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Effects of glutamate-related drugs on marble-burying behavior in mice: Implications for obsessive–compulsive disorder

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Abstract

Clinical evidence demonstrates altered glutamatergic neurotransmission in patients suffering from obsessive–compulsive disorder (OCD). We examined the effects of glutamate-related drugs on marble-burying behavior, which is an animal model of OCD. The uncompetitive *N*-methyl-D-aspartate (NMDA) antagonists memantine (10 mg/kg, i.p.) and amantadine (30 mg/kg, i.p.) significantly inhibited marble-burying behavior without affecting locomotor activity in mice. Similarly, the uncompetitive NMDA receptor antagonist 5*R*,10*S*-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo(*a*,*d*)cyclohepten-5,10-imine hydrogen maleate (MK-801, 0.3 mg/kg, i.p.) inhibited marble-burying behavior. However, MK-801 at the same dose markedly increased locomotor activity. By contrast, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor antagonist 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[*f*]quinoxaline-7-sulfonamide (NBQX) and the glutamate release inhibitor riluzole showed no effect on marble-burying behavior and significant suppression of locomotor activity. MK-801 (0.3 mg/kg, i.p.) and memantine (10 mg/kg, i.p.) significantly disrupted prepulse inhibition as an operational measure of sensorimotor gating. By contrast, amantadine (30 mg/kg, i.p.) did not affect prepulse inhibition. These findings suggest that amantadine could be a useful drug for the treatment of OCD.

Keywords: Marble-burying behavior; Memantine; Amantadine; MK-801; Glutamate; Obsessive–compulsive disorder

1. Introduction

Obsessive–compulsive disorder (OCD) is a psychiatric condition with a lifetime prevalence of 1–3% that is characterized by recurrent and persistent thoughts, impulses or images (obsessions), and/or repetitive, seemingly purposeful behaviors (compulsions) (for example, doubting, checking and washing) (Rasmussen and Eisen, 1992; Sasson et al., 1997). Although classified as an anxiety disorder, patients with OCD demonstrate a high incidence of comorbid depression (Sasson et al., 1997). Currently, serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (SRIs) and selective 5-HT reuptake inhibitors (SSRIs) are considered to be the first choice agents for the pharmacological treatment of OCD (Greist et al., 2003). However, up to 50% of patients with OCD failed to respond in an SSRI trial (Goodman et al., 1989).

Some clinical evidence indicates that glutamatergic abnormalities are associated with OCD symptoms. Brain imaging studies of OCD patients have demonstrated a reversible glutamatergically mediated thalamo-cortical-striatal dysfunction (Rosenberg et al., 2001). Moreover, using proton magnetic resonance spectroscopy, abnormal glutamatergic neurotransmissions were observed in the caudate nuclei of OCD patients (Rosenberg et al., 2000). A recent study also demonstrated that patients with OCD have higher cerebrospinal fluid (CSF) glutamate levels than normal individuals (Chakrabarty et al., 2005). In addition, polymorphisms in the glutamate transporter gene (SLC1A1) and *N*-methyl-D-

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aspartate (NMDA) subunit receptor gene (GRIN2B) regions are associated with OCD (Arnold et al., 2004, 2006). Recently, an uncompetitive NMDA receptor antagonist, memantine, and a glutamate release inhibitor, riluzole, were reported to exhibit augmentation effects in treatment-resistant OCD (Coric et al., 2005; Pasquini and Biondi, 2006; Poyurovsky et al., 2005). Therefore, regulating glutamatergic neurotransmission may result in effective therapy for OCD patients.

Marble-burying behavior is considered to be a potential model of OCD on the basis of behavioral similarity (Ichimaru et al., 1995; Londei et al., 1998; Njung'e and Handley, 1991). Indeed, SSRIs such as fluvoxamine and paroxetine, which have been used to treat human OCD symptoms (Greist et al., 2003), inhibit marble-burying behavior, without affecting locomotor activity (Egashira et al., 2007; Harasawa et al., 2006; Hirano et al., 2005; Ichimaru et al., 1995; Shinomiya et al., 2005). To data, only metabotropic glutamate receptors antagonists have been showed to inhibit marble-burying behavior in mice (Nicolas et al., 2006; Shimazaki et al., 2004; Spooren et al., 2000), while the effects of other glutamate-related drugs such as 5*R*,10*S*-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo(*a*,*d*)cyclohepten-5,10-imine hydrogen maleate (MK-801, dizocilpine), memantine, amantadine, 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[*f*]quinoxaline-7-sulfonamide (NBQX) and riluzole on marble-burying behavior have been not reported on this model. Therefore, we investigated the effects of glutamate-related drugs on marble-burying behavior in mice.

