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# Memantine prevents "bipolar-like" behavior induced by chronic treatment with imipramine in rats

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ABSTRACT

A great deal of evidence suggests that virtually all antidepressant treatments induce a dopaminergic behavioral supersensitivity. We have suggested that this effect may play a key role not only in the antidepressant effect of these treatments, but also in their ability to induce a switch from depression to mania. In 2003-4 we found that the sensitization of dopamine receptors induced by imipramine is followed, after imipramine withdrawal, by a desensitization of these receptors associated with a depressive-like behavior assessed in the forced swimming test. The dopamine receptor sensitization can be prevented by MK-801, an NMDA receptor antagonist, but not by currently used mood stabilizers (lithium, carbamazepine, valproate). These observations led us to suggest – and later confirm - with preliminary clinical observations that memantine may have an acute antimanic and a long-lasting mood-stabilizing effect in treatment-resistant bipolar disorder patients. Here we present data showing that memantine prevents not only the dopamine receptor sensitization induced by imipramine, as observed with MK-801, but also the ensuing desensitization and the associated depressive-like behaviorq observed after antidepressant withdrawal.



## 1. Introduction

A great deal of experimental evidence suggests that virtually all antidepressant treatments (including electroconvulsive shock and REM-sleep deprivation) potentiate dopaminergic transmission by sensitizing dopamine $D_2$ receptors in the mesolimbic system (D'Aquila et al., 2000a; Willner, 1997; Gershon et al., 2007; Collu et al., 1997; Serra et al., 1990; 1992; Serra, 2009; 2010).

In 2003–04 we demonstrated that the sensitization of dopamine receptors induced by chronic treatment with imipramine observed 24 h after imipramine treatment is followed by an opposite phenomenon, i.e. by a desensitization of dopamine receptors, which is associated with a depressive-like behavior assessed in the forced swimming test (D'Aquila et al., 2003, 2004).

On the basis of these observations we suggested that the sensitization of dopamine receptors induced by antidepressants may be involved in the switch from depression to mania (Gessa et al.,1995; D'Aquila et al. 1997; 2001, 2006; Serra, 2010) induced by such treatments in humans, while the desensitization of these receptors might underlie the ensuing depressive relapse (D'Aquila et al., 2003; 2004; Serra, 2010).

Thus, chronic treatment with imipramine induces a behavioral syndrome that appears to reproduce a manic-depressive cycle (mania followed by depression) and can be considered a useful animal model of bipolar disorder.

Indeed, much clinical and experimental evidence strongly suggests a key role of dopamine transmission dysfunction in bipolar mood disorders (Cousins et al., 2009; Berk et al., 2007; Diehl and Gershon, 1992; Dunlop and Nemeroff, 2007; Bennabi et al., 2013; van Enkhuizen et al., 2013): mania seems to be associated with increased dopamine transmission, while a reduced activity of this neurotransmitter appears to underlie depression.

In keeping with these observations it may be suggested that the increased dopaminergic transmission in the mesolimbic system (the reward system) due to $D_2$ receptor sensitization, induced by antidepressants, may contribute to their therapeutic effect, and in particular for such symptoms as anhedonia, loss of motivation, decreased libido and psychomotor retardation (Serra et al., 1992; D'Aquila et al., 2000a).

Moreover, the sensitization of mesolimbic dopamine $D_2$ receptors induced by antidepressants may be responsible, in 'vulnerable subjects' (bipolar disorder, the presence of previous mixed states, early age-at-onset, a cyclothymic or hyperthymic temperament, genetic factors), for the switches from depression to mania/hypomania (Serra et al., 1992; Serra, 2009; 2010; D'Aquila et al., 2000b; Gessa et al., 1995; Collu et al., 1997). In line with this

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hypothesis, in the last five decades, a large body of clinical evidence has been gathered indicating that antidepressant treatments can induce switching from depression to mania/hypomania, not only in bipolar but also in unipolar patients (Peet, 1994; Stoll et al., 1994). In a recent meta-analytic review Tondo and colleagues (Tondo et al., 2010) reported a rate of antidepressant-induced switching of 12.5%.

Currently used mood-stabilizers (lithium, carbamazepine, valproate) fail to prevent the switch from depression to mania in humans (Tondo et al., 2010) as well as the sensitization of dopamine receptors induced by imipramine in rats [actually, the effect of carbamazepine can be attributed to its potent induction of imipramine metabolism] (D'Aquila et al., 2000b; 2001; 2006).

