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Changes in Behavioral Sensitivity to SKF-38393 and Quinpirole Following Withdrawal from Continuous Cocaine Administration in Rats

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NEISEWANDER, J. L., I. LUCKI AND P. McGONIGLE. *Changes in behavioral sensitivity to SKF-38393 and quinpirole following withdrawal from continuous cocaine administration in rats.* PHARMACOL BIOCHEM BEHAV 53(4) 935–942, 1996.—The effects of withdrawal from continuous administration of cocaine on spontaneous locomotor activity and behavioral sensitivity to SKF-38393 and quinpirole were examined in rats. Subdermal minipumps that delivered either saline or 20 mg/kg/day cocaine hydrochloride were implanted for 14 days. Spontaneous locomotor activity, SKF-38393-induced (10 mg/kg, SC) grooming and tongue protrusions, and quinpirole-induced locomotor activity and stereotypy (0.32 and 1.0 mg/kg, SC) were examined either 4–5 h or 7 days after removal of the minipumps. Animals withdrawn from cocaine for 4 h exhibited a decrease in spontaneous locomotor activity relative to saline-pretreated controls, whereas animals withdrawn for 7 days did not differ from controls. Animals withdrawn from cocaine for 4 h did not differ from controls in their sensitivity to SKF-38393, whereas animals withdrawn from cocaine for 7 days exhibited an increase in SKF-38393-induced tongue protrusions relative to controls. In contrast, animals withdrawn from cocaine for 4 h exhibited a decrease in quinpirole-induced locomotion, whereas animals withdrawn for 7 days did not differ from controls. There were no differences in sensitivity to quinpirole-induced stereotypy relative to controls at either withdrawal period. These findings suggest that an increased sensitivity of D_1-like receptors emerges within 7 days during the course of withdrawal from continuous cocaine administration, whereas a change in sensitivity of D_2-like receptors may occur early during withdrawal but normalizes within 7 days.

Sensitization Grooming Oral movements Tongue protrusions Locomotion Stereotypy
Dopamine D_1 receptors Dopamine D_2/D_3 receptors Chronic administration Time course

ABUSE of psychomotor stimulants typically occurs in "binges" during which there is continuous low-level presence of drug over an extended period of time (21,49). Continuous administration regimens have been used as a model of binging, and have been used to investigate behavioral and neurochemical changes that occur following a binge (30,43,59). Continuous administration of cocaine produces tolerance to the stimulant properties of a subsequent cocaine challenge (25,30,46). This tolerance may be due to enhanced sensitivity of presynaptic autoreceptors, because low doses of apomorphine, which are believed to preferentially stimulate presynaptic receptors, produce a decrease in both cocaine-stimulated (29) and electrically stimulated (28) dopamine release. These results suggest that continuous administration of cocaine produces supersensitivity of D_2-like autoreceptors. There is also evidence that continuous cocaine administration may produce supersensitivity at postsynaptic dopamine receptors because enhanced sensitivity to apomorphine-induced stereotypy has also been observed during the course of withdrawal from continuous cocaine administration (43). It remains unclear, however, whether withdrawal from continuous cocaine administration alters the sensitivity of D_1-like (i.e., D_1 and D_5) or D_2-like (i.e., D_2, D_3, and D_4) receptors because both subtypes play a role in apomorphine-induced behavior (14,33,40,41).

The present study examined whether animals infused with cocaine continuously for 14 days would exhibit changes in spontaneous locomotor activity and/or changes in behavioral sensitivity to a challenge injection of either the D_1-selective

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agonist SKF-38393 or the D_2/D_3-selective agonist quinpirole. SKF-38393 elicits grooming and oral movements (4,38,39,42, 48), whereas quinpirole elicits locomotor activity and mild stereotypic behavior (5,6,11,18). These behaviors, as well as spontaneous locomotor activity, were measured either 4–5 h or 7 days following withdrawal from continuous infusion of either cocaine or saline.

METHODS

Drugs and Chemicals

Halothane (Hydrocarbon Labs Inc., N. Augusta, SC) was administered by inhalation. Cocaine hydrochloride (Sigma, St. Louis, MO) was dissolved in sterile saline and was delivered continuously through SC Alzet minipumps (2ML2, Alza Corp., Palo Alto, CA). Quinpirole (Research Biochemicals, Inc., Natick, MA) was dissolved in sterile saline and was injected subcutaneously at a volume of 1 ml/kg. SKF-38393 (Research Biochemicals, Inc., Natick, MA) was dissolved in water and injected subcutaneously at a volume of 2 ml/kg.

