Enhanced Neurobehavioral Effects of Cocaine With Chronic Neuroleptic Exposure in Rats

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Abstract

Individuals with schizophrenia are often treated with medications that block dopamine (DA) neurotransmission. Chronic administration of many DA antagonists alters dopaminergic function, causing a supersensitivity to DA agonists. Because the DA agonist properties of cocaine seem to be involved in its behavioral effects, chronic DA antagonist treatments may enhance these effects of cocaine. This article presents evidence to support this hypothesis, as well as its implications for treating schizophrenia patients who abuse cocaine and suggestions for future research.


Recent clinical studies indicate that cocaine abuse is a significant problem among schizophrenia populations (Brady et al. 1990; Dixon et al. 1991). This dual-diagnosis phenomenon seems inexplicable at first glance, given that cocaine use can cause psychoticlike behaviors, such as paranoia and hallucinations (Satel 1992). Moreover, a widely used animal model of schizophrenia posits a paradigm of chronic exposure to amphetamine, a drug with many pharmacological and behavioral similarities to cocaine. Thus, the abuse of cocaine in a person with a schizophrenia diagnosis does not make sense at any level of explanation, from the neurobiological to the behavioral. However, a recent line of research in our laboratory has begun to explore a possible neuropharmacological route of inquiry that may help explain one basis of this dual diagnosis. Our general hypothesis is that cocaine abuse may be initiated and sustained more easily in persons who have been treated chronically with some neuroleptic drugs. Such treatment seems to alter neural areas subserving drug reward in a way that may make the person more sensitive to the effects of cocaine. Increased sensitivity to the behavioral effects of cocaine may translate into enhanced abuse liability of this drug among neuroleptic-exposed patients with schizophrenia. This article presents evidence in support of this hypothesis.

Dopamine (DA) Theory of Schizophrenia

The antipsychotic effects of neuroleptic drugs were found to be potent treatments for schizophrenia in the 1950s (Delay and Deniker 1952). At that time, however, the mechanisms of their therapeutic effects were unknown. Later research began to focus on the dopaminergic function of these drugs and helped give rise to the DA theory of schizophrenia, which postulated that schizophrenia may be mediated by abnormally high levels of DA. Support for the theory came from the observations that neuroleptics, which block DA transmission, alleviate some psychotic symptoms. Furthermore, the clinical potencies of these neuroleptic drugs were found to be correlated highly with their affinity for DA receptors (Creese et al. 1976). In addition, administration of drugs that increase DA levels, such as amphetamine or L-dopa, sometimes produced symptoms similar to those seen in schizophrenia, such as psychosis and paranoia (Bell 1973). Indeed, this “amphetamine psychosis” effect was the basis of assessing the locomotor activational effects of chronic amphetamine administration in rats as an animal model of schizophrenia (Snyder 1974).

However, some data do not support the idea that the etiology of schizophrenia is related to a surplus of DA in the brain. For example, neuroleptic drugs act at DA receptors by blocking transmission soon after administration, yet their therapeutic effect—a decrease in psychotic symptoms—is usually not seen for several days or weeks (Spohn et al. 1977; Johnstone et al. 1978). There are also
Behavioral Effects of Cocaine

Cocaine has several behavioral effects. Moderate doses stimulate locomotor activity, consistent with cocaine's classification as a psychomotor stimulant. In animals, high doses of cocaine can induce stereotypic responding, a motoric effect characterized by repetitive, in-place movements, such as head bobbing, weaving, or other jerky movements (Lewander 1974). Repeated exposure to the drug can enhance these motoric effects, a phenomenon known as behavioral sensitization, such that lower doses of cocaine can elicit effects that are behaviorally equivalent to those seen originally with a higher dose or increased responding to the same cocaine dose over time. Thus, this phenomenon is often referred to as "reverse tolerance" because these effects are the converse of what is often seen with repeated drug exposure (a decrease in the effectiveness of a dose or decreased responding to the same dose) as found in studies of morphine analgesia. Behavioral sensitization has been suggested to be analogous to the development of cocaine-induced paranoia and hallucinations in that these behavioral effects tend to appear after chronic cocaine use and occur more readily after such exposure (Post and Kopanda 1976). Indeed, behavioral sensitization was first characterized with amphetamine, a drug that is similar to cocaine in its pharmacological and behavioral effects. And because amphetamine-induced psychosis in humans is believed to be related to schizophrenia, the study of the behavioral and pharmacological effects of chronic amphetamine exposure in animals is a good model of this disorder.

