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ORIGINAL INVESTIGATION

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Agomelatine(S 20098) antagonizes the penile erections induced by the stimulation of 5-HT_{2C} receptors in Wistar rats

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Abstract Agomelatine, an antidepressant with melatonin agonist and 5-HT_{2C} antagonist properties, as well as two of its main metabolites, S 21517 (*N*-[2-(7-hydroxy-1-naphtyl)ethyl]acetamide) and S21540 (*N*-[2-(3-hydroxy-7-methoxynaphtalen-1-yl)ethyl]acetamide), have been assessed in vitro on pig choroid plexus preparations to determine their affinities for 5-HT_{2C} receptors and their effects on inositol phosphate production. These compounds were also tested for their ability to inhibit the penile erections induced by the 5-HT_{2C} receptor agonists, *m*-(chlorophenyl)piperazine (mCPP, 0.75 mg/kg, SC) and Ro 60-0175 (2.5 mg/kg, SC) in Wistar rats. These in vivo effects were compared to those of melatonin and the 5-HT antagonists pizotifen and SB 206,553. Agomelatine and S 21517 had moderate affinity for 5-HT_{2C} receptors and behaved in vitro as weak antagonists at this receptor subtype. S 21540 had a 10-fold lower affinity. Pizotifen and SB 206,553 antagonized mCPP- and Ro 60-0175-induced penile erections, suggesting that penile erections induced by mCPP or Ro 60-0175 resulted from the stimulation of 5-HT_{2C} receptors. Whereas increasing doses (from 1.25 to 40 mg/kg, IP) of melatonin were unable to modify the penile erections induced by mCPP and Ro 60-0175, agomelatine (from 1.25 to 40 mg/kg, IP) dose-dependently decreased mCPP- as well Ro 60-0175-induced penile erections. Furthermore, increasing doses (from 1.25 to 40 mg/kg, IP) of S 21517 and S 21540, the two main metabolites of agomelatine, did not affect the penile erections induced by mCPP and Ro 60-0175. Considering the similar activity of melatonin and agomelatine at melatonin receptors, these data suggested that the reported effects were not due to the stimulation of melatonin receptors and that, contrary to melatonin, agomelatine exerted 5-HT_{2C} receptor antagonist properties in addition to its agonist activity at melatonin receptors. Finally, neither S 21517 nor S 21540 seemed to participate to the observed inhibition of penile erections by agomelatine.

Keywords Melatonin · Agomelatine · 5-HT_{2C} receptors · Penile erections · Rats

Dr. Protais died in 2002

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Introduction

Agomelatine (S 20098; *N*[2-(7-methoxy-1-naphthyl)ethyl] acetamide) is a new antidepressant active in rodent models predictive of antidepressant properties (Bertaina-Anglade et al. 2002; Bourin et al. 2002; Papp et al. 2003), and with demonstrated clinical efficacy in major depressive disorders (Lôo et al. 2002). It has been shown that its efficacy cannot be exclusively attributed to its agonist activity on MT_1/MT_2 receptors. Agomelatine has high affinities for cloned human MT_1 and MT_2 melatonin receptor subtypes (K_i=6.15×10^{-11} M and 2.68×10^{-10} M, respectively) comparable to melatonin affinities for these receptors (Yous et al. 1992; Conway et al. 2000). A number of studies have also demonstrated the chronobiotic activity of agomelatine. Thus, agomelatine resynchronized experimentally disrupted circadian rhythms in rodents (Armstrong et al. 1993; Redman et al. 1995; Martinet et al. 1996; Van Reeth et al. 1997), and this effect is related to its agonist activity on melatonin receptors of the SCN (Ying et al. 1996; Redman and Francis, 1998). Though an evaluation of the interaction of agomelatine with a broad range (>80) of receptors and enzymes, it has been demonstrated that agomelatine had

