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Blockade of D1 Dopamine Receptors in the Ventral Tegmental Area Decreases Cocaine Reward: Possible Role for Dendritically Released Dopamine

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This study was designed to assess the involvement of D1 dopamine actions in the ventral tegmental area (VTA) on intravenous cocaine self-administration. Rats were trained to self-administer intravenous injections of cocaine (1.0 mg/kg per injection) on a fixed-ratio 1 (FR-1) schedule or a progressive ratio (PR) schedule of reinforcement and then were tested under the influence of bilateral VTA injections of the D1 dopamine receptor antagonist SCH 23390 or the 5-HT2 receptor antagonist ketanserin. SCH 23390 increased cocaine self-administration on the FR-1 schedule but decreased it on the PR schedule. Injections of ketanserin were ineffective, as were injections of SCH 23390 in a site 1 mm dorsal or 1 mm rostral to the effective VTA site. These data suggest a role for dendritically released dopamine, presumably acting through D1 receptors located on the axons of GABAergic or glutamatergic inputs to the VTA, in the effectiveness of cocaine reward.

Key words: drug abuse; reinforcement; dendritic release; motivation; operant learning; progressive ratio schedule

Brain dopamine (DA) plays important roles in the rewarding effects of natural rewards such as food (Wise et al., 1978; Ettenberg and Camp, 1986a), water (Gerber et al., 1981; Ettenberg and Camp, 1986b), and sexual contact (Pfaus and Phillips, 1989) and in the laboratory reward of lateral hypothalamic electrical stimulation (Fouriezos and Wise, 1976; Franklin, 1978; Wise and Rompré, 1989). The mesocorticolimbic DA system, which originates in the ventral tegmental area (VTA) and terminates in various forebrain structures (Bjorklund and Lindvall, 1986), is also implicated in the rewarding effects of several drugs of abuse, including cocaine, amphetamine, heroin, and nicotine (Wise, 1996; Bardo, 1998). Each of these drug reinforcers causes elevations in extracellular dopamine levels at the axon terminals of the mesocorticolimbic DA system (Zetterström et al., 1983; Di Chiara and Imperato, 1988; Moghaddam and Bunney, 1989). In the case of cocaine, the enhanced extracellular DA concentrations are caused by a blockade of the reuptake of DA back into presynaptic terminals. Destruction of dopaminergic terminals (Roberts et al., 1977) or dopaminergic synaptic targets (Zito et al., 1985) in the nucleus accumbens (NAcc), a mesolimbic terminal region, disrupts responding maintained by cocaine. Injection of D1 dopamine receptor antagonists into the NAcc (Maldonado et al., 1993; McGregor and Roberts, 1993), the medial prefrontal cortex (McGregor and Roberts, 1995), or, to a lesser extent, the amygdala (McGregor and Roberts, 1993), reduces cocaine reward. Thus it is widely assumed that it is dopamine released at the terminals of the mesocorticolimbic system that is important for reward function (Fibiger, 1978; Wise, 1978; Koob and Bloom, 1988; Wise, 1996; Berridge and Robinson, 1998).

In addition to increasing extracellular levels of DA at the level of the axon terminals of the mesocorticolimbic system, cocaine also increases extracellular DA at the level of the dendrites in the VTA (Bradberry and Roth, 1989; Chen and Reith, 1994). Although dendritically released DA has been shown to be involved in the acute locomotor effects of psychostimulants (Jackson and Kelly, 1983; Stewart and Vezina, 1989; LaHoste and Marshall, 1990), a role for dendritically released dopamine in reward function has not been reported. The neurochemical and neuroanatomical arrangements of the VTA, however, suggest that dendritically released DA may indeed be involved in cocaine reward. Dendritically released DA in the VTA acts on D1 receptors located on the terminals of GABAergic and glutamatergic inputs originating in forebrain regions (Sesack and Pickel, 1992; Smith et al., 1996; Steffensen et al., 1998). GABA and glutamate in the VTA modulate the activity of dopaminergic and GABAergic output cells (Albin et al., 1992; Nakanishi, 1992; Overton and Clark, 1992; Kalivas, 1993; Zhang et al., 1994; Christoffersen and Meltzer, 1995). Thus, by modulating the release of GABA and glutamate, which in turn modulate DA cell activity and output, dendritically released DA could play a significant role in cocaine reward. We tested this hypothesis by investigating the effects of intra- and peri-VTA injections of the D1 DA receptor antagonist SCH 23390 or the 5-HT2 receptor antagonist ketanserin on cocaine self-administration in rats. Ketanserin was tested as a control because, in addition to being a potent antagonist at the D1 DA receptor, SCH 23390 is a weak antagonist at the 5-HT2 receptor, which is also found in the VTA. Our results support the hypothesis that dendritically released DA in the VTA affects the rewarding effectiveness of cocaine.

