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Locomotor Activity and Dopamine Synthesis Following 1 and 15 Days of Withdrawal from Repeated Apomorphine Treatments

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ROWLETT, J. K., B. A. MATTINGLY AND M. T. BARDO. *Locomotor activity and dopamine synthesis following 1 and 15 days of withdrawal from repeated apomorphine treatments.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 13–18, 1997.—In two experiments, the effects of repeated apomorphine treatments on locomotor activity and terminal field dopamine synthesis was assessed after either a 1- or 15-day withdrawal period. In the first experiment, rats (n = 11/group) were treated with apomorphine (1.0 mg/kg, s.c.) or vehicle and tested for locomotor activity daily for 10 days. Fifteen days after the last repeated treatment, all rats received 1.0 mg/kg apomorphine and were tested for locomotor activity. Locomotor sensitization developed over the 10 day period and was still evident after the 15-day withdrawal period. In the second experiment, rats (n = 11/group) were treated with apomorphine (1.0 mg/kg, s.c.) or vehicle and tested for locomotor activity daily for 10 days. Dopamine synthesis was assessed following 1 or 15 days of withdrawal by measuring dihydroxyphenylalanine (DOPA) accumulation (after DOPA decarboxylase inhibition with NSD-1015) in striatum and nucleus accumbens-olfactory tubercle. As in the first experiment, rats treated with repeated apomorphine showed locomotor sensitization over the 10 days, relative to controls. Dopamine synthesis was reliably enhanced in the striatum, but not nucleus accumbens-olfactory tubercle, following both 1- and 15-day withdrawal periods. These results indicate that enhanced basal dopamine synthesis following repeated apomorphine treatments, similar to locomotor sensitizaton, is a persistent phenomenom. © 1997 Elsevier Science Inc.

Behavioral sensitization Locomotor activity Apomorphine Autoreceptor 3,4-Dihydroxyphenylalanine (DOPA)

REPEATED treatments with direct- or indirect-acting dopamine agonists often produce a progressive increase in acute behavioral effects of the drugs, a phenomenon known as behavioral sensitization (10,14). Although the mechanism of action responsible for behavioral sensitization is not known, available evidence indicates involvement of the mesocorticolimbic dopamine system (10). One critical factor identified in the development of sensitization to dopamine agonists is dopamine receptor stimulation (11,16,21), suggesting that repeated treatments with these agonists result in alterations in the dopamine receptor system.

Locomotor sensitization has been demonstrated after repeated treatments with the non-selective agonist apomorphine (2,13,14,27), the D2-type agonist bromocriptine (29), and the D3-preferring agonists, quinpirole (3) and 7-OH-DPAT (12). Examination of dopaminergic neurochemistry has revealed very few effects of repeated treatment with these agonists; indeed, the only consistent neurochemical change observed is an increase in basal dopamine synthesis in the terminal fields (24–26). That is, one day after a repeated daily treatment regimen with a dopamine agonist, dihydroxyphenylalanine (DOPA) accumulation (measured after inhibition of DOPA decarboxylase) is enhanced relative to vehicle-treated controls. This enhanced basal dopamine synthesis effect has been observed following repeated treatments with apomorphine (24,25,27) and quinpirole (26), but not with the D1-type ago-

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nist SKF 38393 (25) or the D3-preferring agonist 7-OH-DPAT (12).

A possible explanation of enhanced basal dopamine synthesis after repeated dopamine agonist treatment is that repeated stimulation induces subsensitivity of dopamine autoreceptors. Consistent with this notion, repeated indirect and direct agonist treatments result in a reduction in the inhibitory effects of dopamine or dopamine agonists on impulse flow (1,4,6,23) and dopamine release (22). However, this autoreceptor subsensitivity is transient, in most cases lasting less than a week (1,22,31), while the long-term changes in dopamine receptor sensitivity responsible for behavioral sensitization appear to be modulated by long-term changes in postsynaptic D1 receptors (5). After repeated amphetamine or cocaine treatments, basal firing rates and the number of spontaneously active A10 dopamine neurons are enhanced, a finding consistent with decreased autoreceptor sensitivity (4,28). Previously, we have noted that if dopamine neuron impulse flow is similarly enhanced after repeated apomorphine treatments, then basal dopamine synthesis may be enhanced indirectly (24,25). If, in fact, enhanced DOPA accumulation reflects autoreceptor subsensitivity, we predicted that enhanced basal dopamine synthesis following direct dopamine agonist treatments would be a transient phenomenon, dissipating at a more rapid rate than locomotor sensitization to the agonist. To test this hypothesis, the present study examined locomotor activity and dopamine synthesis following a 15-day withdrawal period after a regimen of repeated apomorphine treatments previously shown to produce both sensitization and enhanced dopamine synthesis after one day of withdrawal (25). The 15-day withdrawal period was chosen because autoreceptor subsensitivity after repeated psychomotor stimulant treatments consistently has been shown to have dissipated by this time (1,31).