The reported euphorogenic effects of cocaine in humans and its subsequent abuse potential are believed to be related to other behavioral properties of cocaine studied in animals (Johanson and Fischman 1989). These behavioral characteristics include its ability to positively reinforce self-administration behavior (Pickens and Thompson 1968), to support place conditioning (Carr et al. 1989), and to act as a discriminative stimulus (Colpaert et al. 1978). Cocaine self-administration is a widely used model of cocaine abuse (Pickens and Thompson 1968; Schuster and Thompson 1969). In this operant conditioning paradigm, animals learn to make a response (e.g., pressing a lever in an operant chamber) to receive an intravenous infusion of the drug. This behavior increases, presumably due to the positively reinforcing effect of these drug injections. Once established, cocaine self-administration behavior shows an inverted U-shaped dose response pattern that lower doses lead to low responding, moderate doses are associated with increased response rates, and higher doses decrease the response rate. The positive reinforcing or rewarding effects of cocaine are thought to underlie its ability to support place conditioning, another widely used animal model of cocaine effects (Carr et al. 1989). In this model, cocaine administration is paired with specific environmental cues. How much the animal approaches or avoids the cocaine-associated environment is then assessed. In my experience, cocaine place conditioning also is associated with an inverted U-shaped curve, with moderate doses supporting the greatest degree of place conditioning. A third widely used animal model of the behavioral effects of cocaine is drug discrimination. In this model, animals are trained to discriminate the presence or absence of a cocaine stimulus by differential lever selection using a two-lever, food-reinforced operant task (Colpaert et al. 1978). Once discriminative stimulus control of behavior is established, the cocaine-occasioned responding to other cocaine doses occurs in a dose-related manner, shows dose-related generalization to drugs of a similar type (e.g., amphetamine), and does not generalize to drugs that are dissimilar to it such as (pentobarbital).

Some of these animal models have been translated into the human laboratory. Researchers have found that cocaine is self-administered in a dose-related manner (Foltin and Fischman 1992), and its discriminative stimulus effects occasion dose-related responding in experienced cocaine users (Oliveto et al. 1995). Many studies use these models to test the involvement of neuropharmacological factors in the behavioral effects of cocaine.

Evidence for the Role of DA in the Behavioral Effects of Cocaine

Many of the prominent behavioral effects of cocaine are believed to involve the mesolimbocortical DA system
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Leads to Neurobehavioral Chronic DA Antagonist Treatment et al. 1991) and place-conditioning effects (Spiraki et al. 1989). This pathway consists of DA cell bodies in the ventral tegmental area (VTA) and its projection areas, including the nucleus accumbens (NAcc), medial prefrontal cortex (mPFC), and other brain regions. Cocaine inhibits DA uptake into the presynaptic terminals through its actions at the DA transporter (Harris and Baldessarini 1973). The result is an accumulation of DA in the synapse of the NAcc (Pettit and Justice 1989) and an enhanced stimulation of these postsynaptic receptors. This ability of cocaine to enhance synaptic DA levels in this neural system is thought to be related to its reinforcing (Ritz et al. 1987) and other behavioral effects (Spealman et al. 1989).

