Antidepressant-like effect of combined treatment with selective σ receptor agonists and a 5-HT$_{1A}$ receptor agonist in the forced swimming test in rats

Grażyna Skuza, Zofia Rogóź

Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Smeńna 12, PL 31-343 Kraków, Poland

Correspondence: Grażyna Skuza, e-mail: skuza@f-pan.krakow.pl

Abstract:
The interaction between the selective sigma (σ) receptor agonists and 8-OH-DPAT, a serotonin (5-HT)$_{1A}$ receptor agonist, was examined in the forced swimming test in rats. The results indicate that joint administration of DTG (5 mg/kg) or SA4503 (3 mg/kg), the selective σ$_1$/σ$_2$- or σ$_1$-receptor agonists, respectively, and 8-OH-DPAT (0.1 or 0.3 mg/kg) induces an antidepressant-like effect. The doses of sigma agonists and 8-OH-DPAT used in the study were inactive per se in this model. The effect of DTG and 8-OH-DPAT co-administration was partly counteracted by WAY 100635 (0.1 mg/kg) as well as by BD 1047 (3 mg/kg), a 5-HT$_{1A}$ and σ$_1$ receptor antagonists, respectively, suggesting the involvement of both receptor types in the anti-immobility effect in rats.

Key words: σ ligands, 8-OH-DPAT, WAY 100635, forced swimming test, rats

Introduction

The ability of antidepressant drugs (ADs) to interact with σ receptors in nanomolar range appears to be relevant to the mechanism of antidepressant action [3, 25]. Preclinical studies have shown that targeting σ receptors alone is sufficient (but not requisite) to produce antidepressant-like actions. As shown previously, σ receptor agonists (e.g. igmesine, SA4503, (+)-pentazocine, and recently UMB23 and UMB82) produce anti-immobility effect in animal models of depression such as forced swimming test or tail suspension test [3, 25, 35]. Moreover, the high-affinity σ receptor agonist igmesine is promising as AD in humans (phase II clinical trials) [34]. It is believed that σ receptors represent an initial target (similarly to monoamine transporters) in a cascade of events that results finally in an antidepressant action.

It is generally accepted that serotonin (5-HT) and noradrenaline systems are directly involved in the pathogenesis of depression and in the mechanism by which ADs exert their therapeutic action. In particular, the disturbance in the function of pre- and post-synaptic 5-HT$_{1A}$ receptors is an important factor in the development of depression [5, 10, 18]. The change in somatodendritic and/or postsynaptic 5-HT$_{1A}$ receptor responsiveness is involved in adaptation to stress [24]. The latter is one of the main agents in the onset of depression. The 5-HT$_{1A}$ receptor agonists, e.g. 8-OH-DPAT, induce rapid and effective antidepressant-like action in the forced swimming test (FST) [9, 13, 31]. As shown
recently, 8-OH-DPAT reveals also the affinity for 5-HT$_7$ receptors [15, 30] but as commonly accepted its anti-immobility effect in the FST is related to the activation of 5-HT$_1A$ receptors [11, 13]. In addition, 5-HT$_1A$ receptor may be of interest in augmentation strategies for antidepressant treatments [1, 16].

It is well established that all the currently used ADs show therapeutic efficacy in a maximum of 60–70% of depressive patients, thus the problem of AD-resistant depression has been the subject of an extensive studies and alternative treatments have been proposed. As we have shown previously, the combined treatment with ADs (representing different mechanism of action after their single administration) or σ receptor agonists (SA4503, DTG) and amantadine (an uncompetitive NMDA receptor antagonist) induced synergistic effect in the forced swimming test in rats [23, 26].

The aim of the present study was to find out if the combined treatment with DTG (the σ$_1$/σ$_2$ receptor agonist) or SA4503 (the σ$_1$ receptor agonist) and 8-OH-DPAT may affect the immobility time of rats in the FST. The doses of substances used in the study were chosen on the basis of our previous results [e.g. 22, 26, 27].

Materials and Methods

Animals

The experiments were carried out on male Wistar rats (250–300 g) housed in groups of 6 per cage in a controlled environment at a temperature of 22 ± 2°C under a 12-h light/dark cycle (the light on at 7 a.m.). The animals had free access to food and water. The 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

The following substances were tested: BD 1047 ((N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino) ethylamine, Tocris, UK), DTG (1,3-di(2-tolyl)-guanidine, Research Biochemical Inc., USA), 8-OH-DPAT ((±)-8-hydroxy-2(di-n-propylamino)-tetralin-hydrobromide, Research Biochemical Inc., USA), SA4503 (1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride, Santen Pharmaceutical Co. Ltd., Japan), WAY 100635 (N-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-N-2-pyridinyl)cyclohexane-carboxamide trihydrochloride, synthesized by Dr. J. Boksa, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland).

The compounds were dissolved in distilled water (except for DTG, which was suspended in 1% Tween 80) and administered perorally (po, SA4503), subcutaneously (sc, WAY 100635) or intraperitoneally (ip, BD 1047, DTG, 8-OH-DPAT) in a volume of 2 ml/kg. Each experimental group consisted of 6–10 naive rats used only once in each test.

Forced swimming test (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-h interval between the first and the second trial. The first trial lasted 15 min, while the second one was carried out for 5 min. The total duration (s) of immobility was measured throughout the second trial [20].

DTG (5 mg/kg) or SA4503 (3 mg/kg) and 8-OH-DPAT (0.1 or 0.3 mg/kg) were given separately or in combination three times: at 24, 5, and 0.5 h before the test. WAY 100635 (0.1 mg/kg) or BD 1047 (3 mg/kg) were given 15 min before joint administration of DTG and 8-OH-DPAT. Each group consisted of 6–10 rats.