METHOD

Animals

Male Wistar albino rats (250–300 g, Harlan Industries, Indianapolis) were used in the experiments. All rats were housed individually in a colony room (artificial lighting from 0700 to 1900 h) and maintained with food and water available continuously. Behavioral testing and brain tissue collection were conducted during the light phase of the cycle.

Locomotor Activity Apparatus

Activity measures were taken in two Model 145-03 BRS/Lehigh Valley cylindrical activity drums as described previously (12). Briefly, each activity drum had two banks of three infrared photocells mounted on the wall of the drum (60 cm diameter, 43 cm high). Movement of the rat through a photocell beam was quantified as a single "count" recorded by electromechanical equipment in an adjoining room. Simultaneous pulses (i.e., spaced less than 0.05 s apart), such as might occur when two beams were broken near their intersection, were recorded as a single count by this method. Thus, activity was defined as the cumulative number of photobeam interruptions per unit of time.

Tissue Dissections and Assay for DOPA

For tissue dissections, rats were killed by rapid decapitation and the brains were removed and placed on an ice-cold dissection plate. Striatal and mesolimbic (nucleus accumbens and olfactory tubercle combined, NAOT) samples were dissected from a coronal slice that extended from approximately 2–3 mm anterior to bregma (20). Each sample was weighed and placed in 0.1 M $HClO_4$ (100 mg tissue/ml) and stored at −70°C.

On the day of the assay, the tissue samples were thawed and sonicated (Vibracell, setting 80). The tissue homogenates then were centrifuged at 30,000 X g for 15 min (4°C). Supernatants (20 μl) were injected into an high-performance liquid chromatograph (HPLC) system. The HPLC consisted of a Bioanalytical Systems LC4B electrochemical detector (working electrode = +750 mV against the Ag/AgCl reference electrode), PM-11 pump and a temperature-controlled column (35°C, 3 μm). The mobile phase consisted of 50 mM Na_2HPO_4, 124 mM citric acid, 0.1 mM EDTA and 10% methanol (pH 3.0). The amount of DOPA was determined by comparison with the peak heights of DOPA standards, which were assayed daily. Peak identity was verified by retention times and by sometimes spiking a tissue sample with a small amount of DOPA standard.

Drugs

Apomorphine hydrochloride (Sigma) was dissolved daily in 0.001 N HCl and injected in a volume of 1.0 ml/kg via the s.c. route. The DOPA decarboxylase inhibitor NSD-1015 (M-hydroxybenzylhydrazine dihydrochloride, Sigma) was dissolved daily in distilled water at a volume of 1.0 ml/kg and injected via the i.p. route. DOPA standards (Research Biochemicals) were mixed in 0.1 M $HClO_4$.

Procedure

In Experiment 1, 22 rats were randomly divided into two treatment groups (vehicle group, apomorphine group; $n = 11$ for both). The dose of apomorphine was 1.0 mg/kg, the vehicle group received 1 ml/kg 0.001 N HCl. During the repeated treatment phase of the study, each rat was removed from the home cage, injected with drug or vehicle, then returned to the home cage for 15 min. After 15 min, each rat was placed in an activity drum, and locomotor activity was recorded for 20 min, after which time the rat was returned to its home cage. This procedure was carried out for 10 days, with 24 hours separating each session. After the 10 days, all treatments stopped and the rats remained in the home cage for a 15-day withdrawal period. After the withdrawal period, on day 26, all rats received an apomorphine challenge test. Thus, all rats received the same injection and activity testing protocol as during the repeated treatment phase, except that all rats received 1.0 mg/kg apomorphine.

