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ORIGINAL INVESTIGATION

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Acute administration of amitriptyline and mianserin increases dopamine release in the rat nucleus accumbens: possible involvement of serotonin$_{2C}$ receptors

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Abstract Previous studies of conventional tricyclic and non-tricyclic antidepressants have suggested that a number of these drugs display considerable pharmacological activity at 5-HT$_{2C}$ receptors in the brain. There is evidence that 5-HT$_{2C}$ receptors are involved in the control of the activity of the central dopaminergic system. Therefore, the effects of amitriptyline (5 mg/kg and 10 mg/kg i.p.) and of the atypical antidepressant mianserin (2.5 mg/kg and 5 mg/kg i.p.) were studied on the extracellular concentration of dopamine (DA) in the nucleus accumbens of chloral hydrate-anesthetized rats, using intracerebral microdialysis. Amitriptyline and mianserin significantly increased DA release (+31.1±7.9% and +33.6±4.3%, respectively) at the higher doses. In addition, lower doses of mianserin (2.5 mg/kg i.p.) and amitriptyline (5 mg/kg i.p.) blocked the inhibitory action of RO 60-0175 (1 mg/kg i.p.), a selective 5-HT$_{2C}$ receptor agonist, on DA release. The effect of RO 60-0175 (1 mg/kg i.p.) was completely blocked by SB 242084 (2.5 mg/kg i.p.), a selective and powerful 5-HT$_{2C}$ receptor antagonist. Taken together, these data indicate that amitriptyline and mianserin increase DA release in the nucleus accumbens by blocking 5-HT$_{2C}$ receptors.

Key words Amitriptyline · Mianserin · Dopamine release · Nucleus accumbens · Microdialysis

Introduction

There is considerable evidence that the functional status of central dopamine (DA)-containing neurons is modulated by serotonin (5-HT)-containing neurons originating from the midbrain raphe nuclei (Kalivas 1993; White 1996; Di Matteo et al. 1998a). Anatomical studies have shown that serotonergic neurons innervate both the substantia nigra, pars compacta (SNc) and the ventral tegmental area (VTA) (Van Der Kooy and Hattori 1980; Steinbusch 1984; Hervé et al. 1987; Van Bockstaele et al. 1993, 1994; Moukhles et al. 1997). In addition, terminal areas of the SNc and VTA, such as the corpus striatum or the nucleus accumbens, receive an input from serotonergic neurons of the raphe nuclei (Azmitia and Segal 1978; Van Bockstaele et al. 1993). The existence of a functional relationship between 5-HT and DA neurons in the brain has been confirmed by a number of biochemical studies that showed either inhibition or facilitation of DA release in the presence of 5-HT agonists (Saito et al. 1996). Electrical stimulation of 5-HT-containing neurons in the dorsal raphe inhibited meso-accumbens DA neurons (Kelland et al. 1993). Moreover, the firing rate of DA neurons in the VTA was reduced by *m*-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP), two mixed 5-HT$_{2C/1B}$ receptor agonists, whereas these neurons were stimulated by mesulergine, suggesting that 5-HT exerts an inhibitory action on DA neurons in the VTA by acting through 5-HT$_{2C}$ receptors (Prisco et al. 1994). More recent studies have shown that SB 206553 [5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-f]indole)], 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. 1997, 1999; Lejeune et al. 1997) and enhances DA release in the rat prefrontal cortex and nucleus accumbens (Di Giovanni et al. 1997, 1999; Lejeune et al. 1997; Di Matteo et al. 1998b), while neither 5-HT$_{2A}$ nor 5-HT$_{2B}$ receptor antagonists seem to have any effect on central DA function (Di Giovanni et al. 1997, 1999; Lejeune et al. 1997; Di Matteo et al. 1998b).