negligible affinity ($IC_{50}>10^{-5}$ M) for all tested receptors, including dopamine D_1–D_5 and adrenergic receptors, but interacted with 5-HT_{2C} receptors. This observation is of particular interest inasmuch as 5-HT_{2C} receptors are implicated in the etiology and treatment of depressive states. A variety of established antidepressants including classical tricyclics, mianserin, trazodone and fluoxetine display moderate to high affinity for 5-HT_{2C} receptors and play a modulatory role on brain 5-HT_{2C} receptor function (Jenck et al, 1993; Palvimaki et al. 1996). Moreover, efficient antidepressants like amitriptyline, imipramine, desipramine, maprotilin and mianserin are antagonists of this receptor subtype. Clinical data also indicate that non-specific antagonists of 5-HT_{2C} receptors are effective in the treatment of depression (Strauss and Klieser 1991; Staner et al. 1992). Therefore, it is relevant to consider whether agomelatine can exert in vivo effects through its blockade of 5-HT_{2C} receptors.

Penile erections in rats can be induced by the 5-HT_{2C} receptor agonists mCPP (Humphrey et al. 1993), a metabolite of trazodone, or Ro 60-0175 [(*S*)-2-(6-chloro-5-fluoroindol-1-yl)-1-methylamine] (Berendsen et al. 1990; Protais et al. 1995; Millan et al. 1997). We therefore decided to first study the interaction of mCPP and Ro 60-0175 with melatonin, agomelatine and two of its main metabolites, S 21517 (*N*-[2-(7-hydroxy-1-naphtyl) ethyl] acetamide) and S21540 (*N*-[2-(3-hydroxy-7-methoxynaphtalen-1-yl) ethyl] acetamide), on the model of penile erections in Wistar rats. In a preliminary step, we also tested the efficacy of the 5-HT_{2C} receptor antagonists pizotifen and SB 206,553 [(5-methyl-1-(3-pyridil-carbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*] indole)]. Subsequently, we have performed in vitro binding studies with agomelatine, S 21517 and S21540 to investigate their affinities for 5-HT_{2C} receptors, and determine their effects on the production of inositol-phosphates.

Materials and methods

Ethical statement

The experiments of this study were carried out in accordance with the French Regulations for the Use and Care of Experimental Animals.

In vitro binding

Agomelatine and its three metabolites S 21540, S 21517 and S 22380 (10^{-9} to 10^{-4} M) were assessed on pig choroid plexus membranes incubated with ^{3}H-mesulergine. Pig choroid plexi were homogenized with a Polytron homogenizer in 10 vol of 0.32 M sucrose in 50 mM TRIS HCl (pH 7.7 at 25°C) and were centrifuged at 900 *g* for 10 min. Supernatant was centrifuged at 70,000 *g* for 15 min and the pellet re-suspended in 10 vol buffer. The suspension was vortexed and incubated at 37°C for 15 min and centrifuged again at 70,000 *g* for 15 min. The final pellets were re-suspended in 50 mM TRIS HCl (pH 7.7 at 25°C) containing 4 mM $CaCl_2$, 0.1% ascorbic acid and 10 μM pargyline (Fluka, Switzerland).

^{3}H-Mesulergine (Amersham, TRK 845, 85 Ci/mmol) was used to measure 5-HT_{2C} receptors following the method of Pazos et al. (1984). ^{3}H-Mesulergine (0.5 nM) was incubated with choroid plexi membranes in 500 μl of buffer in the absence or presence of agomelatine or the metabolites, or 1.0 μM serotonin (5-HT, Sigma), which was used to define the non-specific binding. The incubation was carried out for 30 min at 37°C before the reaction was stopped by filtration through Whatman GF/C glass fiber filters. Filters were washed quickly with three 5 ml portions of ice-cold 50 mM TRIS buffer and were counted in 5 ml Ready Safe by scintillation counting at an efficiency of 45%. The ten concentrations of agomelatine and its metabolites were tested in duplicate assays. Inhibition curves were analysed with the software EBDA (Cambridge, UK) and results were expressed as IC_{50} and K_i values.