Uncompetitive NMDA receptor antagonists, including phencyclidine (PCP), ketamine and MK-801, produce psychosis in healthy humans (Breier et al., 1997; Javitt and Zukin, 1991; Krystal et al., 1999; Malhotra et al., 1996). Uncompetitive NMDA receptor antagonists such as MK-801 and memantine have also been reported to disrupt prepulse inhibition of acoustic startle in rats (Wiley et al., 2003). Prepulse inhibition is defined as a reduction in the startle reflex because of a weak sensory pre-stimulation. Braff and colleagues (1990, 1992) have firmly established prepulse inhibition as an operational measure of sensorimotor gating. Importantly, prepulse inhibition of the acoustic startle response has been reported to be impaired in patients with OCD (Hoenig et al., 2005; Swerdlow et al., 1993). Therefore, we examined whether uncompetitive NMDA receptor antagonists at effective doses affect prepulse inhibition of the startle reflex.

2. Materials and methods

2.1. Animals

Five-week-old male ICR mice (Nihon SLC, Shizuoka, Japan) were used in each experiment. The mice were housed in groups of five per cage. The total number of animals used was 207. For at least 7 days before the behavioral tests, the mice were housed in a room under controlled temperature (23±2 °C), 60±10% relative humidity, and a cycle of 12 h light and 12 h dark, with the period of light starting at 07:00 h. The animals had free access to food (CE-2, Crea Japan, Tokyo, Japan) and water in their home cages. All procedures regarding animal care and use were performed in compliance with the regulations established by the Experimental Animal Care and Use Committee of Fukuoka University.

2.2. Drugs

MK-801 was purchased from Research Biochemicals Inc. (Natick, MA, USA). Memantine hydrochloride, amantadine hydrochloride, NBQX and riluzole were purchased from Sigma-Aldrich (St. Louis, MO, USA). MK-801, memantine and amantadine were dissolved in saline. NBQX and riluzole were suspended in 0.5% CMC-Na. All drugs were administered intraperitoneally (i.p.) 30 min before the test.

2.3. Marble-burying behavior test

The marble-burying behavior test was performed as described previously (Matsushita et al., 2005). All experiments were conducted between 10:00 and 17:00 h. Mice were placed individually in clear plastic boxes (30×30×28 cm), containing 25 glass marbles (1.5 cm in diameter) evenly spaced on sawdust 5 cm deep, without food and water. At the same time, the locomotor activity of mice was measured using an automated activity counter (NS-AS01; Neuroscience, Tokyo, Japan) placed 15 cm above the same plastic boxes. Activity was measured under the illumination of a 100 W bulb. The results of marble-burying behavior were expressed as the number of marbles buried to at least two-thirds of the depth, within 30 min. The observer did not know which agent was being tested.

2.4. Prepulse inhibition of the startle reflex

Prepulse inhibition of the startle reflex was measured as described previously (Egashira et al., 2005). The startle responses were measured in an illuminated startle chamber (39 cm×38 cm×58 cm; SR-LAB System; San Diego Instruments, San Diego, CA, USA), consisting of a Plexiglas cylinder (diameter: 8 cm; length: 16 cm) mounted on a removable frame with a base unit. Movement of a mouse within the cylinder was detected by a piezoelectric accelerometer attached below the frame. A loudspeaker mounted 25 cm above the cylinder provided background white noise and acoustic stimuli. The acoustic stimuli and piezoelectric responses from the accelerometer were controlled and digitized by SR-LAB software and an interface system. The startle amplitude was defined as the average of 100 m s^{-1} readings collected from the beginning of the startle stimulus onset. During the session, the background noise was kept constant at 65 dB. The mice were placed in the cylinders 10 min prior to the initial startle stimuli, and only background noise was offered during this acclimation period. To measure the acoustic startle response and prepulse inhibition, five trials were carried out: no stimulus, two types of startle stimulus only (100 and 120 dB, 20-ms broadband burst), and two types of startle stimulus preceded by a prepulse (a 20-ms broadband burst). The onset of the prepulse was separated from the startle onset by a 100-ms prepulse–startle interval, and the prepulse intensity used was 80 dB. Each trial was repeated 9

times in a random order, and separated by an average interval of 30 s (15–35 s). The prepulse inhibition was calculated as a percentage of the pulse-alone startle amplitude using the following formula: [1 − (startle amplitude following prepulse–pulse pair / startle amplitude following pulse only)] × 100.

