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In vivo and *in vitro* activity of selective 5-hydroxytryptamine$_2$ receptor antagonists

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1 The abilities of ketanserin, ritanserin, R56413 and LY53857 to inhibit 5-hydroxytryptamine (5-HT) and noradrenaline-induced vasoconstrictor responses both *in vitro* and *in vivo* and to lower blood pressure in the rat, were compared.

2 In the isolated perfused mesenteric artery preparation of the rat all of the compounds tested were found to be potent inhibitors of 5-HT-induced vasoconstrictor responses. Ritanserin was the most potent compound, producing more than 50% inhibition of a near maximal response to 5-HT at a concentration of 10^{-11}M. All four compounds were found to be competitive antagonists of noradrenaline; ketanserin being the most potent with a pA_2 value of 7.64 ± 0.06.

3 5-HT-induced pressor responses in the pithed rat were inhibited by low doses ($0.3-10\,\mu g\,kg^{-1}$) of the four compounds. Ketanserin, at doses of $0.1-3.0\,mg\,kg^{-1}$, resulted in rightward shifts of the control dose-response curve to noradrenaline in the pithed rat. None of the other compounds had any significant effect on the noradrenaline-induced pressor responses.

4 Ketanserin ($0.1-1\,mg\,kg^{-1}$) produced a dose-dependent decrease in the mean arterial blood pressure of anaesthetized rats. The maximum decrease in blood pressure observed following a dose of $1\,mg\,kg^{-1}$ ketanserin was 73.7 ± 4.7 mmHg. The other compounds at doses of $1.0-3.0\,mg\,kg^{-1}$ produced a decrease in blood pressure of a lesser magnitude than that following ketanserin. In addition, this effect did not appear to be dose-dependent.

5 It is suggested that the acute hypotensive effect of ketanserin results predominantly from α_1-adrenoceptor blockade. The involvement of antagonism of 5-HT$_2$ receptors in the hypotensive effect of the other compounds tested cannot be excluded.

Introduction

On the basis of radioligand binding studies, Peroutka & Snyder (1979) defined two distinct binding sites for 5-hydroxytryptamine (5-HT), designated 5-HT$_1$ and 5-HT$_2$. Ketanserin, a potent and selective inhibitor of binding at the 5-HT$_2$ site (Leysen *et al.*, 1981), is also able to inhibit the vasoconstrictor effects of 5-HT in a variety of isolated tissues at low concentrations (Van Nueten *et al.*, 1981b). In addition, the observation that ketanserin is able to lower blood pressure in experimental animals (Van Nueten *et al.*, 1981a; Persson *et al.*, 1982) and in man (De Cree *et al.*, 1981; Wenting *et al.*, 1982) has renewed interest in the involvement of 5-HT in hypertension. However, the mechanism of the hypotensive effect of ketanserin remains controversial since ketanserin also possesses appreciable α_1-adrenoceptor antagonist activity and it appears that the acute administration of ketanserin in rats produces a hypotensive effect at doses similar to those required to block α_1-adrenoceptors (Fozard, 1982; Kalkman *et al.*, 1982). Further, other 5-HT$_2$ receptor antagonists with lower affinity for the α_1-adrenoceptor than ketanserin do not lower blood pressure in the rat (Fozard, 1982; Cohen *et al.*, 1983).

On the other hand, chronic administration of ketanserin in the spontaneously hypertensive rat has been shown to lower blood pressure in the absence of any direct involvement of α_1-adrenoceptor blockade (Pettersson *et al.*, 1984). In man, the mechanism of the hypotensive effect of ketanserin is also unclear as there are conflicting reports concerning the importance of α_1-adrenoceptor blockade (Ball *et al.*, 1983; Reimann & Frölich, 1983; Wenting *et al.*, 1984).

In the present study we have compared the ability of ketanserin and other 5-HT$_2$ receptor antagonists such as ritanserin, R56413 (Janssen, 1985) and LY53857 (Cohen *et al.*, 1983) to inhibit 5-HT- and noradren-

aline-induced vasoconstriction both *in vitro* and *in vivo*. In addition, their ability to lower blood pressure in the anaesthetized rat was investigated.

Methods

Male albino Wistar rats weighing 300.8 ± 5.3 g ($n = 128$) were used in this study.

