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Short communication

NMDA and AMPA receptors are involved in the antidepressant-like activity of tianeptine in the forced swim test in mice

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Abstract:
It is known that tianeptine exhibits antidepressant-like activity. Its influence on the glutamatergic system is also known, but the mechanisms involved in this activity remain to be established. The aim of this study was to investigate the involvement of the glutamate pathway in the antidepressant-like action of tianeptine. We investigated the effects of *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor ligands on tianeptine-induced activity in the forced swim test (FST) in mice. The antidepressant-like activity of tianeptine (30 m/kg, *ip*) was significantly antagonized by D-serine (100 nmol/mouse *icv*) and NBQX (10 mg/kg, *ip*). Moreover, low, ineffective doses of the glycine/NMDA site antagonist L-701,324 (1 mg/kg, *ip*) administered together with low, ineffective doses of tianeptine (20 mg/kg, *ip*) exhibited a significant reduction of immobility time in the FST. These doses of the examined agents, which did have an effect in the FST, did not alter locomotor activity. The present study indicates that the antidepressant-like activity of tianeptine in the FST involves both NMDA and AMPA receptors and suggests that the interaction between serotonergic and glutamatergic transmission may play an important role in the action of tianeptine.

Key words:
tianeptine, forced swim test, NMDA, AMPA, receptors, mice

Introduction

Tianeptine is an atypical antidepressant drug. Clinical data show that treatment with tianeptine has a positive influence on the main symptoms of depression. It has been shown to produce thymoanaleptic and anxiolytic effects without any pronounced sedative effects, to promote the normalization of sleep and to be effective in the treatment of mild to moderate depression [9]. The main pharmacologic mechanism of action of tianeptine is connected to serotonergic neurotransmission. It selectivity enhances serotonin (5-HT) reuptake [23] and has no effect on the noradrenergic or dopaminergic systems [9]. Moreover, recent preclinical data indicated that glutamatergic transmission may have an important role in the antidepressant-like activity of tianeptine [9, 10, 22].

Glutamate is accepted as the major excitatory neurotransmitter in the nervous system, which is released from presynaptic neurons and interacts with postsynaptic glutamate receptors, including kainate, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), and *N*-methyl-D-aspartate (NMDA) receptors. There is a large body of evidence showing that the glutamatergic system plays an important role in the mechanism and treatment of depression [7, 32]. The preclinical data demonstrated that blockade of the NMDA receptor complex produced antidepressant-like activity in animal tests and models of depression [26, 35]. In clinical studies, high glutamate levels were found in the central nervous system (CNS) of depressed patients [3, 13, 21], and NMDA receptor abnormalities were observed in both human suicide victims [25] and major depressives [12]. The side effects produced by competitive and noncompetitive NMDA antagonists limit their applicability as antidepressant drugs in humans [42]. However, antagonists of the NMDA receptor complex, ketamine and memantine, are effective in treating human depression [5, 43, 44]. Numerous previous studies indicated the role of serotonergic transmission in the antidepressant-like activity of NMDA ligands [18, 27, 40]. Moreover, relationships between NMDA and metabotropic glutamatergic receptors in the forced swim test (FST) have been demonstrated [30]. Recent data also documented the role of AMPA receptors in the etiology and treatment of depression [1, 34]. It was shown that the positive modulators of AMPA receptors exerted antidepressant-like effects in animal models of depression [33, 38]. Drugs such as imipramine, fluoxetine and tianeptine increased the phosphorylation of the GluR1 (S831, S845) subunit of the AMPA receptors in the frontal cortex and/or hippocampus but with different patterns [8, 36, 37]. The activity of tianeptine in the FST in mice is dependent on the presence of phosphorylated serine residues in the GluR1 subunit [36].

Thus, based on the above information, the aim of the present work was to assess the effects of both NMDA and AMPA ligands on the antidepressant-like activity of tianeptine in the FST in mice.

Materials and Methods

Animals

The experiments were carried out using male albino Swiss mice (25–30 g) purchased from a licensed breeder (Kołacz, Warszawa, Poland). The animals were housed in Makrolon cages under strictly controlled laboratory conditions (ambient temperature 22–23°C, relative humidity approximately 45–55%, 12/12-h light/dark cycle, lights on at 6:00 am); chow pellets and tap water were provided *ad libitum*. They were used in experiments after 7 days of acclimatization to laboratory conditions. Each experimental group consisted of 8–12 animals. The experiments were carried out between 9:00 am and 2:00 pm. All procedures were approved by the Ethical Committee of the Medical University, Lublin.

