Pharmacology Biochemistry and Behavior, Vol. 62, No. 4, pp. 591–599, 1999

0091-3057/99/$–see front matter

PII S0091-3057(98)00180-4

Effects of Chronic Antidepressants in an Operant Conflict Procedure of Anxiety in the Rat

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Received 30 January 1998; Revised 1 September 1998; Accepted 1 September 1998

BEAUFOUR, C. C., N. BALLON, C. LE BIHAN, M. HAMON AND M.-H. THIÉBOT. *Effects of chronic antidepressants in an operant conflict procedure of anxiety in the rat.* PHARMACOL BIOCHEM BEHAV. **62**(4) 591–599, 1999.— The effects of chronic antidepressants were investigated in an animal procedure for the study of anxiety and anxiolytics, the conditioned suppression of operant behavior in rats. In daily 18-min sessions, three periods of nonpunished lever pressing for food alternated with two 4-min periods signaled by a light-on conditioned stimulus during which 50% of the responses were randomly punished by electric foot shocks. Antidepressants were administered once daily for 7–8 weeks to trained, food-restricted rats. Desipramine (dose regimen increase from 4 to 16 mg/kg/day) induced a gradual (4–5-week latency) release of response suppression during punished periods over the course of several weeks of testing. This anxiolytic-like effect was still present 3 weeks following drug discontinuation. In contrast, chronic imipramine (dose regimen increase from 4 to 16 mg/kg/day), maprotiline (4 to 16 mg/kg/day), phenelzine (2 to 4 mg/kg/day), and fluoxetine (1 or 8 mg/kg/day; constant dose), resulted in no change in punished responding, suggesting that no anxiolytic-like effect developed in the course of chronic treatment with these compounds. The largest dose of all antidepressants studied (except fluoxetine) induced a moderate to marked reduction of nonpunished performance that disappeared within 1 week after the last injection. A transient release of conditioned response suppression emerged during the week that followed discontinuation of imipramine, maprotiline, and fluoxetine (8 mg/kg/day). This apparent anxiolytic-like activity might be due to a reduction of some adverse effect induced by the high doses used, and/or might have resulted from a new dynamic equilibrium between monoamine release, reuptake processes, and sensitivity of postsynaptic receptors. In conclusion, operant conflict procedures in rats seem not particularly able to model human anxiety sensitive to chronic antidepressant treatments. © 1999 Elsevier Science Inc.

Anxiety Chronic treatment Conditioned behavioral suppression Desipramine Fluoxetine Imipramine Maprotiline Phenelzine Rat

THE current classifications of mental disorders, DSM IV (2) and ICD-10 (30), clearly distinguish depressive illness from anxiety-related disorders. Pharmacological treatments, however, seem to be less specific to each type of pathology than initially assumed. In particular, clinical studies have shown that some (but not all) antidepressants, either tricyclics, monoamine oxidase inhibitors (MAOIs), or selective serotonin reuptake inhibitors, may be more efficient than benzodiazepines to alleviate anxiety associated with panic disorders (14,34). Even in generalized anxiety disorders, on chronic treatment, imipramine can be more effective than benzodiazepines (32).

In animal procedures devoted to the study of anxiety and anxiolytics, the effects of antidepressants are not unequivocal. This is probably due to several factors, among which is the fact that these experimental procedures were developed and optimized primarily for evaluating benzodiazepines and were further validated by their sensitivity to this class of compounds. Differences in pharmacological properties and pharmacokinetic characteristics of antidepressants can also play a crucial role in the observed variety of results.

On acute injection, antidepressants failed to induce anxiolytic-like effects in various procedures, such as the two-com-

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partment test (15), the elevated plus-maze (11,18), and the potentiated startle reflex (9). Moreover, anxiogenic-like effects were sometimes observed (8,17,26), consistent with the exacerbation of anxiety frequently reported by patients at the initiation of the treatment (37). On chronic administration, antidepressants have been shown to exert anxiolytic-like effects in some studies. For instance, chronic treatment with antidepressants induced a release of behavioral blockade in procedures such as the conditioned suppression of drinking (7–8 weeks) (19,20), the novelty-induced suppression of feeding (3 weeks) (7), or the antipredator defense test battery (3 weeks) (5), in rats, and the social behavior in mice (12–16 days) (21). However, negative results have been reported in the elevated plus-maze (3 weeks) (18), the fear-enhanced acoustic startle (3 weeks) (9), and even the conditioned suppression of drinking task (at least 8 weeks) (12). Therefore, an anxiolytic-like effect cannot be induced by all antidepressants on chronic injection, and/or not all relevant animal procedures allow the demonstration of such a property.

Surprisingly, the anxiolytic potential of antidepressants has never been assessed in operant conflict procedures, such as the Geller-Seifter (22) or the Cook-Davidson (13) paradigms, although they are among the most usual tests devoted to the experimental study of anxiety. This consideration led us to investigate the effects of chronic treatment with a variety of antidepressants (imipramine, desipramine, maprotiline, fluoxetine, phenelzine) in rats subjected to an operant paradigm of conflict behavior. In this procedure, blockade of lever pressing for food was induced by a conditioned signal for punishment and electric foot shocks, contingent on responding. To closely match the clinical conditions, compounds were administered for at least 7 weeks and their effects examined, both during the treatment and after its discontinuation.

