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)

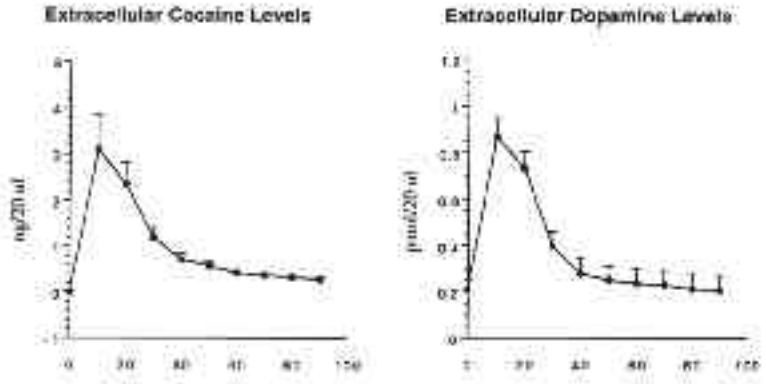

FIGURE 1. *In vivo extracellular concentrations of cocaine and dopamine in the striatum of rats following an intravenous injection of cocaine (2.0 mg/kg).*

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.

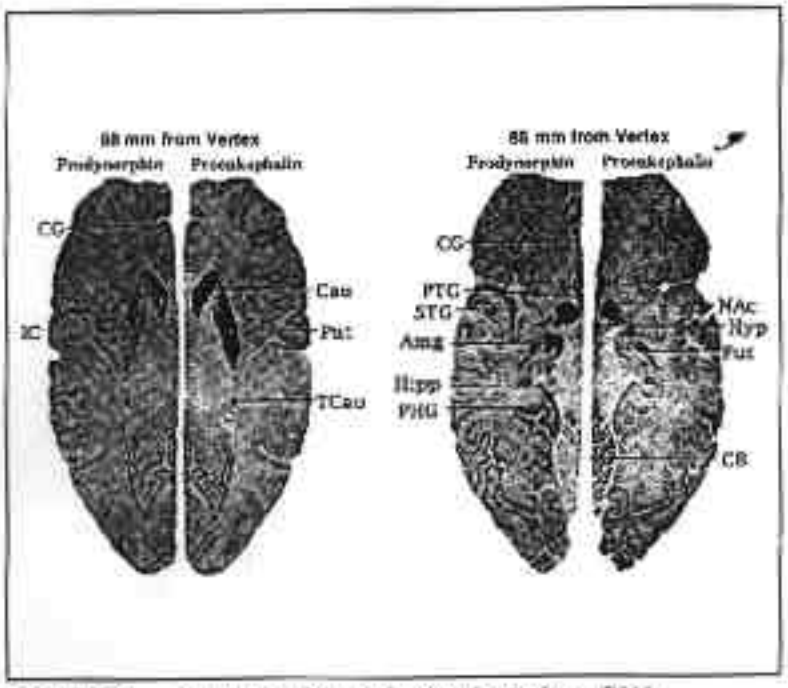

FIGURE 2. *Prodynorphin and proenkephalin mRNA expression in postmortem whole hemisphere human brain sections.*

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.

REFERENCES

Akimoto, K.; Hamamura, T.; and Otsuki, S. Subchronic cocaine treatment enhances cocaine-induced dopamine eflux studies by in vivo intracerebral dialysis. Brain Res 490:339-344, 1989.

Alexander, G., and Crutcher, M. Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. Trends Neurosci 13:266-271, 1990.

Ambre, J.J.; Belknap, S.M.; Nelson, J.; Ruo, T.I.; Shin, S.-G.; and Atkinson, A.J. Acute tolerance to cocaine in humans. Clin Pharmacol Ther 44:1-8, 1988.

Attig, E.; Amyot, R.; and Botez, T. Cocaine induced chronic tics. J-Neurol Neurosurg Psychiat 9:1143-1144, 1994.

Bain, G.T., and Kornestsky, C. Naloxone attenuation of the effect of cocaine on rewarding brain stimulation. Life Sci 40:1119-1125, 1987.

