Neurotoxicity and Neuropathology Associated with Cocaine Abuse

Editor:

Maria Dorota Majewska, Ph.D.

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Cocaine Addiction as a Neurological Disorder: Implications for Treatment

Maria Dorota Majewska

INTRODUCTION

Addiction to stimulants such as cocaine or amphetamine is a chronic, difficult-to-treat psychiatric disorder characterized by very high rates of relapse that can occur following many months or even years of abstinence. Years of diagnostic observations of drug addicts have shown that chemical dependency, including dependency on stimulants, is associated with a variety of coexisting psychiatric and neurological disorders.

This monograph grew out of a technical review sponsored by the National Institute on Drug Abuse (NIDA) in July 1994 that evaluated the existing clinical and preclinical evidence of neurotoxicity and neuro-pathology associated with chronic abuse of stimulants, particularly cocaine. The individual chapters presented in this publication discuss different facets of this topic and together provide convincing proof of neurotoxic effects of stimulants.

The present chapter describes the logic underlying the notion that addiction to cocaine/stimulants could be viewed as a neurodegenerative or neuro-logical disorder and that treatment should address problems of coexisting neurochemical abnormalities. The proposed concept aims to stimulate thoughts and further research in this area, which may ultimately aid the development of effective medications for the treatment of stimulant addiction.

SYSTEMIC COCAINE TOXICITY

Medical complications and deaths associated with cocaine abuse are common. Cocaine toxicity manifests itself at the level of nearly every organ system, with the most dramatic changes observed in the cardio-vascular system, liver, and the brain.

In the cardiovascular system, tachycardia, hypertension, ruptures of blood vessels, arrhythmias, and arteriosclerotic lesions are typical

complications of cocaine abuse that often precede myocardial ischemia and infarction (Karch 1993). Cocaine seems to be hepatotoxic in humans (Marks and Chapple 1967) and animals (Mehanny and Abdel-Rahman 1991; Thompson et al. 1979); this hepatotoxicity is enhanced by drugs such as barbiturates, alcohol, and cocaine adulterants. Cocaine also induces pulmonary disorders, which are particularly severe in cocaine smokers. These disorders include barotrauma, inflammation and lung infections, pulmonary congestion, edema, hypertrophy of pulmonary arteries, and pulmonary necrosis (Karch 1993). The systemic toxicity of cocaine may indirectly contribute to neurological impairments resulting from chronic cocaine abuse.

COCAINE-INDUCED NEUROLOGICAL IMPAIRMENTS

Findings from animal and clinical studies have shown that chronic use of cocaine can produce serious neuropathies. In humans, cocaine abuse can lead to seizures, optic neuropathy, cerebral infarction, subarachnoid and intracerebral hemorrhage, multifocal cerebral ischemia, cerebral atrophy, and myocardial infarction leading to global brain ischemia and edema (Daras et al. 1991; Fredericks et al. 1991; Klonoff et al. 1989; Lathers et al. 1988; Lichtenfeld et al. 1984; Mody et al. 1988; Pascual-Leone et al. 1991). Morphological, physiological, and neurochemical abnormalities in chronic drug abusers have been demonstrated by using modern diagnostic techniques such as positron emission tomography (PET), computed axial tomography (CAT), magnetic resonance imaging (MRI), and single photon emission computed tomography (SPECT) (Bartzokis et al., this volume; Cascella et al. 1991; Pascual-Leone et al. 1991). Various degrees of cere-bral atrophy and brain lesions, particularly in the frontal cortex and basal ganglia, were found in cocaine abusers (Bartzokis et al., this volume; Langendorf et al., this volume; Pascual-Leone et al. 1991). Several investi-gators also noticed patchy deficits in cerebral blood perfusion in the fron-tal, periventricular, and temporal/parietal areas in cocaine/polydrug abusers (Holman et al. 1993; Strickland et al. 1993; Volkow et al. 1988); these deficits are acutely aggravated by cocaine (Kosten et al., this volume). These circulatory deficits may ensue directly from cocaine-induced vaso-constriction of cerebral blood vessels as well as increased platelet aggrega-tion and blood clotting (Kosten et al., this volume; Rinder et al. 1994).

In addition, marked abnormalities in cerebral glucose metabolism in several brain areas were noted in cocaine/polydrug abusers as compared to normal individuals, with variable direction of metabolic changes dependent on the stage of cocaine use, withdrawal, or abstinence. London and colleagues (1990, this volume) showed that intravenous (IV) injections of cocaine in human volunteers globally reduced cerebral glucose metabolism in the neocortex, basal ganglia, hippocampus, thalamus, and midbrain, and that this metabolic decrease was temporally correlated with euphoria. The acute effect of IV cocaine contrasted with marked increases of metabolic activity in orbitofrontal cortical regions and basal ganglia, measured during early phase of cocaine abstinence (1to 3 weeks) (Flowers et al. 1994; Volkow et al. 1991). The protracted period of cocaine abstinence was characterized by decreased metabolic activity in the prefrontal cortex, particularly in the left hemisphere (Volkow et al. 1992a), and was accompanied by impaired cerebral blood flow that persisted for at least 3 to 6 months after detoxi-fication from cocaine (Strickland et al. 1993; Volkow et al. 1988). London and colleagues (this volume) demonstrated that polydrug abusers in early stages of cocaine withdrawal had statistically decreased glucose metabo-lism in visual cortex when measured in absolute values; when values were normalized for global glucose metabolism, a relative increase in metabo-lism was noticed in the orbitofrontal area. The dynamics of metabolic changes associated with cocaine withdrawal and abstinence vary for different brain regions (Flowers et al. 1994) and may, to a certain degree, be correlated with cocaine craving (Grant et al. 1994).

Furthermore, utilization of 31P magnetic resonance spectrometry recently revealed that chronic cocaine abusers show marked reduction in ß-ATP/Pi ratio, particularly in the cerebral cortex, which is strong evidence of the bioenergetic deficits in cocaine addicts (Christiansen et al. 1994, submit-ted). Such deficits are typically observed in individuals who have experi-enced cerebral hypoxia or ischemia, and suggest that chronic cocaine/ stimulant abusers may have dysfunctional brain mitochondria which can subsequently lead to disintegration of cellular membranes and neuronal death. The above data are consistent with observations by others, des-cribing patchy deficits in cerebral perfusion and ischemic episodes in stimulant addicts.

Taken together, the increasing body of evidence indicates that chronic cocaine abusers show signs of neurological deficiencies, particularly dysfunctional basal ganglia and hypofrontality, which appear similar tothose found in variety of neurological/psychiatric disorders. For

example, frontal-cortical hypometabolism has been measured in patients with unipolar and bipolar depression (Baxter et al. 1986). Severe hypofrontality is also typical for schizophrenic patients and for patients with frontal lobe degeneration or atrophy resulting from ischemia, seizures, stroke, or injury (Bauchsbaum et al. 1982; Wegener and Alavi 1991). Typically, frontal lobe degeneration is accompanied by dementia, neuropsychological deficits, apathy, depression, and social disinhibition (Heiss et al. 1992; Miller et al. 1991). Several of the latter psychiatric symptoms are also characteristic of long-term stimulant abusers and they may represent psychobehavioral evidence of frontal lobe impairments in addicts. Functional implications of this phenomenon in continuous drug abuse will be discussed later.

Evidence of Dopamine Deficiency in Cocaine Addicts

Dackis and Gold (1985) have postulated that chronic use of cocaine appears to lead to dysregulation of brain dopaminergic systems. This hypothesis is clinically supported by preliminary findings showing a lasting decrease in dopamine (DA) in the brains of cocaine addicts (Wilson et al. 1992) and reported hyperprolactinemia (Dackis and Gold 1985; Mendelson et al. 1988). More recent studies showed multiphasic changes in prolactin release that are temporally correlated with different phases of cocaine abstinence: High plasma prolactin levels were observed during the immediate abstinence (crash) phase, reduced levels during early withdrawal, and modestly increased levels during the later phases of withdrawal (Gawin et al. 1993). Deficiency of dopaminergic functions in cocaine abusers is suggested by observed reduced uptake of dopa to presynaptic dopamine neurons in the striatum (Baxter et al. 1988), and by decrease of dopamine type 2 (D2) receptor density in the cerebral cortex measured by PET (Volkow et al. 1993). Moreover, the incessant hypodopaminergia accompanied by possible lesions in basal ganglia are implicated in chronic cocaine abusers by persistent extra-pyramidal symptoms including dystonic and choreoathetoid movements, tics, and increased resting hand tremor, resembling those manifestations seen in Parkinson's disease (Bartzokis et al., this volume; Bauer 1993, this volume; Daras, this volume).

Possible degeneration (or dysregulation) of dopaminergic terminals in the brains of cocaine addicts is suggested by the results of PET study that revealed significant decrease of cocaine binding to DA transporters in the basal ganglia and thalamus in cocaine addicts as compared with control individuals (Volkow et al. 1992b). Presynaptic degeneration of DA neurons is also implied by reduced density of DA

transporters in the human striatum (Hurd and Herkenkam 1993) and in the prefrontal cortex (Hitri et al. 1994) as measured postmortem in cocaine addicts, although some studies found an increased density of these transporters in abusers dying of cocaine overdose (Staley et al. 1994). The apparent discrepancy illustrates the dynamic nature of changes in densities of DA transporters, determined by subject heterogeneity and differences in stages of cocaine intoxication, withdrawal, or abstinence (Kosten et al., this volume). Finally, it has been suggested that a sign of extreme DA deficiency in cocaine abusers may be a neuroleptic malignant-like syndrome that can lead to rapid death in this population (Kosten and Kleber 1988). Because DA plays a vital role in central nervous system (CNS) reward mechanisms, the data indicating either degeneration or persistent downregulation of DA pathways in long-term cocaine abusers suggest that hypodopa-minergia may be an underlying cause of anhedonia and a driving force for relapse in this population.

PSYCHIATRIC IMPAIRMENTS AND COMORBIDITY IN COCAINE ABUSERS

Psychopathology of Cocaine Abuse

Cocaine abusers exhibit an array of cognitive deficits, particularly in attention, problemsolving, abstraction, arithmetic performance, and short-term memory (Herning et al. 1990; O'Malley et al. 1992). These deficits seem to correspond to findings of neurological impairments, particularly hypofrontality, in stimulant addicts. Cocaine/polydrug abusers also show deviant brain electrical activity manifested in anomalous EEG patterns, particularly an increase in ß activity in frontal cortical areas, and delays or reduced amplitudes of evoked potentials (Braverman et al. 1990; Herning and King, this volume; Pickworth et al. 1990). Such patterns of deficien-cies are characteristic of brain aging and dementia, and they constitute convincing evidence of neurological impairments, accelerated brain aging, and/or possible cerebral atrophy in chronic cocaine/polydrug abusers (Herning and King, this volume).

The most significant psychopathologies observed in cocaine addicts include anhedonia, anxiety, anergia, paranoia, depression, and bipolar mood disorder, which may predispose to suicide and are believed to contribute to cocaine craving and relapse. These changes most likely have a neurochemical basis, and persist for months or years after initiation of cocaine abstinence in some former abusers (Gawin 1991;

Gawin and Ellinwood 1988; Gawin and Kleber 1986; Mackler and O'Brien 1991). These persistent, possibly permanent, disorders of affect may be manifestations of brain damage induced by chronic exposure to stimulants or, to some degree, may antecede stimulant abuse. While it is debated whether and which neurological/psychiatric deficits observed in stimulant addicts were preexisting and which are a consequence of drug abuse, the diagnostic surveys of drug addicts suggest that both cases might be true. Nonetheless, it is current clinical consensus that induction or aggravation of depression, anhedonia, and paranoia, as well as impair-ment of cognitive capacities and motoric dysfunction, result from long-term cocaine abuse (Gawin 1991; O'Malley et al. 1992).

Rarely does cocaine/stimulant addiction exist as a sole disorder, and more often it is comorbid with other psychiatric diseases. An epidemiological study of about 300 treatment-seeking cocaine addicts revealed that, in more than 70 percent of those addicts, cocaine/stimulant dependency coexisted with other lifetime psychiatric disorders such as alcoholism, major depression, bipolar depression, anhedonia, anxiety, phobias, anti-social personality, and history of childhood attention deficit disorder (Rounseville et al. 1991). While anxiety, phobias, attention deficit dis-order, and antisocial personality usually preceded the onset of cocaine addiction, depression and alcoholism frequently followed it. Other studies found similar psychiatric comorbidity of cocaine addiction, particularly with alcoholism, depression, bipolar disorder, anxiety, anhedonia, suicidal ideations, and posttraumatic stress disorders (PTSD) (Deykin et al. 1987; Kosten and Kleber 1988; Marzuk et al. 1992; O'Connor et al. 1992). Although psychosis, hallucinations, and delirium are typical features of cocaine overdose, schizophrenic disorders were not highly correlated with cocaine abuse. However, paranoia, which is common in long-term cocaine abusers, appears to be induced by chronic use of stimulants and has been linked to the animal model of sensitization (Gawin and Khalsa-Denison, this volume).

Attention Deficit-Hyperactivity Disorder (ADHD) and Cocaine Abuse

A strong correlation between stimulant abuse and ADHD, manifested by hyperactivity, distractibility, mood lability, learning disability, and con-duct disorder (Rounseville et al. 1991), is of special interest to researchers. The etiology of ADHD is not known, but it is believed that it may result from perinatal hypoxia, trauma, exposure to neurotoxins, or from genetic defects of corticogenesis (Benson 1991; Heilman et al. 1991). Modern diagnostic techniques have revealed an

association between ADHD and prefrontal/frontal dysfunction, reduced cerebral perfusion and metabo-lism, as well as morphological abnormalities in the frontal lobes (Benson 1991; Hynd et al. 1991). Electroencephalographic (EEG) studies showed abnormal EEG patterns in frontal and temporal cortical regions in hyper-active children (Mann et al. 1992). Hypofrontality associated with ADHD may correspond to the apparent hypofrontality observed in chronic stimu-lant abusers (Volkow et al. 1988, 1992a).

Attention deficits and motor restlessness seem to reflect dysfunction in the frontal-striatal dopaminergic systems (Heilman et al. 1991), which is supported by the fact that ADHD symptoms are controlled by psycho-stimulants (amphetamine, methylphenidate) that increase catecholamine neurotransmission. The link between dopaminergic deficiency and ADHD is also supported by findings from preclinical studies in which administration of the neurotoxin N-methyl-4-phenyltetrahydropyridine (MPTP) (which destroys DA neurons) to nonhuman primates produced neuropsychiatric impairments similar to those observed in ADHD (Roeltgen and Schneider 1991). DA deficiency observed in chronic stimulant abusers and that associated with ADHD may have a common biological substrate, which may suggest that the high percentage of stimulant abusers diagnosed with ADHD represents a population that is self-medicating for DA deficits.

Posttraumatic Stress Disorder

Epidemiological studies suggest a strong relationship between drug abuse and PTSD (Cottler et al. 1992). The etiology of PTSD is complex, as this disorder can be triggered by various physical or psychological traumas that can produce long-lasting or permanent changes in the brain morphol-ogy and function (Post 1992).

Stress-induced overactivity of the hypothalamic-pituitary-adrenal (HPA) axis may contribute to the development of neurological deficits and/or increased vulnerability to stimulant addiction. Exposure of animals to stress increases the turnover and extracellular concentration of DA (Abercrombie et al. 1989), as would a small "priming" dose of cocaine, and may result in priming the animal or human to cocaine use. On the other hand, administration of cocaine, similar to stress, stimulates the HPA axis (Calogero et al. 1989) and ensues in release of adrenal hor-mones. There are several commonalities between cocaine and stress with respect to activation of the catecholaminergic systems and the HPA axis. An intriguing connection between drug addiction and stress has been revealed by

studies which showed that rats subjected to stress learned to self-administer amphetamine much faster than control rats (Piazza et al. 1989, this volume). Increased vulnerability to stimulant addiction has been linked to release of high levels of glucocorticoids, and acquisition of amphetamine or cocaine self-administration in rats could be abolished by adrenalectomy (Goeders and Guerin 1993; Piazza et al. 1991, this volume).

While the neurochemical bases of those phenomenon are not clearly established, several mechanisms may be considered. Piazza and colleagues (this volume) proposed that stress-induced sensitization to stimulants may be mediated by glucocorticoid-induced increased activity of mesencephalic DA neurons. In addition, high levels of glucocorticoids have been shown to induce degeneration of hippocampal neurons (Sapolsky et al. 1985), suggesting that prolonged stress could result in atrophy and functional deficits of certain brain regions, subsequently increasing vulnerability to stimulant addictions. Indeed, lesions to the medial prefrontal cortex in rats were shown to produce supersensitivity to the reinforcing effects of cocaine (Schenk et al. 1991). Along with glucocorticoids, stress stimulates the release of other adrenal steroids and activates synthesis of certain neuro-steroids in the brain (Majewska 1992). The author and colleagues have shown that several of the stress-induced steroids are potent, bimodal modulators of gamma-aminobutyric acid A (GABA-A) receptors in the brain. Reduced metabolites of progesterone and deoxycorticosterone act as allosteric agonists of GABA-A receptors (Majewska et al. 1986), whereas pregnenolone sulfate and dehydroepiandrosterone sulfate act as antagonists (Majewska and Schwartz 1987; Majewska et al. 1988, 1990). Because GABA controls the excitability of neurons and indirectly modulates vir-tually all CNS functions, including learning and memory, the stress-induced GABA-modulatory steroids may play an important role in drug addictions, for which learning is integral.

Childhood Lead Exposure

Recent studies also point to a disturbing link between drug addiction and poisoning with lead, a known neurotoxicant. Chronic or acute exposure to environmental lead during childhood produces encephalopathy in many brain regions including the cerebral cortex, hippocampus, and cerebellum, as well as general axo-dendritic disorganization. This encephalopathy is accompanied by deficient intellectual development, attention deficits, hyperactivity, aggression, behavioral deficits, and general developmental impairments (Vega et

al. 1990; Verity 1990). Lead exposure has been linked to disturbances of the HPA axis and cardiovascular system (Boscolo and Carmignani 1988) as well as to abnormalities in glutamate, DA, and GABA neurotransmission which may result in part from impaired mito-chondrial energy metabolism in the brain (Verity 1990).

Associations between lead exposure during childhood, encephalopathy, and ADHD suggest that lead poisoning may be a factor contributing to the etiology of drug abuse. This notion is supported by results from preclinical studies which documented that chronic exposure of weanling rats to low levels of lead increased their sensitivity to, and self-adminis-tration of, stimulants as compared with control animals (Cory-Slechta and Widzowski 1992).

COCAINE-INDUCED PLASTICITY AND NEUROTOXICITY: ANIMAL STUDIES

The concept that chronic cocaine/stimulant abuse creates lasting neurochemical deficits which may be underlying causes of affective disorders, cognitive impairments, and relapse in addicts is supported by animal studies.

Cocaine-Induced DA Deficiency

Powerful reinforcing effects of cocaine are believed to ensue from its actions to increase extracellular DA levels in the striatum (Pettit et al. 1982; Roberts et al. 1989). Although cocaine binds to biogenic amine transporters and inhibits the reuptake of DA, noradrenaline, and serotonin, its reinforcing properties appear to correlate primarily with inhibition of DA uptake (Pettit et al. 1982; Ritz et al. 1987).

Chronic use of cocaine seems to lead to persistent hypodopaminergia, which may ensue from factors such as prevention of neuronal DA reuptake by cocaine, the compensatory downregulation of DA systems involving supersensitivity of presynaptic DA receptors (Gawin and Ellinwood 1988), and degeneration of DA neurons. This concept is supported by both the clinical evidence (discussed earlier) and results of preclinical studies. Although some investigators reported lack of long-term monoamine depletion following chronic treatment of rats with cocaine (Kleven et al. 1987), the majority of studies point to the existence of DA deficiency. Trulson and colleagues (1987) reported that chronic cocaine treatment induced persistent reduction

in tyrosine hydroxylase (TH) immunoreactivity in the mesolimbic DA system in the rat brain.

Beitner-Johnson and Nestler (1991) observed changes in TH activity in rats chronically exposed to cocaine. In the nucleus accumbens (NA) cocaine decreased the state of phosphorylation of TH, consistent with decreased DA synthesis (Beitner-Johnson and Nestler 1991; Beitner-Johnson et al. 1992). Chronic administration of cocaine to rats consis-tently produced a marked reduction of DA synthesis in the NA (Brock etal. 1990) and decreased DA turnover in the hypothalamus, NA, and frontal cortex, in which depletion of DA lasted for up to 6 weeks after the administration of cocaine (Karoum et al. 1990). Convincing evidence of cocaine-induced DA deficiency was rendered by Hurd and colleagues (1989, 1990), who showed that IV cocaine self-administration produced marked DA overflow in NA and caudate-putamen in naive rats, but DA overflow was attenuated in animals chronically exposed to cocaine. Other investigators also reported that withdrawal from chronic cocaine administration decreased the basal level and release of DA in the limbic system, particularly in the NA of rats (Parsons et al. 1991; Robertson et al. 1991; Segal and Kuczenski 1992). Imperato and colleagues (1992) described a biphasic effect of chronic cocaine treatment on extracellular levels of DA in the ventral striatum: Cocaine administration for up to 5days increased DA levels, consistent with behavioral sensitization, whereas treatment for more than 6 days produced DA deficit. DA deficiency may explain the phenomenon of cocaine tolerance observed 7days after withdrawal from 14 days of continuous cocaine infusion and associated supersensitivity of somatodendritic DA autoreceptors on nigral neurons, in contrast to the behavioral sensitization observed in rats treated by daily cocaine injections (King et al. 1992; Zhang et al. 1992).

In addition to cocaine-induced changes in brain DA levels, several investi-gators observed alterations in presynaptic DA transporters. After chronic cocaine treatment, a reduced density of DA transporters in mesolimbic/ mesocortical brain regions in rats has been reported (Goeders et al. 1990). In rats, decreased density of DA transporters, lasting for at least 12 weeks after cocaine withdrawal, was also found in the frontal cortex (Hitri and Wyatt 1993) and in the NA 10 days after withdrawal from chronic cocaine administration (Sharpe et al. 1991). These lasting, often delayed changes induced by chronic cocaine treatment, including decreased DA synthesis and release and reduced density of DA transporters, suggest either a compensatory

downregulation of the dopaminergic systems or neuronal degeneration.

Cocaine Neurotoxicity

While the neurotoxic effects of amphetamine have been easy to document in animal models, cocaine-induced neurotoxicity has been controversial. However, recent findings of Ellison (1992; Ellison et al., this volume) clearly established that cocaine is also neurotoxic: Continuous exposure to cocaine for 3 to 5days (pellets releasing 103 milligrams (mg) of cocaine over 5 days), in a regimen that mimics bingeing in addicts, produced strik-ing axonal degeneration extending from lateral habenula along the fascic-ulus retroflexus toward the ventral tegmentum.

In rats exposed to continuous cocaine, persistent changes in acetylcholine (ACh) and GABA receptors in the caudate were observed, implying damage to structures postsynaptic to DA neurons (Ellison et al., this volume). These neurodegenerative changes resembled effects of amphet-amine and were observed 30 days after removal of cocaine pellets, sugges-ting that they were long lasting or permanent. In contrast to continuous cocaine infusion, daily injections of 20 mg of cocaine for 5 days failed to produce neurodegeneration but did result in behavioral sensitization. Neurochemical evidence of cocaine-induced neurodegeneration was also furnished by other investigators. Hurd and colleagues (1990) showed that repeated cocaine self-administration produced decreased levels of extra-cellular ACh in rat caudate-putamen in addition to DA deficiency. Contin-uous administration of cocaine was also shown to produce a persistent reduction in binding of the muscarinic receptor ligand and an increase in binding of the central benzodiazepine receptor ligand in the caudate, NA, olfactory tubercle, dorsal hippocampus, amygdala, and cerebral cortex (Zeigler et al. 1991). The upregulation of benzodiazepine receptors (coupled to the GABA-A receptors) could result from decreased GABA synthesis and may suggest degeneration of GABAergic neurons. This concept is supported by findings that repeated administration of ampheta-mine decreases glutamate decarboxylase messenger ribonucleic acid (mRNA) and GABA release in the brain (Lindefors et al. 1992).

The brain regions that degenerated after continuous cocaine exposure are very rich in ACh and are the crossroads for DA, GABA, and ACh inner-vations (Angevine and Cotman 1981); therefore their lesions are likely to cause impairment of neuronal functions mediated by these

neurotrans-mitters. Such effects were, in fact, observed behaviorally in rats in the forms of exaggerated fear, anxiety, and reduced exploratory behavior (Zeigler et al. 1991). Perhaps similar neurodegeneration takes place in cocaine abusers, contributing to the observed cognitive deficits, anxiety, paranoia, psychosis, and the disturbance of reward pathways and affect (Gawin 1991) that may indicate permanently altered neuronal pathways.

Changes in Neuropeptidergic Systems

Several persistent changes in neuropeptidergic transmission have been reported as resulting from chronic cocaine exposure in animals and humans. Hurd and Herhenham (1993) examined the neostriatum of human cocaine addicts postmortem and found marked reduction of enkephalin mRNA as well as decrease of DA transporter, concomitant with an eleva-tion of dynorphin levels and k receptors. Reduction of enkephalinergic systems and potentiation of dynorphinergic systems have been interpreted as contributing to dysphoria and craving in cocaine addicts, because activation of k receptors in the mesolimbic system seems to exert aversive effects (DiChiara and Imperato 1988; Herz 1988). Part of aversive and anhedonic effects mediated via dynorphin may be due to its interaction with the DA system, where kappa agonists have been shown to decrease DA release (DiChiara and Imperato 1988). Rats that either self-adminis-tered cocaine or were chronically treated with cocaine had higher levels of mRNA for dynorphin and substance P in the brain areas innervated by DA (Hurd et al. 1992; Sivam 1989; Smiley et al. 1990). Chronic cocaine injec-tions were also reported to upregulate μ receptors in several brain areas rich in dopaminergic terminals such as cingulate cortex, caudate-putamen, NA, and amygdala (Unterwald et al. 1992).

Pilotte and colleagues (1991) described persistent changes in the density of neurotensin (NT) receptors following chronic cocaine administration and withdrawal, including decrease of presynaptic receptors in the ventral tegmental area (VTA) containing the dopaminergic pericarya and an increase of postsynaptic NT receptors in the prefrontal cortex containing DA terminals. Because DA and NT are colocalized in mesocorticolimbic neurons and NT in the VTA depolarizes DA-releasing neurons, the changes in density of NT described above seem consistent with loss of dopaminergic function.

The persistent alterations in neuropeptidergic transmission seen after chronic cocaine use may signal either lasting neuroadaptions or

neuro-degeneration that may underlie abnormal neuropsychological functioning in cocaine addicts.

Biochemical Mechanism of Cocaine Neurotoxicity

Although the neurochemical processes involved in cocaine-induced neurotoxicity are not well characterized, there are several pathogenic phenomena that may be considered. Cocaine transiently increases extracellular levels of catecholamines. The excessive concentrations of DA can be neurotoxic (Filloux and Wamsley 1991), and catecholamines have been shown to cause neuronal death in tissue cultures (Rosenberg 1988). The mechanisms of DA cytotoxicity may involve its autoxidation in the extracellular environment which generates extremely reactive free radicals and toxic quinones (Ben-Shachar et al. 1995; Graham et al. 1978; Slivka and Cohen 1985). Cocaine, and the episodic excessive synaptic activity of catecholamines that it produces, may also induce neurotoxicity via interference with mitochondrial electron transport and oxidative phosphorylation (Ben-Shachar et al. 1995; Fantel et al. 1990; Leon-Valarde et al. 1992), leading to bioenergetic deficits and subsequent activation of a host of neurodegenerative and necrotic events.

An important factor of cocaine-induced neurotoxicity is vasoconstriction of cerebral blood vessels and coronary arteries combined with increased platelet aggregation, which can lead to focal or general ischemic episodes and cerebral infarctions. The ischemic episodes may additionally impair mitochondrial function, and by compromising brain energy metabolism (Majewska et al. 1978) may lead to neurodegeneration and development of brain edema (Bartzokis et al., this volume). Moreover, subarachnoid or intracerebral hemorrhages in chronic cocaine abusers may lead to accumulation of iron in neuronal and glial plasma membranes, which stimulates free radical peroxidation of membrane lipids and damages cellular integrity (Bartzokis et al., this volume).

In addition, cocaine-induced neurotoxicity may be mediated by uncon-trolled release of glutamate provoked by ischemic episodes. Glutamate activates ionotropic and metabolotropic glutamate receptors; overactivity of those receptors leads to the excessive excitation of neurons and accumu-lation of intracellular Ca++, which may induce neuronal death (Majewska and Bell 1990; Simon et al. 1984). Because DA has been shown to potentiate the neurotoxic effects of excitatory amino acids (Filloux and Wamsley 1991; Wood et al. 1992), the neurotoxicity produced by chronic cocaine use may

involve synergistic actions of DA and glutamate. In part, cocaine-induced neurotoxicity may be also mediated by dynorphin whose levels increase after chronic cocaine treatment/use and which was suggested to be neurotoxic (Faden, this volume). It is possible that in cocaine addicts who coabuse alcohol the neurotoxic effects are more robust than those observed in animal models as a result of formation of cocaethylene, which appears to be more toxic than cocaine (Hearn et al. 1991).

SUMMARY

Clinical and preclinical studies provide convincing evidence for persistent neurological/psychiatric impairments and possible neuronal degeneration associated with chronic cocaine/stimulant abuse. These impairments include multifocal and global cerebral ischemia, cerebral hemorrhages, infarctions, optic neuropathy, cerebral atrophy, cognitive impairments, and mood and movement disorders. These findings may encourage the place-ment of stimulant addiction into the category of organic brain disorders. Functional and microanatomical anomalies in the frontal and temporal cortex as well as other brain regions may be responsible for certain aspects of phenomenology and neuropsychopathology that are characteristic of stimulant polydrug addictions. These may include broad spectrum of deficits in cognition, motivation, and insight; behavioral disinhibition; attention deficits; emotional instability; impulsiveness; aggressiveness; depression; anhedonia; and persistent movement disorders. Although it is still debated whether the hypofrontality and other brain anomalies observed in stimulant abusers are a consequence or an antecedent of drug abuse, this debate seems purely academic and irrelevant with respect to the importance of compensating for these deficits in the development of treatment strategies.

The neuropsychiatric impairments accompanying stimulant abuse may contribute to the very high rate of relapse in addicts that can take place after long periods (years) of abstinence. It is possible that the neurological deficits present in stimulant addicts, whether they are primary or secondary to stimulant abuse, are responsible for perpetual drug abuse which may be a form of self-medication (Weiss et al. 1991, 1992). In this context, addiction to stimulants, once fully developed, may represent a true biological dependency on drugs that temporarily compensate for existing neurological deficits. The concept of self-medication by drug addicts is supported by major theories of biological psychiatry. While a majority of drug addicts are polydrug users, there seems to be a prefer-

ence for a particular type of drug among different populations of addicts. Addicts who experience distress, anxious dysphoria, and turbulent anger prefer the calming actions of opiates, whereas addicts with preceding attention deficit disorder, depression, or bipolar disorder often prefer stimulants (Khantzian 1985). Figure 1 presents conceptual relationships between brain damage and cocaine/stimulant abuse.

More clinical studies are needed to establish unequivocally the epidemiological relationships between preexisting neurological deficits—resulting either from genetic, developmental, traumatic, or neurotoxic factors—and vulnerability to drug addictions. Nonetheless, deducing from the results of preclinical studies, it is conceivable that individuals with neurological deficits associated with attention deficit disorder, developmental neuroanatomical abnormalities, lead poisoning, alcoholism, posttraumatic brain lesions, and PTSD may be more vulnerable to stimulant addiction. This notion has significant empirical support as preclinical studies have shown that animals with lesioned prefrontal cortex became supersensitive to cocaine (Schenk et al. 1991) and animals with lesions at the amygdala, VTA, or raphe nuclei manifest more rapid acquisition of amphetamine self-administration than control rats (Deminiere et al. 1989).

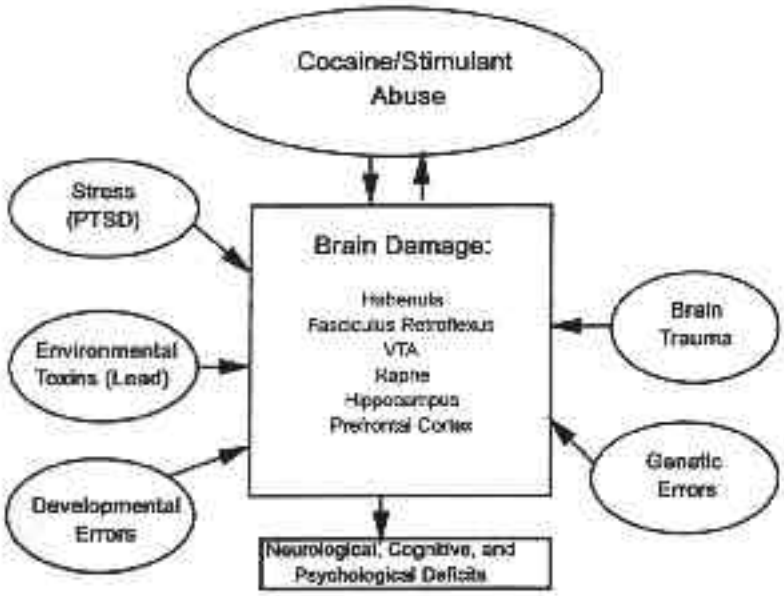

FIGURE 1. *Conceptual relationships between brain damage and cocaine/stimulant abuse.*

The above arguments, postulating neuropathology as an intrinsic com-ponent of stimulant addiction, should be taken into consideration with the caveat that the clinical manifestations of the disease are heterogenous and addicts may express varying stages and degrees of the disease as deter-mined by environmental and genetic factors. Therefore, it is likely that stimulant addicts who have less advanced neuropathology may recover spontaneously after detoxification with proper nutritional and psychother-apeutic support if they can sustain abstinence. On the other hand, it is conceivable that the effective treatment for addicts with more advanced neuropathology may require not only essential psychotherapy and deconditioning of patients (O'Brien et al. 1992), but also a medication that targets the problems of accompanying neurological deficits. Theo-retically, medications that would repair the neurological damage and/or compensate for neurochemical deficits might be effective. Such medica-tions should possibly be fashioned after those prescribed for stroke, trauma, ischemia, neurodegeneration, Parkinson's disease, or dementias, and may include treatments that promote neuronal regeneration. In NIDA's Medications Development Division, clinical trials are underway to test several medications that address these problems.

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AUTHOR

Maria Dorota Majewska, Ph.D.
Special Expert
Clinical Trial Branch
Medications Development Division
National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

Brain Atrophy and Chronic Cocaine Abuse: Background and Work in Progress

Frederick G. Langendorf, David C. Anderson, David E. Tupper, David A. Rottenberg, and Irwin D. Weisman

INTRODUCTION

The crack epidemic, now a decade old, disabused neurologists of the idea that cocaine was a relatively safe drug. Acute neurologic complications of cocaine intoxication such as headaches, delirium, seizures, and strokes have now been amply delineated. Less clear is whether long-term cocaine use, uncomplicated by acute problems, can lead to structural or functional changes in the human brain. Brain atrophy is a potential consequence of alcohol abuse (Cala and Mastaglia 1980; Fox et al. 1976; Harper et al. 1988; Ron et al. 1982), inhalant abuse (Hormes et al. 1986; Rosenberg et al. 1988), and use of nonrecreational substances such as corticosteriods (Bentson et al. 1978; Gordon 1980) and valproic acid (McLachlan 1987). This chapter summarizes some earlier work linking long-term cocaine abuse to brain atrophy, and it describes an ongoing investigation of brain atrophy and dysfunction in chronic cocaine abusers using volumetric brain magnetic resonance imaging (MRI).

PRIOR STUDIES

The use of cocaine in Minneapolis and St. Paul took off in 1986, about a year after the crack epidemic arrived in New York. Admissions to Hennepin County Medical Center (HCMC) for cocaine-related illness quadrupled within a year, with neurologic complications accounting for about a tenth of these admissions. A link between brain atrophy and cocaine first surfaced in a retrospective study of patients admitted with the then relatively novel diagnosis of cocaine-related seizure (Pascual-Leone etal. 1990). This study covered 1985 to 1987, during which time 474patients were admitted to HCMC with a primary diagnosis of acute cocaine intoxication corroborated by a positive urine toxicology screen for-cocaine. Thirty-two of these patients had a first-ever seizure within 90minutes of using cocaine. Thirteen of these 32 were first-time

cocaine users. Computed tomographic (CT) head scans were performed in all 32patients with new-onset seizures. Among the 13 first-time users, there was a single abnormal scan; it showed a subarachnoid hemorrhage. Among the 19 habitual cocaine users, two scans revealed cerebral infarc-tion and 10 (53 percent) showed diffuse cerebral atrophy. All 10patients with atrophy were human immunodeficiency virus (HIV) negative. None was older than 38 years. Their experience with alcohol and other drugs could not be accurately determined.

In a second retrospective study covering a similar time interval, the focus was on brain volume, itself quantified by linear CT measurements (Pascual-Leone et al. 1991). This study included patients at HCMC and the University of Minnesota Hospital admitted with cocaine intoxication or addiction who underwent a CT scan. The presenting problem was head-ache (about half), seizure, delirium, or movement disorder. Patients with the following potentially confounding variables were excluded: polydrug or alcohol abuse (by self-report), alcohol dependence (by "Diagnostic and Statistical Manual of Mental Disorders," 3d ed. (DSM-III) criteria), HIV seropositivity, decreased serum albumin, and age less than 20 or greater than 40 years. Of the 51 patients studied, 16were first-time cocaine users. Planimetric measurements were performed on the CT scans of the first-timeand habitual cocaine groups as well as a control group of 54 patients admitted for headache with the same exclusions. There were seven mea-surements (see figure 1) plus four indices derived from these measures.

The habitual cocaine abuser group differed significantly from both the first-use and control groups on all but two of the measurements and all four indices. This finding implies cerebral atrophy in the habitual user group (table 1). There was no significant difference on any of the measures or derived indices between the first-use cocaine subgroup and the controls. There was no relationship between CT measurements and age in this two-decade age range. There was a correlation between duration of cocaine abuse and atrophy on one measure, the maximal frontal horn width, suggesting a dose-effect relationship (figure 2).

There is little additional information on the effect of cocaine abuse on human brain volume. Studies involving cocaine and CT or MRI brain imaging have featured abusers of multiple drugs (including alcohol) besides cocaine. In a study from Johns Hopkins University and the National Institute on Drug Abuse (NIDA) Addiction Research Center, three planimetric CT measures were made on a group of abusers of

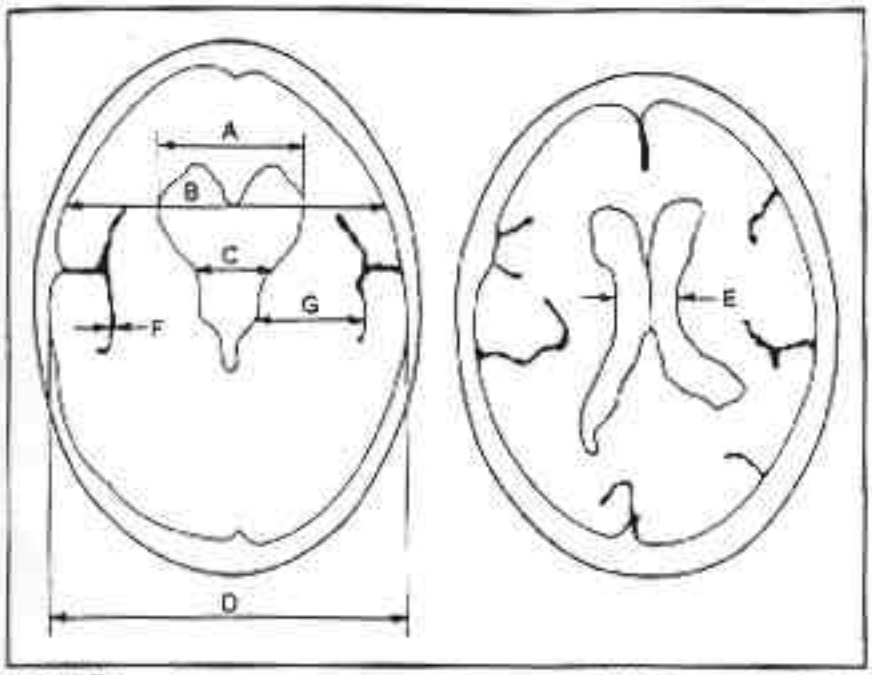

FIGURE 1. *Linear measurements taken on axial CT slices. Maximal width of the frontal horns of the lateral ventricles (A), frontal brain width (B), minimal intercaudate distance (C), maximal width of the brain (D), minimal width of the ventricular bodies (E), maximal width of the sylvian fissure (F), and mean distance between the third ventricle and the sylvian fissure (G).*

multiple substances, including cocaine (Cascella et al. 1991). A severity score was established for each drug, based on frequency and quantity of use. Substance abusers and controls differed significantly on third ventricular width, suggesting atrophy in the substance abuser group. For individual substances, however, only alcohol severity scores could be correlated with any measure of atrophy, after taking into account the effect of age.

There is a single study that includes volumetric MRI measures performed at the University of Trondheim, Norway. The study group consisted of polysubstance abusers with experience in, or abuse of, a mean of 5.3 drugs, including heavy alcohol consumption in each case (Aasley et al. 1993). There were planimetric and volumetric measures of the cerebral hemispheres and cerebellum; the substance abuser and control groups

TABLE 1. Values of the linear measurements and calculated indices of cerebral atrophy on CT in controls (N = 54) and first-time (N = 16) and habitual (N = 35) cocaine abusers.

		Cocaine abusers	
	Controls	1st time	Habitual
Max. frontal horns width (A)	3.06±0.20	3.04±0.26	3.63±0.32*
Frontal brain width (B)	10.77±0.37	10.68±0.44	10.69±0.47
Min. intercaudate distance (C)	0.83±0.14	0.80±0.22	1.14±0.32*
Max. brain width (D)	12.76±0.66	12.96±0.57	12.17±0.63
Min. ventricular bodies width (E)	2.30±0.30	2.40±0.41	2.81±0.37*
Max. sylvian fissure width (F)	0.22±0.06	0.21±0.11	0.28±0.08†
Distance third ventricle-sylvian fissure (G)	3.88±0.20	3.88±0.21	3.73±0.36‡
Frontal lobe index (A/B)	0.29±0.02	0.29±0.03	0.34±0.03*
Evans ratio (A/D)	0.24±0.02	0.23±0.02	0.28±0.03*
Bicaudate index (C/D)	0.07±0.01	0.06±0.02	0.09±0.02*
Huckman number (A+C)	3.88±0.26	3.84±0.39	4.76±0.54*

NOTE: All measurements given in cm as mean ± standard deviation.

KEY: * = $p < 0.005$ habitual cocaine addicts versus controls and versus first-time cocaine users; † = $p < 0.005$ habitual cocaine addicts versus controls, $p < 0.05$ versus first-time cocaine users; ‡ = $p < 0.05$ habitual cocaine addicts versus controls and versus first-time cocaine users; max = maximum; and min. = minimum.

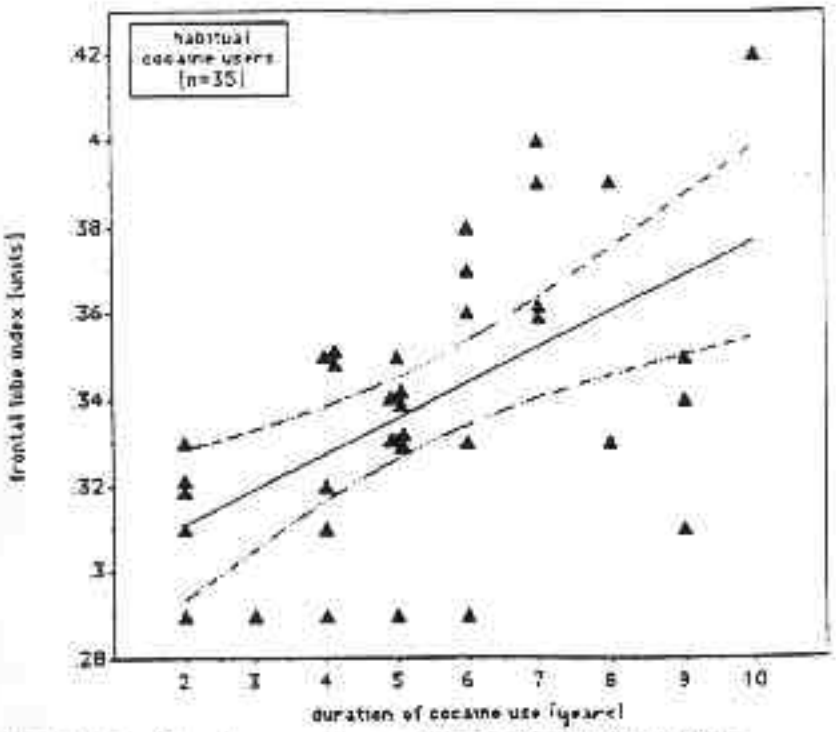

FIGURE 2. *Simple regression analysis for frontal lobe index (A/B) and duration of cocaine abuse in years in the 35 habitual cocaine abusers. Regression line and 90 percent confidence bands for the true mean of the frontal lobe index are displayed.*

differed only on a measure of the volume of the cerebellar vermis, the site of alcoholic cerebellar degeneration.

In two studies of single photon emission computed tomography (SPECT) in cocaine abusers, many subjects abused additional substances, including alcohol. In one of these, CT scans were also obtained, supplementing SPECT data (Tumeh et al. 1990). Diffuse cerebral atrophy was found in 2 of 10 subjects, one of whom used alcohol heavily. In the second SPECT study, MRI revealed diffuse cerebral atrophy in one subject of eight, whose substance abuse profile is not described (Strickland et al. 1993).

The reported HCMC studies were limited. Their retrospectivity prevented adequate control for the confounding influence of alcohol or other substances, nutritional status, and other neurologic problems

such as multiple head injuries. Brain atrophy was inferred from linear measure-ments in a single plane. No conclusions about preferential involvement of grey or white matter were possible, and no mechanism for atrophy was suggested. In other studies, alcohol appeared to be a potent confounder. It would also be important to consider whether any brain atrophy due to cocaine brings brain dysfunction in its wake, and whether either atrophy or dysfunction prove to be reversible with abstinence from cocaine.

THE BRAIN ATROPHY AND DYSFUNCTION IN CHRONIC COCAINISM (BADCO) STUDY

The BADCO Study has been undertaken to investigate brain atrophy and its functional consequences in a manner that will overcome some of the methodological problems that have afflicted earlier studies. The study is driven by four hypotheses: Long-term use of cocaine induces cerebral atrophy; atrophy has functional consequences detectable as cognitive and electrophysiological dysfunction; the pathogenic basis for atrophy is cerebral ischemia; and consequences are partially reversible with abstinence from cocaine.

Subjects are recruited among inpatients at four Twin Cities chemical dependency treatment centers. The need for inpatient treatment, defined with increasing stringency in recent years, represents the imprimatur of severe abuse. Total duration of substance abuse must be 6 months or longer. Subjects must be 20 to 40 years old, have at least a 10th grade education, and be 1 to 4 weeks out from their last substance use. Poly-substance abusers, who predominate at these treatment centers, are excluded, along with monosubstance abusers of inhalants and alcohol. Subjects are screened for potentially confounding neurologic, cardiac, metabolic, toxic, and nutritional problems with a neurologic history, physical examination, HIV antibody test, liver function tests, serum albu-min, body mass index, and urine toxicology. Total substance exposure is quantified, and an additional index of functional severity based on the Global Assessment of Function (GAF) Scale (DSM-IV) is assigned.

Subjects are divided into two experimental groups: cocaine abusers and abusers of a single other substance (monosubstance abusers) excluding cocaine, alcohol, and inhalants. (Those who abuse cocaine only are also considered monosubstance abusers.) The group of other monosubstance abusers provides a match for the cocaine abusers in terms of lifestyle. The experimental protocol involves

volumetric MRI, neuropsychological testing, electrophysiological testing and, for some cocaine abusers, SPECT or positron emission tomography (PET). In BADCO's cross-sectional wing, comparisons will be drawn between these two experi-mental groups and normative data for each element of the experimental protocol. Cross-sectional comparisons will address the first two study hypotheses. A longitudinal wing will feature a 6-month reassessment and retest of the cocaine abusers, not all of whom will have continued to abstain from cocaine. Longitudinal data will address the fourth study hypothesis. The functional imaging techniques, SPECT and PET, will be used to address the third study hypothesis.

MRI data are acquired on a 1.5 Tesla unit that also produces standard, clinically useful images. Volumetric analysis is performed using a novel three-compartment model (Bonar et al. 1993). For each subject, a "slab" of brain tissue consisting of 15 to 20 3-millimeter-thick MRI brain slices (including most of the cerebral hemispheres but excluding the posterior fossa) is analyzed. Percentages of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) are calculated for a slab by summing across slices; a fourth (other) compartment consisting mostly of meninges and blood vessels is accounted for. The combined GM+WM compartment can be taken as a relative measure of brain volume; a small GM+WM compartment implies cerebral atrophy. The reproducibility of the method has been investigated in a group of nine normal volunteer subjects aged 20 to 40 years who were scanned two to six times over a period of several years; this group serves as the normal control group for the brain volume aspect of the study. The fractional volume of the GM+WM compartment is extremely stable over time, although the fractional volumes in the individual GM and WM compartments vary somewhat.

The neuropsychological wing of the study involves a battery of tests constructed to evaluate a broad range of cognitive abilities, with a focus on information processing speed and efficiency and on mechanisms of attention. There are tests of general intelligence, including reading ability and vocabulary, that can be expected to reflect baseline function; verbal and visual memory tasks to test immediate memory span, short-term processing, delayed retention, and rate of new learning and retrieval; tests of attention, response time, and impulsivity; tests of executive function; and tests of psychomotor function. A depression inventory is also included. This battery, of course, addresses the question of brain dys-function due to chronic cocaine abuse, and in the specific context of BADCO it permits correlation with anatomic changes revealed by MRI.

The electrophysiological arm of BADCO consists of a quantitative electroencephalogram (EEG). Recording is performed during eyes-open and eyes-closed relaxed wakefulness, as well as during a mental arith-metic task. Artifact is edited out in this system, so that lengthy epochs are available for analog-to-digital conversion and fast Fourier transform analysis. Power in each of six defined frequency bands can be derived for each electrode site. Like the neuropsychological arm of BADCO, the electrophysiological arm affords the possibility of assessing the func-tional correlates of imaging data.

Preliminary Results

For purposes of this chapter, a partial analysis of early BADCO data was undertaken. In keeping with a focus on brain atrophy, volumetric MRI data were analyzed and compared with measures of substance abuse severity. Results from the neuropsychological and electrophysiological arms are not presented.

Forty-five substance abusers have been entered to date (see table 2). Most cocaine abusers smoked crack. The other monosubstance abuser group, at present, includes predominantly opiate abusers. The cocaine abuser and other monosubstance abuser groups are very closely matched for age and education. For each substance, an approximate value for total quantity of substance used was calculated from average quantity per unit time and duration; a rating is based on a scale of 1 to 5. The GAF func-tional outcome rating is based on a scale of 10 to 100, with 100 implying no effect of substance abuse on family or social and occupational function. (Both rating scales are available upon request.) Not surprisingly, the BADCO requirement of inpatient chemical dependency treatment status produced subjects with considerable social and occupational problems. Table 2 reflects the entire BADCO population divided between groups.

MRI data are currently available from 24 cocaine abusers and 6 other monosubstance abusers. These subgroups do not differ significantly from their parent groups, as presented in table 2.

Figure 3 contains illustrative data for a single cocaine abuser who was studied twice, 6 abstinent months apart. In this figure, transaxial slice number (abscissa) is plotted against percentage of brain slab volume (ordinate). Brain slice numbers increase in a caudal-rostral direction. Summing the compartmental contributions of each slice across all

TABLE 2. BADCO Study population to date. Some cocaine abusers have no single preferred route of administration. Lifetime quantity of single substance used is scored on a scale of 1to 5. The measure of functional outcome, scored on a scale of 10 to 100, is described in the text; higher figures imply better function.

	SUBJECTS	
	Cocaine*	Other substance**
Number		
Age		
Education (y)	13.2 (11-19)	12.7 (12-14)
Duration of abuse (y)	4.7 (.6-14)	4.7 (.5-15)
Quantity used	3.2 (1-5)	3.5 (3-4)
Functional outcome	50.4 (15-70)	47.8 (30-70)

KEY: * = route of administration: smoked, 21; insufflated, 8; IV, 1.
** = heroin, 7; prescription opiates, 1; marijuana, 2; benzodiazepines, 1.

15 slices yields the overall percentage composition for each tissue compartment. The large GM contribution (solid line) at slice 25 corresponds to deep grey nuclei (thalamus and basal ganglia), the WM peak at slice 35 (dot-dash line) corresponds to the centrum semiovale, and the CSF peak at slice 33 corresponds to the lateral and third ventricles. In this subject, the GM+WM compartment is within normal limits on both occasions. The significance, if any, of the scan-to-scan variation in GM and WM composition is unclear.

In figure 4, grand means (horizontal dashes) for the GM+WM fraction (for each of 20 brain slices) are displayed for the cocaine abuser group; individual subject values are represented by small closed circles. The continuous solid line represents the slice means for the normal control group; the dashed lines correspond to plus or minus 2 standard deviations (SD). The cocaine abusers appear to be atrophic (cocaine abuser slice means are below normal control means). The atrophy implied by these preliminary data appears to be generalized. Data from separate GM and WM plots are, at this stage, inconclusive, but they suggest greater volume loss in the WM compartment.

Brain volume has been defined here as (GM+WM)/(GM+WM+ CSF+"other") across all brain slices comprising the slab; in table 3, the

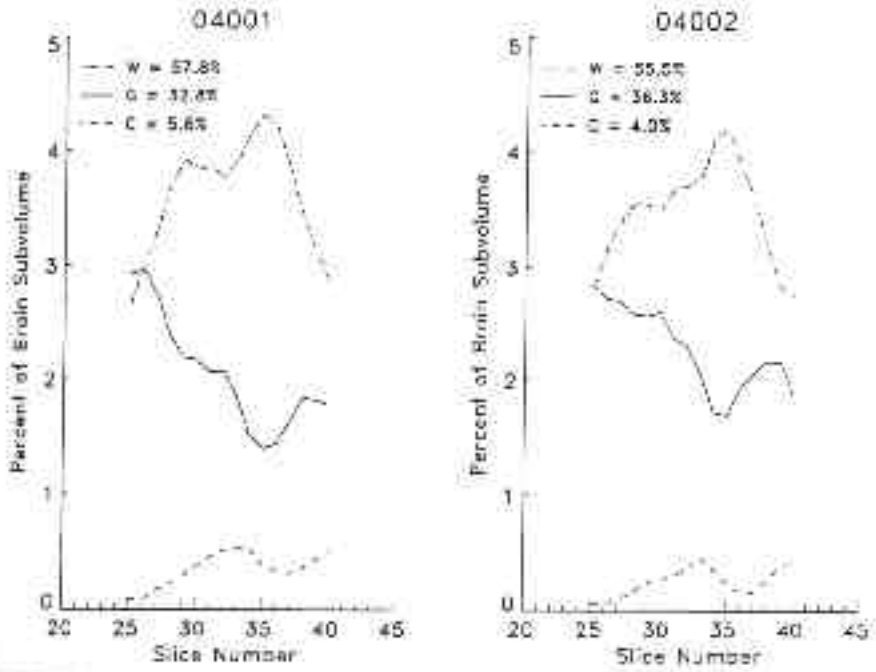

FIGURE 3. *MRI data from abstinent cocaine abuser.*

mean brain volume (SD) is shown for each experimental group and for the normal control group. Each experimental group differs significantly from the normal control group. There is no difference on this measure between the cocaine abuser and other monosubstance abuser groups. In the cocaine abuser group, there is no significant correlation between brain volume and three measures of severity of abuse: duration of abuse, quantity of substance used, and functional outcome.

Discussion

Data from the ongoing BADCO Study are preliminary and cannot at this time support any definite conclusions. There is an early indication that the cocaine abuser group will differ from normal controls on a volumetric

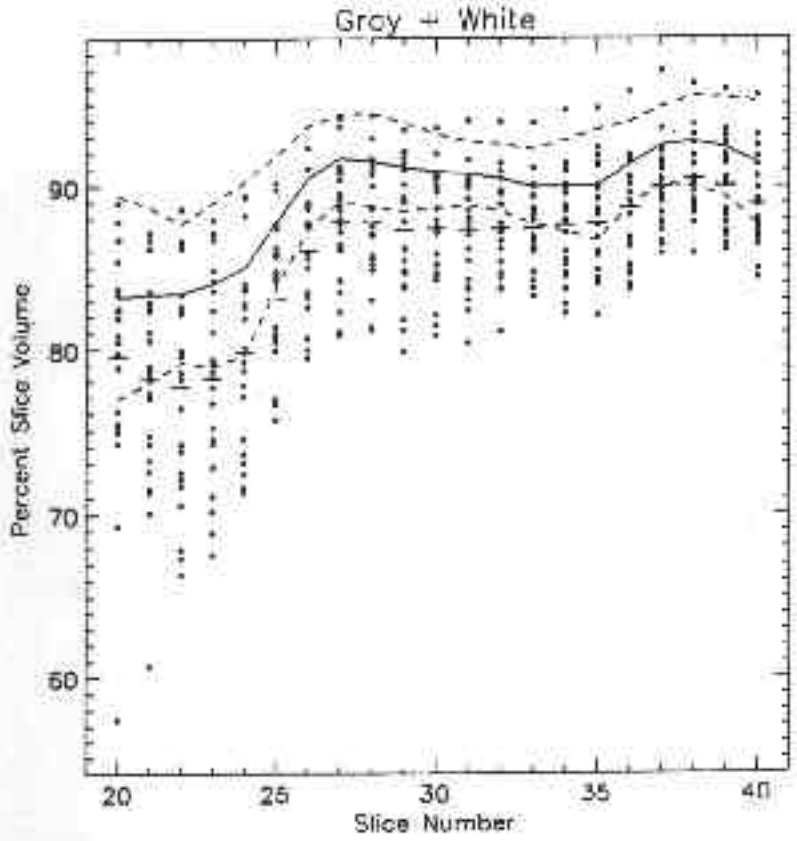

FIGURE 4. *Grand means for GM+WM fraction, cocaine abuser group.*

MRI measure of brain volume, suggesting cerebral atrophy in the cocaine abuser group and corroborating earlier retrospective studies of cocaine abusers at the same institution.

The measure of atrophy here is a relative one, with brain (WM+GM) volume expressed as a percentage of total intracranial contents. Absolute volumes in the WM and GM compartments have not yet been investi-gated, but they might provide an alternate measure if corrected for height. Atrophy appeared widespread, but it may be evenly distributed only with respect to the horizontally oriented slices that make up a slab.

TABLE 3. $p < 0.01$ for cocaine group versus normal controls and for other monosubstance abuser group versus normal controls.

BRAIN VOLUME FRACTIONS			
	White matter	Grey matter	White & grey
Cocaine (24)	0.510 (0.048)	0.350 (0.049)	0.860 (0.036)
Other (6)	0.505 (0.054)	0.353 (0.027)	0.858 (0.045)
Norms	0.539 (0.046)	0.359 (0.048)	0.898 (0.010)

The MRI technology used in this study affords the opportunity to reorient the plane of slicing. An analysis of coronally oriented slices, for exam-ple, might demonstrate atrophy that preferentially involves particular lobes. There is also the possibility of investigating specific regions rather than a whole brain slab.

If cocaine does induce cerebral atrophy, the association between cocaine and ischemic stroke provides one possible mechanism. Predominantly WM atrophy, as suggested by early results here, is in keeping with small-vessel ischemic disease. The SPECT studies already cited do show per-fusion defects in cocaine abusers, though not associated with atrophy onMRI (Strickland et al. 1993) or CT (Tumeh et al. 1990) in the great majority of cases. The correlation of SPECT with quantitative MRI, as in the BADCO Study, may be more fruitful. Radiologic evidence of small-vessel ischemic disease will also be looked for on the standard clinical MR images that are generated during volumetric MRI data acquisition. Alternatively, a direct, widespread cytotoxic effect of cocaine, for which there is no compelling evidence, may account for atrophy.

The BADCO Study's MRI data are presented here in stand-alone fashion, but the functional tests in the study, especially the neuropsychological battery, will supply critical context for any imaging findings. The idea of drug-induced brain atrophy is chilling (and shrunken cerebral hemis-pheres would make an eye-catching "this is your brain on drugs" display), but atrophy independent of functional decline may represent an anatomic curiosity, with no dire consequences for the cocaine abuser. More light will be shed on the importance of anatomic or functional changes by the longitudinal wing of the study.

The BADCO Study may find atrophy without implying a specific causal relationship to cocaine, since there is, so far, no difference in brain volume between cocaine abusers and noncocaine, nonalcohol,

noninhalant mono-substance abusers. If both groups do exhibit similar atrophy, common factors must be considered. Volumetric MRI-demonstrable atrophy may be a toxic effect of a variety of substances whose ability to cause brain volume loss was never suggested by less elaborate imaging techniques. Addiction itself, independent of the substance involved, may produce changes in the brain beyond the dopaminergic system that directly participates in addictive behavior. Minor head injuries, past nutritional deficits, stress and other lifestyle factors, and genetic influences may mediate brain volume in substance abusers.

The factors common to abusers of various single substances are no doubt well represented or even exaggerated in the polysubstance abuser, whom the BADCO Study has struggled mightily to exclude. Only a study of thepure cocaine abuser has the ability to establish causal links to cocaine. This approach can demonstrate specific actions of cocaine, uncover spe-cific deficits, and suggest specific treatments. But there are conceivable advantages to the less pure study of polysubstance abusers, aside from avoiding the logistical problem of ferreting out the uncommon single-substance abuser. If polysubstance abusers predominate at chemical dependency treatment centers, then they are worthy of study. If addiction itself might account for many of the behavioral and biological changes due to substance abuse, then fractionating addicts by substance may not help. If the social causes and consequences of the substance abuse problem in this country are similar for many substances, then a focus on cocaine may provide only a sidelight.

