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THE SYNERGISTIC EFFECT OF SELECTIVE SIGMA RECEPTOR AGONISTS AND UNCOMPETITIVE NMDA RECEPTOR ANTAGONISTS IN THE FORCED SWIM TEST IN RATS

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Data acquired to date show that some sigma receptor ligands reveal "antidepressant-like" activity in the forced swim test in mice and rats. Moreover, our preliminary results suggested that joint administration of sigma receptor ligands and amantadine (AMA, a glutamatergic/NMDA receptor antagonist) caused a positive interaction in the Porsolt test in rats, as had already been observed in the case of co-treatment with clinically active antidepressants and AMA. The aim of the present study was to examine the effect of combined administration of sigma₁ or sigma₂ receptor agonists, SA4503 or siramesine, respectively, and AMA or memantine (MEM) (uncompetitive NMDA receptor antagonist). SA4503 or siramesine given jointly with MEM (as well as with AMA) decreased the immobility time in rats. The effect of SA4503 and AMA co-administration was antagonized by progesterone, a sigma₁ receptor antagonistic neurosteroid. Combined treatment with siramesine and AMA was modified by neither progesterone nor BD1047 (a novel sigma antagonist with preferential affinity for sigma₁ sites); but it was counteracted by sulpiride and prazosin (a dopamine D₂- and an α_1 -adrenergic receptor antagonist, respectively). The "antidepressant-like" effect induced by siramesine and MEM was not antagonized by progesterone, but was attenuated by BD1047, sulpiride and prazosin. The obtained results give support to the hypothesis that sigma (particularly sigma₁) receptors may be one of the possible mechanisms by which drugs induce antidepressant-like activity in the forced swim test, and that this effect may be enhanced by NMDA receptor antagonists. Combined treatment with sigma ligands and AMA or MEM (applied in the clinic) may be an alternative to the treatment of antidepressant-resistant depressive patients in the future.

Key words: *sigma agonists, memantine, amantadine, synergistic effect, forced swim, rats*

INTRODUCTION

Sigma receptors had first been described by Martin et al. (1) as one of the opiate receptor subtypes, but were later considered to be a distinct class of receptors. Recently, a sigma₁ receptor was cloned and found to be different from all known mammalian receptors (2). Two different sigma receptor subtypes, sigma₁ and sigma₂, were distinguished on the basis of their pharmacological profiles (3). Since several antidepressants (ADs) show high affinity for sigma receptors, the sigma binding sites may be relevant to the mechanism of antidepressant action (4-6). Moreover, sigma receptor agonists (especially sigma₁ ones) display antidepressant-like activity in animal models (7-9).

It is commonly accepted that sigma receptor ligands can modulate neurotransmission mediated by central neurotransmitter systems, including dopaminergic and glutamatergic/NMDA ones, which are seemingly important for the mechanism of action of ADs (10-12). The antidepressive properties of NMDA receptor antagonists were postulated more than ten year ago and their antidepressant-like action was shown in a number of animal models (e.g. 11, 13-15). Our earlier studies showed that ADs (imipramine, citalopram, mianserin) potentiated the antidepressant-like effect of MK-801, uncompetitive NMDA receptor antagonist, indicating the existence of synergism between ADs and MK-801 (13). Moreover, ADs administered in combination with amantadine, memantine or neramexan, uncompetitive NMDA receptor antagonists, display a positive interaction in the forced swimming test in rats. Therefore it is possible that co-administration of ADs and NMDA receptor antagonists may induce a more pronounced antidepressive activity in clinic than treatment with ADs alone (16). The latter observation may be of particular importance in the case of drug-resistant patients and may suggest a method of obtaining significant antidepressive actions with limited side-effects.

Our preliminary results indicated that selective sigma₁ and sigma₂ receptor agonists given jointly with AMA decreased the immobility time of rats (8). The present study was aimed at determining whether combined treatment with SA4503 or siramesine on the one hand and MEM (another uncompetitive NMDA receptor antagonist) on the other, led to an increase in antidepressant-like activity compared to the effects of those compounds given separately. Additionally, we used progesterone, a sigma₁ receptor antagonistic neurosteroid, and BD 1047, a novel sigma antagonist with preferential affinity for sigma₁ sites (17, 18), to determine the role of the sigma₁ receptor in the effect induced by joint treatment with sigma ligands and the uncompetitive NMDA receptor antagonists - AMA and MEM.