Animals

Male Sprague–Dawley rats (Charles River Breeding Labs, Wilmington, MA) weighing 250–300 g were housed three per cage in a climate-controlled facility with a 12 L : 12 D cycle. They were acclimated to handling for 3 days prior to beginning the experiments.

Surgery

Animals were anesthetized by halothane inhalation and the skin rostral to the flank was shaved and cleaned. An incision was made in the shaved area and a burrow was made through the connective tissue using hemostats. A minipump was implanted into the burrow and the incision was closed using surgical staples. Fourteen days later, the animals were again anesthetized by halothane inhalation, another incision was made, and the pump was removed. The incision was flushed with sterile saline and then closed using surgical staples. The animals regained consciousness within 1–2 min following these surgeries. The content of the minipumps was measured after removal to verify successful infusion. Cocaine-treated animals with failed minipumps were eliminated from the study. The condition of the skin was also observed, and none of the animals had exhibited necrosis that is sometimes observed following bolus SC injections. Animals were studied only once after chronic infusion of saline or cocaine.

Sensitivity to SKF-38393

The design of this experiment was a 2 × 2 factorial in which animals were randomly assigned to groups receiving either sterile saline or cocaine hydrochloride (20 mg/kg/day) for 14 days via minipump, and were then tested for sensitivity to the behavioral effects of SKF-38393-HCl (10 mg/kg, SC) either 4 h or 7 days after removal of the minipumps. The design yielded the following four groups: saline-pretreated animals tested after a 4-h withdrawal period (n = 7), saline-pretreated animals tested after a 7-day withdrawal period (n = 9), cocaine-pretreated animals tested after a 4-h withdrawal period (n = 7), and cocaine-pretreated animals tested after a 7-day withdrawal period (n = 8). The animals were placed into a clear Plexiglas cage (44 × 24 × 20 cm high) that had a wire mesh floor and a perforated metal lid. They were allowed to habituate to the cage for 30 min. They were then injected subcutaneously with SKF-38393 and immediately placed back into the cages for 30 min. The amount of time (i.e., seconds) the animals were engaged in grooming and the incidence of tongue protrusions were recorded continuously by an observer unaware of the animals' previous treatment. Observers recorded behavior for one to two rats at a time depending on their level of competancy.

Spontaneous locomotor activity and sensitivity to quinpirole. The design of this experiment was a 2 × 2 × 2 factorial in which animals were randomly assigned to groups receiving either sterile saline or cocaine hydrochloride (20 mg/kg/day) for 14 days via minipump, and were then tested for sensitivity to the behavioral effects of quinpirole (0.32 or 1.0 mg/kg, SC) either 5 h or 7 days after removal of the minipumps. The design yielded the following 8 groups: saline-pretreated animals tested following 0.32 mg/kg quinpirole after a 5-h withdrawal period (n = 7), saline-pretreated animals tested following 0.32 mg/kg quinpirole after a 7-day withdrawal period (n = 8), saline-pretreated animals tested following 1.0 mg/kg quinpirole after a 5-h withdrawal period (n = 6), saline-pretreated animals tested following 1.0 mg/kg quinpirole after a 7-day withdrawal period (n = 7), cocaine-pretreated animals tested following 0.32 mg/kg quinpirole after a 5-h withdrawal period (n = 6), cocaine-pretreated animals tested following 0.32 mg/kg quinpirole after a 7-day withdrawal period (n = 7), cocaine-pretreated animals tested following 1.0 mg/kg quinpirole after a 5-h withdrawal period (n = 6), cocaine-pretreated animals tested following 1.0 mg/kg quinpirole after a 7-day withdrawal period (n = 8).