2.5. Statistical analysis

The results obtained in the marble-burying behavior test were analyzed using one-way analysis of variance (ANOVA), followed by the Tukey–Kramer post-hoc test to determine whether there were differences between the groups. Data on the prepulse inhibition of the startle reflex were evaluated for statistical significance using two-way (with repeated measures) ANOVA (factors: drugs and pulse) followed by the Student *t*-test to determine differences among the groups. A probability level of $P<0.05$ was accepted as statistically significant. Values are expressed as means ± S.E.M.

3. Results

3.1. Effects of glutamate-related drugs on marble-burying behavior

To examine whether glutamate-related drugs exhibit therapeutic effects on OCD, their effects were examined using an animal model of OCD. The uncompetitive NMDA receptor antagonist MK-801, at a dose of 0.3 mg/kg, significantly reduced the number of buried marbles and increased locomotor activity [number of buried marbles: $F(3,30)=49.305$, $P<0.0001$ by one-way ANOVA; $P<0.01$; locomotor activity: $F(3,30)=8.822$, $P<0.001$ by one-way ANOVA; $P<0.01$, Fig. 1]. Memantine at a dose of 10 mg/kg significantly reduced the number of buried marbles, without affecting locomotor activity [$F(3,29)=19.218$, $P<0.0001$ by one-way ANOVA; $P<0.01$; locomotor activity: $F(3,29)=1.737$, $P>0.1$ by one-way ANOVA, Fig. 2]. Similarly, amantadine, at a dose of 30 mg/kg, significantly reduced the number of buried marbles without affecting locomotor activity [number of buried marbles: $F(3,28)=14.454$, $P<0.0001$ by one-way ANOVA; $P<0.01$; locomotor activity: $F(3,28)=2.162$, $P>0.1$ by one-way ANOVA, Fig. 3].

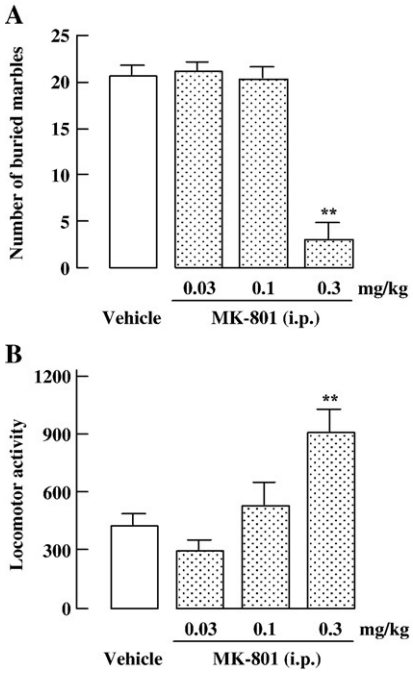

Fig. 1. Effect of MK-801 on marble-burying behavior in mice. (A) Number of buried marbles; (B) locomotor activity. MK-801 was administered i.p. 30 min prior to the test. Values are expressed as means ± S.E.M. ($n=8$–9). **$P<0.01$ compared with the vehicle-treated group (Tukey–Kramer post-hoc test).

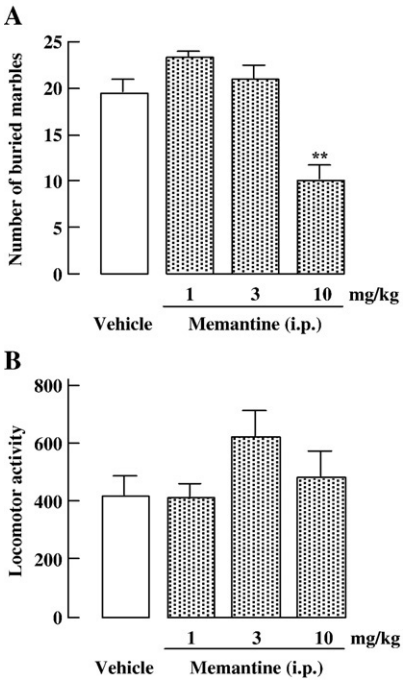

Fig. 2. Effect of memantine on marble-burying behavior in mice. (A) Number of buried marbles; (B) locomotor activity. Memantine was administered i.p. 30 min prior to the test. Values are expressed as means ± S.E.M. ($n=8$–9). **$P<0.01$ compared with the vehicle-treated group (Tukey–Kramer post-hoc test).