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MATERIALS AND METHODS

Subjects and surgery. Subjects were male Long–Evans rats (Charles River Canada, Saint Constant, Québec, Canada; and Harlan, Indianapolis, IN) weighing between 350 and 400 gm at the time of surgery. Each was kept on a 12 hr light/dark cycle with the dark phase starting at 7 A.M. and had free access to food (Purina rat chow) and water except during self-administration sessions. Each rat was implanted, under sodium pentobarbital anesthesia (65 mg/kg, i.p.), with bilateral guide cannulas (20 gauge) aimed at the VTA or at control sites either 1 mm rostral or 1 mm dorsal to the VTA. For guide cannula implantations into the VTA, the flat-skull (Paxinos and Watson, 1986) coordinates were 5.6 mm caudal to bregma, ±2.2 mm lateral to the midline (angled at 10° toward the midline to bypass the sagittal sinus), and 7.3 mm below the surface of the skull. For the rostral control site, the coordinates were 4.6 mm caudal to bregma, ±2.2 mm from the midline, and 7.3 mm below the surface of the skull. For the dorsal control site, the coordinates were 5.6 mm caudal to bregma, ±2.2 mm from the midline, and 6.3 mm below the surface of the skull. Obturators extended 1 mm beyond the guide cannulas and were kept there until the time of testing.

While under anesthesia, each rat was fitted with a permanently indwelling jugular catheter. An incision was made in the neck and the jugular vein was isolated and opened. A Silastic intravenous catheter (Dow Corning, Midland, MI) was inserted into the vein so that the tip penetrated to a position just short of the right atrium. The other end of the catheter was fed subcutaneously to the back of the neck and exited through an opening at the back of the skull. A bent 22 gauge stainless steel tube was inserted into the catheter and secured to the rat's skull with dental cement anchored by stainless steel screws. This tube served as a connector between the intravenous catheter and the drug infusion line. The catheter was flushed with a heparin-saline solution (200 U/ml) immediately after surgery and daily thereafter.

Cocaine self-administration training. One day after surgery, the animals began cocaine self-administration training. All self-administration sessions (training and test) were conducted during the dark phase. Each animal was placed daily in a 26 × 26 × 30 cm operant chamber equipped with an operant lever mounted 10 cm from the floor. A white cue light was mounted 3 cm above the lever, and each cage had a hanging water bottle. The rat was connected by polyethylene tubing, through a fluid swivel, to a syringe in a syringe pump (Razel; 1 rpm). Each lever press activated the syringe pump and cue light for 14 sec, causing the intravenous delivery of 1.0 mg/kg cocaine in a 0.125 ml volume of saline. During drug delivery, lever presses were counted but had no other consequence. Thus, the rats learned to lever press under a fixed ratio 1 (FR-1) schedule of reinforcement. Some rats were tested on this schedule of reinforcement, whereas others were switched, after responding stabilized, to a progressive ratio (PR) schedule. Stable responding on the FR-1 schedule was defined as three consecutive sessions during which the total number of responses did not vary by >10% from the mean of the three sessions; rats met this criterion between 11 and 20 training sessions.

On a PR schedule of reinforcement, the ratio of responses per infusion was increased after each infusion according to an exponential function. In the present study, the response requirements in the progression were calculated by the formula, responses $= 5 \times e^{(\text{inj } \# \times 0.2)} - 5$. The ratios in the progression were 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, and so on. Eventually, as the ratio requirement increased, the rats ceased to respond. The step at which rats stopped responding was referred to as the break point (BP). For the present experiments, the BP was operationally defined as the final ratio completed within 1 hr of the previously earned injection. A stable BP was operationally defined as three consecutive BPs that did not differ by >10% from their mean; rats met this criterion between 15 and 20 training sessions.