In Experiment 2, 44 rats were randomly divided into four treatment groups in a 2 (apomorphine or vehicle) × 2 (1- or 15-day withdrawal) design ($n = 11$/group). The repeated treatment phase was conducted exactly as in the first experiment, except that 22 rats received apomorphine and 22 rats received vehicle treatment. Although the rats in each withdrawal condition received the same treatment, this variable was assessed during repeated treatments to assure that these groups did not differ in their activity counts. Twenty-four hours after the cessation of the 10-day repeated treatment regimen, all animals in the apomorphine/1-day withdrawal and vehicle/1-day withdrawal groups were injected with 100 mg/kg NSD-1015 and were decapitated 30 min later. Fifteen days after the cessation of the 10-day repeated treatment regimen (day 26), all animals in the apomorphine/15-day withdrawal and vehicle/15-day withdrawal groups were injected with 100 mg/kg NSD-1015 and decapitated 30 min later.

Data Analysis

Locomotor activity counts in Experiment 1 were analyzed initially with a mixed factor analysis of variance (ANOVA) with drug as the between-groups factor and day as the repeated measure. Separate one-way ANOVAs were performed on data from days 10 and 26 with drug as the factor. A one-within ANOVA was performed comparing day 10 to day 26 on the apomorphine group only, in order to assess any changes in apomorphine-induced activity due to the 15-day withdrawal period.

Locomotor activity counts in Experiment 2 were analyzed with a mixed factor analysis of variance (ANOVA) with drug and withdrawal period as the between-groups factors and day as the repeated measure. DOPA levels (μg/g tissue) were analyzed with 2 (apomorphine, vehicle) × 2 (1-day withdrawal, 15-day withdrawal) ANOVAs performed on data from the striatum and NAOT separately. For all ANOVAs, the alpha level was $p \leq 0.05$.

RESULTS

Experiment 1: Apomorphine-induced Sensitization After a 15-day Withdrawal Period

Repeated apomorphine treatments resulted in a progressive increase in activity counts relative to vehicle treatments across the 10 days of testing [see Fig. 1, drug main effect, $F(1, 20) = 47.87$, $p < 0.0001$; day main effect, $F(9, 180) = 11.82$, $p < 0.0001$; drug × day interaction, $F(9, 180) = 37.83$, $p < 0.0001$]. Activity counts for the apomorphine-treated rats were significantly higher than vehicle-treated rats on both day 10 and the day 26 challenge test [$F(1, 20) = 88.76$, $p < 0.0001$ and $F(1, 20) = 15.62$, $p < 0.001$; respectively]. However, there was no reliable change in activity counts in the apomorphine group comparing day 10 to day 26 [$F(1, 20) = 1.79$, $p > 0.05$]. Thus, repeated apomorphine treatments produced locomotor sensitization after 10 days of treatment, and sensitization was evident after a 15-day withdrawal period, since rats treated with repeated apomorphine showed significantly higher activity counts after apomorphine challenge than rats treated with repeated vehicle injections. Moreover, the activity counts in apomorphine-treated rats did not differ from day 10 of repeated treatment to day 26, indicating that the magnitude of the sensitization effect had not changed significantly after withdrawal.

Experiment 2: Dopamine Synthesis After 1 or 15 Days of Withdrawal from Repeated Apomorphine

Repeated apomorphine treatments resulted in a progressive increase in activity counts relative to vehicle treatments across the 10 days of testing [see Fig. 2, drug main effect, $F(1, 42) = 209.97$, $p < 0.0001$; day main effect, $F(9, 358) = 14{,}41$, $p < 0.0001$; drug × day interaction, $F(9, 358) = 40.96$, $p < 0.0001$]. Neither the main effect of withdrawal period nor interactions involving withdrawal as a factor were significant [withdrawal main effect, $F(1, 42) = 0.52$; drug × withdrawal interaction, $F(1, 42) = 0.88$; withdrawal × day interaction, $F(9, 358) = 1.01$; drug × withdrawal × day interaction, $F(9, 358) = 1.14$; all $p > 0.05$]. Thus, the rats in the two withdrawal period groups did not differ in their activity counts or sensitivity to apomorphine treatments prior to the withdrawal intervals.

