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Effects of daily SKF 38393, quinpirole, and SCH 23390 treatments on locomotor activity and subsequent sensitivity to apomorphine*

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Abstract. In three experiments, male Wistar rats (250–350 g) were injected (SC) daily with the D_1-type dopamine receptor agonist, SKF 38393 (0.0, 4.0, 8.0, or 16.0 mg/kg), the D_2-type dopamine receptor agonist, quinpirole (0.0, 0.3, or 3.0 mg/kg), and/or the D_1-type dopamine receptor antagonist, SCH 23390 (0.0 or 0.5 mg/kg) for 8–10 days. After each daily injection, the rats were tested for locomotor activity in photocell arenas for 20 min. Following this subchronic pretreatment, all rats were challenged with the mixed dopamine receptor agonist apomorphine (1.0 mg/kg, SC) and tested for locomotor activity. SKF 38393 treatments produced a dose-dependent decrease in locomotor activity which did not significantly change across days. Quinpirole also depressed locomotor activity when first injected, but this quinpirole-induced inhibition of activity progressively decreased across days. When subsequently challenged with apomorphine, rats in both the SKF 38393 and the quinpirole pretreatment groups displayed greater locomotor activity than rats pretreated with only vehicle. Although SCH 23390 pretreatments did not affect subsequent sensitivity to apomorphine, SCH 23390 completely blocked the effect of quinpirole. These results suggest that although repeated D_1 receptor stimulation may be sufficient to induce behavioral sensitization to apomorphine, D_2 receptor stimulation also contributes to the effect.

Key words: Behavioral sensitization – Apomorphine – SKF 38393 – Quinpirole – SCH 23390 – Locomotor activity

The repeated administration of drugs that stimulate dopamine receptors often results in the development of behavioral sensitization (see Robinson and Becker 1986; Kalivas and Weber 1988). This behavioral sensitization effect has been demonstrated in rats with both direct (e.g., apomorphine) and indirect (amphetamine, cocaine) dopamine agonists and is characterized by a progressive augmentation of various drug-induced motor behaviors (e.g., Kalivas and Weber 1986; Robinson and Becker 1986; Mattingly et al. 1988). Although recent evidence clearly indicates that stimulation of dopamine receptors is neccessary for the development of behavioral sensitization (e.g., Kuczenski and Leith 1981; Mattingly and Rowlett 1989; Peris and Zahniser 1989), the specific drug-induced neurobiological changes mediating the development of behavioral sensitization are unknown.

Dopamine agonists which induce the development of behavioral sensitization (e.g., apomorphine, amphetamine, and cocaine) result in an increased stimulation of both D_1-type and D_2-type dopamine receptors. In a recent study of apomorphine-induced sensitization, we found that concurrent treatments of rats with the D_1-type dopamine antagonist, SCH 23390, blocked both the acute locomotor-activating effects of apomorphine and the development of behavioral sensitization. In contrast, the D_2-type dopamine receptor antagonist, sulpiride, blocked the acute effects of apomorphine, but did not prevent the development of behavioral sensitization (Mattingly et al. 1991). Similarly, amphetamine-induced behavioral sensitization may be blocked by D_1, but not D_2-type, dopamine receptor antagonists (Stewart and Vezina 1989; Vezina and Stewart 1989). These findings, of course, suggest that repeated stimulation of the dopamine D_1-type receptor is both necessary and sufficient to induce the development of behavioral sensitization. In the present study, we tested this assumption by treating rats daily with either the selective D_1-type dopamine agonist, SKF 38393 (expt 1) or the D_2-type agonist, quinpirole (expt 2), and testing for locomotor activity. Following this subchronic pretreatment, all rats were then tested for locomotor activity after a challenge injection of the mixed D_1/D_2 agonist, apomorphine. Based upon our prior work, we expected the rats pretreated with SKF 38393, but not quinpirole, to demonstrate behavioral sensitization to apomorphine.

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Experiments 1 and 2

Materials and methods

Subjects. Seventy-three male Wistar albino rats (Harlan Industries, Indianapolis, IN) weighing between 250 and 350 g served as subjects. All rats were housed individually in hanging wire-mesh cages in a colony room with a 12-h light-dark cycle and food and water available continuously. All behavioral testing was conducted during the light phase of the cycle.

