Pergamon

Pharmacology Biochemistry and Behavior, Vol. 50, No. 2, pp. 147-151, 1995

0091-3057/95 $9.50 + .00

0091-3057(94)00274-6

Crucial Role of D_1 Dopamine Receptors in Mediating the Antidepressant Effect of Imipramine

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Received 22 February 1994

GAMBARANA, C., O. GHIGLIERI, A. TAGLIAMONTE, N. D'ALESSANDRO AND M. G. DE MONTIS. *Crucial role of D_1 dopamine receptors in mediating the antidepressant effect of imipramine.* PHARMACOL BIOCHEM BEHAV **50**(2) 147-151, 1995. – Although the neurochemical effects of chronic imipramine (IMI) treatment have been related to an increased adrenergic as well as dopaminergic transmission, no clear-cut evidence exists on whether one of these two neuronal systems mediates the behavioral effects of the tricyclic compound. Because a large body of evidence favors the role of dopamine, the interference of a selective inhibition of D_1 or D_2/D_3 dopamine receptors on IMI effect upon the learned helplessness behavior (LH) in rats was studied. A 2-week treatment with SCH 23390, followed by a 24-h washout, showed almost the same efficacy as chronic IMI in preventing LH induction. Moreover, SCH 23390 given acutely before the pretest completely antagonized the effect of chronic IMI. Furthermore, SKF 38393 administered to drug-naive animals prior to the unavoidable shocks completely neutralized its behavioral sequelae. Finally, the inhibition of D_2/D_3 dopamine receptors by acute sulpiride did not modify IMI efficacy. These results strongly suggest that D_1 dopamine receptor function controls the reactivity of animals exposed to a prolonged unavoidable stress, and mediates IMI antidepressant effect.

Depression Imipramine Dopamine agonists Dopamine antagonists Learned helplessness

A PARTIAL inhibition of catecholamine synthesis as produced by the daily administration of 50 mg/kg of α-methyl-para-tyrosine (α-MT), completely prevents the long-term effects of imipramine (IMI) in rats. Thus, animals receiving IMI for 3 weeks associated to α-MT do not develop hypersensitivity to the excitatory effects of dopamine agonists (6), and acquire the learned helplessness behavior (LH) if exposed to repeated inescapable shocks (8). Moreover, they do not show down regulation of β-adrenoceptor number and decreased response of adenylyl cyclase to β-adrenoceptor stimulation in the cerebral cortex (8). Finally, they do not present reduction of D_1 dopamine receptor number, decrease of adenylyl cyclase response to D_1 agonists, nor increase of the enzyme V_{max} in the limbic areas (6).

The neurochemical effects of chronic IMI treatment have been related to an increased neuronal transmission produced by the tricyclic compound on the adrenergic (29) as well as the dopaminergic (7) system. On the other hand, whereas no clear-cut relationship has been demonstrated between the increased β-adrenergic transmission and the antidepressant effects of iprindole, imipramine, and pargyline (9,19), evidence indicates that dopamine plays a relevant role in the mechanism of action of different antidepressant treatments. In fact, the hypersensitivity to dopamine agonists (1,15,27), the selective increase of dopaminergic transmission in the limbic areas (6,7), and the increased intracranial self-stimulation (10) produced in rats by long-term exposure to different antidepressants constitute a strong theoretical ground for such a role of dopamine. Moreover, it is well established that D_2 dopamine receptor supersensitivity mediates the increased behavioral response to dopamine agonists after chronic imipramine (24). However, little is known about whether a selective dopamine receptor subtype has a prominent part in the process of neuronal adaptation to chronic antidepressants. Thus, the present study examined how a selective inhibition of D_1 or D_2/D_3 dopamine receptors would affect the ability of IMI to prevent the acquisition of LH in rats. D_1 dopamine receptor function seems to play a key role in such an effect of IMI.

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METHOD

Animals

Experiments were carried out on male Sprague-Dawley rats (Charles River, Como, Italy). Animals were kept in a controlled environment with a constant temperature of 22°C, on a 12L : 12D cycle, with free access to food and water.

All the procedures used in this study were in strict accordance with the European legislation on the use and care of laboratory animals (CEE No. 86/609).