Analysis of the DOPA data in the striatum (Fig. 3, left panel) revealed a main effect of drug only [drug main effect, $F(1, 40) = 11.18$, $p < 0.002$; withdrawal main effect, $F(1, 40) = 1.75$, $p > 0.05$; drug × withdrawal interaction, $F(1, 40) = 0.37$, $p > 0.05$]. Although DOPA levels were greater in the NAOT for rats previously given repeated apomorphine treatments compared to vehicle-treated rats (Fig. 3, right panel), this difference did not reach significance [drug main effect, $F(1, 40) = 3.83$, $p = 0.057$]. Also, neither the main effect of withdrawal period nor the drug × withdrawal interaction were significant [$F(1, 40) = 0.98$, $p > 0.05$ and $F(1, 40) = 0.32$, all $p > 0.05$; respectively]. Thus, repeated apomorphine treatments resulted in significantly enhanced basal dopamine synthesis in the striatum after 1- and 15-day withdrawal periods.

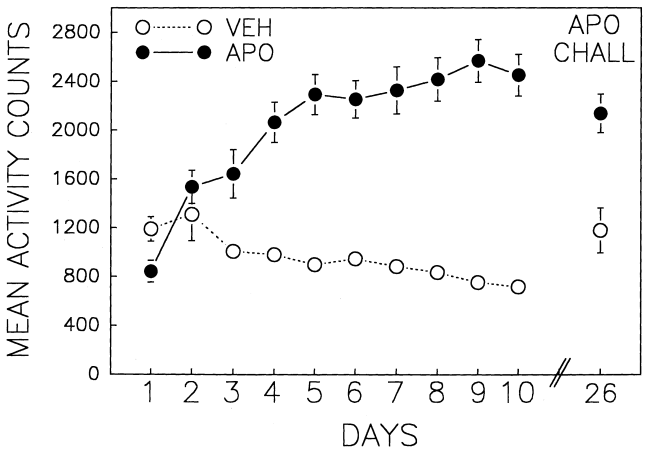

FIG. 1. Activity counts (mean &plm; SEM) for rats (n = 11/group) treated with apomorphine (APO, 1.0 mg/kg, s.c.) or vehicle (VEH, 0.001 M HCl, 1 ml/kg, s.c.) daily for 10 days. Fifteen days after the 10-day daily treatment regimen (day 26), all rats were injected with a challenge dose of apomorphine (APO CHALL, 1.0 mg/kg, s.c.). For all sessions, each rat was injected with drug or vehicle and returned to the home cage for 15 min. Activity was recorded as photobeam interruptions during a 20 min session.

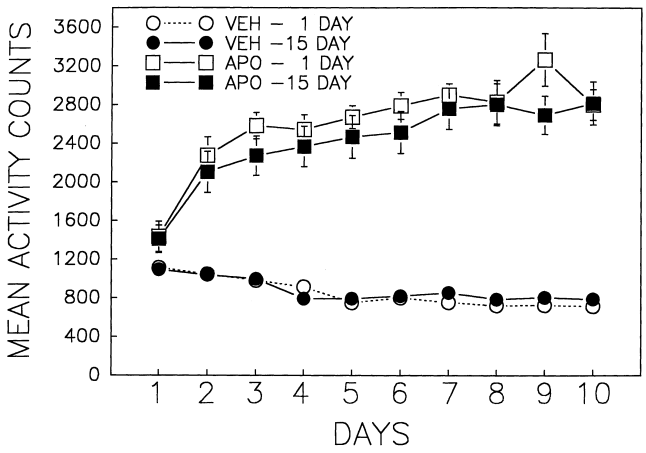

FIG. 2. Activity counts (mean &plm; SEM) for rats (n = 11/group) treated with apomorphine (APO-1 DAY, APO-15 DAY; both 1.0 mg/kg, s.c.) or vehicle (VEH-1 DAY, VEH-15 DAY; 0.001 M HCl, 1 ml/kg, s.c.) daily for 10 days. The subdivision of rats into the 1 DAY or 15 DAY conditions represents animals that were killed for DOPA determination either 1 day or 15 days after withdrawal, respectively. Other details as in Fig. 1.

