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Role of serotonin$_{2C}$ receptors in the control of brain dopaminergic function

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Abstract

There is substantial evidence that the functional status of mesocorticolimbic dopaminergic (DA) system originating in the ventral tegmental area (VTA) is under a phasic and tonic inhibitory control by the serotonergic system, which acts by stimulating serotonin$_{2C}$ (5-HT$_{2C}$) receptor subtypes. This assertion is based upon a number of electrophysiological and biochemical data showing that 5-HT$_{2C}$ receptor agonists decrease, while 5-HT$_{2C}$ receptor antagonists enhance mesocorticolimbic DA function. On the other hand, it does not seem that 5-HT$_{2C}$ receptors play a relevant role in the control of nigrostriatal DA system originating in the substantia nigra pars compacta (SNc). The authors of this article review the most relevant data regarding the role of 5-HT$_{2C}$ receptors in the control of brain DA function and underline the importance of this subject in the search of new therapies for neuropsychiatric disorders such as depression, schizophrenia, drug addiction, and Parkinson's disease.

Keywords: 5-HT$_{2C}$ receptors; Dopaminergic function; Mesolimbic system; Nigrostriatal system; Antidepressants; Antipsychotics

1. Introduction

Serotonin (5-HT)-containing neurons originating from the midbrain raphe nuclei innervate both the substantia nigra (SN) and the ventral tegmental area (VTA). Thus, neuroanatomical studies have shown a high density of 5-HT immunoreactive fibers both in the substantia nigra pars compacta (SNc), pars reticulata (SNr), and the VTA (Hervé et al., 1987; Moukhles et al., 1997). Serotonergic terminals make synaptic contacts with both dopaminergic (DA) and non-DA neurons in the SNc, SNr, and the VTA (Hervé et al., 1987; Moukhles et al., 1997). Interestingly, the ventral mesencephalic tegmentum including the SN contains the highest brain concentrations of 5-HT, and both the SNc and the SNr receive a dense 5-HT input, which is higher in the SNr (9×10^6 varicosities/mm^3) than in the SNc (6×10^6 varicosities/mm^3) (Moukhles et al., 1997). Moreover, virtually all 5-HT varicosities form synaptic specialization in the SNr, whereas only 50% do so in the SNc (Moukhles et al., 1997). In addition, terminal areas of the SNc and VTA, such as the striatum or the nucleus accumbens, receive an input from serotonergic neurons originating in the raphe nuclei (Azmitia and Segal, 1978). Several 5-HT receptor subtypes have been shown to be present in the basal ganglia. Thus, a high density of 5-HT$_{1B}$ receptors has been found in the SN, VTA, globus pallidus, and entopeduncular nucleus (Pazos and Palacios, 1985; Barnes and Sharp, 1999). In contrast, levels of 5-HT$_{1A}$ binding sites and mRNA encoding the 5-HT$_{1A}$ receptor are barely detectable in the basal ganglia (Barnes and Sharp, 1999). On the other hand, high to moderate levels of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor binding and the corresponding mRNA are present in several forebrain areas including the basal ganglia and the limbic system. Thus, high levels of 5-HT$_{2A}$ and 5-HT$_{2C}$ binding sites are found in the caudate nucleus, nucleus accumbens, olfactory tubercle, and pyriform cortex (Pazos and Palacios, 1985). There is a good concordance between the distribution of 5-HT$_{2A}$ and 5-HT$_{2C}$ binding sites distribution and their relative mRNA (Pompeiano et al., 1994). However, the relative distribution of mRNA for 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors is different. Thus, moderate levels of both 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor mRNA have been detected in the SN, while the VTA contains 5-HT$_{2C}$ but not 5-HT$_{2A}$ receptor mRNA (Pompeiano et al., 1994; Eberle-Wang et al., 1997; Abramowski et al., 1995). There is large

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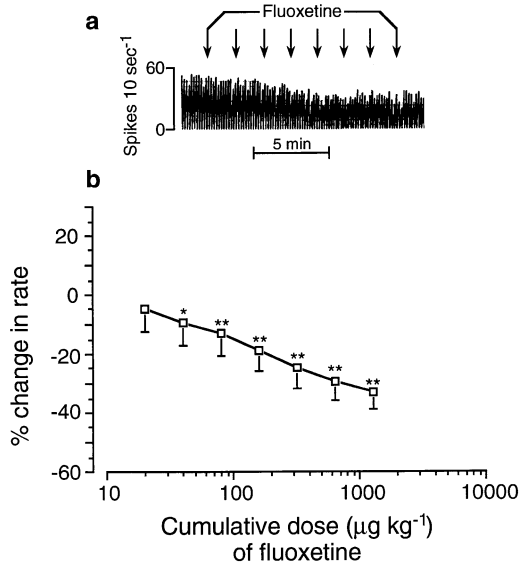

Fig. 1. Effect of fluoxetine on the firing rate of VTA dopaminergic neurones; (a) representative rate histogram showing the typical inhibitory effect of intravenous fluoxetine (20, 20, 40, 80, 160, 320, 640, 1280 μg/kg, at arrows); (b) cumulative dose–response curve showing mean percentage of change (±S.E.M.) in firing rate of VTA dopaminergic neurons after intravenous fluoxetine. * $P<.05$; ** $P<.01$ compared to basal firing rate (one-way analysis of variance, followed by Tukey's test). (Taken from Prisco and Esposito, 1995.)