MATERIALS AND METHODS

Animals and drug treatment

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 on a 12- hour light/dark cycle (the

light on at 7 a.m.). The animals had free access to food and water. AMA, MEM, SA4503, BD 1047 and sulpiride were dissolved in distilled water (sulpiride with a slight addition of citric acid), progesterone in a 10% DMSO + a 1% aqueous solution of carboxymethylcellulose; siramesine and prazosin were suspended in a 1% aqueous solution of Tween 80. The compounds were administered *i.p.* (AMA, MEM, BD 1047, prazosin, siramesine, sulpiride), *s.c.* (progesterone) or *p.o.* (SA 4503) at a volume of 2 ml/kg. Studies were conducted between 8 a.m. and 3 p.m. Experimental protocols were approved by the Local Bioethics Commission and to comply with the guidelines of the agency in charge at the Institute of Pharmacology, Polish Academy of Sciences.

Drugs

Amantadine hydrochloride (AMA, Sigma-Aldrich Chemie GmbH, Germany), BD 1047 (N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino) ethylamine, Tocris, UK), memantine hydrochloride (MEM, Sigma-Aldrich Chemie GmbH, Germany), prazosin (hydrochloride, Research Biochemicals Inc., USA), progesterone (4-pregnene 3, 20-dione, Serva Feinbiochemica, Germany), SA4503 (1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride, Santen Pharmaceutical Co. Ltd., Japan), siramesine hydrochloride (Lundbeck, Denmark), (-) sulpiride (Research Biochemicals Inc., USA).

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) up to a height of 15 cm. There was a 24-hour interval between the first and the second trial; the first trial lasted 15 min, the second 5 min. The total duration (s) of immobility was measured throughout the second trial (19).

SA4503 (3 mg/kg) and siramesine (1 mg/kg) were given separately or in combination with AMA (10 mg/kg) or MEM (2.5 mg/kg) three times: at 24, 5, and 1 h before the test. In some experiments, progesterone (20 mg/kg) or BD1047 (3 mg/kg) was given at 15 min, sulpiride or prazosin - at 30 min before joint treatment with sigma ligands and NMDA antagonists. Each group consisted of 8 rats.

Locomotor activity test

The locomotor activity of rats was studied with photoresistor actometers (two light beams; LxWxH = 40x40x25 cm) for 30 min. Drug treatments were carried out according to the same experimental schedule as described above (three injections). Each group consisted of 6-8 rats.

Statistical analysis

The data were evaluated by an analysis of variance (ANOVA), followed - when appropriate - by individual comparisons with the control using Dunnett's test.

RESULTS

Forced swim (Porsolt's) test

SA4503 at the doses used (1, 3 and 10 mg/kg) did not modify the immobility time of rats in a statistically significant manner. Co-administration of SA4503 and MEM (in a dose of 2.5 mg/kg, inactive per se) induced a decrease in the

