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A comparison of the behavioral effects of minaprine, amphetamine and stress

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Abstract Different types of clinically effective antidepressants prevent the behavioral effects of experimental stress, and some of these treatments affect mesolimbic dopamine (DA) functioning. Animal studies have demonstrated that repeated psychostimulant administration and repeated or chronic stressful experiences also affect mesolimbic DA functioning. These results could suggest homologies among stress, psychostimulants and antidepressants. The present experiments show that either repeated stress (120 min restraint daily for 10 consecutive days) or subchronic treatment with the antidepressant minaprine (5 mg/kg daily for 10 consecutive days) significantly reduced the inhibitory effect of 120 min of restraint on climbing, a behavioral response dependent on mesolimbic DA functioning. However, the antidepressant did not induce the altered sensitivity of presynaptic DA receptors promoted by repeated stress. Chronic stressful experience (13 days of food restriction) and repeated amphetamine (2.5 mg/kg daily for 10 consecutive days) were as effective as subchronic minaprine in reducing immobility in the Porsolt's swimming test. However, whilst both stress and amphetamine enhanced struggling, minaprine promoted swimming. Finally, chronically stressed mice and mice pretreated with amphetamine showed enhanced sensitivity to amphetamine-induced locomotion, whilst this effect was absent in animals pretreated with the antidepressant. These results indicate that although chronic and repeated stress as well as amphetamine have some antidepressant-like behavioral effects, their mode of action could be different from that of clinically active substances.

Key words Antidepressants · Behavioral sensitization · Dopamine · Mesolimbic system · Swimming test · Apomorphine

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Introduction

The contribution of stress to the induction or exacerbation of depression has been increasingly emphasised in recent years (see Bidzinska 1984; Anisman and Zacharko 1990; Willner 1991 for review). Moreover, animal studies have revealed that stressors induce behavioral, neurochemical and hormonal alterations which are reminiscent of those observed in depressed patients (see Bidzinska 1984; Corwell et al. 1985; Anisman and Zacharko 1990; Willner 1991 for review). Consequently, several animal models of clinical depression which focus on the behavioral effects of stressors have been developed. Most of these models share a fundamental characteristic: the behavioral effects under study are observable in animals exposed to unavoidable and uncontrollable stressors but not in those exposed to aversive events of identical intensity and duration that can be either controlled or escaped (see Weiss et al. 1981; Anisman and Zacharko 1990; Zacharko and Anisman 1991 for review).

It has been demonstrated recently that unavoidable and uncontrollable stressful experiences induce profound inhibition of dopamine (DA) release in the nucleus accumbens (Puglisi-Allegra et al. 1991; Rossetti et al. 1993; Cabib and Puglisi-Allegra 1994), thus suggesting that at least part of the behavioral alterations observed following experimental stress depend on inhibition of mesolimbic DA release. The involvement of disturbed mesolimbic DA transmission in the behavioral alterations promoted by stressful experiences would be in line with evidence from preclinical and

clinical investigations, which suggest altered mesolimbic DA functioning in the pathophysiology of depression (see Willner 1983; Swerdlow and Koob 1987; Zacharko and Anisman 1991 for review).

Different types of clinically effective antidepressants prevent the behavioral effects of acute stress (see Borsini and Meli 1988; Anisman and Zacharko 1990 for review) and some of these treatments may affect mesolimbic DA functioning (Plaznik and Kostowsky 1987; Muscat et al. 1990; Delini-Stula et al. 1988; Serra et al. 1990). Antidepressants have been suggested to promote subsensitivity of inhibitory presynaptic DA receptors (Carlsson 1975; Serra et al. 1979; Chiodo and Antelman 1980; Muscat et al. 1988), and might thus reduce the inhibitory effects of stressful experiences on mesolimbic DA functioning.

