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Repeated Treatments with 7-OH-DPAT: Context-Independent Behavioral Sensitization and Conditioned Hyperactivity

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MATTINGLY, B. A., L. L. RICE, M. LANGFELS AND S. E. FIELDS. *Repeated treatments with 7-OH-DPAT: Context-independent behavioral sensitization and conditioned hyperactivity.* PHARMACOL BIOCHEM BEHAV **65**(2) 241–246, 2000.—The primary objective of this study was to determine whether the expression of behavioral sensitization to the putative dopamine D_3 receptor agonist 7-OH-DPAT is context dependent. Three groups (n = 8 each) of male Wistar rats (250–350 g) were given nine injections (at 48-h intervals) of 7-OH-DPAT (1.0 mg/kg, SC) or vehicle 15 min before and after activity testing. The paired group received 7-OH-DPAT before activity testing and vehicle after testing. The unpaired group received vehicle before and 7-OH-DPAT after testing, and the vehicle control group received two vehicle injections. Locomotor activity was measured in photocell arenas for 2 h. After the first seven sessions, all rats were tested for activity following a vehicle injection to test for possible conditioning effects. Prior to the 11th session, all rats were given a challenge injection of 7-OH-DPAT (1.0 mg/kg, SC) to test for sensitization. Major findings were as follows: (a) the 7-OH-DPAT/paired group displayed a progressively greater increase in locomotor activity with repeated treatments; (b) the 7-OH-DPAT/paired group was significantly more active than either the vehicle control group or the 7-OH-DPAT/unpaired group during the vehicle test session; and (c) after the 7-OH-DPAT challenge injection, the paired and unpaired 7-OH-DPAT groups were significantly, and equally, more active than the vehicle control group. In contrast to previous findings with the D_2-type dopamine agonists bromocriptine and quinpirole, these results suggest that the expression of behavioral sensitization to 7-OH-DPAT is not context dependent. Moreover, these results suggest that the apparent conditioned hyperactivity and context dependency often observed after repeated dopamine agonist treatments may not be related to the same associative and/or nonassociative mechanisms. © 2000 Elsevier Science Inc.

Behavioral sensitization 7-OH-DPAT Locomotor activity Dopamine D_3 receptors

WITH repeated intermittent administration, the behavioral effects of both direct (e.g., apomorphine, quinpirole) and indirect (e.g., amphetamine, cocaine) dopamine agonists, progressively increase. This phenomenon, termed behavioral sensitization, has been extensively documented for the locomotor-activating effects of psychostimulants (1,27,34), and accumulating evidence suggests that the rewarding effects of psychostimulant drugs also become sensitized with repeated drug administration [e.g., (25,32)]. This phenomenon has received considerable research attention because the neurochemical mechanisms mediating the development and persistence of behavioral sensitization are thought to be involved in the development of stimulant-induced paranoid psychosis (27), as well as in the maintenance of compulsive drug-seeking behavior and relapse in recovering addicts (6,28).

Although the repeated administration of psychostimulant drugs produces a number of neurochemical alterations (15, 17), the development and expression of behavioral sensitization is also influenced by a number of environmental or associative factors [e.g., (9,23,29,34)]. For example, the expression of behavioral sensitization following repeated treatments with amphetamine or cocaine is often either not observed, or

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is significantly reduced, if the repeated drug treatments are associated with the animal's homecage rather than the activity test apparatus [e.g., (9,26,34)]. This context dependency of behavioral sensitization has usually been attributed to Pavlovian conditioning processes (3,34). Consistent with this view, a conditioned hyperactivity response to apparatus and injection/handling cues associated with repeated amphetamine or cocaine exposure has often been reported (8,9,14,19,35). Similarly, context-dependent behavioral sensitization along with a conditioned hyperactivity response has been observed after repeated treatments with the D_2-type dopamine agonist, bromocriptine (16). In contrast, conditioned hyperactivity responses are usually not observed in rats sensitized to either the mixed D_1/D_2-type dopamine agonist, apomorphine (11,21,30), or the selective D_2/D_3 dopamine agonist, quinpirole (13,37, 40), even though the expression of sensitization to these agonists appears to be context dependent (12,21,37,38). These latter findings, of course, are inconsistent with a Pavlovian interpretation of the context-dependent behavioral sensitization observed with direct dopamine agonists.

