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Reversal of antidepressant-induced dopaminergic behavioural supersensitivity after long-term chronic imipramine withdrawal

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Abstract

Chronic antidepressant treatments enhance dopaminergic neurotransmission in the mesolimbic dopamine system. We suggested that this potentiation might underlie both the antidepressant therapeutic effect and the antidepressant-induced switch from depression to mania, which in turn, might be involved in the development of rapid cycling in bipolar patients. In this study, we investigated the changes occurring in the sensitivity of the mesolimbic dopamine system up to 40 days after antidepressant withdrawal. Male Sprague–Dawley rats were treated for 3 weeks with imipramine (20 mg/kg) and tested for motor activity 24 h, 12, 33 and 40 days after treatment withdrawal. Ambulatory activity and rearing counts were recorded after challenge with the dopamine D2-like receptor agonist quinpirole (0.15 mg/kg). Imipramine increased the motor response to quinpirole, 24 h after treatment discontinuation. No relevant differences between the groups were found after 12 and 33 days. After 40 days, a decreased level of rearing was observed in the group treated with imipramine. These results show a reversal of the imipramine-induced dopaminergic supersensitivity after 40 days of chronic imipramine withdrawal and suggest that the mood-switches observed in bipolar patients following antidepressant treatment and subsequent withdrawal, i.e. mania followed by rebound depression, might depend upon parallel changes in the mesolimbic dopamine system sensitivity.
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Keywords: Antidepressant; Bipolar disorder; Imipramine; Mania; Rapid cycling; Supersensitivity

1. Introduction

A number of experimental observations suggest that a decreased dopaminergic neurotransmission might be associated with depression, whereas an increased dopaminergic neurotransmission might be associated with mania (see Jimerson, 1987). In particular, dopamine receptor antagonists, which are effective in the treatment of mania (Baldessarini, 1996), have been reported to induce depressive states (see Randrup et al., 1975; Willner, 1983). Conversely, dopamine receptor agonists, which can be effective in the treatment of depression (e.g. Angrist et al., 1975; Bouras and Bridges, 1982; Colonna et al., 1979; Corrigan et al., 2000), have been reported to precipitate mania in bipolar patients (Randrup et al., 1975; Jimerson, 1987). Moreover, decreased and increased cerebrospinal fluid levels of homovanillic acid, a major dopamine metabolite, have been detected in depressive and manic patients, respectively (Jimerson, 1987; Willner, 1983).

Antidepressant treatments enhance dopaminergic neurotransmission by increasing the behavioural sensitivity to the stimulation of dopamine receptors in the mesolimbic dopamine system (Collu et al., 1997; D'Aquila et al., 1992, 1997a,b,c, 2000a,b, 2001; Maj et al., 1989; Serra et al., 1979, 1990, 1992; Spyraki and Fibiger, 1981). We suggested that such supersensitivity might underlie, on the one hand, the antidepressant therapeutic effect (see D'Aquila et al., 2000b; Serra et al., 1992), and, on the other hand, the antidepressant-related manic states (D'Aquila et al., 2000a, 2001; Serra et al., 1990, 1992), such as antidepressant-induced switch from depression to mania, which in turn, might be one of the critical events leading to the development of rapid cycling in bipolar patients (Koukopoulos et al., 1995).

The potentiation of dopamine transmission by antidepressant treatments, as revealed by the increased motor

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stimulant response to dopamine agonists, takes place after 2–3 weeks of treatment (see D'Aquila et al., 2000b), and it is still present 3 days (Serra et al., 1990), but not 10 days (Spyraki and Fibiger, 1981) after treatment discontinuation. No information is available in the literature as to what happens after long-term withdrawal.

In this study, we investigated the changes in the sensitivity of the mesolimbic dopamine system up to 40 days after antidepressant withdrawal, by measuring, in four different groups of animals, the motor response to the dopamine D2-like receptor agonist quinpirole 24 h, 12, 33 and 40 days after discontinuation of a 3-week imipramine treatment.

2. Materials and methods

The present study was carried out in accordance to the Italian law, which allows experiments on laboratory animals only after submission of a research project to the competent authorities, and in accordance to the "Principles of laboratory animal care" (NIH publication no. 85–23, revised 1985).

