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BRIEF COMMUNICATION

The Dopamine D-2 Agonist Quinpirole Produces Environment-Specific Conditioned Activity

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MAZURSKI, E. J. AND R. J. BENINGER. *The dopamine D-2 agonist quinpirole produces environment-specific conditioned activity.* PHARMACOL BIOCHEM BEHAV 30(2) 525–527, 1988.—The stimulant effects of various dopamine agonists can become conditioned to the particular environment with which they are repeatedly paired. The present study assessed the ability of the selective dopamine D-2 agonist quinpirole (2.5 mg/kg) to similarly show environment-specific conditioning. Rats in Paired and Unpaired groups (both n=12) received 12 pairings of a unique environment with quinpirole or saline, respectively. Horizontal and vertical activity were automatically measured during the 60-min sessions. Home cage injections were given after each session and involved administration of saline or quinpirole to rats, whichever they did not have during the session. Intermittent tests for conditioned activity were given wherein both groups received saline prior to being placed in the chambers for 60 min. Quinpirole enhanced horizontal activity. Stimulant effects on vertical activity were also observed although they appeared after an initial suppression of the response. Conditioned activity was observed on the saline tests as the Paired group was significantly more active than the Unpaired group on each measure. The present findings suggest that enhanced stimulation of the D-2 receptor can produce environment-specific conditioned activity. Consequently, researchers using quinpirole should take this factor into consideration, particularly if utilizing chronic drug treatment.

Dopamine D-2 receptor Quinpirole Horizontal and vertical activity Environment-specific conditioning

CLASSICAL conditioning using pharmacological agents as the unconditioned stimuli has been widely demonstrated using a variety of their effects as the measured response. A frequently used paradigm, environment-specific conditioning, involves the repeated pairing of drug effects with a unique environment. If the response to saline of the subjects with the pairing history exceeds control levels, conditioning is said to have occurred. It is of interest that a number of stimulant drugs used in this paradigm enhance transmission within the dopaminergic system. For example, (+)-amphetamine, cocaine, methylphenidate and apomorphine have all been shown to produce conditioned effects in such studies [2, 3, 6–9]. Furthermore, administration of the dopamine specific antagonist pimozide can block the establishment of conditioning with (+)-amphetamine and cocaine [2,3], further supporting the notion that dopamine is critically involved.

Recently, it has been discovered that there are at least two distinct receptor subtypes for dopamine, termed D-1 and D-2 [5]. Stimulation of the D-1 receptor enhances the production of cyclic AMP whereas stimulation of the D-2 site either does not affect, or may inhibit cyclic AMP formation [4,5]. The behavioral significance of the two receptor subtypes is still under extensive investigation. Although the early research suggested that the behavioral effects of DA agonists were mediated primarily by the D-2 receptor recent evidence suggests that stimulation of the D-1 receptor is also critical for expression of some behaviors [12].

The recent availability of dopamine agonists specific to the D-2 receptor, such as quinpirole [11], make it feasible to enhance transmission at this receptor while leaving the D-1 receptor relatively unaffected. Thus, behavioral responses to preferential D-2 receptor stimulation can be examined. The current study was conducted to determine if administration of quinpirole without concurrent enhanced stimulation at the D-1 receptor could produce environment-specific conditioning. Quinpirole was considered an ideal candidate for examination of this effect as it is known to act as a stimulant in rats, increasing locomotion, sniffing and grooming [12].

METHOD

Subjects

Twenty-four male Wistar rats had free access to food (Purina Rat Chow) and water for the duration of the study. They were individually housed in a climatically controlled environment (21±1°C) kept on a 12 hr light (0600–1800)/dark cycle.

Apparatus

Activity was measured in six Plexiglas chambers (41×50×37 cm), each encased in black styrofoam. A 2.5 W bulb was placed on the ceiling of each box and a fan circulated air while providing constant masking noise. Each chamber was equipped with two sets of 7 infrared emitters and detectors placed at 5 and 15 cm above the wire rod floor, which assessed horizontal and vertical activity independently. Further details of the apparatus have been previously reported [1].

