The mechanism of the sympathoinhibitory action of urapidil: role of 5-HT_{1A} receptors

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1 An investigation was carried out to determine if the sympathoinhibition caused by urapidil is due to activation of 5-HT_{1A} receptors by investigating whether it could be reversed by the non-selective 5-HT_{1A} receptor antagonist spiperone. To control for the possibility of functional antagonism by spiperone, the ability of spiperone to reverse the sympathoinhibition caused by clonidine was also investigated. These experiments were carried out in anaesthetized prazosin-pretreated cats to prevent the α_1 -adrenoceptor antagonist action of urapidil and spiperone from masking any effects observed.

2 Cats were anaesthetized with α -chloralose and simultaneous recordings were made of whole cardiac, splanchnic and renal nerve activities, blood pressure, heart rate and femoral arterial flow (from which conductance was derived). All animals were initially pretreated with prazosin (1 mg kg⁻¹, i.v.) given in divided doses (0.75 followed 10 min later by 0.25 mg kg⁻¹), then either urapidil (0.75 mg kg⁻¹, i.v.) or clonidine (10 μ g kg⁻¹, i.v. in two divided doses) followed by 3 separate injections of spiperone (1 mg kg⁻¹, i.v.). In another set of experiments urapidil was given followed by injections of the appropriate vehicle for spiperone, while in another set urapidil was replaced with an injection of the appropriate vehicle followed by injections of spiperone. In the experiments with clonidine, the α_2 -adrenoceptor antagonist Wy 26392 (0.3 mg kg⁻¹) was given after the last injection of spiperone.

3 The prazosin pretreatment caused a fall in blood pressure associated with femoral vasodilatation, a small bradycardia and little change in cardiac, splanchnic or renal nerve activities. Urapidil or clonidine injection after prazosin caused sympathoinhibition associated with an additional bradycardia. However, only urapidil caused an additional fall in blood pressure. Spiperone injections reversed the sympathoinhibition caused by urapidil but not that caused by clonidine. The sympathoinhibition caused by clonidine was reversed by the α_2 -adrenoceptor antagonist Wy 26392.

4 These results show that the sympathoinhibition caused by urapidil in prazosin-pretreated cats can be reversed by spiperone. The reversal of this sympathoinhibition is not due to functional antagonism. It is concluded that urapidil can cause sympathoinhibition by activation of 5-HT_{1A} receptors.

Keywords: 5-HT_{1A} receptors; sympathoinhibition; blood pressure; urapidil; clonidine; prazosin; spiperone; anaesthetized cats

Introduction

The central sympathoinhibitory action of urapidil cannot simply be explained by its ability to block central α_1 -adrenoceptors (Kellar *et al.*, 1984; Sanders & Jurna, 1985; Van Zwieten *et al.*, 1985; Ramage, 1986b). Instead, the similarity of the cardiovascular and central sympathoinhibitory actions of urapidil to those of the 5-hydroxytryptamine_{1A} (5-HT_{1A}) receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), have led to the suggestion that it may be activation of 5-HT_{1A} receptors that is responsible for the central sympathoinhibition caused by urapidil (Ramage, 1986b). Urapidil has since been shown to bind to 5-HT_{1A} receptors (Fozard & Mir, 1987; Groß *et al.*, 1987) and to show agonist activity at this receptor (Fozard & Mir, 1987; Schoeffter & Hoyer, 1988) supporting such a hypothesis.

