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Cataleptogenic effect of subtype selective 5-HT receptor antagonists in the rat

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Abstract

5-HT receptor antagonists with selectivity for 5-HT_{1A} WAY-100635 (*N*-[2-[-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl)cyclohexanecarboxamide), 5-HT_{1B} GR 127935 (*N*-[methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′(5-methyl-1,2,4-oxadiazol-3-yl)[1,1-biphenyl]-4-carboxamide · HCl), 5-HT_{2C} SB 200646A (*N*-(1-methyl-5-indolyl)-*N*′-(3-pyridyl)urea · HCl) and 5-HT_{2A} (ketanserin, fananserin and MDL 100,151 [1] ((±)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol) receptors were tested for cataleptogenic responses in rats. WAY-100635 (0.1–3 mg/kg, s.c.), ketanserin (0.1–3 mg/kg, s.c.), MDL 100,151 (0.3–3 mg/kg, s.c.) and fananserin (RP 62203; 3 mg/kg, s.c.) induced a significant catalepsy. GR 127935 (1 mg/kg, s.c.), SB 200646A (without effect per se at 10 mg/kg, s.c.) and MDL 100,151 (0.3 mg/kg, s.c.) did not inhibit the cataleptic response to the dopamine D_2 receptor antagonist, loxapine (0.3 mg/kg, s.c.). Catalepsy induced by MDL 100,151 (3 mg/kg) was blocked by co-treatment with clozapine, but not by SB 200646A (both at 10 mg/kg, s.c.). Although clozapine displays significant affinity to 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C} receptors, the present results suggest that blockade of these receptors is not responsible for clozapine's anticataleptic activity.

Keywords: Catalepsy; 5-HT receptor antagonist; Receptor subtype; Clozapine

1. Introduction

5-HT receptor agonists and antagonists modulate in a complex manner the cataleptogenic effect of dopamine D_2 receptor antagonists in rats. Thus, serotonin re-uptake inhibitors such as citalopram, CGP 6085, clomipramine or zimeldine have been consistently found to enhance catalepsy provoked by haloperidol or raclopride (Waldmeier and Delini-Stula, 1979; Balsara et al., 1979; Wadenberg and Ahlenius, 1995). On the other hand, the directly acting 5-HT_{1A} receptor agonists 8-hydroxy-2-(di-*n*-propylamino)tetraline (8-OH-DPAT), ipsapirone, gepirone and flesinoxan (Invernizzi et al., 1988; McMillen et al., 1988; Elliott et al., 1990; Hicks, 1990; Wadenberg and Ahlenius, 1991; Neal-Beliveau et al., 1993; Lucas et al., 1997) and the preferential 5-HT_{2A} receptor agonists, DOB (1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane) and DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane)(Elliott et al., 1990; Hicks, 1990; Neal-Beliveau et al., 1993; Wadenberg and Ahlenius, 1995) consistently inhibit D_2-receptor-mediated catalepsy. The somewhat preferential 5-HT_{2C} receptor agonists, mCPP (*m*-chlorophenylpiperazine) and quipazine were reported either not to affect (McMillen et al., 1988; Elliott et al., 1990) or to enhance the cataleptogenic effect of haloperidol (Balsara et al., 1979). In contrast, the literature regarding the effects of mixed 5-HT_{2A}/5-HT_{2C} receptor antagonists (mianserin, ritanserin, mesulergine) on dopamine D_2 receptor-mediated catalepsy is particularly inconsistent and results vary between inhibition (Hicks, 1990; Bligh-Glover et al., 1995; Lucas et al., 1997), no effect (Wadenberg, 1992; Bligh-Glover et al., 1995) or potentiation (Elliott et al., 1990).

During the last few years several excellent subtype-selective 5-HT receptor antagonists have become available. In the present series of experiments, we tested the novel 5-HT_{1A} receptor selective antagonist, WAY-100635 (Forster et al., 1995), the 5-HT_{1B} receptor-selective antagonist GR 127935 (Skingle et al., 1994), three 5-HT_{2A} receptor-selective antagonists, ketanserin (Leysen et al., 1982),

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[1] The active (+)-enantiomer is known as MDL 100,907.