2.1. Subjects

Male Sprague–Dawley rats (Harlan, Italy), weighing initially 180–200 g, were used as subjects. They were housed 2–3 per cage in air-conditioned rooms. The rooms were lit between 8 a.m. and 8 p.m. and maintained at a temperature of 22 ± 2 °C and humidity 50–60%.

2.2. Drugs and treatments

The animals ($N = 80$) were treated for 3 weeks with either imipramine (20 mg/kg), $n = 40$, or vehicle (distilled water, 1 ml/kg), $n = 40$. At the end of the treatment, they have been divided into four groups, with each group, including 10 imipramine-treated and 10 vehicle-treated animals, to be challenged with quinpirole and tested for motor activity at different times after the end of chronic treatment. Testing times for the four groups were 24 h, 12, 33 and 40 days, respectively, after the end of imipramine treatment.

Quinpirole HCl and imipramine HCl (Sigma, St. Louis, USA) were dissolved in distilled water. Imipramine was administered intraperitoneally in daily injections, at the dose of 20 mg/kg in a volume of 1 ml/kg. Quinpirole was administered subcutaneously at the dose of 0.15 mg/kg in a volume of 1 ml/kg.

2.3. Motor activity

Motor activity was measured by an apparatus consisting of a mobile rack (height 180 cm, width 100 cm and depth 60 cm) with eight compartments (height 40 cm, width 45 cm, depth 50 cm), into which a transparent Perspex cage (height 19 cm, floor area 23 × 33 cm) was placed (Imetronic, Pessac, France). Motor activity is detected by a system of photocell infrared beams, dividing the cage area into two sectors, rear and front sector. In particular, the interruption of two photocell beams belonging to two different sectors is recorded as an ambulatory activity count. A "barrier" of

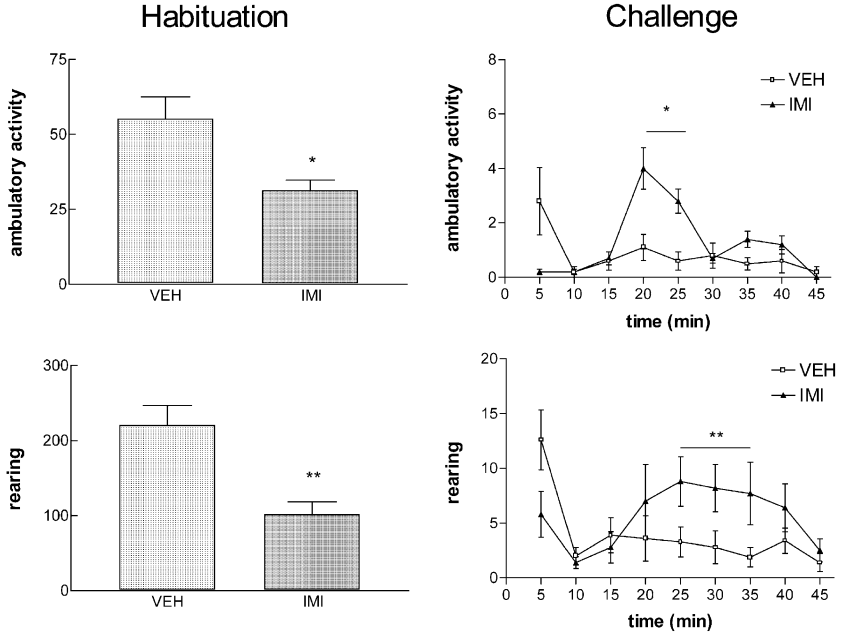

Fig. 1. Motor response to quinpirole after 24 h chronic imipramine withdrawal. VEH: vehicle, IMI: imipramine. After 60 min habituation to the motility cages (left panels), ambulatory activity (top panels) and rearing (low panels) were recorded for 45 min following a 0.15 mg/kg s.c. quinpirole injection (right panels). *$P < 0.05$; **$P < 0.01$ (habituation: ANOVA, main effect of imipramine; quinpirole challenge: ANOVA followed by F-tests for contrasts).