Procedure

The rats were randomly separated into two equal sized groups, termed Paired and Unpaired. Prior to experimentation they were handled daily over a five day period. The study began the following day, and included a series of 60-min sessions in the activity monitoring chambers. Sessions were of two types: conditioning and test. Conditioning sessions included intraperitoneal administration of quinpirole (2.5 mg/kg) or saline (0.9%) to the Paired and Unpaired groups respectively, prior to placement in the chambers. Pilot studies had suggested that maximal stimulant effects of quinpirole were exhibited after 90 min, thus injections were given 90 min before the sessions. Three Paired and three Unpaired rats were always tested simultaneously. Between 30 and 60 min after the rats had been replaced in their home cages following the conditioning sessions they were each administered a second injection. At this time the Paired rats received saline and the Unpaired rats the drug. This procedure ensured that all rats had similar exposure to quinpirole, although the groups differed with respect to the environment with which the drug was associated. Test sessions were similar to conditioning; however, rats in both groups received saline 90 min before the session. No home cage injections were administered on test days.

Sessions occurred on a daily basis except where indicated below. There were three rounds of four conditioning sessions, each followed by one test. However, after the second and third rounds of sessions all rats had two days without experimentation followed by another test session. Thus, there were a total of 12 conditioning and five test sessions.

RESULTS

The data were analysed separately for pairing and testing sessions and for horizontal and vertical activity. In each case, a three-way analysis of variance with time (6 10-min intervals), session (12 for conditioning or 5 for test), and group (Paired and Unpaired) as the factors was conducted. Figure 1 shows the average activity in each 10 min period during the average of the conditioning and test sessions for each activity level.

Horizontal Activity

During conditioning sessions analysis of horizontal activity yielded significant time, $F(5,110)=18.60$, $p<0.01$, group, $F(1,22)=65.69$, $p<0.01$, and time by group, $F(5,110)=9.37$, $p<0.01$, effects. The time effect suggested that activity levels tended to decrease across the session. The group effect indicated that, overall, the Paired group was more active than the Unpaired group, thus demonstrating a stimulant effect of quinpirole. Simple main effects analyses determined that the Paired group was significantly more active than the Unpaired group during the last forty minutes (see Fig. 1).

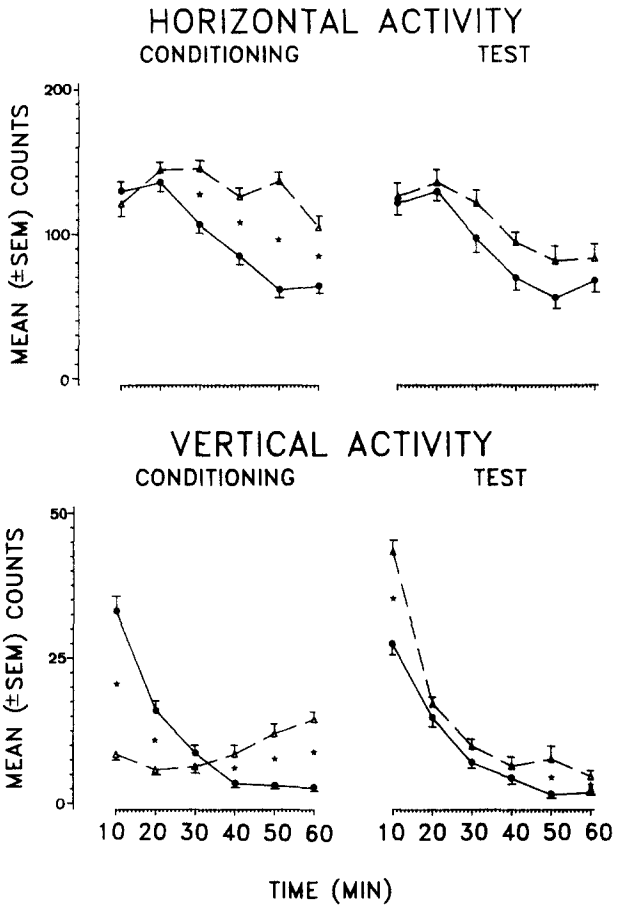

FIG. 1. Mean (±SEM) activity scores in each 10 min for Paired (△) and Unpaired (●) groups during the average of 12 conditioning and 5 test sessions for horizontal and vertical activity. N=12 per group. *Indicates group difference with $p<0.05$ at a time interval.

