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Effect of acute treatment with YM992 on extracellular norepinephrine levels in the rat frontal cortex

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Abstract

The effects of acute treatment with (*S*)-2-[[(7-fluoroindan-4-yl)oxy]methyl]morpholine monohydrochloride (YM992), venlafaxine, fluoxetine and citalopram on extracellular norepinephrine levels were examined in the rat frontal cortex by in vivo microdialysis. YM992 (3, 10, 30 mg/kg, i.p.) dose-dependently increased extracellular norepinephrine levels (3-fold at 10 mg/kg, 5.5-fold at 30 mg/kg). While venlafaxine and 30 mg/kg fluoxetine also produced significant increases in norepinephrine levels, 30 mg/kg citalopram had no effect. The combined administration of MDL100,907 (a selective 5-HT_{2A} receptor antagonist) and citalopram did significantly increase norepinephrine levels compared with either saline or citalopram treatment. Therefore, a synergistic effect due to 5-HT reuptake inhibition and 5-HT_{2A} receptor antagonism of YM992 may partly contribute to the increase of extracellular norepinephrine levels. YM992 enhances the neurotransmission of not only 5-HT system but also norepinephrine, and as such may have a preclinical profile different from that of a selective serotonin reuptake inhibitor.

Keywords: Norepinephrine; 5-HT_{2A} receptor antagonist; Microdialysis; YM992; Venlafaxine; Antidepressant

1. Introduction

Several studies have shown the dysfunction of serotonergic and noradrenergic systems in depression (Sugrue, 1983; Blier and De Montigny, 1994; Leonard, 1999). Clinical results have suggested a potential therapeutic benefit of enhancing neurotransmission mediated by both serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine. It was reported that the combination of a selective serotonin reuptake inhibitor and a norepinephrine reuptake inhibitor resulted in a more rapid and robust antidepressant effect than those observed with mono therapy (Nelson et al., 1991; Seth et al., 1992). Also, venlafaxine, having both 5-HT and norepinephrine reuptake inhibitory action (Artigas, 1995), was shown to display an early onset of antidepressive action (Derivan et al., 1995; Benkert et al., 1996), and to be effective in treatment-resistant depression when used at high doses (Nierenberg et al., 1994; De Montigny et al., 1999).

There is much evidence, including results from in vivo microdialysis studies, that noradrenergic neurons are functionally modulated by serotonergic systems in the brain (Clement et al., 1992; Saito et al., 1996; Haddjeri et al., 1997; Hamamura et al., 1997; Barnes and Sharp, 1999). Several 5-HT_{1A} receptor agonists increase the extracellular norepinephrine levels in many brain areas including the hypothalamus (Suzuki et al., 1995), hippocampus (Done and Sharp, 1994; Hajós-Korcsok and Sharp, 1996) and frontal cortex (Gobert et al., 1997). These effects can be antagonized by the selective 5-HT_{1A} receptor antagonists, *N*-tert-butyl-3-(4-(2-methoxyphenyl)piperazin-1-yl)-2-phenyl-propariamide (WAY100135) and *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexane carboxamide (WAY100635) (Suzuki et al., 1995; Hajós-Korcsok and Sharp, 1996). Also, it has been reported that 5-HT_{2A} receptor agonist inhibits norepinephrine release in the rat hippocampus (Done and Sharp, 1992), and ritanserin, a 5-$HT_{2A/2C}$ receptor antagonist, increases the norepinephrine levels (Done and Sharp, 1994). However, Gobert and Millan (1999) reported that the extracellular norepinephrine levels in the rat frontal cortex are increased by 5-HT_{2A} receptor activation but not

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changed by a selective 5-HT_{2A} receptor antagonist, *R*-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol (MDL100,907).

YM992 ((*S*)-2-[[(7-fluoroindan-4-yl)oxy]methyl]morpholine monohydrochloride) is a putative antidepressant that has 5-HT reuptake inhibitory activity and 5-HT_{2A} receptor antagonism (Hatanaka et al., 1996; Takeuchi et al., 1997). In this study, to investigate the involvement of YM992 on noradrenergic systems, the effects of acute treatment with YM992 on extracellular norepinephrine levels were examined in the rat frontal cortex using in vivo microdialysis. The effect of YM992 was compared with the effect of venlafaxine, a serotonin and norepinephrine reuptake inhibitor, and two selective serotonin reuptake inhibitors, fluoxetine and citalopram. In addition, a combination study of MDL100,907 (a selective 5-HT_{2A} receptor antagonist) and citalopram (a selective serotonin reuptake inhibitor) was performed to investigate the synergistic effect due to the 5-HT reuptake inhibition and 5-HT_{2A} receptor antagonism of YM992 on extracellular norepinephrine levels.