scientific literature concerning the role of the different 5-HT receptor subtype in the control of brain DA transmission. For example, there is evidence that 5-HT_{1B} receptors underlie the 5-HT-induced inhibition of $GABA_B$ receptor mediated IPSPs in rat midbrain DA neurons in vitro (Johnson et al., 1992). However, in vivo electrophysiological experiments have shown that selective activation of 5-HT_{1B} receptors do not cause any significant change in the basal activity of VTA DA-containing neurons, thus suggesting that 5-HT_{1B} receptors do not play a relevant role in the control of mesolimbic DA system in vivo (Prisco et al., 1994). Moreover, systemic administration of the potent and selective 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), causes a pronounced excitatory effect on the firing and bursting activity of neurons within a subpopulation of VTA DA-containing neurons (Prisco et al.,1994). Microiontophoretic application of 8-OH-DPAT into the VTA does not have any effect on the basal firing rate of DA-containing neurons, and selective lesions of serotonergic neurons by 5,7-dihydroxytryptamine (5,7-DHT) abolish the excitatory effects of systemic 8-OH-DPAT (Prisco et al., 1994). These data indicate that stimulation of 5-HT_{1A} receptors by 8-OH-DPAT disinhibits DA-containing neurons by reducing a tonic inhibitory activity exerted by the serotonergic system (Prisco et al., 1994). A series of studies have shown that 5-HT exerts a tonic and phasic inhibitory control mainly on the mesolimbic and mesocortical DA system, by stimulating 5-HT_{2C} receptors. On the other hand, 5-HT_{2A} receptors seem to have an opposite effect on these systems in that there is evidence that 5-HT_{2A} receptor agonists enhances 3,4-methylenedioxymethamphetamine-induced DA release (Gudelsky et al., 1994).

In this paper, the most relevant findings regarding the role of 5-HT_{2C} receptors in the control of nigrostriatal and mesocorticolimbic DA function will be reviewed.

2. Effects of drugs enhancing 5-HT synaptic levels on the electrical activity of DA neurons in the SNc and the VTA

Acute administration of fluoxetine causes a dose-dependent inhibition of the firing rate of VTA DA neurons, but it does not affect the activity of DA cells in the SNc (Prisco and Esposito, 1995) (Fig. 1). A similar effect, though less pronounced, has been observed with citalopram (Prisco and Esposito, 1995). Furthermore, mesuler-

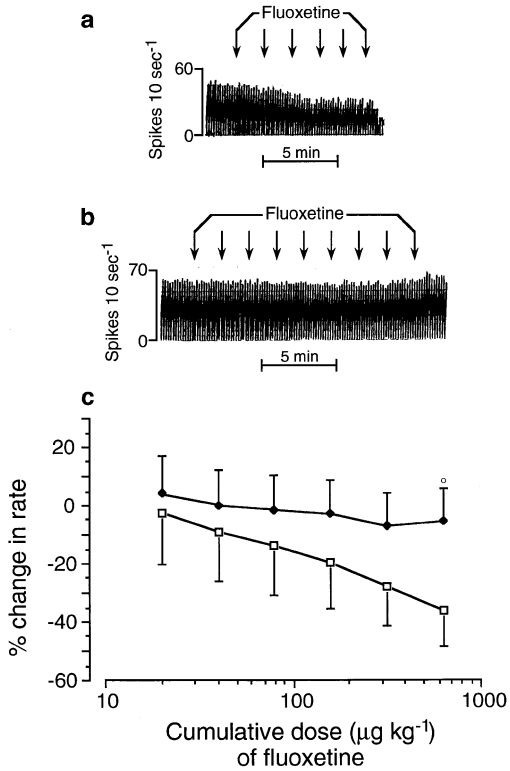

Fig. 2. Effects of chronic treatment with intraperitoneal fluoxetine (10 mg/kg, for 21 days) on the response of VTA dopaminergic neurones to acute intravenous fluoxetine: (a) representative rate histogram showing the typical inhibitory effect of acute intravenous fluoxetine (20, 20, 40, 80,160,320 μg/kg, at arrows) in a control rat; (b) typical rate histogram showing the prevention by chronic intraperitoneal fluoxetine of the inhibitory response to acute intravenous fluoxetine (20, 20, 40, 80, 160, 320, 640, 1280, 2560 μg/kg, at arrows); (c) cumulative dose–response curves showing mean percentage of change (±S.E.M.) in the firing rate of VTA dopaminergic neurones after acute intravenous fluoxetine in control rats (□) and in animals treated chronically with fluoxetine (■). Complete tolerance developed after chronic fluoxetine administration. ° $P<.05$ [$F(6,84)=6.27$, two-way analysis of variance, split-plot design, followed by Tukey's test]. (Taken from Prisco and Esposito, 1995.)

gine, an unselective 5-HT_{2C} receptor antagonist (Boess and Martin, 1994), as well as the destruction of 5-HT neurons by the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT), prevents the flouxetine-induced inhibition of VTA DA cells (Prisco and Esposito, 1995). These results indicate that flouxetine inhibits the mesolimbic DA pathway by enhancing the extracellular level of 5-HT, which would act through 5-HT_{2C} receptors (Prisco and Esposito, 1995). This study also demonstrated that fluoxetine-induced inhibition of DA neurons in the VTA was no longer observed after chronic treatment (21 days) with this drug (Fig. 2). Interestingly, *m*-chlorophenylpiperazine (mCPP), a mixed 5-$HT_{2A/2B/2C}$ receptor agonist (Barnes and Sharp, 1999; Hoyer et al., 1994), inhibited the firing activity of VTA DA neurons in control animals but not in those chronically treated with flouxetine (Prisco and Esposito, 1995). The authors suggested that 5-HT_{2C} receptors might be downregulated after repeated fluoxetine administration. Consistent with this hypothesis is the evidence that chronic treatment with sertraline and citalopram, two selective serotonin reuptake inhibitors (SSRIs), induce tolerance to the hypolocomotor effect of mCPP (Maj and Moryl, 1992). This hyposensitivity of 5-HT_{2C} receptors might be a key step for the achievement of an antidepressant effect. Indeed, it is possible to argue that the acute inhibitory effect of flouxetine on mesolimbic DA system would mask its clinical efficacy in the early stage of treatment. This masking effect would disappear when the hyposensitivity of 5-HT_{2C} receptors occurs. A series of studies carried out in our laboratory have shown that acute administration of SSRIs such as paroxetine, sertraline, and fluvoxamine causes a slight but significant decrease in the basal firing rate of VTA DA neurons (Di Mascio and Esposito, 1997). Therefore, it is conceivable that, similar to fluoxetine, these three SSRIs could reduce mesocorticolimbic DA transmission by activating 5-HT_{2C} receptors.

