5-HT_{2C} RECEPTOR ACTIVATION INDUCES GROOMING BEHAVIOUR IN RATS: POSSIBLE CORRELATIONS WITH OBSESSIVE-COMPULSIVE DISORDER

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5-HT2C RECEPTOR AKTIVÁCIÓJA SZTEREOTIP MOSAKODÁST VÁLT KI PATKÁNYBAN: LEHETSÉGES KAPCSOLAT A KÉNYSZERBETEGSÉGGEL

A kényszerbetegség experimentális állatmodelljeiben megfigyelt fokozott sztereotip mosakodást (self-grooming) egyes kutatók az emberi kényszeres cselekvések (pl. rituális kézmosás) megfelelőjének tekintik. Korábbi farmakológiai kísérletek alapján feltételezhető volt bizonyos szerotonin$_2$ (5-HT_2) receptor altípusok szerepe a self-grooming szabályozásában. Kényszerbetegekkel folytatott klinikai vizsgálatokban egyes 5-HT_2 receptor agonisták fokozták a betegség tüneteit. Jelen vizsgálatunk azt igazolja, hogy a központi idegrendszeri szerotonin$_{2C}$ (5-HT_{2C}) receptorok szelektív aktiválása fokozza a patkányokban a sztereotip mosakodást. Eredményeink alátámasztják azt a feltételezést, hogy az 5-HT_{2C} recepor aktivációja felelős a fent említett klinikai vizsgálatokban tapasztalt kényszeres tünetek fokozódásáért. Kísérleteink segíthetnek megérteni a kényszerbetegségben szerepet játszó szerotonerg mechanizmusokat, és hozzájárulhatnak e pszichiátriai zavar hatékonyabb gyógyításához.

KULCSSZAVAK: sztereotip mosakodás, kényszerbetegség, szerotonin, 5-HT_{2C} receptor, 5-HT_{2B} receptor

SUMMARY

Excessive self-grooming in animal models of obsessive-compulsive disorder (OCD) is regarded as an equivalent of compulsive behaviour in OCD patients. Previous studies have suggested a key modulatory role of certain serotonin$_2$ receptor subtypes both in grooming behaviour and OCD. Certain 5-HT_2 receptor agonists were reported to exacerbate symptoms in OCD patients. Here we report that activation of the serotonin$_{2C}$ (5-HT_{2C}) receptor induces self-grooming in rats, which result supports the hypothesis that selective stimulation of central 5-HT_{2C} receptors exacerbates symptoms also in OCD. The present findings may help to understand serotonergic mechanisms underlying psychiatric disorders of the obsessive-compulsive spectrum and may progress the development of novel anxiolytic and anti-OCD medications.

KEYWORDS: self-grooming, obsessive-compulsive disorder, serotonin, 5-HT_{2C} receptor, 5-HT_{2B} receptor

Introduction

Self-grooming – rubbing, scratching, preening, licking, nibbling, stroking and otherwise lavishing attention on the body surface – is a common part of any rodent's daily routine; it helps to keep the animal's fur clean, to keep cool and probably to help wounds heal. Self-grooming in rodents is stereotypically sequenced and naturally occurs after arousal, novelty or stress.

Under laboratory conditions (e.g. the social interaction test or the elevated plus-maze test) anxiety-provoking situations or anxiogenic compounds (e.g. cholecystokinin or corticotropin-releasing hormone) induce self-grooming in rats [41,42]. The 5-$HT_{2C/2B}$ receptor agonist *m*-CPP is also known to produce dose-dependent self-grooming [4]. *m*-CPP-induced self-grooming can be attenuated by mianserin, LY-53857 and metergoline which are antagonists with high affinity for the 5-HT_{2C} and the 5-HT_{2B} receptor site [4].