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AUTHORS

Frederick G. Langendorf, M.D.
Department of Neurology
Hennepin County Medical Center
701 Park Avenue South
Minneapolis, MN 55415

and

Assistant Professor
University of Minnesota Medical School
Minneapolis, MN 55415

David C. Anderson, M.D.
Department of Neurology
Hennepin County Medical Center
701 Park Avenue South
Minneapolis, MN 55415

and

Professor
University of Minnesota Medical School
Minneapolis, MN 55415

David E. Tupper, Ph.D.
Director, Neuropsychological Section
Department of Neurology
Hennepin County Medical Center
701 Park Avenue South
Minneapolis, MN 55415

David A. Rottenberg, M.D.
Director, PET Imaging Service
Department of Neurology
Veterans Administration Medical Center
54th Street and 49th Avenue South
Minneapolis, MN 55417

and

Professor of Neurology and Radiology
University of Minnesota Medical School
Minneapolis, MN 55415

Irwin D. Weisman, M.D., Ph.D.
Department of Radiology
Hennepin County Medical Center
701 Park Avenue South
Minneapolis, MN 55415

and

Clinical Assistant Professor
University of Minnesota Medical School
Minneapolis, MN 55415

Neurologic Complications of Cocaine

Michael Daras

INTRODUCTION

Coca leaves have been chewed by South American Indians for several centuries, and cocaine hydrochloride (HCl) has been used since it was isolated in the middle of the 19th century by Niemann (Grinspoon and Bakalar 1981; Holmstedt and Fredga 1981; Petersen 1977). However, untoward effects related to the chewing of the leaves or intranasal insufflation of cocaine HCl had been rare. When used for the only remaining medical indication, local anesthesia, complications are uncommon. In a survey of over 100,000 rhinoplasties performed using cocaine HCl as a local anesthetic, 191 mild and 34 severe reactions were reported, and 5 deaths were attributed to its use (Feehan and Mancusi-Ungaro 1976).

The introduction in 1983 of the alkaloidal form of cocaine known as crack (Jekel et al. 1986) has led to a tremendous increase in its use followed by a rise in the incidence of medical, neurologic, and psychiatric complications. From the lung epithelium, the effect on the central nervous system (CNS) of inhaled free-base cocaine is faster than that produced by intranasal or intravenous (IV) routes and results in a higher serum concentration (Johanson and Fischman 1989; Jones 1984; Verebey and Gold 1988). Local vasoconstriction in the oral or nasal mucosa slows down the absorption of cocaine and, therefore, produces lower plasma levels than IV administration of cocaine HCl or intrapulmonary absorption of crack. The mucosal (oral or nasal) administration has been associated with less intense excitement but also has a lower incidence of complications.

The rise in the rate of complications related to the increasing use of crack cocaine has been reflected in the medical literature: Initial isolated case reports were replaced by a series of accounts of medical and neuro-psychiatric complications of crack cocaine. These accounts were followed by publications describing specific complications such as strokes, seizures, myocardial infarctions, and rhabdomyolysis (Brust 1993; Sanchez-Ramos 1993).
The CNS effects of cocaine seem to result from the reuptake blockade of NE DA, and serotonin, which can potentiate the action of these

three neurotransmitters, leading to serious complications (Dackis and Gold 1988; Johanson and Fischman 1989). Although emergency room visits and hospital admissions due to cocaine-induced symptoms are more commonly related to medical and psychiatric problems, neurologic sequelae are frequent and severe. In two studies of cocaine-related emergency room visits (Brody et al. 1990; Rich and Singer 1991), neurologic symptoms accounted for 17.4 percent and 39.1 percent, respectively, of patients' complaints.

Neurologic complications related to cocaine use can be classified as neurovascular events (cerebral or spinal), seizures, abnormal movements, headache, hyperpyrexia, and rhabdomyolysis, as well as rarer miscellaneous complications involving the nervous system.

NEUROVASCULAR COMPLICATIONS

The first report of a cocaine-related stroke by Brust and Richter (1977) was accepted with skepticism. The few isolated case reports in the next few years (Caplan et al. 1982; Lichtenfeld et al. 1984; Lundberg et al. 1977; Schwartz and Cohen 1984) suggested that this was an extremely rare complication. However, since 1985 the incidence of cocaine-related strokes has reached epidemic proportions (table 1).

Although intracranial hemorrhages following cocaine use were more frequent in the early reports, the number of ischemic and hemorrhagic strokes seem to be equal in the more recent series of reviews (Daras et al. 1994b; Jacobs et al. 1989; Levine et al. 1990, 1991; Peterson et al. 1991; Van Viet et al. 1990). This probably reflects the change in the preferred route of administration, since hemorrhagic strokes seem to be more frequent with cocaine HCl while use of the alkaloidal form of cocaine is equally associated with both ischemic and hemorrhagic events (Levine et al. 1991).

Cocaine abuse is a significant risk factor for cerebrovascular complications in young adults (Kaku and Lowenstein 1990) in whom traditional risk factors are frequently missing (Daras et al. 1994a; Levine et al. 1990). Anticardiolipin antibodies, which increase the risk for stroke (Asherson et al. 1989), have been detected in 27.3 percent of asympto-matic cocaine users (Fritsma et al. 1991) and some patients with

TABLE 1. Reports of cocaine-related strokes.

Year	Types and # of Strokes	Reporting Researchers and Incidents Reported
1977	Infarct: 1	Brust and Richter
	SAH: 1	Lundberg et al.
1982	ICH: 1	Caplan et al.
1984	Infarct: 1	Schwartz and Cohen
	SAH: 2	Schwartz and Cohen; Lichtenfeld et al.
	ICH: 2	Schwartz and Cohen; Lichtenfeld et al.
1986	Infarcts: 2	Chasnoff et al.; Golbe and Merkin
	SAH: 2	Rogers et al.; Cregler and Mark
1987	Infarcts: 4	Levine et al.,3; Lowenstein et al.,1
	TIA: 8	Lowenstein et al.
	SAH: 6	Altes-Capella et al.,1; Wojak and Flamm,2; Kaye and Fainstat,1; Mittleman and Wetli,1; Lowenstein et al.,1
	ICH: 11	Wojak and Flamm,4; Mittleman and Wetli,4; Lowenstein et al.,2; Lehman,1
1988	Infarcts: 9	Devenyi et al.,1; Mody et al.,4; Weingarten,1; Toler and Anderson,1; DeVore and Tucker,1; Tenorio et al.,1
	TIA: 2	Mody et al.
	SAH: 6	Mangiardi et al.,5; Henderson and Torbey,1
	ICH: 7	Mangiardi et al.,4; Mody et al.,3
1989	Infarcts: 27	Mast et al.,8; Rowley et al.,2; Jacobs et al.,8; Engstrand et al.,8; Meza et al.,1
	TIA or infarcts: 21	Moore and Peterson
	SAH: 4	Jacobs et al.
	ICH: 19	Nalls et al.,4; Mast et al.,6; Rowley et al.,1; De Broucker et al.,1; Jacobs et al.,4, Mercado et al.,1; Nolte and Gelman,1; Spires et al.,1
	IVH: 7	Mast et al.
	ICRH: 29	Peterson and Moore,13; Tardiff et al.,9; Klonoff et al.,7
	Strokes: 13	Dixon and Bejar

TABLE 1. Reports of cocaine-related strokes (continued).

Year	Types and # of Strokes	Reporting Researchers and Incidents Reported
1989	Unspecified Periventr. Leuko-malacia: 5	Mast et al.
1990	Infarcts: 38	Seaman,1; Levine et al.,18; Deringer et al.,1; Krendel et al.,2; Hall,1; Petty et al.,1; Kaku and Lowenstein,7; Hoyme et al.,1; Kramer etal.,1; Guidotti and Zanasi,2; Sloan et al.,3
	SAH: 31	Levine et al.,5; Kaku and Lowenstein,6; Hoyme et al.,1; Simpson et al.,17; Sloan etal.,2
	ICH: 16	Levine et al.,5; Green et al.,1; Kaku and Lowenstein,10
1991	Infarcts: 62	Peterson et al.,19; Sauer,1; Daras et al.,18; Hamer et al.,1; Heier et al.,17; Fredericks etal.,1; Dominguez et al.,5
	SAH: 10	Peterson et al.,8; Hamer et al.,1; Chadan etal.,1
	ICH: 10	Harruff et al.,2; Peterson et al.,7; Ramadan etal.,1
1992	Infarcts: 3	Sloan and Mattioni,1; Konzen et al.,1; Nwosu et al.,1
1993	TIA: 1	Libman et al.
	Infarct: 2	Massachusetts General Hospital; Morrow and McQuillen
1994	Infarcts: 25	Daras et al.
	SAH: 9	"
	ICH: 16	"
	IVH: 5	"

KEY: SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage; ICRH = intracranial hemorrhage; IVH = intraventricular hemorrhage; TIA = transient ischemic attack.

cocaine-related strokes (Daras et al. 1994b; Sloan et al. 1990; Toler and Anderson 1988). Ethanol intoxication has also been associated with strokes (Gorelick 1987). Combining cocaine with ethanol, the drug most commonly used with cocaine, leads to formation of cocaethylene (benzoylecgonine ethyl ester) (Dean et al. 1992), which induces more adverse cardiovascular effects than cocaine alone in healthy volunteers (Perez-Reyes and Jeffcoat 1992) and leads to higher mortality in mice (Hearn et al. 1991).

Several reports describe cerebrovascular accidents in neonates exposed in utero to cocaine (Chasnoff et al. 1986; Dixon and Bejar 1989; Dominguez et al. 1991; Heier et al. 1991; Hoyme et al. 1990; Kramer et al. 1990; Mast et al. 1989; Spires et al. 1989). Low serum cholinesterase levels in the fetus (Johanson and Fischman 1989) may increase susceptibility to the vascular effects of cocaine. Although pregnancy is also associated with low cholinesterase levels (Johanson and Fischman 1989), reports of strokes in pregnant women are rare (Henderson and Torbey 1988; Levine et al. 1991; Mercado et al. 1989; Tuchman et al. 1992).

The exact mechanism of cocaine-related stroke remains incompletely understood because of the multiple effects of cocaine on the cardiovascular system. By blocking the reuptake of norepinephrine (Herrting et al. 1961), cocaine increases sympathetic activity leading to hypertension, tachycardia, and vasoconstriction (Johanson and Fischman 1989). A dose-related rise in arterial pressure and heart rate has been noted in humans (Fischman et al. 1976) and experimental animals (Wilkerson 1988).

Subarachnoid hemorrhage (SAH) from rupture of an underlying aneurysm or arteriovenous malformation (AVM) (Daras et al. 1994b; Levine et al. 1990; Mangiardi et al. 1988; Tardiff et al. 1989; Wojak and Flamm 1987) may be due to acute hypertension induced by cocaine. The absence of hypertension in the initial emergency room examination in most cases of cocaine-induced intracranial hemorrhage can be explained by the short half-life of cocaine (Johanson and Fischman 1989).

Intracerebral hemorrhage may be due to an underlying lesion such as AVM (Daras et al. 1994b; Jacobs et al. 1989; Kaku and Lowenstein 1990; Levine et al. 1990; Lichtenfeld et al. 1984; Lowenstein et al. 1987; Mangiardi et al. 1988; Mittleman and Wetli 1987; Mody et al. 1988; Simpson et al. 1990) or a glioma (Wojak and Flamm 1987). The location of hemorrhages in the territory of penetrating arteries,

such as the basal ganglia/internal capsule or pons, in a large number of patients suggests a pathophysiology similar to that of hypertensive intracerebral hemorrhage. Habitual cocaine abuse may expose small vessels to episodic hyper-tension, leading to accelerated arteriosclerotic changes. Advanced atherosclerosis has been observed in the aorta and the renal arteries of cocaine users (Bacharach et al. 1992; Fogo et al. 1992) and in rabbits exposed to cocaine (Langner et al. 1988). An alternate explanation for the occurrence of intracerebral bleeding is hyperperfusion in an area made ischemic by cocaine-induced vasoconstriction (Caplan 1988). These two pathogenetic mechanisms are not necessarily mutually exclusive and may, in fact, coexist.

Ischemic infarctions related to cocaine use can involve any level of the neuraxis, including the spinal cord (Daras et al. 1991; Mody et al. 1988; Peterson et al. 1991) and the retina (Devenyi et al. 1988; Libman et al. 1993). Multiple overlapping mechanisms may be responsible. The vasoconstriction from sympathetic overstimulation due to blocking of epinephrine reuptake may be aggravated by the simultaneous increase of systemic arterial pressure, which can alter cerebral autoregulation (Burke et al. 1987). Changes in autoregulation have been observed in the rat neocortex following cocaine administration (Kelly et al. 1993). Hypertensive opening of the blood-brain barrier may increase vasocon-striction (Owman and Hardebo 1985). Cocaine may also block the reuptake of serotonin (Dackis and Gold 1988), the most potent vasoconstrictor amine in the brain (Edvinson and MacKenzie 1976), particularly in large and medium-size vessels (Hardebo et al. 1978). Cocaine-induced vasoconstriction has been observed in the retinal artery of a patient with monocular blindness (Libman et al. 1993) and cerebral arterioles of rats (Altura et al. 1988), and it can be ameliorated by mag-nesium ion (Mg^{2+}) (Huang et al. 1990). However, the observation that topical cocaine application dilated pial arterioles in cats (Dohi et al. 1990) contradicts previous findings and has added confusion.

Experimentally, cocaine enhances the response of platelets to arachidonic acid, which leads to increased production of thromboxane A and promotes platelet aggregation (Togna et al. 1985). Thrombocytopenia has been reported in six human immunodeficiency virus (HIV)-negative cocaine users, none of whom developed a stroke (Leissinger 1990).

Myocardial infarction, cardiac arrhythmias, and cardiomyopathy increase the risk of embolic infarcts, but only two cases of proven

embolic strokes have been reported (Petty et al. 1990; Sauer 1991). Vasculitis, which is common in strokes related to other drugs and particularly amphetamines (Citron et al. 1970), has been attributed to cocaine on the basis of angiographic findings (Kaye and Fainstat 1987). These findings, however, could also indicate vasospasm following undiagnosed SAH (Levine et al. 1988). Biopsy-proven vasculitis has been documented in only five cases (Fredericks et al. 1991; Krendel et al. 1990; Massachusetts General Hospital 1993; Morrow and McQuillen 1993); all had normal cerebral angiography.

COGNITIVE DEFICITS

The question of mental impairment in cocaine users was brought up first by Gordon (1908). Sixty years later, Buck and colleagues (1968) described psychological impairment and poor work performance in South American coca leaf chewers. Subsequent studies demonstrated subtle deficits in auditory recall, concentration, and reaction time (Ardila et al. 1991; O'Malley et al. 1992; Weinrieb and O'Brien 1993). The main problem in all these studies is the unavailability of information about the premorbid performance of the patients.

Electroencephalographic investigation of cocaine users revealed diffuse theta activity that increased with continuous use (Pascual-Leone and Dhuna 1990a). Cerebral atrophy has been reported in chronic habitual cocaine users on computed tomography (Pascual-Leone et al. 1991). The exact explanation of these findings is not clear. It is, however, tempting to speculate that the atrophy is ischemic in origin based upon several positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies performed on cocaine users. Studies have demonstrated decreased cerebral blood flow, particularly in the frontal and temporal cortex of cocaine users (Tumeh et al. 1990; Volkow et al. 1988), small focal cortical defects (Holman et al. 1991), and decreased glucose utilization (London et al. 1990). Cognitive impairment accompanied by cerebral hypoperfusion on SPECT has been noted even after 6 months of abstinence (Strickland et al. 1993).

HEADACHES

The incidence of headaches related to cocaine use varies significantly from study to study. Among cocaine users, up to 60 percent reported

headaches following its use (Washton and Gold 1984). Lipton and colleagues (1989) reported that 13.1 percent of hospitalized cocaine users complained of headaches. Lowenstein and colleagues (1987) found that only 0.8 percent of emergency room patients suffered from headaches. Among patients with cocaine intoxication, 1.8 percent presented with acute headache (Dhuna et al. 1991a). Migraine-like headaches occasionally complicated by neurological deficit have been reported (Lipton et al. 1989; Satel and Gawin 1989). In one case report, a patient became dependent on cocaine because it relieved migraines (Brower 1988).

Dhuna and colleagues (1991a) identified three patterns of headaches following cocaine use: acute onset of headaches within minutes of cocaine use, increasing headache during a binge, and headaches during abstinence. Withdrawal headaches have been reported as late as 4 weeks to 9 months after cessation of cocaine use (Baker and Dilavou 1989). A possible connection between cocaine-induced headaches and serotonin may exist, in view of the blocking of serotonin reuptake by cocaine (Cunningham and Lakoski 1988). Acute headache following use of cocaine is not always benign. It may be an ominous sign and herald the onset of an acute cerebrovascular event, particularly hemorrhage (Daras et al. 1994a; Levine et al. 1990).

Seizures

Although seizures have been known to occur following cocaine use since 1922 (Pulay 1922) and have been notoriously associated with the "body packer" syndrome (Wetli and Mittleman 1991), it was only recently realized that seizures can be associated with recreational cocaine use (Alldredge et al. 1989; Choy-Kwong and Lipton 1989a; Harden et al. 1992; Kramer et al. 1990; Lowenstein et al. 1987; Myers and Earnest 1984; Pascual-Leone et al. 1990). In questionnaires given to adolescent cocaine users, loss of consciousness was reported by 2 percent and seizures by 1 percent of the light users, while 27 percent of heavy users reported loss of consciousness and 4 percent reported seizures (Schwartz et al. 1988). In clinical studies, the reported occurrence of cocaine-related seizures is also relatively low. Lowenstein and colleagues (1987) reported 29 seizures (2.8 percent) in 1,275 emergency room visits or admissions for cocaine-related complications. Pascual-Leone and colleagues (1990) reported 32 (7.9 percent) seizures among 403 cocaine- intoxicated patients. In two New York studies, seizures were found less frequently: 1.4 percent in the series reported by Choy-Kwong and Lipton (1989a)

and 0.6 percent by Harden and colleagues (1992). The majority of patients develop generalized tonic-clonic convulsions, but partial simple or complex seizures may occur. Seizures are usually isolated, but generalized status epilepticus can occur (Alldredge et al. 1989; Lowenstein et al. 1987). One case of complex partial status epilepticus has been described after crack use (Ogunyemi et al. 1989).

The mechanism of cocaine-related convulsions remains unclear. Eidelberg and colleagues (1963) postulated that cocaine produced seizures by blocking the reuptake of catecholamines. Their finding that dibenamine, chlorpromazine, and reserpine prevented cocaine-induced seizures in experimental animals further supported this hypothesis. They also documented onset of cocaine-related seizures in the temporal region in cats similar to lidocaine-induced seizures (Post et al. 1981).

Recurrent seizures have been described in experimental animals after repeated doses of subconvulsant levels of cocaine administered intraperitoneally; the term "pharmacologic kindling" has been proposed by Post and Kopanda (1975) to describe this phenomenon. In spite of the controversy surrounding kindling in humans, the finding by Harden and colleagues (1992) that 9 of 22 patients had recurring seizures only after repeated use of cocaine and the case report by Dhuna and colleagues (1991b) of possible kindling-induced epilepsy in a habitual cocaine user support this notion.

ABNORMAL MOVEMENTS

A possible association between cocaine and abnormal movements was first reported by Kumor and colleagues (1987), who noted an increased incidence of dystonic movements in cocaine users treated with neuro-leptics. This observation was also made by Hegarty and colleagues (1991). Dystonic reactions have been observed during both cocaine intoxication (Farrell and Diehl 1991; Merab 1988) and withdrawal (Choy-Kwong and Lipton 1989b; Rebischung et al. 1990) without use of neuroleptics.

Exacerbation of other abnormal movements, such as tics induced by cocaine in previously controlled patients with Tourette syndrome, has been noted (Cardoso and Jankovic 1993; Factor et al. 1988; Mesulam 1986; Pascual-Leone and Dhuna 1990b). Occurrence of tics has also been reported in previously asymptomatic patients (Pascual-Leone

and Dhuna 1990b). One case of opsoclonus-myoclonus following cocaine use has been reported (Scharf 1989).

Choreoathetoid movements clinically indistinguishable from those observed in Huntington's disease and lasting up to 6 days have been reported recently (Daras et al. 1994a). By blocking the reuptake of dopamine, cocaine produces a high availability of dopamine at the synaptic cleft, which can trigger choreoathetoid movements. Further inability to downregulate dopamine concentration may be responsible for the recurrence of these movements with repeated cocaine use in some patients. The existence of street names to describe these movements (crack dancing and boca turcida) suggests that they may be more common than physicians recognize.

RHABDOMYOLYSIS AND HYPERPYREXIA

The alkaloidal form of cocaine has been added to the list of drugs that produce rhabdomyolysis. However, the other routes of administration can also trigger muscle damage (Daras et al., in press-b; Merigian and Roberts 1987; Nolte 1991; Parks et al. 1989; Roth et al. 1988; Skluth et al. 1988). Rhabdomyolysis can occasionally recur (Horst et al. 1991) or can occur simultaneously with skin infarction (Zamora-Quezada et al. 1988). Elevated serum creatine kinase levels may be present in up to 34percent of cocaine users without other muscle symptoms (Welch et al. 1991).

Hyperpyrexia, which has been described in cocaine intoxication, has been noted in several cases of cocaine-induced rhabdomyolysis (Merigian and Roberts 1987; Roth et al. 1988; Skluth et al. 1988). Hyperthermia alone or in combination with agitation may cause muscle damage. In addition, ischemia from cocaine-induced vasoconstriction of muscle arteries has been proposed to induce muscle injury (Roth et al. 1988; Skluth et al. 1988). A direct toxic effect has been shown on cardiac (Peng et al. 1989) but not on striated muscle. High catecholamine levels from cocaine- induced reuptake blockade may release calcium from the sarcoplasmic reticulum, leading to high intracellular calcium. This can trigger a series of events leading to cell death (Parks et al. 1989).

The association of hyperthermia, rhabdomyolysis, and agitation has led Kosten and Kleber (1988) to propose a mechanism similar to that responsible for the neuroleptic malignant syndrome (NMS). Chronic use of cocaine may produce dopamine depletion (Dackis and Gold

1985) or decrease dopamine receptors (Volkow et al. 1990) and lead to inadequate dopamine availability. The observation of higher incidence of NMS in cocaine abusers treated with neuroleptics (Akpaffiong and Ruiz 1991) supports this notion. It seems, however, that these multiple mechanisms are not mutually exclusive but may combine to produce this frequently fatal complication.

MISCELLANEOUS COMPLICATIONS

In addition to the increased risk of infection associated with IV use, non-IV cocaine users tend to expose themselves to the risk of HIV and other sexually transmitted infections because of their sexual practices. Increased sexual activity, promiscuity, or exchange of sex for crack can lead to higher incidence of infection (Marx et al. 1991). Cocaine has immunosuppressant properties and IV cocaine users are at a higher risk of infectious endocarditis than are other parenteral drug users (Chambers et al. 1987). Enhancement of HIV-1 replication by cocaine has been noted in human peripheral mononuclear blood cells (Peterson et al. 1993).

Anosmia, rhinitis, and perforation of the nasal septum are well known complications of cocaine-induced vasoconstriction from nasal insufflation, but extreme cases of cerebrospinal fluid rhinorrhea from erosion of the cribriform plate (Sawicka and Trosser 1983) and bilateral optic neuritis with osteolytic sinusitis have also been reported (Newman et al. 1988).

In addition to the cases of anterior spinal artery infarction (Daras et al. 1994a; Mody et al. 1988; Peterson et al. 1991), spinal cord involvement from a spinal epidural hematoma has been described (Huff 1994).

Impairment of the neuromuscular junction by cocaine would not be expected, but cocaine use unmasked and then exacerbated symptoms of myasthenia gravis in a young woman (Berciano et al. 1991). The author has also observed recurrent exacerbation of myasthenic symptoms with repeated cocaine use in a young man (Daras et al., in press-a).

CONCLUSIONS

The neurologic complications of cocaine abuse may be the tip of an iceberg in view of the medical and psychiatric side effects as well as the social problems related to its use. In particular, the violence associated with crack surpasses that of other illegal drugs and makes cocaine not a panacea, as Freud had suggested, but a societal nightmare.

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AUTHOR

Michael Daras, M.D.
Professor of Clinical Neurology
New York Medical College

and

Chief of Service
Department of Neurology
Metropolitan Hospital
1901 First Avenue
New York, NY 10029

Psychomotor and Electroencephalographic Sequelae of Cocaine Dependence

Lance O. Bauer

INTRODUCTION

Cocaine is abused because it affects brain function. It would therefore not be surprising to discover that functional brain impairments figure prominently as a consequence, and perhaps an antecedent (Bauer and Hesselbrock 1993; Bauer et al. 1994; O'Connor et al. 1994), of chronic abuse. It would also not be surprising to discover that these impairments persist after the chronic cocaine abuse has ended. Yet, there are relatively few studies published in the human research literature that either support or refute these assumptions. Much of what is hypothesized about the consequences of chronic cocaine abuse in human patients is based on clinical impressions, case reports (Cardoso and Jankovic 1993; Choy-Kwong and Lipton 1989; Farrell and Diehl 1991; Merab 1988; Mesulam 1986; Pascual-Leone and Dhuna 1990; Satel and Swann 1993), or extrapolations from studies of cocaine's acute effects (Fischman and Schuster 1980; Herning et al. 1985; Morgan et al. 1993; Sherer 1988). As a consequence, some disagreements have arisen in the clinical literature, and there is little consensus (Cottler et al. 1993; Gawin and Kleber 1986; Satel et al. 1991; Weddington et al. 1990) regarding the nature, severity, and/or duration of the postcocaine abuse syndrome.

One factor confounding discussions over the residua of cocaine abuse is the nature of the data. Studies focusing on subjective symptoms and mood (Satel et al. 1991; Weddington et al. 1990) have typically described the postcocaine abuse syndrome as mild in severity and approximately 3to 4 weeks in duration. In contrast, studies focusing on objective signs of functional brain impairment (Alper et al. 1990; Bauer 1993a, 1993b, 1994a, 1994b, 1994c; Herning et al., this volume; O'Malley et al. 1992; Roberts and Bauer 1993; Roemer et al., unpublished data; Volkow et al. 1992) point to a syndrome that is significantly more severe and persistent. These different conclusions are likely the result of method-related differ-ences in measurement sensitivity and/or error. Yet, one should not con-clude that the postcocaine abuse syndrome is therefore a statistically significant but clinically trivial entity. Several studies have associated poor clinical

outcomes, such as relapse to alcohol (Bauer 1994a; Rohsenow et al. 1994) or nicotine (Niaura et al. 1989) dependence, with subtle neurophysiological deficits that are not always expressed in a symptom or mood disturbance. Relapse to cocaine abuse represents another clinically significant psychiatric outcome that may be related to subtle cocaine-induced neurophysiological deficits (Carroll et al. 1993). Thus, there must be important, measurable sequelae of cocaine abuse, which have been largely underestimated or missed in the extant studies of psychiatric symptomatology (Satel et al. 1991; Weddington et al. 1990).

The goal of the present chapter is to review objective neurophysiological evidence for a postcocaine abuse syndrome. The focus is on the author's studies of psychomotor function and electroencephalographic (EEG) activity, or evoked EEG responses. Many of these studies were described in journals published during 1993 and 1994. Since that time, more sub-jects have been added to the data set and one can now report a replication of the original findings in an expanded sample.

METHODOLOGICAL CONSIDERATIONS

Before reviewing the specific details of these studies, it may be valuable to offer several general comments concerning the methodological problems attendant to conducting research with this population. Similar comments have been offered (Reed and Grant 1990) regarding neuro-psychological studies of substance abusers. These comments are also germane to studies of resting EEG activity, event-related potentials (ERPs), and most other clinical and basic science studies of recovering cocaine abusers.

Table 1 provides a list of disorders or conditions that often co-occur with cocaine dependence. It is by no means a complete list. Some would add attention deficit-hyperactivity disorder (ADHD) to the list of premorbid risk factors (Barkley et al. 1990; Gittleman et al. 1985). However, the association of childhood ADHD and adult drug abuse is controversial (Halikas et al. 1990; Kaminer 1992). Nonetheless, all of the cited varia-bles have been shown to affect psychomotor function or EEG activity (Bauer and Hesselbrock 1993; Bauer et al. 1994; Jabbari et al. 1993; Pollock and Schneider 1990; Smiley 1987). They therefore represent potential confounds in any study that professes to examine the sequelae of cocaine dependence and must be considered.

TABLE 1. Potential threats to causal inference.

Premorbid factors
Antisocial personality/conduct disorder
Aggression
Family history
Medical factors
Head injury
Seizures (including drug-related seizures)
HIV/AIDS
Other major medical disorders
Psychoactive medications
Psychiatric factors
Polysubstance abuse
Depression (including moderate depression)
Other DSM-III-R Axis I disorders

Although the variables listed in table 1 do represent confounds in deter-mining the specific effects of chronic cocaine abuse, they are also impor-tant variables for study because they may amplify, moderate, or entirely explain cocaine's purported effects. Indeed, one goal of the University of Connecticut research program is to add such variables incrementally to the existing, uncomplicated sample of cocaine abusers so that additive or interactive relationships can be studied. A popular alternative method for accomplishing the same goal involves the recruitment of a heterogenous subject sample and the post hoc "removal" of unwanted variance through analysis of covariance or regression. But these statistical methods rest on tenuous assumptions (Adams et al. 1985; Cronbach et al. 1977) which are frequently violated in clinical research. Furthermore, the level of control that can be achieved through post hoc statistical methods will always fall short of what can be achieved through a priori means (i.e., by construc-ting narrow inclusion criteria).

This desire for strict experimental control and narrow inclusion criteria challenges the clinical reality and speaks to a common controversy in drug abuse research. The result of using highly restrictive inclusion criteria can be a finding that does not generalize to the larger cocaine-dependent population. However, the findings are less ambiguous in origin. Furthermore, through the use of such criteria, it becomes possible to define and validate homogenous subtypes of cocaine abusers (Ball et al. 1995) and develop hypotheses regarding subtype-specific inter-ventions (Kosten 1989).

For example, antisocial personality disorder (ASPD) and a family history of alcoholism have recently been found to be associated with different patterns of EEG and neuropsychological impairment (Bauer and Hesselbrock 1993; Bauer et al. 1994; Gillen and Hesselbrock 1992; O'Connor et al. 1994). ASPD and a family history of alcoholism are both risk factors for the development of cocaine dependence (Bauer and Kranzler 1994; Miller et al. 1989; Rounsaville et al. 1991). Yet, if each is associated with a different neurophysiological path toward the same endpoint, then a different type of preventive intervention may be required.

Method

For the past 5 to 6 years, a group based at the University of Connecticut School of Medicine has been conducting research funded by the National Institute on Drug Abuse (NIDA) to examine EEG activity and psycho-motor functioning among cocaine-dependent patients during their initial 3months of abstinence. One concern that arose early in formulating the study design was the specification of an appropriate control group. As table 2 indicates, two separate control groups were included. One group consisted of alcohol-dependent patients who were matched to the cocaine-dependent group on a variety of premorbid variables such as the number of ASPD characteristics and the prevalence of a family history of alcoholism. The groups were also matched on a number of symptom measures such as the Beck Depression Inventory (BDI) and Spielberger State-Trait Anxiety Inventory (STAI). All of the groups were screened to exclude individuals with other drug dependence; other Axis I diagnoses; seizures (including drug-related seizures); head injury; intravenous (IV) drug use; current medication use; and neurological, cardiovascular, or liver disease. The cocaine abusers were no more dependent or medically complicated than the alcoholics, as measured by their number of previous hospitalizations. The cocaine abusers and alcoholics were also recruited from the same treatment facilities. While these two groups of patients differed significantly from an age- and socioeconomic status (SES)-matched nondrug-dependent control group, they were quite similar in many other respects, thereby making it easier to attribute any psycho-motor or EEG differences between them to the effects of either cocaine or alcohol.

TABLE 2. Demographic and clinical features of study groups.

Variable	Cocaine dependence	Alcohol dependence	Control
Age (SD)	31.3 (1.8)	31.0 (1.7)	32.1 (1.2)
Gender (M/F)	24/4	19/3	26/2
# ASP criteria**			
before age 15	2.3 (1.1)*	2.0 (1.3)*	0.2 (0.5)
after age 15	3.7 (0.7)*	3.1 (0.5)*	0.3 (0.1)
Proportion FHA+	0.3 (0.2)*	0.4 (0.1)*	0.1 (0.2)
BDI Score	9.3 (8.2)*	8.9 (8.4)*	2.6 (5.2)
STAI Score			
State anxiety	42.3 (12.4)*	40.8 (13.1)*	31.3 (9.3)
Trait anxiety	38.8 (8.7)*	37.0 (11.3)*	32.7 (9.1)
# Prev. detox.	0.9 (0.2)*	1.3 (0.3)*	0.0 (0)
Avg. # days/week last 6 months			
used cocaine	3.0 (0.5)*	0.3 (1.5)	0.0 (0.1)
used alcohol	4.0 (2.6)	6.2 (0.7)*	3.2 (2.4)
used opiates	0.0 (0)	0.0 (0)	0.0 (0)
Avg. amount/occasion			
cocaine (g)	0.9 (0.3)*	0.1 (0.4)	0.1 (0.2)
alcohol (# drinks)	4.0 (1.8)	16 (2.4)*	2.3 (1.6)

KEY: * = $p < 0.05$ versus control group; ** = excluding substance abuse related items; BDI = Beck Depression Inventory; STAI=State-Trait Anxiety Inventory; FHA+ = family history of alcoholism; ASP = antisocial personality.

The cocaine-dependent group consisted of individuals who primarily used cocaine in its freebase form. None were IV users. Only six met criteria for alcohol abuse; none met lifetime criteria for alcohol dependence. Cocaine use during the month preceding treatment exceeded 5 grams. The alcohol-dependent group was likewise uncomplicated.

The study design was longitudinal. Patients were evaluated repeatedly: 7to 10 days (session 1), 16 to 21 days (session 2), and 94 to 100 days (session 3) after their last use of cocaine or alcohol. Abstinence was verified through frequent and irregularly scheduled urine screens. Limiting the variability in abstinence was important since, at least among alcohol-dependent patients, there are electrophysiological data (Begleiter and Porjesz 1979; Begleiter et al. 1974) suggesting a transition in the early phases of abstinence from central nervous system (CNS) hyper- to hypoexcitability. Among cocaine abusers, CNS excitability is hypothe-sized (Gawin and Kleber 1986) to change in the opposite direction. Accordingly, assessments that were imprecisely timed relative to the initiation of either alcohol or cocaine abstinence would result in contradictory findings or, on average, no findings at all. The normal control group was also repeatedly tested to control for the effects of practice or familiarization.

Each subject participated in a 2-hour evaluation that included assessments of motor system functioning and EEG reactivity, among others. A particu-lar emphasis was placed on the assessment of motor system functioning. This emphasis was inspired by an early report (Volkow et al. 1988) of altered blood flow in the frontal brain of human cocaine abusers, as well as numerous reports of locomotor hyperactivity, sterotypy, and altered nigro-striatal dopamine turnover among cocaine-exposed animals (for a review see Johanson and Fischman 1989). Indeed, of all the tests included in the present battery, tests of motor system functioning have proven to be the most robust and persistent discriminators of cocaine-dependent patients.

A description of the test battery follows. The description of each test includes a verbal summary of the major findings resulting from an analysis of the expanded sample. For a detailed description of previous findings, data analysis techniques, and test parameters, the reader should consult recent publications (Bauer 1993a, 1993b, 1993c, 1994b, 1994c; Roberts and Bauer 1993).

Psychomotor Sequelae

Hand Tremor and Body Sway. Hand tremor was the simplest test in the battery to administer. It was transduced using an accelerometer taped to the subject's forefinger (Bauer 1993a). Other techniques could have been used; however, many of these techniques (e.g.,-electromyography, infrared or magnetic position sensors, and touch-activated electric circuits) are difficult to engineer or provide unwanted feedback cues to the patient.

Hand tremor is actually a complex phenomenon. Because it possesses an inherent rhythmicity, tremor can be objectively analyzed in the frequency domain using quantitative techniques such as Fourier analysis and the fast Fourier transform. The output of this transformation is a power spectral density function that provides estimates of tremor amplitude (power) as a function of the underlying frequency.

The advantage of applying Fourier analysis to tremor rests on the assumption that tremor frequency bears an important relationship to the underlying generator. This position was most strongly advocated by Holmes (1904) and more recently by Findley and colleagues (1981). A more conservative view is probably appropriate, however. The reason for conservatism derives from the fact that there is usually more than one type of tremor associated with a given neurological disease. These multiple tremors may be a direct effect of the disease process itself, or may reflect the gradual recruitment of multiple tremor generators due to chronic inflammation, edema, or tumor growth.

In the case of Parkinson's disease, for example, there is evidence of a characteristic hand tremor (Findley et al. 1981) occurring at rest at a stable frequency of 4 to 5 hertz (Hz). Postural and kinetic tremors have also been observed in Parkinson's-diseased patients, although at a different predominant frequency and with a lower prevalence than rest tremor. These latter tremors may therefore reflect a secondary process of the disease.

There is an additional type of tremor that can be detected in some disease states and in normal individuals with no significant neuropathology. This normal physiologic tremor (Young 1984) has a peak frequency of approxi-mately 9 Hz and is not significantly altered by intention or action. Normal physiologic tremor is

exaggerated by anxiety states or other factors that arouse peripheral adrenergic systems.

An analysis of hand tremor (figure 1) in substance abusers revealed significantly more hand tremor among the two patient groups relative to the normal controls. However, the types of tremor exhibited by the two patient groups were different. In both cases, the predominant frequency of tremor was in a slower, abnormal range (i.e., < 9 Hz). Therefore, it is unlikely that their hand tremors were a consequence of enhanced adrenergic outflow, anxiety, fatigue, or the other benign processes that 9Hz tremor is believed to index.

Alcohol-dependent patients exhibited significantly more low frequency (<4 Hz) tremor than the other two groups, but only during the first laboratory session (i.e., after 7 to 10 days of abstinence). The eliciting stimulus for this tremor was a task that required rapid ballistic pointing movements toward a moving visual target, alternating with periods of sustained posture. Thus, the amount of tremor recorded during the task was actually a combination of true action tremor with tremor of the postural type. Both types of tremor have previously been reported in

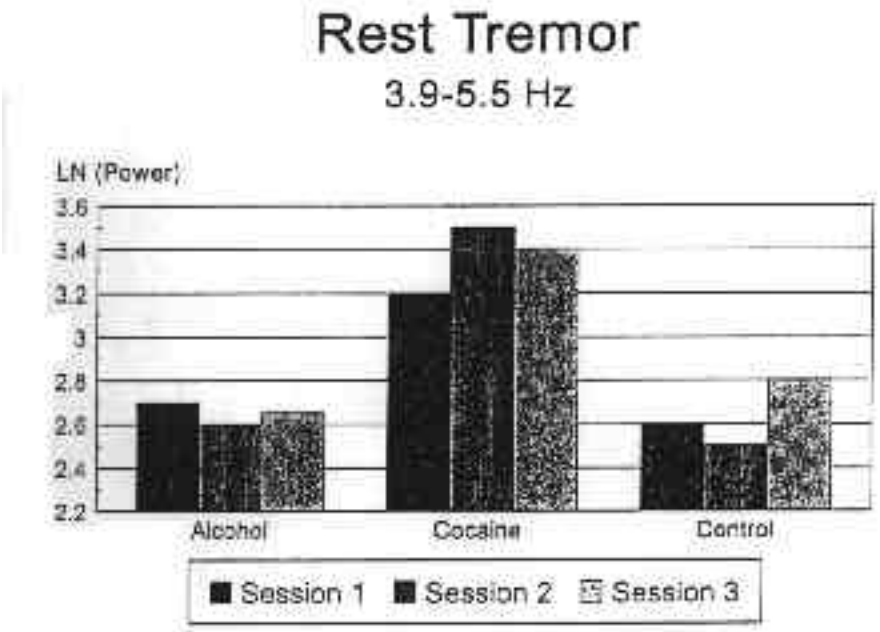

FIGURE 1. *Hand tremor as a function of subject group and session. Differences greater than 0.38 units are significant (Tukey critical difference, $p < 0.05$).*

alcohol-dependent patients (Neiman et al. 1990; York and Biederman 1991) and in patients with known cerebellar pathology (Victor et al. 1959).

The hypothesis of cerebellar dysfunction as the source of postural/action tremor among 1-week abstinent alcohol-dependent patients was further supported by the demonstration of enhanced body sway among these same patients, also during the first week of abstinence. Of course, enhanced body sway can be produced by other alcohol abuse-related factors, including peripheral neuropathy (Scholz et al. 1986) and some premorbid factors (Bauer and Hesselbrock 1993). But the young age and relatively excellent health of study patients, and the careful matching of the two patient groups on the prevalence of ASPD and family history of alcoholism, argue against these alcohol-related factors as significant contributors.

Cocaine-dependent patients exhibited a 4 to 6 Hz tremor that appeared while the hand rested in a supine position. The hand tremor was not accompanied by signs of cerebellar dysfunction, such as the enhanced body sway found in alcoholic patients, or nystagmus (Bauer 1993b). It was also not present during posture or movement. Most importantly, the exaggerated resting hand tremor of the cocaine-dependent patients did not diminish in amplitude, even after 94 to 100 days of verified cocaine abstinence (figure 1).

It is tempting (but still premature) to draw an analogy between the resting hand tremor observed in the present study and the characteristic resting hand tremor of Parkinson's disease. As noted above, numerous case reports have suggested an association between the effects of chronic cocaine abuse and the effects of Parkinsonism. These reports imply that cocaine can exacerbate preexisting extrapyramidal movement disorders or produce a Parkinsonian-like extrapyramidal disorder where none existed previously (Cordoso and Jankovic 1993; Choy-Kwong and Lipton 1989; Farrell and Diehl 1991; Merab 1988; Mesulam 1986; Pascual-Leone and Dhuna 1990; Satel and Swann 1993). Controlled studies demonstrating altered basal ganglia glucose metabolism in cocaine-exposed brain (Volkow et al. 1991) and altered cocaine receptor binding in Parkinson's-diseased striatal tissue (Kaufman and Madras 1991) reinforce the cocaine abuse-Parkinsonism analogy.

Despite the superficial similarity of tremors associated with cocaine abuse and Parkinsonism, it is important to recognize that the resting hand tremor exhibited by cocaine-dependent patients in the present study was far more subtle than described in the aforementioned case reports of cocaine abusers or in Parkinson's disease patients. In fact, the hand tremor detected in the present study was not visually obvious and would not have been detected without sensitive recording devices. Therefore, it is probably not significant in their daily lives, except for a subset of patients whose occupations require fine motor control and/or rapid motor responses.

Yet, it would be clinically and scientifically valuable to follow a group of cocaine-dependent patients as they enter middle age or senescence and determine if the subclinical tremor evolves into a significant clinical entity. For the same reason, it would also be valuable to follow a group of cocaine-dependent patients receiving neuroleptics for the management of schizophrenic symptoms and determine if they are more likely to develop clinically significant dystonic reactions or tardive dyskinesias. Kumor and colleagues (1986) have already reported data supportive of this hypothesis.

Reaction Time Performance. The very mild hand tremor exhibited by abstinent cocaine-dependent patients appears to bear a relationship to the slower-than-normal reaction times (RT) exhibited by these same patients. In fact, within this group, there is a significant correlation ($r = 0.43$, $p<0.05$) between rest tremor and simple reaction time.

The reaction times shown in figures 2a and 2b (Roberts and Bauer 1993) were measured during visual and auditory divided attention tasks. The tasks are similar to those used in the Reitan-Klove Sensory Perceptual Exam (Golden et al. 1981). During each task, a 20-millisecond (ms) stimulus (light flash or tone) is presented in either the right or left sensory field or in both sensory fields simultaneously. The stimulus location is varied randomly from trial to trial. Trials occur at the rate of one every second. Subjects are instructed to press one of two horizontally aligned response keys to indicate the spatial location of the stimulus, or both keys simultaneously when stimuli occur bilaterally. Reaction time and errors are calculated.

In clinical applications of this or similar variants of the Reitan-Klove Sensory Perceptual Exam in brain-damaged patients, neuropsychologists have focused on a particular type of performance error, an inability to detect simultaneous bilateral stimulation. Errors of this type are most often associated with posterior parietal lobe disease (i.e., the sensory neglect syndrome). Neither cocaine- nor alcohol-dependent patients

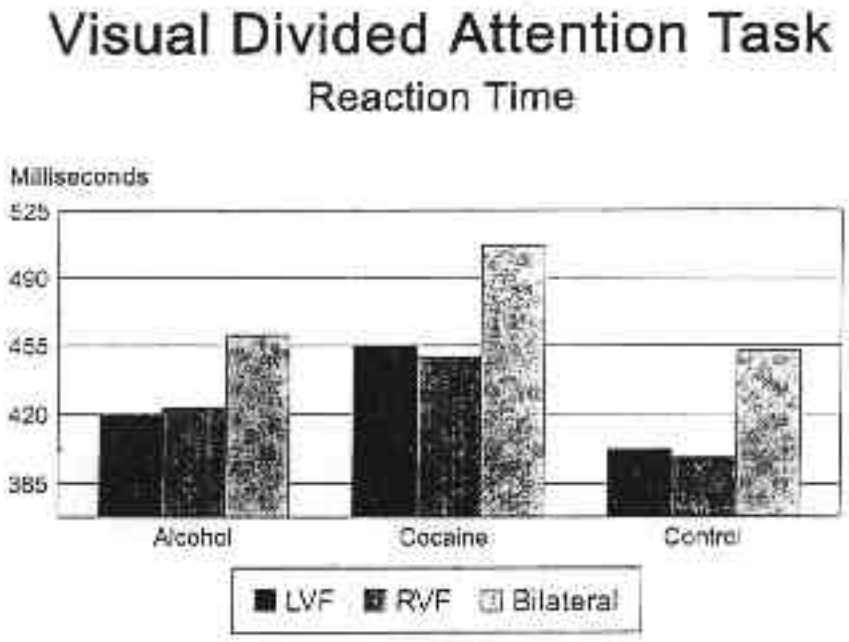

FIGURE 2a *Reaction time (in ms) during the visual divided attention task plotted as a function of subject group and stimulus location (visual field). The session effect was not significant and the data are accordingly collapsed over sessions. Differences greater than 27 ms are significant.*

exhibited a pattern of errors consistent with this clinical syndrome. Rather, cocaine-dependent patients were just slower than the other two groups during all three laboratory sessions. The magnitude of the slowing did not change as a function of the complexity of the discrimination (uni-lateral versus bilateral) or as a function of the sensory modality of the task (visual or auditory). Thus, the slowing appeared limited to the motor side of the reflex arc.

In a different experiment (Bauer 1994c) employing the same subjects, reaction time, performance errors, and EEG activity were examined during a vigilance task 30 minutes in duration. The justification for evaluating vigilance derived from clinical observations of disordered arousal (e.g.,the postcocaine use "crash," alcohol withdrawal insomnia)

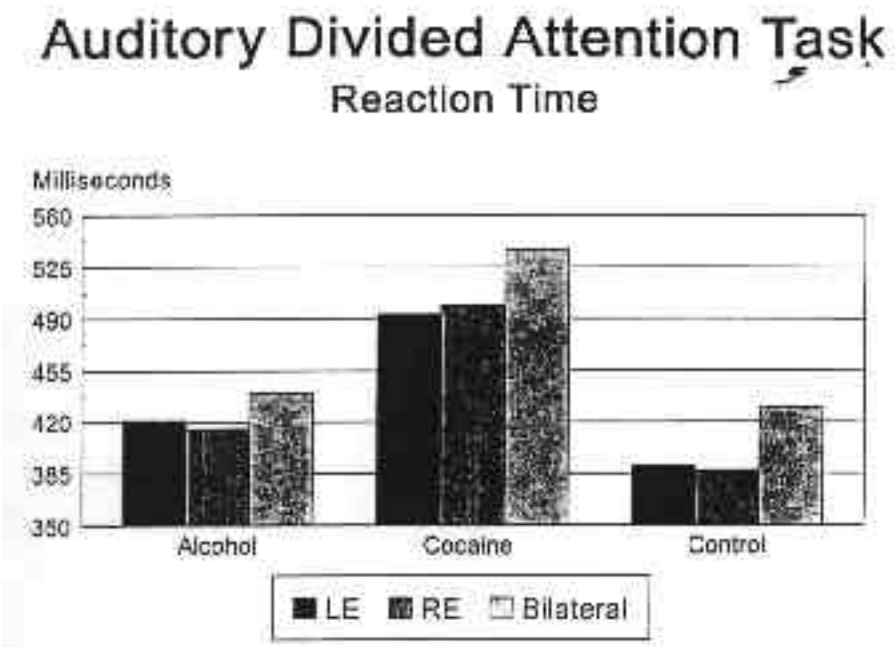

FIGURE 2b. *Reaction time (in ms) during the auditory divided attention task plotted as a function of subject group and stimulus location (ear). The session effect was not significant. Differences greater than 22 ms are significant.*

and more systematic demonstrations (Gawin and Kleber 1986; Gillin et al. 1990) of disrupted sleep among patients in the early phases of cocaine or alcohol withdrawal. Therefore, it was logically of interest to determine if these disruptions were reflected in patients' daytime alertness and if altered alertness persisted into the later phases of the withdrawal and recovery period.

The vigilance task was a conventional signal detection paradigm (Davies and Parasuraman 1982) in which subjects listened to 100 ms duration of pure tones occurring at a rate of 30 per minute. On one-third of the trials, a 1,000 Hz tone was substituted for the 500 Hz standard tone. Subjects were instructed to press a response key upon detecting the rare 1,000 Hz tone and to ignore the other. EEG activity and performance were monitored continuously and summarized separately for each 10-minute period during the 30-minute vigil.

As expected, omission errors increased with time on task, as did reaction time and EEG alpha (7 to 13 Hz) power. However, there were no differences among the cocaine-dependent, alcohol-dependent, and control groups with respect to the magnitude or rate of these time-related changes. At the risk of interpreting the null hypothesis, these null findings suggest that recovering cocaine- or alcohol-dependent subjects are no more vulner-able to the effects of mental fatigue, at least in the present task setting, than are controls. Indeed, available data indicate that acute doses of cocaine and alcohol also have little (Fischman and Schuster 1980) or no effect (Erwin et al. 1978) on time-related reductions in vigilance. Rather, acute cocaine and alcohol primarily affect the average level of performance.

The only variable to differentiate groups was reaction time averaged across the 30-minute vigil. As in the divided attention task (see above), the reaction times of the cocaine-dependent patients were 50 to 75 ms slower than the other groups. The magnitude of the reaction time slowing, also as above, did not change as a function of duration of abstinence (figure 3).

ERP Correlates of Motor Function. In a new study in which subjects are tested after 3 and 9 months of verified abstinence, the author is examining P300 ERPs during various information-processing tasks. In one such task (after Knight 1984), subjects hear a 5-minute train of discrete 50-ms duration tones (presentation rate 40 per minute). The tones are mostly uniform in pitch. However, in 10 percent of the trials, the filtered and shaped sound of a dog bark is substituted for the tone. The subject is instructed to ignore this change. In another 10 percent of the trials, a higher pitched tone is substituted for the standard tone. The subject is instructed to press a key when this event occurs.

Thus, there are two types of rare events during the task: a rare nontarget (the dog bark) and a rare target (the higher pitched tone). Figure 4 shows averaged ERPs for the two patient groups for these two events. Prelim-inary analyses of the P300 evoked by the rare nontarget revealed it to be similar in the cocaine-dependent and alcohol-dependent groups and only slightly reduced relative to the normal control group (not shown). The P300 evoked by this rare nontarget event consisted of only one wave with a peak latency of approximately 300 ms.

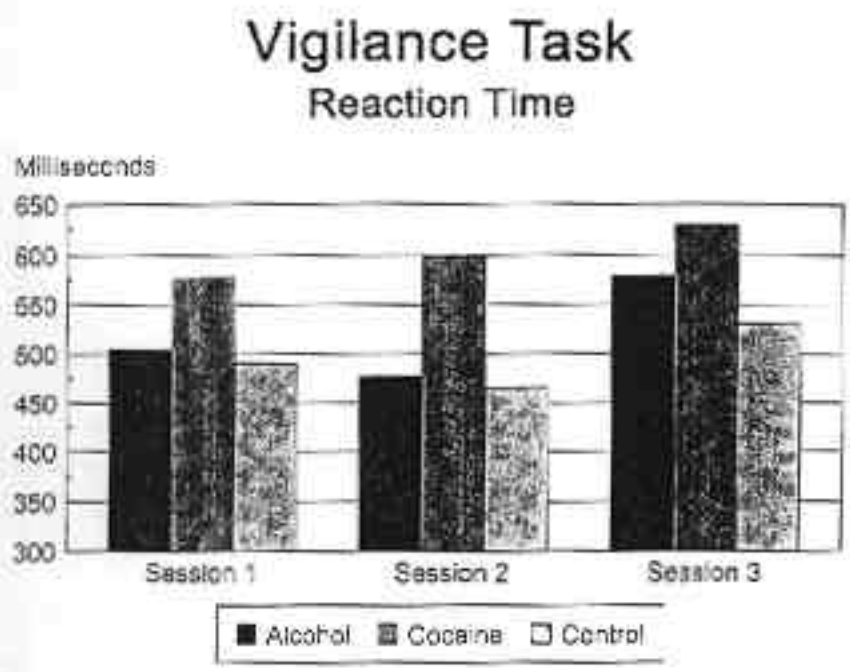

FIGURE 3. *Reaction time (in ms) during the auditory vigilance task. Differences greater than 43 ms are significant.*

In contrast, the rare target event evoked a complex of two positive waves, hereafter called P300a and P300b, among both alcohol-dependent patients and normal controls. But, among the cocaine-dependent patients, the P300b wave was significantly reduced in amplitude. In other words, when a motor response was required, cocaine abusers showed a reduced P300. This decrement was present after 3 months of verified abstinence. Later phases of the study will examine whether the P300 decrement is detectable after 9 months of cocaine abstinence.

One can plot the scalp topography of the difference between the alcohol-dependent and cocaine-dependent patient groups in the later P300 component. Topographic maps of ERPs are based on several assumptions that may not always hold (Burgess and Gruzelier 1993; Jayakar et al. 1991). Nonetheless, as figure 5 shows, the P300b reduction in abstinent cocaine abusers was greatest at frontal electrode sites. This finding is consistent with the frontal locus of glucose metabolism

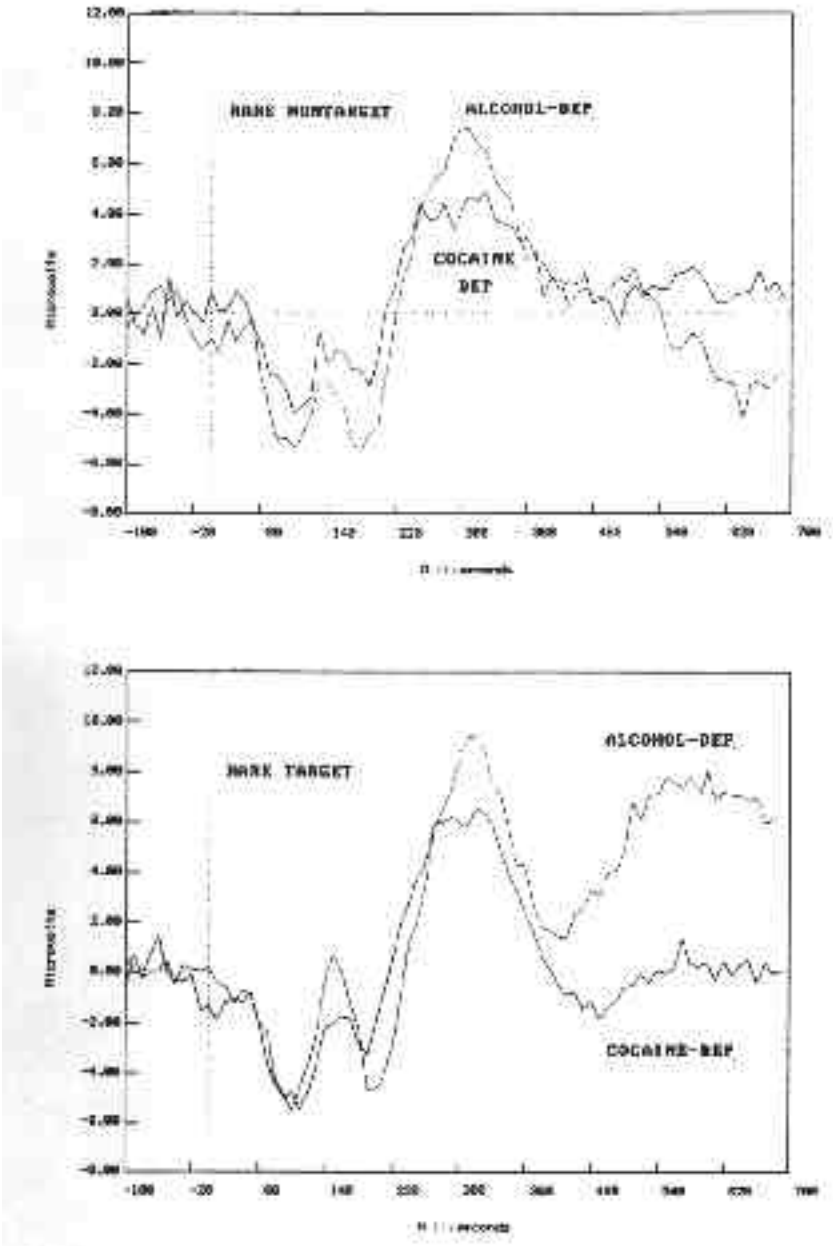

FIGURE 4. *Averaged event-related potentials elicited by rare nontarget (above) and rare target (below) stimuli.*

abnormalities detected among 3- to 4-month abstinent cocaine abusers by Volkow and colleagues (1992).

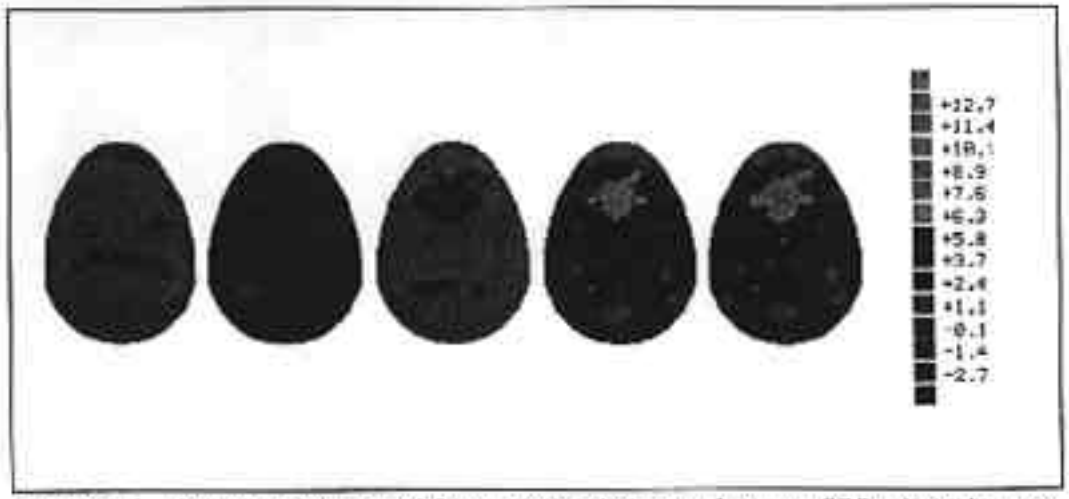

FIGURE 5. *Topographic map of the amplitude difference between ERPs elicited among alcohol-dependent and cocaine-dependent patients in response to rare target stimuli. Note that the maximum difference between the patient groups occurs at frontal electrode sites in a latency range that encompasses the P300b.*

The demonstration of P300 amplitude decrements among abstinent cocaine-dependent patients is not unprecedented in the literature (Amass et al. 1990; Branchey et al. 1993; Herning and colleagues, this volume). However, most previous demonstrations of P300 decrements have used the conventional two-stimulus P300 "oddball" task, which confounds P300a and P300b components as well as the effects of stimulus novelty and motor responding. Another distinguishing feature of the present P300 study (Branchey et al. 1993) was the attempt to control for the effects of ASPD and a family history of alcoholism (Bauer et al. 1994; Polich et al. 1994). Since these two premorbid variables were held constant in the present comparison of cocaine- versus alcohol-dependent patients and the P300 decrement was specific to the cocaine-dependent group, one can more convincingly attribute the decrement to the effects of chronic cocaine dependence. It is important to recognize that the same conclusion cannot be drawn regarding alcohol dependence, where P300 decrements are more reliably related to premorbid variables (Pfefferbaum et al. 1991). Thus, at least with respect to P300, cocaine appears more neurotoxic than alcohol.

Eye Movements. As the last measure of motor system functioning among recovering cocaine-dependent patients, eye movements were recorded (Bauer 1993b). Eye movement recording is an especially powerful technique for studying brain function. Eye movement control can be disrupted by a wide range of family history (Holzman et al. 1984), neurological (Leigh and Zee 1991), and drug-use variables. The avail-able armamentarium of quantitative eye movement measures is also wide ranging, from assessments of resting nystagmus to reflexive movements elicited by caloric, rotoric, or optokinetic challenges.

For a variety of reasons, both smooth pursuit and saccadic eye movements were examined. The scientific justification was provided by previous studies of acute drug effects in normal controls. In such studies, alcohol has been shown to interfere with both smooth pursuit (Levy et al. 1981) and saccadic (Baloh et al. 1979; Fuster et al. 1985) tracking. Ampheta-mine has the opposite effect (Filip et al. 1978; Tedeschi et al. 1983).

Only two studies have examined eye movements among patients chroni-cally exposed to cocaine. Demer and colleagues (1989) examined a variety of eye movement parameters among cocaine-abusing patients and normal controls. No group differences were found, except for a slight reduction in the gain of the vestibulo-ocular

reflex among the cocaine abusers. Unfortu-nately, only nine patients were tested, and four of the nine patients were receiving antidepressant or antipsychotic medications. The likelihood of detecting eye movement abnormalities was accordingly low.

Rosse and colleagues (1992) contrasted the smooth pursuit eye movements of crack cocaine abusers, schizophrenic patients, and a normal control group. A reduction in smooth pursuit gain and an increase in large ampli-tude saccadic intrusions were detected among both schizophrenic and cocaine-abusing patients. Due to the brevity of the report, it is unclear whether the difference between patients and controls could be explained by some other variable such as a group difference in the prevalence of familial schizophrenia (Holzman et al. 1984). To eliminate this potential confound from the present subject sample, it was important to exclude from the analy-sis any individual with a parent or sibling affected with Axis I schizophrenia, schizophrenia-like disorders, or Axis II Cluster A personality disorders as described in the "Diagnostic and Statistical Manual of Mental Disorders," 3d. ed. rev. (DSM-III-R) (American Psychiatric Association 1987).