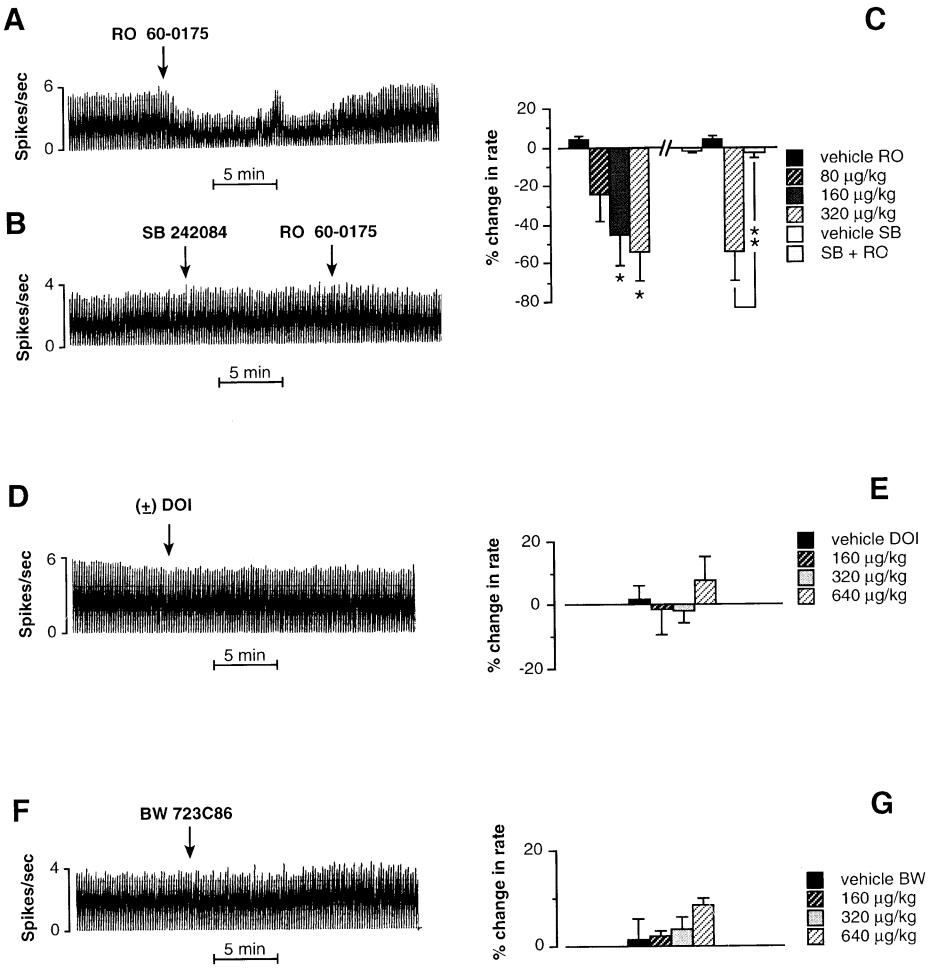

Fig. 3. Effects of various agonists on the firing rate VTA dopaminergic neurons. Representative rate histograms showing the typical effect of intravenous RO 60-0175 (320 μk/kg) (A), (±)-DOI (640 μg/kg) (D), and BW 723C86 (640 μg/kg) (F). Histograms showing mean percentage change (±S.E.M.) in the firing rate of DA neurons after intravenous RO 60-0175 (80–320 μg/kg) (C, left), (±)-DOI (160–640 μg/kg) (E), and BW 723C86 (160–640 μg/kg) (G). * $P < .05$ compared to the vehicle group (one-way analysis of variance, followed by Turkey's test) (C, left). Representative rate histogram showing that intravenous SB 242084 (200 μg/kg) prevents the inhibitory effects of RO 60-0175 (320 μg/kg, iv) (B). The arrows indicate the time of drug injection. (C, right) Histograms showing that pretreatment with SB 242084 (200 μg/kg, iv) abolished the inhibitory effects of RO 60-0175 (320 μg/kg, iv) on the firing rate of DA neurons. $F(1,13) = 14.52$; ** $P < .01$ (two-way analysis of variance, split-plot design, followed by Tukey's test). (Taken from Di Matteo et al., 2000a.)