Rat mesenteric artery preparation

Mesenteric arteries were excised from rats anaesthetized with pentobarbitone sodium (60 mg kg^{-1}, i.p.) and prepared for perfusion by the method of McGregor (1965). The superior mesenteric artery was cannulated and perfused with a modified Krebs-Henseleit solution of the following composition (mM): NaCl 117.5, $NaHCO_3$ 25.3, KCl 5.4, NaH_2PO_4 1.15, $CaCl_2$ 2.52, $MgSO_4$ 0.57 and glucose 11.1. The solution was gassed with a mixture of 95% O_2 and 5% CO_2 and was maintained at a temperature of 37°C. The tissues were perfused at a constant rate of 2 ml min^{-1} and the perfusion pressure was recorded continuously via a side-arm of the arterial cannula by means of a Statham pressure transducer attached to a Grass 79D Polygraph. Responses to noradrenaline and 5-HT were obtained by perfusing the tissue with a known concentration of either agonist for 10 s as described by Coupar & McLennan (1978). Each tissue was equilibrated for 30 min before construction of a dose-response curve to either of the agonists. Doses of noradrenaline and 5-HT were delivered at 5 min intervals. To examine the effects of the antagonists, the tissues were perfused with a known concentration of the antagonist for 30 min before the construction of a second dose-response curve.

Pithed rats

Rats were anaesthetized by inhalation of halothane, the trachea cannulated and the brain and spinal cord destroyed by introducing a blunt needle through the right eye orbit. Immediately after pithing the animals were artificially respired by use of an air pump at the rate of 60 strokes min^{-1} and a volume of 20 ml $stroke^{-1}\,kg^{-1}$. Systemic arterial pressure was measured from the right common carotid artery with a Statham Pressure Transducer and recorded on a Grass 79D Polygraph. The right jugular vein was cannulated for intravenous administration of drugs.

Following an initial 30 min equilibration period, dose-response curves were constructed to either noradrenaline or 5-HT. To examine the effects of the antagonists, rats were injected with one dose of the antagonist and after a further 20 min the dose-response curve was repeated.

Anaesthetized rats

Rats were anaesthetized by an i.p. injection of pentobarbitone sodium (60 mg kg^{-1}). The carotid artery and jugular vein were cannulated as described above. At the completion of the surgical procedures the rats received an intravenous (i.v.) injection of pentobarbitone sodium (12 mg kg^{-1}). Following a 30 min equilibration period the rats were injected with one dose each of one of the antagonists or the vehicle and their blood pressure and heart rate were recorded for a further 60 min.

Drugs

The following drugs were used: ketanserin (R41468, 3[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-2,4(1H,-3H)-quinazolinedione as tartrate salt), (gift: Janssen); LY53857 [4-isopropyl-7-methyl-9-(2-hydroxy-1-methylpropoxycarbonyl)-4, 6, 6A, 7, 8, 9, 10, 10A-octahydroindolo(4,3-FG)quinoline maleate], (gift: Eli Lilly); ritanserin (R55667, 6-[2-[4-*bis*(4-fluoro-phenyl) methylene]-1-piperidinyl]ethyl-7-methyl-5H-thiazolo-[3,2-a]-pyrimidin-5-one); R56413 (3-[2-[4-*bis*(4-fluorophenyl)-methylene]-1-piperidinyl]ethyl]-2-methyl-4H-pyrido-[1,2-a] pyrimidin-4-one 2 HCl; both Janssen); 5-HT creatinine sulphate and noradrenaline hydrochloride (Sigma). In the *in vitro* studies all of the antagonists were prepared in stock solutions of 1 mM in distilled water with the exception of ritanserin which was suspended in distilled water and dissolved with the addition of a minimum amount of HCl. 5-HT was prepared in a stock solution of 10 mM in Krebs-Henseleit solution. Noradrenaline was prepared in a stock solution of 32 mM in distilled water adjusted to pH 2 by the addition of HCl. Ascorbic acid (0.3 mg ml^{-1}) was added to dilute noradrenaline solutions to protect against oxidation. For the *in vivo* studies, solutions of 1 mg ml^{-1} of the antagonists were prepared. Ketanserin, LY53857 and R56413 were dissolved in saline. Ritanserin was dissolved in saline adjusted to pH 2.6 with HCl. 5-HT and noradrenaline were prepared as 2 mg ml^{-1} solutions in saline. The stock solution of noradrenaline and all dilutions were protected against oxidation by the addition of 0.3 mg ml^{-1} ascorbic acid. All drug concentrations refer to the base.