Drug administration

Tianeptine (Sigma-Aldrich, Poznań, Poland) was dissolved in normal saline and administered intraperitoneally (*ip*) 60 min before the test. L-701,324 (7-chloro-4-hydroxy-3-(3-phenoxy)phenylquinolin-2[1H]-one; Sigma-Aldrich, Poznań, Poland) was suspended in a 1% aqueous solution of Tween 80 and administered *ip* 60 min before the test. NBQX (2,3-dihydroxy-6-nitro-7-sulfoamoylbenzo(f)-quinoxaline; Tocris Bioscience, Bristol, UK) was dissolved in 0.9% saline and administered *ip* 40 min before the test. Control animals received an *ip* injection of saline (vehicle). D-serine (Sigma-Aldrich, Poznań, Poland) was also dissolved in normal saline and administered intracerebroventricularly (*icv*) 15 min before the test. *Icv* administration was performed on unanesthetized mice

according to a modified method described by Lipman and Spencer [16]. Briefly, a 10 µl type 701 glass Hamilton microsyringe with the 26 gauge needle shortened to a length of 7 mm was used. Rigid PVC tubing was put on the needle to limit its penetration to 3 mm. The injection site was approximately 2 mm posterior to and 1 mm lateral (left) of the bregma. Control animals received an *ip* or *icv* injection of saline (vehicle). The volumes of vehicle or drug solutions for *ip* and *icv* administrations were 10 ml/kg and 5 µl per mouse, respectively.

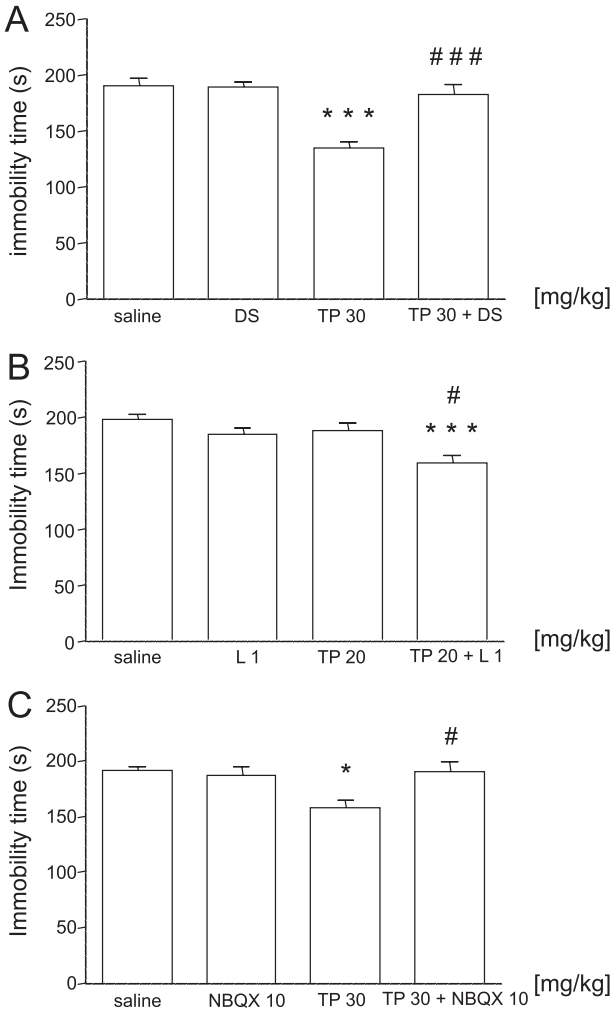

Fig. 1. Effect of joint administration of tianeptine (TP) and (**A**) D-serine (DS), (**B**) L-701,324 (L) or (**C**) NBQX on the total duration of immobility in the forced swim test in mice. Tianeptine (20 or 30 mg/kg, *ip*) and L-701,324 (1 mg/kg, *ip*) were administered 60 min before the test, and D-serine (100 nmol/mouse *icv*) was administered 15 min before the test. The values represent the means ± SEM of 8–12 mice. * $p < 0.05$, *** $p < 0.001$ *vs.* the respective saline control group; # $p < 0.05$, ### $p < 0.001$ *vs.* the respective tianeptine-treated group (Bonferroni's *post-hoc* test)

FST

The studies were carried out on mice according to the method described by Porsolt et al. [31]. The mice were dropped individually into glass cylinders (25 cm high, 10 cm diameter) containing 10 cm of water maintained at 23–25°C. The animals were left in the cylinder for 6 min. After the first 2 min, the total duration of immobility was measured during a 4-min test period. The mouse was judged to be immobile when it remained floating passively in the water.