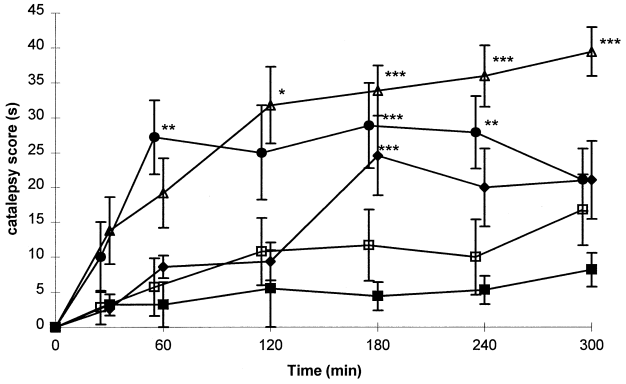

Fig. 1. Cataleptic effect of the 5-HT_{1A} receptor antagonist WAY-100635 (0.1–3 mg/kg, administered s.c. at $t = 0$), expressed in s, determined in during 300 min at 60 min intervals. Key to the symbols: filled squares: WAY-100635 0 mg/kg (controls); open squares: 0.1 mg/kg; filled diamonds: 0.3 mg/kg; open diamonds: 1.0 mg/kg and open triangles: 3.0 mg/kg. Data represent mean values ± S.E.M. of groups of 10 rats. WAY-100635 induced significant catalepsy at 0.3, 1 and 3 mg/kg (*t*-test with Bonferroni correction for multiple comparisons; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$).

MDL 100,151 (the racemic mixture containing the (+)-enantiomer known as MDL 100,907; Sorensen et al., 1993; Arnt, 1996), fananserin (RP 62203; Malgouris et al., 1993) and the novel 5-HT_{2C} receptor selective antagonist, SB 200646A (Kennett et al., 1994) for their cataleptogenic activity per se and for their ability to influence catalepsy induced by loxapine.

The atypical antipsychotic drug clozapine has high affinity for 5-HT_{2A} and 5-HT_{2C} receptors (Meltzer et al., 1989; Coward, 1992). According to one theory, the absence of dopamine D_2 receptor-mediated catalepsy with clozapine, is due to its concomitant potent 5-HT_{2A} receptor blockade (Meltzer et al., 1989; Meltzer, 1995). In the present experiments all three 5-HT_{2A} receptor antagonists unexpectedly induced a cataleptic response. In order to learn more about the mode of action of clozapine, it was therefore tested whether the catalepsy induced by MDL 100,151 would be susceptible to inhibition by clozapine. In view of the variable effects obtained with mixed 5-HT_{2A}/5-HT_{2C} receptor antagonists and the consistent cataleptogenic responses with selective 5-HT_{2A} receptor antagonists, it was also tested whether the 5-HT_{2C} receptor antagonist SB 200646A would inhibit the response to MDL 100,151.

2. Materials and methods

2.1. Animals

Male Wistar rats (220–250 g) were housed in groups of 5 with food and water freely available.

2.2. Experimental procedure

Catalepsy was measured at $t = 0$, 0.5, 1 h and then at hourly intervals up to 5 h in a quiet, dimly lit laboratory. Rats were placed with the forepaws on a wooden block (7 cm high) and the time, up to a maximum of 45 s, spent with the forepaws on the wooden block, without a deliberate move to step down, was determined. Three consecutive attempts to place the rat onto the wooden block were made at each time point with the longest latency taken as the reading. Data are expressed as means ± S.E.M. Each experimental group consisted of 10 animals. The experiments were performed strictly according to a protocol accepted by the Basel Stadt Cantonal Veterinary Service.

2.3. Statistics

The Student *t*-test with Bonferroni correction for multiple comparisons was used to compare groups.