Production of inositol-phosphates

Accumulation of inositol phosphate in pig choroid plexi cell preparations was carried out as described by Hoyer et al. (1989). agomelatine, S 21517, S 21540 (10^{-7} to 10^{-4} M), mesulergine (10^{-9} to 10^{-6} M) and 5-HT (10^{-8} to 10^{-5} M) were applied to pig choroid plexi cell preparations incubated with ^{3}H-inositol and EC_{50} values for stimulation or inhibition of inositol phosphates were determined. Choroid plexi were dissected and placed into ice-cold Krebs Ringer bicarbonate buffer (containing 123 mM NaCl, 5 mM KCl, 0.8 mM $CaCl_2$, 1.3 mM $MgSO_4$, 1.4 mM KH_2PO_4, 26 mM $NaHCO_3$, 50 mM glucose). The tissue was sieved through a strainer (pore size 250 μm) and cells were obtained by centrifugation at 400 *g*, 3 min, 4 °C. Cells were collected in 50 ml Krebs buffer gassed with 95% O_2/5% CO_2 and incubated for 30 min at 37 °C. The cells were allowed to settle, the medium was removed and replaced by 6 ml fresh Krebs buffer containing ^{3}H-myo-inositol (3.33 μCi/ml, Amersham). Following a 1 h incubation at 37°C, cells were washed, then suspended in Krebs buffer containing 10 mM LiCl and 10 μM pargyline (Fluka). Aliquots of 50 μl test drugs, 50 μl Krebs buffer and 400 μl cell suspension were added to the suspension and incubated for 1 h at 37°C. The reaction was stopped by 1 ml hot (80°C) 10 mM Na_2 EDTA. Samples were centrifuged at 1500 *g* for 5 min. One ml of the supernatant was placed on column of Dowex 1×8 resin (Fluka), Cl^- form and columns were rinsed twice with 5 ml ultra-pure water. Then, 3 ml of 1 M HCl were added to the columns in order to elute ^{3}H-inositol phosphate into scintillation vials. Samples were counted in a Beckman 6500LS liquid scintillation counter. Experiments were performed in triplicate.

Saturation and inhibition curves were analysed with the software EBDA (Cambridge, UK) to determine EC_{50} values.

Penile erections

Penile erections were measured in male Wistar rats (WI, Charles River, weighing 200–250 g) using experimental conditions described previously (Protais et al. 1983, 1995). Briefly, rats housed in an air-conditioned room under controlled 12-h light-dark cycle (light on at 8 a.m.) were injected IP with 5-HT antagonists or melatonin derivatives. Thirty minutes later, they received an SC injection of mCPP (0.75 mg/kg) or Ro 60-0175 (2.5 mg/kg). Dosages of mCPP and Ro 60-0175 were chosen from dose-response curves performed in previous experiments (Protais et al. 1995; Millan et al. 1997). For the observations, rats were introduced into rectangular cages (L=25 cm; W=18 cm; H=30 cm) with vertical walls of wire netting. Immediately after the injection of the 5-HT_{2C} agonists, penile erections (rats in an upright position presenting an emerging and engorged penis) were counted by direct observation during 60 min. All the experiments were carried out between 9 a.m. and 7 p.m., without taking care of phases of circadian rhythms of rats. Melatonin, agomelatine and its metabolites were suspended in a 1% hydroxyethylcellulose solution. Other drugs were dissolved in saline or in distillated water. All the solutions were prepared extemporaneously. All doses, expressed as the free base of respective salts, were injected in a volume of 5 ml/kg. An analysis

of variance (ANOVA), followed by Student's *t*-test, was applied to evaluate the significance of means.

Results

In vitro binding and production of inositol-phosphates

Agomelatine and S 21517 have moderately high affinities for 5-HT_{2C} receptors (K_i=2.1×10^{-7} and 1.3×10^{-7} M, respectively). The metabolite S 21540 has a 10-fold lower affinity (K_i=1.8×10^{-6} M) (Table 1).

Whereas 5-HT stimulated the production of inositol phosphates in cell preparations of pig choroid plexi with mean EC_{50} values of 4.0±1.1×10^{-7} M, agomelatine, S 21517 and S 21540 (up to 10^{-4} M) were inactive to stimulate the production of inositol phosphates.

