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ORIGINAL INVESTIGATION

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Locomotor sensitization to quinpirole: environment-modulated increase in efficacy and context-dependent increase in potency

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Abstract This study examines whether behavioural sensitization to the dopamine agonist, quinpirole, reflects an increase in the drug's potency and/or efficacy to induce locomotion, and how these parameters are influenced by environmental context. Three experiments were conducted in which animals received either chronic quinpirole (10×0.5 mg/kg, twice weekly) or saline injections in either the home cage environment, an alternate environment or the testing environment (activity monitors), followed by a dose-response test for the expression of sensitization in the activity monitors. Compared to the acute dose-response relationship, chronic quinpirole increased the maximum response. This increase in efficacy was significantly higher in animals treated with quinpirole in a non-home cage environment compared to those that received chronic treatment in the home cage. A leftward shift in the dose-effect function was observed only in animals with prior drug experience in the testing environment. Results indicate that locomotor sensitization to quinpirole reflects an environment-modulated increase in the drug's efficacy, and an environment-dependent increase in drug potency. Efficacy and potency may be subject to sensitization by non-associational and associational mechanisms, respectively.

Key words Locomotion · Dose-response · Context-dependent sensitization · Context-independent sensitization · Rats · Efficacy · Potency · D_2/D_3 agonist

Introduction

Certain responses to psychostimulant drugs increase when the drug is administered repeatedly. For instance, the locomotor responses to the indirect dopamine agonists, amphetamine and cocaine, and the direct dopamine agonists, apomorphine, quinpirole and bromocriptine, are higher in rats treated chronically with these drugs compared to animals receiving an acute drug injection (Segal and Schuckit 1983; Mattingly and Gotsick 1989; Hirabayshi et al. 1991; Hoffman and Wise 1992; Szechtman et al. 1994b). This phenomenon of enhanced responding is generally called "sensitization", although terms such as reverse tolerance, up-regulation, supersensitivity, behavioural augmentation, behavioural sensitization, and facilitation, have been applied as well (see Robinson and Becker 1986, for review). These shifts in terminology reflect, in part, attempts to identify a satisfactory perspective for a phenomenon that, at first glance, appears to lie outside the framework of homeostasis. Sensitization is a phenomenon that challenges "our understanding of the nature of adaptive changes in the nervous system" (Willner et al. 1993). This is because psychostimulant-induced sensitization has been implicated in contributing to the development of psychopathologies such as psychosis, mania, post-traumatic stress disorder, panic disorder, and addiction (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 putative relationship between sensitization and psychopathology has sparked a vigorous search for common mechanisms, but it now appears that sensitization probably represents a collection of complex changes (Wise and Leeb 1993; Szechtman et al. 1994b).

Sensitization is often contrasted with tolerance as representing, respectively, leftward and rightward shifts of the dose-response curve with respect to the acute dose-effect function (Stewart and Badiani 1993). A shift of the curve along the x-axis is generally monitored as a change in ED_{50}, a measure of the drug's *potency*. However, besides increasing the drug's potency to yield an augmented drug effect, chronic drug treatment could also increase the maximum response to the drug, that is, the drug's *efficacy*. Presumably, a change in potency or efficacy would reflect a different mechanism producing the enhanced drug response (e.g. Levine 1990).

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The first purpose of the present study was to determine which parameters of the relationship between quinpirole dose and locomotor responding are altered by chronic treatment with this D_2/D_3 dopamine agonist. Previous studies have shown that chronic treatment with quinpirole induces a large and robust locomotor sensitization (e.g. Einat and Szechtman 1993a; Szechtman et al. 1994a,b), and that the response to chronic quinpirole is usually characterized by a predominance of locomotor activity, uncontaminated by the influence of mouthing behaviour (Zhou et al. 1991; Szechtman et al. 1994b). Moreover, locomotor sensitization induced by quinpirole seems representative of the general phenomenon of drug-induced behavioural sensitization because, like the sensitization to other psychostimulants, it is influenced by non-pharmacological factors (Willner et al. 1992; Einat and Szechtman 1993b; Szechtman et al. 1993; Einat et al. 1996; Franklin and Tang 1996). One such factor is the environment in which the rat repeatedly experiences a drug (e.g. Tilson and Rech 1973; Post et al. 1981; Mattingly and Gotsick 1989; Stewart and Vezina 1991; Hoffman and Wise 1992; Szechtman et al. 1993; Einat et al. 1996). Consequently, the second purpose of the present study was to assess how the parameters of the quinpirole dose-locomotor response relationship are influenced by environmental history of chronic treatment in sensitized animals. Our results show that locomotor sensitization to quinpirole reflects an increase in both the drug's efficacy and potency, and that the change in efficacy is modulated by environmental variables whereas the change in potency is environment-dependent.

