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Long-Term Sensitization of Apomorphine-Induced Rotation Behavior in Rats With Dopamine Deafferentation or Excitotoxin Lesions of the Striatum

JENNIFER M. KLUG AND ANDREW B. NORMAN[1]

Division of Neuroscience, Departments of Psychiatry, Anatomy, and Physiology, University of Cincinnati College of Medicine, 231 Bethesda Avenue, Cincinnati, OH 45267

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KLUG, J. M. AND A. B. NORMAN. *Long-term sensitization of apomorphine-induced rotation behavior in rats with dopamine deafferentation or excitotoxin lesions of the striatum.* PHARMACOL BIOCHEM BEHAV **46**(2) 397–403, 1993.—Following unilateral 6-hydroxydopamine (6-OHDA)-induced deafferentation or unilateral kainic acid (KA) lesions of the striatum, rats displayed rotation behavior in response to apomorphine (0.25 or 1 mg/kg, SC, for 6-OHDA- and KA-lesioned rats, respectively). Three days following the initial apomorphine injection, rats were challenged under identical conditions with the same dose of apomorphine received previously. A third trial with apomorphine was again repeated after 3 days. Two more sets of behavioral data, each consisting of three trials, were collected under the same conditions as the first. Each set was separated by a period of 5–6 weeks. Following the second trial of the first set, rats showed a significant increase in the maximal number of rotations, demonstrating behavioral sensitization. Following the two 5-week intervals, rats were still sensitized to apomorphine, showing behavioral responses similar to the sensitized responses observed after the initial trials. Thus, the postsynaptically mediated sensitization of apomorphine-induced rotation behavior in 6-OHDA- or KA-lesioned rats is a long-lasting phenomenon. That lesions producing postsynaptic dopaminergic hypersensitivity and hyposensitivity can both show long-lasting sensitization may indicate multiple mechanisms underlying the sensitization.

Reverse tolerance Supersensitivity Behavioral facilitation 6-Hydroxydopamine Kainic acid

EXPOSURE of animals to psychomotor stimulants such as amphetamine (25,28) and cocaine (24) induce an increase in the behavioral effects of these drugs upon subsequent exposure. This sensitization to the behavioral effects of these psychomotor stimulants has been suggested to be mediated by an increase in the release of dopamine in the basal ganglia (5,7,22,26). However, it has also been reported that sensitization of apomorphine or selective D_1 or D_2 dopamine receptor agonist-induced rotation behavior has been observed in rats with 6-hydroxydopamine (6-OHDA)-induced deafferentation of dopaminergic neurons to the striatum (1,14,15,19). As no dopamine is present in lesioned animals, these data indicate that a postsynaptic rather than a presynaptic mechanism is involved in the sensitization response.

The relationship between the behavioral sensitization elicited by presynaptically acting dopamimetic agents such as amphetamine and cocaine in unlesioned animals and the sensitization elicited by directly acting dopamine receptor agonists in dopamine-deafferented rats is uncertain at present. The postsynaptically mediated sensitization response may be distinct from that produced by amphetamine and cocaine. Alternatively, the mechanisms of the amphetamine- and cocaine-induced sensitization may be postsynaptic and similar to those mediating sensitization to dopamine receptor agonists. Psychomotor stimulant-induced sensitization is characterized as being long lasting in that a single administration will produce sensitization to a subsequent administration for many days or weeks following the first administration (9,25). We, therefore, examined the longevity of the sensitization response to apomorphine in 6-OHDA-lesioned animals to determine whether it is also a short- or a long-term phenomenon.

Unilateral excitotoxin lesions of the striatum produce a deficit in dopaminergic neurotransmission that results in rotation behavior in response to dopamine receptor agonists (6, 18,19,27). The direction of apomorphine-induced rotation behavior is dependent upon the location of the excitotoxin lesion in the basal ganglia (18). It has been previously shown that rats with anterior excitotoxin lesions rotate contralateral to the lesion and are sensitized to apomorphine upon repeated challenges (19). We, therefore, investigated whether rats with

[1] To whom requests for reprints should be addressed.

posterior excitotoxin lesions, which rotate ipsilateral to the lesion (18), also develop sensitization to apomorphine and whether this sensitization is a transient or long-lasting phenomenon.

