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Interaction studies of 5-HT_{1A} receptor antagonists and selective 5-HT reuptake inhibitors in isolated aggressive mice

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Abstract

Recently published studies have suggested that behavioral and neurochemical changes induced by selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors are potentiated by coadministration of a 5-HT_{1A} receptor antagonist. The potentiating effect is hypothesized to be due to antagonism of somatodendritic 5-HT_{1A} autoreceptors. In the present study the effects of concomitant administration of a selective 5-HT reuptake inhibitor with a 5-HT_{1A} receptor antagonist (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-*N*-(2-pyridinyl) cyclo-hexanecarboxamide (WAY 100635) or a β-adrenoceptor and 5-$HT_{1A/1B}$ receptor antagonist (pindolol or (−)-penbutolol) were studied in isolated aggressive mice. WAY 100635 was inactive, but high doses of WAY 100635 produced a marked anti-aggressive effect when combined with a non-effective dose of citalopram or paroxetine. Low doses of pindolol, but not (−)-penbutolol, produced a minor but significant anti-aggressive effect in combination with citalopram or paroxetine. High doses of pindolol or (−)-penbutolol inhibited aggressive behavior, an effect which was reversed by citalopram or paroxetine. The β-adrenoceptor antagonist, metoprolol, but not the α_1-adrenoceptor antagonist, prazosin, facilitated the anti aggressive effect of citalopram. The significance of these findings is discussed relative to the above hypothesis. © 1997 Elsevier Science B.V.

Keywords: Isolation-induced aggression; 5-HT_{1A} receptor; 5-HT (5-hydroxytryptamine, serotonin) reuptake inhibitor; (Mouse)

1. Introduction

There is extensive evidence that serotonin (5-hydroxytryptamine, 5-HT) receptors play an important role in mediating aggressive behavior (e.g. reviews by Eichelman, 1990; Miczek et al., 1994; Bell and Hobson, 1994). Aggressive behavior can be reversed by 5-HT receptor stimulation, e.g. by administration of a selective 5-HT reuptake inhibitor (Olivier et al., 1989; Ögren et al., 1980; Sánchez and Hyttel, 1994) or a 5-HT_1 receptor agonist (McMillen et al., 1988, 1989; Olivier et al., 1990; Sánchez et al., 1993).

A number of recent studies suggest that selective 5-HT reuptake inhibitor-induced behavioral and neurochemical effects are potentiated by coadministration of a 5-HT_{1A} receptor antagonist. The potentiating effect is ascribed to antagonism of presynaptic somatodendritic 5-HT_{1A} receptors. These receptors control neuronal firing activity and thereby terminal 5-HT release, and activation of somatodendritic autoreceptors after administration of a selective 5-HT reuptake inhibitor consequently tends to diminish the selective 5-HT reuptake inhibitor-induced increase of serotonergic activity (Matos et al., 1996). A number of microdialysis studies have demonstrated that the selective 5-HT reuptake inhibitor-induced increase in extracellular 5-HT concentration is increased several fold after coadministration of a 5-HT_{1A} receptor antagonist, e.g. (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-*N*-(2-pyridinyl) cyclo-hexanecarboxamide (WAY 100635), or a β-adrenoceptor/5-$HT_{1A/1B}$ receptor antagonist, e.g. (−)-penbutolol or pindolol (e.g. Bel and Artigas, 1992; Invernizzi et al., 1992; Hjorth, 1993; Hjorth et al., 1996). The 5-HT_{1A} receptor antagonist-induced potentiation of selective 5-HT reuptake inhibitor-induced effects has also been demonstrated in a few behavioral studies; e.g. WAY 100635

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potentiates selective 5-HT reuptake inhibitor-induced inhibition of marble burying behavior (Dourish et al., 1996).

The purpose of the present study was to investigate the interaction between selective 5-HT reuptake inhibitors and the 5-HT_{1A} receptor antagonist WAY 100635 or the mixed β-adrenoceptor and 5-$HT_{1A/1B}$ receptor antagonists pindolol or (−)-penbutolol in isolated aggressive mice.