Consistent with these neuropharmacological findings, DA antagonists tend to attenuate the behavioral effects of cocaine, whereas DA agonists generally enhance these behavioral effects (Woolverton and Johnson 1991). For example, the neuroleptic and DA antagonist, haloperidol, partially blocks the behavioral effects of cocaine, including its effects on intravenous self-administration (Roberts and Vickers 1984), drug discrimination (Colpaert et al. 1978; Kleven et al. 1990; Callahan and Cunningham 1993), schedule-controlled behavior (Bergman and Spealman 1988), locomotor activity (Weiss et al. 1989; Martin-Iverson and Reimer 1994), and place conditioning (Kosten et al. 1996). In general, these behavioral studies find that short-term haloperidol treatment is associated with a partial attenuation of cocaine effects that may be due to the specific actions of haloperidol within the mesolimbocortical DA system. That is, haloperidol may act at postsynaptic DA receptors in the NAcc, but not in the mPFC. DA afferents projecting to the mPFC differ in many characteristics from those of the NAcc (see Roth et al. 1987), and haloperidol does not seem to affect these mPFC afferents as it does those projecting to the NAcc (Thierry et al. 1986). This specific action of haloperidol in the NAcc, but not in the mPFC, may be why some studies have failed to find an acute effect of haloperidol on the discriminative stimulus (Barrett and Appel 1989; Witkin et al. 1991) and place-conditioning effects (Spiraki et al. 1989) of cocaine.

Chronic DA Antagonist Treatment Leads to Neurobehavioral Supersensitivity

Neurobiological research suggests that, whereas the behavioral effects of cocaine may be attenuated partially by short-term administration of many DA antagonists, long-term treatment may enhance these effects. For example, heightened functional responsiveness, including increases in postsynaptic receptor binding (Burt et al. 1977; Seeger et al. 1982) and density in nigrostriatal (Müller and Seeman 1978) and mesolimbic (i.e., NAcc) structures (see et al. 1989), occurs in some dopaminergic regions after long-term haloperidol treatment. In addition to these postsynaptic effects, studies examining presynaptic DA neurons in the VTA suggest that long-term DA antagonist treatment reduces the number of spontaneously active cells, perhaps because of a state of depolarization inactivation produced by the chronic blockade of postsynaptic DA receptors (Chiodo and Bunney 1983; White and Wang 1983). This depolarization inactivation seems to be limited to DA neurons projecting to the NAcc and does not include those projecting to the mPFC (Chiodo and Bunney 1983).

Long-term haloperidol treatment has several functional consequences, including enhanced stereotypic responses to DA agonists, such as apomorphine (Tarsy and Baldessarini 1974; Seeger et al. 1982), amphetamine (Rebec et al. 1982), quinpirole (LaHoste and Marshall 1992), and cocaine (see below). Moreover, long-term haloperidol treatment enhances the sensitivity to the behavioral effects of cocaine in the place-conditioning and drug-discrimination procedures (Kosten et al. 1996; see below). Consistent with these data are recent studies that find more rapid locomotor sensitization to cocaine with long-term haloperidol treatment (LeDuc and Mittleman 1993) and enhanced sensitivity to the effects of cocaine on schedule-controlled behavior after cessation of long-term administration of the DA antagonists, raclopride and spiperone (Howell and Byrd 1992). Long-term administration of the DA antagonist, SCH 23390, heightens stereotypic responses to apomorphine (Vaccheri et al. 1987) and enhances sensitivity to the discriminative stimulus effects of the DA agonist, SKF 38393 (Gui-Hua et al. 1992). Moreover, enhanced behavioral effects of cocaine have been found after long-term administration of SCH 23390 in some studies (Emmett-Oglesby and Mathis 1988; Kleven and Woolverton 1990), but not in another (Howell and Byrd 1992).

Long-Term Haloperidol Enhances the Sensitivity to the Place-Conditioning Effects of Cocaine