METHODS

Animals

The experiments were carried out on 288 male Wistar AF rats (C.E.R.J., Le Genest, France) weighing 100 ± 10 g at the beginning of the training and 350–425 g at the time of the initiation of the treatments. They were housed eight per cage under standard laboratory conditions (12-h light–dark cycle, lights on at 0730 h; room temperature 21 ± 1°C) with free access to water in their home cage. One week prior to the beginning of the training, rats were placed on a daily schedule of food restriction (13 g of standard chow per day per rat), which was maintained until the end of the experiments. The experiments were carried out in compliance with the European Communities Council Directive for animal care (86/609/EEC).

Apparatus

The experiments were conducted in four standard ventilated, sound-attenuated operant chambers (Campden Instruments Ltd., UK). Each chamber was fitted with an electrified grid floor and an automatic magazine delivering food pellets (45 mg, Campden) in a tray located between two response levers. The chambers were supplied with three lights (24 V; 3 W) located above each lever and in the middle of the ceiling (house light).

Procedure

Rats were submitted to operant sessions 5 days a week. They were initially trained, during daily 18-min sessions, to press the right lever to obtain food pellets according to a fixed ratio 1 (FR1) schedule of food reinforcement, which was progressively raised to an FR8 schedule. Pressing the left lever had no consequence throughout the experimental procedure. The stimulus light situated above the right lever was illuminated during these initial training sessions. After stabilization of FR8 responding (about 18 sessions), two 4-min punished periods, signaled by the illumination of the light situated above the left lever, were introduced in the course of the sessions. They started 4 and 11 min after the beginning of the session. During these periods, presses were reinforced with food pellets according to an FR1 schedule, and were also associated with scrambled electric foot shocks according to a random ratio 50% (RR50%) schedule (50 ± 15% of the presses were randomly punished). The shock intensity, initially set at 0.5 mA (45-ms duration), was increased gradually and adjusted for each rat to cause a similar degree of response suppression (range 0.5–2 mA). Shock intensity was not modified after punished responding stabilized to a level, whereby rats received six shocks or less during the punished periods (total 8 min). The nonpunished periods were signaled by the illumination of the right stimulus light as during the initial training. Visual stimuli were maintained throughout the appropriate periods.

The numbers of pellets obtained and shocks received by each rat were automatically recorded every minute. Approximately 20 sessions after the initiation of the punishment contingency were necessary to obtain stable response baselines, i.e., 50–80 presses/min during nonpunished periods (corresponding to 6–10 pellets earned/min) and zero to two presses/min during punished periods. At this time, rats of each experimental series were divided into two groups, which were matched according to the average number of shocks received and also the number of pellets earned during the last four training sessions (baseline). Chronic drug (or saline) treatment was then initiated.

Drugs

The drugs used were imipramine-HCl, desipramine-HCl (Ciba-Geigy, Basel, Switzerland), fluoxetine-HCl (Eli-Lilly, Indianapolis, IN), maprotiline-HCl, phenelzine-SO_4 (Sigma, St. Louis, MO). Rats received one daily injection of either the drug studied or saline, between 1730 and 1930 h, and the operant sessions took place 15–18 h after the last injection. Except otherwise specified, the daily dose regimen was progressively increased to reduce the intensity of adverse effects (essentially hypophagia) frequently observed at the initiation of the treatment and with large doses (Fig. 1). To control for the effects of an established anxiolytic, diazepam (1 and 2 mg/kg IP; Hoffmann–La Roche, Basel, Switzerland) or vehicle was given acutely to additional groups of drug-naive rats (n = 10/group), in the course of the experiments. Drugs were dissolved in saline (0.9% NaCl), except diazepam, which was suspended in a drop of Tween 80 in saline. The doses are expressed as the salt or the base, as appropriate. Drugs or vehicle were administered IP in a volume of 0.5 ml/100 g b.wt. The number of animals per group is indicated in Fig. 1.

Statistical Analyses

The performance of rats was recorded 5 days a week. The statistical analyses were performed on data obtained 6, 13, 20, 34, 48, and eventually 55 days following the initiation of the chronic treatments and during 6 or 20 days following discontinuation of drug injection. The total number of pellets obtained during the nonpunished periods (1, 3, and 5; total 10

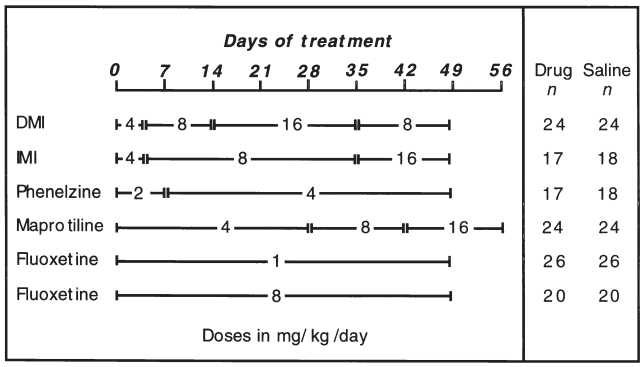

FIG. 1. Chronic antidepressant treatment: doses (mg/kg, IP) administered once a day to independent groups of rats during 7 or 8 weeks. A control group of rats given saline was paired with each treated group (n = number of rats/group).

min) and during the punished periods (2 and 4; total 8 min) by antidepressant- and saline-injected rats were compared independently by two-tailed Student's t-test. Any data that did not fit in with normality of distribution or homogeneity of variance were subjected to the nonparametric Mann–Whitney z-test. The acute effects of diazepam were analyzed by one-way analysis of variance (ANOVA) and pair-wise comparisons between treated and control groups were made using Dunnett's t-test using the appropriate error variance term from ANOVAs.

