Relationship of Alpha Receptor Types to Hypotension and Renal Vasodilation Caused by Alpha Blockers in Conscious Dogs

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SUMMARY In conscious instrumented normotensive and two-kidney, one clip Goldblatt hypertensive dogs, we compared the effects of the α-receptor blocking agent, urapidil, on blood pressure, renal vascular resistance, heart rate, and plasma renin activity with those of prazosin and phentolamine. Urapidil (2 mg/kg) and prazosin (0.25 mg/kg) decreased blood pressure and renal vascular resistance in both groups of animals, and urapidil caused a small increase in renal blood flow. Heart rate, but not plasma renin activity, was increased at the peak of the hypotension. Phentolamine had no significant effect on any of these parameters. All three agents markedly inhibited the renal vasoconstrictor responses to intraarterially administered phenylephrine and norepinephrine, and thus exhibited an α1-receptor blocking action. Only urapidil significantly antagonized the response to B-HT 933, a selective α2-receptor agonist, indicating that it also interacts at α2-receptor sites. Since both normotensive and hypertensive animals exhibited similar hypotensive responses after both urapidil and prazosin, the degree of α-receptor blockade achieved did not reveal greater sympathetic tone in renal hypertension. (Hypertension 5 (suppl I): I-170-I-174, 1983)

Key Words • urapidil • renal blood flow • hypotension • sympathetic nervous system • prazosin

Evidence suggests that α1-receptors are concentrated at the adrenergic neuroeffector junction, and therefore α1-blocking agents are particularly effective in inhibiting sympathetic vascular tone.1 Adrenergic blocking agents such as prazosin act selectively on α1-receptors, inhibiting almost completely the vasoconstrictor action of the α1-agonist phenylephrine.2 Agents such as phentolamine, which block both α1- and α2-receptors, have complex effects since they can inhibit sympathetic vascular tone postjunctionally, but also enhance adrenergic transmitter release through blockade of α2-mediated negative feedback.3

Urapidil, a phenyl piperazine derivative,4 possesses alpha1-blocking properties and may also stimulate α2-receptors in the central nervous system.5 Thus, this agent has the potential capacity to inhibit sympathetic vascular tone at central and peripheral sites. The main purpose of the present investigation was to examine the effects of urapidil on blood pressure and renal hemodynamics in conscious instrumented normotensive and two-kidney, one clip Goldblatt hypertensive dogs and to ascertain the renal α-adrenergic receptor upon which it acts.

Methods Twelve dogs of either sex weighing 16–30 kg were used in this investigation. Throughout the study, dogs were fed puppy chow, which provided 67 mEq of sodium chloride daily. While anesthetized with pentobarbital, the dogs underwent two separate operations for implantation of femoral arterial and venous catheters, and approximately 1–2 weeks later for placement of a Zepeda blood flow probe (4–5 mm in diameter) around the left renal artery and a PE 10 catheter in the artery. Details of this technique have been published elsewhere.6 The flow probe was located on the artery as close to the aorta as possible, and the catheter inserted retrograde into the artery at the site of branching so that the catheter tip lay in the artery 3–5 mm proximal to the location of the flow probe. This differs from our previous procedure in which the catheter was inserted orthograde. Flow probe leads and the catheter ends were passed subcutaneously, emerging high on the dog’s back; they were covered with a jacket. Intraarterial injections and infusions of pharmacologic agents were made into the renal artery catheter; the catheter end was enlarged in heated sesame oil to facilitate injection of the agents. Intravenous administration was made into the femoral venous catheter, and systemic arterial pressure was monitored and blood samples withdrawn from the femoral arterial catheter.

Experiments were conducted on the dogs after they were trained to lie quietly on a padded table. Blood pressure and renal blood flow were monitored for ap-
proximately 10 minutes until stable, and the hematocrit was determined. Balancing the probe was done electronically and checked periodically during the experiment. An arterial blood sample (2.5–3 ml) was withdrawn into a chilled plastic syringe containing 1 mg/ml disodium EDTA. Plasma was separated in the cold, and the sample was frozen at −20°C for later radioimmunoassay of plasma renin activity (PRA). Only urapidil and prazosin increased heart rate, 64 ± 3 to 84 ± 7 bpm (p < 0.05) and from 70 to 76 ± 5 bpm after urapidil (p < 0.05). As in the normotensives, phentolamine had no significant effect on blood pressure or renal hemodynamics in the normotensive dogs. Urapidil and prazosin increased heart rate, 64 ± 3 to 84 ± 7 bpm (p < 0.05) and from 70 to 76 ± 5 bpm after urapidil (p < 0.05). For the remainder of the experiment, which lasted 30 to 60 minutes after administering the agent, phentolamine caused no significant effect on blood pressure or renal hemodynamics in the normotensive dogs. Urapidil and prazosin increased heart rate, 64 ± 3 to 84 ± 7 bpm (p < 0.001) and 69 ± 3 to 82 ± 6 bpm (p < 0.05), respectively at the time that the blood pressure was elevated earlier, had returned toward the control level. Hypertensive Dogs