Materials and methods

Subjects

A total of 462 experimentally naive male Long-Evans rats (Charles River, Canada; weighing 150–200 g at the start of the experiment) were housed individually in polyethylene cages (35×30×16 cm) in a temperature controlled (22°C) colony room under a 12-h day-12-h night cycle. Food and water were available ad libitum. Rats were allowed to acclimatize to the colony room for 1 week following arrival and were handled 2 min daily for 5 days before the start of the experiment. All treatment sessions occurred during the light phase of the day-night cycle.

Apparatus

The *testing environment* consisted of a Plexiglas locomotor activity chamber (40×40×35 cm) located in a non-colony room. Six such testing chambers were interfaced to a Digiscan 16 monitor and an IBM PC computer that provided automated recording of locomotor distance (Omnitech Electronics, Columbus, Ohio, USA). The *home cage environment* was the rat's own housing cage described above. The *alternate cage environment* was an empty polyethylene cage with identical dimensions as the home cage. Alternate cages were placed on separate shelves in the colony room, away from the racks used to shelve housed rats.

Drugs

Quinpirole hydrochloride (Research Biochemicals, Natick, Mass., USA) was dissolved in normal saline and injected SC under the nape of the neck at a volume of 1.0 ml/kg. For injections one to ten, the dose of quinpirole administered was 0.5 mg/kg, and for injection 11 (the test injection), the dose of quinpirole varied from 0.005 to 5 mg/kg according to group. Saline injections were also at a volume of 1.0 ml/kg SC.

Design and procedure

The influence of chronic treatment with quinpirole on the dose-response profile of the locomotor response to quinpirole was assessed in three separate experiments. The three experiments utilized three distinct environments for chronic drug treatment: the rat's own home cage; a similar but clean empty cage (that is, containing no cage bedding, food or water); and a larger empty Plexiglas cage. The home cage was situated at its usual location in the colony room; the empty cage (also referred to as an alternate cage/environment) was located on a separate rack in the colony room; and the Plexiglas cage was in a separate testing room. The larger Plexiglas cage served also as the testing chamber in all experiments. Each experiment consisted of two phases. In the first phase, chronic treatment was administered in the particular environment to induce sensitization. In the second phase, various doses of quinpirole were administered in the testing chamber to determine the relationship between quinpirole dose and the amount of locomotion induced by the drug. The environments were selected based on findings from previous studies that different levels of sensitization are expressed in the activity cages following chronic quinpirole treatment in either the home cage, an alternate cage or the activity cage (see Einat and Szechtman 1993a,b; Einat et al. 1996).

To induce sensitization, chronic treatment in all experiments consisted of ten injections of quinpirole, administered twice weekly. This regimen was chosen because quinpirole sensitization was previously shown to reach a plateau after eight to ten injections, and was unaffected by interdose intervals ranging from 2 to 8 days (Szechtman et al. 1994a,b). Control rats received equivalent chronic treatment with saline. To determine the dose-response profile to quinpirole, groups of rats from each treatment received one of 13 quinpirole doses (0, 0.005, 0.01, 0.02, 0.04, 0.05, 0.06, 0.07, 0.08, 0.1, 0.2, 1.0, and 5.0 mg/kg). Assignment to treatment with chronic quinpirole or chronic saline was random, except that for the experiments involving chronic treatment in the home and alternate cages, groups had equivalent mean body weight, and for the experiment involving chronic treatment in the locomotor cage, they had equivalent mean locomotor performance on injections eight to ten.

The procedure to induce sensitization in each experiment was as follows. For the experiment in which chronic treatment was administered in the home cage, animals were removed from their home cage, weighed, injected, and replaced into the cage. The procedure for the alternate cage experiment was similar, except that animals were put into an empty cage for 90 min. For the experiment involving chronic treatment in the locomotor activity chamber, rats were weighed in the colony room, transported in their home cage to the experimental room, injected, and placed into the activity monitors for 90 min.