However, evidence from *in vivo* experiments that urapidil lowers blood pressure by a 5-HT_{1A} receptor agonist action is contradictory. Doods *et al.* (1988) were unable to prevent the central hypotensive action caused by urapidil using (–)-pindolol, which is known to block 5-HT_{1A} receptors (Schoeffter & Hoyer, 1988; Hoyer, 1988). On the other hand, spiroxatrine, another putative 5-HT_{1A} receptor antagonist (Nelson & Taylor, 1986) was found to attenuate the hypotensive effect of urapidil (Sanders *et al.*, 1988; Kolassa *et al.*, 1989). However, spiroxatrine alone caused a fall in blood pressure which may have contributed to the apparent antagonism of the hypotension caused by urapidil, while in the experiments of Doods *et al.* (1988) it is possible that the α_1 -adrenoceptor antagonist action of urapidil was masking the ability of (–)-pindolol to attenuate the hypotensive action of urapidil.

The present experiments were designed to overcome these problems by trying to reverse the sympathoinhibitory action of urapidil in prazosin pretreated animals with the non-selective 5-HT_{1A} antagonist spiperone (see Hoyer, 1988), which has been reported to reverse the sympathoinhibitory action of the 5-HT_{1A} agonist 8-OH-DPAT (McCall *et al.*, 1987). Prazosin pretreatment has the advantage of preventing any haemodynamic effects, caused by the ability of both urapidil (Sanders *et al.*, 1984) and spiperone (Feniuk *et al.*, 1985) to block α_1 -adrenoceptors, from masking any of the responses observed. Further, as there are many pathways involved in the central control of sympathetic outflow (Coote, 1988), the reversal of any sympathoinhibition caused by urapidil could be due to spiperone causing disinhibition in an unrelated central sympathoinhibitory pathway i.e. spiperone causing functional antagonism. To overcome this problem, the ability of spiperone to reverse the sympathoinhibitory action of clonidine in prazosin pretreated cats was also investigated. Finally, as 5-HT_{1A} receptor agonists cause differential sympathoinhibition (Ramage & Wilkinson, 1989), recordings were made from more than one sympathetic outflow.

A preliminary account of some of these observations has been published (Ramage, 1989).

Methods

Experiments were performed on 20 male adult cats (2.5–4.2 kg) anaesthetized with a mixture of α -chloralose (70 mg kg⁻¹, i.v.)

and pentobarbitone sodium (12 mg per animal). Supplementary doses of α -chloralose (10–15 mg kg⁻¹) were given as required. The animals were artificially ventilated using positive pressure after neuromuscular blockade with vecuronium bromide (200 μ g kg⁻¹). Arterial blood gases, pH, body temperature, blood pressure, heart rate and femoral arterial conductance were monitored as previously described (Ramage, 1984). Drugs were given by bolus injection into the jugular vein.

Simultaneous recordings were made of whole nerve activity from the inferior cardiac, splanchnic and renal nerves as previously described (Ramage & Wilkinson, 1989). Nerve activity was quantified by rectifying and integrating the signal above noise over 5 s using solid state electronic integrators. The validity of the threshold setting was verified at the end of the experiment by administration of sodium pentobarbitone (60 mg per animal) or by crushing the nerve to block all activity. The outputs of the integrators were displayed on a Grass polygraph. Sympathetic nerve activity was tested to ensure that it was under baroreceptor modulation, by checking that activity in these nerves was increased by a fall in blood pressure caused by sodium nitroprusside (2 μ g kg⁻¹) and decreased by a rise in blood pressure caused by noradrenaline (0.25 μ g per animal).