Apparatus. Activity measures were taken in two BRS/Lehigh Valley cylindrical activity drums (Model 145–03). The floor of each drum was made of 4 cm diamond-shaped wire mesh and was 60 cm in diameter. The interior wall of each drum was painted flat black and was 43 cm high. Each drum was located in a separate sound-attenuated experimental cubicle that was kept dark during testing.

Two banks of three infrared photocells were mounted on the outside of each drum. The six photocell beams were approximately 12 cm apart arranged in a criss-cross pattern 2.5 cm above the drum floor. The photocell banks were connected to back-path eliminator diodes. Movement of the rat through a photocell beam sent a single pulse to the counters. Simultaneous pulses (i.e., pulses spaced less than 0.05 s apart) such as might occur when two beams are broken at their intersection were recorded as a single count by this method. Thus, locomotor activity was operationalized as the cumulative number of photocell interruptions per unit time.

Drugs. Apomorphine hydrochloride (Sigma) and SKF 38393 (Research Biochemicals) were dissolved daily in 0.001 N HCL. Apomorphine was injected in a volume of 1.0 ml/kg and SKF 38393 was injected in a volume of 1.5 ml/kg. Quinpirole hydrochloride (Research Biochemicals) was mixed in distilled H_2O and injected in a volume of 1.0 ml/kg. All injections were SC. Control injections were given using the appropriate vehicle using the same route and volume as the corresponding drug injection.

Design and procedure. At the beginning of experiment 1, 48 rats were randomly assigned, in equal numbers, to one of four treatment groups: 0 (vehicle), 4.0, 8.0, or 16.0 mg/kg SKF 38393. On each of the first 10 days of the experiment (pretreatment phase), the rats were injected with the appropriate dose of SKF 38393 and then tested for locomotor activity 15 min after the injection. Locomotor activity measurements were taken for 20 min each day. On day 11 of the experiment all rats were given a challenge injection of apomorphine (1.0 mg/kg) and then tested for activity 15 min later. Experiment 2 was the same as experiment 1 except three groups of rats (N=8–9/group) were given either 0 (vehicle), 0.3, or 3.0 mg/kg quinpirole during the pretreatment phase.

Data analysis. Significant differences among the groups in mean activity counts across days were determined with mixed-factor analyses of variance (ANOVA) using drug treatment group as a between factor and daily test session as a repeated measure. When appropriate, additional one-way ANOVAs or Neuman-Keuls post hoc test were performed.

Results

Expt 1: chronic SKF 38393 and activity. The mean activity counts for the four groups injected daily with various doses of SKF 38393 across the first ten test days are shown in Fig. 1. As may be seen in this figure, rats injected with SKF 38393 were significantly less active than the vehicle control rats on the first test day. Moreover, this drug-induced decrease in locomotor activity was dose-dependent and was maintained relatively unchanged across the ten daily injection-test sessions. That is, although the groups gradually decreased activity with repeated testing, the activity of the SKF 38393 groups, particularly the 8.0 and 16.0 mg/kg groups, remained significantly lower than that of the vehicle control rats. The ANOVA performed on these data revealed a significant drug effect [$F(3, 44) = 12.10$, $P < 0.0001$], day effect, [$F(9, 396) = 50.64$, $P < 0.0001$], and Drug × Day interaction, [$F(27,396) = 1.89$, $P < 0.01$]. This latter interaction was largely due to the fact that the groups decreased activity at slightly different rates over the first 3 test days.