Excessive grooming in animals is regarded similar to the symptoms of obsessive-compulsive disorder (OCD) and other obsessive-compulsive (OC)-spectrum disorders in humans including trichotillomania [20,21,36,39]. A growing body of evidence about OCD, including neuropharmacologic studies, links this classic psychiatric syndrome to 5-HT_2 receptors. The behavioural and neuroendocrine effects of the 5-$HT_{2B/2C}$ agonist m-CPP were studied in patients with OCD and healthy controls. Twelve patients and 20 controls were given a single dose of 0.5 mg/kg of *m*-CPP, administered orally under double-blind, placebo-controlled, random-assignment conditions. Following *m*-CPP, but not following placebo, patients with OCD experienced a transient but marked exacerbation of obsessive-compulsive symptoms [44]. Some indication that this symptom exacerbation did not simply represent a nonspecific response to the anxiogenic effects of *m*-CPP comes from studies using anxiogenic agents in OCD patients. Unlike patients with panic disorder in whom panic attacks occured when exposed to yohimbine, lactate or carbon dioxide, patients with OCD did not manifest significantly greater anxiety or panic attacks with these other agents, nor did they manifest any exacerbation of OCD symptoms [35]. Pretreatment with orally administered metergoline, a non-selective 5-HT_{2C} antagonist, obliterated the increases in *m*-CPP-induced exacerbation of OCD symptoms [37].

The 5-HT_{2C} and the 5-HT_{2B} receptor are members of the 5-HT_2 receptor family. It is generally accepted that 5-HT_2 receptors are coupled to G-proteins and activate phospholipase C and release calcium via phosphatidylinositol hydrolysis in the brain and other tissues [12,23]. 5-HT_{2C} receptors are most likely involved in several neurobehavioural processes including anxiety, stereotype movements, and penile erection [4,25,30,43]. Activation of this receptor subtype efficiently alters the release of other neurotransmitters like noradrenaline, adrenaline, dopamine, glutamate or gamma-amino butyric acid (GABA) [13,14,33] and the release of neuropeptides like corticotropin releasing hormone (CRH), oxytocin and vasopressin [3,4,10]. However, there are little available data on the functional effects of central 5-HT_{2B} receptors. Studies on the actions of the 5-HT_{2B} receptor agonist BW 723C86 indicate a role for the 5-HT_{2B} receptor in anxiety. BW 723C86 has been reported to have an anxiolytic-like profile in the rat social interaction test after subcutaneous administration or after direct injection into the medial amygdala, which contains detectable amounts of 5-HT_{2B} receptor-like immunoreactivity [15,16, 28]. In a recent experiment BW 723C86 was reported to reduce the frequency of grooming bouts of rats in observation cages [27].

As mentioned before, a restraining aspect of previous inspections on role of the various 5-HT receptors involved in grooming behaviour has been the lack of subtype-selective agents [17,23, 31]. The purpose of our study was to explore the role of 5-HT_{2C} and 5-HT_{2B} receptors in self-grooming in rats observed in single cages, using the selective 5-HT_{2C} antagonist SB-242084 [8,9, 31] the selective 5-HT_{2B} antagonist SB-215505 [29] and the 5-$HT_{2C/2B}$ agonist *m*-CPP [23,25].

Materials and Methods

All procedures used were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals. The protocols were approved by the local Ethical Committee. Male Sprague-Dawley rats (280-340 g, Crl:CD^RBR, Charles River, Hungary), were used in the studies. The animals (4 per cage) were kept under standard condition, with standard food and water freely available. The temperature was 21±1°C, the 12 hour light-dark cycle started at 06.00 hour. In these experiments animals were placed to single observation cages immediately after *m*-CPP or vehicle injections. Display of grooming behaviour was scored every 15 s by a trained person, beginning with the injection of the compounds [4]. Vibration, face and head washing, body grooming, scratching, paw licking, head shaking and genital grooming were included as components of grooming behaviour. Animals were scored for 30 min, thus, the maximum of the available score during the observation period was 120.

1-[3-chlorophenyl]piperazine hydrochloride (*m*-CPP) was dissolved in physiological saline. SB-242084 (6-chloro-5-methyl-1-[2-(2-methyl-pyridyl-3-oxy) pyrid-5-yl carbamoyl] indoline) was dissolved in a solution of 25 mM citric acid and 10% hydroxypropyl-β-cyclodextrin and neutralised by diluted NaOH. SB-215505 (6-chloro-5-methyl-1-[5-quinolylcarbamyl]indoline) was dissolved in a solution of 25 mM citric acid and 40% hydroxypropyl-β-cyclodextrin and neutralised by diluted NaOH. All drugs were injected

intraperitoneally in a volume of 1 ml/kg. SB-242084 and SB-215505 were administered 20 min before the agonist as a pretreatment.

