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Effect of combined administration of 5-HT$_{1A}$ or 5-HT$_{1B/1D}$ receptor antagonists and antidepressants in the forced swimming test

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Abstract

In the present study, we examined effects of the selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor citalopram, the 5-HT/noradrenaline reuptake inhibitor imipramine, the selective noradrenaline reuptake inhibitor desipramine or the monoamine oxidase-A inhibitor moclobemide, administered in combination with the 5-HT$_{1A}$ receptor antagonist *N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridynyl)cyclohexanecarboxamide (WAY 100635) or the 5-HT$_{1B/1D}$ receptor antagonist *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)-phenyl]-2′-methyl-4′-(5-methyl-[1,2,4]oxadiazol-3-yl)1,1′-biphenyl-4-carboxamide (GR 127935) and the 5-HT$_{1B}$ receptor antagonist *N*-[3-(2-dimethylamino) ethoxy-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-(1,1′-biphenyl)-4-carboxamide (SB 216641) in the forced swimming test in rats. When given alone, citalopram (20 and 30 mg/kg), imipramine (20 mg/kg), desipramine (20 mg/kg), moclobemide (20 mg/kg), WAY 100635 (0.1 and 1 mg/kg), GR 127935 (10 and 20 mg/kg) or SB 216641 (2 mg/kg) did not shorten the immobility time of rats. Co-administration of WAY 100635 (0.1 and 1 mg/kg) and citalopram (20 mg/kg), or imipramine (20 mg/kg), or moclobemide (20 mg/kg) did not affect the immobility time of rats, whereas WAY 100635 given jointly with desipramine (20 mg/kg) induced a weak anti-immobility effect. GR 127935 (10 and 20 mg/kg) or SB 216641 (2 mg/kg) co-administered with imipramine, desipramine or moclobemide, but not citalopram, produced a significant anti-immobility action in the forced swimming test in rats. These results indicate that the blockade of 5-HT$_{1B}$ rather than 5-HT$_{1A}$ receptors may facilitate the anti-immobility effect of imipramine, desipramine or moclobemide in the forced swimming test. No interaction was observed between 5-HT$_{1A}$ or 5-HT$_{1B/1D}$ receptor antagonists and citalopram.

Keywords: Citalopram; Imipramine; Desipramine; Moclobemide; 5-HT$_{1A}$/5-HT$_{1B}$ receptor antagonist; Forced swimming test in rats

1. Introduction

The involvement of serotonin (5-hydroxytryptamine, 5-HT) in the pathogenesis of depression and its role in the action of antidepressant drugs have been well established (Briley and Moret, 1993). Drugs acting on the 5-HT system have been shown to be effective in the treatment of depression. However, the onset of antidepressant activity requires a period of chronic treatment—usually 2–4 weeks—before this activity can be observed. A delay in the onset of the therapeutic effect of antidepressants, as well as the fact that not all patients respond to a particular antidepressant drug, are characteristic of antidepressants with different mechanisms of action (Thase and Rush, 1995).

The results of rat microdialysis studies indicate relative importance of 5-HT$_{1A}$ and 5-HT$_{1B}$ autoreceptors to the mechanism of action of selective serotonin reuptake inhibitors or monoamine oxidase inhibitors; moreover, these data suggest that it is possible to accelerate the onset and, probably, to increase the efficacy of treatment with these drugs by their combined administration with autoreceptor-blocking drugs (Gardier et al., 1996; Hjorth et al., 2000; Moret and Briley, 2000). Some clinical evidence has suggested that pindolol, a 5-HT$_{1A}$/5-HT$_{1B}$ receptor/β-adrenoceptor antagonist (Lucki, 1992), may be effective in accelerating the onset of antidepressant activity, and that it may enhance beneficial effects in therapy-resistant depression when co-administered with selective serotonin reuptake inhibitors, 5-HT and/or noradrenaline reuptake inhibitors, or monoamine oxidase inhibitors (Artigas et al., 1994; Blier and Bergeron, 1995; Perez et al., 1997).

A few papers have reported an interaction between antidepressants and 5-HT$_{1A}$ and/or 5-HT$_{1B/1D}$ receptor

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ligands in animal models of depression. One of the most widely used preclinical tests for detecting antidepressant-like activity is the forced swimming test (Porsolt et al., 1978, 1979). It has been shown that pretreatment of mice with pindolol significantly enhances the anti-immobility effects of subactive doses of the selective serotonin reuptake inhibitors fluoxetine, citalopram or paroxetine, but does not induce any interaction with the 5-HT and/or noradrenaline reuptake inhibitors imipramine, maprotiline or desipramine in the forced swimming test (Redrobe et al., 1996, 1998). In rats, neither pindolol nor the selective 5-HT_{1A} receptor antagonist *N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridynyl) cyclohexanecarboxamide (WAY 100635) enhanced the effects of fluoxetine, paroxetine or the monoamine oxidase-A inhibitor befloxatone (Moser and Sanger, 1999; Tatarczyńska et al., 2002), whereas a combination of the 5-HT/noradrenaline reuptake inhibitor duloxetine and WAY 100635 resulted in the shortening of immobility time (Millan et al., 1998). The results of our earlier study also showed that the 5-$HT_{1B/1D}$ receptor antagonist *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-[1,2,4]oxadiazol-3-yl)1,1′-biphenyl-4-carboxamide (GR 127935), and the 5-HT_{1B} receptor antagonist *N*-[3-(2-dimethylamino)ethoxy-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-(1,1′-biphenyl)-4-carboxamide (SB 216641), given jointly with paroxetine (but not fluoxetine), produced an anti-immobility effect in the forced swimming test in rats (Tatarczyńska et al., 2002). It is noteworthy that the effects of combined administration of 5-HT_{1A} and/or 5-$HT_{1B/1D}$ receptor antagonists (WAY 100635, GR 127935, pindolol) and antidepressants (paroxetine, fluoxetine, fluvoxamine, citalopram, imipramine) were also evaluated in other animal models of depression; however, the obtained results turned out to be equivocal (Cousins and Seiden, 2000; Cryan et al., 1998, 1999; Mayorga et al., 2001; O'Neill et al., 1996; Papp et al., 2002; Służewska and Szczawińska, 1996).