LH Induction

The procedure used has been described previously (17). In brief, the apparatus consisted of a Plexiglas cage (30 × 60 × 30 cm) with dark walls and covers. The floor was fitted with stainless steel rods spaced 1 cm apart. The cage was divided into two equal chambers (by a dark Plexiglas partition with a 10 × 10 cm sliding door), one having an electrified and the other a nonelectrified floor. The grid of the electrified floor was connected to one pole of a S 44 Grass stimulator; the second pole was connected to an electrode applied to the rat's tail. The apparatus was made by D.F. of D. Gambelli, Siena, Italy.

For the shock session, which lasted about 50 min, rats weighing a maximum of 250 g (however of constant weight within each experiment) were individually placed in the chamber with the electrified floor having the sliding door closed. Eighty inescapable electric shocks (1 mA × 5 s) were delivered (one every 30 s) through the electrode attached to the rat's tail and protected by a rigid plastic tube (pretest). Twenty-four hours later, animals were tested in a shock/escape paradigm in the same apparatus of the inescapable session. Rats were individually placed in the electrified floor chamber where, after a 5-min habituation period, they received 30 consecutive electric shocks (1 mA × 5 s), at 30-s intervals. Shocks were delivered to the rat's tail in coincidence with a 5-s opening of the door (10 × 10 cm) connecting the electrified chamber to the nonelectrified one (escape test). Animals that succeeded in escaping were immediately replaced in the electrified floor chamber, where they spent the next 30-s interval. Those that failed to escape awaited in the test chamber for the next 5-s trial.

Experimental Protocols

For chronic drug treatments, animals initially weighing 125–150 g were utilized.

1) Fifty rats were divided into five groups of 10 animals each. A group of 10 rats was treated with imipramine (10 mg/kg, IP) twice a day for 2 weeks. A second group of animals received *l*-sulpiride (25 mg/kg, IP) twice a day. Rats of the third group were implanted with a SC minipump (Alzet 2002) delivering 0.03 mg/kg/day of SCH 23390 for 14 days. The remaining 20 animals received saline for the same period of time: half of these rats were injected IP, twice a day (1 ml/kg), and the other half were implanted with SC minipumps (Alzet 2002).

2) A group of 30 rats was treated for 14 days with imipramine (10 mg/kg, IP, twice a day), and then was divided into three subgroups of 10 animals each. Twenty rats (controls) received saline (1 ml/kg, IP, twice a day) for 2 weeks. Each group, 20 min before the exposure to inescapable shocks, received an acute injection of either saline, SCH 23390 (0.03 mg/kg/day, SC), or sulpiride (25 mg/kg, IP).

3) Acute behavioral experiments were carried out in groups of at least 10 rats each (weight 200–250 g).

Animals underwent the pretest 2 h after the last treatment with IMI and 24 h after the last administration of *l*-sulpiride or the cessation of SCH 23390 infusion. Acute treatments were administered 20 min before the pretest or the test session, unless differently specified. The escape test was carried out 24 h later.

For each group of control rats, half of the animals did not receive the unavoidable shocks (naive).

Drugs

Imipramine hydrochloride, SCH 23390, SKF 38393, and quinpirole were dissolved in 0.9% saline. *l*-Sulpiride was dissolved in saline with a few drops of glacial acetic acid; pH was adjusted to 6–6.5 with a Tris saturated solution. All drugs were injected in a volume of 0.1 ml/100 g rat body weight. For long-term SCH 23390 administration, the drug was dissolved in saline and administered by osmotic minipump (Alzet 2002). Each treated group had its proper controls that received the vehicle by the same route of administration. Imipramine hydrochloride, SCH 23390, and SKF 38393 were purchased from commercial sources; *l*-sulpiride was generously supplied by Ravizza, Italy; quinpirole was a gift from Ely Lilly, USA.

Statistics

All data are expressed as mean ± SEM. Because multiple drug treatments were compared with values from a single control group, statistical comparisons were made by ANOVA followed by post hoc analysis using the Bonferroni test ($p < 0.05$) (18).

RESULTS

Long-Term IMI Treatments

In the first set of experiments, the effects of a chronic IMI administration on LH acquisition were compared to those induced by a chronic treatment with SCH 23390 or *l*-sulpiride, selective D_1 and D_2/D_3 dopamine receptor antagonists, respectively. The administration of IMI was interrupted the day of the inescapable shock session, whereas that of the antagonists ceased 24 h earlier. As shown in Fig. 1, IMI completely prevented the acquisition of LH; SCH 23390 was slightly less potent than the tricyclic compound. On the other hand, animals treated with *l*-sulpiride showed a clearcut LH. Sham-operated control rats, subjected or not to the pretest, did not perform differently on the escape test from saline-injected controls. Thus, data from sham and control animals belonging to the same subgroup were pooled in the final results.