Recently, locomotor sensitization has been demonstrated with the putative selective dopamine D_3 receptor agonist, 7-OH-DPAT (20,22). In many respects, the acute and chronic locomotor effects of 7-OH-DPAT are similar to those of the dopamine D_2/D_3 agonist quinpirole (20). Unlike quinpirole, however, rats sensitized to 7-OH-DPAT appear to display conditioned hyperactivity when placed into the activity test apparatus without the drug (22). In the present study, therefore, we wanted to determine whether the expression of behavioral sensitization to 7-OH-DPAT, like quinpirole and bromocriptine, is context dependent. Consequently, three groups of rats were given repeated injections of 7-OH-DPAT or vehicle either paired or unpaired with the activity test apparatus and then tested for conditioning after a vehicle injection, and for sensitization after a 7-OH-DPAT challenge injection.

METHOD

Subjects

Twenty-four male Wistar albino rats (Harlan Industries, Indianapolis, IN) weighing between 250 and 350 g served as subjects. All rats were housed individually in hanging stainless steel rectangular cages (35 cm L $\times$ 18 cm W $\times$ 18 cm H). The front wall and floor of the cages was constructed 2-mm wire mesh in a square (12 $\times$ 12 cm) pattern. Food and water was available continuously through dispensers attached to the cages. The colony room was maintained on a 12 L:12 D schedule. 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) that were 60 cm in diameter and 43 cm high. The interior of each drum was painted flat black, and the floor was made of 4-cm diamond-shaped wire mesh. Each drum was located in a separate sound-attenuated experimental room that was kept dark during testing.

Two banks of three infrared photocells were mounted on the outside of each drum. The photocells were approximately 12 cm apart and 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 defined as the cumulative number of photocell interruptions per unit time.

Drugs

(±)-7-Hydroxy-dipropylaminotetralin hydrobromide (7-OH-DPAT; Research Biochemicals) was dissolved in distilled H_2O and injected SC in a dose of 1.0 mg/kg. Doses were calculated based upon the salt form of the drug. Vehicle injections were given using the same route and volume (1.0 ml/kg).

Design and Procedure

At the beginning of the experiment, 24 rats were randomly assigned in equal numbers to one of three treatment groups: vehicle, 7-OH-DPAT/paired, and 7-OH-DPAT/unpaired. During the training phase (sessions 1–7), each rat received an injection 15 min before and after activity testing. Rats in the vehicle group were given two vehicle injections. The 7-OH-DPAT/paired group rats were given an injection of 7-OH-DPAT before activity testing and a vehicle injection after activity testing. Rats in the 7-OH-DPAT/unpaired condition received vehicle before testing and 7-OH-DPAT after testing. On session 8 (conditioning test), all rats were treated the same as during the training phase except all rats were given two vehicle injections. On sessions 9 and 10 (retraining phase), all rats were treated the same as in the training phase. On session 11 (sensitization test), all rats received an injection of 7-OH-DPAT (1.0 mg/kg) prior to activity testing. In all phases of the experiment the rats were returned to their home cage after the injections. All activity test sessions were 120 min in duration, and separated by 48-h drug-free intervals.

Data Analysis

Significant differences among the groups in mean activity counts during the training phase (sessions 1–7) and the retraining phase (sessions 9–10) were determined with mixed three-factor analyses of variance (ANOVAs) using drug treatment condition as a between-groups factor and test session, and blocks of 20 min within sessions, as repeated measures. Significant interactions were analyzed with additional ANOVAs performed on individual session and/or block data, followed by Newman–Keuls post hoc tests. Mean activity counts of the groups on the conditioning test (session 8) and sensitization test (session 11) were analyzed using mixed two-factor ANOVAs.

