European Journal of Pharmacology 647 (2010) 90–96

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Neuropharmacology and Analgesia

Sertraline increases extracellular levels not only of serotonin, but also of dopamine in the nucleus accumbens and striatum of rats

Yuji Kitaichi [a,b], Takeshi Inoue [b,*], Shin Nakagawa [b], Shuken Boku [b], Aya Kakuta [b], Takeshi Izumi [c], Tsukasa Koyama [b]

[a] Department of Molecular Stressphysiology, Max Planck Institute of Psychiatry, Kraeperinstr. 2-10, Munich, 80804, Germany
[b] Department of Psychiatry, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan
[c] Department of Neuropharmacology, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan

ARTICLE INFO

Article history:
Received 7 March 2010
Received in revised form 11 July 2010
Accepted 24 August 2010
Available online 9 September 2010

Keywords:
Sertraline
Fluvoxamine
Paroxetine
Dopamine
Serotonin
Noradrenaline

ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are a first-line treatment for depression. Recent reports in the literature describe differences in antidepressant effects among SSRIs. Although each SSRI apparently has different pharmacological actions aside from serotonin reuptake inhibition, the relations between antidepressant effects and unique pharmacological properties in respective SSRIs remain unclear. This study was designed to compare abilities of three systemically administered SSRIs to increase the extracellular levels of serotonin, dopamine, and noradrenaline acutely in three brain regions of male Sprague–Dawley rats. We examined effects of sertraline, fluvoxamine, and paroxetine on extracellular serotonin, dopamine, and noradrenaline levels in the medial prefrontal cortex, nucleus accumbens and striatum of rats using *in vivo* microdialysis. Dialysate samples were collected in sample vials every 20 min for 460 min. Extracellular serotonin, dopamine, and noradrenaline levels were determined using high-performance liquid chromatography with electrochemical detection. All SSRI administrations increased extracellular serotonin levels in all regions. Only sertraline administration increased extracellular dopamine concentrations in the nucleus accumbens and striatum. All SSRI administrations increased extracellular noradrenaline levels in the nucleus accumbens, although fluvoxamine was less effective. These results suggest that neurochemical differences account for the differences in clinical antidepressant effects among SSRIs.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) have antidepressant effects equal to those of tricyclic antidepressants. However, they have better tolerability and lower rates of treatment discontinuation than tricyclic antidepressants do (Montgomery and Kasper, 1995; Anderson, 2000). Most treatment guidelines for depression recommend SSRIs as a first-line treatment (Rush et al., 1998; Janicak et al., 2001; Kennedy et al., 2001). Several SSRIs have been developed and put on the market. Various SSRIs have common pharmacological characteristic of inhibiting serotonin reuptake on serotonin transporters. However, clinical reports describe that switching to another SSRI is effective for the treatment of depression, for which one SSRI is ineffective (Joffe et al., 1996; Thase et al., 1997, 2001). In STAR*D trial—which elucidated clinical efficacies of switching to sertraline, bupropion-SR, and venlafaxine-XR in nonresponders or patients intolerant to citalopram, an SSRI—the remission rate of switching to sertraline, an SSRI, was shown to be 17.6% by the 17-item Hamilton Depression Rating Scale. It was not different from those of other treatments (Rush et al., 2006). Recently, Ruhé et al. (2006) reviewed that response rates of switching to a second SSRI were about 50–70% after the first SSRI treatment had failed. In a meta-analysis study, Cipriani et al. (2009) reported that mirtazapine, escitalopram, venlafaxine, and sertraline exhibited greater effectiveness in unipolar depressive patients than duloxetine, fluoxetine, fluvoxamine, and paroxetine, which suggests that antidepressant effects of various SSRIs might differ despite their shared classification as antidepressants.