Based on the literature discussed above that long-term DA antagonist treatment leads to neuronal supersensitivity and is associated with enhanced sensitivity to the behavioral effects of DA agonists, my colleagues and I conducted the following experiments. We tested whether long-term administration of the classic DA antagonist,
haloperidol, would enhance sensitivity to the behavioral effects of cocaine using a place-conditioning procedure. This procedure was logical to use because we have had extensive experience with this paradigm using cocaine (Kosten and Nestler 1994; Kosten et al. 1994, 1996). Haloperidol was the logical DA antagonist to try first, given the vast literature on its short- and long-term effects. Rats were administered haloperidol (1 mg/kg, subcutaneously) or vehicle for 21 days before and during training and testing of cocaine place conditioning in the first study described below. In the second study, we administered haloperidol in the drinking solution, based on the method of See and Ellison (1990), for 30 days before and during training and testing of cocaine place conditioning. (This oral administration procedure resulted in an average daily dose of 2.2 mg/kg, which was set higher due to first-pass metabolism.) Continuation of haloperidol administration during the cocaine training distinguishes these studies from many previous ones in which the antagonist treatment was withdrawn before the effects of the DA agonist were examined. Maintenance of the antagonist treatment is a better model of the clinical situation in which stimulant abuse may occur while patients are on medications. Thus, these studies examined the combined effects of long-term pretreatment of a DA antagonist, which presumably enhances the sensitivity of at least certain aspects of the DA system, and of its short-term effect of antagonizing certain effects of cocaine.

In the first study, separate groups of rats (4 in each group) were assigned to receive haloperidol or vehicle injections as stated above. After 21 days of drug exposure, the rats were trained in the place-conditioning procedure, as described previously (Kosten and Nestler 1994; Kosten et al. 1994, 1996) with 15 mg/kg cocaine intraperitoneal (i.p.). Rats received four training trials with cocaine and four with saline in which the cocaine administration was paired with one side of the place-conditioning apparatus and saline administration was paired with the other side on separate days. During test days, the rats had access to both sides, which differed in their visual and tactile cues, for 30 minutes. We recorded the amount of time spent on each side and compared the change in time spent on the cocaine-paired side after training with the time spent on that side before training. As shown in figure 1, rats that had received haloperidol spent more time on the cocaine-paired side after training than the group that had received vehicle. This haloperidol group effect was significant, \( t(6) = 2.5; p < 0.05 \), suggesting that chronic DA receptor blockade with haloperidol administration enhances the rewarding properties of cocaine.

We also assessed the effects of long-term (30 days), orally administered haloperidol on the place-conditioning effects of cocaine using lower cocaine doses (2.0 mg/kg). Because these doses are normally below the threshold for supporting place conditioning in vehicle-treated rats, this study assessed whether chronic haloperidol administration would enhance the sensitivity to cocaine. Our findings indicate that long-term haloperidol treatment does enhance the sensitivity to the place-conditioning effects of cocaine, as these low doses were able of supporting place conditioning in the haloperidol treated groups, but not in the vehicle-treated group (Kosten et al. 1996).

Because these studies used a regimen of long haloperidol administration that continued throughout cocaine training and testing period, it was necessary to assess the effects of place conditioning to cocaine the haloperidol was given during the training period (i.e., acquisition) or during the testing period only (expression). To study the effects of short-term haloperidol treatment on the acquisition of place conditioning cocaine, haloperidol or vehicle solutions were given during the training phase. Note that haloperidol (or its vehicle) was present during all training sessions (cocaine vehicle training days); thus, any possible behavioral differences were due to chronic haloperidol.
Cocaine Discrimination was completing at least 90 percent of the cocaine sessions. The criterion for acquisition of the discrimination was meeting at least two reinforcers in a session for six consecutive sessions. Once cocaine demonstrated stimulus control over behavior, a cocaine dose-response function (0.3–17 mg/kg) was determined during one test session using a multiple dosing procedure. In this procedure, rats were injected with the first cocaine dose, and 10 minutes later, a 10-minute test session began during which a maximum of 10 reinforcers could be earned for completing FR10 response requirements on either lever. Five minutes later, the second cocaine injection was given to bring the cumulative cocaine dose up to the second dose level, and testing continued as before. This procedure was continued until the cumulative cocaine dose reached either 10 or 17 mg/kg.

Testing occurred under three conditions: vehicle, short-term, and long-term haloperidol administration. Rats were given the vehicle haloperidol solution to drink for 3 days. On the third day, a cocaine dose-response function was generated using the multiple dosing procedure. Discrimination training continued for 4 days after this test day. At this point, the vehicle solutions were replaced by the haloperidol solution for 3 days. On the third day, a second cocaine dose-response function was generated as before. This 3-day administration procedure was used to allow enough time for DA receptor blockade to occur. At the completion of this short-term haloperidol phase of the study, discrimination training was suspended, and the rats were maintained on haloperidol and food deprivation for 28 days. On the 28th day, a third cocaine dose-response function was determined as before.

