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Short communication

Enhancement of the anti-immobility action of antidepressants by a selective 5-HT$_7$ receptor antagonist in the forced swimming test in mice

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Abstract

Using the forced swimming test in mice, we examined the effect of the following antidepressants: citalopram, imipramine, desipramine and moclobemide (which are characterized by different mechanisms of action), administered in combination with the selective 5-HT$_7$ receptor antagonist (2*R*)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]-pyrrolidine (SB 269970). All those drugs were given in doses which did not shorten the immobility time of mice. Citalopram (1.25 mg/kg), imipramine (10 mg/kg), desipramine (5 mg/kg) or moclobemide (10 mg/kg) administered jointly with SB 269970 (5 mg/kg), produced a significant antidepressant-like effect. None of the compounds studied, given alone or in combination, increased the spontaneous locomotor activity of mice. The obtained results indicate that blockade of 5-HT$_7$ receptors may facilitate the anti-immobility effect of antidepressants in mice.

Keywords: Citalopram; Imipramine; Desipramine; Moclobemide; 5-HT$_7$ receptor antagonist; Forced swimming test in mice

1. Introduction

It has been well documented that serotonin (5-hydroxytryptamine, 5-HT) is implicated in the pathogenesis of depression and in the action of antidepressant drugs. Drugs acting on the 5-HT system, e.g. selective serotonin reuptake inhibitors (SSRIs), are frequently used for treating depression; however, no early signs of therapeutic improvement are observed before the second week of treatment with these drugs. It is generally accepted that antidepressants with another mechanism of action than SSRIs share a similar delay in their onset of action, and that not all patients respond to a particular antidepressant drug (see Thase and Rush, 1995). Clinical evidence suggests that combined administration of some antidepressants with pindolol, a 5-HT$_{1A/1B}$ receptor/β-adrenoreceptor partial agonist, may be effective in accelerating the action of antidepressants (Artigas et al., 1994). An alternative approach to improve the treatment of depression is a search for multitarget agents that combine monoamine uptake with the actions at 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_2$ receptors or α_2-adrenoreceptors; in preclinical studies, some of them show a potential antidepressant-like profile (see Millan, 2004). Several studies have indicated an interaction between antidepressants and antagonists of different 5-HT receptor subtypes in animal models of depression. It has been reported that subactive doses of antidepressants with different mechanisms of action, co-administered with selective and nonselective antagonists of 5-HT$_{1A}$/5-HT$_{1B}$ as well as 5-HT$_{2A}$/5-HT$_{2C}$ or 5-HT$_3$ receptors, produce significant antidepressant-like effects in animal models of depression including the forced swimming test (Ago et al., 2005; Da-Rocha et al., 1997; Marek et al., 2005; Mayorga et al., 2001; Millan et al., 1998; Redrobe and Bourin, 1997; Redrobe et al., 1996; Tatarczyńska et al., 2002, 2004). However, several other data do not support these findings (Da-Rocha et al., 1997; Moser and Sanger, 1999; O'Neill et al., 1996; Papp et al., 2002; Redrobe et al., 1996; Tatarczyńska et al., 2002, 2004).

Recently it has been suggested that 5-HT$_7$ receptors may play a role in mood disorders including depression (for reviews, see Hedlund and Sutcliffe, 2004; Thomas and Hagan, 2004). In fact, these receptors are concentrated in corticolimbic structures which are involved in affective processes (see Thomas and Hagan, 2004); chronic treatment with antidepressants down-regulates 5-HT$_7$ receptor expression in rat hypothalamus (Mullins et al., 1999) and reduces the effectiveness of rat

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hippocampal 5-HT$_7$ receptor activation (Tokarski et al., 2005). Furthermore, experiments conducted on 5-HT$_7$ receptor knock-out mice have shown an antidepressant-like behaviour of these animals, i.e. reduction of immobility, when compared with wild-type mice in the forced swimming (Guscott et al., 2005; Hedlund et al., 2005) and the tail suspension (Hedlund et al., 2005) tests. A significant antidepressant-like effect was also observed after administration of the selective 5-HT$_7$ receptor antagonist (2*R*)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]pyrrolidine (SB 269970) in the two above-mentioned animal models (Hedlund et al., 2005; Wesołowska et al., 2006).