Taking account of the above observations, the present study was designed to further evaluate the interaction between 5-HT_{1A} or 5-$HT_{1B/1D}$ receptor antagonists and antidepressant drugs in the forced swimming test in rats. 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 effects of those drugs given at non-active (citalopram) or subactive (imipramine, desipramine, moclobemide) doses in combination with either the 5-HT_{1A} receptor antagonist WAY 100635 (Forster et al., 1995) or the 5-$HT_{1B/1D}$ receptor antagonist GR 127935 (Skingle et al., 1995; Starkey and Skingle, 1994), or the 5-HT_{1B} receptor antagonist SB 216641 (Hagan et al., 1997; Schlicker et al., 1997) in the forced swimming test in rats. Citalopram was investigated at doses higher than those inducing marked functional changes in central 5-HT neurotransmission in vivo (Invernizzi et al., 1992; Maj and Moryl, 1992). WAY 100635 was used at doses effective in blocking the in vivo and in vitro effects induced by 5-HT_{1A} receptor agonists, resulted from the stimulation of both pre- and postsynaptic 5-HT_{1A} receptors (Assié and Koek, 1996, 2000; Forster et al., 1995). Similarly, both 5-$HT_{1B/1D}$ and 5-HT_{1B} receptor antagonists GR 127935 and SB 216641, respectively, were used in a dose range in which they produced effects related to the blockade of 5-HT_{1B} receptors (Cervo et al., 2002; Hagan et al., 1997; Lin and Parsons, 2002; Mansbach and Rovetti, 1996).

2. Materials and methods

2.1. Animals and housing

The experiments were carried out on male Wistar rats weighing 220–240 g. The animals were kept in groups of eight to a cage (60 × 38 × 20 cm) at a temperature of

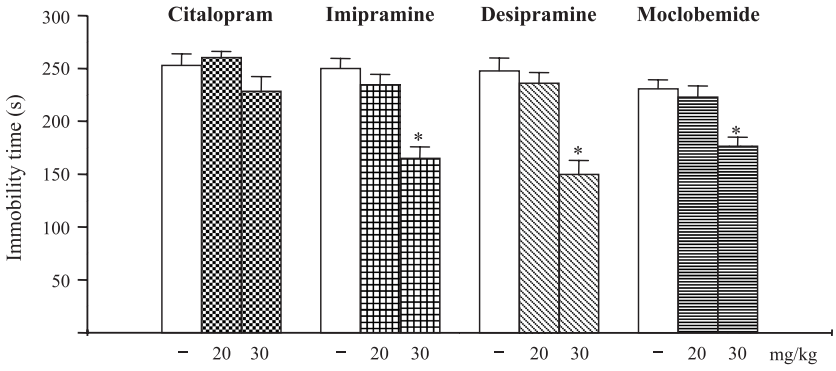

Fig. 1. Effects of citalopram, imipramine, desipramine and moclobemide on the immobility time in the forced swimming test in rats. All drugs were administered 60 min before the test. All values are mean ± S.E.M. for $n = 8$. *$P < 0.01$ compared to respective vehicle group using Dunnett's test following a significant ANOVA (citalopram: $F(2,21) = 2.46$, n.s.; imipramine: $F(2,21) = 21.54$, $P < 0.001$; desipramine: $F(2,21) = 20.58$, $P < 0.001$; moclobemide: $F(2,21) = 10.33$, $P < 0.001$).

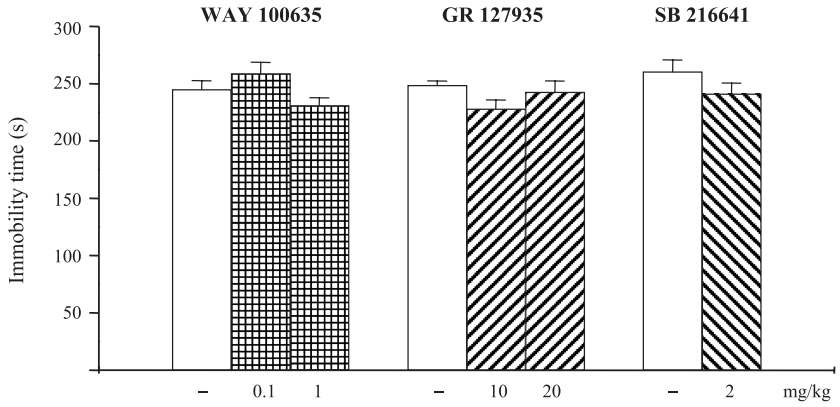

Fig. 2. Effects of WAY 100635, GR 127935 and SB 216641 on the immobility time in the forced swimming test in rats. All compounds were administered 75 min before the test. All values are mean ± S.E.M. for $n = 8$. Values of ANOVA (WAY 100635: $F(2,21) = 2.56$, n.s.; GR 127935: $F(2,21) = 1.89$, n.s.; SB 216641: $F(1,14) = 1.88$, n.s.).

