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Potential antidepressant-like effect of MTEP, a potent and highly selective mGluR5 antagonist

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Abstract

The involvement of glutamate in the pathophysiology of depression has been suggested by a number of experiments. It was well established that compounds, which decreased glutamatergic transmission *via* blockade of NMDA receptor, produced antidepressant-like action in animal tests and models. The present study was carried out to investigate whether a selective mGluR5 antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP) induces antidepressant-like effects after intraperitoneal injections in male Wistar rats or male C57BL/6J mice. Potential antidepressant-like activity of MTEP was evaluated using the forced swimming test (FST) in rats, the tail suspension test (TST) in mice and the olfactory bulbectomy (OB) model of depression in rats. The results of our studies showed, that MTEP (0.3–3 mg/kg) produced a significant dose-dependent decrease in the immobility time of mice in the TST, however, at doses of 1 or 10 mg/kg, it did not influence the behavior of rats in the FST in rats. Moreover, the repeated administration of MTEP (1 mg/kg) attenuated the OB-related hyperactivity of rats in the open field test, in the manner similar to that seen following chronic (but not acute) treatment with typical antidepressant drugs. These data suggest that MTEP, which is considered to be a potential therapeutic agent, may play a role in the therapy of depression.

Keywords: mGluR5; MTEP; Depression; Olfactory bulbectomy; Tail suspension test; Forced swimming test

1. Introduction

A variety of antidepressant drugs, acting *via* distinct mechanisms, including serotonergic, noradrenergic and/or dopaminergic systems, have been used for several past decades. Nonetheless, conventional antidepressants have many limitations, which hinder the effective treatment, producing several adverse effects and requiring a few weeks of treatment to evoke therapeutic effects (Potter and Hollister, 2004). Such a profile of these drugs has encouraged ongoing research aimed to develop new compounds, which may yield more efficacious and faster acting therapeutic agents. In recent years, attention has focused on glutamate and glutamatergic system, which is considered to be one of the promising targets for a novel antidepressant therapy.

Glutamate, the principal excitatory neurotransmitter in the central nervous system (CNS) acts *via* ionotropic glutamate receptors (iGluR), including NMDA, AMPA and kainate receptors. However, it also plays the major role in activating modulatory pathways through G-protein-coupled metabotropic glutamate receptors (mGluRs) (Nakanishi, 1992). Eight mGluR subtypes: mGluR1-mGluR8 have been distinguished and subdivided into three groups according to their sequence homology, signaling pathways and selectivity for agonists. Group I mGlu receptors, which contain mGluR1 and mGluR5, initiates cellular responses through Gq/11 protein coupled to phospholipase C and

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stimulation of phosphoinositide hydrolysis/Ca^{2+} signal transduction pathway (Conn and Pin, 1997).

The studies concerning glutamate implication in affective disorders, including depression, have shown that functional NMDA receptor antagonists exhibit antidepressant-like effects in animal tests and models of depression. It became clear that NMDA receptor could be one of promising targets of a novel antidepressant therapy (for review see: Paul and Skolnick, 2003; Pilc et al., 2002b; Skolnick, 1999). However, potential clinical application of NMDA receptor antagonists was hampered by the fact that these drugs produce several adverse effects, including memory impairment, ataxia, muscle relaxation and psychotomimetic effects (Danysz et al., 1996). Discovery of selective agonists/antagonists, which activate/inhibit CNS function via mGluRs, provides a novel target for development of therapeutic agents. Behavioral studies of the last few years have confirmed that compounds, which modulate glutamatergic neurotransmission via mGluRs, produce antidepressant-like activity in several tests and models in rodents (Chaki et al., 2004; Cryan et al., 2003; Pałucha et al., 2004; Pilc et al., 2002a; Tatarczyñska et al., 2001; Wierońska et al., 2002).

