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Effects of acute and chronic administration of venlafaxine and desipramine on extracellular monoamine levels in the mouse prefrontal cortex and striatum

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ABSTRACT

Prefrontal catecholamine neurotransmission plays a key role in the therapeutic actions of drugs for attention-deficit/hyperactivity disorder (ADHD). We have recently shown that serotonin/noradrenaline reuptake inhibitors and the noradrenaline reuptake inhibitor desipramine attenuated horizontal hyperactivity in spontaneously hypertensive rats, an animal model of ADHD, and that these drugs are potential pharmacotherapeutics for ADHD. In this study, we used *in vivo* microdialysis to study the effects of acute and chronic (once daily for 3 weeks) administration of the serotonin/noradrenaline reuptake inhibitor venlafaxine and the noradrenaline reuptake inhibitor desipramine on noradrenaline, dopamine, and serotonin levels, and the expression of the neuronal activity marker c-Fos in the mouse prefrontal cortex and striatum. Both acute and chronic venlafaxine administration increased prefrontal noradrenaline, dopamine, and serotonin levels and striatal noradrenaline and serotonin levels. Both acute and chronic desipramine administration increased prefrontal noradrenaline and dopamine levels and striatal noradrenaline levels, with chronic administration yielding stronger increase. Chronic desipramine did not affect striatal dopamine and serotonin levels. Both acute and chronic venlafaxine administration increased the expression of c-Fos in the prefrontal cortex, whereas chronic, but not acute, desipramine administration increased the expression of c-Fos in the prefrontal cortex. Both acute and chronic venlafaxine administration increased the striatal c-Fos expression to some degree, whereas desipramine administration did not. These results suggest that acute and chronic venlafaxine and chronic desipramine administration maximally activate the prefrontal adrenergic and dopaminergic systems without affecting striatal dopaminergic systems in mice.

1. Introduction

Serotonin/noradrenaline reuptake inhibitors (SNRIs) are widely used for the treatment of major depressive disorder. Several clinical trials have examined the effectiveness of the SNRIs venlafaxine (Olvera et al., 1996; Findling et al., 2007; Zarinara et al., 2010) and duloxetine (Mahmoudi-Gharaei et al., 2011) for treating the attention-deficit/hyperactivity disorder (ADHD) symptoms including inattention, oppositionality, and hyperactivity. We have recently found that the SNRIs duloxetine, venlafaxine, and milnacipran, the noradrenaline reuptake inhibitors (NRIs) reboxetine and desipramine, like the ADHD medications atomoxetine and methylphenidate, have reduced the horizontal locomotor activity and increased extracellular levels of noradrenaline and dopamine in the prefrontal cortex in spontaneously hypertensive rats, an animal model of ADHD (Umehara et al., 2013a). Moreover, we showed that the effects of methylphenidate and venlafaxine on hyperactivity were blocked by the α_2-adrenoceptor antagonist idazoxan, suggesting a role for this receptor in these anti-hyperactivity effects (Umehara et al., 2013b). These studies suggest that SNRIs and NRIs are potential pharmacotherapeutics for ADHD.

Since patients suffering from ADHD are medicated with ADHD medications for relatively long periods of time (Vitiello, 2001; Hechtman and Greenfield, 2003), it is important to study the effect of chronic administration of ADHD medications. Kihara and Ikeda (1995) reported in rats that chronic administration of duloxetine increased prefrontal serotonin, but not noradrenaline, to a greater

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extent than to a single dose of duloxetine administration alone. In contrast, Kitaichi et al. (2005) reported that the subchronic treatment of milnacipran, an SNRI, increased basal noradrenaline levels in the prefrontal cortex and enhanced milnacipran challenge-induced increase in prefrontal noradrenaline, but not serotonin, levels in rats. These studies suggest differences in the effects on monoamine levels of different SNRIs. Furthermore, Millan et al. (2001) reported that acute administration of venlafaxine increased prefrontal noradrenaline, dopamine, and serotonin levels in rats, whereas Dawson et al. (1999) showed that venlafaxine increased prefrontal noradrenaline, but not serotonin, levels in rats. It should be noted that the effects of venlafaxine on prefrontal noradrenaline and serotonin levels appear to differ between species (rats versus mice). In contrast to results in rats (Dawson et al., 1999; Millan et al., 2001; Umehara et al., 2013a), venlafaxine increased prefrontal serotonin levels to a greater extent than to noradrenaline levels in mice (David et al., 2003). Chronic administration of venlafaxine does not affect the basal levels of noradrenaline, dopamine, or serotonin in the rat prefrontal cortex (Gur et al., 1999; Millan et al., 2001), but it is not known whether chronic administration of venlafaxine affects venlafaxine challenge-induced increase in brain monoamine levels. In this study, we examined the effects of acute and chronic administration of the SNRI venlafaxine on extracellular noradrenaline, dopamine, and serotonin levels and the expression of the neuronal marker c-Fos in the mouse prefrontal cortex and striatum. The effects of chronic administration of the NRI desipramine on prefrontal monoamine levels and c-Fos expression were examined as a comparison in this study, because they have never previously been reported in the mouse.

