Anxiety-like effects induced by acute fluoxetine, sertraline or m-CPP treatment are reversed by pretreatment with the 5-HT₂C receptor antagonist SB-242084 but not the 5-HT₁A receptor antagonist WAY-100635

Gyorgy Bagdy, Marton Graf, Zsuzsanna E. Anheuer, Edit A. Modos and Sandor Kantor

Laboratory of Neurochemistry and Experimental Medicine, and Department of Neurology, Faculty of Health Sciences, Semmelweis University, National Institute of Psychiatry and Neurology, Budapest, Huvosvolgyi ut 116, H-1021, Hungary

Abstract

The possible role of 5-HT₁A and 5-HT₂C receptors in the anxiety induced by fear, acute treatment with SSRI antidepressants or the 5-HT receptor agonist m-CPP were tested in the social interaction anxiety test in male Sprague–Dawley rats. Fluoxetine (2.5–10 mg/kg, i.p.), sertraline (15 mg/kg, i.p.) and m-CPP (0.5–2.0 mg/kg, i.p.) all had an anxiogenic-like profile (decrease in time of total social interaction and increase in self-grooming compared to vehicle) under low-light, familiar arena test conditions. All these effects were reversed by pretreatment with the highly subtype-selective 5-HT₂C receptor antagonist, SB-242084 at doses of either 0.05 or 0.2 mg/kg, i.p. In contrast, the selective 5-HT₁A receptor antagonist WAY-100635 (0.05 and 0.2 mg/kg, s.c.) failed to reverse SSRI-induced decrease in time of total social interaction, further, it augmented self-grooming response. SB-242084 (0.2 mg/kg) and WAY-100635 (0.05 and 0.2 mg/kg) reversed hypo-locomotion caused by the SSRI antidepressants. SB-242084, tested alone against vehicle under high-light, unfamiliar arena test conditions associated with fear, caused significant anxiolysis at 0.2 mg/kg and higher doses. These results suggest that increased anxiety in rodents, and possibly, also in humans (e.g. agitation or jitteriness after SSRIs and panic after m-CPP), caused by acute administration of SSRI antidepressants or m-CPP, are mediated by activation of 5-HT₂C receptors. Blockade of 5-HT₁A autoreceptors may exacerbate certain acute adverse effects of SSRI antidepressants. Both 5-HT₁A and 5-HT₂C receptors are involved in the SSRI-induced decrease in locomotor activity. In addition, our studies confirm data that subtype-selective 5-HT₂C receptor antagonists have strong anxiolytic actions.

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Introduction

SSRI antidepressants are therapeutically active in several anxiety disorders (Nutt and Glue, 1989; Papp, 1999; Westenberg and Den Boer, 1993). Clinically, the effect of these agents is characterized by delayed onset with the likelihood of initial exacerbation, e.g. agitation or jitteriness, especially in panic disorder patients, and that may cause a decrease in treatment acceptance (Nutt and Glue, 1989; Papp, 1999; Pohl et al., 1988; Westenberg and Den Boer, 1993). In animal models of anxiety SSRI antidepressants are, in general, characterized by an anxiogenic-like profile after acute administration (Griebel, 1995; Handley et al., 1993). A transient anxiogenic-like effect of fluoxetine in the social interaction test that disappeared after chronic treatment was described by our group in earlier studies (To and Bagdy 1999; To et al., 1999). Pharmacological characterization of the effects of the 5-HT agonist m-chlorophenylpiperazine (m-CPP) led to the hypothesis that activation of 5-HT₂C receptors may mediate anxiety in humans and rodents although pharmacological tools used in these studies were not able to differentiate between 5-HT₁A and 5-HT₂C receptors.
Figure 1. Effects of different doses of (a) fluoxetine (2.5–10.0 mg/kg, i.p.) and (b) m-CPP (0.5–2.0 mg/kg, i.p.) in the social interaction anxiety test under low-light, familiar arena conditions. Significant effects (p < 0.05) compared to vehicle are denoted by *.