In our previous studies we evaluated potential antidepressant-like effects of a potent and systemically active mGluR5 antagonist MPEP (2-methyl-6-(phenylethynyl)-pyridine). Our results strongly indicated antidepressant-like effects of this drug in behavioral tests in rats and mice (Pilc et al., 2002a; Tatarczyñska et al., 2001; Wierońska et al., 2002). It should be noticed, however, that MPEP has some disadvantages as a pharmacological tool, including a poor aqueous solubility and possibly its limited solubility in cerebrospinal fluid, which is supposed to contribute to the reduced in vivo efficacy of that compound (Cosford et al., 2003). Furthermore, MPEP application may lead to several off-target activities, including NMDA receptor blockade (O'Leary et al., 2000), inhibition of norepinephrine transporter (Heidbreder et al., 2003) and positive allosteric modulation of mGlu4 receptor (Mathiesen et al., 2003). All these effects might, at least in part, account for antidepressant-like activity of MPEP. Thus, it is questionable whether in vivo effect of MPEP, which we observed in our studies, is mediated by antagonistic action at mGlu5 receptors.

The recently discovered MPEP analogue, MTEP (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine) seems to be free of the most of disadvantages described for MPEP (Cosford et al., 2003). Wide-range counterscreening in a large number of in vitro assays was performed, which demonstrated no activity of MTEP in functional assays at NMDA NR2B receptors (at >300 μM), mGlu1, mGlu2, mGlu3 or mGlu7 receptors (10 μM), and, moreover, it showed no activity in binding assays of a large variety of receptors including glutamatergic (AMPA, NMDA), GABA, adenosine, adrenergic, dopamine, histamine, muscarinic, nicotinic and serotonergic (10 μM) (Busse et al., 2004; Cosford et al., 2003). It was also shown that MTEP (100 μM), unlike MPEP (10 μM), did not potentiate L-AP4-induced responses in CHO_{nfat} cells expressing mGluR4 (Busse et al., 2004). Thus, MTEP seems to be a considerably better pharmacological tool for investigating mGluR5-related effects than MPEP. These data prompted us to investigate potential antidepressant-like effect of a potent and highly selective mGluR5 antagonist, MTEP, in the behavioral tests and a model of depression in rats and/or mice.

2. Materials and methods

2.1. Animals and housing

Male Wistar rats (250–300 g) were used to assess antidepressant-like effects in the FST and in the OB model of depression, while male C57BL/6J mice (23–25 g) were used to determine antidepressant-like activity in the TST. The animals were kept under standard laboratory conditions of lighting (06:00–18:00 h) and temperature (19–21 °C). Food and water were freely available. Each experimental group consisted of 8–12 animals. All the subjects were experimentally naive and used only once in each test. Separate groups of animals were used in the locomotor studies from those used in the TST and FST tests. Experiments were performed during the light period (10:00–14:00 h) by an observer unaware of the treatment. All procedures were conducted according to the guidelines of the National Institutes of Health Animal Care and Use Committee, and were approved by the Ethics Committee of the Institute of Pharmacology, Polish Academy of Sciences in Kraków.

2.2. Drug administration

Imipramine (Polfa, Poznañ, Poland) and MTEP (Merck Research Laboratories, San Diego, USA) were dispersed in a suspension of Tween 80 (1% v/v in 0.9% w/v NaCl). For chronic administration, MTEP was freshly prepared daily. Solution of Tween 80 (1% v/v in 0.9% w/v NaCl) was used as a vehicle. Drugs were injected intraperitoneally (ip) at a constant volume of 2 ml/kg (rats) or 10 ml/kg (mice).

2.3. Tail suspension test

The studies were carried out according to the method of Steru et al. (1985). C57BL/6J mice were individually suspended by their tails to a plastic string positioned horizontally 75 cm above the table top, using adhesive tape placed ~ 1 cm from the tip of the tail. Total duration of immobility was measured over a period of 6 min. MTEP was given ip at doses of 0.3, 1 and 3 mg/kg, 1 h before the test. Mice were considered immobile only when they hanged down passively and completely motionless.