Microinjections of SCH 23390 or ketanserin. On test days, the animals were pretreated with VTA microinjections of SCH 23390 or ketanserin. Fifteen rats were tested under the influence of intra-VTA injections of SCH 23390, and 10 were tested under intra-VTA ketanserin under the FR-1 schedule of reinforcement. Ten rats were tested with intra-VTA injections of SCH 23390 under a PR schedule of reinforcement. Four rats were tested under a PR schedule with microinjections of SCH 23390 in sites just rostral to the VTA, and five were tested with SCH 23390 in sites just dorsal to the VTA site.

Just before these test sessions, the obturator was removed from one of the guide cannulas, and a stainless steel injector cannula was inserted into that guide cannula for each animal. The injector extended beyond the guide cannula by 1 mm. The injector was connected through polyethylene tubing to a 10 μl Hamilton (Reno, NV) syringe that was preloaded with SCH 23390 (1, 2, or 4 μg/0.5 μl), ketanserin (2, 4, or 8 μg/0.5 μl) or vehicle (of which 96% of the volume consisted of artificial CSF and the rest of methanol). The test compound was delivered by motorized syringe pump in a volume of 0.5 μl over 30 sec. The injector was kept in place for an additional 60 sec. The injector was then removed, and the obturator was replaced into the guide cannula. This procedure was repeated for the contralateral side. At the end of the second microinjection, the rat was placed in the operant chamber, and the test session (either FR-1 or PR) was started.

The animals were tested at 4 d intervals with as many of the doses or vehicle as possible; 3 d of treatment-free testing intervened between microinjection treatments. If the total number of injections on the session after the test session did not fall within 10% of the mean of the three sessions preceding the test session, then the data from that test session were not used. If after a test session, baseline response rates did not meet the stability criterion (three consecutive sessions in which the total number of injections per session was within 10% of the mean for the three sessions), treatment-free testing continued. If more than seven sessions passed in which the stability criterion was not met, the rat was removed from the experiment; two animals were removed for this reason. Animals were also removed from the experiment when catheters were blocked or began to leak or when head assemblies became dislodged. Sixteen of the FR-1 animals and seven of the PR animals failed to complete testing at one or more dose levels.

Histology. After its last test session, each rat was anesthetized with sodium pentobarbital, perfused with saline followed by 10% formalin, and decapitated. The brains were removed and stored in 10% formalin for at least 7 d before being cut in 40 μm serial sections, stained with thionin, and inspected for cannula implantation and injection sites.

Data analysis. The total number of infusions per session for the FR-1 or PR schedule was analyzed. Separate one-way ANOVAs were conducted on the data from the groups receiving intra-VTA doses of SCH 23390 or ketanserin under the FR-1 schedule of reinforcement. A separate one-way ANOVA was conducted on the data from the group receiving intra-VTA doses of SCH 23390 under the PR schedule. A final one-way ANOVA was conducted on the data from the groups receiving the 4.0 μg/0.5 μl dose of SCH 23390 in the VTA, the site just dorsal to the VTA, and the site just rostral to the VTA. Site comparisons were made using Scheffé tests. Because not all animals completed every treatment condition in either experiment, we used a between-subjects ANOVA model. A within-subjects model would have overestimated statistical significance; the between-subjects model is more conservative.

Drugs. Cocaine hydrochloride (National Institute on Drug Abuse, Rockville, MD) was dissolved in saline. SCH 23390 and ketanserin (Research Biochemical Inc., Natick, MA) were dissolved in 4% methanol and 96% artificial CSF.

RESULTS

Microinjections of SCH 23390 into the VTA produced a dose-orderly increase in the number of cocaine infusions self-administered on an FR-1 schedule of reinforcement (Fig. 1*a*) ($F_{(3,17)} = 13.86$; $p < 0.001$). At the highest dose, SCH 23390 increased cocaine intake to values twice as high as were observed after control vehicle injections. Response records taken in the baseline (no injection) and SCH 23390 conditions both showed well spaced cocaine intake that continued to be regular throughout the period of cocaine availability (Fig. 1*b*). However, the rate of cocaine intake was higher in the SCH 23390 condition than in the baseline or vehicle condition, especially during the first half of the test sessions. On average, the animals responded approximately once every 4 min under the high-dose SCH 23390 condition and once every 7 min under the baseline or vehicle condition. Microinjections of ketanserin into the VTA did not affect rate of cocaine self-administration (Fig. 1*a*) ($F_{(3,18)} = 0.23$; $p > 0.9$).