Consistent with these findings, SB 242084 [6-chloro-5-methyl-1-[2-(2-methylpyridiyl-3-oxy)-pyrid-5-yl carbamoyl] indoline], the most powerful and selective 5-

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HT_{2C} receptor antagonist now available (Kennett et al. 1997), selectively enhanced the mesocorticolimbic DA function with respect to that of the nigrostriatal system, while RO 60-0175 [(S)-2-(chloro-5-fluoro-indol-1-yl)-1-methylethylamine 1:1 $C_4H_4O_4$], a 5-HT_{2C} receptor agonist (Martin et al. 1998), reduced it (Millan et al. 1998; Di Matteo et al. 1999).

Previous studies of conventional tricyclic and non-tricyclic antidepressants suggested that a number of these drugs display considerable pharmacological activity on 5-HT_{2C} receptors in the brain. Binding and behavioral studies have shown that several antidepressant drugs bind with micromolar or nanomolar affinity to 5-HT_{2C} receptors in the pig brain and antagonize mCPP-induced penile erection in rats (Jenck et al. 1993, 1994), a behavioral model used to test agonistic and antagonistic properties of drugs acting on 5-HT_{2C} receptors (Berendsen et al. 1990; Millan et al. 1997). Interestingly, chronic mianserin, an atypical antidepressant which shows similar antagonistic properties on both 5-HT_{2A} and 5-HT_{2C} receptors, caused a paradoxical downregulation of both receptors in different systems of cell culture, due to its direct action on these receptors (Barker and Sanders-Bush 1993; Pranzatelli et al. 1993; Newton and Elliott 1997), and decreased the density of 5-HT_{2C} sites in the choroid plexus, producing a desensitization of 5-HT-stimulated phosphoinositide hydrolysis (Sanders-Bush and Breeding 1988). Because mesocorticolimbic DA pathways are involved in physiological functions regarding motivation and reward (Fibiger 1995), they are an obvious candidate as a neurobiological substrate of depressive syndrome. Since, as reported above, there is evidence that 5-HT_{2C} receptors control the activity of mesolimbic DA function, we have tested the effect of amitriptyline and mianserin on DA release in the nucleus accumbens of anesthetized rats. For this purpose, extracellular DA levels were monitored in the rat nucleus accumbens using intracerebral microdialysis coupled to high-performance liquid chromatography (HPLC) with electrochemical detection.

Materials and methods

Animals

Male Sprague-Dawley rats (Consorzio Mario Negri Sud, Italy) weighing 300–380 g were used. The animals were kept at constant room temperature (21±1°C) and relative humidity (60±5%) under a regular light/dark schedule (light 0800–2000 hours). Food and water were freely available. Procedures involving animals and their care were conducted in conformity with the institutional guidelines that are in compliance with national (D.L. n. 116, G.U., suppl. 40, 18 Febbraio 1992) and international (*EEC Council Directive* 86/609, OJ L 358,1, Dec. 12, 1987; *NIH Guide for the Care and Use of Laboratory Animals*, NIH Publication N. 85–23, 1985; and *Guidelines for the Use of Animals in Biomedical Research*, Giles 1987) laws and policies.

Microdialysis

Rats were anesthetized with chloral hydrate (400 mg/kg i.p.) and then placed on a stereotaxic instrument (David Kopf Instruments, Tujunga, Calif.). Supplemental doses of anesthetic were administered i.p. during the experiment. A microdialysis probe (CMA/12, 2-mm length, 500-µm outer diameter; Carnegie Medicin, Stockholm, Sweden) was implanted into the left nucleus accumbens (AP=2.5; L=1.4; V=–8 from the dura surface and with respect to the bregma), according to the atlas of Paxinos and Watson (1986). The probe was perfused at a constant rate of 1 µl/min by means of a microperfusion pump (Harvard Apparatus syringe infusion pump 22, Mass.) with artificial cerebrospinal fluid (aCSF) composed of 147 mM Na^+, 2.7 mM K^+, 1 mM Mg^{2+}, 1.2 mM Ca^{2+}, 154.1 mM Cl^-, adjusted to pH 7.4 with 2 mM sodium-phosphate buffer. The aCSF was filtered through type-GS (0.22 µm) Millipore glass filters before use. Every 20 min, samples of perfusate were collected and immediately assayed by means of HPLC with electrochemical detection.