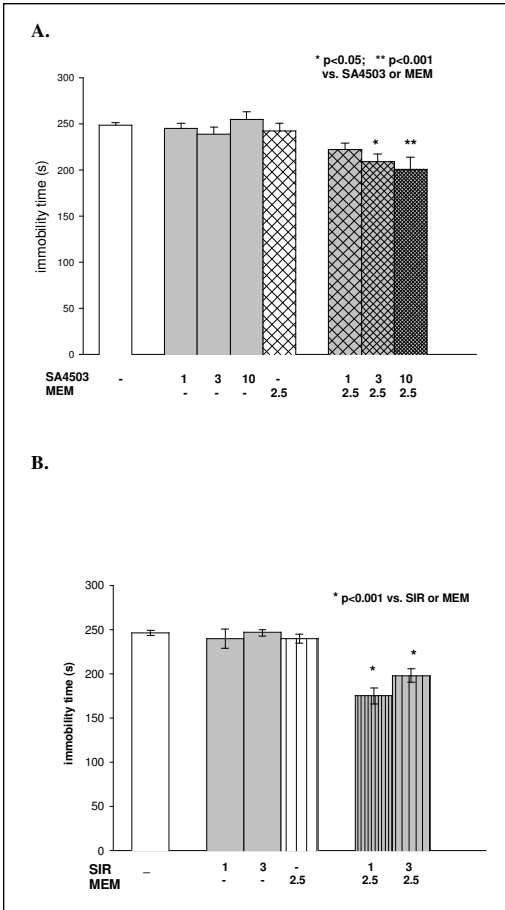


Fig. 1. The effect of combined treatment with memantine (MEM) and SA4503 (A) or siramesine (SIR) (B) in the forced swimming test in rats. MEM (2.5 mg/kg) and SA4503 (1, 3, 10 mg/kg) or SIR (1, 3 mg/kg) were given three times at 24, 5 and 1 h before the test. The obtained results represent the mean ± SEM; n=8. The data were statistically evaluated by ANOVA, followed by individual comparisons using Dunnett's test.

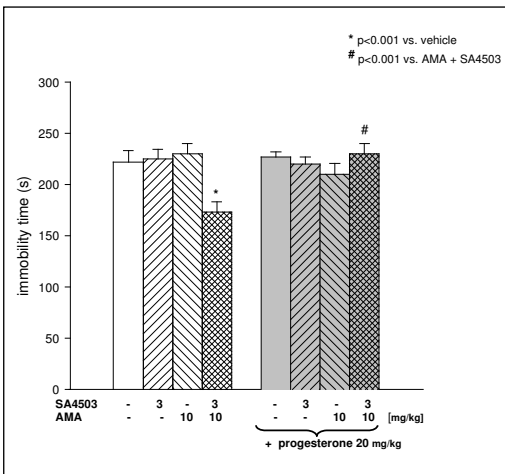


Fig. 2. The influence of progesterone on the anti-immobility effect of SA4503 and amantadine (AMA). SA4503 (3 mg/kg) or AMA (10 mg/kg), or both compounds jointly were given three times at 24, 5 and 1 h before the test. The right side of the columns (gray background) represents the groups pretreated with progesterone (20 mg/kg; 15 min before each injection of SA4503, AMA, or their co-administration). The obtained results show the mean ± SEM; n=8. The data were statistically evaluated by ANOVA, followed by individual comparisons using Dunnett's test.

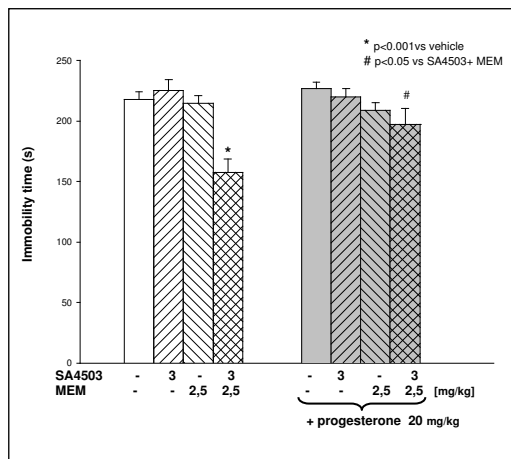


Fig. 3. The influence of progesterone on the anti-immobility effect of SA4503 and MEM. SA4503 (3 mg/kg) or MEM (2.5 mg/kg), or both compounds jointly were given three times at 24, 5 and 1 h before the test. The right side of the columns (gray background) represents groups pretreated with progesterone (20 mg/kg; 15 min before each injection of SA4503, MEM, or their co-administration). The obtained results show the mean \pm SEM; $n=8$. The data were statistically evaluated by ANOVA, followed by individual comparisons using Dunnett's test.

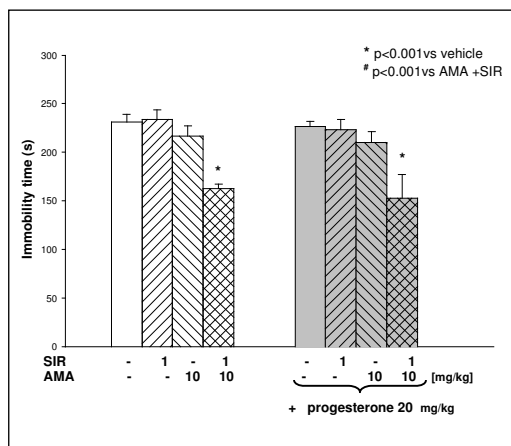


Fig. 4. The influence of progesterone on the anti-immobility effect of SIR and AMA. SIR (1 mg/kg) or AMA (10 mg/kg), or both compounds jointly were given three times at 24, 5 and 1 h before the test. The right side of the columns (gray background) represents groups pretreated with progesterone (20 mg/kg; 15 min before each injection of SIR, AMA, or their co-administration). The results show the mean \pm SEM; $n=8$. The data were statistically evaluated by ANOVA, followed by individual comparisons using Dunnett's test.