SB 269970 has been found to be a potent ligand of human cloned (Lovell et al., 2000) and guinea-pig (Hagan et al., 2000) 5-HT$_7$ receptors (pK_i=8.9 and 8.7, respectively). It shows excellent selectivity (>250-fold) over 5-HT$_1$, 5-HT$_2$, 5-HT$_4$, 5-HT$_6$, α_1, D$_2$ and D$_3$ receptors, apart from 5-HT$_{5A}$ ones (50-fold), and has been found to be over 100-fold selective over a total of 50 receptors, enzymes or ion channels (Lovell et al., 2000). SB 269970 has good central nervous system penetration (Hagan et al., 2000) and shows features of a 5-HT$_7$ receptor antagonist (Hagan et al., 2000; Guscott et al., 2003; Lovell et al., 2000; Tokarski et al., 2003).

In the present study we investigated the interaction between the selective 5-HT$_7$ receptor antagonist SB 269970 and antidepressant drugs with different mechanisms of action in the forced swimming test in mice. The antidepressants chosen included the selective serotonin reuptake inhibitor citalopram, the tricyclic 5-HT/noradrenaline reuptake inhibitor imipramine, the selective noradrenaline reuptake inhibitor desipramine and the monoamine oxidase-A inhibitor moclobemide. We examined the effect of those drugs (given in subactive doses selected on the basis of the present experiment) administered in combination with SB 269970 (given in an inactive dose of 5 mg/kg, chosen on the basis of our earlier (Wesołowska et al., 2006) and present studies) in the forced swimming test in mice. To the best of our knowledge, the effect of joint administration of selective 5-HT$_7$ receptor antagonists and antidepressants in animal models of depression has not been studied so far.

2. Materials and methods

2.1. Animals and housing

The experiments were performed on male Albino Swiss mice (24–26 g), purchased from a licensed dealer (Staniszewska; Ilkowice, Poland). The animals were kept in groups of twenty to a cage (60×38×20 (height) cm) at a temperature of 20±1 °C and had free access to food (standard laboratory pellets) and tap water before the experiment. All the investigations were conducted in the light phase on a natural light/dark cycle (September to December) between 9 AM and 2 PM. Each experimental group consisted of 10 animals per drug dose. All experiments were performed on separate groups of animals, each animal was used only once in the test. The experiments were carried out by an observer unaware of a treatment. All the experimental procedures were approved by the Local Bioethics Commission at the Institute of Pharmacology, Polish Academy of Sciences in Kraków.

2.2. Drugs

The following drugs were used: citalopram (hydrobromide; H. Lundbeck, Copenhagen, Denmark), desipramine (hydrochloride; Research Biochemicals, Natic, MA, USA), (2*R*)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]pyrrolidine (hydrochloride; SB 269970; Tocris, Cookson, Bristol, UK), imipramine (hydrochloride; Polfa-Stargard, Poland) and moclobemide (Ro 11-1163; F. Hoffman-La Roche, Basel, Switzerland). Citalopram, desipramine and imipramine were dissolved in distilled water, while SB 269970 and moclobemide were suspended in a 1% aqueous solution of Tween 80 immediately before administration. All the compounds were injected intraperitoneally (i.p.) in a volume of 10 ml/kg. Citalopram, desipramine, imipramine, SB 269970 were given 30 min and moclobemide 60 min before the test. Moclobemide administered 30 min before the test did not induce any significant effect in the forced swimming test in mice. In an interaction study the drugs – when administered at the same pre-treatment time – were given in two separate injections (SB 269970 first, and immediately afterwards an antidepressant). Control mice received vehicle according to the same schedule. The doses of drugs refer to their salt forms.

2.3. Forced swimming test in mice

The experiment was carried out according to the method of Porsolt et al. (1977). Briefly, the mice were individually placed in a glass cylinder (25 cm high, 10 cm in diameter) containing 6 cm of water maintained at 23–25 °C, and were left therein for 6 min. A mouse was regarded as immobile when it remained floating in water, making only small movements to keep its head above it. The total duration of immobility was measured during the final 4 min of a 6-min test session, after a 2-min habituation period.

2.4. Locomotor activity in mice

The spontaneous locomotor activity of mice was recorded in photoresistor actometers (24 cm in diameter) illuminated by two light beams, which were connected to a counter for the recording of light-beam interruptions. The mice were placed individually in the actometers, and the number of crossings of the light beams was counted during a 6-min experimental session (i.e. at the time equal to the observation period in the forced swimming test).

2.5. Statistical analysis

The obtained data were presented as the mean±S.E.M. Comparisons between groups were carried out by a one-way analysis of variance (ANOVA), followed by intergroup comparisons using the Dunnett's test (when only one drug was given), or by the Newman–Keuls post-hoc test (when two drugs were used).

