CNS Drug Reviews
Vol. 6, No. 3, pp. 195–205

SB 242084: A Selective 5-HT_{2C} Receptor Antagonist

Vincenzo Di Matteo, Giuseppe Di Giovanni, and Ennio Esposito

Istituto di Ricerche Farmacologiche "Mario Negri,"
Consorzio "Mario Negri" Sud, Santa Maria Imbaro (Chieti), Italy

Key Words: 5-HT_{2C} receptors — Anxiety — Depression — Dopaminergic function — SB 242084 — Schizophrenia.

ABSTRACT

SB 242084 is the most potent and selective 5-HT_{2C} receptor antagonist thus far available. Thus, SB 242084 has high affinity for the cloned human 5-HT_{2C} receptor with a pK_i of 9.0, a much lower affinity for the human cloned 5-HT_{2B} (pK_i 7.0) and 5-HT_{2A} (pK_i 6.8) receptors, and low affinity for other 5-HT, dopamine, and adrenergic receptors. In the 5-HT-stimulated PI hydrolysis model of 5-HT_{2C} receptor function, SB 242084 was found to be a competitive antagonist with a pK_B of 9.3. A series of *in vivo* studies have shown that SB 242084 is a very effective antagonist of behavioral responses mediated by 5-HT_{2C} receptors such as penile erections, and the hypophagic and hypolocomotor effect of mCPP in rats. In addition, this compound has anxiolytic-like properties. Moreover, SB 242084 increases the basal activity of dopaminergic neurons in the VTA and the *in vivo* DA release in the nucleus accumbens, and it is capable of blocking the inhibitory effects of mCPP and RO 60-0175 on mesolimbic dopaminergic activity. These data are consistent with the evidence that 5-HT_{2C} receptors exert an inhibitory control upon the mesolimbic dopaminergic system.

Taken togheter, the available data on SB 242084 might have implication for the possible use of this compound in the treatment of anxiety, depression, and the negative symptoms of schizophrenia.

INTRODUCTION

An increasing amount of evidence indicates that serotonin (5-HT) is involved in the regulation of several physiological functions, including affective behavior, sleep, food

Address correspondence and reprint requests to: Dr. E. Esposito, Istituto di Ricerche Farmacologiche "Mario Negri," Consorzio "Mario Negri" Sud, 66030 Santa Maria Imbaro (Chieti), Italy.
Phone: +39 (872) 570-274; Fax: +39 (872) 578-240.

intake, sexual behavior, memory, and thermoregulation (47). Moreover, a dysregulation of the serotonergic system is thought to underly the pathogenesis of psychiatric illnesses, such as depression, anxiety, obsessive compulsive disorder (OCD), eating disorders, and schizophrenia (12,13,48). 5-HT probably attains such a variety of functions by acting on distinct receptor subtypes, most of which have been sequenced and cloned (7,20,41). The availability of compounds that act on various 5-HT receptor subtypes has allowed progress in the understanding of the relative contribution of these receptors in the control of various aspects of behavior. For example, 5-HT_{1A} receptor agonists stimulate locomotor activity and increase food intake, whereas 5-HT_{2C} agonists cause hypolocomotion and reduce eating (6,26,28,31). Recently, 5-HT_{2C} receptor antagonists have been proposed to be potential anxiolytic and antidepressant agents (4,27), whereas 5-HT_{2A} blockers might be helpful in the treatment of psychotic disorders (21). Most of the serotonergic agents used in pharmacological tests, however, are not selective enough to permit an accurate investigation of the role of various 5-HT receptors. The lack of selectivity is probably due to structural similarities between 5-HT receptor subtypes. This fact is particularly evident in the case of 5-HT_2 receptors, which form a closely related subgroup (4).

5-HT_2 receptors are G-protein-coupled receptors, functionally linked to the phosphatidylinositol (PI) hydrolysis pathway and are currently classified as 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} subtypes (3,7,23) based on their close structural homology and pharmacology (3,7,23). The amino acid sequence of the 5-HT_2 receptors shares a high degree of homology within the seven transmembrane domains (3,7,23); thus, it is not surprising that many compounds bind with high affinity to all three of these receptor subtypes. Presently, there is evidence that the 5-HT_{2C} receptor is located mainly postsynaptically, with a high degree of cellular heterogeneity within dopaminergic, GABAergic, cholinergic, substance P, dynorphin, and other neuronal systems (3,18,46). There is also high sequence homology (>80% in the transmembrane regions) between mouse, rat, and human 5-HT_{2C} receptors (3). They are widely distributed throughout the brain and have been proposed to be mediators of the different actions of 5-HT in the central nervous system (CNS) (3,7,23). High levels of 5-HT_{2C} mRNA or protein expression have been found in the choroid plexus, rat frontal cortex, hippocampus, septum, hypothalamus, striatum, rhombencephalon, and spinal cord (36,42,44), while the 5-HT_{2A} receptor showed a more widespread localization in the CNS, with higher levels in the cortical areas (42). Recently several groups have shown, using more sensitive techniques, the presence of both 5-HT_{2B} receptor mRNA (19) and protein (17) in the rat brain.