METHOD

Surgical Procedures

Male Sprague–Dawley rats (200–250 g) were used for these studies. All animals were housed in pairs with food and water available ad lib and on a 12 L : 12 D cycle. All testing was during the light phase of the cycle. One group of rats was administered desipramine (25 mg/kg, IP) and pargyline (40 mg/kg, IP) 30 min prior to surgery. Rats were anesthetized with pentobarbital (50–55 mg/kg, IP) and mounted in a Kopf stereotaxic frame (Kopf, Topanga, CA). The rats received a unilateral injection of 8 μg 6-OHDA (Sigma Chemical Co., St. Louis, MO) in 4 μl 0.9% saline containing 0.02% ascorbate. The solution was injected over 4 min and the needle left in place an additional 5 min before withdrawal. Stereotaxic coordinates were AP = 4.4 mm posterior and ML = 1.2 mm relative to bregma and DV = 8.0 mm from dura according to the atlas of Paxinos and Watson (21) with bregma and lambda at the same height. A second group of rats were unilaterally lesioned with kainic acid (KA; 5 nmol; Sigma) in 1 μl 0.9% saline. The solution was injected over 1 min and the needle left in place an additional 2 min before withdrawal. Stereotaxic coordinates were AP = 0.3 mm anterior and ML = 2.3 mm relative to bregma and DV = 5.1 mm from dura.

Behavioral Testing

Behavioral testing began for 6-OHDA-lesioned rats 4–5 weeks postsurgery and for KA-lesioned rats 4–6 weeks postsurgery.

Animals were individually placed in an open-field environment consisting of a Plexiglas box (dimensions 40 × 40 cm) or a Rotoscan Rotometer (Omnitech Electronics) and left to habituate for 20 min. During the habituation period, rats were observed and any spontaneous rotation behavior recorded. Animals were then injected with apomorphine (Sigma) dissolved in normal saline containing 0.02% ascorbate. 6-OHDA-lesioned rats were administered 0.25 mg/kg apomorphine SC; KA-lesioned rats were administered 1.0 mg/kg apomorphine SC. Rotations were continually counted in 5-min periods until all rotation behavior ceased. Rotations were defined as complete 360° turns and reported as the net difference between the two directions. Rats were then returned to their home cage.

For 6-OHDA-lesioned rats, 3 days following the first injection with apomorphine (Trial 1) rats were returned to the same box or rotometer in which they were placed for Trial 1. After a 20-min habituation period, rats were administered apomorphine (Trial 2) in the same dose as received in Trial 1 and rotations measured. Rats were again returned to their home cage. Three days later, the procedure was repeated (Trial 3) as in Trials 1 and 2. These three trials constituted the first set of trials (Set 1). Five to 6 weeks later, the procedures were repeated with three trials separated by 3-day intervals as for Set 1. This constituted Set 2. Five to 6 weeks after the completion of Set 2, the procedures were repeated. This constituted Set 3. Three to 5 days following the last apomorphine challenge (Trial 3 of Set 3), rats were placed into the same boxes or rotometers as previously and after a 20-min habituation period administered vehicle solution (1 ml/kg, SC) and any rotation behavior measured. For KA-lesioned rats, the behavioral testing procedure was as for 6-OHDA-lesioned rats but the period between the three trials in each set varied between 3 and 5 days.

Immunocytochemistry

Three hours following the last injection, 6-OHDA-lesioned rats were intracardially perfused with isotonic saline for 2 min followed by 30 min of ice-cold 4% paraformaldehyde under pentobarbital (65 mg/kg) anesthesia. Brains were postfixed overnight in 4% paraformaldehyde and then stored in a 20% sucrose solution for 24 h. Brains were sectioned (60 μm) on a freezing microtome and placed in cold 0.1 M phosphate buffer with 0.2% Triton X-100 (PB with TX) overnight.

Sections were processed for tyrosine hydroxylase (TH) immunocytochemistry. The primary antibody used was monoclonal mouse anti-TH (Incstar, Stillwater, MN) at a 1 : 2,000 dilution. After a rinse in PB with TX containing 0.5% hydrogen peroxide, tissue was incubated for 48 h with primary antibody in PB with TX containing 1% normal horse serum. After washing three times in PB with TX, sections were incubated for 1 h in biotinylated [horse antimouse immunoglobulin (Ig)G] secondary antibody (Vector Laboratories, Burlingame, CA). After three rinses, sections were incubated for 1 h in avidin–biotin–horseradish peroxidase conjugate from ABC rabbit kits (Vector), washed, and incubated with 3,3′-diaminobenzidine tetrachloride and hydrogen peroxide. Sections were rinsed in PB and mounted onto slides.

Histology

At the end of the behavioral studies, KA-lesioned rats were intracardially perfused as before. Brains were removed and placed in 20% sucrose for 24–48 h and then sectioned and stained with cresyl violet.

Statistics

Differences in the magnitude of rotation behavior were assessed using a one-way repeated-measures analysis of variance (ANOVA) with preplanned comparisons.