The respective SSRIs have different pharmacological actions aside from their serotonin reuptake inhibition (Carrasco and Sandner, 2005). These different actions might be related to differences in antidepressant effects of SSRIs. In receptor binding studies, some SSRIs display marked affinity for noradrenaline transporters, dopamine transporters, muscarinic receptors, and sigma receptors (Sánchez and Hyttel, 1999; Owens et al., 2001; Narita et al., 1996). Notably, sertraline is capable of dopamine reuptake inhibition; paroxetine shows the capability of noradrenaline reuptake inhibition in rats

* Corresponding author. Tel.: +81 11 706 5160; fax: +81 11 706 5081.
E-mail address: tinoue@med.hokudai.ac.jp (T. Inoue).

0014-2999/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2010.08.026

(Goodnick and Goldstein, 1998). However, the relations between antidepressant effects and unique pharmacological properties in respective SSRIs remain unclear.

The biological basis of depression is hypothesized as a lack of neurotransmitters such as serotonin and noradrenaline. The increases in extracellular serotonin and noradrenaline levels in the brain are thought to be related closely to the antidepressant effect. However, recent evidence suggests that dopamine might be related also to the pathogenesis and treatment of depression (Kapur and Mann, 1992; Papakostas, 2006). Several drugs that stimulate dopamine have antidepressant effects (Papakostas, 2006). Several lines of evidence suggest that the medial prefrontal cortex, nucleus accumbens and striatum—the projection regions of three main dopamine systems (Björklund and Dunnett, 2007)—are closely related to depression (Konarski et al., 2008; Nestler and Carlezon, 2006). Particularly, some reports have described that dopaminergic neurons in the nucleus accumbens are related to depression-like behaviors in animal models (Nestler and Carlezon, 2006) and anhedonia, which is a core symptom of major depressive disorder (Gorwood, 2008). The relations between dopaminergic neurons in the nucleus accumbens and depression have been receiving increasing attention.

To clarify differences in the antidepressant effects among SSRIs, we examined the effects of three SSRIs (sertraline, fluvoxamine, and paroxetine) not only on extracellular serotonin and noradrenaline levels, but also on extracellular dopamine levels in the medial prefrontal cortex, nucleus accumbens, and striatum of rats using *in vivo* microdialysis.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats weighing 270–400 g, obtained from the Shizuoka Laboratory Animal Center (Shizuoka, Japan), were housed in groups of four and maintained on a 12 h light–dark cycle (light phase: 06:30–18:30) in a temperature-controlled environment (22 ± 1 °C) with free access to food and water. Experiments began after a 10-day period of acclimatization. The Hokkaido University School of Medicine Animal Care and Use Committee approved all procedures, which complied with the Guide for the Care and Use of Laboratory Animals, Hokkaido University School of Medicine.

2.2. Drugs

Sertraline hydrochloride (a gift from Pfizer Inc., USA), fluvoxamine maleate (a gift from Solvay Pharmaceuticals S.A., The Netherlands), and paroxetine hydrochloride (a gift from GlaxoSmithKline plc., UK) were used. Sertraline hydrochloride, fluvoxamine maleate and paroxetine hydrochloride were dissolved, respectively, in distilled water adding 2 drops of Tween 80 to achieve a final concentration of 10 mg/ml, 15 mg/ml and 5 mg/ml. Those were injected intraperitoneally (i.p.) as a volume of 2 ml/kg. The dosages of sertraline hydrochloride (20 mg/kg), fluvoxamine maleate (30 mg/kg), and paroxetine hydrochloride (10 mg/kg) were chosen based on earlier *in vivo* and *ex vivo* studies explained below. From the inhibitory potency (ED_{50}) of serotonin reuptake of sertraline, fluvoxamine, and paroxetine in human (9.1, 18.6, and 5.0 mg/day *in vivo*, respectively) (Suhara et al., 2003; Meyer et al., 2004) and rats (3.1, 10.4, and 1.9 mg/kg *ex vivo*, respectively) (Koe et al., 1983; Thomas et al., 1987), sertraline 20 mg/kg, fluvoxamine 30 mg/kg and paroxetine 10 mg/kg in rats are estimated, respectively, as equivalent to 59 mg/day, 54 mg/day, and 26 mg/day in human (clinical daily doses of sertraline, fluvoxamine, and paroxetine are, respectively, 50–200 mg/day, 50–250 mg/kg, and 20–60 mg/kg) (Bauer et al., 2002).