2. Materials and methods

2.1. Animals and drugs

All animal studies were approved by the Animal Care and Use Committee of the Graduate School of Pharmaceutical Sciences, Osaka University. All experimental procedures were conducted in accordance with the guidelines of the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). Every effort was made to minimize animal suffering, and to reduce the number of animals used. 5-week-old male Institute of Cancer Research (ICR) mice were obtained from SHIMIZU Laboratory Supplies Co., Ltd. (Kyoto, Japan) and housed in cages (24 cm × 17 cm × 12 cm) in groups of five or six animals under controlled environmental conditions (22 ± 1 °C; 12:12-h light-dark cycle, lights on at 0800 h, food and water ad libitum) for 1 week before the use in experiments. The following drugs were used: venlafaxine hydrochloride (Tocris Bioscience, Bristol, UK) and desipramine hydrochloride (Sigma, St. Louis, MO, USA). Venlafaxine was dissolved in distilled water containing 5% glucose. Desipramine was dissolved in saline (0.9% solution of NaCl). All drugs were administered in a volume of 10 ml/kg intraperitoneally (i.p.). The doses used here were chosen on the basis of the dose level that attenuated enhanced locomotion and increased prefrontal noradrenaline and dopamine levels in spontaneously hypertensive rats (Umehara et al., 2013a). 6-week-old mice were injected once daily with vehicle (5% glucose solution), saline, venlafaxine (30 mg/kg), or desipramine (10 mg/kg) for 21 consecutive days. The microdialysis and c-Fos immunohistochemistry experiments were carried out 24 h after the last injection (day 22) at 9 weeks of age. The challenge doses of venlafaxine and desipramine were 30 and 10 mg/kg, respectively. All acute and chronic drug administration experiments were conducted at the same time, and different mice were used in each experiment.

2.2. In vivo microdialysis

One day before the last injection of vehicle, saline, venlafaxine, or desipramine, mice were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and stereotaxically implanted with a guide cannula (one site per animal) for a dialysis probe (Eicom Corp., Kyoto, Japan) in the prefrontal cortex (A +1.9 mm, L −0.5 mm, V −0.8 mm, from the bregma and skull) or striatum (A +0.4 mm, L −1.7 mm, V −2.5 mm) (Franklin and Paxinos, 1997) as previously described (Ago et al., 2007, 2011; Koda et al., 2010). The cannula was cemented in place with dental acrylic, and the animal was kept warm and allowed to recover from anesthesia. Postoperative analgesia was performed with a single injection of buprenorphine (0.1 mg/kg, i.p.) (Ago et al., 2007, 2011; Koda et al., 2010). The active probe membranes were 3 mm long in the prefrontal cortex and 2 mm long in the striatum. 2 days after the surgery, the probe was perfused with Ringer's solution (147.2 mM NaCl, 4.0 mM KCl, and 2.2 mM $CaCl_2$; pH 6.0; Fuso Pharmaceutical Industries, Ltd., Osaka, Japan) at a constant flow rate of 1 μl/min. A stabilization period of 3 h was established before the onset of each experiment. Microdialysis samples (20 μl) were collected every 20 min and injected immediately onto a high-performance liquid chromatography (HPLC) column for simultaneous assay of noradrenaline, dopamine, and serotonin. The concentrations of noradrenaline, dopamine and serotonin in brain microdialysates were determined by HPLC with an electrochemical detector (HTEC-500; Eicom Corp., Kyoto, Japan) (Ago et al., 2011; Hiramatsu et al., 2013; Koda et al., 2010). An Eicompak CAX column (2.0 mm i.d. × 200 mm; Eicom) was used, and the potential of the graphite electrode (Eicom) was set to +450 mV against an Ag/AgCl reference electrode. The mobile phase contained 100 mM ammonium acetate buffer (pH 6.0), 30 mM sodium sulfate, 134 μM EDTA, and 30% methanol. After the experiments, Evans Blue dye was microinjected through the cannula to histologically verify the position of the probe, and only data from animals with correct probe placements were used in the analysis.

2.3. c-Fos immunohistochemistry

c-Fos immunostaining was performed as described previously (Ago et al., 2011; Hiramatsu et al., 2013; Koda et al., 2010). After challenge injection of vehicle, saline, venlafaxine (30 mg/kg), or desipramine (10 mg/kg), mice were placed back into their home cages. Two hours after injection, mice were deeply anesthetized with pentobarbital and then perfused transcardially with saline, followed by a solution of 4% paraformaldehyde in phosphate-buffered saline (PBS). The brain was fixed with 4% paraformaldehyde in PBS over 1 day and then transferred to 20% sucrose in PBS for 2 days. Serial 20-μm-thick coronal sections containing the prefrontal cortex (+ 2.0 through +1.8 mm with respect to bregma) and striatum (+ 0.5 through +0.3 mm with respect to bregma) were cut using a cryostat microtome at −20 °C. Free-floating sections were preincubated for 30 min in 0.3% hydrogen peroxide in PBS to remove endogenous peroxidase activity. The sections were washed in PBS and then blocked in 1.5% goat serum in PBS for 20 min at room temperature. Thereafter, the sections were incubated with an anti-c-Fos rabbit polyclonal primary antibody (1:1000 dilution; sc-52, Santa Cruz Biotechnology, Santa Cruz, CA, USA) overnight at room temperature. Subsequently, the sections were washed in PBS and incubated with a secondary antibody solution containing biotinylated anti-rabbit IgG (1:500 dilution; Vector Laboratories, Burlingame, CA, USA) for 30 min at room temperature. The sections were then incubated with avidin–biotin–horseradish peroxidase complex (Vectastain ABC kit; Vector Laboratories) for 30 min at room temperature. Brown cytosolic products were obtained by reacting with 3,3′-diaminobenzidine (Histofine SAB-PO