2. Material and methods

2.1. Animals

Male mice (NMRI/BOM, SPF, Møllegård) weighing 18–20 g at the beginning of the experiment were used. The mice were housed under a 12 h light/dark cycle (light on at 6 a.m.). The aggressive mice were single-housed in Macrolon type II cages and intruder mice were housed in plastic cages (35 × 30 × 12 cm) 10 in each. The room temperature (21 ± 2°C), relative humidity (55 ± 10%), and air exchange (16 times per h) were automatically controlled. The animals had free access to commercial food pellets and tap water between test sessions.

2.2. Procedure

The test was conducted as described by Sánchez et al. (1993). Briefly, the aggressive mice were kept isolated for about 21 days. After the isolation period the mice were trained to attack a non-aggressive intruder mouse of the same strain. An attack was defined as biting or an attempt to bite the intruder mouse. The training and the testing sessions took place in the home cage of the aggressive mouse. Attack latencies of 10 s or less were reached after daily training sessions for 5–7 days. Only mice with attack latencies of less than 10 s were included in the studies.

In the test sessions the mice were tested immediately before drug treatment and 30 min later. The attack latency was measured with a maximum observation time of 180 s. Each group consisted of 8 aggressive and 16 non-aggressive (for pre- and post-drug testing) mice. A total of two or three separate experiments, each including a control group and three or four doses, were conducted with each drug.

2.3. Drugs

(−)-Penbutolol molecular weight (mw) 292; (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-*N*-(2-pyridinyl) cyclo-hexanecarboxamide trihydrochloride (WAY-100635), mw 513, citalopram hydrobromide mw 405 (all synthesized at Department of Medicinal Chemistry, H. Lundbeck A/S); metoprolol tartrate mw 685 (Sigma, USA) were dissolved in saline. Paroxetine acetate, mw 373 (SmithKline Beecham, UK), and prazosin hydrochloride, mw 417 (Pfizer, USA), were dissolved in distilled water. Pindolol mw 248 (Dumex A/S, Denmark) was dissolved in a minimum amount of 0.1 M citric acid.

Injection volumes were 10 ml/kg and the route was s.c.

2.4. Statistics

Attack latencies were expressed as means (± S.E.M.), and two-way analysis of variance (ANOVA) was used for assessing the effects of combining selective 5-HT reuptake inhibitor with antagonist. Post hoc pair wise comparisons of means were performed by applying the Newman–Keuls method. The statistical analyses were performed by means of the Sigmastat program (version 1.0).

3. Results

The 5-HT_{1A} receptor antagonist WAY 100635 did not increase the attack latency by itself (Fig. 1a and B). A marked increase in the attack latency was achieved when high doses of WAY 100635 were administered in combi-

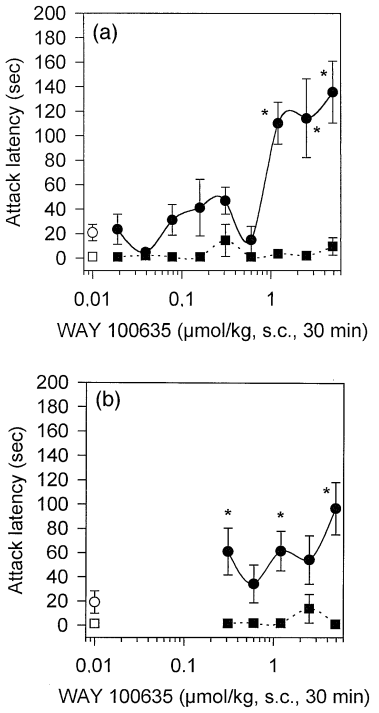

Fig. 1. (a) Anti-aggressive effect of WAY 100635 + saline (■) or WAY 100635 + citalopram 25 µmol/kg (10 mg/kg, s.c.) (●) in socially isolated male mice. Saline + saline (□) and citalopram 25 µmol/kg + saline (○). Mean increase in attack latency (± S.E.M.) versus dose is shown. Both compounds were administered 30 min before testing. (b) Anti-aggressive effect of WAY 100635 + saline (■) or WAY 100635 + paroxetine 27 µmol/kg (10 mg/kg, s.c.) (●) in socially isolated male mice. Saline + saline (□) and paroxetine 27 µmol/kg + saline (○). Mean increase in attack latency (± S.E.M.) versus dose is shown. Both compounds were administered 30 min before testing. * $P < 0.05$; two-way ANOVA followed by pairwise comparisons of dose groups. $N = 8–24$ per dose group.