The tasks used to elicit smooth pursuit and saccadic eye movements have been described previously (Bauer 1993b). In brief, the smooth pursuit eye movement task required subjects to visually track a pendulum oscil-lating at 0.4 Hz. Eye movements were recorded electro-oculographically and analyzed in the frequency domain to yield Holzman and colleagues' (1984) log (signal to noise) (LN(S/N)) statistic.

The saccadic eye movement task involved visual tracking of the apparent motion of light emitting diodes briefly illuminated at one of four eccen-tricities (20 or 35 degrees left or right of center) determined randomly. To increase the number of saccadic eye movements, subjects were required to perform a visual discrimination at these locations. Only the initial (i.e., elicited) saccade was measured.

Analyses revealed different types of eye movement dysfunction in the two patient groups. During the step-tracking task, alcohol-dependent patients exhibited longer saccadic reaction times than the other groups. This delay in the ability to establish fixation on a new visual target endured throughout the first 94 to 100 days of abstinence. It may account for the alcohol-dependent patients' longer-than-normal visual search times (Bertera and Parsons 1978) during

neuropsychological tests. Whether it also contributes to reading and comprehension problems is an open question.

In contrast, cocaine-dependent patients exhibited a persistent change in smooth pursuit eye tracking. Somewhat surprisingly, however, the smooth pursuit tracking accuracy of these patients was found to be superior to that of alcohol-dependent patients and normal controls, even after 3 months of abstinence. Since acute amphetamine administration has been shown to improve eye-tracking accuracy (Filip et al. 1978), the supranormal tracking of abstinent cocaine abusers could represent a residual cocaine-like effect. This stands in contrast to cocaine-opposite effects such as their slower-than-normal reaction times (see above). Thus, cocaine appears capable of inducing hyper- or hypoexcitability in different portions of the motor system.

EEG Sequelae

Cocaine's apparent ability to induce simultaneous, directionally opposite changes in neurononal excitability in the motor system also extends into the sensory systems. Figure 6 shows the magnitude of an EEG response to a light flickered at the subject's dominant resting alpha frequency, between 7 and 13 Hz. Photic driving is an old clinical technique still used in clinical EEG assessments. A variety of patient groups, including schizophrenics (Jin et al. 1990) and Alzheimer's disease (Politoff et al. 1990) patients, have been shown to exhibit reduced driving responses; cocaine abusers are no exception. As the intensity of flicker is increased, only normal controls show an increase in response amplitude.

Figure 6 contrasts with the results of another photic driving experiment (figure 7) in which the flicker is produced by means of a sine wave, not a square wave. In many sensory systems, these two types of stimulation are encoded differently and activate different neuronal circuits. In the visual system, for example, high frequency transient events (square waves) and steady states (sine waves) are differentiated at levels as low as retinal ganglion cells and follow different pathways. Thus, as can be seen in the figure, increasing the intensity (modulation depth) of sine wave flicker elicits an exaggerated response in cocaine-dependent patients, while square wave flicker does the opposite (figure 6). These exaggerated and inhibited responses persist even after 3 months of abstinence.

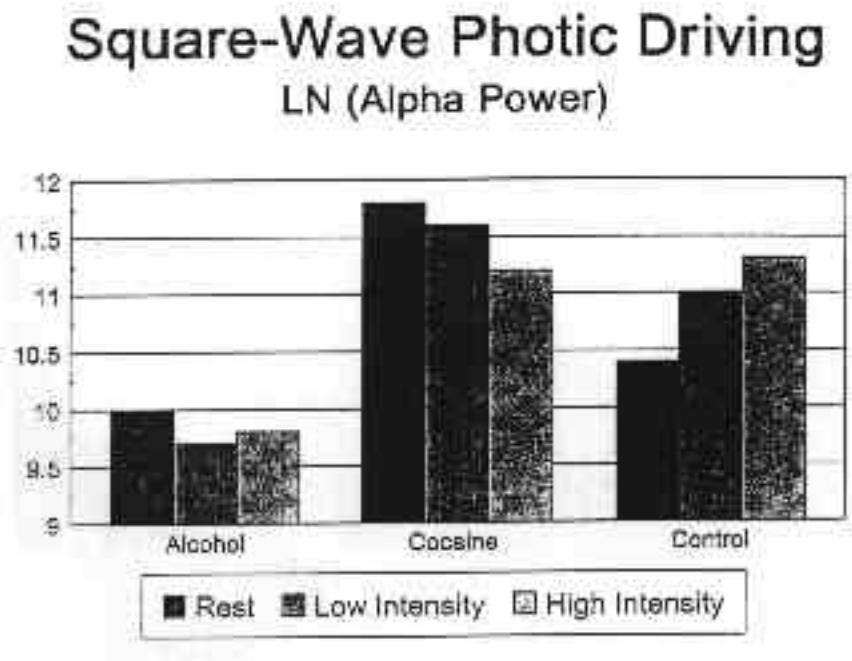

FIGURE 6. *EEG alpha power in the three subject groups as a function of the intensity of a square wave modulated photic stimulus. Differences greater than 0.6 units are significant. The session effect was not significant. The data are accordingly collapsed across the levels of that variable.*

SUMMARY

In conclusion, there appears to be strong evidence from these studies supporting the existence of a postcocaine abuse syndrome. The general hypothesis stated that cocaine-dependent patients would exhibit impaired performance on tests of motor system functioning. It was further hypothe-sized that these impairments would be more severe and persistent than impairments in other areas. These hypotheses were confirmed. Cocaine-dependent patients were found to exhibit a statistically significant resting hand tremor, which did not remit despite 3 months of verified abstinence. In contrast, alcohol-dependent patients exhibited an enhanced action tremor and enhanced body sway that remitted after 1week. Cocaine-dependent, but not alcohol-dependent, patients also exhibited slower reaction times than controls during a protracted vigilance task and during simpler tasks requiring visual or auditory divided attention. The reaction time slowing

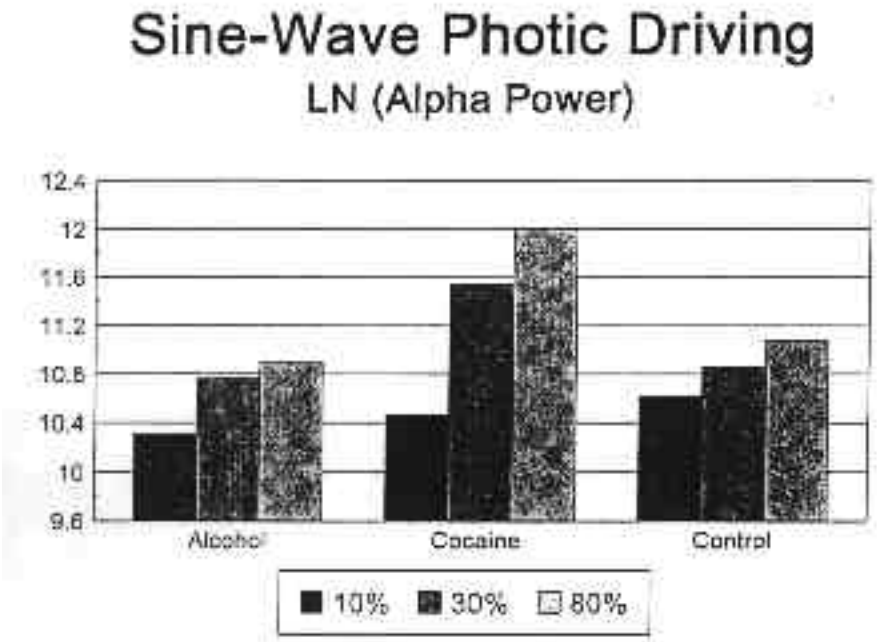

FIGURE 7. *EEG alpha power in the three subject groups as a function of the intensity of a sine wave modulated photic stimulus. Differences greater than 0.9 units are significant. The session effect was not significant. The data are accordingly collapsed across the levels of that variable.*

was substantial (approximately 50 to 75 ms), task independent, and, like resting tremor, did not remit after 3 months of abstinence.

The demonstration of smooth pursuit eye movement irregularities in the cocaine-dependent group further reinforced the motor system hypothesis. During visual tracking of an oscillating pendulum, the tracking accuracy of cocaine-dependent patients was superior to that of controls at all three time points. Studies that have administered acute amphetamine to nor-mal, nondrug-dependent individuals have reported a similar finding. Collectively, these findings suggest that chronic cocaine use may induce a hyperexcitability of the smooth pursuit eye movement control system, which persists into abstinence.

Evidence for EEG abnormalities among recovering cocaine-dependent patients was provided by a variety of experiments. In a new and ongoing experiment, cocaine-dependent patients exhibit

reduced P300b ERPs to rare stimuli, which they must acknowledge with a motor response. Evidence for a nonmotor CNS dysfunction was provided by examining EEG responses to a simple flickering light. However, the nature of the dysfunction was complex. EEG responses to square wave modulated light revealed diminished reactivity among both cocaine-dependent and alcohol-dependent patients at all three time points. In contrast, EEG responses to sine wave modulated light revealed enhanced reactivity among the cocaine-dependent patients only. The coexistence of diminished or enhanced EEG reactivity and diminished or enhanced motor system functioning implies that cocaine dependence can simulta-neously depress and enhance different aspects of brain function in the same individual. The diversity of cocaine's EEG and psychomotor effects may have an analog in demonstrations of the simultaneous development of sensitization and tolerance among animals chronically exposed to cocaine.

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AUTHOR

Lance O. Bauer, Ph.D.
Associate Professor of Psychiatry
Director, Neural Dynamics Laboratory
Department of Psychiatry
University of Connecticut School of Medicine
Farmington, CT 06030

Cocaine Effects on Dopamine and Opioid Peptide Neural Systems: Implications for Human Cocaine Abuse

Yasmin L. Hurd

INTRODUCTION

Cocaine induces a wide range of emotions in humans, from an initial high (euphoric state) to severe anxiety, paranoia, depression, and anhedonia. As a psychomotor stimulant, cocaine has a potent effect on motor behavior, increasing locomotion and causing stereotyped repetitious behavior, tics, and uncontrollable tremors. Despite the fact that the psychological and behavioral effects of cocaine use in humans have been well documented for over 100 years, the current knowledge of the neurobiological events underlying the abuse of cocaine in humans is still limited.

Much of the information obtained thus far about cocaine's effects on brain function have derived from a large number of animal studies carried out within the past 20 years. Such studies have clearly demonstrated that activation of the neurotransmitter dopamine (DA) is necessary for initiation of many of the behavioral properties associated with cocaine, including reinforcement and motor activation. However, a one-neurotransmitter hypothesis to account for the complexity of drug abuse is improbable. Many investigations into the neurobiological actions of cocaine abuse have thus begun to focus attention on neural systems linked with that of DA. Of these DA-related neural systems, a strong case can be made for a role of the endogenous opioid neuropeptides dynorphin and enkephalin in cocaine abuse. These endogenous endorphins are not only involved in the regula-tion of emotion and emotional expression but also tightly integrated in basal ganglia motor circuits.

This chapter outlines some of the neuroanatomical and pharmacological data generated from both human and animal studies that together lend support for a DA/opioid peptide hypothesis for the psychological and behavioral properties of cocaine abuse. This neuroanatomical and neurochemical background is the foundation for understanding results obtained from recent postmortem studies of

human cocaine users which reveal an imbalance in the gene expression of specific opioid pepties.

DOPAMINE INVOLVEMENT IN HUMAN COCAINE ABUSE

Not surprisingly, the data to support a central role for DA in cocaine abuse is abundant. Pharmacologically, cocaine, an indirect DA agonist, is a potent inhibitor of the DA transport carrier, effectively potentiating in vivo extracellular DA concentrations (Church et al. 1987; Hurd and Ungerstedt 1989; Pettit and Justice 1989). Cocaine has a relatively short plasma and brain half-life—intravenous (IV) in humans, 16 to 87 minutes (Inaba 1989; Javaid et al. 1978); in rats, 18 to 30 minutes (Hurd et al. 1988; Nayak et al. 1976)—with in vivo brain cocaine levels linearly correlated to extracellular levels of DA (Hurd et al. 1988; Nicolaysen et al. 1988; figure 1). Therefore, an acute IV administration of cocaine typically produces a fast "hit-and-run" effect on the potentiation of extracellular levels of DA, with the peak DA elevation observed within 10 minutes and a return to baseline levels by 20 to 30 minutes in rats (Hurd and Ungerstedt 1989; figure 1).

Such findings lend support to the belief that it is the short half-life of cocaine that accounts for the rapid euphorogenic properties of the drug. In fact, the in vivo DA overflow induced by an acute IV injection of cocaine in rats is not only temporally correlated to in vivo cocaine binding (presum-ably binding to DA transport carriers) measured in human brains by posi-tron emission tomography (PET) (Fowler et al. 1989), but also temporally correlated to the subjective high and rush reported by humans (Fischman et al. 1983; Fowler et al. 1989; Kumor et al. 1989).

Unfortunately, a one-to-one correlation between the amount of cocaine in the brain and elevated extracellular levels of DA cannot solely account for the diverse psychological and behavioral effects of the drug. While the elevation of DA is critical for initiation of the acute stimulatory actions of cocaine, the actual presence of the drug in the brain and the subsequent potentiation of synaptic DA levels do not always appear to be correlated with all the psychological aspects of cocaine abuse, especially those associated with aversive emotions. Fifteen minutes after an IV injection of cocaine, craving is experienced although a high concentration of cocaine should still be present in the brain (Jaffe et al. 1989). Moreover, the rush feelings in response to IV cocaine still return rapidly (within 10 minutes) to baseline even during the active infusion of the drug (Kumor et al. 1989)

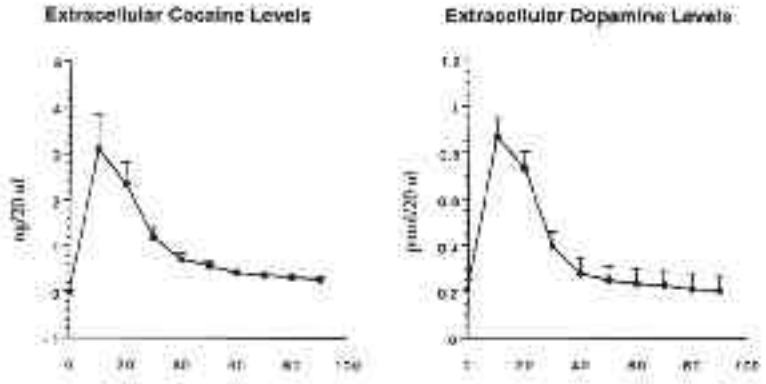

FIGURE 1. *In vivo extracellular concentrations of cocaine and dopamine in the striatum of rats following an intravenous injection of cocaine (2.0 mg/kg).*

SOURCE: Hurd et al. 1988.

when extracellular levels of DA would be expected to remain elevated (Hurd and Ungerstedt 1989). It is also apparent that after the self-reported rush has diminished, continuous IV infusion of cocaine can induce negative feelings such as dysphoria, anxiety, and paranoia; these can be intermixed with positive feelings of well being (Kumor et al. 1989; Sherer 1988).

Clinically, there are a number of studies showing the development of tolerance to the positive subjective high with repeated cocaine use (Fischman and Schuster 1982; Fischman et al. 1985) and during the continuous infusion of the drug (Ambre et al. 1988). The cocaine abuse disorder is therefore characterized as a state in which negative dysphoric events become a larger part of the drug abuse phenomena, while the positive euphorogenic properties that initiated cocaine abuse attenuated, even with cocaine present in the body.

Although the literature is in agreement about potentiated DAergic function during acute administration of cocaine, there are debates about the responsivity of DAergic transmission during chronic cocaine abuse. Recent PET experiments carried out by Volkow and coworkers (this volume) have revealed that indices of in vivo DA overflow are attenuated in cocaine-dependent human patients compared with control subjects following a challenge administration of the stimulant drug methyl-phenidate. These clinical findings are complemented by animal data showing attenuation of extracellular

levels of DA in the nucleus accumbens of previously exposed rats directly self-administering cocaine as compared with cocaine-naive rats receiving the drug for the first time (Hurd et al. 1989). Furthermore, a number of animal studies have reported reduced basal extracellular levels of DA as a consequence of repeated cocaine administration (Imperato et al. 1992; Parsons et al. 1991) and a functional tolerance of the DAergic responsiveness to cocaine despite elevated concentrations of the transmitter (Weiss et al. 1992). Altogether these findings would be consistent with the DA depletion theory of cocaine addiction proposed to account in part for the underlying dysphoric effects associated with chronic cocaine abuse (Dackis and Gold 1985). However, in addition to tolerance (Hurd et al. 1989; Imperato et al. 1992; Inada et al. 1992; Maisonneuve and Kreek 1994; Robinson et al. 1990; Segal and Kuczenski 1992), in vivo animal studies have also reported sensitization (Akimoto et al. 1989; Kalivas and Duffy 1990; Pettit et al. 1990; Robinson et al. 1988) of striatal DA overflow as a consequence of the repeated administration of psychomotor stimulants.

The contradictions reported in the animal literature about DA responsivity to repeated cocaine administration may be resolved if the experimental factors within these studies that shed some light on the dynamic nature of cocaine-induced DA effects are considered. These factors include differences in the dose, route of administration, duration of drug use, timing of drug administration, drug withdrawal time period, and the environment associated with cocaine use. Each of these factors can significantly contribute to differences in DAergic sensitivity to repeated cocaine administration (Johanson and Fischman 1989). In fact, a second challenge administration of cocaine following just one previous injection of the stimulant can cause different effects on cocaine-induced elevation of striatal DA levels in rats depending on the time between testing: 1 day, sensitization; 10 days, attenuation; and 20 days, no change in cocaine-induced DA overflow compared with the first cocaine exposure (Guix, Hurd, and Ungerstedt, unpublished data). Consistent with time-dependent alterations in DAergic sensitivities to cocaine implied by the animal literature, clinical hypoprolactinemia (considered an index of increased DA tone) has been found after acute cocaine use (Gawin and Kleber 1985), whereas hyperprolactinemia (an index of decreased DA tone) has been documented during intermittent periods of cocaine withdrawal (Dackis and Gold 1985; Mendelson et al. 1988). Nevertheless, based on the complexity of the behaviors associated with cocaine (some show tolerance while others show sensitization) (Johanson and Fischman 1989), it is necessary to explore other

affected neuro-chemicals in an attempt to explain the myriad cocaine abuse behaviors, especially those associated with craving, dysphoria, paranoia, and anxiety, which dominate chronic cocaine abuse compared with euphoria.

OPIOID NEUROPEPTIDES INVOLVEMENT IN HUMAN COCAINE ABUSE

Although relatively few studies have directly investigated the involvement of opioid peptides in cocaine abuse, the neurobiological and behavioral actions of opioid compounds have been extensively studied. Similar to cocaine, opiate drugs are highly addictive, and endogenous opioid peptides have a physiological role in a wide variety of behaviors, including mood, motivation, and extrapyramidal motor function (Herz 1993).

There are three major classes of endogenous opioid peptides in the brain—dynorphins, enkephalins, and endorphins—derived from three distinct precursor genes: prodynorphin, proenkephalin, and pro-opiomelanocortin. Of these, dynorphin and enkephalin peptides are the most abundant in the brain (Khachaturian et al. 1985). Several lines of preclinical and clinical evidence suggest a significant involvement of opioid peptides in cocaine abuse. In human cocaine abusers, the street combination of heroin and cocaine (speedball) potentiates the subjective reinforcing effects of cocaine alone. Moreover, it appears that cocaine abusers self-medicate opiate agonists (e.g., heroin) to attenuate some of the negative dysphoric and anxious feelings induced by cocaine (Kreek 1988). Animal studies also show a strong involvement of the opioid system in the reinforcing actions of cocaine. Administration of the opiate antagonist naloxone reduces the rewarding effects of cocaine on self-stimulation behavior (Bain and Kornestsky 1987) and, within a critical cocaine dose range, also reduces the rewarding effects associated with cocaine self-administration (Carroll et al. 1986; De Vry et al. 1989).

Opioid neuropeptides produce their effects through interactions at the specific opiate receptors μ, d, and k. Enkephalin peptides have a high affinity for μ and d opiate receptors (Lord et al. 1977), whereas dynorphin peptides have a high affinity for k opiate receptors (Chavkin et al. 1982). Administration of enkephalins and/or stimulation of μ and d opiate recep-tors are rewarding (Shippenberg et al. 1987), whereas stimulation of k receptors are aversive (Bals-Kubik et al. 1992; Shippenberg et al. 1987) and experienced as

dysphoric in humans (Pfeiffer et al. 1986). Thus, there appears to be a functional balance within the opioid system such that dynorphin mediates opposite behaviors to enkephalin in regard to mood and motivation. There is also a growing body of evidence showing a functional dichotomy of opioids in the behavioral effects of cocaine.

Animal studies have demonstrated that k agonists can block both the acute and chronic effects of cocaine on locomotor activity and stereotypy in rats (Heidbreder et al. 1993). Moreover, k agonists or μ antagonists effectively block cocaine reward in place preference paradigm in rats (Suzuki et al. 1992). Likewise, k agonists impair, whereas μ agonists potentiate, the reward stimulus properties of cocaine in monkeys (Spealman and Bergman 1993). These data validate the attempts to manipulate the opposing proper-ties of the opioid system as a new approach to the treatment of cocaine abuse. The effectiveness of buprenorphine, a partial μ agonist and k antag-onist, to reduce cocaine self-administration in monkeys (Mello et al. 1989) has recently brought such pharmacological manipulations to the clinic. Although buprenorphine has proven effective in treating opiate abuse (Mello and Mendelson 1980; Schottenfeld et al. 1993), the duration of buprenorphine treatment may be a critical factor for its reduced effective-ness in suppressing cocaine use in cocaine-dependent subjects (Mendelson et al. 1992; Schottenfeld et al. 1993).

NEUROANATOMICAL INTERACTIONS OF DOPAMINE AND OPIOID SYSTEMS

Mesolimbic and mesostriatal brain regions have been shown to be neuroanatomical substrates for the drug reward and motor stimulatory effects of drugs of abuse (Koob 1992). The limbic system comprises a collection of brain structures believed to be involved in the experience and expression of emotion, and as such are central to drug reward and the wide spectrum of emotional pathology induced by cocaine. The basal ganglia, in contrast, are a group of structures involved in motor coor-dination; a central component of this system, the neostriatum (caudate, putamen, and nucleus accumbens (ventral striatum)), integrates informa-tion related to sensorimotor functions, emotion, and motivation. Identifi-cation of the basal ganglia as a critical anatomical site of action for cocaine is substantiated not only by increased motor activation after administration of the drug but also by the development of movement dis-orders in human cocaine users that are similar to neurological manifesta-tions associated with abnormal basal ganglia DA function (e.g.,tremors, involuntary

movements, shakes, crack dancing, and tics) (Attig et al. 1994; Bauer 1993; Daras et al. 1994). The fact that the striatum is richly innervated by DA neurons, is organized into distinct motor- and limbic-related subregions, and is abundant in the opioid neuropeptides dynor-phin and enkephalin makes it an important brain structure for examining the interaction of DA and opioid peptides in cocaine abuse.

Basal Ganglia

Brain regions normally included in the basal ganglia are the striatum, globus pallidus, subthalamic nuclei, and substantia nigra. DA is predominantly synthesized in cells of the substantia nigra pars compacta, which sends massive projections to the striatum (Björklund and Lindvall 1984). DA nerve terminals in the striatum synapse predominantly onto medium spiny cells rich in the opioid neuropeptides dynorphin and enkephalin as well as the inhibitory amino acid gamma aminobutyric acid (GABA) and the tachykinin neuropeptide substance P (Freund et al. 1984; Kubota et al. 1986). Medium spiny striatal neurons are the predominant cell type in this brain structure (human, 70 to 80 percent (Graveland et al. 1985); rat, 90 to 95 percent (Somogyi et al. 1981)) and serve as the major output pathways from the striatum.

There are two primary striatal efferent pathways that are discernible based on their neuropeptide content. Striatal neurons innervating the mesen-cephalic substantia nigra area predominantly contain dynorphin and substance P (Brownstein et al. 1977; Vincent et al. 1982). In contrast, enkephalin-containing striatal neurons project predominantly to the globus pallidus (external segment) (Del Fiacco and Cuello 1982), which in turn sends projections to the subthalamic nuclei and subsequently onto the substantia nigra. Most striatal neurons contain GABA (Kita and Kitai 1988), and thus this neurotransmitter is present in both striatonigral and striatopallidal pathways. Of the striatal neurochemicals, opioid neuro-peptides have become useful markers for dissociating striatal efferent pathways: Dynorphinergic neurons serve as a central component of the direct striatal output pathway back to the substantia nigra, whereas enkephalinergic neurons indirectly influence nigral activity via the globus pallidus.

Functionally, the two striatal opioid efferent pathways differentially modulate the activity of basal ganglia target nuclei (substantia nigra pars reticulata and thalamus) and consequently mediate opposing

actions on motor control. The striatonigral pathway exerts a tonic inhibition onto basal ganglia output nuclei, whereas the striatopallidal pathway exerts a tonic excitation in regulating movement (Alexander and Crutcher 1990). Consequently, potentiation of the striatonigral and/or inhibition of the striatopallidal pathway lead to increased behavioral activation. In contrast, inhibition of striatonigral and/or potentiation of striatopallidal pathway leads to reduced motor activation. A consistent finding in both human and animal cocaine users is an augmentation of the dorsal striatonigral dynor-phin system with weak or no changes of the enkephalin striatopallidal pathway (Daunais et al. 1993; Hurd and Herkenham 1993; Hurd et al. 1992). Such alterations in the striatal pathways would lead to hyper-activity, compatible with the potent motor stimulatory effects of cocaine.

The functional interaction between the DA and opioid system is also evident at the receptor level. Dynorphin striatonigral neurons preferentially express the messenger ribonucleic acid (mRNA) for DA type 1 (D1) receptors, whereas enkephalin striatopallidal neurons primarily express the mRNA for DA type 2 (D2) receptors (Gerfen et al. 1990; LeMoine et al. 1990). Recent experiments have demonstrated that knockout mice deficient in D1 receptors have reduced dynorphin immu-noreactivity in the striatum, primarily in the limbic-related compartment (Hiroi et al. 1994), and reduced responsivity to cocaine (White et al. 1994). However, both D1 and D2 DA antagonists have been shown to impair cocaine self-administration behavior (Bergman et al. 1990; Koob et al. 1987; Roberts and Vickers 1984).

Considerable data have been accumulated from lesion and pharmacological animal studies showing that DA differentially modulates the regulation of striatal opioid peptides (Gerfen et al. 1991; Young et al. 1986), but it is also apparent that opioids, in turn, can modulate DAergic activity. While kappaergic agents decrease dopamine release, μ agonists in contrast increase DA levels in the striatum (Di Chiara and Imperato 1988; Spangel et al. 1990). The reduction of striatal DA release upon application of the dynorphin peptide into the substantia nigra (Herrera-Marschitz et al. 1986) further supports the hypothesis that dynorphin mediates a negative striatonigral feedback modulation of DA neurons, and as such behavior.

Limbic System

Limbic and limbic-related brain regions include the hippocampus, amygdala, parahippocampal gyrus (entorhinal cortex), cingulate (medial prefrontal) cortex, insular cortex, septum, nucleus accumbens, and ventral tegmental area (VTA). In the limbic system, DA-synthesizing cells are found predominantly in the VTA, which sends terminal projections to the nucleus accumbens, amygdala, and prefrontal cortex (Björklund and Lindvall 1984). It has been well documented in animal studies that the forebrain structures innervated by VTA DA neurons are involved in the rewarding effects of cocaine. Lesions of the VTA (Roberts and Koob 1982), nucleus accumbens (Zito et al. 1985), and amygdala (McGregor and Roberts 1994) all impair cocaine self-administration. Of the forebrain structures studied for their role in drug reward, however, most attention has been given to the nucleus accumbens. Based on its localization in the ventral striatum and its strong anatomical connection with the amygdala, hippocampus, cingulate, and other limbic areas, the nucleus accumbens has the capacity of integrating functions related to emotion, motivation, and motor coordination (Heimer et al. 1982; Mogenson et al. 1980; Nauta 1986) that are relevant to cocaine abuse.

In addition to D1 and D2 receptors, the nucleus accumbens is characterized by preferential expression of D3 receptor mRNA expression in both rats (Bouthenet et al. 1991; Landwehrmeyer et al. 1993a) and humans (Hurd et al., unpublished observations; Landwehrmeyer et al. 1993b) as compared with the dorsal striatum. Consistent with D1 and D2 receptor antagonists, administration of 7-hydroxy-N, N-di-n-propyl-2-aminotetralin (7-OHDPAT), a D3 antagonist, also increases cocaine self-administration behavior in rats; this is interpreted as a partial blockade of the rewarding effects of cocaine (Caine and Koob 1993). Thus, all three subtypes of DA receptors appear to be involved to some extent in the self-administration of cocaine. However, it remains to be determined whether the various DA receptors subserve different aspects of cocaine self-administration behavior that may be unrelated to reinforcement and reward.

Aside from the dorsal and ventral dichotomy, the striatum is heterogeneously organized into distinct neurochemical and anatomical compartments differentially associated with limbic and sensorimotor functions. The two striatal compartments, patch (or striosome) and matrix, are linked respectively to limbic and sensorimotor brain areas (Graybiel 1990). Neurochemically, cells localized to the patch compartment in the human striatum are characterized by high μ opiate receptors (Hurd and Herkenham 1993,

1995), high D1 mRNA expression (Rappaport et al. 1993), and low DA transporter sites (Donnan et al. 1991; Graybiel and Moratalla 1989; Hurd and Herkenham 1993). Moreover, it has been demonstrated that high prodynorphin mRNA expression is predominantly restricted to the most limbic-related regions of the human striatum, namely the patch compartment and nucleus accumbens (Hurd and Herkenham 1993, 1995).

Of the neurosubstances localized within the limbic patch compartment, only prodynorphin has been shown to have a striking association to limbic regions of the human brain. As shown in figure 2, high prodynor-phin mRNA is found to be preferentially expressed in traditionally defined limbic areas such as the hippocampal formation (most preferably in the dentate gyrus), amygdala, parahippocampal gyrus (entorhinal cortex), and cingulate and insular cortices. Interestingly, limbic regions in the human brain that show a preferential expression of prodynorphin mRNA also show enhanced activation (e.g., glucose metabolism and blood flow) during exposure to cocaine stimuli (London et al., this volume; Volkow et al., this volume). The preferential association of high prodynorphin gene expression within limbic brain structures is not matched by other opioid neuropeptides. Instead, proenkephalin mRNA is extremely low in the amygdala and hippocampus but widely expressed throughout the striatum and hypothalamus (figure 2). Overall, there is a distinct anatomical organization of the gene expression of prodynorphin and proenkephalin systems in the human brain that should signify distinct involvement of the opioid peptides in different brain functions.

POSTMORTEM DA AND OPIOIDS ALTERATIONS IN HUMAN COCAINE USERS

Direct examination of cocaine's effects on the human brain through both postmortem and in vivo imaging analyses is necessary to extend the advances being made in knowledge of the neurobiology of human cocaine abuse. Neuroadaptations in both DA and opioid peptides neural systems have been reported in the few postmortem human studies carried out thus far. At the DAergic level, the most profound alterations present in post-mortem brains of human subjects with a positive toxicology of cocaine use are with the DA transporter.

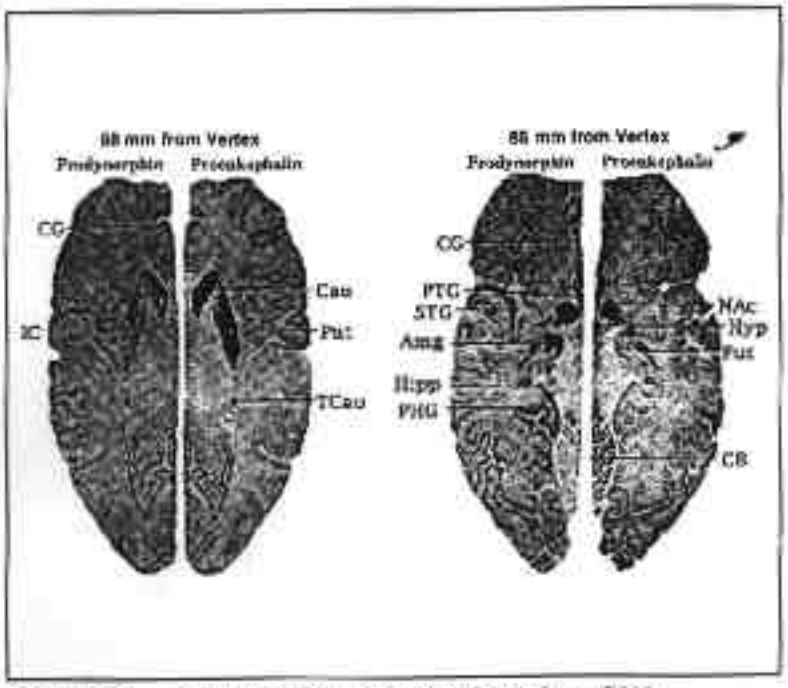

FIGURE 2. *Prodynorphin and proenkephalin mRNA expression in postmortem whole hemisphere human brain sections.*

KEY: Amg = amygdala; Cau = caudate nucleus; CB = cerebellum; CG = cingulate gyrus; Hipp = hippocampus; Hyp = hypothalamus; IC = insular cortex; PHG = parahippocampal gyrus; PTG = paraterminal gyrus; Put = putamen; STG = superior temporal gyrus; Tcau = tail of caudate nucleus.

Similar to the animal literature (Pilotte and Sharpe, this volume), there are contradictions in the reported direction of change. While some postmortem human studies have observed a decreased number of DA transporter sites in the caudate, putamen (Hurd and Herkenham 1993), and prefrontal cortex (Hitri et al. 1994), others have reported an increase in the striatum (Little et al. 1993; Staley et al. 1994). Decreased DA transporter sites have also been observed in vivo with PET studies of human cocaine users (Volkow et al. 1992, this volume).

Moreover, at the MRNA level, only reductions of the DA transporter have been found thus far in animals repeatedly administered cocaine (Cerruti et al. 1994; Xia et al. 1992). Interestingly, mesencephalic brain specimens obtained from some of the subjects who showed

reduced DA transporter binding sites in the striatum (Hurd and Herkenham 1993) had a 10 to 25percent reduction of DA transporter mRNA expression, though no significance was achieved (probably due to small sample size) (Hurd et al., unpublished observations).

Some of the contradictions reported about the alterations of DA transporter binding following cocaine administration may be attributed to the drug withdrawal time period and/or duration of treatment (Pilotte and Sharpe, this volume). However, determining the adaptive responses of the DA transporter protein to the effects of repeated cocaine use may be more complex since it has recently been discovered that the human DA transporter has multiple functional sites as revealed by different ligands for labeling the transporter sites (Pristupa et al. 1994). In that sudy, it was demonstrated that some ligands (e.g., WIN 35 428) bind to two sites of the human DA transporter, only one of which seems to represent the func-tional state of the protein. Moreover, different ligands (e.g., WIN 35 428 (cocaine-like) and GBR 12935 (noncocaine-like)) appear to bind to dif-ferent conformational states/forms of the human transporter. The con-flicting postmortem human studies described above used different ligands (cocaine-like versus noncocaine-like transport inhibitors) for assessing DA transporter alterations in the brain tissue of human cocaine users, and as such may have revealed different conformational states of the DA transporter. These issues need to be resolved.

In contrast to the postmortem evidence implying presynaptic alterations of cocaine binding sites, no changes in D2 receptors, either at the level of mRNA expression (Hurd and Herkenham 1993; Meador-Woodruff et al. 1993) or binding site densities (Meador-Woodruff et al. 1993), have been found thus far in the postmortem striatal tissue of human cocaine users. However, a temporary decrease of presumably postsynaptic D2 receptors has been observed in human cocaine abusers using PET analysis (Volkow et al. 1990). In the one primate study investigating the effects of cocaine on DAergic markers relevant to the human studies, DA transporter sites were shown to be decreased and D2 receptor densities were unchanged (Farfel et al. 1992). However, in that study D1 binding sites were reduced only in the caudate, a finding not matched in postmortem striatal tissue of human cocaine users (Meador-Woodruff et al. 1993).

Only one postmortem human study to date has directly investigated the opioid peptide system in relation to cocaine use. In the striatum of human cocaine users, prodynorphin mRNA expression was found

to be elevated in the patch compartment, whereas proenkephalin mRNA expression was decreased (Hurd and Herkenham 1993). The elevation of prodynorphin mRNA expression in human cocaine users is consistent with results obtained in rats that had been allowed to self-administer cocaine (Daunais et al. 1993; Hurd et al. 1992). In fact, elevated dynorphin mRNA expression (Daunais et al. 1993; Hurd et al. 1992; Hurd and Herkenham 1992; Spangler et al. 1993) and peptide levels (Sivam 1989; Smiley et al. 1990) are thus far the most consistent reproducible results obtained after the administration of cocaine, a finding that emphasizes the strong role of the dynorphin opioid peptide in cocaine abuse. In contrast to these results in human cocaine users, the animal literature reports very weak or no changes in striatal enkephalin mRNA expression following cocaine administration (Branch et al. 1992; Hurd et al. 1992; Spangler et al. 1993). Such differences could be due to the chronicity of cocaine use, since in general no animal study has mimicked the long-term use of cocaine found in the average human cocaine abuser. In addition, most human cocaine users have also administered other psychoactive drugs that could have long-term effects and influence enkephalin mRNA expression.

The differential changes observed in opioid gene expression in postmortem brains of human cocaine users were also complemented by consistent direction of change in their selective receptors. k receptors were increased (primarily in the caudate nucleus), while μ receptors were found to be reduced in the striatum (primarily in the patch compartment) (Hurd and Herkenham 1993). A hypothesis of neurochemical craving and dysphoria in the brains of human cocaine users (Hurd and Herkenham 1993) has been put forth based on the fact that neural systems associated with euphoria (μand enkephalin) are reduced, whereas neural systems associated with dysphoria (k and dynorphin) are elevated. Interestingly, neurochemical alterations were more pronounced in the caudate and putamen than in the nucleus accumbens in both human (Hurd and Herkenham 1993) and rat (Daunais et al. 1993; Hurd et al. 1992; Hurd and Herkenham 1992) studies, which might reflect the strong motor-activating actions of cocaine. However, the limbic-related component of cocaine's action is perhaps reflected in the finding that the changes observed with prodynorphin mRNA expression in the human study were restricted to the limbic patch compartment.

In considering the possible interpretations about the role of opioid peptides in cocaine abuse based on the postmortem findings, it cannot be over-looked that these changes might also reflect to some extent

neurotoxicity induced by repeated cocaine use. Endogenous opioids appear to be markers of injury within the central nervous system (CNS). A significant number of studies have provided evidence that tissue damage (e.g.,follow-ing spinal cord or brain injury) is associated with the increased presence of dynorphin in the area at the level of peptide production, mRNA expres-sion, and k receptor binding sites (Faden 1989; Faden et al. 1990; Vink et al. 1991). These findings have led to the conclusion that increased dynorphin is neurotoxic, whereas decreased dynorphin and increased enkephalin may be neuroprotective (Faden, this volume). In fact, dynorphin accumulation in local tissue after traumatic brain injury is correlated with a regional decline in cerebral blood flow (McIntosh et al. 1987), a consistent phenomena observed in humans following admini-stration of cocaine (London et al., this volume; Volkow et al. 1988). If indeed the opioid changes theorized following injury hold true for other CNS function, then perhaps the increased dynorphin mRNA expression and k receptor binding sites (with a concomitant decreased enkephalin mRNA expression and μ binding sites) found in the postmortem tissue of human cocaine users indicate heightened neurotoxic opioid substances and a reduction in neuroprotective substances. Altogether, this would imply greater toxicity in the brains of human cocaine users. However, animal studies have failed to find any evidence of neurotoxicity following chronic cocaine administration when estimating toxicity based on the degeneration of DA terminals (Ryan et al. 1988). Nevertheless, the absence of degen-erated DA terminals does not exclude the fact that toxicity could have occurred due to repeated cocaine use.

In summary, although acute activation of DAergic systems might initiate reinforcement neural circuits, differential alteration of opioid neuro-peptides, elevated dynorphin, and reduced enkephalin might underlie the negative aversive properties of cocaine abuse. While it is clear that additional studies are necessary to fully elucidate the role of dynorphin and enkephalin peptides during the different stages of the drug abuse cycle, it is feasible, based on the evidence accumulated thus far, that treatments targeted at correcting the imbalance of the opioid peptide system might prove beneficial for treatment of cocaine abuse.

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AUTHOR

Yasmin L. Hurd, Ph.D.
Karolinska Institute
Dept. of Clinical Neuroscience
Psychiatry and Psychology Section
Karolinska Hospital
S-171 76 Stockholm,Sweden

The Neurotoxic Effects of Continuous Cocaine and Amphetamine in Habenula: Implications for the Substrates of Psychosis

Gaylord Ellison, Scott Irwin, Alan Keys, Kevin Noguchi, and Giri Sulur

INTRODUCTION: THE STIMULANT PSYCHOSES

The experiments described in this chapter have grown out of attempts to develop animal models of psychosis, especially schizophrenia. Because of the difficulties inherent in identifying and quantifying hallucinatory episodes in nonhumans, it is necessary to develop third-order models of psychoses when using animals. Thus, there are endogeneous psychotic states in humans such as occur in schizophrenia and other dementias, there are certain drug-induced states in humans that can be indistinguish-able in many aspects from endogeneous psychoses, and finally there are attempts to replicate similar drug-induced states in animals and thereby clarify the altered neural mechanisms that underlie these abnormal states.

It could be argued that studies attempting to develop heuristic animal models of psychoses by chronically administering those drugs known to induce schizophrenia-like symptoms in humans are inevitably flawed because the symptomatology produced does not mimic schizophrenia in all aspects. But, although these models have limitations, they have proved valuable both in clinical and research settings. Animal models have proved sufficiently reliable that modern psychiatric admission procedures now typically withhold neuroleptic medications for several days in new cases of psychosis to determine whether the psychosis clears rapidly (in which case it was drug-induced) or not (in which case it is treated as an endogenous psychosis). Presently, these drug models in humans are the best available models of schizophrenia, and consequently the derived animal models should be invaluable research tools.

It is generally recognized that there are two principal drug models of psychosis in humans: the stimulant-induced psychoses and

phencyclidine (PCP)-induced psychosis (table 1). The stimulant psychoses are observed following chronic amphetamine or cocaine abuse. The authors have previously reviewed (Ellison and Eison 1983; Ellison 1991) the extensive literature indicating the emergence of a paranoid-like psychosis in chronic amphetamine and cocaine addicts, the chief symptoms of which are motor stereotypies, paranoid delusions, sensory hallucinations (including parasitosis, or the delusion of bugs or snakes on the skin), and a loose-ning of associations. This literature on amphetamine abuse has been reviewed by Connell (1958), Bell (1965), and Ellinwood (1967), and on cocaine abuse by Siegal (1977), Lesko and colleagues (1982), Gawin (1986), and Manschreck and colleagues (1988). A particularly interesting feature of stimulant psychosis is the pronounced parasitosis (Brady et al. 1991; Elpern 1988; Mitchell and Vierkant 1991). The parasitotic groom-ing that develops in animals given stimulants is discussed below.

TABLE 1. Two drug models of psychosis.

Stimulant psychoses
Produced by chronic amphetamine or cocaine abuse
Well documented in addicts who develop speed runs
Chief symptoms are stereotypies, paranoid delusions, parasitosis and other sensory hallucinations, and loosening of associations.
Evidence of persisting alterations in nervous system (Reactivation)
Phencyclidine and ketamine psychosis
Produced by NMDA antagonists (phencyclidine, ketamine)
Bingeing intake pattern develops in addicts
Chief symptoms are flat affect, depersonalization, body image distortion, amnesia, catatonia, and thought disturbances
Evidence of persisting memory deficits

To induce a model of stimulant psychosis in animals it is of paramount importance not only to give the proper drugs but also to do so in the proper drug regimen. The development of speed runs appears to be a key factor for the induction of stimulant psychoses. It

was recognized long ago (Connell 1958) that most amphetamine addicts eventually come to self-administer amphetamine every few hours for up to 5 days and that, towards the end of these binges, they reliably develop paranoid delusions and hallucinations (Kramer et al. 1967). There is a similarly extensive literature from cocaine addict populations of speed runs leading to para-noia. Furthermore, virtually every controlled study eliciting an overt amphetamine psychosis in humans has involved continuous, low-dose administration of the drug every hour for days (Griffith et al. 1972; Angrist et al. 1974); the explanation for the one apparent exception (Bell 1973) is discussed by Ellison (1994). Similarly, Satel and colleagues (1992) found that every one of their subjects who had experienced cocaine-induced paranoia did so while on a binge ranging from 6 hours to5-days in duration.

In an effort to mimic speed runs in animals, the authors developed a slow-release silicone pellet containing amphetamine base (in 300 gram (g) rats this pellet releases 20 milligrams (mg) over a 5-day period). Rats and nonhuman primates implanted with this pellet showed stages of behavioral alterations that were similar in sequence to those reported in the controlled studies in humans, although the precise behaviors elicited were much more complex in the higher organisms. In rats, continuous amphetamine administration initially resulted in a period during which sensitization to amphetamine-elicited motor stereotypies developed (Ellison and Morris 1981), followed by a late stage (3 to 5 days after pellet implantation) when the motor stereotypies decreased and certain distinctive late-stage behaviors emerged (e.g., limb-flicks, wet-dog shakes, spontaneous startle responses, and abnormal social behaviors) (Ellison et al. 1978b). A similar progression, but with even more distinctive and varied late-stage behaviors, occurs in monkeys (Ellison et al. 1981; Ellison and Eison 1983). Many of these behaviors have been called hallucinogen-like because they are normally induced by hallucin-ogens, whereas they are suppressed by acute injections of amphetamine. Another distinctive late-stage behavior is excited parasitotic grooming episodes. In monkeys this is expressed as rapid, slapping hand move-ments directed at the skin surface and moving from limb to limb (Ellison et al. 1981); in rats this is expressed as a change from the normal body washing and grooming behavior to a body-biting sequence similar to that of a dog afflicted with fleas (Nielsen et al. 1980b). There are close similarities between the amphetamine- and cocaine-induced parasitotic effects in humans and those found in animal studies (De Leon et al. 1992).

NEUROTOXIC EFFECTS IN CAUDATE OF CONTINUOUS AMPHETAMINE ADMINISTRATION

Late-stage behaviors induced by continuous amphetamine administration have a number of distinct neurochemical correlates in brain. Amphetamine continuously administered for 5 days induces alterations, including down-regulation of dopamine (DA) type 2 (D2) receptors in striatum (Nielsen et al. 1980a) and a progressive shift of heightened glucose metabolism away from striatal and towards mesolimbic structures (Ellison and Eison 1983). But one of the most striking effects of continuously administered amphet-amine is its well-documented neurotoxic effects on DA terminals in caudate. Studies of catecholamine fluorescence in animals administered continuous amphetamine (Ellison et al. 1978b; Nwanze and Jonsson 1981; Ryan et al. 1990) reveal the appearance of swollen, distinct axons with multiple enlarged varicosities and stump-like endings; similar observations were made using silver stains on degenerating axons (Ryan et al. 1988). These abnormalities did not occur if the same amount of amphetamine was given in daily injections. The unique capability of continuous ampheta-mine administration to induce degeneration of DA terminals in the caudate nucleus has been validated using a variety of techniques. The ampheta-mine can be delivered by slow-release silicone pellets, minipumps, very frequent injections, or by substantial and frequent doses of methampheta-mine, which has a slower rate of clearance and is considerably more potent at releasing DA (Hotchkiss and Gibb 1980; Ricaurte et al. 1980; Steranka and Sanders-Bush 1980). Furthermore, Fuller and Hemrick-Luecke (1980) found that an amphetamine injection administered in combination with drugs that slow its metabolism becomes neurotoxic to caudate DA termi-nals. The amphetamine- or methamphetamine-induced damage to DA endings can be prevented by pretreatment or concurrent administration of drugs such as a tyrosine hydroxylase inhibitor (Wagner et al. 1983), DA uptake inhibitor (Fuller and Hemrick-Leucke 1982; Hanson et al. 1987), and noncompetitive antagonists of N-methyl-D-aspartate (NMDA) (Sonsalla et al. 1989; Fuller et al. 1992). Studies of methamphetamine-induced neurotoxicity (reviewed by Seiden and Ricaurte 1987) typically employ doses that are comparatively higher than those using d-ampheta-mine; these doses also induce damage to serotonin cells, are lethal to some of the animals, and induce widespread neuronal degeneration in a variety of other structures (Ellison and Switzer 1994).

One of the most interesting aspects of this neurotoxic effect is that it is only induced by continuous amphetamine administration. If exactly the same amount of amphetamine (20 mg over 5 days, or about 12-mg/kg/day) is given in daily injections once a day over 5 days, no neurotoxicity is observed. This was initially a rather surprising finding, for the peak brain levels achieved after such large single injections are enormously greater than brain levels found when the drug is administered continuously. However, it now appears that, for a number of pharmacological agents, prolonged plasma levels are more crucial in producing neurotoxicity than higher but more transient plasma levels. Apparently neuronal systems have developed more effective ways to cope with sudden and brief insults than with progressive, more prolonged ones.

NEUROTOXIC EFFECTS IN FASCICULUS RETROFLEXUS OF CONTINUOUS STIMULANT ADMINISTRATION

The authors recently attempted to determine if the findings with amphetamine administration (discussed above) could be generalized to cocaine psychosis. Like amphetamine, cocaine also potentiates DA at the receptor, is a sympathomimetic, and leads to speed runs in chronic addicts who, in some cases, develop a paranoid psychosis similar in many aspects to that induced by amphetamine. The question for the DA model of psychosis that grew out of the amphetamine literature was whether continuous cocaine administration would also have a neurotoxic effect on DA terminals in caudate (i.e., if this was an anatomical correlate of the paranoia). Since continuous cocaine cannot be reliably administered via osmotic minipumps due to local vasoconstrictive and necrosis-inducing properties, an alternative drug delivery system was needed.

Consequently, the authors developed (Lipton et al. 1991) a silicone pellet with a release rate of 103 mg cocaine base over 5 days. Administration induced behavioral stages similar to those caused by continuous amphet-amine (initial hyperactivity, the evolution of stereotypies, a crash stage, and finally late-stage behaviors including limb flicks, wet-dog shakes, and parasitotoic grooming episodes) (Lipton et al. 1991). The authors then looked for persisting alterations in DA receptors produced by continuous cocaine administration as would be expected following DA terminal damage in striatum. No such changes were found at 14 days following continous cocaine administration, although a parallel group that had received continuous amphetamine showed large changes in striatal D1 and D2 receptors (Zeigler et al. 1991). However, the rats that had received

continuous cocaine did show persisting alterations in acetyl-choline (ACh) and gamma-aminobutyric acid (GABA) receptors in caudate, perhaps indicating that continuous cocaine had produced a somewhat different kind of neurotoxicity in caudate and possibly postsynaptic to DA receptors. At this point, the authors began collab-orative studies using silver stain to assess neural degeneration (Switzer 1991; de Olmos et al. 1981). These studies have proved to be very fruitful. By using minimally toxic doses and then searching for selective degeneration in brain, one can search for the weak links in neuronal circuitry induced by continuous stimulant administration. Those path-ways overdriven by incessant drug-induced activity may eventually degenerate, leaving the brain in a persistently altered state.

In the silver-stain studies, rats were given continuous amphetamine, continuous cocaine, or no drugs for 5 days, and then their brains were removed and examined for degeneration at various times following cessation of drug administration. The entire brain from the olfactory nucleus to the mesencephalon was screened. The animals administered continuous amphetamine were found to evidence quite substantial degeneration in caudate, but there was essentially no degeneration observed in caudate in the cocaine-administered animals. However, a very distinctive pattern of extensive degeneration after either continuous amphetamine or cocaine administration was observed in a totally unexpected brain region: the lateral habenula (LHb) and fasciculus retroflexus (FR) (Ellison 1992). Many of these long degenerating axons, when observed several days following pellet removal, showed classical anatomical signs of disintegration (e.g., axons beginning to fragment, the appearance of corkscrew or stump-like endings). These degenerating axons were almost exclusively in the mantle (as opposed to the core) of FR. Figure 1 shows this dramatic degeneration in a saggital section of FR after 5 days of continuous cocaine administration.

These results, coupled with the existing literature, have implications for models of stimulant-produced psychosis and paranoia. It is clear that amphetamine and cocaine are similar in that they are both strong stimulants with potent actions in potentiating DA, and both lead to a pattern of repeated drug intake by addicts over prolonged periods. With both drugs, these runs or binges produce a progressive dysphoria and paranoia followed by a rebound depression upon drug discontinuation. Furthermore, when given continuously to animals, both drugs eventually induce comparable late-stage behaviors. However, these two drugs are markedly different in their persisting effects in caudate. Continuous amphetamine has neurotoxic effects on DA terminals and DA receptors in caudate; continuous cocaine does not. Continuous cocaine produces

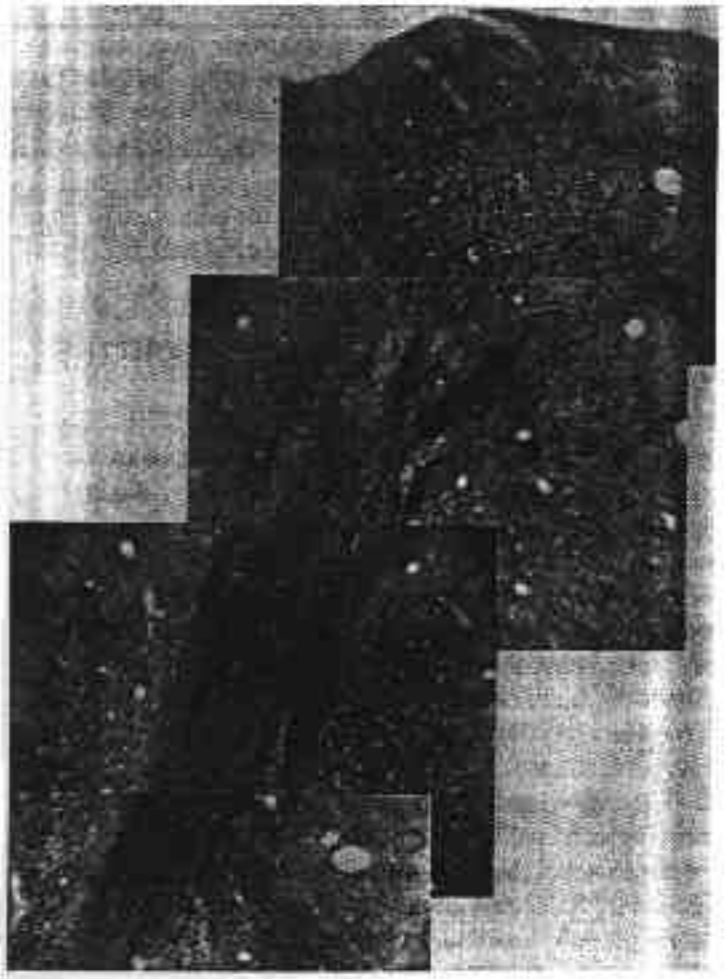

FIGURE 1. *Photomontage showing degeneration in habenula and fasciculus retroflexus following 5 days of continuous cocaine. At the top of the figure is lateral habenula; the more ventral three sections follow fasciculus retroflexus. Because fasciculus retroflexus moves laterally slightly as it projects more ventrally, the bottom two sections are from a section slightly more lateral than the top two. Multiple long darkly stained axons and swollen varicosities can be traced throughout fasciculus retroflexus.*

persisting alterations in GABA and ACh receptors whereas continuous amphetamine does not. However, the two drugs are quite similar in their ability to induce degeneration of axons in LHb extending ventrally into FR. A logical conclusion would be that the neurotoxic alterations in LHb and FR play a critical role in mediating the paranoid psychosis that follows the continuous use of these stimulants and the persistently altered paranoid reactions to the drug that develop in chronic addicts.

THE HABENULA, FASCICULUS RETROFLEXUS, AND THE ANATOMY OF PARANOIA

The recent findings described above suggest a need to reevaluate the role of the LHb and FR in the mediation of DA-related circuitry. Figure 2 illustrates the principal connections of the habenula as described in the classical anatomical studies by Herkenham and Nauta (1977, 1979) and others. The inputs consist predominantly of pathways traveling in stria medullaris terminating in either the medial or lateral habenular nuclei, with two subdivisions: medial septal-limbic and lateral pallidal-limbic. The principal input for medial habenula is cholinergic fibers arising from the septal area (nearly every septal cell projects to the medial habenula), but there are also projections from nucleus accumbens and the diagonal band of Broca. The major input to LHb are GABA fibers from the medial (or internal) globus pallidus (in primates) or its homolog in rat, the entopeduncular nucleus, but there are also inputs from limbic forebrain, including the lateral hypothalamus, diagonal band of Broca, substantia innominata, lateral preoptic area, nucleus accumbens, frontal cortex, and the suprachiasmatic nucleus. Both nuclei also receive less extensive ascending afferents from the central grey and medial raphe, and the LHb receives dopaminergic inputs from the substantia nigra (SN) and ventral tegmental area (VTA).

The principal efferent fibers from the medial habenula, including cholinergic, glutaminergic, and substance P fibers, travel in the core of FR to the interpeduncular nucleus, VTA, raphe nuclei, and SN. The LHb has more varied outputs, with axons travelling principally in the periphery or mantle region of the FR sending projections to several thalamic (mediodorsal and ventromedial) and hypothalamic (lateral, septal, and preoptic) nuclei. But the principal efferents from LHb are to midbrain nuclei such as the dorsal and medial raphe nuclei (constituting one of the major inputs to raphe), to the VTA and SN pars compacta, and also to central grey.

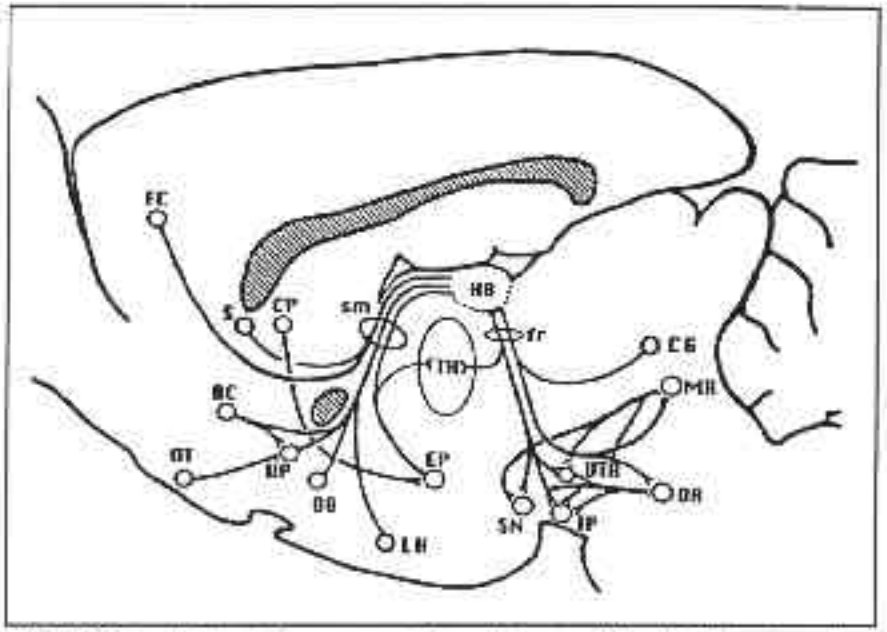

FIGURE 2. *Schematic representation of some of the chief inputs and outputs of the habenular complex. Major descending pathways as shown entering sm, passing through or synapsing in habenula, and descending in fr to a variety of mesencephalic structures. Collaterals from EP and HB to thalamus are also shown.*

KEY: FC = frontal cortex; OT = olfactory tubercle; AC = nucleus accumbens; CP = caudate-putamen; DB = nucleus of the diagonal band; VP = ventral pallidum; sm = stria medullaris thalami; EP = entopeduncular nucleus; fr = fasciculus retroflexus; TH = thalamic nuclei, including dorsalmedial, ventral anterior, and ventral lateral; HB = habenula; SN = substantia nigra; VTA = ventral tegmental area; IP = interpeduncular nucleus; MR = medial raphe nucleus; DR = dorsal raphe nucleus.

Sutherland (1982) described some of the functional roles of what was termed the "dorsal diencephalic conduction system." It has anatomical and functional connections to modulate important functions such as sensory gating through the thalamus, pain gating through the central grey and raphe, and mediation of motor stereotypies and reward mechanisms through the SN and VTA. Lesions of habenula produce a wide variety of behavioral alterations, including alterations in self-stimulation, pain inhibition, avoidance learning, and sexual and maternal behaviors (Ellison 1994).

Studies of glucose utilization have consistently shown the habenula to be highly sensitive to DA agonists and antagonists; in fact, it is the most sensitive region in brain to agonists such as cocaine (London et al. 1986). The dorsal diencephalic system has major and predominantly inhibitory connections onto DA-containing cells. The descending control of mono-amine and other mesencephalic cells carried in FR appears to consist largely of inhibitory influences. Sasaki and colleagues (1990) found that they could markedly attenuate methamphetamine-induced inhibition of SN cells by making lesions of the habenula, of the entopeduncular nucleus, or transections of the stria medullaris. These studies support an important role of the dorsal diencephalic conduction system in inhibiting DA cell bodies and in mediating part of the negative feedback from limbic and striatal DA receptors onto DA cell bodies. These are ideal connections for the media-tion of psychosis on both anatomical and functional grounds. The descen-ding influences from DA-rich and limbic structures are quite unique in brain in that striatal and limbic inputs directly converge. In addition, this circuitry apparently mediates a major part of the descending control over serotonin cells of the raphe complex (in fact, they represent the chief input in all of brain to raphe). An implication of this circuitry is that due to the amphetamine- or cocaine-induced degeneration of the FR fibers, the higher brain areas might no longer be able to regulate dopaminergic and seroto-ninergic cell firing.

DO THE FIBERS IN FR THAT DEGENERATE AFTER COCAINE BINGES CARRY NEGATIVE FEEDBACK FROM DA-RICH-REGIONS ONTO DA CELL BODIES?

There is additional evidence that the LHb and FR mediate part of the negative feedback from DA-rich regions onto DA cell bodies. Lesions of either stria medullaris, LHb, or FR increase DA turnover in prefrontal cortex, nucleus accumbens, and striatum (Lisoprawski et al. 1980; Nishikawa et al. 1986), and electrical stimulation of the habenula inhibits DA-containing cells in SN and VTA (Christoph et al. 1986).

