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Reversal of stress-induced anhedonia by the atypical antidepressants, fluoxetine and maprotiline

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Abstract. Chronic exposure to mild unpredictable stress has previously been found to depress the consumption of palatable sweet solutions. In the present study this effect was reversed by chronic (9 weeks) treatment with the atypical antidepressants, fluoxetine and maprotiline (5 mg/kg/day); the non-antidepressant chlordiazepoxide was ineffective. Stressed animals were also subsensitive to food reward in the place conditioning procedure; however, fluoxetine and maprotiline treated animals showed normal place preference conditioning. Acute pretreatment with raclopride (100 μg/kg) selectively reversed the recovery of sucrose drinking in antidepressant-treated stressed animals. These results extend previous reports of the efficacy of tricyclic antidepressants in this paradigm, and support the hypothesis of a dopaminergic mechanism of antidepressant action.

Key words: Stress – Sucrose drinking – Place preference conditioning – Reward – Fluoxetine – Maprotiline – Chlordiazepoxide – Rats

Chronic sequential exposure to mild unpredictable stress has been found to depress the consumption of, and preference for, palatable sweet solutions; these deficits, which may represent a decrease in sensitivity to rewards, are reversed by chronic administration of tricyclic antidepressants (Willner et al. 1987; Muscat et al. 1988, 1990; Sampson et al. 1991). As stress is implicated in the etiology of depression (Lloyd 1980; Kanner et al. 1981; Anisman and Zacharko 1982; Brown and Harris 1988), the chronic mild stress paradigm may provide a relatively realistic animal model of the decreased response to rewards (anhedonia) that characterizes melancholia (Klein 1974; Nelson and Charney 1981; Fawcett et al. 1983; American Psychiatric Association 1987). The main purpose of the present study was to investigate the activity in this model of two non-tricyclic antidepressants, the specific serotonin (5HT) uptake inhibitor fluoxetine (Bremner 1984; Asberg et al. 1986) and the specific noradrenaline (NA) uptake inhibitor maprotiline (Maitre et al. 1975; Montgomery 1980). The non-antidepressant anxiolytic drug chlordiazepoxide was also included, as a negative control.

The place conditioning paradigm, in which animals increase their preference for a distinctive environment in which the reward is administered, has been used extensively to study the rewarding properties of natural rewards and of drugs of abuse (Bozarth 1987; Carr et al. 1989). In support of the interpretation that decreased sucrose consumption in animals subjected to chronic mild stress results from subsensitivity to reward, we have previously reported that the suppression of sucrose intake by chronic mild stress is associated with a decrease in the rewarding properties of natural rewards (food pellets or sweet solutions) and drug rewards (amphetamine, morphine), as assessed by their ability to support conditioned place preferences (Papp et al. 1991, 1992). A second objective of this study was to investigate whether, in addition to restoring normal sucrose consumption, antidepressant drugs also normalize place preference conditioning in chronically stressed animals.

Antidepressant drugs have traditionally been assumed to exert their clinical effects through an interaction with noradrenergic or serotonergic systems. However, after chronic administration, antidepressants have also been found to potentiate the locomotor stimulant effects of dopamine (DA) D2 agonists. These effects are apparent following systemic administration (Willner and Montgomery 1981; Martin-Iverson et al. 1983; Arnt et al 1984; Maj et al. 1984a, b; Maj 1988) or direct injection of D2 agonists into the nucleus accumbens (Maj and Wedzony 1985, 1988; Maj et al. 1987; Maj 1988). We have previously demonstrated that acute administration of DA receptor antagonists reduced the consumption of a sweet solution in chronically stressed rats successfully treated with imipramine, desmethylimipramine (DMI) or amitriptyline, but did not reduce consumption in non-stressed animals

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or in untreated stressed animals. These data argue strongly that an increase in DA receptor responsiveness may be responsible for the therapeutic action of tricyclic antidepressants in this model (Muscat et al. 1990; Sampson et al. 1991). We have therefore investigated the role of dopaminergic mechanisms in the actions of fluoxetine and maprotiline, using an acute challenge with a highly selective D2 receptor antagonist, raclopride (de Paulis et al. 1986).

Materials and methods

Subjects. Male Lister hooded rats, weighing approximately 290 g at the start of the experiment, were obtained from the National Institute for Medical Research (UK). The animals were singly housed, except where grouped as part of the stress procedure (see below).