(Bagdy, 1996, 1998; Bagdy et al., 1992; Bristow et al., 2000; Kennett et al., 1989; Murphy et al., 1991). Furthermore, the role of either 5-HT, namely 5-HT\textsubscript{1A}, 5-HT\textsubscript{2A}, 5-HT\textsubscript{2B}, and 5-HT\textsubscript{2C} receptors, or other mechanisms, e.g. noradrenergic and neuropeptide systems have been suggested in acute and/or chronic effects of SSRI antidepressants (Bristow et al., 2000; Dekeyne et al., 2000; Handley et al., 1993; Kennett et al., 1994; Lerer et al., 1999; Matto et al., 1996; Quested et al., 1997; Szabo et al., 2000; To and Bagdy 1999; To et al., 1999), but only one study used a 5-HT\textsubscript{2C} receptor subtype-selective antagonist (Dekeyne et al., 2000). To study the possible role of 5-HT\textsubscript{1A} and 5-HT\textsubscript{2C} receptors in acute SSRI administration-induced anxiety, WAY-100635, a subtype-selective 5-HT\textsubscript{1A} receptor antagonist (Fletcher et al., 1996; Griebel, 1999) and SB-242084, a subtype-selective 5-HT\textsubscript{2C} receptor antagonist (Kennett et al., 1997) were used as a pretreatment before administration of SSRI antidepressants. In addition to social interaction another measure of anxiety, self-grooming, and the anxiolytic-like actions of SB-242084 per se were also tested.

Method

All procedures used in this study were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals. The protocol of the study was approved by the local Ethical Committee. Male Sprague–
Dawley rats (240–330 g, Crl: CD\textsuperscript{BR}, Charles River, Hungary), were used in the studies. The animals (4 per cage) were kept under standard conditions, with standard food (CRLT/AM, Charles River, Hungary) and water freely available. The temperature was 21 ± 1 °C, the 12 h light–dark cycle started at 06:00 hours.

The social interaction test was performed as described previously (To and Bagdy, 1999). Rats were housed in a room adjacent to the testing room at least for 2 wk before the tests. The animals were randomly assigned to treatments. In the low-light (5 lx), familiar arena conditions animals were individually pre-exposed to the test box and the injections three times on days preceding the test. In the high-light (300 lx), unfamiliar arena conditions animals were not habituated to the test box. Rats were tested for social interaction with an unknown test partner that did not differ by more than 15 g in weight. At the end of each test the box was thoroughly wiped with detergent and dried to remove odours. The animals were tested in a random order between 09:00 and 13:00 hours in an...
adjacent room for 7.5 min. The evenly illuminated box (60 × 60 × 40 cm), was marked in 10 cm compartments by lines on the floor.

The behaviour of animals was recorded on videotape. It was scored later by a person unaware of the drug treatment as described earlier (To and Bagdy, 1999). The following behaviours were included in total social interaction: sniffing partner, anogenital sniffing, peaceful following, grooming partner, crawling under, climbing over, chasing, aggressive grooming, dominant posture, submissive posture, biting, boxing, kicking, pushing, wrestling. Rearing, crossing of lines and self-grooming were also scored.

SB-242084 (6-chloro-5-methyl-1-[(2-[2-methylpyrid-3-yloxy]pyrid-5-yl)carbamoyl]indoline dihydrochloride, Sigma-Aldrich, Budapest, Hungary), sertraline hydrochloride and fluoxetine hydrochloride (both kindly donated by EGIS Pharmaceuticals Ltd, Budapest, Hungary) were dissolved in 10% solution of 2-hydroxypropyl-β-cyclodextrin (Research Biochemicals International, Natick, MA, USA). WAY-100635 maleate (N-[2-[(4-[2-methoxyphenyl]-1-piperazinyl)ethyl]-N-2-pyridinyl cyclohexanecarboxamide maleate, Research Biochemicals International) and m-CPP (meta-chlorophenylpiperazine hydrochloride, Research Biochemicals International), were dissolved in physiological saline. WAY-100635 was administered s.c., all other drugs i.p., in a volume of 1 ml/kg. SB-242084 was administered 5 min before the SSRI antidepressants, WAY-100635 20 min before the SSRI antidepressants or m-CPP, which was administered 20 min before the test.

The data were analysed using one- or two-way ANOVA followed by Tukey–Kramer and Kruskal–Wallis tests followed by the Mann–Whitney rank sum test (Super ANOVA and StatViewSE + Graph, Abacus Concepts, Berkeley, CA, USA). Each treatment group consisted of 10–14 animals that is, 5–7 pairs of rats. Each rat was tested only once. Data on the figures and in the text are expressed as mean ± S.E.M.