On the test day (injection 11), rats were weighed in the colony room, transported to the experimental room, injected, and placed in the locomotor activity chambers for 90 min. Following each session, activity cages were wiped clean with paper towels moistened with an ammonium fluid (Windex).

Data analysis

Locomotor distance served as the dependent variable. Statistical analyses were performed separately for each experiment, using a Treatment by Test Dose analysis of variance (ANOVA), followed by tests for simple effects as appropriate. The Treatment factor had two levels (chronic quinpirole versus chronic saline) and the Test Dose factor had eight or nine levels of quinpirole dose, depending on the experiment. A priori contrasts were used to statistically compare at each level of Treatment, the inhibitory response

(Eilam and Szechtman 1989) at the 0.04 mg/kg dose of quinpirole with the saline response. Across experiments comparison of the maximum response was evaluated by a one-way ANOVA, followed by post hoc comparisons (Duncan multiple range test); a similar procedure was used to compare the locomotor response to the 0.07 mg/kg dose of quinpirole across experiments. Statistical significance was set at $P<0.05$, two-tailed.

To describe the dose-effect function, the parameters providing the best fit for the following asymmetric sigmoid equation were estimated using a nonlinear curve-fitting algorithm (Fig. P Version 6.0, Fig. P Software Corporation, Durham, N.C., USA):

$$R = \frac{R_{max} \times D^n}{D^n + ED_{50}^n}$$

where R is the locomotor response at quinpirole dose D, and the estimated parameters are the maximum response at an infinite quinpirole dose (R_{max}), the quinpirole dose yielding the half-maximum response (ED_{50}) and a coefficient (n) representing sigmoidicity. In computing R, the lowest response was set to zero. The equation is a function describing linear dose versus effect relationship. Sufficient data points were available to fit the function only to the locomotor scores of rats treated chronically with quinpirole in the testing environment. Estimates of the maximum response and the ED_{50} for the other treatments were obtained directly from the data by identifying on the graph, respectively, the highest response and the dose which would yield 50% of the maximum response observed. ED_{50} and R_{max} are taken as estimates of drug potency and efficacy, respectively.

Results

Induction of sensitization by chronic treatment

As shown in Fig. 1, the experience of ten quinpirole injections (0.5 mg/kg every 3–4 days) increased the overall locomotor response to quinpirole compared to an acute injection of the drug. Moreover, this effect did not depend on a particular environmental history of chronic drug administration. Specifically, the main effect of treatment was significant regardless of whether animals received chronic injections in their home cage [$F(1,160)=6.212$, $P=0.014$; Fig. 1, top], an alternate cage similar in size to the home cage [$F(1,125)=35.6$, $P<0.001$; Fig. 1, middle], or in the same locomotor activity chamber [$F(1,125)=56.9$, $P<0.001$; Fig. 1, bottom] as used for the testing of sensitization on injection 11.

Dose-effect profile of sensitized locomotion

Inspection of Fig. 1 suggests that the expression of locomotor sensitization depended on the test dose of quinpirole, with higher but not lower test doses of the drug revealing a difference between the chronic and acute injections of quinpirole. Statistical analysis supported this impression for rats which received chronic treatment in the alternate cage [Treatment by Test Dose interaction, $F(7,125)=7.1$, $P<0.001$] and for those receiving chronic injections in the testing chamber [interaction effect, $F(8,125)=2.7$, $P=0.009$]. The interaction effect failed to reach statistical significance for the rats treated chronically in their home cage [$F(8,160)=1.3$, $P=0.238$], although a trend for group differences at the 0.2 and