The regional and cellular distribution of 5-HT_{2C} receptors has been investigated also in the human brain. The main sites of mRNA 5-HT_{2C} receptors or protein expression are the choroid plexus, cerebral cortex, hippocampus, amygdala, some components of the basal ganglia, and other limbic structures (1,39), suggesting that this receptor may be involved in the regulation of different human brain functions. The presence of 5-HT_{2C} receptors in the prefrontal cortex and in different components of the limbic system suggests this receptor has a direct involvement in anxiety and/or mood disorders. Moreover, this receptor has been implicated in the serotonergic control of appetite (27,45). Studies of conventional tricyclic and nontricyclic antidepressants suggest that a number of these drugs display considerable pharmacological activity at 5-HT_{2C} receptors in the brain (24,25), and the possible involvement of 5-HT_{2C} receptors in the pathogenesis of depressive disorders and in the mechanism of action of antidepressants is further substantiated by several other studies (37,38). In addition, selective serotonin reuptake inhibitors (SSRIs)

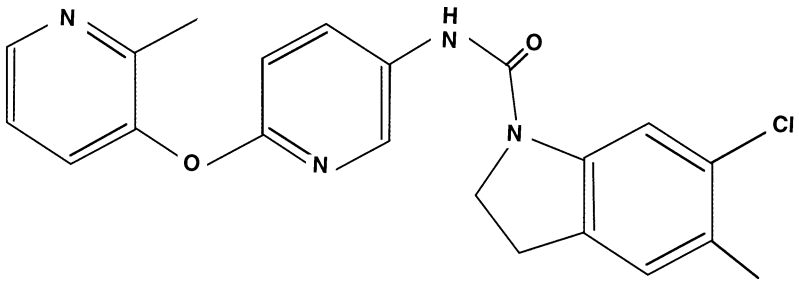

Fig. 1. Chemical structure of SB 242084, 6-chloro-5-methyl-1-{[2-(2-methyl-3-pyridyl)oxy]-5-pyridyl carbamoyl} indoline.

decrease 5-HT_{2C} receptor responsiveness (27). Other pharmacological studies have shown that central 5-HT_{2C} receptors are involved in the pathogenesis of panic disorder, OCD, eating disorders, alcoholism, migraine, sleep disorders, and obesity (for review see ref. 27). Therefore, 5-HT_{2C} receptor ligands may have therapeutic applications in a variety of illnesses (27). In particular, preclinical and early phase clinical studies have shown that 5-HT_{2C} antagonists may be useful in the treatment of anxiety, depression, and sleep disorders (4).

SB 242084 is the most selective and brain penetrant 5-HT_{2C} receptor antagonist (8,29). Herein its preclinical pharmacology and its possible applications in human neuropsychiatric disorders are reviewed.

CHEMISTRY

SB 242084, ($C_{21}H_{19}ClN_4O_2$), 6-chloro-5-methyl-1-{[2-(2-methyl-3-pyridyl)oxy]-5-pyridyl carbamoyl} indoline (Fig. 1) has a molecular weight of 394.860 (free base). The compound is a white powder, soluble in dimethyl sulfoxide or in *N*,*N*-dimethylformamide. SB 242084 was prepared by coupling 6-chloro-5-methylindoline with phenyl carbamate in a four-step synthesis described by Bromidge et al. (8). For *in vivo* studies, SB 242084 was dissolved in 0.9% saline containing 8% hydroxypropyl-β-cyclodextrin by weight and 25 mM citric acid and was given either i.p. or i.v.(16,29).

SELECTIVITY FOR 5-HT_{2C} RECEPTORS AND *IN VITRO* PHARMACOLOGY

In the 5-HT-stimulated PI hydrolysis model of 5-HT_{2C} receptor function using human cloned receptors expressed in HEK 293 cells, SB 242084 was found to be a competitive antagonist with a pK_B of 9.3, which is consistent with its binding affinity (pK_i 9.0) (8). Thus, SB 242084 has an increased affinity for cloned human 5-HT_{2C} receptors compared with previously available compounds, such as SB 206553 {5-methyl-1-[(3-pyridylcarba-

moyl)-1,2,3,5-tetrahydropyrrolo(2,3-f)indole]} (pK_i 7.9) and SB 200646A [*N*-(1-methyl-5-indolyl)-*N′*-(3-pyridyl) urea hydrochloride] (pK_i 6.9) (8,29,30). Moreover, SB 242084 shows at least 160- and 100-fold selectivity over the 5-HT_{2A} and 5-HT_{2B} receptor subtypes, respectively (8,29). In addition, SB 242084 displays a greater than 100-fold selectivity over a range of other 5-HT, dopamine, and adrenergic receptors (8,29). Similar results were obtained in another binding study using human neuroblastoma cells (SH-SY5Y) transfected with the human cloned 5-HT_{2C} receptor (29). SB 242084 showed high affinity for the cloned human 5-HT_{2C} receptor with a pK_i of 9.0, a much lower affinity for the human cloned 5-HT_{2B} (pK_i 7.0) and 5-HT_{2A} (pK_i 6.8) receptors, and low affinity for all other receptors tested (29). In the same cellular line, 5-HT caused a concentration-dependent increase in PI hydrolysis that was fully antagonized by SB 242084 (29). In a 5-HT_{2C} receptor model constructed on the basis of the structure of bacteriorhodopsin, the central pyridyl ring of SB 242084 occupies a lipophilic pocket surrounded by Phe 508 and Phe 616, while the terminal pyridyl ring occupies another lipophilic pocket formed by Ile 305 and Ile 410 (8). In this model, the terminal pyridyl nitrogen may form a hydrogen bond with Ser 413; this interaction is not possible in the case of the 5-HT_{2B} receptor since the corresponding residue in the protein sequence is alanine (8). In addition, the substituted indoline is placed in another pocket, the boundary of which is defined by residues Val 212, Val 608, Met 612, and Tyr 715. In the 5-HT_{2B} receptor model, the corresponding 608 residue is leucine, and in the 5-HT_{2A} receptor both the 212 and 608 residues are leucine (8). These differences are expected to lead to smaller binding pockets. Consequently, steric differences among receptors of the 5-HT_2 family may contribute to the observed 5-HT_{2C} selectivity of SB 242084 (8).