Figure 2 presents the mean percent of cocaine-appropriate responding as a function of cocaine dose for two rats. The three dose-response functions shown are the vehicle condition, the effects of acute (3 days) haloperidol administration, and the effects of chronic (28 days) haloperidol administration. After acute haloperidol administration, the cocaine dose-response curve shifted to the right of that determined in the absence of haloperidol administration. After chronic haloperidol administration, the cocaine dose-response curve shifted to the left of that determined in the absence of haloperidol administration. These data suggest that acute haloperidol administration attenuates the discriminative stimulus effects of cocaine, consistent with previous studies (Colpaert et al. 1978; Kleven et al. 1990; Callahan and Cunningham 1993), although not with some other studies (Barrett and Appel 1989; Witkin et al. 1991). In contrast, chronic haloperidol administration enhances these effects, consistent with our place-conditioning data and with a previous report on the effects of chronic SCH 23390 on cocaine discrimination (Emmett-Oglesby and Mathis 1988).

Differential Effects of Chronic Versus Acute Haloperidol Treatment on Cocaine Discrimination

In this study, rats were trained to discriminate cocaine (10 mg/kg) from saline under a fixed ratio 10 (FR10) schedule of food presentation. Fifteen minutes after cocaine injections, the completion of 10 responses on one lever produced the delivery of a food pellet in a 15-minute session during which a maximum of 50 reinforcements could be earned. After i.p. saline injections, completion of 10 responses on the other lever produced a food pellet (times and maximum reinforcement were identical to the cocaine sessions). The criterion for acquisition of the discrimination was completing at least 90 percent of the responses on the injection-appropriate lever and receiving at least two reinforcers in a session for six consecutive sessions. Once cocaine demonstrated stimulus control over behavior, a cocaine dose-response function (0.3–17 mg/kg) was determined during one test session using a multiple dosing procedure. In this procedure, rats were injected with the first cocaine dose, and 10 minutes later, a 10-minute test session began during which a maximum of 10 reinforcers could be earned for completing FR10 response requirements on either lever. Five minutes later, the second cocaine injection was given to bring the cumulative cocaine dose up to the second dose level, and testing continued as before. This procedure was continued until the cumulative cocaine dose reached either 10 or 17 mg/kg.

Testing occurred under three conditions: vehicle, short-term, and long-term haloperidol administration. Rats were given the vehicle haloperidol solution to drink for 3 days. On the third day, a cocaine dose-response function was generated using the multiple dosing procedure. Discrimination training continued for 4 days after this test day. At this point, the vehicle solutions were replaced by the haloperidol solution for 3 days. On the third day, a second cocaine dose-response function was generated as before. This 3-day administration procedure was used to allow enough time for DA receptor blockade to occur. At the completion of this short-term haloperidol phase of the study, discrimination training was suspended, and the rats were maintained on haloperidol and food deprivation for 28 days. On the 28th day, a third cocaine dose-response function was determined as before.

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Figure 2. Percent of cocaine-appropriate responding as a function of cocaine dose in rats trained to discriminate cocaine (10 mg/kg intraperitoneal) from vehicle in a two-lever, food-reinforced discrimination procedure.

Cocaine discrimination was assessed under three conditions: vehicle (open squares), acute or 3 days (closed squares), and chronic or 28 days (closed circles) of orally delivered haloperidol administration. Compared to vehicle conditions, acute haloperidol administration was associated with a rightward shift, whereas chronic haloperidol administration was associated with a leftward shift in the cocaine dose-response function. The former effect likely reflects the ability of the DA antagonist, haloperidol, to block the behavioral effects of cocaine in the short-term. The latter effect can be explained as a chronic DA receptor blockade leading to a supersensitivity to the effects of the DA agonist, cocaine. This effect, in turn, enhanced the sensitivity to the discriminative stimulus effects of cocaine.