nation with a non-effective dose of citalopram (25 μmol/kg = 10 mg/kg, Fig. 1a). Similarly, a significant increase in the attack latency was achieved in mice treated with paroxetine (27 μmol/kg = 10 mg/kg) plus WAY 100635 (Fig. 1b).

Combined treatment with citalopram (25 μmol/kg = 10 mg/kg) or paroxetine (27 μmol/kg = 10 mg/kg) and low (i.e. inactive) pindolol doses increased the attack latency significantly (two-way ANOVA). However, the effect of pindolol was less pronounced than that of WAY 100635. Pindolol by itself increased the attack latency significantly at high doses, and citalopram or paroxetine reversed this effect (Fig. 2a and b).

A high dose of the β-adrenoceptor and 5-HT_{1A} and 5-HT_{1B} receptor antagonist, (−)-penbutolol, increased the attack latency significantly (Fig. 3a). Citalopram (25 μmol/kg = 10 mg/kg) did not interfere with the effect of low doses of (−)-penbutolol, whereas it reversed the effect of a high dose of (−)-penbutolol.

The β-adrenoceptor antagonist, metoprolol, did not increase the attack latency, whereas citalopram (25 μmol/kg = 10 mg/kg) in combination with metoprolol resulted in a small but statistically significant increase in the attack latency (Fig. 3b).

The α_1-adrenoceptor antagonist, prazosin (0.024–0.74 μmol/kg = 0.01–0.31 mg/kg), either alone or in combi-

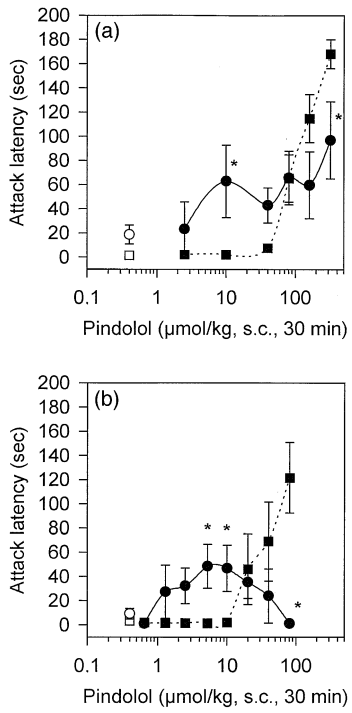

Fig. 2. (a) Anti-aggressive effect of pindolol + saline (■) or pindolol + citalopram 25 μmol/kg (10 mg/kg, s.c.) (●) in socially isolated male mice. Saline + saline (□) and citalopram 25 μmol/kg + saline (○). Mean increase in attack latency (± S.E.M.) versus dose is shown. Both compounds were administered 30 min before testing. (b) Anti-aggressive effect of pindolol + saline (■) pindolol + paroxetine 27 μmol/kg (10 mg/kg, s.c.) (●) in socially isolated male mice. Saline + saline (□) and paroxetine 27 μmol/kg + saline (○). Mean increase in attack latency (± S.E.M.) versus dose is shown. Both compounds were administered 30 min before testing. $^{*}P < 0.05$; two-way ANOVA followed by pairwise comparisons of dose groups. $N = 8$–24 per dose group.