In all 20 experiments variables were recorded over a 20 min period before injection of prazosin (0.75 mg kg⁻¹) followed 10 min later by a second injection of prazosin (0.25 mg kg⁻¹). In one group of 10 experiments, urapidil (0.75 mg kg⁻¹) was injected 5 min later followed, in 5 of these experiments, 7 min later by 3 separate injections of spiperone (1 mg kg⁻¹) at 2–3 min intervals while in the other 5 experiments the vehicle for spiperone (vehicle 2; 0.4 M lactic acid plus 10% 1 M bicarbonate) was given instead of spiperone over the same time intervals. Of the remaining 10 experiments, in 5, the vehicle for urapidil (vehicle 1; 0.04 M lactic acid) was given instead of urapidil after prazosin, while in the other 5 experiments clonidine (10 μ g kg⁻¹) was given instead of urapidil followed, in both cases, by 3 separate injections of spiperone (1 mg kg⁻¹) at 2–3 min intervals. Clonidine was administered in divided doses (5 μ g kg⁻¹) approximately 5 min apart. In these experiments spiperone was given between 11–16 min after the first injection of clonidine, followed, 3 min after the last dose of spiperone, by the α_2 -adrenoceptor antagonist Wy 26392 (0.3 mg kg⁻¹). The doses of urapidil and clonidine used were chosen as the doses that were found to cause an approximately equal degree of sympathoinhibition, which was submaximal, in preliminary experiments. The time between the injections represents the time taken for the change in blood pressure caused by these drugs to stabilize. All drugs except prazosin, urapidil and spiperone were dissolved in saline. Prazosin and urapidil were dissolved in 0.04 M lactic acid (vehicle 1) while spiperone was dissolved in 0.4 M lactic acid then 10% (by volume) of 1 M bicarbonate was added to bring the pH to approximately 4 (vehicle 2). All doses except noradrenaline, prazosin and urapidil refer to the salts of the drug.

Analysis of data

All results are expressed as changes from baseline values. Changes caused by prazosin are taken from the first set of baseline values i.e. the values obtained prior to injection of the first dose of prazosin, while changes caused by remaining treatments are taken from the second set of baseline values i.e. just prior to the injection of urapidil, clonidine or vehicle 1. All data are presented as changes (mean $\pm$ s.e.mean) from either of these sets of baseline values. Responses for all variables were measured just prior to the next injection. The changes that occurred after the final injection were measured 3 min after spiperone or vehicle and between 2 and 6 min after Wy 26392. These times represent the times when the effects on the above variables had stabilized. Nerve activity was taken as the mean level over 1 min in arbitrary units. Comparison of changes caused by prazosin with that of initial baseline values and changes caused by the second dose of prazosin from the first dose were carried out by Student's paired *t* test on the absolute values obtained before and after the injections of prazosin. Comparisons of the data obtained in the urapidil and clonidine experiments were carried out by two way analysis of variance and the least significant difference for comparisons between the means (Sokal & Rohlf, 1969). The effect of spiperone on vehicle 1 (0.04 M lactic acid) pretreatment was analysed by a one way analysis of variance and again the least significant difference for comparison between the means (Sokal & Rohlf, 1969). Differences were considered significant when *P* < 0.05.

Drugs

α -Chloralose and sodium nitroprusside were purchased from Sigma and pentobarbitone sodium from May & Baker Ltd. The following drugs were kindly donated by the companies indicated, prazosin (Pfizer U.K. Ltd.), urapidil (Byk Gulden Pharmazeutika), clonidine HCl (Boehringer Ingelheim), spiperone (Janssen, Belgium) and Wy 26392 (N-((2 β , 11 β)-1, 3,4,6,7,11b-hexahydro-2H-benzo-(a)-quinolizin-2-yl)-N-methylpropanesulphonamide, HCl; Wyeth Lab. U.K.).

Results

Effects of prazosin pretreatment

The initial injection of prazosin (0.75 mg kg⁻¹) caused a significant fall in blood pressure along with a significant increase in femoral arterial conductance and a small bradycardia. This was not associated with a significant change in nerve activity (see Table 1). A further injection (i.v.) of prazosin (0.25 mg kg⁻¹) had no significant additional action on the variables being recorded (see Table 1). Baseline values for all groups of experiments after prazosin pretreatment are shown in Table 2.