RESULTS

Training Sessions 1–7

Mean activity counts of the three groups across the six 20-min time blocks on sessions 1, 4, 7, and 10 are displayed in Fig. 1. As may be seen in this figure, 7-OH-DPAT treatment produced a biphasic effect on locomotor activity, relative to vehicle, on session 1 (cf., DPAT/paired group), with an initial period of inhibition being followed by locomotor stimulation. As expected, the 7-OH-DPAT/unpaired rats did not significantly differ from the vehicle control rats, and the activity of both groups significantly declined across both sessions and blocks within sessions. In contrast, rats given 7-OH-DPAT prior to each session (i.e., DPAT/paired group) displayed a progressive increase in activity across sessions, especially

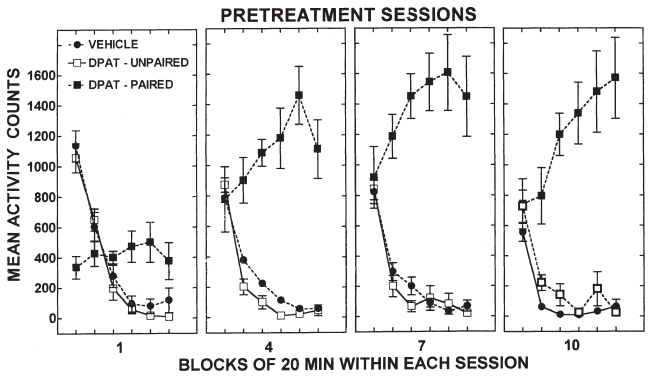

FIG. 1. Mean activity counts (±SEM) across blocks of 20 min on sessions 1, 4, 7, and 10 for rats treated 15 min before each session with either vehicle (vehicle, DPAT-unpaired) or 1.0 mg/kg 7-OH-DPAT (DPAT-paired), and 15 min after each session with either vehicle (vehicle, DPAT-paired) or 1.0 mg/kg 7-OH-DPAT (DPAT-unpaired).

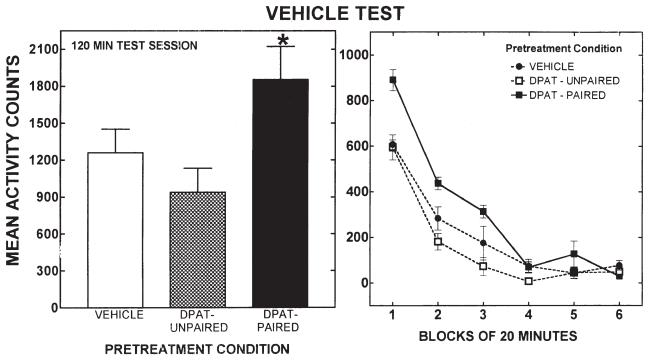

FIG. 2. Mean activity counts (±SEM) after a vehicle injections (session 8) for rats previously treated subchronically with either vehicle or 7-OH-DPAT (1.0 mg/kg, DPAT) either paired or unpaired with activity testing. The left panel represents the total session activity, and the right panel presents the same data as a function of six 20-min blocks within the session. Left panel: $*p < 0.05$ compared to the VEH-VEH group.

during the second hour of each test session [condition main effect: $F(2, 21) = 39.20$, $p < 0.0001$; condition × session interaction, $F(12, 126) = 30.25$, $p < 0.0001$; condition × block interaction, $F(10, 105) = 24.77$, $p < 0.0001$].