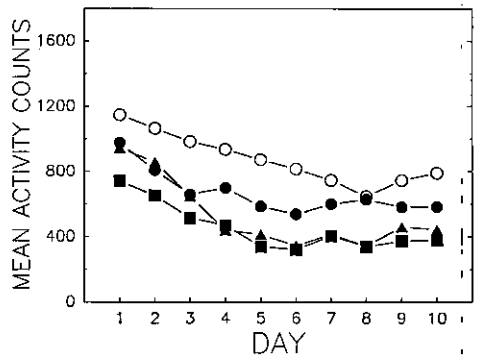

Fig. 1. Mean activity counts per 20 min session across the 10 pretreatment days for rats (N=12/group) injected with either vehicle (○—○) or SKF 38393. SKF 38393: 4.0 mg/kg (●—●); 8.0 mg/kg (▲—▲); 16.0 mg/kg (■—■). The standard error of the mean for the groups' activity on day 10 was 65.25

Expt 1: apomorphine challenge of SKF 38393 pretreated rats. The mean activity counts of the four pretreatment groups after a challenge injection of apomorphine (1.0 mg/kg) on test day 11 are shown in Fig. 2. As shown in this figure, rats previously given ten daily injections of SKF 38393 displayed significantly greater levels of locomotor activity in response to the apomorphine challenge injection than rats previously treated with only vehicle. As expected, the ANOVA performed on these data revealed a significant drug effect, [$F(3, 44) = 3.55$, $P < 0.05$]. Subsequent analysis of this drug effect with Newman-Keuls post hoc tests indicated that all three SKF 38393

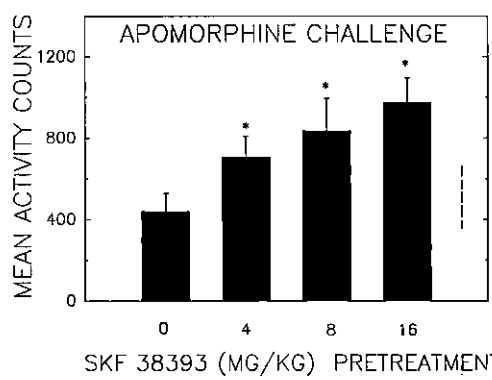

Fig. 2. Mean activity counts (+SEM) during the 20 min session following a challenge injection of apomorphine for rats (N=12/group) previously treated daily with either vehicle or SKF 38393. (*$P < 0.05$ vs 0 mg/kg group)

pretreatment groups were significantly more active following apomorphine than the vehicle control group ($Ps < 0.05$).

Expt 2: chronic quinpirole and activity. The mean activity counts for the three groups of rats injected daily with either quinpirole or vehicle are displayed in Fig. 3. As may be seen in this figure, quinpirole induced a significant depression in locomotor activity following the first injection. This quinpirole-induced inhibition of locomotor activity, however, progressively decreased with repeated injections. Indeed, by day 4 of testing the rats injected with quinpirole did not differ significantly from those injected with vehicle, and by the end of testing quinpirole-treated rats were more active than vehicle-treated rats. The ANOVA performed on these data indicated that the main effect of drug was not significant. As expected, however, both the main effect of day and the Drug × Day interaction were significant [$F(9,198) = 13.95$, $P < 0.0001$, and $F(18, 198) = 9.49$, $P < 0.0001$, respectively]. To further analyse this interaction, a one-way ANOVA was performed on the rats' activity scores on the last pretreatment test day (10). The results of this analysis revealed no significant differences in activity among the groups ($P > 0.05$). Thus, the quinpirole-treated rats were not significantly more active than the vehicle-treated rats on this test day.

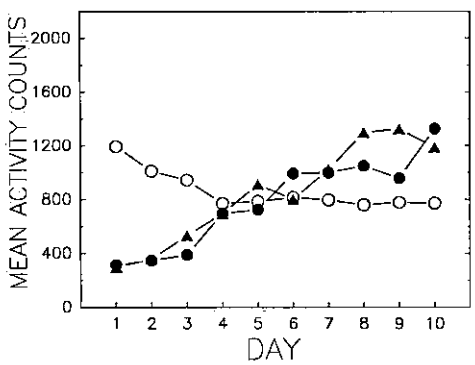

Fig. 3. Mean activity counts per 20 min session across the 10 pretreatment days for rats ($N = 8$–9/group) injected with either vehicle (○—○) or quinpirole. Quinpirole: 0.3 mg/kg (●—●); 3.0 mg/kg (▲—▲). The standard error of the mean for the groups' activity on day 10 was 179