Table 1 Changes caused by divided doses of prazosin (0.75 mg kg⁻¹ followed by 0.25 mg kg⁻¹) given i.v. on: mean blood pressure (BP), heart rate (HR), femoral arterial conductance (FAC), cardiac nerve activity, splanchnic nerve activity and renal nerve activity in anaesthetized cats

	Baseline value	Prazosin (0.75 mg kg ⁻¹)	Prazosin (0.25 mg kg ⁻¹)
BP (mmHg)	125 $\pm$ 4	-44 $\pm$ 3***	-42 $\pm$ 3
HR (beats min ⁻¹)	235 $\pm$ 6	-16 $\pm$ 4**	-22 $\pm$ 5
FAC (ml mmHg ⁻¹ min ⁻¹ $\times$ 10 ⁻³)	85 $\pm$ 10	+49 $\pm$ 12***	+49 $\pm$ 11
Cardiac nerve activity (%)		-13 $\pm$ 12	-17 $\pm$ 12
Splanchnic nerve activity (%)		-10 $\pm$ 9	-18 $\pm$ 8
Renal nerve activity (%)		+3 $\pm$ 7	-6 $\pm$ 6

Baseline values for BP, HR and FAC are also shown. All results are shown as the mean $\pm$ s.e.mean; *n* = 20. ***P* < 0.01; ****P* < 0.001. Although data are presented as the mean changes from baseline values, statistical analysis was performed on the absolute values measured before and after administration of prazosin.

Table 2 Anaesthetized cats: baseline values of mean blood pressure (BP), heart rate (HR) and femoral arterial conductance (FAC) after prazosin pretreatment for each group of experiments: vehicle 1 plus spiperone, urapidil plus spiperone, urapidil plus vehicle 2 and clonidine plus spiperone

Experimental groups:	Vehicle 1 + spiperone	Urapidil + spiperone	Urapidil + vehicle 2	Clonidine + spiperone
BP (mmHg)	77 ± 8	82 ± 4	86 ± 6	91 ± 10
HR (beats min ⁻¹)	227 ± 11	231 ± 13	205 ± 10	189 ± 8
FAC (ml mmHg ⁻¹ min ⁻¹ × 10 ⁻³)	120 ± 23	138 ± 19	214 ± 37	91 ± 10

All results are shown as the mean ± s.e.mean; *n* = 5.

Effects of urapidil and clonidine in prazosin pretreated animals

Urapidil (0.75 mg kg⁻¹) or clonidine (10 µg kg⁻¹; in divided doses) caused significant (*P* < 0.05) sympathoinhibition in all nerves being recorded of between 50 and 96% (Figures 1 and 2). This was associated with a significant bradycardia for both drugs. In the urapidil groups of experiments, both in those which went on to receive spiperone and those which went on to receive vehicle alone, there were significant falls in blood pressure of 12 ± 4 and 12 ± 3 mmHg, respectively. The sympathoinhibition caused by clonidine was associated with a significant decrease in femoral arterial conductance but no change in blood pressure (Figure 2).

Effects of divided doses of spiperone on the changes caused by urapidil and clonidine in prazosin pretreated cats

From Figure 1 it can be seen that spiperone given in divided doses (i.v.) of 1 mg kg⁻¹ reversed the sympathoinhibition caused by urapidil but not that caused by clonidine. The latter

was reversed by Wy 26392. The combined results are shown in Figure 2. Comparison of the abilities of spiperone and vehicle (2) control to increase nerve activity show that spiperone began to increase cardiac and splanchnic nerve activity significantly (*P* < 0.05) after the first dose but renal nerve activity was not significantly increased until after the second dose of spiperone (data not illustrated). The additional fall in blood pressure caused by urapidil, in prazosin pretreated animals, was nearly maximally reversed by the first dose of spiperone (data not illustrated). Further, spiperone caused a significant increase in femoral arterial conductance only in the urapidil group, again reaching near maximum after the first dose. In this respect the vehicle used to dissolve spiperone also caused a significant increase in femoral arterial conductance but that caused by spiperone was significantly larger at all doses.