Retraining Sessions 9–10

As may be seen in Fig. 1, the activity of the three groups on session 10 was similar to that observed on the last training session (session 7) prior to the vehicle conditioning test. The ANOVA performed on sessions 9–10 revealed, as expected, significant main effects of condition, $F(2, 21) = 63.77$, $p < 0.0001$, and a significant condition × block interaction, $F(10, 105) = 11.81$, $p < 0.0001$. However, neither the main effect of session nor any of the interactions involving session as a factor approach significance. Thus, the within-session activity of the various groups was stable from session 9 to 10.

Conditioning Test—Session 8

The mean activity counts of the three groups after receiving the same vehicle injection are shown in Fig. 2. As may be seen in the left panel, rats previously treated with 7-OH-DPAT paired with the test environment were significantly more active over the 120-min test session than rats previously treated with only vehicle [condition main effect, $F(2, 21) = 16.92$]. As may be seen in the right panel of Fig. 2, the increased activity of the 7-OH-DPAT/paired rats, relative to vehicle controls, diminished across time blocks [block main effect, $F(5, 105) = 147.15$, $p < 0.0001$; condition × block interaction, $F(10, 105) = 423$, $p < 0.0001$]. Rats previously treated with 7-OH-DPAT not paired with the test environment did not significantly differ from rats previously given only vehicle.

Sensitization Test—Session 11

The mean activity counts of the three pretreatment groups following a 7-OH-DPAT challenge injection are shown Fig. 3. As may be seen in this figure, rats previously treated with 7-OH-DPAT paired with the test environment were significantly more active after the 7-OH-DPAT challenge injection than rats previously given only vehicle [condition effect, $F(2, 21) = 3.54$, $p < 0.05$]. More important, rats previously treated with 7-OH-DPAT unpaired with the test environment were also more responsive to the 7-OH-DPAT challenge injection than vehicle control rats, and did not differ in activity from the 7-OH-DPAT/paired group on this test (ps > 0.05). As may be seen in the right panel of Fig. 3, although the groups increased activity across blocks [block main effect, $F(5, 105) = 10.14$, $p < 0.001$], the rats previously treated with 7-OH-DPAT were more active than the rats previously given only vehicle on all blocks, [condition × block interaction, $F(10, 105) < 1.00$].

DISCUSSION

Consistent with previous studies (20,22), the acute administration of 7-OH-DPAT produced a biphasic effect upon locomotor activity, with a period of locomotor inhibition being followed by a period of locomotor stimulation. With repeated administration, however, the initial inhibitory effects diminished and the secondary excitatory effects progressively increased [cf., (20,22)]. The within- and between-session pattern of activity generated by repeated 7-OH-DPAT treatments was similar to that previously observed with the dopamine D_2-type agonists, quinpirole and bromocriptine (16,36). This similarity to quinpirole and bromocriptine, along with the fact that lower doses of 7-OH-DPAT do not produce behavioral sensitization (20), suggests that the development of behavioral sensitization to 7-OH-DPAT may not be exclusively mediated by dopamine D_3 receptor stimulation (20,33).

As expected, based upon our previous work, rats treated repeatedly with 7-OH-DPAT paired with the test environment were significantly more active than either the 7-OH-DPAT/unpaired rats or the vehicle control rats when tested after a vehicle-only injection on session 8. This finding is consistent with a conditioning explanation of behavioral sensitization, which suggests that environmental cues associated with drug exposure become capable of eliciting hyperactivity in the absence of the drug [see (34)]. Similar evidence of conditioned hyperactivity has been observed after repeated bromocriptine treatments (16), but as mentioned, conditioned hyperactivity is usually not observed after repeated quinpirole or apomorphine treatments (13,21,30,37,40).