2.4. Forced swimming test

The experiments were performed according to the procedure of Porsolt et al. (1978). Briefly, the rats were placed individually in glass cylinders (40 cm high, 18 cm in diameter) containing 15 cm of water, maintained at 25 °C. The water column was deep enough so that rats could not support themselves by placing their paws on the base of the cylinder. After 15 min, they were removed to a drying room (30 °C) for 30 min. They were placed again in the cylinder 24 h later and the total duration of immobility was measured during a 5-min test. The rat was considered to be immobile when it remained floating passively in the water. MTEP (1 or 10 mg/kg) and imipramine (30 mg/kg, used as a positive standard) were administered as a series of 3 ip injections: 24, 5 and 1 h before the 5-min test on the second day. The first injection was given at the end of a drying period (i.e. 30 min after removal from the water).

2.5. Locomotor activity

The spontaneous locomotor activity of mice was measured in photoresistor actometers (circular cages, 25 cm in diameter, 15 cm high, two light sources, two photoresistors), where the animals were placed individually 1 h after injection of MTEP solution. The number of crossings of light beams was measured within 30 min of experimental session. First measurement was performed 6 min after placing animals into actometers.

The spontaneous locomotor activity of rats was measured in photoresistor actometers ($40 \times 40 \times 25$ cm, two light sources, two photoresistors), where the animals were placed individually after a series of 3 ip injections of MTEP (24, 5 and 1 h before the test). The number of crossings of light beams was measured within 30 min of experimental session. First measurement was performed 5 min after placing animals in actometers.

2.6. Olfactory bulbectomy

2.6.1. Surgical procedure

After a 2-week acclimatization period, bilateral OB was performed under pentobarbital/chloral hydrate anesthesia (Equithesin) in rats. The head was shaved and povidone–iodine (1%) was applied. A midline sagittal incision was made extending at least 1 cm rostral to the bregma. Two drill holes 2-mm in diameter were made 7 mm anterior to the bregma and 2 mm lateral to the midline. The olfactory bulbs were removed by suction. Care was taken to avoid damaging the frontal cortex. After the operation, bleeding was controlled, by plugging the holes with hemostatic sponge. In sham-operated animals, the skull was carefully pierced and the wound was closed. The mixture of antibiotics (penicillin and streptomycin, Polfa, Tarchomin, Poland) was applied on the wound prior to closure. After surgery, the rats were kept four per cage (two OB+two sham), and allowed to recover for 14 post-surgery days. They were handled daily throughout the recovery period to eliminate any aggressiveness that would otherwise arise. Two weeks after the surgery, drug treatment began. MTEP was administered once daily for 14 days, at a dose of 1 mg/kg, ip. Control animals received a vehicle solution. There were a total of four groups of rats: OB+Vehicle, OB+MTEP, sham+Vehicle, sham+MTEP.

2.6.2. Open field test

Twenty four hours after the last injection of MTEP, the open field test was performed, using apparatus consisting of an arena 90 cm in diameter, divided with white lines into eight regular, symmetric sectors. Experiments were conducted in the dark room and the apparatus was illuminated with a 60 W bulb, positioned 1 m above the center of the circle. The animals were placed individually in the center of the open field and allowed to explore freely for 3 min. The behaviors expressing interest, i.e. episodes of peeping and rearing, defined as raising of forepaws from the floor, and the number of sector lines crossed (ambulation score), defined as crossing the line with all four paws, were determined.

2.7. Data analysis

The data were presented as the means±SEM and evaluated by one-way analysis of variance (ANOVA) followed by Dunnett's test (FST, TST) or by two-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test (OB model of depression), using GraphPad Prism version 4.00 for Windows 2000 (GraphPad Software, San Diego CA, USA).

