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Short communication

WAY 100,635 enhances both the 'antidepressant' actions of duloxetine and its influence on dialysate levels of serotonin in frontal cortex

Mark J. Millan *, Mauricette Brocco, Sylvie Veiga, Laetitia Cistarelli, Christophe Melon, Alain Gobert

I.D.R.S., 125, Chemin de Ronde, 78290 Croissy-sur-Seine, France

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Abstract

The mixed serotonin and noradrenaline reuptake inhibitor, duloxetine, (5.0 mg/kg, s.c.), increased levels of serotonin (220%), dopamine (180%) and noradrenaline (470%) in individual dialysates of frontal cortex of freely moving rats. Its influence on serotonin, but not dopamine or noradrenaline, levels was enhanced by the 5-HT_{1A} receptor antagonist, WAY 100,635 (*N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl) cyclo-hexanecarboxamide 3HCl) (0.16 mg kg^{-1}, s.c). In the forced swimming test, although duloxetine was inactive alone, it dose dependently reduced immobility in the presence of WAY 100,635. Thus, blockade of 5-HT_{1A} (auto)receptors selectively facilitates the influence of duloxetine on serotonin levels in the frontal cortex in rats and, in the forced swimming model, enhances its 'antidepressant' properties in parallel. © 1998 Elsevier Science B.V.

Keywords: Serotonin reuptake inhibitor; Frontal cortex; Antidepressant; 5-HT_{1A} receptor; 5-HT (5-hydroxytryptamine, serotonin); Depression

1. Introduction

The antidepressant actions of serotonin reuptake inhibitors involve reinforcement of corticolimbic serotoninergic transmission (Maes and Meltzer, 1995; Artigas et al., 1996) and desensitization of 5-HT_{1A} autoreceptors may be related to the delayed start of action of the inhibitors (Artigas et al., 1996). This desensitization process is mimicked by 5-HT_{1A} autoreceptor antagonists which enhance the increase in serotonin levels provoked by serotonin reuptake inhibitors (Artigas et al., 1996; Gobert et al., 1997). Nevertheless, there is no functional evidence from experimental models that the antidepressant actions of serotonin reuptake inhibitors are potentiated by antagonism of 5-HT_{1A} autoreceptors. The present study addressed these issues, using the selective 5-HT_{1A} receptor antagonist, WAY 100,635 (*N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl) cyclo-hexanecarboxamide 3HCl) (Artigas et al., 1996) and the mixed serotonin and noradrenaline reuptake inhibitor, duloxetine (Engleman et al., 1995).

2. Materials and methods

Male Wistar rats (220–220 g) were implanted under pentobarbital anesthesia with a guide cannula in the frontal cortex (Gobert et al., 1997). Five days later, a concentric probe was introduced and 2 h later, dialysis commenced. Three basal samples (20 μl) were collected, WAY 100,635 was injected, then, 20 min later, duloxetine was injected and samples (20 μl) were taken for 3 h. Serotonin, dopamine and noradrenaline were measured simultaneously by HPLC/colorimetric detection with an assay sensitivity of 0.2, 0.1 and 0.1 pg/sample, respectively. In the forced swimming test (Porsolt et al., 1977; Schreiber et al., 1994), rats were placed in cylinders with 15 cm deep water at 25°C for 15 min. The following day, the rats were replaced therein and immobility was recorded over 15 min. Duloxetine and WAY 100,635 were injected, respectively, 20 and 40 before testing. Drugs were dissolved in sterile distilled water and injected s.c..

* Corresponding author. Tel.: +33-1-41182200; fax: +33-1-41182470.

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3. Results

Duloxetine increased levels of serotonin, dopamine and (markedly) noradrenaline in frontal cortex (Fig. 1). In the presence of WAY 100,635 (inactive alone), the influence of duloxetine on serotonin, but not dopamine or noradrenaline, levels was enhanced (Fig. 1). In the forced swimming test, duloxetine was inactive alone (Fig. 2). However, in the presence of WAY 100,635, it dose dependently reduced immobility (Fig. 2).