3. Effects of various 5-HT_{2C} receptor agonists and antagonists on nigrostriatal and mesocorticolimbic DA function

A series of studies carried out in our laboratory has clearly shown that 5-HT_{2C} receptors play a prominent role in the control of mesocorticolimbic DA function. Initially, it was found that the firing rate of DA neurons in the VTA was reduced by mCPP and trifluoromethylphenylpiperazine (TFMPP), two mixed 5-$HT_{2A/2B/2C}$ receptor agonists (Hoyer et al., 1994), whereas these neurons were stimulated by mesulergine (Prisco et al., 1994). Based on those findings, it was suggested that 5-HT could exert an inhibitory action on DA neurons in the VTA by acting through 5-HT_2 receptors (Prisco et al., 1994). However, these data did not allow to distinguish the relative contribution of each 5-HT_2 receptor subtype in the control of central DA function. Subsequent studies clearly indicated a selective involvement of 5-HT_{2C} receptors on the basis of the evidence that the inhibitory effect of the mixed 5HT_2 receptor agonists mCPP and 6-chloro-2-(1-piperazinyl)piperazine (MK 212) on the activity of VTA DA-containing neurons and on accumbal DA release was completely prevented by 6-chloro-5-methyl-1-[2-(2-methylpyridiyl-3-oxy)-pyrid-5-yl carbamoyl] indoline (SB 242084), a selective 5-HT_{2C} receptor antagonist (Di Giovanni et al., 2000). Moreover, SB 242084 blocked the inhibitory action of (*S*)-2-(chloro-5-flouro-indol-yl)-l-methylethylamine 1:1 $C_4H_4O_4$ (RO 60-0175), a selective 5-HT_{2C} receptor agonist (Di Matteo et al., 2000a) (Figs. 3 and 4).

Another series of studies have shown that 5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole) (SB 206553), a selective 5-$HT_{2C/2B}$ receptor antagonist (Kennett et al., 1996), increases the basal firing rate and the bursting activity of VTA DA neurons (Di Giovanni et al., 1999) and enhances DA release in the rat nucleus accumbens and prefrontal cortex (Di Giovanni et al., 1999; Di Matteo et al., 1998; Gobert et al., 2000). Consistent with these findings, 6-chloro-5-methyl-l-[2-(2-methylpyridiyl-3-oxy)-pyrid-5-yl carbomoyl] indoline (SB 242084), the most powerful and selective 5-HT_{2C} receptor antagonist now available (Kennett et al., 1997), selectively enhanced the mesocorticolimbic DA function (Figs. 5 and 6), while RO 60-0175 and MK 212, two 5-HT_{2C} receptor agonists, reduced it (Di Matteo et al., 1999; Millan et al., 1998). Moreover, SB 242084 was found to potentiate the phencyclidine-induced increase in accumbal DA release (Hutson et al., 2000). On the one hand, it does not seem that 5-HT_{2C} receptors exert a relevant role in the control of nigrostriatal DA system. Thus, there is evidence that 5-HT_{2C} receptor

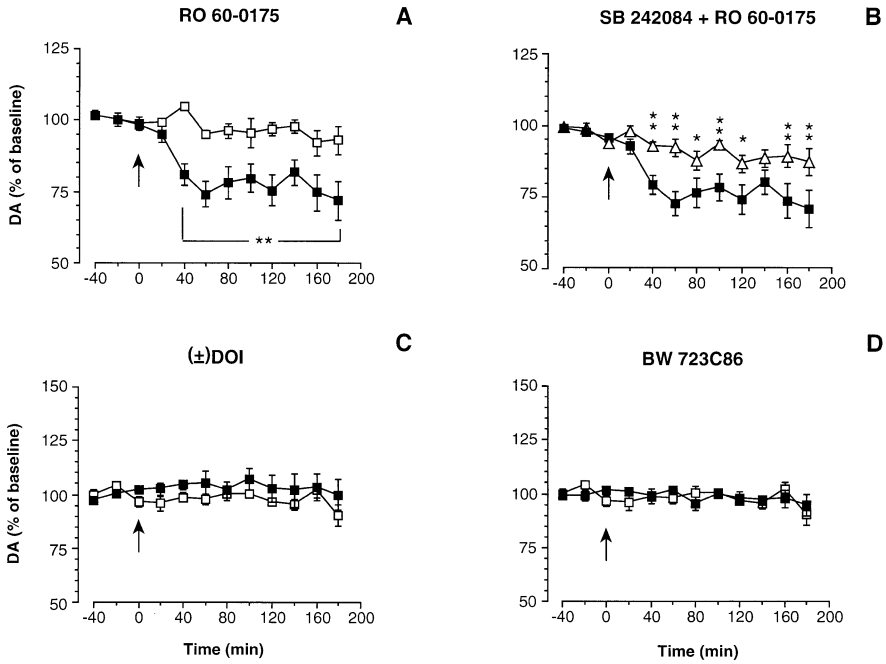

Fig. 4. Time course of the effect of intraperitoneal administration of 1 mg/kg of RO 60-0175 (A), 1 mg/kg of (±)-DOI (C), and 1mg/kg of BW 723C86 (D) on extracellular DA levels in the rat nucleus accumbens. (□) Control groups treated with the vehicle. Drugs were administered at the time indicated by vertical arrows. Each data point represents mean percentage ± S.E.M. of the baseline value calculated from three samples before drug injection. Each experiment was carried out on five to six animals per group. ** $P < .01$ versus control group (two-way analysis of variance followed by Tukey's test). (B) Time course of the effect of RO 60-0175 (■) (1 mg/kg, ip) and pretreatment of SB 242084 (△) (2.5 mg/kg, ip) on extracellular DA levels in the nucleus accumbens. RO 60-0175 was administered at the time indicated by vertical arrow. SB 242084 was given 10 min before RO 60-0175. Each data point represents mean percentage ± S.E.M. of the baseline value calculated from three samples before RO 60-0175 injection. Each experiment was carried out on five to six animals per group. $F(1,10) = 10.252$, * $P < .05$, ** $P < .01$ RO 60-0175 versus SB 242084 + RO 60-0175 (two-way analysis of variance, split-plot design, followed by Tukey's test). (Taken from Di Matteo et al., 2000a.)