Several recent observations from this laboratory clarify some of the long-lasting effects of continuous cocaine administration and also provide indirect evidence consistent with the hypothesis that the degenerating axons carry part of the DA-mediated negative feedback. The authors have found that there are long-lasting sequelae of 5 days

of continuous treatment with the cocaine pellet which suggest correlates of the neuro-toxicity observed in brain. Cocaine pellet pretreated rats, when tested several weeks following pellet explant, act frightened in open-field tests. At the beginnning of the test they initially "freeze," remaining immobile for prolonged periods (Zeigler et al. 1991), and when tested over pro-longed periods in novel environments they remain hyperactive far longer than the controls (figure3). These observations suggest a lack of habitu-ation to novel sensory stimulation in these animals. It has also been reported that FR lesions in rats lead to decreased spontaneous alternation (Corodimas et al. 1992). The authors have begun to examine if cocaine pellet pretreated rats evidence persisting effects in spontaneous alteration, and figure 4 shows results that suggest long-lasting deficits. All of these observations are highly consistent with increased DA turnover after lesions of LHb.

Using microdialysis techniques, the authors recently attempted to test the hypothesis that the axons which degenerate in FR and LHb following continuous cocaine mediate part of the negative feedback from DA receptors onto DA cell bodies (Keys and Ellison 1994). Rats were pre-treated with either cocaine or control pellets for 5 days, and then 14days later, microdialysis probes were lowered into the caudate nucleus. Baseline DA and GABA levels were not significantly different in the two groups. However, when the animals were perfused locally with the D1 agonist SKF 38393, the controls showed a large decrease in striatal DA overflow and dopaminergic metabolites compared with the cocaine-treated animals (figure 5). Because D1 receptors are largely postsynaptic in caudate, where DA release is governed largely by presynaptic mechanisms, this result suggests a deficiency in the negative feedback pathways extending from caudate onto SN and VTA cell bodies, or locally within striatum. A general conclusion from all of these observations is that animals treated with the cocaine pellet and then given a recovery period show a number of behavioral and biochemical alterations similar to those of animals following lesions of LHb or FR.

REPEATED COCAINE BOUTS: PROGRESSIVE EFFECTS ON BEHAVIOR AND TOXICITY

The authors have also made some very interesting observations on progressive effects of repeated cocaine administration bouts. These arose

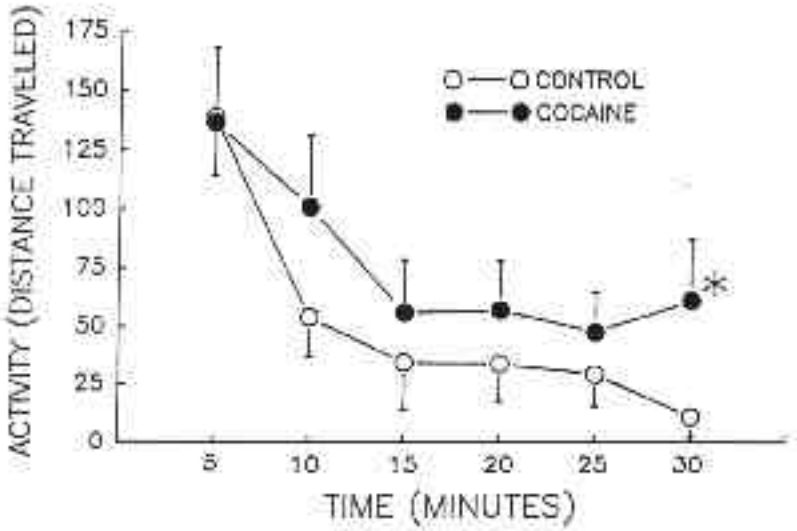

FIGURE 3. *When tested in a novel environment several weeks after pellet removal, cocaine-treated animals remain hyperactive longer than the controls.*

KEY: * = different from controls, $p < 0.05$

from a study that did not work out as had been predicted, but which yielded enormously provocative results. The original experimental design represented an initial attempt to determine if there is any regenera-tion of the degenerating fibers in FR following the cocaine pellet. An experiment was designed to determine if any signs of axonal regeneration could be detected in LHb and FR following the cocaine pellet adminis-tration. Four groups were prepared. A single-pellet exposure group was implanted with cocaine pellets and sacrificed 6 days later, 1 day after pellet removal. The amount of degeneration in LHb and FR in this group was compared with that in a second group of rats implanted with a cocaine pellet for 5days, given a 10-day recovery period, implanted with a second cocaine pellet for 5days, and sacrificed 1 day later. The authors hypothesized that little further degeneration would be observed in this group, since the tracts in these animals had recently degenerated and minimal recovery time had been given. A third group was implanted with a 5-day pellet, given a 3-month drug-free recovery period, implanted with a second 5-day pellet, and sacrificed 1day after the second pellet was removed. It was hypothesized that if any regeneration occurred, this

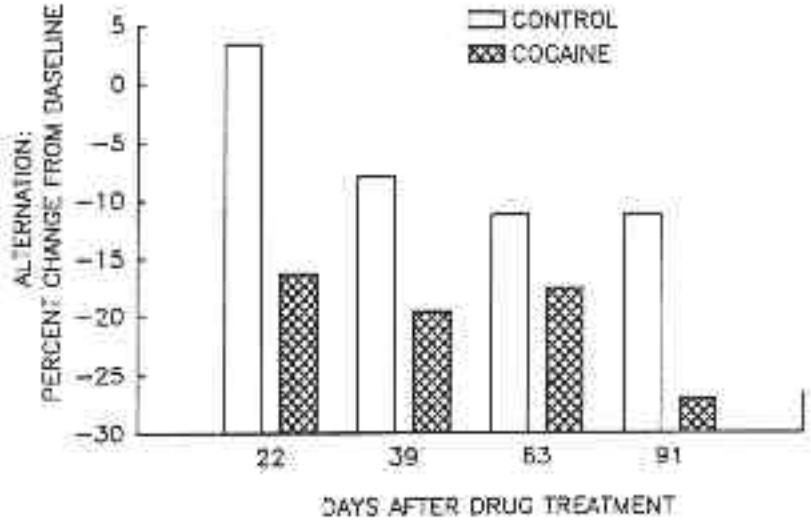

FIGURE 4. *Rats pretreated with the cocaine pellet for 5 days also show extremely persisting deficits in spontaneous alternation in a t-maze. This test is related to immediate memory.*

group would show more degeneration in FR. A fourth group was given 14 daily injections of cocaine, a 10-day drug-free period, implanted with the cocaine pellet for 5 days, and sacrificed 1 day after pellet removal. This type of intermittent drug regimen has quite different effects on behavior than continuous cocaine administration, and so comparisons of degeneration in this group with that in the pellet, 10-day recovery, second pellet group were also of interest.

The actual study results were quite different from those expected. Compared with the single pellet exposure group, there was appreciably more degeneration in the LHb and FR in both of the two-pellet groups. In fact, the degeneration in the 10-day recovery group was slightly greater than in all other groups (figure 6). Thus, rather than providing evidence for any regeneration, this result seems to imply that the single cocaine pellet exposure causes degeneration in only a proportion of the vulnerable fibers since a second pellet administered shortly thereafter (the pellet, 10-day recovery, second pellet group) induces further degeneration. This is an important finding, for it indicates that repeated bouts of cocaine administration in rats spaced 1 or 2 weeks apart appear to be

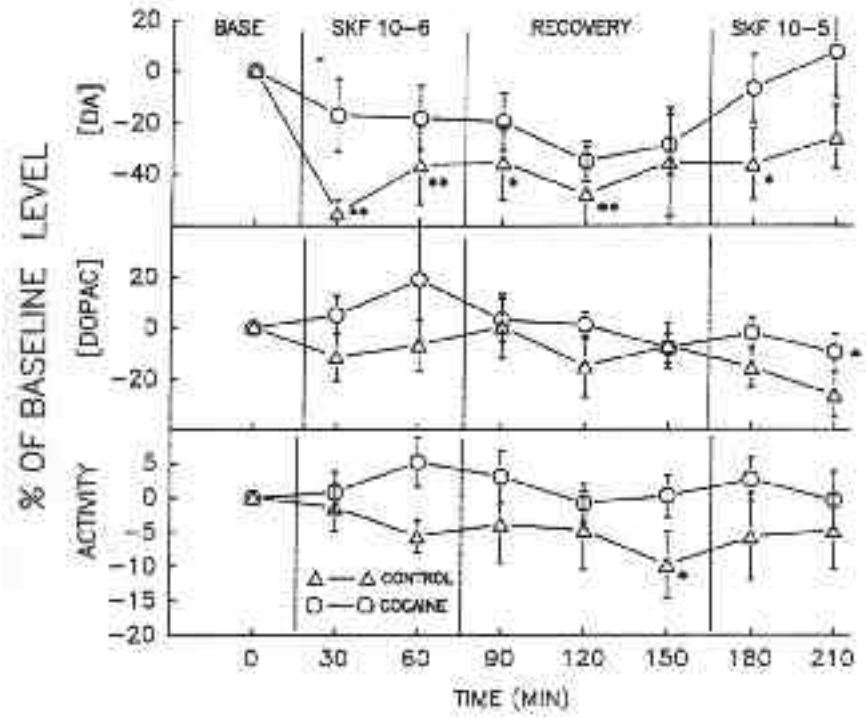

FIGURE 5. *Percent change from baseline levels in striatal DA, DOPAC, GABA, and gross activity during and after local striatal infusion of SKF 38393 10^{-6} followed by a recovery period and then local infusion of SKF 38393 10^{-5}. The cocaine-treated group had been given a 5-day simulated binge several weeks prior to the experiment.*

KEY: * = $p < 0.05$; ** = $p < 0.01$.

extraordinarily neurotoxic. These results imply that a simulated binge induced by a single cocaine pellet clearly does not induce degeneration in all the susceptible fibers, but leaves some of these fibers in a weakened and vulnerable state. It is clear that prior to this study the authors had never really observed animals with the full extent of cocaine-induced degeneration. A second unexpected finding was that pretreatment by spaced daily injections (14 daily injections, each of 10 milligrams per kilogram (mg/kg) cocaine) actually produces an appreciable tolerance to neurotoxic effects induced by the drug given continuously, even though

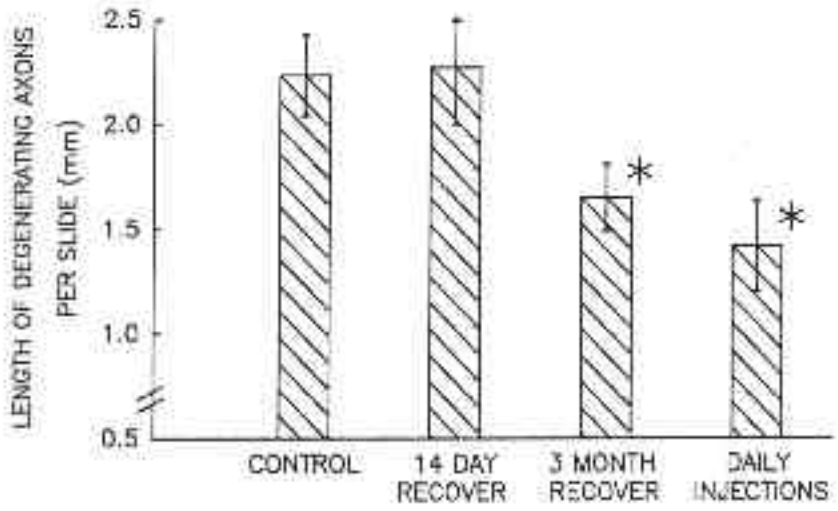

FIGURE 6. *Total amount of unilateral degeneration (sum of all axon lengths) from one slide through LHb and FR. A "blind" observer sketched degenerating fibers using camera lucida, and the resulting ink traces were quantified for total length using imaging software.*

KEY: * = significantly less than control, $p < 0.05$; control = cocaine sham pellet, 14 days recover, cocaine pellet; 14 day = cocaine pellet, 14 days recover, cocaine pellet; 3 month = cocaine pellet, 3 month recover, cocaine pellet; daily inject = 14 inj, 14 days recover, cocaine pellet.

the rats showed a marked potentiation of stereotyped behaviors induced by subsequent pellet administration (see below).

This study also measured behavior during the pellet implant, videotaping the animals automatically every 2 hours throughout the 5 days of the cocaine pellet exposures. Figure 7 shows that, as reported previously, rats implanted with the cocaine pellet go through stages of behavior, from initial exploratory behavior best measured by cage crossings, to motor stereotypies, and finally to late-stage behaviors, including what appears to be parasitotic grooming. The results revealed substantially heightened behavioral alterations in both reimplant groups, both heightened stereotypies and then increased late-stage behaviors. In other words, the behavior was highly

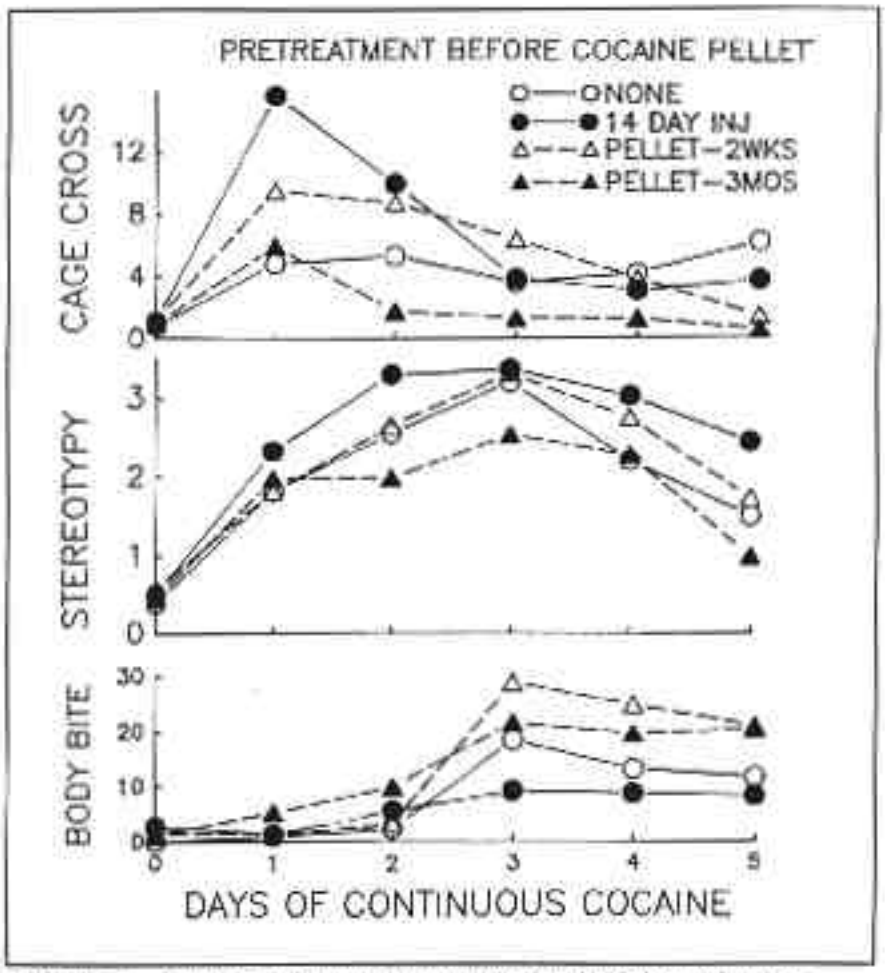

FIGURE 7. *Amount of three behaviors during the 5 days of cocaine pellet action in the four groups. Locomotion was measured as number of cage crossings, motor stereotypy using a conventional rating scale, and duration of body biting quantified as total amount of time computer key depressed.*

correlated with the amount of degeneration observed. Thus, upon implantation with the second pellet, both the 10-day recovery and the 3-month recovery animals showed even more intense stereotypy than the single-pellet treated rats, and then even more late stage behavior upon reimplantation following their first pellet exposure. The 3-month recovery rats showed the greatest degree of parasitotic grooming behavior the authors have ever observed.

Figure 7 shows the total duration of body biting in the four experimental groups during the first or second cocaine pellet exposure (other two groups). This shows the potentiation of the distinctive parasitotic-like behavior, especially in the rats given a 3-month recovery period between implantation of the first and second pellet. While cocaine pretreatments with injections or pellets generally induce tolerance to neurotoxic effects induced by the drug (unless they are too closely spaced), there is a com-plete lack of correlation between various behavioral indices (e.g., motor stereotypies) and neurotoxic effects. In addition to replicating the stages of continuous stimulant exposure (i.e., initial hyperactivity, stereotypy, and late-stage behaviors), these findings add a new twist to the abundant literature on tolerance and sensitization induced by continuous and inter-mittent stimulant exposure. While cocaine pretreatment with intermittent injections led to heightened hyperactivity and motor stereotypies but lessened late-stage behaviors induced by a subsequent pellet implant, the pellet pretreatment led to lessened steroeotypies but heightened parasi-totic grooming. Clearly, the persisting effects of these different drug regimens are much more complex than previously imagined.

It appears that repeated bouts of cocaine exposure in rats may produce progressive alterations in brain and behavior. The authors have never really observed the fully developed late-stage hallucinatory syndrome of behavior, nor have they investigated the full ramifications of how exten-sive the correlated alterations in brain can be. Yet, a recurrent theme in studies of both amphetamine and cocaine addicts (Satel et al. 1992) is how paranoia and parasitosis evolve in the confirmed addict, eventually reaching the point where the initial drug intake can induce them. The cocaine addicts studied by Satel and colleagues (1992) who showed the full syndrome of binge-limited paranoia had been addicts for over 2years and had each consumed an enormous estimated quantity of cocaine (1.34±1.7 kg). The repeated pellet implantation regimen may develop into an extraordinarily interesting paradigm not only for the study of chronic cocaine abuse but also for more general models of sensory hallucinations (such as parasitosis) and of paranoia. These findings may have therapeutic and general scientific implications; the progressive development of parasitosis and paranoia is often cited by addicts as a critical factor in seeking treatment. This repeated binge regimen should prove perfect for the study of metabolic and other regional brain changes correlated with late-stage behaviors.

WHERE ARE THE CELL BODIES THAT GIVE RISE TO FR DEGENERATION?

There are two distinct possibilities for the site of the cell bodies that give rise to the degenerating axons following continuous amphetamine or cocaine administration. They could be located in LHb, projecting ven-trally through FR, but they could also be in midbrain cell groups. The dopaminergic cells of the SN or VTA give rise to ascending DA axons terminating in habenula. The raphe nuclei also project to habenula, as does the central gray.

Three lines of evidence point to the cell bodies in LHb as the source. The first relates to the fact that the degenerating axons are quite highly con-centrated in the mantle of FR. When the anterograde tracer PHAL is injected into LHb (Araki et al. 1988), the pattern of staining observed mirrors almost exactly that seen in the degenerating fibers: a high con-centration of descending fibers in the mantle of FR, with some fibers then entering thalamic nuclei but the majority terminating in regions such as VTA. The ascending fibers such as from SN and VTA projecting to LHb are not so rigidly confined to FR.

A second line of evidence comes from studies in the authors' laboratory. Rats were injected with PHAL in LHb using the Araki and colleagues (1988) protocol, then given 7 days for anterograde transport to occur. The rats were then implanted with either amphetamine or cocaine pellets for 5days. When the animals were sacrificed 2 days after pellet removal, PHAL-stained fibers were observed in FR that had the distinctive characteristics of degenerating fibers (fragmented axons, corkscrew shaped axons, and end stumps). This finding means that at least some of the degenerating axons have cell bodies in LHb.

The third line of evidence comes from the present study of animals that experienced repeated bouts of cocaine administration. When the brains of these animals were stained for degeneration, only a few stained cell bodies were observed (principally in the repeated pellet groups). Most of stained cell bodies were concentrated in the most lateral part of the LHb, with a few in the more medial portion of LHb (figure 8). Furthermore, cell counts of cresyl violet sections from these same animals indicated a decreased number of cells in LHb in the animals repeatedly exposed to cocaine as compared with the controls. When considered altogether, these data support the hypothesis that most, if not all, of the degenerating axons are from cells in LHb.

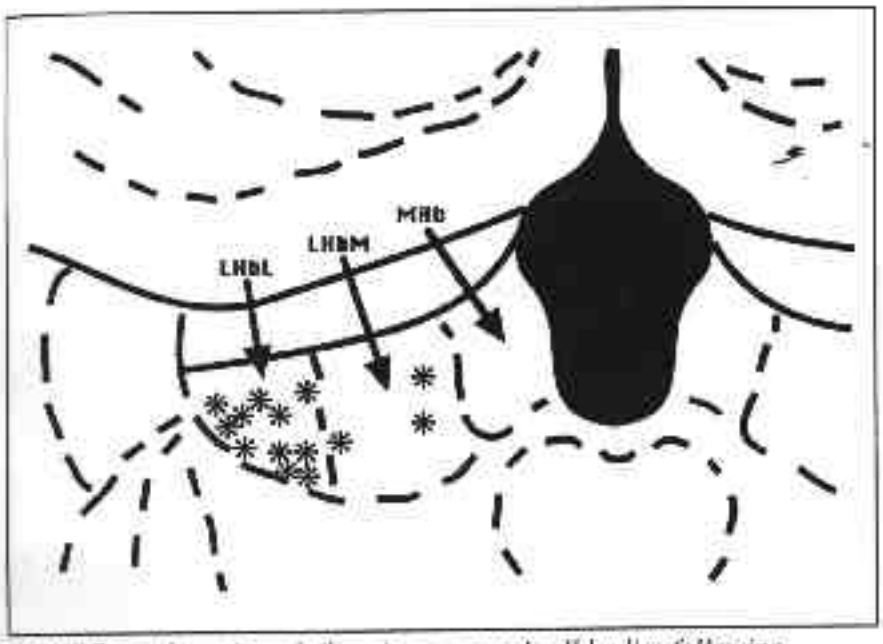

FIGURE 8. *Location of silver-impregnated cell bodies following repeated bouts of cocaine administration. These degenerating cells were palely stained but are concentrated in LHb in the same regions as the c-fos stained cells observed following acute cocaine injections.*

What Are the Mechanisms of this Neurotoxicity?

In LHb and FR, the neurotoxic effects of continuous cocaine and amphetamine administration are unusual in that they are so strongly correlated with a decrease in glucose metabolism in the affected structures. An immense number of studies of glucose utilization have consistently shown that while virtually all DA agonists increase glucose metabolism in DA-rich regions such as caudate nucleus, nucleus accumbens, SN, and VTA, they markedly decrease glucose metabolism in the habenula (reviewed in Ellison 1994). Indeed, some studies reported glucose metabolism in the habenula to be the most sensitive region in all of brain to low doses of DA agonists such as cocaine. Another characteristic of the toxicity in LHb is that the drug administration sufficient to induce this effect must be con-tinuous and extremely prolonged, on the order of many days. This was dramatically validated when it was found that very high doses of metham-phetamine over 8to 10 hours, while producing extraordinary

degeneration in caudate-putamen, are relatively ineffective in producing degeneration in LHb and FR (Ellison and Switzer 1994).

In most other cases of neurotoxicity induced by drugs of abuse, the neuro-toxic effects are observed in brain regions where glucose metabolism is markedly heightened by the drug. Examples are the neurotoxicity pro-duced in caudate by continuous amphetamine administration (Ellison 1994) and the toxicity in several limbic regions produced by NMDA antagonists (Ellison 1995). The possibility that this is an inhibotoxic effect (i.e., that neurons must operate within a normal range, and when they are dramati-cally inhibited for very prolonged periods they begin to show toxic effects) was discussed in Ellison (1994). According to this notion, prolonged inhibition of LHb cells, presumably produced by the powerful GABAergic fibers from entopeduncular nucleus, is responsible for the damage.

More recent data suggest an alternative possibility is more likely to be true. Glucose metabolism, as reflected by 2-deoxyglucose (2DG) uptake, typi-cally reflects the activity in terminals rather than cell bodies (Sharp et al. 1993). Consequently, it is possible that striatal GABAergic efferents to the entopeduncular nucleus are stimulated by the DA agonist administration and, thus, produce a strong inhibition of the entopeduncular efferents to the LHb. The reduced activity in the terminals of these LHb afferents would result in both the reduction of 2DG uptake and the disinhibition of haben-ular cells. This hypothesis (reviewed by Wirtshafter and colleagues (1994)) is supported by the finding that DA agonists induce fos-like immuno-reactivity in cells in the most lateral LHb. In fact, the pattern of induction produced by amphetamine in that study was almost identical to the pattern of cells staining for degeneration (see figure 8).

Wirshafter and colleagues (1994) further found that this fos-like induction could be abolished by 6-hydroxydopamine (6-OHDA) lesions of the nigro-striatal bundle. In collaboration with researchers from the National Insti-tute of Mental Health (NIMH), the authors recently obtained virtually identical findings. Acute injections of cocaine led to an induction of c-fos messenger ribonucleic acid (mRNA) in a large number of cells of the most lateral portions of the LHb. In both of these studies, cells in the more medial aspects of LHb appeared to show c-fos mRNA induction more correlated with general stress, rather than dopaminergic activity. These findings suggest that the neurotoxicity in the LHb and FR induced by continuous

amphetamine or cocaine may be due to the prolonged hyper-activity of the LHb cells produced by the removal of GABAergic inhibitory influences.

DEGENERATION PATTERNS AFTER PSYCHOTOMIMETIC DRUGS OF ABUSE

These findings suggest that the roles of LHb, FR, and the dorsal diencephalic system in general need to be reconsidered in the generation of stimulant-induced and other psychotic states such as schizophrenia. It can be argued that alterations in these pathways are ideal candidates for producing the behaviors that occur during psychosis, and that future considerations of the circuitry underlying psychoses need to include this highly important but relatively neglected system. Because these struc-tures are not large in humans, it is presently very difficult to resolve them in scanning studies. But, the clear prediction is alterations in these struc-tures in cocaine addicts and perhaps in schizophrenics.

It is of considerable interest to determine if similar alterations are present in the second drug model of psychosis, that produced by PCP and the other NMDA antagonists such as ketamine and perhaps dizocilpine. The model psychoses that PCP and ketamine induce mimic a variety of schizo-phrenic symptoms, including flattened affect, a dissociative thought dis-order, depersonalization, and catatonic states. These symptoms can per-sist for prolonged periods, and there is evidence in chronic PCP and ketamine addicts of persisting memory deficits.

PCP, ketamine, and dizocilpine are quite similar in many of their effects, and they all have a neurotoxic effect on neurons in the most posterior cin-gulate cortex (Olney et al. 1989). When the authors administered PCP or dizocilpine to rats in a 5-day binge regimen, there was minimal degener-ation in LHb and FR; however, both of these drugs further induced neur-onal degeneration in a variety other limbic structures. These structures included not only posterior cingulate (retrosplenial) cortex but also rat brain regions related to olfaction such as the olfactory tubercle, anterior olfactory nucleus, and tenia tecta. Additional limbic structures affected were the piriform cortex and the most posterior regions of entorhinal cortex and its projections through the perforant pathway to dentate gyrus and, to a lesser extent, other cells in ventral hippocampus. This finding suggests anatomical substrates for a second drug model of psychosis because most of these same structures are among the

clearest areas where anatomical alterations occur in dementias such as schizophrenia and Alzheimer's disease (Ellison 1995).

THE ANATOMY OF PSYCHOSIS

Although the stimulant and PCP drug models of psychosis have long been recognized as one of the most promising avenues for determining the mechanisms underlying dementias, hallucinogens, and schizophrenia, the insights that have come from these models have been largely pharma-cological rather than neuroanatomical. The study of selective degeneration in brain induced by simulated binges of psychomimetic drugs of abuse lead to some quite unexpected predictions of what parts of brain are the "weak links" in the structures basic to these abnormal states. In the case of the stimulant psychoses, they point toward a pathway almost totally neglected in the "dopamine theory of schizophrenia," while with the NMDA antagonist psychoses, they direct attention toward limbic struc-tures for which the evidence of involvement in schizophrenia is well documented, but which have not been linked with this drug model. Thus, studies of selective degeneration in brain after psychomimetics offer con-siderable promise for the development of new conceptions of the anatomy of psychosis.

CONCLUSION

1. There are alterations in parahippocampus and hippocampus in schizophrenia and Alzheimer's disease. Disordered cell arrangements, decreased cell number, and decreased total area in hippocampus and entorhinal cortex are found in schizophrenia (Kovelman and Scheibel 1984; Bogerts 1993; Jeste and Lohr 1989). Roberts (1991) concluded that probably all schizophrenics have abnormalities in medial temporal lobe structures centering about entorhinal cortex. Positron emission tomography (PET) studies (Liddle et al. 1992) of brain blood flow found that the left parahippocampal region, which includes the ento-rhinal cortex, correlated highest with total schizophrenic symptoma-tology; the authors conclude that alterations in this area are central in schizophrenia.

Entorhinal cortex shows the earliest evidence of neurofibrillary tangles, and remains the most severely affected brain region in Alzheimer's disease throughout the progression of the disease (Braak and Braak 1991). Extent of degeneration in hippocampus and

entorhinal cortex of Alzheimer's patients correlates highly with performance on the Mini-Mental State Examination (Kesslak et al. 1991).

2. There is evidence for anatomical and functional alterations in olfactory regions in schizophrenia and Alzheimer's disease. Olfactory dysfunc-tion is well documented in schizophrenia (Kopala et al. 1993). This is not due to chronic antipsychotic medications (Wu et al. 1993). Schiz-ophrenic patients have decreased glucose metabolism in most brain regions, but it is greatest in patients with olfactory agnosia (Clark et al. 1991).

There is a substantial loss of olfactory functions present in Alzheimer's disease (Feldman et al. 1991; Serby et al. 1991), and this is among the first signs of Alzheimer's (Doty 1991). This is reflected as decreased metabolic rates in medial-temporal cortex, especially during olfactory memory tasks (Buchsbaum et al. 1991). In Alzheimer's disease, a sizable increase has been reported in neurofibrillary tangles and neuritic plaques in olfactory cortex compared to many other brain regions (Reyes et al. 1993); the olfactory bulb also shows substantial pathology (Struble and Clark 1992).

3. There is also evidence for alterations in posterior cingulate cortex in schizophrenia and Alzheimer's disease. Across a variety of brain regions in schizophrenics, the largest alterations in serotonin receptor number are in posterior cingulate, hippocampus, and temporal cortex (increases in both 5-HT1A and 5-HT2 receptors) (Joyce et al. 1993).

The highest concentration of neuritic plaques and neurofibrillary tangles in retrosplenial cortex of Alzheimer's disease patients are in lamina III and V (Chun et al. 1994), corresponding well with the location of the degenerating pyramidal cells following NMDA antagonists. Substantial alterations occur in receptor binding in posterior cingulate cortex in Alzheimer's patients (Vogt et al. 1990), as well as dramatically decreased glucose metabolism in posterior cingulate in Alzheimer's (Minoshima et al. 1994).

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AUTHORS

Gaylord Ellison, Ph.D.
Professor of Psychology

Scott Irwin, B.S.
Research Associate

Kevin Noguchi, B.S.
Research Associate

Giri Sulur, Ph.D.
Research Associate
Department of Psychology
University of California, Los Angeles
405 Hilgard Avenue
Los Angeles, CA 90024

Alan Keys, Ph.D.
Research Associate
Oregon Health Sciences University
Portland, OR 97201

PET Studies of Cerebral Glucose Metabolism: Acute Effects of Cocaine and Long-Term Deficits in Brains of Drug Abusers

Edythe D. London, June M. Stapleton, Robert L. Phillips, Steven J. Grant, Victor L. Villemagne, Xiang Liu, and Rebeca Soria

Positron emission tomography (PET) is a nuclear imaging technique that can be employed to assess regional brain function noninvasively. When used with [18F]fluorodeoxyglucose (FDG), a radiotracer for glucose metabolism, it can provide quantitative maps of global and regional cerebral metabolic rates for glucose (Phelps et al. 1979; Reivich et al. 1979). The FDG method has been used to assess changes in regional brain function in a variety of physiological and pathological states (Buchsbaum et al. 1990; Martin et al. 1992; Reiman et al. 1986), including the acute responses to psychoactive drugs (London and Morgan 1993). Measure-ments using PET with FDG also have demonstrated persistent differences in the metabolism of brains of substance abusers as compared with those of control subjects without significant histories of illicit drug abuse (Stapleton et al. 1995; Volkow et al. 1992a, 1992b). This chapter focuses on the acute effects of cocaine on cerebral glucose metabolism and how they relate to other physiological and behavioral states. It also discusses the long-term differences in the brains of substance abusers and the extent to which such differences may relate to cocaine abuse.

Prior to human studies of the effects of cocaine on cerebral metabolism, theacute effects of amphetamine on regional metabolic rate for glucose (rCMRglc) were studied with FDG. An oral dose of d-amphetamine (0.5milligrams per kilogram (mg/kg)) decreased cortical and subcortical rCMRglc in schizophrenic as well as control subjects (Wolkin et al. 1987). The magnitude of amphetamine-induced change was uniform across brain regions, and was related to the concentration of the drug in plasma. These results were in marked contrast to those from a study of subjects with attention deficit-hyperactivity disorder who were given either d-ampheta-mine or methylphenidate (Matochik et al. 1993). Although there were no significant effects on global metabolic rate for glucose, each drug produced differential regional effects. A single oral dose of d-amphetamine (0.25mg/ kg), equal to half the dose given to the

subjects in the study by Wolkin and colleagues (1987), improved performance on an auditory continuous per-formance task (CPT) and significantly increased rCMRglc in anterior medial frontal cortex, right temporal cortex, right caudate nucleus, and right thalamus, but caused decreases in left and right anterior frontal cortices. In contrast, a single oral dose of methylphenidate (0.35mg/kg) did not improve performance on CPT and decreased the rCMRglc in anterior medial frontal, left parietal, and left parietal/occipital cortices. Differences in the effects of the two stimulants on rCMRglc as well as on CPT performance may be attributable to the mechanisms by which the drugs stimulate the release of dopamine and/or norepinephrine (McMillen 1983). Whereas methyl-phenidate promotes the release of catecholamines from reserpine-sensitive vesicular storage pools, amphetamine releases the amines from reserpine-insensitive pools. Both drugs also block amine reuptake. The contrast between results found by Matochik and colleagues (1993) as compared with those of Wolkin and colleagues (1987) for amphetamine-induced changes in rCMRglc may be related to the dose of amphetamine or to the pathology of the respective subject populations.

In a study aimed at elucidating the neuroanatomical substrates of the positive effects of cocaine on mood, the FDG method was used to study the effects of cocaine on cerebral metabolism (London et al. 1990a). Subjects with histories of polysubstance abuse, including intravenous (IV) self-administration of cocaine, were given an IV injection of cocaine hydrochloride (40 mg). They manifested characteristic effects of cocaine, including significant elevations in self-reports of positive mood and cardiovascular stimulation. Cocaine significantly decreased global glucose metabolism by 8.59±3.4 (mean±SEM) percent ($p = 0.02$ by matched pair t-test) and reduced rCMRglc in 35 of 56 regions analyzed ($p< 0.05$ by matched pair t-test) (table 1). Statistically significant decrements ranged in magnitude from 5.8 to 16 percent of values obtained when subjects received placebo. Although the cocaine-induced decrements in cerebral glucose metabolism were global, the magnitude of the metabolic change in the right amygdala was negatively correlated with the positive quality and strength of the subjective response.

These findings were extended in a study by Morgan and colleagues (1993) that investigated the relationship between subjective responses to cocaine and ventricle-to-brain ratio (VBR), an index of cerebral atrophy (Ron 1983; Wilkinson 1982). In subjects with histories of polydrug abuse, this parameter of ventriculomegaly has been correlated with the amount of alcohol consumed during the period of peak alcohol use (Cascella et al. 1991). The results from Morgan and colleagues (1993)

TABLE 1. Effect of cocaine on rCMRglc.

	Placebo		Cocaine	
	Left	Right	Left	Right
Neocortex				
Superior frontal gyrus	8.18±1.38	8.67±1.35	7.75±0.81	8.14±1.27
Orbitofrontal cortex (19)	8.93±1.43	8.83±1.41	8.57±1.15	8.34±1.03
Insula	10.26±1.56	10.70±1.72	9.15±1.66*	9.23±2.01*
Temporal pole (19)	5.83±1.01	5.90±1.01	5.40±0.82*	5.60±0.78
Primary visual cortex	9.50±1.82	10.10±1.78	8.53±1.56*	9.06±1.72*
Lateral occipital gyrus	7.94±1.34	6.40±1.41	7.27±0.90*	7.60±1.20*
Basal ganglia				
Caudate nucleus	8.44±1.28	8.85±1.19	7.91±1.28*	7.76±1.47*
Putamen	9.47±1.21	10.10±1.36	8.57±1.27*	8.35±1.57

Each value is the mean±SD regional cerebral metabolic rate for glucose (rCMRglc, mg/100g/min) for 20 subjects, except where indicated in parentheses.

KEY: * = Statistically significant effect of cocaine as determined by t-test using the difference between rCMRglc measured in cocaine and in placebo conditions, uncorrected for the number of comparisons, $p<0.05$.

indicated that selective measures of the effects of cocaine, including self-report ratings of intensity of drug effect, scores on the morphine-benzedrine group subscale of the Addiction Research Center Inventory, and several items on visual analog scales of subjective self-reports were negatively correlated with VBR. VBR also differed significantly between subjects who were grouped according to scores (rush and crash) on the cocaine sensitive scale (larger VBR in subjects with weaker responses). Changes in global and regional cerebral metabolic rates for glucose were not significantly related to VBR. Thus, the effects of cocaine on mood but not cerebral glucose metabolism were related to the structural integrity of the brain.

Findings that cocaine and other stimulants reduce cerebral glucose metabolism seem inconsistent with the behavioral effects of these drugs in humans, and they are at variance with reported effects of d-ampheta-mine (Wechsler et al. 1979) and l-cocaine on rCMRglc in rats (London et al. 1986). However, the effects of stimulants on rCMRglc in the human brain are consistent with observations that other drugs which produce positive affective states, such as diazepam (De Wit et al. 1990; Foster et al. 1987), ethanol (De Wit et al. 1990; Volkow et al. 1992a), morphine (London et al. 1990b), nicotine

(Stapleton et al. 1992), and buprenor-phine (Walsh et al. 1994) also reduce rCMRglc, particularly in cortical areas. The mechanism for producing decreases in cerebral glucose metabolism may be related to the interaction between euphoriant drugs and the mesolimbic dopamine system (Gardner 1992; Koob and Bloom 1988; London and Morgan 1993). Thus, the reduced cortical metabolism seen in response to euphoriants may be a consequence of an action on mesolimbic areas that are important to reward and that provide the reinforcement for continued drug self-administration. Alternatively, decrements in rCMRglc may be a response to positive affect induced by drugs of abuse.

A recent study by Herning and colleagues (1994) that used a group of subjects drawn from the same population studied with FDG and cocaine (London et al. 1990a; Morgan et al. 1993) indicated that acute cocaine significantly increased frontal and central electroencephalographic (EEG) activity in the beta range (13.6 to 32.8 hertz (Hz)). Although increased beta activity is usually considered to be indicative of increased brain activ-ity, the finding that other drugs of abuse, such as barbiturates (Benowitz et al. 1980) and benzodiazepines (Manmaru and Matsura 1989), also increase EEG beta activity while reducing rCMRglc (Buchsbaum et al. 1987; deWit et al. 1990; Foster et al. 1987; Theodore et al. 1986) suggested that increases in beta activity may be related to decreased cortical function and metabolic demand (Bunney and Aghajanian 1978; Siggins 1978).

Aside from assessment of the acute effects of cocaine, recent investi-gations have been directed at determining if the brains of substance abusers manifest deficits that may reflect long-term consequences of the use of cocaine or other drugs of abuse. A study of VBR, determined volumetrically by magnetic resonance imaging, demonstrated that relative to normal controls, subjects with histories of polydrug abuse did not have larger VBR, nor was there any tendency toward relative ventriculomegaly (Liu et al. 1995). In contrast, patterns of rCMRglc differed in polydrug abusers as compared with those in controls (Stapleton et al. 1995). Comparisons of absolute values of rCMRglc indicate that polydrug abusers have statistically lower metabolism in the visual association cortex than controls. When values of rCMRglc were normalized for global glucose metabolism (a technique used to reduce the effect of interindividual differences on group comparisons of rCMRglc), rCMRglc was significantly higher in the orbitofrontal cortex in the drug abuse group as compared with controls. These metabolic differences, which are more robust than

structural deficits in the brains of substance abusers, may represent long-term consequences of the self-administration of cocaine or other drugs of abuse. Nonetheless, the degree to which these differences predate drug abuse is not known.

Other studies have been designed specifically to test the effects of cocaine withdrawal on rCMRglc. A study of two groups of male polydrug abusers, who used an average of 4 grams (g) of cocaine per week, indicated that abstinence from cocaine for less than 1 week was associated with increased rCMRglc in orbitofrontal cortex and basal ganglia, whereas abstinence for 2 to 4 weeks was associated with a return to normal rCMRglc (Volkow et al. 1991). The subjects were polydrug abusers who were dependent on nicotine and cocaine, but not other drugs of abuse. Cocaine dependence was established using criteria from the "Diagnostic and Statistical Manual of Mental Disorders," 3d ed. revised (DSM-III-R), and all but three of the cocaine-dependent patients had depressive symptoms at the time of the study. In a second study by the same group, male cocaine-dependent volunteers were recruited from a detoxification unit. This study revealed lower levels of rCMRglc in the frontal cortex of cocaine abusers after 1 to 6 weeks of abstinence as compared with values in controls. The difference persisted in a subset of subjects who were retested after 3 to 4 months (Volkow et al. 1992b). A more recent, preliminary study of cocaine absti-nence involved three groups of six subjects each, studied with FDG on three occasions relative to cocaine withdrawal (Flowers et al. 1994). Factor analysis indicated that early cocaine abstinence (7 to 20 days) was asso-ciated with increased metabolism in ventral striatum, orbitofrontal cortex, and amygdala, with a decline in rCMRglc to these regions during middle abstinence (21 to 41 days). In addition, the dorsal caudate and putamen were less activated early in abstinence, but rCMRglc in these regions showed peak rCMRglc in middle abstinence. Finally, rCMRglc in the anterior cingulate and dorsolateral frontal cortex declined only late in abstinence (100 days to 10 years). Data from these studies indicate that the early stage of cocaine withdrawal (1 to 3 weeks) appears to be associated with increased rCMRglc in orbitofrontal cortex and basal ganglia. This hypermetabolic condition is followed by decreased rCMRglc in frontal cortex at a later stage (> 4 weeks). Furthermore, the decrease in rCMRglc of the frontal cortex persists for at least 3 to 4 months.

The long-term changes in brain function seen during active drug use and during periods of abstinence also may include alterations that underlie behavioral responses to conditioned cues. It has been

suggested that stimuli which reliably signal drug use may come to elicit conditioned responses (Siegel 1979; Stewart et al. 1984). For example, heroin users manifest decreased skin temperature and skin resistance, as well as increased self-reported craving and withdrawal, when presented with stimuli related to heroin use, but not during presentation of cues that are not related to drug abuse (Childress et al. 1986; O'Brien et al. 1986). Several studies have examined whether stimuli associated with cocaine use produce different responses in cocaine abusers compared with subjects with no history of cocaine use (Bauer and Kranzler 1994; Childress et al. 1988; Ehrman et al. 1992; O'Brien et al. 1990). These studies indicate that patients who have abused cocaine show increased physiological and subjective responses to cocaine-related stimuli when compared to subjects who have no history of cocaine use.

A prominent response to presentation of cocaine-related stimuli is an increase in subjective reports of craving for cocaine. Although craving has been difficult to define precisely (Kozlowski et al. 1989; Markou et al. 1993; Newlin 1992; Tiffany et al. 1993), it has been conceptualized as an intervening variable that motivates continued drug use or resumption after abstinence. In particular, increased craving during withdrawal from chronic cocaine use is believed to contribute substantially to relapse (Gawin and Kleber 1986). Although the physiological responses to cocaine-related stimuli are believed to be the product of a Pavlovian conditioning process that generates craving, the neural substrates of craving are largely unknown (Koob 1992).

Preliminary data from a PET study using the FDG method suggest a potential neural mechanism for the long-term changes in brain that underlie the production of craving (Grant et al. 1994). Consistent with previous studies, polydrug abusers who are currently using cocaine show an increase in self-reports of craving and overall EEG arousal during presentation of visual cocaine-related stimuli. PET scans reveal increases in rCMRglc in portions of the prefrontal cortex and the occipital lobe. These cortical responses to conditioned cues point to a potential dif-ference between polydrug abusers and individuals who have no histories of drug abuse, and may reflect cerebral substrates that are targets for therapies aimed to antagonize drug craving and relapse.

In conclusion, cocaine abuse is associated with a number of acute and long-term effects that are both behavioral and physiological. To summarize, acute cocaine administration produces a constellation of

effects that are similar to those produced by other euphoriant drugs. These physiological effects include decreases in regional and global metabolic rates for glucose and increases in EEG beta power. Current literature suggests that a common brain mechanism, which may be attributable to an interaction with the mesolimbic dopaminergic system, underlies the euphoriant actions of these drugs.

The data presented in this chapter also indicate that cerebral functional differences in the brains of substance abusers include reduced rCMRglc of visual association cortex and increased rCMRglc in orbitofrontal cortex and basal ganglia in polydrug abusers relative to nonabusing controls. In addition, rCMRglc in several brain regions in cocaine abusers seems to be related to the length of abstinence from cocaine. Furthermore, long-term cocaine use is associated with the development of conditioned responses that may include craving, a behavioral state which may contribute to relapse. Preliminary data indicate that these condi-tioned responses include specific changes in rCMRglc. Thus, metabolic mapping with PET and FDG has been useful in providing information on brain function in several states of the cycle of cocaine addiction, from acute euphorigenic responses to persistent differences in brain function after cessation of drug use. The major challenge of the human studies described has been the lack of control over drug history and other envi-ronmental factors that may confound the interpretation of the findings. Such problems could be obviated in studies of primates, and the develop-ment of PET scanners with improved spatial resolution would enhance such efforts.

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AUTHORS

Edythe D. London, Ph.D.
Chief
Neuroimaging and Drug Action Section
Neuroscience Branch
Intramural Research Program
National Institute on Drug Abuse
National Institutes of Health
Baltimore, MD 21224

and

Associate Professor of Radiology
Department of Radiology
School of Medicine
The Johns Hopkins University
Baltimore, MD 21204

and

Adjunct Associate Professor
Department of Pharmacology and Experimental Therapeutics
School of Medicine
University of Maryland
Baltimore, MD 21201

June M. Stapleton, Ph.D.
Brooklyn Veterans Affairs Medical Center
Neurology Service (127)
Brooklyn, NY 11209

Steven J. Grant, Ph.D.
Robert L. Phillips, Ph.D.
Victor L. Villemagne, M.D.
Xiang Liu, M.D.
Rebeca Soria, Ph.D.
Neuroimaging and Drug Action Section
Neuroscience Branch
Intramural Research Program
National Institute on Drug Abuse
National Institutes of Health
Baltimore, MD 21224

Cardiotoxic Properties of Cocaine: Studies With Positron Emission Tomography

Nora D. Volkow, Joanna S. Fowler, and Yu-Shin Ding

INTRODUCTION

The frequent use of cocaine in the United States has resulted in a high degree of morbidity and mortality. Although cocaine was initially believed to be a relatively safe drug, there is now evidence that cocaine is one of the most toxic drugs of abuse (Johanson and Fishman 1989). In fact, laboratory animals given free access to cocaine will self-administer until death (Koob and Bloom 1988). Though cocaine is toxic to various organs in the body, the most frequently involved are the brain and the heart (Dackis and Gold 1990).

Cardiac toxicity is the most frequent complication of cocaine abuse. Cocaine use can trigger myocardial infarction (Huester 1987; Isner et al. 1986) and lethal cardiac arrhythmias (Gradman 1988). Both central (Jones and Tackett 1990; Wilkerson 1988) and peripheral mechanisms (Beckman et al. 1991; Hale et al. 1988; Pitts and Marwah 1989) are responsible for cocaine's cardiotoxic properties. Cocaine's peripheral actions involve the release of adrenaline and noradrenaline from the adrenals (Chiueh and Kopin 1978), inhibition of noradrenaline reuptake sites in myocardial tissue (Iversen 1965), and local anesthetic effects in myocardial cells (Seifen et al. 1989).

Cocaine is directly toxic to the myocardium (Peng et al. 1989; Przywara and Dambach 1989), and its anesthetic properties can trigger cardiac asystole (Nanji and Filipenko 1984). There is evidence from postmortem studies in subjects who died of cocaine overdose that there is significant accumulation in myocardial tissue (Poklis et al. 1987). Therefore, it is important to determine the extent to which there is an accumulation of cocaine in the human heart in vivo. One approach is to measure the distribution and behavior of cocaine in the living heart and compare it with that of its distribution in other organs of the human body. Another approach is to assess the effects of cocaine on specific physiologic and neurochemical processes in the heart.

This chapter describes positron emission tomography (PET) studies that investigated the pharmacokinetics of cocaine in the heart and the dynamics for cocaine-induced inhibition of the norepinephrine (NE) transporter. PET was used in two separate studies: One study assessed the pharmaco-kinetics of cocaine in the living heart, and the other evaluated the effects of cocaine in the NE transporter.

PHARMACOKINETICS OF COCAINE IN THE HEART

[11C]Cocaine was used to assess the kinetics and binding of cocaine in the baboon and human heart. Baboon studies were done in order to assess the effects of various pharmacological challenges on the binding of cocaine in heart. This approach was used to characterize the pattern of cocaine binding in myocardial tissue in vivo. [N-11C-methyl] cocaine was prepared by the methylation of nor-cocaine with [11C]methyl iodide (Langstrom and Lundqvist 1976) as previously described (Fowler et al. 1989).

Baboon Studies

Studies were done in adult female baboons (Papio Annubis). For each of the seven paired studies, the baboons were scanned twice, 2-hours apart. The first scan for each animal was always done with no pharmacological intervention and was used as baseline to compare the effects of the interventions on the second scan. The following interventions were done prior to the second scan:

1. For one of the animals, the second scan was also done with no pharmacological intervention to assess test-retest reproducibility of [11C]cocaine in heart.

2. The second scan of one animal was done 2 minutes after intravenous (IV) administration of 2 milligrams per kilogram (mg/kg) cocaine to assess the specificity of cocaine's binding to the heart.

3. For two animals, the second scan was done 30 minutes after IV administration of 0.5 mg/kg desipramine. Another animal was scanned 30 minutes after administration of tomoxetine (0.5 mg/kg) to determine the extent of [11C]cocaine binding to the NE transporter.

4. For one animal, the second scan was done 30 minutes after IV administration of nomifensine (2mg/kg) to assess binding to dopamine transporters.

5. For one animal, the second scan was done 60 minutes after IV administration of benztropine mesylate (0.1 mg/kg) to assess binding to muscarinic receptors as well as to dopamine transporters.

Human Studies

Ten healthy human volunteers (male, age range 21 to 47 years) were studied. Five of the subjects received two scans with a 2- to 3-hour time interval between doses. For one subject, the scans were done with no pharmacological intervention to assess the reproducibility of the cardiac uptake of [11C]cocaine between measurements. For four subjects, the second scan was done 40 minutes after the IV injection of 2 mg benztropine mesylate (Dewey et al. 1990) to determine the extent to which uptake of cocaine in the heart represented binding to muscarinic receptors and/or dopamine transporters.

Dynamic scans were done inmediately after IV administration of 5 to 10millicuries (mCi) of [11C]cocaine to (7 to 13 micrograms (µg) cocaine per injection). In the human subjects, dynamic scans were obtained for a total of 45 minutes, and in the baboons for a total of 54 minutes. The baboons were anesthetized, catheterized, and prepared for the PET study as previously described (Dewey et al. 1990). Details on scanning procedure and preparation have been published both for the human (Volkow et al. 1992) as well as for the baboon studies (Dewey et al. 1990). Arterial blood was sampled to measure total radioactivity concentration as well as unchanged tracer in plasma as previously described. Regions in left atrium, left ventricle, and septum were obtained as described (Fowler et al. 1994; Volkow et al. 1992). Time-activity curves for tissue concentration in heart were plotted for the various interventions.

EFFECTS OF COCAINE ON THE MYOCARDIAL NOREPINEPHRINE TRANSPORTER

[18F]Norepinephrine, a ligand for which uptake in heart reflects the func-tion of the NE transporter, was used to evaluate the function of the NE transporter. The effects of cocaine on the uptake of [18F]norepinephrine in the baboon heart were evaluated with PET (Fowler et al. 1994). Studies were done in two adult female baboons: One was scanned five different times, and the other four different times, with a 9- to 14-day interval between scans. The first scan was

done with no pharmacological intervention and was used as baseline. The experimental strategies were as follows:

1. In one baboon, the four additional [18F]fluoronorepinephrine scans were done 5 minutes, 30 minutes, 66 minutes, and 24 hours after IV administration of 2 mg/kg cocaine.

2. In the second baboon, the three additional [18F]fluoronorepinephrine scans were performed 30 minutes, 78 minutes, and 24 hours after IV administration of 2 mg/kg cocaine.

Dynamic scans were started inmediately after injection of 0.9 to 4.2 mCi of [18F]fluoronorepinephrine (0.17 mg/mCi) and were continued for a total of 100 minutes. Arterial plasma input functions were measured for each study as described previously (Ding et al. 1993). Heart and res-piratory rates were monitored during the PET study. Details on scanning protocol for the [18F]fluoronorepinephrine and synthesis of [18F]norepine-phrine have been published (Ding et al. 1993).

For the analysis of the PET images, regions of interest were drawn directly on the myocardial emission images as previously described (Ding et al. 1993). The activity in these regions of interest was used to obtain the time activity curve for regional tissue concentration. The time-activity curves for tissue concentration and for unchanged tracer in plasma were used to calculate the transport constant between plasma and tissue (K1) and to obtain the retention fraction (ratio of heart radioactivity to integral of plasma radioactivity at 30 minutes) (Ding et al. 1993).

RESULTS

Pharmacokinetics of Cocaine in the Heart

There was high uptake of radioactivity into the human and baboon heart after IV injection of [11C]cocaine (figure 1). Regional analysis of radioactive isotope in the heart showed homogeneous distribution with similar uptake in left ventricle, atrium, and septum.

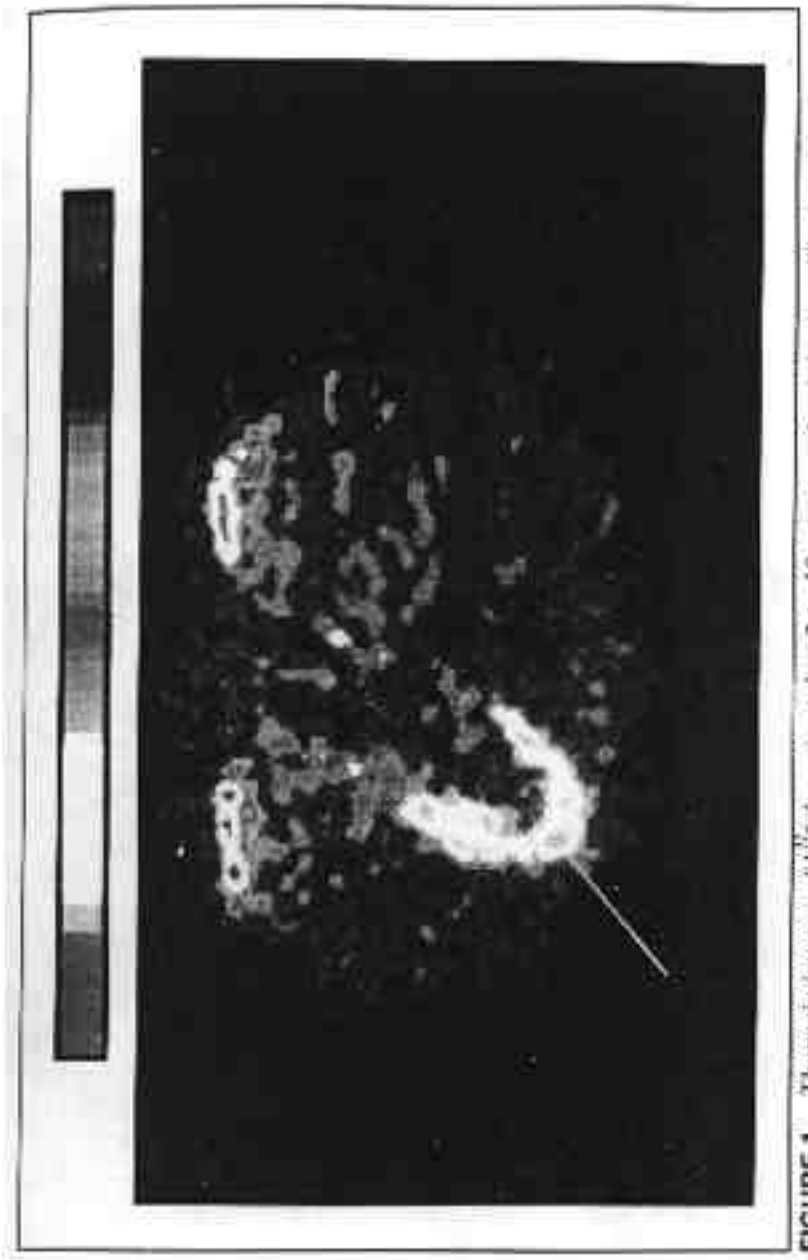

FIGURE 1. *Thoracic images of ^{11}C-ivomine taken 2 to 10 minutes after injection. The image corresponds to an axial plane showing the long axis views of the heart.*

In the human heart, peak carbon-11 concentrations for the left ventricle, septum, and atrium corresponded to 0.007 (standard deviation (SD) 0.001), 0.006 (SD 0.002), and 0.007 percent (SD 0.001) dose/cc of tissue respectively. The peak uptake is equivalent to that observed for the basal ganglia, which also corresponded to 0.007 percent dose/cc tissue. Peak uptake of carbon-11 in the heart occurred 2 to 3 minutes after admini-stration of the tracer. The clearance of [11C] cocaine from the heart was also very fast, with half-peak activity seen 10 minutes after injection (figure 2). In contrast, there was no retention of radioactivity by the lung, where the activity paralled that of the tracer in plasma. Figure 2 shows the kinetics of carbon-11 uptake in heart, lung, and arterial plasma for one representative subject.

Benztropine mesylate, a drug that binds to muscarinic receptors and dopamine transporters, did not change binding of [11C]cocaine in the human heart (figure 3).

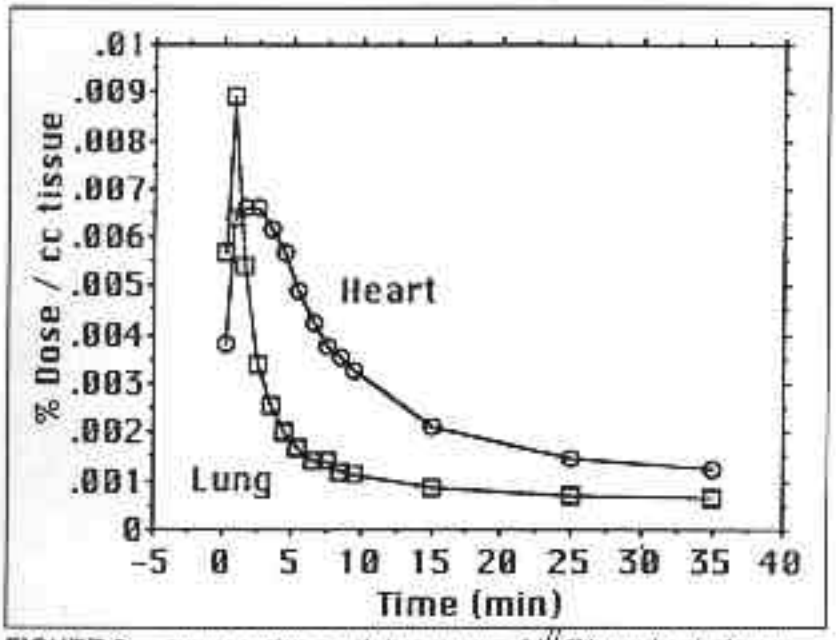

FIGURE 2. *Average time-activity curves of [11C]cocaine in heart and lung for the baseline studies in the normal controls. Uptake in lung paralleled the radioactivity of plasma. In the heart, peak uptake occurred 2 to 3 minutes after injection. Half of the peak activity remained at 10 minutes.*

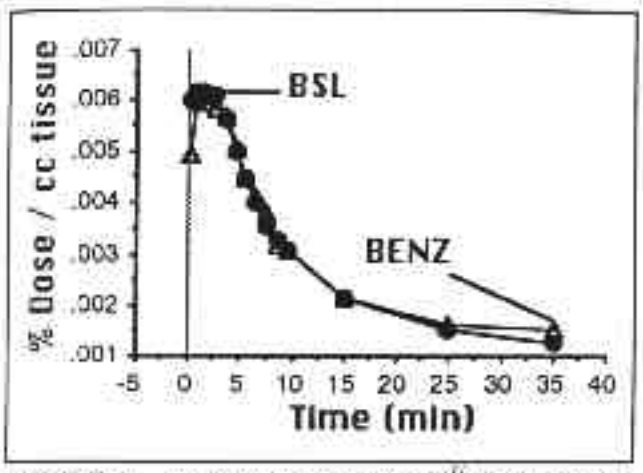

FIGURE 3. *Time-activity curves of [^{11}C]cocaine in heart for a normal control tested at baseline (BSL) and after pretreatment with benztropine mesylate (BENZ). Benztropine did not affect [^{11}C]cocaine binding.*

In the baboon, peak [11C]cocaine concentration ranged from 0.036 to 0.055percent dose/cc tissue, which (as in humans) was also similar to peak uptake in basal ganglia (0.05 percent (SD 0.01) dose/cc tissue). Serial PET studies showed a test-retest variability of less than 5 percent for the uptake of [11C]cocaine in heart. The time-activity curves for both studies were super-imposable on each other (data not shown). Preadministration of cocaine prior to tracer injection decreased the clearance of [11C]cocaine (half-life (t_): 12.3 minutes (cocaine) versus 9 minutes (baseline)) (figure 4).

Slowing of the clearance may have reflected a higher plasma concentra-tion of [11C] cocaine throughout the study, when the animal was pre-administered pharmacological doses of cocaine (figure 5). This plasma increase probably reflects a larger bioavailability of [11C]cocaine, as a result of the occupation by cocaine of its binding sites.