20 ± 1 °C, and had free access to food (standard laboratory pellets) and water. All the investigations were conducted in the light phase, on a natural light cycle (from September to March), between 9 a.m. and 2 p.m. The animals were used only once in each test. All the experimental procedures were approved by the Animal Care and Use Committee at the Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland.

2.2. Drugs

The following drugs were used: citalopram (hydrobromide; H. Lundbeck, Copenhagen, Denmark), desipramine (hydrochloride; Research Biochemicals, Natick, MA, USA), *N*-[3-(2-dimethylamino)ethoxy-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-(1,1′-biphenyl)-4-carboxamide (hydrochloride, SB 216641; Tocris,

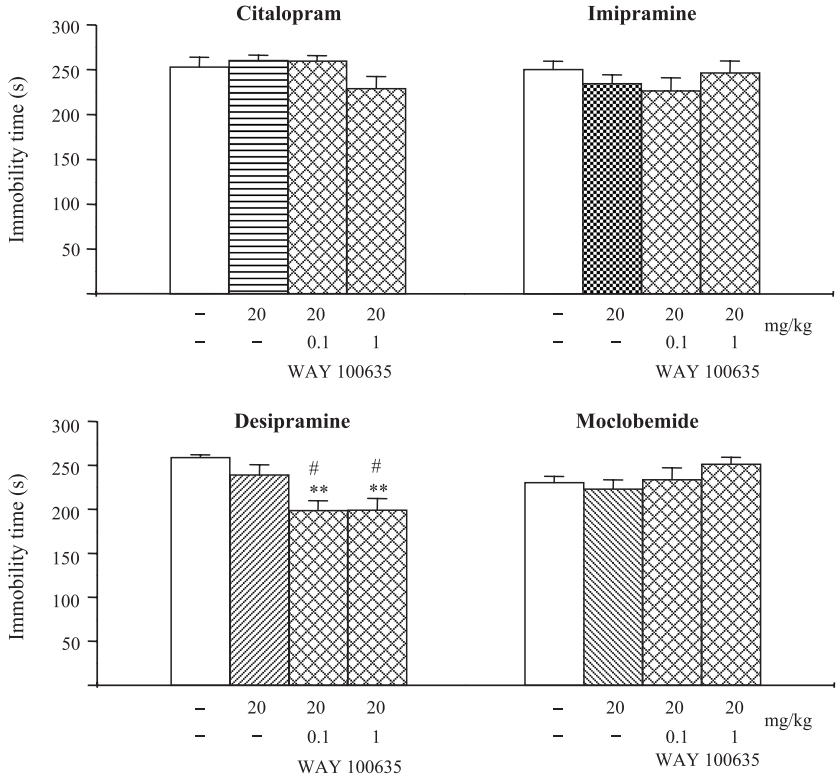

Fig. 3. Interaction of WAY 100635 with citalopram, imipramine, desipramine or moclobemide in the forced swimming test in rats. WAY 100635 and antidepressants were administered 75 and 60 min before the test, respectively. All values are mean ± S.E.M. for $n = 8$. $^{**}P < 0.01$ compared to respective vehicle group; $^{\#}P < 0.05$ compared to group receiving the same dose of antidepressant without WAY 100635, Newman–Keuls test following a significant ANOVA (citalopram: $F(3,28) = 2.418$, n.s.; imipramine: $F(3,28) = 0.839$, n.s.; desipramine: $F(3,28) = 8.194$, $P < 0.01$; moclobemide: $F(3,28) = 1.458$, n.s.).

Cookson, Bristol, UK), imipramine (hydrochloride, Polfa-Starogard, Poland), *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-[1,2,4]oxadiazol-3-yl)1,1′-biphenyl-4-carboxamide (hydrochloride, GR 127935; GlaxoSmithKline, Stevenage, UK), *N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridynyl)cyclohexanecarboxamide (trihydrochloride, WAY 100635; synthesized by Dr J. Boksa, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland) and moclobemide (Ro 11-1163; F. Hoffman-La Roche, Basel, Switzerland). Citalopram, imipramine, SB 216641 and WAY 100635 were dissolved in distilled water; desipramine, GR 127935 and moclobemide were suspended in a 1% aqueous solution of Tween 80 immediately before administration. All the compounds were administered in a volume of 2 ml/kg, WAY 100635 was injected subcutaneously (s.c.), the remaining compounds—intraperitoneally (i.p.). Citalopram, desipramine, imipramine and moclobemide were given 60 min before the test, GR 127935, SB 216641 and WAY 100635—75 min before. Control rats received a vehicle according to the same schedule. The dosage, time schedules and routes of administration were based on in vivo experiments using those compounds (Borsini and Meli, 1988; Cervo et al., 1990; Eroğlu and Güven, 1998; Przegaliński et al., 1997; Tatarczyńska et al., 2002).

2.3. Forced swimming test

The studies were carried out on rats according to the method of Porsolt et al. (1978). On the first experimental day, the animals were gently placed individually in plexiglas cylinders (40 cm in height, 18 cm in diameter), containing 15 cm of water maintained at 25 °C for a 15-min habituation period. On removal from the water, they were placed in a plexiglas box under a 60-W bulb to dry for 30 min. On the following day, the rats were replaced in the cylinders, and the total duration of immobility was measured for a 5-min test period by an experimenter who was unaware of the treatment the rats had received.

