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Associational and nonassociational mechanisms in locomotor sensitization to the dopamine agonist quinpirole

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Abstract A pairing paradigm was employed to explore the contribution of associational mechanisms to the expression of sensitization to the dopamine agonist quinpirole. Rats received ten quinpirole injections in the test environment (Group Paired) or in the home cage (Group Unpaired), and saline in the alternate environment. A third group received saline injections in both environments (Group Acute). Subjects received quinpirole on the 11th injection as a test for locomotor sensitization, and saline on the next injection as a test for conditioned activity. The range of discriminative stimuli predicting a drug versus a non-drug injection was increased across three independent experiments in an effort to detect a possible associational effect. Regardless of the strength of discriminative stimuli, both Paired and Unpaired groups showed locomotor sensitization to 0.5 mg/kg quinpirole compared with the Acute group. However, the Paired group showed more locomotion than the Unpaired group in the last minutes of the sensitization test. With a lower sensitizing dose of quinpirole (0.1 mg/kg) used in one experiment, only the Paired group showed locomotor sensitization. For both doses, the Paired, but not the Unpaired groups showed conditioned locomotion. It is suggested that with moderate doses of quinpirole, expression of locomotor sensitization does not require drug-signalling cues though such signals may have a modulatory influence. With lower quinpirole doses, however, quinpirole sensitization is context-dependent.

Key words Hyperactivity · Rats · Reverse tolerance · Context-dependent sensitization · Context-independent sensitization · Conditioned locomotion · D_2/D_3 agonist

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Introduction

Repeated administration of many psychostimulant drugs leads to an increase or sensitization of the drug-induced behavioral response (Robinson and Becker 1986; Stewart and Badiani 1993). The phenomenon has received much experimental attention, sparked in part by the hypothesis that psychostimulant-induced sensitization and psychopathologies such as psychosis, mania, post-traumatic stress disorder, panic disorder, and addiction, result from similar mechanisms (Ellinwood 1968; Ellison 1979; Kokkinidis and Anisman 1980; Post and Contel 1981; Angrist 1983; Segal and Schuckit 1983; Robinson and Becker 1986; Antelman 1988; Post and Weiss 1988; Piazza et al. 1989; Robinson and Berridge 1993). The contribution of non-pharmacological factors, and of learning in particular to sensitization remains controversial, however.

At one extreme is the position that behavioral sensitization reflects entirely the contribution of a conditioned response. Support for this position has come from the use of paradigms which maximize the ability of environmental cues to signal drug injection. Typically, three groups of rats receive chronic injections of the drug and/or saline. One group receives the drug paired with the same environment as that later used for sensitization testing (test environment), and saline in the home cage (Group Paired). A second group receives the drug paired with the home cage and saline in the test environment (Group Unpaired). A third group receives saline in both environments (Control group). Following chronic treatment (considered to be the Training period), a test for the expression of sensitization is administered, in which all groups receive an injection of the drug in the test environment. To test for conditioned activity, all groups are challenged with saline. When such a paradigm was employed to examine sensitization to amphetamine (Tilson and Rech 1973), bromocriptine (Hoffman and Wise 1992), or cocaine (Post et al. 1981), the Paired group showed more locomotor activity during a test for sensitization than both the Unpaired and Control groups, while

the Unpaired and Control groups did not differ from each other. Furthermore, only the Paired group showed conditioned activity. These results suggest that conditioning of discriminative environmental stimuli entirely accounts for locomotor sensitization.

A more moderate position holds that learning merely modulates sensitization. This position is based on the evidence that by removing conditioned environmental cues or abolishing the conditioned locomotor response, the sensitized response is altered but still present (Mattingly and Gotsick 1989; Stewart and Vezina 1991; Szechtman et al. 1993; but see Ahmed et al. 1993).