The data were analyzed using Kruskal-Wallis test followed by Mann-Whitney rank sum test. Groups consisted of 6-8 animals. Each rat was tested only once. Data in the figures and in the text are expressed as mean±SEM.

Results

Effect of different doses of the 5-HT$_{2C/2B}$ receptor agonist *m*-CPP (0.1-2.5 mg/kg, i.p.) on self-grooming is shown in Figure 1. *m*-CPP caused dose-dependent increase of self-grooming ($H_{5,41}$= 14.81, P<0.02). The effect showed a bell-shaped, bimodal dose-response curve. Maximal effect was observed at the dose of 0.6 mg/kg of *m*-CPP.

Effect of the selective 5-HT2C receptor antagonist SB-242084 (20 min pretreatment) on m-CPP-induced self-grooming is shown in Figure 2. SB-242084 (0.5 mg/kg, i.p.) inhibited *m*-CPP-induced (0.6 mg/kg) self-grooming ($H_{3,27}$=13.98, P<0.02). SB-242084 alone did not alter self-grooming.

Effect of the selective 5-HT$_{2B}$ antagonist SB-215505 (20 min pretreatment) on *m*-CPP-induced self-grooming is shown in Figure 3. Pretreatment with SB-215505 (1 mg/kg, i.p.) did not change the effect of *m*-CPP (0.6 mg/kg) on self-grooming ($H_{3,27}$=11.47, P<0.01). SB-215505 alone did not induce self-grooming.

Discussion

As reported in previous studies, in our present work we provide further evidence that the 5-HT$_{2C/2B}$ receptor agonist *m*-CPP dose-dependently produces self-grooming [4]. The affinities of the 5-HT$_2$ receptor agonist *m*-CPP for receptor subtypes are 5-HT$_{2B}$>5-HT$_{2C}$>5-HT$_{2A}$ [7,35], but functional characterization on recombinant human receptors showed that, compared to 5-HT, *m*-CPP has 65%, 24% and 22% relative efficacies on 5-HT$_{2C}$, 5-HT$_{2B}$ and 5-HT$_{2A}$ receptors, respectively [38]. Pharmacological studies with different antagonists revealed that most effects of *m*-CPP on the central nervous system are mediated by 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors rather than by 5-HT$_{2A}$ receptors [4,6,30]. This is true also for anxiety-type effects and self-grooming, behaviours that are evident at low, 0.3-0.6 mg/kg doses of *m*-CPP [4,26,30].

Figure 1.
Effect of different doses of m-CPP compared to vehicle control (saline) on self-grooming

Each column represents the mean±SEM of 6-8 animals. *= Significant effect of *m*-CPP compared to vehicle, Mann-Whitney rank sum test, P<0.05. Results of the Kruskal-Wallis tests are given in the text.

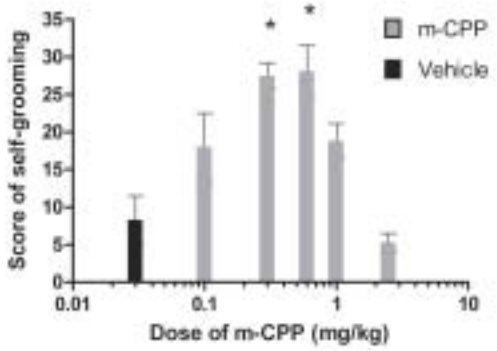
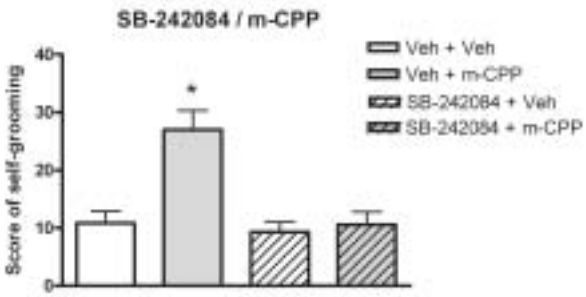


Figure 2.
Effect of SB-242084 pretreatment (0.5 mg/kg, i.p.) compared to vehicle (10% hydroxypropyl- -cyclodextrin) on m-CPP-induced (0.6mg/kg, i.p., vehicle: saline) self-grooming

Each column represents the mean±SEM of 6-8 animals. Veh= appropriate vehicle control, *= Significant effect compared to vehicle/vehicle, Mann-Whitney rank sum test, P<0.05. Results of the Kruskal-Wallis tests are given in the text.

