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).

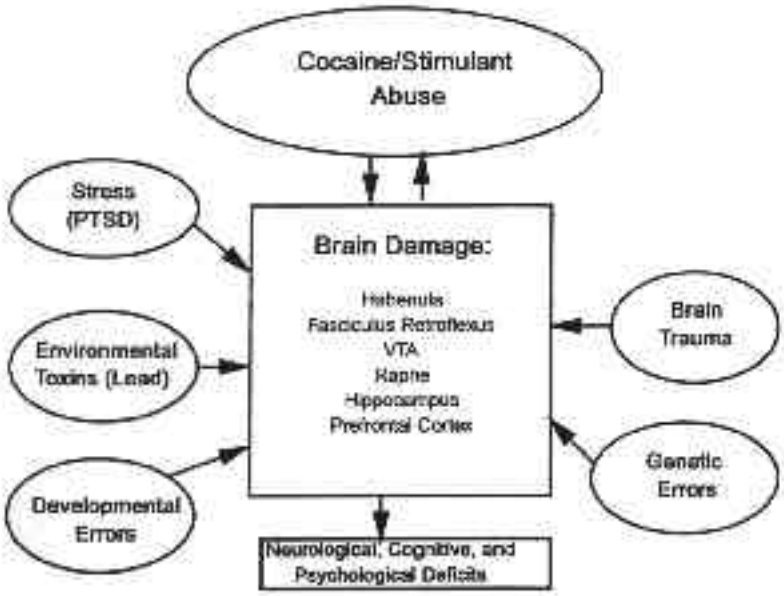

FIGURE 1. *Conceptual relationships between brain damage and cocaine/stimulant abuse.*

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

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