To further clarify the reciprocal role of D_1 and D_2/D_3 dopamine receptors on the mechanism of action of IMI, SCH 23390 and *l*-sulpiride were administered acutely 20 min before the pretest session to rats treated for 2 weeks with the tricyclic antidepressant. Figure 2 shows that whereas SCH 23390 (0.03 mg/kg, SC) completely antagonized the protective effect of IMI on the behavioral consequences of inescapable shocks, *l*-sulpiride (25 mg/kg, IP) was ineffective.

Acute Treatments Before the Pretest

In the second series of experiments, the selective D_1 agonist SKF 38393 and the D_2/D_3 agonist quinpirole were acutely administered to drug-naive rats before the inescapable shocks. When tested for escape 24 h later, rats that had received SKF 38393 (2.5 mg/kg, IP) 20 min prior to the pretest showed a number of escapes similar to that of naive animals (Fig. 3). Interestingly, only half of the animals treated with quinpirole

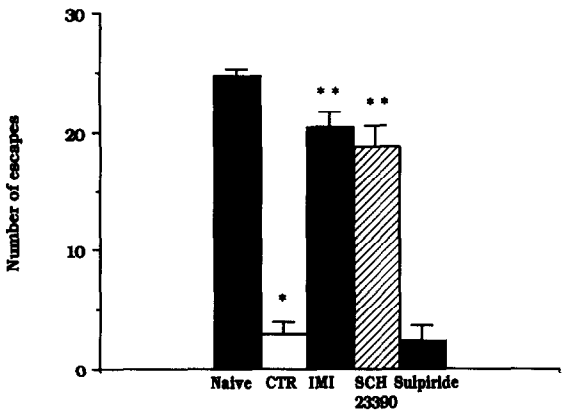

FIG. 1. Effect of chronic treatment with imipramine (IMI), SCH 23390, or *l*-sulpiride on the acquisition of LH by rats. IMI (10 mg/kg, IP, twice a day), SCH 23390 (0.03 mg/kg, SC, daily), and *l*-sulpiride (25 mg/kg, IP, twice a day) were administered to rats for 2 weeks, as described in the Method section. Animals underwent the inescapable shock session 2 h (IMI) or 24 h (SCH 23390 and *l*-sulpiride) after the end of treatment. Behavioral scores are expressed as average number of escapes ± SEM in 30 consecutive trials. *Significantly different ($p < 0.001$) from naive animals. **Significantly different ($p < 0.001$) from control animals.

(0.25 mg/kg, SC) 15 min before the unavoidable shock session escaped during the test (Fig. 3, inset).

Acute Treatments Before the Escape Test

To examine whether the stimulation of D_1 and/or D_2/D_3 dopamine receptor activity could antagonize the "depressant" effect of the repeated unavoidable shocks, SKF 38393 or quinpirole was injected 20 and 15 min, respectively, before the escape test to naive and conditioned rats. Neither compound modified the performance of naive animals (data not shown). However, both of them completely antagonized the behavioral sequelae of inescapable shocks (Fig. 4).

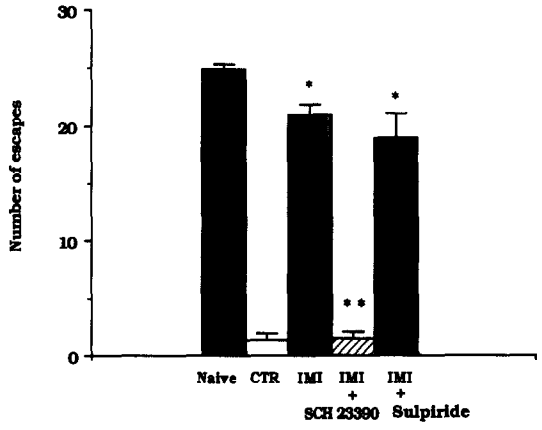

FIG. 2. Effects of the acute blockade of D_1 or D_2/D_3 dopamine receptors on imipramine (IMI) prevention of LH acquisition. Rats treated with IMI for 2 weeks received an injection of SCH 23390 (0.03 mg/kg, SC) or *l*-sulpiride (25 mg/kg, IP) 20 min before the inescapable shocks. Behavioral scores are expressed as average number of escapes ± SEM in 30 consecutive trials. *Significantly different ($p < 0.001$) from control animals. **Significantly different ($p < 0.001$) from naive animals.