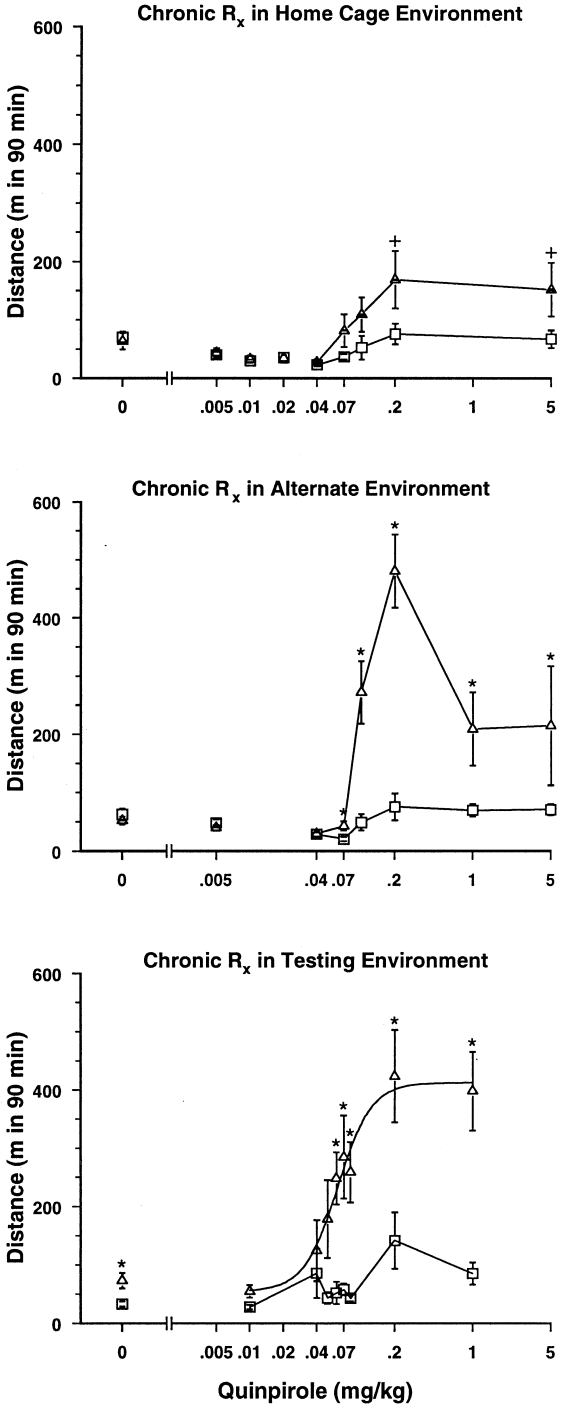

Fig. 1 Influence of treatment environment on the locomotor response to various doses of quinpirole. Rats received ten injections of saline (*squares*) or 0.5 mg/kg quinpirole (*triangles*) either in their home cages (*top panel*), alternate cages (*middle panel*) or activity monitors (*bottom panel*). On the test of sensitization shown in the figure, rats were administered one of the test doses of quinpirole and their locomotion measured for 90 min in the activity monitors. Values are means±SEM. * And + indicate $P<0.05$ and $P<0.10$ versus chronic saline group

5 mg/kg doses did exist ($P<0.05$, one-tailed probability, *t*-tests).

To characterize the sensitized dose-effect profile, an asymmetric sigmoid function (see Methods) was fitted to the data obtained from rats treated chronically with quinpirole in the testing environment (Fig. 1, bottom). In that group of rats, the range of test doses employed to determine the dose-response curve permitted a reliable estimate of the drug's potency (ED_{50}) and of its efficacy (maximum response, R_{max}). The estimate of ED_{50} was found to be 0.0617+0.004 mg/kg, and the estimate for the maximum response was 412.6+20.2 m. The maximum response was equivalent to the effect obtained at 0.2 mg/kg quinpirole, suggesting that this drug dose was sufficient to produce the near maximum effect. The available data did not permit a reliable estimate of the potency and efficacy of the acute drug effect. However, inspection of the dose-response graph (Fig. 1, bottom) suggests a rough estimate. Specifically, the ED_{50} for the acute response seems to be about 0.1 mg/kg, and the acute maximum response (as indexed by the locomotor response to 0.2 mg/kg quinpirole) to be about one-quarter of the sensitized maximum. It would appear, therefore, that chronic treatment in the testing environment increased both the potency and the efficacy of quinpirole to elicit locomotion.