2. Materials and methods

2.1. Materials and administration

(*S*)-2-[[(7-fluoroindan-4-yl)oxy]methyl]morpholine monohydrochloride) (YM992) and *R*-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol (MDL100,907) were synthesized by the Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd. (Ibaraki, Japan). Fluoxetine (Eli Lilly and Co.; Indianapolis, IN), citalopram (H. Lundbeck; Copenhagen, Denmark) and venlafaxine (Wyeth-Ayerst; Princeton, NJ) were obtained from commercially available preparations by extraction, refining and purity-checking at the Institute. All other chemicals were obtained from standard commercial sources. For the in vivo microdialysis study, YM992, venlafaxine and citalopram were dissolved in saline; MDL100,907 was dissolved in saline to which a few drops of Tween 80 was added (Kehne et al., 1996); and fluoxetine was dissolved in distilled water. Acute systemic administration of each drug was carried out intraperitoneally (1 or 2 ml/kg).

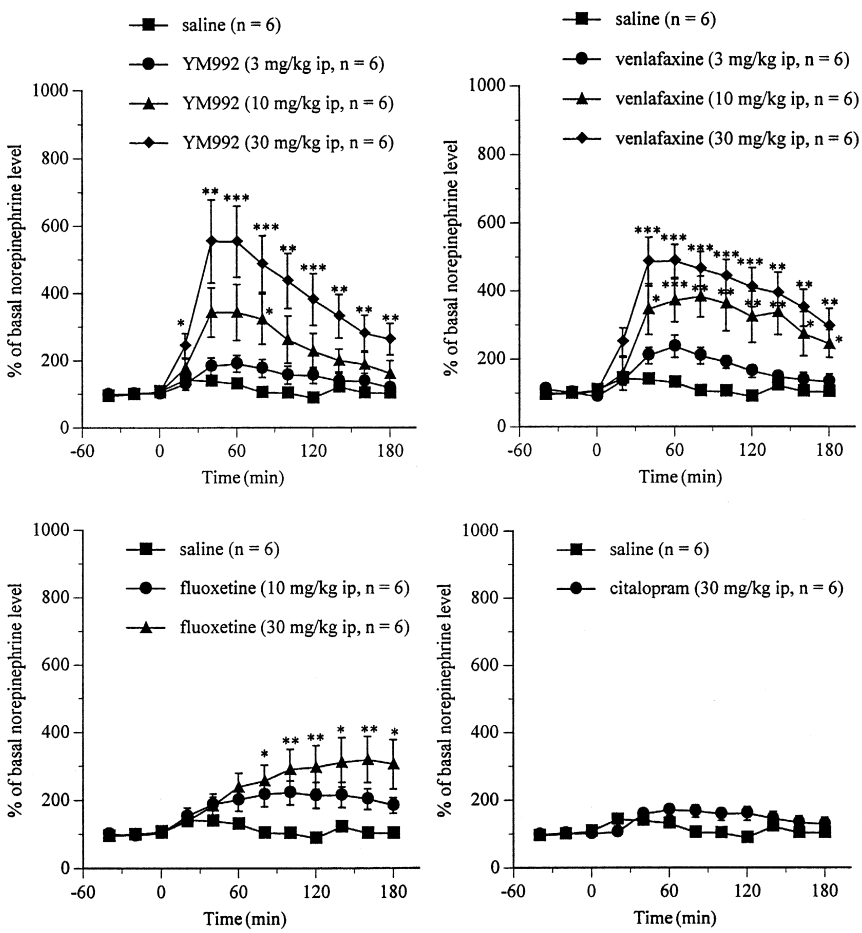

Fig. 1. Effects of acute treatment with YM992, venlafaxine, fluoxetine or citalopram on in vivo extracellular norepinephrine levels in the frontal cortex of freely moving rats. Saline, YM992 (3, 10, 30 mg/kg, i.p.), venlafaxine (3, 10, 30 mg/kg, i.p.), fluoxetine (10, 30 mg/kg, i.p.) and citalopram (30 mg/kg, i.p.) were injected at Time 0. Results are expressed as a percentage of the mean norepinephrine levels of the last three measurements taken before drug administration. Each value represents the mean ± S.E. of six rats. Significant differences from corresponding saline-treated rats were assessed by two-way repeated-measures ANOVA followed by Dunnett's test ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$).