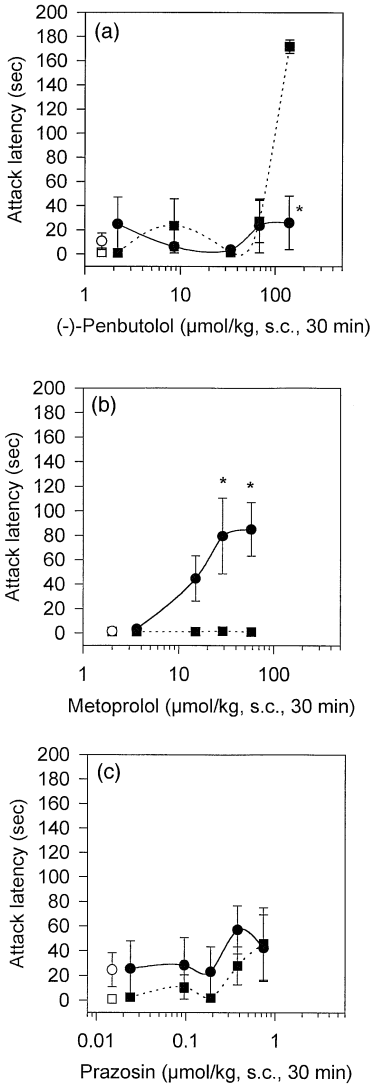

Fig. 3. (a) Anti-aggressive effect of (−)-penbutolol + saline (■) or (−)-penbutolol + citalopram 25 μmol/kg (10 mg/kg, s.c.) (●) in socially isolated male mice. Saline + saline (□) and citalopram 25 μmol/kg + saline (○). Mean increase in attack latency (± S.E.M.) versus dose is shown. Both compounds were administered 30 min before testing. (b) Anti-aggressive effect of metoprolol + saline (■) or metoprolol + citalopram 25 μmol/kg (10 mg/kg, s.c.) (●) in socially isolated male mice. Saline + saline (□) and citalopram 25 μmol/kg + saline (○). Mean increase in attack latency (± S.E.M.) versus dose is shown. Both compounds were administered 30 min before testing. (c) Anti-aggressive effect of prazosin + saline (■) or prazosin + citalopram 25 mol/kg (10 mg/kg, s.c.) (●) in socially isolated male mice. Saline + saline (□) and citalopram 25 μmol/kg + saline (○). Mean increase in attack latency (± S.E.M.) versus dose is shown. Both compounds were administered 30 min before testing. $^{*}P < 0$ 05; two-way ANOVA followed by pairwise comparisons of dose groups. $N = 8$–24 per dose group.

nation with citalopram (25 μmol/kg = 10 mg/kg) did not affect the attack latency significantly (Fig. 3c).

4. Discussion

The 5-HT_{1A} receptor antagonist, WAY 100635, failed to show anti-aggressive effects, even at very high doses (present study and Sánchez et al., 1996a), but facilitated the anti-aggressive effect of the selective 5-HT reuptake inhibitors, citalopram and paroxetine. Former studies of citalopram and paroxetine have demonstrated weak and no, respectively, anti-aggressive potency of these drugs (Sánchez and Hyttel, 1994). However, potent effects were achieved with citalopram or paroxetine in combination with sub-effective doses of the 5-HT precursor L-5-hydroxy-tryptophan (L-5-HTP), suggesting that an overall increase in serotonergic activity inhibits aggressive behavior (Sánchez and Hyttel, 1994). As discussed in the introduction, antagonism of somatodendritic 5-HT_{1A} receptors after treatment with WAY 100635 is suggested to augment the selective 5-HT reuptake inhibitor-induced increase in serotonergic output. This effect could be involved in the anti-aggressive effect observed in studies of WAY 100635 given in combination with a selective 5-HT reuptake inhibitor. However, the potency of WAY 100635 in the present study was surprisingly low compared to its very high 5-HT_{1A} receptor antagonistic potency in other studies. WAY 100635 reversed 8-OH-DPAT-induced inhibition of aggressive behavior in isolated mice with an ED_{50} value of 0.012 μmol/kg, s.c. (0.0062 mg/kg; Sánchez et al., 1996a). The minimal effective dose (MED) of WAY 100635 was 1.2 μmol/kg (0.63 mg/kg) in the present study. This low potency does not suggest that the potentiation can be ascribed to antagonism at somatodendritic 5-HT_{1A} receptors alone.