On the other hand, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor antagonist NBQX did not affect the number of buried marbles [$F(3,32)=0.672$, $P>0.1$ by one-way ANOVA, Fig. 4A]. However, NBQX at doses of 0.3 and 1 mg/kg significantly reduced locomotor activity [$F(3,32)=4.562$, $P<0.01$ by one-way ANOVA; $P<0.05$, Fig. 4B]. Similarly, the glutamate release inhibitor riluzole had no effect on the number of buried marbles [$F(3,26)=1.218$, $P>0.1$ by one-way ANOVA, Fig. 5A], but significantly reduced locomotor activity at a dose of 10 mg/kg [$F(3,26)=3.991$, $P<0.05$ by one-way ANOVA; $P<0.05$, Fig. 5B].

3.2. Effects of uncompetitive NMDA receptor antagonists on prepulse inhibition of the startle reflex

We next investigated whether uncompetitive NMDA receptor antagonists at effective doses affected prepulse inhibition of the startle reflex. MK-801 (0.3 mg/kg, i.p.) and memantine (10 mg/kg, i.p.) significantly reduced the % prepulse inhibition [drugs: $F(3,38)=2.770$, $P>0.05$; pulse: $F(1,38)=4.950$, $P<0.05$;

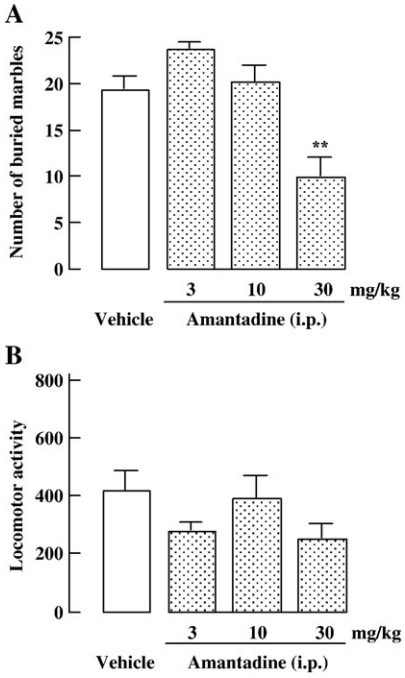

Fig. 3. Effect of amantadine on marble-burying behavior in mice. (A) Number of buried marbles; (B) locomotor activity. Amantadine was administered i.p. 30 min prior to the test. Values are expressed as means±S.E.M. (n=8). **P<0.01 compared with the vehicle-treated group (Tukey–Kramer post-hoc test).

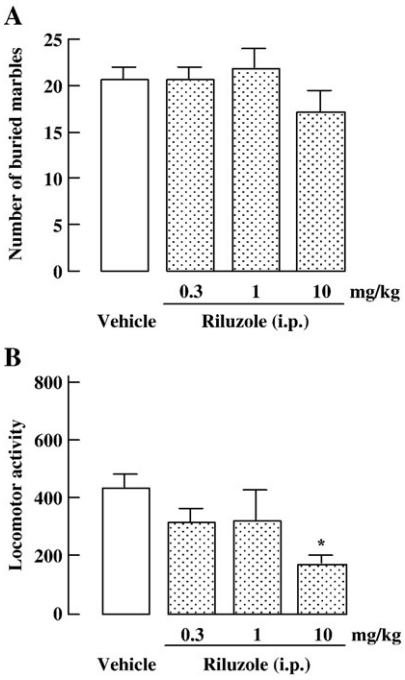

Fig. 5. Effect of riluzole on marble-burying behavior in mice. (A) Number of buried marbles; (B) locomotor activity. Riluzole was administered i.p. 30 min prior to the test. Values are expressed as means±S.E.M. (n=6–12). *P<0.05 compared with the vehicle-treated group (Tukey–Kramer post-hoc test).

interaction: $F(3,38)=1.259$, $P>0.1$ by two-way (with repeated measures) ANOVA; MK-801: 80–100 dB, $P<0.01$, 80–120 dB, $P<0.01$; memantine: 80–100 dB, $P<0.05$, Fig. 6A], whereas amantadine (30 mg/kg, i.p.) had no effect on the % prepulse inhibition. On the other hand, MK-801, memantine and amantadine at the same doses significantly increased the startle amplitude [drugs: $F(3,38)=3.298$, $P<0.05$; pulse: $F(1,38)=$