Neither tomoxetine, desipramine, nomifensine, nor benztropine mesylate inhibited the uptake of [11C]cocaine in the heart, nor did they change its pharmacokinetics (figure 6 shows the time-activity curves for the tomoxetine study).

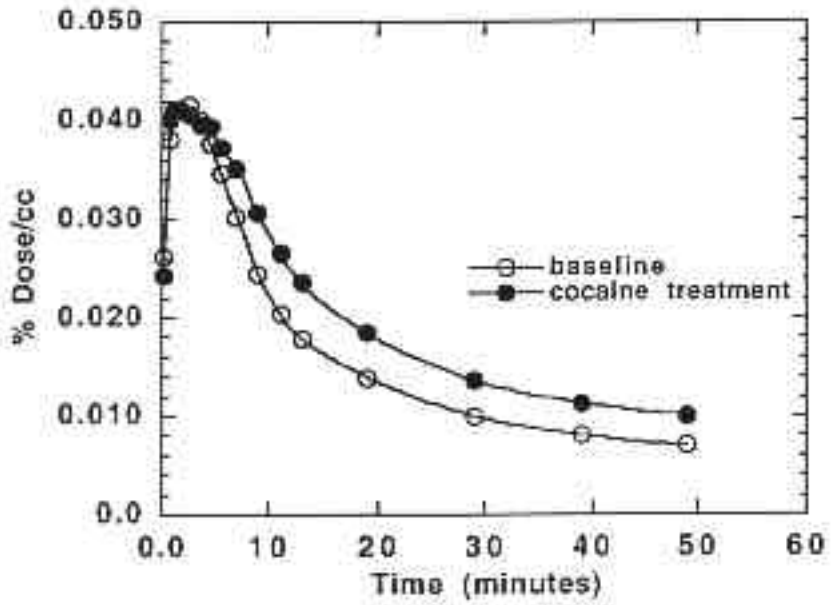

FIGURE 4. *Time-activity curves for [^{11}C]cocaine in baboon heart at baseline and after administration of cocaine (2 mg/kg IV). Cocaine preadministration decreased uptake of [^{11}C]cocaine in heart.*

Effects of Cocaine on the Myocardial Norepinephrine Transporter

Studies with [18F]norepinephrine revealed the characteristic pattern of high uptake of radioactive isotope into the heart that peaks almost immediately after injection and plateaus thereafter (Ding et al. 1993). Cocaine preadministration inhibited [18F]norepinephrine uptake into the heart by 90 percent when the studies were done 5 minutes after cocaine administration. This profound inhibition of [18F]norepinephrine uptake is equivalent to that observed after pretreatment with desipramine using doses that had failed to inhibit [11C]cocaine in heart (Ding et al. 1993). In contrast to the fast pharmacokinetics of cocaine in the heart, cocaine-induced inhibtion of the NE transporter was prolonged. Sixty-six minutes after cocaine administration, the retention fraction for [18F]norepinephrine was 29 percent of the baseline value for one baboon. At 78minutes after cocaine administration, the retention fraction for [18F]norepinephrine was 57 percent of the baseline value for the other baboon. By 24 hours, the retention fraction for [18F]norepinephrine approached baseline values.

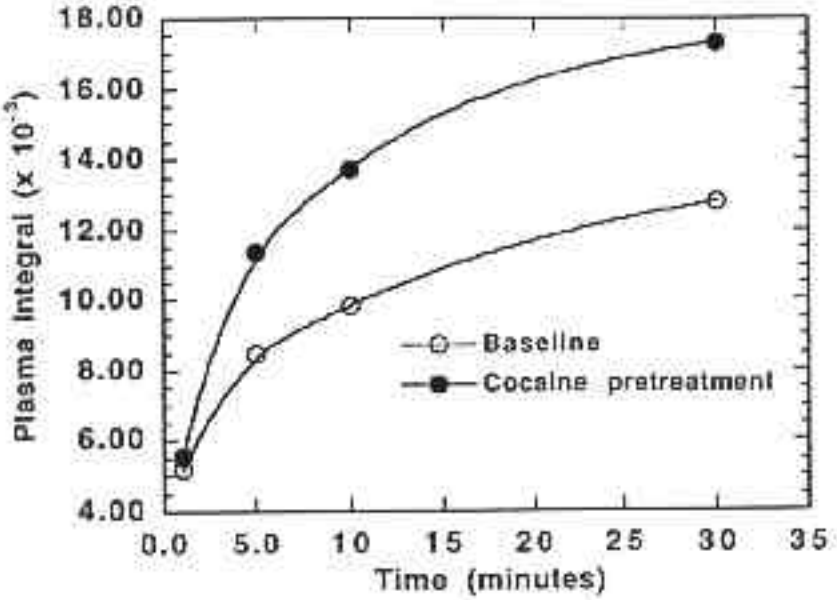

FIGURE 5. *Plasma integrals for the concentration of ^{11}C]cocaine (nCi/cc minute) for the study done at baseline and after cocaine preadministration (2 mg/kg IV).*

Time-activity curves for [18F]norepinephrine are shown in figure 7 for [18F]fluoronorepinephrine scans done at baseline and at 5 minutes, 30minutes, 66 minutes, and 24 hours after administration of cocaine to one baboon.

Discussion

This study documented significant uptake of [11C] cocaine by the human heart. In a heart weighing 350 gm, 2.5 percent of the injected dose was in the heart 2 to 3 minutes after IV administration. The uptake and clearance of carbon-11 from the heart were faster than in the brain (Fowler et al. 1989). In the heart, the time for clearance to 50percent of maximum uptake was 10 minutes, whereas in the brain it was 25 minutes (Fowler et al. 1989). The 2- to 3-minute postinjection peak corresponds with the time required to reach maximal chronotropic response after IV cocaine (Rowbotham et al. 1987). However, the kinetics of cocaine clearance from the heart do not correspond to the longer lasting chronotropic effects of cocaine (Foltin

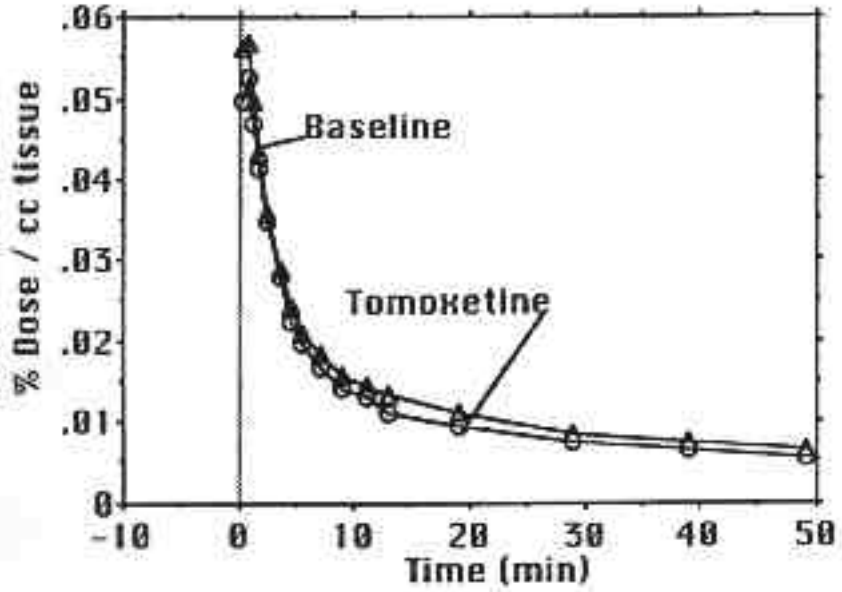

FIGURE 6. *Time activity curves for [^{11}C]cocaine in baboon heart at baseline and after administration of tomoxetine. Tomoxetine did not affect [^{11}C]cocaine binding in heart.*

and Fischman 1991). Similarly, the chronotropic effects of cocaine are of much longer duration than the kinetics of cocaine in brain.

The discrepancy in the duration of the chronotropic effects of cocaine and the kinetics of cocaine in heart or brain suggests either that cocaine induces a prolonged change in the transporters and/or receptors with which it inter-acts or that the actions are indirect. Indirect chronotropic effects on the heart could be due to central effects and/or to catecholamine release from the adrenal (Nahas et al. 1991). Alternatively, these effects could be the results of a cocaine metabolite.

The finding that there is significant accumulation of cocaine in the human heart suggests that cocaine could affect myocardial tissue directly via its interaction with noradrenergic transporters in myocardial cells (Lew and Angus 1981) or via its local anesthetic properties at this site (Boni et al. 1991). Both of these properties may act synergistically to enhance cocaine's toxic effects. Although the cardiac accumulation of cocaine is

TABLE 1. [^{18}F]Norepinephrine ([^{18}F]NE) heart uptake after cocaine pretreatment (2 mg/kg) at different times prior to tracer injection. Heart uptake is expressed as retention fraction (the ratio of the heart uptake to the arterial plasma integral for [^{18}F]NE at 30 minutes). The peak uptake of the tracer in heart for this study (0.060 percent dose/cc tissue) was 10percent lower than that for the baseline (0.067 percent dose/cc tissue).

	Intervention	Intervention time prior to [18F]NE	Retention fraction (RF)	% inhibition
Baboon 1	baseline	NA	0.41	100
	cocaine	5 minutes postcocaine	0.032	92
	cocaine	30 minutes postcocaine	0.090	78
	cocaine	66 minutes postcocaine	0.12	71
	cocaine	1440 minutes postcocaine	*	*
Baboon 2	baseline	NA	0.28	100
	cocaine	30 minutes postcocaine	0.089	68
	cocaine	78 minutes postcocaine	0.16	43
	cocaine	1440 minutes postcocaine	0.24	14

KEY: * = Blood measurements lost due to technical error; NA = not applicable.

transient after a single administration, under conditions of repeated administration (as in the cocaine abuser), one would expect high concentrations throughout the period of drug administration.

Pretreatment with desipramine, nomifensine, and benztropine did not affect the binding of [11C]cocaine to the heart. These results could be interpreted as showing no binding of cocaine to NE transporters, dopa-mine transporters, or to muscarinic receptors, but it is unlikely since postmortem studies have demonstrated binding of cocaine to NE trans-porters (Lew et al. 1981) and to muscarinic receptors (Sharkey et al. 1988) in the heart. It is more likely that these results reflect insufficient sensitivity of PET to detect binding when the concentration (Bmax) or the affinity (Kd) of the transporters or the receptors is low.

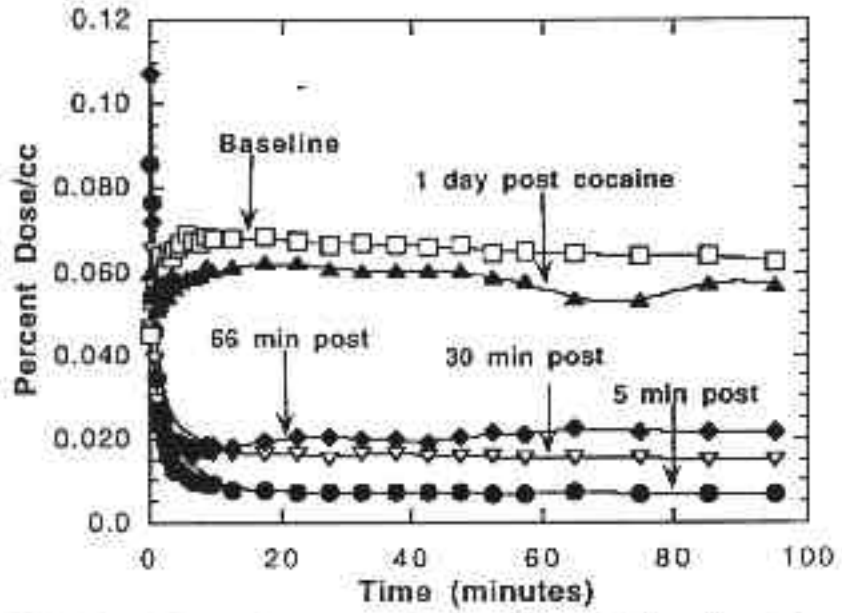

FIGURE 7. *Time-activity curves for five different PET studies with (-)-6[18] FINE in one of the baboons at baseline, and at 5 minutes, 30 minutes, 66 minutes, and 24 hours after pretreatment with cocaine (2 mg/kg IV).*

Even though the authors were unable to document binding of cocaine into the NE transporter as assessed by the inability of desipramine to block [11C]cocaine uptake, inhibition of the NE transporter by cocaine was demonstrated by the blockade of [18F]norepinephrine uptake. This apparent discrepancy could be due to the lack of PET sensitivity to detect binding sites with relatively low concentration per cc of tissue, but it may also indicate different sites of interaction of desipramine and cocaine at the NE transporter site. These results highlight the importance of com-bining more than one tracer in imaging studies that investigate the actions of a given drug in a receptor or transporter.

Another interesting finding from this investigation was the discrepancy between the short pharmacokinetics of cocaine in heart and the long-lasting cocaine-induced inhibition of the NE transporter. At 66 minutes, when there was no [11C]cocaine left in the myocardium, there was still 71percent inhibition of the transporter. Even 24 hours after adminis-tration of cocaine, there still appeared to be some functional inhibition of the NE transporter. The long-lasting inhibition of the NE transporter by cocaine despite its short

pharmacokinetics could represent competition for the transporter by circulating catecholamines induced as a result of cocaine's actions in the adrenals (Powis et al. 1989). However, it is also possible that the long-lasting NE transporter inhibition reflects a cocaine-induced change in the conformation of the transporter. Further work is required to evaluate if acute cocaine administration does in fact alter the conformation of the NE transporter.

SUMMARY

This study documented marked accumulation of cocaine in the human and baboon heart, which was not inhibited by desipramine pretreatment. However, cocaine inhibited 6-[18F]fluoronorepinephrine uptake in heart to the same degree as did desipramine (Fowler et al. 1994). Since uptake of [18F]norepinephrine in the heart is a function of its uptake by the NE transporter (Fowler et al. 1994), its inhibition by cocaine corroborates in vivo a significant interaction of cocaine with this transporter.

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AUTHORS

Nora D. Volkow, M.D.
Director, Nuclear Medicine
Associate Chief of Staff
Clinical Research Center
Brookhaven National Laboratory
and
Associate Professor
Department of Psychiatry
State University of New York at Stony Brook
Stony Brook, NY 11794-8101

Joanna S. Fowler, Ph.D.
Director, PET Program
Chemistry Department

Yu-Shin Ding, Ph.D.
Chemist
Chemistry Department

Brookhaven National Laboratory
Building 490
30 Bell Avenue
Upton, NY 11793

Neuropsychological Abnormalities in Cocaine Abusers: Possible Correlates in SPECT Neuroimaging

Thomas R. Kosten, Robert Malison, and Elizabeth Wallace

INTRODUCTION

Neuropsychological abnormalities in cocaine dependence fall into two broad categories: mood and cognitive disorders. The mood disorders include both acute anhedonic symptoms, which are associated with cocaine abstinence, and sustained depressive disorders, which occur at about five times the community rates (32 percent versus 6percent) (Gawin and Kleber 1986; Rounsaville et al. 1991). The neurobiology of these mood disorders may be related to abnormalities in catecholamine receptors and reuptake carriers induced by chronic cocaine usage. These changes are probably reversible, although they may leave a permanent diathesis towards underlying psychiatric disorders. For example, cocaine-associated panic disorders appear to lead to spontaneous panic attacks in many individuals for years after they stop taking cocaine (Aronson and Craig 1986; Louie et al. 1989; Rosen and Kosten 1992). Cognitive disorders appear to be related to neuronal loss.

In order to examine these two disorders associated with chronic cocaine usage, single photon emission computed tomography (SPECT) neuro-imaging has been employed. Correlates of mood dysfunction might be examined using iodinated probes for dopamine (DA) receptors and the DA reuptake carrier; both the receptors and the reuptake carrier can be affected by chronic cocaine use in animal models (Alburges et al. 1993). Correlates of cognitive deficits can be examined with agents that assess blood flow such as technetium-99-hexamethyl-propylamine oxime (HMPAO) (Holman et al. 1989; Holmes et al. 1985).

SPECT CEREBRAL BLOOD FLOW STUDIES AND COGNITIVE FUNCTIONING

In a series of studies, Holman and colleagues (1991, 1993) have shown that cocaine-dependent patients may have patchy perfusion defects in cerebral cortical blood flow. These defects appear to be relatively persistent over several weeks after cessation of cocaine use, although recent work suggests a potential improvement in blood flow of up to 30percent during 4 weeks of treatment with the partial opioid agonist buprenorphine (Holman et al. 1993; Mendelson et al. 1995). Other investigators have noted these perfusion defects in cocaine-dependent patients, but because of the small number of subjects in most studies, the general prevalence of these defects among cocaine abusers is unknown (Strickland et al. 1991; Tumeh et al. 1990; Volkow et al. 1988).

Brain Perfusion Defects

In the first study by Holman and colleagues (1991), 18 male polydrug abusers who had used an average of 2.2 grams (g) of cocaine per week for an average of 7.7years were examined. Seven of the 18 meet current abuse or dependence criteria for alcoholism, and 7 met dependence cri-teria for opioids. The subjects reported their last use of cocaine from 1 to 16 days prior to the SPECT study, and nine of the subjects were positive for cocaine metabolites on the study day. The neuropsychological test battery included the Wechsler Memory Scale and its subtests of digit span and visual reproduction, the Stroop Color Word Test, the Rey-Osterreith Complex Figure Test, the California Verbal Learning Test, the Wisconsin Card Sorting Test, and the Luria Three-Step Motor Sequence Test. The imaging protocol used a brain imager with a resolution of 8.2millimeters (mm) and imaging was done using 20 millicuries (mCi) of HMPAO. Perfusion defects in cortical regions were identified as any area with less than 60percent of the maximum cerebellar activity, as determined from computer-generated isocount maps. The defects were then described as large if they involved more than 1 centimeter (cm) of cortex. Sixteen of the 18 cocaine-dependent subjects had abnormal brain perfusion patterns with the most frequent perfusion abnormalities seen in the parietal cortex (16/18), temporal cortex (15/18), frontal cortex (14/18), and basal ganglia (11/18). Only one subject had large focal deficits without additional small perfusion deficits. Amount or frequency of previous cocaine use was not associated with the number or size of these focal defects, although the two subjects who had no defects on scanning reported only infrequent

alcohol use. All of the other subjects reported moderate to severe alcohol abuse or dependence, suggesting an association of defects with combined alcohol and cocaine abuse, an issue addressed later in this chapter.

The subsequent study by Holman and colleagues (1993) included 10 cocaine-dependent polydrug abusers who were imaged with HMPAO 2 to 3 days after admission to an inpatient treatment facility and then again at 7to 8 days and 17 to 29 days after beginning abstinence from illicit drugs. Beginning on day 10, the patients also received buprenorphine (a mixed opioid agonist/antagonist), which was continued until the end of the study. The details of image acquisition and analysis were the same as the previous study, but with some simplification in the categorization. The cortical regions were classified as "abnormal" if the activity ratio was less than 0.6and "borderline" if they fell between 0.6 and 0.72 relative to cerebellar activity. In the abnormal zones, regional cerebral blood flow increased 11percent ± 9 percent at 7 to 8 days and 24 percent ± 9 percent at 17 to 29days after initiation of treatment. In the borderline cortex areas, the increase in cerebral blood flow was 5 percent on day 7 to 8 and 11 percent on day 17 to 29. Blood flow showed virtually no change in the normal areas. The increase in cerebral blood flow did not vary significantly by location in the cortex. An interesting conclusion of the investigators was that the perfusion defects observed in these chronic cocaine- and opioid-dependent patients were partially reversible with short-term abstinence and treatment using buprenorphine. Overall, the amount of improvement across subjects was variable, but all patients showed an increase in cerebral blood flow in abnormal regions during the 3 to 4 weeks of the study, with a range of increase between 11 and 37percent.

Holman's work has suggested that these perfusion deficits are more common in patients dependent on cocaine and either alcohol or opioids than on cocaine alone. In a 20-subject study, the authors' research group has found that patients dependent on alcohol and cocaine are more likely to have perfusion deficits than those dependent on cocaine alone (Woods et al., submitted). In the frontal and parietal cortex of cocaine- and alcohol-dependent patients, blood flow is particularly reduced and the mean decrease is four times greater than the variation in blood flow across normal subjects. The "pure" cocaine abusers showed no differ-ences from normals. The role of cocaethylene in producing these lesions is of interest, since the authors' studies have shown a potentiation of cocaine's cardiovascular effects by alcohol. With alcohol plus cocaine, cocaethylene is formed,

and heart rates and blood pressures are higher and sustained twice as long as with cocaine alone (McCance-Katz et al. 1993). Thus, alcohol abuse in the context of heavy cocaine dependence may predispose to the development of these perfusion defects.

Mechanisms Leading to Perfusion Defects

In acute cocaine administration studies, the authors and other investigators have found a decrease in cortical cerebral blood flow and general metabolic activity as assessed by fluorodeoxyglucose studies using positron emission tomography (PET) (London et al. 1990; Pearlson et al. 1993; Wallace et al. 1994). The blood flow study by Pearlson and colleagues (1993) involved the administration of 48 milligrams (mg) of intravenous (IV) cocaine to eight abstinent cocaine users in a double-blind, crossover design. The investigators examined blood flow using SPECT and 20 mCi of HMPAO. The cocaine produced significant decreases in frontal cortical and basal ganglia blood flow, which corre-lated negatively with increases in self-ratings of rush and high. The sta-tistically significant mean percentage changes by region were 6.5percent in the left caudate, 5.5-percent in the left putamen, 9.9 percent in the inferior cingulate, and 9percent in the right frontal area. Changes within individual patients included decreases in blood flow of up to 25percent during cocaine administration.

Subjective responses, including high and rush, were also significantly elevated after cocaine administration. Because HMPAO has more than 80percent first-pass extraction with an estimated 90-second time window reflecting regional cerebral blood flow changes, this activity corresponds rather closely to the time of peak subjective effects, which for IV cocaine is typically 3 to 5 minutes after administration. Thus, a reasonably close correspondence might be expected between the blood flow measures and these subjective responses. However, it is not clear what these blood flow changes reflect, since these regional cerebral blood flow changes could reflect direct effects of cocaine on cerebrovasculature. The regional locali-zation that was observed makes this nonspecific blood flow alteration unlikely. All of the regional changes were observed in areas connected neuroanatomically to the dopaminergic system. Thus, cocaine in humans may produce regional decreases in cerebral blood flow corresponding to sites enriched in dopaminergic terminals.

A similar study by Wallace and colleagues (1994) calculated absolute changes in blood flow during cocaine administration. Four male

cocaine abusers were given IV cocaine at 0.5 milligrams per kilogram (mg/kg) followed by an injection of HMPAO to assess regional cerebral blood flow. Arterial levels of the HMPAO metabolite were also measured in order to calculate absolute blood flow, which was compared for placebo injection versus cocaine injection. Substantial decreases of up to 40per-cent in whole brain blood flow were detected during acute cocaine injec-tion with regional differences in blood flow similar to the findings of Pearlson and colleagues (1993). These greater changes in absolute blood flow suggest that the relative blood flow changes calculated in com-parison to cerebellum in the Pearlson study (1993) underestimated the decrease in blood flow caused by cocaine. The actual decreases in blood flow within particularly vulnerable areas in the basal ganglia and cortex appear to be as much as twofold greater than those estimates made by Pearlson. The implication of this greater reduction in blood flow is that the pathophysiological consequences for highly localized perfusion deficits could be substantial. Particularly with repeated cocaine dosing or in the presence of cocaethylene, which has a substantially longer half-life than cocaine itself (McCance-Katz et al. 1993), blood flow reductions could be substantial and sustained.

In these controlled studies by Wallace and colleagues (1994), it was further observed that all four of the subjects had patchy cortical perfusion deficits when administered placebo rather than cocaine. These deficits were similar to those previously observed by Holman in cocaine abusers (1991, 1993). When cocaine was acutely administered, these patchy perfusion deficits had a further reduction in blood flow, which in many cases leads to complete reduction in blood flow for small focal defects. Again, the implication for the pathophysiology of persistent blood flow defects in cocaine abusers is obvious. In subjects who already have cerebral perfusion deficits from chronic cocaine abuse, the hypoperfusion is enhanced by acute cocaine administration. This enhancement of chronic perfusion deficits by acute cocaine administration suggests the pathophysiology that leads to the development of structural brain deficits in cocaine abusers (Jacobs et al. 1989; Klonoff et al. 1989). These structural brain lesions have been noted in patients who present to the emergency room typically after very large dosages of cocaine. These doses might produce severe and persistent cerebral vasoconstriction and perfusion deficits. Thus, a vascular basis for neuronal loss is evident.

While direct vasoconstriction of cerebral blood flow by cocaine may decrease cerebral perfusion (Isner and Cholski 1990), another effect of

cocaine that may decrease cerebral perfusion has been described by Rinder and colleagues (1994) based on platelet adhesion. Platelets are granular cells lacking a nucleus, but still having active metabolism (Marcus 1969). When a blood vessel is injured, platelets aggregate at the site and form a viscous plug prior to formation of a clot. Aggregation of platelets is produced by small amounts of thrombin as well as by adeno-sine diphosphate (ADP), which is released from the platelets themselves. As part of their structure, platelets include dense granules and a-granules. The dense granules contain large amounts of serotonin leading to vaso-constriction as well as ADP, which recruits other platelets and activates the a-granules. Release of the dense granules occurs in the early stages of this clot formation and can be blocked by aspirin, which inhibits cyclo-oxygenase, a key enzyme for the adhesive process. The a-granules are involved in the next phase of platelet aggregation and thrombus forma-tion. They are activated by ADP and release fibrinogen, thrombospon-din, and prostaglandins. Platelets that have already partially released some of their a-granules attract other platelets, leading to the formation of platelet thrombi. The a-granule includes a membrane protein called P-selectin, which becomes an integral part of the platelet membrane when the a-granule is released. P-selectin mediates adhesion of these platelets to leukocytes and serves as a marker for platelet activation. P-selectin positive platelets can be identified and quantified using monoclonal antibody assays.

Using this antibody assay, Rinder and colleagues (1994) found that platelets of chronic cocaine abusers are in a partially activated state, making them substantially more adherent to each other and to blood vessel walls. In a series of 92 baseline and 18 ADP-stimulated blood studies, the percentage of P-selectin positive platelets was significantly higher in cocaine abusers at baseline (12 percent versus 5 percent in normals), and the cocaine abusers' platelets had a significantly smaller response to ADP activation (3.5 percent versus 22 percent in normals). This lower percentage of activation simply reflects the already partially activated state of the platelet pool (e.g., the baseline differences from normals) due to a-granule release in the cocaine abusers' platelets. Because of this activation, any stimulus leading to dense granule release in these platelets results in rapid and substantial platelet clumping and thrombus formation in small cerebral blood vessels. This critical action of cocaine was recently confirmed by Kugelmass and colleagues (1993). This platelet clumping may also be reversible by aspirin, leading to a resolution of the cerebral perfusion defects noted earlier with SPECT scans. Figure 1 shows perfusion defects in a cocaine abuser reversed by 4weeks of aspirin treatment. Row (a) images were taken before treat-ment; row (b) shows blood flow following 2 weeks of treatment with 325-mg aspirin per day.

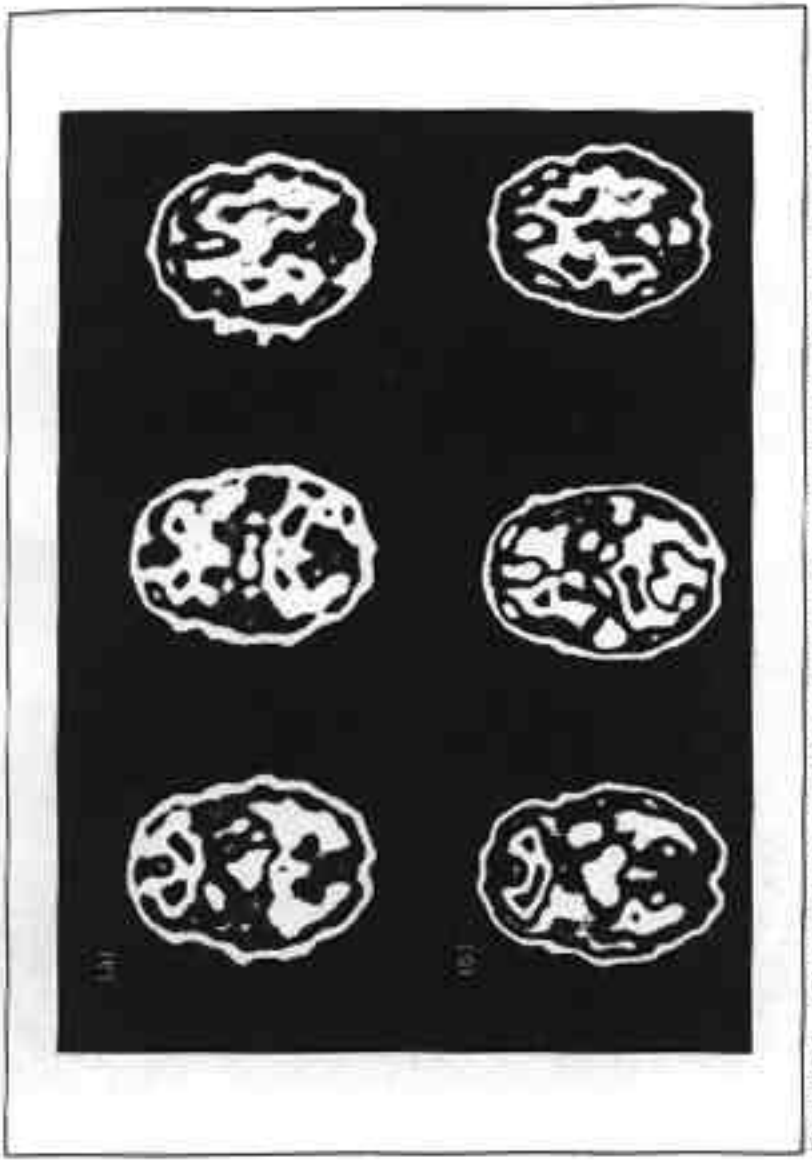

FIGURE 1. *Change in cerebral blood flow in cocaine abusers following 2 weeks of aspirin treatment.*

Neuropsychological Deficits

The functional consequences of these cerebral perfusion deficits have not been directly shown, but several studies have demonstrated neuropsycho-logical deficits in chronic cocaine dependence. O'Malley and colleagues (1990, 1992), in two separate studies, have shown that chronic cocaine-dependent patients who have been abstinent for up to 18months can show persistent difficulty in tasks requiring concentration and recent memory. Herning and colleagues (1990) have had similar findings and, most recently, others (Bauer 1993; Roberts and Bauer 1993) have demonstrated abnormalities in a variety of motor tasks suggestive of Parkinsonian symptoms in abstinent cocaine-dependent patients.

Holman and colleagues' SPECT neuroimaging studies (1991, 1993) found no specific correlation between areas of neuroanatomical abnormalities and specific neuropsychological deficits, but found that the patients with perfu-sion deficits had overall neuropsychological impairment on a variety of tests. All the subjects showed abnormalities on psychometric testing, with 5 of the 18 subjects having moderate deficits. The most common deficits involved spatial learning and organization in 12 out of 18 subjects. There was no detailed correspondence between the site of the perfusion defects and the character of the neuropsychological defects. No attempt was made to relate the number and severity of perfusion defects to the number of neuropsychological tests showing impairment. Thus, there does not appear to be a precise correlation between specific neuropsychological impairments and specific cerebral perfusion deficits, but there is an overall association between psychological impairment in memory and concentration and the occurrence of multiple cerebral perfusion deficits.

The association between the degree of neuropsychological impairment and cerebral blood flow was examined in a study of methadone-maintained cocaine abusers by Woods and colleagues (1991). In this study, human immunodeficiency virus (HIV)-negative and HIV-positive patients who did not have clinically diagnosed acquired immunodeficiency syndrome (AIDS) and were not treated with azidothymidine (AZT) were examined and compared. Two interesting associations were demonstrated. Among the HIV-negative patients, the ratio of blood flow in the striatum to the whole brain was inversely correlated with the percentage of 13 neuropsycho-logical tests showing impairment ($R = -0.77$, $p < 0.05$). Thus, more impairment was associated with reduced blood flow. A second

interesting finding was the relationship of striatal blood flow to the percentage of neuropsychological tests showing impairment for the HIV-positive patients. Previous neuroimaging studies have suggested that the identification of blood flow deficits is difficult in HIV-positive cocaine abusers, because both conditions can be associated with patchy cortical blood flow deficits (Holman et al. 1991). However, in the early stages of HIV infection of the central nervous system (CNS), the basal ganglia and striatum frequently show metabolic hyperactivity rather than the blood flow deficits that are observed with chronic cocaine abuse. This association between increased striatal blood flow and greater levels of neuropsychological impairment was observed in the Woods study (Woods et al. 1991) (R=0.55). Thus, cocaine-abusing methadone patients who were HIV negative shared a strong negative correlation between striatal blood flow and neuropsycho-logical impairment, while those who were HIV positive showed a strong positive correlation between striatal bloodflow and neuropsychological impairment. This finding is of particular importance in differential diag-nosis during the early stages of HIV infection among IV cocaine users, since brain infection with the AIDS virus is an indication for initiation of chemotherapies such as AZT.

SPECT RECEPTOR STUDIES AND AFFECTIVE DISTURBANCES

Postsynaptic DA Receptors

While cerebral blood flow deficits in cocaine abusers appear to be associated with cognitive dysfunction, the underlying neuropathology for affective disturbances may reside in receptor changes induced by chronic cocaine. Cocaine binds to the DA transporter and blocks reuptake of DA back into the presynaptic dopaminergic neuron, leading to an accumu-lation of DA in the synapse. This accumulation of DA in the synapse can have opposite effects on the pre- and postsynaptic neurons. The post-synaptic neuron's DA receptors may be downregulated from chronic stimulation. The animal studies on this issue have not clearly demon-strated downregulation of dopamine type 2 (D2) receptors, but have consistently found downregulation of dopamine D1 receptors (Alburges et al. 1993). In studies using a carbon-11 labeled D2 antagonist in humans, Volkow and colleagues (1990) demonstrated a reduction in D2 receptors during acute abstinence among chronic cocaine abusers. Other human studies by Childress (1995) used SPECT imaging with the ligand iodo-benzamide (IBZM) to examine the D2 and possibly D3 receptor during sustained abstinence among cocaine abusers. While these

studies have not involved comparisons with matched normal controls, the DA receptors do not appear to be downregulated in these patients. No SPECT studies have examined DA receptors during acute abstinence from cocaine. However, in primate studies the authors have demon-strated that IBZM has good specific affinity for the D2 receptor in the caudate and that it is readily displaceable by haloperidol, a potent D2 antagonist (Innis et al. 1992). This ligand, IBZM, can also be displaced by the endogenous DA that is released by amphetamine administration. This amphetamine effect can be blocked by the administration of reser-pine, which depletes endogenous DA (Innis et al. 1992). Human studies with a D2 ligand using SPECT in cocaine abusers are being started.

DA Transporters

The authors' most recent work with SPECT involves imaging the DA transporter using [123I]-methyl-3ß-(4-iodophenyl) trophane-2ß-carboxylate (iodinated ß-CIT), a cocaine analog in which the ester linkage has been removed between the tropane and benzene rings. Binding to dopaminergic cells in the striatum appears highly specific and can be displaced by other cocaine analogs or GBR 12909, another DA transporter ligand. Binding of CIT in the striatum is not displaced by citalopram, a serotonin reuptake inhibitor. In normal human subjects, CIT takes approximately 24 hours to reach maximal binding in the striatum and remains stable there for about 1day.

In human studies, the authors have examined regulation of the DA transporter and the percentage of transporter occupancy using cocaine displacement. Transporter regulation was examined by comparing cocaine addicts to healthy controls and by comparing binding after acute versus sustained drug abstinence within the same subjects scanned at 1, 14, and 28 days after stopping cocaine. The rationale for these studies are that although preclinical research demonstrates conflicting results about the effects of chronic cocaine administration on the DA transporter, post-mortem studies in humans have shown an increase of 50 to 100percent among cocaine abusers dying of overdose (Little et al. 1993; Staley et al. 1992, 1993).

The subjects in the present study comparing cocaine abusers to normals included five male and three female cocaine-dependent patients with a mean age of 32 years. They smoked an average of 6 g per week of cocaine and had been abstinent for 30 to 96 hours prior to the first imaging session. They were compared to age- and gender-matched controls. Using V3", which is defined as the ratio of specific

striatal binding over nonspecific occipital binding, the authors found that the cocaine-dependent patients had much greater amounts of CIT binding, as shown in figure 2. In comparing specific patients with their matched controls, in only one case was the control subject slightly higher in CIT binding. In the most dramatic difference, a cocaine-dependent patient had a V3" of 15.0 while a matched healthy control had a V3" of 10.8, indicating a 40percent increase in DA transporters.

When the authors compared acute versus sustained abstinence among six patients examined serially over 2 to 4 weeks after stopping cocaine abuse, a reduction in CIT binding was found. In every subject, there was a reduc-tion in binding from initial imaging until the followup. Upon initial imaging the average V3" was 11.6; this measurement decreased about 20percent over the 2- to 4-week followup. This drop was slightly less than the 30 percent difference between the healthy controls and the cocaine abusers at the initial imaging. Thus, normalization in the number of reuptake carriers appears to take 2 to 4 weeks, which corresponds very well with the time course of depressive symptomatology following dis-continuation of cocaine (Satel et al. 1991; Weddington et al. 1990).

In studies with CIT, the authors have determined whether euphorigenic dosages of cocaine occupy measurable levels of DA transporters in human cocaine abusers. In this preliminary study, the authors adminis-tered cocaine to five cocaine abusers who smoked an average of 6g of cocaine per week. The IV cocaine administration studies used dosages of-20 and 40 mg while monitoring both physiological and subjective responses. In these studies, specific displacement of CIT was only about 25percent with a cumulative cocaine dose of 60 mg. This dosage of cocaine produced substantial euphoria and physiological effects on heart rate and blood pressure. An unusual characteristic of these studies was that maximal displacement of CIT did not occur for about 40 to 60-minutes after cocaine administration. Since the subjective effects of cocaine peaked within a few seconds and subsided within 15 minutes, this temporal dissociation suggested an underestimate of the percentage of reuptake carrier occupied by cocaine in order to produce euphoria. In order to produce the 40 to 100 percent upregulation of reuptake carriers as well as the substantial downregulation of postsynaptic DA receptors, a much greater percentage in occupancy of reuptake carriers would be expected during chronic and repeated cocaine usage. Since these studies involved only two relatively modest dosages of cocaine, it is possible that repeated higher dosages of cocaine over more sustained periods of time might occupy a substantially greater proportion of reuptake carrier.

FIGURE 2. *CIT binding in healthy control and cocaine addict.*

Affective Disturbances

The substantial neuroreceptor and transporter abnormalities that appear to persist during cocaine abstinence may have their clinical correlates in affective disturbance. A study by Weddington and colleagues (1990) found that over the course of a 30-day inpatient stay, Beck Depression Inventory scores declined from a mean of 9 to 2. Satel and colleagues (1991) found that depression scores declined from a mean of 15 to about 8 after 10 days, with a secondary peak at about day 14 when the scores rose to 12. During this period, craving for cocaine went from a high of 80 out of 100 down to a low of 5 by day 30 (Weddington et al. 1990). In both of these studies, the majority of the decline occurred during the first 2 weeks of hospitalization and included substantial reductions in anxiety, depression, hostility, fatigue, and general physical symptoms. One symp-tom that appeared to show greater persistence among inpatient cocaine abusers was difficulty falling asleep, which continued for about 3weeks. In the Satel study (Satel et al. 1991), serial blood samples were also obtained three times weekly for prolactin, growth hormone, and homo-vanillic acid, a DA metabolite. None of these hormonal measures differed from those of normal subjects. Both studies concluded that symptoms after inpatient cessation of

uncomplicated cocaine addiction were relatively mild and decreased linearly over the first month.

Both of these inpatient studies have several limitations. First, these symptoms of cocaine abstinence may be somewhat more persistent in an outpatient setting where cues associated with cocaine use recur and there-by increase both anxiety and cocaine craving (Gawin and Kleber 1986). Second, both studies involved relatively small numbers of subjects, with 12 cocaine-dependent patients in the Weddington study and 22 patients inthe Satel study. Third, further studies need to examine correlations between the amount of receptor dysregulation and subjective dysphoria and cocaine craving. Since the Satel study found no hormonal abnor-malities in these subjects, it is possible that patients with documented neurobiological abnormalities on SPECT or other scanning will show more severe symptoms during abstinence. Future studies can examine these correlates as researchers accumulate data from more brain-scanned subjects.

Future Prospects for SPECT

Future receptor imaging work with cocaine abusers might focus on sensitization and noradrenergic receptors as well as on tolerance from chronic cocaine abuse. Recent studies by the authors' group suggest significant dysregulation of noradrenergic systems during cessation of cocaine use (McDougle et al. 1994). During an inpatient stay, 14 subjects were given 2 mg/kg of intranasal cocaine three times daily for a 3-day period. One or 2 days after the last dose of cocaine, subjects received a double-blind, randomized IV infusion of yohimbine at 0.4-mg/kg. These cocaine treated subjects had significantly greater placebo corrected methoxyhydroxyphenylglycol (MHPG) response to yohimbine and rated themselves as significantly more nervous following yohimbine than following placebo. When these challenges were repeated 2 weeks later, cocaine-treated subjects reported significantly less nervousness. In addition, at the initial yohimbine challenge, 71 percent of the subjects developed a panic attack, whereas none of them developed a panic attack during the challenge session 2 weeks later. These results suggest an underlying dysregulation in noradrenergic function and a vulnerability to panic/anxiety during early cocaine cessation in cocaine dependence. Thus, future studies using SPECT imaging might examine whether noradrenergic receptors are upregulated by chronic cocaine use. Because this upregu-lation may occur on presynaptic receptors, which have a relatively lower density than postsynaptic receptors, these changes induced by cocaine may be difficult to detect with SPECT imaging.

However, the general concept of receptor upregulation as a possible correlate of the sensitization associated with cocaine holds promise for the future of SPECT receptor imaging.

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AUTHORS

Thomas R. Kosten, M.D.
Professor

Robert Malison, M.D.
Assistant Professor

Elizabeth Wallace, M.D.
Assistant Professor

Division of Substance Abuse
Department of Psychiatry
Yale University School of Medicine
27 Sylvan Avenue
New Haven, CT 06519

Cocaine Withdrawal Alters Regulatory Elements of Dopamine Neurons

Nancy S. Pilotte and Lawrence G. Sharpe

Cocaine is an extremely reinforcing drug that is readily self-administered by both animals and humans. Although cocaine affects many transmitter systems in the brain, the best characterized are the dopaminergic neurons that originate in the midbrain and innervate areas in the forebrain. These include the nigrostriatal, mesolimbic, and mesocortical dopaminergic systems. Adequate characterization of these systems includes not only cocaine's acute effects and the effects of long-term exposure but also the functional, biochemical, and neuronal changes after its long-term withdrawal. The reinforcing effects of cocaine have been linked to its ability to block dopamine uptake (Kuhar et al. 1991; Ritz et al. 1987), particularly at the nucleus accumbens (Koob 1992; Woolverton and Johnson 1992). The focus of the work described below is the changes that emerge in the regulatory elements of dopamine neurons after repeated cocaine administration and its withdrawal.

One immediate consequence of the administration of cocaine is an increase in the extracellular concentration of dopamine in areas innervated by dopaminergic neurons (Hurd et al. 1989; Weiss et al. 1992a, 1992b). Cocaine prolongs the action of dopamine in the synapse by blocking its presynaptic uptake, the normal mechanism that terminates dopaminergic activity (Harris and Baldessarini 1973). In the mesolimbic system, repeated daily administration of cocaine apparently reduces the ability of the dopamine neurons to respond to changes in its micro-environment. This functional impairment is marked by a subsensitivity of dopamine autoreceptors that lasts for several days (Henry et al. 1989) and a corresponding increase in the spontaneous activity of dopamine neurons (Ackerman and White 1992). Together, these alterations in the neuronal regulatory elements lead to increased basal dopamine concen-trations in the nucleus accumbens within the hours after the last exposure to cocaine in animals that self-administer cocaine (Weiss et al. 1992a). However, in cocaine-acclimated rats, the extracellular concentrations of dopamine fall below the basal levels measured in cocaine-naive rats a few days after cocaine is withdrawn (Imperato et al. 1992; Parsons et al. 1991; Rossetti et al. 1992).

The authors have examined the effects of repeated cocaine administration and, importantly, its withdrawal on another regulatory element, the dopamine transporter, using rats given multiple intermittent intravenous (IV) injections of cocaine that are timed to mimic the patterns of self-injection reported previously (Porrino et al. 1988). Cocaine, at a dose of 1 milligram per kilogram (mg/kg) given over 5 seconds, was infused into a catheterized jugular vein every 12 minutes for 2 hours each day, resulting in 10 daily injections of cocaine totaling 10 mg/kg/day. The administration of cocaine in this way coupled with an appropriate withdrawal period reduced the binding of [3H]mazindol (Sharpe et al. 1991) or [3H]WIN 35,428 (Pilotte et al. 1994) to the dopamine transporter in the nucleus accumbens. Under this regimen, apparent binding to the dopamine transporter is within the range seen in saline-treated controls from 1 to 6 days after the last exposure to cocaine. However, following longer periods of withdrawal ranging from 10 to 60 days, binding to this regulatory element is significantly and persistently reduced (figure 1). It is especially interesting that a similar reduction does not occur in the caudate-putamen, a major dopaminergic projection field, but instead is limited to the nucleus accumbens, an area associated with the rewarding effects of abused substances. Similar reductions in the nucleus accum-bens of the binding of ligands selective for the dopamine transporter also have been reported after 2 weeks of withdrawal in animals that self-administered cocaine (Wilson et al. 1994). Additionally, the reduction in transporter occurs in the medial-most or shell division of the nucleus accumbens (Zahm 1992; Zahm and Heimer 1993), and does not occur in the core region (Pilotte et al., in press).

These long-term changes in transporter binding reflect a reduction in the number of dopamine transporter sites rather than a change in binding affinity (Pilotte et al. 1994). They reflect an apparent decrease in the expression of messenger ribonucleic acid (mRNA) for the dopamine transporter that occurs selectively in neurons that project from the medial aspects of the ventral tegmental area to the nucleus accumbens (Cerruti et al. 1994). This decrease in the mRNA can be seen as early as 10 days after the last exposure to cocaine, and does not occur in neurons originating in the substantia nigra.

The pattern of cocaine administration also seems to be a critical factor for determining whether the long-term reduction in transporter binding occurs upon withdrawal of the drug. The pattern of cocaine admini-stration that the authors employ closely resembles the behavioral pattern of rats that self-administer the same unit dose of cocaine in the

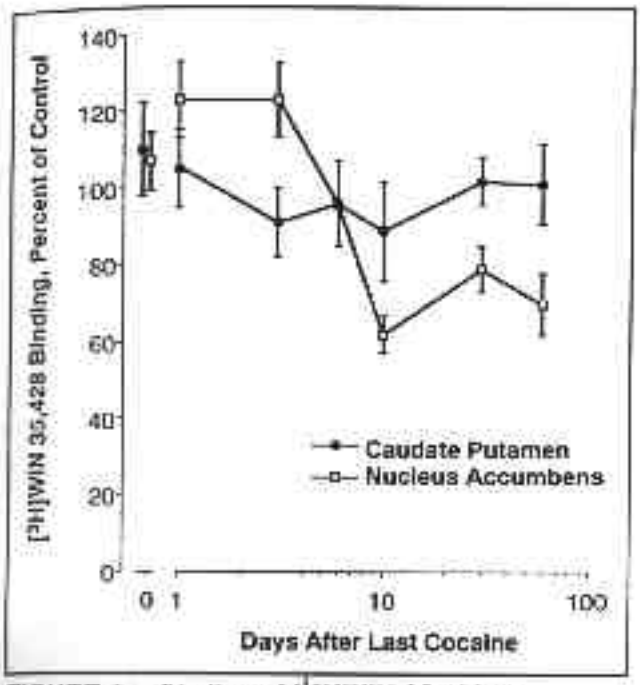

FIGURE 1. *Binding of [³H]WIN 35,428 to dopamine transporters in the nucleus accumbens and to the caudate putamen of rats at different times after the last infusion of cocaine or saline. There was a significant effect of withdrawal on binding in the nucleus accumbens on days 10, 20, and 60. Five to 10 cocaine-treated rats and an equal number of saline-infused rats were used at each time point.*

same time period. Actively self-administered cocaine (Wilson et al. 1994) and passively administered, experimenter-controlled infusions of cocaine (Pilotte et al. 1994; Sharpe et al. 1991) produce similar reduc-tions in the dopamine transporter in the nucleus accumbens after 10 to 14days of withdrawal. Interestingly, 10 days of intraperitoneal (IP) administration of cocaine (doses of 15 or 30 mg/kg given at the begin-ning and end of a 2-hour period) that cumulatively total 3 to 6 times the total daily dose of cocaine given IV (10 x 1 mg/kg) does not reduce binding to the dopamine transporter (figure 2) (Pilotte, Sharpe, Kuhar,

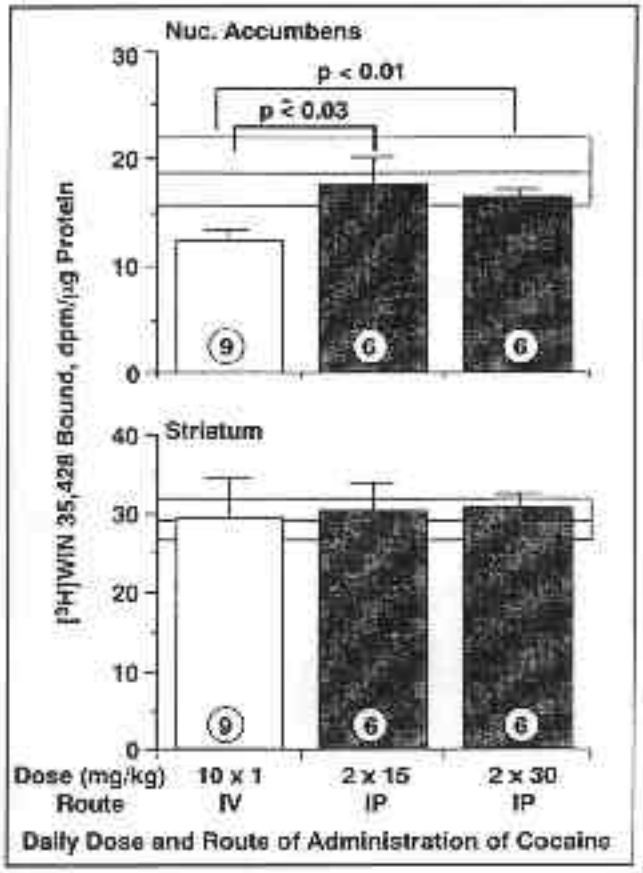

FIGURE 2. *Dopamine transporters in the nucleus accumbens and the caudate-putamen 10 days after withdrawal of IV or IP cocaine. Numbers at the base of each column refer to the numbers of cocaine-treated rats. The clear horizontal bars refer to the mean dpm (and SEM) of saline-treated rats.*

and Cone, unpublished observations). Accordingly, the pattern of repeated cocaine delivery achieved by this method of passively administered multiple infusions of cocaine may have unique properties that contribute to the regulation of the dopamine neuron. It seems possible that the pattern of delivery in rats self-administering cocaine in this manner is also a signif-icant determinant of the rewarding properties of cocaine.

Withdrawal of repeated, intermittently administered cocaine leads to long-lasting reductions in dopamine transporters within the nucleus accumbens

that may be consistent with neuronal dysfunction. However, the authors do not know if these changes have functional consequences for the regulation of the neuron. Coupled with the other transient neuronal changes, it seems that the decrease in the number of dopamine transporters in the nucleus accumbens may be associated with a global reduction in dopaminergic neural activity as measured by basal dopamine efflux (Imperato et al. 1992; Robertson et al. 1991; Rossetti et al. 1992) and subsequent response to challenges with cocaine (Weiss et al. 1992b). However, the persistence of these signs beyond 60 days is not known.

Dopaminergic neurons that originate in the ventral tegmental area and project to the prefrontal and cingulate cortices also have a role in cocaine self-administration (Goeders and Smith 1983; Goeders et al. 1986). These dopaminergic neurons are noteworthy because large vesicles containing a peptide, neurotensin, are localized within them (Studler et al. 1988). Graded electrical stimulation of these neurons can release preferentially dopamine, neurotensin, or both (Bean et al. 1989a, 1989b). Dopamine and agents that affect dopamine, such as cocaine, appear to regulate neuronal neurotensin (Hanson et al. 1989; Merchant et al. 1988). Possible interactions between neurotensin and cocaine are suggested by the observation that pretreatment with a neurotensin antagonist retards the development of sensitization to the repeated injections of cocaine (Horger et al. 1994). Reports of this type led the authors to hypothesize that cocaine administration and withdrawal might modulate neurotensin in mesocorticolimbic dopaminergic neurons.

The authors gave cocaine to rats during a single 10-day infusion regimen as previously described and measured the binding of [3H]neurotensin to receptors in terminal areas of these neurons immediately after or 10 days after the last exposure to cocaine. Withdrawal of cocaine decreased the binding of neurotensin in the ventral tegmental area immediately after cocaine exposure, and binding at the cell bodies did not recover even after 10 days of withdrawal (Pilotte et al. 1991). In contrast, binding at the terminal fields of the mesocorticolimbic neurons was twice that of saline-treated rats right after the last cocaine administration and three times greater than that of the controls 10 days after the last exposure to cocaine (Pilotte et al. 1991). This observation suggested that the content of neurotensin in these neurons might be decreased after cocaine withdrawal. However, assay of the neurotensin content of these tissues revealed that there was more neurotensin in rats withdrawn from cocaine

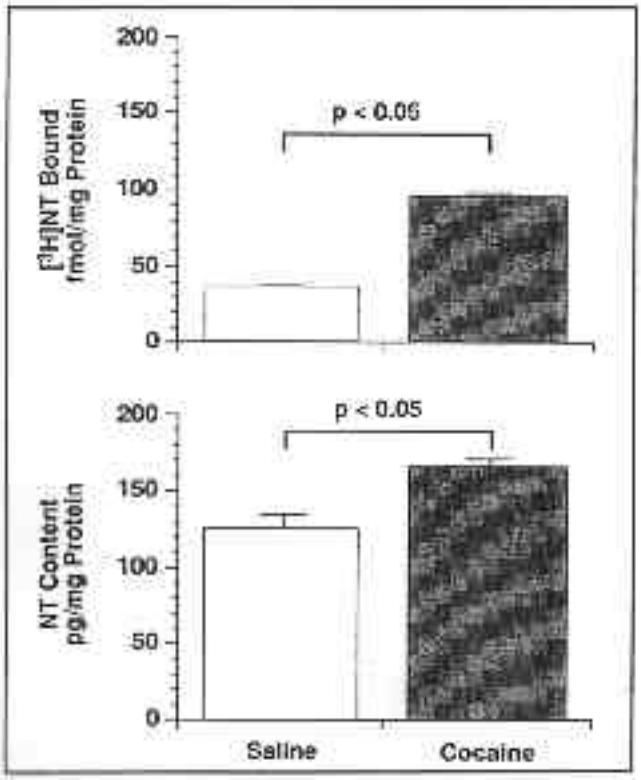

FIGURE 3. *Neurotensin binding and content increased 10 days after cocaine withdrawal. Ten animals were used in each group.*

than in rats withdrawn from saline (figure 3). This finding of an apparently disrupted regulatory relationship between an agonist and its receptor was unexpected, and suggests that there may be a deficit in the ability of these neurons to release their contents after withdrawal of cocaine. Additionally, the pattern of neurotensin binding after withdrawal of cocaine (Pilotte et al. 1991) is strikingly similar to that of rats bearing 6-hydroxydopamine lesions of the ventral tegmental area (Herve et al. 1986). Together, these observations suggest an intimate association of neurotensin and dopamine within tightly delineated neural circuits such that neurotensin and dopamine can each modulate the activity of the other. Thus, altered function in one component may be indicative of abnormal function in the other.

It is important to note that no overt neurotoxicity, pathology, or cellular damage has been reported in the nucleus accumbers of animals given cocaine. However, the findings described above seem to suggest that functional changes may occur. The nature of this change is an increase in dopaminergic activity during chronic intake followed by a reduction in activity several days after the withdrawal of cocaine. This interpretation is consistent with the changes in regulatory elements of dopamine neurons noted previously. Such a reduction may be part of a physiological basis for cocaine dependence, craving, and relapse to additional drug usage and its concomitant psychological states (Gawin, this volume; Gawin and Ellinwood 1988; Gawin and Kleber 1986).

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AUTHORS

Nancy S. Pilotte, Ph.D.
Staff Fellow
Neuroscience Branch

Lawrence G. Sharpe, Ph.D.
Research Psychologist
Molecular Biology Branch

Addiction Research Center
National Institute on Drug Abuse
P.O. Box 5180
Baltimore, MD 21224

EEG and Evoked Potentials Alterations in Cocaine-Dependent Individuals

Ronald I. Herning and Deborah E. King

INTRODUCTION

After two decades of epidemic cocaine use and extensive animal research, what is known about the effects of prolonged exposure to cocaine on the central nervous system (CNS) comes from human findings. Reports of neurological and cerebrovascular infarcts attributed to cocaine abuse and studies investigating CNS function of abstinent cocaine-dependent patients provide important insights into prolonged effects of cocaine on the human brain. The neurological and cerebrovascular infarcts investi-gated include strokes (Sloan and Mattioni 1992), seizures (Holand et al. 1992), transient ischemic attacks (Spivey and Euerle 1990), and headaches (Dhopesh et al. 1990). The studies of abstinent cocaine-dependent patients used neuropsychological evaluations, electroencephalogram (EEG), single photon emission computed tomography (SPECT), and positron emission tomography (PET) methodologies. The neurological infarcts appear to be at the one end of a continuum with subtle, but not trivial, CNS alterations at the other. These alterations, whether residual or permanent, may complicate treatment for cocaine dependence. The importance of treating these alterations needs to be addressed.

This chapter reviews EEG and event-related potential (ERP) data from cocaine-dependent subjects who are not seeking treatment. This research is ongoing at the National Institute on Drug Abuse (NIDA) Intramural Research Program (IRP). The results are compared to other published studies. Some of the data are in the process of being published elsewhere, and some of the data are very preliminary.

There are some problems in studying CNS alterations in abstinent cocaine abusers. First, cocaine use is often linked to other substance abuse, comorbidity with other psychiatric disorders is often present, and it is possible that the deficits observed predated cocaine abuse. Although these difficulties exist, it is possible to remove the confounds of polysubstance abuse and comorbidity statistically or by the use of appropriate experimental and control groups. If the

deficits predated substance abuse, they may be similar to those observed in populations at risk for substance abuse. If the deficits are different from those seen in at-risk populations, they may be due to prolonged drug abuse. Certainly, prospective research is needed to clarify this issue.

The EEG and ERP changes examined here do not parallel the dysphoric mood effects observed in abstinence. Dysphoric mood symptoms occur in abstinent cocaine-dependent patients and dissipate after 1 to 2 weeks (Satel et al. 1991; Weddington et al. 1990). The CNS alterations appear to persist beyond the dysphoric mood state and may be linked to relapse. The cocaine craving, which also persists, may be related to these CNS alterations.

BACKGROUND: PET, SPECT, AND EEG STUDIES

Changes in the cerebral glucose metabolism of cocaine abusers have been observed, and are reviewed elsewhere (London et al. and Volkow et al., this volume). SPECT studies of blood flow show areas of reduced cortical blood flow in cocaine abusers (Holman et al. 1991; Mena et al. 1990; Tumeh et al. 1990; Volkow et al. 1988; Weber et al. 1990). In these studies the sample size was often small, and the cocaine abuser may not have meet the criteria for cocaine dependence. The subjects also abused drugs other than cocaine. However, these studies do suggest the possibility of cortical perfusion deficits in cocaine abusers; further research with larger sample sizes and more clearly defined populations of cocaine-dependent patients are needed.

EEG studies in cocaine-dependent individuals appear to paint an inconsistent picture. In terms of the resting EEG, Alper and colleagues (1990) found increased EEG alpha and to a lesser extent increased EEG beta in cocaine abusers, while Bauer (1994) found no baseline differences in EEG between cocaine-dependent subjects and control subjects. Roemer and colleagues (1994) reported decreases in EEG delta activity. The present authors found increased EEG beta in cocaine-dependent subjects relative to established norms, and the percentage of EEG beta was corre-lated to self-reported cocaine drug history measures (Herning et al., under review). Thus, the four groups appear to have different findings.

EEG hyperactivity to modulated sensory stimuli was reported by Bauer (1993). The EEG studies suffer from the same problems as the

PET and SPECT studies. That is, the subjects are polysubstance abusers and the sample sizes are also small, but not as small as in PET and SPECT studies. The differences in EEG findings observed in cocaine-dependent subjects can possibly be explained in part by differences in EEG recor-ding and analysis procedures, but they may also be due to the heterogeneity of cocaine-dependent patients.

The neuropsychological investigations of cocaine-dependent patients suggest a possible underlying deficit in information processing (Herning et al. 1990; O'Malley et al. 1992; Roberts and Bauer 1993). Thus, the authors examined the ERPs of cocaine-dependent patients and compared them to control subjects. Bauer (this volume) also used the ERP metho-dology to study brain processing deficits in cocaine-dependent patients.

No attempt has been made in previous EEG studies to relate the magni-tude of the observed CNS alterations to the specific amount of cocaine used or the duration of cocaine abuse. The authors studied the EEG and cognitive ERPs of cocaine-dependent individuals, not currently depen-dent on other illicit drugs or alcohol, during monitored abstinence on a closed research ward. The hospitalized cocaine-dependent patients were tested at about 8 days of abstinence. The subjects' EEG and ERP findings were compared with that of control subjects or normative data and corre-lated with their self-reported drug histories.

METHOD

Subjects

The subjects (N = 37) were cocaine-dependent by "Diagnostic and Statistical Manual of Mental Disorders," 3d ed. rev. (DSM-III-R) criteria and were studied after about 9 days of monitored abstinence. An addi-tional sample of 31 subjects who abused cocaine but did not have a struc-tured psychiatric interview were included in the resting EEG tests. The cocaine-dependent subjects resided on a closed residential research unit. Abstinence was monitored by testing randomly obtained urine samples. The control subjects (N = 17) who had no substance use disorders except nicotine dependence and no other psychiatric disorders using DSM-III-R criteria were tested as outpatients. The nondrug-using status of the out-patient control subjects was verified by urine toxicology. The drug his-tory was obtained using the Addiction Severity Index (ASI). The ASI drug

history for cocaine-using subjects is presented in tables 1 to 3. All subjects were seronegative for human immunodeficiency virus (HIV).