Results
Fluoxetine (Figure 1a; 2.5–10 mg/kg, i.p.) and m-CPP (Figure 1b; 0.5–2.0 mg/kg, i.p.) caused dose-dependent decrease in time of total social interaction [F(3,42) = 7.68, p < 0.001 and F(3,36) = 11.01, p < 0.001 for fluoxetine and m-CPP, respectively], increase in self-grooming and decrease in line crossings (Figure 1a, b). Minimal effective doses for time of total social interaction were 5.0 and 0.5 mg/kg, for fluoxetine and m-CPP, respectively. At these doses fluoxetine, but not m-CPP, caused a significant decrease in the number of line crossings. The dose–response curves for self-grooming were clearly different, namely, a biphasic response was found for m-CPP but not for fluoxetine.

Pretreatment with SB-242084 (0.05 and 0.2 mg/kg, i.p.) significantly reversed effects of fluoxetine (Figure 2a) and sertraline (Figure 3) on time of total social interaction [F(2,68) = 6.14, p < 0.01 and F(2,60) = 7.19, p < 0.01 for pretreatment × treatment interaction for fluoxetine and sertraline, respectively]. Effect of m-CPP (0.5 mg/kg,
i.p.) on time of total social interaction was also significantly reversed by pretreatment with SB-242084 [Figure 4; pretreatment × treatment interaction, $F(1,36) = 12.64$, $p < 0.01$]. SB-242084 also reversed other effects, thus, self-grooming and decrease in line crossings induced by fluoxetine (Figure 2a) and sertraline (Figure 3) and self-grooming induced by m-CPP (Figure 4), but the dose–response effects of SB-242084 on the various parameters were different. Anxiety-related effects, like social interaction and self-grooming responses, were reversed by 0.05 mg/kg of SB-242084, but a higher dose was needed for the reversal of hypolocomotion.

Pretreatment with WAY-100635 (Figure 2b; 0.05 and 0.2 mg/kg, s.c.) failed to reverse the effects of fluoxetine on time of total social interaction or self-grooming [pretreatment × treatment interactions, $F(2,68) = 0.71$, $p = 0.49$ and $F(2,68) = 0.37$, $p = 0.69$, for the two parameters, respectively]. Even more, WAY-100635 alone slightly increased self-grooming, and, as a pretreatment, it augmented self-grooming response caused by fluoxetine [Figure 2b; pretreatment effect, $F(2,68) = 3.30$, $p < 0.05$]. In contrast, it reversed the effect of fluoxetine on line crossings very efficiently [Figure 2b; pretreatment × treatment interaction, $F(2,68) = 5.81$, $p < 0.005$. WAY-
1000635 alone did not have any effect on time of total social interaction or line crossings (Figure 2b).

Possible anxiolytic effects of SB-242084 alone (Figure 5; 0.05–0.5 mg/kg, i.p.) were tested in separate experiments under high-light, unfamiliar arena conditions. SB-242084 had significant effects on time of total social interaction and self-grooming. The minimal effective dose for both social interaction and self-grooming was 0.2 mg/kg. Locomotor activity was not significantly altered, although a strong trend, a 41% increase was found in the number of line crossings at 0.5 mg/kg SB-242084 compared to vehicle (Figure 5).

Discussion

Anxiogenic-like effect of fluoxetine (Bristow et al., 2000; Griebel, 1995; To and Bagdy 1999; To et al., 1999) and citalopram (Dekeyne et al., 2000) in the social interaction test was described in earlier studies. Acute administration of these compounds caused significant decrease in the time of total social interaction and fluoxetine caused also a decrease in the number of line crossings, and an increase in time of self-grooming (G. Bagdy, Z. E. Anheuer and S. Kantor, personal communication; Bristow et al., 2000; Dekeyne et al., 2000; To and Bagdy 1999; To et al., 1999). Under low-light, familiar arena conditions the surrounding is comfortable for the animals, and thus, basal anxiety is low, so anxiogenic compounds, including, e.g. corticotropin-releasing hormone (CRH) or m-CPP efficiently alter parameters like social interaction (File and Hyde, 1978; Guy and Gardner, 1985; Kantor et al., 2000; Kennett et al., 1998; Kennett et al., 1989; To et al., 1999) or self-grooming (Dunn and File, 1987; Kantor et al., 2000; To et al., 1999). The number of line crossings, a measure of locomotor activity, is decreased by some, e.g. cholecystokinin (CCK) or higher doses of m-CPP, but not all compounds that increase anxiety (File and Hyde, 1978; Guy and Gardner, 1985; Kennett et al., 1989; To and Bagdy 1999). Anxiogenic action of SSRI antidepressants is also supported by data that fluoxetine caused significant c-fos-like immunoreactivity in the central nucleus of amygdala, and paraventricular nucleus and increased ACTH and corticosterone secretion (Gibbs and Vale, 1983; Overstreet et al., 2000).