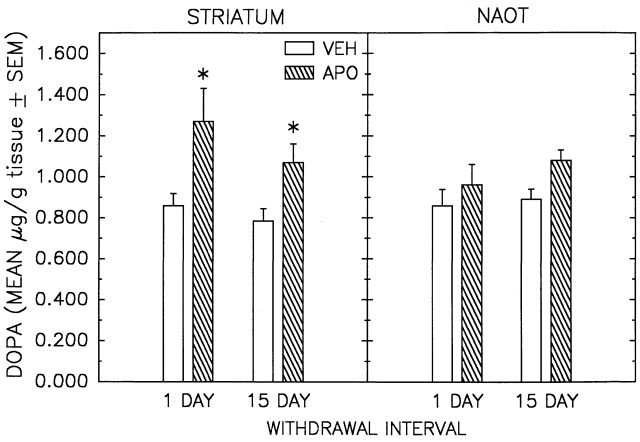

FIG. 3. DOPA accumulation (mean μg/g tissue &plm; SEM) in rat (n = 11/group) striatum and nucleus accumbens-olfactory tubercle (NAOT) following 1 or 15 days of withdrawal from repeated apomorphine treatment (APO, 1.0 mg/kg, once daily for 10 days) or vehicle treatment (VEH, once daily for 10 days). All rats were injected with NSD-1015 (100 mg/kg, i.p.) 30 min prior to decapitation.

Moreover, this effect did not significantly dissipate after 15 days of withdrawal.

DISCUSSION

In the present study, repeated apomorphine treatments resulted in locomotor sensitization, consistent with previous findings (2,13,14). More important, the magnitude of this apomorphine-induced sensitization effect did not significantly decrease over a 15-day withdrawal period (cf., 13). The finding of apomorphine-induced locomotor sensitization after long withdrawal periods is consistent with research assessing psychomotor stimulant-induced sensitization (10). Taken together, these results indicate that locomotor sensitization to both direct and indirect dopamine agonists is a persistent phenomenon.

Twenty-four hours after the last injection of apomorphine, DOPA levels, following injection of a DOPA decarboxylase inhibitor, were enhanced in the striatum. This enhanced dopamine synthesis effect has been observed after repeated apomorphine treatment in rats (24,25) and mice (27), as well as after repeated quinpirole treatments in rats (26). Also, this enhanced basal dopamine synthesis effect has been reported in the NAOT, although the effect has been shown to be lower in magnitude than in the striatum (24-27). Consistent with this, in the data reported herein only trends for increased DOPA accumulation were apparent in the NAOT. The present study extends previous work by examining DOPA accumulation after a 15-day withdrawal period. Indeed, to our knowledge, this paper is the first to assess basal neurochemical changes in dopamine function after greater than one day of withdrawal from repeated apomorphine treatments. After 15 days of withdrawal, DOPA levels were still significantly elevated in the striatum of rats previously treated with apomorphine, compared to rats previously treated with vehicle. Indeed, the enhanced striatal DOPA levels of apomorphine-treated rats after the 15-day withdrawal period did not significantly differ from the enhancement observed after the 1-day withdrawal period. Thus, enhanced basal dopamine synthesis, similar to locomotor sensitization, after repeated apomorphine treatments appears to be a persistent phenomenon.

Autoreceptor subsensitivity has been proposed as an initial event in the cellular cascade associated with the development of behavioral sensitization to psychomotor stimulants (4,31). According to this hypothesis, sensitization may involve at least two cellular alterations in the mesocorticolimbic dopamine system: an initial and transient decrease in the sensitivity of D2 autoreceptors followed by an increase in sensitivity of D1 postsynaptic receptors. Consistent with this hypothesis, after repeated cocaine treatments, the inhibitory effects of dopamine or D2 dopamine agonists were significantly reduced (1,4), an effect that dissipated by 8 days after the repeated treatments (1). In contrast, increased sensitivity to inhibitory effects of the D1 agonist SKF 38393 on cell firing was evident 1 month after repeated cocaine treatments (5). Similar and concordant findings have been observed with other techniques [e.g., in vivo microdialysis (8,9,22)] and after repeated amphetamine treatments (31). For example, suppression of extracellular dopamine levels by local administration of quinpirole into the nucleus accumbens of rats treated with repeated cocaine was attenuated (relative to controls) 1-2 days, but not 21–22 days after cessation of repeated cocaine treatment (22). Finally, electrophysiological evidence for subsensitivity of D2 receptors has been obtained following a short withdrawal interval after repeated apomorphine treatments (6,23).