Indirect support of a relationship between hyposensitivity of presynaptic DA receptors and reduction of the behavioral impairment induced by stress comes from results obtained following repeated exposures to stressors. Indeed repeated restraint experiences lead to reduction of the initial impairing effects of this stressor on climbing (Puglisi-Allegra et al. 1990), a behavioral response mediated by the mesolimbic DA system (Costall et al. 1980, 1981), as well as to hyposensitivity of DA autoreceptors in this system (Cabib and Puglisi-Allegra 1991).

The aim of the first part of this paper was to test whether subchronic treatment with the antidepressant minaprine (Biziere et al. 1982, 1985; Montgomery et al. 1991; Wheatly 1992), can prevent the inhibitory effects of a single restraint experience on climbing behavior, and also induces hyporesponsivity of presynaptic DA receptors to the direct agonist apomorphine.

Another way in which antidepressants could prevent the behavioral impairing effects of stressful experiences is by promoting DA release. Indeed, enhanced DA release in the ventral striatum in response to minaprine has been observed following subchronic treatment with the antidepressant that reduces immobility in the Porsolt test (forced swimming test) (Imperato et al. 1994).

Several lines of evidence suggest that enhanced mesolimbic DA release in response to pharmacological and environmental stimuli represents the neurobiological substratum of behavioral sensitization, a phenomenon induced by repeated psychostimulant administration as well as by repeated or chronic stressful experiences (see Robinson 1988; Kalivas and Stewart 1991; Robinson and Berridge 1993 for review). At the behavioral level, this phenomenon is revealed by an enhanced response to psychostimulant challenge. For instance, the behavioral response to amphetamine may be enhanced following chronic treatment with antidepressants (Willner and Montgomery 1981; Martin-Iverson et al. 1983; Maj and Wedzony 1985). It is thus possible that antidepressants promote central alterations similar to those induced by psychostimulants and stress.

The second set of experiments presented in this paper will evaluate this possibility. To do so, we assessed whether two treatments, chronic stress and repeated amphetamine, known to produce behavioral sensitization, share the behavioral effects of the antidepressant minaprine in the Porsolt's test. Moreover, we investigated whether the antidepressant promotes behavioral sensitization to amphetamine challenge.

Materials and methods

Animals and housing

Male mice of the outbred NMRI strain (Plaisant, Rome, Italy) were used to test the effects of single or repeated restraint and acute or subchronic minaprine on climbing behavior.

Male mice of the inbred DBA/2 strain (IFFA CREDO, Monticello B. za, Como, Italy) were used to test the effects of chronic stress, amphetamine and minaprine on behavior in the Porsolt's test and on amphetamine-induced locomotion. This strain of mice was chosen for these experiments because it is highly susceptible to behavioral sensitization (Robinson 1988; Badiani et al. 1992).

All mice were purchased at 6 weeks of age. Upon their arrival, they were housed in groups of five or six in standard breeding cage ($27 \times 21 \times 13.5$ cm) with food and water ad lib on a 12/12-h dark/light cycle (light on between 7.00 a.m. and 7.00 p.m.). Experiments started 2 weeks after arrival.

Tests were always conducted in the second half of the light period in naive subjects.

Drugs

Minaprine (Sanofi Winthrop) was dissolved in saline (0.9% NaCl) and injected subcutaneously (SC) in a volume of 10 ml/kg.

Apomorphine hydrochloride (Sigma) was dissolved in distilled water and injected subcutaneously (SC) in a volume of 10 ml/kg.

d-Amphetamine sulphate was dissolved in saline (0.9% NaCl) and injected intraperitoneally (IP) in a volume of 10 ml/kg.

Restraint and minaprine pretreatments

Male NMRI mice were randomly assigned to three different pretreatments: repeated restraint, repeated minaprine, repeated saline; or unhandled until the day of testing. Mice assigned to repeated stress (Rep. Restraint) were restrained daily for 120 min in a snug-fit apparatus, in a room separate from the colony room, for 10 consecutive days (Puglisi-Allegra et al. 1990; Cabib and Puglisi-Allegra 1991). Mice assigned to repeated minaprine (Minaprine) received one daily injection of minaprine (5 mg/kg, SC) for 10 consecutive days, whereas saline-pretreated mice (Saline) received one daily injection of saline (10 ml/kg, SC) for 10 consecutive days. Mice not assigned to any pretreatment (Unhandled) were left undisturbed until the day of testing.