2.4. Open field test

The studies were carried out on rats according to the slightly modified method of Janssen et al. (1960). The

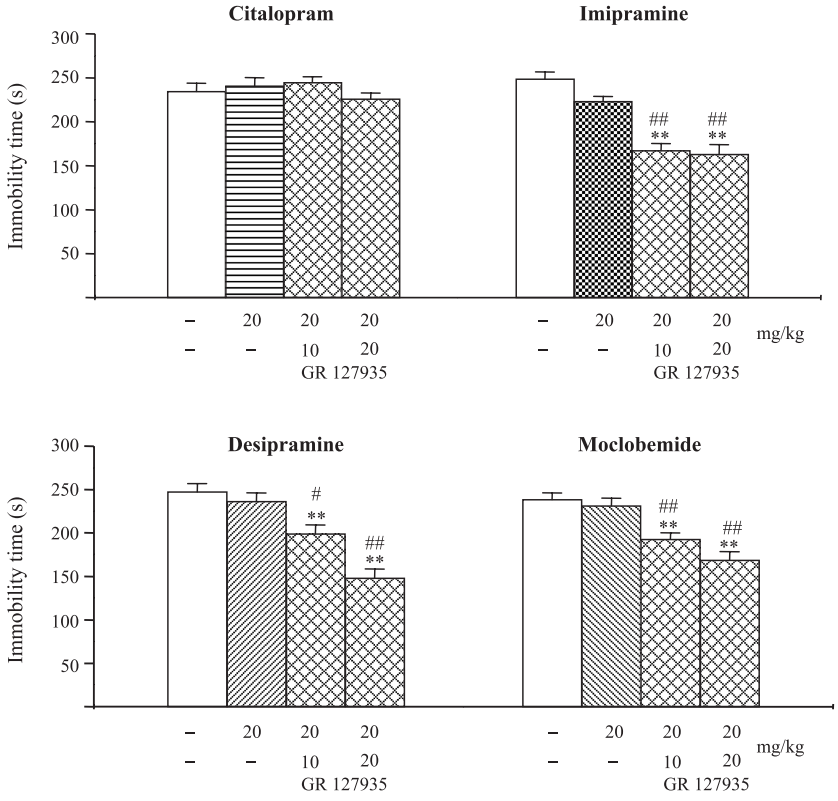

Fig. 4. Interaction of GR 127935 with citalopram, imipramine, desipramine or moclobemide in the forced swimming test in rats. GR 127935 and antidepressants were administered 75 and 60 min before the test, respectively. All values are mean ± S.E.M. for $n = 8$., $^{**}P < 0.01$ compared to respective vehicle group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared to group receiving the same dose of antidepressant without GR 127935, Newman–Keuls test following a significant ANOVA (citalopram: $F(3,28) = 0.988$, n.s.; imipramine: $F(3,28) = 24.757$, $P < 0.001$; desipramine: $F(3,28) = 19.663$, $P < 0.001$; moclobemide: $F(3,28) = 14.834$, $P < 0.001$).

centre of the wooden open arena (1 m in diameter; black in colour; divided with white lines into six symmetrical sectors without walls) was illuminated with a 75-W bulb hanging 75 cm above it. The open area was elevated to a height of 50 cm above the floor. Individual control or drug-injected animals were gently placed in the centre of the arena and were allowed to explore freely. The time spent walking, ambulation (the number of crossings of sector lines) and the number of rearing and peeping (looking under the edge of the arena) episodes were recorded for 3 min. Behavioral responses were recorded by an experimenter unaware of the treatment.

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. Effects of antidepressants and 5-HT_{1A}, 5-$HT_{1B/1D}$ or 5-HT_{1B} receptor antagonists given alone in the forced swimming test

The selective serotonin reuptake inhibitor citalopram (20 and 30 mg/kg) did not have any significant effect on the immobility time of rats in the forced swimming test. The 5-HT/noradrenaline reuptake inhibitor imipramine, the noradrenaline reuptake inhibitor desipramine and the monoamine oxidase-A inhibitor moclobemide, administered at the dose of 20 mg/kg, were inactive, but when given at 30 mg/kg, they significantly reduced the immobility time (Fig. 1). Therefore, the dose of 20 mg/kg of all the antidepressants tested was chosen for interaction studies. Neither the selective 5-HT_{1A} receptor antagonist WAY 100635 (0.1 and 1 mg/kg) nor the 5-$HT_{1B/1D}$ receptor antagonist GR 127935 (10 and 20 mg/kg) nor the 5-HT_{1B} receptor antagonist SB 216641 (2 mg/kg) induced a significant effect (Fig. 2). As was demonstrated in an earlier study, a larger dose of SB 216641 (4 mg/kg)