3. Results

3.1. Tail suspension test

MTEP, administered ip, at doses of 0.3, 1 and 3 mg/kg significantly decreased the immobility time of mice in the TST (by 24%, 41% and 48%, respectively), [$F(4,57) = 13.15$, $p < 0.0001$]. The efficacy of MTEP used at doses of 1 and 3 mg/kg was not significantly different from that of imipramine (20 mg/kg, ip), used as a positive standard (Fig. 1).

3.2. Forced swimming test

MTEP, administered ip, at doses of 1 and 10 mg/kg did not change the behavior of rats in the FST (Table 1). Imipramine, used as a positive standard at a dose of 30 mg/kg ip, significantly decreased the immobility time of rats in this test [$F(2,21) = 14.1$, $p < 0.001$].

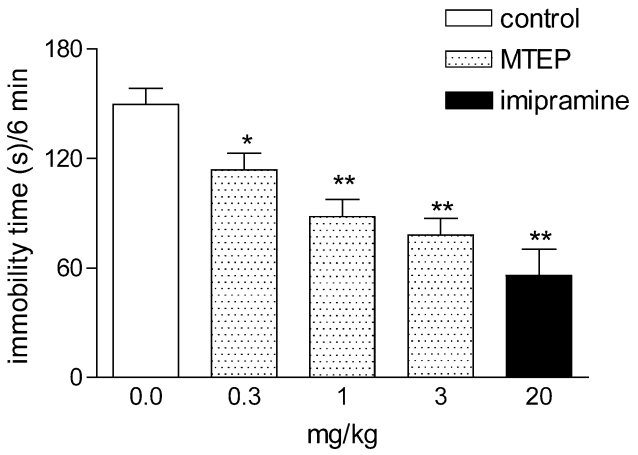

Fig. 1. The effects of MTEP and imipramine in the tail suspension test in mice. MTEP and imipramine were administered ip, 1 h before the test. Values are expressed as the means±SEM, $n=10-12$, *$p<0.05$, **$p<0.01$ vs. control group (Dunnett's test).

3.3. Locomotor activity

MTEP, administered ip, at a dose of 10 mg/kg did not change the locomotor activity of rats within 5-min experimental session, i.e. a period of time identical to the observation period in the FST, or within 30-min experimental session (Table 1). Similarly, no changes in the locomotor activity of mice were observed within 6-min experimental session, i.e. a period of time identical to the observation period in the TST, or 30-min experimental session, after administration of MTEP, given ip at doses of 1 or 10 mg/kg (Table 2).

3.4. Open field test in OB rats

The effect of chronic MTEP administration on the number of line crossings in the open field is shown in Fig. 2a. Two-way ANOVA revealed significant OB effect compared to sham-operated animals [$F(1,30)=6.269$), $p=0.018$]. MTEP, reduced the effect of olfactory bulbectomy [$F(1,30)=4.499$, $p=0.0423$] and had no effect on behavior of sham-operated rats.

Table 1
The effects of MTEP on the behavior of rats in the forced swimming test (a) and in the locomotor activity test (b)

Compound	n	Dose (mg/kg)	(a) Immobility time (s)	(b) Number of crossings	
			5 min	5 min	30 min
Vehicle	8	–	170±12	78±5	103±8
MTEP	8	1	150±12	nt	nt
MTEP	8	10	179±4	87±5	106±7
Imipramine	8	30	73±24*	nt	nt

Values are expressed as the means±SEM; *n*—number of rats per group, nt—not tested.
* $p<0.01$ vs. respective vehicle (Dunnett's test).

Table 2
The effect of MTEP on the locomotor activity of mice

Compound	n	Dose (mg/kg)	Number of crossings	
			6 min	30 min
Vehicle	9	–	66±11	162±15
MTEP	8	1	73±8	158±18
	8	10	81±6	183±23

Values are expressed as the means±SEM, *n*—number of mice per group.

As shown in Fig. 2b, OB produced a significant increase in the number of rearings+peepings compared to sham operated animals [$F(1,30)=4.271$, $p=0.0475$]. Two-way ANOVA revealed also the effect of repeated MTEP administration, which significantly reduced OB-related increase in the number of rearings+peepings [$F(1,30)=8.535$, $p=0.006$]. Moreover, there was a significant interaction between the groups, [$F(1,30)=5.726$, $p=0.023$].