Locomotor activity

The locomotor activity of the mice was measured with photoresistor actimeters (circular cages, diameter 25 cm, two light beams). The animals were placed individually in an actimeter for 10 min. Activity was measured at 5-min intervals to characterize the dynamics of the changes. The number of crossings of the light beams by the mice was recorded as the locomotor activity.

Statistical analysis

The obtained data were evaluated by a one-way analysis of variance (ANOVA) followed by Bonferroni's *post-hoc* test. All results are presented as the means ± standard error of the mean (SEM). A p-value less than or equal to 0.05 was considered to be a statistically significant difference.

Results

Effect of joint administration of tianeptine and D-serine on total immobility duration in the FST

The effects of the combined administration of tianeptine and D-serine (a glycine B receptor agonist) on the total duration of immobility in mice are shown in Figure 1A (ANOVA: $F(3,35) = 15.20$; $p < 0.0001$).

Tianeptine at a dose of 30 mg/kg significantly ($p < 0.001$) reduced the immobility time in mice. D-serine given alone at a dose of 100 nmol/mouse had no effect on the immobility time; however, when combined with tianeptine, it abolished the tianeptine-induced antidepressant-like effect.

Tab. 1. Effect of combined treatment with NMDA and AMPA ligands and tianeptine on spontaneous locomotor activity in mice

Treatment	Dose	Activity counts	
		5 min	10 min
A: vehicle + vehicle	—	115.4 ± 11.38	202.7 ± 20.07
tianeptine + vehicle	30 mg/kg	131.4 ± 12.63	223.4 ± 23.94
D-serine	100 nmol/mice	96.0 ± 8.25	141.1 ± 17.02
tianeptine + D-serine	30 mg/kg + 100 nmol/mice	127.3 ± 13.64	189.9 ± 22.8
B: vehicle + vehicle	—	153.1 ± 11.57	227.3 ± 18.58
tianeptine + vehicle	20 mg/kg	134.0 ± 9.03	210.3 ± 13.23
L-701,324 + vehicle	1 mg/kg	125.1 ± 11.22	171.8 ± 19.22
tianeptine + L-701,324	20 mg/kg + 1 mg/kg	122.0 ± 11.22	171.9 ± 29.72
C: vehicle + vehicle	—	69.38 ± 14.36	114.0 ± 19.29
tianeptine + vehicle	20 mg/kg	58.5 ± 15.33	88.40 ± 30.15
NBQX + vehicle	10 mg/kg	63.10 ± 11.99	114.8 ± 22.09
tianeptine + NBQX	20 mg/kg + 10 mg/kg	76.4 ± 10.68	140.1 ± 19.65

The values represent the means ± SEM of 8–10 mice per group. **A**: ANOVA $F(3,32) = 1.725$; $p = 0.1817$ for 5 min; $F(3,32) = 1.151$; $p = 0.3437$ for 10 min. **B**: ANOVA $F(3,34) = 0.3649$; $p = 0.7788$ for 5 min; $F(3,34) = 0.8356$; $p = 0.4838$ for 10 min. **C**: ANOVA $F(3,35) = 1.133$; $p = 0.3490$ for 5 min; $F(3,35) = 1.858$; $p = 0.1548$ for 10 min

Effect of joint administration of tianeptine and L-701,324 on the total immobility duration in the FST

The effects of the combined administration of tianeptine and L-701,324 (a glycine B receptor antagonist) on the total duration of immobility in mice are shown in Figure 1B (ANOVA: $F(3,30) = 7.586$; $p = 0.0006$). Both tianeptine at a dose of 20 mg/kg and L-701,324 at a dose of 1 mg/kg had no effect on the immobility time in mice. The combined administration of tianeptine with L-701,324 significantly reduced the immobility time in the FST ($p < 0.05$).

Effect of joint administration of tianeptine and NBQX on the total immobility duration in the FST

The effects of combined administration of tianeptine and NBQX (an AMPA receptor antagonist) on the total duration of immobility in mice are shown in Figure 1C (ANOVA: $F(3,31) = 5.086$; $p = 0.0056$). Tianeptine at a dose of 30 mg/kg significantly shortened the immobility time in mice ($p < 0.05$). NBQX, given alone at a dose of 10 mg/kg, had no effect on the immobility time; however, when combined with tianeptine, it abolished the tianeptine-induced antidepressant-like effect.