Values of blood pressure, renal blood flow, and renal vascular resistance in the control period and after urapidil, prazosin, or phentolamine in normotensive dogs are shown in figure 3. Urapidil and prazosin caused similar decreases in blood pressure and renal vascular resistance, but only urapidil increased renal blood flow significantly. The peak changes occurred shortly after terminating the 10-minute infusion of the blocker, and the hypotensive effect persisted usually for the remainder of the experiment, which lasted 30 to 60 minutes after administering the agent. Phentolamine caused no significant effect on blood pressure or renal hemodynamics in the normotensive dogs. Urapidil and prazosin increased heart rate, 64 ± 3 to 84 ± 7 bpm (p < 0.001) and 69 ± 3 to 82 ± 6 bpm (p < 0.05), respectively at the time that the blood pressure was elevated earlier, had returned toward the control level. Hypertensive Dogs

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Results

Relative α₁- and α₂-Receptor Blockade by Urapidil, Prazosin, and Phentolamine in the Renal Vascular Bed

Renal vasoconstrictor responses in the control period and after urapidil, prazosin, or phentolamine in normotensive dogs are depicted in figure 1. A representative experiment with urapidil is shown in figure 2. The responses to norepinephrine and phenylephrine generally consisted of a sharp decrease in blood flow, whereas that to B-HT 933 showed a rapid decrease followed in some cases by a longer lasting (1 minute or more) decrease in blood flow. Data were analyzed based on the change in the initial sharp reduction in blood flow only. Urapidil and prazosin were equally effective in almost totally abolishing the response to phenylephrine. Phentolamine was somewhat less potent in this respect. All three agents were approximately equal in their ability to antagonize responses to norepinephrine. None of the blockers markedly affected the responses to B-HT 933, a reported α₁ agonist. Only urapidil significantly depressed the response to this agent.

Effect of Alpha Blockers on Blood Pressure, Renal Hemodynamics, Heart Rate, and PRA in Normotensive Dogs

Values of blood pressure, renal blood flow, and renal vascular resistance in the control period and after urapidil, prazosin, or phentolamine in normotensive dogs are shown in figure 3. Urapidil and prazosin caused similar decreases in blood pressure and renal vascular resistance, but only urapidil increased renal blood flow significantly. The peak changes occurred shortly after terminating the 10-minute infusion of the blocker, and the hypotensive effect persisted usually for the remainder of the experiment, which lasted 30 to 60 minutes after administering the agent. Phentolamine caused no significant effect on blood pressure or renal hemodynamics in the normotensive dogs. Urapidil and prazosin increased heart rate, 64 ± 3 to 84 ± 7 bpm (p < 0.001) and 69 ± 3 to 82 ± 6 bpm (p < 0.05), respectively at the time that the blood pressure was elevated earlier, had returned toward the control level. Hypertensive Dogs

Effects of Alpha Blockers and Blood Pressure, Renal Hemodynamics, Heart Rate, and PRA in Hypertensive Dogs

At this stage of the hypertension, 14 to 53 days after renal artery constriction, PRA was 2.48 ± 1.08 and 2.25 ± 0.75 ng AI/ml/hr in the urapidil and prazosin experiments, respectively. Blood pressure was 22 mm Hg higher in the hypertensives than in the normotensives, and renal vascular resistance varied between these groups of experiments. Urapidil and prazosin produced significant decreases in blood pressure and renal vascular resistance (fig. 3), a slight tachycardia, and no change in PRA. Heart rate increased from 66 ± 4 to 76 ± 5 bpm after urapidil (p < 0.05) and from 70 ± 6 to 84 ± 9 bpm after prazosin (p < 0.05). As in the normotensives, phentolamine had no significant effect on any of these parameters.
FIGURE 1. A. Renal vasoconstrictor responses to phenylephrine, B-HT 933, and norepinephrine in conscious normotensive dogs in the control period and after administration of urapidil, 2 mg/kg, i.v. In one experiment the doses of phenylephrine were 1, 2, and 4 μg, and in one experiment the doses of norepinephrine were 0.25, 0.5, and 1 μg. Figures within the parentheses represent the number of experiments. *p < 0.05 and ***p < 0.001, compared to control responses. B. Responses in normotensive dogs in the control period and after administration of prazosin, 0.25 mg/kg, i.v. In one experiment, the doses of norepinephrine were 0.25, 0.5, and 1 μg. **p < 0.01, and ***p < 0.001. C. Responses in normotensive dogs in the control period and after administration of phentolamine, 1 mg/kg, i.v. In one experiment, the doses of phenylephrine were 4, 8, and 16 μg, and in one experiment, the doses of norepinephrine were 0.25, 0.5, and 1 μg.

