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Effect of the selective 5-HT$_7$ receptor antagonist SB 269970 in animal models of anxiety and depression

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Abstract

The aim of the present study was to examine the effect of the selective 5-HT$_7$ receptor antagonist SB 269970 (0.25–20 mg/kg) in the behavioral tests commonly used for predicting anxiolytic- and antidepressant-like activity. Diazepam and imipramine were used as standard drugs. SB 269970 (in one medium dose of 0.5 or 1 mg/kg) exerted a specific antianxiety-like effect in the Vogel drinking test in rats, in the elevated plus-maze test in rats and in the four-plate test in mice. Moreover, SB 269970 (in one medium dose of 5 or 10 mg/kg) showed antidepressant-like activity in the forced swimming and the tail suspension tests in mice. At the same time, the tested compound at doses of 1–20 mg/kg did not change the spontaneous locomotor activity of mice. The potential anxiolytic and antidepressant effects produced by SB 269970 were weaker than those of the reference drugs employed. It is noteworthy that the active doses of SB 269970 were devoid of any visible motor side-effects. In conclusion, the results of our studies indicate that 5-HT$_7$ receptor antagonists may play a role in the therapy of both anxiety and depression.

Keywords: 5-HT$_7$ receptor antagonist; SB 269970; Anxiolytic-like activity; Antidepressant-like activity; Mouse; Rat

1. Introduction

It has been well documented that the serotonergic (5-HT) system of the brain is involved in mental illnesses such as anxiety and depression (Blier and de Montigny, 1999; Mann, 1999). The neurotransmitter 5-HT mediates its effects by interacting with seven distinct families of the receptors located pre- and/or postsynaptically (Barnes and Sharp, 1999; Hoyer et al., 2002). However, the role of different 5-HT receptor subtypes in the pathophysiology and treatment of mood diseases has still to be clarified. Recently it was suggested that 5-HT$_7$ receptors (whose biological functions are poorly understood) may play some role in the control of circadian rhythms, sleep, cognitive processes, pain and migraine, as well as in the pathophysiology of many psychiatric disorders including depression and anxiety (Hedlund and Sutcliffe, 2004; Thomas and Hagan, 2004).

The 5-HT$_7$ receptor has been cloned from human, rat, mouse and guinea-pig cDNA libraries and it shows a distinct pharmacological profile, different from that of other 5-HT receptors; successively, four isoforms of the 5-HT$_7$ receptor, all of them being positively coupled to adenylyl cyclase (presumably via G_s) and having analogous pharmacology, have been identified (Barnes and Sharp, 1999). The distribution of 5-HT$_7$ receptor mRNA, the immunolabelling and radioligand binding studies are consistent across species, the highest 5-HT$_7$ receptor densities being found in the thalamus, hypothalamus, hippocampus, frontal cortex and amygdala (Hedlund and Sutcliffe, 2004; Thomas and Hagan, 2004). Neurochemical studies indicate that at least in the hypothalamus the 5-HT$_7$ receptor is located postsynaptically to 5-HT nerve terminals (Clemett et al., 1999; Belenky and Pickard, 2001). Electrophysiological studies show that activation of 5-HT$_7$ receptors increases neuronal excitability in a number of brain regions (Tokarski et al., 2003; Thomas and Hagan, 2004).

Although 5-HT$_7$ receptor selective agonists have not been reported to date, recent development of selective 5-HT$_7$ receptor antagonists and the possibility of using 5-HT$_7$ antisense

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oligonucleotides, as well as the availability of a 5-HT_7 receptor knockout mouse strain make it possible to better test the effects produced by 5-HT_7 receptor manipulation in different experimental models. However, conclusive evidence for the 5-HT_7 receptor function in vivo is still insufficient. It was demonstrated that the 5-HT_7 receptor was involved in the hypothermia induced by the non-selective 5-HT_7 agonist 5-carboxytryptamine (5-CT) in guinea-pigs (Hagan et al., 2000) and mice (Guscott et al., 2003); furthermore, it was shown that 5-HT and 5-CT failed to induce hypothermia in 5-HT_7 receptor knockout mice (Guscott et al., 2003; Hedlund et al., 2003). Additionally, 5-HT_7 knockout mice showed antidepressant-like activity in the Porsolt forced swimming test (Guscott et al., 2005; Hedlund et al., 2005) and in the tail suspension test (Hedlund et al., 2005) as their immobility was reduced compared to wild-type controls. Administration of the 5-HT_7 receptor antagonist (*R*)-3,*N*-dimethyl-*N*-[1-methyl-3-(4-methyl-piperidine-1-yl)propyl]benzene-sulfonamide (SB 258719) to wild-type mice caused only a small, non-significant decrease in immobility time in the forced swimming test, measured in the light phase; in the dark phase, however, it induced an effect similar to that observed in knockout mice (Guscott et al., 2005). Recently Hedlund et al. (2005) demonstrated that the 5-HT_7 receptor antagonist (2*R*)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]-pyrrolidine (SB 269970) exhibited antidepressant-like activity (in the light phase) in both the mouse forced swimming and the tail suspension tests. It is noteworthy that only one dose of either 5-HT_7 antagonist was examined (Guscott et al., 2005; Hedlund et al., 2005). In view of the fact that acute restraint stress up-regulates 5-HT_7 receptor mRNA in the hippocampus (Yau et al., 2001), and that chronic treatment with antidepressants down-regulates 5-HT_7 receptor binding in rat hypothalamus (Sleight et al., 1995; Mullins et al., 1999), the above-quoted results suggest some role of 5-HT_7 receptors in depression.