All animals were tested for climbing behavior 24 h after the end of the different pretreatments.

Climbing test

Climbing behavior was scored as previously described (Cabib and Puglisi-Allegra 1991). Each mouse was placed in a cylindrical cage with walls made of vertical steel bars. Behavior was scored as follows: 0 = four paws on the bottom of the cage; 1 = two paws

holding the bars; 2 = four paws holding the bars. Scores were evaluated by an experienced observer unaware of which treatment the animal had received. Behavior was scored every 2 min starting 5 min after introduction in the test cage over a 60-min test session. All tests were carried out in sound-attenuated cubicles where a 30-W lamp was the only source of illumination and temperature was maintained constant.

One group (n = 10–12) from each pretreatment and one unhandled group were tested immediately following 120 min of restraint (STRESS). Three matched groups were used as controls (CONTROL).

Six groups (n = 10–12) of unhandled mice were tested for climbing behavior following either a single minaprine injection (0, 5, 10 mg/kg, SC) (CONTROL) or minaprine plus 120 min of restraint (STRESS).

Three groups (n = 10–12) of mice pretreated with minaprine (Minaprine) and three groups of mice pretreated with saline (Saline) were tested for climbing behavior following different doses of apomorphine (0, 0.25, 2 mg/kg, SC).

Chronic stress, amphetamine, and minaprine pretreatments

Mice of the DBA/2 strain were assigned to four different conditions: chronic stress, repeated amphetamine, repeated minaprine, repeated saline.

Chronic stress (Stress) consisted of singly housing the mice with water ad lib, but restricted access to food. Food was delivered once daily (1.00 p.m.) in a quantity adjusted to induce a 25% weight loss within the first 5 days and to maintain the animals at 75% of the original weight for the following 8 days (Table 1). On day 13, mice were allowed free access to food and tested 24 h thereafter. The 24 h of free access to food was offered to let the mice recover from the physically debilitating effects of weight loss.

All other groups were left in groups of six in standard breeding cage.

Mice pretreated with amphetamine (Amph) received one daily injection (2.5 mg/kg IP) of the psychostimulant for 10 consecutive days, then allowed 7 days of withdrawal and tested on day 8. The drug-free period was chosen, since it is required for behavioral sensitization induced by psychostimulants to be expressed (Robinson 1988; Badiani et al. 1992).

Mice pretreated with minaprine (Mina) received one daily injection (5 mg/kg, SC) for 10 consecutive days and tested 24 h after the last injection. Saline-pretreated mice (Sal) received one daily injection of saline (10 ml/kg, SC) for 10 consecutive days.

Porsolt test

One group (n = 6) of mice from each of the four pretreatments was subjected to the Porsolt forced-swimming test. Testing was performed in a glass cylinder (height 40 cm, diameter 18 cm) containing 10 cm of water at 25° C. The cylinder was placed inside a sound-attenuated cubicle where a 60-W lamp was the only source of illumination. Mice were initially exposed to the apparatus for 10 min (pretest) then placed in a 30–32° C drying room for 30 min. Twenty-four hours later, the animals were again exposed to the apparatus (test session) for 5 min.

Table 1 Weight (mean g±SE) variations observed in food-restricted (stressed) or control mice

	Day 0	5	13	14 (24 h food)
Controls	23.4 ± 0.5	24.1 ± 0.3	24.7 ± 0.2	25.0 ± 0.3
Stressed	23.4 ± 0.4	18.0 ± 0.5	17.8 ± 0.4	22.5 ± 0.5

The test session was videotaped and an observer unaware of the treatment each animal received, subsequently recorded different behavioral items with a keyboard system connected to an Apple computer. The behavioral items recorded were: struggling (attempts at climbing the glass walls), swimming, paddling (quite movements of the posterior paws), immobility (absence of movements).