WAY 100635 has a moderate affinity for α_1-adrenoceptors with an in vitro selectivity ratio of about 50 relative to its 5-HT_{1A} receptor affinity (Sánchez et al., 1996a). Ptosis in mice is mediated by peripheral α_1-adrenoceptors, and induction of ptosis is suggested as an in vivo model for determination of α_1-adrenoceptor antagonistic potency (Millan et al., 1994). In this model the α_1-adrenoceptor antagonistic doses of WAY 100635 were comparable to the doses that potentiated the anti-aggressive effect of citalopram in the present study, i.e. ED_{50} = 5.3 μmol/kg (2.7 mg/kg, Sánchez, unpublished observations). The ptosis-inducing potency of the α_1-adrenoceptor antagonist, prazosin, was ED_{50} = 0.082 μmol/kg (Sánchez, unpublished observations), whereas prazosin increased the attack latency of isolated aggressive mice at much higher doses, i.e. ED_{50} = 1.3 μmol/kg (Sánchez et al., 1993). This difference in potency may indicate that the anti-aggressive effect is mediated by central adrenoceptors as prazosin penetrates the blood–brain barrier poorly. Recent in vivo microdialysis studies in rats have shown that systemic administration of either a 5-HT_{1A} receptor agonist or an α_1-adrenoceptor antagonist reduces hippocampal 5-HT release (Hjorth et al., 1995), suggesting that there is a close interaction between the two neurotransmitter systems. In the present study prazosin in doses up to 0.74 μmol/kg failed to induce an anti-aggressive effect in combination with citalopram (Fig. 3C). This suggests that α_1-adrenoceptor antagonism alone cannot explain the WAY 100635-induced facilitation of the effect of a selective 5-HT reuptake inhibitor. However, a combined effect of α_1-adrenoceptor antagonism and the presynaptic 5-HT_{1A} receptor antagonism of WAY 100635 may be involved in the anti-aggressive effect when the drug is given together with citalopram.

Both pre- and postsynaptic 5-HT receptors are involved in mediation of aggressive behavior in isolated aggressive mice. An earlier study using the same test procedure showed that 5-HT depletion by treatment with *p*-chlorophenylalanine methyl ester did not affect the attack latency by itself, but attenuated the anti-aggressive effect of the 5-HT-releasing agent fenfluramine and potentiated the anti-aggressive effect of the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamin) tetralin (8-OH-DPAT) (Sánchez and Hyttel, 1994). This suggests that postsynaptic 5-HT_{1A} receptors play an important role in the mediation of aggressive behavior in the present model. Thus antagonism at postsynaptic 5-HT_{1A} receptors after treatment with WAY 100635 probably counteracts the anti-aggressive effect achieved by combined 5-HT uptake inhibition and antagonism of somatodendritic 5-HT_{1A} autoreceptors.

Other 5-HT receptor subtypes than 5-HT_{1A} receptors are likely to be involved in mediating aggressive behavior. 5-HT_{1B} receptor stimulation is found to play a specific role in the control of aggressive behavior (reviews by Olivier et al., 1989; Bell and Hobson, 1994). Former studies applying the procedure of the present study have shown that the 5-HT_1 receptor agonist 1-(trifluoromethylphenyl)piperazine (TFMPP) increases the attack latency significantly and that this effect is likely to be mediated by 5-HT_{1B} receptors (Sánchez et al., 1993, 1996a). 5-HT_{2A} or 5-HT_{2C} receptors may also be involved in mediating aggressive behavior (Olivier and Mos, 1992; Bell and Hobson, 1994). With the present procedure it was shown that the 5-$HT_{2A/2C}$ receptor antagonist, ritanserin, potentiated the 8-OH-DPAT-induced increase in attack latency (Sánchez and Meier, 1997). Ritanserin was inactive by itself and the 5-$HT_{2A/2C}$ receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) increased the attack latency significantly, but only at high and probably non-selective doses (Sánchez et al., 1993). This suggests a modulatory role of 5-$HT_{2A/2C}$ receptors on 5-HT_{1A} receptor-mediated effects.