The animals were first tested for changes in spontaneous locomotor activity either 4 h or 7 days after removal of the minipumps. The animals were placed into Plexiglas test cages (41 × 19 × 19 cm) that were contained within a rack that had two sets of photocells and light sources mounted opposite each other. The photocells were located 13 cm from each end and 4 cm above the floor of the cage. A computer-automated relay system described by Lucki et al. (32) recorded the number of times the photobeams were interrupted consecutively by the animal moving from one end of the cage to the other (i.e., crosses). Crosses were recorded in 10-min intervals and provided a measure of locomotor activity. Spontaneous locomotor activity was measured for a total of 60 min. The animals were then injected with their assigned dose of quinpirole and placed back into the test cage, and crosses were recorded in 20-min intervals for a total of 2 h. Stereotypic behavior was also measured by an observer unaware of the animals' previous treatment. The observer rated stereotypic behavior every 2.5 min based on a 10-s observation period using a modified version of the Creese and Iversen (15) scale. Scores ranging from 0–6 were assigned to the following behaviors: 0 = inactive, 1 = normal activity, 2 = normal activity with intermittent stereotypic sniffing, 3 = continuous stereotypic sniffing, 4 = stereotypic sniffing with occasional stereotypic licking or gnawing, 5 = stereotypic sniffing with frequent stereotypic licking or gnawing, and 6 = continuous stereotypic licking or gnawing. The presence or absence of sniffing, oral stereotypies (i.e., licking and gnawing), and grooming was also recorded for each of the 10-s observation periods.

Data Analyses

The amount of time (i.e., s) the animals were engaged in grooming and the incidence of tongue protrusions following SKF-38393 administration were analyzed using a 2 × 2 factorial ANOVA with pretreatment (i.e., saline vs. cocaine) and

withdrawal period (i.e., 4 h vs. 7 day) as between-subjects factors. Post hoc pair-wise comparisons were made using the Fisher LSD test. Spontaneous locomotor activity was analyzed using a 2 × 2 × 6 repeated measures ANOVA with pretreatment (i.e., saline vs. cocaine) and withdrawal period (i.e., 4 h vs. 7 day) as between-subjects factors and time course in 10-min intervals as a repeated measure. Quinpirole-induced locomotor activity was analyzed using a 2 × 2 × 2 × 6 repeated measures ANOVA with pretreatment, withdrawal period, and dose as between subjects factors, and time course in 20-min intervals as a repeated measure. In addition, separate ANOVAs of the data from each withdrawal period were conducted as planned comparisons [(26), p. 240] because the focus of this study was to examine withdrawal-dependent changes in sensitivity to quinpirole. Interactions were further analyzed using factorial ANOVAs at each 20-min interval [(26), p. 213]. Stereotypy ratings were analyzed using nonparametric Kruskal-Wallis ANOVAs and the number of time-sampled observations of sniffing, oral stereotypy, and grooming were analyzed by 2 × 2 × 2 ANOVAs with pretreatment, withdrawal period, and dose of quinpirole as between subjects measures.

RESULTS

Sensitivity to SKF-38393

Animals pretreated with cocaine exhibited no change in sensitivity to SKF-38393-induced tongue protrusions following a 4-h withdrawal period, but enhanced sensitivity following a 7-day withdrawal period (Fig. 1). The ANOVA revealed a significant interaction between pretreatment and withdrawal variables, $F(1, 27) = 5.86$, $p < 0.05$. Post hoc analyses revealed that animals withdrawn from cocaine for 4 h did not differ significantly from their respective control group. In contrast, animals withdrawn from cocaine for 7 days exhibited significantly more tongue protrusions relative to their respective control group (Fisher LSD test, $p < 0.05$). Neither of the groups tested after the 7-day withdrawal period, however, differed significantly from the groups tested after the 4-h withdrawal period. Although there was no significant difference between the two saline-pretreated groups, there was a trend for an increased number of tongue protrusions in the group tested after the 4-h withdrawal period relative to the group tested after the 7-day withdrawal period. It is possible that the proximity of surgery and testing in the 4-h withdrawal group may have led to a slight increase in baseline number of tongue protrusions. An increase in baseline tongue protrusions can present difficulty in detecting drug-induced increases in tongue protrusions due to a potential ceiling effect. However, cocaine-treated animals did not even exhibit a trend for enhanced sensitivity to SKF-38393 at the 4-h time point, suggesting that the increased baseline did not obscure detecting an effect. In contrast to the effects of SKF-38393 on tongue protrusions, there were no significant differences among the groups in the amount of time spent grooming (Fig. 1).