ELECTROPHYSIOLOGICAL AND BIOCHEMICAL CHARACTERIZATION

Electrophysiological techniques and *in vivo* microdialysis were used to investigate the effect of SB 242084 in the control of nigrosriatal and mesolimbic dopaminergic function in rat brain. Extracellular single unit recordings were performed from neurochemically identified dopamine neurons in the substantia nigra pars compacta (SNc), and the ventral tegmental area (VTA). SB 242084 dose-dependently (160–640 μg/kg, i.v.) and significantly increased the basal firing rate of VTA dopaminergic neurons, and the bursting activity was also enhanced in the same area (Fig. 2) (16). On the other hand, SB 242084 did not cause any significant change in the basal firing rate and bursting activity of dopaminergic neurons in the SNc (Fig. 2) (16). Consistently, basal dialysate dopamine (DA) and dihydroxyphenylacetic acid (DOPAC) were significantly increased in the nucleus accumbens of anesthetized rats after intraperitoneal injection of SB 242084 (5–10 mg/kg) (Fig. 3) (16). Moreover, the inhibitory effects of *m*-chlorophenylpiperazine (mCPP) and MK 212 [6-chloro-2-(1-piperazinyl)piperazine], two nonselective 5-HT_{2C} receptors agonists, were prevented by SB 242084, suggesting an inhibitory action of 5-HT on mesolimbic dopaminergic activity through stimulation of 5-HT_{2C} receptors (15). Interestingly, SB 242084 also prevented the inhibitory influence of RO 60-0175 [(*S*)-2-(chloro-5-fluoro-indol-1-yl)-1–methylethylamine 1:1 $C_4H_4O_4$], a selective 5-HT_{2C} agonist (32), on me-

