Cocaine Withdrawal Alters Regulatory Elements of Dopamine Neurons

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

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concentrations of dopamine fall below the basal levels measured in cocaine-naive rats a few days after cocaine is withdrawn (Imperato et al. 1992; Parsons et al. 1991; Rossetti et al. 1992).

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

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

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

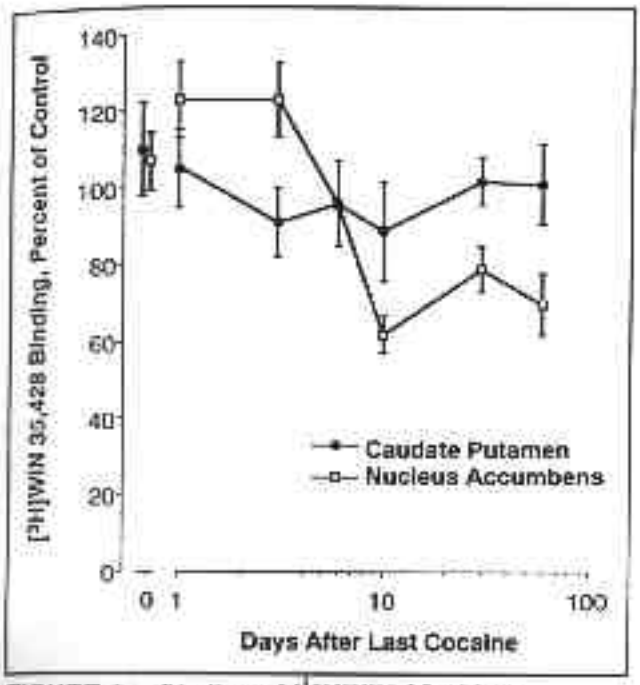

FIGURE 1. *Binding of [³H]WIN 35,428 to dopamine transporters in the nucleus accumbens and to the caudate putamen of rats at different times after the last infusion of cocaine or saline. There was a significant effect of withdrawal on binding in the nucleus accumbens on days 10, 20, and 60. Five to 10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

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

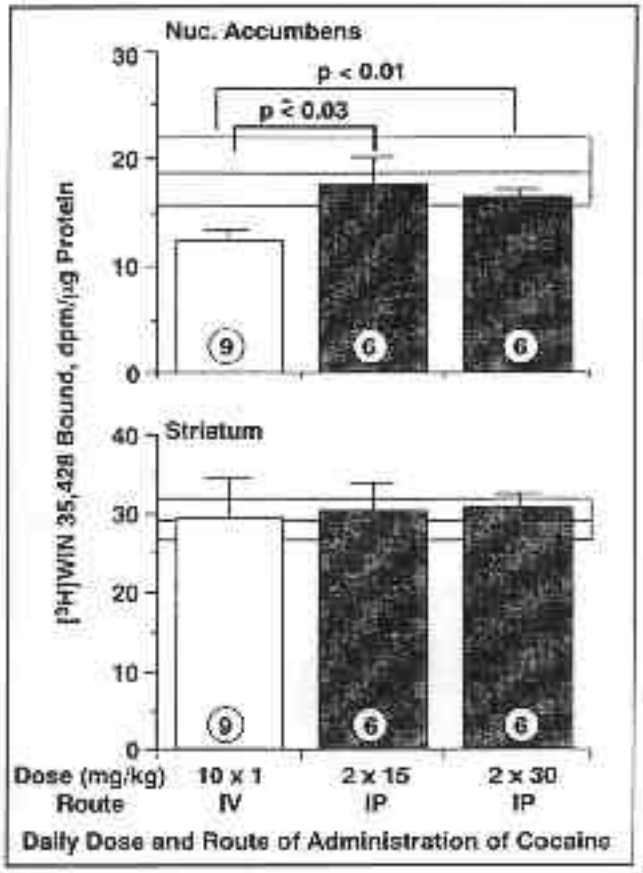

FIGURE 2. *Dopamine transporters in the nucleus accumbens and the caudate-putamen 10 days after withdrawal of IV or IP cocaine. Numbers at the base of each column refer to the numbers of cocaine-treated rats. The clear horizontal bars refer to the mean dpm (and SEM) of saline-treated rats.*

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

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

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

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

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

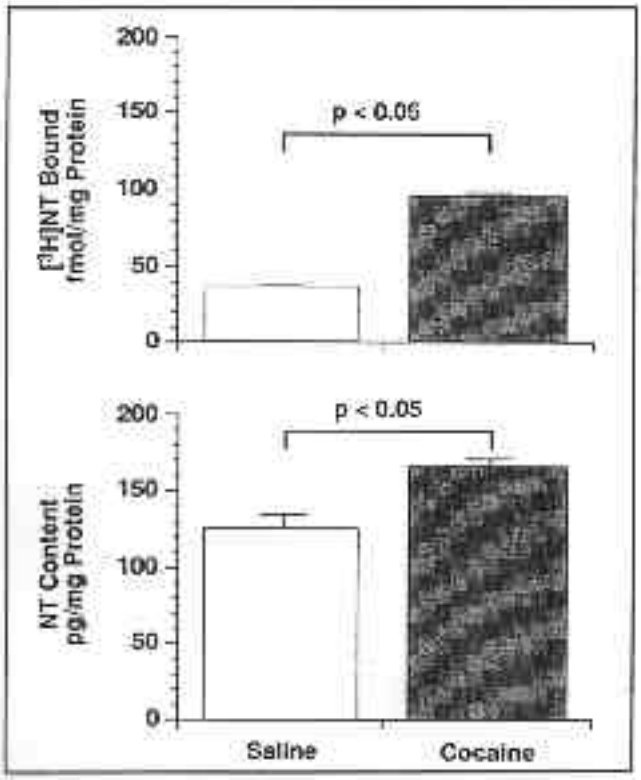

FIGURE 3. *Neurotensin binding and content increased 10 days after cocaine withdrawal. Ten animals were used in each group.*

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

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

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