Inspection of the dose-response profiles for rats treated chronically in the home and alternate cage environments (Fig. 1, top and middle) suggests no change in potency due to chronic drug treatment (it appears to be about 0.09–0.1 mg/kg in both the acute and sensitized groups). However, chronic treatment in these environments did appear to increase quinpirole's efficacy to elicit locomotion, as evidenced by a higher maximum response in the sensitized than the acutely treated animals (all maxima were at the 0.2 mg/kg dose). The comparison of the maximum responses was statistically significant for the alternate cage environment ($P<0.05$; Fig. 1, middle) and a similar trend existed for the home cage environment ($P<0.05$, one-tailed; Fig. 1, top).

Environmental influence on efficacy and potency

To compare more formally the impact of different treatment environments on the sensitized efficacy of quinpirole, Fig. 2 (left) plots the maximum response obtained in each experiment (from Fig. 1). Similarly, to compare impact of environment on potency, Fig. 2 (left) shows the locomotor response to the 0.07 mg/kg dose of quinpirole, the dose closest to the sensitized ED_{50} dose found in the testing cage environment (from Fig. 1). As is evident, treatment environment had relatively independent effects on the efficacy and potency of quinpirole: chronic quinpirole in the non-home cage environments increased the efficacy of quinpirole significantly more than the same treatment in the rat's home cage [$F(2,26)=7.3$, $P=0.003$], but chronic quinpirole in the testing environment increased the potency of quinpirole significantly more than the same treatment in the other two environments [$F(2,29)=9.5$, $P=0.001$].

Low dose inhibitory effects of quinpirole and conditioned locomotion

Finally, to assess changes in the locomotor inhibitory effects of quinpirole (Eilam and Szechtman 1989), Fig. 2 (right) displays for each treatment environment the response to 0.04 mg/kg quinpirole relative to the saline level. As indicated in the figure, a significant inhibition of locomotion was present in rats that received their chronic treatment in the home and alternate cage environments, but not in those that received their chronic treatment in the testing environment. It is also noteworthy that only in rats treated in the testing environment

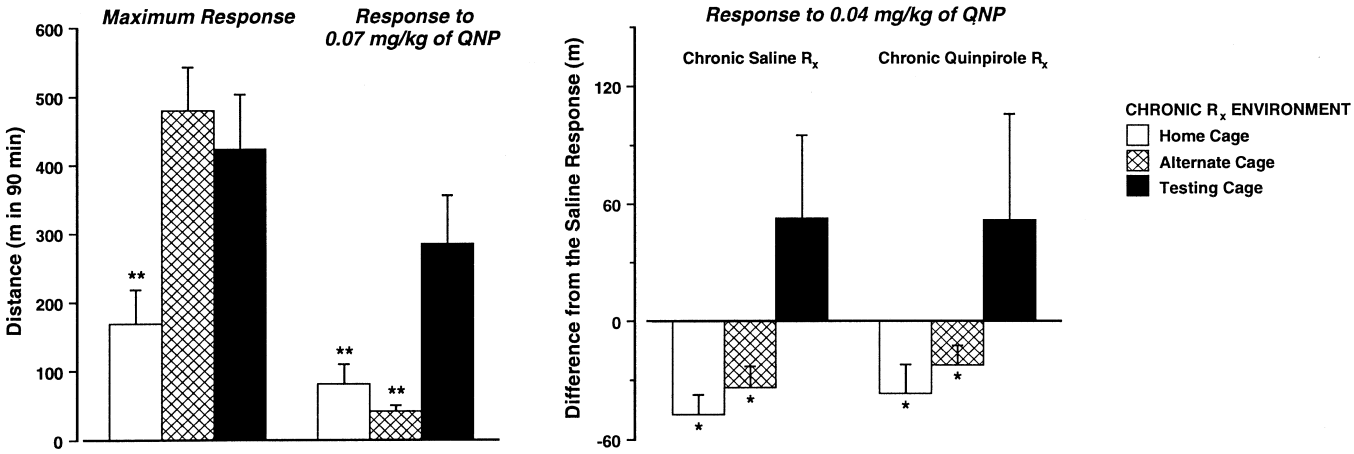

Fig. 2 Impact of treatment environment on the efficacy and potency of quinpirole to elicit locomotion in sensitized rats (*left*) and on the inhibitory effects induced by a low dose of quinpirole (*right*). Efficacy is indexed by the maximum response found in Fig. 1 and potency by the response to an injection of 0.07 mg/kg quinpirole. The inhibitory effect is shown as the difference between the locomotor response to the 0.04 mg/kg dose of quinpirole and to saline. Values are means±SEM. $^{**}P<0.05$ versus group without stars; $^{*}P<0.05$ for drug minus saline comparison

was there a significant difference between the saline controls and the sensitized group injected with saline (Fig. 1, bottom), suggesting that the drug-paired environment induced conditioned locomotion.