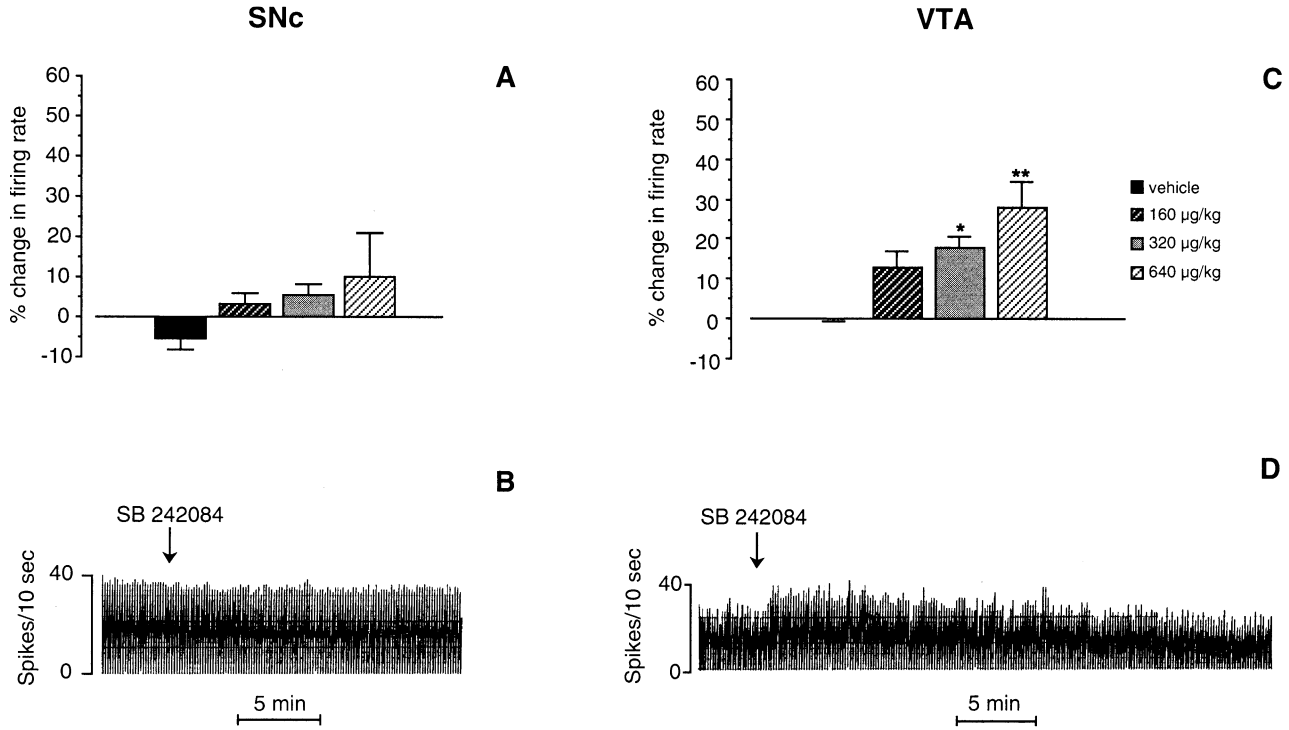

Fig. 2. Effect of SB 242084 on the firing rate of SNc and VTA DA neurons (16). (**A**, **C**) Histograms showing mean percentage of change (±S.E.M.) in firing rate of DA neurons in the SNc (**A**) and the VTA (**C**) after i.v. SB 242084 ($n = 6–8$). (**B**, **D**) Representative rate histograms showing the lack of effect of i.v. SB 242084 (640 µg/kg) in the SNc (**B**) and the typical excitatory response in the VTA (D). $*P < 0.05$, $**P < 0.01$ vs. control group; one-way ANOVA followed by Tukey's test.

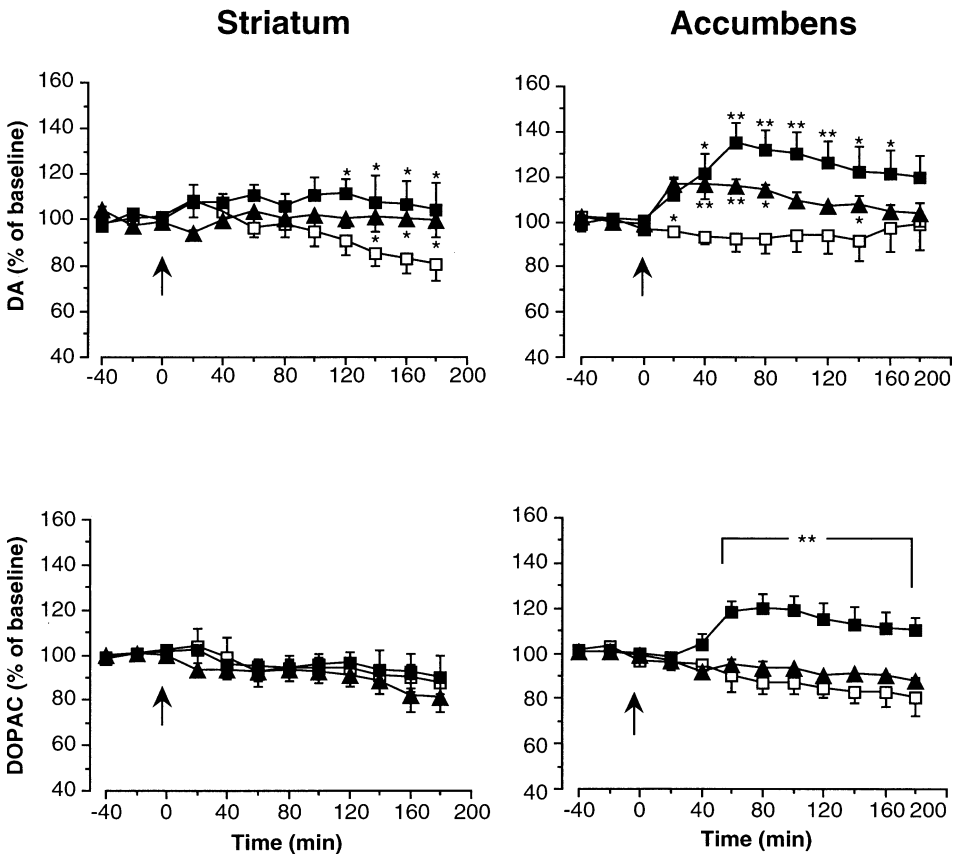

Fig. 3. Time course of the effect of i.p. administration of SB 242084 5 (▲) and 10 mg/kg (■) on extracellular DA and DOPAC levels in the striatum (left column) and the nucleus accumbens (right column) (16). Control group (□) was treated with vehicle. SB 242084 was administered at the time indicated by vertical arrows. Each data point represents mean change ± S.E.M. from the baseline value calculated from three samples before SB 242084 injection. Each experiment was carried out on 5–6 animals per group. $*P < 0.05$, $**P < 0.01$ vs. control group; two-way ANOVA followed by Tukey's test.

solimbic dopaminergic activity (Figs. 4 and 5). RO 60-0175 (2.5 mg/kg, s.c.) markedly reduced DA and noradrenaline (NA) release in the frontal cortex of freely moving rats without affecting 5-HT release (35). In contrast, SB 242084 (10 mg/kg, i.p.) markedly increased dialysate DA and NA levels without affecting 5-HT outflow in the frontal cortex, suggesting a tonic inhibitory influence of 5-HT upon frontocortical dopaminergic and noradrenergic transmission by stimulating 5-HT_{2C} receptors (35).