Statistical analysis

In the rat mesenteric artery studies, the antagonist activities of the agents were compared by use of pA_2 values determined by the method of Arunlakshana & Schild (1959) or of IC_{50} values against noradrenaline or 5-HT. In the *in vivo* preparations, values are expressed as the mean ± s.e.mean.

Table 1 The antagonist activity of 5-HT$_2$ antagonists against noradrenaline and 5-hydroxytryptamine (5-HT) determined in the rat mesenteric artery preparation

Compound	*Noradrenaline* (pA_2)	*5-HT* (IC_{50}M)	*5-HT selectivity ratio**
Ketanserin	7.64 ± 0.06 (4)	3×10^{-11} (4)	760
Ritanserin	7.28 ± 0.07 (3)	$< 10^{-11}$ (4)	>5250
R56413	7.14 ± 0.14 (3)	1×10^{-11} (4)	7240
LY53857	6.12 ± 0.08 (4)	3×10^{-10} (4)	2530

*The 5-HT selectivity ratio is obtained by dividing the antilog ($-pA_2$) (noradrenaline) by the IC_{50} (5-HT) value. A higher value represents greater selectivity for 5-HT as opposed to noradrenaline antagonism. The number in parentheses is the number of tissues used to determine each value.

Results

Rat mesenteric artery preparation

Perfusion of the rat mesenteric artery preparation with solutions containing noradrenaline or 5-HT increased the perfusion pressure in a dose-dependent manner, the maximum responses being 200.4 ± 11.0 ($n = 14$) or 57.9 ± 4.1 ($n = 16$) mmHg, respectively. In control tissues, the dose-response curves for noradrenaline- and 5-HT-induced vasoconstriction were, following a 30 min equilibration period, reproducible with no change evident in the maximum response obtained. In addition no change in the ED_{50} dose for either agonist was observed. Antagonist drugs, at the concentrations used, did not alter the basal perfusion pressure. The antagonists did however inhibit the noradrenaline- and 5-HT-induced increase in perfusion pressure.

The antagonism of the noradrenaline-induced vasoconstriction was competitive in nature. Ketanserin was found to be the most potent antagonist and the least potent was LY53857. The pA_2 values determined against noradrenaline are shown in Table 1.

The antagonism of the 5-HT response appeared to be non-competitive in nature. The maximum response to 5-HT was reduced in the presence of each antagonist. This is in agreement with the results of McLennan & Taylor (1984), who demonstrated that ketanserin was an apparently non-competitive antagonist of 5-HT-induced vasoconstriction in the isolated perfused mesenteric artery preparation of the rat. In an attempt to quantify the 5-HT antagonism, IC_{50} values were determined. The IC_{50} is defined as the concentration of antagonist required to reduce by 50% the response to a dose of 5-HT that resulted in a near maximum response (Table 1). Ritanserin was the most potent and LY53857 was the least potent antagonist of the 5-HT-induced vasoconstriction. All of the antagonists required more than a 700 fold increase in concentration to inhibit noradrenaline responses (Table 1).

Pithed rats

In pithed rats, the resting mean arterial blood pressure was 38.4 ± 1.5 mmHg ($n = 54$). Intravenous (i.v.) injection of 5-HT and noradrenaline produced dose-dependent transient increases in mean arterial blood pressure. All of the antagonists inhibited the 5-HT-induced pressor responses in an apparently non-competitive manner (Figure 1). Doses of 1.0 to 3.0 $\mu g\,kg^{-1}$ of ketanserin, ritanserin, R56413 or LY53857 reduced the 5-HT responses by approximately 50%. Ritanserin, R56413 and LY53857 did not alter the noradrenaline-induced pressor response up to doses of 3.0 $mg\,kg^{-1}$. Ketanserin (0.1 to 3.0 $mg\,kg^{-1}$) resulted in a rightward shift of the noradrenaline dose-response curve (Figure 2).