RESULTS

Drug Effects During Chronic Treatment

Imipramine (Fig. 2). Punished responding in rats given daily injections of imipramine during 7 weeks did not differ from control performance, whatever the dose regimen received during the preceding days (4, 8, or 16 mg/kg/day). The number of pellets obtained during the nonpunished periods was reduced in rats given imipramine compared to the saline-injected rats; except on day 13, this effect reached a statistically significant level (day 6: $t = 2.66$; day 20: $t = 2.45$; day 27: $t = 4.55$; day 34: $t = 3.26$; day 41: $t = 4.19$; day 48: $t = 3.91$; at least $p < 0.02$). Body weight of treated rats did not significantly differ from that of controls throughout the chronic treatment (not shown).

Desipramine (Fig. 3). Chronic desipramine induced a progressive increase in punished responding and rats obtained more pellets than controls from the 34th day onwards (day 34: $z = 2.00$, $p < 0.05$; day 41: $z = 2.52$, $p < 0.01$; day 48: $z = 2.97$, $p < 0.01$). The number of nonpunished responses was reduced, and this effect reached a significant level on day 20 ($z = 2.05$, $p < 0.05$), day 27 ($z = 3.04$, $p < 0.01$) and day 34 ($z = 2.93$, $p < 0.01$).

As illustrated in Fig. 4, the body weight of rats given desipramine (4 and then 8 mg/kg/day), was significantly lower than that of controls by the end of the first 2 weeks of treatment. During the subsequent 3 weeks, this difference was further marked and treated rats lost ~32 g, while they received the dose of 16 mg/kg/day. Because of this weight loss and of the reduction in nonpunished responding, the daily dose of desipramine was reversed back to 8 mg/kg/day during the last 2 weeks of treatment.

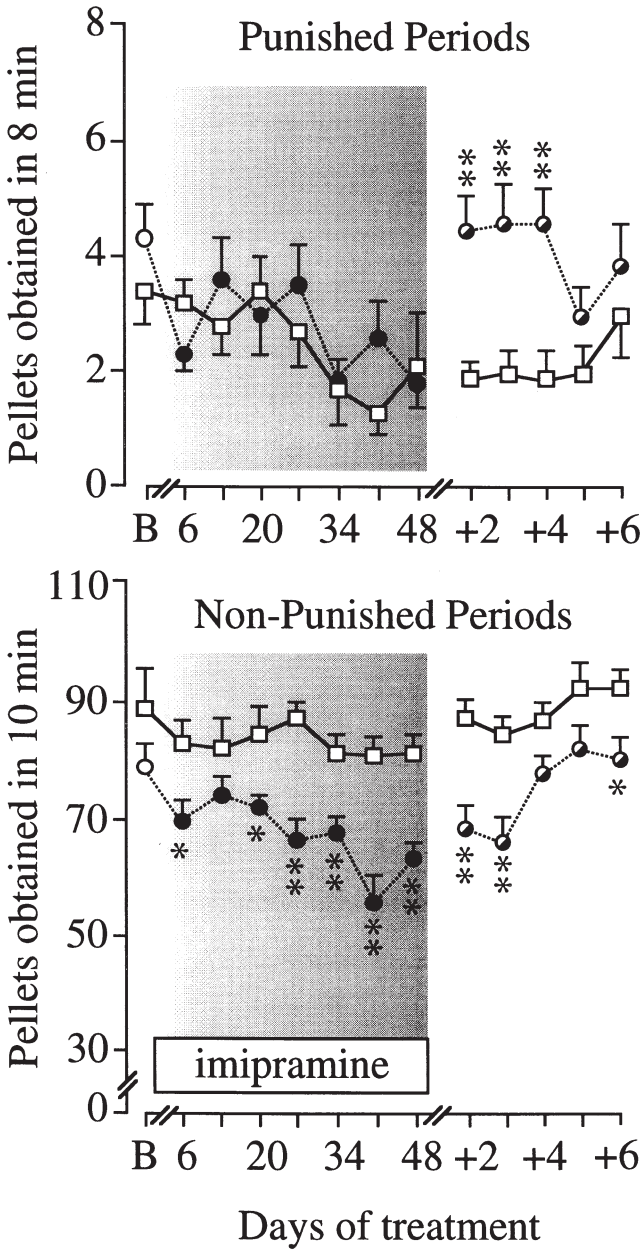

FIG. 2. Effect of chronic administration of imipramine at increasing doses from 4 to 16 mg/kg/day, IP, during 7 weeks (illustrated at weekly intervals from day 6 to 48) and of drug discontinuation (illustrated at days +2 to +6 after the final injection) on the total number (mean ± SEM) of food pellets obtained during the punished (top) and nonpunished (bottom) periods of the operant conflict procedure. □ Saline; ● Imipramine; ◑ Imipramine discontinuation; B = baseline. *$p < 0.05$; **$p < 0.01$, vs. paired saline-injected rats (Student's t-test).