Procedure. All animals ($n = 80$) were first trained to consume a highly palatable weak (1%) sucrose solution; training consisted of an initial 48 h exposure to sucrose in place of water, followed by five 1 h tests in which sucrose was presented, in the home cage, following 20 h food and water deprivation; intake was measured by weighing pre-weighed bottles at the end of the test. Subsequently sucrose consumption was monitored, in 1 h tests following 20 h food and water deprivation, at weekly intervals throughout the experiment, with the exception of 1 week during which place preference conditioning was carried out (see below).

On the basis of their sucrose intakes in the final baseline test, the animals were divided into two matched groups ($n = 40$). One group of animals was subjected throughout the experiment to chronic unpredictable mild stress; a variety of mild stressors were applied, each for a period of between 0.5 and 20 h. Stressors could occur at any time of day, except during weeks 10 and 11, when stressors were administered at night only, in order not to impinge directly on place preference conditioning procedures conducted during the day. A control group in each experiment was deprived of food and water for 20 h preceding each sucrose intake test, and as required by the place conditioning procedure (see below), but otherwise food and water were freely available in the home cage.

The stress regime used in each of weeks 1 and 2, was similar to that used previously (Muscat et al. 1987, 1990; Willner et al. 1987; Sampson et al. 1991) and consisted of: two 20 h periods of food and water deprivation, one immediately prior to the sucrose intake test, the other followed by 2 h of resricted access to food (scattering of a few 45 mg precision pellets in the cage); one additional 16 h period of water deprivation; two periods of continuous overnight illumination; two periods (7 and 17 h) of 45 degree cage tilt; one 17 h period of paired housing; one 17 h period in a soiled cage (100 ml water in sawdust bedding); two periods (3 and 5 h) of intermittent white noise (85 dB); three periods (7, 9 and 17 h) of low intensity stroboscopic illumination (300 flashes/min). During weeks 10 and 11 the stress regime consisted of overnight exposures to: continuous illumination; soiled cage; white noise; paired housing; stroboscopic illumination; cage tilt. All of the individual stressors used were classified as being, at worst, mildly stressful, under the terms of the relevant (UK) legislation, the Animals (Scientific Procedures) Act of 1986.

On the basis of their sucrose intake scores following 4 weeks of stress, each group was divided into four matched subgroups ($n = 10$); a computer programme was written to optimize the matching procedure, as a result of which the subgroups differed in their mean sucrose intakes by less than 0.1 g. Subsequently, separate groups of control and stressed animals were treated chronically with fluoxetine (5 mg/kg), maprotiline (5 mg/kg), chlordiazepoxide (5 mg/kg) or vehicle. Drugs were injected daily, between 17.00 and 19.00 hours, for a total of 9 weeks. In addition, all animals received a single, once-only injection of raclopride (100 µg/kg) 20 min before the week 12 sucrose intake test (i.e. after 8 weeks of chronic drug treatment).

During weeks 10 and 11 of stress (i.e. weeks 6–7 of drug treatment) eight animals in each group were randomly selected for training in a food-rewarded place preference conditioning procedure (it was not practicable to run all 80 animals). Place conditioning was conducted in six identical wooden chambers containing white and black arms ($30 \times 15 \times 15$ cm), with different floor textures (plain wood or wire mesh, respectively), and a central gray area ($15 \times 15 \times 15$ cm). For the first 3 days the animals were allowed freely to explore the whole chamber for 10 min daily. On day 4 the time spent in each arm was measured in a 10-min pre-conditioning test. On days 5–10, the animals received a series of 120-min training trials, preceded by 22 h food deprivation, in which the animals were confined on alternate days in each of the two arms. Food pellets (standard lab chow) and a water bottle were freely available in the white arm; the amount of food eaten was measured by weighing the food remaining at the end of each session. No food (or water) was available in the black arm; following confinement in the black arm, the animals were fed for 2 h on their return to the home cage. Changes in side-preference were measured on day 11 in a 10 min post-conditioning test; no rewards were available during this test, and the animals were not food deprived.

Drugs. The following agents were used in this study: fluoxetine hydrochloride (Lilly, Indianapolis); maprotiline hydrochloride (Sigma, St Louis); chlordiazepoxide hydrochloride (Roche, Welwyn); raclopride tartrate (Astra, Sodertalje). All drugs were dissolved in distilled water, which was used for control injections, and injected IP in a volume of 1 ml/kg body weight. Fluoxetine, maprotiline and chlordiazepoxide were administered chronically at 5 mg/kg and raclopride was administered acutely at 100 µg/kg; doses refer to the salts.