Effects of divided doses of spiperone in prazosin pretreated cats which had received vehicle instead of urapidil

Divided doses of spiperone caused no significant increases in sympathetic nerve activity. However, spiperone did cause a

Figure 1 Traces of recordings of cardiac nerve activity (CNA), splanchnic nerve activity (SNA), renal nerve activity (RNA) and blood pressure (BP) from two separate anaesthetized prazosin (1 mg kg⁻¹) pretreated cats. Trace (a) shows the effect of injection (i.v.) of urapidil followed by 3 consecutive injections (i.v.) of spiperone on these variables. Trace (b) shows the effect of the first i.v. injection of clonidine followed by that of first injection of spiperone. It should be noted that this injection of spiperone is after a second injection of clonidine (5 µg kg⁻¹) which has been omitted for clarity as has the part of the trace showing the second injection of spiperone. The last portion of trace (b) shows the effect of a single (i.v.) injection of the α₂-adrenoceptor antagonist, Wy 26392, which was given after the last dose of spiperone. cumul. = cumulative. It should be noted that the initial sympathoinhibition observed (first part of trace b) on injection of clonidine is baroreceptor-mediated due to the rise in blood pressure caused by the peripheral vasoconstrictor action of clonidine.

Figure 2 Prazosin (1 mg kg^{-1}) pretreated anesthetized cats showing changes in renal (RNA), splanchnic (SNA) and cardiac nerve activity (CNA), heart rate (HR), blood pressure (BP) and femoral arterial conductance (FAC) caused by the following injections (i.v.). Group 1 shows the effect of 3 mg kg^{-1} (cumulative) of spiperone (closed columns) on changes caused by vehicle 1 (urapidil vehicle; cross hatched columns). Group 2 shows the effect of 3 mg kg^{-1} (cumulative) of spiperone (closed columns) on changes caused by urapidil (0.75 mg kg^{-1} , open columns). Group 3 shows the effect of urapidil (0.75 mg kg^{-1} , open columns) on changes caused by spiperone vehicle (cross hatched columns). Group 4 shows the effect of 3 mg kg^{-1} (cumulative) of spiperone (closed columns) on changes caused by clonidine ($10 \mu\text{g kg}^{-1}$, heavily stippled columns) plus the effect of the α_2 -adrenoceptor antagonist Wy 26393 (0.3 mg kg^{-1} , lightly stippled columns) given after 3 mg kg^{-1} spiperone on the above variables. All changes (Δ) are from the prazosin pretreatment values. All values are mean ($n = 5$) with s.e.mean shown by vertical bars above the columns. The effects of spiperone on vehicle 1 pretreatment (Group 1) were analyzed by using a one way analysis of variance and the least significance difference test to compare the means. The effects of spiperone on the above variables in the urapidil and clonidine groups (Groups 2 & 4) have been compared with those of vehicle 2 (Group 3) using a two way analysis of variance and the least significance difference test to compare the means, $*P < 0.05$; $**P < 0.01$. The data for each single injection of spiperone have been omitted for the sake of clarity.

dose-related fall in heart rate, which was significant after the last dose, plus an increase in femoral arterial conductance although this was only significant at the second dose of spiperone (not illustrated). There was a tendency for blood pressure to decline but this was not significant.