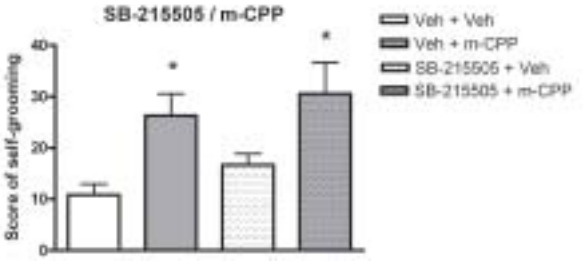


Although compounds used in previous studies could not clearly differentiate between 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors, data about low concentration and expression of 5-HT$_{2B}$ receptors in the central nervous system and the opposite for the 5-HT$_{2C}$ receptor supported the role of the latter [1,22,24,32,34]. However, additional studies confirmed the expression of 5-HT$_{2B}$ receptors in the rat brain [15] and activation of the 5-HT$_{2B}$ receptor was reported to inhibit grooming behaviour [27].

In our study we demonstrate that pretreatment with low doses of the selective 5-HT$_{2C}$ receptor antagonist SB-242084 effectively reverses actions of *m*-CPP, and pretreatment with SB-215505, a

Figure 3. Effect of SB-215505 pretreatment (1 mg/kg, i.p.) compared to vehicle (40% hydroxypropyl- -cyclodextrin) on m-CPP-induced (0.6 mg/kg, i.p., vehicle: saline) self-grooming

Each column represents the mean±SEM of 6-8 animals. Veh= appropriate vehicle control, *= Significant effect compared to the appropriate control, Mann-Whitney rank sum test, P<0.05. Results of the Kruskal-Wallis tests are given in the text.



selective 5-HT_{2B} receptor antagonist does not alter m-CPP induced grooming. These results confirm that 5-HT_{2C} and not 5-HT_{2B} receptor activation is responsible for *m*-CPP-induced self-grooming. Our results are in line with recent studies, which reported that the 5-HT_{2B} agonist BW 723C86 did not produce any of the behavioural effects associated with administration of *m*-CPP [27]. Furthermore, the selective 5-HT_{2B} antagonists, LY 202146 and LY 266097, failed to block *m*-CPP-induced hypolocomotion in mice [18,27]. Thus, there is compelling evidence that predominantly 5-HT_{2C} and not 5-HT_{2A} or 5-HT_{2B} receptors mediate the in vivo effects of m-CPP in the CNS. Therefore we can conclude that *m*-CPP is a useful tool for testing 5-HT2C receptor function in vivo.

We can assume that 5-HT_{2C} receptors also play a role in obsessive-compulsive disorder in humans. *m*-CPP was reported to exacerbate symptoms of OCD [44] and pretreatment with metergoline, an antagonist with very high affinity to 5-HT_{2C} receptors obliterated this effect [37]. Thus, it seems plausible that activation of 5-HT_{2C} receptors is responsible for *m*-CPP-induced exacerbation of OCD symptoms.

Recent studies have found further intriguing similarities between excessive self-grooming in animals and compulsive symptoms in OCD patients [20,21,36,39]. Previous studies report, that *m*-CPP-induced self-grooming is in whole, or in part mediated via the hypothalamic paraventricular nucleus [2,5]. The role of the paraventricular nucleus has been postulated also in OCD [40]. Furthermore, the localization of 5-HT_{2C} receptors show a remarkable association with the so-called "OCD-circuit". Studies on the immunohistochemical distribution of 5-HT_{2C} receptors in the rat brain [11] show that 5-HT_{2C} receptors are highly represented in the orbitofrontal cortex, the anterior cingulate cortex, and the caudate nucleus. These structures are referred to as the "OCD-circuit", because they show abnormal metabolic activity in OCD patients [19]. Therefore, we can truly expect that our findings on self-grooming may also be relevant to clarifying serotonergic mechanisms involved in OCD. Furthermore, the future development of drugs selectively targeting 5-HT_{2C} receptors could offer new treatment possibilities for OC-spectrum disorders.