In the case of the PR schedule, microinjections of SCH 23390 decreased responding (Fig. 2*a*) ($F_{(3,30)} = 12.38$; $p < 0.001$). At the highest dose, SCH 23390 reduced the mean number of cocaine infusions to 27% of the mean observed under vehicle control conditions. Cumulative response records taken in the vehicle condition showed alternations between periods of high response

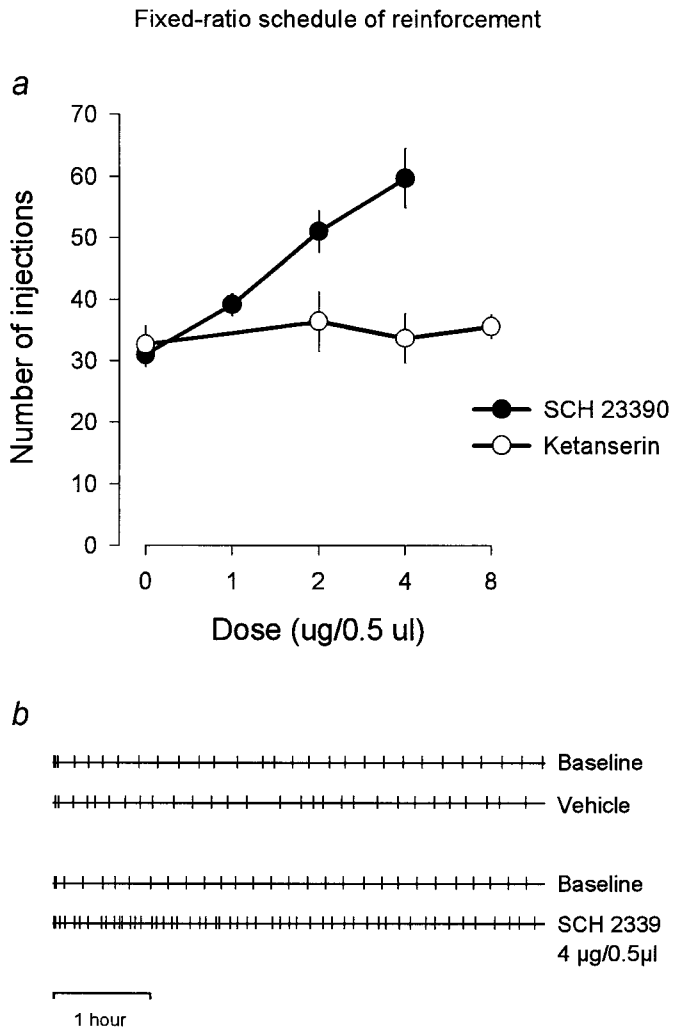

Figure 1. *a*, Mean ± SEM effects of SCH 23390 (and ketanserin) on cocaine self-administration under an FR-1 schedule of reinforcement. *b*, Event records reflecting the response rate and pattern of responding for a subject under baseline conditions and after vehicle or SCH 23390 treatment. Note the immediate acceleration and subsequent return toward a normal response rate after SCH 23390 treatment.

rates followed by postreinforcement pauses (no responding) that are typically seen during cocaine self-administration on PR schedules of reinforcement. Cumulative response records taken in the SCH 23390 condition also showed this typical PR pattern of responding, except that responding ended earlier in the session at lower final response ratios (Fig. 2*b*). Whereas the animals made a mean of 57 lever presses for the final earned injection under the vehicle condition, they made means of only 33, 14, and 4 responses for the final earned injections under the 1, 2, and 4 μg/0.5 μl SCH 23390 conditions, respectively (Table 1).

Microinjections of the 4 μg/0.5 μl dose of SCH 23390 into a site 1 mm dorsal or into a site 1 mm rostral to the VTA injection site also produced decreases in PR responding, but these reductions were significantly smaller than those observed after microinjection of this dose of SCH 23390 into the VTA (Fig. 3) ($F_{(2,15)} = 13.62$; $p < 0.001$). Scheffé comparisons between the VTA and the dorsal site and between the VTA and the rostral site confirmed that responding was significantly less depressed when SCH 23390 was injected dorsal or rostral to the VTA site ($F_{(1,15)} = 21.07$; $p < 0.001$; and $F_{(1,15)} = 14.94$; $p < 0.01$, respectively).