2.4. Compounds

Loxapine and ketanserin were purchased from RBI, whilst all other compounds were synthesised at Novartis. It should be noted that MDL 100,151 is the racemate of

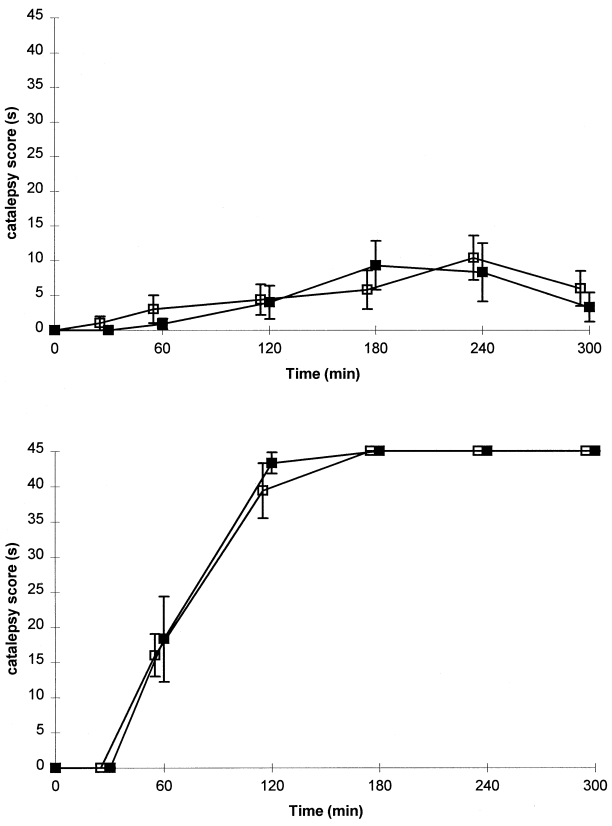

Fig. 2. The 5-HT_{1B} receptor antagonist GR 127935 (1 mg/kg s.c. at $t = 0$; open squares) was not significantly more cataleptogenic than its solvent (filled squares; top panel). Bottom panel: the cataleptic response to loxapine (0.3 mg/kg s.c.; filled squares) was not significantly suppressed by co-administration of GR 127935 (1 mg/kg s.c.; open squares). Catalepsy is expressed in seconds and was measured during 300 min at 60 min intervals. Data represent mean values ± S.E.M. of groups of 10 rats.

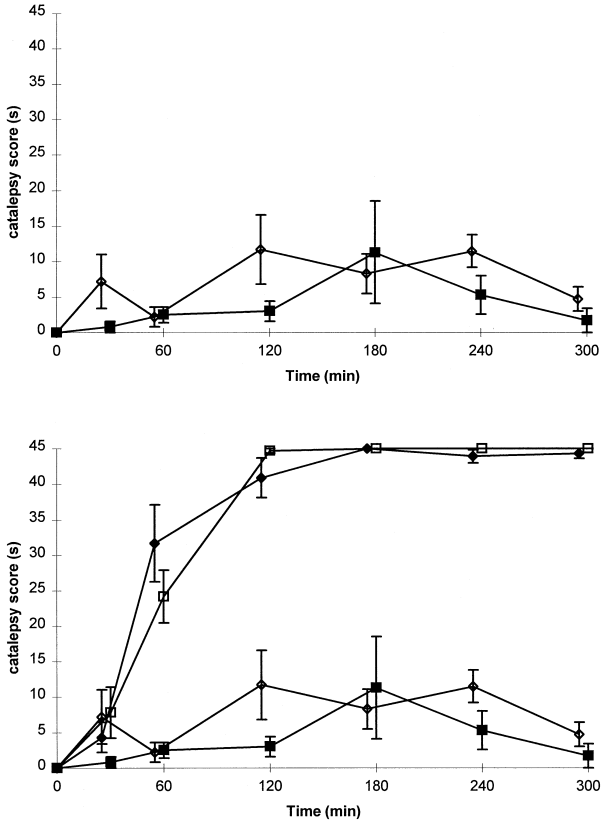

Fig. 3. The 5-HT_{2C} receptor antagonist SB 200646A (10 mg/kg s.c. at $t = 0$; open diamonds) was not significantly more cataleptogenic than its solvent (filled squares; top panel). Bottom panel: the cataleptic response to loxapine (0.3 mg/kg s.c.; filled squares) was not significantly suppressed by the co-administration of SB 200646A (10 mg/kg s.c.; open squares). Catalepsy is expressed in s and was measured during 300 min at 60 min intervals. Data represent mean values ± S.E.M. of groups of 10 rats.