One group of chronically stressed (n = 6) and one group of control (repeated saline) (n = 5) mice were examined for their behavioral responses in the forced-swimming test during the pretest session.

Amphetamine-induced locomotion

One group (n = 6) of mice from each of the four pretreatments was tested for sensitization to the locomotor effects of amphetamine. Locomotor activity was measured by an automated apparatus consisting of eight toggle-floor boxes (Badiani et al. 1992), each divided into 20 × 10 cm compartments. For each mouse, the number of crossings from one compartment to the other was recorded by means of a micro switch connected to the tilting floor of the box. The apparatus was placed inside a sound attenuated cubicle where a 30-W lamp was the only source of illumination.

Mice were allowed 1 h habituation to the testing cages, then removed and left undisturbed in their home cages for the following hour. Testing sessions started immediately after injection of a challenge dose (1 mg/kg, IP) of amphetamine and lasted 60 min.

Statistics

Two-way ANOVAs for independent measures were conducted for data obtained following repeated restraint, repeated minaprine and acute minaprine (Pretreatment: two levels = Rep. Restraint, Unhandled or Minaprine, Saline or three levels: Minaprine 0, 5, 10 mg/kg; Treatment: two levels = STRESS, CONTROL). Whenever a significant interaction was attained, post-hoc comparisons were performed using Duncan's test.

The effects of repeated minaprine on apomorphine-induced climbing were evaluated by a two-way ANOVA for independent measures (Pretreatment: two levels = Minaprine, Saline; Treatment: three levels = 0, 0.25, 2 mg/kg Apomorphine).

Data collected from the Porsolt's test were analysed by four one-way ANOVAs for independent measures (four levels: Sal, Stress, Amph and Mina); one for each behavioral item. Post-hoc comparisons were performed by Duncan's test.

Two-way ANOVAs with repeated measure (pretreatment as between factor: 2 levels = Control, Stress; time as within factor: two levels = 0–5; 6–10 min) was run to analyse immobility in mice during pretest exposure.

Locomotor effects of the challenge dose of amphetamine were analysed by one-way ANOVA for independent measures (four levels: Sal, Stress, Amph and Mina). Post-hoc comparisons were performed by Duncan's test.

Results and discussion

Effects of minaprine and restraint on climbing behavior

The effects of repeated restraint experiences on climbing behavior are reported in Fig. 1A. ANOVA revealed a significant interaction between single and repeated restraint [$F(1, 22) = 4.42$; $P < 0.05$]. Post hoc individual between-groups comparisons indicated that a single

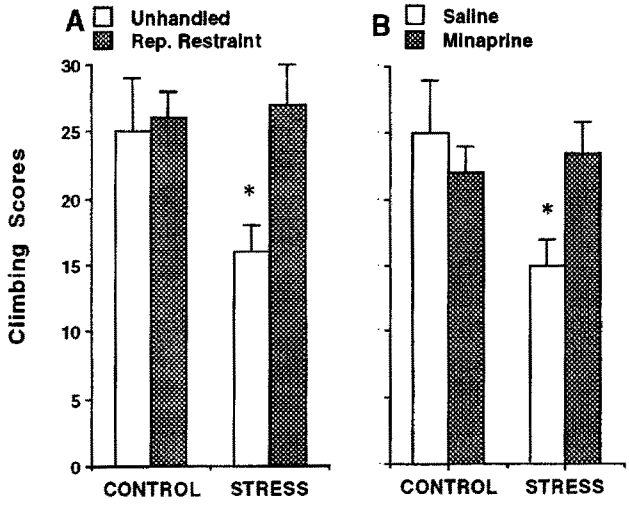

Fig. 1 Effects of repeated stress experiences (*Rep. Restraint*) or no handling (*Unhandled*) (**A**); and repeated minaprine (*Minaprine*) or repeated saline (*Saline*) (**B**) on climbing behavior exhibited by mice exposed to 120 min of restraint (*STRESS*) before test or control mice (*CONTROL*). Data are expressed as mean (± SE) climbing scores. *Significantly ($P < 0.05$) different from all other groups