Discussion

The present findings show that chronic treatment with 0.5 mg/kg quinpirole elevated the maximum locomotor response to the drug compared to an acute drug injection. The magnitude of this elevation was greater when chronic treatment was administered outside the home cage compared to rats that received chronic injections in their home cage environment. Chronic treatment also produced a leftward shift in the dose-response curve of quinpirole, but only in rats that experienced all their drug injections in the testing environment. These findings suggest that locomotor sensitization to quinpirole reflects relatively independent changes in the drug's efficacy and potency to induce locomotion, and that these effects of chronic drug treatment are modulated by the environmental history of drug experience. Below, we consider possible mechanisms for the observed increase in the efficacy and potency of quinpirole, in the context of environmental modulation.

Increase in efficacy

An increase in the maximum response to excess concentrations of the drug is usually interpreted as an increase in the available number of receptors with which the drug can interact. Indeed, chronic administration of another psychostimulant, cocaine, may produce an upregulation of D_2 receptors in the nucleus accumbens (Peris et al. 1990; Zeigler et al. 1991), a brain region implicated in the locomotor-activating effects of quinpirole (Van Hartsveldt et al. 1992). However, chronic quinpirole treatment produces a decrease, rather than an increase, in brain D_2 receptor density as measured by a spiperone binding assay (Subramaniam et al. 1992). Therefore, the elevation of maximum response probably occurred through an increase in the efficiency of transductional mechanisms, either due to the release of the D_2 receptor from an inhibitory interaction with another receptor system, or due to induction of long-lasting transcriptional changes that amplify the effect of quinpirole binding to its receptor.

The first possibility is consistent with previous suggestions that quinpirole-induced locomotion is negatively controlled by D_1 receptor stimulation (Eilam et al. 1991, 1992) and that desensitization of D_1 receptors or uncoupling of D_1/D_2 interaction may be involved in behavioural sensitization and other effects (Stewart and Vezina 1989; Eilam and Szechtman 1990; Engber et al. 1993; Marshall et al. 1993; Szechtman et al. 1994b; LaHoste et al. 1996). It is also consistent with a D_1/D_2 interactional model proposed to account for the observation that in mice bearing unilateral striatonigral lesions, the maximum number of rotations induced by apomorphine is increased by sulpiride pretreatment, without a change in potency of apomorphine to induce rotations (Randall 1988; Mandel et al. 1993). The second possibility is consistent with findings that chronic administration of a number of psychostimulants induces immediate-early genes and second messengers (Graybiel et al. 1990; Dragunow et al. 1991; Terwilliger et al. 1991; Chen et al. 1995; Nestler 1995). The present study does not distinguish which of these possibilities accounts for the increase in maximum response.

Nevertheless, it is clear that the increase in efficacy is not just a consequence of pharmacological treatment because the magnitude of the increase varied with the treatment environment. We can suggest two possibilities for the observation that the maximum locomotor response was not as high in the home cage treated rats, compared to those that were treated outside the home cage.

One possibility is that the amount of locomotion during chronic treatment determines the maximum capacity to respond to quinpirole. A previous study found that repeated quinpirole administration to rats in the home cage produced less locomotion across injections than the same treatment in a non-home cage environment, and that on a subsequent test in the activity monitors the home cage treated rats showed less locomotor sensitization than the rats treated in the non-home cage environment (Einat and Szechtman 1993b). The differential display of locomotion was ascribed to the presence versus absence of cage bedding in the two treatment environments, favouring drug-induced mouthing and locomotion, respectively. A similar differential display in the home and non-home environments probably occurred in the present study, though direct confirmation is lacking. Locomotion during chronic treatment could increase efficacy of quinpirole by elevating the performance capacity of the locomotor system either because of locomotor practice itself (motor learning) (Einat and Szechtman 1993b; Szechtman et al. 1993); operant reinforcement of locomotion by quinpirole (Willner et al. 1993); or both. According to this view, sensitization of the maximum performance capacity is not general but is confined to a specific response system, and environment affects efficacy by differentially promoting the activation of this response system during chronic treatment.