On the contrary, the blockade of NMDA receptors by administration of the uncompetitive antagonist MK-801, completely prevents the behavioral sensitization of dopamine receptors induced by imipramine (D'Aquila et al., 1992) and electroconvulsive shock (D'Aquila et al., 1997).

These observations led us to suggest (Serra, 2009; 2010) the use of memantine, an uncompetitive NMDA receptor antagonist currently used in the treatment of Alzheimer's disease, as an antimanic and mood-stabilizing agent in treatment-resistant bipolar disorders.

Preliminary clinical observations strongly suggest that memantine has a clinically relevant antimanic effect and a sustained mood-stabilizing action, both as augmenting agent (Koukopoulos et al., 2010; 2012; Serra et al., 2012; 2013a; 2014a; Sani et al., 2012) in treatment-resistant bipolar disorder, and as a monotherapy (Keck et al., 2009; Serra et al., 2013b; 2014b, 2014; De Chiara et al., 2014) in a small sample of "naïve" patients.

Here we present data showing that memantine prevents not only, as observed with MK-801, the sensitization of dopamine receptors induced by chronic imipramine, but also the ensuing desensitization of those receptors and the associated depressive-like behavior assessed in the forced swimming test (FST).

## 2. Materials and methods

The present study was carried out in accordance with Italian law, which allows experiments on laboratory animals only after submission of a research project to the competent authorities, and in accordance with the "Guide for the Care and Use of Laboratory Animals" 8th Edition (National Research Council of Academies, The National Academies Press, Washington DC, 2011).

## 3. Subjects

Male Sprague-Dawley rats (Harlan, Italy), weighing initially 125–149 g, were housed in groups of 2 per cage in controlled environmental condition (temperature 22–24 °C, humidity 50–60%; light on at 8:00, off at 20:00), with free access to food and water.

## 4. Drugs and treatments

The animals ($N=40$) were divided into four groups ($n=10$) and treated with vehicle (distilled water), memantine HCl (Ebixa sol. Lundbeck Italy s.p.a), imipramine HCl (Sigma-Aldrich) and memantine plus imipramine for 3 weeks.

Memantine and imipramine (dissolved in distilled water) were administered intraperitoneally in daily injections, at the dose of 10 mg/kg and 20 mg/kg, respectively, in a volume of 1 ml /kg.

Twenty-four hour and 21 days after chronic-treatment withdrawal, the rats were tested for locomotor response to quinpirole (dopamine $D_2$-like receptor agonist) and on day 2 and 22 after treatment withdrawal animals were tested in the forced swimming test.

## 5. 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 (h 40 cm, w 45 cm, d 50 cm), into which a transparent perspex cage (height 19 cm, floor area $23 \times 33$ cm$^2$) was placed (Imetronic, Pessac, France).

Motor activity was 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 was recorded as a "long movement" motility count.

A "barrier" of 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 0900 and 1500 h. After 2 h habituation to the motility cages, rats were subcutaneously injected with 0.15 mg/kg quinpirole (Sigma-Aldrich) and the motor response was recorded for the following 30 min; data were collected in 5-min time bins.

## 6. Forced swimming test

According to the method described by Porsolt (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 video camera. Experiments were performed between 0900 and 1200. The videotapes were observed by experimenters unaware of the treatment received by the subjects, and the immobility time was recorded. 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.

## 7. Statistical analysis

The results were analyzed by analysis of variance (ANOVA), supplemented by *F*-tests for contrasts.

All data are presented as mean ± S.E.M; *P*-values $< 0.05$ were considered to be statistically significant.

## 8. Results

Chronic treatment with imipramine, as expected, potentiates locomotor activity induced by the administration of quinpirole 24 h after imipramine withdrawal (Fig. 1), measured as long movements [$F(1,29)=9.27$, $P=0.0049$] and rearing behavior [$F(1,29)=17.76$, $P=0.0002$].

The administration of memantine does not influence quinpirole effect, but prevents the potentiation of quinpirole effect induced by imipramine on the long movements [$F(1,29)=5.40$, $P=0.027$], and rearing behavior [$F(1,29)=9.94$, $P=0.0037$].

On the contrary (Fig. 2), 21 days after chronic imipramine withdrawal, the locomotor activity induced by quinpirole is significantly reduced in the long movements [$F(1,30)=3.94$, $P=0.05$] and in the rearing behavior [$F(1,30)=3.87$, $P=0.05$].

The administration of memantine does not affect the quinpirole response while it prevents the reduction of the quinpirole effect observed in the imipramine treated animals, on the long movements [$F(1,30)=11.08$, $P=0.0023$] and rearing [$F(1,30)=8.75$, $P=0.0063$].