Anaesthetized rats

The mean arterial blood pressure and heart rate of pentobarbitone anaesthetized rats was 125.2 ± 3.7 mmHg ($n = 44$) and 390.2 ± 6.2 beats min^{-1} ($n = 44$), respectively. Ketanserin decreased blood pressure and heart rate in a dose-dependent manner (Figure 3a). Injection of 1.0 $mg\,kg^{-1}$ ketanserin resulted in a maximum (73.7 ± 4.7 mmHg) decrease in blood pressure within 5 min. The heart rate of ketanserin (1.0 $mg\,kg^{-1}$)-treated rats decreased by approximately 125 beats min^{-1}. Ritanserin, R56413 and LY53857 produced a hypotensive effect of lesser magnitude than did ketanserin. Ritanserin, which may be taken as representative of these compounds, induced a maximum hypotensive effect of 28.8 ± 7.4 mmHg at a dose of 3.0 $mg\,kg^{-1}$ (Figure 3b). Ritanserin decreased heart rate by approximately 70

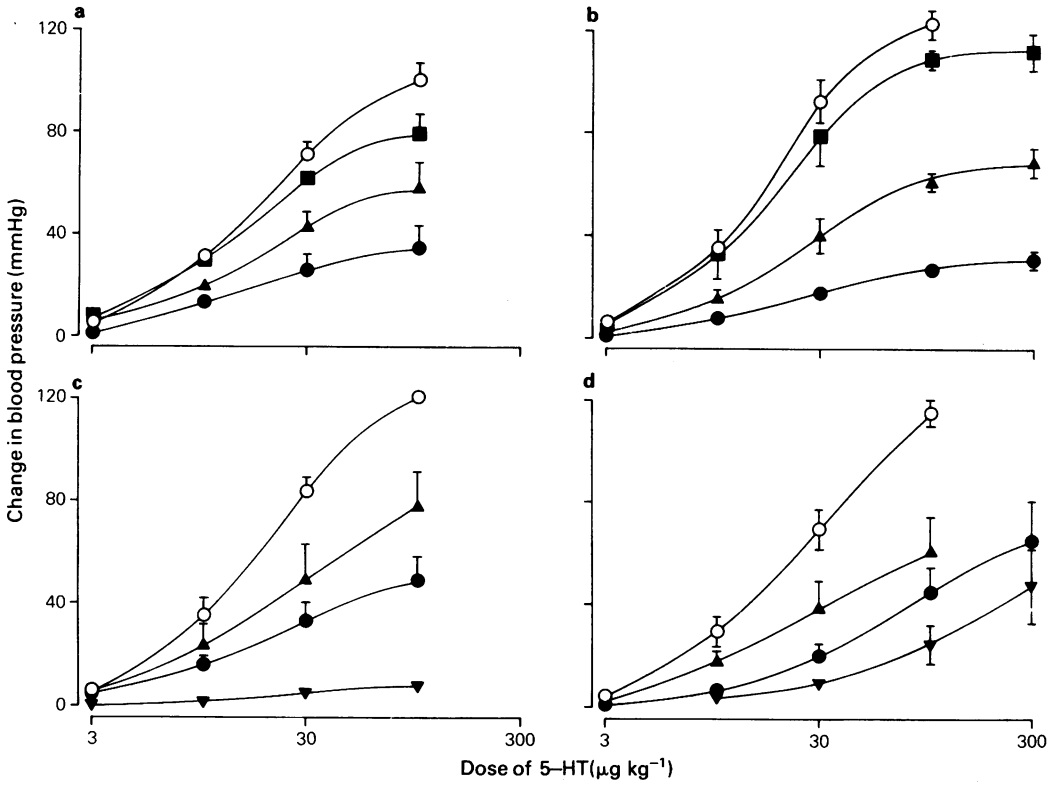

Figure 1 Effect of 5-hydroxytryptamine (5-HT) on the mean arterial blood pressure of pithed rats in the presence of (a) ketanserin, (b) ritanserin, (c) R56413 and (d) LY53857. Symbols: control (○), 0.3 μg kg^{-1} (■), 1.0 μg kg^{-1} (▲), 3.0 μg kg^{-1} (●), 10.0 μg kg^{-1} (▼). Vertical bars indicate s.e.mean and each value is the mean from at least 3 experiments. Absence of vertical bars indicates that the s.e.mean fell within the outline of the symbol.