restraint experience significantly reduced climbing behavior and that this effect was lost following ten daily experiences with the stressor. The effects of repeated minaprine on climbing behavior are reported in Fig. 1B. ANOVA revealed a significant interaction between minaprine pretreatment and single restraint [$F(1, 42) = 4.14$; $P < 0.05$]. Post hoc individual between-groups comparisons revealed that a subchronic treatment with 5 mg/kg of the antidepressant was devoid of effects per se, but significantly reduced climbing inhibition induced by restraint.

A single injection of minaprine (5 or 10 mg/kg) did not affect inhibition of climbing response induced by 120 min of restraint; ANOVA revealed only a significant Stress main effect [$F(1, 54) = 15.41$; $P < 0.0005$], although a reduction of climbing was observable at the highest dose of minaprine in control animals (Fig. 2).

These results, confirming previous ones obtained in a different strain of mice (Puglisi-Allegra et al. 1990), indicate that a single exposure to stress has inhibitory effects on behavior and that this effect is lost upon repeated experience with the stressor. Moreover, it appeared that the inhibitory effect of stress on behavior was absent in mice pretreated with subchronic minaprine; a finding consistent with previously reported data concerning the protective effects of antidepressants against behavioral effects of stress (see Anisman and Zacharko 1990 for review).

Effects of subchronic minaprine on apomorphine-induced climbing

Subchronic minaprine did not modify sensitivity to the behavioral effects of either a low or a high dose of apomorphine [ANOVA revealed only a significant effect of

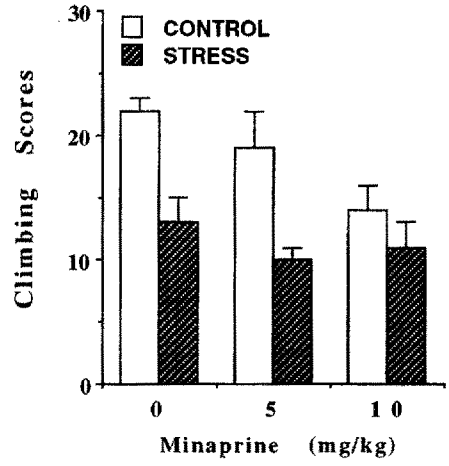

Fig. 2 Effects of pretreatment with a single injection of different doses of minaprine on climbing behavior of control mice (*CONTROL*) or mice exposed to 120 min of restraint (*STRESS*) before test. Data are expressed as mean (± SE) climbing scores

apomorphine challenge: $F(2, 63) = 57.43$; $P < 0.0001$]. The absence of significant interaction between factors did not allow individual between-groups comparison. However, comparisons among overall means (REP SAL + REP MIN) revealed a significant inhibitory effect of the low dose of apomorphine and a significant stimulatory effect of the high dose on behavior on climbing (Fig. 3).

These dose-dependent effects of the DA agonist on climbing have been previously described and are thought to depend on preferential activation of the inhibitory autoreceptors and stimulatory postsynaptic receptors by low and high doses of apomorphine respectively (Martres et al. 1977; Marcais et al. 1978; Cabib and Puglisi-Allegra 1991 for review). Repeated stressful experiences have been shown to reduce the

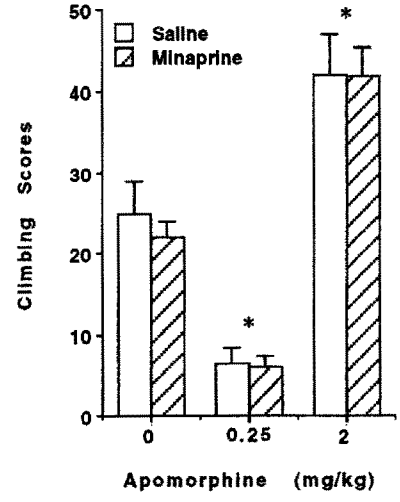

Fig. 3 Effects of a repeated minaprine (*Minaprine*) or repeated saline (*Saline*) on climbing behavior in response to different doses of apomorphine. Data are expressed as mean (± SE) climbing scores. *Significantly ($P < 0.05$) different from vehicle (O) (comparison among overall means)