Analysis. Results were analyzed by analysis of variance, supplemented by tests of simple main effects and F-tests for contrasts, using the appropriate analysis of variance error term (Winer 1971). The analyses involved two between-subjects factors (stress/control and drug treatment) and where appropriate, one within-subjects factor (successive tests). Separate analyses were conducted on sucrose intake data collected before and after place preference conditioning (weeks 0–5 of drug treatment and weeks 7–9 of treatment, respectively).

Results

Sucrose intake

In the final baseline test, sucrose intake (mean ± standard error) was 12.8 (± 0.4) g in both groups. Following 4 weeks of stress, intake remained at 12.3 (± 0.4) g in controls, but fell to 9.0 (± 0.3) g in stressed animals [$F(1, 72) = 78.0$, $P < 0.001$]. In animals treated with vehicle or chlordiazepoxide, this difference persisted for the remainder of the experiment (Fig. 1). Body weight fell significantly during the first 4 weeks of stress (control: 312 ± 4 g; stress: 289 ± 3 g), but this difference had largely disappeared by the final week of the experiment (322 versus 312 g in vehicle-treated groups). At this time, body weights were similar in animals treated with vehicle, fluoxetine or maprotiline, and somewhat (but nonsignifiantly) higher in both chlorodiazepoxide-treated groups.

Fluoxetine and maprotiline had no significant effects on sucrose intake in control animals, but in stressed animals both drugs caused a gradual recovery of performance (Fig. 1), resulting in significant stress X weeks interactions over the first analysis period [weeks 0–5: fluoxetine, $F(3,216) = 5.96$, $P < 0.001$; maprotiline, $F = 2.78$, $P < 0.05$]. Sucrose intake in fluoxetine-treated stressed animals was increased significantly from baseline

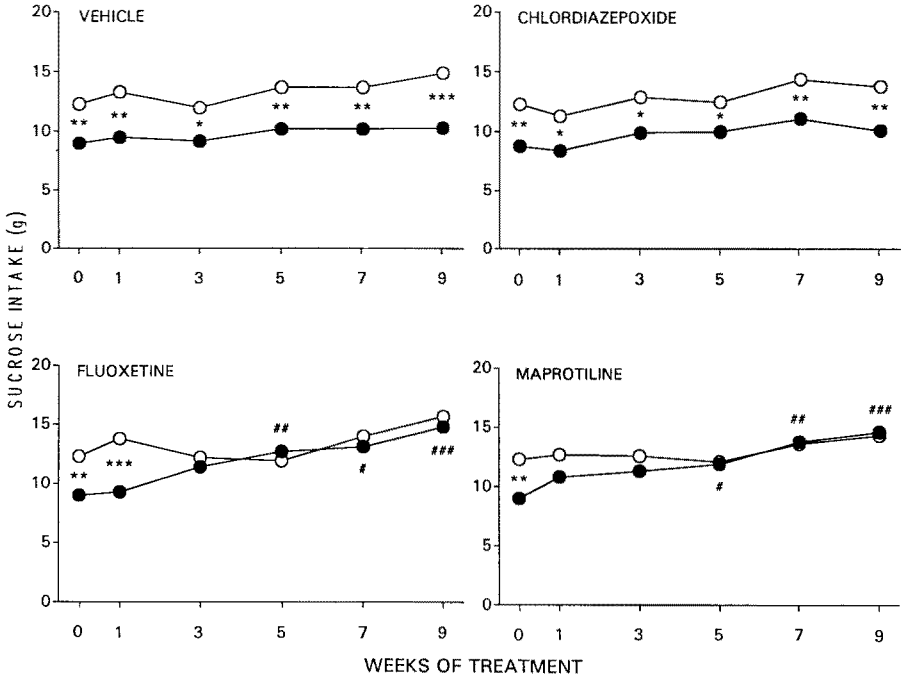

Fig. 1. The effect of exposure to chronic unpredictable mild stress and chronic drug treatment on consumption of 1% sucrose in a 1-h test. Drug treatment commenced following 4 weeks of stress. *Stars* represent comparisons between controls (*open circles*) and stressed animals (*closed circles*): * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. *Hatches* represent comparisons between drug- and vehicle-treated stressed animals: # $P < 0.05$; # # $P < 0.01$; # # # $P < 0.001$