2.2. Animals and surgery

All experiments conformed with the regulations of the Animal Experimentation Ethics Committee of Yamanouchi Pharmaceutical Co., Ltd., Male Wistar rats (SLC; Shizuoka, Japan), weighing 250 to 380 g, were maintained on a 12-h light/dark cycle, with food and water available ad libitium. Rats were anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and placed in a stereotaxic frame (David Kopf Instruments; Tujunga, CA). The skull was exposed and a small hole was drilled to allow implantation of a guide cannula (Eicom; Kyoto, Japan) in the frontal cortex (A: 3.7 mm, L: 2.0 mm, V: 1.5 mm, coordinates relative to bregma [Paxinos and Watson, 1986]). The guide cannula was fixed in the skull with dental cement.

2.3. In vivo microdialysis and chromatographic analysis

At least 5 days after surgery, microdialysis probes (0.22 mm outer diameter, 3 mm exposed membrane; Eicom) were implanted into the frontal cortex and perfused with Ringer's solution (mM: NaCl, 147; KCl, 2.7; $CaCl_2$, 1.2; $MgCl_2$, 0.8) at a flow rate of 2 μl/min. Dialysates collected from the frontal cortex were directly injected into the high-performance liquid chromatography system every 20 min by an autoinjector (AS-10; Eicom). Norepinephrine in the dialysate was separated on a reverse-phase column (Eicompak CA-5ODS; Eicom) and detected with an electrochemical detector (ECD-100 or ECD-300; Eicom). The mobile phase consisted of 0.1 M phosphate buffer (pH 6.0), containing 400 mg/l of sodium-1-octanesulfonate, 50 mg/l of Na_2EDTA, and 5.5–6% methanol. The flow rate of the mobile phase was 1 ml/min. After basal norepinephrine levels stabilized, each drug was administered to freely moving rats at Time 0. Values are expressed as a percentage of the mean of the last three measurements taken before drug administration in each animal.

2.4. Statistics

Basal norepinephrine levels in rat frontal cortex were evaluated by one-way analysis of variance (ANOVA) by treatment group. For in vivo microdialysis studies, the effects of drugs were analyzed by two-way repeated-measures ANOVA. When significant differences were found, post-hoc comparisons were made with Dunnett's or Tukey's test.

3. Results

3.1. Effects of YM992, fluoxetine, citalopram and venlafaxine on in vivo extracellular norepinephrine levels in the rat frontal cortex

Basal norepinephrine levels in rat frontal cortex were 121.6 ± 6.0 fmol/40 μl dialysate ($n = 72$). These basal values did not differ significantly (one-way ANOVA) among treatment groups (data not shown). The administration of YM992 produced a dose-dependent increase in extracellular norepinephrine levels in the rat frontal cortex (two-way repeated-measures ANOVA; treatment: F (3,20) $= 7.5$; $P < 0.01$, time: F (9,180) $= 23.15$; $P < 0.001$, interaction: F (27,180) $= 5.37$; $P < 0.001$, Fig. 1); Norepinephrine levels increased by about three times at a dose of 10 mg/kg, and about 5.5 times at a dose of 30 mg/kg (Fig. 1). Venlafaxine also dose-dependently increased norepinephrine level (two-way repeated-measures ANOVA;