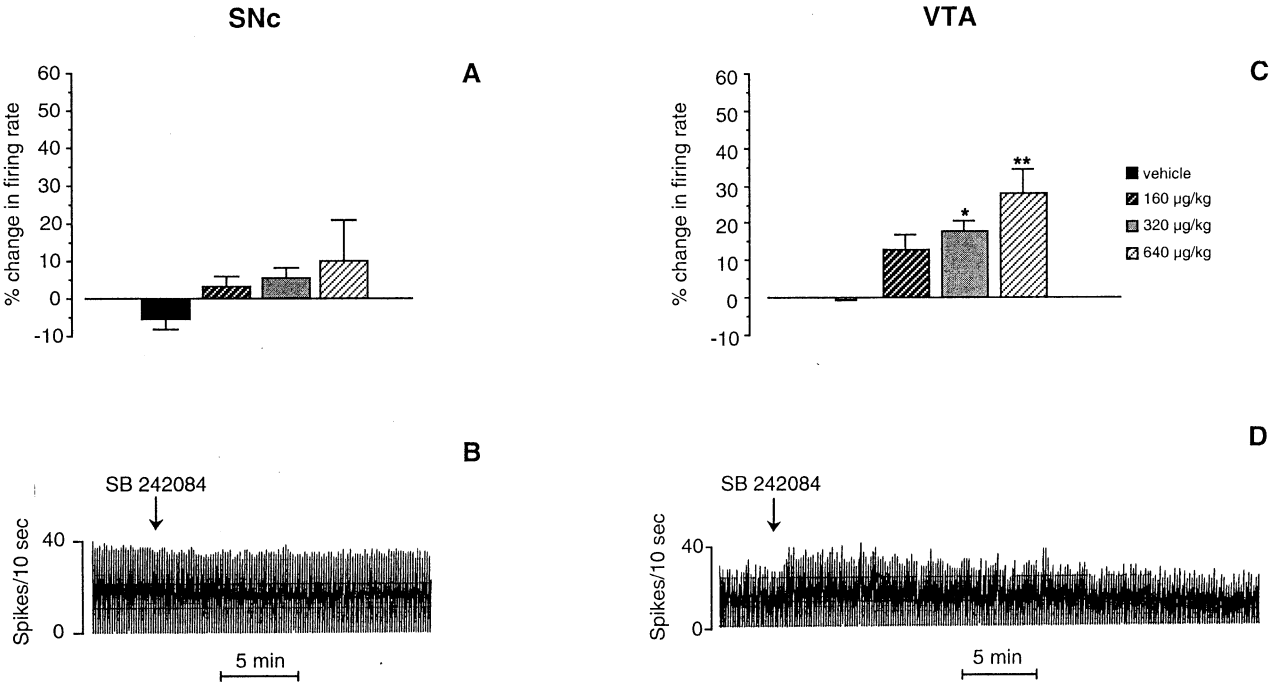

Fig. 5. Effect of SB 242084 on the firing rate of SNc and VTA dopamineric neurons. (A, C) Histograms showing mean percentage of change (±S.E.M.) in the firing rate of DA neurons in the SNc (A) and the VTA (C) after intravenous SB 242084 ($n=6–8$). (B, D) Representative rate histograms showing the lack of effect of intravenous SB 242084 (640 µg/kg) in the SNc (B) and the typical excitatory response in the VTA (D). * $P<.05$, ** $P<0.01$ compared with the control group (one-way analysis of variance, followed by Tukey's test). (Taken from Di Matteo et al., 1999.)

agonists such as mCPP, MK 212, and RO 60-0175 do not significantly affect the activity of SNc DA neurons and the in vivo DA release in the striatum (Di Giovanni et al., 2000; Di Matteo et al., 1999). On the other hand, the mixed

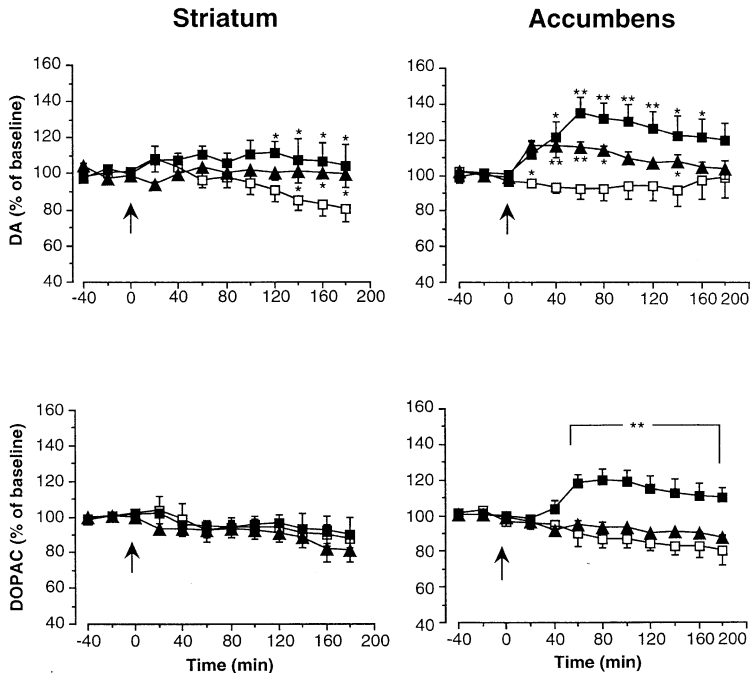

Fig. 6. Time course of the effect of intraperitoneal administration of 5 (▲) and 10 mg/kg SB 242084 (■) on extracellular DA and DOPAC levels in the striatum (left column) and the nucleus accumbens (right column). (□) Conrol group treated with vehicle. SB 242084 was administered at the time indicated by vertical arrows. Each data point represents mean percentage±S.E.M. of the baseline value calculated from three samples before SB 242084 injection. Each experiment was carried out on five to six animals per group. * $P<.05$, ** $P<0.01$ compared with the control group (two-way analysis of variance, followed by Tukey's test). (Taken from Di Matteo et al., 1999.)

