World Journal of Psychiatry

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DOI: 10.5498/wjp.v6.i2.215

World J Psychiatr 2016 June 22; 6(2): 215-220
ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Basic Study

Failure of memantine to "reverse" quinpirole-induced hypomotility

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Author contributions: All authors contributed to this work.

Supported by Fondazione Banco di Sardegna, Italy (Grant no 2013 U718/AI.642.MGB).

Institutional animal care and use committee statement: 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).

Conflict-of-interest statement: Dr. Gino Serra has applied for a patent for the use of memantine to treat bipolar disorder. No other author or immediate family member has current financial relationships with commercial entities that might represent or appear to represent potential conflicts of interest with the material presented here.

Data sharing statement: Original data are reported.

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Received: October 13, 2015
Peer-review started: October 14, 2015
First decision: January 15, 2016
Revised: January 28, 2016
Accepted: March 14, 2016
Article in press: March 16, 2016
Published online: June 22, 2016

Abstract

AIM: To evaluate antidepressant-like effect of memantine in a rat model.

METHODS: Male Wistar rats were treated intraperitoneally with either vehicle, memantine (10 mg/kg) or imipramine (20 mg/kg), for 3 wk. Twenty-four hour after the last treatment animals were challenged with quinpirole (0.3 mg/kg s.c.) and tested for motor activity. After 1 h habituation to the motility cages, the motor response was recorded for the following 45-min and the data were collected in 5-min time bins.

RESULTS: As expected, chronic treatment with imipramine potentiated the locomotor stimulant effect of quinpirole. On the contrary, chronic memantine administration failed to induce the behavioral supersensitivity to the dopamine agonist.

CONCLUSION: The results show that memantine, at variance with antidepressant treatments, fails to induce dopaminergic behavioral supersensitivity. This observation is consistent with the results of preclinical and clinical studies suggesting that memantine does not have an acute antidepressant action but does have an antimanic and mood-stabilizing effect.

Key words: Memantine; Bipolar disorder; Depression; Mood stabilizer; Imipramine; D_2 sensitization

Core tip: Memantine at variance with virtually all antidepressant treatments, fails to induce dopaminergic behavioral supersensitivity. This observation is consistent with the results of preclinical and clinical studies suggesting that memantine does not have an acute antidepressant action but does have an antimanic and mood-stabilizing effect.

Demontis F, Serra G. Failure of memantine to "reverse" quinpirole-induced hypomotility. *World J Psychiatr* 2016; 6(2): 215-220 Available from: URL: http://www.wjgnet.com/2220-3206/full/v6/i2/215.htm DOI: http://dx.doi.org/10.5498/wjp.v6.i2.215

INTRODUCTION

The blockade of serotonin and noradrenaline reuptake by tricyclic antidepressants or the inhibition of monoaminoxidase (MAO) by MAO inhibitors has been considered responsible for the therapeutic action of the first generation of antidepressant drugs. On the contrary, the role of dopamine in the mechanism of action of these drugs has been neglected for long time. However, in 1979[1] we first reported that chronic treatment with antidepressant drugs activates dopaminergic transmission.

In the last few decades numerous studies have confirmed that virtually all antidepressant (AD) treatments (including electroconvulsive shock and REM-sleep deprivation) increase the motor-stimulant effect of dopamine receptor agonists by sensitizing D_2 dopamine receptors in the mesolimbic system[2-9].

In these last few years, it has been hypothesized that glutamate and NMDA receptors play a role in the neurobiology of depression[10-14]. Moreover, it has been reported that the NMDA receptor blocker, memantine, reduces immobility time in the forced swimming test (FST), a widely used animal model of depression, suggesting that it could have a potential antidepressant effect[15-17].

However, it has been recently reported that memantine fails to reduce immobility time in the FST after chronic treatment[18], and to reverse anhedonia in the chronic mild stress model of depression[19], suggesting that the antidepressant-like effect observed in the FST after acute treatment should be considered a "false positive"[20].

These observations are consistent with clinical studies that failed to find an acute antidepressant effect of memantine in humans[21-29].

Moreover, we have recently reported preclinical and clinical evidence suggesting that memantine has an antimanic and mood-stabilizing action[18,30-39].

Thus, to further clarify the effect of memantine in animal models of depression, we compared the effect of chronic administration of memantine and imipramine on the locomotor response to the dopamine D_2-like receptor agonist quinpirole, as a measure of dopamine D2-like receptor sensitivity[40].

As expected, chronic administration of imipramine potentiated the locomotor stimulant effect of quinpirole, while memantine failed to affect the quinpirole action.