after 3 weeks of treatment [$F(1,216) = 5.9$, $P < 0.025$]; after 5 weeks of treatment, these animals drank significantly more than vehicle-treated stressed animals [simple main effect: $F(1,72) = 7.7$, $P < 0.01$], and this increase was maintained thereafter (Fig. 1). After only 1 week of maprotiline treatment, there was no longer a significant difference between stressed animals and controls [$F(1,72) = 2.3$, N.S]; at 3 weeks, maprotiline-treated stressed animals were significantly improved from baseline [$F(1,216) = 5.9$, $P < 0.025$]; after 5 weeks of treatment, they drank significantly more than vehicle-treated stressed animals [simple main effect: $F(1,72) = 4.7$, $P < 0.05$]; and this increase was maintained thereafter (Fig. 1).

Analysis of sucrose intake data from weeks 7–9 of drug treatment (Fig. 2) revealed a significant 3-way interaction [drug × stress × weeks: $F(6,144) = 6.3$, $P < 0.001$]. The administration of raclopride in week 8 significantly reduced sucrose intake in fluoxetine and maprotiline treated stressed animals [$F(1,144) = 107.0$, 124.5, respectively, $P < 0.001$], but had no significant effect in vehicle or chlordiazepoxide treated stressed animals, or in any of the four control groups [max $F(1,144) = 3.2$, N.S.].

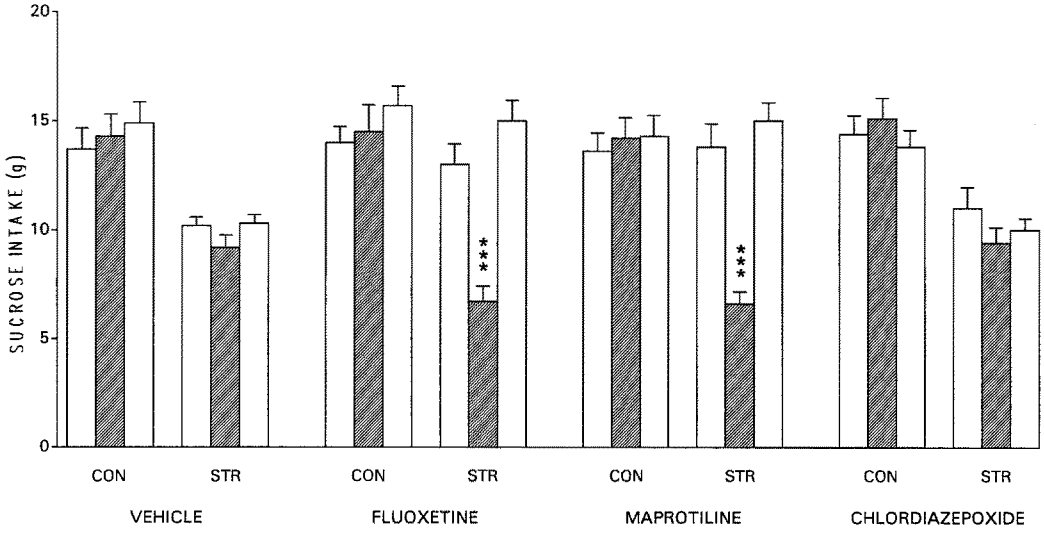

Fig. 2. Effect of raclopride (100 µg/kg) on consumption of 1% sucrose in 1-h tests, in controls (*CON*) and animals exposed to chronic mild stress (*STR*). Control data (*white bars*) are the same as those shown in Fig. 1 for weeks 7 and 9 of chronic drug treatment. Raclopride (*hatched bars*) was administered acutely prior to the sucrose test in week 8 of chronic treatment. *** $P < 0.001$ relative to control data collected in the immediately preceding and immediately following weeks