The locomotor activity test

The locomotor activity of rats was recorded for each animal in Opto-Varimex cages (Columbus Instruments, USA) for 5 min. Horizontal locomotor activity, defined as distance travelled was expressed in cm. Drug treatments were carried out according to the same experimental schedule as described above (three injections). Each group consisted of 6–8 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

FST is widely used as a quick and reliable behavioral test in rodents which detects all major classes of antidepressant treatments [6, 12, 20]. In this study, neither DTG (5 mg/kg) nor 8-OH-DPAT (0.1 or 0.3 mg/kg) per se changed rats’ immobility [F(3, 28) = 0.79; ns vs. vehicle] (Fig. 1). Combined treatment with DTG (5 mg/kg) and 8-OH-DPAT (0.1 or 0.3 mg/kg) dose-dependently decreased the immobility duration [DTG × 8-OH-DPAT (0.3 mg/kg) interaction: F(1, 28) = 4.29, p < 0.05]. The anti-immobility effect of joint treatment with DTG and 8-OH-DPAT (0.3 mg/kg) was partly counteracted by WAY 100635 (0.1 mg/kg) (Fig. 2A) [F(1, 14) = 63.89, p < 0.001] and by BD 1047 (3 mg/kg) (Fig. 2B) [F(1, 14) = 8.78, p < 0.05]. This finding indicates that both σ1- and 5-HT1A receptor activation is involved in anti-immobility effect in rats observed in this study. Similar decrease in rats’ immobility was observed also after co-administration of 8-OH-DPAT (0.3 mg/kg) and σ1 receptor agonist, SA4503 (Fig. 3) [F(1, 28) = 6.44, p < 0.05]. It should be emphasized that these synergistic effects were not an expression of a change in general locomotor activity, since it was unaltered after co-administration of both σ ligands and 8-OH-DPAT as well as after pretreatment with BD 1047 or WAY 100635 (control = 470.7 ± 93; DTG + 8-OH-DPAT (0.3 mg/kg) = 513.2 ± 105; WAY 100635 + DTG + 8-OH-DPAT = 395.1 ± 80). As mentioned in the Introduction, a number of σ1 agonists induced the antidepressant-like effect in the FST in rats and mice, which was antagonized by the σ1 antagonists (for review see [28]). In particular, a potential antidepressant activity of OPC-14523 has been demonstrated in preclinical studies [2, 33]. OPC-14523 binds at nanomolar concentrations to σ receptor (to both its subtypes to similar degree) and to 5-HT1A receptor. Investigations of Tottori et al. [33] suggested that its action in the FST appeared earlier than after fluoxetine and even imi-
pramine, since it could be observed already after a single dose of this compound (with the lack of influence on basic locomotor activity). The antidepressant-like effect of OPC-14523 was antagonized both by NE-100, a σ1 receptor antagonist, and by WAY-100635, a 5-HT1A receptor antagonist. It was concluded that unique mechanism of action of OPC-14523, combining agonism at 5-HT1A and σ receptors, amplified its antidepressant potential and could manifest itself as a quicker and more efficient clinical effect.

It is accepted that the antidepressant-like action of 8-OH-DPAT in the FST (as well as buspirone or gepirone, the 5-HT1A receptor partial agonists), is related to the activation of 5-HT1A receptors [9, 11, 13, 17]. In contrast to some literature data [8, 9], 8-OH-DPAT at doses used in our studies (0.1 and 0.3 mg/kg) failed to produce statistically significant decrease in the immobility time. This discrepancy may be due to some differences in the methodological details (e.g. strains of rats, way and time of drug administration, depth of water in cylinders, etc.).

The data concerning the role of 5-HT1A receptor in facilitation of antidepressant effect are conflicting. Some clinical data suggested that co-administration of pindolol (a 5-HT1A/1B and β-adrenoceptor antagonist) and SSRIs shortened the time of onset of clinical action and enhanced beneficial effect in the therapy-resistant depression [1, 4]. Pindolol potentiated the anti-immobility effect of fluoxetine, citalopram, fluvoxamine and paroxetine in the FST in mice as well as accelerated an antidepressant-like action of fluvoxamine in chronic mild stress model in rats [7, 29]. On the other hand, some other results did not support these findings [19, 32]. Co-treatment with SSRIs (selective serotonin reuptake inhibitors) or desipramine and 5-HT1A agonists (8-OH-DPAT, buspirone) enhanced the antidepressant-like action [21].

As mentioned in the Introduction, ca. 30% of depressed patients do not respond the AD treatment. In recent years, numerous studies have been undertaken in order to find out the possibilities of potentiating the efficacy of ADs and accelerating the onset of clinical improvement. In addition to our previous studies concerning the co-administration of ADs or σ receptor antagonists and amantadine (mentioned in the Introduction), co-treatment with pramipexole and sertraline also induces antidepressant-like effect in rats, antagonized by σ1 receptor antagonists (BD 1047 and progesterone) [22]. It was concluded that σ1-receptors may constitute one of the possible mechanisms by which joint treatment with pramipexole and sertraline induces antidepressant-like activity. As was demonstrated recently, (+)-pentazocine, a selective σ1 receptor agonist, produced synergism with subeffective doses of venlafaxine in FST in mice [14].

In summary, the results obtained in this study allow to suppose that joint administration of σ1- and 5-HT1A receptor agonists may be an alternative to the treatment of AD-resistant depressive patients but this conclusion requires further studies.

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