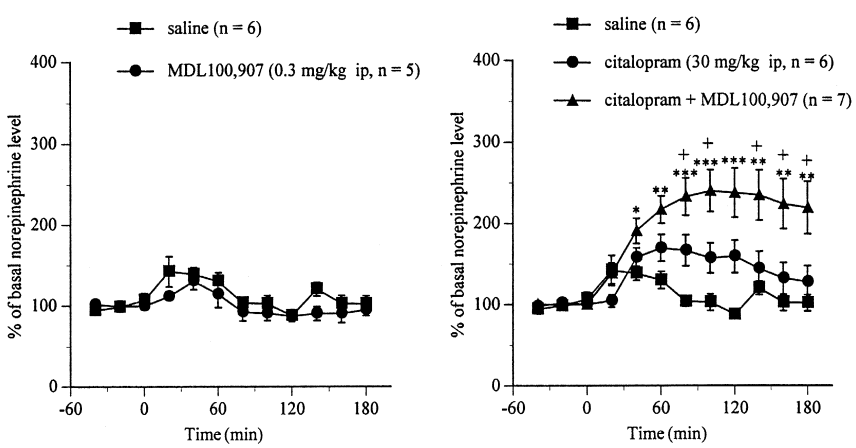

Fig. 2. Effects on in vivo extracellular norepinephrine levels due to acute treatment with MDL100,907 alone and in combination with citalopram. Saline, MDL100,907 (0.3 mg/kg, i.p.), citalopram (30 mg/kg, i.p.) or MDL100,907 (0.3 mg/kg, i.p.) plus citalopram (30 mg/kg, i.p.) were injected at Time 0. Results are expressed as a percentage of the mean norepinephrine levels of the last three measurements taken before drug administration. Each value represents the mean ± S.E. of five to seven rats. There was no significant difference in norepinephrine levels between MDL100,907 treatment and saline treatment (F (1,9) $= 3.01$; $P > 0.10$) according to two-way repeated-measures ANOVA. Significant differences between MDL100,907 plus citalopram and saline ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$) or between MDL100,907 plus citalopram and citalopram alone ($^{+}P < 0.05$) were assessed by two-way repeated-measures ANOVA followed by Tukey's test.

treatment: $F(3,20) = 12.39$; $P < 0.001$, time: $F(9,180) = 22.11$; $P < 0.001$, interaction: $F(27,180) = 4.26$; $P < 0.001$, Fig. 1). Fluoxetine also produced a significant but smaller increase in norepinephrine levels at 30 mg/kg (two-way repeated-measures ANOVA; treatment: $F(2,15) = 4.5$; $P < 0.05$, time: $F(9,135) = 10.76$; $P < 0.001$, interaction: $F(18,135) = 5.8$; $P < 0.001$, Fig. 1). However, citalopram (30 mg/kg) had no effect on norepinephrine levels (two-way repeated-measures ANOVA; $F(1,10) = 3.61$; $P > 0.05$, Fig. 1).

3.2. Effects of MDL100,907 and combined treatment of MDL100,907 and citalopram on extracellular norepinephrine levels in the rat frontal cortex

MDL100,907 induced no significant change in extracellular norepinephrine levels (two-way repeated-measures ANOVA; treatment: $F(1,9) = 3.01$; $P > 0.10$, Fig. 2). Combined administration of MDL100,907 and citalopram significantly increased norepinephrine levels compared with both saline (two-way repeated-measures ANOVA; treatment: $F(1,11) = 16.16$; $P < 0.01$, time: $F(9,99) = 8.68$; $P < 0.001$, interaction: $F(9,99) = 11.19$, $P < 0.001$) and citalopram (two-way repeated-measures ANOVA; treatment: $F(1,11) = 5.65$; $P < 0.05$, time: $F(9,99) = 18.53$; $P < 0.001$, interaction: $F(9,99) = 3.69$, $P < 0.001$) (Fig. 2).

4. Discussion

The present study showed that YM992 dose-dependently increased extracellular norepinephrine levels in the rat frontal cortex, exhibiting better efficacy than the selective serotonin reuptake inhibitors fluoxetine and citalopram, and similar efficacy to the serotonin and norepinephrine reuptake inhibitor venlafaxine.

Fluoxetine, which is a well-known selective serotonin reuptake inhibitor, produced a significant threefold increase in the norepinephrine level at a dose of 30 mg/kg. It has been reported that fluoxetine significantly increased (by about twofold) the norepinephrine level at a dose of 10 mg/kg, s.c. (Gobert et al., 1997) or by local infusion (5 μM) into the rat frontal cortex (Hughes and Stanford, 1996). The data from our study are consistent with these results. Fluoxetine at micromolar concentrations inhibits the reuptake of norepinephrine (Wong et al., 1995), and this brain concentration of fluoxetine is thought to occur after several systemic doses of 10 mg/kg (Dailey et al., 1992; Caccia et al., 1993). Thus, the increase of norepinephrine caused by fluoxetine may be due to reuptake inhibition of norepinephrine. The potency and selectivity of YM992 for inhibition of 5-HT and norepinephrine uptake into rat brain synaptosomes was similar to that of fluoxetine in vitro (Hatanaka et al., 1996). Additionally, the brain concentration of YM992 after oral administration of a 30 mg/kg dose reaches micromolar concentrations (Kawakami and Noguchi, unpublished data). Therefore, the increase of norepinephrine by YM992 also may be partly due to reuptake inhibition of norepinephrine in vivo.