MATERIALS AND METHODS

Subjects

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).

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

Treatments

The animals (n = 60) were divided into three groups (n = 20) and treated with vehicle (distilled water) controls, memantine HCl (Ebixa sol. Lundbeck Italy s.p.a) and imipramine HCl (Sigma, Haldrich) for 3 wk.

They were challenged with quinpirole and tested for motor activity 24 h after the end of this treatment. Imipramine HCl and quinpirole HCl (Sigma, Haldrich) were dissolved in distilled water. Memantine and imipramine 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. Quinpirole was administered subcutaneously at the dose of 0.30 mg/kg in a volume of 1 mL/kg.

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 cm^2 × 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. The interruption of two photocell beams belonging to the same sector was recorded as a "short movement" motility count. A "barrier" of infrared photocell beams, placed at the height of 15 cm, detected rearing activity. The apparatus was connected to a personal computer by an electronic interface. Experiments were performed between 0900 and 1500 h. After 1-h habituation to the motility cages, the rats were divided into 2 groups and treated s.c. with control vehicle (n = 30) and quinpirole (n

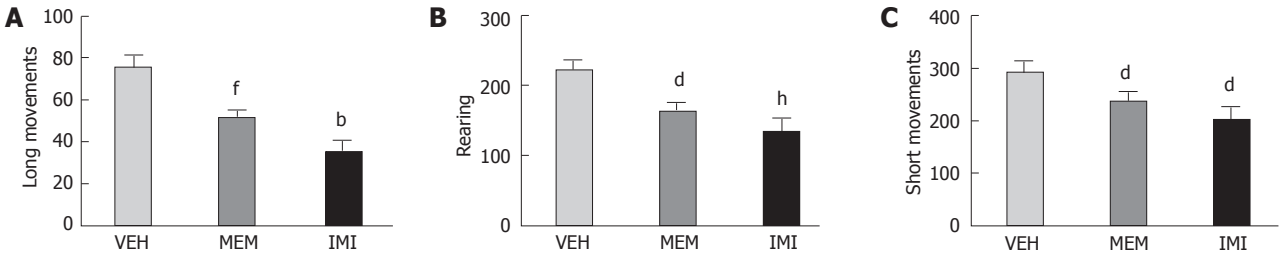

Figure 1 Spontaneous motor activity after 24 h discontinuation of chronic treatments (60 min habituation to the motility cage). Each value represents the mean ± SEM from 20 rats: Vehicle (VEH), memantine (MEM), imipramine (IMI). Number of long movements (A), rearing (B) and short movements (C) measured as indicated in the materials and methods: Motor activity. A: $^{f}P < 0.001$, memantine *vs* vehicle [F (1.51) = 12.21; $P = 0.0009$]; $^{b}P < 10^{-6}$, imipramine *vs* vehicle [F (1.51) = 31.71; $P = 0.000001$]; B: $^{d}P < 0.01$, memantine *vs* vehicle [F (1.51) = 10.58; $P = 0.0020$]; $^{h}P < 10^{-4}$, imipramine *vs* vehicle [F (1.51) = 19.90; $P = 0.000045$]; C: $^{d}P < 0.01$, memantine *vs* vehicle [F (1.51) = 11.57; $P = 0.0013$]; $^{d}P < 0.01$, imipramine *vs* vehicle [F (1.51) = 10.13; $P = 0.0024$]; ANOVA followed by Newman-Keuls-test.