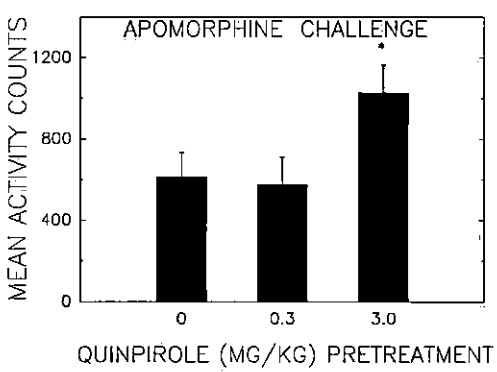

Fig. 4. Mean activity counts per 20 min session (+SEM) following a challenge injection of apomorphine for the three groups of rats ($N = 8$–9 each) previously treated daily with either vehicle or quinpirole. (*$P < 0.05$ vs 0 mg/kg group)

Expt 2: apomorphine challenge of quinpirole pretreated rats. The mean activity counts of the three quinpirole pretreatment groups after a challenge injection of apomorphine on day 11 of testing are shown in Fig. 4. It is evident from this figure that the rats pretreated for 10 days with 3.0 mg/kg quinpirole displayed significantly greater locomotor activity in response to a challenge injection of apomorphine than did either the vehicle-control group or the 0.3 mg/kg quinpirole pretreatment group. As expected, the ANOVA performed on these data revealed a significant drug effect [$F(2,24) = 3.75$, $P < 0.05$].

Experiment 3

In experiment 2, rats pretreated with the D_2 receptor agonist, quinpirole displayed significantly greater levels of locomotor activity following an apomorphine injection than did rats pretreated with vehicle. This finding was unexpected because our previous work had indicated that rats repeatedly treated with the mixed D_1/D_2 dopamine receptor agonist, apomorphine, along with the selective D_1 dopamine antagonist SCH 23390 do not become sensitized to apomorphine (Mattingly et al. 1991). This apparent discrepancy in the effects of repeated D_2 receptor stimulation may be related to the presence or absence of D_1 "tone". That is, repeated D_2 receptor stimulation may have been effective in expt 2 because the D_1 receptors were not blocked as they were in our previous study. If so, then the effects of repeated quinpirole treatments, like apomorphine treatments, should be blocked by concurrent treatments with the D_1 receptor antagonist, SCH 23390. In experiment 3, therefore, groups of rats were injected daily with quinpirole and/or SCH 23390 for 8 days and then tested for locomotor activity after a challenge injection of apomorphine.

Materials and methods

Subjects, apparatus, and drugs. The subjects were 32 male Wistar albino rats (Harlan Industries, Indianapolis, IN) weighing between 250 and 300 g at the beginning of the experiment. The apparatus was the same as in the preceding experiments. Likewise, quinpirole and apomorphine were obtained, prepared, and administered as described previously. SCH 23390 (Research Biochemicals, Inc.) was dissolved daily in distilled H_2O and injected SC in a volume of 1.0 ml/kg.

Design and procedure. The rats were randomly assigned, in equal numbers, to one of four groups comprising the two (SCH 23390 dose: 0 or 0.5 mg/kg) × two (quinpirole dose: 0 or 3.0 mg/kg) factorial design. On day 1 of the pretreatment phase each rat was first injected with either vehicle or SCH 23390 and returned to its home cage. Fifteen minutes later each rat was injected with either quinpirole or vehicle and again returned to its home cage. Fifteen minutes after the second injection each rat was placed into the activity drum and activity counts were recorded for 20 min. This injection-test procedure was repeated daily for 8 days. On day 9, all

rats were given a challenge injection of apomorphine (1.0 mg/kg) and tested for activity 15 min after the injection.