Since these compounds did not stimulate inositol-phosphate formation, their effects on 10 μM 5-HT-induced production of inositol-phosphates were tested. Agomelatine, S 21517 and S 21540 (10^{-7} to 10^{-4} M) were antagonists at 5-HT_{2C} receptors, with a rank order of efficacy as follows: S 21517>agomelatine>S 21540. By comparison, mesulergine (10^{-9} to 10^{-6} M) potently inhibited the 5-HT stimulated accumulation of inositol phosphates (Table 2).

Effects of pizotifen and SB-206,553 on penile erections induced by mCPP or Ro 60-0175

At the dose of 0.75 mg/kg (SC), mCPP induced a mean of three or four penile erection episodes in 1 h; some yawns were also observed. Penile erections induced by mCPP were significantly antagonized by pizotifen at doses of 3.5 and 14 mg/kg (IP) [$F(2,27)$=21.20, P<0.0001] and by SB 206,553 at doses of 2 and 8 mg/kg (IP) [$F(2,21)$=22.07, P<0.0001; Fig. 1].

Table 1 K_i and IC_{50} (M) values for the displacement of ^{3}H-mesulergine binding to 5-HT_{2C} receptors of pig choroid plexus cell preparations. Values are from displacement curves with ten concentrations performed in duplicate

	IC_{50} (M)	K_i (M)
Agomelatine	3.8×10^{-7}	2.1×10^{-7}
S 21517	2.4×10^{-7}	1.3×10^{-7}
S 21540	3.2×10^{-6}	1.8×10^{-6}
5-HT	2.4×10^{-8}	1.3×10^{-8}

Table 2 Effect of agomelatine, S 21517, S 21540 and mesulergine on 5-HT-stimulated inositol phosphate production in pig choroid plexus cell preparations. Agomelatine, S 21517 and S 21540 were tested at increasing concentrations from 10^{-7} M to 10^{-4} M, and mesulergine from 10^{-9} M to 10^{-6} M. Experiments were performed in triplicate

	K_i (M)
Agomelatine	1.1±0.3×10^{-6}
S 21517	0.7±0.9×10^{-6}
S 21540	3.8±3.0×10^{-6}
Mesulergine	0.9±0.2×10^{-9}

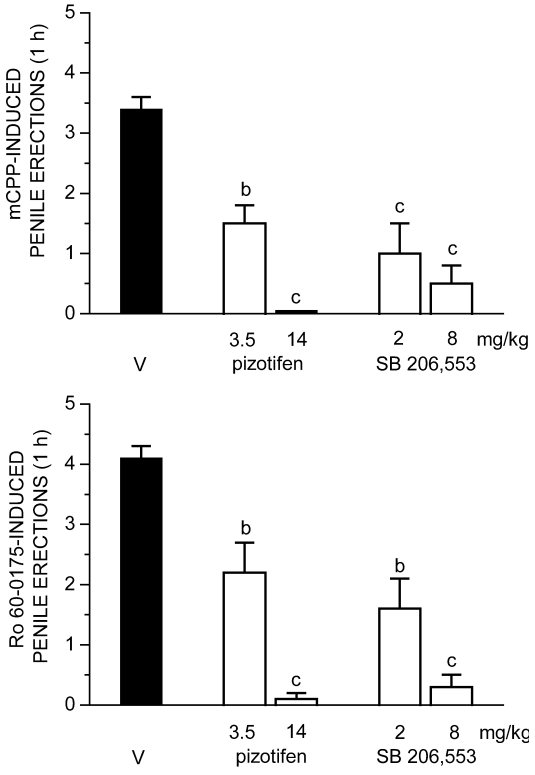

Fig. 1 Interaction of pizotifen and SB 206,553 with mCPP or Ro 60-0175 on penile erections in Wistar rats. Pizotifen and SB 206,553 were injected IP 30 min before the SC injection of mCPP (0.75 mg/kg) or Ro 60-0175(2.5 mg/kg) and the counting of penile erections during a 60-min period starting from the injection of mCPP or Ro 60-0175. Mean±SEM from 8–10 rats per group. ^bP<0.01; ^cP<0.001 as compared to rats receiving vehicle (*V*) in place of 5-HT antagonists