The present study examines the contribution of learning to the expression of locomotor sensitization induced by the D_2/D_3 dopamine agonist quinpirole. Locomotor sensitization to quinpirole is of interest for at least three reasons. First, chronic treatment with quinpirole induces locomotor sensitization that is about six times the acute response (e.g., Einat and Szechtman 1993b). The magnitude of the quinpirole effect is larger than that obtained with amphetamine (e.g. Ellinwood et al. 1972), apomorphine (e.g. Druhan et al. 1993), cocaine (e.g. Badiani et al. 1995) or bromocriptine (e.g. Hoffman and Wise 1992). Second, the response to chronic quinpirole is usually characterized by a predominance of locomotor activity (Zhou et al. 1991; Szechtman et al. 1994b). In contrast, most psychostimulants induce additional behaviors including repetitious sniffing, licking, gnawing, biting or chewing. Thus, chronic treatment with quinpirole is conducive to relatively uncontaminated measurement of sensitization of a single response (locomotion). Finally, locomotor sensitization induced by quinpirole is influenced by non-pharmacological factors (Willner et al. 1992; Einat and Szechtman 1993a; Szechtman et al. 1993), and in that sense at least seems representative of the general phenomenon of drug-induced behavioral sensitization.

It is not known whether the locomotor sensitization induced by quinpirole is entirely dependent on conditioned environmental stimuli, as is the case for the expression of locomotor sensitization induced by another D_2 agonist, bromocriptine (Hoffman and Wise 1992). In one study in which this question was explicitly examined, the findings were ambiguous: a conditioned effect was found for quinpirole-induced rearing but not locomotion (Mazurski and Beninger 1991) or rotation (Silverman 1991). In the present study, we used the drug pairing paradigm described above in three independent experiments in an effort to find conditioned environmental control. Because the results of the first experiment were ambiguous in terms of demonstrating robust conditioned environmental control, we reasoned that by employing stronger discriminative stimuli this should promote environment-drug conditioning, and thus reveal conditioned environmental control over the expression of quinpirole-induced locomotor sensitization, should it exist.

The strength of discriminative stimuli was increased by virtue of providing more cues that signalled drug and non-drug injections. If locomotor sensitization depends on environmental learning, then the Paired group would demonstrate more locomotion than both the Unpaired and Acute groups, and no difference would be evident between the Unpaired and Acute groups. If environmental learning is not necessary for sensitization, then both the Paired and the Unpaired group would show more locomotion than the Acute group, and would not differ from each other. Finally, if learning is not necessary but can modulate sensitization, then the Paired group would show more locomotion than the Unpaired group, and this group in turn would locomote more than the Acute group.

Materials and methods

Subjects

One hundred and fourteen experimentally naive Long-Evans rats (Charles River, Canada) weighing 230–306 g at start of treatment were used. Rats were housed individually in polyethylene cages (35×30×16 cm) with beta-chip bedding (Northeastern Products Corp, Warrensburg, N.Y.), in a colony room (22°C) with a 12:12 h light cycle, and with free access to food and water. Rats were handled by the experimenter for 5 days (2 min each day) prior to the beginning of treatment. All treatments and testing were administered during the light hours. Subjects were allocated to activity-equivalent groups (n=9–10 per group) based on a 30-min pre-test in running wheels.

Apparatus

In experiments 1 and 2, the test environment was a Plexiglas activity chamber (40×40×35 cm) located in non-colony room. Six of such chambers were interfaced to a Digiscan 16 monitor and a computer that provided automated recording of locomotor distance (Omnitech Electronics, Columbus, Ohio). The floors of the test chambers were covered with a layer (approximately 1 cm deep) of clean beta-chip bedding.

In experiment 3, the test environment was a large open-field made of a mirrored glass table (160×160 and 60 cm high) placed at least 70 cm from the walls of a non-colony room. The open field was subdivided into 25 rectangular places (locales) used to define the location of the animal in the field. Four small Plexiglas/glass boxes (approximately 8×8×7.5 cm) were present at the same fixed locations of the open field throughout the study; the objects were placed there to enhance the opportunity for exploration. Behavior was videotaped continuously on a video-cassette recorder together with a computer-readable time code (Telcom Research, Burlington, Ontario, Canada). A computer, interfaced with the video recorder, was used to score behavior during playback of the video records, with a resolution of 1/30 s, providing measures of distance traveled as described previously (Eilam et al. 1991, 1992; Szechtman et al. 1994b).

In all experiments, the home cage environment was the rat's polyethylene cage situated in the animal colony room.