A few papers are available so far on the effect of 5-HT_7 receptor manipulation in animal models of anxiety. Treatment with 5-HT_7 antisense oligonucleotides had no significant effect on the percentage of either open entries or the time spent in the open arms in the elevated plus-maze in rats (Clemett et al., 1998). In the same model, both wild-type and 5-HT_7 receptor knockout mice showed no difference in the time spent exploring the open arms or in the number of entries into the open arms of the maze (Guscott et al., 2005). Similarly, innate anxiety-like behavior, determined by the light/dark transfer test, was not altered in 5-HT_7 knockout mice (Roberts et al., 2004a). No data have been available so far on the effect of selective 5-HT_7 receptor antagonists in animal models of anxiety.

Therefore the aim of the present study was to investigate the role of SB 269970, a selective 5-HT_7 receptor antagonist (Lovell et al., 2000), administered in a wide range of doses (30 min prior to the test), in behavioral models commonly used to predict anxiolytic- and antidepressant-like activities. We used different experimental procedures to determine the potential anxiolytic-like activity of SB 269970: two conflict procedures (the conflict drinking test in rats and the four-plate test in mice) and one exploratory model (the elevated plus-maze test in rats), since parameters recorded in anxiety models may reflect different emotional states (File, 1992; Belzung and Le Pape, 1994; Rodgers, 1997). The forced swimming test and the tail suspension test in mice were used to evaluate antidepressant-like activity. We applied diazepam and imipramine as reference drugs. Moreover, the effect of SB 269970 on the spontaneous locomotor activity of mice was tested. The time schedule of SB 269970 administration was based on pharmacokinetic results described by Hagan et al. (2000). In fact, the latter authors showed that SB 269970 at a dose of 3 mg/kg i.p. reached the highest concentration (87 nM) in rat brain at 30 min post dose time point which would be predicted to attain a substantial occupancy of 5-HT_7 receptors. The doses of SB 269970 (0.25–20 mg/kg) used were based on the literature data obtained in in vivo studies with mice and rats (Guscott et al., 2003; Hedlund et al., 2004, 2005), as well as on the findings of a pilot experiment.

SB 269970 was shown to be a potent ligand of human cloned (Lovell et al., 2000) and guinea-pig (Hagan et al., 2000) 5-HT_7 receptors ($pK_i = 8.9$ and 8.7, respectively). It had excellent selectivity (>250-fold) over 5-HT_1, 5-HT_2, 5-HT_4, 5-HT_6, α_1, D_2 and D_3 receptors, apart from 5-HT_{5A} ones (50-fold). Furthermore, in a commercial screening package, SB 269970 was found to be over 100-fold selective over a total of 50 receptors, enzymes or ion channels (Lovell et al., 2000). Pharmacokinetic studies demonstrated that SB 269970 had good central nervous system penetration (Hagan et al., 2000). SB 269970 showed features of a 5-HT_7 receptor antagonist. Indeed, it inhibited the activity of adenylyl cyclase, stimulated by the non-selective 5-HT_7 receptor agonist 5-CT (Lovell et al., 2000) or by 5-HT (Mahé et al., 2004). Also in electrophysiological assays, SB 269970 blocked the excitability evoked by 5-CT in the CA_1 (Tokarski et al., 2003) and CA_3 (Gill et al., 2002) regions of rat hippocampal slices, as well as the 5-HT-induced inward current in neurons of the anterodorsal nucleus of rat thalamus (Chapin and Andrade, 2001). Furthermore, in vivo functional studies indicated that SB 269970 antagonized the 5-CT-evoked hypothermia in guinea-pigs (Hagan et al., 2000) and mice (Guscott et al., 2003).

2. Materials and methods

2.1. Subjects

The experiments were performed on male Wistar rats (250–300 g), male Albino Swiss mice (24–28 g), and male C57BL/6J mice (23–24 g). The animals were kept in groups of eight (rats) or twenty (mice) to a cage (60 × 38 × 20 cm) at a temperature of 20 ± 1 °C, and had free access to food (standard laboratory pellets) and water. All the experimental procedures were approved by the Local Bioethics Commission at the Institute of Pharmacology, Polish Academy of Sciences in Kraków.

2.2. Experimental procedures

All the experiments were conducted in the light phase, on a natural light cycle (from March to June), between 09:00 and 14:00 h. The rats were handled