BEHAVIORAL STUDIES

To evaluate its *in vivo* antagonist activity, SB 242084 was used in a model of penile erection in rats, which is mediated by activation of 5-HT_{2C} receptors (35). SB 242084

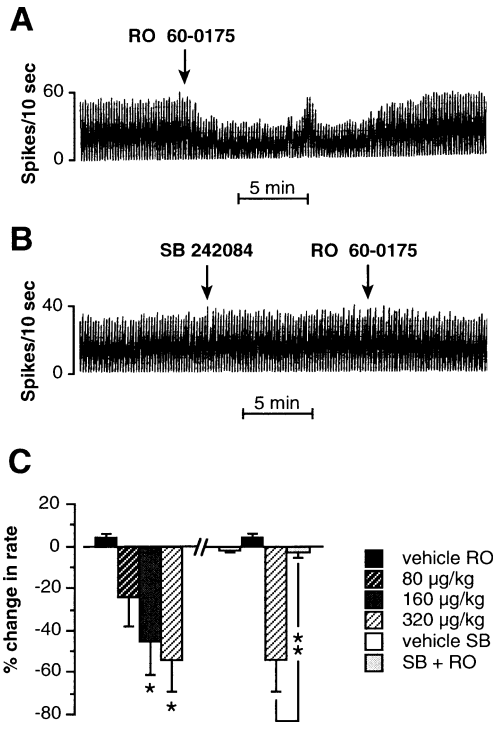

Fig. 4. Effects of RO 60-0175 on the firing rate of VTA DA neurons. (**A**) Representative rate histogram showing the typical effect of i.v. RO 60-0175 (320 µg/kg). (**B**) Representative rate histogram showing that i.v. SB 242084 (200 µg/kg) prevents the inhibitory effect of RO 60-0175 (320 µg/kg, i.v.). Arrows indicate the time of drug injection. (**C**) Histograms showing mean change (±S.E.M.) in firing rate of DA neurons after i.v. RO 60-0175 (80–320 µg/kg) (left). $*P < 0.05$ compared to the vehicle group (one-way ANOVA, followed by Tukey's test). Pretreatment with SB 242084 (200 µg/kg, i.v.) abolished the inhibitory effects of RO 60-0175 (320 µg/kg, i.v.) on the firing rate of DA neurons (C, right). $F_{1,13} = 14.52$; $**P < 0.01$ (two-way ANOVA, split plot design, followed by Tukey's test).

dose-dependently antagonized penile erections induced by RO 60-0175 (2.5 mg/kg, s.c.) with an ID_{50} of 0.7 mg/kg, i.p. (35). Moreover, pretreatment with SB 242084 completely attenuated the reduction in locomotor activity induced by *m*-chlorophenylpiperazine (mCPP), a behavioral response which is mediated by the stimulation of central 5-HT_{2C} receptors (29). Thus, administration of mCPP (7 mg/kg, i.p.) caused a marked reduction in locomotor activity, and pretreatment with SB 242084 either i.p. (0.01–0.3 mg/kg) or p.o. (0.5–5 mg/kg) completely blocked the effect of mCPP (29). In the social interaction test, SB 242084 (0.1–1 mg/kg, i.p.) increased the amount of time rats spent in social interaction without affecting locomotor activity and also markedly increased punished responses in a rat Geller–Seifter conflict test (0.1–3 mg/kg, i.p.), suggesting anxiolytic-like properties of this compound (29). Furthermore, the ability of SB 242084 (2 and 6 mg/kg, p.o.) to antagonize the hypophagic action of mCPP (5 mg/kg, i.p.) (29) confirms the hypothesis that 5-HT_{2C} receptors are involved in the control of food intake (27). Finally, SB 242084 had no effect on convulsant activity in the rat maximal electroshock seizure threshold test (29).

DISCUSSION

SB 242084 is the most potent and selective 5-HT_{2C} receptor antagonist that has been developed to date (8,29). Receptor binding studies have shown that this compound has