Bals-Kubik, R.; Ableitner, A.; Herz, A.; and Shippenberg, T.S. Neuroanatomical sites mediating the motivational effects of opioids as mapped by the conditioned place preferences paradigm in rats. J-Pharm Exp Therap 264:489-495, 1992.

Bauer, L.O. Motoric signs of CNS dysfunction associated with alcohol and cocaine withdrawal. Psychiat Res 47:69-77, 1993.

Bergman, J.; Kamien, J.B.; and Spealman, R.D. Antagonism of cocaine self-administration by selective dopamine D1 and D2 antagonists. Behav Pharmacol 1:355-364, 1990.

Björklund, A., and Lindvall, O. Dopamine-containing systems in the CNS. In: Björklund, A., and Hökfelt, T., eds. Handbook of Chemical Neuroanatomy. Vol. 2: Classical Transmitters in the CNS, Part I. Amsterdam: Elsevier, 1984. pp. 55-122.

Bouthenet, M.-L.; Souil, E.; Martres, M.-P.; Sokoloff, P.; Giros, B.; and Schwartz, J.-C. Localization of dopamine D3 receptor mRNA in the rat brain using in situ hybridization histochemistry: Comparison with dopamine D2 receptor mRNA. Brain Res 564:203-219, 1991.

Branch, A.D.; Unterwald, E.M.; Lee, S.E.; and Kreek, M.J. Quantitation of preproenkephalin mRNA levels in brain regions from male Fischer rats following chronic cocaine treatment using a recently developed solution hybridization assay. Mol Brain Res 14:231-238, 1992.

Brownstein, M.J.; Mroz, E.A.; Tappaz, M.L.; and Leeman, S.E. On the origin of substance P and glutamic acid decarboxylase in the substantia nigra. Brain Res 135:315-323, 1977.

Caine, S.B., and Koob, G.F. Modulation of cocaine self-administration in the rat through D-3 dopamine receptors. Science 260:1814-1816, 1993.

Carroll, M.E.; Lac, S.T.; Walker, S.T.; Kragh, M.J.; and Newman, T. Effects of naltrexone on intravenous cocaine self-administration in

rats during food satiation and deprivation. J Pharmacol Exp Ther 238:1-7, 1986.

Cerruti, C.; Pilotte, N.S.; Uhl, G.; and Kuhar, M.J. Reduction in dopamine transporter mRNA after cessation of repeated cocaine administration. Mol Brain Res 22:132-138, 1994.

Chavkin, C.; James, I.F.; and Goldstein, A. Dynorphin is a specific endogenous ligand for the k-opioid receptor. Science 215:413-415, 1982.

Church, W.H.; Justice, J.B.; and Byrd, L.D. Extracellular dopamine in rat striatum following uptake inhibition by cocaine, nomifensine, and benztropine. Eur J Pharmacol 139:345-348, 1987.

Dackis, C.A., and Gold, M.S. New concepts in cocaine addiction: The dopamine-depletion hypothesis. Neurosci Behav Rev 9:469-477, 1985.

Daras, M.; Koppel, B.S.; and Atos-Radzion, E. Cocaine-induced choreoathetoid movements ("crack dancing"). Neurology 44:751-752, 1994.

Daunais, J.B.; Roberts, D.C.S.; and McGinty, J.F. Cocaine self-administration increases prodynorphin, but not c-fos, mRNA in rat striatum. Neuroreport 4:543-546, 1993.

De Vry, J.; Donselaar, I.; and Van Ree, J.M. Food deprivation and acquisition of intravenous cocaine self-administration in rats: Effect of naltrexone and haloperidol. J Pharmacol Exp Ther 251:735-740, 1989.

Del Fiacco, M., and Cuello, A.C. Neostriatal enkephalin-immunoreactive neurones project to the globus pallidus. Brain Res 231:1-17, 1982.

Di Chiara, G., and Imperato, A. Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. J Pharm Exp Ther 244:1067-1080, 1988.

Donnan, G.A.; Kaczmarczyk, S.J.; Paxinos, G.; Chilco, P.J.; Kalnins, R.M.; Woodhouse, D.G.; and Mendelsohn, F.A.O. Distribution of catecholamine uptake sites in human brain as determined by quantitative [3H]mazindol autoradiography. J Comp Neurol 304:419-434, 1991.