HPLC analysis

Dialysate samples were analyzed using reverse-phase HPLC coupled with electrochemical detection. The mobile phase was composed of 70 mM NaH_2PO_4, 0.1 mM Na_2 ethylene diamine tetraacetic acid (EDTA), 0.7 mM triethylamine, 0.1 mM octylsulfonic acid, and 10% methanol, adjusted to pH 4.8 with orthophosphoric acid. This mobile phase was delivered at a 1-ml/min flow rate (Pump 420, Kontron Instruments, Milano, Italy) through a Hypersil column (C18, 4.6×150 mm, 5 µm, Sigma Aldrich Chemicals, Mo.). Samples were injected manually into the HPLC unit, and detection of DA was carried out using a coulometric detector (Coulochem II, ESA, Bedford, Mass.) coupled to a dual electrode analytic cell (model 5014). The potential of the first electrode was set at –175 mV and the second at +175 mV. Under these conditions, the sensitivity for DA was 0.95 pg/20 µl, with a signal to noise ratio of 3:1.

Drug treatments

All pharmacological treatments were performed following the stabilization of DA levels in the perfusate. A stable baseline, defined as three consecutive samples in which DA content varied by less than 10%, was generally obtained 150–180 min after the beginning of the perfusion (stabilization period). Amitriptyline and mianserin were dissolved in distilled water. SB 242084 was dissolved in 0.9% saline containing 8% hydroxypropyl-β-cyclodextrin by weight and 25 mM citric acid, before injecting. RO 60-0175 was dissolved in 200 µl 10% acetic acid, made up to almost required volume with 0.9% saline and brought to pH 6.5. All drugs were given i.p. at a volume of 2 ml/kg body weight. Control rats were injected with an equal volume of vehicle only.

Histology

At the end of the experiment, the rats were perfused transcardially with 0.9% saline solution (60 ml), followed by 4% paraformaldehyde–saline solution (60 ml). The brains were removed and stored in 4% paraformaldehyde for a few days. Coronal sections (40 µm) were cut using a cryostat microtome and stained with formal-thionin. The placement of the probe was verified under a microscope.

Data analysis

In dialysis experiments, DA content in each sample was expressed as a percentage of the average baseline level calculated from three fractions collected before drug administration. Data correspond to mean±SEM values of the percentage obtained in each experimental group. The statistical analysis of the time course was performed by two-way analysis of variance (ANOVA; split-plot design) treatment × time or pretreatment × treatment, followed by Tukey's test to permit adequate multiple comparisons.

Drugs

Amitriptyline was from Research Biochemicals Incorporated (RBI) (Natick, Mass.), mianserin was purchased from Sigma Chemical Co., SB 242084 was a gift from Dr. Guy A. Kennett (SmithKline Beecham Pharmaceuticals, Harlow, UK). RO 60-0175 was kindly donated by Dr. Eva-Maria Gutknecht (F. Hoffmann-La Roche Ltd, Basel, Switzerland).

Results

Effects of amitriptyline and mianserin on DA release

Absolute basal levels of dialysate DA content, without considering probe recovery, was 5.15±0.5 pg/20 µl (n=11). As reported in Fig. 1, the injection of 10 mg/kg i.p. amitriptyline produced a significant increase in DA release, 40 min after administration, reaching the maximal effect of 31.1±7.9% relative to baseline values 100 min after administration of the drug (n=6) and producing a prolonged effect during the whole time of the experiment, without returning to baseline levels. Amitriptyline, at the dose of 5 mg/kg i.p., induced a small non-significant increase of DA efflux, whose levels rose to 16.1±4.4% relative to baseline at 160 min (n=6) (Fig. 1).