RESULTS

6-OHDA-Lesioned Rats

Rotation behavior. Following all injections of apomorphine (0.25 mg/kg, SC), rats displayed rotations contralateral to the lesioned side. As shown in Fig. 1, there was a significant increase ($p < 0.01$) in the total mean number of rotations in Trial 2 of Set 1 (339 ± 58 rotations) compared to Trial 1 of Set 1 (176 ± 50 rotations).

There was a significant increase ($p < 0.01$) in the total mean number of rotations in Trial 1 of Set 2 (358 ± 45 rotations) and Trial 1 of Set 3 (377 ± 101 rotations) compared to Trial 1 of Set 1.

Time course. The increase in the total number of rotations in all trials following the first challenge with apomorphine (Trial 1 of Set 1) were characterized by changes in the time course and maximal responses. An example of these changes is shown in Fig. 2. Following the first challenge with apomorphine, the maximal rate of rotation was observed during the second 5-min postinjection period. In Trial 3 of Set 3, the maximal rate of rotation was observed during the first 5-min postinjection period.

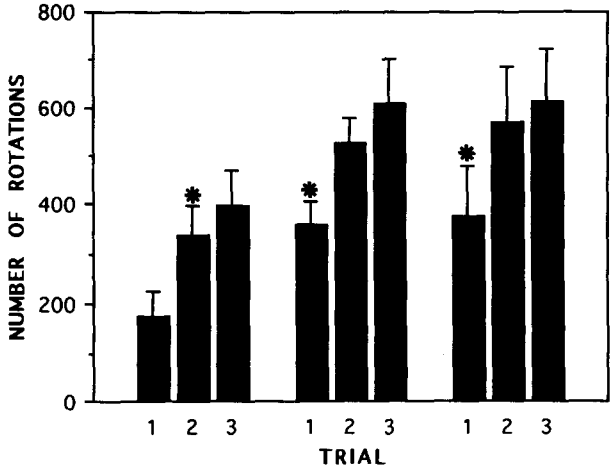

FIG. 1. Long-term sensitization of apomorphine-induced rotation behavior in animals with unilateral 6-hydroxydopamine lesions. Rats received apomorphine (0.25 mg/kg, SC) and rotation behavior was measured until animals stopped rotating. Three days later, rats received the same dose of apomorphine in the same box or rotometer and using the same procedure as previously. A third injection with apomorphine was repeated after 3 days. These three trials with apomorphine constituted Set 1. Two more sets of behavioral data, each consisting of three trials separated by 3 days, were collected under the same conditions as Set 1. Each set was separated by a period of 5-6 weeks. Values represent the mean ± SEM total number of rotations contralateral to the lesion. The data is from nine individual rats. *Significantly different from Trial 1 of Set 1, $p < 0.01$, analysis of variance.

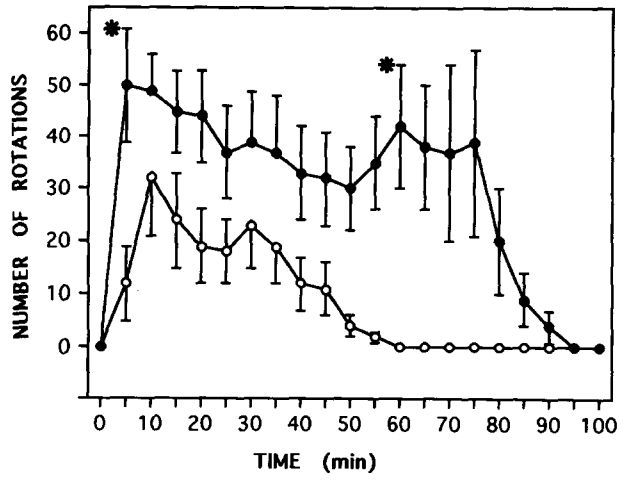

FIG. 2. Time course of apomorphine-induced rotation behavior in unilateral 6-hydroxydopamine-lesioned rats. Rats were administered apomorphine (0.25 mg/kg, SC) and rotation behavior was measured. Rats were rechallenged with apomorphine as described for Fig. 1. Values represent the mean ± SEM number of rotations from nine rats observed in each 5-min period. Data from Trial 1 of Set 1 (○) and Trial 3 of Set 3 (●). *Significantly different from Trial 1 of Set 1, at least $p < 0.05$, analysis of variance.