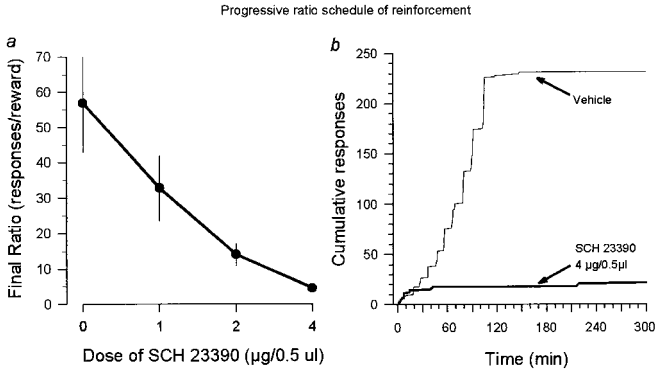

Figure 2. *a*, Mean ± SEM effects of SCH 23390 on BP for cocaine self-administration under a PR schedule of reinforcement. *b*, Cumulative response records reflecting the total number of responses and the pattern of responding for a subject after vehicle or SCH 23390 (4 μg/0.5 μl) treatment.

Figure 4 shows the locations of the cannula tips. Microinjections aimed at the anatomical control sites were ~1 mm rostral and 1 mm dorsal to the VTA region (Fig. 4).

DISCUSSION

Microinjections of SCH 23390 into the VTA increased rates of cocaine self-administration on an FR-1 schedule of reinforcement and, at the same doses, decreased BPs on a PR schedule of reinforcement. Together these data suggest that blockade of D1 DA receptors in the VTA reduces the rewarding effectiveness of self-administered cocaine. The fact that intra-VTA injections of SCH 23390 affected response rates in opposite directions depending on the schedule of reinforcement under which the rats were responding argues against the possibility that VTA SCH 23390 had a simple, nonspecific effect on motoric output. Had SCH 23390 enhanced or impaired the ability of animals to perform the lever press response, then it would have produced changes in the same direction under the two schedules of reinforcement. Rather, the data suggest a motivational interpretation.

In the present study, animals responding under the FR-1 schedule and pretreated with intra-VTA SCH 23390 continued to display the pattern of regularly spaced infusions that was seen after no or vehicle pretreatment. Thus cocaine was still sufficiently rewarding to maintain stable responding under the SCH 23390 conditions. However, each earned injection satisfied (satiated) the animal for a shorter duration under SCH 23390 conditions than under normal conditions. Cocaine is thought to be effective because it elevates extracellular dopamine levels, and the generally accepted interpretation of neuroleptic-induced increases in stimulant self-administration is that increased dopamine concentrations are needed to overcome the competitive

Table 1. Effects of intra-VTA SCH 23390 on mean final ratios completed in the progressive ratio series and on mean cumulative responses

Dose of SCH 23390 (μg/0.5 μl)	Final ratio completed	Cumulative responses
Vehicle	56.86 ± 14.04	255.25 ± 71.63
1	32.78 ± 9.10	136.56 ± 44.02
2	14.13 ± 3.11	47.00 ± 12.66
4	4.44 ± 0.85	9.11 ± 2.24

Values are mean ± SEM.

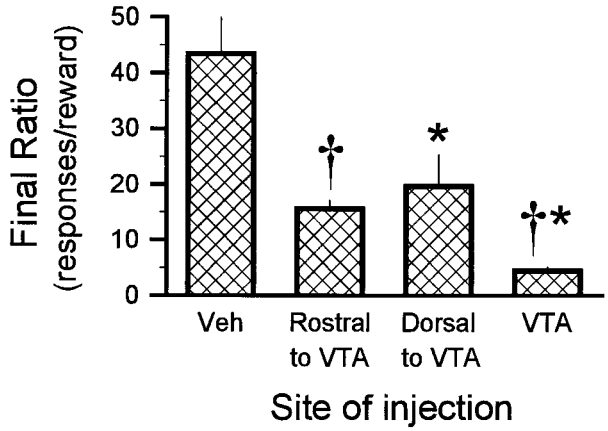

Figure 3. Depression of progressive ratio BP as a function of site of microinjection. The dorsal and rostral control sites were each 1 mm from the VTA site where the drug was most effective. The vehicle value represents the average of the vehicle data taken from the VTA and the dorsal and rostral sites. * or † indicate paired comparisons that showed significant differences.

antagonism of dopamine receptors (Yokel and Wise, 1975, 1976; de Wit and Wise, 1977; Ettenberg et al., 1982).