EEG Recording Procedures

The EEG was collected during a resting recording session with the eyes closed. The EEG was recorded from the following International 10/20 scalp sites: F3, C3, P3, O1, F4, C4, P4, and O2. The ERPs were recorded from the following International 10/20 scalp sites: F3, Fz, P3, F4, Cz, P4, and Pz. The EEG recording was monopolar with the reference ipsilateral site at A1 or A2. Silver-silver chloride electrodes were used at all loca-tions. The EEG was amplified using a signal conditioning unit with 1 to 50 hertz (Hz) half-amplitude bandpass. The output from the amplifier was recorded on a personal computer with an analog-to-digital convertor. The EEG was displayed on the computer monitor as it was collected and the raw EEG data were saved on the computer disk. The EEG during the ERP tasks was amplified with 0.1 Hz to 100 Hz half-amplitude bandpass amplifiers and 60 Hz notch filter. Monitoring of EEG artifact was per-formed during both on-line collection and off-line processing.

During the recording of the EEG and ERPs, subjects sat in a reclining chair located in a sound-attenuated electronically shielded chamber. A minimum of 3 minutes of EEG was recorded during the eyes-closed

TABLE 1. ASI drug history: Number of days used in the last 30 days.

Drug	Substance abusers Mean and SD		Cocaine dependent Mean and SD	
Cocaine	5.7	6.6	20.2	7.6
Alcohol	8.7	7.3	9.6	8.1
Heroin	3.9	7.1	2.6	3.8
Marijuana	5.6	7.7	1.7	3.8
Amphetamines	0.6	2.9	0.1	0.2
Barbiturates	0.1	0.4	0.3	1.8
Benzodiazapines	0.3	1.9	0.3	1.2

TABLE 2. ASI drug history: Drug of use (number of months).

Drug	Substance abusers Mean and SD		Cocaine dependent Mean and SD	
Cocaine	87.0	75.8	93.0	75.8
Alcohol	168.9	89.9	121.9	102.2
Heroin	90.7	158.0	52.1	90.6
Marijuana	143.8	106.4	93.1	88.0
Amphetamines	34.4	78.1	12.0	43.8
Barbiturates	32.8	71.1	12.4	47.2
Benzodiazapines	21.8	61.8	13.2	38.4

TABLE 3. ASI drug history: Cocaine use.

Cocaine Measure	Substance abusers Mean and SD		Cocaine dependent Mean and SD	
g/week	0.61	0.99	3.66	5.40
g/month	2.38	3.91	12.40	14.36
Day/30 days	5.73	6.64	20.30	7.57
Months used	87.40	75.82	92.96	76.81

condition. During these 3-minute recordings, the percentage of EEG activity was determined for delta (1.3-3.5 Hz), theta (3.6-7.5 Hz), alpha (7.6-13.5 Hz), and beta (13.6-50.0 Hz) EEG bands using the clinical zero-cross method.

The EEG for the ERP collection was recorded on a personal computer with an analog-to-digital convertor. Each channel was sampled at 5.0-millisecond (ms) intervals using software developed by NIDA's IRP for this purpose. The sampling interval began 150 ms before stimulus onset and ended 850 ms after onset. An average ERP was calculated separately for the target and nontarget stimuli. The amplitude and latency for N1, P2, and P3 were measured for the target and nontarget ERPs.

ERP Tasks

During the auditory rare event monitoring (AREM) task, the subject was asked to count the number of rare tones in a series of rare and frequent tones. At the end of the series the researcher obtained the

subject's count of the rare tones. The tones were presented at the rate of one every 2seconds using the Neurological Workload Test Battery (NWTP). The task lasted about 4 minutes. Rare tone frequency was 1000 Hz, and the frequent tone frequency was 2000 Hz. Twenty percent of the tones were of the rare type. Both tones were 70 decibels (dB) standard pressure level (SPL) and 100 ms long. The tones were presented to the subject through a headset.

For the continuous performance task (CPT) and Sternberg Memory Task, event-related responses were elicited visually using letters presented on aTV monitor by the NWTB system. For the CPT task, the subject monitored a series of letters displayed on the screen, one at a time, and was required to press a button with the preferred hand when any letter repeated itself. For the Sternberg Memory Task, three or six letters were shown for 30 seconds and the subject was required to monitor a series of letters. When a letter from the test set appeared, the subject was to press a button with the preferred hand. When any other letter appeared, the subject was required to press another button with the nonpreferred hand. Each task lasted about 5 minutes. The letters subtended 100 of visual angle, were on the screen for 600 ms, and were presented at a rate of one every 2 seconds. The mean luminance of the screen was 40 candela per square meter (cd/m2). The TV monitor was 30 centimeters (cm) from the subject's eyes.

RESULTS

The mean percentage for the EEG beta band for the resting eyes-closed session is shown in table 4. The mean data for cocaine-dependent individuals (Herning et al., under review) and 31 additional substance abusers is compared with 30- and 40-year-old male norms. A description of the sample from which the norms were obtained is included elsewhere (Herning et al., under review). The mean percentages for both the

TABLE 4. Percentage of activity in beta band.

Electrode	30-year-old norms1		40-year-old norms1		Sustance abusers and cocaine-dependent subjects (N = 68)	
	Mean	1 SD	Mean	1 SD	Mean	1 SD
F3	23.0	2.3	23.0	3.0	38.4*	12.9
F4	21.0	2.0	22.0	2.9	37.0*	13.4
C3	22.0	2.3	23.0	2.9	39.0*	12.4
C4	23.0	2.3	24.0	3.0	39.2*	11.7
P3	21.0	2.3	20.0	2.0	34.8*	10.7
P4	22.0	2.3	21.0	2.9	34.2*	11.1
O1	20.0	2.3	20.0	2.9	35.3*	13.1
O2	20.0	2.3	20.0	2.9	32.4*	10.9

KEY: 1 = Commercial norms are from HZI Research Center (see Herning et al. 1994 for demographic information on this sample); * = indicates value is more than 3 SD above norms.

substance abusers and the cocaine-dependent patients were greater than the age-matched norms. The percentage of EEG beta was elevated at all electrode sites.

The authors tested whether the increased percentage of EEG beta was correlated with drug history variables from the ASI. If these increases in EEG beta were indeed due to cocaine use, a strong positive correlation with cocaine drug history measures should be present in the data. Since 13 drug history measures were used, the Bonferroni corrected probability was used to preserve a 0.05 confidence level for each electrode site ($p<-0.05/13$ or 0.0042). Table 5 lists these correlations for the cocaine drug history measures for all the subjects (N = 68). The increase in EEG beta at F3 and F4 was significantly correlated with the number of grams of cocaine these subjects used the week before admission to the research study. Correlations with other cocaine drug history measures approached significance. EEG alpha was correlated with months of cocaine use for

TABLE 5. Correlation between EEG beta and self-reported cocaine use: All subjects (N = 68).

	Electrode							
Self-report measure	F3	C3	P3	O1	F4	C4	P4	O2
Day/30 days	0.25	0.16	0.06	0.02	0.26	0.06	0.08	-0.02
Months of use	-0.13	0.06	0.00	-0.04	-0.06	0.03	0.01	-0.11
g/week	0.46*	0.31	0.07	0.07	0.45*	0.09	0.03	-0.03
g/month	0.30	0.13	-0.05	-0.08	0.28	-0.03	-0.09	-0.11
Age	0.05	0.04	0.12	-0.07	0.07	-0.07	0.10	0.00

KEY: * = $p < 0.05$ (13 drug history measures) = 0.0042.

C4 and P4 electrode sites. However, none of the other substances used by these subjects was correlated with EEG beta.

The grand means waveforms are plotted for the AREM, CPT, and Sternberg tasks for both the cocaine-dependent subjects and control sub-jects in figures 1-4. The cocaine-dependent individuals had longer N1 (group by electrode: $F(2,82) = 9.24$, $p < 0.005$) and P2 (group: $F(1,38)=3.96$, $p < 0.05$) latencies in the AREM task and reduced P2 amplitudes in the CPT (group: $F(1,38) = 11.75$, $p < 0.005$) and Sternberg Memory Tasks (group by electrode interaction: $F(2,84) = 4.95$, $p<0.01$). The cocaine-dependent subjects had reduced P3 amplitudes in all tasks (AREM group by electrode interaction: $F(2,82) = 3.12$, $p < 0.05$; CPT group: $F(1,38)= 24.13$, $p < 0.001$; Sternberg group: $F(1,38) = 3.42$, $p<0.07$). These differences can be observed in the grand averages. The ERP measures that significantly differed between groups were correlated with drug history measures (see table 6). The N1 latency delay in the AREM task was correlated with the number of days alcohol was used in the last 30days, and the P2 latency delay was correlated with self-reports of the number of months of cocaine and alcohol use. The reduction in P3 amplitude was modestly, but not significantly, correlated with self-reported alcohol, marijuana, and opiate use, but not with cocaine use. Perhaps as the sample size in this study increases, these latter correlations will become significant.

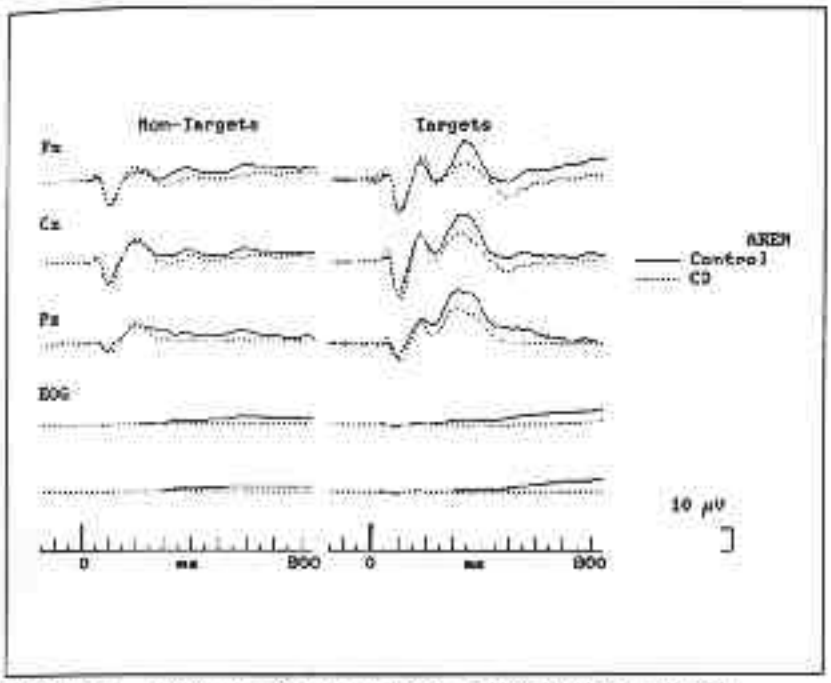

FIGURE 1. *The grand average ERPs are plotted for control subjects (N = 17) and cocaine-dependent subjects (CD)(N = 27) for the AREM task. The left column presents the ERP for the nontargets and the right column presents the ERP for the targets. The N1 is the negative-going component (down) at about 100 ms, the P2 is the positive-going (up) component at about 200 ms, and P3 the postive-going component at about 350 ms. The bottom two waveforms in each column are eye movements (EOG) recorded from above to the side of the left eye and from above the left eye to A$_1$.*

KEY: Fz = frontal scalp position; Cz = central scalp position; Pz = parietal scalp position.

DISCUSSION

The amount of beta activity in the resting EEG was elevated, and the N1, P2, or P3 component of the ERP to task-relevant stimuli was reduced or delayed in this sample of abstinent cocaine abusers. The percentage of

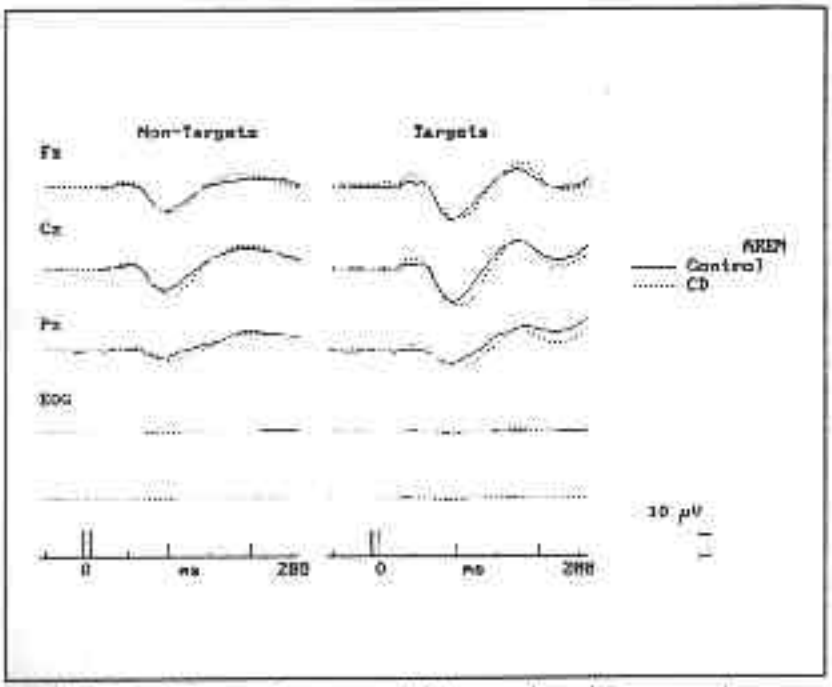

FIGURE 2. *The grand average ERPs are plotted for control subjects (N = 17) and cocaine-dependent subjects (CD)(N = 27) for the AREM task. The first 200 ms after the onset of the stimuli is shown so that the latency delays in N1 and P2 can be observed. The left column presents the ERP for the nontargets, and the right column presents the ERP for the targets. The N1 is the negative-going component (down) at about 100 ms, and the P2 is the positive-going (up) component at about 200 ms. The bottom two waveforms in each column are eye movements (EOG) recorded from above to the side of the left eye and from above the left eye to A$_1$.*

KEY: Fz = frontal scalp position; Cz = central scalp position; Pz = parietal scalp position.

beta in the EEG of the sample exceeded age-matched norms. The N1 and P2 components, as well as the P3 component of the ERPs elicited in several cognitive tasks, were altered when compared to a sample of control subjects. The percentage of EEG beta and P2 latency was correlated with the self-reported amount of cocaine use. The amount of cocaine used in the last week before admission was correlated with EEG

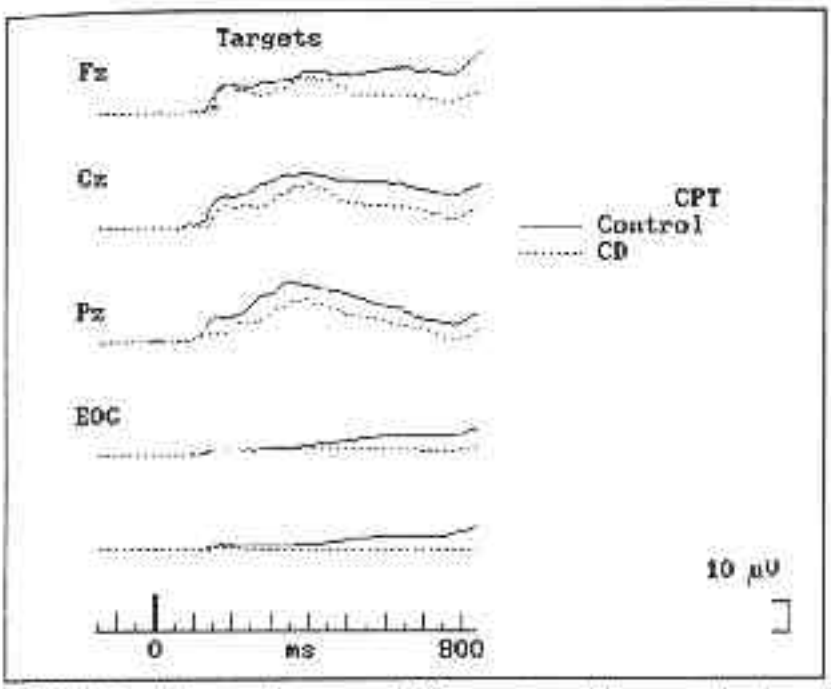

FIGURE 3. *The grand average ERPs are plotted for control subjects (N = 17) and cocaine-dependent subjects (CD) (N = 27) for the CPT. Only the targets are shown. The P2 is the positive-going (up) component at about 200 ms, and P3 is the positive-going component at about 350 ms. The bottom two waveforms in each column are eye movements (EOG) recorded from above to the side of the left eye and from above the left eye to A$_1$.*

KEY: Fz = frontal scalp position; Cz = central scalp position; Pz = parietal scalp position

activity in the beta band at both frontal electrode sites. P2 latency was correlated with the number of months of cocaine and alcohol use. P3 amplitude was only weakly correlated with self-reported drug history measures.

The EEG findings agree in part with those of Alper and colleagues (1990) and Roemer and colleagues (1994), but not with Bauer (1993, 1994, this volume). In the Alper study, the EEG of the cocaine-dependent indi-viduals was also compared to age-matched norms. Those researchers

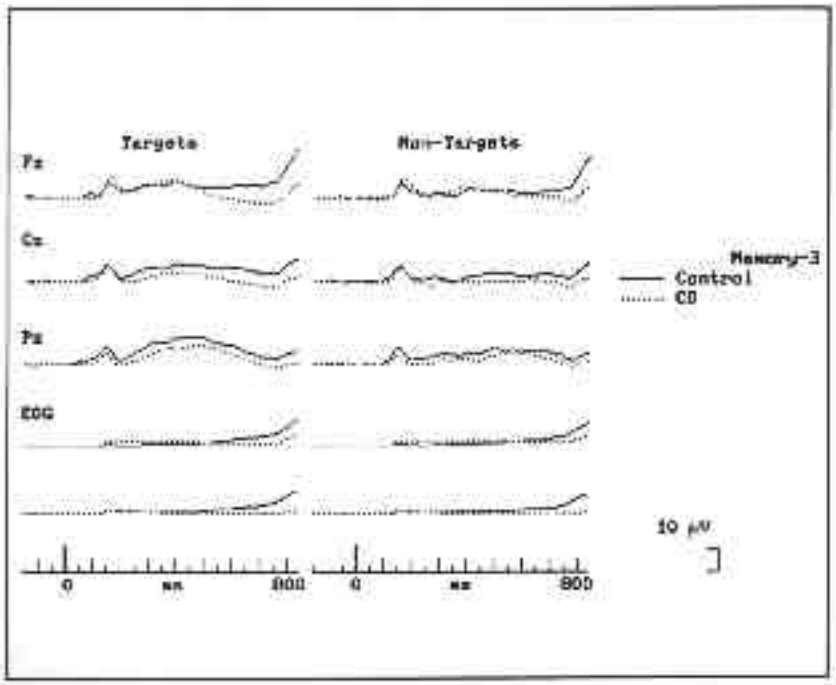

FIGURE 4. *The grand average ERPs are plotted for control subjects (N = 17) and cocaine-dependent subjects (CD) (N = 27) for the Sternberg Memory Task with a 3-letter set size. The left column presents the ERP for the targets, and the right column presents the ERP for the nontargets. The P2 is the positive-going (up) component at about 200 ms, and P3 is the postive-going component at about 350 ms. The bottom two waveforms in each column are eye movements (EOG) recorded from above to the side of the left eye and from above the left eye to A$_1$*

KEY: Pz = frontal scalp position; Cz = central scalp position; Pz = parietal scalp position.

found elevated levels of beta at frontal electrode sites and increased EEG alpha over the cortex in seven cocaine-dependent crack users. The time of recording relative to the self-reported last use of cocaine varied considerably. Roemer reported reduced EEG delta and theta. The authors found increased EEG beta with reduced delta and theta, but the self-reported use measures were correlated with the increase in beta and not

TABLE 6. Correlation between ERP measures and self-reported drug use: Cocaine-dependent subjects (N = 27).

	Task and ERP measure						
Self-report measure	Oddball			Paired CPT		Sternberg Memory	
	N1L	P2L	P3A	P2A	P3A	P2A	P3A
Cocaine							
Days/30 days	0.20	0.24	-0.11	0.01	0.07	-0.38	-0.13
Months of use	-0.10	0.57*	0.13	-0.05	0.31	0.32	0.08
g/week	0.32	-0.12	-0.08	-0.18	-0.26	-0.22	-0.27
g/month	0.43	-0.15	0.04	-0.11	-0.15	-0.23	-0.19
Alcohol							
Days/30 days	0.62*	-0.25	-0.24	0.01	-0.36	-0.25	-0.38
Months of use	-0.18	0.53*	0.15	0.11	0.35	-0.10	0.04
Marijuana							
Days/30 days	0.11	0.04	0.20	-0.06	0.14	-0.22	0.42
Months of use	-0.25	0.47	0.22	-0.12	0.42	0.35	0.12
Heroin	0.04	0.31	-0.39	-0.25	-0.08	-0.34	-0.37
Days/30 days	0.04	0.31	-0.39	-0.25	-0.08	-0.34	-0.37
Months of use	-0.10	0.41	-0.31	-0.12	-0.07	-0.15	-0.16

KEY: * = $p < 0.005$ or 0.05 for 10 drug history measures; N1L=-N1latency; P2L = P2 latency; P2A = P2 amplitude; P3A=P3-amplitude.

with the decreases in delta and theta (Herning et al., under review). Bauer reported no difference in the resting EEG activity in a sample of cocaine-dependent patients when they were compared to control subjects. Bauer reported EEG hyperactivity to modulated sine, but not square, wave sensory stimuli in cocaine-dependent patients. In the present sample of cocaine-dependent individuals, the authors found higher levels of beta activity in the resting EEG after about 10 days of monitored abstinence on a closed research ward.

Several factors may have contributed to the differences in results. First, a major difference among the studies was the frequency range of the EEG beta band. Alper used 12.5 to 25.0 Hz beta band and Bauer used 12.5 to 30.0 Hz band, while the authors used 13.6 to 50.0 Hz. Roemer may have also used a small EEG beta band, but these details were not reported. The peak frequency in the authors' subjects' individual beta bands was about 26 Hz. With the smaller beta band,

the Alper group and Bauer eliminated an important part of the EEG beta activity in their samples. Second, the subjects in the Alper, Bauer, and Roemer studies were seeking treatment; the majority of the authors'subjects were not. It is unclear how this may have contributed to the difference in results. As the authors continue to monitor the EEG of larger samples of cocaine-dependent subjects, the differences may be resolved or explained.

Bauer (this volume) and Amass and colleagues (1990) reported a reduced P3 component in cocaine-dependent subjects. P3 or P300 is an electro-physiological measure related to the intensity of stimulus evaluation observed during the updating of working memory (Donchin and Coles 1988; Johnson 1993). In this preliminary study, the P3 was reduced in cocaine-dependent subjects as compared with control subjects. However, the magnitude of the reduction was not correlated with self-reported cocaine drug history measures. The reduction in P3 may have predated the cocaine abuse. A reduced P3 amplitude was also observed in adoles-cent boys who used cocaine or heroin (Herning et al. 1989). Reduced P3 amplitudes were observed in young sons of alcoholic fathers (Polish et al. 1994), children diagnosed as having attention deficit-hyperactivity disorder (Holcomb et al. 1986; Klorman et al. 1979, 1990; Loiselle et al. 1980; Satterfield et al. 1988; Taylor and Keenan 1990), and in antisocial boys (Raine and Venables 1987). These groups of children are at increased risk for substance abuse (Kofoed and MacMillan 1986; Lewis 1984; Mannuzza et al. 1993; Sutker 1984; Weiss et al. 1985). Thus, the reduction in P3 amplitude may have predated substance abuse.

N1 and P2 alterations in cocaine-dependent individuals have not previously been reported. In the AREM task, both N1 and P2 components were delayed in the cocaine-dependent subjects. These delays were correlated with cocaine and alcohol use. While visual P2 amplitudes in the CPT and Sternberg Memory Tasks were reduced, these decreases were not correlated with drug history measures. Reduced visual P2 components were observed in children diagnosed with attention deficit-hyperactivity disorder (Halliday et al. 1976; Klorman et al. 1979, 1990; Prichep et al. 1976), sons of opiate-abusing mothers (Guo et al. 1994), and sons of alcoholic fathers (Begleiter et al. 1987). Thus, only the delays in the auditory P2 components may be related to prolonged cocaine abuse, but the reduction of visual P2 observed in this study may have predated the subjects' drug abuse.

Excess EEG beta activity appears to be a sign of cocaine dependence (Herning et al., under review). The authors' study extends these findings using a much larger sample. Both the EEG alpha and beta activity in these cocaine abusers were correlated with self-reported recent cocaine use. The abundance of EEG alpha and beta was not correlated with depression as measured by the Beck Depression Inventory. These EEG alterations in cocaine abusers are due to prolonged effects of cocaine on the brain, and they may be related to the reduced blood flow in frontal, central, and temporal cortical areas reported in cocaine abusers (Holman et al. 1991; Mena et al. 1990; Tumeh et al. 1990; Volkow et al. 1988; Weber et al. 1990).

Niedermeyer (1963) first reported that vertebrobasilar artery insufficiency was associated with increased EEG beta. This interpretation is supported by reported correlations between decreases in regional cortical blood flow and increased levels of EEG beta observed in patients with spinocerebellar degeneration (Nagata et al. 1993). The reductions in cortical perfusion may lead to neuron death, and the increased EEG beta may be related to this neuron loss. Chronic use of cocaine was associated with cortical atrophy (Pascual-Leone et al. 1991). Increases in EEG beta were reported to increase with age and to be related to neuron loss (Iyma et al. 1992; Shearer et al. 1989).

Further support for the notion that the increases in EEG beta and, perhaps, the information processing alterations are due to reductions in cortical perfusion come from the authors' work with nimodipine (Herning et al., in press-a, in press-b.). Nimodipine is a dihydropyridine calcium channel blocker used in the treatment of cerebrovascular vasospasm associated with subarachnoid hemorrhage. Nimodipine increased cerebral blood flow by dilatation of cortical arterioles (Godfraind et al. 1990; Oliver et al. 1993) and reduced vasospasm (Fleckenstien-Gruin and Fleckenstien 1990). The EEG of elderly patients was normalized after chronic nimodipine treatment (Ulrich and Stieglitz 1988). Acute doses of nimodipine reduced EEG beta and increased EEG alpha in substance abusers (Herning et al., under review). Nimodipine also blocked the decline of the P3 component with repeated testing of auditory and visual ERP in two cognitive tasks (Herning et al., under review). The relation-ship between normalizing CNS function and reducing craving needs to be investigated. The authors' data provide a strong rationale for treatment of cocaine dependence with nimodipine at doses that produced changes in EEG and ERP measures.

Cocaine-induced euphoria is associated with the reduction of cortical activity and perhaps with the loss of cortical inhibition in subcortical areas (Herning et al. 1994). Given the cortical perfusion deficits and neurophysiological alterations observed in abstinent cocaine-dependent patients, it is tempting to suggest that cocaine craving is the result of reduced cortical inhibition in subcortical areas. With reduced cortical regulation of these areas, subcortical areas may be more responsive to cocaine-related cues. Improving cortical perfusion and restoring neural functioning to borderline neurons may reduce craving.

In conclusion, the relative abundance of EEG beta is increased and ERP information processing components are delayed in cocaine-dependent individuals. These alterations in CNS function may be related to the reduced cortical blood flow observed in cocaine abusers using SPECT and PET methodologies. These observations suggest that the repeated use of cocaine may be associated with abnormal brain functioning, resulting in cognitive deficits. Further studies are needed to assess whether these changes are associated with craving for cocaine and the implications they have for treatment.

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AUTHORS

Ronald I. Herning, Ph.D.
Research Psychologist
Intramural Research Program
National Institute on Drug Abuse
Baltimore, MD 21224

Deborah E. King, R.N., M.S.
Instructor
School of Nursing
University of Maryland Baltimore County
Baltimore, MD 21228

Is Craving Mood-Driven or Self-Propelled? Sensitization and "Street" Stimulant Addiction

Frank H. Gawin and M. Elena Khalsa-Denison

INTRODUCTION: SENSITIZATION AND PSYCHOSES

Pharmacological sensitization is defined as an increasing effect of a given drug dose after repeated administrations. Detected over 65 years ago during observations of animal behavior, sensitization provided an anti-thesis to the concept of pharmacological tolerance. In modern neuro-science, the sensitization concept has evolved to reflect neuroadaptive, or perhaps neurotoxic, processes and pharmacodynamics, rather than pharmacokinetic changes in plasma or brain concentrations of a drug.

Sensitization was first observed as gradual increases in motor activation following daily readministration of stimulant drugs (e.g., cocaine, amphet-amines). Sensitization has subsequently been demonstrated, assessed, and extended in multiple research domains, including hundreds if not thou-sands of preclinical neurophysiological and neurochemical studies in monoaminergic systems. Sensitization is evoked by some but not all dosages and administration patterns. Sensitization has also been demon-strated in both nonstimulant drugs of abuse and in medications without abuse potential. Hence, neither stimulant properties nor addictive proper-ties are required to produce sensitization.

Both the pursuit of basic pharmacological knowledge and clinical psychiatric and neurophysiological observations drove the extensive work in sensitization research. Clinical observations yielded theoretical impli-cations for sensitization in mental illness, indicating that the neurophysi-ology of sensitization might be part of, or similar to, the pathophysiology of paranoid psychoses. These observations included multiple cases of stimulant-induced paranoid psychoses in stimulant users that appeared soon after clinical use of cocaine and amphetamine became established (Lasagna et al. 1955; Lewin 1924; Maier 1926). The psychotic episodes occurred during or immediately after amphetamine self-administration of substantial doses throughout sustained binges, but in only some abusers. The episodes followed a near-uniform sequence, emerging and

intensifying over time and mimicking a sensitization-like dose-response paradigm, usually occurring only after chronic abuse and repeated binge administrations (Ellinwood 1967; Kramer et al. 1967; Smith 1969). The similarities between sensitization evoked in animals and stimulant-induced psychoses led to an enduring animal model for research on human psychosis and schizophrenia (Borrison et al. 1979; Post et al. 1976).

SENSITIZATION AND ADDICTION

Sensitization has had dramatically less prominence in addiction theory and research, despite the fact that the prototype stimulants used in early sensitization studies had addictive properties. Recently, researchers in basic rather than clinical sciences, particularly behavioral pharmacology, have advanced an entirely new clinical domain for pharmacological sensitization—drug seeking in addiction—speculating that the crucial clinical phenomenon of drug craving is mediated by pharmacological sensitization.

Earlier clinical speculation, although limited, also held that sensitization may play a role in cocaine abuse and craving. A series of clinical pharma-cotherapy studies ensued that evaluated carbamazepine, an agent that limits the acquisition of sensitization, for treatment of cocaine dependence (Hallikas et al. 1991, 1992). However, several controlled trials failed to demonstrate any therapeutic efficacy for carbamazepine in cocaine abstinence initiation (Kranzler et al. 1993). Before the recent extensions in the sensitization concept occurred, it should be noted that 50 years of clinical observation and research during several amphetamine and cocaine abuse epidemics had not resulted in serious suggestions that sensitization-like clinical phenomena were integral to drug seeking and addiction.

Dissimilarities Between Sensitization and Craving

The authors have previously held (Gawin 1991) that the dosing and temporal patterns associated with sensitization do not match the clinical dose patterns displayed in stimulant addiction, and that there is no con-vincing evidence that sensitization is involved in the essential neuro-physiological, neuroadaptive, or neurotoxic processes that subserve maintenance of drug seeking in active addiction. Although the authors' position is based on many considerations, three are preeminent.

1. Clinical reports on the progression of stimulant addiction are quite consistent. They reveal that drug seeking in cocaine or amphetamine addiction does not demonstrate uniform increases in gradual increments as stimulant re-administrations accrue, as occurs in animal sensitization experiments. Development of the craving and bingeing associated with intensive stimulant dependence is instead describedby addicts as occurring almost immediately after switching to smoking or intravenous (IV) administration or after dramatic increases in intranasal dosage (Gawin and Ellinwood 1988). When this stage (named the "high intensity transition") occurs, craving increases abruptly immediately following the experience of dramatically more intensive dose effects and euphoria. In recent years, this transition has produced the near instant and devastating addiction often noted when an individual's first exposure to cocaine is to "crack."

2. Clinical reports indicate that, in the subpopulation of stimulant abusers who experience stimulant-induced paranoia, the paranoia follows a sensitization-like pattern of gradually increasing intensity or evocation by decreasing dose, similar to sensitization patterns found in animal experiments. But, as just noted, this accumulation is different from the pattern of abrupt change in craving. Stimulant-induced paranoia is an extremely unpleasant experience that is by no means desired or craved, but is instead endured because of the competing desire for a euphoric high. For example, addicts often destroy cocaine supplies in response to delusional fears of imminent arrest. Discarding the object of addiction is not consistent with sensitization of the neurobiological substrates of addiction or drug seeking. Sensitization may thus underlie stimulant paranoia, but paranoia does not co-vary with the patterns or qualities of craving or drug seeking. Paranoia is entirely absent in stimulant users despite extreme use (Satel et al. 1991). Thus paranoia and craving are dissimilar.

3. The dosage and administration patterns in addictive street stimulant use(i.e., high dose; very rapid absorption administration routes; and extended binges characterized by multiple, frequent new superimpo-sitions of drug boluses) differ profoundly from the experimental administration paradigms that foster sensitization in animal research (low, single doses by slow absorption routes). Because the immediate psychological effects and limbic neurophysiological effects of cocaine vary as a function of the acceleration of plasma cocaine concentration and not as a function of simple plasma level (Van Dyke et al. 1982), the intracellular central nervous system (CNS) effects of cocaine exposure may be 1,000 times

greater in multidose street cocaine smoking (crack) or injection than in intraperitoneal (IP) dosing in animals (50-fold difference in plasma acceleration rate x 10 to 20 versus 1 dose/day). Thus, extrapolation from slow-absorption, single, low-dose administration in animal research to human street drug use is profoundly uncertain. Only effects that are minimally dose related and uniformly result from virtually any route of repeated cocaine exposure should begeneralized from animal models of sensitization to addicts. It is crucial to be aware that conservative estimates indicate that 5,000,000 to 10,000,000 individuals (almost exclusively low-dose intranasal users) have repeatedly used cocaine without seeking treat-ment; most are free of severe addiction or uncontrollable craving. Thus extensive human exposure has occurred that at least parallels the slow-onset animal sensitization dosing paradigm without any evidence of clinically significant consequences.

Persistence of Sensitization and of Craving

The above points notwithstanding, the persistence of craving as well as itsresistance to therapy are crucial issues in stimulant abuse treatment. Sensitization persists months after its appearance in animals—a characteristic shared by both the vulnerability to stimulant paranoia in human addicts and by vulnerability to stimulant craving in addiction. Thus, despite important dissimilarities implying that sensitization is not the neurophysiological equivalent of subjective craving, it is critical that sensitization be carefully considered in relationship to addiction and craving, not prematurely dismissed. It is plausible that sensitization may somehow contribute to aspects of the neuroadaptive or neurotoxic matrix underlying chronic drug craving and addiction.

IS CRAVING MOOD-DRIVEN OR SELF-PROPELLED?

Robinson and Berridge (1993) have most extensively developed the hypothesis that addiction is linked to sensitization. They suggest that craving for abused drugs results from drug-induced pharmacological sensitization in hypothesized neurophysiological substrates of incentive salience (or, from Robinson and Berridge, the biological substrate for the psychological perception of wanting) to produce frequent, intense per-ceptions that abused drugs are necessary. Put simply, Robinson and Berridge posit that craving is not mood-driven, or equated with a desire to escape dysphoria and/or to experience pleasure by using a drug, but is instead self-propelled, or equated with a toxically upregulated psychological measurement system (sensitized

by drug use) that mis-measures the importance (salience) of further drug use, resulting in more drug use and further propagation of toxicity and craving. Most important, the subjective mood or expected mood of the addict is not a factor; this separates Robinson and Berridge's hypothesis from previous major theories of addiction. The incentive salience hypothesis thus accepts a determinism, but one based on judgment, via a sensitization process, to escape the classic mood-based determinism that is inherent in previous reward theory.

The incentive salience hypothesis encompasses complexly arrayed but largely traditional epistemological, historical, and philosophical arguments, as well as psychological arguments in the traditions of operant and classical conditioning and reward theory. It is less traditional in that it interposes arrays of neuroreceptor, neurophysiological, pharmacological, and clinical medical-psychiatric generalizations and arguments that extend the scope of the hypothesis and its potential influence well beyond academic meaning and discourse. Since desire and craving are crucial components of addiction theory, research, and treatment practices, any importance attributed to sensitization could either advance or misguide addiction treatment and research.

Assessing the full scientific validity of an incentive salience sensitization hypothesis for craving would require extensive experiments on contro-versial preclinical issues in reward and behavioral neuropharmacology, neurophysiology, and psychology, as well as their clinical research correlates. Completing these experiments would require formidable effort and resources. Is such effort warranted in preclinical or clinical addiction treatment research efforts in warring against drugs (rather than basic research)? The authors believe that this can be justified only if it meaning-fully improves clinical understanding and ultimately, treatment. Note that only selected clinical anecdotal citations and generalizations of unclear origin and validity have been used as support in attempts to establish that sensitization-like patterns exist in addictive behavior and that sensitization actually sustains clinical addiction. The authors therefore focus the remainder of this chapter on the most fundamental question: "What is the clinical accuracy of claims made regarding sensitization and the actual clinical foundation for a sensitization-craving-addiction hypothesis?" While exhaustive evaluation of the complex, multidomain incentive salience hypothesis is implausible here, as it exceeds the scope of a single chapter, its foundations can be assessed by examining the fidelity of the theory to current clinical research findings.

Systematically derived, empirical data from clinical and human laboratory research on many characteristics of cocaine dependence are now emerging from recent, often large studies of the characteristics, phenomenology, and natural history of cocaine addiction. These data may aid in assessment of anecdotal observations that were previously reported. Concordance with a sensitization model is not a priority in clinical research; the reports cited were focused on descriptions of cocaine dependence written for a clinical and treatment research audience, and not on the reports' fit with sensiti-zation theory. Nonetheless, these reports provide far superior data on sensitization and stimulant addiction than prior anecdotes; unfortunately, previously published reviews on addiction and sensitization have not attended to this literature.

CLINICAL PHENOMENA AND STIMULANT SENSITIZATION

Clinical Research on Cocaine Paranoia

Satel and colleagues (1991) recently reported the first systematic evaluation of stimulant paranoia. They assessed 50 unselected cocaine- dependent subjects consecutively admitted to inpatient treatment. A structured, 57-item paranoia assessment interview was used as well as standard cocaine history assessments. Two-thirds (68 percent) of the sample described experiencing paranoid psychosis during the cocaine high and postcocaine crash, a greater-than-expected prevalence that has heightened concern over sensitization and possible neurotoxicity in cocaine dependence.

The reported characteristics of cocaine-induced paranoia were uniform and consistent with a sensitization process. One hundred percent of the subsample who experienced paranoia had been paranoia-free early in cocaine dependence, averaging years of binge use before paranoid symptoms gradually became troubling. All described multiple stimulant binges with intensifying anxiety during binges before experiencing frank paranoid delusions; once paranoia appeared, every subsequent cocaine binge induced its reexperience. All subjects described intensification of the paranoia with continued cocaine use. No subject reported any amelio-ration or tolerance of their anxiety or paranoia, and half used anxiolytic street drugs to reduce their intensity. The onset of paranoid delusions after starting a binge accelerated over time, first ranging from 10 to 90minutes after the binge start and decreasing to between 5 and 15minutes by the time

of admission. Half of the subsample engaged in bizarre activities, such as hiding or protracted compulsive rechecking, driven by the paranoia. Thirty-eight percent secured weapons, and six percent had fired weapons to protect themselves from imagined pursuers. The total duration of paranoia averaged about 12 hours, with near total resolution (97 percent) of paranoid symptoms before awakening after the postcocaine crash (sleep). These systematically derived clinical data are consistent with a century of uniform case descriptions. Recently Angirst (1994) and, in part, Brady and colleagues (1991) have reported nearly identical data that replicate and also extend these findings.

The characteristics of irrational fear and paranoid ideation induced by cocaine in chronic street abuse match characteristics of sensitization in animal models: First a dose threshold exists, in a minimal amount and/or duration of use before sensitization, as anxiety and later frank paranoia appear. Second, sensitization inevitably persists and reappears on cocaine readministration, as does paranoia when binges reoccur. Third, symptoms intensify over repeated binges, as do the behavioral effects of sensitization. Fourth, noted acceleration of onset occurs over repeated binges, which should be equivalent to gaining an effect earlier, at lower dose, as in sensiti-zation. Combined, the anecdotal accounts and systematic investigations are unequivocal regarding the characteristics of stimulant-induced paranoia and provide convincing evidence that sensitization, manifested as paranoia, does occur in street cocaine abusers.

The subsamples that did not experience paranoia may have substantial research significance for psychosis in mental illness (one-third of the Satel and colleagues (1991) sample; similar proportions were reported byBrady and colleagues (1991) and Angirst (1994)). Such individuals appeared to have greater immunity to sensitization and stimulant-induced paranoia rather than insufficient cocaine exposure. Lifetime cocaine exposure in the nonparanoid subsample (Satel et al. 1991) was almost twice that preceding onset of frank delusions in the paranoid subsample (1,400 versus 820 grams). The paranoid and nonparanoid subgroups didnot differ on sociodemographics, administration route, settings for cocaine use, and amount or prevalence of other drug use. They were also equivalent in the intensity of cocaine-seeking behavior or craving for cocaine (operationalized as length of use or dependence), intensity of abuse (grams/hr), the rapidity of the transition from use to dependence, and subjective self-reports and ratings.

In preclinical research, the homogenous animal strains used in experimental samples demonstrate much less intersubject variation in sensitization than is evident in stimulant abusers. However, substantial between-strain differences in animal acquisition of sensitization have recently been demonstrated, suggesting that animals can be bred to be sensitization vulnerable or sensitization resistant. Neurobiological contrasts of such animals would provide a powerful model for understanding the genetics and neurobiology of paranoid psychosis and, if resistance to sensitization could be induced, for the potential prevention or treatment of schizophrenia.

Clinical Research on Cocaine Seeking and Addiction: Euphoria, Withdrawal, Craving, and Relapse

Drug seeking in addiction has long been largely attributed to avoidance of unpleasant sensations of drug or alcohol withdrawal combined with the expectation that euphoric sensations would follow drug use. As noted, the hypothesis that sensitized, incentive neurophysiology mediates drug seeking, however, requires neither euphoria nor unpleasant withdrawal symptoms. Clinical data on cocaine seeking and craving in relation to possible sensitization exist in at least four clinical research areas: treatment effects on craving; laboratory experiments on euphoria and craving; inves-tigations of stimulant withdrawal; and large-sample natural history studies of cocaine addiction, its longitudinal course, and abstinence patterns.

Clinical Research on Euphoria

Addicts sometimes complain that they achieve little or none of the high that accompanied earlier drug use and question why, with less compelling reward, they endure the pain and hardship of career drug addiction. Such individuals nonetheless most often continue to pursue drugs, and this paradox constitutes a major stanchion in the clinical foundation for sensi-tization theory on drug seeking. The sensitization view argues that since no reward is experienced, a process other than reward compels drug seeking and abuse in addiction. Alleviation of withdrawal dysphoria is considered a failed explanation largely because drug seeking in addiction frequently occurs before or after classic withdrawal symptoms occur. The logical void is then deemed filled by the concept of sensitization via incentive motivational neurophysiology.

But is drug euphoria truly absent in addiction? This belief is based purely on anecdotal assertion of unclear origin and validity.

Moreover, the assertion is not critically assessed and its meaning for the addict is not considered. No laboratory studies documenting the absence (or presence) of euphoria in addicted drug abusers are cited, nor have clinical survey data been interpreted or presented.

Language, Euphoria, and Drug Abuse Research

The assertion that euphoria does not occur in addicts represents, at best, great clinical naivete. It presupposes the validity of interchanging precise scientific terms with anecdotal street slogans. In clinical research, such terms as “high” are unusable unless they are precisely defined and assessed within structured research parameters, and they are suspect until validated. Statements by addicts about drug euphoria reflect word choices defined within specific addict subcultures, the addict’s level of expectations or wishes regarding drug experiences, and the immediate state of intoxication or withdrawal. In the language of street stimulant addicts, "high" can refer to many disparate constructs, such as experiences of other’s intoxication (e.g., "contact high"); drug-induced agitation or altered perception (e.g., a "trash high"); or transient, peak-intensity drug experiences after rapid administration of potent drugs (e.g., "I got off but it wasn't good enough to get me a real high").

The difficulty of ascribing specific meaning to terms denoting euphoria or other acute drug effects in addicts is best illustrated by the variations in terminology used to distinguish peak versus sustained stimulant euphoria. Transient, overwhelming euphoria occurs seconds after stimulant injection or smoking, as plasma drug concentration elevation accelerates. The onset of this extreme euphoria is termed the "high" by many addicts (but also the "slam," "rush," "wire," "ride," "rip," and others). Nonescalating, sustained euphoria occurs with lower dosages or slowed absorption as plasma drug concentration increases decelerate after intranasal or oral stimulant use,or after the peak injection or smoking effects begin to dissipate. Such euphoria is also termed the "high" by many addicts (also the "ride," "cruise," "wire," "stoke," "rip," and others). Upon recurrent acute use late within a binge, acute tolerance or tachyphylaxis results in greatly diminished peak and sustained effects that pale in comparison with initial doses, but initial doses remain euphorigenic. With chronic use and tolerance, maximal initial peak effects may diminish unless the dosage is increased, but sustained euphoria is still experienced. Thus, for example, addicts alleging that a high was missing acknowledge a positively perceived subjective intoxication and are readily able to ascribe a dollar street value to that experience, but complain of the

lack in abrupt euphoric intensity compared with peak effects of early stimulant intoxications. Similarly, addicts in adjoining urban drug microcultures with inverted but parallel terminology have described the same experience after stimulant use—the relative absence of peak effects but presence of sustained effects—in exactly opposite terms; not getting a high (peak effects) but still enjoying a ride (sustained effects), or as not getting a ride (peak effects) but still enjoying the high (sustained effects).

Hence, complaints about the absence of a high almost invariably reflect acute and/or chronic tolerance with diminished peak effects that suffer in subjective comparison to the euphoric glory of initial doses and preneuro-adaptation peak effects. In light of the long accrual of mounting adverse consequences of addiction, the value of continued drug use becomes increasingly problematic (e.g., "I don't know why I get high").

Laboratory Experiments: Euphoria in Chronic Dependence

The preceding assertions that drug euphoria does occur in addiction are substantiated by the entirety of two decades of human subject research on stimulant and opiate administration. Human subject investigations of illegal addictive drugs have been conducted almost exclusively in chron-ically dependent subjects since the late 1970s. These studies exclude normal or nondependent subjects because of restrictions instituted due to ethical concerns over exposing drug-naive or nonaddicted individuals to powerful, addicting euphoriants. Euphoria, high, dollar value, and similar ratings are the principle subjective measures in such research and have been used to define psychological dose-response relationships of stimulants (Van Dyke et al. 1982).

Numerous human subject studies using balanced, placebo-controlled, double-blind drug administration have been reported. These studies have uniformly confirmed that chronically dependent subjects experience euphoria. The sensitization hypothesis of euphoria or reward in addiction would predict that either human subject research would require preselec-tion of less addicted subjects who still had the capacity to experience a high, or that absence of euphoria would occur repeatedly and plague such research. Yet there are no reports in the experimental human subject literature that support these predictions.

Clinical evidence that diminished drug effects and tolerance occur in addiction has been accumulating for over a century. That euphoric effects can dissipate with tolerance is rudimentary clinical knowledge. For example, both heroin addicts and ex-addicts working as methadone counselors recognize that methadone, via cross-tolerance, blocks the heroin high and that purer heroin or higher doses restore the high. With tolerance, euphoria is harder to achieve; but neither euphoria nor the associated reward motivation disappears. Furthermore naltrexone, an opiate antagonist used in treatment of opiate addiction, does block euphoria. If euphoria is absent, as the sensitization perspective contends, why is naltrexone needed or useful? If sensitization mediates craving without any effect of reward, then craving should be unaffected by naltrexone blockade of reward. However, the clinical research findings are the opposite of the incentive salience prediction regarding reward. Craving comes closer to elimination during naltrexone treatment than during any other pharmacotherapy for addiction and, contrary to incen-tive sensitization theory, returns immediately upon discontinuation of naltrexone with the perception that the drug high is available (Meyer and Mirin 1979).

Euphoria with Craving?

The sensitization view makes one additional anecdotal point in attempting to refute the classic view that drug reward or mood effects are involved in craving or addiction. Reports that cocaine craving in addicts is frequently induced by acute cocaine administration (Jaffe et al. 1989) are cited as evidence of an internal contradiction (presumably fatal) in current addiction theory based on mood effects. The contradiction is that the acute experience of cocaine-induced euphoria and the simultaneous craving for that euphoria are logically incongruous. Sensitization theory proponents then hold that euphoria and craving have been misunderstood. They first refer to the assertion presented above that euphoric mood effects are absent in addiction. Alternatively, they also contend that even if drug effects that increase positive mood do exist in severe addiction, the contradiction means such mood effects are relatively unimportant in drug seeking. Mood is reasoned to be unimportant because if craving is not eliminated by euphoria, then craving must therefore reflect another neurophysiological process independent of mood. This "other process" notion introduces a conceptual void that is then filled by the hypothesized neurophysiological sensitization of incentive motivation to produce craving.

Once again, evidence from nonanecdotal clinical and human subject research literature that has not been previously cited in sensitization and craving discussions better informs consideration of whether and how cocaine-induced mood elevation and craving might coexist. Prior citation of anecdote is clinically correct in that cocaine induces craving with great consistency. This factor is essential to produce day- or days-long binges. Such binges are sustained by an agent, cocaine, that has a half-life for euphoria measured in minutes. Decade-old clinical accounts of patterns of cocaine use during binges describe frequent, regularly spaced episodes of craving as cocaine's very brief euphoria dissipates, resulting in mul-tiple, serial readministrations (Gawin and Kleber 1985). However, it is erroneous to assume that cocaine-induced craving for cocaine occurs at the same time as mood elevation, and that euphoria does not reduce craving. (Rarely, cocaine-induced craving for cocaine is a consequence of low purity and/or doses that are inadequate to produce euphoria, but that instead induce mild sympathetic activation that focuses the absence of expected euphoria, thereby increasing craving. This parallels a priming dose in animal self-administration research). Nearly invariably, induction of craving by cocaine administration escalates as euphoria rapidly dissipates. Such induced craving, however, never appears in the clinical literature as an acute stimulant effect directly covarying with either euphoric, sympathomimetic, or psychomotor activation, or with other effects of ascending plasma cocaine concentrations. Classic clinical descriptions depict cocaine readministration and craving as occurring 20to 60 minutes after IV or smoking administration, not at 5 to 10minutes when euphoria peaks. The timecourses of these parameters, originally observed before the turn of the century, have been supported by sys-tematic assessments of clinical samples (Gawin and Kleber 1984, 1986). These timecourses have recently been experimentally substantiated by several human subject investigations of cocaine that assessed the time-course of craving, cocaine readministration, and euphoria (Fischman et al. 1990; Kosten et al. 1992; Sherer et al. 1988). These experiments clearly documented an inverted temporal relationship between high or rush and craving or drug readministration.

Research on Withdrawal

Based on the following clinical generalizations, the sensitization view of addiction considers withdrawal unimportant in regard to craving and sustaining addiction. First, even though relief from withdrawal symptoms clearly motivates drug seeking during opiate and alcohol withdrawal, effective pharmacological treatments exist that reverse

opiate and alcohol withdrawal. Such treatments, while helpful, do not eliminate all drug craving and drug seeking during withdrawal. Second, addicts very fre-quently crave an abused agent in the absence of appreciable withdrawal symptoms, either before the onset of classic withdrawal when intoxication is minimal but withdrawal has not yet started, or after withdrawal has run its course and relapse occurs. Third, the sensitization viewpoint contends that extreme drug seeking and craving occurs without commensurate withdrawal in several addictive disorders, such as cocaine and nicotine addiction, which they contend have minimal or no withdrawal syndromes.

The first two generalizations are acceptable portrayals of extant clinical phenomena. The last, however, does not reflect current clinical consen-sus or research. It conflicts with current understanding that psycho-logically expressed withdrawal syndromes that produce little objectively observable classic withdrawal symptomatology may nonetheless often be primary determinants of clinical outcomes.

Cocaine withdrawal, in symptom structure if not timecourse, closely parallels nicotine withdrawal; both parallel the subtle psychological distress of the protracted withdrawal syndrome that has been described as persisting beyond resolution of classic physical symptoms of opiate or alcohol withdrawal. These psychological withdrawal syndromes are consistently comprised of anhedonia within a dysphoric cluster of varying psychological symptoms including anergia, anxiety, and nonmelancholic depression. These syndromes have been used to partially explain early relapse, but after classic withdrawal symptoms have waned.

It is essential to note that, contrary to the sensitization viewpoint, such symptoms are deemed subtle only from the standpoint of ease of overt observation. Current clinical consensus holds that these nonphysical with-drawal syndromes explain much of the drug seeking, craving, and relapse that occurs in cocaine dependence in the absence of dramatic physical withdrawal symptoms, particularly in treatment-resistant subpopulations (Gawin 1991; Gawin and Ellinwoood 1988). Psychologically expressed withdrawal thus counters the arguments of incentive sensitization by sug-gesting that dysphoric symptoms drive relapse. Similarly, classic physical opiate and alcohol withdrawal symptoms are treatable with established pharmacotherapies but cocaine, nicotine, and protracted opiate and alcohol withdrawal are not eliminated by the same agents. Thus these withdrawal conditions must be considered along with euphoria

seeking or sensitization of incentive salience in assessing explanations for drug seeking in addiction. It should also be noted, as discussed more fully below, that attempts to combat such symptoms have opened new avenues for promising pharma-cological strategies in treatment of alcohol, cocaine, and nicotine depen-dence (Covey et al. 1993; Gawin et al. 1989; Mason and Kocsis 1991). The efficacy of these treatments is difficult to attribute to any mechanism other than amelioration of dysphoric psychological symptoms.

Dopaminergic Neurophysiology: Withdrawal or Craving? Reward and Anhedonia or Incentive Perception and Sensitization?

The current theoretical foundation of cocaine withdrawal is that neuro-physiological reward systems exposed to chronic exogenous activation by euphorigenic drugs respond through subsequent compensatory down-regulation of these systems, resulting in subsensitive reward responses. This subsensitivity is clinically expressed as anhedonia (Gawin and Kleber 1986), and a substantial body of preclinical research literature reports decreased electrophysiological and neurochemical sensitivity of brain dopaminergic reward systems (Leith and Barrett 1976; Markou and Koob 1991; Robertson et al. 1991).

The sensitization view, which holds that prevailing hypotheses of addiction misinterpret both the significance of reward and of withdrawal anhedonia, dismisses the pivotal association between clinical anhedonia and preclinical electrophysiology. Instead, the sensitization view considers mesocorticolimbic dopaminergic systems, previously imputed to mediate reward and anhedonia, to mediate incentive attributions or salience. The sensitization hypothesis emphasizes that underappreciated components of this system are sensitized and that it is these sensitized components, rather than electrophysiological decrements diminishing well being, that are important in drug seeking. In this view, acute drug administration diminishes incentive motivation and thereby reduces craving, rather than reducing craving by producing euphoria; nonadministration (abstinence) increases incentive motivation and thereby amplifies craving, rather than unveiling anhedonia.

This distinction initially appears academic and perhaps arcane; crack smokers struggling to initiate abstinence will readily declare they care little about the difference between whether very few things feel good or whether, instead, very few things seem important. Most addicts would hold that what feels good is what's important, and effectively

refute this emotional/ cognitive distinction with demonstrative behavior in ensuing relapses.

In populations less philosophically sophisticated than addicts, however, the sensitization perspective on withdrawal and craving has received substantial attention and has the potential to both influence policy and guide future clinical treatment and research. The sensitization view replaces the fundamental significance of perceived suffering with impaired judgments of salience or the broken brain machinery of judging impor-tance. If withdrawal is incorrectly deemed absent or unimportant, further development of effective psychotherapeutic or pharmacotherapeutic tools to assist recovery would suffer.

On the level of public attitude and perception, it has not yet been recognized that the incentive sensitization view unintentionally opens an avenue for moralistic mistreatment of addicts. The false medical belief of the late 1970s that cocaine produced no withdrawal resulted in the percep-tion of cocaine abuse as a moral problem throughout the first 6 years of escalating epidemic use. This perception resulted in disregard of the pain caused by cocaine abuse, rather than a constructive recognition of a societal problem of uncontrolled craving warranting addiction treatment.

Craving in Clinical Cocaine Withdrawal

The sensitization perspective largely considers the current clinical term "withdrawal" to be a euphemism for craving that suffers, from the stand-point of clinical pertinence, from overuse in describing myriad, poorly substantiated symptoms that form a withdrawal syndrome which is only vaguely related to drug seeking. Unfortunately, anecdotal clinical general-izations that equate only easily observable, largely physical, classic symp-toms and that equate withdrawal intensity and importance are cited as a clinical foundation for the sensitization hypothesis of addiction. Recent systematic clinical research has escaped note or appeared too recently to inform prior discussions of these issues.

Classic perspectives on withdrawal consider craving a part of withdrawal. Such perspectives also consider that craving is more than withdrawal, and can be based in memory and anticipated drug reward without the presence of dysphoric withdrawal. In earlier prevailing views of addiction the possi-bility of euphoric experience, amplified by drug availability and by condi-tioned associations that evoke

memories of that drug euphoria (conditioned craving), were believed to drive one component of craving through antici-pation of positive mood changes. This concept subsumes so-called con-ditioned craving. (Conditioned craving is almost wholly absorbed as the craving acknowledged by the sensitization viewpoint, but is altered in sensitization theory by the proposition that such craving is not driven by memories of drug-induced positive mood changes, but rather is prompted by conditioned misattribution of incentive importance.) Dysphoric withdrawal symptoms that are time limited, usually lasting weeks to months, drive another (second) component of craving by anticipated elimination of negative mood.

When withdrawal symptoms are prominent, both sources of craving are considered to exist and interact; as withdrawal symptoms dissipate, euphoria seeking and conditioned craving predominate. The interactions of these components of craving and other variables are complex and include substantial interindividual differences that vary in intensity depending upon perceived drug availability, and follow a variable and fluctuating timecourse. In alcohol or (to some extent) opiate withdrawal, superimposition of dangerous physical symptoms for up to 2 weeks can be a further complication.

The chasm between the sensitization and withdrawal views focuses attention on three crucial questions that require evaluation before the validity of the sensitization view of stimulant withdrawal can be fully assessed. These questions include whether withdrawal exists as a syndrome, whether its symptoms contribute to cocaine seeking, and whether detectable symptoms beyond craving exist that independently create a withdrawal syndrome.

Investigations of cocaine withdrawal have included semistructured clinical assessments disclosing symptom constellations (Ellinwood and Petrie 1977; Gawin and Kleber 1986; Smith 1969) and inpatient assess-ments. These assessments consistently identified subtle withdrawal syndromes. However, these studies had eliminated cocaine availability (but gave low doses of cocaine at study onset, thus inadvertently tapering cocaine exposure and perhaps blunting craving), and used instruments that had not been validated and perhaps were not sensitive enough to measure stimulant withdrawal. Subsequent studies of cocaine withdrawal have used factor analysis and multisymptom inventories in assessing 200to 300 outpatients (Gawin et al. 1992; Margolin et al. 1994).

The later studies confirm that a syndrome exists which is linked to, but different from, cocaine seeking and craving. Several symptom factors exist in cocaine withdrawal. Five 3- to 6-symptom factors have been identified: dysphoria/depression, anergia, anxiety/irritability, pain/nausea, and anhedonia as well as a distinct, separable craving factor. These factors, and the syndrome they constitute, are differentially and significantly linked to cocaine seeking and use. Hence, clinical research data contradict the predicted findings of an incentive sensitization viewpoint for each of the three critical assessment questions noted above. Further, unexpected findings are readily explained by classic withdrawal views but not incentive salience. In pure cocaine addicts carefully selected for an absence of alcohol dependence, the craving for cocaine (but not for alcohol) was correlated first with anhedonia and second with dysphoria, while craving for alcohol (but not for cocaine) was most highly correlated with anxiety/ irritability (Gawin et al. 1992).

These findings illustrate a remarkable specificity of craving, withdrawal symptoms, and drug choice. They further contradict the incentive sensitization viewpoint, since it predicts absence of pertinence to any withdrawal symptoms and could not account for symptom-specific craving linked to a specific drug, while linkage of a withdrawal factor (e.g., anxiety/irritability) to craving for a specific anxiolytic drug that is not the drug of choice (e.g., alcohol) can be simply explained by prior theory as an attempt to alleviate the individual's specific dysphoric component of psychological withdrawal.

Clinical Research on Craving

Systematic research in cocaine, nicotine, opiate, and alcohol abuse treatment has explored multiple assessment instruments as they relate to drug craving. Such research not only evaluates treatment outcome, but also discloses fundamental relationships in addiction through naturalistic assessments in conditions that are uninfluenced by experimental treat-ments. Hence, untreated single timepoint evaluations of craving are available from intake assessments, and repeated assessments of control (placebo) groups can provide data on the stability of symptom or factor relationships to craving over several months. Such data are available from multiple studies of psychotherapies and pharmacotherapies for all agents of abuse. These data are too extensive to fully review here. To summarize, they indicate that craving is complexly related to drug use in stimulant, opiate, alcohol, and nicotine abuse. Preeminent among drug-use factors beyond craving are drug availability (i.e., near absence of craving if drug euphoria is unavailable due to hospitalization or pharma-cological blockade in the absence of acute physical opiate or alcohol withdrawal), the euphorigenic potency of the drug,

psychological with-drawal symptom type and intensity, the prevalence and potency of environmental conditioned cues and alternative nondrug reinforcers, and the prevalence and potency of negative reinforcers (work required for drug use or the punishment potential and type).