Administration of mianserin (5 mg/kg i.p.) caused an increase in DA release in the nucleus accumbens (n=6). The increase in DA was significant and reached the maximum of 33.6±4.3% with respect to baseline 60 min after injection of the drug. However, the lower dose (2.5 mg/kg i.p.) of mianserin did not cause any significant modification of DA outflow (n=5) (Fig. 1). The i.p. administration of the vehicle used to dissolve amitriptyline and mianserin in a group of control rats (n=6) did not cause any change in extraneuronal DA levels (Fig. 1).

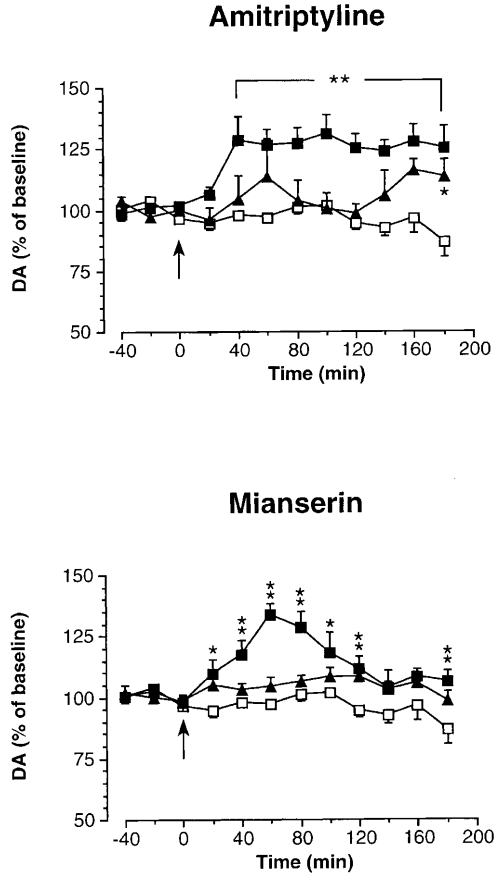

Fig. 1 Time course of the effect of i.p. administration of 5 mg/kg (▲) and 10 mg/kg (■) amitriptyline (*upper panel*) and 2.5 mg/kg (▲) and 5 mg/kg (■) mianserin (*lower panel*) on extracellular dopamine (DA) levels in the nucleus accumbens. (□) Control group treated with vehicle. Amitriptyline and mianserin were administered at the time indicated by *vertical arrows*. Each *data point* represents mean percentage±SEM of the baseline value calculated from three samples before drug injection. Each experiment was carried out on 5–6 animals per group. **P*<0.05, ***P*<0.01 versus control group; two-way ANOVA followed by Tukey's test