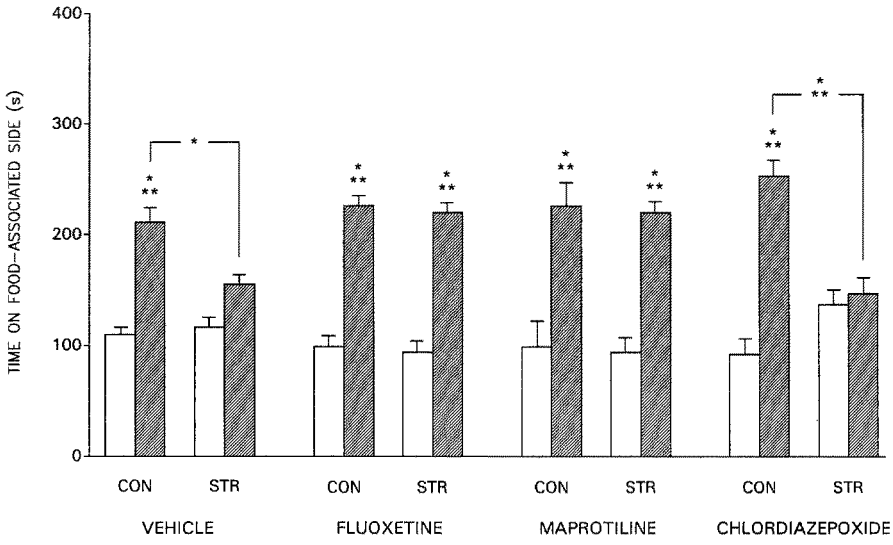

Fig. 3. Effects of chronic mild stress on food rewarded place preference conditioning in controls (*CON*) and stressed animals (*STR*). The data are time spent in the food-associated (*white*) side of the chamber before (*open bars*) and after (*hatched bars*) conditioning. * $P < 0.05$; ** $P < 0.001$; comparisons are between pre- and post-conditioning scores except where indicated

Table 1. Food intake on place conditioning trials[1,2]

	Trial 1		Trial 2		Trial 3	
	CON	STR	CON	STR	CON	STR
Vehicle	7.2 (0.2)	9.4 (0.4)	9.8 (0.3)	11.5 (0.6)	10.8 (0.3)	11.7 (0.5)
Fluoxetine	8.4 (0.6)	10.4 (0.5)	9.9 (0.7)	12.3 (0.5)	11.5 (0.6)	12.4 (0.8)
Maprotiline	8.6 (0.5)	11.1 (0.8)	9.3 (0.2)	11.9 (0.4)	9.5 (0.3)	11.7 (0.6)
Chlordiazepoxide	7.7 (0.5)	9.0 (0.4)	9.6 (0.6)	11.3 (0.3)	9.7 (0.5)	11.6 (0.3)

[1]Values are means (g) with standard error in parentheses, $n = 8$
[2]STR, stress; CON, control

Place preference conditioning

Prior to place conditioning animals spent more time on the black side of the apparatus (mean = 353 s) than on the white side (mean = 107s), but there were no significant effects of either stress or drug treatment (all F-values for main effects and interactions < 1.0). Analysis of time spent on the white side before and after conditioning (Fig. 3) revealed a significant 3-way interaction [drugs × stress × tests: $F(1,56) = 4.4$, $P < 0.01$]. Post-conditioning scores increased in all four control groups [$F(1,56) = 83.4$, $P < 0.01$] and in fluoxetine and maprotiline treated stressed animals [$F(1,56) = 16.3$, 23.3, respectively, $P < 0.001$]. However, no significant increases were observed in the vehicle and chlordiazepoxide treated stressed groups [$F(1,56) = 2.3$, 0.1, respectively, N.S.], with the result that post-conditioning scores in these two groups of animals were significantly lower than in their respective control groups [vehicle: $F(1,56) = 4.5$, $P < 0.05$; chlordiazepoxide: $F(1,56) = 17.0$, $P < 0.001$].

Food intake on the three place conditioning trials is shown in Table 1. Intake increased significantly over the 3 days [$F(2,112) = 84.0$, $P < 0.001$]. Stressed animals ate significantly more than controls on all three trials [$F(1,56) = 30.0$, $P < 0.001$], but there was no significant effect of drug treatment [$F(3,56) = 2.0$, N.S.].