3. Results

3.1. Effect of the antidepressants and the 5-HT$_7$ receptor antagonist SB 269970 given alone in the forced swimming test in mice

In agreement with our previous study (Wesołowska et al., 2006), the selective 5-HT$_7$ receptor antagonist SB 269970 at a dose of 5 mg/kg did not affect the immobility time of mice in the forced swimming test; its higher dose (10 mg/kg) induced a significant anti-immobility effect in that test (Fig. 1). The results presented in Figs. 1 and 2 show that citalopram (1.25 mg/kg), imipramine (10 mg/kg), desipramine (5 mg/kg) and moclobemide (10 mg/kg) did not affect the immobility time of mice in the forced swimming test. When the antidepressants were administered in higher doses, i.e. citalopram at 2.5, 5 and 10 mg/kg (Fig. 1), imipramine at 20 mg/kg, desipramine at 10 mg/kg and moclobemide at 20 mg/kg (Fig. 2), they significantly reduced the immobility time of mice in that test. Therefore the following doses: 1.25 mg/kg of citalopram, 10 mg/kg of imipramine or moclobemide, and 5 mg/kg of desipramine were chosen for interaction studies.

3.2. Interaction of the antidepressants with the 5-HT$_7$ receptor antagonist SB 269970 in the forced swimming test in mice

The results presented in Figs. 1 and 2 show that SB 269970 (5 mg/kg) co-administered with subactive doses of citalopram (1.25 mg/kg), imipramine (10 mg/kg), desipramine (5 mg/kg) or moclobemide (10 mg/kg) revealed a pronounced, statistically significant anti-immobility effect.

3.3. Effects of the antidepressants, given alone or in combination with the 5-HT$_7$ receptor antagonist SB 269970, on spontaneous locomotor activity of mice

Neither the antidepressants studied nor SB 269970, given alone in doses used in interaction experiments, affected the spontaneous locomotor activity of mice during a 6-min experimental session. Citalopram (1.25 mg/kg), imipramine (10 mg/kg) and desipramine (5 mg/kg) co-administered with SB 269970 (5 mg/kg) had no effect on the locomotor activity of mice, while moclobemide (10 mg/kg) given with SB 269970 (5 mg/kg) slightly, but significantly, reduced that activity. The mean±S.E.M. values for the number of crossings were as follows: control 94.8±4.1, citalopram 112.4±6.6, citalopram+SB 269970 101.6±5.7 ($F(2,27)=2.515$, n.s.); control 94.8±4.1, imipramine 94.4±6.3, imipramine+SB 269970 88.8±5.1 ($F(2,27)=0.406$, n.s.); control 83.8±7.4, desipramine 65.7±3.8, desipramine+SB 269970 84.7±7.1 ($F(2,27)=2.863$, n.s.); control 83.8±7.4, moclobemide 93.9±6.4, moclobemide+SB 269970 61.5±3.7 ($P<0.05$ vs control, $P<0.01$ vs moclobemide) ($F(2,27)=7.548$, $P<0.01$); control 100.9±5.9, SB 269970 112.0±6.5 ($F(1,18)=1.607$, n.s.).

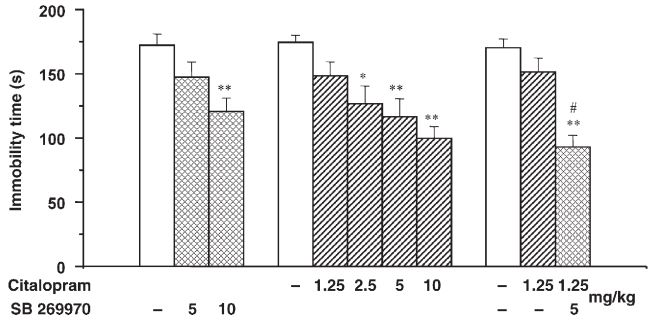

Fig. 1. Effects of SB 269970 and citalopram administered alone or in combination on the immobility time in the forced swimming test in mice. SB 269970 and citalopram were administered 30 min before the test. All values are mean±S.E.M. for $n=10$. *$P<0.05$, **$P<0.01$ compared to respective vehicle group, Dunnett's test following a significant ANOVA (SB 269970: $F(2,27)=6.121$, $P<0.01$; citalopram: $F(4,45)=6.681$, $P<0.001$); #$P<0.01$ compared to group receiving citalopram at 1.25 mg/kg without SB 269970, Newman–Keuls test following a significant ANOVA ($F(2,27)=16.803$, $P<0.001$).

