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PRELIMINARY COMMUNICATION

SIGMA$_1$ RECEPTOR ANTAGONISTS ATTENUATE ANTIDEPRESSANT-LIKE EFFECT INDUCED BY CO-ADMINISTRATION OF 1,3 DI-o-TOLYLGUANIDINE (DTG) AND MEMANTINE IN THE FORCED SWIMMING TEST IN RATS

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Sigma$_1$ receptor antagonists attenuate antidepressant-like effect induced by co-administration of 1,3 di-o-tolylguanidine (DTG) and memantine in the forced swimming test in rats. G. SKUZA, Z. ROGÓŻ. Pol. J. Pharmacol., 2003, 55, 1149–1152.

The obtained results show that DTG, the σ_1/σ_2 receptor agonist, exerts a synergistic effect with memantine, an uncompetitive NMDA receptor antagonist, in the forced swimming test in rats, and that progesterone and BD 1047, the σ_1 receptor antagonists, counteract this effect. The results suggest that the σ_1 receptor subtype may contribute to the behavioral response induced by combined administration of DTG and memantine in Porsolt's test in rats.

Key words: *sigma ligands, DTG, memantine, synergistic effect, progesterone, BD 1047, forced swimming test, rats*

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INTRODUCTION

The sigma (σ) receptors were first described by Martin et al. [4] as one of the opiate receptor subtypes, but they were later determined to be a distinct class of receptors. Recently, the σ_1 receptor was cloned and found to be different from all known mammalian receptors [12]. Two different σ receptor subtypes, σ_1 and σ_2, have been distinguished [9]. Since several antidepressants have high affinity for σ receptors, the σ_1 binding sites may be relevant to the mechanism of antidepressant action [3, 11]. It is widely accepted that σ receptor ligands can modulate neurotransmission mediated by central neurotransmitter systems, including glutamatergic/NMDA [7].

Our preliminary results indicated that combined treatment with SA4503 and siramesine (selective σ_1 and σ_2 receptor agonists, respectively) on the one hand, and amantadine on the other, showed synergistic effect in the forced swimming test in rats [13].

The aim of the present study was to support this finding using another σ receptor ligand, DTG (σ_1/σ_2 receptor agonist) and NMDA antagonist, memantine (MEM). Additionally, we used progesterone, a σ_1 receptor antagonistic neurosteroid and BD 1047, a novel σ antagonist with preferential affinity for σ_1 sites [5, 6], to determine the role of σ_1 receptor in the effect induced by joint treatment with DTG and MEM.

MATERIALS and METHODS

The experiments were carried out on rats (male Wistar, 250–300 g) housed in groups (6 per cage) in a controlled environment at a temperature of 22 ± 2°C under a 12-hour light/dark cycle (the light on at 7 a.m.). The animals had free access to food and water. Studies were conducted between 8 a.m. and 3 p.m. Experimental protocols were approved by the local Ethics Committee and complied with guidelines of the responsible agency of the Institute of Pharmacology.

Substances

1,3-Di-*o*-tolylguanidine (DTG, Research Biochemicals Inc., USA), memantine hydrochloride (MEM, Merz Pharmaceuticals, Germany), progesterone (4-pregnene-3,20-dione, Serva, Feinbiochemica, Germany), N-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine (BD 1047, Tocris, UK).

MEM and BD 1047 were dissolved in distilled water, DTG was suspended in 1% aqueous solution of Tween 80 and progesterone in 1% aqueous solution of carboxymethylcellulose. The compounds were administered intraperitoneally (*ip*) (MEM and DTG) or subcutaneously (*sc*) (progesterone, BD 1047) in a volume of 2 ml/kg.

Forced swimming (Porsolt's) test

The animals were subjected to two trials during which they were forced to swim in a cylinder (40 cm high, 18 cm in diameter) filled with water (23–25°C) to a height of 15 cm. There was a 24-hour interval between the first and second trial; the first trial lasted 15 min, the second 5 min. The total duration (s) of immobility was measured throughout the second trial [8]. DTG (2.5 and 5 mg/kg) was given separately or in combination with MEM (2.5 mg/kg) three times: at 24, 5, and 1 h before the test; progesterone or BD 1047 were given 15 min before the every injection of MEM and DTG. Each group consisted of 8 rats.

Open field test

The center of an open platform (divided into sectors, without walls) was illuminated with a 75 W bulb, hung directly 75 cm above it. During all experiments the rest of the laboratory room was dark. To start the test, animals were placed gently in the center of the platform and were allowed to explore it freely. Ambulation (the number of crossings of sector lines), peeping (the number of times the animals peeped down from the edge of the arena) or rearing and the time of walking were recorded directly for 5 min. Drug treatments were carried out according to the same experimental schedule as described above (three injections). Each group consisted of 6 rats.

Data analysis

The data were evaluated by two-way ANOVA, followed, when appropriate, by individual comparisons with the control using Dunnett's test.