Faden, A.I. Opioid and nonopioid mechanisms may contribute to dynorphin's pathophysiological actions in spinal cord injury. Ann Neurol 27:67-74, 1989.

Faden, A.I.; Reizo, S.; Chang, L.-H.; James, T.L.; Lemke, M.; and Weinstein, P.R. Opiate-receptor antagonist improves metabolic recovery and limits neurochemical alterations associated with reperfusion after global brain ischemia in rats. J Pharm Exp Ther 255:451-458, 1990.

Farfel, G.M.; Kleven, M.S.; Woolverton, W.L.; Seiden, L.S.; and Perry,B.D. Effects of repeated injections of cocaine on catecholamine receptor binding sites, dopamine transport binding sites and behavior in rhesus monkey. Brain Res 578:235-242, 1992.

Fischman, M.W., and Schuster, C.R. Cocaine self-administration in humans. Fed Proc 41:241-246, 1982.

Fischman, M.W.; Schuster, C.R.; and Hatano, Y. A comparison of the subjective and cardiovascular effects of cocaine and lidocaine in humans. Pharmacol Biochem Behav 18:123-127, 1983.

Fischman, M.W.; Schuster, C.R.; Javaid, J.I.; Hatano, Y.; and Davis, J. Acute tolerance development to the cardiovascular and subjective effects of cocaine. J Pharm Exp Ther 133:41-51, 1985.

Fowler, J.S.; Volkow, N.D.; Wolf, A.P.; Dewey, S.L.; Schlyer, R.R.M.; Hitzemann, R.; Logan, J.; Bendriem, B.; Gatley, S.J.; and Christman,D. Mapping cocaine binding sites in human and baboon brain in vivo. Synapse 4:371-377, 1989.

Freund, T.F.; Powell, J.F.; and Smith, A.D. Tyrosine hydroxylase-immunoreactive boutons in synaptic contacts with identified striatonigral neurons, with particular reference to dendritic spines. Neuroscience 13:1189-1216, 1984.

Gawin, F.H., and Kleber, H.D. Neuroendocrine findings in chronic cocaine abusers: A preliminary report. Br J Psychiat 147:569-573, 1985.

Gerfen, C.R.; Enber, T.M.; Susel, Z.; Chase, T.N.; Monsma, F.J.; Mahan,L.C.; and Sibley, D.R. D1 and D2 dopamine receptor regulated gene expression of striatonigral and striatopallidal neurons. Science 250:1429-1432, 1990.

Gerfen, C.R.; McGinty, J.F.; and Young, W.S., III. Dopamine differentially regulates dynorphin, substance P and enkephalin expression in striatal neurons: In situ hybridization histochemistry analysis. J Neurosci 11:1016-1031, 1991.

Graveland, G.A.; Williams, R.S.; and Di Figlia, M. A golgi study of the human neostriatum: Neurons and afferent fibers. J Comp Neurol 234:317-333, 1985.

Graybiel, A.M. Neurotransmitters and neuromodulators in the basal ganglia. Trends Neurosci 13:244-254, 1990.

Graybiel, A.M., and Moratalla, R. Dopamine uptake sites in the striatum are distributed differentially in striosome and matrix compartments. Proc Natl Acad Sci U S A 86:9020-9024, 1989.

Heidbreder, C.A.; Goldberg, S.R.; and Shippenberg, T.S. The kappa-opioid receptor agonist U-69593 attenuates cocaine-induced behavioral sensitization in the rat. Brain Res 616:335-338, 1993.

Heimer, L.; Switzer, R.C., III; and Van Hoesen, G.W. Ventral striatum and ventral pallidum: Components of the motor systems? Trends Neurosci 5:83-87, 1982.

Herrera-Marschitz, M.; Christennon-Nylander, I.; Sharp, T.; Staines, W.; Reid, M.; Hökfelt, T.; Terenius, L.; and Ungerstedt, U. Striato-nigral dynorphin and substance P pathways in the rat. II. Functional analysis. Exp Brain Res 64:193-207, 1986.

Herz, A. Opioids. New York: Springer-Verlag, 1993.