Drugs

Quinpirole hydrochloride (RBI, Natick, Mass.) was dissolved in physiological saline (0.5 mg/ml or 0.1 mg/ml, according to dose regimen) and injected subcutaneously under the nape of the neck. Equivalent volumes of saline were used for non-drug injections. The 0.5 mg/kg dose of quinpirole was selected because it is representative of the locomotor sensitization effects induced by doses of the drug from 0.25 to 2.5 mg/kg (Szechtman et al. 1994a), and

was previously used to demonstrate the influence of environment on quinpirole sensitization (Einat and Szechtman 1993b; Szechtman et al. 1993). The 0.1 mg/kg dose of quinpirole was chosen because it is at the low end of the acute dose-response curve for evoking locomotor excitation (Eilam and Szechtman 1989).

Design and procedure

Three separate experiments were conducted employing the same pairing paradigm. The Paired group received ten injections of quinpirole (every 2–4 days) in the test environment and saline injections in the home cage on alternate days. The Unpaired group received the same treatment except that quinpirole was administered in the home cage and saline in the test environment. The third group received saline in both environments during the training period (Group Acute). The particular number of injections and inter-dose interval were chosen because quinpirole sensitization was previously shown to reach a plateau after eight to ten injections, and was unaffected by interdrug spacing ranging from 2 to 8 days apart (Szechtman et al. 1994a,b). Injection 11 served as the test for sensitization, with all rats receiving quinpirole in the test environment. Injection 12 served as the test for conditioned locomotion, with all groups receiving saline in the test environment. An exception occurred in experiment 1 where the Paired and Unpaired groups received quinpirole instead of saline on injection 12, to assess the reliability of any sensitization effect found on injection 11.

The three experiments differed in the range of discriminative stimuli that were present to distinguish the drug and saline injections. In experiment 1, room cues and the slightly different size, shape and smell of the test environment served as discriminative stimuli because the same pre-injection ritual was followed before injections of quinpirole and saline. In particular, for injections in the test environment, rats were wheeled on a cart (in their home cages) from the colony room to the activity monitors room, injected with quinpirole or saline, and placed into the activity chambers. Similarly, for injections in the home cage, subjects were wheeled on a cart out of the colony room and back (for a distance equivalent to the one from the colony room to the activity monitors room) before injection. To reduce the possibility that time of day could become a discriminative cue, the daily time of injection was nonsystematically varied between 9 a.m. and 3 p.m. In experiment 2, the pre-injection ritual was a discriminative cue because for injections in the test environment the rats were taken through the same ritual as in experiment 1, whereas for injections in the home cage, they were not wheeled out of the colony room before home injections but were removed from the cage, injected, and returned into the home cage without ever leaving the colony room. Finally, in experiment 3, the discriminative cues included room cues, distinct environments (a large glass table versus polyethelene home cage with bedding), distinct pre-injection rituals (as in experiment 2), and distinctive time of injection (subjects were injected with quinpirole at one set time of the day and with saline at another set time). We refer to the discriminative cues in experiments 1–3 as "small environment", "small environment+handling", and "large environment+handling+time", respectively.

The procedure for all experiments was identical except for the following: a) during the training period, each session in the test apparatus lasted 90 min in experiment 1 and 60 min in experiments 2 and 3; b) rats were injected with quinpirole three times a week during the training period in experiment 1 and twice a week in experiments 2 and 3; and, c) the test for sensitization was 90 min long in experiments 1 and 2 and 60 min long in experiment 3. Finally, in all studies the dose of quinpirole was 0.5 mg/kg; in experiment 2, additional sets of Paired, Unpaired and Acute groups were treated and tested using a lower dose of quinpirole, 0.1 mg/kg. The variation across experiments in the duration of exposure to the test apparatus was considered of minor importance because 45-min exposures yielded equivalent sensitization as 2-h exposures to the test apparatus (Szechtman and Dai, unpublished observations); similarly, a previous study did not find that varying the interdose interval from 2 to 4 days influenced sensitization (Szechtman et al. 1994a); finally, it should be noted that these variations do not introduce a systematic bias across the three experiments.

Statistics

Locomotor distance served as the dependent variable. Statistical analyses were performed separately for each test in each experiment, using a Group by Time analysis of variance (ANOVA) with repeated measures on the Time factor. A significant Group, or Group by Time interaction, was followed by post hoc comparisons (Duncan multiple range test). The Group factor had three levels (Paired, Unpaired and Acute), and the Time factor consisted of 12 or 18 5-min bins, depending on length of test. Statistical significance was set at $P<0.05$.