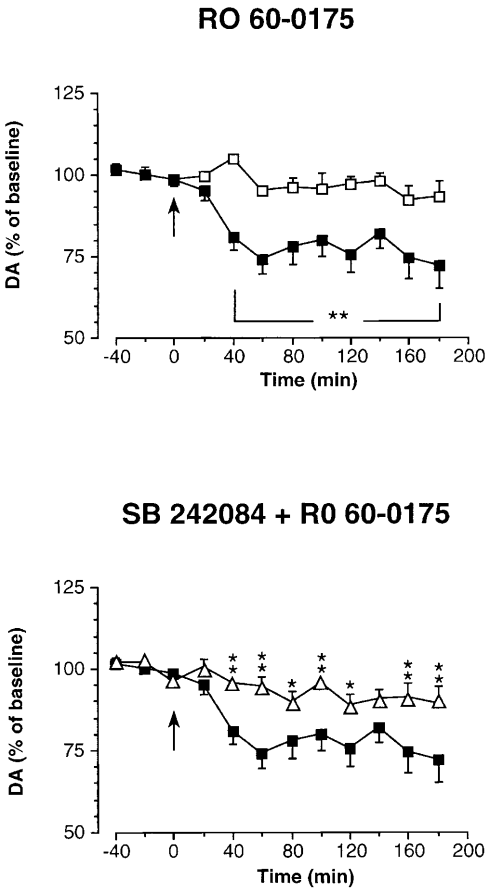

Fig. 2 *Upper panel*: time course of the effect of i.p. administration of 1 mg/kg RO 60-0175 (■) on extracellular dopamine (DA) levels in the nucleus accumbens. (□) Control group treated with vehicle. RO 60-0175 was administered at the time indicated by *vertical arrow*. Each *data point* represents mean percentage±SEM of the baseline value calculated from three samples before drug injection. Each experiment was carried out on 5–6 animals per group. ***P*<0.01 versus control group; two-way ANOVA followed by Tukey's test. *Lower panel*: time course of the effect of RO 60-0175 (1 mg/kg i.p.; ■) and effect of 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 *vertical arrow*. SB 242084 was given 10 min before RO 60-0175. Each *data point* represents mean percentage±SEM of the baseline value calculated from three samples before RO 60-0175 injection. Each experiment was carried out on 5–6 animals per group. $F_{1,10}$=10.25, **P*<0.05, ***P*<0.01; RO 60-0175 versus SB 242084 + RO 60-0175; two-way ANOVA followed by Tukey's test

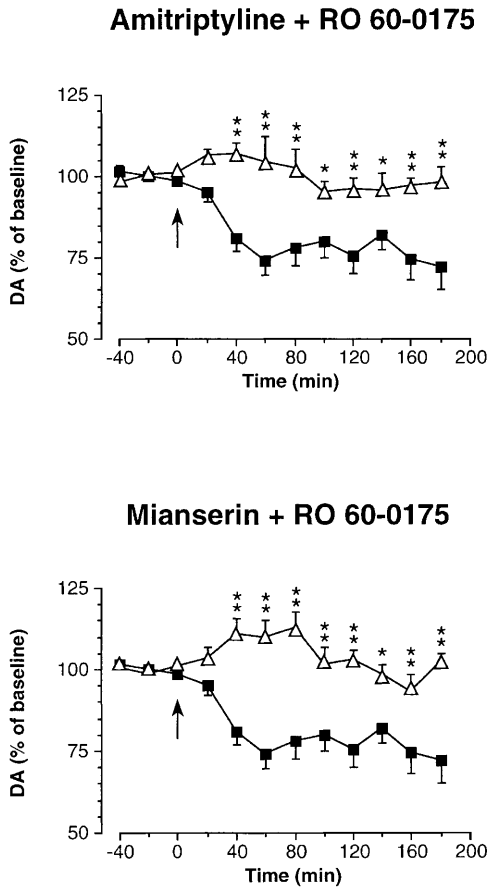

Fig. 3 *Upper panel*: time course of the effect of RO 60-0175 (1 mg/kg i.p.; ■) and pretreatment of amitriptyline (5 mg/kg i.p.; △) on extracellular dopamine (DA) levels in the nucleus accumbens. RO 60-0175 was administered at the time indicated by *vertical arrow*. Amitriptyline was given 10 min before RO 60-0175. Each *data point* represents mean percentage±SEM of the baseline value calculated from three samples before RO 60-0175 injection. Each experiment was carried out on five animals per group. $F_{1,9}$=15.77, **P*<0.05, ***P*<0.01; RO 60-0175 versus amitriptyline + RO 60-0175; two-way ANOVA followed by Tukey's test. *Lower panel*: time course of the effect of RO 60-0175 (■; 1 mg/kg i.p.) and pretreatment of mianserin (△; 2.5 mg/kg i.p.) on extracellular DA levels in the nucleus accumbens. RO 60-0175 was administered at the time indicated by *vertical arrow*. Mianserin was given 10 min before RO 60-0175. Each *data point* represents mean percentage±SEM of the baseline value calculated from three samples before RO 60-0175 injection. Each experiment was carried out on five animals per group. $F_{1,9}$=23.67, **P*<0.05, ***P*<0.01; RO 60-0175 versus mianserin + RO 60-0175; two-way ANOVA followed by Tukey's test