Results

Expt 3: quinpirole, SCH 23390, and activity. The mean activity counts of the four groups across the eight pretreatment sessions are presented in Fig. 5. As may be seen in this figure, rats injected with SCH 23390 and/or quinpirole were significantly less active on day 1 than rats injected with only vehicle. Further, the SCH 23390-induced inhibition of locomotor activity did not significantly change across the 8 pretreatment days. In contrast, the quinpirole-induced inhibition of locomotor activity decreased significantly across the pretreatment days for rats injected with vehicle, but not for those injected with SCH 23390. That is, concurrent SCH 23390 treatments completely blocked the increase in activity observed across days in quinpirole-injected rats. The three-factor ANOVA performed on these data revealed a significant main effect for SCH 23390 [$F(1, 28) = 74.60$, $P < 0.0001$], and several significant interactions including the SCH 23390 × Quinpirole × Day interaction [$F(7, 196) = 8.35$, $P < 0.0001$]. To further analyse this latter interaction, a separate ANOVA was performed on the last pretreatment day (day 8) alone. Consistent with the above interpretation, this analysis revealed a significant main effect of SCH 23390 [$F(1, 28) = 50.37$, $P < 0.0001$], however, neither the main effect of quinpirole nor the SCH 23390 × Quinpirole interaction was significant [$Fs < 1.00$]. Thus, at the end of the pretreatment phase, rats injected with SCH 23390 remained significantly less active then the vehicle control rats, whereas rats treated daily with only quinpirole did not significantly differ from rats injected daily with only vehicle.

Expt 3: apomorphine challenge of SCH 23390/quinpirole pretreated rats. The mean activity counts of the four groups of rats after the challenge injection of apomorphine on day 9 of testing are presented in Fig. 6. Consistent with the results of experiment 2, rats pretreated for 8 days with only quinpirole displayed significantly

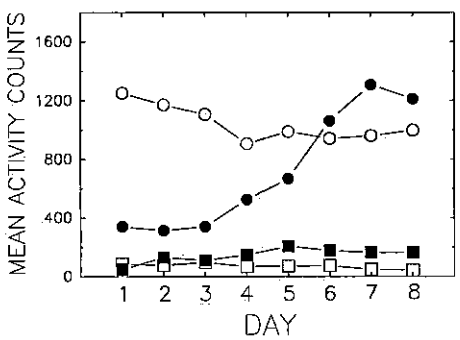

Fig. 5. Mean activity counts per 20 min session across the 8 pretreatment days for the four groups of rats ($N = 8$/group) injected daily with either vehicle (V) or SCH 23390 (S) followed by either vehicle or quinpirole (Q) (○—○) V–V; (●—●) V–Q; (□—□) S–V; (■—■) S–Q. The stardard error of the mean for the groups' activity on day 8 was 101

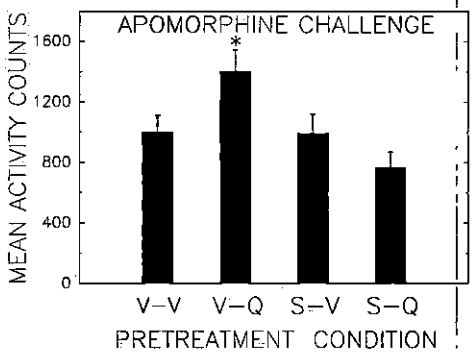

Fig. 6. Mean activity counts per 20 min session (+SEM) following a challenge injection of apomorphine for groups of rats ($N = 8$/group) previously treated for 8 days with either vehicle (V) or SCH 23390 (S) followed by either vehicle (V) or quinpirole (Q). (*$P < 0.05$ vs V–V group)

greater locomotor activity following an injection of apomorphine than did rats pretreated with only vehicle. In contrast, the activity of rats pretreated with only SCH 23390 for 8 days did not differ significantly from the vehicle-only group on this test day. More important, rats pretreated with both SCH 23390 and quinpirole for 8 days did not differ from the vehicle control group. In other words, concurrent treatments of rats with SCH 23390 blocked the effects of repeated quinpirole treatments on apomorphine-induced activity. Consistent with this interpretation, the ANOVA performed on these data revealed a significant main effect of SCH 23390 [$F(1, 28) = 8.44$, $P < 0.01$] and a significant SCH 23390 × Quinpirole interaction [$F(1, 28) = 8.01$, $P < 0.01$]. A Neuman-Keuls analysis of this significant interaction indicated that the vehicle-quinpirole rats were significantly more active than the other three groups, [$Ps < 0.05$]. None of the other group comparisons were significant.