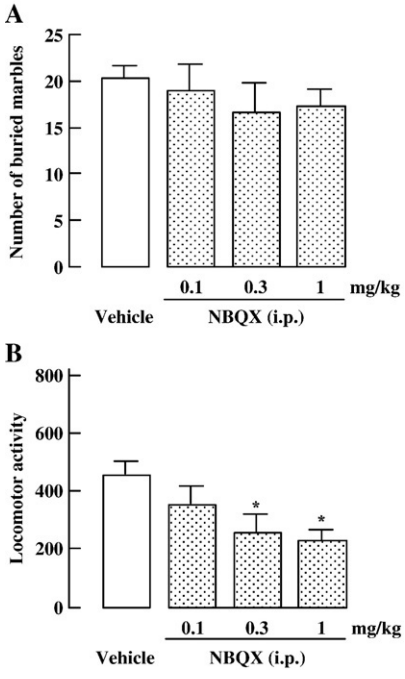

Fig. 4. Effect of NBQX on marble-burying behavior in mice. (A) Number of buried marbles; (B) locomotor activity. NBQX was administered i.p. 30 min prior to the test. Values are expressed as means±S.E.M. (n=8–12). *P<0.05 compared with the vehicle-treated group (Tukey–Kramer post-hoc test).

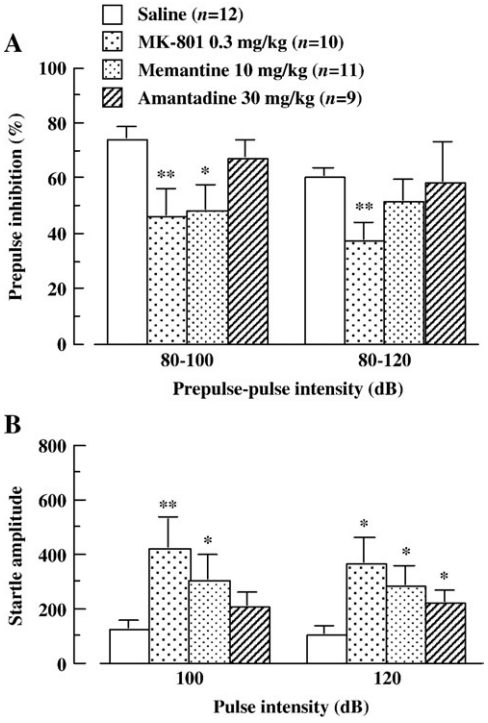

Fig. 6. Effects of MK-801, memantine and amantadine on prepulse inhibition of the startle reflex in mice. (A) Prepulse inhibition %; (B) startle amplitude. MK-801, memantine and amantadine were administered i.p. 30 min prior to the test. Values are expressed as means±S.E.M. (n=9–12). *P<0.05, **P<0.01 compared with the saline-treated group (Student t-test).

20.777, $P<0.0001$; interaction: $F(3,38)=1.609$, $P>0.1$ by two-way (with repeated measures) ANOVA; MK-801: 100 dB, $P<0.01$, 120 dB, $P<0.05$; memantine: 100 and 120dB, $P<0.05$; amantadine: 120 dB, $P<0.05$, Fig. 6B].

4. Discussion

In the present study, we demonstrated that the uncompetitive NMDA antagonists memantine (10 mg/kg, i.p.) and amantadine (30 mg/kg, i.p.) inhibited marble-burying behavior, which is considered to be an animal model of OCD (Ichimaru et al., 1995; Londei et al., 1998; Njung'e and Handley, 1991), without affecting locomotor activity in mice. Therefore, these effects were not attributable to non-specific sedative effects or a deficit of motor function. Similarly, SRIs and SSRIs, which have been used to treat the symptoms of human OCD (Greist et al., 2003), have also been reported to inhibit marble-burying behavior in mice without affecting locomotor activity (Egashira et al., 2007; Harasawa et al., 2006; Hirano et al., 2005; Ichimaru et al., 1995; Njung'e and Handley, 1991; Shinomiya et al., 2005). These findings suggest that memantine and amantadine may exhibit therapeutic effects on OCD. Similarly, MK-801 (0.3 mg/kg, i.p.) inhibited marble-burying behavior. However, MK-801 at the same dose markedly increased locomotor activity. In rodents, MK-801 has been known to elicit behavioral abnormalities, including hyperactivity and disruption of prepulse inhibition (Irifune et al., 1995; Mansbach and Geyer, 1989). Therefore, it is unlikely that these inhibitory effects on marble-burying behavior are specific effects. By contrast, the AMPA receptor antagonist NBQX and the glutamate release inhibitor riluzole showed no effect on marble-burying behavior, but reduced locomotor activity. In fact, NBQX and riluzole have been reported to inhibit locomotor activity in rodents (Lourenço Da Silva et al., 2003; Maj et al., 1995). Thus, glutamate-related drugs, in particular uncompetitive NMDA receptor antagonists such as memantine and amantadine, could inhibit marble-burying behavior without affecting locomotor activity.