Finally, the effects of dopamine D_1 or D_2/D_3 receptor inhibition on the number of escapes of naive rats were studied. Figure 4 shows that, whereass SCH 23390 completely inhibited the avoidance behavior in the tested animals, *l*-sulpiride had no apparent effect.

DISCUSSION

A large body of pharmacological and neurochemical evidence supports the hypothesis that dopamine plays a considerable role in affective disorders. In fact, dopamine metabolites are reduced in the cerebrospinal fluid of depressed patients (21), and the administration of dopamine agonists improves mood in bipolar patients [for review see (13)]. Moreover, it is well accepted that the clinical efficacy of neuroleptics in mania is related to dopamine receptor blockade, that depressive states have been reported among the side effects of neuroleptics, and that rebound improvement of mood and even hypomania might follow their abrupt withdrawal [for review see (13)]. Sulpiride, an atypical neuroleptic that rather selectively inhibits D_2/D_3 dopamine receptors, is considered effective in depression (2), and its activating effects have been associated with preferential blockade of presynaptic dopamine receptors. Anhedonia, a pathognomonic symptom of depression, has been related to a decreased dopaminergic transmission in the limbic areas mediating reward (11). Such data are further strenghtened by the findings that long-term exposure of rats to different antidepressant treatments results in marked supersensitivity to the effects of central stimulants on motility (26), downregulation of the D_1 dopamine receptor complex in the limbic areas (5,14), and increased dopamine release in the nucleus accumbens (22).

However, no clear indications are available on a possible prominent role played by a single subtype of dopamine receptors in the stability of mood, although the increased behavioral response to central stimulants produced by a chronic treatment with IMI is clearly induced by D_2 dopamine receptor supersensitivity (24). Moreover, others have reported that D_2 dopamine receptor agonists appear to be active in some animal models of depression, like the forced swimmig test (3) and LH (12).

The present data provide circumstantial evidence that the D_1 dopamine receptor system is essential in the antidepressant action of IMI. In fact, a long-term inhibition of D_1 dopamine receptors, followed by a 24-h wash-out, had almost the same efficacy in preventing the acquisition of LH by rats as a chronic treatment with IMI. This finding may be easily explained in terms of D_1 dopamine receptor supersensitivity (20). Moreover, long-term *l*-sulpiride administration failed to affect LH acquisition. The pivotal role of D_1 dopamine receptors in LH is further supported by the fact that: (i) SCH 23390, given acutely before the pretest, completely antagonized the effect produced by a chronic IMI treatment; (ii) SKF 38393, administered to drug-naive animals just prior to the unavoidable shock session, completely prevented its behavioral sequelae. Furthermore, the selective inhibition of D_2/D_3 dopamine receptors as produced by *l*-sulpiride administered immediately before the pretest did not modify the antidepressant effect of IMI. These results strongly suggest that D_1 dopamine receptor function controls the reactivity of animals exposed to a prolonged unavoidable stress.

Both SKF 38393 and quinpirole administered acutely 30 min before the test session to pretested rats produced a complete reversal of LH. The result obtained with SKF 38393 is in agreement with previous data showing that this compound is

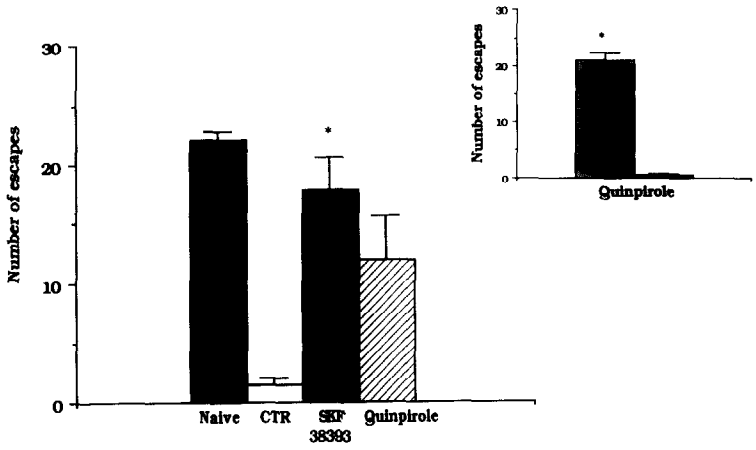

FIG. 3. Antagonism of LH development by acute administration of SKF 38393 or quinpirole in control (pretested) rats. Animals received SKF 38393 (2.5 mg/kg, IP) or quinpirole (0.25 mg/kg, SC) 20 and 15 min, respectively, prior to the inescapable shock session. Behavioral scores are expressed as average number of escapes ± SEM in 30 consecutive trials. Quinpirole-treated rats could be divided into two subpopulations (inset): animals that failed to escape (0.5 ± 0.3 escapes) and animals that escaped (21.0 ± 1.4 escapes). *Significantly different ($p < 0.001$) from control animals.