MDL 100,907 (Sorensen et al., 1993), which is the active (+)-enantiomer.

WAY-100635 and GR 127935 were dissolved in physiological saline. MDL 100,151, loxapine, ketanserin and clozapine were dissolved in a small volume of 0.2 ml acetic acid (10%) and further diluted with physiological saline. SB 200646A and fananserin were dissolved in *N*-methylpyrrolidone and diluted with H_2O. In combination experiments, drugs were administered consecutively, at $t = 0$ min.

3. Results

The selective 5-HT_{1A} receptor antagonist, WAY-100635 (0.3–3 mg/kg, s.c.) dose-dependently increased catalepsy scores with several rats in the highest dose-group reaching the cut-off level of 45 s (Fig. 1). The 5-HT_{1B} receptor antagonist, GR 127935 (1 mg/kg, s.c.) neither induced catalepsy when given alone (Fig. 2; top panel) nor inhibited catalepsy induced by loxapine (Fig. 2; bottom panel). Similar results were obtained with the selective 5-HT_{2C} receptor antagonist, SB 200646A (10 mg/kg, Fig. 3). In contrast, the three putatively selective 5-HT_{2A} receptor antagonists, MDL 100,151, fananserin and ketanserin were clearly cataleptogenic under the present test conditions. Thus, ketanserin dose-dependently increased catalepsy scores at doses between 0.1 and 3 mg/kg (Fig. 4). Fananserin (3 mg/kg) was also clearly cataleptogenic (Fig. 5), although tested at only one dose due to a limited availability of compound. MDL 100,151 provoked significant catalepsy at the doses of 0.3–3 mg/kg with the maximum response occurring at 1 mg/kg (Fig. 6; top panel). MDL 100,151 (0.3 mg/kg) failed to modify loxapine-induced catalepsy (Fig. 6; bottom panel), but clozapine (10 mg/kg) suppressed the cataleptic response to MDL 100,151 (3 mg/kg; Fig. 7; top panel). SB 200646A (10 mg/kg) did not affect the cataleptic response to MDL 100,151 (3 mg/kg; Fig. 7; bottom panel).

4. Discussion

Many 5-HT_{1A} receptor agonists differ markedly in their intrinsic agonist activity and, depending on the test used, the same compound can appear as an agonist, partial agonist or 'silent' antagonist (Fletcher et al., 1993; Assié and Koek, 1996). As described in Section 1, 5-HT_{1A} receptor agonists, including those with relatively low intrinsic activity, invariably have been found to inhibit the cataleptic response induced by dopamine receptor antagonists. WAY-100635 is the first selective 5-HT_{1A} receptor antagonist which lacks partial agonist activity even in models with a high receptor reserve (Forster et al., 1995; Assié and Koek, 1996). Since partial agonists are anti-

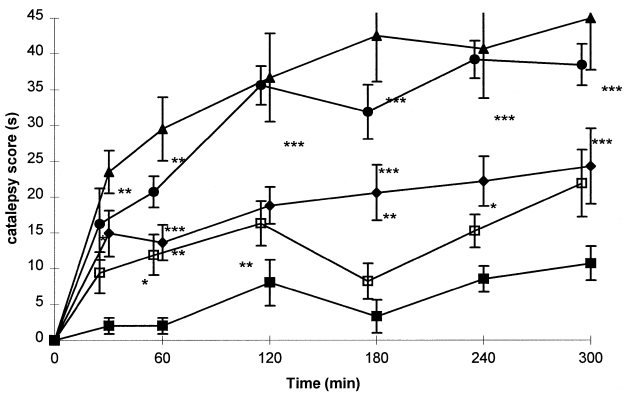

Fig. 4. Cataleptic effect of the 5-HT_{2A} receptor antagonist ketanserin (0.1–3 mg/kg, administered s.c. at $t = 0$), expressed in seconds, determined in during 300 min at 60 min intervals. Key to symbols: filled squares: ketanserin 0 mg/kg (controls); open squares: 0.1 mg/kg; filled diamonds: 0.3 mg/kg; open diamonds: 1.0 mg/kg; filled triangles: 3.0 mg/kg. Data represent mean values ± S.E.M. of groups of 10 rats. Ketanserin induced significant catalepsy at 0.1, 0.3, 1 and 3 mg/kg (*t*-test with Bonferroni correction for multiple comparisons; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$).