At the dose of 2.5 mg/kg (SC), Ro 60-0175 induced a mean of about four penile erection episodes in 1 h, but did not induce yawns. Penile erections induced by Ro 60-0175 were also significantly antagonized by pizotifen at doses of 3.5 and 14 mg/kg (IP) [$F(2,27)$=2.55, P<0.0001] and by SB 206,553 at doses of 2 and 8 mg/kg (IP) [$F(2,21)$=18.97, P<0.0001; Fig. 1].

Effects of increasing doses of melatonin, agomelatine, S 21517 and S 21540 on mCPP- or Ro 60-0175-induced penile erections in Wistar rats

Increasing doses of melatonin from 1.25 to 40 mg/kg (IP) were unable to affect mCPP-induced penile erections [$F(6,63)$=1.15, P>0.05]. In contrast, penile erections induced by mCPP were inhibited by increasing doses of agomelatine [$F(6,113)$=22.17, P<0.0001]. A significant antagonism of mCPP-induced penile erections was observed from 10 mg/kg agomelatine (IP), and at the dose of 40 mg/kg agomelatine, mCPP-induced penile erections

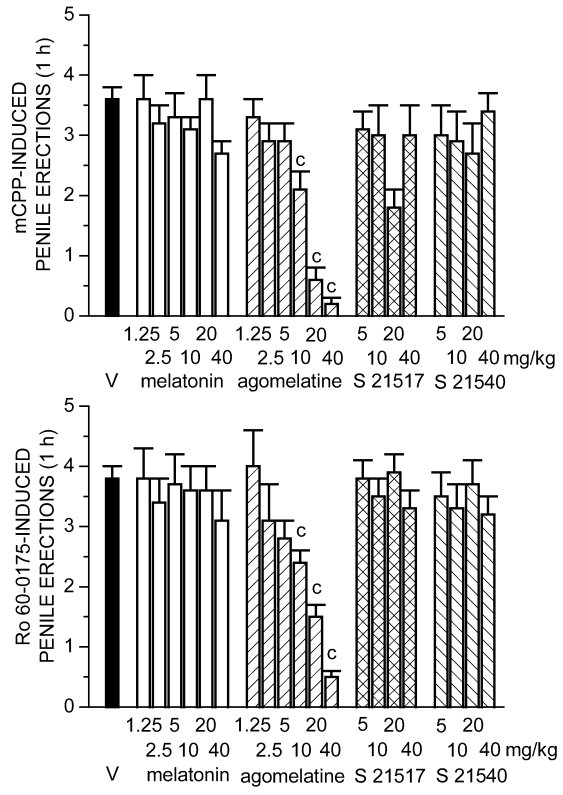

Fig. 2 Effects of increasing doses of melatonin, agomelatine, S 21517 and S 21540 on penile erections induced by mCPP or Ro 60-0175 in Wistar rats. Melatonin, agomelatine, S 21517 and S 21540 were injected IP 30 min before the SC injection of mCPP (0.75 mg/kg) or Ro 60-0175 (2.5 mg/kg) and the counting of penile erections during a 60-min period starting from the injection of mCPP or Ro 60-0175. Mean±SEM from 10–20 rats per group. $^{c}P<0.001$ as compared to rats receiving 1% hydroxy-ethylcellulose solution (*V*) in place of melatonin derivatives

were almost completely prevented. The ID_{50} of agomelatine was 10.2±1.4 mg/kg. Dosages of S 21517 or of S 21540 from 5 to 40 mg/kg (IP) were unable to modify significantly mCPP-induced penile erections [$F(4,45)=1.96$, $P=0.116$, NS; $F(4,45)=0.33$, $P>0.8$, NS, respectively; Fig. 2].