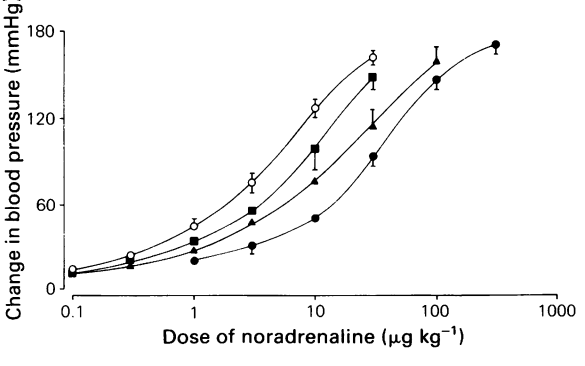

Figure 2 Effect of ketanserin on the noradrenaline-induced pressor responses in the pithed rat. The control curve is represented by open circles. Ketanserin doses were 0.1 mg kg^{-1} (■), 1.0 mg kg^{-1} (▲) and 3.0 mg kg^{-1} (●). Each point shows mean and vertical bars s.e.mean of results from at least 3 animals. Absence of vertical bars indicates that the s.e.mean fell within the outline of the symbol.

beats min^{-1}. At a dose of 1.0 mg kg^{-1}, ketanserin produced a hypotensive effect of greater magnitude and longer duration than the other antagonists.

Discussion

In the present study we have examined the effects of four 5-HT$_2$ receptor antagonists both *in vitro* and *in vivo* against 5-HT and noradrenaline. We have also examined the ability of these compounds to lower blood pressure in normotensive rats. Ketanserin was found to be an antagonist of both 5-HT and noradrenaline and was also able to lower blood pressure. Ritanserin, R56413 and LY53857 were antagonists *in vitro* of noradrenaline and 5-HT; however, *in vivo* although they did not inhibit the effect of noradrenaline, they did evoke a hypotensive effect of lesser magnitude than that of ketanserin.

Considerable interest in the role of 5-HT in the control of blood pressure has arisen from numerous

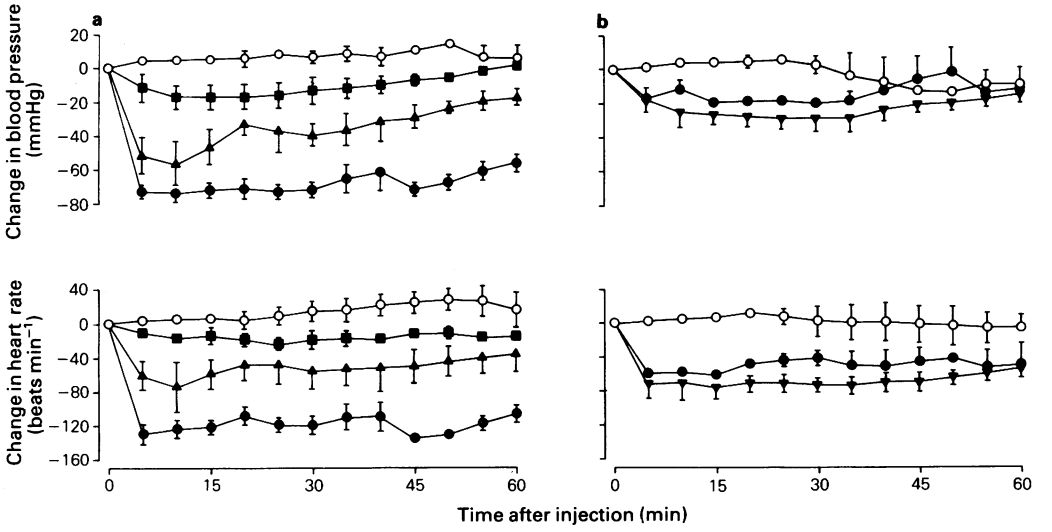

Figure 3 Effect of ketanserin (a) and ritanserin (b) on the blood pressure and heart rate responses of pentobarbitone-anaesthetized rats. Symbols: control (○), 0.1 mg kg^{-1} (■), 0.3 mg kg^{-1} (▲), 1.0 mg kg^{-1} (●) and 3.0 mg kg^{-1} (▼). Vertical bars indicate s.e.mean and each value is the mean from 3–5 experiments. Absence of vertical bars indicates that the s.e.mean fell within the outline of the symbol.

reports that have shown ketanserin to be an effective antihypertensive agent in various experimental animal models (Van Nueten *et al.*, 1981a) and in man (De Cree *et al.*, 1981). The proposal that 5-HT$_2$ receptor blockade is responsible for the hypotensive effect of ketanserin is controversial, since ketanserin also possesses α_1-adrenoceptor blocking activity. The present results confirm that ketanserin is able to lower blood pressure.