5-$HT_{2B/2C}$ antagonist SB 206553 caused only a slight increase in the basal activity of DA neurons in the SNc and striatal DA release (Di Giovanni et al., 1999). Therefore, on the basis of the above mentioned data, it is possible to conclude that the serotonergic system exerts both phasic and tonic control of mesocorticolimbic DA function by acting through 5-HT_{2C} receptors.

A recent study carried out in our laboratory has shown that mCPP excites non-DA (presumably GABA-containing) neurons both in the SNr and the VTA by activating 5-HT_{2C} receptors (Di Giovanni et al., 2001). One interesting finding of that study was the differential effect exerted by mCPP on subpopulations of SNr neurons. Thus, mCPP caused a marked excitation of the so-called P(0) SNr non-DA neurons, whereas it did not affect the P(+) neurons. These neurons are identified on the basis of the presence [P(+)] or the absence [P(0)] of an excitatory response to a noxious stimulus (footpinch) (Di Giovanni et al., 2001). There is evidence that P(+) SNr neurons are GABA-containing interneurons that exert a direct inhibitory influence on DA neurons in the SN, whereas P(0) cells represent GABA-ergic SNr projection neurons (Di Giovanni et al., 2001). On the other hand, all non-DA neurons in the VTA were equally excited by mCPP. It is tempting to speculate that this differential response to mCPP might be the basis of the preferential inhibitory effect of 5-HT_{2C} agonists on the mesocorticolimbic versus the nigrostriatal DA function.

4. Therapeutic potential of drugs acting through the 5-HT_{2C} receptors

In view of the hypothesis that disinhibition of the mesolimbic DA system underlies the mechanism of action of several antidepressant drugs (Cervo and Samanin, 1988) the disinhibitory effect of SB 206553 and SB 242084 on the mesolimbic DA system might 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 might exert antidepressant activity (Baxter et al., 1995). 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 (Jenck et al., 1994). Based on those findings, Di Matteo et al. (2000b) have carried out experiments showing that acute administration of amitriptyline and mianserin, two antidepressants with high affinity for 5-HT_{2C} receptors, enhances DA release in the rat nucleus accumbens probably by blocking these receptor subtypes. Interestingly, amitriptyline and mianserin have been tested in the chronic, mild, stress-induced anhedonia model of depression and were found to be effective in reversing the stress effects (Sampson et al., 1991; Moreau et al., 1994). The antianhedonic effects of tricyclic antidepressants, mianserin, and fluoxetine were abolished by pretreatment with D_2/D_3 receptor antagonists, thus indicating an involvement of DA in the antidepressant effect of various drugs in this model (Sampson et al., 1991; Willner, 1995). Although DA has received little attention in biological research on depression, with respect to other monoamines such as 5-HT and noradrenaline, it is now well established that disturbances of mesolimbic DA function are implied in the pathophysiology of depression (Brown and Gershon, 1993; Fibiger 1995). However, future experiments aimed at investigating the effects of chronic administration of 5-HT_{2C} receptor antagonists on mesolimbic DA function will help to clarify the role played by this receptor subtype in their putative antidepressant action.

The preferential disinhibition of mesocorticolimbic DA function by 5-HT_{2C} antagonists might be relevant for the possible use of these compounds 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 (Deutch et al., 1991). Moreover, it is noteworthy to mention recent data showing that atypical antipsychotic drugs (clozapine, sertindole, olanzapine, ziprasidone, risperidone, zotepine, tiospirone, fluperlapine, tenilapine), which produce little or no extrapyramidal side effects while improving negative symptoms of schizophrenia, exert substantial inverse agonist activity at $5HT_{2C}$ receptors (Herrick-Davis et al., 2000). Thus, 5-HT_{2C} receptor inverse agonism might underlie the unique clinical properties of atypical antipsychotic drugs (Herrick-Davis et al., 2000). However, in vivo experiments are necessary to confirm the relevance of this action of atypical antipsychotics on 5-HT_{2C} receptors.

In addition, the evidence of selective reduction of mesocorticolimbic DA function by 5-HT_{2C} receptor agonists might be exploited for therapeutical purposes. Thus, it has recently been found that RO 60-0175 reduces cocaine-reinforced behavior by stimulating 5-HT_{2C} receptors (Grottick et al., 2000). Moreover, these authors have also shown that RO 60-0175 reduces ethanol- and nicotine-induced self-administration and hyperactivity (Grottick et al., in press; Tomkins et al., submitted). These data are consistent with biochemical studies showing that 5-HT_{2C} receptor agonists inhibit morphine-induced DA release in the rat nucleus accumbens (Willins and Meltzer, 1998). Therefore, it is conceivable that 5-HT_{2C} receptor agonists might be useful for the treatment of drug addiction.