There was a significant increase ($p < 0.05$) in the peak number of apomorphine-induced rotations for Trial 3 of Set 3 (50 ± 11 rotations) compared to that observed for Trial 1 of Set 1 (32 ± 11 rotations). There was a significantly greater ($p < 0.001$) number of rotations at 60-min postinjection at Trial 3 of Set 3 compared to Trial 1 of Set 1, indicating that the duration of the apomorphine-induced behavioral response was increased between Trial 3 of Set 3 (80–85 min) and Trial 1 of Set 1 (50–55 min).

Spontaneous rotation. No spontaneous rotation behavior was observed for any of the rats during the 20-min habituation period during the three trials of Set 1 (Table 1). However, spontaneous rotation contralateral to the lesion was observed in six of nine rats during Trial 1 of Set 2. This spontaneous rotation behavior occurred during the first 1-3 min of the 20-min habituation period and then ceased. After rats stopped rotating spontaneously, they did not rotate again until after receiving the apomorphine injection. Spontaneous rotation was also observed in the same six rats in Trial 1 of Set 3 (Table 1). No spontaneous rotation was seen in any of the rats in Trials 2 and 3 of Sets 2 and 3 (Table 1).

Three to 5 days after Trial 3 of Set 3, when all rats were placed back into the boxes in which they were previously tested no spontaneous rotation behavior was observed and the injection of the same volume of vehicle produced no injection-induced rotation behavior in any of the rats.

Immunocytochemistry. Immunocytochemical staining of rat striatum using anti-TH primary antibody showed intense immunoreactivity in the striatum contralateral to the lesion (Fig. 3). Ipsilateral to the lesion, there was little, if any, immunoreactivity present.

KA-LESIONED RATS

Rotation behavior. Following all injections of apomorphine (1.0 mg/kg, SC), rats displayed rotations ipsilateral to the lesioned side. As shown in Fig. 4, there was a significant increase ($p < 0.005$) in the total mean number of rotations

TABLE 1

SPONTANEOUS ROTATION BEHAVIOR IN UNILATERAL 6-HYDROXYDOPAMINE-LESIONED RATS

Set	Trial	Spontaneous Rotation
1	1	No
1	2	No
1	3	No
2	1	Yes, $n = 6$
2	2	No
2	3	No
3	1	Yes, $n = 6$
3	2	No
3	3	No

Before receiving apomorphine, rats were placed into Plexiglas boxes or a Rotometer and allowed to habituate for 20 min. Values represent the number of rats demonstrating spontaneous rotation behavior for the first 1-3 min of the habituation period. After rats stopped rotating spontaneously, they did not rotate again until receiving the apomorphine injection.

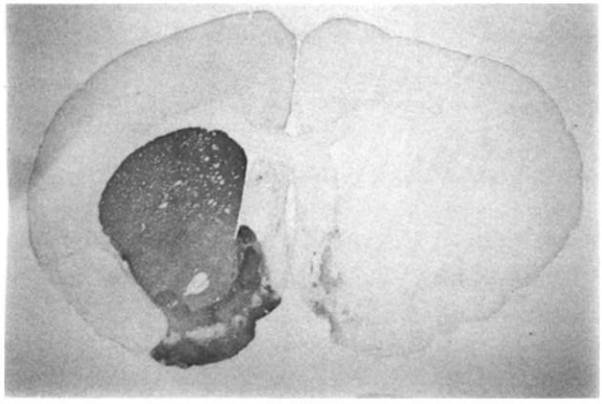

FIG. 3. Tyrosine hydroxylase immunocytochemistry in a unilateral 6-hydroxydopamine-lesioned rat brain. Dense tyrosine hydroxylase immunoreactivity was observed in the striatum contralateral to the lesion. Ipsilateral to the lesion, there was little, if any, tyrosine hydroxylase immunoreactivity present.

between Trial 1 of Set 1 (93 ± 13 rotations) and Trial 2 of Set 1 (299 ± 44 rotations).

There was a significant increase ($p < 0.005$) in the total mean number of rotations between Trial 1 of Set 1 and Trial 1 of Set 2 (680 ± 128 rotations).

There was a significant increase ($p < 0.005$) for the total mean number of rotations between Trial 1 of Set 1 and Trial 1 of Set 3 (572 ± 88 rotations).