Effect of RO 60-0175 on DA release and its antagonism by SB 242084

Administration of the selective 5-HT_{2C} receptor agonist RO 60-0175 (1 mg/kg i.p.) (*n*=5) caused a significant decrease of DA release up to 60 min after administration (26.0±4% below baseline). The reduction in extraneuronal DA concentrations remained stable for up to 3 h after treatment (Fig. 2). Administration of the vehicle used to dissolve RO 60-0175 did not cause any significant change in DA outflow (*n*=5) (Fig. 2). Pretreatment (10 min before RO 60-0175) with the selective 5-HT_{2C} receptor blocker SB 242084 (2.5 mg/kg i.p.), at a dose that did not change basal DA release, completely blocked the inhibitory effect of RO 60-0175 (1 mg/kg i.p.) ($F_{1,10}$=10.25, *P*<0.01; *n*=6; Fig. 2).

Effect of pretreatment with amitriptyline and mianserin on the inhibitory action of RO 60-0175

Administration of the lower doses of amitriptyline (5 mg/kg i.p.) (*n*=5) and mianserin (2.5 mg/kg i.p.) (*n*=5) 10 min before RO 60-0175 (1 mg/kg i.p.) significantly prevented the inhibitory action of RO 60-0175 on the DA release in the nucleus accumbens ($F_{1,9}$=15.77, *P*<0.01 and $F_{1,9}$=23.67, *P*<0.001, respectively; Fig. 3).

Discussion

Several antidepressant drugs, including amitriptyline and mianserin, have been shown to bind with micromolar to nanomolar affinity to the 5-HT_{2C} receptor subtype in the pig brain and to antagonize mCPP-induced penile erections in rats (Jenck et al. 1993, 1994), an effect mediated through stimulation of central 5-HT_{2C} receptors (Berendsen et al. 1990; Millan et al. 1997). The present study shows that amitriptyline and mianserin, significantly enhance in vivo DA release in the nucleus accumbens. The action of amitriptyline was more prolonged than that of mianserin, which reached a peak at 60 min and then returned to baseline levels. Thus, we propose that the stimulatory action of amitriptyline and mianserin on DA release in the nucleus accumbens may be mediated through the 5-HT_{2C} receptor subtypes. This hypothesis is based on the evidence that the central 5-HT system exerts a tonic and phasic inhibitory control on mesocorticolimbic DA function by acting on 5-HT_{2C} receptors (Prisco et al. 1994; Di Giovanni et al. 1997, 1999; Lejeune et al. 1997; Di Matteo et al. 1998b; Millan et al. 1998). However, mianserin was found to enhance extracellular DA in the medial prefrontal cortex as a result of the concurrent blockade of α_2 and 5-HT_{2A} receptors (Tanda et al 1996). In addition, several typical and atypical antipsychotic drugs with prominent 5-HT_{2A} antagonistic properties were shown to increase DA release in the nucleus accumbens (Nomikos et al. 1994; Hertel et al. 1996; Marcus et al. 1996). Nevertheless, it is unlikely that, under our experimental conditions, mianserin could have enhanced DA release by blocking 5-HT_{2A} receptors, inasmuch as the highly selective 5-HT_{2A} antagonists RP 62203, MDL 100907, and SR 46349B failed to modify mesocorticolimbic DA function (Sorensen et al. 1993; Schmidt 1996; Di Matteo et al. 1998b; Di Giovanni et al. 1999). Moreover, selective blockers of α_2 receptors did not change basal DA release in the nucleus accumbens, thus ruling out an involvement of this receptor subtype in the control of mesolimbic DA function (Tanda et al 1996; Hertel et al. 1999).

With regard to amitriptyline, it is well known that it blocks α_1 adrenergic, H_1 histaminergic, and muscarinic acetylcholine receptors (Richelson 1996; Frazer 1997). Although high doses of H_1 antagonists were found to cause a transient increase in DA release in the nucleus accumbens (Dringenberg et al. 1998), neither α_1 nor muscarinic antagonists affected DA release (Meltzer et al. 1994; Mathe et al. 1996). Therefore, considering that amitriptyline causes a sustained increase in DA outflow in the nucleus accumbens, it is unlikely that this effect is mediated by blockade of H_1 histaminergic receptors.