It might be noted that in this experiment the rats previously given only vehicle displayed greater activity following the apomorphine challenge injection than in either of the preceding two experiments. Moreover, in contrast to the first two experiments, apomorphine did not produce a decrease in activity in vehicle rats relative to their activity level following vehicle on the preceding day. This variability in the initial effects of apomorphine is not unusual. Moreover, the lack of an apomorphine-induced increase in activity following the first injection of apomorphine is consistent with our previous work (see Mattingly et al. 1988, 1991; Mattingly and Gotsick 1989; Rowlett et al. 1991). It should be emphasized, however, that the development of behavioral sensitization to apomorphine is a highly reliable and robust phenomenon, and despite changing baselines, the relative effects of various treatments on apomorphine-induced locomotor activity have also been reliable across experiments (cf, quinpirole groups in Figs. 4 and 6).

Discussion

It is evident from the present results that selective stimulation of the D_1-type dopamine receptor with SKF 38393

in rats significantly inhibited locomotor activity, Moreover, this inhibition was dose-dependent and did not significantly change with repeated treatments. The D_2-type dopamine receptor agonist, quinpirole, also decreased locomotor activity when first administered, but this inhibition rapidly decreased with repeated treatments. In fact, with repeated treatments quinpirole appeared to have a stimulating effect on locomotor activity relative to the vehicle treated rats. Whether this increase in activity with repeated quinpirole treatments should be interpreted as tolerance or sensitization, however, is unclear, since the quinpirole treated rats were not significantly more active than the vehicle treated rats at the end of training. Although the time course is quite different, the direct D_2-type dopamine receptor agonist bromocriptine also depresses locomotor activity when first presented, but with repeated treatments results in an increase in locomotor activity (Hoffman and Wise 1992).

The inhibition of locomotor activity induced by quinpirole was expected and may be related to the stimulation of D_2-type autoreceptors. Dopamine autoreceptors appear to be part of a negative feedback loop which, when stimulated, result in a decrease in the synthesis and release of dopamine as well as a decrease in the firing rate of dopamine cells (see Wolf and Roth 1987; Drukarch and Stoof 1990; Lynch 1991, for reviews). Dopamine autoreceptors are generally considered to be of the D_2-type (but see Diana et al. 1991) and appear to be more sensitive to various dopamine agonists compared to postsynaptic D_2-type receptors (see Skirboll et al. 1979; Drukarch and Stoof 1990). Thus, although high doses of direct agonists such as apomorphine often increase locomotor activity, low doses typically result in an inhibition of activity due to selective autoreceptor stimulation (e.g., Mattingly et al. 1988). The initial inhibition of activity induced by quinpirole in the present study is consistent with this view. Moreover, the rapid tolerance that developed to the inhibitory effects of quinpirole also suggests autoreceptor involvement. That is, a number of electrophysiological studies have demonstrated that autoreceptors rapidly become subsensitive to dopamine agonists with repeated exposure (e.g., Rebec and Lee 1982). Hence, the progressive increase in activity observed in the present study with repeated quinpirole treatments may be related to the development of autoreceptor subsensitivity.

As discussed above, low doses of the mixed D_1/D_2 dopamine receptor agonist apomorphine usually produce hypoactivity and this decrease in activity has generally been attributed to selective D_2 autoreceptor stimulation (e.g., Radhakishun and Van Ree 1987). The present results, however, indicate that stimulation of D_1-type dopamine receptors with SKF 38393 can also produce locomotor hypoactivity. This finding suggests that the inhibitory effects of low doses of some dopamine agonists might be due to D_1 postsynaptic receptor stimulation rather than to simply D_2 autoreceptor activation. Consistent with this view, other recent work suggests that the behavioral effects of low dose apomorphine treatments cannot be explained exclusively by selective autoreceptor activation (see Stahle and Ungerstedt 1989, 1990; Lynch 1991). Alternatively, it is possible that SKF 38393 reduced activity in the present study because the doses used stimulated both postsynaptic D_1 receptors and D_2 autoreceptors. If this were the case, however, the SKF 38393-induced inhibition of activity should have progressively diminished over days in a manner similar to quinpirole. As noted previously, the SKF 38393-induced decrease in locomotor activity did not significantly change with repeated treatments. Likewise, SKF 38393-induced grooming behavior in rats does not significantly increase with daily treatments (White et al. 1990; Niesewander et al. 1991). Thus, the possibility exists that the hypoactivity observed after mixed agonist treatments is mediated in part by D_1 receptors (cf, Vezina et al. 1991).