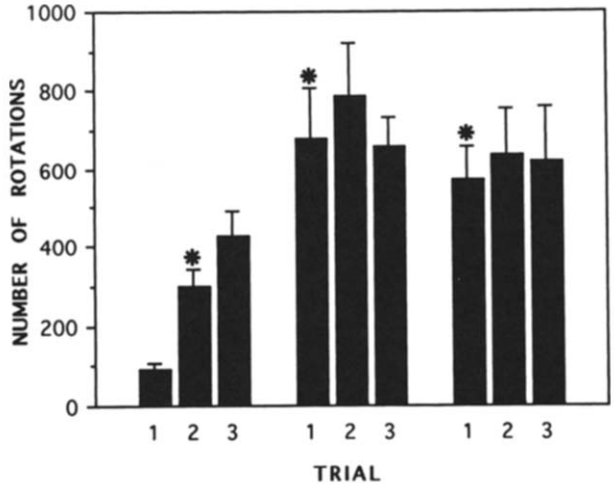

FIG. 4. Long-term sensitization of apomorphine-induced rotation behavior in animals with unilateral kainic acid lesions. Rats received apomorphine (1.0 mg/kg, SC) and rotation behavior was measured until animals stopped rotating. Three days later, rats received the same dose of apomorphine in the same box and using the same procedure as previously. A third injection with apomorphine was repeated after 3 days. These three trials constituted Set 1. Two more sets of behavioral data, each consisting of three trials separated by 3–5 days, were collected under the same conditions as Set 1. Each set was separated by a period of 5–6 weeks. Values represent the mean ± SEM total number of rotations ipsilateral to the lesion. The data is from eight individual rats. *Significantly different from Trial 1 of Set 1, $p < 0.005$, analysis of variance.

Spontaneous rotation. No spontaneous rotation behavior was observed during the 20-min habituation period in any of the rats in any of the trials.

Three to 5 days following Trial 3 of Set 3, when all rats were placed back into the boxes in which they were previously tested, injections of the same volume of vehicle produced no spontaneous rotation or induced rotation behavior in any of the rats.

Histology. Histological analysis revealed that the extent of the KA-lesioned damage in a rat was detectable from +1.2 mm to −2.12 mm from bregma according to the atlas of Paxinos and Watson. A representative section is shown in Fig. 5. The neurodegeneration was restricted to the lesioned side of the brain and was characterized by a shrinkage of the striatal parenchyma with a concomitant enlargement of the lateral ventricle. All rats turned ipsilateral to the lesioned side of the brain.

DISCUSSION

The sensitization of apomorphine-induced rotation behavior that has previously been characterized in 6-OHDA- and KA-lesioned rats (19) was found in the present study to persist for at least 20 weeks (the approximate time between Trial 1 of Set 1 and Trial 3 of Set 3). This long-term aspect of the sensitization response is similar to that demonstrated for psychomotor stimulants, such as amphetamine and cocaine in unlesioned (24,25) and in 6-OHDA-lesioned (9) animals. The magnitude of the sensitization response appears to reach a plateau, indicating a maximal response, after three or four injections of apomorphine. The sensitized behavioral response to apomorphine appears to persist for a significant portion of the animal's lifetime.

We previously demonstrated that the 3-day interval between injections provides a marked and reproducible sensitization response (19). We also previously reported that there was no significant difference in the total number of rotations between the third and fourth injections of apomorphine (18). However, in the present study the maximal response was not reached by the third injection, and four or five challenges with apomorphine were required to produce the maximal response.

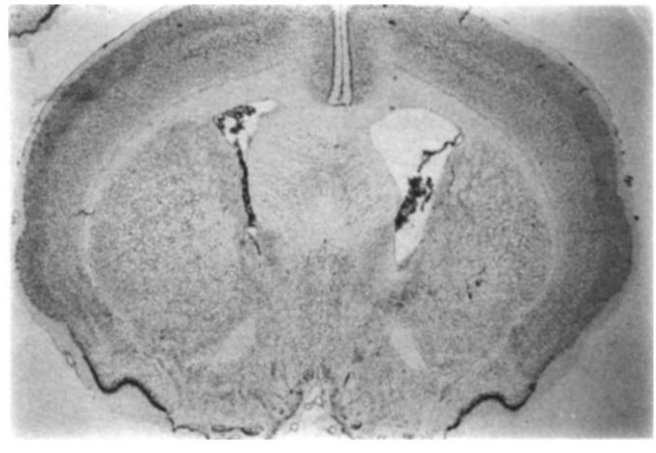

FIG. 5. Nissl stain of a coronal section through the striatum of an animal receiving a kainic acid lesion. Section is located at approximately 1.0 mm posterior to bregma according to the atlas of Paxinos and Watson.

Interestingly, after rats in the present study had received nine injections of apomorphine there was no evidence of a desensitization of the behavioral response. It has previously been reported that sensitization to apomorphine and other psychomotor stimulants appears to be related to the time intervals between administrations of the drug, with continuous administration more likely to produce desensitization and intermittent administration producing sensitization (23). Although tolerance to the behavioral effects of apomorphine analogs have been reported following repeated administration (32), the intermittent administration used in the present studies was not conducive to producing tolerance to the behavioral effects of apomorphine. The sensitization to apomorphine observed in our studies was consistent with the sensitization to apomorphine observed in unlesioned animals (10,11,13).