We also have observed several findings consistent with the hypothesis of autoreceptor subsensitivity followed by enhanced D1 receptor sensitivity drawn from experiments examining electrophysiological effects of repeated psychomotor stimulant treatments. For example, enhanced dopamine synthesis occurred after repeated treatments with quinpirole (26) but not SKF 38393 (25), suggesting a role for D2-type autoreceptors in the development of enhanced dopamine synthesis. Likewise, co-treatments with a D2-type, but not a D1-type, dopamine antagonist blocked quinpirole-induced increases in basal dopamine synthesis (26). However, a D1-type dopamine antagonist blocked the development of behavioral sensitization to the D1-type/D2-type agonist apomorphine (18) and the D2-type agonists quinpirole and bromocriptine (19,29). Thus, it appears that D1 receptor stimulation is critical to the development of behavioral sensitization.

Autoreceptor subsensitivity appears to contribute to the development of sensitization indirectly by increasing D1 receptor stimulation as a result of enhanced basal dopamine synthesis and release (see ref. 12). We have postulated that enhanced basal dopamine synthesis may reflect increased basal cell firing (25,26), which has been shown to be enhanced after repeated cocaine and amphetamine treatments, and is likely due to subsensitive autoreceptor function (4,28). However, after repeated psychomotor stimulant treatments, autoreceptor subsensitivity dissipates after approximately 1 week (1,9,31), whereas in the present study, enhanced dopamine synthesis after repeated apomorphine was still evident after 15 days of withdrawal. This finding suggests that if enhanced dopamine synthesis reflects enhanced impulse flow, then autoreceptor subsensitivity following repeated apomorphine treatments may not be a transient phenomenon.

Alternatively, there are several possible cellular events that may explain the present findings. First, different subsets of autoreceptors (30) may be differentially regulated by repeated apomorphine treatments. That is, changes in basal impulse flow may reflect a transient decreased sensitivity of impulse-regulating autoreceptors, whereas decreased sensitivity of synthesis-modulating autoreceptors may not be transient. Differ-

ential regulation of subsets of autoreceptors could not be addressed in the present study, as DOPA levels in the absence of impulse flow inhibition (i.e., after gamma-butyrolactone treatments, 30) do not differentiate between the activity of synthesis-modulating and impulse-modulating autoreceptors. A second explanation of the results is that enhanced DOPA levels may not reflect changes in autoreceptor function. Changes in dopamine synthesis may reflect non-receptor changes, such as direct effects on tyrosine hydroxylase and/or end-product inhibition. Indeed, if autoreceptors were subsensitive, then a challenge with a direct agonist should result in a diminished ability of the agonist to decrease DOPA accumulation. We (24) and others (27) have not found any significant changes in the effects of acute agonist challenge on DOPA accumulation as a result of repeated apomorphine treatments. However, this lack of effect of agonist challenge may reflect the existence of spare D2 autoreceptors masking down-regulation (6). Finally, the transivity of autoreceptor subsensitivity following repeated treatment with a direct agonist may not be as pronounced as that observed after repeated treatments with an indirect agonist. That is, the effect may dissipate, but only after longer withdrawal periods. Indeed, the cellular events modulating sensitization to apomorphine may differ from those involved with sensitization to other drugs that do not directly stimulate dopamine receptors. Consistent with the notion that the underlying mechanisms involved in sensitization may differ depending on the sensitizing drug, we (15,17) and others (7) have found marked differences in the ability of dopamine antagonists to prevent the development of sensitization to such diverse agonists as apomorphine, cocaine and morphine. Despite these issues, the data in the present experiment demonstrate that enhanced dopamine synthesis after repeated apomorphine treatments is not a transient phenomenon, and therefore may contribute to the persistent locomotor activity changes observed after repeated apomorphine treatments.

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