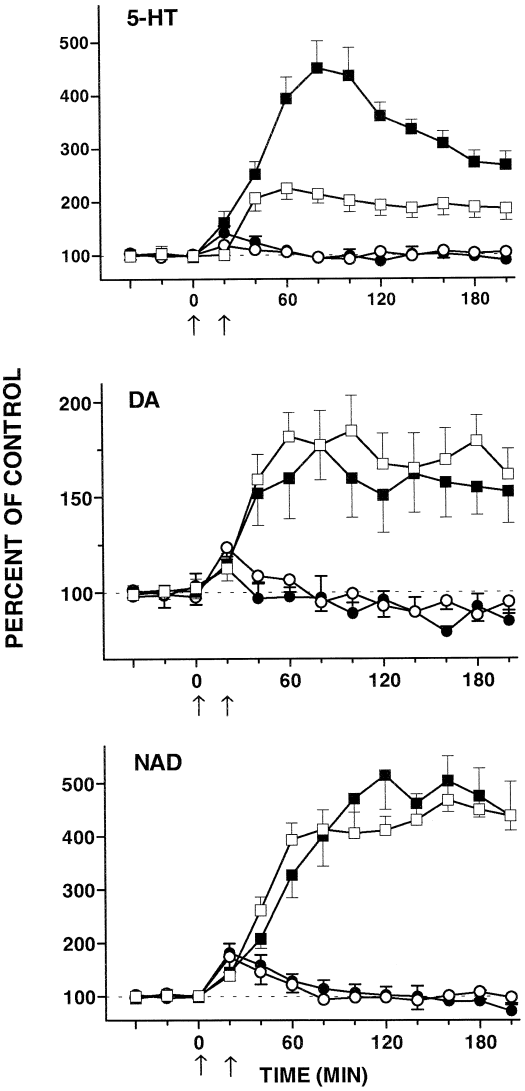

Fig. 1. Modulation by WAY 100,635 (0.16 mg/kg, s.c.) of the influence of duloxetine (5.0 mg/kg, s.c.) upon dialysate levels of serotonin, dopamine (DA) and noradrenaline (NAD) in the frontal cortex of freely moving rats. Data are means ± S.E.M. $N = 8–9$ per value. ANOVA (60–200 min), serotonin: influence of WAY 100,635, $F(1,15) = 35.1$, $P < 0.001$; time, $F(7,105) = 6.1$, $P < 0.001$ and interaction, $F(7,105) = 3.7$, $P < 0.01$. Dopamine: WAY 100,635, $F(1,15) = 0.4$, $P > 0.05$; time, $F(7,105) = 1.9$, $P > 0.05$ and interaction, $F(7,105) = 0.9$, $P > 0.05$. Noradrenaline: influence of WAY 100,635, $F(1,15) = 0.1$, $P > 0.05$; time, $F(7,105) = 2.6$, $P < 0.05$ and interaction, $F(7,105) = 1.2$, $P > 0.05$. For serotonin, all WAY 100,635/duloxetine (■) versus vehicle/duloxetine (□) values were significant in Dunnett's test ($P < 0.05$). Vehicle/vehicle (○) and WAY 100,635/vehicle (●).

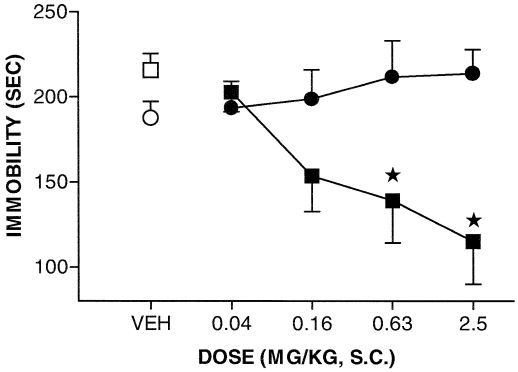

Fig. 2. Influence of WAY 100,635 on the action of duloxetine (5.0 mg/kg, s.c.) in the forced swimming test. Data are means ± S.E.M. N = 7–9 per value. ANOVA: Influence of duloxetine, $F(1,65) = 5.8$, $P < 0.05$; WAY 100,635, $F(4,65) = 1.6$, $P > 0.05$ and interaction, $F(4,65) = 5.1$, $P < 0.01$. Asterisks indicate significance of differences of WAY 100,635/duloxetine (■) from vehicle/duloxetine (□) values in Dunnett's test ($P < 0.05$). Vehicle/vehicle (○) and WAY 100,635/vehicle (●).

4. Discussion

The present findings extend studies suggesting that duloxetine exerts a more marked influence on reuptake of noradrenaline than of serotonin (Engleman et al., 1995; Kihara and Ikeda, 1995). As concerns the increase in dopamine levels, indirect mechanisms such as excitatory 5-HT_3 receptors on dopaminergic terminals may be involved (Tanda et al., 1995). WAY 100,635 potentiated the increase in levels of serotonin, but not noradrenaline or dopamine, provoked by duloxetine in individual dialysate samples, allowing for the virtual exclusion of pharmacokinetic factors in this interaction. Thus, 5-HT_{1A} receptor blockade may selectively modify the influence of serotonin reuptake inhibitors upon serotonin levels in frontal cortex (Gobert et al., 1997). Various effects of drugs inhibiting serotonin reuptake in the forced swimming test have been described (Porsolt et al., 1977; Borsini and Meli, 1988, 1990) and duloxetine was ineffective alone in this model. However, it did reduce immobility time in the presence of WAY 100,635. This observation parallels findings of clinical studies where (−)-pindolol enhanced the antidepressant actions of serotonin reuptake inhibitors (Artigas et al., 1996). Inasmuch as postsynaptic 5-HT_{1A} receptors may contribute to the antidepressant actions of serotonin reuptake inhibitors (Schreiber et al., 1994), the potentiating effects of 5-HT_{1A} receptor blockade might appear paradoxical. However, it has been suggested that (−)-pindolol may not markedly block postsynaptic 5-HT_{1A} sites (Artigas et al., 1996) while the marked increase in serotonin levels seen with duloxetine plus WAY 100,635 might 'override' 5-HT_{1A} receptor blockade at the postsynaptic level. Alter-

natively, 5-HT_{1A} receptors may not underlie the antidepressant activity of duloxetine under the present conditions. Identification of the key serotonin receptor type(s) involved in the antidepressant actions of serotonin reuptake inhibitors remains an important challenge (Maes and Meltzer, 1995).

The present study had several limitations. First, regional differences in modulation of serotonin reuptake inhibitor actions by 5-HT_{1A} antagonists have been reported (see Artigas et al., 1996). Second, we employed acute administration of a single antidepressant agent and only one 5-HT_{1A} antagonist. Third, we employed a single functional model of antidepressant activity. It will be of interest to extend the present work along these lines.

In conclusion, blockade of 5-HT_{1A} (auto)receptors selectively facilitated both the increase in levels of serotonin — but not of noradrenaline or dopamine — elicited by duloxetine in frontal cortex, and its functional antidepressant properties in the forced swimming model. These findings are consistent with the strategy of co-administering 5-HT_{1A} autoreceptor antagonists to improve the antidepressant efficacy of serotonin reuptake inhibitors. However, the present data require extension to other antidepressant agents and to other models of potential antidepressant activity before general conclusions can be reached.

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