able to reverse LH and to reduce immobility time in the forced swimming test (23). Interestingly, cocaine (10 mg/kg, IP) was able to reverse completely LH if administered 15 min before the test session, whereas it failed to prevent LH induction when given before the shock session (data not shown). Thus, although LH reversal seems generically related to a central stimulant effect, the prevention of LH acquisition appears to be mediated by a rather selective D_1 dopamine receptor activation.

The present results are at variance with those reported by Borsini et al. (3). These authors, using the forced swimming test as a model of depression, concluded that D_2 dopamine receptor activation plays a crucial role in restoring animal reactivity and in mediating the antidepressant effect of DMI. Indeed, in that experimental setting, D_1 dopamine receptor activity appears almost irrelevant. The discrepancy between such findings and ours might derive from the use of different animal models and protocols. For instance, 5-HT uptake inhibitors are able to antagonize LH (16), whereas they are almost inactive on the forced swimming test (4). Moreover, the effect of tricyclics on LH takes at least 3 days to develop (25) and is maximal after 2–3 weeks of chronic treatment (17); thus, it can be better evaluated in terms of preventive activity. On the other hand, in the forced swimming test DMI appears significantly effective also if administered during the 24-h interval between the stress and the test session (3). Thus, due to the short duration of the LH syndrome compared to the slow development of IMI effect, we focused our attention and experiments more on the prevention of stress behavioral sequelae than on their reversal.

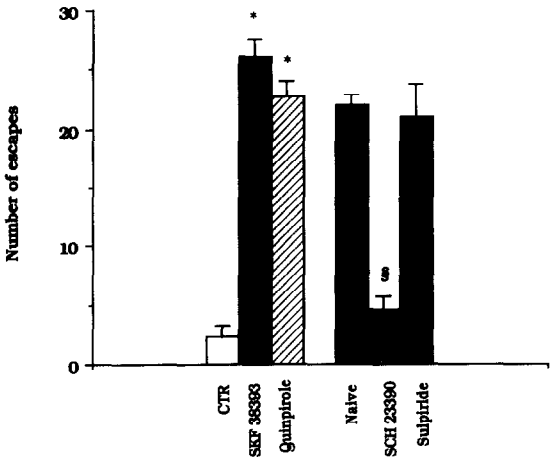

FIG. 4. Effects of acute treatments with dopaminergic agonists or antagonists on LH. Control (pretested) animals received SKF 38393 (2.5 mg/kg, IP) or quinpirole (0.25 mg/kg, SC) 20 and 15 min, respectively, prior to the escape test. Naive rats were treated with SCH 23390 (0.03 mg/kg, SC) or *l*-sulpiride (25 mg/kg, IP) 20 min before the escape test. Behavioral scores are expressed as average number of escapes ± SEM in 30 consecutive trials. *Significantly different ($p < 0.001$) from control rats. §Significantly different ($p < 0.001$) from naive rats.

The prominent role played by D_1 dopamine receptors in preventing the behavioral consequences of a prolonged unavoidable stress was questioned by the findings obtained with quinpirole. In fact, 50% of rats receiving the D_2/D_3 agonist before the pretest performed similarly to naive animals at the test session. However, the importance of D_2/D_3 receptors in reversing the behavioral deficits of pretested rats was weakened by the failure of acute sulpiride treatment to modify the escape rate of naive animals, whereas SCH 23390 pretreatment completely inhibited avoidance.

In conclusion, the role of D_1 dopamine receptor activation in rats seems to be crucial in preventing the development and in eliminating the behavioral sequelae of repeated inescapable shocks, as well as in mediating the antidepressant effect of IMI. In such a context, the D_2/D_3 dopamine receptors appear to play a facilitatory, ancillary role.

ACKNOWLEDGEMENTS

This work was supported by grants from the M.U.R.S.T. and from the C.N.R.

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