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Short communication

Antidepressant-like effect of PRE-084, a selective σ_1 receptor agonist, in Albino Swiss and C57BL/6J mice

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Abstract:
PRE-084, a selective σ receptor agonist, exhibited an antidepressant-like effect in the forced swim test (FST) in Albino Swiss and C57BL/6J mice. This effect was counteracted by BD 1047 (5 and 10 mg/kg) but not by SM-21 (3 and 10 mg/kg), which are σ_1- and σ_2-receptor antagonists, respectively. The results indicated that PRE-084 has an antidepressant-like effect in C57BL/6J and, to a lesser extent, in Albino Swiss mice. These results support the idea that σ_1-receptors, but not σ_2-receptors, contribute to the mechanism of antidepressant activity of σ agonists in FST.

Key words:
σ_1 receptor agonist, PRE-084, σ_1- and σ_2-receptor antagonists, BD 1047, SM 21, forced swim test, mice

Introduction

σ Receptors were first described in the literature by Martin et al. [7] as a subtype of opiate receptors. However, subsequent work showed that they define a distinct class of receptors composed to two subtypes, σ_1 and σ_2, which are distinguished by their pharmacological profiles. The σ_1 receptor was cloned and found to be different from all known mammalian proteins [for review: 3, 6, 11].

Several antidepressant drugs (ADs) have high affinities for σ receptors, and the binding of σ receptors may be relevant to their mechanism of antidepressant action [1, 17]. Preclinical studies have shown that targeting σ receptors alone is sufficient (but not requisite) to produce antidepressant-like effects. As shown previously, the σ receptor agonists (e.g., igmesine, SA4503, (+)-pentazocine, and recently UMB23 and UMB82) produces an anti-immobility effect in animal models of depression such as the forced swim test (FST) in rats and mice, or the tail suspension test in mice [1, 10, 17, 22]. Moreover, the high-affinity σ receptor agonist igmesine is a promising AD agent in humans (phase II clinical trials) [23]. It is believed that σ receptors represent an initial target (similarly to monoamine transporters) in a cascade of events that results in antidepressant action.

Differences in behaviors between mouse strains in response to drugs, including the effects of ADs in the FST in mice, have been described previously [2]. It was suggested that the antidepressant-like effect of σ receptor agonists depends on the brain content of neu-

rosteroids, especially progesterone, which is proposed to be an endogenous ligand for σ receptors [12, 13]. As was shown by Phan et al. [12] the brain progesterone level of C57BL/6J mice is two-fold lower than that of Albino Swiss mice, suggesting that the availability to σ receptor agonists is higher in C57BL/6J mice.

The aim of the study was to compare the effect of 2-(4-morpholinethyl)-1-phenylcyclo- hexanecarboxylate hydrochloride (PRE-084), a potent and selective σ agonist [19], in Albino Swiss and C57BL/6J mice. Moreover, N-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine (BD1047) and (±)-tropanyl 2-(4-chlorophenoxy)butanoate maleate (SM 21), which are σ_1- and σ_2-receptor antagonists, respectively, were used to estimate the contribution of these receptors on the anti-immobility effect of PRE-084.

Materials and Methods

Animals

The experiments were carried out on male Albino Swiss mice (25 ± 5 g) (Charles River Laboratories, Sulzfeld, Germany) or C57BL/6J (licensed animal breeder IF PAS, Kraków, Poland). The animals were housed 8 per cage (57 × 35 × 20 cm) in a colony room maintained at 21 ± 1°C and 40–50% humidity under a 12-h light-dark cycle (the light on at 7 a.m.). The animals had free access to food and water before the experiment. All experiments were conducted during the light phase and performed in accordance with the European Communities Council Directive of 24 November 1986 (86/609 EEC). All experimental protocols were approved by the Local Bioethics Commission for the Animal Experiments at the Institute of Pharmacology, Polish Academy of Sciences.

Chemicals

BD 1047 (Tocris Cookson Ltd., UK), PRE-084 (Tocris Cookson Ltd., UK), SM 21 (Tocris Cookson Ltd., UK). The compounds were dissolved in distilled water and injected intraperitoneally (*ip*).

The locomotor activity test

The locomotor activity of mice was recorded using the Opto-M3 System (Columbus Instruments, Columbus, OH, USA), which is a multi-channel activity monitor that supports sensors (0.5" beam spacing) attached to a computer and calculates both ambulatory activity and total counts. Each group consisted of 10 mice.

FST in mice

FST in mice was evaluated according to the method of Porsolt et al. [13] with slight modifications. Briefly, each mice was placed individually in a glass cylinder filled up to 9 cm with water at 22–23°C. The immobility time was recorded for the last 5 min of a 6 min FST. The animals were used only once in each experiment. Groups consisted of 8–10 mice each.