immobility time (Fig. 1A). Siramesine, 1 and 3 mg/kg, as well as MEM, did not influence the immobility time of rats. Joint treatment with siramesine and MEM produced an antidepressant-like effect (Fig. 1B).

SA4503 (3 mg/kg) administered in combination with AMA (10 mg/kg) decreased the immobility time of rats compared to the control (vehicle) group, as well as to SA4503 (3 mg/kg) or AMA (10 mg/kg) group. Progesterone (20 mg/kg) completely abolished that effect (Fig. 2).

Co-administration of SA4503 (3 mg/kg) and MEM (2.5 mg/kg) induced an antidepressant-like effect, which was partly antagonized by progesterone (20 mg/kg) (Fig. 3).

Siramesine (1 mg/kg) given jointly with AMA (10 mg/kg) shortened the time of immobility. Progesterone (20 mg/kg) did not modify that effect (Fig. 4). Similar lack of effect was observed when the rats were pretreated with BD 1047

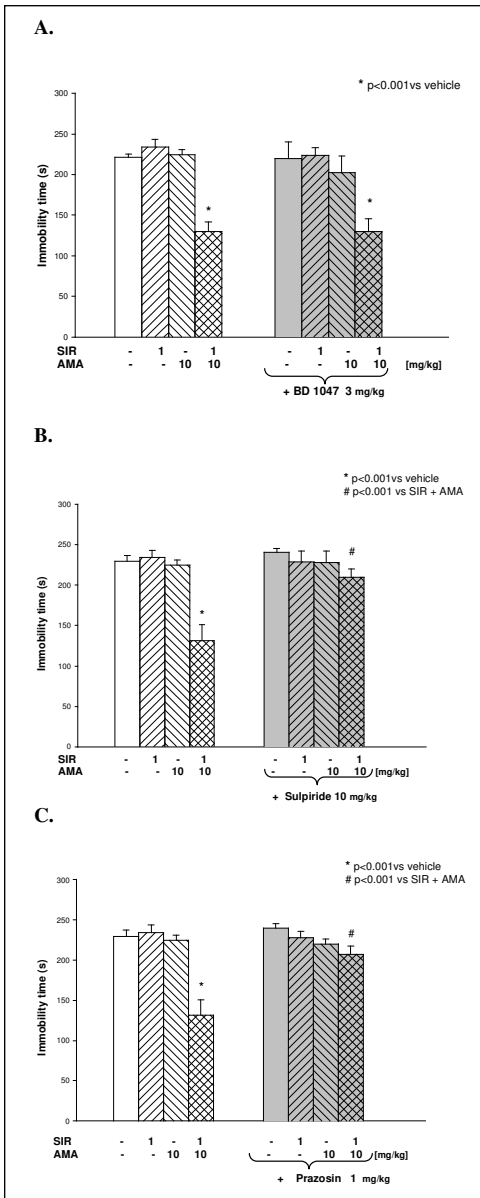


Fig. 5. The influence of BD 1047 (**A**), sulpiride (**B**), or prazosin (**C**) on the anti-immobility effect of SIR and AMA. SIR (1 mg/kg) and AMA (10 mg/kg) were given three times at 24, 5 and 1 h before the test. The right side of the columns (gray background) represents groups pretreated with BD 1047 (**A**) (3 mg/kg; 15 min before each injection of SA4503, AMA, or their co-administration), sulpiride (**B**) (10 mg/kg, 30 min before each injection of SA4503, AMA, or their co-administration), or prazosin (**C**) (1 mg/kg, 30 min before each injection of SIR, AMA, or their co-administration). The obtained results show the mean \pm SEM; $n=8$. The data were statistically evaluated by ANOVA, followed by individual comparisons using Dunnett's test.