Although repeated pairing of 7-OH-DPAT with the test

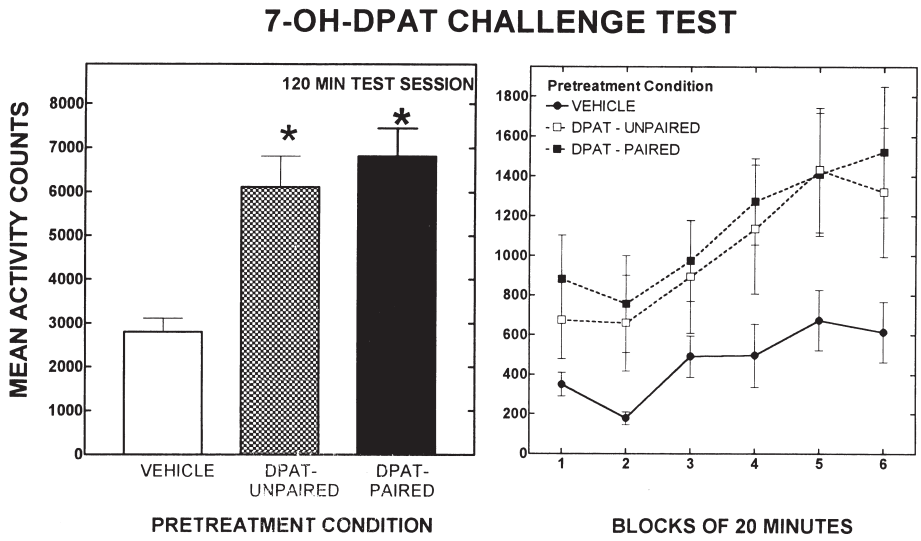

FIG. 3. Mean activity counts (±SEM) after a 7-OH-DPAT challenge injection (session 11) for rats previously treated subchronically with either vehicle or 7-OH-DPAT (1.0 mg/kg, DPAT) either paired or unpaired with activity testing. The left panel represents the total session activity, and the right panel presents the same data as a function of six 20-min blocks within the session. Left panel: $*p < 0.05$ compared to the VEH-VEH group.

environment produced what appeared to be conditioned hyperactivity, the development and/or expression of behavioral sensitization to 7-OH-DPAT was not context dependent. That is, rats previously treated with 7-OH-DPAT paired with the test chambers were significantly more active than rats previously treated with only vehicle. However, rats previously treated with 7-OH-DPAT unpaired with the test chambers were also more active than the vehicle control rats after the 7-OH-DPAT challenge injection, and did not differ in activity from the 7-OH-DPAT/paired rats. In other words, repeated 7-OH-DPAT treatments appeared to produce the same degree of behavioral sensitization regardless of whether the treatments were paired or unpaired with the activity test chambers. Thus, unlike other selective dopamine D_2-type agonists, behavioral sensitization to 7-OH-DPAT does not appear to be context specific.

Although 7-OH-DPAT is often considered to be a selective dopamine D_3 receptor agonist, recent research suggests that the in vivo selectivity of 7-OH-DPAT for D_3 receptors compared to D_2 receptors may be relatively small (18,33). Consistent with the in vivo findings, the acute and chronic behavioral effects of 7-OH-DPAT are, for the most part, similar to those of other prototypical dopamine D_2-type agonists [cf., (20)]. The present results, along with our previous findings, however, reveal a number of important behavioral and neurochemical differences between the effects of 7-OH-DPAT and the D_2-type agonists, bromocriptine and quinpirole. For example, rats sensitized to quinpirole display cross-sensitization to apomorphine (24) and cocaine (15). In contrast, rats sensitized to 7-OH-DPAT do not display cross-sensitization to either apomorphine or cocaine (20). Further, chronic quinpirole treatments produce an increase in basal dopamine synthesis in both nigrostriatal and mesolimbic terminal fields, presumably due to the development of autoreceptor subsensitivity (31). Although 7-OH-DPAT treatment acutely decreases dopamine synthesis, chronic 7-OH-DPAT treatments do not affect basal dopamine synthesis in either area (20). Finally, the development of behavioral sensitization to either quinpirole or bromocriptine can be prevented by concurrent treatments with the D_1-type dopamine antagonist SCH 23390 (24,41), whereas SCH 23390 treatment does not prevent the development of sensitization to 7-OH-DPAT (22). Together with the current findings, these differences suggest that the development of behavioral sensitization to these D_2-type agonists (i.e., bromocriptine, quinpirole, and 7-OH-DPAT) may not be mediated by a common neurochemical mechanism [cf., (20,22)].