Maprotiline (Fig. 5). Punished responding in rats given daily injections of maprotiline for 8 weeks never significantly differed from performance of the saline-injected rats, whatever the dose regimen received during the preceding days (4, 8, or 16 mg/kg/day). The number of pellets obtained during the nonpunished periods was reduced in treated animals, espe-

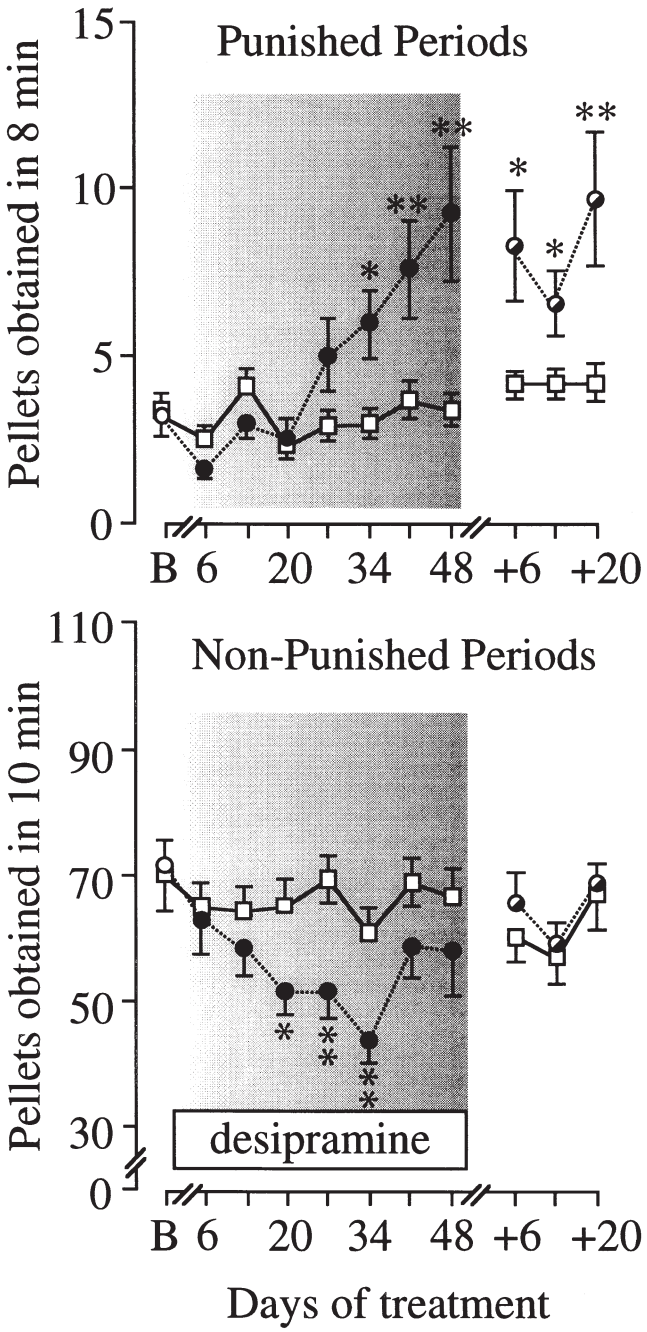

FIG. 3. Effect of chronic administration of desipramine at increasing doses from 4 to 16 mg/kg/day, IP, during 7 weeks (illustrated at weekly intervals from day 6 to 48) and of drug discontinuation (illustrated at days +6, +13, and +20 after the final injection) on the total number (mean ± SEM) of food pellets obtained during the punished (top) and nonpunished (bottom) periods of the operant conflict procedure. □ Saline; ● desipramine; ◑ desipramine discontinuation; B = baseline. *$p < 0.05$; **$p < 0.01$, vs. paired saline-injected rats (Mann–Whitney z-test).

cially during the last 2 weeks, while animals received 16 mg/kg/day of maprotiline (day 48: $t = 3.39$; day 55: $t = 3.61$; $p < 0.01$).

Rats given 4 and then 8 mg/kg/day of maprotiline gained less weight than controls. During the subsequent 2 weeks,

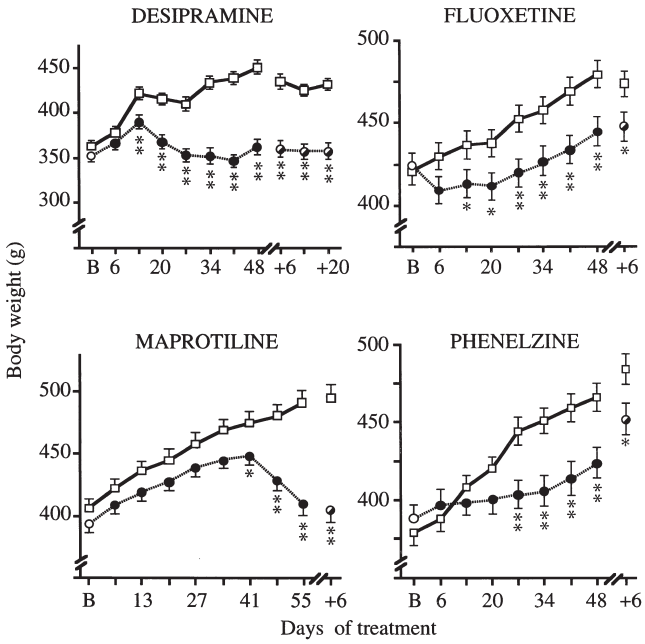

FIG. 4. Time course of changes in body weight during chronic administration of desipramine, fluoxetine (8 mg/kg/day), maprotiline, or phenelzine, and following treatment discontinuation. □ Saline; ● drug; ◑ drug discontinuation; B = baseline. *$p < 0.05$; **$p < 0.01$, vs. paired saline-injected rats (Student's t-test).

while they received 16 mg/kg/day (see Fig. 1), their body weight was significantly lower than that of controls. Indeed, treated rats lost approximately 30 g during this period (Fig. 4).

Fluoxetine (Fig. 6). Chronic fluoxetine (1 or 8 mg/kg/day) did not affect performance during either the punished or the nonpunished periods.