Another possibility is that a substantial lack of familiarity with the test environment lowers the capacity for maximum performance. This possibility stems from the observation that on the test for sensitization, the home cage rats would have experienced a larger change from the chronic treatment days than the other rats: it was the first time that they were placed into a cage without bedding and it was the first time that they were taken outside their home environment to receive a drug injection. Conceivably, performance capacity to drugs is reduced in unfamiliar circumstances due to inhibitory or competing re-

actions to novelty (Bardo et al. 1990). According to this view, a lower sensitized efficacy is only an apparent effect, as the introduction of novelty precludes a true measure of the sensitized maximum.

Although further studies are necessary, we favour the first possibility as having the greater impact because there was no difference in the maximum response between the alternate and testing cage treated rats. If attenuation by novelty were a crucial factor, the alternate cage rats should have exhibited a lower maximum response compared to rats treated and tested in the testing environment.

Increase in potency

With regard to the observation that the potency of quinpirole was increased only in rats that received chronic treatment in the testing environment, we suggest that this indicates a role for drug-predictive cues in increasing sensitivity to stimulant drugs. For the rats treated and tested in the testing environment, the test day was no different from other injection days except for the dose of the drug administered. Thus, only in these rats could the environment reliably predict an injection of the drug on the test day, a property which it presumably acquired due to environment-drug pairing (Beninger and Hahn 1983; Hinson and Siegel 1983; Gold et al. 1988; Stewart and Ahmed et al. 1993; Badiani 1993; Einat et al. 1996) as evidenced by conditioned locomotion. Consequently, the finding that the increase in potency was confined to rats treated and tested in the same environment and thus was context-dependent, may be related to the presence of drug-signalling stimuli.

An increase in potency implies that chronic treatment increased the affinity of quinpirole for its receptor. Quinpirole binds not only to the D_2 receptor but also to an MAOI-displaceable site that may allosterically modulate D_2 receptor binding (Levant et al. 1996). Since chronic quinpirole does not appear to affect the affinity of the D_2 receptor as measured by spiperone binding (Subramanian et al. 1992), the increase in potency may reflect a change at the MAOI-displaceable quinpirole site. The possibility exists that activity at that site may be subject to control by drug-predictive cues.

Tolerance to depressive drug effects and sensitization

Because dopamine agonists have both depressive and excitatory effects, it has been postulated that sensitization reflects tolerance of the drug depressive effects (Hinson and Siegel 1983; Baker and Tiffany 1985), possibly due to tolerance or “desensitization” of presynaptic dopamine autoreceptors (Muller and Seeman 1979; Antelman and Chiodo 1983; Castro et al. 1985). The present data suggest that for the locomotor sensitization to quinpirole, such a mechanism is unlikely because low doses of quinpirole continued to induce locomotor inhibition even in sensitized rats.

Relevance of sensitization to psychopathology and summary

Although development of sensitization to drugs can be seen as a biologically negative process because of possible links to psychopathology, the present findings suggest another viewpoint. The more robust effect of chronic treatment, in the sense of being more independent of environmental context, was to increase the efficacy rather than the potency of quinpirole. Such an effect suggests that instead of an increase in sensitivity to drugs, sensitization reflects an increase in the performance capacity of the organism to respond to the drug (and presumably to similar drug-like stimuli). An increase in the capacity to perform motor output is generally a desired goal of exercise and practice. From this vantage point, sensitization to quinpirole can be seen as a positive process of enhancing motor capacity, as suggested previously (Szechtman et al. 1994b). It is not clear, however, whether the same applies to the sensitization induced by other psychostimulants, since the impact of environment on their efficacy and potency has not been determined.

In summary, sensitization to quinpirole reflects an increase in the efficacy and potency of quinpirole to induce locomotion. These effects are modulated, however, by the environmental history of chronic drug exposure. Thus, the increase in efficacy appears related to the opportunity to engage in locomotion during chronic treatment and/or may require situational familiarity for full expression. The increase in potency appears to be dependent, instead, on environment stimuli serving as reliable drug-predictive cues. Therefore, efficacy and potency may be subject to sensitization by non-associational and associational mechanisms, respectively.

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