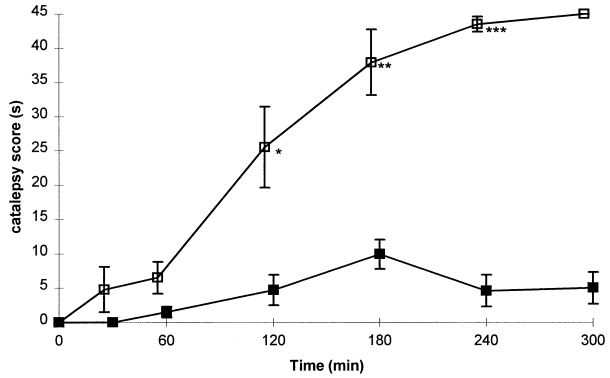

Fig. 5. Cataleptic effect of the 5-HT_{2A} receptor antagonist fananserin (RP 62203; 3 mg/kg, administered s.c. at $t = 0$; open squares), expressed in s, determined in during 300 min at 60 min intervals. Controls: filled squares. Data represent mean values ± S.E.M. of groups of 10 rats. Fananserin induced significant catalepsy (*t*-test with Bonferroni correction for multiple comparisons; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$).

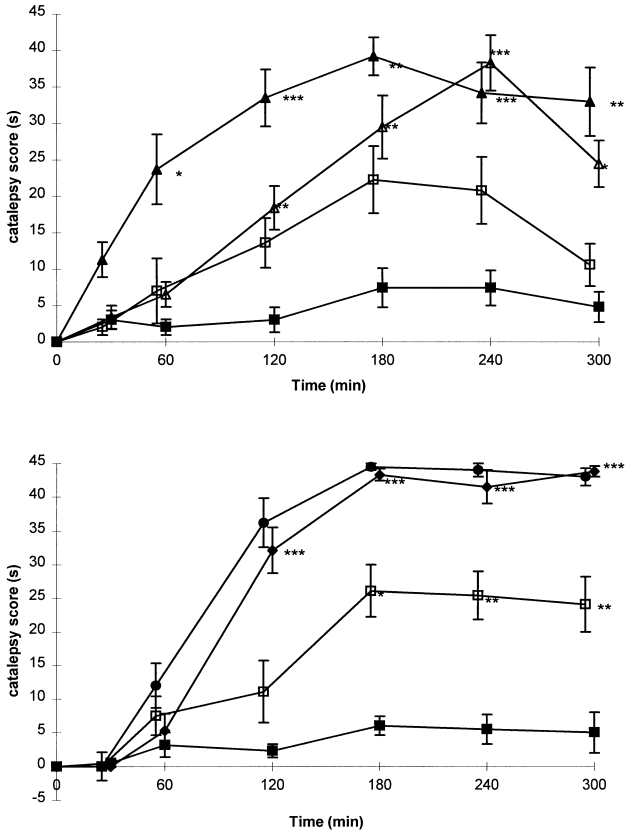

Fig. 6. Top panel: Cataleptic effect of the 5-HT_{2A} receptor antagonist MDL 100,151, administered s.c. at $t = 0$), expressed in s and measured during 300 min at 60 min intervals. Key to symbols: MDL 100,151 (0 mg/kg): filled squares; 0.3 mg/kg: open squares; 1.0 mg/kg filled triangles; 3.0 mg/kg open triangles. Data represent mean values ± S.E.M. of groups of 10 rats. Statistically significant cataleptic responses (*t*-test with Bonferroni correction) were obtained at 1 and 3 mg/kg, but not with 0.3 mg/kg. In the lower panel it is shown that MDL 100,151 (0.3 mg/kg; open squares) was cataleptic in this particular experiment. The cataleptic response to loxapine (0.3 mg/kg, s.c.; filled diamonds) was not suppressed by co-administration of MDL 100,151 (open diamonds); Control animals (filled squares) received the two solvents. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