Another interesting application of the data regarding the functional role of 5-HT_{2C} receptors in the basal ganglia is the possible use of 5-HT_{2C} receptor antagonists in the treatment of Parkinson's disease. The neural mechanisms underlying the generation of parkinsonian symptoms are thought to involve reduced activation of primary motor and premotor cortex and supplementary motor areas, secondary to overactivation of the output regions of the basal ganglia, i.e. SNr and globus pallidus internus (Gpi) (Albin et al., 1989), largely because of excessive excitatory

drive from the subthalamic nucleus (STN). Therapy of Parkinson's disease consists mainly of amelioration of the symptoms with classical dopaminomimetics (Hagan et al., 1997). This treatment, however, is characterized by declining efficacy and occurrence of disabling side-effects (Agid, 1998). Functional inhibition of GPi or STN, has provided an alternative to lesioning, by deep brain stimulation associated with modest side-effects (Rodriguez et al., 1998). As already mentioned, 5-HT_{2C} receptors are located in the SNr and medial segment of the pallidal complex in the rat and human brain (Abramowski et al., 1995; Eberle-Wang et al., 1997). In addition, 5-HT_{2C}-like receptor binding is increased in a rat model of parkinsonism (Radja et al., 1993) and in human parkinsonian patients (Fox and Brotchie, 2000). Given that 5-HT_{2C} receptor activation leads to excitation of SNr, it is tempting to speculate that excessive 5-HT_{2C} receptor stimulation may contribute to the increased activity of the output regions of the basal ganglia and thus to the symptoms of parkinsonism. In this respect, it is noteworthy that preliminary experiments carried out in our laboratory show that SB 242084 reduces the basal firing rate of P(0) neurons in the SNr. Thus, based on these findings, it would be very interesting to test the effects of 5-HT_{2C} receptor antagonists on the basal activity of GABA-ergic neurons in the SNr, and on in vivo GABA release in the SNr and the thalamus (which is a projection area of the SNr) of normal and 6-OHDA-lesioned rats, which represent a suitable animal model of Parkinson's disease.

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References

Abramowski D, Rigo M, Duc D, Hoyer D, Staufenbiel M. Localization of 5-hydroxytryptamine$_{2C}$ receptor protein in human and rat brain using specific antisera. Neuropharmocology 1995;34:1635–45.

Agid Y. Levodopa: is toxicity a myth? Neurology 1998;50:858–63.

Albin R, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989;12:366–75.

Azmitia EC, Segal M. An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. J Comp Neurol 1978;179:641–68.

Barnes NM, Sharp T. A review of central 5-HT receptors and their function. Neuropharmacology 1999;38:1083–152.

Baxter G, Kennett G, Blaney F, Blackburn T. 5-HT_2 receptor subtypes: a family reunited? Trends Pharmacol Sci 1995;16:105–10.

Boess FG, Martin IL. Molecular biology of 5-HT receptors. Neuropharmacology 1994;33:275–317.

Brown AS, Gershon S. Dopamine and depression. J Neural Transm: Psychiatr Sect 1993;91:75–109.

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;40:155–6.

Deutch A, Moghaddam B, Innis RB, Krystal JH, Aghajanian GK, Bunney BS, Charney DS. Mechanisms of action of atypical antipsychotic drugs: implications for novel therapeutic strategies for schizophrenia. Schizophr Res 1991;4:121–56.

Di Giovanni G, De Deurwaerdére P, Di Mascio M, Di Matteo V, Esposito E, Spampinato U. Selective blockade of serotonin$_{2C/2B}$ receptors enhances mesolimbic and mesostriatal dopaminergic function: a combined in vivo electrophysiological and microdialysis study. Neuroscience 1999;91:587–97.

Di Giovanni G, Di Matteo V, Di Mascio M, Esposito E. Preferential modulation of mesolimbic versus nigrostriatal dopaminergic function by serotonin$_{2C/2B}$ receptor agonists: a combined in vivo electrophysiological and microdialysis study. Synapse 2000;35:53–61.

Di Giovanni G, Di Matteo V, La Grutta V, Esposito E. *m*-Chlorophenylpiperazine excites non-dopaminergic neurons in the rat substantia nigra and ventral tegmental area by activating serotonin-2C receptors. Neuroscience 2001;103:111–6.

Di Mascio M, Esposito E. The degree of inhibition of dopaminergic neurons in the ventral tegmental area induced by selective serotonin reuptake inhibitors is a function of the density-power-spectrum of the interspike interval. Neuroscience 1997;79:957–61.

Di Matteo V, Di Giovanni G, Di Mascio M, Esposito E. Selective blockade of serotonin$_{2C/2B}$ receptors enhances dopamine release in the rat nucleus accumbens. Neuropharmacology 1998;37:265–72.

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;38:1195–205.

Di Matteo V, Di Giovanni G, Di Mascio M, Esposito E. Biochemical and electrophysiological evidence that RO 60-0175 inhibits mesolimbic dopaminergic function through serotonin$_{2C}$ receptors. Brain Res 2000a;865:85–90.

Di Matteo V, Di Mascio M, Di Giovanni G, Esposito E. Acute administration of amitriptyline and mianserin increases dopamine release in the rat nucleus accumbens: possible involvement of serotonin$_{2C}$ receptors. Psychopharmacology 2000b;150:45–51.

Eberle-Wang K, Mikeladze Z, Uryu K, Chesselet M-F. Pattern of expression of the serotonin$_{2C}$ receptor messenger RNA in the basal ganglia of adults rats. J Comp Neurol 1997;384:233–47.

Fibiger HC. Neurobiology of depression: focus on dopamine. In: Gessa G, Fratta W, Pani L, Serra G, editors. Depression and mania: from neurobiology to treatment. New York: Raven Press, 1995. pp. 1–17.

Fox SH, Brotchie JM. 5-HT_{2C} receptor binding is increased in the substantia nigra pars reticulata in Parkinson's disease. Mov Disord 2000;15:1064–9.

Gobert A, Rivet J-M, Lejeune F, Newman-Tancredi A, Adhumeau-Auclair A, Nicolas J-P, Cistarelli L, Melon C, Millan MJ. Serotonin$_{2C}$ receptors tonically suppress the activity of mesocortical dopaminergic and adrenergic, but not serotonergic, pathways: a combined dialysis and electrophysiological analysis in the rat. Synapse 2000;36:205–21.