Although SKF 38393 treatments decreased locomotor activity across the 10 pretreatment days, SKF 38393-pretreated rats displayed significantly greater levels of activity in response to an apomorphine-challenge injection than rats pretreated with only vehicle. This finding is consistent with our previous work in which rats were treated daily with the mixed dopamine agonist apomorphine along with the D_2 receptor antagonist sulpiride (Mattingly et al. 1991). Although this combination of drugs resulted in an acute decrease in locomotor activity across days, rats treated in this manner displayed a sensitized locomotor response to a subsequent challenge injection of apomorphine. Together these results suggest that repeated stimulation of the dopamine D_1-type receptor alone is sufficient to induce the development of behavioral sensitization to the mixed dopamine agonist apomorphine. Based upon both behavioral and electrophysiological data, other researchers have also concluded that repeated dopamine D_1 receptor stimulation may be the crucial factor neccessary for the induction of agonist-induced behavioral sensitization (e.g., Braun and Chase 1988; Criswell et al. 1989; Henry et al. 1989; Stewart and Vezina 1989; Vezina and Stewart 1989; White et al. 1990; Henry and White 1991). It should be noted, however, that SKF 38393 is not a full but rather a partial D_1 dopamine receptor agonist. Consequently, it might be argued that the increase in sensitivity to apomorphine observed in the present study following repeated SKF 38393 treatments could be due to an upregulation of D_1 dopamine receptors. There are at least two arguments against this alternative interpretation. First, although an increase in dopamine D_1 receptors in the substantia nigra has been reported following chronic methamphetamine treatments (Ujike et al. 1991), chronic administration of SKF 38393 alone does not alter either the number or affinity of D_1 receptors (Rowlett, Mattingly, and Bardo, submitted for publication; Neisewander et al. 1991). Second, if the increase in sensitivity to apomorphine was due to the partial agonist effects of SKF 38393, then repeated SCH 23390 treatments should produce a similar increase in sensitivity to apomorphine. Repeated treatment with the dopamine D_1 receptor antagonist SCH 23390, however, does not result in an increased activity response to a subsequent challenge injection of apomorphine (see expt 3; Mattingly et al. 1991).

As discussed previously, we have found that the de-

velopment of behavioral sensitization to the mixed D_1/D_2 dopamine agonist apomorphine could be completely blocked by the concurrent administration of the dopamine D_1 receptor antagonist SCH 23390 (Mattingly et al. 1991). This finding suggests that repeated stimulation of the D_2 receptor alone is not sufficient to induce behavioral sensitization. In the present study, however, rats previously given daily quinpirole (3.0 mg/kg) treatments displayed a greater activity response to apomorphine than rats pretreated with only vehicle. Consistent with this result, it has recently been reported that rats are also more sensitive to the locomotor-activating effects of cocaine after subchronic quinpirole pretreatments (Horger and Schenk 1991). These results, of course, clearly suggest the involvement of D_2 receptors in the development of behavioral sensitization. One possible explanation of these findings is that repeated quinpirole treatments induce autoreceptor subsensitivity. Thus, when subsequently challenged with a mixed dopamine agonist such as apomorphine or cocaine, there is a greater net increase in postsynaptic dopamine receptor stimulation, which in turn, leads to greater locomotor activity. Interestingly, autoreceptor tolerance or subsensitivity was one of the earliest explanations for the development of behavioral sensitization (Muller and Seeman 1979; Robinson and Becker 1986), and a number of behavioral, electrophysiological, and neurochemical effects of repeated agonist treatments are consistent with this view (Rebec and Lee 1982; Henry and White 1991; Rowlett et al. 1991). But while an autoreceptor subsensitivity argument appears plausible, this explanation cannot account for the fact that the 0.3 mg/kg dose of quinpirole used in the present study did not increase subsequent sensitivity to apomorphine. Like the 3.0 mg/kg dose, this low dose of quinpirole resulted in a significant inhibition in activity that diminished across the 10 pretreatment days (see Fig. 3). This finding suggests that the 0.3 mg/kg dose of quinpirole also induced autoreceptor subsensitivity. Yet, this dose of quinpirole did not increase subsequent sensitivity to apomorphine. Thus, although autoreceptor subsensitivity may be a contributing factor to the development of sensitization, this latter finding suggests that some minimal level of postsynaptic D_2 receptor stimulation is also necessary to produce this effect. Consistent with this view, other evidence suggests that autoreceptor tolerance cannot account exclusively for the development of behavioral sensitization to mixed dopamine agonists (see Robinson and Becker 1986; Mattingly et al. 1991; Rowlett et al. 1991). Dopamine D_2 antagonists, for example, do not block the development of sensitization to either apomorphine or amphetamine (Stewart and Vezina 1989; Vezina and Stewart 1989; Mattingly et al. 1991).