The mechanism for the sensitization response is unknown at present. The sensitization to the behavioral effects of cocaine and amphetamine has been correlated with an increase in the release of dopamine in the basal ganglia following repeated administration (5,7,22,26). Although the characteristics of the apomorphine-induced sensitization response with respect to the permanence of the effect are similar to those of amphetamine, an increase in the release of dopamine following repeated administration is unlikely to provide a mechanism for the apomorphine-induced sensitization response. The ipsilateral striata of 6-OHDA-lesioned animals are essentially devoid of dopaminergic terminals. Even if the 6-OHDA lesion is not complete, apomorphine has been demonstrated to inhibit (16,31,32) rather than enhance dopamine release. These data, therefore, indicate that a postsynaptic mechanism may mediate the apomorphine-induced sensitization of rotation behavior.

Other investigators reported that a conditioned learning behavior can produce an increase in apomorphine-induced rotations (2–4) or produce spontaneous rotations (29,30) in rats with unilateral 6-OHDA lesions. This is unlikely to account for the sensitization phenomenon observed in our experiments. Injection of saline following long-term intermittent exposure to apomorphine did not produce any rotation behavior in any of the animals. Therefore, a conditioned learning response to the injection itself cannot be responsible for the increases in rotation behavior produced by apomorphine.

It was reported that rats with unilateral 6-OHDA lesions exhibit spontaneous rotation when placed back into the environment in which they previously displayed apomorphine-induced rotation behavior (29,30). This spontaneous rotation behavior has been assumed to represent a conditioned response to the environment. This demonstrates that environmental contextual cues can induce rotation behavior and also demonstrates a long-term learning response. In the current experiments, we also observed this spontaneous rotation phenomenon. Interestingly, to observe this response required a long time period (5 or 6 weeks) following the initial set of apomorphine injections. The response was transient and occurred only for 2–3 min immediately after the animal was placed in the testing chamber. The behavior was not observed 3 days later, when rats were placed back into the same environment. Not every animal exhibited spontaneous rotation behavior, although all animals exhibited rotation behavior in response to apomorphine. Importantly, when rats were injected with apomorphine they were no longer displaying spontaneous rotations. Further, in Trials 2 and 3 of Sets 1, 2, and 3, when rats were sensitized to the behavioral effects of apomorphine compared to Trial 1 of Set 1, no spontaneous rotation behavior was observed. Although conditioned responses can occur as previously described (29,30), they do not appear to be relevant to the sensitization of rotation behavior produced by repeated treatments with apomorphine. It is, however, important to habituate rats to their environment prior to drug injection so that the spontaneous rotation behavior is not a confounding factor in the measured sensitization response. It has also been demonstrated that the behavioral sensitization to apomorphine in unlesioned rats develops with repeated challenges in the absence of drug-associated contextual environmental stimuli (12). Therefore, the sensitization response to apomorphine is distinct from the contextual environmental conditioning in both lesioned and unlesioned animals.

It is unlikely that the long-lasting sensitization observed in the current experiments could be produced by modifications of receptors or second messenger systems as the proteins constituting these systems are constantly degraded and resynthesized (17). As dopamine receptors have a half life on the order of days (17), any receptors modified during the initial apomorphine challenge would eventually be degraded and replaced by newly synthesized receptors. Therefore, the sensitization response, if it was related to modified receptors, would be relatively short lived. It may be speculated that newly synthesized receptors may have been modified in some manner and that the mechanism for this posttranslational modification could be permanent. It might also be speculated that a novel gene may have been induced and it is a new gene product that alters the sensitivity of cells to dopaminergic stimulation. Indeed, there are preliminary reports that protooncogene expression may be altered following repeated treatments with apomorphine (20) and amphetamine (8). However, it is unclear at present whether these neurochemical changes are related to the behavioral sensitization.

Rats with unilateral kainic acid lesions of the striatum also display a sensitization of the apomorphine-induced rotation behavior. The characteristics of the sensitized responses were similar to those observed in 6-OHDA-lesioned rats. The plateau in the magnitude of the sensitized response was observed following the third or fourth injection. The sensitized response was also present for a protracted period. We previously reported that rats with KA lesions of the striatum can turn contralateral to the lesion depending upon the anterior/posterior placement of the lesion (18). Rats with anterior KA lesions displayed sensitization of contralateral rotation behavior in response to apomorphine (19). In our present studies, we found that rats with posterior KA lesions rotate ipsilateral to the lesion and also display a sensitization of the ipsilateral rotation behavior. The rotation behavior ipsilateral to the lesion (6,18,27) is generally assumed to represent a hyposensitivity of dopamine receptor-mediated responses on the lesioned side of the brain with normosensitive dopamine receptor-mediated responses on the unlesioned side of the brain (27).