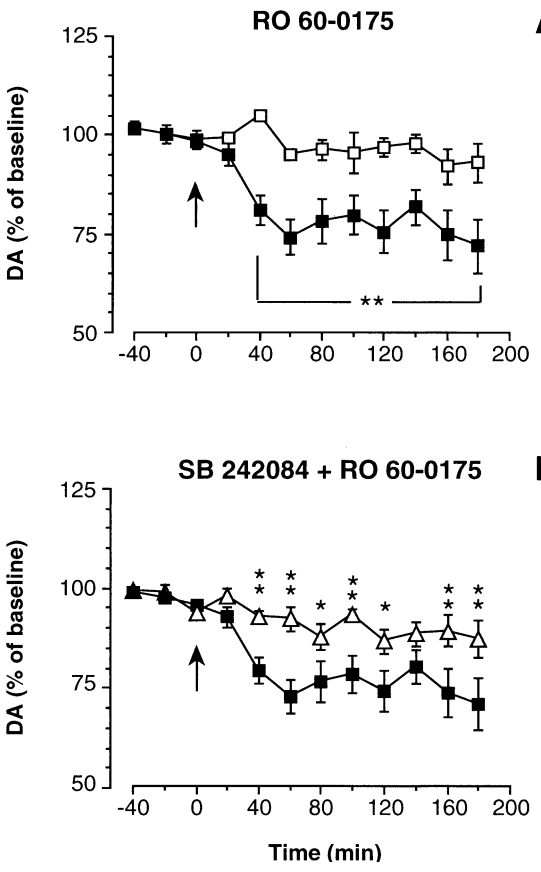

Fig. 5. (**A**) Time course of the effect of i.p. RO 60-0175 (1 mg/kg) (■) on extracellular DA levels in the rat nucleus accumbens. Control groups (□) were treated with the vehicle. RO 60-0175 was administered at the time indicated by the arrow. Each data point represents mean change ± S.E.M. from the baseline value calculated from three samples before drug injection. Each experiment was carried out on 5–6 animals per group. $^{**}P < 0.01$ vs. control group; two-way ANOVA followed by Tukey's test. (**B**) Time course of the effect of RO 60-0175 (1 mg/kg, i.p.) (■) and pretreatment of SB 242084 (△) (2.5 mg/kg, i.p.) on extracellular DA levels in the nucleus accumbens. RO 60-0175 was administered at the time indicated by the arrow. SB 242084 was given 10 min before RO 60-0175. Each data point represents mean change ± S.E.M. from the baseline value calculated from three samples before RO 60-0175 injection. Each experiment was carried out on 5–6 animals per group. $F_{1,10} = 10.252$, $^{*}P < 0.05$, $^{**}P < 0.01$ RO 60-0175 vs. SB 242084 + RO 60-0175; two-way ANOVA followed by Tukey's test.

100- and 160-fold selectivity over the closely related, cloned human 5-HT_{2B} and 5-HT_{2A} receptor subtypes, respectively (8,29). Moreover, systemic administration of SB 242084 blocks the hypolocomotor response to mCPP (29), an effect which is mediated by stimulation of 5-HT_{2C} receptors in the CNS. This finding indicates that SB 242084 is a brain-penetrant compound which is capable of blocking central 5-HT_{2C} receptors *in vivo*.

A series of experiments conducted in our laboratory have shown that SB 242084 causes a dose-dependent increase in the basal firing rate of DA neurons in the VTA (16). In addition, SB 242084 increases the bursting activity of DA neurons in the VTA. In agreement with these data, basal DA output is also enhanced in the nucleus accumbens following the administration of SB 242084 (16). Consistent with the fact that bursting activity of midbrain DA neurons is associated with a much larger increase in DA output in the terminal regions than single-spike firing (5,22), a robust enhancement of basal DA release was found in the nucleus accumbens (16). Moreover, a recent report has shown that selective 5-HT_{2C} blockade by SB 242084 causes a marked increase in dialysate levels of DA in the rat prefrontal cortex (35). The finding that SB 242084 is capable of changing the basal activity of mesocorticolimbic DA neurons is consistent with the presence of 5-HT_{2C} receptors within these brain regions (1,33,36,40,42,46). Furthermore, it has re-

cently been shown that 5-HT_{2C} receptor mRNA is expressed by γ-aminobutyric acid (GABA)-containing cells but not by DA neurons within the SN and the VTA (18). It is, therefore, conceivable that the effect of SB 242084 on DA neuronal activity would be indirect and resulting from the removal of a tonic inhibitory action of GABAergic neurons. Nevertheless, the extent that 5-HT_{2C} receptors located in other brain areas, such as the nucleus accumbens, participate in the observed excitatory effect on DA neurons remains to be established.

In view of the hypothesis that disinhibition of the mesolimbic DA system underlies the mechanism of action of several antidepressant drugs (9,10,11), the stimulatory effect of SB 242084 on the mesolimbic DA system may open new possibilities for the employment of 5-HT_{2C} receptor antagonists as antidepressants. This hypothesis is consistent with the suggestion that 5-HT_{2C} receptor blockers may exert antidepressant activity (4,27). In this respect, it is interesting to note that several antidepressant drugs have been shown to bind with submicromolar affinity to 5-HT_{2C} receptors in the pig brain and to antagonize mCPP-induced penile erections in rats, an effect mediated through the stimulation of central 5-HT_{2C} receptors (24,25). However, the hypothesis that selective 5-HT_{2C} receptor antagonists may have antidepressant properties is apparently in contrast with the evidence that 5-HT_{2C} agonists show antidepressant activity in animal models of depression (37). The authors suggest that the potential antidepressant effect of 5-HT_{2C} agonists may result from their ability to down-regulate 5-HT_{2C} receptors following chronic treatment (37). Interestingly, chronic administration of both agonists and antagonists of 5-HT_{2C} receptors causes a down-regulation of this 5-HT receptor subtype (2,43). Therefore, it is possible to argue that a reduced function of 5-HT_{2C} receptors may be the common mechanism by which 5-HT_{2C} agonists and antagonists may alleviate depression.

It has recently been reported that SB 242084 is active in various animal tests predictive of anxiolytic activity in humans, such as the social interaction test and the Geller–Seifter procedure (29). The ability of SB 242084 to enhance mesolimbic DA function is of interest, especially in view of the evidence that increased DA release may be involved in the anxiolytic effect of buspirone and low doses of sulpiride and haloperidol (34). Interestingly, it has been proposed that 5-HT_{2C} receptor antagonists might be provided with therapeutic activity in several clinical forms of anxiety, such as generalized anxiety, panic disorder, and OCD (27). In addition, selective 5-HT_{2C} receptor antagonists may be useful in the treatment of the negative symptoms of schizophrenia, a clinical condition in which a reduced function of the mesocorticolimbic DA system has been hypothesized (14).

In conclusion, preclinical studies with SB 242084 indicate that selective 5-HT_{2C} receptor antagonists may be useful in the treatment of neuropsychiatric disorders, such as anxiety, depression, and the negative symptoms of schizophrenia.