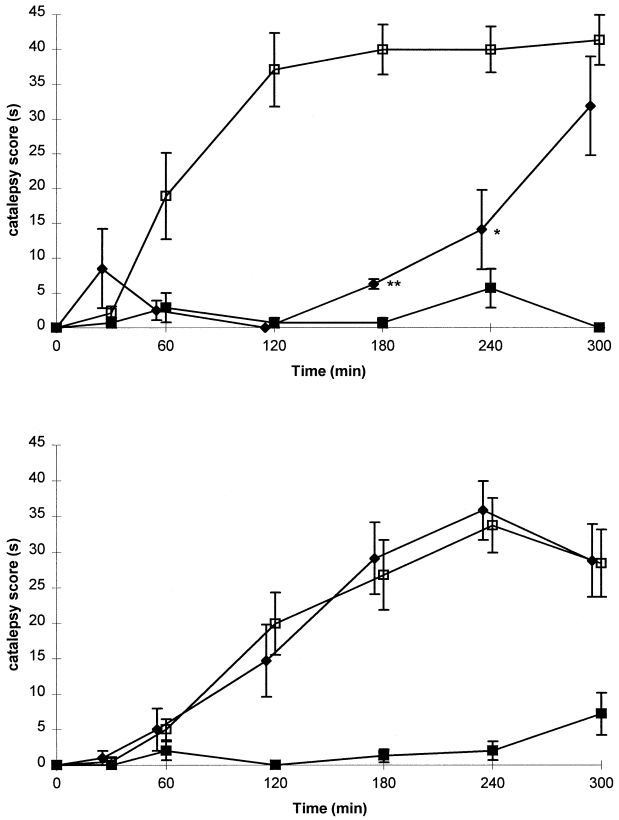

Fig. 7. Cataleptic response to MDL 100,151 (3 mg/kg s.c. at $t = 0$) with (filled diamonds) or without co-treatment (open squares) with clozapine (10 mg/kg s.c. at $t = 0$; top panel) or SB 200646A (10 mg/kg s.c. at $t = 0$; bottom panel). Control animals (filled squares) were co-administered the respective solvents. Catalepsy is expressed in s and was measured during 300 min at 60 min intervals. Data represent mean values ± S.E.M. of groups of 10 rats. Clozapine, but not SB 100646A, significantly inhibited the response to the 5-HT_{2A} receptor antagonists (*t*-test with Bonferroni correction; $^{*}P < 0.05$; $^{**}P < 0.01$).

cataleptic, the observation that the silent 5-HT_{1A} receptor antagonist, WAY-100635, caused catalepsy may not be, therefore, too surprising. To our knowledge, such an observation has not, however, been reported previously. Admittedly, the doses of WAY-100635 required are certainly at the high end of the dose range that has been found to inhibit the behavioural or endocrine response to selective 5-HT_{1A} receptor agonists (an ID_{50} of 0.01 mg/kg has been found for inhibition of the 8-OH-DPAT induced behavioural syndrome in rats and guinea-pigs, for example). On the other hand, even at 100-fold higher doses WAY-100635 maintains its selectivity (Forster et al., 1995; Table 1). It is conceivable that full 5-HT_{1A} receptor occupation is required for the induction of catalepsy, hence, explaining why even low efficacy 5-HT_{1A} receptor agonists, such as ipsapirone, are consistently anticataleptic (see Section 1).

The preferential 5-HT_{2A} receptor agonists, DOI and DOB, inhibit neuroleptic drug-induced catalepsy (Elliott et al., 1990; Hicks, 1990; Neal-Beliveau et al., 1993; Wadenberg and Ahlenius, 1995). However, the responses ob-

Table 1
In vitro receptor binding affinities (pK_d) at selected binding sites

	Receptor					
	5-HT_{2A}	5-HT_{2C}	5-HT_{1A}	D_2	D_4	α_1
MDL 100,151	8.4[a]	7.0[a]	4.9[a]	3.9[a]	5.7[a]	6.8[a]
Fananserin	9.9[b]	7.6[b]	7.1[b]	6.4[c]	8.8[c]	8.4[b]
Ketanserin	8.7[d]	7.0[e]	5.9[e]	6.7[d]	—	8.0[d]
WAY-100635	6.0[f]	6.0[f]	8.9[f]	< 6.9[f]	—	6.6[f]

pK_d values (nM) are from the following sources: [a]Hoyer, unpublished; [b]Malgouris et al. (1993); [c]Heuillet et al. (1996); [d]Leysen et al. (1981); [e]Hoyer (1988); [f]Forster et al. (1995).