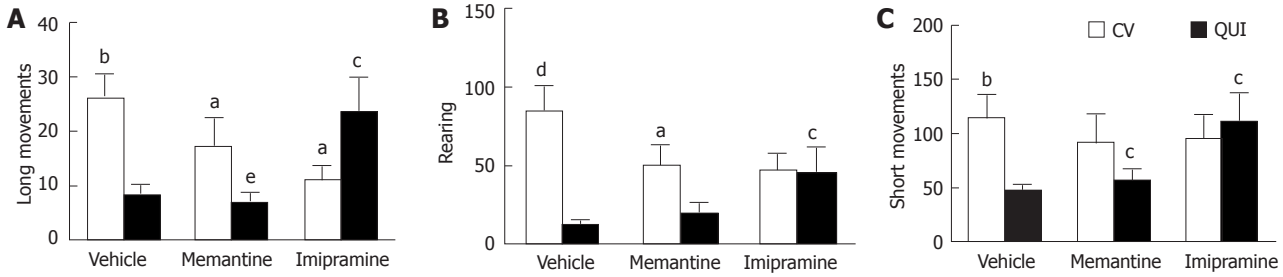

Figure 2 Motor response to quinpirole after 24 h chronic imipramine and memantine withdrawal. Number of long movements (A), rearing (B) and short movements (C) measured as indicated in the materials and methods: Motor activity. Each value represents the mean ± SEM from 10 rats (ANOVA followed by F test for contrast). Control vehicle (CV), quinpirole (QUI). A: $^{b}P < 0.01$, Vehicle-CV *vs* vehicle-QUI [F (1.48) = 11.20; $P = 0.0015$]; $^{a}P \leqslant 0.05$, memantine-CV *vs* memantine-QUI [F (1.48) = 3.74; $P = 0.05$]; $^{a}P \leqslant 0.05$, imipramine-CV *vs* imipramine-QUI [F (1.48) = 3.74; $P = 0.05$]. $^{c}P \leqslant 0.05$, vehicle-QUI *vs* imipramine-QUI [F (1.48) = 6.39; $P = 0.014$]; $^{e}P < 0.01$, memantine-QUI *vs* imipramine-QUI [F (1.48) = 7.74; $P = 0.007$]; vehicle-QUI *vs* memantine-QUI [F (1.48) = 0.07; n.s]; B: $^{d}P < 10^{-4}$, vehicle-CV *vs* vehicle-QUI [F (1.48) = 22.73; $P = 0.000018$]; $^{a}P \leqslant 0.05$, memantine-CV *vs* memantine-QUI [F (1.48) = 4.10; $P = 0.048$]; imipramine-CV *vs* imipramine-QUI [F (1.48) = 0.006; n.s.]. $^{c}P \leqslant 0.05$, vehicle-QUI *vs* imipramine-QUI [F (1.48) = 3.80; $P = 0.05$]; vehicle-QUI *vs* memantine -QUI [F (1.48) = 22.48; n.s]; C: $^{b}P \leqslant 0.01$, vehicle-CV *vs* vehicle-QUI [F (1.48) = 6.83; $P = 0.01$]; imipramine-CV *vs* imipramine -QUI [F (1.48) = 0.24; n.s.]. $^{c}P \leqslant 0.05$, vehicle-QUI *vs* imipramine-QUI [F (1.48) = 4.83; $P = 0.032$]; $^{c}P \leqslant 0.05$ memantine-QUI *vs* imipramine-QUI [F (1.48) = 3.75; $P = 0.05$].

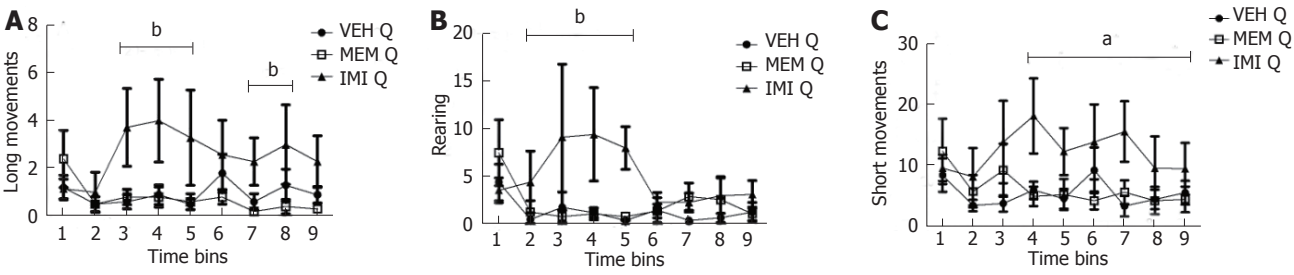

Figure 3 Time course of quinpirole effect on motor activity after 24 h chronic imipramine and memantine withdrawal. Long movements (A), rearing (B) and short movements (C) measured as indicated in the materials and methods: Motor activity. Each value represents the mean ± SEM from 10 rats: vehicle + quinpirole (VEH Q), memantine + quinpirole (MEM Q), imipramine + quinpirole (IMI Q). A, B: $^{b}P < 0.01$ imipramine-quinpirole *vs* vehicle-quinpirole and memantine-quinpirole; C: $^{a}P < 0.05$ imipramine-quinpirole *vs* memantine-quinpirole (ANOVA followed by F test for contrast; horizontal lines represent contrast involving consecutive times).

= 30).

The motor response was recorded for the following 45 min and data were collected in 5-min time bins.

Statistical analysis

The results were analysed by analysis of variance, supplemented by F tests for contrasts. Habituation and quinpirole challenge data were analysed separately. All data are presented as mean ± SEM; $P < 0.05$ is considered to be statistically significant.