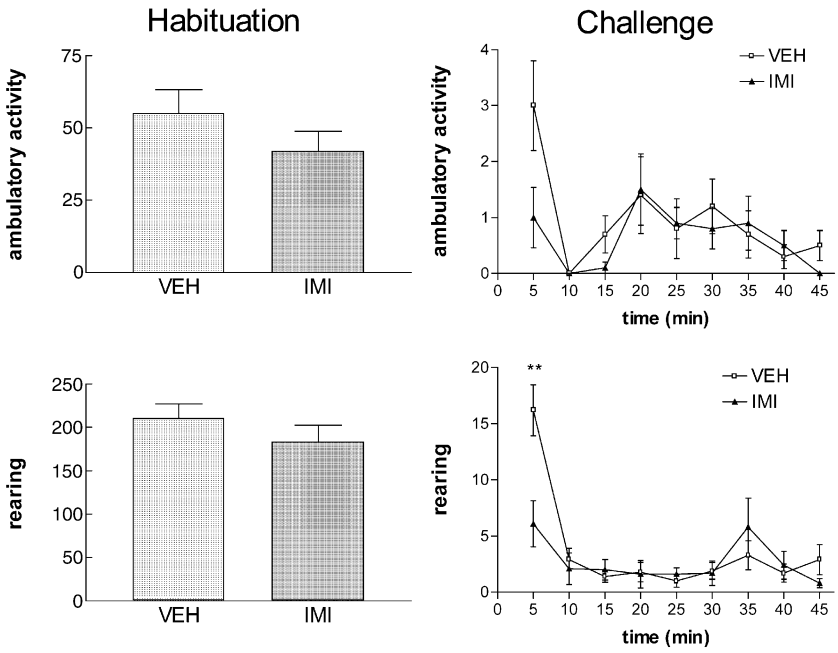

Fig. 2. Motor response to quinpirole after 12 days chronic imipramine withdrawal. VEH: vehicle, IMI: imipramine. After 60 min habituation to the motility cages (left panels), ambulatory activity (top panels) and rearing (low panels) were recorded for 45 min following a 0.15 mg/kg s.c. quinpirole injection (right panels). $^{**}P < 0.01$ (ANOVA followed by F-test for contrasts).

infrared photocell beams, placed at the height of 15 cm, detects rearing activity. The apparatus was connected to a personal computer by an electronic interface.

Experiments were performed between 9 a.m. and 3 p.m. After 1-h habituation to the motility cages, all the rats were subcutaneously injected with 0.15 mg/kg quinpirole and the motor response was recorded for the following 45 min. Data have been collected in 5-min time bins.

2.4. Statistics

The results were analysed by analysis of variance (ANOVA), supplemented by F-tests for contrasts, using the appropriate ANOVA error term (Winer, 1971). Habituation and quinpirole challenge data have been analysed separately. The analysis involved one between groups factor, imipramine (with two levels: vehicle and imipramine),

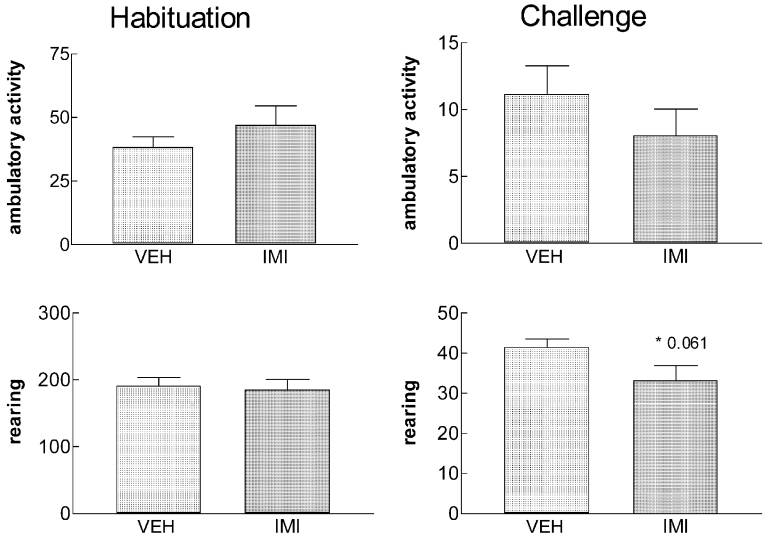

Fig. 3. Motor response to quinpirole after 33 days chronic imipramine withdrawal. VEH: vehicle, IMI: imipramine. After 60 min habituation to the motility cages (left panels), ambulatory activity (top panels) and rearing (low panels) were recorded for 45 min following a 0.15 mg/kg s.c. quinpirole injection (right panels). $^{*}P < 0.061$, not significant (ANOVA, main effect of imipramine).

and a within group factor, time (habituation, 12 levels and quinpirole challenge, 9 levels, with each level corresponding to a 5-min time bin).