To illustrate, data from a cocaine abuse pharmacotherapy trial have been published that elucidate relationships between euphoria, withdrawal, and craving (Brown et al. 1993). At intake, the relationships among standard psychiatric assessment instruments, cocaine craving, and cocaine use were evaluated in 63 cocaine-dependent individuals without dependence on other agents. The study evaluated overall symptomatic distress using a standard symptom checklist, a global severity scale, and the Beck Depression Inventory (a focused index of symptoms associated with severe clinical depression). Standard craving assessments were also used. Cocaine usage, a prima facie index of drug seeking, is shown in relation-ship to these instruments in the correlation matrix of figure 1. Note that craving, overall symptomatic distress, and depression are substantially correlated with reasonable explanation of variance (~30percent explained by each direct relationship). Each of these, however, has substantially less linear relationship to actual cocaine usage (individually explaining an average variance of 7 percent). Patient attributions of craving, but not their actual drug use, are thus strongly related to indices of withdrawal as reflected in both overall symptomatic distress and severity of depression. This example thus directly contradicts the incentive sensitization view that withdrawal dysphoria does not drive craving. These data further reinforce the need for preclinically derived theories of addiction to be assessed against clinical research data rather than relying upon anecdotal evidence.

The absence of a substantial relationship between craving and actual cocaine use refutes a fundamental unstated assumption of the incentive sensitization theory on addiction: craving is presumed to be the equiva-lent of addiction or drug seeking and use. In most outpatient substance abuse treatment trials that demonstrate a pharmacological effect of tricyclic antidepressants, a significant change in craving appears after a delay, occurring 1 to 3 weeks after, not before, a decrease in drug use (Covey et al. 1993; Gawin et al. 1989; Mason and Kocsis 1991). This delayed reduction craving has sometimes been explained as a secondary self-attribution that follows observation of decreased drug taking. It is also possible that decreases in drug use usually, without pharmaco-therapy, increase craving and withdrawal symptom frequency and severity, and that the absence of an immediate rise in craving when cocaine use decreases is direct evidence of the pharmacotherapeutic effect. Further, these studies found that diminished craving generally follows decreases in drug use so substantial that abstinence or near abstinence precludes further reduction in drug intake; the diminished craving thus can no longer be reversed by decreased drug intake, and

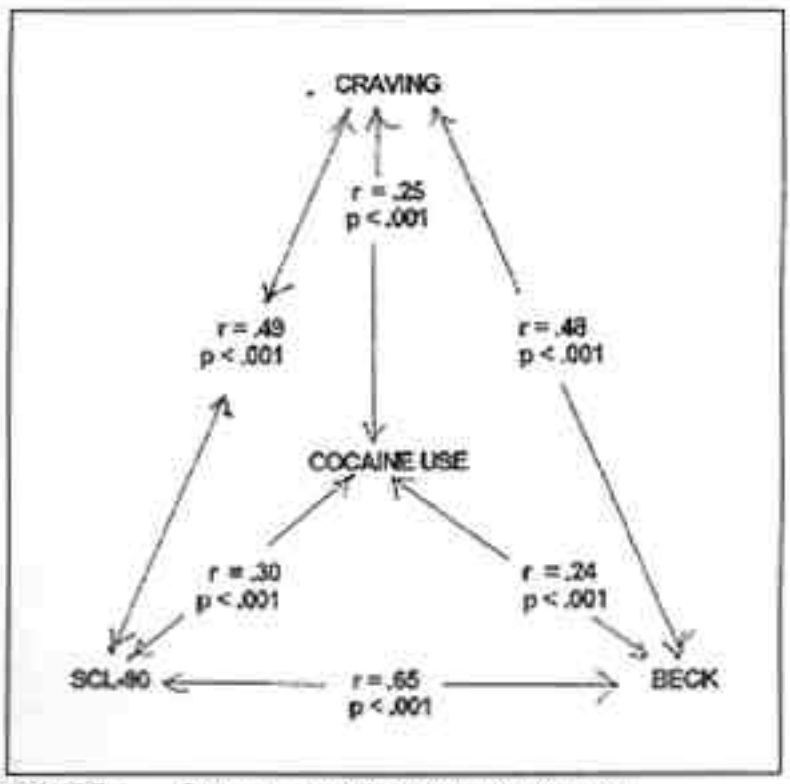

FIGURE 1. *Cocaine use and symptom assessments.*

reduced craving scores follow. As noted previously, the therapeusis associated with reduced drug seeking and craving also decreases depres-sion. This effect supports a withdrawal perspective; because there is no evidence that antidepressants decrease incentive motivation—direct evidence to the contrary exists—the incentive sensitization theory regarding craving and addiction is contradicted.

Human subject research into craving's complexity in relation to addiction has recently begun. A study by Fischman and colleagues (1990) on the effect of the tricyclic antidepressant desipramine on cocaine self-adminis-tration found that human subjects in an experimental laboratory, when denied alternative reinforcers, chose the highest available IV dose of cocaine significantly less frequently when also treated with chronic desi-pramine than with placebo, although they did not cease self-administra-tion. The efficacy of desipramine in decreasing craving for the highest dose can be explained as a result of reduced withdrawal depression that requires a high dose to overcome dysphoria and produce euphoria. Other interpretations are also plausible, such as the medication increasing the

effect of the lower dose to produce greater peak euphoric effects or also blunting peak effects of the higher dose; further investigation is thus under way. It should be noted that these explanations are all based on a reward/anhedonia model of addiction. An incentive sensitization view cannot readily interpret these findings. In a similar single-dose human laboratory study by Kosten and colleagues (1992), desipramine substan-tially accelerated the disappearance of cocaine-induced (or primed) craving for cocaine. This finding can be readily interpreted as evidence that desipramine and not placebo decreases dysphoric craving, resulting in experience of only that craving component related to the desire to re-experience the recent intensity of the high. Again, these data are not consistent with an incentive sensitization hypothesis.

The incentive sensitization perspective places substantial currency in the observation that sensitization and conditioned craving can both be linked to classical conditioning. Sensitization occurs in the environment where prior drug administrations occurred, and can be minimized in animals by shifts from the room and cage where sensitization was instituted. Incentive sensi-tization holds that craving in addiction reflects conditioned associations that evoke memories of the importance of using drugs. If the word "importance" in the preceding sentence were replaced by the word "euphoria," this view would be consistent with current clinical consensus regarding conditioned craving. Further, the commonality of classical conditioning indicates only that associative memory is part of either sensitization and conditioned craving and not that the two are linked. This also does not present a particularly discriminating distinction, since reward and punishment are integral factors that directly affect the strength of both instrumental and associative learning and memory. Further, other basic dissimilarities between conditioned craving and sensitization are discussed below.

Clinical Research on Relapse

Beginning over a century ago, clinicians reported that relapse after long- sustained abstinence in those chronically addicted to stimulants often leads to near-immediate resumption of high-intensity stimulant abuse rather than following the pattern of intermittent and slow abuse escalation that charac-terizes initial oral or intranasal stimulant use prior to the high-intensity transition to binge addiction. If relapse always occurs this way, such clini-cal data would display a pattern similar to sensitization, in that relapse to drug use results in reinstatement of the previously incrementally developed patterns of

severe cocaine use. Of course, such a pattern would not clearly substantiate that sensitization was associated with the effect; many crack abusers do not experience a sensitization-like timecourse but instead immediately display high-intensity abuse patterns.

In the first large-sample natural history evaluation of cocaine dependence patterns, recently completed by Khalsa and colleagues (1994), extensive structured interviews assessed temporal development of cocaine depen-dence, longitudinal abuse patterns, and postabstinence relapse to cocaine use. Subjects were males requesting treatment at an urban Veterans' Administration hospital. These data provide objective, systematic measure-ment of major variables in cocaine addiction that previously have been investigated in small clinical samples and anecdote. The data clearly demonstrate that many (76percent) but not all former addicts who relapse immediately resume the level of drug abuse that existed just prior to initiating abstinence, rather than returning to earlier use patterns. The data thus are consistent with prior anecdote; however, in the 24 percent who gradually resume use, no putative sensitization-like phenonon appear, and addiction remains.

CONCLUSIONS

Evaluation of systematic research findings rather than selected anecdotal evidence substantially alters conclusions regarding the pertinence of sensi-tization to addiction and craving. The research reviewed here objectively substantiates that stimulant-induced paranoia is extremely consistent with classic sensitization. Incentive sensitization is not, however, consistent with research findings on euphoria, withdrawal, drug seeking, or craving as a general concept. The authors conclude that while sensitization provides a superbly fitting model for paranoia, it fails completely as a model to fully explain addiction.

Incentive Sensitization and Pharmacological Sensitization - Logical Discordance

Within stimulant addiction there are parallels to sensitization in conditioned craving and the intensity of abuse resumed after relapse. These data demonstrate the persistence and reinstatement of effects that develop after repeated stimulant administrations.

However, the authors believe that incentive sensitization theory contains severe logical flaws that render these commonalities meaningless. The incentive sensitization view of addiction lacks fidelity to the classically defined preclinical sensitization concept. Pharmacological sensitization differs profoundly from incentive sensitization in one underappreciated respect: it requires that the sensitized effect be an increased acute action of the drug inducing the sensitization. In this regard, all of the clinical effects cited as reflecting sensitization by incentive sensitization theory fail; none of the purported sensitization effects is an acute action produced by a dose of stimulant, but all are instead accompaniments to chronic addiction. Similarly, while severe abuse intensity is unveiled by the resumption of stimulant use, this effect does not occur uniformly upon stimulant readmin-istration, nor is it an acute effect of a single dose. Rather, severe abuse occurs in a logically different category, after acute effects of a first dose have dissipated, when binges are extended, and as the drug is sequentially administered in defining an abuse pattern. This behavior is not an increased acute effect of one drug dose itself.

The absence of fidelity to the sensitization concept as defined in classic pharmacology alters the basic heuristic and logical concordances of incentive sensitization theory, and thus renders the preceding review unnecessary. Nonetheless, the authors believe that the review is instruc-tive and worthwhile because of the attention given this view among nonclinicians, as well as because it illustrates the problems of selective use of clinical anecdote, rather than rigorously examining empirical clinical research data to subserve theory.

Because the fundamental reference of incentive sensitization theory is not an acute drug effect but rather an increasing accompaniment of addiction, the theory can be observed to be based in semantics and epistemology rather than pharmacology or clinical neurophysiology, as follows: Incentive sensitization theory has its focus only on repeated drug admin-istration, increasing something over time in common with classic pharmacological sensitization, and thus has negligible linkage to its claimed foundation in preclinical sensitization research (which, again, uniformly involves the experimental evaluation of acute effects on re-dosing). The label "incentive sensitization" is thus a partial misnomer from the standpoint of classical pharmacology. Incentive sensitization can be distilled as positing that some drugs produce changes in neuro-physiology over repeated administration (previously termed neuroadap-tation). Losing any

linkage to acute redosing with the drug, the statement that “sensitization of the neurophysiology subserving "incentive" processes occurs after chronic drug reapplication" is logically equivalent to the statement that "adaptation of the neurophysiology subserving psychological processes occurs after chronic drug reapplication." The statements differ only in that incentive sensitization specifies a particular sort of adaptation, increases (sensitization rather than desensitization), and a particular type of psychological process, that termed "incentive."

Incentive sensitization is thus simply a logical special case within the psychological component of a broader and much more completely researched concept in pharmacological and toxicological neuroscience: neuroadaptation. Thus incentive sensitization theory is half (the half that goes up and not down) of a theoretical part of neuroadaptation, the part which is limited to the neurophysiology of a putative discriminable neuroanatomical system regulating incentive intent and judgment. Furthermore, the system appears to occupy the identical neurophysio-logical and neuroanatomical locus as that previously identified as the central locus of the reward dimension of mood. Hence the "part" of neuroadaptation defined by incentive sensitization was fully recognized previously. The essential issue reduces to whether attention should be directed at the feeling itself, or at its motivation. At heart, the issue is semantic and epistemological: Should this system be called a "reward" or "incentive" system?

The authors wish to make clear, however, that the most important consequence of this realization is not in the realm of academic discourse, but instead is its effects on policy. There exists substantial risk that theories such as incentive sensitization are not recognized as oversigni-fying terminology. Such theories have the potential to deflect the effort and resources that are likely to advance therapeusis and alleviate clinical distress. The authors are thus in absolute agreement with the basic premise of their patients: How one feels is what’s important, not the terms employed in description.

Is it rational to consider that sensitization is not clinically relevant to craving and drug seeking, but to fear that it might be misinterpreted as such? As noted, carbamazepine has been employed in pharmacotherapy research on cocaine addiction because of a theorized association between craving and sensitization; the rationale for using a drug that had been previously demonstrated to have no effect on expression of cocaine-induced sensitization was not questioned. Although carbamazepine does limit the acquisition and

development of sensitization to cocaine, it is only effective when used to pretreat cocaine-naive animals prior to serial cocaine administrations. Carbamazepine was nonetheless chosen for clinical trials based on the hypothetical hope, never demonstrated in research, that it would affect expression of sensitization, along with hope that craving was manifest sensitization. Chronic crack addicts, who were far from drug naive, were chosen as the sample. (This work has not been directly linked to the more carefully constructed craving/sensitization hypotheses of Robinson and Berridge 1993.) Although poorly piloted and highly ques-tionable from the standpoint of theoretical integrity and preclinical know-ledge, clinical carbamazepine research was rapidly extensively supported and evaluated in controlled, randomized trials with several hundred cocaine-using patients. Resulting double-blind efficacy findings were wholly negative, after not inconsiderable patient risk, research effort, and expense.

The pressures of "wars" declared on drug abuse and epidemic expansion of cocaine smoking partially fueled the fact that decisions regarding carbam-azepine were made without prior systematic data assessment or evidence of a link between sensitization and sustained clinical addiction. The atmosphere demanded new approaches and exaggerated the significance of sensitiza-tion at the probable expense of other preclinical or treatment research with greater likelihood of producing eventual societal gain. This clinical prece-dent illustrates the need to critically assess claims of pertinence in sensiti-zation research, and it stands as a clear warning.

Objective evaluation and careful assessment of the true significance of sensitization itself in addiction is equally, if not more, important in preclinical research. Such significance must be established before its relevance to addiction, based on an extrapolated theory that does not actually reflect sensitization, is used to justify further pharmacological studies of sensitization that use low doses and administration patterns which never occur in humans. Such studies would again result in a misallocation of limited research resources at the expense of other research areas having greater potential for ultimate clinical benefit in addiction treatment.

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AUTHORS

Frank H. Gawin, M.D.
Director of Research
The Mood and Addiction Neuroscience Foundation
11901 Santa Monica Boulevard
Suite 523
West Los Angeles, CA 90025

Laboratory For The Study Of Addictions
Drug Abuse Research Center
University of California at Los Angeles
1100 Glendon Avenue - Suite 763
Los Angeles, CA 90024

M. Elena Khalsa-Denison, M.D., Ph.D.
Laboratory For The Study Of Addictions
Drug Abuse Research Center
University of California at Los Angeles
1100 Glendon Avenue - Suite 763
Los Angeles, CA 90024

Methamphetamine and Methylenedioxymethamphetamine Neurotoxicity: Possible Mechanisms of Cell Destruction

Lewis S. Seiden and Karen E. Sabol

BACKGROUND

Methamphetamine and Related Drugs Have High Abuse Liability

Methamphetamine and amphetamine, potent indirectly acting sympatho-mimetic amines and related compounds, are self-administered by experi-mental animals and abused by humans. Methylenedioxymethamphet-amine (MDMA) shares some discriminative properties with amphetamine and has been reported to be heavily used for recreational purposes among certain groups. Although the abuse liability of methamphetamine and its congeners was recognized shortly after the recognition of their pharmaco-logical properties, a concerted effort to assess long-term effects in the central nervous system (CNS) was only made in the last 15years. The effort to determine possible neurotoxic effects was in part prompted by epidemics of methamphetamine abuse between 1950 and 1970 in Japan, Sweden, Great Britain, and the United States (Brill and Hirose 1969; Jonsson and Gunne 1970; Kramer et al. 1967). Since the middle 1970s, cocaine abuse has increased to epidemic proportions. The acute psycho-active effects of methamphetamine are similar to those of cocaine, but the effects of methamphetamine last longer (Seiden et al. 1993).

Data are available on the neurotoxic effects of long-term administration of high doses of methamphetamine to experimental animals, but there are no similar data for cocaine. Although some of the potentially dangerous effects of methamphetamine on the human brain are known, the duration of these effects and/or their physiological and behavioral consequences are not well understood. Such information would provide valuable insight and guidance for treatment and prevention programs, and it would further the understanding of neurobiological principles of drug-induced CNS injury. Understanding how these drugs' biochemical and pharmacological inter-actions lead to cell death may enhance

understanding of cell death in the CNS caused by disease, environmental toxins, and aging, and lead to preventive or ameliorative therapies.

The social problems caused by abuse of these drugs may result from or be compounded by their neurotoxic effects. While the neurotoxic doses of amphetamine and methamphetamine are between 10 and 20 times the dose required to affect behavior (Koda and Gibb 1973; Seiden and Ricaurte 1987), the toxic dose of MDMA is only 2 to 4 times that required to affect behavior. Methamphetamine (100 milligrams per kilogram (mg/kg)) and MDMA (40 mg/kg) can cause the same toxic response with only one injection of the drug at a somewhat higher unit dose than the eight injections over 4 days used in the authors' original paradigm (Seiden and Ricaurte 1987).

Methamphetamine and MDMA Have Toxic Effects on Monoamine-Containing Nerve Cells

Methamphetamine is selectively toxic to dopamine (DA) and 5-hydroxy-tryptamine (5-HT) nerve terminals in the CNS, while MDMA is selectively toxic to 5-HT terminals. The neurotoxicity is evidenced by: 1) long-lasting depletions of the specific neurotransmitter in the CNS (Seiden and Ricaurte 1987); 2) reduction of Vmax for the rate-limiting enzymes (in the case of destruction of DA and 5-HT terminals the enzymes are tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH), respectively); 3)reduction in the number of DA and 5-HT uptake sites (Commins et al. 1987b; Wagner et al. 1980b); 4) morphological evidence of neurotoxicity showing that cells in DA and 5-HT regions are argyrophyllic after metham-phetamine or MDMA treatment (Steranka and Sanders-Bush 1980; Wagner et al. 1980a, 1980b); and 5) immunohistochemical evidence showing swelling and fragmentation of axons in the short term, and decreased immunoreactivity in the long term, with morphology that is consistent with cell death being the result of necrosis (Axt and Molliver 1991; O'Hearn et al. 1988) as opposed to programed cell death or apoptosis.

An important issue with respect to neurotoxicity involves the long-term effects of methamphetamine and MDMA as indicated by the length of time these effects are observed after drug treatment, which engenders depletion of the transmitter. In the rhesus monkey, there are data showing that changes persist for over 3 years (Woolverton et al. 1989). Several reports exist in which the long-term effect of MDMA on the 5-HT system in the rat was investigated. 5-HT tissue concentrations show a pattern of partial recovery, but continue to be

significantly reduced at 52 weeks posttreatment (De Souza et al. 1990). De Souza and colleagues (1990) used a treatment regimen of 20 mg/kg administered eight times at 12-hour intervals. Using a lower dose (10 mg/kg four times at 1-hour intervals), Scanzello and colleagues (1993) found significant reductions of 5-HT tissue concentrations at 2 to 32 weeks (depending on the region), but complete recovery at 52 weeks post-treatment. The number of cortical 5-HT uptake sites (as measured by specific binding to the transporter) was completely recovered (Battaglia et al. 1988; Scanzello et al. 1993) at 52 weeks posttreatment, while hippo-campal 5-HT uptake sites were still significantly decreased after 52 weeks (Scanzello et al. 1993). Functional uptake (as measured by the transport of 5-HT across the cell membrane), while showing a pattern of recovery, was found to be significantly reduced 1 year posttreatment (20 mg/kg eight times at 12-hour intervals) (Lew et al. 1993). Although these three reports are not in complete agreement on the extent of recovery of the 5-HT system at 52 weeks post-MDMA treatment, they do agree that each demonstrates a pattern of serotonergic recovery after high-dose MDMA treatment. Whether this recovery persists or reverses (see Zaczek et al. 1990) remains to be determined.

In addition to the measures discussed above, the long-term effects of methamphetamine and related compounds on DA receptors have been investigated. The results obtained are equivocal; increases, decreases, and lack of effects have been reported (Robinson and Becker 1986). The absence of consistent results may be attributable to the use of slightly different binding techniques (e.g., use of different displacing agents) as well as varying dosing regimens. Since most previous studies also used low repeated doses of methamphetamine, it is difficult to determine whether the changes observed were related to neurotoxicity. Several studies using high doses of methamphetamine have demonstrated decreases in DA receptor binding (McCabe et al. 1987; Schmidt et al. 1985a, 1985b). Interestingly, McCabe and colleagues (1987) reported that DA type 1 (D1) receptors remained decreased in the substantia nigra as long as 21 days after a neurotoxic methamphetamine regimen.

PROPOSED MECHANISMS OF METHAMPHETAMINE AND MDMA NEUROTOXICITY

In an overview of selective neurotoxicity, Baumgarten and Zimmerman (1992) proposed general mechanisms that can cause cell death. These are conceptually useful as a framework for

understanding the mechanisms underlying nerve cell death engendered by drugs. As noted by Baumgarten and Zimmerman (1992), specific types of pathology were observed in different neuroanatomical regions of the CNS resulting from hypoxia and ischemia. Baumgarten and Zimmerman (1992) discussed three types of trauma that induce neurotoxicity that are not mutually exclusive. First, an inadequate supply of glucose and/or oxygen to the CNS depletes energy stores and results in cell death. Second, synaptic transmission mediated by excitatory transmitters such as glutamate may lead to high Ca++ influx into neurons which, if high enough, can cause cell death. Third, specific neurotoxicity is engendered by a toxin that has high and specific affinity for the membrane transporter, which is respon-sible for uptake of the transmitter. Toxins transported into neurons may be formed by auto-oxidation of endogenous neurotransmitters (e.g., DA and 5-HT) to form hydroxy derivatives. Although the mechanism by which these (6-hydroxydopamine and 5,7-dihydroxytryptamine) compounds cause neurotoxicity is uncertain, these transporter-specific toxins are highly reactive and may themselves generate destructive free radicals or cross-link proteins that contain reactive sulfhydryl groups.

A Toxic Metabolite of the Amphetamine Analog Is Formed

An approach used in the search for a toxic metabolite of amphetamine-like compounds was to directly inject the parent drug into the brain. If the parent drug is effective, then one can rule out metabolites that are formed in the periphery (Sherman et al. 1975); however, a toxic metabo-lite may be formed in the brain. Direct injections of MDMA into the brain did not mimic peripheral injections in its acute (Schmidt and Taylor 1988) or long-term effects (Paris and Cunningham 1991). However, when MDMA was infused into the brain over a 1-hour period, the behavioral and neurochemical acute effects were observed (Schmidt and Taylor 1988).

Intracerebral injections of two metabolites of parachloroamphetamine (PCA), 3-chloro-4-hydroxy amphetamine and 4-chloro-3-hydroxy amphetamine, were minimally effective in changing serotonin levels. Only the 4-Cl-3-OH compound was active, and only at 24 hours postinjection, not at 2weeks. McCann and Ricaurte (1991) showed that intracerebral injections of two metabolites of methylenedioxyamphetamine (MDA) (which itself is a metabolite of MDMA), alpha-methyldopamine and 3-O-methyl-a-methyldopamine, did not cause MDA-induced serotonergic neurotoxicity. In addition,

systemic injection of the two MDA metabolites did not cause long-term effects on the serotonin system (McCann and Ricaurte 1991).

Steele and colleagues (1991) found that alpha-methylepinine, a metabolite of MDMA formed by demethylenation, failed to damage the 5-HT system in rats. In addition, Lewander (1971) reported that guinea pigs, a species that does not metabolize amphetamine by para-hydroxyl-ation, still showed neurotoxic damage from amphetamine. Finally, when iprindol treatment (which inhibits para-hydroxylation of the parent drug) (Freeman and Sulser 1972) precedes PCA (Sherman et al. 1975), the short-term and long-term effects on the 5-HT system are not blocked or attenuated. Ricaurte and colleagues (1984a) showed that at a dose of amphetamine which was ineffective in producing long-term DA deple-tions, the combination of amphetamine plus iprindol resulted in long-lasting DA depletions, suggesting that the prolongation of the half-life of amphetamine caused the toxicity of amphetamine (Ricaurte et al. 1984a). Based on the above discussion, the toxic drug metabolite theory of amphet-amine (and related compounds) neurotoxicity has little support. It should be noted, however, that an exhaustive study of all possible metabolites of the amphetamine class of drugs has not been done.

DA Is Important for Neurotoxicity Induced by Amphetamine-Like Drugs

An intact DA system appears to be necessary for methamphetamine- and MDMA-induced neurotoxicity to the DA and 5-HT systems of the brain (Nash et al. 1990; Schmidt et al. 1985a, 1992b). Inhibition of DA syn-thesis with alpha methyltyrosine (AMT) blocks MDMA- and metham-phetamine-induced damage to both the DA and 5-HT systems (Axt et al. 1990; Schmidt et al. 1985b). Administration of l-dihydroxyphenylalanine (L-dopa), thus replacing the AMT-depleted DA, blocks the protective effects of AMT (Schmidt et al. 1985b). The induction of DA depletion with 2,3,5-trihydroxyphenethylamine (6-OHDA) also blocks MDMA toxicity to the 5-HT system (Schmidt et al. 1990b; Stone et al. 1988). These results led to the theory that DA mediates methamphetamine- or MDMA-induced 5-HT neurotoxicity (Schmidt et al. 1985b). One diffi-culty with this hypothesis is that much of the 5-HT terminal damage occurs in brain regions which have essentially no dopaminergic innervation (e.g.,hippocampus) (Verhage et al. 1992). The anatomical location for a putative DA and 5-HT interaction is not presently understood, but may occur in the brainstem.

An Excitatory Feed-Forward Loop Enhanced by Methamphetamine May Produce Metabolic Conditions That Cause Neurotoxicity

Carlsson (1992, 1995; Carlsson et al. 1995) has elaborated on the feed-forward neural circuit, which coincides with the extrapyramidal motor system. Carlsson proposes that when the system is stimulated by metham-phetamine, the excessive neural activity may mediate methamphetamine-induced neurotoxicity to the DA system. Theoretically, the pathway involved (cortex-striatum-palladus-thalamus-subthalamus-cortex) is excited by methamphetamine or related compounds, causing a continued excitation of 5-HT and DA neurons. This maintained activity of the DA and 5-HT systems demands excess energy. During repeated activity, the cell is depolarized and repolarized; Na+ and Ca++ move into the cell and must be removed. The cells cannot maintain homeostasis and therefore die. This theory is discussed in detail elsewhere (Carlsson 1992, 1995; Carlsson et al. 1995), and is consistent with the some of the data (see below) concerning pharmacological treatments that prevent methamphetamine-induced neurotoxicity.

NMDA Receptor Mediation of Neurotoxicity Induced by Amphetamine-Like Compounds: A Role for Glutamate

Sonsalla and colleagues (1989) first reported that MK-801 (a noncom-petitive antagonist at the N-methyl-d-aspartate (NMDA) glutamatergic site) could antagonize the methamphetamine-induced neurotoxicity to DA neurons. The protective effects of MK-801 are consistent with a Ca++ theory of methamphetamine neurotoxicity. MK-801 blocks Ca++ entry into the cell; this blockade may be important for two reasons. Keeping extracellular Ca++ from entering the neuron would diminish the proba-bility of Ca++-induced cell death (Nicotera et al. 1990). In addition, by blocking Ca++ entry into the cell, subsequent Ca++-induced Ca++ release from intracellular stores could also be blocked (Frandsen and Schousboe 1992; Lei et al. 1992).

MK-801's protective effect may also be related to temperature regulation. Schmidt and colleagues (1990a) and Bowyer and colleagues (1992) have shown that lowering ambient temperature can protect against MDMA and methamphetamine neurotoxicity. In a series of studies, Bowyer and colleagues (Bowyer et al. 1992, 1993, 1994) have shown that rats injected with methamphetamine at an ambient temperature of 23°C had signifi-cant depletions of striatal

DA, whereas rats that were injected in an ambient temperature of 4°C did not show any depletion in striatal DA. In addition, they have shown that rats which became very hyperthermic in response to methamphetamine treatment, but were cooled to prevent death, had larger DA depletions than rats that did not show the same degree of methamphetamine-induced hyperthermia. Bowyer and colleagues con-cluded that the hyperthermia induced by methamphetamine is related to the DA depletions, but hyperthermia alone does not cause the DA depletions produced by methamphetamine.

The noncompetitive NMDA receptor antagonist MK-801 attenuates depletions of 5-HT induced by MDMA. MK-801 has been shown to induce hypothermia in rat models of ischemia. The question arose as to whether MK-801 and two other glutamate antagonists, CGS 19755 (CGS) and NBQX, protect against MDMA-induced 5-HT depletions by induction of hypothermia. Male Sprague-Dawley rats were injected with either saline (SAL), MK-801 (2.5 mg/kg), CGS (25.0 or 50.0 mg/kg x 2), or NBQX (30.0 mg/kg x 2 or 55.0 mg/kg x 3) followed by either MDMA (40.0 mg/kg) or SAL. Core body temperature was monitored for 4 hours or longer using radiotelemetry. Baseline temperature was between 37.0° and 37.6°C. Administration of MK-801 with MDMA significantly decreased temperature to 34.0+0.39°C within 2 hours of the MDMA injection, and it also protected against serotonergic toxicity. Neither MDMA alone nor MK-801 alone had a significant effect on temperature over the same time period. When rats were treated with MK-801 plus MDMA and temperature was maintained between 38.4°C and 40.4°C for 4 hours, protection against 5-HT depletion was abolished. Coadmini-stration of the competitive NMDA antagonist CGS with MDMA resulted in a decrease in temperature to 34.5+0.27°C and provided partial pro-tection against 5-HT depletions. When the AMPA receptor antagonist NBQX was administered with MDMA, temperature did not differ from rats treated with saline plus MDMA, and NBQX did not protect against 5-HT depletions.

The data from this study (Farfel 1993) show that coadministration of NMDA antagonists with MDMA induces hypothermia in dose com-binations which protect against serotonergic toxicity, and neuro-protection is abolished when temperature is maintained above 38.4°C (Farfel 1993). These data indicate that hypothermia induced by NMDA receptor antagonism plays a role in protection against serotonergic toxicity. MK-801, when given in combination with MDMA, decreases body temperature by 3 to 5°C (Farfel 1993). In addition, if rats are kept at normal body temperature through artificial

heating, the protective effect of MK-801 is reversed. Therefore, MK-801 may be protecting against methamphetamine- and MDMA-induced neurotoxicity by slowing down cellular processes, including the toxic process.

Holson and colleagues (1993) have reported that haloperidol and diazepam, which protect against amphetamine neurotoxicity, also lower core body temperature. As suggested by these authors, any compound that is shown to protect against toxicity may have an effect on tempera-ture regulation mechanisms. This is a developing issue in the field of amphetamine-analog neurotoxicity. By determining which compounds protect by cooling alone, researchers may be able to narrow the field of possible mechanisms of neurotoxicity.

Hydroxy Radical Formation and Methamphetamine Neurotoxicity

Senoh and Wiktop (1959) observed the presence of trihydroxyphenethyl-amines in the urine of some schizophrenic patients, which suggested the formation of an unusual metabolite of DA. Substitution of a hydroxy group in the fifth position on the phenyl ring of DA leads to the forma-tion of 6-OHDA. Cohen and Heikkila (1974) showed that DA could be converted to one of three trihydroxyphenethylamines via the Fenton-Huber-Weiss reactions in a system where there was Fe++, hydrogen peroxide, ethylenediaminetetraacetic acid (EDTA), and DA.

Fenton-Huber-Wise reactions:

Fe2+-EDTA + H202 --> Fe3+-EDTA + OH- + OH.
2Fe3+-EDTA + (H2)-ascorbate --> 2Fe2+-EDTA-dehydroascorbate + 2H+
2Fe2+-EDTA + 2H+ + 02 --> 2(Fe3+-EDTA) + H202
02 + 2H+ + Fe2+-EDTA --> H202 + Fe3+-EDTA
02 + Fe3+-EDTA --> 02 + Fe2+-EDTA
02 + H202 --> 02 + OH- + OH.

Based on the reports of Senoh and colleagues (1959) and Cohen and Heikkila (1974), the authors hypothesized that injections of large doses of methamphetamine could result in the formation of a toxic metabolite of DA. The in vivo condition seemed close to the in vitro conditions described by Cohen and Heikkila. Riederer and colleagues (1989) and Halliwell (1989) showed that there is Fe++ stored in many regions of the brain. Hydrogen peroxide is a product of monoamine oxidase metabolism, and its concentration is normally kept small by catalase. If there is excess hydrogen peroxide, however, it could

undergo Fe++ catalysis and result in hydroxy radical formation. Hydroxy radicals are characterized by single unpaired electrons in their outer orbit and are, therefore, highly reactive (Cohen and Heikkila 1974; Halliwell and Gutteridge 1984). The hydroxy radical, once formed, could react with DA to form 6-OHDA. It is possible that with large amounts of DA in the synaptic cleft after high-dose methamphetamine treatment, a small proportion of DA could be metabolized to 6-OHDA and be transported back into the DA neuron through the DA transporter. Once inside the neuron, it can be converted to a semiquinone. The reactive semiquinone seeks an electron donor such as the sulfhydryl groups on cysteine or methionine (components of long-chain proteins). When the semiquinone and long-chain proteins are cross-linked through sulfhydryl bonds, the proteins are denatured and no longer functional (Fornstedt and Carlsson 1989; Fornstedt et al. 1986).

Seiden and Vosmer (1984) have detected 6-OHDA in the striatum of rats and 5,6-dihydroxytryptamine (5,6-DHT) in the hippocampus (Commins et al. 1987a) after a single large dose of methamphetamine. The authors assumed that both conversions proceeded according to a Fenton-type reaction. Attempts to replicate this work have proved difficult; there were instances when neither 6-OHDA nor 5,6-DHT could be detected in any of the rats treated with methamphetamine. Rollema and colleagues (1986) failed to detect extracellular 6-OHDA in rats treated with metham-phetamine using the in vivo dialysis technique. In addition, other investi-gators have tried to measure tissue concentrations of 6-OHDA after meth-amphetamine treatment, but then either found the results inconsistent from rat to rat or could not detect any of the hydroxylated derivatives of DA (Cohen and Gibb, personal communication, 1989). Recently, Wagner and colleagues (1993) reported the formation of 6-OHDA in the micro-gram range after the rats were treated with methamphetamine; in this experiment a monoamine oxidase (MAO) inhibitor and a catechol-O-methyltransferase inhibitor were administered before treatment with methamphetamine. Similar results have been obtained with the use of an MAO inhibitor (Marek et al. 1990c). Although the data are inconclusive at present, the in vivo formation of the neurotoxins 6-OHDA and 5,6-DHT would account for the specificity of methamphetamine effects on DA and 5-HT neurons.

Zigmond and colleagues (Hastings and Zigmond 1992; Zigmond and Hastings 1992) investigated the role of endogenous DA in DA neuro-toxicity induced by methamphetamine. They reported the oxidation

of DA and the formation of cysteinyl-DA adducts using both in vitro and in vivo systems. Although DA oxidation can proceed nonenzymatically (see table 1), they examined the formation of the hydroxy radical as an enzymatic reaction. Peroxidase enzymes are capable of catalyzing the conversion of DA to reactive DA quinones. Since peroxidase enzymes are not present in brain, they tested a similar enzyme, prostaglandin (PG) synthase, which is present in brain. When purified PG synthase was combined with DA and bovine serum albumin, they identified a DA quinone and a cysteinyl-DA adduct. It was inferred from this reaction that hydroxy radicals could be formed (see enzymatic reaction in table 1). They concluded that DA oxidation could be catalyzed by PG synthase and, importantly, that the oxidized quinone was a potential mechanism for cytotoxicity.

TABLE 1. Toxic metabolite formation.

Nonenzymatic reaction	Enzymatic reaction
H202 + Fe2+ ----> OH + OH-	H202 + DA PG syn> Quinone + OH + OH-
OH +DA ----> 6-OHDA	Quinone + Cysteine -> Cysteinyl-DA adduct
6-OHDA ----> Semiquinone	
Semiquinone + Cysteine ---> Cysteinyl-DA adduct	

Hydroxy radicals in rat brain have recently been detected by allowing them to react with injected salicylates to form 2,5-dihydroxybenzoic acid (Liang et al. 1992). This proves to be a useful technique for measurement of hydroxy radical formation in vivo (Giovanni et al. 1992). Metham-phetamine (12.5 mg/kg 4 x 2 hour) caused an increase in free hydroxy radicals as measured by the salicylate techniques, and the increase in free radicals was blocked by AMT. These results again suggest that high neurotoxic doses of methamphetamine promote the formation of free radicals and that DA plays a role in the formation of free radicals when methamphetamine is given in neurotoxic doses.

METHAMPHETAMINE- AND MDMA-INDUCED NEUROTOXICITY CAN BE ANTAGONIZED PHARMACOLOGICALLY

AMT Attenuates Methamphetamine and MDMA Neurotoxicity

AMT prevents methamphetamine-induced depletion of DA and 5-HT (Axt et al. 1990; Ricaurte et al. 1984b; Schmidt et al. 1985b; Wagner et al. 1983). AMT also prevents the MDMA-induced depletion of 5-HT (Stone et al. 1988) and partially attenuates PCA depletion of 5-HT (Axt and Seiden 1990). An interpretation of these findings is that DA release is necessary for methamphetamine- or MDMA-induced neurotoxicity to DA and 5-HT neurons (Schmidt et al. 1985b). The data obtained with AMT are also consistent with the idea that DA is important in driving a potentially toxic, feed-forward, striatal-thalamic-cortical loop (Carlsson 1992, 1995; Carlsson et al. 1995). The AMT results are also consistent with the proposal that the release of DA engenders the formation of neurotoxic metabolites of DA (Commins et al. 1987a; Giovanni et al. 1992; Hastings and Zigmond 1992; Liang et al. 1992; Seiden and Vosmer 1984; Zigmond and Hastings 1992). AMT pretreatment has been shown to decrease amphetamine-induced DA release (Butcher et al. 1988); AMT, therefore, decreases the availability of DA for hydroxy radical reactions. The AMT results do not provide direct support for the drug metabolite or NMDA receptor hypotheses. However, there are preliminary results from the authors' laboratory (unpublished observations) that the combination of methamphetamine plus AMT causes a decrease in core temperature in rats; therefore, the mechanism of action of AMT may be similar to that of MK-801.

DA Receptor Antagonists Block Methamphetamine and MDMA Neurotoxicity

DA antagonists (haloperidol, chlorpromazine) prevent methamphetamine- and MDMA-engendered neurotoxicity (Hotchkiss and Gibb 1980; Schmidt et al. 1990a; Sonsalla et al. 1986). The most parsimonious explanation for DA antagonism by haloperidol in the context of current theories is that the antagonist alters output of the striatal-thalamic-cortical circuit as described above (Carlsson 1992, 1995; Carlsson et al. 1995). By blocking striatal DA receptors, one could theoretically interrupt the dopaminergic influence on the striatal-thalamic-cortical loop. The protection afforded by DA antagonists is difficult to integrate with other theories of neurotoxicity. Haloperidol does not block amphetamine-induced DA

release (Nash and Yamamoto 1992), and in fact it increases DA synthesis (Carlsson and Lindqvist 1963). The haloperidol result, therefore, does not fit well with the hydroxy radical theory because the synthesis of DA as well as its release are increased. Nor does the neuroprotection of haloperidol fit well with the idea that an intact DA system is needed for neurotoxicity: With haloperidol, the DA neuron itself and its ability to release DA remain intact. Finally, the haloperidol results provide no direct support for the toxic drug metabolite and the NMDA receptor theories of amphetamine-analog toxicity.

5-HT2 Antagonists Block Methamphetamine- and MDMA-Induced Neurotoxicity

The 5-HT2 antagonist ketanserin protects against MDMA-induced damage to the serotonin system (Azmitia et al. 1990; Nash et al. 1990). Nash and colleagues (1990) also found that ketanserin inhibits DA synthesis after MDMA treatment, and they suggested that MDMA-induced neurotoxicity involves the activation of DA neurons via 5-HT2 receptors on DA cell bodies. In addition, Nash (1990) demonstrated that ketanserin attenuated MDMA-induced DA release in vivo. The neuro-protective effects of 5-HT2 antagonists were reproduced with other 5-HT2 antagonists (Schmidt et al. 1991, 1992a, 1992b). In addition to blocking MDMA-induced neurotoxicity, MDMA-induced DA release, and MDMA-induced increases in DA synthesis, 5-HT2 antagonists also block the MDMA-induced decreases in DA cell firing (Schmidt et al. 1992a). This series of experiments support the view that DA mediates the MDMA-induced damage to the 5-HT terminal, and the 5-HT2 blocking agents prevent this neurotoxicity by interacting with DAergic activity.

The neuroprotective effects of 5-HT2 antagonists are also consistent with a Ca++ theory of methamphetamine and MDMA neurotoxicity. 5-HT2 receptors are linked to the second messenger inositol-1-4-5-trisphosphate (IP3) (Minchin 1985). IP3 in turn stimulates the release of intracellular Ca++ from sequestration compartments (Berridge and Irvine 1989; Gandhi and Ross 1987). Blockade of the 5-HT2 receptor should, therefore, diminish the amount of intracellular free Ca++ and decrease the likelihood of Ca++-induced cell death (Azmitia et al. 1990). 5-HT2 antagonists administered with MDMA (e.g., MK-801, AMT) also cause a substantial decrease in core temperature that may be responsible for its protective effects (Malberg et al. 1994; Schmidt et al. 1992a). The 5-HT2 antagonist result is consistent with the excitatory feed-forward loop hypothesis in that the 5-HT2

receptors are probably involved in the circuitry (e.g., on the DA cell body). The 5-HT2 antagonist result is also consistent with the hydroxy radical theory since it has been shown that the 5-HT2 antagonist ketanserin attenuates the MDMA-induced release of DA (Nash 1990). The toxic drug metabolite theory and the NMDA receptor theory do not receive direct support from the 5-HT2 antagonist result.

MK-801 and Other NMDA Antagonists Block Methamphetamine- and MDMA-Induced Neurotoxicity

Sonsalla and colleagues (1989) reported that MK-801 protects against methamphetamine-induced damage to DA terminals, and other noncom-petitive as well as competitive NMDA antagonists protected against methamphetamine-induced neurotoxicity (Sonsalla et al. 1991). MK-801 also protects against methamphetamine- and MDMA-induced damage to the serotonin system (Farfel et al. 1992; Johnson et al. 1989a). These results are consistent with an NMDA receptor-mediated calcium mecha-nism of neurotoxicity. Alternatively, MK-801 may protect against methamphetamine- and MDMA-induced neurotoxicity by interacting with temperature regulation mechanisms (Bowyer et al. 1994; Farfel and Seiden 1992); that is, the protection afforded by MK-801 may be due to lowering of body temperature rather than blockade of an NMDA receptor-mediated toxic process (see above).

The protective effects of MK-801 could be consistent with the DA mediation and the hydroxy radical theory of methamphetamine and MDMA neurotoxicity. MK-801 has been shown to decrease metham-phetamine-induced DA release in vivo (Weihmuller et al. 1991), diminishing the availability of DA for conversion into a neurotoxic DA metabolite. However, Kashihara and colleagues (1991) failed to replicate this finding in vivo, and Bowyer and colleagues (1991) failed to block methamphetamine-induced DA release in vitro. These issues will remain controversial until the relationship between glutamate release and DA release as mediated by the glutamate NMDA receptor is clarified.

The protection afforded by MK-801 is consistent with the idea of interrupting an excitatory feed-forward loop. The MK-801 results do not provide direct support for the toxic drug metabolite theory.

Antioxidants Can Block Methamphetamine-Induced Neurotoxicity

Ascorbic acid (Wagner et al. 1986) protects against the DA damage induced by methamphetamine, and cysteine (Schmidt and Kehne 1990; Steranka and Rhind 1987) protects against PCA- and MDMA-induced serotonergic toxicity. The protective effects of these antioxidants are consistent with the hydroxy radical theory of amphetamine-analog neurotoxicity, insofar as the antioxidant would neutralize the hydroxy radical before it can oxidize DA. Whether auto-oxidation occurs enzyma-tically or nonenzymatically, the antioxidants could function in a similar manner by forming a nonreactive complex with the hydroxy radical or protecting DA from quinone formation. The antioxidant results could support the toxic drug metabolite theory in that antioxidants may block the conversion of the parent drug to a toxic metabolite; they could also support the DA mediation theory. The antioxidant results provide no direct support for the excitatory feed-forward loop and NMDA receptor theories.

DA and 5-HT Transporter Inhibitors Block Methamphetamine and MDMA Neurotoxicity

DA uptake inhibitors protect against methamphetamine-induced damage to the DA system, but not against serotonergic damage (Marek et al. 1990b; Schmidt and Gibb 1985b). Similarly, 5-HT uptake inhibitors protect against methamphetamine- or MDMA-induced damage to the 5-HT system, but not the DA system (Ricaurte et al. 1983; Schmidt 1987; Schmidt and Gibb 1985b). Mazindol, which blocks both DA and 5-HT uptake, protects against both DA and 5-HT depletions (Marek et al. 1990b). Amfonelic acid blocks methamphetamine-induced DA toxicity when administered up to 8 hours after methamphetamine (Fuller and Hemrick-Luecke 1982; Marek et al. 1990b). Fluoxetine blocks MDMA-induced 5-HT damage when administered 3 to 6 hours post-MDMA (Schmidt 1987).

Since uptake inhibitors have been shown to block or attenuate the trans-mitter release induced by amphetamine-like compounds (Butcher et al. 1988), these results suggest that DA release is important for DA toxicity, and 5-HT release is important for 5-HT toxicity. This interpretation is consistent with the hydroxy radical theory of amphetamine toxicity: Uptake inhibitors result in less extracellular DA or 5-HT available for conversion to the toxin 6-OHDA or 5,6-DHT. The inhibition of metham-phetamine-induced neurotoxicity

with uptake inhibitors is also consistent with the idea that methamphetamine-induced neurotoxicity is dependent on a striatal-thalamic-cortical loop. Decreasing methamphetamine-induced DA release diminishes DA's influence on this circuit, resulting in protection against methamphetamine- or MDMA-induced neurotoxicity.

The pattern of protection afforded by uptake inhibitors does not completely generalize, however. The DA uptake inhibitor benztropine does not protect against either methamphetamine-induced DA or 5-HT depletion (Marek et al. 1990b); the DA uptake inhibitor GBR 12909 partially protects against MDMA-induced decreases in the serotonin synthetic enzyme TPH (Stone et al. 1988); and finally, the DA uptake inhibitor amfonelic acid has been shown to protect against methamphet-amine-induced damage to the serotonin system (Schmidt and Gibb 1985a). These inconsistencies may reflect some limitations in pharmaco-logical understanding of the drugs being used as specific tools, or they may suggest that the DA and 5-HT systems are somewhat interactive in the mechanism of amphetamine toxicity. For example, the protection against serotonergic damage by the DA uptake inhibitor GBR 12909 (Stone et al. 1988) supports the view that DA release is important for 5-HT toxicity. In addition, the failure of the selective DA uptake inhibitor benztropine (Marek et al. 1990a) to protect against methamphet-amine-induced DA depletion brings into question the parallel between release and toxicity within a given transmitter system. The uptake inhibitor results would support the toxic drug metabolite hypothesis if it could be demonstrated that the uptake inhibitor blocked uptake of the toxic drug metabolite into the neuron. The uptake inhibitor results do not support the NMDA receptor theory in any direct manner.

6-OHDA Lesions Protect Against MDMA-Induced Damage to the 5-HT System

Bilateral 6-OHDA lesions of the substantia nigra partially block MDMA-induced deficits to the 5-HT system (Schmidt et al. 1990b; Stone et al. 1988). These results are consistent with the DA mediation theory of serotonergic toxicity and the excitatory feed-forward loop theory. They provide no support for the NMDA receptor and hydroxy radical theories, but more work is needed for clarification. These results are not consistent with a toxic drug metabolite theory of amphetamine-analog neurotoxicity.

GABA Transaminase Inhibitors and GABA Agonists Protect Against Methamphetamine-Induced Neurotoxicity

Amino-oxyacetic acid inhibits gamma-aminobutyric acid (GABA) transaminase, an enzyme responsible for GABA degradation. Chlormethiazole, an agonist at the GABA-A receptor, also protects against methamphetamine-induced DA and 5-HT damage (Green et al. 1992). GABA is an important inhibitory transmitter in the striatal-thalamic-cortical circuit. It can be postulated that as the levels of GABA increase, the toxic overexcitation of this circuit is diminished, allowing for protection against methamphetamine or MDMA treatment. Since GABA is an ubiquitous inhibitory transmitter, any agent that increases GABA activity will possibly decrease or counteract glutamate activity. In this way the GABA transaminase inhibitor results would be consistent with a glutaminergic mechanism (NMDA receptor-mediated) theory of amphetamine toxicity. The GABA transaminase inhibitor results provide no obvious support for the hydroxy radical theory, the DA theory, or the toxic drug metabolite theory of amphetamine-analog neurotoxicity.

The list of agents discussed above that can affect amphetamine neuro-toxicity is not exhaustive. For example, adrenalectomies (Johnson et al. 1989b) and protein synthesis inhibitors (Finnegan and Karler 1992) both protect against amphetamine analog toxicity, while acetone, which activates several cytochrome P450 enzymes, enhances MDA toxicity (Michel and George 1993). This list of protective agents is likely to grow with future research.

SUMMARY

Methamphetamine and MDMA as well as similar substituted phenethyl-amines are toxic to DA and/or 5-HT neurons. The duration and magni-tude of these effects are dose dependent and are accompanied by different degrees of recovery. MDMA-induced 5-HT damage persists for up to 52weeks in the rat, and methamphetamine-induced DA damage persists for up to 3 years in the rhesus monkey.

Several possible mechanisms of amphetamine-analog toxicity have been reviewed. The excitatory feed-forward loop theory is best supported by the literature. This theory, however, is very wide ranging and difficult to prove or disprove. The hydroxy radical and DA mediation theories are both well supported by the data reviewed.

It should be noted that these two hypotheses are closely related to each other. The DA mediation theory is based on the requirement of an intact DA system for metham-phetamine and MDMA neurotoxicity to occur. The hydroxy radical theory is also based on the presence of DA and 5-HT; in addition, it suggests the formation of toxic hydroxy radicals from DA or 5-HT as thespecific mechanism for the amphetamine-analog neurotoxicity. The hydroxy radical theory also accounts for the fact that amphetamine-analog neurotoxicity is selectively toxic to the DA and/or 5-HT systems of the brain; that is, the toxin is formed either in the synapse or within the neurons that release DA and/or 5-HT as a result of amphetamine analog treatment.

The toxic drug metabolite theory, while not exhaustively studied, has little support from the literature at present. Similarly, the NMDA receptor mediation theory, in its most straightforward form, also has little support from the literature. The protective effects of the NMDA receptor antagonist MK-801 may be a modulatory effect resulting from changes in temperature regulation, rather than a direct effect of antagonizing a link in the toxic mechanism itself. It should be noted that the effects of the pro-tective agent plus amphetamine-analog combinations on body tempera-ture, when thoroughly investigated, may serve to separate agents which protect through a cooling mechanism from agents that protect by inter-fering with the toxic process itself.

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AUTHORS

Lewis S. Seiden, Ph.D.
Professor
Department of Pharmacological and Physiological Sciences
University of Chicago
947 East 58th Street
Chicago, IL 60637

Karen E. Sabol, Ph.D.
Assistant Professor
University of Mississippi
Department of Psychology
301 Peabody
University, MS 38677

Stress, Glucocorticoids, and Mesencephalic Dopaminergic Neurons: A Pathophysiological Chain Determining Vulnerability to Psychostimulant Abuse

Pier Vincenzo Piazza, Michela Marinelli, Françoise Rougé-Pont, Véronique Deroche, Stefania Maccari, Hervé Simon, and Michel Le Moal

INTRODUCTION: VULNERABILITY TO DRUGS AND DRUG ABUSE

It is common knowledge that enormous individual differences exist in drug intake by humans (De Wit et al. 1986). A large number of people have tried drugs at least once, but for most of them drug use experiences are restricted to a single or a few incidents. Among those who persist in taking drugs, drug use can remain an occasional behavior limited, for example, to weekends or parties. Only some drug users develop drug abuse (i.e., a compulsive drug use that becomes the principal goal-directed behavior of the subject) (O'Brien et al. 1986). The origin of the peculiar vulnerability to develop drug abuse observed in some individuals is one of the principal questions to be answered about addiction.

Individual differences in the vulnerability to drug abuse may be explained from two very different points of view. The first is a drug-centered vision of addiction that sees drug abuse as the consequence of the modifications induced in the brain by repeated drug intake. Through the development of tolerance, sensitization, and conditioning, repeated exposure to the drug induces drug dependence—the real cause of abuse. In this viewpoint, vulnerable individuals are those who have greater chances to be, and actually are, the most exposed to the drug because of the environment that surrounds them (peer and/or social pressure are the most often cited causes). The second view may be considered an individual-centered theory of addiction that regards drug abuse as the consequence of a peculiar, pathological reaction to the drug. From this perspective, vulnerable individuals are those who, because of a specific functional

state of the biological substrates that interact with the drug, can experience such a peculiar drug effect.

Understanding the role of the drug and the role of the individual in determining drug abuse is fundamental to defining the goals of addiction therapies. If a drug-centered vision can fully explain drug abuse, then addiction should be considered a neurotoxic disease and the treatment should be achieved by combining two strategies. The first is to suppress the drug's availability, and the second is to reverse the biological effects of repeated drug intake. Conversely, if drug abuse originates from the interaction of the drug with a peculiar individual substrate, the treatment approach should not differ from that of other behavioral pathologies. A therapy should be developed to counteract the biological peculiarity that makes some subjects respond to the drug in a pathological way.

An Experimental Approach to Individual Vulnerability to Drugs

The ideal experiment designed to understand the role of individual biological features in determining vulnerability to drug abuse must fulfill one essential requirement: All subjects should have equal access to the drug under identical environmental conditions. This condition is almost impossible to realize in human studies, but it can be easily achieved in experimental research in animals. Animal research may actually contrib-ute to the understanding of drug abuse because animals self-administer, either intravenously (IV) or orally (Pickens and Harris 1968; Schuster and Thompson 1969; Weeks 1962), almost all the drugs abused by humans (Yokel 1987).

In stable laboratory conditions individual differences in the propensity to develop drug intake are easily evidenced in rodents (Deminière et al. 1989). For example, when low doses of psychostimulant drugs are used and the behavior is studied in the acquisition phase, only some laboratory rats acquire IV self-administration (Piazza et al. 1989, 1990b, 1991b, 1993b). Propensity to develop psychostimulant self-administration not only exists, but can also be predicted by the individual behavioral re-sponse to stressful situations such as exposure to a novel environment (Piazza et al. 1989, 1990b, 1991b). Indeed, a positive correlation exists between locomotor response to novelty and the amount of amphetamine taken during the first days of testing for IV self-administration.

Individual differences in the propensity to develop drug self-adminis-tration can be illustrated by dividing animals into subgroups on the

basis of their locomotor responses to novelty (Piazza et al. 1989,-1990b,1991b). The first subgroup, the high responders (HRs), contains all the animals with an activity score above the median of the entire group. The second subgroup, the low responders (LRs), contains all the rats with an activity score below the group median. When HR and LR animals are tested for IV self-administration of amphetamine (between 10 and 30 micrograms per injection (µg/inj)), HRs will acquire self-administration whereas LRs will not (Piazza et al. 1989, 1990b, 1991b). Similar results have been obtained when HRs and LRs are tested for self-administration of cocaine (100µg/inj) (Piazza et al., unpublished data).

Differences in psychostimulant self-administration between HRs and LRs do not simply reflect differences in threshold sensitivity to the reinforcing effects of this class of drugs. In fact, during the first days of testing for self-administration, both groups self-administer amphetamine or cocaine at similar rates. However, this behavior rapidly extinguishes in LRs whereas it is stabilized and maintained in HRs (Piazza et al. 1990b, 1991b, 1993b). This result suggests that LRs are not insensitive to the reinforcing effects of the drugs at the dose used, but that psychostimu-lants have a higher efficacy as reinforcers in HRs.

HR and LR rats also differ in other psychostimulant-induced behaviors. HRs show a higher sensitivity to the psychomotor effects of amphetamine and cocaine, displaying a higher locomotor response to systemic and intra-accumbens injection of these drugs (Exner and Clark 1993; Hooks et al. 1991, 1992a, 1992b, 1992c; Piazza et al. 1989, 1991b). HRs also seem more prone to develop conditioning of the motor effects of amphet-amine. Following low doses of amphetamine (0.5 milligrams per kilogram (mg/kg)), conditioning of amphetamine-induced locomotion is developed by HRs but not by LRs (Jodogne et al. 1994).

HRs and LRs also differ in amphetamine-induced sensitization, though contrasting results have been found. Some authors have shown that sensitization is exclusively developed by HRs (Hooks et al. 1992c), whereas in other laboratories (Exner and Clark 1993; Piazza et al. 1989) sensitization appears more prevalent in LRs. In these experiments, after sensitization LRs no longer differed from HRs in amphetamine-induced locomotion and self-administration (Exner and Clark 1993; Piazza et al. 1989). Variation in sensitization of HR and LR animals under different experimental conditions may be explained by uncontrolled differences in the establishment of a stimulus control

of sensitization (Stewart and Badiani 1993). Thus, it has been shown that the expression of sensiti-zation in HRs is under the control of the environmental cues associated with the effect of the drug, whereas sensitization is not under such control in LRs (Jodogne et al. 1994). In other words, in conditions that facilitate a stimulus control of sensitization, HRs should show a higher sensitization than LRs; when the influence of conditioning is minimized, sensitization may appear exclusively in LRs.

Animal research has shown that vulnerability to develop drug abuse may depend on preexisting individual differences, and propensity to develop self-administration can vary among individuals having equal access to the drug under identical laboratory conditions. This propensity can also be predicted in rodents by unconditioned spontaneous behaviors such as locomotor response to novelty. Prediction of drug intake by independent behavioral measures is an important finding for three reasons. First, it identifies that individual differences in drug intake are not due to uncon-trolled experimental errors. Second, it supports the hypothesis that indi-vidual differences in drug intake result from differences in the biological substrates interacting with the drug. Third, it provides an essential tool for the study of the biological basis of individual vulnerability to drugs. Indeed, the comparison of vulnerable and resistant subjects after repeated testing for self-administration or other drug-mediated responses would not allow differentiation between drug-induced and preexisting differences.

Factors Determining Individual Vulnerability to Psychostimulants

Research on the origins of individual vulnerability to drugs has principally focused on psychostimulant drugs. However, individual differences in the vulnerability to self-administer opioids have also been reported (Glick et al. 1992) and may correlate with differences in vulner-ability to psychostimulants (Deroche et al. 1993b). In particular, the specific roles of mesencephalic dopaminergic neurons, stress, glucocorti-coids, and the interactions between these three factors have been exten-sively studied in determining vulnerability to cocaine and amphetamine. The observed effects of these three factors upon vulnerability to psycho-stimulant use are briefly reviewed below.

Mesolimbic Dopaminergic Neurons. These neurons, and in particular an increase in the activity of their projection to the nucleus accumbens, may be a crucial factor in determining a greater vulnerability to the reinforcing effects of psychostimulants. Indeed,

the reinforcing properties of this class of drugs seem to be mediated by the psychostimulant-induced increase in extra-cellular concentration of dopamine (DA) in the nucleus accumbens (Koob and Bloom 1988; LeMoal and Simon 1991). Specific neurochemical lesions of the dopaminergic projection to the nucleus accumbens decrease or are extinguished depending on the self-administered dose of IV psycho-stimulants (Roberts et al. 1977, 1980, 1982). Furthermore, animals will self-administer psychostimulants directly into the nucleus accumbens (Hoebel et al. 1983). Specific agonists or antagonists of dopaminergic receptors may respectively increase or decrease the reinforcing properties of psychostimulants (Davis and Smith 1977; Risner and Jones 1976; Roberts and Vickers 1984, 1987). In this respect 7-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OHDPAT), a dopaminergic agonist showing the highest affinity for dopamine type 3 (D3) receptors, is more potent than agonists with a higher affinity for D1 or D2 dopaminergic receptors (Caine and Koob 1993). D3 receptors are localized primarily in the nucleus accumbens, whereas D1 and D2 receptors have a widespread distribution throughout the brain (Sokoloff et al. 1990).

Stressful Situations. Stressful situations affect the activity of mesencephalic dopaminergic neurons, which in turn modify behavioral response to stress. Three main interactions between stress and DA can be identified. First, following the pioneer work of Thierry and coworkers (1976), it is now widely accepted that acute exposure to most situations that are considered experimental models of stress increases the activity of mesencephalic dopaminergic neurons. Second, repeated exposure to stress induces a long-term sensitization of the response of mesencephalic dopaminergic neurons to subsequent activation, and in particular a sensitization of their response to psychostimulants (Kalivas and Stewart 1991; Robinson and Becker 1986; Robinson and Berridge 1993). Third, behaviors that are specifically elicited by situations that may be interpreted as stressful depend on the activity of mesencephalic dopaminergic neurons. For example, the polydipsia (Falk 1961) displayed by food-deprived rats on a fixed interval of food reinforcement schedule (schedule-induced polydipsia) or the compulsive eating induced in satiated rats by a mild pinching of the tail (Antelman et al. 1976) are decreased by neurochemical lesions of dopaminergic mesencephalic neurons (Antelman et al. 1975; Robbins and Koob 1980).

Glucocorticoids. Glucocorticoids may be one of the factors that mediate the increase in stress-induced dopaminergic activity. First, glucocorticoid secretion by the adrenal gland is one of the principal

biological responses to stress (Selye 1950), and an increase in corticosterone secretion is observed in all those situations that increase the activity of dopaminergic neurons (Bohus et al. 1982; Dantzer and Mormède 1983; Knych and Eisenberg 1979; Sachser 1986). Second, mesencephalic dopaminergic neurons contain corticosteroid receptors (Härfstrand et al. 1986), and glucocorticoids can modify the metabolic activity of aminergic neurons (Rothschild et al. 1983, 1985). Third, suppression of corticosterone secretion suppresses DA-dependent behavioral responses to stress such as schedule-induced polydipsia (Levine and Levine 1989) or wheel running (Lin et al. 1988).

Working Hypothesis. On the basis of these observations it has been hypothesized (Piazza et al. 1991a) that stress, glucocorticoids, and dopaminergic neurons may be organized in a pathophysiological chain that determines vulnerability to develop drug abuse. In order to develop this hypothesis, the authors first review the relationship that exists between each of these factors and the propensity to develop IV self-administration of psychostimulants. Then the possible interactions in a pathophysiological chain are examined.