Hiroi, N.; Xu, M.; Moratalla, R.; Tonegawa, S.; and Graybiel, A.M. Absence of dynorphin-immunoreactive striosomes in the caudoputamen of mice mutant for the dopamine D1 receptor. Neurosci Abstr 20:786, 1994.

Hitri, A.; Cassanova, M.F.; Kleinman, J.E.; and Wyatt, R. Fewer dopamine transporter receptors in the prefrontal cortex of cocaine users. Am J Psychiat 151:1074-1076, 1994.

Hurd, Y.L.; Brown, E.; Finlay, J.; Fibiger, H.C.; and Gerfen, C. Cocaine self-administration differentially alters mRNA expression of striatal peptides. Mol Brain Res 13:165-170, 1992.

Hurd, Y.L., and Herkenham, M. Influence of a single injection of cocaine, amphetamine or GBR 12909 on mRNA expression of striatal neuropeptides. Mol Brain Res 16:97-104, 1992.

Hurd, Y.L., and Herkenham, M. Molecular alterations in the neostriatum of human cocaine addicts. Synapse 13:357-369, 1993.

Hurd, Y.L., and Herkenham, M. The human neostriatum shows compart-mentalization of neuropeptide gene expression in dorsal and ventral regions: An in situ hybridization histochemical analysis. Neuroscience 64:571-586, 1995.

Hurd, Y.L.; Kehr, J.; and Ungerstedt, U. In vivo microdialysis as a technique to monitor drug transport: Correlation of extracellular cocaine levels and dopamine overflow in rat brain. J Neurochemistry 51:1314-1316, 1988.

Hurd, Y.L., and Ungerstedt, U. Cocaine: An in vivo microdialysis evaluation of its acute action on dopamine transmission in rat striatum. Synapse 3:48-54, 1989.

Hurd, Y.L.; Weiss, F.; Andén, N.E.; Koob, G.F.; and Ungerstedt, U. Cocaine reinforcement and extracellular dopamine overflow: An in vivo microdialysis study. Brain Res 498:199-203, 1989.

Imperato, A.; Mele, A.; Scrocco, M.G.; and Puglisi-Allegra, S. Chronic cocaine alters limbic extracellular dopamine. Neurochemical basis for addiction. Eur J Pharmacol 212:299-300, 1992.

Inaba, T. Cocaine: Pharmacokinetics and biotransformation in man. Can J Physiol Pharmacol 67:1154-1157, 1989.

Inada, T.; Polk, K.; Purser, C.; Hume, A.; Hoskins, B.; Ho, I.K.; and Rockhold, R.W. Behavioral and neurochemical effects of continuous infusion of cocaine in rats. Neuropharmacology 31:701-708, 1992.

Jaffe, J.H.; Cascella, N.G.; Kumor, N.M.; and Sherer, M.A. Cocaine-induced cocaine craving. Psychopharmacology 97:59-64, 1989.

Javaid, J.I.; Fischman, M.W.; Schuster, C.R.; Dekirmenjian, H.; and Davis, J.M. Cocaine plasma concentration: Relation to physiological and subjective effects in humans. Science 202:227-228, 1978.

Johanson, C.L., and Fischman, M.W. The pharmacology of cocaine related to its abuse. Pharmacol Rev 41:3-52, 1989.

Kalivas, P.W., and Duffy, P. Effect of acute and daily cocaine treatment on extracellular dopamine in the nucleus accumbens. Synapse 5:48-58, 1990.

Khachaturian, H.; Lewis, M.E.; Schafer, M.K.-H.; and Watson, S.J. Anatomy of the CNS opioid system. Trends Neurosci 8:111-118, 1985.

Kita, H., and Kitai, S.T. Glutamate decarboxylase immunoreactive neurons in rat neostriatum: Their morphological types and populations. Brain Res 447:346-352, 1988.

Koob, G.F. Drugs of abuse: Anatomy, pharmacology and function of reward pathways. Trends Pharmacol 13:177-184, 1992.

Koob, G.F.; Le, H.T.; and Creese, I. The D1 dopamine receptor antagonist SCH 23390 increases cocaine self-administration in the rat. Neurosci Lett 79:315-320, 1987.

Kreek, M.J. Multiple drug abuse patterns and medical consequences. In:Meltzer, H., eds. Psychopharmacology: The Third Generation of Progress. New York: Raven Press, 1988. pp. 1597-1604.