The body weight of animals given 8 mg/kg/day of fluoxetine (but not 1 mg/kg/day), was significantly lower than that of controls by the end of the first week of treatment, and this difference persisted up to at least 1 week after cessation of the 7-week treatment (Fig. 4).

Phenelzine (Fig. 7). The number of responses emitted during the punished periods was not significantly modified by chronic phenelzine. During the nonpunished periods, a reduction of lever presses was observed in treated rats. This effect reached the level of statistical significance during sessions performed at days 13, 20, 27, and 41 ($t = 2.83$; $= 2.36$; $= 4.47$; and $= 2.17$, respectively; at least $p < 0.05$).

The gain in body weight of rats given chronic phenelzine was lower than in controls. The difference between the two groups was significant from the end of the fourth week of treatment onwards (Fig. 4).

Effects of Acute Diazepam

In the course of the experiments conducted with chronic desipramine, additional groups of drug-naive rats were given an acute injection of diazepam (DZP 1–2 mg/kg, $n = 10$). Diazepam induced a significant increase of lever presses during punished periods (controls: 3.2 ± 0.5; DZP 1: 10.5 ± 3.0, $t = 2.40$, $p < 0.05$; DZP 2: 15.6 ± 3.8, $t = 3.41$, $p < 0.01$) and a moderate reduction of responding during the nonpunished periods (number of pellets obtained—controls: 78 ± 6; DZP 1: 70 ± 8, NS; DZP 2: 60 ± 4, $t = 2.50$, $p < 0.05$).

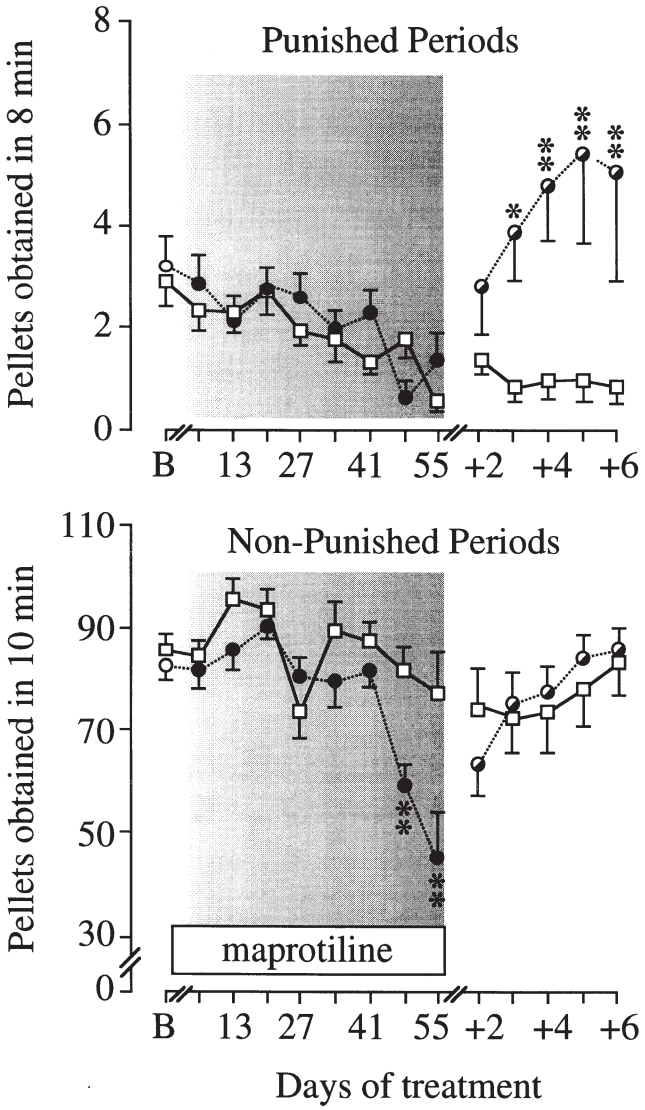

FIG. 5. Effect of chronic administration of maprotiline at increasing doses from 4 to 16 mg/kg/day, IP, during 8 weeks (illustrated at weekly intervals from day 6 to 55) and of drug discontinuation (illustrated at days +2 to +6 after the final injection) on the total number (mean ± SEM) of food pellets obtained during the punished (top) and nonpunished (bottom) periods of the operant conflict procedure. □ Saline; ● maprotiline; ◑ maprotiline discontinuation; B = baseline. *$p < 0.05$; **$p < 0.01$, vs. paired saline-injected rats (Student's *t*-test or Mann–Whitney *z*-test).

Effects Following Treatment Discontinuation

Imipramine (Fig. 2). Two, 3, and 4 days after imipramine discontinuation, treated rats emitted more responses than did control rats during the punished periods ($t = 3.82$; $= 3.33$; $= 3.65$, respectively, $p < 0.01$). The number of nonpunished pellets obtained progressively returned to control values within the 6 posttreatment days.

Desipramine (Fig. 3). During a 3-week period following drug discontinuation, rats previously given chronic desipramine emitted significantly more punished responses than did their saline counterparts (day 6, $z = 1.64$, $p < 0.05$; day 13, $z = 1.67$, $p < 0.05$; day 20, $z = 2.68$, $p < 0.01$). Nonpunished responding did not differ between the two groups of rats during the same period.