Long-Term Effects of Haloperidol on Cocaine-Induced Stereotypy and Locomotor Activity

We have assessed the effects of long-term haloperidol treatment on the stereotypic and locomotor effects of cocaine. Rats (in groups of 4 each) were maintained on vehicle or haloperidol solutions, orally delivered as described above, for 30 days. The stereotypic effects of two doses of cocaine (10 and 15 mg/kg) were rated using a scale modified from Ellinwood and Balster (1974) that ranges from 1 (asleep) to 9 (dyskinetic-reactive). The presentation of cocaine doses was counterbalanced across rats, and 1 week separated the two cocaine exposures. Rats were brought into the test room and adapted to the clear, Plexiglas testing containers for at least 15 minutes. Cocaine injections were given and stereotypy ratings were made every 5 minutes for a 30-minute session by a rater blind to treatment condition. Long-term haloperidol exposure enhanced the stereotypic effects of cocaine. The sums of the stereotypic ratings across the test sessions (six 5-minute rating periods each) are shown in figure 3. The group given chronic haloperidol treatment showed significantly greater stereotypy compared with the veh treated group, $F = 23.67; df = 1,12; p < 0.0005$. The dose had no effect. These results suggest that long-term haloperidol enhances the stereotypic effects of the DA agonist, cocaine, similar to previous studies effects of other DA agonists (Tarsy and Baldi 1974; Rebec et al. 1982; Seeger et al. 1982; LaHc Marshall 1992).

In contrast, we found that similar treatment enhanced the sensitivity to the locomotor activating of cocaine. In fact, long-term haloperidol treatment lowered horizontal, ambulatory activity. In the separate groups of rats (8 in each group) were given either haloperidol solutions for 30 days. This administration continued throughout the subsequent test. During the last week of the chronic haloperidol administration, the rats were adapted to the locomotor chamber for at least three 30-minute sessions. These chambers are circular and are designed to measure horizontal, ambulatory stereotypy activity, as described previously (Kosten et al. After 30 days of haloperidol (or vehicle) administration rats received one i.p. cocaine injection per week at the following doses: 0, 2.5, 5.0, or 7.5 mg/kg. cocaine doses were given in a counterbalanced design. The sums of the stereotypic ratings across the test sessions (six 5-minute rating periods each) are shown in figure 3.

The stereotypy rating scale ranged from 1 (asleep) to 9 (dyskinetic-reactive). One group received orally delivered haloperidol (Hal) administration for at least 30 days (closed squares), and the other group was given vehicle (Veh) administration (open squares). Each group was tested once each with one of the two cocaine doses (10 and 15 mg/kg i.p.) in a counterbalanced design with 1 week separating the sessions. The Hal-treated rats showed significantly greater cocaine-induced stereotypy than the Veh-treated rats.
Locomotor activity was assessed in 30-minute sessions. As shown in figure 4, total locomotor counts over these sessions increased by increasing cocaine dose, $F = 8.28, df = 3.52, p < 0.0001$. The haloperidol-treated group showed a small, but significant decrease in cocaine-induced activation overall, as evidenced by the significant group effect, $F = 5.53; df = 1.52, p < 0.05$. Although we used different cocaine doses in the stereotypy and locomotor studies and only one of these effects was measured per study, the enhancement of cocaine-induced stereotypy that occurs with chronic haloperidol exposure may have interfered with the animals' ambulatory activity. The expressions of these two motoric effects are incompatible with each other, as stereotypic responding disrupts ambulatory activity. Nonetheless, the enhanced behavioral responding seen in drug discrimination, place conditioning, and stereotypy with chronic haloperidol administration occurs despite the tendency for this treatment to lower ambulatory activity.