2.3. Experimental procedures

All experiments were performed with nonrestrained, freely moving rats. Sertraline (20 mg/kg), fluvoxamine (30 mg/kg), paroxetine (10 mg/kg), and distilled water with Tween 80 were administered i.p. 120 min after the first dialysate samples were collected. In every experiment, eight rats (two rats for each treatment group) were examined, with all experiments subsequently repeated. Extracellular serotonin, dopamine, and noradrenaline levels were determined using high-performance liquid chromatography with electrochemical detection (HPLC-ECD) (Eicom Corp., Kyoto, Japan).

2.4. Microdialysis procedures

Experiments were performed according to a procedure described in a previous report (Kitaichi et al., 2008). Stereotaxically and under pentobarbital anesthesia (30 mg/kg i.p.), AG-4, AG-8, and AG-8 guide cannulae (Eicom Corp.) were implanted respectively into rats, leading to the surface of the medial prefrontal cortex, nucleus accumbens, and striatum at the following coordinates relative to the bregma from the stereotaxic atlas of Paxinos and Watson (1997): A + 3.2, ML + 0.8, DV + 1.0 mm; A + 1.7, ML + 0.8, + DV 6.0 mm; and A + 0.5, ML + 3.0, DV + 3.5 mm. Dialysis probes with 0.22 mm outer diameter (A-I-4-03, A-I-8-02, A-I-8-03; Eicom Corp.) were then inserted into the guide cannulae so that 3.0, 2.0, and 3.0 mm of the probes were exposed, respectively, to the medial prefrontal cortex, nucleus accumbens, and striatum tissues. Only one probe was implanted in each rat. Rats were housed individually after these operations. Experiments were performed in freely moving rats. On the next day, 24 h after surgery, perfusion was started using artificial cerebrospinal fluid (CSF) (145 mM NaCl, 3.0 mM KCl, 1.3 mM $CaCl_2$, and 1.0 mM $MgCl_2$) at a flow rate of 2 μl/min. Following initial perfusion for 2 h, dialysate samples were collected in sample vials containing 50 μl of 0.05 M acetic acid every 20 min for 460 min.

2.5. Analytical procedures for serotonin and dopamine

The HPLC system consisted of a liquid chromatograph pump (EP-300; Eicom Corp.), a degasser (DG-300; Eicom Corp.), a reverse-phase ODS column (Eicompak PP-ODS 30 4.6 mm; Eicom Corp.), an electrochemical detector (ECD-300; Eicom Corp.), and a data acquisition system (PowerChrom; AD Instruments Pty. Ltd., Sydney, Australia). For serotonin and dopamine analysis, 20 μl of dialysate was injected into the HPLC system that used a 0.1 M phosphate buffer (pH 6.0) mobile phase containing 1% (v/v) methanol, 50 mg/l Na_2EDTA, and 500 mg/l sodium L-decanesulfonate. Separations were conducted at 25 °C with a flow rate of 0.5 ml/min. In the electrochemical detector, an oxidation potential was set at 400 mV. Standard solutions for serotonin and dopamine were injected every working day, and the peak heights for the standards were used for comparison to determine the amounts of serotonin and dopamine in the samples.

2.6. Analytical procedures for noradrenaline

To determine noradrenaline concentrations, we used identical equipment to that used for the serotonin and dopamine analysis, with the exception that a different reverse-phase ODS column (Eicompak CA-5ODS 150 2.1 mm; Eicom Corp.) was used. For noradrenaline analysis, 30 μl of dialysate was injected into the HPLC system that used a 0.1 M phosphate buffer (pH 6.0) mobile phase containing 5% (v/v) methanol, 50 mg/l Na_2EDTA and 500 mg/l L-octanesulfonic acid. Separations were conducted at 25 °C with a flow rate of 0.23 ml/min. The electrochemical detector was set at an oxidation potential of 550 mV. Noradrenaline standard solutions were injected every working day and the peak heights for the standard were used for comparison to determine the amount of noradrenaline in the samples.