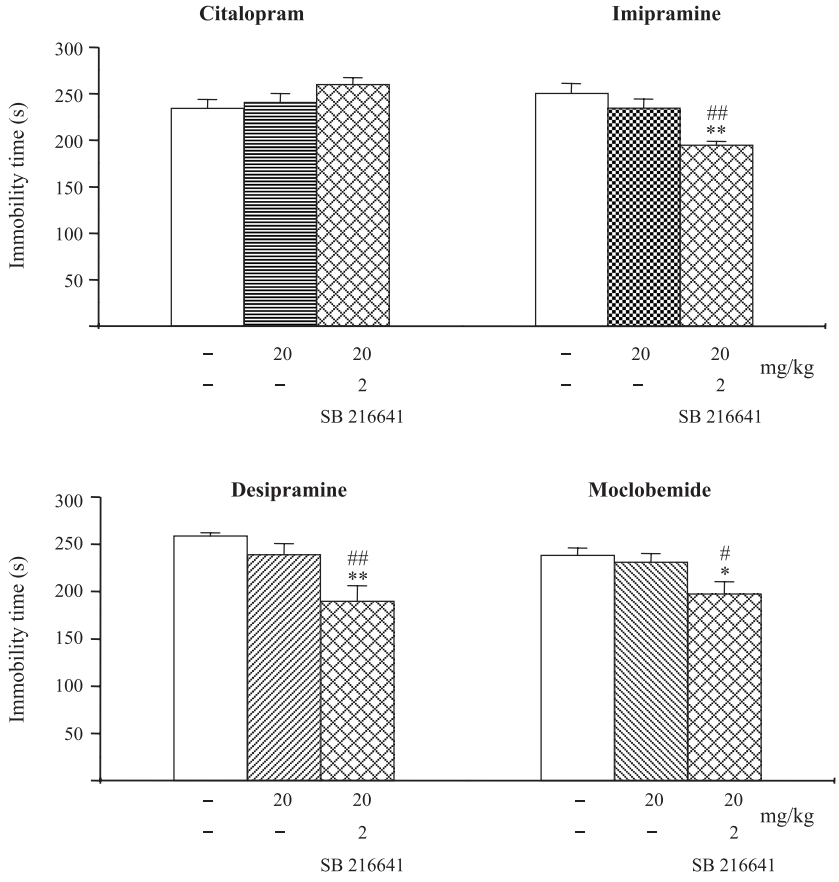

Fig. 5. Interaction of SB 216641 with citalopram, imipramine, desipramine or moclobemide in the forced swimming test in rats. SB 216641 and antidepressants were administered 75 and 60 min before the test, respectively. All values are mean ± S.E.M. for $n=8$. *$P<0.05$, **$P<0.01$ compared to respective vehicle group; $^{\#}P<0.05$, $^{\#\#}P<0.01$ compared to group receiving the same dose of antidepressant without SB 216641, Newman–Keuls test following a significant ANOVA (citalopram: $F(2,21)=2.054$, n.s.; imipramine: $F(2,21)=11.300$, $P<0.001$; desipramine: $F(2,21)=9.275$, $P<0.01$; moclobemide: $F(2,21)=4.703$, $P<0.05$).

Table 1
The effect of WAY 100635, GR 127935, SB 216641, imipramine, desipramine and moclobemide, given alone or in combination, on exploratory activity during a 180-s open field test in rats

Treatment (mg/kg)	Exploratory activity		
	Walking time (s)	Ambulation	Peeping + rearing
Vehicle + vehicle	41.0 ± 1.9	17.0 ± 1.8	16.2 ± 2.4
WAY 100635 (0.1) + vehicle	40.8 ± 3.2	14.8 ± 1.4	10.3 ± 1.4
WAY 100635 (1) + vehicle	36.7 ± 4.3	13.0 ± 2.7	10.5 ± 1.9
GR 127935 (10) + vehicle	40.5 ± 3.5	16.2 ± 2.0	14.8 ± 1.9
GR 127935 (20) + vehicle	41.5 ± 3.0	15.8 ± 1.8	14.2 ± 2.8
SB 216641 (2) + vehicle	42.2 ± 3.4	16.8 ± 1.3	12.8 ± 2.8
	$F(5,30) = 0.343$ n.s.	$F(5,30) = 0.627$ n.s.	$F(5,30) = 1.242$ n.s.
Vehicle + vehicle	37.8 ± 3.9	16.8 ± 2.6	11.5 ± 1.7
Vehicle + imipramine (20)	34.6 ± 2.5	14.8 ± 1.8	12.5 ± 1.3
GR 127935 (10) + imipramine (20)	39.7 ± 2.9	16.5 ± 2.8	14.5 ± 1.9
GR 127935 (20) + imipramine (20)	40.2 ± 4.6	15.5 ± 2.1	11.7 ± 2.5
SB 216641 (2) + imipramine (20)	46.5 ± 5.0	19.0 ± 2.4	14.8 ± 2.6
	$F(4,25) = 1.238$ n.s.	$F(4,25) = 0.451$ n.s.	$F(4,25) = 0.594$ n.s.
Vehicle + vehicle	38.8 ± 2.0	15.7 ± 1.0	14.5 ± 2.4
Vehicle + desipramine (20)	34.2 ± 4.5	12.3 ± 2.7	9.8 ± 1.7
WAY 100635 (0.1) + desipramine (20)	31.2 ± 3.5	12.5 ± 1.2	11.7 ± 1.9
WAY 100635 (1) + desipramine (20)	34.8 ± 6.3	12.7 ± 2.8	10.7 ± 2.5
GR 127935 (10) + desipramine (20)	39.0 ± 2.2	13.5 ± 2.0	13.2 ± 1.4
GR 127935 (20) + desipramine (20)	36.5 ± 2.9	12.2 ± 1.1	9.3 ± 1.7
SB 216641 (2) + desipramine (20)	41.3 ± 4.8	14.7 ± 3.4	14.0 ± 1.8
	$F(6,35) = 0.739$ n.s.	$F(6,35) = 0.364$ n.s.	$F(6,35) = 1.107$ n.s.
Vehicle + vehicle	41.7 ± 3.0	16.5 ± 1.8	13.0 ± 2.6
Vehicle + moclobemide (20)	48.5 ± 3.5	16.3 ± 2.0	14.0 ± 2.1
GR 127935 (10) + moclobemide (20)	42.3 ± 3.9	19.2 ± 2.1	11.8 ± 3.2
GR 127935 (20) + moclobemide (20)	38.5 ± 4.3	14.8 ± 1.9	14.0 ± 3.2
SB 216641 (2) + moclobemide (20)	39.8 ± 4.5	14.3 ± 2.4	11.0 ± 1.3
	$F(4,25) = 0.973$ n.s.	$F(4,25) = 0.830$ n.s.	$F(4,25) = 0.337$ n.s.