RESULTS and DISCUSSION

As it was shown at Figure 1, DTG (2.5 and 5 mg/kg) as well as MEM (2.5 mg/kg) given sepa-

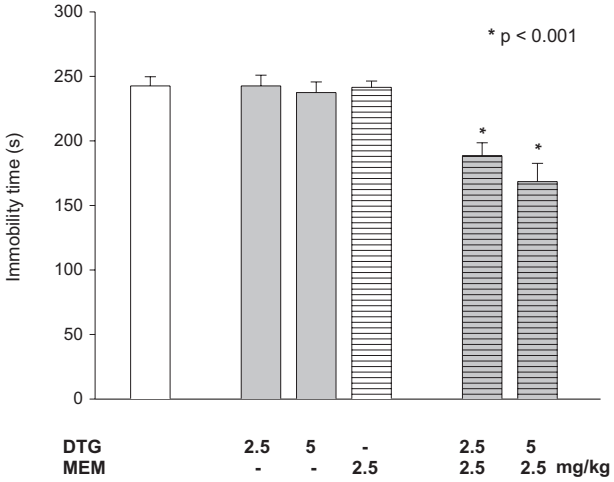

Fig. 1. The effect of joint treatment with DTG and MEM in the forced swimming test in rats. DTG (2.5 and 5 mg/kg *ip*) was given jointly with MEM (2.5 mg/kg *ip*) three times: at 24, 5 and 1 h before the test. The animals were observed for 5 min. The results represent a mean ± SEM (s) from 8 rats. The data were statistically evaluated by ANOVA followed by Dunnett's test

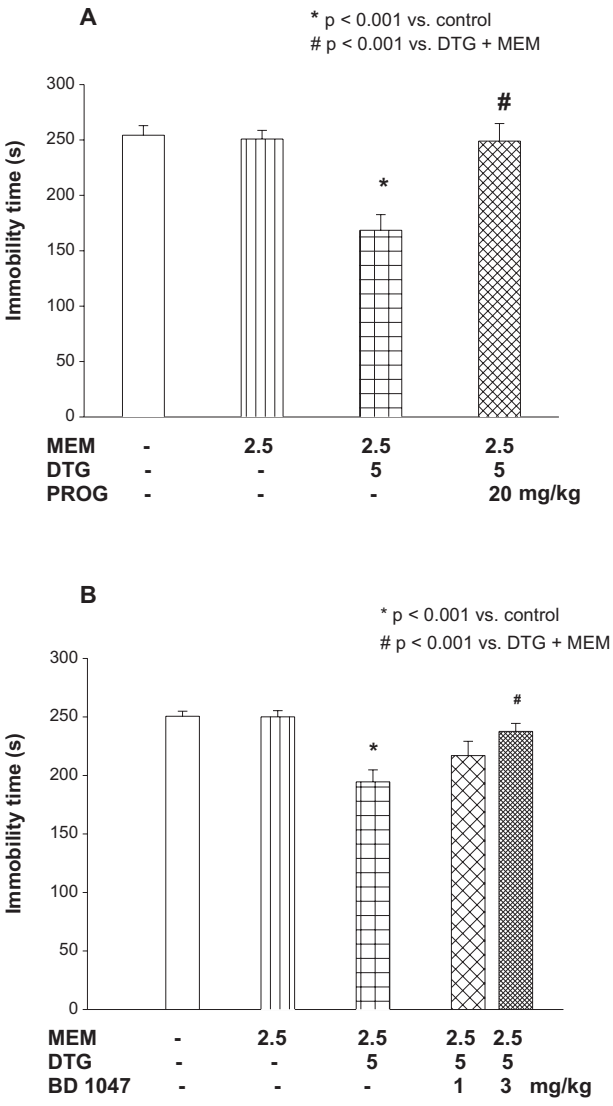

Fig. 2. The influence of progesterone (20 mg/kg) (A) or BD 1047 (1 and 3 mg/kg) (B) on the antidepressant-like effect induced by combined treatment with DTG (5 mg/kg) and MEM (2.5 mg/kg) in the forced swimming test in rats. DTG was given jointly with MEM three times: at 24, 5 and 1 h before the test. Progesterone (20 mg/kg) or BD 1047 (1 and 3 mg/kg) was given 15 min before every injection of DTG + MEM. The animals were observed for 5 min. The results represent a mean ± SEM (s) from 8 rats. The data were statistically evaluated by ANOVA followed by Dunnett's test

rately, did not change the immobility time of rats. Co-administration of DTG (at both doses used) with MEM induced antidepressant-like effect in Porsolt's test. These synergistic effects were not an expression of a general change in locomotor activity, since it was unaltered after co-administration of both σ receptor ligands and MEM (data not shown).

The antidepressant-like effect of DTG at a dose of 5 mg/kg, given jointly with MEM, was antagonized by progesterone (20 mg/kg) (Fig. 2A). Similar antagonistic action was observed when rats were pretreated with BD 1047 (3 mg/kg). Lower dose of BD 1047 (1 mg/kg) failed to affect the immobility time decreased by joint treatment with MEM and DTG (Fig. 2B). Neither progesterone nor BD 1047 showed any activity (data not shown).

Our previous results revealed that combined treatment with NMDA antagonist, amantadine, and σ receptor agonists (particularly σ_1, and to a lesser extent – σ_2) induced a synergistic effect in the forced swimming test in rats, similarly as it was observed in the case of co-administration of the NMDA receptor antagonists and some antidepressants [10, 13].

The present results support our previous finding that σ receptor agonists and uncompetitive NMDA receptor antagonists showed synergistic effect in the Porsolt's test in rats which seems to be related, at least in part, with an activation of σ_1 receptor, since progesterone, a σ_1 receptor antagonistic neurosteroid, and BD 1047, a σ antagonist with preferential affinity for σ_1 sites [5, 6], counteract this antidepressant-like activity. It is noteworthy that amantadine (at therapeutic concentrations) as well as MEM (at higher doses), bind to the σ sites [2].

Moreover, potential antidepressant activity of other σ_1 agonists (igmesine, OPC 14523) has been demonstrated in preclinical studies [1, 14].

Though the precise mechanism of positive interaction of uncompetitive NMDA receptor antagonists and σ_1 receptor agonists in Porsolt's test requires further studies, the above-described results indicate that activation of σ (particularly σ_1) receptor may be one of possible mechanisms by which drugs induce an antidepressant-like activity in the Porsolt's test and that it may be enhanced by NMDA receptor antagonists.

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