inhibitory effects of low doses of apomorphine on climbing (Cabib and Puglisi-Allegra 1991) due to hyposensitivity of central DA autoreceptors (Antelman and Chiodo 1983; Muscat et al. 1988; Cabib and Puglisi-Allegra 1991). Consequently, the absence of a similar effect in mice subchronically treated with minaprine suggests that the mode of action of this antidepressant does not involve altered sensitivity of presynaptic DA receptors.

The absence of changes in DA autoreceptors sensitivity would also explain the lack of sensitization to the stimulatory effects of the high, postsynaptic dose of apomorphine. Indeed, this result appears contrary to previously reported results (Maj et al. 1984) and cannot be explained by ceiling effects, since further dose-dependent increase of climbing is promoted by higher doses of apomorphine (Marcais et al. 1978). It should be noted that postsynaptic effects of apomorphine are dependent on coactivation of DA receptors of the D_1 and D_2 subtypes (Clark and White 1987). Antidepressants do not affect sensitivity of postsynaptic DA receptors of the D_2 type and reduce sensitivity of the D_1 type (Martin-Iverson et al. 1983; Maj and Wedzony 1985; Klimek and Nielsen 1987; Serra et al. 1990; Papp et al. 1994). Consequently, whenever observable, antidepressant-induced sensitization to apomorphine challenge most probably depends on reduced sensitivity of the inhibitory DA autoreceptors (Martres et al. 1977).

Effects of stress, amphetamine and minaprine on behavioral responses in the Porsolt test

Data on the behavioral responses in the Porsolt's test are reported in Fig. 4. ANOVA revealed significant differences among pretreatments for immobility [$F(3, 24) = 3.64$; $P < 0.03$]; for struggling [$F(3, 24) = 18.38$; $P < 0.001$] and for swimming [$F(3, 24) = 5.48$; $P < 0.01$]. Post hoc comparisons revealed a significant reduction of immobility accompanied by a significant increase of struggling in stressed and amphetamine pretreated mice and a reduction of immobility accompanied by a significant increase of swimming in mice pretreated with minaprine.

Results obtained in control and chronically stressed mice during pretest exposure to forced swimming are reported in Table 2. ANOVA revealed only a significant increase of immobility over the test period [$F(1, 10) = 23.06$; $P < 0.001$].

Previous studies have demonstrated both reduced and enhanced immobility in the Porsolt test after repeated or chronic exposure to stressors (Platt and Stone 1982; Prince and Anisman 1984; Hilakivi et al. 1989). These discrepancies could depend on the type of stressor used (Armario et al. 1991). Moreover, methodological differences in the experimental procedure used for the forced swimming test may be fundamental in determining the varied outcomes. Indeed, in the present experiments, chronically stressed mice naive to the test condition (pretest) showed a non-significant enhancement of immobility in the Porsolt