Results

Test for expression of locomotor sensitization

As shown in Fig. 1, chronic treatment with the 0.5 mg/kg dose of quinpirole induced locomotor sensitization in both the Paired and Unpaired groups. Specifically, the Paired group locomoted more than the Acute group in every experiment. Similarly, with the 0.5 mg/kg dose of quinpirole, the Unpaired group demonstrated also more locomotion than the Acute rats. This difference was statistically significant in experiments 2 and 3, but was only

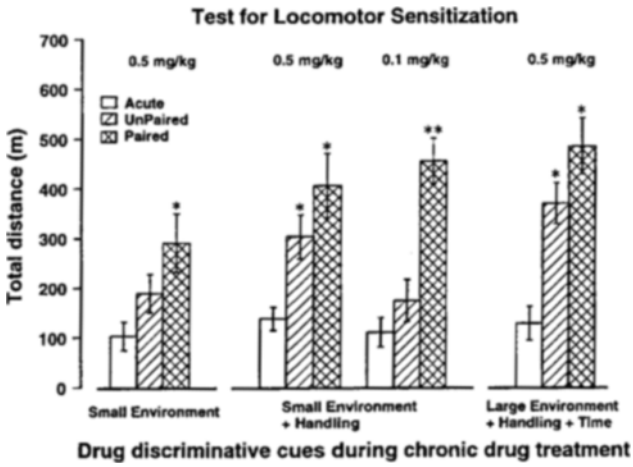

Fig. 1 Relationship between drug-predictive Pavlovian cues and the locomotor sensitization induced by quinpirole. All groups received an injection of quinpirole (0.5 or 0.1 mg/kg) on the test of sensitization shown in the figure. Paired rats (*cross-hatched bar*) were treated chronically with quinpirole in the indicated test environment and with saline in the home cage, the Unpaired group (*hatched bar*) received chronic quinpirole in the home cage and saline in the test environment, and the Acute group (*open bar*) were injected chronically with saline in the test environment and in the home cage. Bars represent the total locomotor distance in 90 min for the tests in the small environment and 60 min for the test in the large environment. Values are mean±SEM. See Materials and methods for description of discriminative cues in each experiment. * Indicates $P<0.05$ compared to the Acute group, and ** indicates $P<0.05$ compared to both the Acute and Unpaired groups, Duncan multiple range test