The same pattern of responses was observed for penile erections induced by Ro 60-0175 (2.5 mg/kg, SC). Whereas increasing doses of melatonin from 1.25 to 40 mg/kg (IP) did not modify Ro 60-0175-induced penile erections [$F(6,63)=0.266$, $P>0.8$, NS], the same dose range of agomelatine dose-dependently decreased Ro 60-0175-induced penile erections [$F(6,113)=7.187$, $P<0.0001$] with a significant inhibition from 10 mg/kg leading to an almost complete abolition at 40 mg/kg. The ID_{50} of agomelatine was 13.0±1.8 mg/kg. Dosages of S 21517 or of S 21540 from 5 to 40 mg/kg (IP) were unable to modify significantly Ro 60-0175-induced penile erections [$F(4,45)=0.82$, $P=0.817$, NS; $F(4,45)=0.25$, $P>0.8$, NS, respectively; Fig. 2].

Discussion

Our data confirm previous studies indicating that the stimulation of 5-HT_{2C} receptors activates specifically neuronal mechanisms involved in rat penile erections (Berendsen et al. 1990; Protais et al. 1995; Millan et al. 1997). Indeed, mCPP and Ro 60-0175, two well known 5-HT_{2C} receptor agonists (Zifa and Fillion 1992; Martin et al. 1998) induced penile erection episodes similar to those observed following the injection of dopamine receptor agonists (Protais et al. 1995), but did not induce yawning behaviour, or a little in the case of mCPP. Furthermore, penile erections induced by mCPP or Ro 60-0175 were antagonized by the non-selective 5-HT antagonist pizotifen (Zifa and Fillion 1992), and by the 5-HT_{2C} antagonist SB 206,553 (Kennett et al. 1996; Millan et al. 1997).

Agomelatine dose-dependently decreased mCPP- as well as Ro 60-0175-induced penile erections. Given the high affinity of agomelatine to MT1/MT2 receptors, the first hypothesis explaining its effects on mCPP- or Ro 60-0175-induced penile erections would be a melatonin receptor mediated mechanism. However, increasing doses of melatonin were unable to modify the penile erections induced by mCPP and Ro 60-0175. The differences between the results observed with melatonin and agomelatine on penile erections induced mCPP and Ro 60-0175 do not seem to reflect different activities at melatonin receptors since both compounds display very close affinities in the picomolar range at melatonin receptor subtypes, and behave as agonist of melatonin receptors (Grassi-Zucconi et al. 1996; Martinet et al. 1996; Ying et al. 1996; Wiley et al. 1998; Conway et al. 2000; Weibel et al. 2000). The effects of melatonin and agomelatine at MT1/MT2 receptors were observed at low doses with a maximal effect at 5 mg/kg (IP) (Ying et al. 1996), whereas the complete inhibition of penile erections induced by 5-HT_{2C} agonists was observed only at 40 mg/kg agomelatine (IP). Furthermore, the observed effects were not related to the phases of circadian rhythms of rats since experiments were performed over a large daily period of time (from 9 a.m. to 7 p.m.). These data suggest that the antagonism of penile erections induced by mCPP and Ro 60-0175 by agomelatine does not depend upon the stimulation of melatonin receptors.

Since mCPP and Ro 60-0175 induce penile erections through the stimulation of 5-HT_{2C} receptors, it seems likely that agomelatine antagonizes penile erections by blocking 5-HT_{2C} receptors, like pizotifen or SB 206,553. This conclusion is strengthened by the in vitro binding studies indicating that agomelatine binds to 5-HT_{2C} receptors ($K_i=2.1\times10^{-7}$ M) and acts as a 5-HT_{2C} antagonist. In fact, agomelatine possesses a dual mechanism of activity in acting as a 5-HT_{2C} receptor antagonist and as an agonist at melatonin receptors, and previous studies have proposed that its antidepressant efficacy is based on its combined engagement of MT_1/MT_2 and 5-HT_{2C} receptors (Bertaina-Anglade et al, 2002; Bourin et al. 2002; Papp et al. 2003).