RESULTS

Habituation

As shown in Figure 1, during 1 h of habituation to the motility cage, animals chronically treated with imipramine and memantine showed a significant reduction of motor activity, measured as long movements, rearing activity and short movements.

Quinpirole challenge

Figure 2 shows that quinpirole reduced the locomotor

activity, assessed as long movements, rearing activity and short movements, in control and memantine-treated rats, On the contrary, in imipramine-treated animals quinpirole stimulated locomotor activity (long movements and short movements) or prevented its sedative effect (rearing). Figure 3 shows the time course of quinpirole effect. Imipramine, but not memantine, stimulates locomotor activity induced by the dopamine agonist.

DISCUSSION

The present results confirm that chronic treatment with imipramine potentiated the locomotor response to the selective dopamine D2 receptor agonist quinpirole.

Quinpirole, as well as other dopamine agonists, has a biphasic effect on locomotor activity. A low doses it stimulates dopamine D2 autoreceptors mediating sedation/reduced motor activity, while at relatively high doses stimulates post-synaptic dopamine D2 receptors and and increases motor activity. In the present experiment the used dose of quinpirole reduces motor activity by stimulating dopamine autoreceptors in control animals. Imipramine, but not memantine, reverses this effect (*i.e.,* increases locomotor activity) because the stimulation of the supersensitive post-synaptic receptors overcomes the sedative effect due to the stimulation of autoreceptors (this issue has been extensively addressed in Serra *et al*[6,41,42]).

These findings are consistent with the large body of studies that strongly suggest that virtually all antidepressant treatments sensitize dopamine D_2 receptors in the mesolimbic system[2-4,6,8,9,41,42]. On the contrary, memantine fails to stimulate the locomotor response to quinpirole, suggesting that, at variance with antidepressant treatments, it does not sensitize D_2 receptors. This observation provides further support to our hypothesis[30,31,42] that the effect observed in the FST is a "false positive" and is in keeping with the failure of clinical studies to demonstrate an acute antidepressant action of memantine in depressed subjects[21-29]. Moreover, the results are consistent with our preclinical and clinical observations that strongly suggest that memantine has an antimanic and mood-stabilizing effect in patients with bipolar mood disorders. Indeed, we found that memantine prevents the dopamine D2 receptor sensitization induced by imipramine[30], that has been suggested to underly antidepressant-induced mania in humans[43,44]. Moreover, Gao *et al*[45] have reported an antimanic-like effect of memantine in two widely used animal models of mania. In addition we found that memantine prevents the bipolar-like behavior (mania followed by depression) induced by imipramine[18] suggesting that the drug may have a mood-stabilizing effect (*i.e.,* the ability to prevent mania/hypomania and depression episodes in manic depressive illness). This effect is the opposite to that observed with antidepressant drugs, which have been defined as "mood destabilizers"[46] because of their ability to induce mania in humans suffering from mood disorders.

Finally, the results are consistent with our[34-39] and Keck *et al*[47] reports of an acute antimanic effect of memantine and our observations of a long-lasting and progressive mood-stabilizing action of memantine in severely ill patients with bipolar disorder[34-39].

ACKNOWLEDGMENTS

The authors thank Denis Greenan for his important contribution to the drafting of this report.

COMMENTS

Background

Chronic antidepressant treatments, including electroconvulsive shock and REM sleep deprivation, potentiate the locomotor activity induced by dopamine D2 receptor agonists, suggesting that they sensitize dopamine D2 receptors in the mesolimbic system.

Research frontiers

Preclinical and clinical evidence suggests that memantine has an acute antimanic and a long-lasting mood stabilizing effect. On the contrary, while has been reported an antidepressant-like effect of the drug in the forced swimming test (FST), the administration of the compound in depressed patients appears to be ineffective.

Innovations and breakthroughs

The authors found that memantine, at variance with virtually all antidepressant treatments, fails to sensitize dopamine D_2 receptors, suggesting that the antidepressant-like effect observed in the FST should be considered a "false positive". This observation is consistent with the clinical reports of the lack of antidepressant action of memantine in depressed patients.

Applications

The authors' observation further support the suggestion to use memantine, as well as lithium, as an acute antimanic and a long-term mood stabilizing treatment.

Terminology

Memantine as a new mood stabilizer for the long-term prophylaxis of bipolar disorders.

Peer-review

A well-written paper, which adds to the evidence for the use of memantine in bipolar disorder.

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P- Reviewer: Chakrabarti S, Marzuillo P, Muneoka K
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