Statistics

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

Results and Discussion

PRE-084 decreased the immobility time of Albino Swiss mice only at its highest dose, 60 mg/kg (Fig. 1A). This effect was counteracted by BD1047 at does of 5 mg/kg (Fig. 1B) and 10 mg/kg (data not shown) but not by SM 21 at 3 mg/kg (Fig. 1C) or 10 mg/kg (data not shown). The antidepressant-like effect of PRE-084 was enhanced in C57BL/6J mice because this effect was present also at the lower dose of 30 mg/kg (Fig. 2A). The effect of PRE-084 (30 mg/kg) was completely antagonized by 5 mg/kg (Fig. 2B) or 10 mg/kg (data not shown) of BD1047 but not by 3 mg/kg (Fig. 2C) or 10 mg/kg (data not shown) of SM 21. It should be emphasized that the effects observed in FST were not due to changes in general locomotor activity, since none of the compounds (given separately or in combination) changed locomotor activity (data not shown).

According to previous reports, PRE-084 does not change the immobility time of Albino Swiss mice in the FST [12, 22]. However, we found that PRE-084 exerts moderately but statistically significantly decreases immobility time (by ca. 27%). This discrepancy may be due to methodological differences, e.g.,

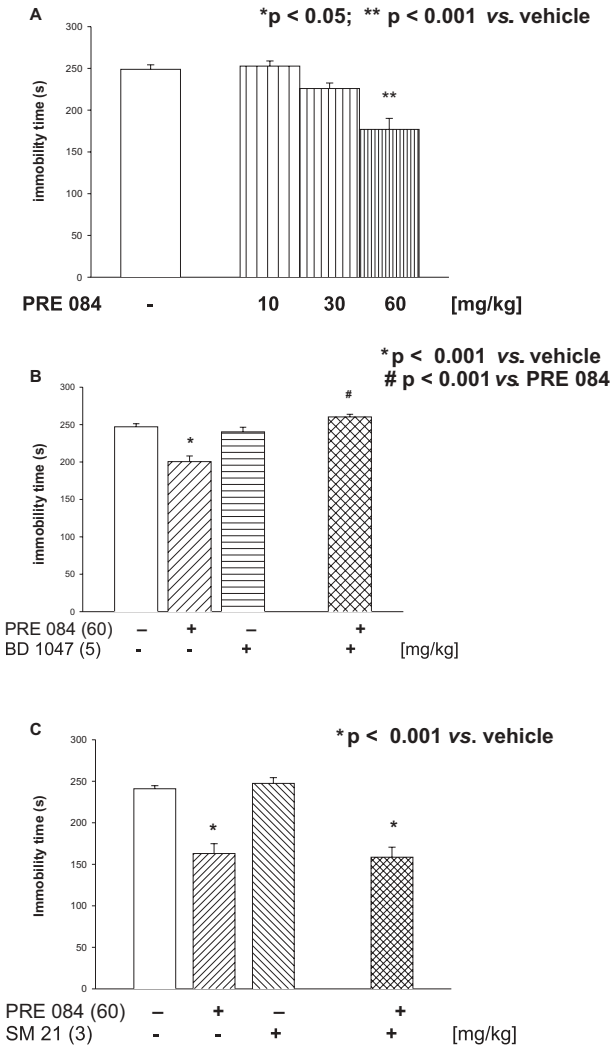

Fig. 1. The effect of PRE-084 on the immobility time of Albino Swiss mice in the FST (**A**) and the influence of BD1047 (**B**) or SM 21 (**C**), the σ_1- and σ_2-receptor antagonists, respectively. PRE-084 (10, 30 and 60 mg/kg) was given 30 min before the test, BD1047 (5 mg/kg) and SM 21 (3 mg/kg) 15 min before PRE-084. The results represent the mean ± SEM (n = 8–10 mice)