Among other hypothesis, agomelatine could affect penile erections through dopaminergic or adrenergic systems. However, several results argue against this hypothesis. Except for MT1/MT2 and 5-HT_{2C} receptors, agomelatine has negligible affinity ($IC_{50}>10^{-5}$ M) for more than 80 tested receptors, including dopamine D_1 to D_5 and adrenergic receptors. Accordingly, agomelatine (as well as melatonin) has no main impact on the rat dopaminergic system since, when administered 2 h before the darkness onset, either acutely (1.25, 5, 10, 20, 40 mg/kg IP) or chronically (10 mg/kg IP for 15 days), both compounds exerted no effect on the apomorphine (0,75 mg/kg SC)-induced spontaneous behaviour, including rearing, sniffing, biting and grooming (unpublished results). Moreover, the almost complete prevention of penile erections observed with the highest dose of agomelatine cannot be related to sensorimotor deficits of rats since, up to the dose of 64 mg/kg, no such deficits are noted in the Irwin test with agomelatine, and particularly no modification of locomotor activity (Porsolt, unpublished results).

In the present study, neither 3-hydroxylated (S 21540) and demethylated (S 21517) metabolites of agomelatine, were able to modify the penile erections induced by mCPP or Ro 60-0175. Both metabolites of agomelatine have at least 100 times less affinity than the native compound to melatonin receptors, and indeed, unlike agomelatine, they cannot re-entrain free running rhythms of Long Evans rats in constant dim light (Redman and Francis 1998). The present in vitro binding results also show that the metabolites' affinities for 5-HT_{2C} receptors were equal or lower than that of agomelatine. It could be suggested that the doses of S 21517 and S 21540 used in the present study (up to 40 mg/kg) were too low to efficiently inhibit mCPP or Ro 60-0175-induced penile erections. However, it seems unlikely that the metabolism of the highest tested dose of agomelatine (40 mg/kg), which completely antagonizes the penile erections induced by 5-HT_{2C} receptor agonists, could lead to plasma concentrations of S 21517 or S 21540 which are higher than those obtained following the administration of 40 mg/kg S 21517 or S 21540. Indeed, metabolism studies at both pharmacological and toxicological doses in rat have shown only a weak plasma amount of non-conjugated S 21517 (<5% of native compound).

In conclusion, our results suggest that the antagonism by agomelatine of penile erections induced by mCPP or Ro 60-0175 is not due to the stimulation of melatonin receptors and that agomelatine, despite its relatively low in vitro affinity for 5-HT_{2C} receptors, is a potent in vivo antagonist at 5-HT_{2C} receptors, a property which is not shared by melatonin. Interestingly, the efficacy of agomelatine in our model is obtained at doses that also support its antidepressant activity (Bertaina-Anglade et al. 2002; Bourin et al. 2002; Papp et al. 2003). In addition, at the effective doses of agomelatine, the 5-HT_{2C} receptor blockade is a pharmacological property of the native product and not of its metabolites.

Clearly, the in vitro affinity of agomelatine at 5-HT_{2C} receptors is substantially lower (>100-fold) than that at MT_1/MT_2 receptors. At the opposite, in vivo chronobiotic effects of agomelatine are generally observed at doses with a maximal effect around 5 mg/kg (Martinet et al. 1996; Ying et al. 1996), whereas inhibition of penile erections was observed at doses between 10 and 40 mg/kg, i.e. in the range of doses that support its antidepressant activity (Bertaina-Anglade et al, 2002; Bourin et al. 2002; Papp et al. 2003). Thus, in vivo, the dose necessary to get a complete 5-HT_{2C}-mediated inhibition of penile erections (40 mg/kg) is only 8-fold higher than for getting its maximal chronobiotic activity. This ratio is far less pronounced than what would be expected from the differential agomelatine affinities at 5-HT_{2C} versus MT_1/MT_2 sites. Accordingly, Ying et al. (1996) have shown that, thanks to its high lipophilicity, agomelatine easily crosses the blood-brain barrier in rodents.

Together with the absence of significant effect of melatonin per se in the present model, these results strongly suggest that the antagonism of penile erections by agomelatine most probably depends on its antagonist property at 5-HT_{2C} receptors.

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