It is clear from previous studies and the present data that in normal rats amphetamine, cocaine, and apomorphine can produce sensitization of various behaviors. In rats with unilateral 6-OHDA lesions, the sensitization of apomorphine-induced rotation behavior indicates a postsynaptically mediated sensitization of an already supersensitive dopaminergic system. Amphetamine sensitization of rotation behavior observed in unilateral 6-OHDA-lesioned animals may be due to a sensitization of the normosensitive dopaminergic system, presumably by a mechanism similar to that observed in unlesioned animals. In rats with unilateral KA lesions of the stria-

tum turning ipsilateral in response to apomorphine, the sensitization of apomorphine-induced rotation may also represent a sensitization of the normosensitive striatum similar to that in unlesioned animals. In rats with unilateral KA lesions of the striatum turning contralateral in response to apomorphine, this sensitization of apomorphine-induced rotations may represent a sensitization of a perturbed neuronal circuitry within the basal ganglia. The sensitization response to amphetamine, cocaine, and directly acting dopamine receptor agonists such as apomorphine may be mediated by multiple mechanisms. These may include an increase in the release of dopamine in addition to a sensitization of the postsynaptic component of dopaminergic neurotransmission within the striatum. However, it is clear that, regardless of its functional status, the dopaminergic system within the basal ganglia displays a fundamental tendency to become sensitized in response to repeated challenges with psychomotor stimulants and directly acting dopamine receptor agonists.