Although PCP has been shown to have direct effect on dopaminergic system, in general other NMDA receptor antagonists have indirect effects on monoamine systems by blocking NMDA receptors located on glutamatergic and γ-aminobutyric acid (GABA)ergic neurons, which in turn could lead to increase in other neurotransmitter release. For example, MK-801 increases dopamine, 5-HT and norepinephrine release in the nucleus accumbens in rats (Yan et al., 1997). Memantine also increases the levels of extracellular dopamine, norepinephrine and their metabolites in the cortex and striatum (Shearman et al., 2006; Spanagel et al., 1994). Moreover, amantadine increases dopamine release in the striatum (Takahashi et al., 1996) and enhances antidepressant drug-evoked changes in the levels of extracellular 5-HT in the frontal cortex (Owen and Whitton, 2005). Therefore, NMDA receptor-mediated changes in monoamine neurotransmission may be involved in the inhibitory effects of NMDA antagonists.

NMDA receptor antagonists like PCP, ketamine and MK-801, have been reported to produce schizophrenic-like symptoms including prepulse inhibition deficits (Breier et al., 1997; Javitt and Zukin, 1991; Krystal et al., 1999; Malhotra et al., 1996). Therefore, in this study, we examined whether uncompetitive NMDA receptor antagonists at doses that were effective in the marble-burying test, affect prepulse inhibition of the startle reflex. MK-801 (0.3 mg/kg, i.p.) and memantine (10 mg/kg, i.p.) significantly disrupted prepulse inhibition. In particular, MK-801 disrupted prepulse inhibition at both prepulse–pulse intensities. On the other hand, amantadine (30 mg/kg, i.p.) did not affect prepulse inhibition. The present findings are consistent with those of previous studies (Wiley et al., 2003). Although amantadine and memantine share the same binding site as PCP, inside the receptor-associated ion-channel (Danysz et al., 1997; Kornhuber et al., 1994), they are well tolerated and have fewer psychotomimetic properties when compared with other uncompetitive NMDA receptor antagonists like MK-801 or PCP. This could be related to their low affinity and their fast voltage-dependent channel blocking properties (Chen et al., 1992; Kornhuber and Weller, 1997). Importantly, prepulse inhibition of the acoustic startle response has been reported to be impaired in patients with OCD (Hoenig et al., 2005; Swerdlow et al., 1993). Therefore, when uncompetitive NMDA antagonists are used to treat OCD, it is necessary to note sensorimotor gating.

In humans, Tourette's syndrome and OCD are frequently (40–75%) comorbid disorders (Frankel et al., 1986; Leonard et al., 1992; Nee et al., 1980). Tourette's syndrome and OCD are also associated with cortical–limbic hyperactivity in somatosensory, orbitofrontal and amygdalar areas, and possible consequent glutamatergic hyperactivation of efferent striatal motor pathways (Kurlan et al., 1990; Sheppard et al., 1999). McGrath et al. (2000) created a transgenic mouse model of comorbid Tourette's syndrome and OCD by expressing a neuropotentiating cholera toxin transgene in a subset of D_1 receptor-expressing neurons, which are thought to induce cortical and amygdalar glutamate output. These transgenic mice exhibit perseverative behaviors (repetitive climbing and leaping) that mimic some aspects of Tourette's syndrome and OCD. MK-801, which may indirectly stimulate cortical–limbic glutamate output, has been shown to worsen these perseverative behaviors (McGrath et al., 2000). Thus, the exacerbation of OCD-like behaviors by glutamatergic agents in this study supports an important role for the glutamatergic neuronal system in the pathogenesis of OCD.

In conclusion, the study presented here demonstrates, for the first time, that memantine and amantadine inhibit marble-burying behavior, which is a model for evaluating clinical potential in the treatment of OCD, without affecting locomotor activity in mice. Moreover, amantadine did not affect prepulse inhibition. In addition, amantadine is a drug of broad clinical utility. These findings suggest that amantadine could be a useful drug for the treatment of OCD.

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