The 5-HT2 receptor family consists of three subtypes, namely, the 5-HT2A, the 5-HT2B and the 5-HT2C (formerly 5-HT1C) receptor, and several antagonists, like ritanserin has similar affinity for all three subtypes (Bonhaus et al., 1997). SB-242084, the first subtype-selective 5-HT2C receptor antagonist, has very high affinity (pK_i = 9.0) for the cloned human 5-HT2C receptor and has over 100- and 158-fold selectivity over the cloned human 5-HT2A and 5-HT2B receptors (Kennett et al., 1997). Furthermore, it has at least 100-fold selectivity for this receptor over all other receptors tested (Kennett et al., 1997). The affinities of m-CPP for these subtypes are 5-HT2B > 5-HT2C > 5-HT2A (Bonhaus et al., 1997; Murphy et al., 1991), but functional characterization on recombinant human receptors showed that, compared to 5-HT, m-CPP has 65, 24 and 22% relative efficacies on 5-HT2C, 5-HT2B and 5-HT2A receptors, respectively (Porter et al., 1999). SB-242084 reversed the actions of SSRI antidepressants and m-CPP very efficiently in our study; in the dose of 0.05 mg/kg it reversed decrease of social interaction and increase in self-grooming caused by all compounds tested. These data, together with a recently published study of Dekeyne et al. (2000), where SB-242084 effectively reversed anxiogenic action of citalopram, strongly suggest that 5-HT2C receptors mediate the anxiogenic actions of SSRI antidepressants caused by increased synaptic 5-HT concentration.

SB-242084 alone failed to alter anxiety-related behaviours, namely, time of total social interaction and self-grooming, but pretreatment with this compound significantly reversed these effects of SSRI antidepressants and m-CPP, and in addition, hypolocomotion caused by fluoxetine and sertraline under low-light, familiar arena conditions. Because of the receptor-binding profile of this compound, these data suggest that SSRIs and m-CPP mediate anxiogenic responses by activation of 5-HT2C receptors. However, other explanations might also be possible, thus first, the effect of the compounds on the locomotion may confound the interpretation of the data, secondly, the anxiolytic effect of SB-242084 per se may lead to a false conclusion. To discuss the first question, our data show that decreases in locomotion caused by fluoxetine are, in some cases parallel to its effect on total social interaction, that might suggest that the decrease in social interaction may be caused by the effects on locomotion. However, these effects showed clear dissociation in the case of m-CPP and citalopram, thus, m-CPP failed to decrease locomotion at the doses of 0.5 mg/kg, but it caused significant decrease on time of total social interaction. A similar dissociation was found in the case of citalopram (G. Bagdy, Z. E. Anheuer and S. Kantor, personal communication; Dekeyne et al., 2000). The efficacies of SB-242084 on SSRI-induced social interaction and locomotion were also dissociated, namely, anxiety-like effects were reversed by 0.05 mg/kg SB-242084, while higher doses of the compound were needed for the reversal of hypolocomotion (see Results). In addition, WAY-100635 completely reversed hypolocomotion caused by fluoxetine but it failed to reverse the decrease in social interaction. Thus, the decrease and reversal in social interaction cannot be considered as a secondary
effect of locomotion. Furthermore, in addition to social interaction, we used another measure of anxiety, namely self-grooming. This stereotypic behaviour is increased by aversive stimuli and anxiogenic compounds like CRH or m-CPP measured either in the social interaction test or in single cages (Bagdy et al. 1992; Dunn and File, 1987; Kantor et al., 2000; To et al., 1999). Conversely, it is attenuated by anxiolytic compounds under high anxiety conditions. Under certain conditions, this parameter is a more sensitive and less variable measure than time of total social interaction (Dunn and File, 1987; Kantor et al., 2000; To et al., 1999). For example, WAY-100635 pretreatment enhanced self-grooming response but not social interaction caused by fluoxetine in this study, and the minimal effective dose for fluoxetine was lower for self-grooming than for social interaction (see Results). It is likely that augmentation of this stereotypical behaviour by WAY-100635 is caused by the enhancement of the effect of fluoxetine on extracellular 5-HT, as was shown in microdialysis studies (Malagie et al., 1996). It has been suggested that m-CPP-induced self-grooming is mediated by 5-HT\textsubscript{2c} (formerly 5-HT\textsubscript{1c}) receptors, although subtype-selective 5-HT\textsubscript{2c} receptor antagonists have not been used, and neuropeptides synthesized by the hypothalamic paraventricular nucleus (Bagdy and Makara, 1995; Bagdy et al., 1992). m-CPP causes significant increase of this response at low doses where absolutely no locomotion effect can be observed (Bagdy et al., 1992). Dose-dependence of self-grooming and locomotion response of m-CPP were also dissociated in this study. Thus, anxiety-like responses of SSRIs and m-CPP, and anxiolytic effects of SB-242084 cannot be explained on the basis of activity changes. A similar conclusion was drawn also by Bristow et al. (2000) who measured anxiety and locomotion after fluoxetine treatment.