Maprotiline (Fig. 5). Two to 6 days following discontinuation from chronic maprotiline, treated rats obtained more pellets during the punished periods than did their saline counterparts. This effect was statistically significant from the third day onwards (day 3, $z = 2.43$, $p < 0.05$; day 4, $z = 3.26$; day 5, $z = 2.99$; day 6, $z = 2.96$; $p < 0.005$). Nonpunished responding no longer differed between the two groups of animals during the same period.

Fluoxetine (Fig. 6). During the week following drug discontinuation, rats previously given chronic fluoxetine (8 mg/kg/day) emitted more responses during the punished periods than did control animals. This effect reached a statistically significant level on day 3 ($z = 2.04$, $p < 0.05$), day 4 ($z = 3.24$, $p < 0.05$), and day 5 ($z = 2.21$, $p < 0.05$). Nonpunished lever presses did not differ between treated and control rats. Punished and nonpunished responding in rats previously given 1 mg/kg/day of fluoxetine did not differ from performance of control animals.

Phenelzine (Fig. 7). Discontinuation from chronic phenelzine did not significantly modify punished lever pressing. Nonpunished responding progressively returned to control values within the 6-day posttreatment period.

DISCUSSION

The aim of this study was to reveal possible anxiolytic-like effects of antidepressants on chronic administration, in rats subjected to a conflict procedure during which lever pressing for food was suppressed by a conditioned signal for punishment and contingent electric foot shocks. For this purpose, imipramine, desipramine, maprotiline, fluoxetine, or phenelzine were administered for 7–8 weeks to independent groups of rats very well trained to the experimental contingencies so that they emitted a large number of presses during nonpunished periods and almost completely blocked their responses when the conditioned signal for punishment was present. Drugs were given once a day, 15–18 h before the operant sessions, at escalating doses (except fluoxetine) to attenuate the adverse effects often observed at the initiation of antidepressant treatment.

Desipramine produced a time-dependent increase in punished responding that occurred with a 4–5-week latency, in keeping with results from other studies (8,19). The release of behavioral suppression was still present 3 weeks after drug discontinuation, indicating that it more likely resulted from neurobiological changes than drug accumulation (see below). However, the magnitude of this anticonflict effect was clearly lower than that observed in the same procedure following acute diazepam.

In contrast with the results obtained in the conditioned suppression of drinking (12,19,20), the novelty-induced suppression of feeding (7,8), and/or the social behavior in mice (21), chronic imipramine, maprotiline, fluoxetine, and phenelzine, were inactive in inducing an anxiolytic-like release of punished responding in the present conflict procedure. The primary neurobiological targets of the drugs studied cannot account for such differences in the observed effects. Indeed, desipramine is a preferential NA reuptake inhibitor, imipramine a nonselective NA/5-HT reuptake inhibitor [exten-