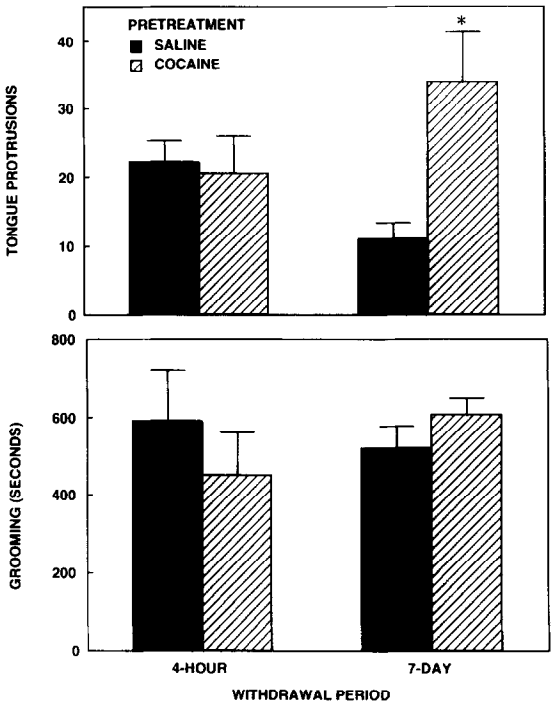

FIG. 1. Effects of withdrawal from continuous cocaine administration on SKF-38393-induced tongue protrusions (top panel) and grooming (bottom panel). Animals were pretreated with either saline or cocaine hydrochloride (20 mg/kg/day) for 14 days via osmotic minipumps. They received a challenge injection of SKF-38393 (10 mg/kg, SC) either 4 h or 7 days after the minipumps were removed. The incidence of tongue protrusions and the time animals spent grooming was then measured for 30 min. Values illustrated represent the mean + SEM for each group. Asterisk represents a significant difference from corresponding saline-pretreated control group, Fisher LSD test, $p < 0.05$.

Spontaneous Locomotor Activity

Animals pretreated with cocaine exhibited a decrease in spontaneous locomotor activity when examined following a 4-h withdrawal period, but no change following a 7-day withdrawal period (Fig. 2). The ANOVA revealed a significant interaction between pretreatment, withdrawal period, and 10-min interval, $F(5, 245) = 5.65$, $p < 0.01$. Subsequent 2 × 2 ANOVAs (i.e., pretreatment by withdrawal) of data from each 10-min interval revealed significant interactions at intervals 1 and 2 ($p < 0.05$). Pair-wise comparisons revealed that during both of these intervals, cocaine-pretreated animals examined following a 4-h withdrawal period exhibited a decrease in locomotor activity relative to saline-pretreated controls (Fisher LSD tests, $p < 0.05$). In contrast, no difference was observed between saline- and cocaine-pretreated animals examined following a 7-day withdrawal period. Analyses of data from intervals 3–6 revealed a significant main effect of withdrawal period ($p < 0.05$), indicating that animals withdrawn for 4 h exhibited less locomotor activity relative to animals withdrawn for 7 days regardless of pretreatment.

Sensitivity to Quinpirole

Animals pretreated with cocaine exhibited a decrease in quinpirole-induced locomotor activity when examined following a 5-h withdrawal period, but no change following a 7-day withdrawal period (Fig. 3). The analysis of locomotor activity at the 5-h withdrawal period revealed significant interactions between pretreatment and 20-min interval, $F(5, 105) = 4.60$, $p < 0.01$, and between dose and 20-min interval, $F(5, 105) = 3.13$, $p < 0.05$. Subsequent pretreatment by dose ANOVAs at each 20-min interval indicated a main effect of dose at interval 1 and 2, where animals given 1 mg/kg quinpirole exhibited more locomotion relative to animals given 0.32 mg/kg ($p < 0.01$). At intervals 3–6, however, there was a