Whilst it is difficult to compare directly IC_{50} and pA_2 values with K_i values from binding experiments, the 5-HT$_2$ receptor antagonist activity of the four compounds determined in the present study is in keeping with previously published data. The IC_{50} values of approximately 10^{-11}–10^{-10}M are in agreement with the reported pA_2 value of 10.4 against 5-HT in the rat jugular vein of LY53857 (Cohen *et al.*, 1983) and K_i values of 0.2–0.4 nM for 5-HT$_2$ binding in rat frontal cortex for ketanserin, ritanserin and R56413 (Janssen, 1985). The *in vitro* potency of the four compounds as antagonists of 5-HT was consistent with their *in vivo* activity. Low doses (1.0 to 3.0 μg kg^{-1}) inhibited 5-HT-induced pressor responses.

A similar consistency was not observed with the antagonist activity against noradrenaline. Firstly in the mesenteric artery, the pA_2 values determined for ketanserin, ritanserin and R56413 against noradrenaline are comparable to their reported affinity for α_1-binding sites (K_i values) (Janssen, 1985), whereas the pA_2 of 4.8 determined by Cohen *et al.* (1983) for LY53857 in the rat aorta was less than the value of 6.1 obtained in the present study. Secondly, although all four compounds had α-adrenoceptor antagonist activity *in vitro*, only ketanserin inhibited the noradrenaline-induced pressor responses in the pithed rat. In addition, ketanserin also produced the most significant hypotensive effect. The doses of ketanserin that lowered blood pressure in the present study are similar to those that have been reported to lower blood pressure in spontaneously hypertensive rats (Persson *et al.*, 1982). Furthermore, similar doses of ketanserin were found to inhibit the increase in blood pressure observed following sympathetic nerve stimulation in pithed rats (Fozard, 1982). It is suggested from these observations that the acute hypotensive effect of ketanserin in anaesthetized normotensive rats results primarily from the blockade of peripheral α_1-adrenoceptors.

The lesser hypotensive effect of ritanserin, R56413 and LY53857, which we presume does not result from *in vivo* α-adrenoceptor antagonism, may result from 5-HT$_2$ receptor blockade either peripherally or centrally. However, there are a number of questions which need to be addressed in order to validate or refute this proposal. The doses of the drugs which lowered blood pressure in the anaesthetized rat were 1000 fold greater than those required to abolish the 5-HT-induced pressor responses in the pithed rat. Similarly, the

hypotensive effect appears to coincide with the observed decrease in heart rate. The results of experiments by Fozard (1982) whereby the hypotensive effect of ketanserin can be separated from the bradycardia by section of the vagosympathetic trunks or treatment with atropine, suggest that these two effects are not linked causally. The hypotensive effects of ritanserin, R56413 and LY53857 are greater than those reported previously (Cohen *et al.*, 1983; Pettersson *et al.*, 1985), a discrepancy that may be related to the use of conscious spontaneously hypertensive rats in the previous reports. The observation that ritanserin had a pA_2 value of approximately 7.3 in the mesenteric artery preparation and yet had no effect on noradrenaline pressor responses *in vivo* might be related to noradrenaline activating different subtypes of α-adrenoceptors in the two preparations that are not inhibited equally by ritanserin. Previously it has been shown that noradrenaline produces vasoconstriction via activation of α_1-adrenoceptors in the mesentery (McPherson *et al.*, 1984), whereas *in vivo* noradrenaline may act via post-junctional α_1- and α_2-adrenoceptors to mediate vasoconstriction (Docherty & McGrath, 1980; Timmermans & Van Zwieten, 1980). In view of the reported affinity of ritanserin for α_2-adrenoceptor binding sites (Leysen *et al.*, 1985), it is unlikely that this is a plausible explanation.

Thus, it is difficult to correlate the *in vivo* and *in vitro* activity of the antagonists. While all of the compounds are α-adrenoceptor antagonists *in vitro*, ritanserin, R56413 and LY53857 did not block the pressor responses to noradrenaline in the pithed rat nor did they decrease blood pressure to the same extent as ketanserin. The mechanism of the hypotensive action of ritanserin, R56413 and LY53857 may involve either a non-specific depressant or a non-adrenergic component. A common property of these compounds is their ability to inhibit 5-HT_2 receptor-mediated responses both *in vivo* and *in vitro*. A speculative suggestion is that the smaller hypotensive effect observed following intravenous injection of ritanserin, R56413 and LY53857 compared to that following the more potent α_1-adrenoceptor antagonist ketanserin, is mediated by 5-HT_2 receptor blockade.

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