(3 mg/kg) (*Fig. 5A*). The antidepressant-like effect evoked by joint treatment with siramesine and AMA was partly counteracted by sulpiride (10 mg/kg) (*Fig. 5B*) and prazosin (1 mg/kg) (*Fig. 5C*). The anti-immobility effect induced by co-administration of siramesine and MEM was not changed by progesterone (*Fig. 6*) but attenuated by BD 1047 (*Fig. 7A*), sulpiride (*Fig. 7B*) and prazosin (*Fig. 7C*).

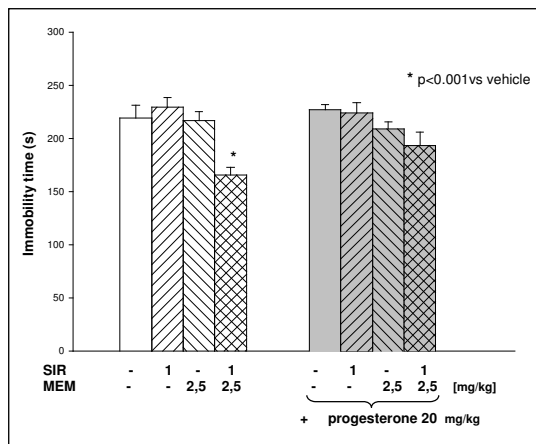


Fig. 6. The influence of progesterone on the anti-immobility effect of SIR and MEM. SIR (1 mg/kg) or MEM (2.5 mg/kg), or both compounds jointly were given three times at 24, 5 and 1 h before the test. The right side of the columns (gray background) represents groups pretreated with progesterone (20 mg/kg; 15 min before each injection of SA4503, MEM, or their co-administration). The obtained results show the mean \pm SEM; $n=8$. The data were statistically evaluated by ANOVA, followed by individual comparisons using Dunnett's test.

The locomotor activity test in rats

The sigma agonists, SA4503 (3 mg/kg) and siramesine (1 mg/kg), or the uncompetitive NMDA receptor antagonists AMA (10 mg/kg) and MEM (2.5 mg/kg), or their combinations did not modify the locomotor activity of rats (data not shown).

DISCUSSION

Although the mechanism of the action of ADs has been studied for many years, it still remains unclear in details and successive new hypotheses are proposed. In accordance with the present opinion, the third generation of ADs should activate monoaminergic transmission and increase the corticolimbic availability of monoamines through indirect mechanisms or by acting "downstream", by cellular substrates controlling gene expression, synaptic plasticity and neurogenesis (20). Such conditions are partly satisfied by selective sigma ligands, which are able to indirectly modulate monoaminergic transmission (21).

As has been proposed by Hayashi et al. (22), sigma receptors control the intracellular levels of Ca^{2+} . Moreover, they can also modulate ion channels, e.g. voltage-dependent Ca^{2+} channels, as well as NMDA receptor and K^+ channels (the former by direct coupling as a modulatory subunit) (23). Such mechanisms, being related to a downstream target, may be involved in the potential antidepressant effect of selective sigma ligands.

On the basis of biochemical *in vitro* experiments, SA4503 was characterized as a σ_1 receptor agonist (24). Preliminary studies indicated that it decreased immobility time in the tail suspension test and Porsolt's test in mice (7, 9). Alleviation of behavioral despair in mice was also observed after another σ_1 agonist, (+)pentazocine, and after the σ_1/σ_2 agonist 1,3di-o-