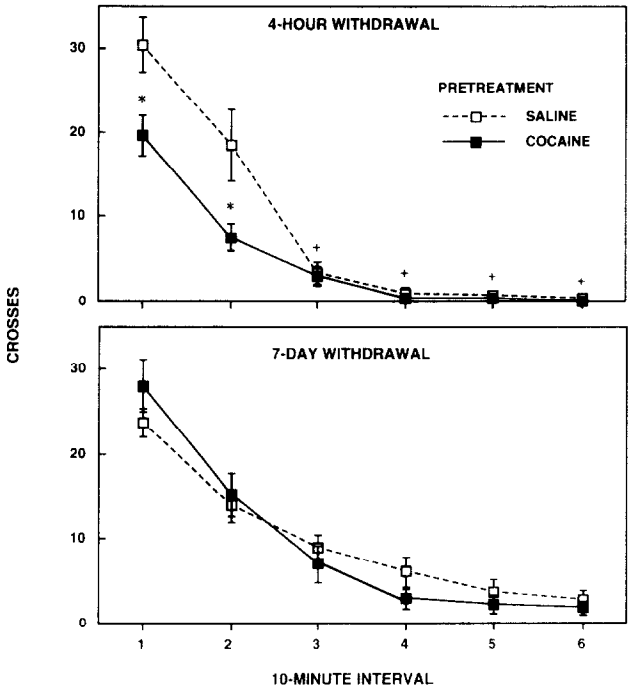

FIG. 2. Effects of withdrawal from continuous cocaine administration on spontaneous locomotor activity. Animals were pretreated with either saline or cocaine hydrochloride (20 mg/kg/day) for 14 days via osmotic minipumps. Spontaneous locomotor activity was measured for 1 h either 4 h (top panel) or 7 days (bottom panel) after the minipumps were removed. Values illustrated represent the mean ± SEM for each group. Asterisk represents a significant difference from corresponding saline-pretreated control group, Fisher LSD test, $p < 0.05$. Plus sign represents a significant difference from groups tested at the 7-day withdrawal time point, ANOVA, main effect of withdrawal period, $p < 0.05$.

main effect of pretreatment ($p < 0.05$), where animals pretreated with cocaine exhibited less locomotor activity relative to animals pretreated with saline. In contrast to the 5-h withdrawal period, there were no significant differences in locomotor activity among groups tested at the 7-day withdrawal period. The overall ANOVA also revealed that regardless of pretreatment, animals tested following a 5-h withdrawal period exhibited less locomotor activity relative to animals tested following a 7-day withdrawal period, $F(1, 44) = 51.3$, $p < 0.01$, and animals given a dose of 1.0 mg/kg exhibited more locomotor activity relative to animals given 0.32 mg/kg, $F(1, 44) = 6.1$, $p > 0.01$.

Neither cocaine pretreatment nor length of the withdrawal period altered quinpirole-induced stereotypy. Animals tested following a 5-h withdrawal period exhibited similar stereotypy ratings following quinpirole challenge as animals tested following a 7-day withdrawal period regardless of pretreatment. There were, however, dose-dependent differences in stereotypy ratings across 20-min intervals (Kruskal-Wallis ANOVAs, $p < 0.05$). Animals given 1.0 mg/kg exhibited higher stereotypy ratings relative to animals given 0.32 mg/kg during the first, fifth, and sixth 20-min intervals (Fig. 4; Mann-Whitney U-tests, $p < 0.05$). Analysis of the number of observations of sniffing and oral stereotypies also revealed a greater incidence of these behaviors in animals given 1.0 mg/kg relative to animals given 0.32 mg/kg, regardless of pretreatment or length of withdrawal, $F(1, 44) = 14.9$, $p < 0.01$, and $F(1, 44) = 15.7$, $p < 0.01$, respectively (data not shown). There were no differences in the number of observations of grooming among the groups (data not shown).

DISCUSSION

Enhanced sensitivity to SKF-38393-induced tongue protrusions emerged during the course of withdrawal from continuous cocaine administration. Animals withdrawn from cocaine for 7 days exhibited an increase in tongue protrusions relative to controls, whereas animals withdrawn for 4 h did not differ from controls. There were no changes in SKF-38393-induced grooming at either withdrawal period. We have previously reported a similar pattern of changes in behavior following repeated administration of SKF-38393 (42). However, others have reported sensitization of SKF-38393-induced grooming following repeated SKF-38393 administration (10,24,57). The reason for discrepancy in these reports may be related to differences in treatment regimens or method of measuring