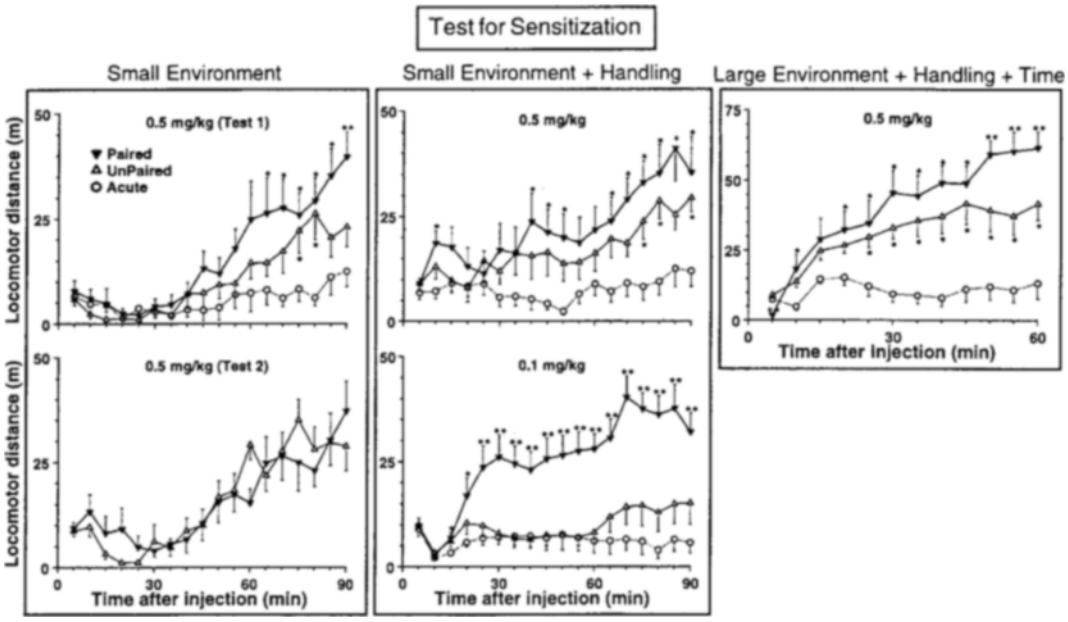

Fig. 2 Time course of locomotor activity on the test for sensitization in three experiments. Same data as in Fig. 1 except that each point represents 5 min of locomotor activity, and also a second sensitization test is shown for experiment 1 ("small environment"); values are mean±SEM. * Indicates $P<0.05$ compared to the Acute group, and ** indicates $P<0.05$ compared to both the Acute and Unpaired groups, Duncan multiple range test

a trend in experiment 1 ($P=0.09$). Furthermore, the Paired and Unpaired groups did not differ from each other in any of the experiments. However, chronic treatment with a lower dose of quinpirole (0.1 mg/kg) used in experiment 2, did induce sensitization in the Paired but not in the Unpaired group.

Figure 2 shows that a difference between the Paired and Unpaired groups may exist in the time course of locomotor activity because (a) in all experiments, a consistent and statistically significant effect of sensitization appeared earlier in the Paired than in the Unpaired group; and, (b) in two experiments (experiment 1 and 3) Paired rats locomoted significantly more than the Unpaired group in the last minutes of the test.

Finally, Fig. 2 shows that the non-significant trend for a difference between Paired and Unpaired rats disappeared upon repetition of the sensitization test in experiment 1. This may indicate that a single drug injection in the test environment is sufficient to eliminate context dependent differential sensitization.

Test for conditioned locomotion

Figure 3 shows the time course of locomotor activity to an injection of vehicle in the activity chambers (experiment 2) and in the large open field (experiment 3). As is evident, for rats pretreated in experiment 2 with 0.5 mg/kg quinpirole, an injection of saline induced an equivalent amount of locomotion in the three groups [for Group, $F(2,27)=1.27$, ns; for Group by Time, $F(22,287)=1.18$, ns], suggesting an absence of conditioned locomotion. In contrast, for animals pretreated chronically with 0.1 mg/kg quinpirole, the Paired group showed significantly more locomotion in the 1-h session than either the Acute or Unpaired groups [for Group, $F(2,26)=3.69$, $P=0.039$; for Group by Time, $F(22,286)=0.95$, ns], suggesting conditioned locomotion. Finally, for the test in the large open field, the main effect of Group did not reach statistical significance [$F(2,24)=2.98$, $P=0.07$] but the Group by Time interaction [$F(22,264)=4.3$ $P<0.001$] was significant. Post hoc tests showed that in the first 5 min of the session, Paired animals locomoted significantly less than the Unpaired and Acute animals. From 10 to 25 min after injection, Paired animals locomoted the most, significantly higher than the Acute group for all these 5-min intervals and significantly higher than the Unpaired rats at the 15-min time point. Thus, results indicate the presence of conditioned locomotion in the Paired group, resembling the biphasic effect of quinpirole injection: initial inhibition followed by locomotor excitation compared to saline treated animals (Eilam and Szechtman 1989; Szechtman et al. 1994a).

Because the Unpaired and Acute groups experienced quinpirole in the test environment on injection 11 (i.e., before the current probe for conditioned locomotion), the performance of Paired animals was compared to the saline behavior of Unpaired and Acute animals on injection 10. The results of this comparison confirmed the presence of conditioned locomotion in the Paired group pretreated with 0.1 mg/kg quinpirole [for Group, $F(2,26)=11.35$, $P=0.0003$] and in the Paired rats tested in the large environment [for Group by Time $F(22,64)=5.08$, $P<0.001$]. Moreover, compared to Unpaired and Acute groups on injection 10, Paired rats pretreated with 0.5 mg/kg quinpirole and challanged with saline in experiment 2 exhibited significantly more