tained with 5-HT_2 receptor antagonists are conflicting (see Section 1). Antagonists which discriminate between 5-HT_{2A} and 5-HT_{2C} receptors have only recently become available. Surprisingly, the first compound in this class, ketanserin evoked a clear-cut and dose-dependent catalepsy at doses between 0.1 and 3 mg/kg (Fig. 4). However, ketanserin also has considerable affinity for the α_1-adrenoceptor (see Table 1) and since the classical α_1-adrenoceptor antagonist, prazosin is weakly cataleptic (unpublished results), a role for α_1-adrenoceptors in the response to ketanserin cannot be entirely excluded. Fananserin (3 mg/kg), like ketanserin evoked a cataleptic response in the present experiments. However, as with ketanserin, an influence of α_1-adrenoceptor blockade cannot be ruled out (see Table 1). In addition, though initially considered to be more selective than ketanserin (see also Table 1) its selectivity has been recently compromised by the discovery of its high affinity for dopamine D_4 receptors (Heuillet et al., 1996). The consequence of dopamine D_4 receptor blockade with respect to the induction of catalepsy is unknown, although the selective D_4 receptor antagonists, L-745,870 and U-101397 are reported to be without cataleptogenic potential at doses thought to fully occupy D_4 receptors (Merchant et al., 1996; Bristow et al., 1997).

Perhaps the best pharmacological tool to test the influence of 5-HT_{2A} receptor blockade is MDL 100,907, a compound which displays high potency to the 5-HT_{2A} site (pK_d 9.1) and 100-fold selectivity over the 5-HT_{2C} site (Kehne et al., 1996). In addition, the selectivity vis-à-vis other receptors such as the α_1-adrenoceptor, the dopamine D_4 or D_2 receptor subtypes is even larger (pK_d values of 6.8, 6.3 and 5.6), respectively (Palfreyman et al., 1993; Kehne et al., 1996). In the present experiments, MDL 100,151, which is the racemate with MDL 100,907 as the active enantiomer, was used. The racemic compound essentially retained its pharmacological selectivity (see Table 1). MDL 100,151 induced cataleptic responses at 0.3, 1 and 3 mg/kg. This result is at variance with Sorensen et al. (1993), who reported that MDL 100,907 was ineffective at 1 mg/kg. Whether the use of the active enantiomer, rather than the racemate explains the discrepancy in results, is presently unknown. The most parsimonious conclusion from the experiments, using three different 5-HT_{2A} receptor antagonists, is that central 5-HT_{2A} receptor blockade leads to a cataleptic response. Inspection of Figs. 4–6 shows that the onset of cataleptic activity, compared to a standard neuroleptic drug like loxapine, is slower, with maximal effects seen towards the end of the 5 h observation period. This may be one explanation why a cataleptic response to 5-HT_{2A} receptor antagonists has not been noted before. Again it must be stated that the doses at which the 5-HT_{2A} receptor antagonists produced catalepsy are relatively high. For instance, blockade of central 5-HT_{2A} receptors in rats by MDL 100,907, quantified as inhibition of 5-HTP-induced head twitches, was achieved at doses of approximately 0.1 mg/kg (Kehne et al., 1996). Similar to the situation with the 5-HT_{1A} receptor antagonist, catalepsy may be seen only after complete occupation of 5-HT_{2A} receptors.

The absence of extrapyramidal side effects with clozapine has been ascribed to its high 5-HT_{2A} antagonist activity relative to its affinity for D_2 receptors (Meltzer et al., 1989). In the literature this possibility has been questioned (Casey, 1993; Kapur, 1996). The present results obtained with ketanserin, fananserin and MDL 100,151 are also inconsistent with this hypothesis. In addition, loxapine and olanzapine have quite similar 5-HT_{2A}/D_2 receptor affinity ratios as clozapine, yet clozapine inhibits the cataleptic response to loxapine, olanzapine (Kalkman et al., 1997) and MDL 100,151. These observations provide a strong argument against the idea that 5-HT_{2A} receptor blockade is the explanation for clozapine's low EPS profile. The argument is further reinforced by the observation that MDL 100,151 at a high, and only weakly cataleptic dose (0.3 mg/kg) failed to modify the catalepsy induced by loxapine.