The β-adrenoceptor and 5-$HT_{1A/1B}$ receptor antagonists pindolol and (−)-penbutolol increased the attack latencies, but only at high doses (Fig. 2A, B and Fig. 3A). This agrees with earlier findings, where both the (+) and

(−) enantiomers of penbutolol showed anti-aggressive effects (Sánchez et al., 1996a). The same study demonstrated that low doses of a β-adrenoceptor antagonist (i.e. (+)-penbutolol, metoprolol or ICI 118,551) potentiated the anti-aggressive effect of 8-OH-DPAT, suggesting a β-adrenoceptor-induced facilitation of serotonergic neurotransmission. In agreement with this, low doses of pindolol produced a modest facilitation of the citalopram- or paroxetine-induced anti-aggressive effect (Fig. 2A and B). A small but significant facilitation of the anti-aggressive effect of citalopram was also achieved with the β-adrenoceptor antagonist metoprolol (Fig. 3B), whereas low doses of (−)-penbutolol failed to affect this effect of citalopram. The lack of effect of (−)-penbutolol compared to pindolol might be ascribed to differences in their efficacy at 5-HT_{1A} receptors. Pindolol failed to reverse the anti-aggressive effect of 8-OH-DPAT (Sánchez et al., 1993), whereas (−)-penbutolol reversed the effect completely (Sánchez and Hyttel, 1994), suggesting that the former might be a low efficacy agonist and the latter an antagonist. Recent studies of pindolol in an anxiety model in rats (inhibition of footshock-induced ultrasonic vocalization) also suggested a partial 5-HT_{1A} receptor agonistic effect of pindolol (Sánchez et al., 1996b), and an electrophysiological study suggested that pindolol was an antagonist at somatodendritic 5-HT_{1A} autoreceptors, but not at postsynaptic 5-HT_{1A} receptors (Blier and Bergeron, 1995). Thus the lack of effect of (−)-penbutolol given together with a selective 5-HT reuptake inhibitor might be ascribed to antagonism of postsynaptic 5-HT_{1A} receptors, and the weak effect observed after pindolol plus a selective 5-HT reuptake inhibitor might be related to a weak stimulatory effect.

The selective 5-HT reuptake inhibitors reversed the anti-aggressive effect induced by high doses of pindolol or (−)-penbutolol. This is not readily explained. Recent studies of the effect of selective 5-HT reuptake inhibitor and pindolol combinations in the rat forced swim test showed facilitatory or inhibitory effects of pindolol depending on the doses used (Detke et al., 1996). Low doses of pindolol potentiated the effect of a threshold dose of fluoxetine, whereas higher doses antagonized fluoxetine-induced immobility in the forced swim test. The latter effect was ascribed to antagonistic effects at postsynaptic 5-HT_{1A} receptors. These receptors play an important role in the mediation of immobility induced by forced swimming.

In conclusion, the attack latency of isolated aggressive mice was increased markedly, moderately or not at all after treatment with a combination of selective 5-HT reuptake inhibitor and the 5-HT_{1A} receptor antagonists WAY 100635, pindolol or (−)-penbutolol, respectively. It is unlikely that the potentiating effect of WAY 100635 can be ascribed to antagonism of presynaptic 5-HT_{1A} receptors alone as the effect was achieved at high doses at which 5-HT_{1A} receptor as well as α_1-adrenoceptor antagonism is present. It is likely that β-adrenoceptor antagonistic as well as 5-HT_{1A} receptor mediated effects are involved in the response to treatment with a selective 5-HT reuptake inhibitor and pindolol or (−)-penbutolol. The different effects achieved with pindolol and (−)-penbutolol may be related to different efficacies at 5-HT_{1A} receptors.

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