The interpretation that blockade of VTA D1 receptors reduced the rewarding effectiveness of cocaine fits well with the decrease in BPs observed in rats responding under the PR schedule of reinforcement. In this paradigm, the number of lever presses required for successive injections was increased exponentially until the animal ceased continuing to respond. The BP, the response requirement at which the animal stops lever pressing, is taken as an index of the animal's motivation under a given reward condition (Richardson and Roberts, 1996). When a treatment reduces the BP for a given reward, it is thought to have done so by reducing the effectiveness of the rewarding event. By this test, again, intra-VTA SCH 23390 appears to reduce the rewarding effectiveness of self-administered cocaine. These findings are the first to suggest a functional role for dendritically released dopamine in reward function.

The present experiments with intra-VTA injections of ketanserin and peri-VTA injections of SCH 23390 were conducted to rule out the possibilities that the effects of intra-VTA injections of SCH 23390 were attributable to blockade of 5-HT2 receptors or to actions in distal sites. Although SCH 23390 is the classic antagonist of D1 DA receptors (Hyttel, 1983; Iorio et al., 1983) it also has high affinity for and antagonist actions at 5-HT2 receptors (Hicks et al., 1984; Bischoff et al., 1986; Hoyer et al., 1989; Briggs et al., 1991; Woodward et al., 1992; Ciccocioppo et al., 1997; Eberle-Wang et al., 1997). Ketanserin shares the ability to block 5-HT2 receptors (Leysen et al., 1981) but does not block D1 DA receptors. It is known that systemic injections of 5-HT2 antagonists fail to affect rate or BP in rats self-administering cocaine (Porrino et al., 1989; Lacosta and Roberts, 1993), suggesting that 5-HT2 receptors, in the VTA or elsewhere, are likely not involved in cocaine reward. However, there are 5-HT2 receptors in the VTA (Kalivas, 1993), and thus we used ketanserin to rule out the possibility that blockade of these receptors was significant in the effects of SCH 23390. The present data argue against this possibility. Ketanserin failed to affect cocaine self-administration, ruling out the possibility that 5-HT2 actions of SCH 23390 played a role in the SCH 23390 effects.

To address the possibility that intra-VTA injections of SCH 23390 diffuse to and act at distal sites, we investigated the effects of two peri-VTA injections of this compound on cocaine self-administration. Injection of substances directly into the brain is associated with a hydraulic pressure that can drive the substance toward the pressure sinks of ventricles and extrapial spaces. The most prominent diffusion is up the cannula shaft, particularly if the cannula penetrates a ventricle (Johnson and Epstein, 1975; Wise and Hoffman, 1992). To assess this possibility, we tested injections just dorsal and just rostral to our VTA site. Although microinjections of SCH 23390 into each of these sites decreased responding on the progressive ratio schedule, in each case the effect was less than was seen with the primary VTA injections. This rules out the possibility of dorsal or rostral diffusion to a distal site of action; rather, it seems likely that diffusion to the VTA accounts for the weaker effects of injections into each of these control sites.