Grottick AJ, Fletcher PJ, Higgins GA. Studies to investigate the role of 5-HT_{2C} receptors on cocaine and food maintained behavior. J Pharmacol Exp Ther 2000;295:1183–91.

Grottick AJ, Corrigall WA, Higgins, GA. Activation of 5-HT_{2C} receptors reduces the locomotor and rewarding effects of nicotine. Psychopharmacology (in press).

Gudelsky GA, Yamamoto BK, Nash JF. Potentiation of 3,4-methylenedioxymethamphetamine-induced dopamine release and serotonin neurotoxicity by 5-HT_2 receptor agonists. Eur J Pharmacol 1994;264:325–30.

Hagan JJ, Middlemiss DN, Sharp PC, Poste GH. Parkinson's disease: prospects for improved drug therapy. Trends Pharmacol Sci 1997;18:156–63.

Herrick-Davis K, Grinde E, Teitler M. Inverse agonist activity of atypical antipsychotic drugs at human 5-hydroxytryptamine2C receptors. J Pharmacol Exp Ther 2000;295:226–32.

Hervé D, Pickel VM, Tong HJ, Beaudet A. Serotonin axon terminals in the ventral tegmental area of the rat: fine structure and synaptic input to dopaminergic neurons. Brain Res 1987;435:71–83.

Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ, Saxena PR, Humprey PPA. International union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). Pharmacol Rev 1994;46:157–203.

Hutson PH, Barton CL, Jay M, Blurton P, Burkamp F, Clarkson R, Bristow LJ. Activation of mesolimbic dopamine function by phencyclidine is enhanced by 5-$HT_{2C/2B}$ receptor antagonists: neurochemical and behavioural studies. Neuropharmocology 2000;39:2318–28.

Jenck F, Moreau JL, Mutel V, Martin JR. Brain 5-HT_{1C} receptors and antidepressants. Progr Neurophsychopharmacol Biol Psychiatry 1994; 18:563–74.

Johnson SW, Mercuri NB, North RA. 5-Hydroxytrypyamine$_{1B}$ receptors block the $GABA_B$ synaptic potential in rat dopamine neurons. J Neurosci 1992;12:2000–6.

Kennett GA, Wood MD, Bright F, Cilia J, Piper DC, Gager T, Thomas D, Baxter GS, Forbes I, Brown AM, Middlemiss DN, Blackburn TP. In vitro and in vivo profile of SB 206553, a potent 5-HT_{2C}/5-HT_{2B} receptor antagonist with anxiolytic-like properties. Br J Pharmacol 1996;117:427–34.

Kennett GA, Wood MD, Bright F, Trail B, Riley G, Holland V, Avenell KY, Stean T, Upton N, Bromidge S, Forbes IT, Brown AM, Middlemiss DN, Blackburn TP. SB 242084, a selective and brain penetrant 5-HT_{2C} receptor antagonist. Neuropharmacology 1997;36:609–20.

Maj J, Moryl E. Effects of sertraline and citalopram given repeatedly on the responsiveness of 5-HT receptor subpopulations. J Neural Transm: Gen Sec 1992;88:143–56.

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;37:953–5.

Moreau J-L, Bourson A, Jenck F, Martin JR, Mortas P. Curative effects of the atypical antidepressant mianserin in the chronic mild stress-induced anhedonia model of depression. J Psychiatr Neurosci 1994;19:51–6.

Moukhles H, Bosler O, Bolam JP, Vallée A, Umbriaco D, Geffard M, Doucet G. Quantitative and morphometric data indicate precise cellular interactions between serotonin and postsynaptic targets in rat substantia nigra. Neuroscience 1997;76:1159–71.

Pazos A, Palacios JM. Quantitative autoradiographic mapping of serotonin receptors in the rat brain: I. Serotonin-1 receptors. Brain Res 1985; 346:205–30.

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.

Prisco S, Esposito E. Differential effects of acute and chronic flouxetine administration on the spontaneous activity of dopaminergic neurons in the ventral tegmental area. Br J Pharmacol 1995;116:1923–31.

Prisco S, Pagannone S, Esposito E. Serotonin–dopamine interaction in the rat ventral tegmental area: an electrophysiological study in vivo. J Pharmacol Exp Ther 1994;271:83–90.

Radja F, Descarrier L, Dewar KM, Reader TA. Serotonin 5-HT_1 and 5-HT_2 receptors in adult rat brain after destruction of nigrostriatal dopamine neurons: a quantitative autoradiographic study. Brain Res 1993;606: 273–85.

Rodriguez MC, Obeso JA, Olanow CW. Subthalamic nucleus-mediated excitoxicity in Parkinson's disease: a target for neuroprotection. Ann Neurol 1998;44:S175–S88 (Suppl).

Sampson D, Willner P, Muscat R. Reversal of antidepressant action by dopamine antagonists in an animal model of depression. Psychopharmacology 1991;104:491–5.

Tomkins DM, Joharchi M, Tampakeras M, Martin, JR, Wichmann J, Higgins GA. An investigation of the role of 5-HT_{2C} receptors in modifying ethanol self-administration behaviour. Pharmacol, Biochem Behav (submitted).

Willins DL, Meltzer HY. Serotonin 5-HT_{2C} agonists selectively inhibit morphine-induced dopamine efflux in the nucleus accumbens. Brain Res 1998;781:291–9.

Willner P. Animal models of depression: validity and applications. In: Gessa G, Fratta W, Pani L, Serra G, editors. Depression and mania: from neurobiology to treatment. New York: Raven Press, 1995. pp. 19–41.