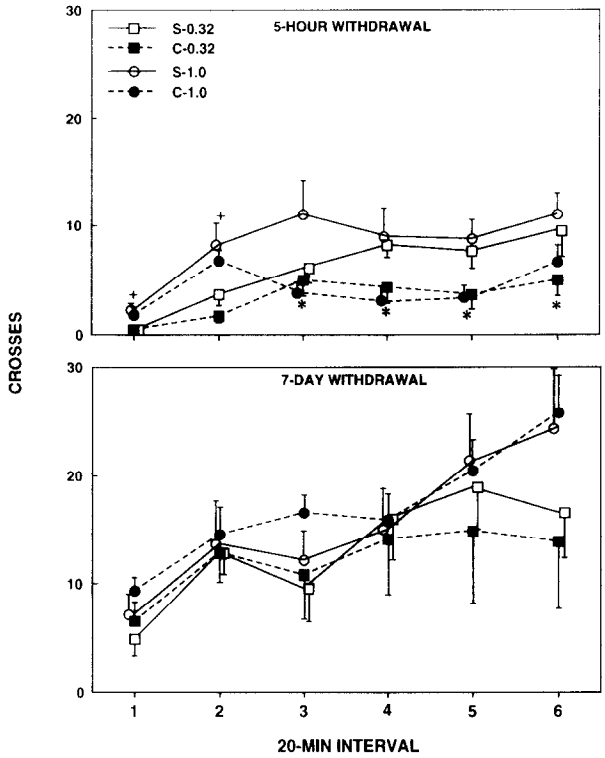

FIG. 3. Effects of withdrawal from continuous cocaine administration on quinpirole-induced locomotor activity. Animals were pretreated with either saline or cocaine hydrochloride (20 mg/kg/day) for 14 days via osmotic minipumps. Locomotor activity was measured for 1 h following administration of quinpirole (0.32 or 1.0 mg/kg) either 5 h (top panel) or 7 days (bottom panel) after the minipumps were removed. The figure legend designates the pretreatment with either saline (S) or cocaine (C) followed by the dose of quinpirole. Values illustrated represent the mean ± SEM for each group. Asterisk represents a significant difference from corresponding saline-pretreated control group, ANOVA, main effect of pretreatment, $p < 0.05$. Plus sign represents a significant difference from groups challenged with 0.32 mg/kg quinpirole, ANOVA, main effect of dose, $p < 0.01$.

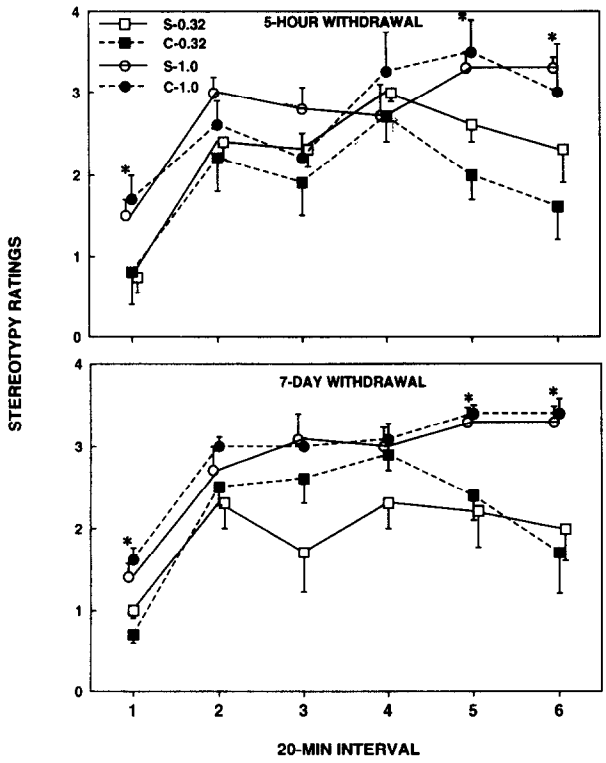

FIG. 4. Effects of withdrawal from continuous cocaine administration on quinpirole-induced stereotypy. Animals were pretreated with either saline or cocaine hydrochloride (20 mg/kg/day) for 14 days via osmotic minipumps. Stereotypy was measured for 1 h following administration of quinpirole (0.32 or 1.0 mg/kg) either 5 h (top panel) or 7 days (bottom panel) after the minipumps were removed. The figure legend designates the pretreatment with either saline (S) or cocaine (C) followed by the dose of quinpirole. Values illustrated represent the mean ± SEM for each group. Asterisk represents a significant difference from groups challenged with 0.32 mg/kg quinpirole, Mann-Whitney *U*-tests, $p < 0.05$.