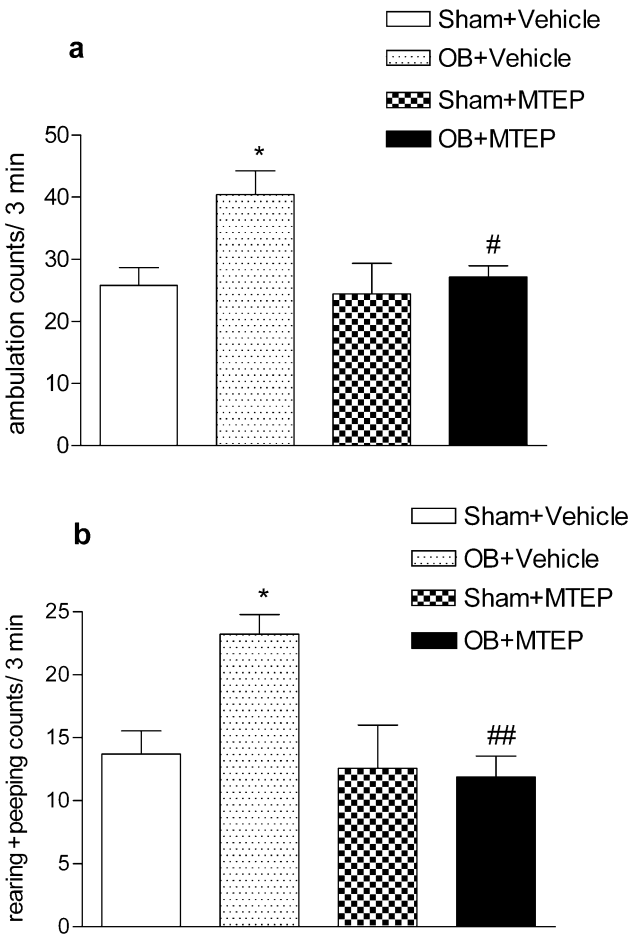

Fig. 2. The effect of repeated MTEP administration on the ambulation (a) and rearing+peeping (b) scores in the open field test following olfactory bulbectomy in rats. MTEP was given ip, at a dose of 1 mg/kg for 14 days. The test was performed 24 h after the last dose of a drug. Values are expressed as the means±SEM, $n=8-10$, *$p<0.05$ vs. sham+vehicle group, $^{\#}p<0.05$ vs. OB+vehicle group, $^{\#\#}p<0.01$ vs. OB+vehicle group (Bonferroni's multiple comparison test).

4. Discussion

Both basic research and some clinical studies indicate that compounds, which reduce transmission at NMDA receptors, exhibit antidepressant-like effects (Paul and Skolnick, 2003). Since mGlu5 receptors have been shown to potentiate the iGluR responses, including potentiation of NMDA receptor currents (Attucci et al., 2001; Awad et al., 2000; Pisani et al., 2001; Ugolini et al., 1999), we hypothesized that compounds, which inhibit mGluR5, may act at a functional endpoint similar to the target of NMDA receptor antagonist. Our previous behavioral studies confirmed that an mGluR5 antagonist, MPEP, displayed antidepressant-like activity in rats and mice (Tatarczyńska et al., 2001; Wierońska et al., 2002). However, in the light of many well-documented off-target effects of MPEP, there is some doubt as to whether antidepressant-like effects of that compound were mediated by its antagonistic action on mGluR5 receptors.