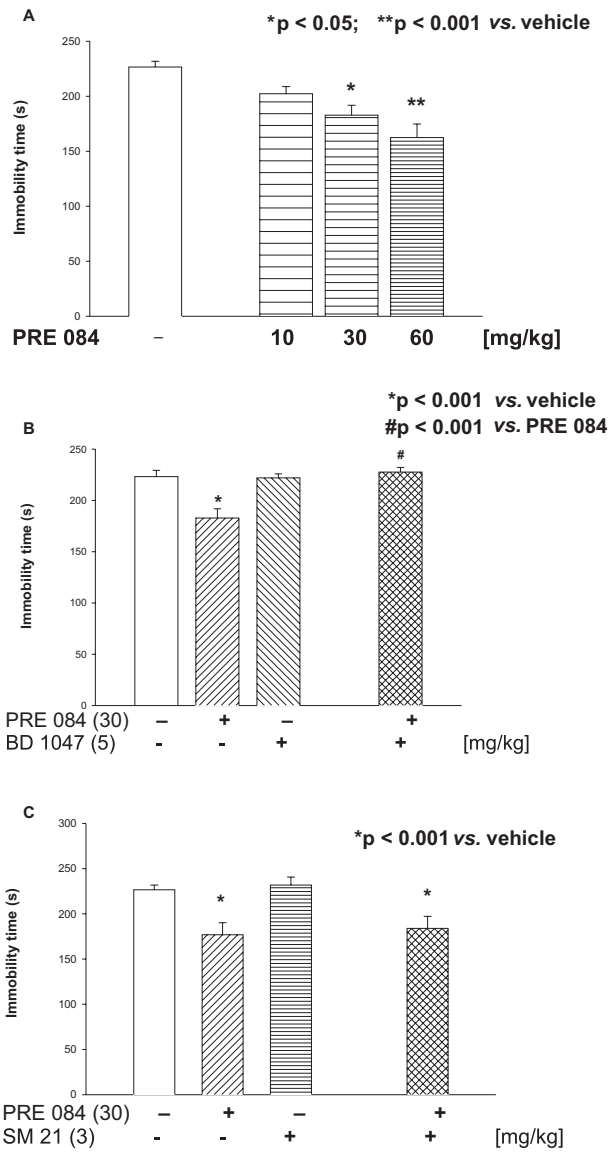

Fig. 2. The effect of PRE-084 on the immobility time of C57BL/6J mice in the FST (**A**) and the influence of BD1047 (**B**) or SM 21 (**C**), the σ_1- and σ_2-receptor antagonists, respectively. PRE-084 (10, 30 and 60 mg/kg) was given 30 min before the test, BD1047 (5 mg/kg) and SM 21 (3 mg/kg) 15 min before PRE-084. The results represent the mean ± SEM (n = 8–10 mice)

depth of water in cylinders or the lack of pretest 24 h prior. The anti-immobility effect of PRE-084 was observed in C57BL/6J mice at a lower dose (30 mg/kg) as compared to Albino Swiss mice (60 mg/kg).

In general, the antidepressant-like effect of σ receptor agonists (including PRE-084) in FST is relatively weaker than that of typical ADs such as imipramine, but it may be potentiated by co-administration with other compounds such as amantadine or 8-OH-DPAT (uncompetitive NMDA receptor antagonist or serotonin $5HT_{1A}$ receptor agonist, respectively) [17, 18]. Moreover, the affinity of PRE-084 for σ_1-receptor is lower than that of other σ_1-receptor agonists such as SA4503 (IC_{50} = 44 nM and 17.4 nM, respectively) [10, 19]. Whereas the effect of PRE-084 was antagonized by BD 1047, a σ_1-receptor antagonist [8, 21], the preferential σ_2-receptor agonist SM 21 [5, 9] did not change the effect of PRE-084, both in Albino Swiss and C57BL/6J mice.

Although the mechanisms underlying the ability of σ receptor agonists to produce antidepressant-like ac-

tions remain to be elucidated, there is evidence suggesting that they stimulate a variety of neural adaptations in the central nervous system relevant to antidepressant action. These include intracellular Ca^{2+} signaling, noradrenergic, serotonergic and glutamatergic NMDA neurotransmission [1, 3, 17]. Recently, it has been demonstrated that σ_1 receptors up-regulate the release of brain derived neurotrophic factor (BDNF) [25]. The role of BDNF/TrkB signaling has been proposed to mediate the therapeutic effect of ADs [4, 14]. Repeated treatment with some σ_1 receptor agonists such as fluvoxamine, significantly potentiate BDNF-triggered glutamate release in cultured cortical neurons as well as NGF (nerve growth factor)-induced neurite sprouting in PC12 cells [16, 20, 25]. Additionally, σ_1 receptor knockout C57BL/6J mice display a depressive-like phenotype with increased immobility time and decreased swim time in FST [15].

According to David et al. [2], Swiss mice are the most sensitive strain for detecting antidepressant-like activity based on serotonin and/or noradrenaline reuptake inhibition, while C57BL/6J are sensitive to dopamine reuptake inhibitors. As mentioned above, σ_1-receptor ligands can modify monoaminergic neurotransmission indirectly, which may be a possible mechanism for their antidepressant-like activity. Moreover, the differences in reactivity of Swiss and C57BL/6J mice in FST may due to differences in brain neurosteroid (progesterone) levels, as previously suggested by Phan et al. [12].

Taken together, our results indicate that the dissimilarity in antidepressant-like effects of PRE-084 in Swiss and C57BL/6J mice is rather quantitative than qualitative. Furthermore, the results support the idea that σ_1- but not σ_2-receptor is involved in the anti-immobility effect of PRE-084 in both species.

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