grooming. In the present study, the beginning of a grooming episode was marked by body contact with either the snout or forepaws. These grooming episodes were typically preceded or followed by a bout of oral movements, including tongue protrusions. This bout of oral movements may have been included in the grooming measurement by others, which would account for the discrepancy. It is also possible that the SKF-38393-induced grooming response was at a maximal level, and therefore, enhanced sensitivity may not be detectable because of a ceiling effect. In any case, the results from the present study suggest that dopamine D_1-like receptors that mediate tongue protrusions become supersensitive following withdrawal from continuous cocaine administration.

The effect of quinpirole on locomotion varies dose dependently; low doses (<0.125 mg/kg) decrease locomotion, whereas intermediate to high doses (≥0.5 mg/kg) produce a decrease within the first 10 min followed by an increase that is most marked during the second hour of testing (18,19,55). The findings from the present study are consistent with the effects reported previously for intermediate to high doses because quinpirole-induced locomotion and stereotypy measures were lower in the first 20 min of testing relative to the rest of the test session. In contrast to the enhancement of SKF-38393-induced behaviors during the course of withdrawal, a decrease in quinpirole-induced locomotion was observed early during withdrawal (i.e., 5 h) and was no longer evident 7 days later. There were no changes in quinpirole-induced stereotypy at either withdrawal period. A decrease in quinpirole-induced (1 mg/kg) locomotion has also been reported following repeated administration of cocaine (54); however, this was associated with an increase in stereotypic rearing and head bobbing that was not observed in the present study.

The decrease in locomotion produced by dopamine agonists is thought to be mediated by preferential stimulation of D_2-like autoreceptors (13). Thus, it is possible that the decrease in quinpirole-induced locomotion observed at the 5-h withdrawal period may have been due to enhanced sensitivity of D_2-like autoreceptors resulting in prolonged inhibition of locomotion by quinpirole. Consistent with this interpretation, low doses of apomorphine produce a decrease in both cocaine-stimulated (29) and electrically stimulated (28) dopamine release in animals following withdrawal from continuous cocaine administration. However, electrophysiological studies indicate that dopamine neurons are subsensitive to the inhibitory effect of apomorphine following withdrawal from continuous cocaine administration (1,2).

Quinpirole has a greater affinity for D_3 receptors relative to D_2 receptors, and therefore, likely occupies more D_3 receptors than D_2 receptors at low doses, as well as initally following intermediate to high doses. Thus, the decrease in quinpirole-induced locomotion may be due to enhanced sensitivity of postsynaptic D_3 receptors in line with the recent suggestion that the decrease in locomotion produced by dopamine agonists may be due to preferential binding to putative postsynaptic dopamine D_3 receptors (50). Similar dose- and time-dependent changes in locomotor activity have been observed following administration of the D_3-preferring agonist 7-hydroxy-*N,N*-di-n-propyl-2-aminotetralin (7-OH-DPAT) (16, 27), and these changes appear to be independent of changes in dopamine release or synthesis (50). Moreover, the D_3-preferring antagonist U99194A increases locomotor activity without increasing dopamine release (56). However, the notion that both quinpirole and 7-OH-DPAT may preferentially stimulate D_3 receptors is complicated by the recent observation that the selectivity for D_3 receptors is less in vivo (8), as well as when compared with the high affinity state of the D_2 receptor (Burris, personal communication).

Lastly, the decrease in quinpirole-induced locomotion at the 5-h withdrawal period may be due to decreased sensitivity of postsynaptic D_2 receptors thought to mediate hyperlocomotion (5,11,18). Indeed, significant decreases in locomotion were observed in cocaine-pretreated animals relative to saline-pretreated animals up to 2 h following quinpirole administration. It is unlikely that these late effects were due to a prolonged inhibitory phase of quinpirole on locomotion because this phase normally lasts only 10 min (18,19,55). However, it is important to note that quinpirole-induced stereotypy, which is though to be mediated in part by postsynaptic D_2 receptors (3,9,12,17), was not altered in the present. Locomotion and stereotypy produced by direct and indirect dopamine agonists are thought to be mediated by postsynaptic receptors in the nucleus accumbens and caudate-putamen, respectively [e.g., see (7) review]. Therefore, receptors in these dopamine terminals may be altered differentially by withdrawal from continuous cocaine administration.