Discussion

These experiments demonstrate that spiperone can reverse the sympathoinhibitory action of urapidil in prazosin-pretreated, anaesthetized cats. However, spiperone failed to reverse the sympathoinhibition caused by clonidine in these prazosin-pretreated cats, the latter being reversed by the α_2 -adrenoceptor antagonist Wy 26392 (Paciorek *et al.*, 1984). Spiperone also did not cause sympathoexcitation in cats pretreated with prazosin alone. These latter two observations make it highly unlikely that spiperone is causing the reversal of urapidil by functional antagonism. Both urapidil and spiperone have in common an affinity for α_1 -adrenoceptors (Schoetensack *et al.*, 1977; Eltze, 1984; Sanders *et al.*, 1984; Feniuk *et al.*, 1985) and 5-HT_{1A} receptors (see Hoyer, 1988). Any interaction between spiperone and urapidil at α_1 -adrenoceptors is extremely unlikely as these receptors would seem to be completely blocked by the prazosin pretreatment, as indicated by the second dose of prazosin failing to cause any further changes in the variables being recorded. Thus, an interaction of spiperone and urapidil at 5-HT_{1A} receptors is the more likely explanation for the ability of spiperone to reverse the sympathoinhibitory action of urapidil. In this respect urapidil has been shown to act as a partial agonist at the 5-HT_{1A} receptors on the guinea-pig ileum (Fozard & Mir, 1987) and on forskolin-stimulated adenylate cyclase activity (Schoeffter & Hoyer, 1988) while spiperone is a silent antagonist in this latter system (Schoeffter & Hoyer, 1988). Thus these combined observations support the view that the sympathoinhibition caused by urapidil is due to activation of 5-HT_{1A} receptors.

The rostral ventrolateral medulla has been identified as a site of action at which urapidil, as well as the 5-HT_{1A} receptor agonist 8-OH-DPAT, act to cause central sympathoinhibition (Gillis *et al.*, 1988; Laubie *et al.*, 1989; Mandel *et al.*, 1989). Local administration of spiperone can prevent the hypotension and bradycardia induced when urapidil is applied to this area and application of spiperone to this area completely reverses the hypotension and bradycardia caused by i.v. urapidil (Mandel *et al.*, 1989), thus supporting the conclusion from the present observations. However, as Mandel *et al.* (1989) point out, their experiments suggest that α_1 -adrenoceptor blockage is not important in the hypotensive action of urapidil, although the dose given in this study (Mandel *et al.*, 1989) is known to block α_1 -adrenoceptors. This could be due to some functional antagonism caused by spiperone.

The observation that spiperone alone had no effect on nerve activity in prazosin pretreated animals suggests that central 5-HT_{1A} receptors, at least in anaesthetized, prazosin pretreated cats, are not under tonic activation. In this respect application of spiperone alone to the ventral surface of the medulla has also been demonstrated to have no effect on blood pressure or heart rate (Mandel *et al.*, 1989). It is conceptually possible that blockade by spiperone of central 5-HT₂ receptors may have masked such an action as central 5-HT₂ receptors are considered to have a sympathoexcitatory action (McCall *et al.*, 1987). However, this seems doubtful as a selective 5-HT₂ receptor antagonist, cinanserin, failed to have any effect on nerve activity in prazosin pretreated, anaesthetized cats (Ramage, 1988a). The increase in femoral arterial conductance caused by spiperone in the present experiments may be related to blockade of central 5-HT₂ receptors as this is a characteristic action of 5-HT₂ receptor antagonists (Ramage, 1985; 1988b). The bradycardic effect of spiperone is not due to an increase in vagal tone as it is not blocked by atropine methonitrate (unpublished observations) and is therefore a peripheral action of unknown mechanism.

The present experiments also demonstrate that α_1 -adrenoceptor antagonists, in addition to causing a fall in blood pressure, prevent the expected reflex rise in sympathetic nerve activity; this would be expected from their ability to have a central inhibitory action on sympathetic outflow

(McCall & Humphrey, 1981; Persson *et al.*, 1981; McCall & Schuette, 1984; Ramage, 1984; 1986a,b).

In conclusion the present results demonstrate that urapidil can activate 5-HT_{1A} receptors to cause sympathoinhibition. This explains why urapidil differs in its action on the cardio-

vascular system compared to other α_1 -adrenoceptor antagonists (Ramage, 1986b).

I wish to thank Mr S. Wilkinson for technical assistance and Byk Gulden Pharmazeutika for support.

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(Received August 20, 1990)

Revised November 19, 1990

Accepted December 3, 1990)