### Conclusions and Future Directions

Most of the behavioral data presented above, in which enhanced behavioral effects of cocaine occurred, are seen with chronic administration of the DA antagonist, haloperidol. Chronic administration of other DA antagonist drugs, such as SCH 23390, raclopride, and sulpiride, has also been associated with enhanced behavioral effects of cocaine. However, unlike in our procedure, the behavioral assessments in those studies were completed after discontinuation of the DA antagonist treatment. Thus, it would be of interest to determine whether such enhanced behavioral effects of cocaine would be seen if DA antagonist treatment is continued throughout the training and test phases. This would be important for two reasons. First, DA antagonists have been suggested as potential treatment agents for cocaine abuse, but these data would suggest that they would not be viable long-term medications for this disorder. Second, perhaps one reason for the phenomenon of cocaine abuse seen in schizophrenia patients is that chronic treatment with neuroleptic medications has likely altered neural areas associated with drug reward (i.e., the mesolimbic DA system). These alterations could make these patients more sensitive to the behavioral effects of cocaine, a DA agonist. Increased sensitivity may underlie an enhanced abuse potential for cocaine in this population.

It would also be of interest to examine the effects of chronic versus acute administration of other neuroleptic drugs. Although most neuroleptic drugs block DA transmission, the degree to which they show affinity for the various types of DA receptors and for other neurotransmitter systems varies (Tamminga and Gerlach 1987). In addition, atypical neuroleptics, which are being developed to avoid tardive dyskinesia and other conditions associated with chronic treatments, differ in their ability to block other neurotransmitter receptors. Chronic administration of one or more of these drugs may not be associated with enhancement of the behavioral effects of cocaine. If so, these medications may be better treatments for the dually diagnosed patient with schizophrenia, but more research is needed to assess this possibility.

One atypical neuroleptic that may be a potentially good treatment choice for this population is clozapine. Clozapine has affinity for $D_1$- and $D_2$-like DA receptors, as well as for $D_3$ and $D_4$ autoreceptors and for serotonin-2 (5-HT$_{2A}$) and 5-HT$_{2C}$ receptor types (Farde et al. 1989; Meltzer 1989; Canton et al. 1990). Our data suggest that short-term clozapine administration attenuates place conditioning to cocaine (Kosten and Nestler 1994), consistent with findings of a partial attenuation of the discriminative stimulus and self-administration effects of cocaine (Vanover et al. 1993; but see Loh et al. 1982). The effects of long-term clozapine administration on behaviors maintained by cocaine are not known. Although the data are ambiguous, some studies suggest that enhanced sensitivity to the behavioral effects of cocaine may not be seen with long-term clozapine. Such treatment enhances $D_1$ receptor binding and does not alter $D_2$ binding in the NAcc (O'Dell et al. 1990). Yet, significant increases in the density of $D_2$...
binding sites are found in the mPFC after both long-term clozapine and haloperidol treatments (Janowsky et al. 1992). Long-term clozapine treatment does not alter basal DA levels and does inhibit amphetamine-induced DA release in the NAcc, in contrast to long-term haloperidol treatment, which decreased basal NAcc levels of DA in one study (Ichikawa and Meltzer 1992), but not another (See and Ellison 1990), and has no effect on amphetamine-induced DA release in the NAcc (See and Ellison 1990; Ichikawa and Meltzer 1992). Behavioral responses to amphetamine after long-term clozapine treatment are altered, but not in a manner consistent with an increase in sensitivity of dopamine receptors, as is seen with long-term haloperidol treatment (Rebec et al. 1982). However, long-term clozapine use is associated with enhanced locomotion induced by the DA agonist, apomorphine, with no effect on stereotypies, in contrast to long-term haloperidol administration that enhances both apomorphine-induced locomotion and stereotypy (Seeger et al. 1982).

Clearly, more research is needed at various levels of investigation from the molecular to the behavioral and clinical areas to ascertain the extent to which chronic administration of antipsychotic medications alters the neural areas subserving drug reward and affects the subsequent behavioral effects to cocaine. Until this phenomenon is better understood, it may be advisable to consider alternative antipsychotic medications for the dually diagnosed schizophrenia patient, such as one of the atypical neuroleptic drugs. These alternative medications may be beneficial because chronic administration may not be associated with the neurobehavioral supersensitivity phenomenon discussed here. In addition, these medications may be effective pharmacotherapies for the cocaine abuse disorder, although this possibility awaits further research.

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