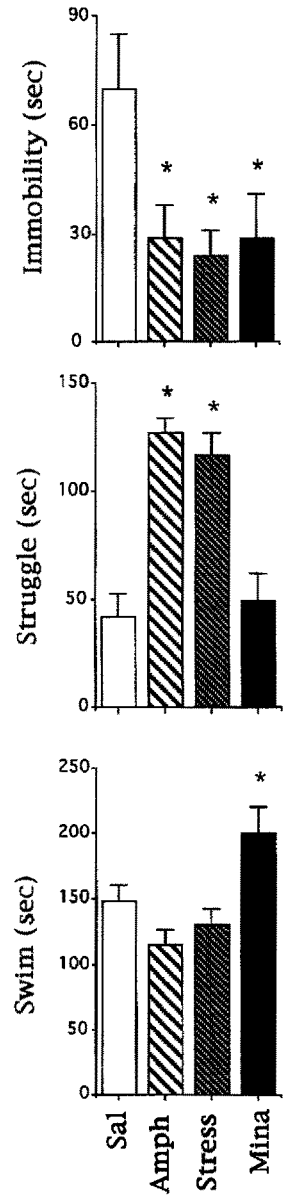

Fig. 4 Effects of repeated saline (*Sal*), repeated amphetamine (*Amph*), chronic stress (*Stress*), or repeated minaprine (*Mina*) on behavioral responses during forced swimming test. Data are expressed as mean seconds (± SE). *Significantly ($P < 0.01$) different from SAL

Table 2 Time spent immobile (mean s ± SE) by control and food-restricted (stressed) mice during pre-exposure to forced swimming test

	min 0–5	6–10
Controls	13.8 ± 3.7	32.6 ± 6.4
Stressed	21.8 ± 5.2	46.6 ± 9.4

Note: see text for statistical results

test. By contrast, a reduction of immobility was evident in chronically stressed mice 24 h after the pretest experience. These results are in line with the observation that different results can be obtained in the swimming test depending on the use of a pretest (Borsini and Meli 1988). Moreover, they extend this observation to experimental conditions in which animals do not receive any treatment immediately before pretest or test.

The anti-immobility effect of minaprine confirms previous results obtained in rats (Imperato et al. 1994) and in mice using a different experimental paradigm (Biziere et al. 1982, 1985). As for the anti-immobility effect of repeated amphetamine, this cannot be ascribed to an agonistic action on a DA system (Borsini and Meli 1988), since the Porsolt test was run after 7 days of withdrawal from the psychostimulant.

The behavioral responses of minaprine-pretreated mice in the Porsolt test differed from that of amphetamine-pretreated or stressed mice. Indeed, whilst both amphetamine and stress enhanced struggling, the antidepressant increased swimming. The difference in the active behaviors promoted by the different treatments indicate that their anti-immobility effect did not depend on forgetting the pretest experience. In this regard, it should be also noted that subchronic minaprine does not impair learning of a single-trial passive avoidance task (Puglisi-Allegra et al. 1994).

Finally, the present results indicate a similar anti-immobility action of stress, minaprine and amphetamine in the Porsolt test. However, they also suggest that the behavioral effects promoted by the three pretreatments in this test are not identical.

Effects of stress, amphetamine and minaprine on amphetamine-induced locomotion

Significant differences among pretreatments were found for locomotor responses induced by amphetamine challenge [$F(3, 24) = 8.13$; $P < 0.001$]. Post hoc comparisons revealed a significant increase of amphetamine-induced locomotion in chronically stressed and amphetamine pretreated mice in comparison with mice pretreated with saline (Fig. 5). These results are consistent with other reports indicating that pretreatments with psychostimulants or stress promote behavioral sensitization to subsequent psychostimulants challenge (see Robinson 1988; Kalivas and Stewart 1991; Badiani et al. 1992 for review).

Instead, no sign of behavioral sensitization was observed in mice pretreated with minaprine. It could be argued that the 24 h of withdrawal was insufficient to reveal this effect, since behavioral sensitization induced by repeated psychostimulants increases as a function of the time interval elapsed from the last injection (Robinson 1988). However, the necessity of fairly prolonged periods of withdrawal to reveal behavioral sensitization has been demonstrated only for psychostimulants. Indeed, repeated or chronic stress (Badiani et al. 1992; Deroche et al. 1993) and, most notably, tricyclic antidepressants (Willner and Montgomery 1981; Maj and Wedzony 1985) have been shown to promote enhanced behavioral response to amphetamine challenge regardless of the time interval elapsed from treatment interruption. Moreover, lack of sensitization to the locomotor effects of amphetamine has been described for other antidepressants such as nomifensine, zimeldine, and fluoxetine (Martin-Iverson et al. 1983). Thus, the present results indicate that minaprine is devoid of behavioral sensitizing effects to psychostimulants.