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REFERENCES

1. Abramowski, D., Rigo, M., Duc, D., Hoyer, D. and Staufenbiel, M., Localization of the 5-hydroxytryptamine2C receptor protein in human and rat brain using specific antisera. Neuropharmacology, 34 (1995) 1635-45.
2. Bagdy, G., Serotonin, anxiety, and stress hormones. Focus on 5-HT receptor subtypes, species and gender differences.PG - 357-63, Ann N Y Acad Sci, 851 (1998).
3. Bagdy, G., Calogero, A.E., Murphy, D.L. and Szemeredi, K., Serotonin agonists cause parallel activation of the sympathoadrenomedullary system and the hypothalamo-pituitary-adrenocortical axis in conscious rats, Endocrinology, 125 (1989) 2664-9.
4. Bagdy, G., Kalogeras, K.T. and Szemeredi, K., Effect of 5-HT1C and 5-HT2 receptor stimulation on excessive grooming, penile erection and plasma oxytocin concentrations, Eur J Pharmacol, 229 (1992) 9-14.
5. Bagdy, G. and Makara, G.B., Paraventricular nucleus controls 5-HT2C receptor-mediated corticosterone and prolactin but not oxytocin and penile erection responses, Eur J Pharmacol, 275 (1995) 301-5.
6. Bagdy, G., Szemeredi, K., Kanyicska, B. and Murphy, D.L., Different serotonin receptors mediate blood pressure, heart rate, plasma catecholamine and prolactin responses to m-chlorophenylpiperazine in conscious rats, J