Consistent with our previous findings (43), animals exhibited a transient decrease in spontaneous locomotor activity after withdrawal from continuous cocaine administration.

The decrease in locomotor activity was evident in animals observed 4 h after cocaine withdrawal, but not in animals observed 7 days after withdrawal. The withdrawal-induced decrease in locomotor activity may parallel the "crash" phase reported to occur 12–48 h after termination of a cocaine binge in humans (21).

Continuous administration regimens typically produce tolerance rather than sensitization to subsequent agonist challenge (45,47). Indeed, continuous administration of quinpirole results in tolerance to quinpirole-induced behavior in mice (58,60). Furthermore, continuous administration of cocaine results in tolerance to subsequent challenge administration of cocaine in rats (25,30,46). The present finding that animals withdrawn from continuous cocaine administration exhibit a decrease in quinpirole-induced locomotor activity may reflect tolerance, consistent with these previous findings. However, the present finding that animals withdrawn from continuous cocaine administration for 7 days exhibit enhanced sensitivity to SKF-38393-induced tongue protrusions suggests that sensitized responses to agonist challenge may emerge during the course of withdrawal from continuous cocaine administration. We have suggested previously that enhanced sensitivity to direct dopamine agonists may emerge during the course of withdrawal from either continuous or repeated cocaine administration, but that the time course varies, depending on the specific parameters of the treatment regimen (43). Consistent with this view, enhanced sensitivity to apomorphine challenge has been observed following relatively short withdrawal periods (i.e., 4 h to 4 days) from either acute or repeated administration of cocaine (31,53), and following a longer withdrawal period (i.e., 7 days) from continuous administration (43).

The present findings that only a D_1 receptor-mediated behavior was sensitized following continuous cocaine administration suggests that the enhanced sensitivity to apomorphine following continuous cocaine administration may be due to enhanced sensitivity of D_1-like receptors. Studies using repeated administration of direct agonists have also suggested that enhanced sensitivity to subsequent agonist challenge may depend on changes in D_1-like receptors rather than D_2-like receptors. For instance, repeated administration of SKF-38393 produces cross-sensitization to apomorphine, whereas repeated administration of quinpirole produces tolerance (10). Furthermore, sensitization produced by repeated administration of apomorphine is blocked by coadministration of a D_1-selective antagonist, but not a D_2-selective antagonist (35). Electrophysiological studies have shown that following repeated cocaine administration neurons in the nucleus accumbens exhibit enhanced sensitivity to the inhibitory effects of apomorphine and SKF-38393, but not quinpirole (22,23). However, repeated administration of quinpirole alone does produce sensitized behavioral responses (20,51,52), but this sensitization may involve an interaction between D_1-like and D_2-like receptors because the effect is blocked by coadministration of a D_1-selective antagonist (36).

The mechanism for enhanced behavioral sensitivity to SKF-38393 following withdrawal from continuous cocaine administration is not likely due to an increase in the number of D_1 receptors, because this treatment has been shown to decrease D_1 receptor density (43). Alternatively, it is possible that chronic stimulation of D_1-like receptors may enhance transduction mechanisms of D_1-like receptors. Consistent with this hypothesis, chronic administration of cocaine in rats increases levels of calmodulin in the striatum, which may promote an increase in dopamine-stimulated adenylate cyclase activity (37). Furthermore, Nestler et al. (44) have reported that chronic administration of cocaine decreases G protein subunits Giα and Goα in the NAc. They suggest this may, in turn, decrease the inhibitory influence of D_2 receptor stimulation of adenylate cyclase, and thereby increase the excitatory influence of D_1 receptor stimulation of adenylate cyclase.

In conclusion, the present findings suggest that prolonged stimulation of dopamine receptors produced by continuous cocaine infusion results in supersensitivity of D_1-like receptors, and either subsensitivity of postsynaptic D_2 receptors, or supersensitivity of either D_2 autoreceptors or D_3 receptors. The time course for these changes differed in that changes in D_2-like receptors occurred early during withdrawal and were no longer evident by day 7, whereas changes in D_1 receptors were not observed until day 7. These changes in sensitivity of dopamine receptors may have implications for developing pharmacological treatment for cocaine withdrawal.

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