In the test sessions on horizontal activity there were significant time, $F(5,110)=16.08$, $p<0.01$, session, $F(4,88)=5.54$, $p<0.01$, and group, $F(1,22)=7.94$, $p<0.01$, effects. Thus, the group effect demonstrated that rats previously having quinpirole-environment pairings were more active than those that did not have such pairings. The time effect again depicted the decline in activity across the session. The session effect reflected the tendency for higher activity scores in both groups following two days without testing (data not shown).

Vertical Activity

The activity profiles during conditioning sessions were quite different for vertical in comparison to horizontal activity (see Fig. 1). The analysis revealed that all effects, except that of group, were significant at $p<0.01$. As the time by group effect suggested that differences between the groups varied depending on the time within the session, the groups were compared at each time interval. These analyses determined that there was a significant suppression of vertical activity in the Paired group in the first twenty minutes followed by a significant enhancement in the last 30 minutes. The session by group interaction was further examined with simple main effects analyses. Significant session effects were observed in both the Paired, $F(11,121)=2.68$, $p<0.01$, and

Unpaired groups, $F(11,121)=13.15$, $p<0.01$. However, activity *decreased* across the course of the study in the Unpaired group, whereas an *increase* over sessions was seen in the Paired group.

The data from vertical activity during the test sessions did not yield a similar profile to those from conditioning. The analysis indicated that there were significant time, $F(5,110)=123.05$, $p<0.01$, session, $F(4,88)=26.11$, $p<0.01$, group, $F(1,22)=9.61$, $p<0.01$, time by session, $F(20,440)=1.88$, $p<0.05$, time by group, $F(5,110)=6.15$, $p<0.01$, and time by session by group effects, $F(20,440)=1.71$, $p<0.05$. Again, the significant time effect illustrated the decline in activity across the session. The significant group effect suggested that the previously Paired group was more active than the Unpaired group. The session effect again illustrated that two days without testing resulted in increased activity in both groups (data not shown). Analysis of the simple main effects comparing the groups at each time determined that the Paired group was significantly more active at the first, fifth and sixth time intervals.

DISCUSSION

The present study suggests that the D-2 agonist quinpirole affects both horizontal and vertical activity in rats. The behavioral profile of rats treated with the drug prior to each session demonstrated a profound difference from those treated with saline before each session. Whereas quinpirole appeared to only stimulate horizontal activity, it produced a biphasic effect on the vertical measure: initially depressing then later enhancing activity. Thus, the assessment method was sensitive to quinpirole-induced alterations in activity across the time period in which the rats were studied.

Rats that previously had the drug paired with the environment showed significantly more horizontal and vertical activity during the tests for conditioning than the control group. This suggested that environment-specific conditioned activity was produced using quinpirole. Although no progressive enhancement of horizontal activity was observed in the Paired group over the course of training (i.e., sensitization), there was such an enhancement in vertical activity. The control group did not exhibit a similar trend but rather their activity decreased over the sessions. This further supports the notion that conditioning was occurring. However, future studies should investigate whether any differences occured in the Unpaired control group in comparison to a group never receiving the UCS (quinpirole) to ensure that the control group's activity in the chambers was unaffected by the drug treatments in the home cage.

As quinpirole was administered to the Paired group 90 min prior to each session, there was not a complete and discrete association of drug-induced behavior and the testing apparatus in the Paired group. Although such a definite association would be desirable, it is often not feasible when using drugs as the UCS due to their gradual onset and inactivation. Nonetheless, the contingency appeared sufficient as conditioned behavior was apparently manifested. In addition to the theoretical significance of this finding, the present data suggest that caution be taken when interpreting the behavioral effects of quinpirole on other paradigms.

A number of previous studies have found that drugs which enhance dopamine transmission, such as (+)-amphetamine, cocaine, methylphenidate and apomorphine are able to produce conditioning in similar paradigms to that used presently [2, 3, 6–10]. The recent finding that multiple receptors for dopamine exist [5] leads to speculation of the functional significance of each in environment-specific conditioning. The study here suggests that enhanced stimulation of the D-2 receptor can produce conditioning, a finding in concordance with recent research on the D-2 receptor suggesting that it has an important behavioral role [12]. However, further research is needed to determine if similar effects would be produced with specific enhancement of the D-1 receptor. Studies have recently been focusing on a possible interaction of the two receptor subtypes. It would be of interest to determine if such an interaction also occurs in the present paradigm.

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