REFERENCES

1. Abramowski D, Rigo M, Due D, Hoyer D, Staufenbiel M. Localization of 5-hydroxytryptamine$_{2C}$ receptor protein in human and rat brain using specific antisera. *Neuropharmacology* 1995;35:1635–1645.
2. Barker EL, Sanders-Bush E. 5-Hydroxytryptamine$_{1C}$ receptor density and mRNA levels in choroid plexus epithelial cells after treatment with mianserin and (–)-1-(4-bromo-2,5-dimethoxy-phenyl)-2-aminopropane. *Mol Pharmacol* 1993;44:725–730.

3. Barnes N, Sharp TA. Review of central 5-HT receptors and their function. *Neuropharmacology* 1999;38:1083–1152.
4. Baxter G, Kennett G, Blaney F, Blackburn T. 5-HT_2 receptor subtypes: A family reunited? *Trends Pharmacol Sci* 1995;16:105–110.
5. Bean AJ, Roth RH. Extracellular dopamine and neurotensin in rat prefrontal cortex *in vivo*: Effects of median forebrain bundle stimulation frequency, stimulation pattern, and dopamine autoreceptors. *J Neurosci* 1991;11:2694–2702.
6. Bendotti C, Samanin R. 8-Hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) elicits eating in free feeding rats by acting on central serotonin neurons. *Eur J Pharmacol* 1986;158:147–150.
7. Boess FG, Martin IL. Molecular biology of 5-HT receptors. *Neuropharmacology* 1994;33:275–317.
8. Bromidge SM, Duckworth M, Forbes IT, et al. 6-chloro-5-methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-indoline (SB-242084): The first selective and brain penetrant 5-HT_{2C} receptor antagonist. *J Med Chem* 1997;40:3494–3496.
9. Cervo L, Grignaschi G, Samanin R. The role of the mesolimbic dopaminergic system in the desipramine effect in the forced swimming test. *Eur J Pharmacol* 1990;178:129–133.
10. Cervo L, Samanin R. Evidence that dopamine mechanisms in the nucleus accumbens are selectively involved in the effect of desipramine in the forced swimming test. *Neuropharmacology* 1987;26:1469–1472.
11. Cervo L, Samanin R. Repeated treatment with imipramine and amitriptyline reduced the immobility of rats in the forced swimming test by enhancing dopamine mechanisms in the nucleus accumbens. *J Pharm Pharmacol* 1988;40:155–156.
12. Charney DS, Woods SW, Goodman WK, Heninger GR. Serotonin function in anxiety. II. Effects of the serotonin agonist mCPP in panic disorder patients and healthy subjects. *Psychopharmacology* 1987;92:14–24.
13. Coppen AJ, Doogan DP. Serotonin and its place in the pathogenesis of depression. *J Clin Psychiatry* 1988;49:4–11.
14. Deutch A, Moghaddam B, Innis RB, et al. Mechanisms of action of atypical antipsychotic drugs: Implications for novel therapeutic strategies for schizophrenia. *Schizophr Res* 1991;4:121–156.
15. Di Giovanni G, Di Matteo V, Di Mascio M, Esposito E. Preferential modulation of mesolimbic vs nigrostriatal dopaminergic function by serotonin$_{2C/2B}$ receptor agonists: A combined *in vivo* electrophysiological and microdialysis study. *Synapse* 2000;35:53–61.
16. Di Matteo V, Di Giovanni G, Di Mascio M, Esposito E. SB 242084, a selective serotonin$_{2C}$ receptor antagonist, increases dopaminergic transmission in the mesolimbic system. *Neuropharmacology* 1999;38:1195–1205.
17. Duxon MS. Flanigan TP, Reavley AC, Baxter GS, Blackburn TP, Fone KCF. Evidence for expression of the 5-hydroxytryptamine-2B receptor protein in the rat central nervous system. *Neuroscience* 1997;76:323–329.
18. Eberle-Wang K, Mikeladze Z, Uryu K, Chesselet MF. Pattern of expression of the serotonin$_{2C}$ receptor messenger RNA in the basal ganglia of adult rats. *J Comp Neurol* 1997;384:233–247.
19. Flanigan TP, Reaveley AC, Carey JE, Leslie RA. Evidence for expression of the 5-HT_{2B} receptor mRNA in rat brain. *Br J Pharmacol* 1995;114:369P.
20. Glennon RA, Lucki I. Behavioral models of serotonin receptor activation. In: Sanders-Bush, ed. *The Serotonin Receptors*. Clifton, NJ: Wiley-Liss, 1988:253–293.
21. Goldstein JM, Litwin LC. Antipsychotic-like activity of ritanserin following chronic treatment in rats. *FASEB J* 1988;2:A1404.
22. Gonon FG. Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by *in vivo* electrochemistry. *Neuroscience* 1988;24:19–28.
23. Hoyer D, Clarke DE, Fozard JR, et al. VII. International union of pharmacology. Classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev* 1994;46:157–203.
24. Jenk F, Moreau JL, Mutel V, Martin JR. Brain 5-HT_{1C} receptors and antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry* 1994;18:563–574.
25. Jenk F, Moreau JL, Mutel V, Martin JR, Haefely WE. Evidence for a role of 5-HT_{1C} receptors in the antiserotonergic properties of some antidepressant drugs. *Eur J Pharmacol* 1993;231:223–229.
26. Kalkman HO, Soar J. Determination of the 5-HT receptor subtype involved in 8-OH-DPAT-induced hyperlocomotion: Potential difficulties arising from inadequate pharmacological tools. *Eur J Pharmacol* 1990;191:383–390.
27. Kennett GA. 5-HT_{1C} receptors and their therapeutic relevance. *Curr Opin Invest Drugs* 1993;2:317–362.
28. Kennett GA, Curzon G. Evidence that hypophagia induced by mCPP and TFMPP requires 5-HT_{1C} and 5-HT_{1B} receptors: Hypophagia induced by RU 24969 only requires 5-HT_{1B} receptors. *Psychopharmacology* 1988;96:93–100.