WAY 100635, GR 127935 and SB 216641 were administered 75 min, imipramine, desipramine and moclobemide 60 min before the test. The values shown are the mean ± S.E.M.; $n = 6$ rats per group.

induced a significant anti-immobility effect in the rat forced swimming test (Tatarczyńska et al., 2002).

3.2. Interaction of antidepressants with the 5-HT_{1A} receptor antagonist WAY 100635 in the forced swimming test

The results presented in Fig. 3 showed that WAY 100635 (0.1 and 1 mg/kg) co-administered with 20 mg/kg of citalopram, imipramine or moclobemide did not produce any significant effect on immobility time in the forced swimming test. A combination of a subactive dose of desipramine (20 mg/kg) and WAY 100635 (0.1 and 1 mg/kg) slightly but significantly reduced the immobility time.

3.3. Interaction of antidepressants with the 5-$HT_{1B/1D}$ receptor antagonist GR 127935, or the 5-HT_{1B} receptor antagonist SB 216641 in the forced swimming test

The results presented in Figs. 4 and 5 revealed that neither GR 127935 (10 and 20 mg/kg) nor SB 216641 (2 mg/kg) given jointly with citalopram (20 mg/kg) induced any significant effect compared to vehicle-treated animals. Co-administration of GR 127935 (10 and 20 mg/kg; Fig. 4) or SB 216641 (2 mg/kg; Fig. 5) with imipramine (20 mg/kg), desipramine (20 mg/kg) or moclobemide (20 mg/kg) resulted in statistically significant anti-immobility effects.

3.4. Effects of antidepressants and 5-HT_{1A}, 5-$HT_{1B/D}$ or 5-HT_{1B} receptor antagonists, given alone or in combination, in the open field test

None of the compounds studied, given alone or in combination (imipramine + GR 127935 or SB 216641; desipramine + WAY 100635 or GR 127935 or SB 216641; moclobemide + GR 127935 or SB 216641), changed the exploratory activity of rats, evaluated by the open field test (Table 1).

4. Discussion

The present study shows that citalopram given alone at doses of 20 and 30 mg/kg does not reduce immobility time in rats in the forced swimming test, whereas imipramine, desipramine and moclobemide at a dose of 30 mg/kg (but not 20 mg/kg) induce anti-immobility effects. These results are in line with the findings of several other studies which indicate that—in contrast to other antidepressants—selective serotonin reuptake inhibitors are devoid of any activity in this test in rats. However, a few other results have shown that some of these drugs may exert antidepressant-like effects in the forced swimming test in rats (Borsini, 1995; Borsini and Meli, 1988; Moser and Sanger, 1999).

Our data clearly prove that 5-HT_{1A} and 5-HT_{1B} receptors play different roles in modulating the action of antidepressant drugs in the rat forced swimming test (Table 2). In fact,

Table 2
Summary of the differential effects of 5-HT_{1A}, 5-$HT_{1B/1D}$ and 5-HT_{1B} receptor antagonists given jointly with antidepressant drugs in the forced swimming test in rats

Antidepressant	WAY 100635	GR 127935	SB 216641
Citalopram	–	–	–
Imipramine	–	+	+
Desipramine	+	+	+
Moclobemide	–	+	+

+ = additive effect; – = no effect.

the obtained results provide no evidence that pretreatment with the silent 5-HT_{1A} receptor antagonist WAY 100635 may help to reveal the anti-immobility activity of the selective serotonin reuptake inhibitor citalopram, the serotonin/noradrenaline reuptake inhibitor imipramine, or the monoamine oxidase-A inhibitor moclobemide. Only the co-administration of WAY 100635 and a subactive dose of the selective noradrenaline reuptake inhibitor desipramine were found to evoke an anti-immobility effect. Interestingly, the 5-$HT_{1B/1D}$ receptor antagonist, GR 127935, and the 5-HT_{1B} receptor antagonist, SB 216641, given jointly with a subactive dose of imipramine, desipramine or moclobemide, but not citalopram, induced anti-immobility effects. All the positive interactions described seem to be specific, since these drugs (given alone or jointly) do not affect the locomotor activity of rats, measured by the open field test.