The selective 5-HT_{2C} receptor agonist RO 60-0175 significantly decreased DA release, while amitriptyline and mianserin, given at doses that did not affect basal DA function, antagonized the effect of RO 60-0175 on accumbal DA outflow, further indicating that the stimulatory effect of these two drugs on DA release may involve a blockade of 5-HT_{2C} receptors. This statement is also strengthened by the evidence that SB 242084, a potent and selective 5-HT_{2C} antagonist (Kennett et al. 1997), completely blocked the inhibitory action of RO 60-0175 on DA release in the nucleus accumbens. In view of the hypothesis that disinhibition of the mesolimbic dopaminergic system underlies the mechanism of action of several antidepressant drugs (Cervo and Samanin 1987, 1988; Plaznik and Kostowski 1987; Cervo et al. 1990; De Montis et al. 1990), the findings of this study that amitriptyline and mianserin raised DA extracellular concentrations by blocking 5-HT_{2C} receptors in the mesolimbic system are of particular interest. These results may suggest that, in addition to other effects on monoaminergic systems, antagonistic properties on brain 5-HT_{2C} receptors are a possible component of the antidepressant properties of these drugs.

The fact that some antidepressants bind to the 5-HT_{2C} receptors might suggest the involvement of this receptor in depressive states. The possible involvement of 5-HT_{2C} receptors in the pathogenesis of depressive disorders and in the mode of action of antidepressants is further substantiated by several other observations. For example, the chronic mild stress procedure, which induces a depression-like state in animals, was shown to enhance 5-HT_{2C} receptor mediated function, as measured in vivo by mCPP-induced penile erections. Conversely, two different antidepressant treatments (72-h REM sleep deprivation and 10-day administration of moclobemide, a reversible inhibitor of monoamine oxidase type A) resulted in a reduction of this 5-HT_{2C} receptor-mediated function (Moreau et al. 1993), supporting the hypothesis that 5-HT_{2C} receptors may be altered, and presumably may exist in a dysregulated (hypersensitive) state in depressive illness. Therefore, it is tempting to speculate that adaptive processes resulting from chronic antidepressant treatment (i.e., desensitization and/or downregulation of 5-HT_{2C} receptors) may normalize this dysregulated state (Moreau et al. 1996). In this respect, it is interesting to note that chronic treatment with 5-HT_{2C} receptor agonists or antagonists resulted in a paradoxical downregulation of 5-HT_{2C} receptors (Barker and Sanders-Bush 1993; Pranzatelli et al. 1993; Moreau et al. 1996; Newton and Elliott 1997). Moreover, in vitro and in vivo binding studies have shown that the downregulation of 5-HT_{2C} receptors observed after chronic exposure to mianserin is a direct receptor-mediated mechanism of this drug at these receptors (Pranzatelli et al. 1993; Barker et al. 1994; Rocha et al. 1994; Newton and Elliott 1997). Therefore, it is conceivable that modifications of 5-HT_{2C} receptor functions might be an important component in the pharmacological effects of some antidepressants, such as mianserin and amitriptyline.

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 anti-anhedonic effects of tricyclic antidepressants, mianserin, and fluoxetine were abolished by pretreatment with the 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 and nigrostriatal DA function are implied in the pathophysiology of depression (Brown and Gershon 1993; Fibiger 1995).

In conclusion, this study provides evidence that antidepressants such as amitriptyline and mianserin act as 5-HT_{2C} receptor antagonists and stimulate in vivo DA release in the nucleus accumbens, when administered acutely. However, it is difficult to evaluate the relevance of this effect in the antidepressant action of amitriptyline and mianserin since the clinical effect of antidepressant drugs becomes evident only after chronic administration. Therefore, it would be of interest to study the effects of chronic treatment with both amitriptyline and mianserin on 5-HT_{2C} receptor function and on DA release in the nucleus accumbens.

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