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Short communication

Long-term imipramine withdrawal induces a depressive-like behaviour in the forced swimming test

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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. In a recent study we have shown a reversal of the imipramine-induced dopaminergic supersensitivity after 40 days of chronic imipramine withdrawal. We interpreted this result suggesting 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. On this basis, one might predict a depressive-like behaviour after long-term interruption of a chronic treatment with imipramine. To test this hypothesis we examined the behaviour of rats treated with chronic imipramine 40 days after treatment interruption in an animal model of depression, the forced swimming test. The results show that animals treated with chronic imipramine, 40 days after treatment interruption, display a depressive-like behaviour in the forced swimming test, as indicated by their increased immobility with respect to the control group.

Keywords: Antidepressant; Depression; Forced swimming test; Imipramine

1. Introduction

Antidepressant treatments enhance dopaminergic neurotransmission by increasing the behavioural sensitivity to the stimulation of dopamine receptors in the mesolimbic dopamine system (D'Aquila et al., 2000, 2001, 2003; Serra et al., 1990, 1992). We suggested that such supersensitivity might underlie, on the one hand, the antidepressant therapeutic effect (see D'Aquila et al., 2000; Serra et al., 1992), and, on the other hand, the antidepressant-related manic states (D'Aquila et al., 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 stimulant response to dopamine receptor agonists, takes place after 2–3 weeks of treatment (see D'Aquila et al., 2000), and persists at least up to 3 days after treatment discontinuation (Serra et al., 1990). In a successive study we investigated the changes occurring in the sensitivity of the mesolimbic dopamine system up to 40 days after antidepressant withdrawal. A reversal of the imipramine-induced dopaminergic supersensitivity after 40 days of chronic imipramine withdrawal was observed (D'Aquila et al., 2003). We interpreted this result suggesting 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. On this basis, one might predict a depressive-like behaviour after long-term interruption of a chronic treatment with imipramine. To test this hypothesis we examined the behaviour of rats treated with chronic imipramine 40 days after treatment interruption in an animal model of depression, the forced swimming test.

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2. Methods and materials

The present study was carried out in accordance with the Italian law, which allows experiments on laboratory animals only after submission of a research project to the competent authorities, and in accordance with 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 two to three per cage in air-conditioned rooms. The rooms were lit between 0800 and 2000 and maintained at a temperature of 22 ± 2 °C and humidity of 50–60%.

2.2. Drugs and treatments

The animals ($N = 24$) were divided into two groups and treated for 4 weeks with either daily intraperitoneal (i.p.) injections of imipramine ($n = 12$), or vehicle ($n = 12$). The dose of imipramine was 20 mg/kg/day, in a volume of 1 ml/kg of distilled water. Forty days after the end of imipramine treatment they were tested in the forced swimming test paradigm.

2.3. Forced swimming test

According to the method described by Porsolt et al. (1978), the animals were placed individually in perspex cylinders (40 cm height; 18 cm diameter) containing 15–16 cm of water at 25 °C, and 15 min later they were moved to a 30 °C drying environment for 30 min (pre-test). The animals were placed again in the cylinder 24 h later for 5 min (test) and this session was recorded by a videocamera. Experiments were performed between 0900 and 1200. The videotapes were observed by experimenters unaware of the treatment received by the subjects, with immobility time as the parameter being measured. A rat was considered immobile when floating and making only the necessary movements to keep its nostrils above the water surface level. An increase or a decrease in immobility time is considered as an antidepressant or a depressive-like effect, respectively.

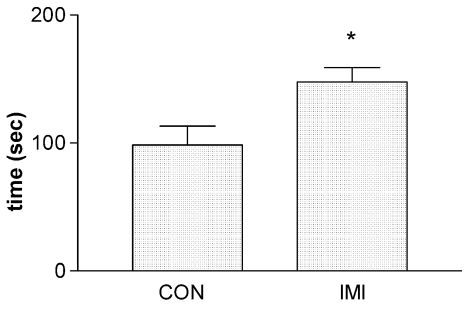

Fig. 1. Effect of 40 days imipramine withdrawal in the forced swimming test: immobility time. Each value represents the mean ± S.E.M. from two groups of animals ($n = 12$). *$P < 0.05$ (ANOVA).

2.4. Statistics

The results were analysed by analysis of variance (ANOVA) using the appropriate ANOVA error term. The analysis involved one between groups factor, with two levels: vehicle and imipramine.

3. Results

ANOVA showed a statistically significant effect [$F(1,20) = 6.66$; $P = 0.017$], due to an increase in immobility-time in the group in 40 days imipramine withdrawal with respect to the control group (Fig. 1).

4. Discussion

The results show that animals treated with chronic imipramine, 40 days after treatment interruption, display a depressive-like behaviour in the forced swimming test, as indicated by their increased immobility with respect to the control group.

We previously suggested that both the manic and the depressive episodes observed in rapid cycling might have as neural correlates the changes in sensitivity of the mesolimbic dopamine system induced by antidepressant treatment and by its discontinuation (D'Aquila et al., 2003). According to this view, the increased sensitivity of the mesolimbic dopamine system induced by antidepressants might underlie the switch from depression to mania, whereas the decreased sensitivity of this system which develops after withdrawal might underlie the precipitation of the 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). The idea that sensitisation of the dopaminergic mesolimbic system might be involved in the frequency of manic episodes and, in particular, in the increased vulnerability to recurrence after each episode, had already been proposed by Post and Weiss (1989), which suggested the involvement on this phenomenon of the same neural substrates underlying the development of cocaine-induced sensitisation and kindling.

The present results, showing a depressive-like behaviour in a condition in which we previously demonstrated a decreased sensitivity of the mesolimbic dopamine system, are in agreement with this hypothesis. 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 receptor 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). The hypothesis that the increased immobility in the forced swimming test might actually depend on a reduced sensitivity of the mesolimbic dopamine system induced by prolonged antidepressant withdrawal (D'Aquila et al., 2003) is also supported by studies demonstrating the role of dopamine, on the one hand, in the anti-immobility effect of antidepressants in this test (Gutierrez-Garcia et al., 2001) and, on the other hand, in the forced-swimming-induced immobility (Yadid et al., 2001).

In spite of a great deal of experimental evidence suggesting the role of different neurotransmitter systems both in the forced-swimming-induced immobility (Nakazawa et al., 2003; Kostowski and Krzascik, 2003) and in the mechanism of its reversal by antidepressant drugs (Harkin et al., 2003; Kostowski and Krzascik, 2003; Schramm et al., 2001), it should be born in mind the difficulty to interpret these results due to the lack of a clear relation between the forced swimming test and any well-defined behavioural dimension. Therefore, further studies in models inducing behavioural impairments which more closely resemble depressive symptoms such as anhedonia are granted to further investigate the proposed hypothesis.

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