Interestingly, in experiment 3, the effect of repeated D_2 receptor stimulation with quinpirole on subsequent sensitivity to apomorphine was completely blocked by the D_1 receptor antagonist, SCH 23390. This finding is consistent with previous work indicating that the development of behavioral sensitization to mixed D_1/D_2 dopamine agonists, such as apomorphine and amphetamine, may also be prevented by the blockade of D_1 dopamine receptors (Stewart and Vezina 1989; Vezina and Stewart 1989; Mattingly et al. 1991). Taken together, these results suggest that repeated dopamine D_2 receptor stimulation is neither necessary nor sufficient for the induction of behavioral sensitization. However, in the presence of D_1 receptor "tone", as in experiment 2, repeated D_2 stimulation may contribute to the magnitude of the sensitization effect. Whereas, in the absence of D_1 "tone", repeated D_2 receptor stimulation will not produce behavioral sensitization (expt 3; Stewart and Vezina 1989; Mattingly et al. 1991). These results are consistent with the idea of an "enabling" function for dopamine D_1-type receptors (see Clark and White 1987, for review).

Although the above interpretation accounts for the present results as well as our previous findings using selective antagonists with repeated apomorphine treatments (Mattingly et al. 1991), at least one alternative explanation should be noted. It could be argued, for example, that the ability of SCH 23390 to block the effects of repeated quinpirole or apomorphine treatments on subsequent sensitivity to apomorphine is due to a general depression of locomotor activity rather than to a specific blockade of dopamine D_1 receptors (cf Hirabayasi et al. 1991). Although this explanation cannot be exclusively ruled out on the basis of the present results, there are several arguments against this view. First, many treatments which significantly reduce locomotor activity do not block the development of behavioral sensitization. For example, the dopamine D_2 antagonist sulpiride depresses activity and blocks the acute locomotor activating effects of apomorphine, but does not prevent the development of behavioral sensitization to apomorphine (Mattingly et al. 1991). Likewise, low doses of apomorphine inhibit locomotor activity but still result in the development of behavioral sensitization (Mattingly et al. 1988). Further, rats repeatedly treated with apomorphine in their home cage without any opportunity to explore the test environment display sensitization when subsequently challenged with apomorphine in the testing environment (Mattingly and Gotsick 1990). Also it may be noted that SKF 38393 treatments decreased activity in a dose-dependent manner in experiment 1, but resulted in a greater activity response to a subsequent challenge dose of apomorphine. Finally, we have recently found that the same dose of SCH 23390 used in the present study does not block the development of behavioral sensitization to cocaine (Mattingly et al. 1992). Thus, treatments that depress locomotor activity in the test chambers do not always prevent the development of behavioral sensitization.

In conclusion, the present results indicate that repeated stimulation of either the D_1-type or D_2-type dopamine receptor can lead to greater activity in response to the mixed dopamine agonist, apomorphine. These findings are consistent with the view that repeated D_1 receptor stimulation is both necessary and sufficient to induce behavioral sensitization to apomorphine. Along with previous findings, the present results suggest that while D_2 receptor stimulation may not be necessary for the development of behavioral sensitization to apomorphine, it does contribute to the magnitude of the

effect. These findings lend additional support to the view that multiple pre- and postsynaptic mechanisms may be involved in the development of behavioral sensitization to dopamine agonists (cf Henry and White 1991).

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