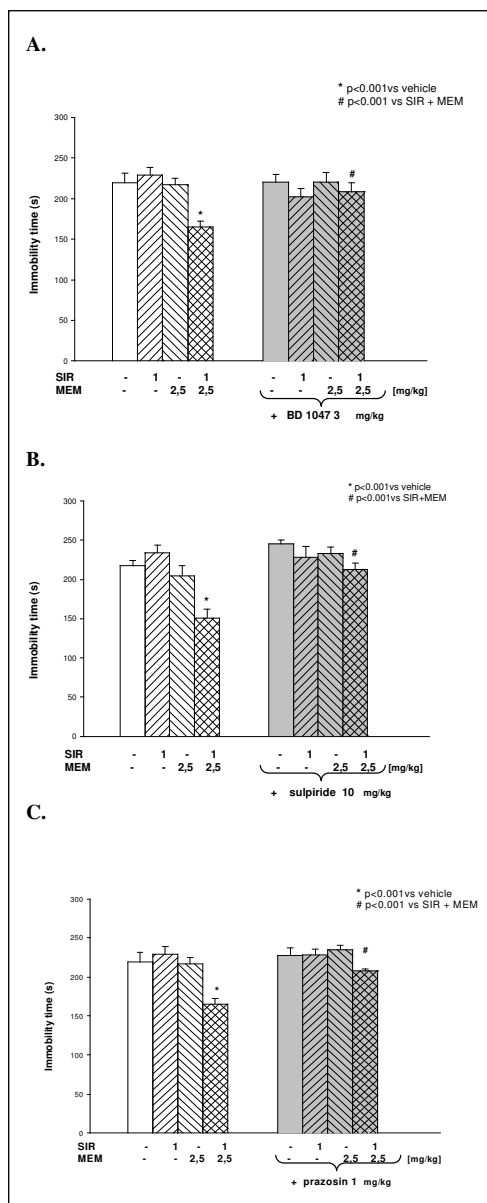


Fig. 7. The influence of BD 1047 (**A**), sulpiride (**B**), or prazosin (**C**) on the anti-immobility effect of SIR and MEM. SIR (1 mg/kg) or MEM (2.5 mg/kg), or both compounds jointly were given three times at 24, 5 and 1 h before the test. The right side of the columns (gray background) represents groups pretreated with BD 1047 (**A**) (3 mg/kg; 15 min before each injection of SIR, MEM, or their co-administration), sulpiride (**B**) (10 mg/kg; 30 min before each injection of SIR, MEM, or their co-administration), or prazosin (**C**) (1 mg/kg; 30 min before each injection of SIR, MEM, or their co-administration). The obtained results show the mean \pm SEM; $n=8$. The data were statistically evaluated by ANOVA, followed by individual comparisons using Dunnett's test.

tolyguanidine (DTG). Moreover, those antidepressant-like effects were antagonized by the sigma₁ antagonist NE-100 (7), or by panamesine, a potential antipsychotic drug with non-selective sigma receptor antagonistic activity (25). The antidepressant-like effect of other sigma₁ agonists, igmesine (JO 1783) and OPC 14523, was recently demonstrated in preclinical studies (26, 27).

However, σ_2 receptors are also likely to modulate emotional responses, since siramesine (a selective σ_2 agonist) showed an anxiolytic-like effect in black-and-white two-compartment box tests in mice and rats, in a social interaction test in rats and in the Vogel conflict test. Moreover, siramesine had moderate antidepressant activity in a chronic mild stress (CMS) model (28, 29). It is noteworthy that no selective antagonists of the σ_2 receptor have been known so far.

Interactions between neuroactive steroids and the σ_1 receptor have been described in *in vitro* and *in vivo* studies (for review see: 30, 31). It was shown that dehydroepiandrosterone (DHEA), pregnenolone or their sulfate esters behaved as agonists of the σ_1 receptor, whereas progesterone - as its antagonist. In the forced swimming test, DHEA sulfate and pregnenolone sulfate caused reduction of immobility, which was reversed by the selective σ_1 receptor antagonist NE-100. On the other hand, progesterone blocked both the σ_1 receptor agonist-mediated effect and neurosteroid effects. A similar cross-reaction between σ_1 receptor ligands and neuroactive steroids was observed at the behavioral level, e.g. in several amnesia models (30, 31).

The anti-immobility effect of SA4503 in the Porsolt's test in rats is not pronounced. It is important to know that a biphasic, bell-shaped dose-response curve has been observed for σ ligands in various behavioral, biochemical and electrophysiological paradigms (32). In the present study, SA4503 did not decrease immobility time in a statistically significant manner (at the doses used). However, when given jointly with AMA or MEM, it produced antidepressant-like activity. Siramesine *per se* failed to show any activity in Porsolt's test in rats. Nevertheless, its co-administration with AMA or MEM caused a decrease in the immobility time of rats, but only at one dose tested (the same as that active in the CMS test) (8). The antidepressant-like effect of combined treatment with SA4503 and AMA was completely antagonized by progesterone. Likewise, progesterone attenuated the anti-immobility effect of joint treatment with SA4503 and MEM.