To date, there has been only sparse information about the interaction beetween WAY 100635 and antidepressants in animal models of depression. Indeed, the effect of WAY 100635 on the antidepressant-like activity of citalopram was previously studied only in the chronic mild stress model in rats, and—like in the present study—no interaction was observed (Papp et al., 2002). In other preclinical studies with rats, WAY 100635 either attenuated or did not affect the action of the other selective serotonin reuptake inhibitors paroxetine or fluoxetine given at active or subactive doses (Cryan et al., 1999; Moser and Sanger, 1999; Tatarczyńska et al., 2002). On the other hand, Cousins and Seiden (2000) demonstrated, using the differential reinforcement of low rates 72-s schedule in rats, that the behaviorally inactive dose of fluoxetine produced an antidepressant-like effect when given in combination with WAY 100635, whereas the effects of the active dose of fluoxetine were blocked by pretreatment with WAY 100635. Furthermore, recent studies by Mayorga et al. (2001) using the tail suspension test demonstrated that fluoxetine and paroxetine failed to decrease immobility in 5-HT_{1A} receptor knockout mice at a dose active in wild-type mice. Accordingly, WAY 100635 blocked the behavioral effects of fluoxetine in wild-type mice. The authors suggested that the presence of 5-HT_{1A} receptors may be critical for the expression of the antidepressant-like behavioral responses of selective serotonin reuptake inhibitors in that test. In the present study, a combination of WAY 100635 and imipramine failed to produce an interaction in the forced swimming test in rats. So far, combined administrations of WAY 100635 and imipramine have not been studied in animal models of depression. However, WAY 100635 has been reported to enhance the anti-immobility activity of duloxetine, another mixed 5-HT and noradrenaline reuptake inhibitor in the rat forced swimming test (Millan et al., 1998). The reason for such a discrepancy between these data and the present results is not clear, since the experimental model, the animals and the range of doses of WAY 100635 are the same, and the mechanism of action of duloxetine and imipramine is similar. On the other hand, in the present study, WAY 100635 potentiated the effect of a subactive dose of desipramine. And again, this finding is in contrast to the results obtained with other 5-HT_{1A} receptor ligands with predominantly antagonistic action 1-(2-methoxyphenyl)-4-[4-(2-phthalimmido)butyl]piperazine (NAN-190), 8-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-8-azaspiro[4.5]decane-7,9dione (BMY-7378) and pindolol, which blocked the effect of desipramine in the forced swimming test in rats and mice (Detke et al., 1995; Redrobe et al., 1996). However, NAN-190 is an antagonist at postsynaptic 5-HT_{1A} receptors (Glennon et al., 1988; Przegaliński et al., 1990) and a partial agonist at presynaptic ones (Gruel and Glaser, 1992; Hjorth and Sharp, 1990); moreover, it also exhibits high affinity for α_1-adrenoceptors (Glennon et al., 1988). Like NAN-190, BMY-7378 is classified as partial agonist at presynaptic 5-HT_{1A}receptors and as antagonist at postsynaptic ones (Sharp et al., 1990), while pindolol is a 5-HT_{1A}/5-HT_{1B} receptor/β-adrenoceptor antagonist which shows a pronounced agonistic effect on central 5-HT_{1A} and 5-HT_{1B} receptors (Arborelius et al., 2000; Clifford et al., 1998; Przegaliński et al., 1995), hence it is actually a partial agonist at these sites. This rather complex receptor binding profile might account for the different interaction of desipramine with NAN-190 or BMY-7378 and the silent 5-HT_{1A} receptor antagonist WAY 100635. Furthermore, it has been found that the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) potentiates the desipramine-induced anti-immobility effect in the forced swimming test in rats (Rénéric et al., 2001) and mice (Redrobe et al., 1996). According to Mayorga et al. (2001), in the tail suspension test, the anti-immobility effect of desipramine is similar in 5-HT_{1A} receptor knockout mice and wild-type animals. It is noteworthy that 5-HT_{1A} receptor mutant mice reveal a decrease in baseline immobility values in the latter test (Mayorga et al., 2001) and in the forced swimming test (Parks et al., 1998, Ramboz et al., 1998). However, the acute blockade of 5-HT_{1A} receptors cannot be compared with their lack in mutant mice, as it induces developmental compensation effects. Although it is very difficult to draw any definite conclusions about the mechanism responsible for the anti-immobility effect of combined administration of WAY 100635 and desipramine, it should be stressed that WAY 100635 exhibits moderate affinity for α_1-adrenoceptors (Forster et al., 1995), and that its main metabolite shows high affinity for these sites in vitro (Pike et al., 1996).

Hence, it is suggested that these receptors may play some role in the positive interaction between WAY 100635 and the selective noradrenaline reuptake inhibitor desipramine. There are no data available on the activity of WAY 100635 given in combination with the monoamine oxidase-A inhibitor moclobemide in animal models of depression. In our experiment, combined administration of those two drugs failed to induce an anti-immobility response. This observation is in the line with the results of Moser and Sanger (1999) indicating that WAY 100635 did not affect the anti-immobility effect of another selective monoamine oxidase-A inhibitor, befloxatone.