In the present study we used the recently described, potent, systemically active mGluR5 antagonist, MTEP, which is free of the most of impediments described for MPEP. Our results showed, that MTEP did not influence the behavior of rats in the FST and in the locomotor activity test in rats (Table 1), while it produced a significant dose-dependent decrease in the immobility time of mice in the TST (Fig. 1), without affecting the locomotor activity (Table 2). Both the FST and the TST are recognized as useful tools to detect antidepressant activity. However, the TST, compared to the FST, shows a higher predictive validity for identifying potentially useful pharmacotherapies, e.g. it detects the antidepressant effects of selective serotonin reuptake inhibitors (Perrault et al., 1992). Furthermore, Belozertseva et al. (2004) have recently shown, that acute blockade of mGluR5 by MTEP exerts antidepressant-like effects in the modified FST in rats. Modification of the test consisted in separate measurements of floating duration, duration of mobile behaviors and duration of escape behaviors. In those studies, MTEP decreased the floating duration (ED_{50} 2.5 mg/kg) and increased the duration of mobile behaviors (paddling and swimming; ED_{50} 5 mg/kg). It was also shown that dose-effect function was biphasic with the highest tested dose (10 mg/kg) being less or no effective. Thus, the doses of MTEP used in our studies (1 and 10 mg/kg) seem to be beyond the range of doses being active in this test. We suppose that discrepancy between the results of Belozertseva et al. (2004) and ours can be attributed to other doses of MTEP used in the studies and differences between "classical" FST and its "modified" version.

In order to further investigate antidepressant-like activity of MTEP, we applied olfactory bulbectomy, which belongs to commonly used models of depression. It has been shown that surgical lesion of olfactory bulbs promotes significant behavioral, physiological, endocrine and immune changes, many of which were qualitatively similar to those observed in depressive patients (for review, see Kelly et al., 1997). Moreover, a variety of OB-related behavioral changes, including well-described hyperactivity in the "open field" and deficit in passive avoidance, respond selectively to antidepressant treatment. However, passive avoidance deficit is known to be susceptible to acute antidepressants administration, while hyperactivity in the "open field" always responds to repeated antidepressants treatment, thus mimicking the clinical time-lag of currently used antidepressant drugs (Harkin et al., 2003). Thus, we used open field test to evaluate a potential antidepressant-like effect of MTEP in OB model of depression.

Our studies confirmed the previously described OB-related hyperactivity of rats in the open field, i.e. an increase in the ambulation counts as well as in the number of rearing+peeping scores, compared to sham operated rats (Fig. 2a,b). Repeated administration of MTEP (1 mg/kg) attenuated the hyperactivity of olfactory bulbectomized rats in this test in the manner similar to that seen following chronic (but not acute) treatment with a variety of typical and atypical antidepressants (Harkin et al., 2003). It was also found that repeated MTEP administration did not result in any behavioral changes in the sham-operated groups, indicating that the effect of MTEP in OB rats is not due to a stimulant or sedative effect of this compound. OB model of depression has been previously used to assess a series of potentially novel antidepressant drugs, including those acting via glutamatergic system (e.g. NMDA receptor antagonist dizocilpine; Redmond et al., 1997).

MTEP turned out to be more potent in our in vivo studies compared to previously studied MPEP, although both drugs have similar potency in vitro (Cosford et al., 2003). This effect results probably from the greater aqueous solubility of MTEP, compared with MPEP, which allows the drug to reach a higher level in plasma, brain and cerebrospinal fluid (Cosford et al., 2003). Busse et al. (2004) showed that the ability of MTEP to occupy mGluR5 after acute ip injection in rats was dose-dependent and at 1 h post-administration its ED_{50} was 1.2 mg/kg, while full receptor occupancy was achieved with the 10 mg/kg dose of MTEP. Thus, it seems that the doses of MTEP, which produced antidepressant-like effects, were appropriate for mGluR5 occupancy in vivo. This observation, together with high selectivity of MTEP strongly suggests that antagonistic action at mGlu5 receptor is responsible for antidepressant-like effects of the tested drug.

We suggest that MTEP, known to be a potent, highly selective mGluR5 antagonist, free of off-target activity, may be considered as a potential therapeutic agent in the treatment of various CNS disorders, including depression.

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