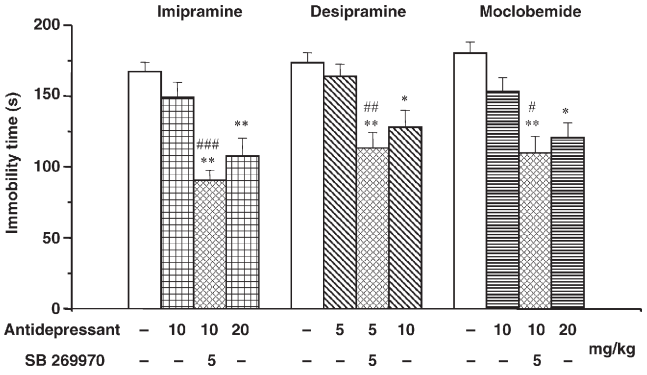

Fig. 2. Effects of imipramine, desipramine and moclobemide administered alone or in combination with SB 269970 on the immobility time in the forced swimming test in mice. SB 269970, imipramine, desipramine and moclobemide were administered 30 and 60 min before the test, respectively. All values are mean±S.E.M. for $n=10$. *$P<0.01$, **$P<0.001$ compared to respective vehicle group; #$P<0.05$, ##$P<0.01$, ###$P<0.001$ compared to the group receiving antidepressant in a lower dose without SB 269970, Newman–Keuls test following a significant ANOVA (imipramine: $F(3,36)=13.839$, $P<0.0001$; desipramine: $F(3,36)=8.718$, $P<0.001$; moclobemide: $F(3,36)=8.977$, $P<0.0001$).

4. Discussion

The major finding of the present study is that low doses of antidepressants: citalopram, imipramine, desipramine or moclobemide (which have no effect of their own) induce anti-immobility effects in mice when used in combination with an inactive dose of SB 269970. All the positive interactions described above seem to be specific, since these drugs (given alone or jointly) do not increase the spontaneous locomotor activity of mice.

To the best of our knowledge, the obtained results constitute the first preclinical report suggesting that the selective blockade of 5-HT$_7$ receptors may have a synergistic effect with the inhibition of 5-HT and/or noradrenaline uptake, as well as with the inhibition of monoamine oxidase-A activity in animal model of depression. Recently, it has been demonstrated that citalopram decreased immobility of 5-HT$_7$ receptor knockout mice and wild-typed controls in the tail suspension test, and that its effect in 5-HT$_7$ receptor knockout mice was additive to that of the genotype alone (Hedlund et al., 2005). This observation seems to

be in line with our results showing that 5-HT_7 receptor blockade facilitates the anti-immobility effect of citalopram. To date, there has been no information on the effect of other antidepressants on behaviour of 5-HT_7 knockout mice in models of depression.

The forced swimming test is one of the most widely used preclinical tests for detecting antidepressant-like activity (see Borsini and Meli, 1988; Porsolt et al., 1977). It has been well established that the shortening of immobility time in the forced swimming test depends primarily on the enhancement of central catecholamine and 5-HT neurotransmission (for reviews, see Borsini, 1995; Borsini and Meli, 1988; Cervo et al., 1990, 1991; Porsolt et al., 1979; Rénéric et al., 2001). Thus it may be assumed that 5-HT or/and noradrenaline and dopamine systems may be involved in mediating the anti-immobility effects of citalopram, imipramine, desipramine or moclobemide co-administered with a 5-HT_7 antagonist. However, to date no findings have been available about the action of SB 269970 on the release of these neurotransmitters in animal brain areas in vivo; it has been found merely that SB 269970 may decrease 5-HT efflux in the dorsal raphe nucleus (Roberts et al., 2004), or that it has no significant effect on 5-HT release in cortical (Roberts et al., 2001) slices. Hence it is unclear how 5-HT_7 receptor blockade can facilitate the anti-immobility action of antidepressants. It is noteworthy that citalopram, imipramine and desipramine (no available data on moclobemide) practically did not exhibit affinity for 5-HT_7 receptors (Shen et al., 1993). Additional studies are necessary to elucidate the mechanism involved in mediating behavioural changes after co-administration of antidepressants and SB 269970 to mice; moreover, at this stage of experimentation it is very difficult to decide whether these synergistic effects may be regarded as a result of pharmacodynamic and/or pharmacokinetic interaction. However, the levels of antidepressants used and SB 269970 (given alone or jointly) have not been analyzed to rule out a pharmacokinetic interaction.

In conclusion, the obtained results indicate that the blockade of 5-HT_7 receptors may facilitate the anti-immobility effects of citalopram, imipramine, desipramine and moclobemide in the forced swimming test in mice. The present data need to be corroborated by further studies conducted in other animal models before any final conclusions are reached.

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