Pharmacol Exp Ther, 250 (1989) 72-8.
7. Barnes, N.M. and Sharp, T., A review of central 5-HT receptors and their function, Neuropharmacology, 38 (1999) 1083-152.
8. Bromidge, S.M., Dabbs, S., Davies, D.T., Davies, S., Duckworth, D.M., Forbes, I.T., Gaster, L.M., Ham, P., Jones, G.E., King, F.D., Mulholland, K.R., Saunders, D.V., Wyman, P.A., Blaney, F.E., Clarke, S.E., Blackburn, T.P., Holland, V., Kennett, G.A., Lightowler, S., Middlemiss, D.N., Trail, B., Riley, G.J. and Wood, M.D., Biarylcarbamoylindolines are novel and selective 5-HT(2C) receptor inverse agonists: identification of 5-methyl-1-[[2-[(2-methyl-3-pyridyl) oxy]-5-pyridyl]carbamoyl]-6-trifluoromethylindoline (SB-243213) as a potential antidepressasnt/anxiolytic agent, J Med Chem, 43 (2000) 1123-34.
9. Bromidge, S.M., Dabbs, S., Davies, S., Duckworth, D.M., Forbes, I.T., Jones, G.E., Jones, J., King, F.D., Saunders, D.V., Blackburn, T.P., Holland, V., Kennett, G.A., Lightowler, S., Middlemiss, D.N., Riley, G.J., Trail, B. and Wood, M.D., 1-[2-[(Heteroaryloxy)heteroaryl]carbamoyl]indolines: novel and selective 5-HT2C receptor inverse agonists with potential as antidepressant/anxiolytic agents, Bioorg Med Chem Lett, 10 (2000) 1863-6.
10. Calogero, A.E., Bernardini, R., Margioris, A.N., Bagdy, G., Gallucci, W.T., Munson, P.J., Tamarkin, L., Tomai, T.P., Brady, L., Gold, P.W. and et al., Effects of serotonergic agonists and antagonists on corticotropin-releasing hormone secretion by explanted rat hypothalami, Peptides, 10 (1989) 189-200.
11. Clemett, D.A., Punhani, T., Duxon, M.S., Blackburn, T.P. and Fone, K.C., Immunohistochemical localisation of the 5-HT2C receptor protein in the rat CNS, Neuropharmacology, 39 (2000) 123-32.
12. Conn, P.J., Sanders-Bush, E., Hoffman, B.J. and Hartig, P.R., A unique serotonin receptor in choroid plexus is linked to phosphatidylinositol turnover, Proc Natl Acad Sci U S A, 83 (1986) 4086-8.
13. Di Matteo, V., Di Giovanni, G., Di Mascio, M. and Esposito, E., SB 242084, a selective serotonin2C receptor antagonist, increases dopaminergic transmission in the mesolimbic system, Neuropharmacology, 38 (1999) 1195-205.
14. Di Matteo, V., Di Giovanni, G., Di Mascio, M. and Esposito, E., Selective blockade of serotonin2C/2B receptors enhances dopamine release in the rat nucleus accumbens, Neuropharmacology, 37 (1998) 265-72.
15. Duxon, M.S., Flanigan, T.P., Reavley, A.C., Baxter, G.S., Blackburn, T.P. and Fone, K.C., Evidence for expression of the 5-hydroxytryptamine-2B receptor protein in the rat central nervous system, Neuroscience, 76 (1997) 323-9.
16. Duxon, M.S., Kennett, G.A., Lightowler, S., Blackburn, T.P. and Fone, K.C., Activation of 5-HT2B receptors in the medial amygdala causes anxiolysis in the social interaction test in the rat, Neuropharmacology, 36 (1997) 601-8.
17. Forbes, I.T., Jones, G.E., Murphy, O.E., Holland, V. and Baxter, G.S., N-(1-methyl-5-indolyl)-N'-(3-methyl-5-isothiazolyl)urea: a novel, high-affinity 5-HT2B receptor antagonist, J Med Chem, 38 (1995) 855-7.
18. Gleason, S.D., Lucaites, V.L., Shannon, H.E., Nelson, D.L. and Leander, J.D., m-CPP hypolocomotion is selectively antagonized by compounds with high affinity for 5-HT(2C) receptors but not 5-HT(2A) or 5-HT(2B) receptors, Behav Pharmacol, 12 (2001) 613-20.
19. Graybiel, A.M. and Rauch, S.L., Toward a neurobiology of obsessive-compulsive disorder, Neuron, 28 (2000) 343-7.
20. Graybiel, A.M. and Saka, E., A genetic basis for obsessive grooming, Neuron, 33 (2002) 1-2.
21. Greer, J.M. and Capecchi, M.R., Hoxb8 is required for normal grooming behavior in mice, Neuron, 33 (2002) 23-34.
22. Hoffman, B.J. and Mezey, E., Distribution of serotonin 5-HT1C receptor mRNA in adult rat brain, FEBS Lett, 247 (1989) 453-62.
23. Hoyer, D., Clarke, D.E., Fozard, J.R., Hartig, P.R., Martin, G.R., Mylecharane, E.J., Saxena, P.R. and Humphrey, P.P., International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin), Pharmacol Rev, 46 (1994) 157-203.
24. Hoyer, D., Pazos, A., Probst, A. and Palacios, J.M., Serotonin receptors in the human brain. II. Characterization and autoradiographic localization of 5-HT1C and 5-HT2 recognition sites, Brain Res, 376 (1986) 97-107.
25. Kahn, R.S. and Wetzler, S., m-chlorophenylpiperazine as a probe of serotonin function, Biol Psychiatry, 30 (1991) 1139-66.
26. Kantor, S., Anheuer, Z.E. and Bagdy, G., High social anxiety and low aggression in Fawn-Hooded rats, Physiol Behav, 71 (2000) 551-7.
27. Kennett, G.A., Ainsworth, K., Trail, B. and Blackburn, T.P., BW 723C86, a 5-HT2B receptor agonist, causes hyperphagia and reduced grooming in rats, Neuropharmacology, 36 (1997) 233-9.
28. Kennett, G.A., Bright, F., Trail, B., Baxter, G.S. and Blackburn, T.P., Effects of the 5-HT2B receptor agonist, BW 723C86, on three rat models of anxiety, Br J Pharmacol, 117 (1996) 1443-8.
29. Kennett, G.A., Trail, B., Riley, G., Bickerdike, M.J., Ranson, J., Forbes, and I.T., P., G.W., Baxter, G.S., Hunter, A.J., SB 215505, a selective 5-HT2B receptor antagonist in rats, Society of Neuroscience Abstracts, 24 (1998) 541.12.
30. Kennett, G.A., Whitton, P., Shah, K. and Curzon, G., Anxiogenic-like effects of mCPP and TFMPP in animal models are opposed by 5-HT1C receptor antagonists, Eur J Pharmacol, 164 (1989) 445-54.
31. Kennett, G.A., Wood, M.D., Bright, F., Trail, B., Riley, G., Holland, V., Avenell, K.Y., Stean, T., Upton, N., Bromidge, S., Forbes, I.T., Brown, A.M., Middlemiss, D.N. and Blackburn, T.P., SB 242084, a selective and brain penetrant 5-HT2C receptor antagonist, Neuropharmacology, 36 (1997) 609-20.
32. Kursar, J.D., Nelson, D.L., Wainscott, D.B. and Baez, M., Molecular cloning, functional expression, and mRNA tissue distribution of the human 5-hydroxytryptamine2B receptor, Mol Pharmacol, 46 (1994) 227-34.
33. Millan, M.J., Dekeyne, A. and Gobert, A., Serotonin (5-HT)2C receptors tonically inhibit dopamine (DA) and noradrenaline (NA), but not 5-HT, release in the frontal cortex in vivo, Neuropharmacology, 37 (1998) 953-5.
34. Molineaux, S.M., Jessell, T.M., Axel, R. and Julius, D., 5-HT1c receptor is a prominent serotonin receptor subtype in the central nervous system, Proc Natl Acad Sci U S A, 86 (1989) 6793-7.