Discussion

These experiments confirm our previous observation that chronic sequential exposure to a variety of mild stressors causes a reduction in the consumption of a palatable (1%) sucrose solution, consistent with a decrease in its rewarding properties (Willner et al. 1987; Muscat et al. 1987, 1990; Papp et al. 1991, 1992; Sampson et al. 1991). Although, in the present study, sucrose intake tests were carried out under conditions of food and water deprivation, the reduction of sucrose consumption by chronic mild stress is also present in nondeprived animals (Muscat and Willner 1992). This effect does not reflect a general decrease in consummatory behaviour, since water intake is unaffected by chronic mild stress (Willner et al. 1987; Muscat and Willner 1992); and food intake (measured during the conditioning trials) was actually higher in the stressed animals (Papp et al. 1991; and present data). There was also no clear relationship between changes in sucrose intake and changes in body weight. The reason for the increase in food intake in stressed animals is uncertain. However, an important consequence is that this should decrease the likelihood of observing an impairment of place preference conditioning. In fact, vehicle-treated stressed animals showed no significant increase in the time they spent on the food-associated side of the place condi-

tioning apparatus, in contrast to the controls, which showed large increases in preference for the food-associated side. A similar impairment of place preference conditioning by chronic mild stress has also been observed with other natural (sucrose solutions) and drug rewards (amphetamine, morphine) (Papp et al. 1991, 1992). Chronic mild stress has also recently been reported to elevate the threshold for intracranial self-stimulation of the ventral tegmental area (Moreau et al. 1992), as previously demonstrated for acute uncontrollable electric shock (Zacharko and Anisman 1991). However, chronic mild stress did not alter the response to aversive drug stimuli in the place conditioning procedure (Papp et al. 1992). Together, these data support the hypothesis that chronic mild stress leads to anhedonia: a generalized insensitivity to rewards (Willner et al. 1991).

We have previously reported that the decreased sucrose intake in animals subjected to chronic mild stress was reversed by chronic (2–5 weeks) treatment with the tricyclic antidepressants imipramine, DMI and amitriptyline (Willner et al. 1987; Muscat et al. 1988, 1990; Sampson et al. 1991). The present data extend this finding to two non-tricyclics, fluoxetine and maprotiline; in addition, they demonstrate, for the first time, that antidepressant treatment also reverses the impairment of place preference conditioning in chronically stressed animals. It should be noted that stress continued throughout the period of chronic drug administration, including the place conditioning phase. Unlike fluoxetine and maprotiline, the non-antidepressant chlordiazepoxide, at the relatively high dose of 5 mg/kg, failed to reverse either the decrease in sucrose intake, or the impairment of place preference conditioning.

Chronic treatment with antidepressant drugs has been reported to increase the psychomotor stimulant effects of DA agonists, administered either systemically or within the nucleus accumbens (See Introduction). Although neither fluoxetine nor maprotiline has been reported to potentiate the psychomotor stimulant effects of DA agonists after chronic treatment, potentiation of locomotor stimulation by DA agonists has been demonstrated after chronic treatment with other specific 5HT (citalopram) and NA (DMI) uptake inhibitors (Plaznik and Kostowski 1987; Maj 1988). Binding studies have revealed a decrease in the number of D1 binding sites in the nucleus accumbens following chronic antidepressant treatment (Klimek and Nielsen 1987), and no change in the number of D2 sites (Martin-Iverson et al. 1983; Klimek and Nielsen 1987); however, an increase in D2 agonist affinity has been observed, which may explain the behavioural data (Klimek and Maj 1989). We have previously reported that DA antagonists, administered acutely, reversed the therapeutic effects of tricyclic antidepressants within the chronic mild stress paradigm (Muscat et al. 1990; Sampson et al. 1991). In the present study, raclopride, a specific D2 antagonist (De Paulis et al. 1986), selectively reversed the therapeutic effect of fluoxetine and maprotiline: at the low dose used, raclopride had no effect on sucrose consumption in any of the four nonstressed control groups, or in the non-recovered vehicle- or chlordiazepoxide-treated stressed groups, but profoundly decreased sucrose intake in the two antidepressant-treated stressed groups. The effect of raclopride was short lasting: recovery of sucrose drinking was again apparent on the following, raclopride-free test.

These results suggest that while the primary pharmacological actions of fluoxetine, a specific 5HT uptake inhibitor, and maprotiline, a specific NA uptake inhibitor, are very different, after chronic treatment they share a common action; and that this common action, potentiation of DA transmission in (probably) the nucleus accumbens, is responsible for the reversal of anhedonia in animals subjected to chronic mild stress. The mechanisms by which acute actions on 5HT and NA systems give rise, after chronic treatment, to sensitization in DA systems, are unknown. The solution to this problem may well provide important insights into the mechanism of clinical action of antidepressant drugs.

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