Effect of tianeptine, NMDA and AMPA ligands on spontaneous locomotor activity in mice

The effects of tianeptine, NMDA and AMPA ligands and their combined administration on locomotor activity are shown in Table 1. The tested agents did not significantly influence the locomotor activity in mice.

Discussion

The antidepressant-like activity of tianeptine has been shown using the classical tests of depression, namely antagonism of reserpine-like compounds, the FST and the isolation test [24], and models of depression, such as the olfactory bulbectomy rat model of depression [11], immobilization stress [41] and learned helplessness [39]. Its antidepressant-like effect is comparable to imipramine and amitriptyline [9, 17]. Furthermore, it has been suggested that the interaction of tianeptine with the glutamatergic system may play a role in its effects [10, 22].

In the present study, we examined the involvement of the NMDA receptor complex in the mechanism of the antidepressant action of tianeptine. We confirmed that tianeptine at a dose of 20 mg/kg, *ip* did not

change the immobility time in the FST [27]. We also demonstrated that an antagonist of the glycine$_B$ site of NMDA receptor, L-701,324, enhanced the antidepressant-like activity of tianeptine. This potentiation manifested as a reduction of the immobility time in the FST without an influence on the locomotor activity. These compounds enhanced the antidepressant-like activity of other antidepressant drugs, i.e., imipramine and fluoxetine, but not reboxetine, in the FST [28]. Thus, the potentiating effect of L-701,324 on tianeptine and other antidepressants is probably connected with serotonergic transmission.

To confirm the role of the glycine$_B$ site of the NMDA receptor in the antidepressant action of tianeptine, we evaluated the influence of D-serine on the activity of tianeptine. We showed that D-serine at a dose of 100 nmol/mouse did not change the immobility time in the FST [29]; however, it blocked the action of tianeptine. Because neither compound alone or in combination influenced the spontaneous locomotor activity of mice, the specificity of the antidepressant-like action of the tianeptine and of the D-serine-induced blockade of this effect is evident. Our results suggest a participation of the glycine$_B$ site of the NMDA receptor in the antidepressant-like activity of tianeptine. It was previously reported that D-serine blocked the antidepressant effects of the following other antidepressants: imipramine, fluoxetine and reboxetine [28]. Thus, we suggest that the antidepressant-like activity of tianeptine may occur *via* an effect on the glycine$_B$ site of NMDA receptor. Therefore, if the glycine$_B$ sites are active, the antidepressant-like effect of tianeptine is blocked, whereas if glycine$_B$ sites are blocked, the activity of tianeptine is enhanced. Our results suggest considerable participation of NMDA glycine$_B$ sites in the antidepressant-like activity of tianeptine.

Several studies have indicated that AMPA receptors may be involved in the therapeutic activity of antidepressant drugs [19]. The highest density of AMPA receptors was found in the prefrontal cortex and hippocampus, i.e., in structures that are responsible for mood regulation and that are thought to be important in depression [6]. Preclinical data have shown that positive AMPA receptor modulators (potentiators) are effective in the FST and tail suspension tests [2]. Several AMPA receptor potentiators have demonstrated efficacy comparable to that of SSRI and tricyclic antidepressants, e.g., LY392098, LY451646, LY451395 and LY404817 [1, 4, 14, 15, 20, 34]. Moreover, the antidepressant-like effects of NMDA antagonists (ketamine and zinc) were prevented by pretreatment with the AMPA receptor blocker NBQX [19, 38], and the AMPA receptor potentiators produced synergistic effects when combined with clinically effective antidepressants, e.g., LY392098, which produced synergistic effects with imipramine, fluoxetine and citalopram in the FST [15].

In the present study, we observed the inhibition of the antidepressant-like activity of tianeptine by NBQX. Thus, we propose that an AMPA receptor blockade is involved in the action of tianeptine. Similar effects were reported for the following other antidepressant drugs: imipramine and citalopram (our unpublished data). Previously published data have shown that some antidepressants influence the AMPA receptor. Fluoxetine has been found to alter AMPA receptor phosphorylation in a manner that is expected to increase AMPA receptor signaling [6], and paroxetine, but not desipramine, enhances synaptic plasticity in the hippocampus by increasing BDNF mRNA expression [19].

In conclusion, the antidepressant-like activity of tianeptine was enhanced by the blockade of the NMDA receptors and antagonized by the activation of glycine$_B$ sites and blockade of AMPA receptors. Based on these results, we hypothesize that an interaction between both NMDA and AMPA receptors plays an important role in the mechanism of the antidepressant action of tianeptine.

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