As discussed previously, context-dependent behavioral sensitization and hyperactivity to drug-associated apparatus cues are generally assumed to be related and mediated by Pavlovian conditioning processes (9,36). Consistent with this view, both context-dependent behavioral sensitization and conditioned hyperactivity are observed after the repeated administration of various direct and indirect dopamine agonist such as amphetamine, cocaine, and bromocriptine [e.g., (9,16,35)]. However, as demonstrated by the present results, these two phenomena are clearly dissociable. In the present study with 7-OH-DPAT, apparent conditioned hyperactivity was observed, but sensitization was not context dependent. In previous work with apomorphine and quinpirole, context-dependent sensitization was observed without conditioned hyperactivity (11,21,37). This double dissociation suggests that these two phenomena may not be mediated by a common associative mechanism.

There are at least two possible explanations for the current apparently discrepant findings. It could be argued, for example, that the hyperactivity of the 7-OH-DPAT/paired rats on the vehicle test was not related to Pavlovian conditioning processes, but rather to a drug-induced disruption of habituation to the cues associated with the activity test environment [see (1,10,22)]. If so, then the hyperactivity of the 7-OH-DPAT/paired rats on the vehicle test may have been due to the relative novelty of the test environment rather than to conditioning. Consistent with this explanation, the level and the pattern

of activity of the 7-OH-DPAT/paired rats on the vehicle test was very similar to that of the vehicle control rats on the first pretreatment session, and markedly different from that observed after a 7-OH-DPAT injection on sessions 7 or 10 (cf., Fig. 1 vs. Fig. 2). If the hyperactivity of this group on the vehicle test was related to the relative novelty of the test environment, rather than to conditioning, then the expression of sensitization would not necessarily be expected to be context specific.

Alternatively, it might be argued that the expression of behavioral sensitization to 7-OH-DPAT is context specific, and the level of activity observed in the 7-OH-DPAT/unpaired rats on the 7-OH-DPAT challenge test simply represents stimulus generalization from the home cage to the test environment. If this view was correct, however, a significant generalization response decrement would have been expected on the sensitization test because the test environment differed significantly from the home cage in size, shape, location, illumination, etc. Although not observed in the present experiment, we previously observed a significant response decrement in apomorphine-treated rats using the same home cages and activity test apparatus as used in the present experiment (21). Thus, although this possibility cannot be eliminated based upon the current experiment, it is unlikely that the sensitized responding of the 7-OH-DPAT/unpaired rats on the 7-OH-DPAT challenge test was due to stimulus generalization.

In recent years there has been growing recognition of the importance of environmental factors in the development and expression of behavioral sensitization (3,7,9,29). Although Pavlovian conditioning processes have long been suggested to influence the development and expression of sensitization (26,39), other associative processes (e.g., operant conditioning, behavioral reorganization) have recently been implicated (10,11,40). Moreover, nonassociative factors such as the relative novelty of the drug-associated test environment (4,5), and as noted above, drug-induced disruptions in habituation processes have also been suggested to influence the development and/or expression of behavioral sensitization (1,10). It appears that a wide variety of associative and nonassociative factors may interact to determine whether: (a) sensitization develops to a particular drug, and (b) to what extent the sensitized response will be expressed (29,38,42). Currently, there is not a systematic model with predictive value that can account for all the various factors influencing the development and/or expression of behavioral sensitization [see (2)]. Clearly, additional research examining the influence of drug/environmental interactions on the development of behavioral sensitization is warranted.

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