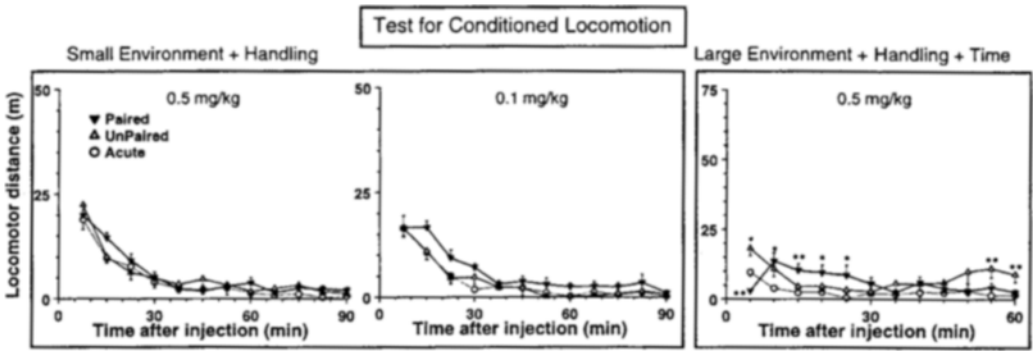

Fig. 3 Time course of locomotor distance on the test for conditioned activity in experiment 2 (small environment+handling) and experiment 3 (large environment+handling+time). Paired, Unpaired and Acute groups are as in Fig. 1; dose of quinpirole refers to the training dose of the drug. The main effect of Group was significant only for rats trained with 0.1 mg/kg quinpirole; the Group×Time interaction was significant in experiment 3. * Indicates $P<0.05$ compared to the Acute group, and ** indicates $P<0.05$ compared to the other groups, Duncan multiple range test

overall locomotion than the other two groups [for Group, $F(2,27)=10.15$, $P=0.001$], suggesting the presence of conditioned locomotion. Inspection of the means suggested that in experiments 2 and 3, the single experience of quinpirole in the test environment altered the Unpaired and Acute rats' subsequent response to saline.

Discussion

Regardless of whether chronic treatment with quinpirole (0.5 mg/kg) was paired or unpaired with the test environment, a challenge injection of quinpirole induced more locomotor activity than an acute injection of the drug. This result suggests that at this dose, locomotor sensitization to quinpirole does not depend on the presence of drug-signalling cues. Two observations strengthen this interpretation. First, it is unlikely that stimulus generalization contributed to sensitization because similar results were obtained in three experiments with varied discriminatory salience between the drug- and non-drug environments. Second, the Unpaired rats did not show conditioned locomotion in any experiment, but the Paired rats did, confirming that the pairing procedure was effective in producing conditioning. Therefore, consistent with previous findings (Szechtman et al. 1993), quinpirole sensitization to a relatively high (0.5 mg/kg) drug dose is context-independent.

With a relatively low chronic dose of quinpirole (0.1 mg/kg), locomotor sensitization was evident in Paired but not in the Unpaired rats. In addition, the Paired, but not the Unpaired rats showed conditioned locomotion. Thus, with a relatively low dose of quinpirole – a dose that acutely does not induce locomotor excitation (Eilam and Szechtman 1989) – locomotor sensitization is context-dependent.

Together, the two sets of findings suggest that locomotor sensitization to quinpirole reflects conditioning at relatively low doses but not at relatively high doses. However, even at relatively high doses, learning may have a modulatory role. First, in all experiments, locomotor sensitization was somewhat higher in the Paired than in the Unpaired rats, and this trend reached statistical significance in the last 15 min of the test in the open field. Second, time course data showed that in all experiments, significant locomotor excitation appeared sooner in the Paired rats compared with the Unpaired rats, suggesting a higher locomotor peak, an advancement in locomotor excitation, or both, in the presence of drug-predictive cues. The time course data also raise the possibility that with longer test duration a significant difference between Paired and Unpaired animals may emerge. Finally, the Paired but not the Unpaired rats showed conditioned locomotion with both low and high sensitizing doses. Thus, learning may contribute to locomotor sensitization induced by relatively high doses of quinpirole. However, this effect is probably relatively small compared to the non-associative one because the difference between Paired and Unpaired rats is marginal and is obliterated by a single drug exposure of the Unpaired rats to the test environment (Fig. 2), and because the magnitude of conditioned activity is several folds lower than sensitized locomotion (compare Figs 2 and 3).