Kubota, U.; Inagaki, S.; Kito, S.; Takagi, H.; and Smith, A.D. Ultrastructural evidence of dopaminergic input to enkephalinergic neurons in rat neostriatum. Brain Res 367:374-392, 1986.

Kumor, K.; Sherer, M.; Gomez, J.; Cone, E.; and Jaffe, J.H. Subjective response during continuous infusion of cocaine. Pharmacol Biochem Behav 33:443-452, 1989.

Landwehrmeyer, B.; Mengod, G.; and Palacios, J.M. Differential visualization of dopamine D2 and D3 receptor sites in rat brain. A comparative study using in situ hybridization histochemistry and ligand binding autoradiography. Eur J Neurosci 5:145-153, 1993a.

Landwehrmeyer, B.; Mengod, G.; and Palacios, J.M. Dopamine D3 receptor mRNA and binding sites in human brain. Mol Brain Res 18:187-192, 1993b.

Le Moine, C.; Normand, E.; Guitteny, A.F.; Fouque, B.; Teoule, R.; and Bloch, B. Dopamine receptor gene expression by enkephalin neurons in rat forebrain. Proc Natl Acad Sci U S A 87:230-234, 1990.

Little, K.Y.; Kirkman, J.A.; Carroll, F.I.; Clark, T.B.; and Duncan, G.E. Cocaine use increases [3H]WIN 35428 binding sites in human striatum. Brain Res 628:17-25, 1993.

Lord, J.A.H.; Waterfield, A.A.; Hughes, J.; and Kosterlitz, H.W. Endogenous opioid peptides: Multiple agonists and receptors. Nature 267:495-499, 1977.

Maisonneuve, I.M., and Kreek, M.-K. Acute tolerance to the dopamine response induced by a binge pattern of cocaine administration in male rats: An in vivo microdialysis study. J Pharmacol Exp Ther 268:916-921, 1994.

McGregor, A., and Roberts, D.C.S. Effect of 6-hydroxydopamine lesions of the amygdala on cocaine self-administration under a progressive ratio schedule of reinforcement. Brain Res 646:273-278, 1994.

McIntosh, T.K.; Hayes, R.L.; and DeWitt, D.S. Endogenous opioids may mediate secondary damage after experimental brain injury. Am J Physiol 253:E565-E574, 1987.

Meador-Woodruff, J.H.; Little, K.Y.; Damask, S.P.; Mansour, A.; and Watson, S.J. Effects of cocaine on dopamine receptor gene expression: A study in the postmortem human brain. Biol Psychol 34:348-355, 1993.

Mello, N.K., and Mendelson, J.H. Buprenorphine suppresses heroin use by heroin addicts. Science 207:657-659, 1980.

Mello, N.K.; Mendelson, J.H.; Breem, M.P.; and Lukax, S.E. Buprenorphine suppresses cocaine self-administration by rhesus monkey. Science 245:859-862, 1989.

Mendelson, J.H.; Teoh, S.K.; Lange, U.; Mello, N.K.; Weiss, R.; Skupny,A.; and Ellingboe, J. Anterior pituitary, adrenal, and gonadal hormones during cocaine withdrawal. Am J Psych 145:1094-1098, 1988.

Mendelson, J.H.; Teoh, S.K.; Mello, N.K.; and Ellingboe, J. Buprenorphine attenuates the effects of cocaine on adrenocorticotropin (ACTH) secretion and mood states in man. Neuropsychopharmacology 7:157-162, 1992.

Mogenson, G.J.; Jones, D.L.; and Yim, C.Y. From motivation to action: Functional interface between the limbic system and the motor system. Prog Neurobiol 14:69-97, 1980.

Nauta, H.J. A simplified perspective on the basal ganglia and their relation to the limbic system. In: Doane, B.K., and Livingston, L.E., eds. The Limbic System: Functional Organization and Clinical Disorders. New York: Raven Press, 1986. pp. 67-77.

Nayak, P.K.; Misra, A.L.; and Mule, S.J. Physiological disposition and biotransformation of (3H)cocaine in acutely and chronically treated rats. J Pharm Exp Ther 196:556-569, 1976.