Till now, only few studies have been concerned with the effect of combined administration of 5-$HT_{1B/1D}$ receptors antagonists and antidepressants in animal models of depression. In the mouse tail suspension test, GR 127935 (10 mg/kg, but not lower doses) blocked the anti-immobility effect of paroxetine (O'Neill et al., 1996); on the other hand, a very low dose of GR 127935 (0.056 mg/kg) enhanced the action of fluoxetine administered in a low dose (2.5 mg/kg), but not at higher dose (20 mg/kg) (Mayorga et al., 2001). Our earlier paper demonstrated that the blockade of 5-HT_{1B} receptors induced by GR 127935 or SB 216641 could evoke the anti-immobility effect of paroxetine, but not fluoxetine, in the forced swimming test in rats (Tatarczyńska et al., 2002). Paroxetine is more potent than fluoxetine in inhibiting noradrenaline reuptake (Hyttel, 1984, 1994), and it displays both 5-HT- and noradrenergic-like activity in functional in vivo studies (Redrobe et al., 1998). In addition, the 5-HT_{1B} receptors located on neuronal terminals act not only as autoreceptors on 5-HT neurons, but also as heteroreceptors on non-serotoninergic neurons where they control the release of other neurotransmitters including noradrenaline and dopamine (for review, see Pauwels, 1997). Therefore, it is speculated that the noradrenaline-mediated neurotransmission may be involved in the anti-immobility effects observed after combined administration of 5-HT_{1B} receptor antagonists and paroxetine. In an unpublished study, we found that the reduction of the time spent immobile, induced by co-administration of GR 127935 and paroxetine, was completely blocked by the α_2-adrenoceptor antagonist idazoxan or the dopamine D2 receptor antagonist sulpiride, which suggest the involvement of catecholamines in this effect. The fact that a putative anti-immobility effect of citalopram, a more selective serotonin reuptake inhibitor (Brunello et al., 2002), was not disclosed by GR 127935 or SB 216641 co-administration, is in keeping with such noradrenergic hypothesis in the forced swimming test. On the other hand, the present data suggest that 5-HT_{1B} receptors may play some role in mediating the anti-immobility effect of imipramine, desipramine and moclobemide. Indeed, co-treatment with the 5-$HT_{1B/1D}$ receptor antagonist GR 127935 or the 5-HT_{1B} receptor antagonist SB 216641 and the above-mentioned antidepressants was found to evoke an anti-immobility effect. However, according to O'Neill et al. (1996), GR 127935 either attenuated or did not affect the anti-immobility action of imipramine (10 or 30 mg/kg, respectively) in the tail suspension test in mice. Such a discrepancy could be accounted for by strain differences (mice vs. rats), the test protocols applied (drug dosage, route of administration) and different experimental models used (tail suspension test vs. forced swimming test). So far, there has been no information available about a possible interaction between 5-$HT_{1B/1D}$ receptor antagonists and selective noradrenaline reuptake inhibitors or monoamine oxidase-A inhibitors in animal models of depression. Only the results obtained by Mayorga et al. (2001) showed that 5-HT_{1B} receptor deletion did not decisively alter the behavioral response to desipramine in the mouse tail suspension test. However, the effects observed in 5-HT_{1B} receptor mutant mice are difficult to compare with our own results obtained with rats treated with 5-HT_{1B} receptor antagonists and desipramine. It is noteworthy that the most potent anti-immobility effect was observed after co-administration of GR 127935 and a subactive dose of desipramine. Although GR 127935 displays mixed 5-$HT_{1B/1D}$ receptor agonist/antagonist properties both in vitro and in vivo (Pauwels, 1997), its agonist properties at 5-HT_{1B} receptors do not seem significant for its positive interaction with desipramine. Indeed, the full 5-HT_{1B} receptor agonist CP-94,253 [3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3,2-b]pyridine] (Koe et al., 1992) at a dose of 5 mg/kg fails to potentiate the anti-immobility effect of desipramine (30 mg/kg; our unpublished data). Summing up, our data indicate that the blockade of 5-HT_{1B} receptors cannot reveal an anti-immobility effect of the selective serotonin reuptake inhibitor citalopram, but may be involved in mediation of the behavioral effect of acute administration of other 5-HT and/or noradrenaline reuptake inhibitors and the monoamine oxidase-A inhibitor tested. It has been well established that the shortening of the immobility time in the rat forced swimming test depends primarily on the enhancement of central catecholamine and—to a lesser extent—5-HT neurotransmission (Borsini, 1995; Borsini and Meli, 1988; Cervo et al., 1990, 1991; Porsolt et al., 1979; Rénéric et al., 2001). Thus, it may be hypothesized that an enhancement of noradrenaline and/or dopamine neurotransmission may be involved in the anti-immobility effects of imipramine, desipramine or moclobemide co-administered with 5-HT_{1B} antagonists. On the other hand, microdialysis studies indicated that the extracellular levels of noradrenaline, dopamine and 5-HT in the frontal cortex were not affected by GR 127935 or other 5-HT_{1B} or 5-HT_{1D} receptor antagonists (Gobert et al., 1998; Millan et al., 2000). The effect of SB 216641 on noradrenaline and dopamine levels has not been tested so far, but like other 5-HT_{1B} receptor antagonists, it failed to alter the extracellular level of 5-HT (Roberts et al., 1997). Unfortunately, no information is available on neurotransmitter substrates that are critical for the positive behavioral effects of antidepressants given jointly with 5-$HT_{1B/1D}$ receptor antagonists, as observed in our experiment.

In conclusion, the obtained results indicate that the blockade of 5-HT_{1B} rather than 5-HT_{1A} receptors may facilitate the anti-immobility effects of imipramine, desipramine and moclobemide in the forced swimming test in rats. No interaction has been found between citalopram and 5-HT_{1A} or 5-$HT_{1B/1D}$ receptor antagonists. The present data need to be corroborated by successive studies conducted in other animal models which are more sensitive to the early onset of effects predictive of clinical antidepressant activity before any final conclusions are reached. Moreover, the evidence presented in our paper does not explain why pindolol potentiates the clinical efficacy of antidepressant drugs.

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