Effects of sertraline and citalopram given repeatedly on the responsiveness of 5-HT receptor subpopulations

J. Maj and E. Moryl
Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland

Accepted January 9, 1992

Summary. The effect of repeated treatment (5 and 10 mg/kg, po, twice daily, 14 days) with sertraline and citalopram (antidepressants which selectively inhibit the reuptake of 5-hydroxytryptamine (5-HT)) on the responsiveness of different 5-HT receptors to their agonists, was examined in rats and mice. Sertraline and citalopram (both at a dose 5 and 10 mg/kg) antagonized (the first one more potently) the hypothermia induced in mice by 8-OH-DPAT (a 5-HT$_{1A}$ agonist), but not the behavioural syndrome induced in rats by this substance. The m-chlorophenylpiperazine-induced hypothermia in mice (a 5-HT$_{1B}$ effect) was increased by sertraline and citalopram (only in a dose of 10 mg/kg). Both antidepressants, given repeatedly (as well acutely) attenuated exploratory hypoactivity induced in rats by m-chlorophenylpiperazine (a 5-HT$_{1C}$ effect). L-5-HTP-induced head twitches in mice (5-HT$_2$ effect) were antagonized dose-dependently by both repeated sertraline and citalopram. Both antidepressants (citalopram only in higher dose) reduced the fenfluramine-induced hyperthermia in rats (5-HT$_2$ effect).

The results indicate that sertraline and citalopram given repeatedly decrease the responsiveness of 5-HT$_{1A}$ (presynaptic) and 5-HT$_2$ receptors but increase the responsiveness of 5-HT$_{1B}$ receptors to respective agonists.

Keywords: Antidepressants, 5-HT receptor subpopulations, mice, rats.

Introduction

Sertraline [1S,4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphtylamine] is a selective inhibitor of serotonin uptake (Koe et al., 1983), with a clinical antidepressant action that can be compared to that produced by tricyclic antidepressant drugs (Reimherr et al., 1988). Sertraline shows no or only very weak affinity for dopamine, $\alpha$-adrenergic, muscarinic, histamine, benzodiazepine, GABA and opioid receptors (Koe et al., 1983; Mol et al., 1990).

Like other antidepressant drugs, sertraline administered repeatedly reduces
the cyclic AMP generation by the noradrenaline receptor-coupled adenylate cyclase in the rat limbic forebrain slices, and decreases the number of \( \beta \)-adrenoceptors in the cerebral cortex of rats (Koe et al., 1987; Byerley et al., 1987). It also diminishes the reactivity of 5-HT\(_2\) receptors in the rat cerebral cortex (Sanders-Bush et al., 1989).

In recent years it has been demonstrated that within the central nervous system exist three main types of serotonin receptors: 5-HT\(_1\), 5-HT\(_2\) and 5-HT\(_3\). Furthermore, serotonin receptors of the 5-HT\(_1\) type are divided into four sub-populations: 5-HT\(_{1A}\), 5-HT\(_{1B}\), 5-HT\(_{1C}\) and 5-HT\(_{1D}\) (Peroutka, 1985; Bradley et al., 1986; Fozard, 1987). Sertraline shows low affinity for 5-HT\(_2\) receptors, but none for the other subpopulations of 5-HT receptors (Mol et al., 1990).

As is well known, antidepressants show a clinical effect after repeated administration only. Therefore we wanted to find out whether sertraline administered repeatedly modifies the reactivity of various types of 5-HT receptors. To this end we examined the effect of sertraline on the responsiveness to agonists of these receptors, having taken into consideration the effects characteristic of them:

- 5-HT\(_{1A}\) receptors – behavioural syndrome in rats and hypothermia in mice both induced by 8-OH-DPAT (Tricklebank et al., 1985; Goodwin and Green, 1985)
- 5-HT\(_{1B}\) receptors – hypothermia induced by m-CPP in mice (Maj et al., 1988; Kennett and Curzon, 1988)
- 5-HT\(_{1C}\) receptors – locomotor hypoactivity induced by m-CPP (Kennett and Curzon, 1988; Kłodzińska et al., 1989)
- 5-HT\(_2\) receptors – head twitches induced by 5-HTP in rats (Arnt et al., 1984); hyperthermia induced by fenfluramine at high ambient temperature in rats (Sulpizio et al., 1978; Pawłowski, 1981).

For the sake of comparison we concurrently carried out studies with citalopram another clinically active selective inhibitor of 5-HT uptake, devoid of any receptor activity (Hyttel et al., 1982; Mol et al., 1990).

**Materials and methods**

**Animals**

The experiments were carried out on Wistar male rats weighing 250–270 g and Albino Swiss male mice weighing 25–30 g. During the whole time of the experiment the animals were kept at room temperature, 20–21 °C, in the natural day-night cycle and had free access to food and water.

**Substances used**

Citalopram hydrobromide (Lundbeck), m-chlorophenylpiperazine dihydrochloride (m-CPP; synthesized by Dr. J. Boksa, Institute of Pharmacology, Polish Academy of Sciences), fenfluramine hydrochloride (Les Laboratoires Servier), (±)-8-hydroxy-2(di-n-propylamino)-tetralin hydrobromide (8-OH-DPAT; Research Biochemicals Inc.), L-5-hydroxytryptophan (L-5-HTP, Sigma), pargyline hydrochloride (Research Biochemicals Inc.), sertraline hydrochloride (Pfizer).