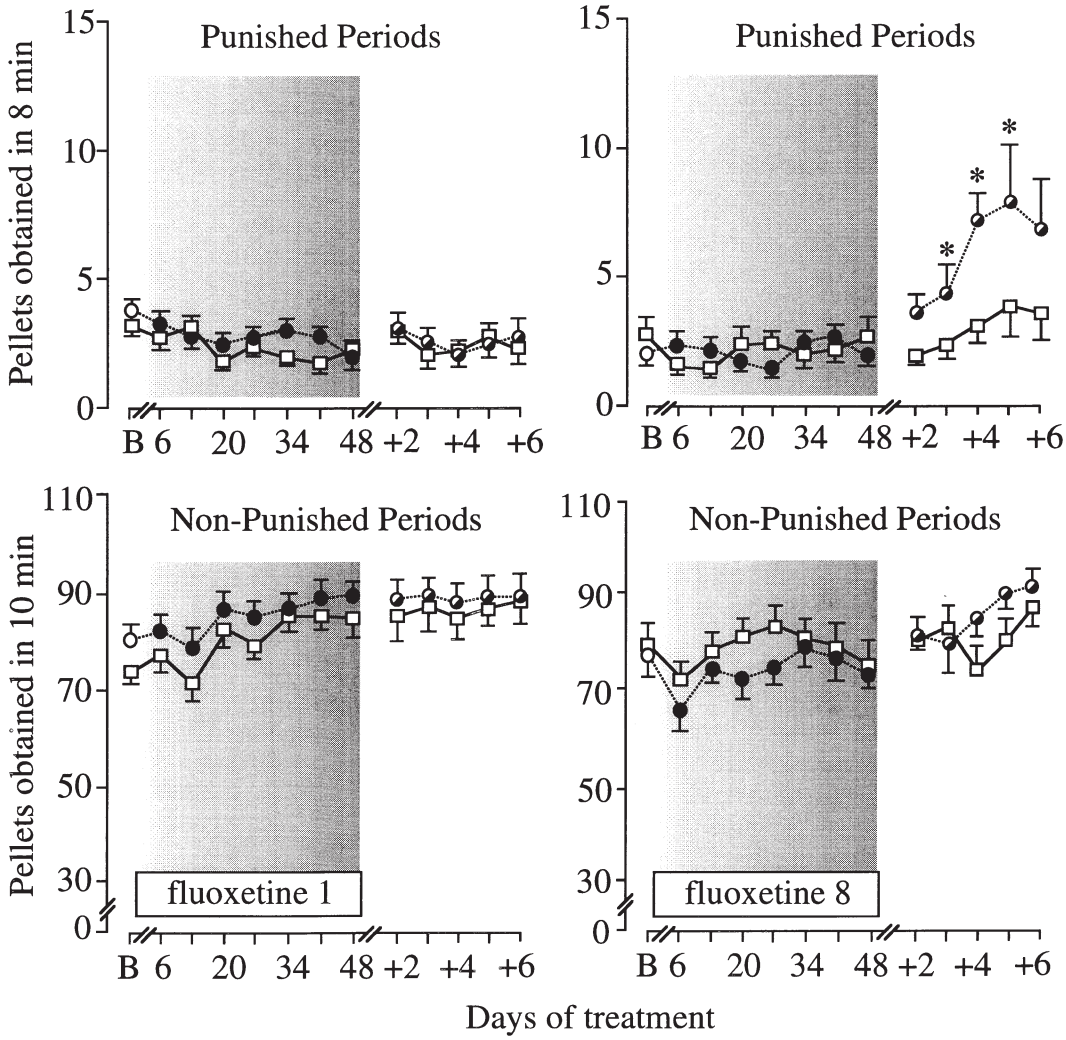

FIG. 6. Effect of chronic administration of fluoxetine 1 mg/kg/day (left-hand part of the figure) or 8 mg/kg/day, IP (right-hand part of the figure) during 7 weeks (illustrated at weekly intervals from day 6 to 48) and of drug discontinuation (illustrated at days +2 to +6 after the final injection) on the total number (mean ± SEM) of food pellets obtained during the punished (top) and nonpunished (bottom) periods of the operant conflict procedure. □ Saline; ● fluoxetine; ◑ fluoxetine discontinuation; B = baseline. *$p < 0.05$, vs. paired saline-injected rats (Student's *t*-test or Mann–Whitney *z*-test).

sively metabolized to desipramine in rats (47)], maprotiline a selective NA reuptake blocker, fluoxetine a selective 5-HT reuptake inhibitor, and phenelzine a nonselective irreversible MAOI. It cannot be excluded that the doses administered, the rhythm of injections, and/or the schedule of dose increase were inappropriate to reach brain concentrations sufficient to induce the neurobiological modifications responsible for an anticonflict effect. However, this seems unlikely, because the highest doses administered were similar to or larger than those active in other paradigms [desipramine: 10 mg/kg (8,12); imipramine: 5 mg/kg (20); fluoxetine: 10 mg/kg (8); phenelzine: 4 mg/kg (19)]. Moreover, they could hardly be further increased because reductions of both nonpunished responding and body weight were observed with most of the compounds tested. The mechanism(s), which would account for the ability of desipramine to release conflict behavior while the other antidepressants tested did not, are not immediately clear. One study reported that, on chronic infusion, desipramine (10 mg/kg × 21 days), but not the same dose of fluoxetine, moclobemide, or maprotiline, desensitized hippocampal 5-HT_3 receptors (35). Because 5-HT_3 receptor antagonists have claimed to exert anxiolytic-like activity in animals (16), such an effect would account for the unique profile of action of desipramine. However, evidence clarifying the differences between the neurobiological consequences of chronic treatment with desipramine by comparison with other antidepressants are necessary before any conclusion can be drawn on this point.

On the other hand, the procedure, based on food motivation, required a chronic food restriction that may have modified the functional status of monoaminergic pathways subserving the action of antidepressants. Indeed, a downregulation of central β-adrenergic receptors (45), modifications of hippocampal 5-HT_{2C} receptor expression (28), and a reduction of 5-HT transporter density in the frontal cortex (48) have been described in food-restricted rats. Such changes might possibly account for the fact that chronic food deprivation attenuated