To address the second question, namely, that the anxiolytic effect of SB-242084 per se may lead to a false conclusion, we performed an experiment with SB-242084 at high-light, unfamiliar arena conditions. Although at low-light, familiar arena conditions, where SB-242084 reversed the effects of m-CPP and the SSRIs, the effects of SB-242084 alone were not significant, additional experiments were necessary, because under low-light, familiar arena conditions anxiolytic compounds per se show weak effects, but their anxiolytic-like effects are enhanced under conditions where the animals sense more fear (File and Hyde, 1978; Guy and Gardner, 1985; Kantor et al., 2000). Under high light, unfamiliar arena conditions SB-242084 alone caused dose-dependent anxiolytic-like activity. Significant effect was found, however, only at 0.2 and 0.5 but not at 0.05 mg/kg. This finding is similar to that described by Kennett et al. (1997), despite the fact that we used a 2-fold shorter observation period, similar to that also used by other groups (File and Hyde, 1978; Guy and Gardner, 1985). In contrast, SB-242084 completely reversed social interaction and self-grooming effects of the SSRIs and m-CPP at the dose of 0.05 mg/kg, thus, this latter effect can not be explained by the anxiolytic action of this compound.

The anxiogenic-like effects of fluoxetine were abolished after chronic treatment (Bristow et al., 2000; To and Bagdy, 1999; To et al., 1999). This finding is in parallel with the clinical and experimental data obtained with chronic SSRI treatment (Handley et al., 1993; Lightowler et al., 1994; Nutt and Glue, 1989; Westenberg and Den Boer, 1993). There is a higher activation of postsynaptic receptors by the excess extracellular 5-HT produced by chronic, compared to acute, SSRI treatment (Artigas, 1993; Bel and Artigas 1993; Invernizzi et al., 1994). Furthermore, disappearance of fluoxetine-induced acute anxiety is accelerated by additional subchronic administration of WAY-100635 (Bristow et al., 2000). The antagonists used for characterization of receptors that mediate the effect of fluoxetine used in the work of Bristow et al. (2000) could not differentiate between 5-HT\textsubscript{2b} and 5-HT\textsubscript{2c} receptors. By the use of the subtype-selective SB-242084, our data show that fluoxetine-induced anxiety is mediated by 5-HT\textsubscript{2c} receptors. Thus, the mechanism of action of delayed attenuation of fluoxetine-induced anxiety possibly includes desensitization of 5-HT\textsubscript{2c} receptors. This is supported also by the clinical data that m-CPP exacerbates symptoms before, but not after chronic treatment with clomipramine (Zohar et al., 1988), and m-CPP-induced neuroendocrine and hyperthermic responses are attenuated after chronic citalopram treatment (Quested et al., 1997). In rats, m-CPP-induced hypolocomotion was attenuated after chronic SSRI treatment (Kennett et al., 1994). The role of 5-HT\textsubscript{2b} or 5-HT\textsubscript{2c} receptors have been suggested in these responses of m-CPP at least in rats (Aulakh et al., 1992; Bagdy, 1996, 1998; Bagdy et al., 1989, 1992; Bristow et al., 2000; Lucki et al., 1989), and, in addition, effectiveness of SB-242084 in self-grooming and social interaction responses in this study provide further evidence for the involvement of 5-HT\textsubscript{2c} receptors in m-CPP-induced anxiety, thus, these data support the view that desensitization of 5-HT\textsubscript{2c} receptors is caused by chronic SSRI treatment.