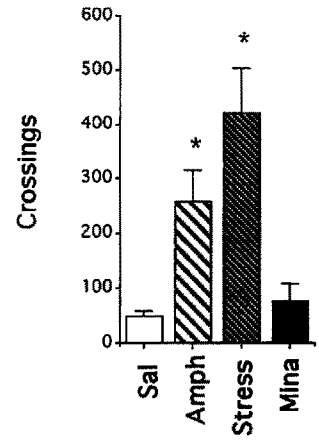

Fig. 5 Effects of repeated saline (*Sal*), repeated amphetamine (*Amph*), chronic stress (*Stress*), or repeated minaprine (*Mina*) on locomotor response elicited by a challenge dose (1 mg/kg) of amphetamine. Data are expressed as mean crossings (± SE). *Significantly ($P < 0.01$) different from SAL

General discussion

The present results indicate that repeated or chronic stressful experiences, repeated psychostimulants and subchronic antidepressant treatment share some behavioral effects. Indeed, all these treatments reduced the inhibitory effects of subsequent stress experiences on behavior. However, some major differences were also evident. Subchronic minaprine did not alter behavioral sensitivity to apomorphine, as reported for repeated stress, and did not induce behavioral sensitization as did repeated amphetamine and chronic stress. Moreover, the active behavioral responses promoted by the different pretreatments in the Porsolt test were different, although they all resulted in a very similar reduction of immobility.

It could be argued that the functional alterations induced by repeated stress are not responsible for the reduction of its inhibitory effects on behavior and that habituation to the stressor could be a more economic explanation. However, the results obtained in the second set of experiments, in line with others (Platt and Stone 1992), indicate cross tolerance among different stressors, ruling out this possibility.

Several lines of evidence point to an involvement of mesolimbic DA in the behavioral effects reported in these experiments. First, the climbing behavior in mice is highly responsive to manipulations of mesolimbic DA functioning (Costall et al. 1980, 1981). Second, repeated stress has been shown to promote parallel strain-dependent alterations of climbing behavior and mesolimbic DA functioning (Puglisi-Allegra et al. 1990; Cabib and Puglisi-Allegra 1991). Third, although minaprine is devoid of the behavioral and central effects of direct and indirect DA agonists (Imperato et al. 1994), altered mesolimbic DA functioning has been shown following subchronic minaprine treatment that has anti-immobility effects in rats (Imperato et al. 1994). Fourth, exposure to forced swimming has been shown to provoke a dramatic decrease of DA release in the nucleus accumbens, that is reduced by pretreatment with antidepressants (Rossetti et al. 1993). Finally, alterations of mesolimbic DA functioning, related to behavioral sensitization, have been observed following repeated psychostimulants (Kalivas and Stewart 1991, for review).

Consequently, the ability to reduce the inhibitory effects of stress on behavior, demonstrated by repeated and chronic stress, repeated amphetamine and minaprine could depend on their shared ability to alter mesolimbic DA functioning. Yet, the difference in the behavioral effects promoted by these treatments suggests the involvement of different alterations. This is not surprising given the complex pre- and postsynaptic changes that could determine altered mesolimbic DA functioning (Kalivas and Stewart 1991, for review).

The latter observation has important clinical implications. Indeed, several lines of evidence suggest that behavioral sensitization in animals could share homologies with psychotic syndromes and drug dependence in humans (Robinson 1988; Robinson and Berridge 1993). Accordingly, preclinical research on antidepressants should acknowledge that behavioral sensitization could be the sign of undesirable side effects. Moreover, since adaptation to repeated and chronic stressful experiences can promote these side effects, pharmacological intervention aimed at preventing them would be therapeutically helpful. Accordingly, preclinical research should look for antidepressants capable of reducing those central effects of stress involved in the development of behavioral sensitization or of promoting alternative adaptive changes. The study of mesolimbic DA functioning in stressful conditions could be the most suited field for this type of researches.

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