In contrast, neither progesterone nor BD1047 counteracted the effect of combined treatment with siramesine and AMA, whereas the antidepressant-like effect of the latter compounds was attenuated by sulpiride and prazosin (a dopamine D_2 - and an α_1 -adrenergic receptor antagonists, respectively). The lack of effect of progesterone and BD1047 seems to be justifiable, considering the σ_1 antagonistic activity of both these compounds. However, besides its high affinity for σ_1 sites ($K_i = 0.93$ nM), BD1047 also binds to the σ_2 receptor ($K_i = 47$ nM) (17). The results obtained in the present study suggest that the anti-immobility effect of combined treatment with siramesine and AMA or MEM is related to noradrenergic and dopaminergic mechanisms, but not to a σ_1 (or a σ_2) one.

Surprisingly, BD1047 attenuated the anti-immobility effect of combined treatment with siramesine and MEM (while progesterone did not modify it in a statistically significant manner). These findings are all the more unexpected as neither progesterone nor BD1047 modifies the antidepressant-like effect of joint

treatment with SIR and AMA. Elucidation of the above discrepancy requires further studies.

Like in the case of siramesine and AMA, sulpiride and prazosin partly antagonized the antidepressant-like effect of combined treatment with siramesine and MEM, which pointed to a complex mechanism of this interaction, including noradrenergic and dopaminergic mechanisms.

Some results suggested that SA4503 - like DTG or (+)pentazocine -facilitated dopaminergic transmission in the frontal cortex, a brain area believed to play an important role in the pathophysiology of depression (e.g. 33, 34, 35). Biochemical and electrophysiological studies demonstrated that the alterations produced by SA4503 resembled those reported for clinically active ADs (e.g. paroxetine, fluoxetine, citalopram, desipramine) (35). Additionally, our earlier results showed that repeated (but not acute) treatment with SA4503 up-regulated D₂-mediated dopaminergic and α_1 -adrenergic transmission, both those effects being important for clinical antidepressant activity (36, 37). According to Rogóž et al. (38), administration of AMA jointly with imipramine induced up-regulation of dopamine D₂ and D₃ receptors in rat brain: that effect may explain the synergistic action observed in behavioral studies. It should be emphasized that combinations of those drugs, administered according to the same experimental schedule, did not increase locomotor activity.

As mentioned in the Introduction, our earlier studies indicated that ADs potentiated the antidepressant-like effect of uncompetitive NMDA receptor antagonists (13). That interaction was particularly interesting in the case of fluoxetine, which - like siramesine - did not show any antidepressant-like activity in Porsolt's test when it has been given alone (8, 16). Moreover, DTG exerted a synergistic effect with MEM, which was counteracted by progesterone and BD 1047, a sigma antagonist with preferential affinity for sigma₁ sites (39).

It is noteworthy that AMA (at therapeutic concentrations), as well as MEM, another uncompetitive NMDA receptor antagonist (at higher doses), bind to sigma sites (40).

In our study, progesterone *per se* did not modify the immobility time of rats, its anti-immobility effect being also observed, though (e.g. 41). The above discrepancy can be explained by numerous essential procedural differences (e.g. sex, doses and the schedule of administration, modifications in Porsolt's test). The lack of progesterone effect in the forced swim test was reported by other authors (30, 31)

It is well established that all the currently used ADs show therapeutic efficacy in a maximum of 60-70% of depressive patients. The problem of AD-resistant depression has been the subject of an extensive study, and alternative treatments have been proposed (e.g. co-administration of ADs and uncompetitive NMDA receptor antagonists or metyrapone, a glucocorticoid synthesis inhibitor) (16, 42). Preliminary clinical trials concerned with combined administration of imipramine and AMA to patients with unipolar drug-resistant depression are promising (43, 44).

The above-described and some earlier results indicate that the activation of sigma (particularly sigma₁) receptor may be one of possible mechanisms by which drugs induce antidepressant-like activity in Porsolt's test, and that this effect may be enhanced by NMDA receptor antagonists. These findings suggest that combined treatment with some sigma ligands and uncompetitive NMDA receptor antagonists may be an alternative to the treatment of antidepressant-resistant depressive patients in the future.

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