Fluoxetine has modest affinity for 5-HT\textsubscript{2c} receptors (Bonhaus et al., 1997; Jenck et al., 1994; Palvimaki et al., 1996). In an in vivo functional model for 5-HT\textsubscript{2c} receptors, however, it failed to have any significant 5-HT\textsubscript{2c} receptor antagonist action (Jenck et al., 1994). This might be explained by its 5-HT-mimetic, reuptake inhibiting effect (Jenck et al., 1994). Indeed, its affinity for the 5-HT uptake site is much higher than its affinity for the 5-HT\textsubscript{2c} receptor.
The dose of fluoxetine used in this study was based on the dose–response curves (Figure 1a), the dose of sertraline on the ratio of clinical doses and affinities for the 5-HT uptake sites of these compounds (Kasper et al., 1994; Palvimaki et al., 1996).

An increase in serotonergic function produced by SSRI antidepressants underlies their clinical effectiveness in anxiety disorders and major depression (Artigas, 1993; Mongeau et al., 1997). Interestingly, acute increase in 5-HT neurotransmission usually increases fear and anxiety-like behaviour (Griebel, 1995), although it may have also an opposite effect depending on the type of the test (Hetem et al., 1996). Increased anxiety-like behaviour was described in Fawn-Hooded rats, a strain with inherited impairment of 5-HT storage and uptake (Kantor et al., 2001). Graeff et al. (1996) suggested that at least three serotonergic pathways are involved in the regulation of anxiety, thus, separate pathways facilitate conditioned fear, inhibit inborn fight–flight reactions and promote resistance to chronic, unavoidable stress. SSRIs and m-CPP increase anxiety in the social interaction test or in the elevated plus maze in rats (Griebel, 1995; Handley et al., 1993; Kantor et al., 2000; Kennett et al., 1989; To and Bagdy, 1999). Anxiogenic effects of m-CPP in clinical studies are also well known (Arato and Bagdy, 1998; Kahn and Wetzler, 1991; Murphy et al., 1991), and anxiety related transient effects of SSRI antidepressants, like agitation or jitteriness have been described (Nutt and Glue, 1989; Papp, 1999; Pohl et al., 1988; Westenberg and Den Boer, 1993). Stress hormones, like ACTH and cortisol or corticosterone are also released after acute administration of these compounds in both humans and rodents (Bagdy et al., 1989; Murphy et al., 1991). However, ritanserin, a non-subtype-selective 5-HT<sub>2</sub> receptor antagonist that reverses some effects of m-CPP, may also increase or decrease anxiety (Bagdy 1998; Guimares et al., 1997; Kahn and Wetzler, 1991). Furthermore, activation of the 5-HT<sub>2c</sub> receptor efficiently alters release of other neurotransmitters like noradrenaline, adrenaline, dopamine or glutamate (Bagdy et al., 1989; Di Matteo et al., 1999; Marcoli et al., 1998; Millan et al., 1998), and neuromodulators like CRH, oxytocin and vasopressin (Bagdy et al., 1989, 1992; Calogero et al., 1989). Some of these neurotransmitters systems may modulate 5-HT<sub>2</sub> receptor-mediated changes. The role of CCK in SSR1-induced anxiety-like effects is supported by the data that citalopram-induced decrease in exploratory behaviour is reversed by a CCK<sub>1</sub> receptor antagonist (Matto et al., 1996). A progressive attenuation of the firing activity of locus coeruleus noradrenergic neurons by sustained SSRI treatment has been shown in electrophysiological studies (Szabo et al., 2000). Furthermore, CCK or CRH-induced anxiety is also decreased after chronic SSRI treatment (To and Bagdy, 1999; To et al., 1999; Van Megen et al., 1997). Thus, different anatomical pathways and other neurotransmitter–neuropeptide systems and receptors may mediate or modulate 5-HT<sub>2c</sub> receptor-induced changes.

In conclusion, our studies provide evidence that acute anxiogenic effects of SSRI antidepressants are reversed by pretreatment with low doses of the subtype-selective 5-HT<sub>2c</sub> receptor antagonist SB-242084, and thus, they suggest that anxiety-related side-effects of acute SSRI treatment, like agitation or jitteriness, may be mediated by 5-HT<sub>2c</sub> receptors.

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