Whereas both clozapine and its *N*-desmethyl metabolite, norclozapine, have high affinity for 5-HT_2 receptors, norclozapine is slightly 5-HT_{2C} receptor-selective vis-à-vis 5-HT_{2A} receptors (Kuoppamäki et al., 1993). These authors suggested that, while attempting to explain the low EPS liability of clozapine, the interaction with the 5-HT_{2C} receptor should not be dismissed. Fox and Brotchie (1996) have used norclozapine in locomotion experiments in rats and suggested that ''5-HT_{2C} receptor antagonists may have a potential as treatment for Parkinsons disease''. However, the 5-HT_{2C} receptor antagonist, SB 200646A, at a dose (10 mg/kg) which is capable of blocking 5-HT_{2C} receptor-mediated responses (Kennett et al., 1994) did not induce catalepsy when tested alone or alter loxapine-induced catalepsy. It therefore seems unlikely that 5-HT_{2C} receptor antagonism influences cataleptogenic mechanisms but other 5-HT_{2C} receptor antagonists need to be tested before a final conclusion can be made.

The selective 5-HT_{1B} receptor antagonist, GR 127935 (1 mg/kg) neither provoked a cataleptic response, nor did it affect loxapine-induced catalepsy. The dose used for these experiments can be considered sufficient to block 5-HT_{1B} receptor-mediated responses. In guinea-pigs, hy-

pothermia induced by stimulation of central 5-HT_{1B} (5-$HT_{1D\beta}$) receptors, was blocked by GR 127935 at oral doses between 0.1 and 1 mg/kg (Skingle et al., 1994). In neurochemical studies in guinea-pigs, GR 127935 (0.1–1 mg/kg, i.p.) significantly increased 5-HT metabolism in forebrain regions (Hutson et al., 1995), whilst the reduction in extracellular 5-HT induced by a 5-HT_1 receptor agonist was abolished by GR 127935 at a dose of 0.05 mg/kg (Skingle et al., 1995). Hypophagia in rats induced with the 5-HT_{1B} receptor agonist, RU 24969, was blocked by GR 127935 (1 mg/kg s.c.; Hartley et al., 1995). Thus, the lack of effect against loxapine-induced catalepsy suggests that this response is not susceptible to central 5-HT_{1B} receptor blockade. Some uncertainty has arisen recently with respect to the intrinsic activity of GR 127935, since it was found that in cells which expressed the human recombinant 5-HT_{1B} receptor, GR 127935 induced an agonist response (Watson et al., 1996; Zgombick et al., 1996). Clearly, other selective and truly 'silent' 5-HT_{1B} receptor antagonists need to be tested.

The present experiments were performed with the aim of learning more about the mechanisms of action of clozapine by using antagonists selective for serotonin receptor subtypes for which clozapine has significant affinity. Clozapine also binds with moderate affinity to other 5-HT receptors such as 5-HT_6 and 5-HT_7 (Roth et al., 1994) and it has been speculated that this could contribute to its unique antipsychotic profile. Unfortunately, selective 5-HT_6 or 5-HT_7 receptor antagonists have still to be disclosed.

Taking the present and previous findings together, a remarkably consistent picture emerges: whilst 5-HT_{1A} and 5-HT_{2A} receptor agonists are anticataleptic, high doses of a selective 5-HT_{1A} and 5-HT_{2A} receptor antagonists induce a cataleptic response. In contrast, 5-HT_{2C} and 5-HT_{1B} receptors seem to have little influence on cataleptogenic mechanisms. Most importantly though, the results indicate that the strong anticataleptic effect of clozapine is probably not caused by blockade of either 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} or 5-HT_{2C} receptors. In this respect it may be worth mentioning that the anticataleptic effect of clozapine can neither be ascribed to an *agonist* effect at 5-HT_{1A} receptors (Bartoszyk et al., 1996).

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