3. Results

In the group of animals tested 24 h after the end of chronic treatment, imipramine induced a decrease both in ambulatory activity and in rearing counts during habituation [long movements, simple main effect of imipramine: $F(1,18)=5.64$, $P=0.028$; rearing, simple main effect of imipramine: $F(1,18)=15.31$, $P=0.001$]. After quinpirole administration, the opposite picture has been observed: the animals treated with imipramine showed a statistically significant increase both in ambulatory activity and in rearing counts [ambulatory activity, imipramine × time interaction: $F(8,144)=3.67$, $P=0.00063$; rearing, imipramine × time interaction $F(8,144)=2.76$, $P=0.007$](Fig. 1).

In the group of animals tested 12 days after the end of chronic treatment, no statistically significant difference between imipramine and control group was revealed, apart from a decreased level of rearing in imipramine-treated animals observed in the first 5 min time bin after quinpirole challenge [imipramine × time interaction $F(8,144)=5.32$, $P=0.000007$](Fig. 2). Similarly, 33 days after withdrawal, neither imipramine effects, nor statistically significant interactions involving imipramine have been shown by statistical analysis, although imipramine main effect in rearing counts after quinpirole challenge was on the verge of statistical significance [$F(1,18)=3.96$; $P=0.061$](Fig. 3).

In the group of animals tested 40 days after the end of chronic treatment, no statistically significant difference between the groups was observed in ambulatory activity counts, either in the habituation period or after challenge with quinpirole. Rearing counts were not affected by imipramine treatment in the habituation period. However, a decreased level of rearing after quinpirole challenge was observed in the group treated with imipramine [simple main effect of imipramine: $F(1,9)=8.84$, $P=0.015$; imipramine × time interaction: $F(8,72)=2.07$, $P=0.049$](Fig. 4).

4. Discussion

The present results confirm the ability of chronic treatment with imipramine to potentiate the motor response to dopamine agonists, as shown by the potentiation of ambulatory activity and rearing counts in imipramine-treated animals challenged with quinpirole 24 h after imipramine withdrawal.

The main finding from this study is the demonstration of the reversal of the imipramine-induced dopaminergic behavioural supersensitivity, which was revealed 40 days after imipramine withdrawal, as shown by the reduction of rearing counts observed in the imipramine-treated animals challenged with quinpirole. A similar trend was also observed in rearing counts in the quinpirole challenge performed 12 and 33 days after withdrawal.

On the basis of experimental evidence, suggesting a link between increased dopaminergic neurotransmission and mania (see Jimerson, 1987), we proposed that the increased sensitivity of the mesolimbic dopamine system induced by repeated treatment with antidepressant drugs might be one of the neural substrates underlying antidepressant-induced switch from depression to mania (D'Aquila et al., 2000a,