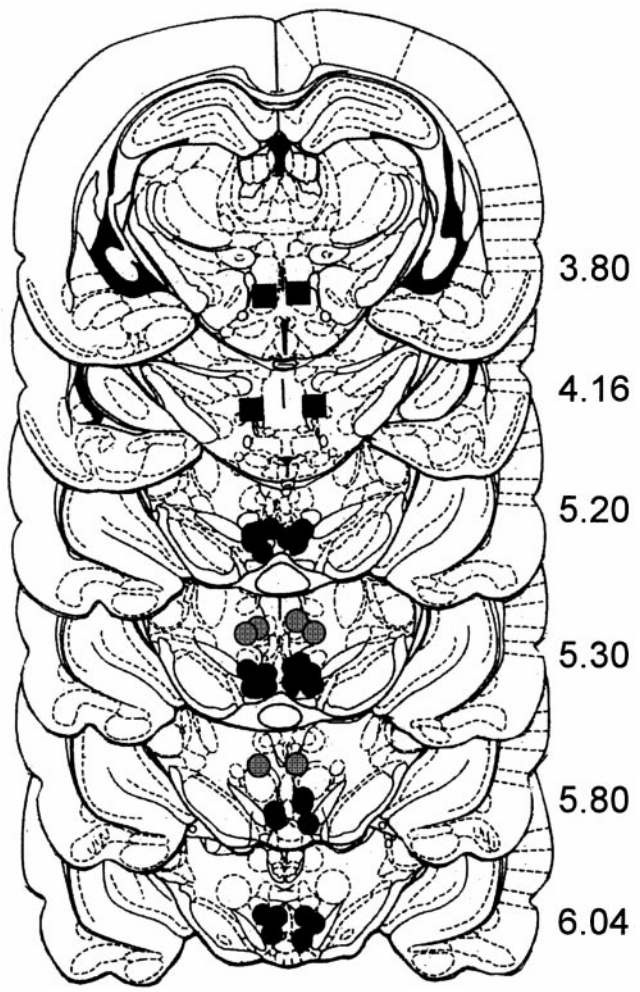

Figure 4. Histological reconstruction of injection sites adapted from Paxinos and Watson (1986). *Black circles*, SCH 23390 or ketanserin; *gray circles*, dorsal controls; *black squares*, rostral controls.

The mechanism of the reward-depressing effects of SCH 23390 in the VTA remains to be determined. The VTA is the site of origin of DA cells projecting to various forebrain structures (Bjorklund and Lindvall, 1986). There are no DA afferents to the VTA; thus the only source of DA here is dendritic release. Cocaine binds to DA transporters on the dendrites and dendritic spines of DA cells in the VTA (Ma et al., 1999). By blocking

dendritic DA uptake, cocaine increases local DA concentrations (Kalivas and Duffy, 1993). There are no D1 DA receptors on dopaminergic (DAergic) neurons, however; D1 DA receptors in the VTA are localized on glutamate and GABA afferents to the VTA (Harrison et al., 1990; Herkenham et al., 1991; Yung et al., 1995; Lu et al., 1997), and the effect of DA at these receptors is to facilitate the release of these neurotransmitters (Starr, 1987; Cameron and Williams, 1993; Kalivas and Duffy, 1995). Glutamate excites VTA DAergic and non-DAergic neurons (Albin et al., 1992; Nakanishi, 1992; Carr and Sesack, 2000) and GABAergic neurons (Overton and Clark, 1992; Zhang et al., 1994; Christoffersen and Meltzer, 1995). GABA inhibits both DAergic neurons (Kalivas, 1993) and nearby GABAergic projection neurons, some of which, in turn, inhibit their dopaminergic neighbors, probably via local collaterals (Tepper et al., 1995). Thus dendritic DA, through D1 receptor activation, can affect local glutamate and GABA concentrations, which can, in turn, control DAergic neurons directly and, through GABA collaterals, indirectly. Given the known role of these DA cells in cocaine reward, any effect on their activity can be predicted to affect cocaine reward one way or the other. The role of GABAergic output cells in cocaine reward is not known, but some of them project to the NAcc, where they, too, might play a role in reward function.

The present finding that dendritically released DA in the VTA can play a significant role in cocaine reward adds a new level of complexity to our understanding of reward circuitry in particular and DAergic circuitry in general. DA transmission in the terminal regions of the mesocorticolimbic system has long been implicated in cocaine reward. The output neurons of NAcc project, through a complex anatomical cascade of GABAergic feedback, back to the VTA. Thus the VTA DAergic somata are positioned to release DA at both the cell bodies and the terminals of descending GABAergic pathways. Similarly, the mesocortical DA system releases DA at both the cell bodies and the descending terminals of the corticotegmental glutamate pathway. The present data support the hypothesis that feedback signals to the VTA contribute to reward function and to other functions of tegmental (both VTA and perhaps similarly substantia nigra) DAergic neurons. The mesocorticolimbic DA system is an important component of a general arousal system that plays significant roles in both the anticipation (Apicella et al., 1992; Schultz, 1997) and the reception (Wise and Rompré, 1989; Berridge and Robinson, 1998) of reward signals. It is not surprising that dysfunction of such a broadly projecting and servoregulated system plays a critical role in motivation and addiction (Fibiger, 1978; Wise, 1978; Koob and Bloom, 1988). Similarly, dysfunction of the nigrostriatal DA system contributes importantly to such divergent phenomena as the motor symptoms of Parkinson's disease and the cognitive and emotional symptoms of schizophrenia. The present findings suggest the possibility that dendritic release of DA in the substantia nigra plays roles in these syndromes as well.

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