Nicolaysen, L.C.; Pan, H.T.; and Justice, J.B., Jr. Extracellular cocaine and dopamine concentrations are linearly related in rat striatum. Brain Res 456:317-323, 1988.

Parsons, L.H.; Smith, A.D.; and Justice, J.B., Jr. Basal extracellular dopamine is decreased in the rat nucleus accumbens during abstinence from chronic cocaine. Synapse 9:60-65, 1991.

Pettit, H.O., and Justice, J.B., Jr. Dopamine in the nucleus accumbens as studied by in vivo microdialysis. Pharmacol Biochem Behav 34:899-904, 1989.

Pettit, H.O.; Pan, H.-T.; Parsons, L.H.; and Justice, J.B., Jr. Extracellular concentrations of cocaine and dopamine are enhanced during chronic cocaine administration. J Neurochem 55:798-804, 1990.

Pfeiffer, A.; Brandt, V.; and Herz, A. Psychotomimesis mediated by kappa opiate receptors. Science 233:774-776, 1986.

Pristupa, Z.B.; Wilson, J.M.; Hoffman, B.J.; Kish, S.J.; and Niznik, H.B. Pharmacological heterogeneity of the cloned and native human dopamine transporter: Disassociation of [3H]WIN 35,428 and [3H]GBR 12,935 binding. Mol Pharmacol 45:125-135, 1994.

Rappaport, M.S.; Sealfon, S.C.; Prikhozhan, A.; Huntley, G.W.; and Morrison, J.H. Heterogenous distribution of D1, D2, and D5 receptor mRNAs in monkey striatum. Brain Res 616:242-250, 1993.

Roberts, D.C.S., and Koob, G.F. Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. Pharmacol Biochem Behav 17:901-904, 1982.

Roberts, D.C.S., and Vickers, G. Atypical neuroleptics increase self-administration of cocaine: An evaluation of a behavioral screen for antipsychotic activity. Psychopharmacology 82:135-139, 1984.

Robinson, T.E.; Jurson, P.A.; Bennett, J.A.; and Bentgen, K.M. Persistent sensitization of dopamine neurotransmission in ventral striatum (nucleus accumbens) produced by prior experience with (+)-amphetamine: A microdialysis study in freely moving rats. Brain Res 462:211-222, 1988.

Robinson, T.E.; Yew, J.; Paulson, P.E.; and Camp, D.M. The long-term effects of neurotoxic doses of methamphetamine on the extracellular concentration of dopamine measured with microdialysis in striatum. Neurosci Lett 110:193-198, 1990.

Ryan, L.I.; Martone, M.; Linder, J.C.; and Groves, P.M. Cocaine in contrast to d-amphetamine does not cause axonal terminal degeneration in neostriatum and agranular cortex of Long-Evans rats. Life Sci 43:421-426, 1988.

Schottenfeld, R.S.; Pakes, J.; Ziedonis, D.; and Kosten, T.R. Buprenorphine: Dose-related effects on cocaine and opioid use in cocaine-abusing opioid-dependent humans. Biol Psych 34:66-74, 1993.

Segal, D.S., and Kuczenski, R. In vivo microdialysis reveals a diminished amphetamine-induced DA response corresponding to behavioral sensitization produced by repeated amphetamine pretreatment. Brain Res 571:330-337, 1992.

Sherer, M.A. Intravenous cocaine: Psychiatric effects, biological mechanisms. Biol Psych 24:865-885, 1988.

Shippenberg, T.S.; Bals, K.R.; and Herz, A. Motivational properties of opioids: Evidence that an activation of delta receptors mediates reinforcement processes. Brain Res 436:234-239, 1987.

Sivam, S.P. Cocaine selectively increases striatonigral dynorphin levels by a dopaminergic mechanism. J Pharmacol Exp Ther 250:818-824, 1989.

Smiley, P.L.; Johnson, M.; Bush, L.; Gibb, J.W.; and Hanson, G.R. Effects of cocaine on extrapyramidal and limbic dynorphin systems. JPharmacol Exp Ther 253:938-943, 1990.