Citalopram, another selective serotonin reuptake inhibitor, induced no significant increase in norepinephrine level at a dose of 30 mg/kg. It has been reported that local infusion of citalopram significantly increased norepinephrine level in the rat ventral tegmental area. However, the concentration of citalopram used was very high (100 μM) (Chen and Reith, 1994). Citalopram has very high selectivity for the 5-HT reuptake site over the norepinephrine reuptake site compared with fluoxetine (Wong et al., 1995). Citalopram significantly increases extracellular 5-HT levels in the rat frontal cortex at doses of 10–30 mg/kg (Hatanaka et al., in press). Thus, our result indicates that citalopram is more selective for the 5-HT system in vivo as well as in vitro.

Although venlafaxine has been described as a serotonin and norepinephrine reuptake inhibitor (Artigas, 1995), the potency and selectivity for 5-HT/norepinephrine system has been questioned (Béïque et al., 1998; Owens et al., 1997). In vitro binding studies, they have shown that venlafaxine binds to the 5-HT reuptake site with a moderate affinity and to the norepinephrine reuptake site with a very low affinity in rats, and the selectivity ratios (5-HT/norepinephrine) are 17-fold to 50-fold. However, in vivo electrophysiological paradigm, venlafaxine has been reported to have potent both 5-HT and norepinephrine reuptake inhibition (Béïque et al., 1999). Also, Dawson et al. (1999) have demonstrated that venlafaxine (3–50 mg/kg) dose-dependently increased extracellular norepinephrine levels in the rat frontal cortex, consistent with our results. Other serotonin and norepinephrine reuptake inhibitors, such as duloxetine and milnacipran, have been shown to increase extracellular norepinephrine levels in the rat frontal cortex (Kihara and Ikeda, 1995) or guinea pig hypothalamus (Moret and Briley, 1997). Thus, in the present study, the increase of extracellular norepinephrine level by venlafaxine is thought to be due to in vivo norepinephrine reuptake inhibition.

The efficacy and potency of YM992 in increasing the norepinephrine level was as same as that of venlafaxine, and was higher than that of fluoxetine and citalopram. As previously mentioned, the potency and selectivity of YM992 for inhibition of 5-HT and norepinephrine uptake into rat brain synaptosomes was similar to that of fluoxetine in vitro (Hatanaka et al., 1996). Thus, some other mechanism of YM992 action contributes the increase of the norepinephrine level. YM992 has 5-HT_{2A} receptor antagonism unlike fluoxetine and citalopram (Takeuchi et al., 1997). Therefore, a combination study of MDL100,907 (a selective 5-HT_{2A} receptor antagonist) and citalopram was performed to investigate the 5-HT_{2A} receptor antagonistic effect of YM992 on extracellular norepinephrine levels in vivo microdialysis.

Extracellular norepinephrine levels significantly increased due to the combined administration of MDL100,907 and citalopram compared with both saline and citalopram. Several studies have demonstrated that systemic 5-HT_{1A} receptor agonists increase norepinephrine release through postsynaptic 5-HT_{1A} receptors (Chen and Reith, 1995; Suzuki et al., 1995; Hajós-Korcsok et al., 1999). Also, it has been reported that 5-HT_{1A} receptor-mediated responses are potentiated by coadministration with 5-HT_{2A} receptor antagonists (Backus et al., 1990; Ashby et al., 1994). Therefore, the stimulation of increased 5-HT in the synaptic cleft by citalopram to 5-HT_{1A} receptors is potentiated by MDL100,907, resulting in increased extracellular norepinephrine levels. YM992 has both 5-HT reuptake inhibitory activity and 5-HT_{2A} receptor antagonisms (Hatanaka et al., 1996; Takeuchi et al., 1997). Thus, although further investigation is needed, this synergistic effect due to its dual action may be responsible for the increase of extracellular norepinephrine levels induced by YM992.

In summary, YM992 induces a significant increase in extracellular norepinephrine levels in the rat frontal cortex. The efficacy of this effect was greater than those of fluoxetine and citalopram, and the same as that of venlafaxine. Additionally, the synergistic effect due to the 5-HT reuptake inhibition and 5-HT_{2A} receptor antagonism caused by YM992 may be responsible for the increase of extracellular norepinephrine levels. Several reports have suggested a potential therapeutic benefit of enhancing neurotransmission mediated by both 5-HT and norepinephrine for depressed patients (Nelson et al., 1991; Seth et al., 1992; Leonard, 1999). YM992 enhances the neurotransmission of not only 5-HT system but also norepinephrine, and as such may have a preclinical profile different from that of a selective serotonin reuptake inhibitor.

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