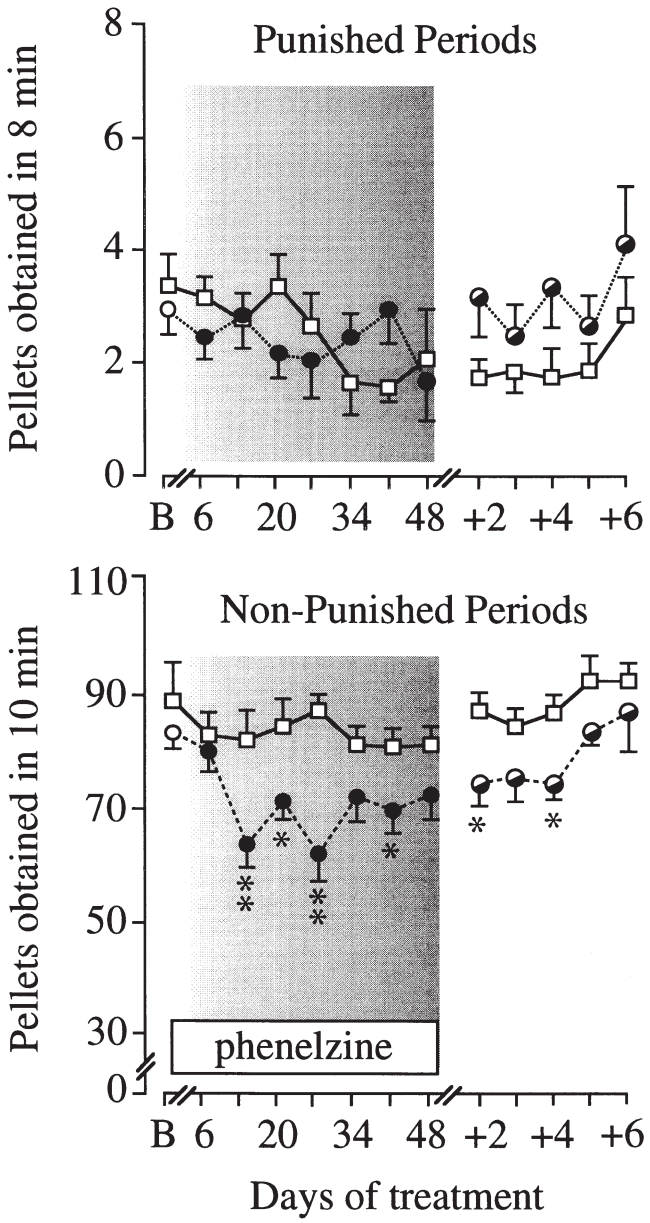

FIG. 7. Effect of chronic administration of phenelzine at increasing doses from 2 to 4 mg/kg/day, IP, during 7 weeks (illustrated at weekly intervals from day 6 to 48) and of drug discontinuation (illustrated at days +2 to +6 after the final injection) on the total number (mean ± SEM) of food pellets obtained during the punished (top) and non-punished (bottom) periods of the operant conflict procedure. □ Saline; ● phenelzine; ◑ phenelzine discontinuation; B = baseline. $*p < 0.05$; $**p < 0.01$, vs. paired saline-injected rats (Student's *t*-test).

the efficacy of antidepressants in reversing behavioral deficits such as failure to escape shocks in the learned-helplessness paradigm (43). However, in the novelty-induced suppression of feeding, starvation did not preclude the reduction in latency to eat by chronic antidepressants (7,8). Furthermore, no anxiolytic-like effects of chronic antidepressants were observed in several procedures that are not based on feeding or drinking responses, including the conditioned defensive burying (4), the elevated plus-maze (11,18), and the fear-enhanced acoustic startle (9), indicating that chronic starvation is not a crucial factor responsible for the inability of several antidepressants to induce anxiolytic-like effects in the present conflict paradigm.

Tricyclic antidepressants are known to induce analgesia, and this effect seemed more pronounced with desipramine than with other tricyclics, whereas it was not observed with fluoxetine (1,42). In addition, some studies (1,41), but not all (25,33), have reported variations in pain responsiveness as a function of age and/or body weight. Therefore, a reduction in sensitivity to shocks could constitute a confounding factor in the present experimental situation, which included punished components. However, several points argue against such a possibility. A tolerance to the desipramine-induced analgesia seemed to develop rapidly during chronic treatment (27). In well-trained rats, as they were in this study, the behavioral blockade was induced not by shocks, but by the presentation of the conditioned signal of shocks. Analgesic doses of morphine and even shock omission did not induce immediate release of responding (13). Finally, contrary to the increase in punished lever presses predicted under the hypothesis that age and/or body weight influence pain sensitivity, responding in control groups did not change or even decreased during the 8–10-week experimental period.

Interestingly, following discontinuation from chronic imipramine, maprotiline and fluoxetine (8 mg/kg/day), a progressive, modest, but significant increase of punished responses appeared with a 2–3-day latency, and peaked by 4–6 days. To the best of our knowledge, such anticonflict effect observed after, but not during a chronic treatment, has never been reported. The mechanism(s) subserving this late-appearing activity are yet unknown. One possibility was that some adverse or toxic effect had rapidly disappeared after the last injection, unmasking an anticonflict activity that had developed during chronic administration. Rats given maprotiline at the dose of 8 mg/kg/day from day 28 to 56 did not exhibit such release from behavioral blockade following treatment discontinuation (results not shown) suggesting that chronic and high doses were necessary for such an effect to be observed. On the other hand, pre- and postsynaptic adaptive processes occurred in the course of chronic administration of antidepressants. For instance, modifications in presynaptic regulatory mechanisms of catecholamine release by α_2-adrenergic, 5-HT_{1A}, and 5-HT_{1B} auto- or heteroreceptors (6), as well as desensitization or downregulation of β-adrenergic and/or 5-HT_{2A} postsynaptic receptors (38,39,46), have been reported. In contrast, 5-HT and NA uptake sites seem to exhibit less adaptive changes to chronic treatments [(10,23,44); but see: (3,29,39)]. Though some of these data remain controversial, it can be hypothesized that drug discontinuation might have resulted in a new equilibrium state between neurotransmitter release and reuptake processes, while postsynaptic sites remained desensitized for a few days (31,40). This would have resulted in a relative reduction of monoaminergic transmission accounting for the anticonflict effect observed within 1 week after the last injection. Indeed, reduced 5-HT or NA transmission has been proposed as a possible mechanism of action of anxiolytic drugs such as benzodiazepines, via their action on GABAergic processes (24). Similar "acute" decreases in monoaminergic transmission probably did not occur during the 6-day period after discontinuation from chronic phenelzine administration, because of the very slow recovery of MAO activity after irre-

versible blockade (36). Such dynamic characteristics in MAO recovery might explain why no release of punished behavior was observed after chronic phenelzine.

In conclusion, a 7–8-week daily administration of most of the antidepressants considered in the present study failed to exert anxiolytic-like effects in an operant conflict procedure in rats. Indeed, only chronic desipramine induced a progressive release of punished responding, which persisted after drug discontinuation. This suggests that, unlike other tests such as the conditioned suppression of drinking, operant conflict procedures in rats are not suitable to model human anxiety sensitive to antidepressant treatments.

ACKNOWLEDGEMENTS

This study was supported by grants from INSERM and DRET (Contract 95-142). Caroline C. Beaufour and Nicolas Ballon were recipients of MESNR and FRM fellowships, respectively, during performance of this study. We would like to thank Novartis for the generous supply of imipramine and desipramine, and Eli-Lilly for the fluoxetine.

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