Somogyi, P.; Bolam, J.P.; and Smith, A.D. Monosynaptic cortical input and local axon collaterals of identified striatonigral neurons. A light and electron microscopic study using the Golgi-peroxidase transport-degeneration procedure. J Comp Neurol 195:567-584, 1981.

Spangel, R.; Herz, A.; and Shippenberg, T.S. The effects of opioid peptides on dopamine release in the nucleus accumbens: An in vivo microdialysis study. J Neurochem 55:1734-1740, 1990.

Spangler, R.; Unterwald, E.M.; and Kreek, M.J. ‘Binge' cocaine administration induces a sustained increase of prodynorphin mRNA in rat caudate-putamen. Mol Brain Res 19:323-327, 1993.

Spealman, R.D., and Bergman, J. Modulation of the discriminative stimulus effects of cocaine by mu and kappa opioids. J Pharmacol Exp Ther 261:607-615, 1993.

Staley, J.K.; Hearn, W.L.; Ruttenber, A.J.; Welti, C.V.; and Mash, D.C. High affinity cocaine recognition sites on the dopamine transporter are elevated in fatal cocaine overdose victims. J Pharm Exp Ther 271:1678-1685, 1994.

Suzuki, T.; Shiozaki, Y.; Masukawa, Y.; Misawa, M.; and Nagase, H. The role of mu- and kappa-opioid receptors in cocaine-induced conditioned place preference. Jpn J Pharmacol 58:435-442, 1992.

Vincent, S.; Hökfelt, T.; Christensson, I.; and Terenius, L. Immunohistochemical evidence for a dynorphin immunoreactive striatonigral pathway. Eur J Pharmacol 85:251-252, 1982.

Vink, R.; Portoghese, P.S.; and Faden, A.I. k-opioid antagonist improves cellular bioenergetics and recovery after traumatic brain injury. Am J Physiol 261:R1527-R1532, 1991.

Volkow, N.D.; Fowler, J.S.; Wang, G.Y.; Hitzemann, R.; MacGregor, R.; Dewey, S.L.; and Wolf, A.D. Decreased binding of 11-C-cocaine in the brain of cocaine addicts. J Nucl Med 33:888, 1992.

Volkow, N.D.; Fowler, J.S.; Wolf, A.P.; Schlyer, D.; Shiue, C.-Y.; Alpert, A.; Dewey, S.L.; Logan, J.; Bendriem, B.; Christman, D.; Hitzemann, R.; and Henn, F. Effects of chronic cocaine abuse on postsynaptic dopamine receptors. Am J Psych 147:719-724, 1990.

Volkow, N.D.; Mullani, N.; Gould, K.L.; Adler, S.; and Krajewski, K. Cerebral blood flow in chronic cocaine users: A study with positron emission tomography. Br J Psychiat 152:641-648, 1988.

Weiss, F.; Paulus, M.P.; Lorang, M.T.; and Koob, G.F. Increases in extracellular dopamine in the nucleus accumbens by cocaine are inversely related to basal levels: Effects of acute and repeated administration. J Neurosci 12:4372-4380, 1992.

White, F.J.; Hu, X.-T.; Xu, M.; and Tonegawa, S. Alterations in mesoaccumbens neuronal responses to dopamine agonists in D1 dopamine receptor "knockout" mice. Neurosci Abstr 20:908, 1994.

Xia, Y.; Goebel, D.J.; Kapatos, G.; and Bannon, M.J. Quantitation of rat dopamine transporter mRNA: Effects of cocaine treatment and withdrawal. J Neurochem 59:1179-1182, 1992.

Young, W.S., III; Bonner, T.I.; and Brann, M.R. Mesencephalic dopamine neurons regulate the expression of neuropeptide mRNAs in the rat forebrain. Proc Natl Acad Sci U S A 83:9827-9831, 1986.

Zito, K.A.; Vickers, G.; and Roberts, D.C.S. Disruption of cocaine and heroin self-administration following kainic acid lesions of the nucleus accumbens. Pharm Biochem Behav 23:1029-1036, 1985.

ACKNOWLEDGMENTS

I thank my collaborators Drs. Miles Herkenham, Göran Sedvall, and Urban Ungerstedt. Preparation of this manuscript was supported by Swedish Medical Research Council Grant no. 11252.

AUTHOR

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

Click here to go to page 117