The inverse relationship between quinpirole dose and contribution of associative learning to locomotor sensitization is reminiscent of a similar inverse relation between morphine tolerance and associative learning. As reviewed by Baker and Tiffany (1985), "the impact of drug-cue contigencies becomes smaller as [morphine] dose increases, relative to the tolerance that accrues when drug is delivered in the absence of predictive signals". In other words, with higher morphine doses, development of tolerance is largely nonassociational or independent of drug-environment contingencies. With lower doses, development of morphine tolerance is more likely to depend on environment-drug contingencies, and thus to involve an associative mechanism. Based on this and other properties of morphine tolerance, Baker and Tiffany proposed the theory that development of drug tolerance conforms to Wagner's model of habituation which has both nonassociative and associative attributes (Wagner 1978). In this view, both habituation and drug

tolerance involve a memory-like system that sets the amount of stimulus processing – relatively little processing if the stimulus is already represented in memory and extensive processing if it is not contained in memory. Thus, when stimulus processing diminishes, responding to the stimulus event declines. This constitutes habituation or, when a drug stimulus is represented in memory, tolerance. The drug stimulus is represented in memory by virtue of presentation of either the drug itself (self-generated priming) or stimuli previously paired with the drug (associatively generated priming), corresponding to context-independent and context-dependent tolerance, respectively.

Though consistent with the research literature on morphine tolerance, the habituation theory makes no provision for an increase in drug effects; consequently, it cannot explain behavioral sensitization. Baker and Tiffany (1985) suggested two possibilities out of this difficulty: 1) there are two simultaneous and opposite drug effects (i.e., a depressive and an excitatory drug effect) such that what appears as sensitization is actually tolerance to the drug depressive effect; 2) there are separate neural systems which subserve habituation and sensitization and an enhanced drug effect is produced by some drugs acting on the sensitization system. Below, we consider the relevance of these possibilities with reference to the locomotor sensitization induced by quinpirole.

The effect of acute quinpirole on locomotion is indeed biphasic, with low doses (< 0.1 mg/kg) reducing and higher drug doses increasing activity. Moreover, with the higher doses, the time course of the locomotor response is also biphasic: hypoactivity followed by hyperactivity (Eilam and Szechtman 1989). It is unlikely, however, that quinpirole sensitization reflects tolerance to the inhibitory effects of the drug, for two reasons. First, chronic treatment elevates the maximum level of performance to several fold of the acute drug response and advances the time of this maximum from late in the course of drug action to within minutes of drug injection (Szechtman et al 1994b). Such a profile is not accountable by the mere removal of an initial depressive effect because that would elevate the maximum response but would not result in the anticipation of the time of the maximum effect. Second, hypolocomotion does not tolerate to chronic treatment with an inhibitory dose of quinpirole (Szechtman et al. 1994a), and is still evident when rats sensitized with excitatory doses of quinpirole are challenged with a low dose of the drug (unpublished observations), suggesting that hypoactivity may be masked at the higher doses by the increase in excitatory drug effects. Thus, chronic treatment produces an increase in the excitatory effects of quinpirole, an increase which appears independent of any tolerance to drug depressive effects.

With regard to the suggestion that drug effects which sensitize involve the stimulation of a unique system "impervious to tolerance mechanisms" (Baker and Tiffany 1985), we consider this possible. Conceptually, such a system is implicit in the habituation model since the model posits that stimulus processing is extensive because of the "surprise" when a representation of the signal does not exist in memory. It follows that the memory/habituation system normally inhibits the "surprise" system. Dopamine-like sensitizing drugs, aside from having cue properties, may stimulate directly the "surprise" system, presumably because D_2/D_3 receptors are present there. If the "surprise" system constitutes, or is part of, an energizing/arousal system, then it is likely that repeated activation will raise the system's efficiency by increasing gain, decreasing setpoint, or both. However, sensitization to quinpirole does not grow unabated with repeated injections but reaches an asymptote, suggesting that "sensitization is a controlled process towards establishing a new level of equilibrium" (Szechtman et al. 1994b). Conceivably, the new level of equilibrium represents the balance between the tolerance mechanism of the habituation/memory system, and the elevated effects of the "surprise" system activated by the drug directly.

In summary, the contribution of learning to locomotor sensitization to quinpirole in rats is dose-dependent: with low sensitizing doses, the expression of sensitization is context-dependent; with moderate doses, expression of locomotor sensitization is context-independent though drug-signalling cues may have a modulatory influence, particularly on the time course of excitation. In this respect, sensitization is influenced by associational and nonassociational variables in a similar manner as is tolerance.

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