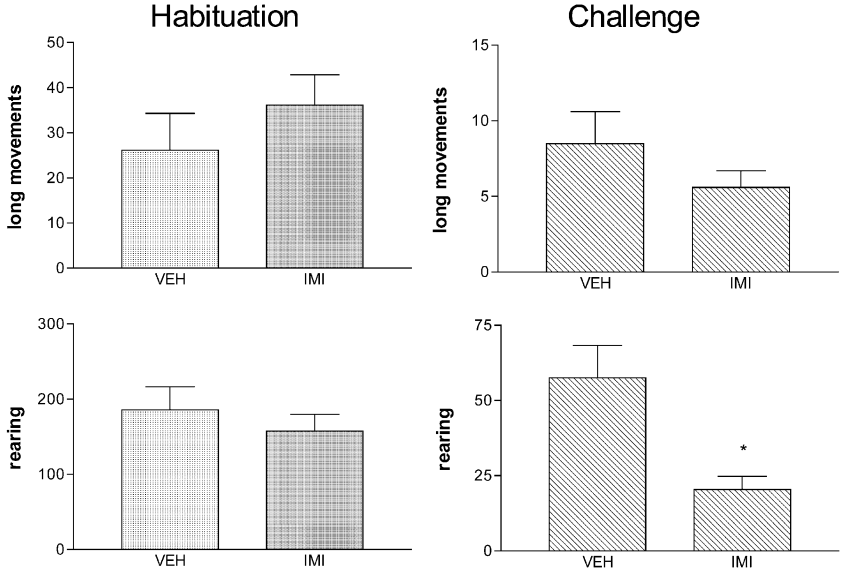

Fig. 4. Motor response to quinpirole after 40 days chronic imipramine withdrawal. VEH: vehicle, IMI: imipramine. After 60 min habituation to the motility cages (left panels), ambulatory activity (top panels) and rearing (low panels) were recorded for 45 min following a 0.15 mg/kg s.c. quinpirole injection (right panels). *$P<0.05$ (ANOVA followed by F-test for contrasts).

2001; Serra et al., 1990), which, in turn, might be one of the critical events leading to the development of rapid cycling in bipolar patients (Koukopoulos et al., 1995).

Consistently with this hypothesis, on the one hand, we found that lithium, which is poorly effective in these pathological conditions (see Koukopoulos et al., 1995; Soares, 2000), failed to prevent the development of such supersensitivity (D'Aquila et al., 2000a). On the other hand, we observed that the anticonvulsant and antimanic drug carbamazepine, which had been shown to be effective in the treatment of rapid cycling in uncontrolled studies and small controlled studies (Joyce, 1988; Post et al., 1983, 1984, 1987), did prevent the development of imipramine-induced dopaminergic behavioural supersensitivity (D'Aquila et al., 2001), although no controlled trials comparing the effects of carbamazepine with those of lithium salts in this category of patients have been ever published (see Soares, 2000).

Including in the framework of this hypothesis the present results, it might be suggested that the increased frequency of mood switches in bipolar patients, eventually leading to rapid cycling, might be triggered, or at least facilitated, by parallel changes in dopamine neurotransmission in the mesolimbic system induced by antidepressant treatment and by its discontinuation. According to this view, the increase in sensitivity of the mesolimbic dopamine system induced by antidepressants might trigger a switch from depression to mania, whereas the decreased sensitivity of this system, which develops after withdrawal might facilitate the precipitation of a depressive episode. This picture provides a suggestive parallel to the mood switches observed in long-term psychostimulant abusers, who may develop a euphoric–hypomanic state when using the drugs, followed by a rebound depressive state during withdrawal (see O'Brien, 1996). Moreover, the observed reversal might also offer a possible explanation to the increased risk of relapse or recurrence of a depressive episode observed after antidepressant treatment discontinuation (Anonymous, 1999; Mirin et al., 1981; Prien and Kupfer, 1986).

According to the proposed hypothesis, one might predict that long-term antidepressant withdrawal result in a depressive-like/anhedonic state, which can be tested in depression models, such as the forced swimming test or learned helplessness, and in models of hedonic behaviour, such as conditioned place preference or intracranial self-stimulation. An association between decreased mesolimbic dopamine system sensitivity and depressive-like/anhedonic state has already been observed in the chronic mild stress model of depression: animals subjected to this experimental procedure display a decreased motor response to dopamine agonists coexisting with deficits in several experimental paradigms measuring hedonic behaviour, and in particular: impairment of conditioned place preference acquisition, increased brain stimulation reward thresholds and decreased consumption and preference for low concentration sucrose solutions (see Willner et al., 1992).

In this study, we dealt with changes in the sensitivity of the mesolimbic dopamine system caused by imipramine treatment (and its discontinuation). Further studies on different antidepressant drugs are necessary in order to better evaluate the relevance of this finding. Moreover, studies on dopamine D2/D3 receptor density and mRNA expression might help to clarify the molecular mechanisms of the observed phenomenon.

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