29. Kennett GA, Wood MD, Bright F, et al. SB 242084, a selective and brain penetrant 5-HT_{2C} receptor antagonist. *Neuropharmacology* 1997;36:609–620.
30. Kennett GA, Wood A, Glen S, et al. *In vivo* properties of SB 200646A, a 5-$HT_{2C/2B}$ receptor antagonist. *Br J Pharmacol* 1994;111:797–802.
31. Lucki I, Ward HR, Frazer A. Effect of 1-(*m*-chlorophenyl)piperazine and 1-(*m*-trifluoromethylpheny)piperazine on locomotor activity. *J Pharmacol Exp Ther* 1989;249:155–164.
32. Martin JR, Bos M, Jenck F, et al. 5-HT_{2C} receptor agonists: Pharmacological characteristics and therapeutical potential. *J Pharmacol Exp Ther* 1998;286:913–924.
33. Mengod G, Nguyen H, Le H, Waeber C, Lubbert H, Palacios JM. The distribution and cellular localization of the serotonin$_{1C}$ receptor mRNA in the rodent brain examined by *in situ* hybridization histochemistry. Comparison with receptor binding distribution. *Neuroscience* 1990;35:577–591.
34. Merlo Pich E, Samanin R. Disinhibitory effects of buspirone and low doses of sulpiride and haloperidol in two experimental anxiety models in rats: Possible role of dopamine. *Psychopharmacology* 1986;89:125–130.
35. Millan MJ, Dekeyne A, 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* 1998;37:952–955.
36. Molineaux SM, Jessell TM, Axel R, Julius D. 5-HT_{1C} receptor is a prominent serotonin receptor subtype in the central nervous system. *Proc Natl Acad Sci USA* 1989;86:6793–6797.
37. Moreau JL, Bös M, Jenck F, Martin JR, Mortas P, Wichmann J. 5-HT_{2C} receptor agonists exhibit antidepressant-like properties in the anhedonia model of depression in rats. *Eur Neuropsychopharmacol* 1996;6:169–175.
38. Moreau JL, Jenck F, Martin JR, Perrin S, Haefely WE. Effect of repeated mild stress and two antidepressant treatments on the behavioral response to 5-HT_{1C} receptor activation in rats. *Psychopharmacology* 1993;110:140–144.
39. Pasqualetti M, Ori M, Castagna M, Marazziti D, Cassano GB, Nardi I. Distribution and cellular localization of the serotonin type 2C receptor messenger RNA in human brain. *Neuroscience* 1999;92:601–611.
40. Pazos A, Cortes R, Palacios JM. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. II. Serotonin-2 receptors. *Brain Res* 1985;346:231–249.
41. Peroutka SJ. 5-Hydroxytryptamine receptor subtypes. *Annu Rev Neurosci* 1988;11:45–60.
42. Pompeiano M, Palacios JM, Mengod G. Distribution of the serotonin 5-HT_2 receptor family mRNAs: Comparison between 5-HT_{2A} and 5-HT_{2C} receptors. *Mol Brain Res* 1994;23:163–78.
43. Pranzatelli MR, Murthy JN, Tailor PT. Novel regulation of 5-HT_{1C} receptors: Down-regulation induced both by 5-$HT_{1C/2C}$ receptor agonists and antagonists. *Eur J Pharmacol* 1993;244:1–5.
44. Sharma A, Punhani T, Fone KCF. Distribution of the 5-hydroxytryptamine$_{2C}$ receptor protein in adult rat brain and spinal cord determined using a receptor-directed antibody: Effect of 5,7-dihydroxytryptamine. *Synapse* 1997;27:45–56.
45. Tecott LH, Sun LM, Akana SF, et al. Eating disorders and epilepsy in mice lacking 5-HT_{2C} serotonin receptors. *Nature* 1995;374:542–546.
46. Ward RP, Dorsa DM. Colocalization of serotonin receptor subtypes 5-HT_{2A}, 5-HT_{2C}, and 5-HT_6 with neuropeptides in rat striatum. *J Comp Neurol* 1996;370:405–414.
47. Zifa E, Fillion G. 5-Hydroxytryptamine receptors. *Pharmacol Rev* 1992;44:401–458.
48. Zohar J, Insel TR, Zohar-Kadouch RC, Hill JL, Murphy DL. Serotonergic responsivity in obsessive-compulsive disorder. Effects of chronic clomipramine treatment. *Arch Gen Psychiatry* 1988;45:167–172.