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REFERENCES

1. Bevan, P. Repeated apomorphine treatment causes behavioural supersensitivity and dopamine D_2 receptor hyposensitivity. Neurosci. Lett. 35:185–189; 1983.
2. Burunat, E.; Castro, R.; Diaz-Palarea, M. D.; Rodriguez, M. Conditioned response to apomorphine in nigro-striatal system-lesioned rats: The origin of undrugged rotational response. Life Sci. 41:1861–1866; 1987.
3. Burunat, E.; Diaz-Palarea, M. D.; Castro, R.; Rodriguez, M. Undrugged rotational response in nigro-striatal system-lesioned rats is related to the previous early response to apomorphine when repeatedly administered. Life Sci. 41:309–313; 1987.
4. Carey, R. J. Application of the unilateral 6-hydroxydopamine rat model of rotational behavior to the study of conditioned drug effects. J. Neurosci. Meth. 22:253–261; 1988.
5. Castaneda, E.; Becker, J. B.; Robinson, T. E. The long-term effects of repeated amphetamine treatment in vivo on amphetamine, KCl and electrical stimulation evoked striatal dopamine release in vivo. Life Sci. 42:2447–2456; 1988.
6. Dunnett, S. B.; Isacson, O.; Sirinathsinghji, D. J. S.; Clark, D. J.; Bjorklund, A. Striatal grafts in rats with unilateral neostriatal lesions. III. Recovery from dopamine-dependent motor asymmetry and deficits in skilled paw reaching. Neuroscience 24:813–820; 1988.
7. Kalivas, P. W.; Duffy, P. Effects of daily cocaine and morphine treatment on somatodendritic and terminal field dopamine release. J. Neurochem. 50:1498–1504; 1988.
8. Klug, J. M.; Lu, S. Y.; Norgren, R. B.; Norman, A. B. Multiple exposure to *d*-amphetamine sensitizes c-fos expression in rat striatum. Soc. Neurosci. Abstr. 18:362; 1992.
9. Lin-Chu, G.; Robinson, T. E.; Becker, J. B. Sensitization of rotational behavior produced by a single exposure to cocaine. Pharmacol. Biochem. Behav. 22:901; 1985.
10. Martres, M. P.; Costentin, J.; Baudry, M.; Marcais, H.; Protais, P.; Schwartz, J. C. Long-term changes in the sensitivity of pre- and postsynaptic dopamine receptors in mouse striatum evidenced by behavioural and biochemical studies. Brain Res. 136: 319–337; 1977.
11. Mattingly, B. A.; Gotsick, J. E.; Marin, C. Locomotor activity and stereotypy in rats following repeated apomorphine treatments at 1-, 3-, or 7-day intervals. Pharmacol. Biochem. Behav. 31:871–875; 1988.
12. Mattingly, B. A.; Gotsick, J. E. Conditioning and experiential factors affecting the development of sensitization to apomorphine. Behav. Neurosci. 108:1311–1317; 1989.
13. Mattingly, B. A.; Rowlet, J. K. Effects of repeated apomorphine and haloperidol treatments on subsequent behavioral sensitivity to apomorphine. Pharmacol. Biochem. Behav. 34:345–347; 1989.
14. Morelli, M.; Chiara, G. D. Agonist-induced homologous and heterologous sensitization to D_1 and D_2-dependent contraversive turning. Eur. J. Pharmacol. 141:101–107; 1987.
15. Morelli, M.; Fenu, S.; Chiara, G. D. Behavioural expression of D_1 receptor supersensitivity depends on previous stimulation of D_2 receptors. Life Sci. 40:245–251; 1987.
16. Muller, P.; Seeman, P. Presynaptic subsensitivity as a possible basis for sensitization by long-term dopamine mimetics. Eur. J. Pharmacol. 55:149; 1979.
17. Norman, A. B.; Battaglia, G.; Creese, I. Differential recovery rates of rat D_2 dopamine receptors as a function of aging and chronic reserpine treatment following irreversible modification: A key to receptor regulatory mechanisms. J. Neurosci. 7:1484–1491; 1987.
18. Norman, A. B.; Norgren, R. B.; Wyatt, L. M.; Hildebrand, J. P.; Sanberg, P. R. The direction of apomorphine-induced rotation behavior is dependent on the location of excitotoxin lesions in the rat basal ganglia. Brain Res. 569:169–172; 1992.
19. Norman, A. B.; Wyatt, L. M.; Hildebrand, J. P.; Kolmonpunporn, M.; Moody, C. A.; Lehman, M. N.; Sanberg, P. R. Sensitization of rotation behavior in rats with unilateral 6-hydroxydopamine or kainic acid-induced striatal lesions. Pharmacol. Biochem. Behav. 37:755–759; 1990.
20. Ouellette, W.; Klug, J. M.; Landen, H. C.; Thompson, H. R.; Norman, A. B. Multiple exposures to apomorphine sensitizes c-fos expression in 6-hydroxydopamine lesioned rat striatum. Soc. Neurosci. Abstr. 18:363; 1992.
21. Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. 2nd ed. New York: Academic Press; 1986.
22. Peris, J.; Zahniser, N. R. One injection of cocaine produces a long-lasting increase in [^{3}H]-dopamine release. Pharmacol. Biochem. Behav. 27:533–535; 1987.
23. Post, R. M. Intermittent vs. continuous stimulation: Effect of time interval on the development of sensitization or tolerance. Life Sci. 26:1275–1282; 1980.
24. Post, R. M.; Weiss, S. R. B.; Pert, A. The role of context and conditioning in behavioral sensitization to cocaine. Psychopharmacol. Bull. 23:425–429; 1987.
25. Robinson, T. E.; Becker, J. B. Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain Res. Rev. 11:157–198; 1986.
26. Robinson, T. E.; Jurson, P. A.; Bennett, J. A.; Bentgen, K. M. Persistent sensitization of dopamine neurotransmission in ventral striatum (nucleus accumbens) produced by prior experience with (+)-amphetamine: A microdialysis study in freely moving rats. Brain Res. 462:211–222; 1988.
27. Schwarcz, R.; Fuxe, K.; Agnati, L. F.; Hokfelt, T.; Coyle, J. T. Rotational behavior in rats with unilateral striatal kainic acid lesions: A behavioral model for studies of intact dopamine receptors. Brain Res. 170:485–495; 1979.
28. Segal, D. S.; Kuczenski, R. Behavioral and neurochemical characteristics of stimulant-induced augmentation. Psychopharmacol. Bull. 23:417–424; 1987.

29. Silverman, P. B. Apomorphine induces latent rotation in lesioned rats, amphetamine does not. Life Sci. 42:2397–2401; 1988.
30. Silverman, P. B.; Ho, B. T. Persistent behavioural effect of apomorphine in 6-hydroxydopamine-lesioned rats. Nature 294:475–477; 1981.
31. Watters, J. R.; Bunney, B. S.; Roth, R. H. Piribedil and apomorphine pre and postsynaptic effects on dopamine synthesis and neuronal activity. Adv. Neurol. 9–273–284; 1975.
32. Worms, P.; Scatton, B. Tolerance to stereotyped behavior and to decrease in striatal homovanillic acid levels after repeated treatment with apomorphine dipivaloyl ester. Eur. J. Pharmacol. 45: 395–396; 1977.