35. Murphy, D.L., Lesch, K.P., Aulakh, C.S. and Pigott, T.A., Serotonin-selective arylpiperazines with neuroendocrine, behavioral, temperature, and cardiovascular effects in humans, Pharmacol Rev, 43 (1991) 527-52.
36. Nordstrom, E.J. and Burton, F.H., A transgenic model of comorbid Tourette's syndrome and obsessive-compulsive disorder circuitry, Mol Psychiatry, 7 (2002) 617-25, 524.
37. Pigott, T.A., Zohar, J., Hill, J.L., Bernstein, S.E., Grover, G.N., Zohar-Kadouch, R.C. and Murphy, D.L., Metergoline blocks the behavioral and neuroendocrine effects of orally administered m-chlorophenylpiperazine in patients with obsessive-compulsive disorder, Biol Psychiatry, 29 (1991) 418-26.
38. Porter, R.H., Benwell, K.R., Lamb, H., Malcolm, C.S., Allen, N.H., Revell, D.F., Adams, D.R. and Sheardown, M.J., Functional characterization of agonists at recombinant human 5-HT2A, 5-HT2B and 5-HT2C receptors in CHO-K1 cells, Br J Pharmacol, 128 (1999) 13-20.
39. Rapoport, J.L., Recent advances in obsessive-compulsive disorder, Neuropsychopharmacology, 5 (1991) 1-10.
40. Scantamburlo, G., Ansseau, M. and Legros, J.J., [Role of the neurohypophysis in psychological stress], Encephale, 27 (2001) 245-59.
41. To, C.T., Anheuer, Z.E. and Bagdy, G., Effects of acute and chronic fluoxetine treatment of CRH-induced anxiety, Neuroreport, 10 (1999) 553-5.
42. To, C.T. and Bagdy, G., Anxiogenic effect of central CCK administration is attenuated by chronic fluoxetine or ipsapirone treatment, Neuropharmacology, 38 (1999) 279-82.
43. Whitton, P. and Curzon, G., Anxiogenic-like effect of infusing 1-(3-chlorophenyl) piperazine (mCPP) into the hippocampus, Psychopharmacology (Berl), 100 (1990) 138-40.
44. Zohar, J., Mueller, E.A., Insel, T.R., Zohar-Kadouch, R.C. and Murphy, D.L., Serotonergic responsivity in obsessive-compulsive disorder. Comparison of patients and healthy controls, Arch Gen Psychiatry, 44 (1987) 946-51.