Dopaminergic Neurons and Vulnerability to Psychostimulants

Comparisons between HRs and LRs have shown that a higher vulnerability to develop drug self-administration is associated with a higher dopaminergic activity in the nucleus accumbens. Postmortem studies have shown that animals vulnerable to develop IV self-administration of psychostimulants (HRs) have a higher 3,4-dihydroxyphenylacetic acid (DOPAC)/DA ratio in the nucleus accumbens compared with more resistant subjects (LRs). The DOPAC/DA ratio, which is considered an indirect index of the release of DA, is higher in HRs than in LRs both under basal conditions and after exposure to novelty (Piazza et al. 1991c). Microdialysis studies have confirmed and extended these results. Quanti-tative microdialysis has shown that, in basal conditions, extracellular concentrations of DA in HR rats are three times higher than that observed in LRs (Hooks et al. 1992a). Furthermore, the percentage increase in extracellular concentrations of DA in response to stress (Rougé-Pont et al. 1993) or to the intraperitoneal (IP) administration of cocaine (Hooks et al. 1991) is also greater in HRs than in LRs.

Greater dopaminergic activity in the nucleus accumbens is not simply associated with a higher propensity to develop amphetamine self-administration; a causal relationship may also exist between these two

variables. Very different experimental manipulations, such as 6-hydroxydopamine (6-OHDA) lesion of the amygdala (Deminière et al. 1988) or electrolytic lesion of the raphe (Simon et al. 1980), that have a common ability to increase dopaminergic activity in the nucleus accum-bens (Hervé et al. 1981; Simon et al. 1988) also increase propensity to acquire amphetamine self-administration.

The possible origins of the hyperactivity of the dopaminergic projection to the accumbens in vulnerable subjects is certainly a very important question. One of the possible causes, a hyperactive hypothalamic-pituitary-adrenal (HPA) axis, is analyzed in detail in the following paragraphs. However, another possible cause that should not be disregarded is the low dopaminergic activity in the prefrontal cortex which characterizes HR rats (Piazza et al. 1991c). This factor may be relevant because dopaminergic activity in the prefrontal cortex exercises inhibitory control on the activity of the dopaminergic projections in the nucleus accumbens (Louilot et al. 1989). Furthermore, lesions of the dopaminergic terminal fields in the prefrontal cortex increase the propensity to self-administer cocaine (Schenk et al. 1991).

Thus, results obtained with multiple approaches converge in suggesting that increased dopaminergic activity in the nucleus accumbens may increase the vulnerability of an individual to develop psychostimulant self-administration.

Stress and Vulnerability to Psychostimulants

An increase in vulnerability to psychostimulants can be induced by several conditions considered as models of stress. The first evidence of the strong control that stressors exercise on psychostimulant self-adminis-tration is probably that from Carroll and coworkers (1979), showing that food restriction increases the efficacy of psychostimulants to act as rein-forcers in a self-administration test. Subsequent research has shown that a large variety of stressful conditions occurring during adult life can increase propensity to self-administer drugs in rodents. For example, a faster acquisition of psychostimulant self-administration has been found in rats subjected to situations that seem relevant from an ethological point of view, for instance social isolation (Deroche et al. 1994; Schenk et al. 1987), social aggression (Haney et al., unpublished results; Miczek et al. 1994), and fixed social hierarchy in highly competitive colonies (Maccari et al. 1991). Furthermore, more artificial and physical stressors such as tail-pinch (Piazza et al. 1990a) or electric foot-shock

(Goeders and Guerin 1994), also increase propensity to develop psychostimulant self-administration.

Very early experiences such as prenatal stress can also increase vulnera-bility to psychostimulants (Deminière et al. 1992). An increase in the propensity to develop amphetamine self-administration has been observed in adult rats (4 months old) whose mothers had been submitted to a re-straint procedure (half an hour twice a day) during the third and fourth week of gestation. Prenatal stress not only increases amphetamine self-administration but also the unconditioned behaviors that characterize spon-taneously vulnerable subjects. Similar to the comparison between HRs and LRs, prenatally stressed rats show a greater locomotor response to novelty and amphetamine as compared with controls (Deminière et al. 1992).

Two recent papers by Shaham and Stewart (1994, 1995) increased the knowledge of the influences of stress on drug self-administration. These authors clearly point out that the effects of stress are not limited to a faster acquisition of self-administration; they also relate to a higher seeking for the drug that can be seen in stressed subjects and in other experimental conditions. These authors found that, over a large range of doses, the breaking point for heroin self-administration is consistently higher in stressed than in control rats (Shaham and Stewart 1994). Furthermore, in rats in which responding for the drug has been extinguished by a long period of extinction, a single stressful experience can induce a relapse in responding for the drug (Shaham and Stewart 1995). Shaham and Stewart (1994) also raised some interesting methodological considera-tions: Although stressed and control rats differ in their breaking points in a progressive ratio schedule, they are almost identical for the rate of self-administration when a fixed ratio (FR) schedule is used. This result indi-cates that when a low fixed ratio is used, measurement of the rate of re-sponding as a function of dose may not reveal differences in vulnerability to the reinforcing properties of drugs.

These results obtained with multiple approaches agree in suggesting thatstressful experiences, either very early in life or during adulthood, may increase the vulnerability of an individual to develop drug self-administration.

Glucocorticoids and Vulnerability to Psychostimulants

Corticosterone, the main glucocorticoid in the rat, seems to have a large influence on the vulnerability to psychostimulants. This hormone facilitates psychomotor and reinforcing effects of amphetamine and/or cocaine, and individual differences in stress-induced corticosterone secretion correlate with individual differences in vulnerability to drugs.

Psychomotor Effects. Psychomotor effects of cocaine depend on basal corticosterone secretion. Suppression of endogenous glucocorticoids by adrenalectomy reduces the locomotor response to cocaine by approxi-mately 50 percent, and a corticosterone replacement treatment, which reinstates diurnal basal levels of the hormone, totally suppresses the effects of adrenalectomy (Marinelli et al. 1994). Suppression of gluco-corticoid secretion similarly reduces the locomotor response to an intra-accumbens injection of cocaine (Marinelli et al. 1994). This result indicates that modulation of sensitivity to cocaine by glucocorticoids involves changes of the mesencephalic dopaminergic transmission in reactivity to the drug. Thus, the locomotor response to the intra-acumbens injection of psychostimulants depends on DA (Delfs et al. 1990; Kelly and Iversen 1976).

Reinforcing Effects. Reinforcing effects of psychostimulants are also increased by corticosterone. Administration of corticosterone induces the acquisition and maintenance of amphetamine self-administration in LR rats that do not acquire this behavior otherwise (Piazza et al. 1991b). Furthermore, in HR rats, 8 days of treatment with metyrapone (the inhibitor of corticosterone synthesis) reduced the intake of cocaine by approximately 50 percent during a testing for relapse (Piazza et al. 1994). More precisely, in this study animals were permitted to acquire and stabilize cocaine self-administration (100 µg/inj) over 10 days. They were then submitted to a drug-free period of 4 days followed by 8 days ofmetyrapone treatment (100 mg/kg twice a day). After this 12-day period (4 days drug free followed by 8 days of metyrapone), the testing for relapse started. Animals had access to cocaine for 5 days during the metyrapone treatment. Metyrapone treatment seemed devoid of major nonspecific motor effects because it did not modify exploratory and food-directed behaviors (Piazza et al. 1994).

Individual Differences. Individual differences in corticosterone secretion can predict vulnerability to drug intake. HR rats have a

longer lasting corticosterone secretion in response to different stressors such as exposure to a novel environment and restraint (Piazza et al. 1991b). Furthermore, the levels of corticosterone 2 hours after exposure to stress are positively correlated with the intake of amphetamine during self-administration (Piazza et al. 1991b). The higher locomotor response to novelty observed in HRs also depends on corticosterone. Suppression of individual differences in stress-induced corticosterone secretion, by fixing corticosterone levels in the range of basal diurnal levels, induces a decrease in HRs' locomotor response to novelty to levels that do not differ from LRs (Piazza et al., unpublished results). Thus, an increase in cortico-sterone secretion may be a factor in increasing individual vulnerability to psychostimulant drugs.

Interactions Between Stress, Corticosterone, and DA in Determining Individual Vulnerability to Psychostimulants

The data outlined in the previous paragraphs show that stress, cortico-sterone, and dopaminergic activity by themselves can influence the propensity of an individual to develop psychostimulant self-adminis-tration. The following paragraphs discuss whether these three factors may be organized in a pathophysiological chain determining vulnerability to drugs. The possible dependence of the effects of one factor upon the activation of the others is considered, including whether stress-induced sensitization of drug effects depends on changes in the reactivity of dopaminergic neurons or stress-induced corticosterone secretion. The authors also discuss whether an increase in corticosterone levels can increase the activity of mesencephalic dopaminergic neurons and the role played by stress-induced corticosterone secretion on the dopaminergic effects of stress.

Stress, Dopamine, and Vulnerability to Psychostimulants

The first step in the study of the possible relevance of the interactions between stress, corticosterone, and DA in determining vulnerability to drugs is to ask if the stress-induced increase in vulnerability to psycho-stimulants may be mediated by an increase in the activity of dopami-nergic neurons.

A large body of evidence indicates that stress-induced sensitization of the behavioral effects of drugs may be mediated by an increase of the response of mesencephalic dopaminergic neurons to the drug. Reviewing this litera-ture it is not the purpose of the present synthesis; the reader is referred to several very good reviews on this subject

(Kalivas and Stewart 1991; Robinson and Becker 1986; Robinson and Berridge 1993; Stewart and Badiani 1993).

Briefly, it is well known that stress activates dopaminergic activity and that repeated stress induces a long-lasting increase in the dopaminergic response to psychostimulants. A criticism to these observations may be that, although stressors increase the activity of dopaminergic neurons, many other neuronal systems are also activated and modified and could mediate the increase in vulnerability to drugs induced by stressors. For this reason, it was important to examine if a stimulation more selective than stress that also activates the dopaminergic neurons may similarly increase vulnerability to psychostimulants. For this purpose, the effects of repeated tail-pinch were compared with those of repeated amphetamine injections. Indeed, repeated stress and repeated amphetamine injections seem to have comparable effects on the activity of dopaminergic neurons (Antelman et al. 1980). It was found that the two treatments had compar-able effects and increased both amphetamine-induced locomotion and self-administration in a similar way (Piazza et al. 1990a).

An increase in the activity of mesencephalic dopaminergic neurons thus may be the neural mechanism through which stressful experiences enhance vulnerability to drugs.

Stress, Corticosterone, and Vulnerability to Psychostimulants

Stress-induced sensitization of the behavioral effects of psychostimulants depends on corticosterone. Three lines of observations support this state-ment. First, blockade of stress-induced corticosterone secretion totally suppresses the increase in the locomotor response to amphetamine induced by different stressful experiences such us repeated restraint (Deroche et al. 1992a) or food restriction (Deroche et al. 1993a). Second, repeated injections of corticosterone, at doses that increase the levels of the hor-mone to the range induced by stress, induce sensitization of the loco-motor response to amphetamine (Deroche et al. 1992b). Third, animals made vulnerable to drugs by previous stressful experiences present an enhanced corticosterone secretion. For example, rats submitted to pre-natal stress (Maccari et al., in press), repeated tail pinch (Piazza et al. 1991b), social aggression (Haney et al., unpublished results; Miczek et al. 1994), or fixed social hierarchy (Maccari et al. 1991) show both a higher propensity to develop amphetamine self-administration and a longer stress-induced corticosterone secretion.

Stress-induced corticosterone secretion seems to control both the development and the expression of stress-induced sensitization to the behavioral effects of psychostimulants. Thus, metyrapone treatment suppresses food restriction-induced sensitization of the locomotor effects of cocaine when administration is started before the beginning of the food restriction or when administration is started 8 days later (i.e., when the sensitization is already established) (Rougé-Pont et al. 1994). These observations suggest that stress-induced corticosterone secretion may be one of the hormonal mechanisms by which stressful experiences enhance vulnerability to drugs.

Corticosterone and Dopamine

The existence of a pathophysiological chain composed of stress, cortico-sterone, and DA implies that glucocorticoids can control the activity of mesencephalic dopaminergic neurons. Although postmortem studies indicate that synthetic glucocorticoids such as dexamethasone can control the metabolism of catecholaminergic neurons, more recent in vivo inves-tigations have provided contrasting results. For example, Imperato and coworkers (1989, 1991) have shown, by means of microdialysis, that although corticosterone can induce a moderate increase in extracellular DA concentrations, such an effect is only obtained with doses that induce plasmatic levels of the hormone that are above the physiological range. In contrast, Mittleman and coworkers (1992), using in vivo voltammetry, have shown an important increase in extracellular DA concentrations following an injection of corticosterone that should maintain the levels of the hormone in the physiological range.

Variability of results in dopaminergic effects of glucocorticoids may be explained by possible state-dependent effects of these hormones. This hypothesis is supported by three observations. First, the effect of cortico-sterone on membrane potentials is dependent on background neuronal activity (Joels and De Kloet 1992). For example, the effects of cortico-sterone on hippocampal CA1 cells are evident only if these neurons are in a depolarized state, whereas glucocorticoids are without effect in resting conditions. Second, behavioral effects of glucocorticoids can differ in different periods of the circadian cycle (Kumar and Leibowitz 1988; Temple and Leibowitz 1989). In adrenalectomized rats, central or systemic corticosterone administration is able to induce intense eating during the first hours of the dark period, but has poor or no effects during the light phase or at the end of the dark period. Third, neurochemical effects of

glucocorticoids may vary among individuals. Rats with a higher predisposition to develop amphetamine self-administration (HRs) are four times more sensitive to the behavioral effects of corticosterone than resistant subjects (LRs) (Piazza et al. 1993a).

Results recently obtained in the authors' laboratory support state-dependent effects of glucocorticoids on the activity of dopaminergic neurons (Piazza et al. 1993c). The administration of corticosterone, at doses that induce an increase in the levels of the hormone similar to those induced by stress, increases extracellular DA levels in the nucleus accum-bens. However, the intensity of the dopaminergic effects of corticoste-rone is influenced by the contingent situation and individual differences. First, the effects of the hormone are influenced by the dark/light cycle, being significant only when the hormone is administered in the dark phase, which corresponds to the period of activity in rodents. Second, in the dark period, the effects of corticosterone on DA are greater (around 80 percent increase) when the hormone is administered contingent to eating than when it is administered in basal conditions (around 20 percent increase). Third, dopaminergic effects of corticosterone vary profoundly among individuals. HR animals, compared with LRs, show a greater increase in extracellular DA concentrations in response to the same dose of corticosterone.

The effects of corticosterone on DA may be proportional to the level of dopaminergic activity at the moment when corticosterone levels rise. Several observations support this hypothesis. First, in the rat, the meta-bolic activity of dopaminergic neurons is greater during the dark period than in the light one (Paulson and Robinson 1994). Second, eating is a behavioral activity that induces an increase in dopaminergic activity (Hoebel et al. 1989). Third, the effects of corticosterone on DA are amplified in animals (such as HRs) that have a higher level of dopami-nergic activity in the nucleus accumbens (Piazza et al. 1991c; Hooks et al. 1991, 1992a).

Corticosterone can thus stimulate the activity of mesencephalic dopaminergic neurons. These effects are greater in animals that are vulnerable to develop psychostimulant self-administration. This interaction between corticosterone and DA is compatible with the hypothesis that these two factors may interact in determining vulnerability to psychostimulants.

Stress, Corticosterone, and Dopamine

In the previous paragraph it has been shown that stress-induced increase in vulnerability to drugs could be mediated by an increase in the activity of dopaminergic neurons and is dependent on stress-induced corticoste-rone secretion. This hormone, in turn, can stimulate the activity of the mesencephalic dopaminergic transmission. In order to complete the picture of the interactions between stress, corticosterone, and dopamine, the dependence of the dopaminergic effects of stress on corticosterone should be analyzed.

Dopaminergic response to stress is decreased in subjects in which stress-induced corticosterone secretion is suppressed (Rougé-Pont et al., unpub-lished results). The increase in extracellular DA concentrations in the nucleus accumbens induced by 10 minutes of tail pinch is less in subjects in which corticosterone levels have been fixed in the basal range by adrenalectomy (ADX) associated with corticosterone pellet implantation (ADX + pellet). Such corticosterone pellets release a stable amount of corticosterone in the range of basal physiological levels (Meyer et al. 1979). In contrast, stress-induced increase in accumbens DA is similar to that of controls if ADX + pellet rats receive, concomitantly with the stress, an IP injection of corticosterone (3 mg/kg). The injection of corticosterone at this dose increases the hormone levels to the range of those observed during stress (Rougé-Pont et al., unpublished results).

Stress-induced corticosterone secretion has different effects on the dopami-nergic response to stress by HR and LR rats (Piazza et al. 1993c). Thus, blockade of stress-induced corticosterone secretion does not modify the dopaminergic response to stress in animals resistant to developing psycho-stimulant self-administration (LRs). In contrast, the enhanced dopami-nergic response to stress that characterizes vulnerable subjects (HRs) is suppressed by blockade of stress-induced corticosterone secretion. In other words, after an adrenalectomy associated with the implantation of a cortico-sterone pellet, HR rats show an identical dopaminergic response to stress as LRs; this response, in turn, is not modified by manipulation of corticoste-rone secretion.

Thus, stress-induced corticosterone secretion may be one of the biological mechanisms by which life experiences increase the activity of dopami-nergic neurons. This last observation supports the hypothesis that stress, corticosterone, and mesencephalic

dopaminergic neurons may be organized in a pathophysiological chain determining vulnerability to psychostimulant abuse.

CONCLUSIONS

The results outlined in this chapter permit one to draw three principal conclusions. First, the development of psychostimulant abuse it is not the simple consequence of the proper effects of these substances, but the result of their interaction with specific individual substrates. Thus, differences in the propensity to develop psychostimulant intake are evidenced in animals having equal access to the drug in stable laboratory conditions. Such individual differences do not arise from uncontrolled experimental errors, since they can be predicted by unconditioned spontaneous behaviors.

Second, stress, corticosterone, and mesencephalic dopaminergic neurons may be organized in a pathophysiological chain determining vulnerability to psychostimulants. More precisely, an increased corticosterone secre-tion, spontaneously present in certain individuals or induced by stress in others, could increase the activity of mesencephalic dopaminergic neurons and thereby enhance the probability (i.e., predispose) that psychostimu-lant administration will result in its abuse.

Third, the possibility of modulating the behavioral and dopaminergic re-sponses to psychostimulants by pharmacological manipulations of cortico-sterone secretion may open new therapeutic strategies for drug abuse.

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AUTHORS

Pier Vincenzo Piazza, M.D., Ph.D.
Chargé de Recherche, INSERM

Michela Marinelli, Pharm.D.
Postdoctoral Fellow

Françoise Rougé-Pont, Ph.D.
Ingegneur D'Etude, INSERM

Véronique Deroche, Ph.D.
Chargé de Recherche, INSERM

Stefania Maccari, Ph.D.
Associate Professor

Hervé Simon, Ph.D.
Professor

Michel Le Moal, M.D., Ph.D.
Professor

Psychobiologie des Comportements Adaptatifs, INSERM U259,
Université de Bordeaux II
Domaine de Carreire
Rue Camille Saint-Saëns,
33077 Bordeaux Cedex
France

Clinical and MRI Evaluation of Psychostimulant Neurotoxicity

George Bartzokis, Mace Beckson, and Walter Ling

PSYCHOSTIMULANT NEUROTOXICITY AND CLINICAL MEDICATION TRIALS

Human and animal data have demonstrated that psychostimulants can cause central nervous system (CNS) neurotoxicity. In addition to gross neurotoxic effects such as infarcts and seizures (Ritz and George 1993; Rodnitzky and Keyser 1992), more subtle cellular toxicity has also been demonstrated and is especially evident in the dopaminergic neurotransmitter system (Gibb et al. 1993).

The Dopaminergic System is believed to be of central importance to the brain processes involved in the development of human addiction to psychoactive substances (Parsons et al. 1991; Robinson and Berridge 1993). Study of animal models of addiction has revealed that mesocorti-colimbic dopaminergic pathways are necessary for the establishment of repetitive self-administration of psychoactive drugs such as cocaine, opiates, and alcohol (Koob and Bloom 1988). Repetitive self-adminis-tration will not occur following disruption of dopaminergic transmission, including lesions to the nucleus accumbens. This nucleus, anatomically distinct in rats but indistinct from the ventral striatum in man, receives dopaminergic input from presynaptic neurons whose cell bodies reside in the ventral tegmental area (VTA) of the midbrain (Fallon 1988). Cocaine and other psychostimulants bind to the dopaminergic transporter of the presynaptic nerve terminal, thereby blocking reuptake and increasing dopaminergic synaptic transmission (Gawin 1991). This presumably applies to all dopaminergic systems, including mesocorticolimbic pro-jections believed responsible for the repetitive behaviors of addiction as well as the nigrostriatal dopamine system responsible for the coordination of complex movements.

The search for a medication to ameliorate or reverse the clinical syndrome of cocaine addiction, including withdrawal, craving, and relapse, has taken on great urgency in the context of both a high prevalence of cocaine depen-dence and the limited efficacy of established treatment strategies (Adams et al. 1986; Kosten et al. 1987). Clinical trials of medications that affect the dopaminergic

systems have been and continue to be conducted to evaluate the potential therapeutic usefulness of such agents. Except for gross neurological abnormalities (e.g., clinical evidence of stroke), these studies generally do not evaluate for the more subtle indicators of neurotoxic damage. Thus, the subject samples recruited for these trials may be hetero-geneous with respect to the functioning and pharmacologic responsiveness of the dopaminergic system. This problem would be compounded by the fact that most trials are short in duration and enroll patients early in their abstinence. These factors may limit any recovery from neurotoxic damage in individuals for whom reversibility of such damage is possible.

The inclusion of highly heterogeneous groups of patients in clinical trials in the absence of any measures of neurotoxicity could greatly hinder the effort to develop pharmacologic treatments in at least two ways. First, heterogeneity of the population reduces the power of clinical trials to detect medication efficacy. Second, the opportunity to detect subgroups of patients in whom a pharmacologic intervention is either especially efficacious or possibly countertherapeutic could be missed if quantitative assessments of neurotoxicity are not done a priori.

The following sections review a hypothesis suggesting new avenues of inquiry into the impact of neurotoxicity on medication trials. The data presented are preliminary and, although supportive of the thesis of neurotoxicity in psychostimulant-addicted populations, they should be interpreted with caution.

Mechanisms of Basal Ganglia Neurotoxicity

Catecholamine metabolism produces free radicals (Halliwell and Gutteridge 1985, 1988) and psychostimulants greatly increase catechol-amine metabolism. Animal data support the hypothesis that the increased levels of catecholamines cause psychostimulant neurotoxicity through free radical mechanisms and that these toxic effects are persistent (Gibb et al. 1993). Metabolic abnormalities, which do not improve with long periods of abstinence, have also been observed in the basal ganglia dopaminergic terminals and in the cortex of cocaine addicts (Baxter et al. 1992; Volkow et al. 1992, 1993), and these abnormalities have been shown to be interrelated (Volkow et al. 1993). One study also reported increased urinary lipoperoxides (breakdown products from oxidative damage of membrane polyunsaturated lipids) in abusers of cocaine (Knight et al. 1988).

The basal ganglia, a region rich in catecholamine terminals, are at high risk for neurotoxicity caused by psychostimulants because increased oxidative stress results from increased dopamine metabolism. Bursts of increased dopamine metabolism increase free radical production and can cause neurotoxicity (Halliwell and Gutteridge 1985, 1988; Gibb et al. 1993). An important additional risk factor for basal ganglia oxidative damage is the high levels of iron present in these structures (Hallgren and Sourander 1958; Morris et al. 1992). As shown in figure 1, iron can catalyze the transformation of free radicals into highly reactive hydroxyl radicals capable of causing neurotoxicity by denaturing biomolecules and initiating lipid peroxidation (Halliwell and Gutteridge 1985, 1988).

Some animal data indicate that amphetamines are more likely to be neurotoxic than cocaine alone (Bennett et al. 1993) or result in different neurotoxicity patterns than cocaine (Ellison and Switzer 1993). Some investigators have even reported a lack of evidence of neurotoxic effects of cocaine in controlled animal experiments (Goodman and Sloviter 1993; Bennett et al. 1993). As these investigators have pointed out, however, this finding should not be interpreted as evidence of lack of toxicity in human addicts because of differences between human and animal physiology, as well as differences between human drug use patterns and animal psychostimulant exposure in laboratory paradigms.

The extent of neurotoxicity in humans can be increased by multiple factors. In the context of cocaine use, even limited exposure to amphetamines can have severe neurotoxic consequences (Kleven and Seiden 1991). Addicts rarely limit themselves to the abuse of a single substance, and, in addition, cocaine is often "cut" with amphetamines. Cocaine may be especially neurotoxic once it enters the CNS (Gu et al. 1993). By bypassing hepatic metabolism, human crack users can achieve very high CNS cocaine levels. Thus, cocaine-induced neurotoxicity may be especially relevant for crack users. In addition, animal data indicate that dopamine metabolism may be markedly increased by significant interactions between cocaine and environmental stress (Kalivas and Duffy 1989). Such interactions would suggest that the psychosocial stressors addicts endure could also increase the likelihood of deleterious effects from cocaine. Finally, considering that human addicts use cocaine for months to years versus the limited exposure in most animal experi-ments, there is an increased likelihood that neurotoxicity is a significant component of the human psychostimulant dependence syndrome.

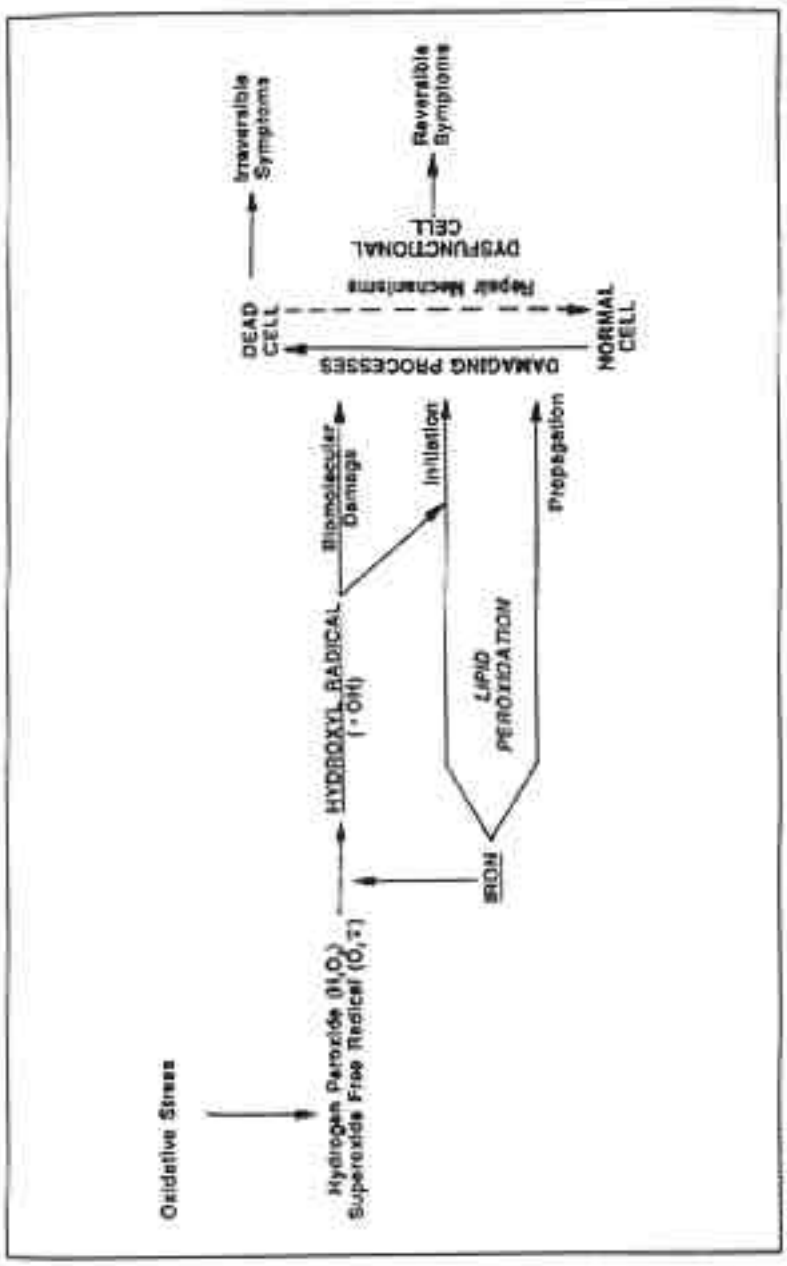
Oxidative Stress
Hydrogen Peroxide (H_2O_2)
Superoxide Free Radical ($O_2^{\cdot-}$)
IRON
HYDROXYL RADICAL
($^{\cdot}OH$)
LIPID PEROXIDATION
Initiation
Propagation
Biomolecular Damage
DAMAGING PROCESSES
NORMAL CELL
DEAD CELL
Repair Mechanisms
DYSFUNCTIONAL CELL
Reversible Symptoms
Irreversible Symptoms

FIGURE 1.

Clinical Evidence of Basal Ganglia Neurotoxicity

Despite the fact that evaluation of neurotoxicity in humans is hampered by the lack of microscopic specimens, evidence is beginning to emerge. Clinical manifestations of subtle neurotoxicity such as deficits in concen-tration and memory (O'Malley et al. 1992; Berry et al. 1993) have been reported. Persistent extrapyramidal movement disorders such as dystonia, chorea, and tics, which are clearly associated with amphetamine and neuroleptic exposure (Rodnitzky and Keyser 1992; Bartzokis et al. 1990), have also been reported with cocaine abuse (Habal et al. 1991; Bauer 1993; Daras et al. 1994). The prevalence of choreoathetoid movements in the cocaine-addicted population is unknown, and it is probably under-appreciated since Daras and colleagues (1994) report that the addicts themselves are aware of the association between crack binges and choreo-athetoid movements, referring to the phenomenon as "crack dancing."

Extrapyramidal movement abnormalities in the cocaine-addicted population may be a useful way of evaluating neurotoxicity in subjects participating in clinical medication trials. A controlled assessment of choreoathetoid movements in cocaine addicts has not been published. Following are preliminary results of an ongoing pilot study on choreo-athetoid movements in male inpatients admitted to the Alcohol and Drug Treatment Program of the West Los Angeles VA Medical Center for treatment of primary cocaine dependence. All patients evaluated were male, with an average age of 41 (range 30 to 60), and had a diagnosis of cocaine dependence according to criteria in the "Diagnostic and Statistical Manual of Mental Disorders," 4th ed. (DSM-IV). Patients were excluded on the basis of a concomitant current or past diagnosis of dependence on other substances, but were not excluded for history of abuse of other sub-stances with the exception of amphetamines. A group of normal controls matched in age, race, and sex to the patient group was also examined. Control subjects had no history of major illness, exposure to neuroleptic medications, severe head trauma (defined as loss of consciousness greater than 15 minutes), or disease or neurologic impairment on routine admis-sion clinical exam. By self-report, the control subjects denied a history of drug dependence or abuse, but some did admit to limited experimentation with cocaine years before the assessment.

Choreoathetoid movements were evaluated using the Abnormal Involuntary Movement Scale (AIMS) and were rated according to the Schooler and Kane (1982) criteria developed for rating tardive

dyskinesia (TD). All but one of the patients were evaluated an average of 8 days after last use. The last patient had been in recovery for 6 years, had a history of severe cocaine dependence similar to the inpatients', and was selected as the first of a new cohort of patients in recovery to evaluate the long-term extrapyramidal sequelae of cocaine dependence.

Nine of the 15 cocaine-dependent patients evaluated were found to have "probable TD" according to Schooler and Kane (1982) criteria, while only 3 of 10 controls met the rating criteria for "probable TD." The amount of movement observed was subtle and none of the patients had severe choreo-athetoid movements of the kind that sometimes is seen in emergency rooms and has been referred to as "crack dancing" (Daras et al. 1994). Interest-ingly, the quantitative differences approached significance between patients and controls only in the body (limbs plus body) AIMS subscore (table 1).

TABLE 1. AIMS in cocaine-dependent patients and normal controls.

	Cocaine patients (N = 15) Mean (SD)		Normal controls (N = 10) Mean (SD)		T	P
Face	3.07	(1.90)	2.80	(1.32)	0.37	0.71
Body	1.67	(1.72)	0.50	(0.71)	2.02	0.055
Total	4.73	(2.58)	3.30	(1.70)	1.54	0.14

Improvement of the choreoathetoid movements during continuous abstinence from cocaine was evaluated. Ten of the inpatients were available to be reexamined an average of 19 days from the first evalua-tion, the entire interim occurring in an inpatient setting, including random urine toxicologic monitoring. As a group, the patients had a decrease in their AIMS scores, which almost reached statistical significance for the total AIMS score (table 2).

Although the data suggest that there are some withdrawal-associated changes in AIMS scores, the choreoathetoid movements are probably not simply an acute withdrawal phenomenon since half of the 10 subjects still had enough movement to be rated as "probable TD" an average of 4weeks from last use. A study of subjects who have been in recovery for long periods and have a history of severe dependence could address the question of whether the extrapyramidal neurotoxicity has permanent sequelae in some patients.

TABLE 2. Choreoathetoid movements in 10 patients withdrawing from cocaine.*

	AIMS score change Mean (SD)		T	P
Face	-0.3	(1.2)	-0.82	0.434
Body	-0.4	(1.5)	-0.84	0.423
Total	-0.7	(1.1)	-2.09	0.066

KEY: * = Cocaine-dependent patients examined an average of 1-week, and reexamined 4 weeks, from the day of last use.

Evidence of Neurotoxicity From Human Brain Imaging Studies

In human studies of cocaine addicts, gross anatomic evidence of neuro-toxicity in the form of increased ventricular brain ratio and cortical atrophy has been observed with magnetic resonance imaging (MRI) and x-ray computed tomography (CT) (Pascual-Leone et al. 1991; Morgan et al. 1993). Some anatomic abnormalities are associated with brain func-tional changes such as decreased sensitivity of individuals with enlarged ventricles to the effects of cocaine itself (Morgan et al. 1993), a phenom-enon also observed in animal models (Schenk et al. 1991). In addition, using positron emission tomography (PET), independent research groups have observed persistent functional abnormalities in striatal dopamine metabolism and cortical glucose metabolism in cocaine addicts (Baxter et al. 1992; Volkow et al. 1992), and these abnormalities have been shown to be interrelated (Volkow et al. 1993).

MRI is an imaging modality that provides excellent resolution and contrast and is essentially a risk-free noninvasive procedure that can assess CNS neurotoxicity. Recently, magnetic resonance spectroscopy and functional magnetic resonance imaging have shown great potential for providing additional biochemical and functional data in a research setting. The discussion is limited to neurotoxicity information obtainable with MRI instruments that are widely available and could be used in the context of medication trials.

Clinical MRI instruments can evaluate both biochemical and structural brain changes. Structural changes such as increased ventricular volumes and lesions such as strokes and CNS bleeds have been reported. More subtle evidence of neurotoxic tissue changes can be evaluated by quantifying tissue relaxation times. Transverse

relaxation times (T2) reflect differences in the immediate molecular environments of water protons and can thus provide biochemical information. T2 lengthening is often associated with increased water content, and T2 shortening in the basal ganglia is often associated with increased iron levels. As noted in this chapters introduction, iron is a possibly important risk factor because it catalyzes free radical-mediated neurotoxic processes (Halliwell and Gutteridge 1985, 1988).

Small differences in water content can have a large impact on T2 values as water T2 is > 1,000 milliseconds (ms) compared with normal brain T2 of < 100 ms. Thus, the inclusion of even a few voxels with increased water content in a region of interest could greatly increase the average T2 measure for the region. An increase in tissue iron would have to be very large to be detected in the context of increased water content since it would have to more than offset the T2 increase caused by increased water concentration. The converse is also true. Increased tissue water will be underestimated if the tissues also contain an increase in iron levels. Since most pathologic tissue changes such as those that may be caused by neuro-toxicity increase the water content of brain tissue, it is likely that neuro-toxicity will result in increased T2 even in the presence of increased iron levels.

Cocaine-dependent patients were examined to investigate whether gross anatomic and T2 evidence of neurotoxicity could be observed using a clinical 1.5 Tesla MRI instrument. Thirteen of the patients who were evaluated with the AIMS agreed to undergo an MRI examination. Despite the fact that the subjects had no history of major illness or severe head trauma and no evidence of disease or neurologic impairment on routine admission clinical exam, two were noted to have severe structural pathology. The first of these, a 53-year-old male, had a very large number of multiple, diffuse, confluent lesions in a classic watershed distribution (figure 2). The second, a 32-year-old male, had a silent occipital stroke (figure 3). The patient group also seemed to have an apparent increase in the prevalence of small hyperintense lesions in the ventral putamen, globus pallidus regions on qualitative evaluation of the scans (figure 4). These lesions were most apparent on coronal scans and corresponded to an area supplied by the anterolateral branches of the mid and anterior cerebral arteries, often a site of intracerebral hemorrhages in this population.

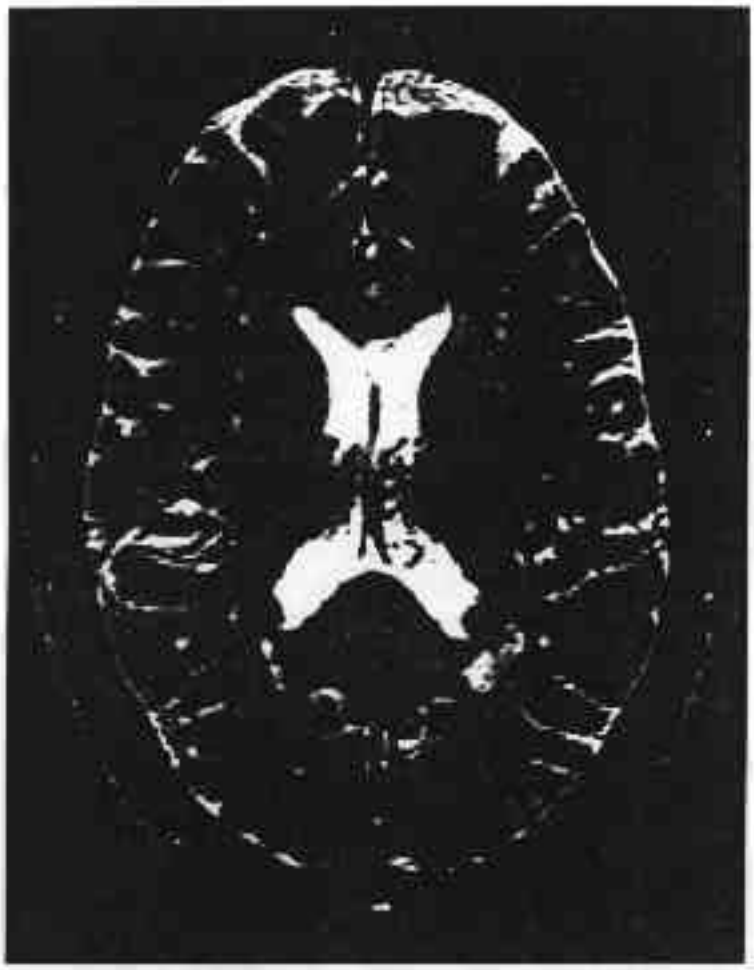

FIGURE 2. *55-year-old cocaine addict with confluent white matter lesions.*

SOURCE: Bartzokis et al. 1994.

FIGURE 3. *37-year-old woman admitted with acute epidural stroke*

SOURCE: Bartzokis et al. 1994.

FIGURE 4. *39-year-old cocaine addict with ventral putamen/globus pallidus hyperintense lesions.*

SOURCE: Bartzokis et al. 1994.

In addition to examining for gross pathology, the average T2 relaxation time of the pixels in the structures of interest (caudate, putamen, and globus pallidus) was measured as described previously (Bartzokis et al. 1994a). Three structures were evaluated for evidence of relationships between clinical evidence of basal ganglia neurotoxicity (choreoathetoid movements as quantified by AIMS) and basal ganglia T2. Preliminary analyses show that cocaine-dependent patients demonstrated an almost statistically significant correlation between AIMS and putamen T2 relaxation times (figure 5). The correlation reached statistical signifi-cance on the right ($r = 0.599$, $p = 0.03$), and almost were statistically signaficant overall ($r=0.56$, $p = 0.06$) and on the left ($r = 0.506$, $p=0.08$). Interestingly, this association was largely due to body (trunk and extremities) AIMS subscores, which approached statistical signifi-cance by themselves at the $p = 0.1$ level on the left, right, and overall ($r=0.52$, $p = 0.07$; $r = 0.50$, $p=0.08$; $r = 0.48$, $p = 0.09$). These corre-lations were not present in the control group or when both controls and cocaine-dependent patients were evaluated together.

Future Directions

As noted above, T2 changes are not specific. The basal ganglia contain high levels of iron that may play a role in neurotoxic processes and could also affect T2 relaxation times. The difficulties of evaluating tissue iron and water in vivo with specificity are not insurmountable. The T2 short-ening effect of ferritin (the iron storage protein that contains up to 90per-cent of non-heme iron in brain (Hallgren and Sourander 1958; Morris et al. 1992) is field-dependent (Bartzokis et al. 1993). This means that MRI is better at detecting T2 shortening caused by ferritin at higher magnetic field strengths (1.5 Tesla (T) and above). At 0.5 T the effect of ferritin is low enough to make it useful as a way of estimating background field-indepen-dent influences on T2 (Bartzokis et al. 1993) and evaluating subtle changes in water content (Bartzokis et al. 1994a, 1994b).

Tissue iron can be evaluated in vivo with specificity by using the unique property of ferritin to shorten T2 in a field-dependent manner (Bartzokis et al. 1993, 1994a, 1994b). This can be done by measuring T2 on two instruments of differing field strengths. The T2 value obtained from the low field-strength instrument reflects the field-independent properties of the tissue. Subtracting the field-independent effects measured by the low field-strength instrument from the effects detected by the high field-strength instrument (composed of both the field-independent tissue effects plus the field-dependent effects of ferritin) produces a measure

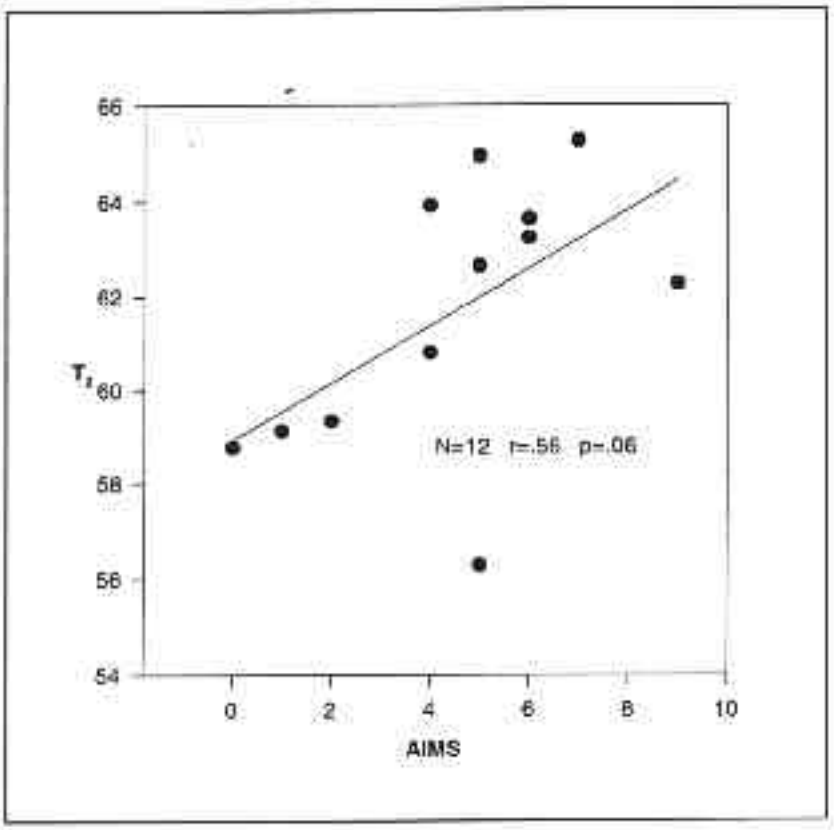

FIGURE 5. *Scatter plot of AIMS score versus putamen T_2 in cocaine addicts.*

that is directly proportional to ferritin levels and is specific for ferritin (Bartzokis et al. 1993, 1994a, 1994b). This approach provides the opportunity to obtain specific measures of both brain water levels and brain iron stores in vivo. Such data may significantly aid efforts to eval-uate both a possible risk factor (high iron levels) and extent of damage (increased water content) in clinical populations and improve the under-standing of amphetamine- and cocaine-mediated neurotoxicity in sub-stance abusers.

CONCLUSIONS

Psychostimulant-induced neurotoxicity has been observed in a variety of human and animal models. Assessing the issue of neurotoxicity and its impact on treatment outcome of cocaine and amphetamine abusers is therefore indicated. Future work should include the continued develop-ment of methodology to evaluate neurotoxic

damage in psychostimulant dependent patients. Such methodology would be incorporated in medi-cation trials for the treatment of substance (particularly psychostimulant) dependence disorders. Some measures such as the AIMS and other stan-dardized clinical assessments can be presently incorporated on a large multicenter scale. More rigorous methods for measuring extrapyramidal movements (Bartzokis et al. 1989; Wirshing et al. 1991), gross brain pathology, and changes in water and iron levels could be evaluated selectively in specialized centers. Identifying and measuring neurotoxic damage mediated by cocaine and amphetamines would help clarify the toxic mechanisms, suggest novel medication strategies, and elucidate the relationship of patient CNS characteristics and associated treatment re-sponse. Such understanding could yield neurobehaviorally based patient-treatment matching and consequently enhance treatment outcome for substance dependence disorders.

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AUTHORS

George Bartzokis, M.D.
The Research Service
West Los Angeles VA Medical Center
Los Angeles, CA 90073

UCLA Department of Psychiatry
Los Angeles, CA 90074

Harbor-UCLA Department of Radiology
Torrance, CA 90509

Mace Beckson, M.D.
The Psychiatry Service
West Los Angeles VA Medical Center
Los Angeles, CA 90073

UCLA Department of Psychiatry
Los Angeles, CA 90074

Walter Ling, M.D.
The Psychiatry Service
West Los Angeles VA Medical Center
Los Angeles, CA 90073

UCLA Department of Psychiatry
Los Angeles, CA 90074

Neurotoxic Versus Neuroprotective Actions of Endogenous Opioid Peptides: Implications for Treatment of CNS Injury

Alan I. Faden

INTRODUCTION

Insults to the central nervous system (CNS) initiate a complex cascade of biochemical alterations that are remarkably consistent across different injury models (Panter and Faden 1992). These reactive changes include both the induction of endogenous autodestructive factors (Faden 1993a; McIntosh 1994) on the one hand and endogenous neuroprotective factors (Mattson and Scheff 1994) on the other. The balance between these opposing processes determines subsequent tissue damage and behavioral recovery.

Endogenous opioid peptides have been implicated as pathophysiological factors in CNS injury since 1981 (Faden et al. 1981a, 1981b). Studies using opioid receptor antagonists support a role for certain endogenous opioids in the pathophysiology of spinal cord trauma, cerebral ischemia, and traumatic brain injury (Faden 1993b). The diversity of endogenous opioids and opioid receptors has complicated the search for the patho-physiological opioids, although solid experimental results implicate dynorphin as one such factor (Faden 1990, 1993b). More recently, studies have demonstrated that certain opioid receptors may mediate neuroprotective actions (Hall et al. 1987; Hayes et al. 1990), suggesting the possible existence of one or more neuroprotective opioids as well. This chapter reviews the literature within the context of developing strategies for treating CNS injury.

ENDOGENOUS OPIOIDS AND OPIOID RECEPTORS

Since the discovery of the pentapeptide enkephalins nearly 20 years ago, a large number of endogenous opioids or opioid fragments have been identified (Cox 1982). These predominantly fall into three large classes: pre-proenkephalin A, pre-proenkephalin B (pre-

prodynorphin), and pre-proopiomelanocortin. In addition, at least three classes of opioid receptors have been found: μ, d, and k.

Enkephalins show some selectivity for μ and d receptors, whereas dynorphin is relatively selective for k receptors. ß-endorphin has activity at each of these receptors. The development of selective synthetic agonists and antagonists to these receptors has provided tools to examine the role of endogenous opioids and their receptors in a variety of physiological and pathophysiological functions, including CNS injury (Faden 1993b).

Endogenous Opioids as Pathophysiological Factors: Studies Using Opioid Receptor Antagonists

Faden and colleagues provided the first evidence to suggest a pathophysiological role for endogenous opioids by demonstrating that treatment with the opioid antagonist naloxone significantly reduced posttraumatic ischemia and improved behavioral recovery following impact injury to cat cervical spinal cord (Faden et al. 1981a, 1981b). This work was subsequently replicated by many laboratories using a variety of experimental animals, CNS injury models, and outcome measures (for review, see Faden 1993b). The high doses of naloxone required for optimal therapeutic actions in CNS injury suggested that non-μ receptors were involved, most likely d or k. Failure to observe a beneficial effect with a d-selective antagonist, combined with strong protective actions for k-active or k-selective opiate antagonists, provided support for the concept that k opioid receptors might mediate the pathophysiological actions of endogenous opioids (Faden et al. 1987).

Dynorphin as a Neurotoxic Factor: Its Potential Role in the Pathophysiology of CNS Injury

Many groups have demonstrated that intrathecal administration of dynorphin causes pathophysiological changes, including hind limb paralysis, decreased spinal cord blood flow, neurochemical changes (i.e.,release of fatty acids and excitatory amino acids), and histological changes (Bakshi et al. 1990; Faden and Jacobs 1983; Herman and Goldstein 1985; Long et al. 1987; Przewlocki et al. 1983). Whether these toxic effects of dynorphin are mediated by opioid receptors has been debated, but best evidence now suggests that both opioid receptor-mediated and nonopioid mechanisms are involved (Bakshi et al. 1990; Faden 1990). At low doses of intrathecal dynorphin, pathophysiologic effects are largely reversed by a variety of opioid

receptor antagonists, including k-active and k-selective antagonists (Bakshi et al. 1990, 1992; Faden 1990). However, at higher doses of dynorphin, paralysis and other physiological effects are not reversed by opioid receptor antagonists, and these actions are duplicated by dynorphin 2-17 or dynorphin 3-13, which are inactive at opioid receptors (Faden 1990; Long et al. 1987).

That dynorphin may be involved in the pathophysiology of CNS injury has been suggested by several observations. Dynorphin administered at subinjury levels significantly shifts the curve of traumatic injury to the left, both after spinal cord injury (Faden 1990) and brain trauma (McIntosh et al. 1994). In addition, following brain or spinal cord trauma, dynorphin increases in injured tissue in direct proportion to injury severity, and it is well localized to those sites showing maximal injury (Faden et al. 1985; McIntosh et al. 1987a). Perhaps more critically, however, treatment with polyclonal antibodies to dynorphin but not antisera to other endogenous opioids significantly attenuates behavioral deficits following traumatic spinal cord injury (Faden 1990).

The responses to trauma and ischemia may differ. Ischemic brain injury has not been associated with accumulation of dynorphin immunoreactive material in injured tissue (Andrews et al. 1989; Fried and Nowak 1987). Moreover, several groups have reported protective, albeit inconsistent, effects of treatment with high systemic doses of dynorphin in experi-mentally induced cerebral ischemia (Baskin et al. 1984; Handa et al. 1988; Tang 1985). However, k opioid receptors appear to be upregulated after both cerebral ischemia (Scavini et al. 1990) and spinal cord trauma (Krumins and Faden 1986), yet downregulated after brain trauma (Perry et al. 1992).

Mechanism for Dynorphin's Neurotoxic Actions

Caudle and Isaac (1988) first suggested that the pathophysiologic actions of dynorphin following intrathecal administration may result from induction of N-methyl-d-aspartate (NMDA)-mediated receptor actions. This concept is supported by results from a number of investigators (Bakshi and Faden 1990a, 1990b; Bakshi et al. 1992; Long et al. 1989). These studies have shown that NMDA antagonists, including competitive, noncompetitive, and glycine modulatory site antagonists, can antagonize the paralytic effects of intrathecal dynorphin (Bakshi and Faden 1990a, 1990b; Bakshi et al. 1992; Long et al. 1989).

NMDA antagonists have also been found to attenuate electrophysiological (Isaac et al. 1990) and histological changes (Bakshi et al. 1992) produced by dynorphin. A possible mechanism may well be that endogenous opioids presynaptically modulate the release of excitatory amino acids. For example, dynorphin administered through a microdialysis probe caused dose-dependent release of glutamate in both brain (Faden 1992) and spinal cord (figure 1). In addition, an opioid receptor antagonist administered prior to brain ischemia attenuated postischemic glutamate release in a stereospecific fashion (Graham et al. 1993).

IS THERE ALSO A NEUROPROTECTIVE ACTION MEDIATED BY ENDOGENOUS OPIOIDS OR OPIOID RECEPTORS?

Hayes and colleagues suggested that μ opioid receptors may modulate neuroprotective actions in brain injury. This is based upon the observation that very low doses of naloxone may exacerbate effects of traumatic brain injury (Hayes et al. 1990) in contrast to very high doses of naloxone, which are protective (Hayes et al. 1983). In addition, this group has shown that μ agonist compounds such as morphine sulfate or D-Ala2-MePhe4Gly-ol5 enkephalin (DAGO) can attenuate the behavioral consequences of traumatic brain injury. Interestingly, DAGO attenuates the behavioral deficits produced by intrathecal dynorphin administration in a dose-dependent fashion (Faden, unpublished observations).

In addition to a potentially protective role provided by μ receptors, a number of studies have shown that certain k agonists may also protect against both brain and spinal cord injury (Birch et al. 1991; Cordon et al. 1990; Hall et al. 1987). Although this would seem to contradict studies showing protective effects of k-selective antagonists such as norbinaltorphimine (Faden et al. 1987; Vink et al. 1991), these differences most likely relate to the well-established existence of k isoreceptors (Horan et al. 1993; Rothman et al. 1990; Zukin et al. 1988). Considerable evidence supports the existence of both high- and low-affinity k receptors. Whereas dynorphin is active at both types of k receptors (Zukin et al. 1988), kagonist compounds showing neuro-protective actions may be selective for the high affinity k1 site. In contrast, the neurotoxic actions of dynor-phin that are mediated by opioid receptors may involve the low-affinity or k2 site, which itself may have distinct subpopulations (k2a, k2b) (Rothman et al. 1990). Interestingly, the benzomorphan opioid antagonist WIN44,441-3, which has perhaps the highest potency and effectiveness of any opioid antagonist in CNS injury (Faden and Jacobs

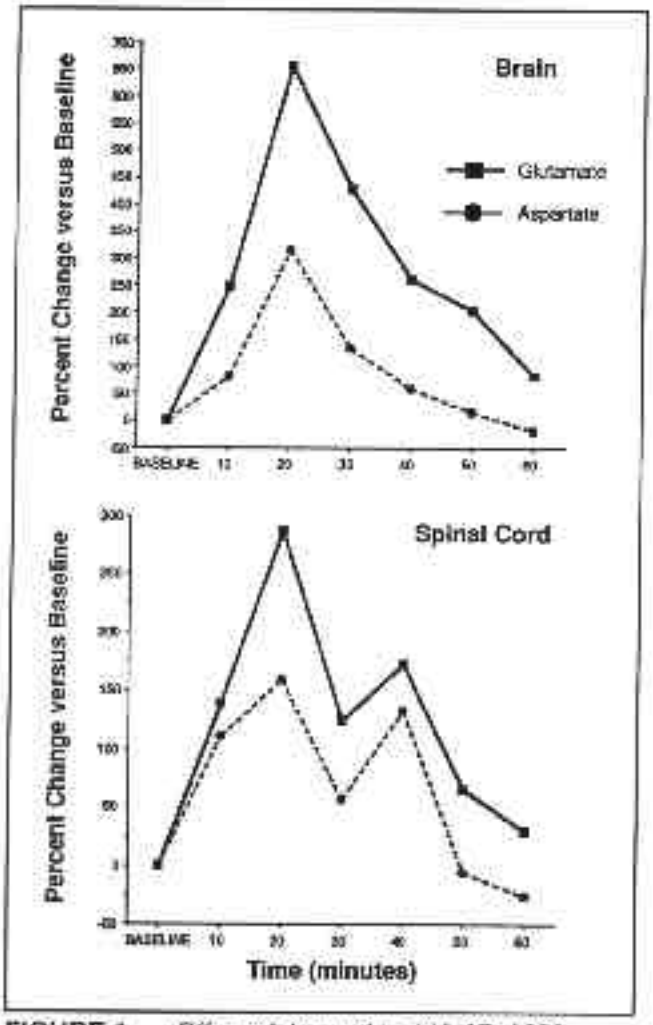

FIGURE 1. *Effect of dynorphin A(1-17) }100 nanomolars (nmol)] on extracellular glutamate and aspartate levels following administration through microdialysis probe in rat hippocampus (top) or spinal cord (bottom). Other studies showed these effects to be dose dependent.*

1985; McIntosh et al. 1987b), has high affinity for the k2b receptor (Horan et al. 1993; Rothman et al. 1990). Moreover, the author and colleagues have recently found that traumatic spinal cord injury in rats selectively upregulates k2 receptors (Sun and Faden, unpublished observations).

LESSONS LEARNED: IMPLICATIONS FOR FUTURE PHARMACOTHERAPY

If one accepts the existing data regarding the protective actions of μ-agonists and k antagonists, then it would seem logical to consider treating patients either with a combination of such agents or with a compound that has this pharmacological profile. Buprenorphine is a mixed μ-agonist/k-antagonist compound (Leander 1987; Sadée et al. 1982) that has been used to treat various forms of addiction in humans (Bracken and Holford 1993; Kosten et al. 1989). In preliminary studies (Johnson et al. 1989), buprenorphine administered 30 minutes after fluid percussion-induced traumatic brain injury in rats significantly improved neurological outcome at 4 weeks as compared to saline-treated controls (figure 2).

Opiate antagonists have been shown to be of benefit in spinal cord injury (Bracken and Holford 1993) and possibly cerebral ischemia (Adams et al. 1986; Estanol et al. 1985) in humans. Given these preliminary experi-mental data and the established safety of buprenorphine treatment in humans, buprenorphine appears to be a potentially attractive therapy for acute brain or spinal cord injury in humans.

Potential Implications for Addiction Treatment

Dynorphin peptides have been found to suppress opiate withdrawal as well as antinociceptive tolerance in morphine-dependent mice (Takemori et al. 1992). Similar observations have been made in a variety of other species, including rats (Green and Lee 1988), monkeys (Aceto et al. 1982), and humans (Wen et al. 1984). From these studies it has been suggested that "Usage of an endogenous opioid peptide may be a safe and useful way to manage opiate withdrawal in human opiate addicts" (Takemori et al. 1992, p. 223). However, given the neurotoxic effects of dynorphin administered intrathecally as well as the ability of dynorphin to shift the curve of CNS trauma to the left, the issue of dynorphin's safety must be considered. Particularly relevant in this regard are the

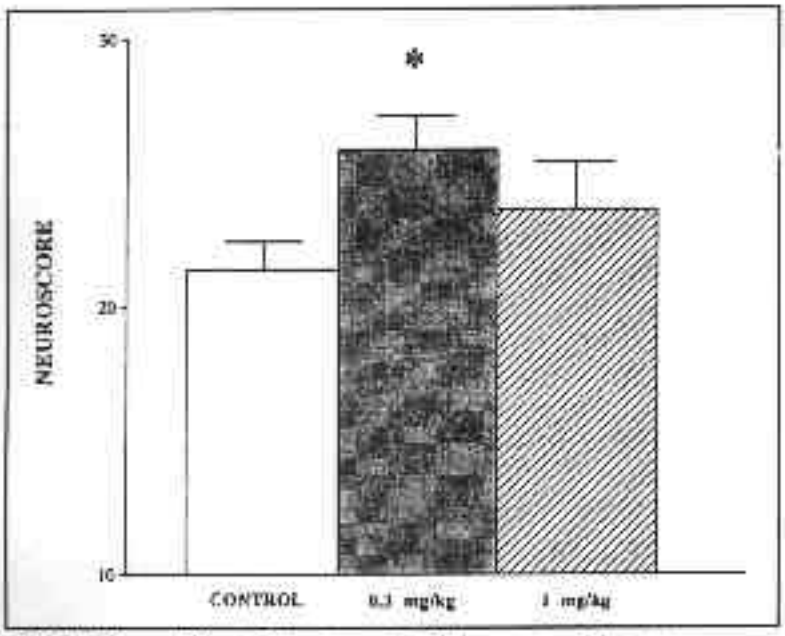

FIGURE 2. *Effect of treatment with buprenorphine on neurological outcome 2 weeks after fluid percussion-induced traumatic brain injury in rats. Neuroscore represents the summation of 7 separate motor function scores, each ranging from 0 (no function) to 5 (normal function). Treatment was administered as single bolus injection at 30 minutes after injury.*

structure-activity studies by Takemori and colleagues (1992) relating to dynorphin suppression of the expression of opiate withdrawal and tolerance in morphine-dependent mice. This therapeutic profile is remarkably similar to that which produces paralytic injury following intrathecal dynorphin administration in rats. Given the other forms of therapy for opiate withdrawal currently being studied, it would be wise to carefully evaluate its safety before proceeding with this form of therapy. Another finding that may be relevant is the recent work by Hurd and Herkenham (1993) demonstrating increases in dynorphin-like immuno-reactive material as well as upregulation of k opiate receptors in cocaine addicts shortly after death. Animal studies have also shown that cocaine administration increases dynorphin levels (Hurd et al. 1992; Sivam 1989).

SUMMARY

Endogenous opioid systems seem to have both neurodestructive and neuroprotective roles in CNS injury. Whereas μ and k1 receptors appear to mediate neuroprotective actions, k2 receptors may be involved in secon-dary injury responses. Among the endogenous opioids, dynorphin has marked neurotoxic effects when given intrathecally to rats; when admin-istered in subinjury doses, dynorphin exacerbates the response to brain or spinal cord trauma. Because of the neurotoxic effects of dynorphin, one should employ this compound with great caution in human studies of addiction treatment. It has not been established which endogenous opioids might be protective. Taken together, these observations may suggest novel approaches to the treatment of CNS injury using selective mixed opioid agonist-antagonist compounds such as buprenorphine.

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AUTHOR

Alan I. Faden, M.D.
Georgetown University School of Medicine
Washington, DC 20007

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