FIGURE 2. Representative experiment demonstrating the effect of urapidil on the responses to α-receptor agonists and on blood pressure and renal blood flow. Calibration represents 1 minute. The blood pressure tracing is the full pulse at some points, and damped at other points in the experiment.
HYPOTENSION FROM ALPHA-RECEPTOR BLOCKADE

FIGURE 3. Blood pressure, renal blood flow, and renal vascular resistance in the control period and after α-receptor blockers in normotensive and hypertensive dogs. Figures within parentheses represent the number of experiments. Standard error of the differences are indicated. *p < 0.05; **p < 0.01; and ***p < 0.001 compared to control.

Discussion

It is now generally accepted that sympathetic vascular tone, levels of PRA, and other circulating vasoactive substances are increased under the conditions in which blood pressure and vascular regulation are usually studied in anesthetized animals. Because of this, we carried out the present study in conscious dogs while they were in a relaxed state. Our main intent was to determine the relative effectiveness of urapidil, a newly introduced antihypertensive agent, in lowering blood pressure and renal vascular resistance in normotensive and renal hypertensive dogs. We utilized two-kidney, one clip Goldblatt hypertensive dogs after the peak in PRA had waned, at which time we presumed they had increased sympathetic tone. Antihypertensive agents that decrease renal vascular resistance, particularly when this is a long-term effect, would be efficacious in the treatment of hypertension. We compared an equally effective α₁-receptor blocking dose of urapidil with the more well-characterized blockers, prazosin and phentolamine. We also hoped to define the subtype(s) of α-receptor blocked by urapidil and to determine whether one or both receptor subtypes were concerned with the blood pressure and renal hemodynamic changes obtained in normotensive and hypertensive dogs.

Several pertinent findings were made in this investigation. Urapidil exerted a significant hypotensive effect, approximately a 13 mm Hg decrease in mean blood pressure, in both normotensive and two-kidney, one clip Goldblatt hypertensive dogs. This hypotensive response is attributable to a decrease in sympathetic vascular tone; and the degree of tone, based on the blood pressure fall, is similar in both the normotensive and hypertensive dogs. Blockade of α₁-receptors appears to primarily mediate the hypotension, since the renal vasoconstrictor response to the α₁-agonist phenylephrine was nearly abolished by urapidil and prazosin, and both agents caused approximately the same blood pressure decrease. Previously it had been shown that the hypotensive response to prazosin is proportional to the degree of vascular α₁-receptor blockade. Postjunctional α₂-receptors rather than α₁-receptors are considered to be mainly under adrenergic neural control, and thus their blockade would be expected to lower blood pressure. Urapidil, but not prazosin, also depressed to a limited degree renal vasoconstriction mediated by α₂ postjunctional receptors. This was suggested by the reduction in the response to the "specific" α₂ agonist B-HT 933 after urapidil. The vasoconstrictor response to this agonist as well as to the more potent α₂ agonists, B-HT 920 and guanabenz are resistant to blockade in the kidney (unpublished results) and it is possible that activation of α₁ receptor in addition to the α₂ type is involved.

Our results with phentolamine were surprising in view of the fact that this agent that blocks both α₁ and α₂ receptors was ineffective in producing significant decreases in blood pressure or renal vascular resistance in either the normotensive or hypertensive dogs. Phenolamine was effective in blocking renal vasoconstrictor responses to norepinephrine and phenylephrine, although the latter was not blocked to the same extent as by the other antagonists. Two possibilities can be offered to explain the failure of phenolamine to lower blood pressure. Postjunctional blockade of α₁-receptors by phenolamine may be overridden by increased adrenergic transmitter release due to interruption of α₂-mediated negative feedback, or α₁ receptors may be incompletely blocked by phenolamine.

The two-kidney, one clip Goldblatt hypertensive dogs did not exhibit greater sympathetic tone than the normotensives under the conditions of these experiments. A similar decrease in mean arterial pressure was obtained in the chronic phase of the hypertension with both urapidil and prazosin, as in the normotensive state. Amann and coworkers demonstrated a greater...
decrease in forearm vascular resistance in essential hypertensive subjects than in normotensives using prazosin. Thus, in essential hypertension increased sympathetic tone is demonstrable by α-adrenergic blockade.

A similar degree of hypotension to that produced by adrenergic blockade in two-kidney, one clip hypertensive dogs has been reported by us previously, using guanethidine treatment. In that study, however, guanethidine did not affect the blood pressure of the normotensive controls. Differences in the schedule of drug administration or the agents utilized in the present and previous studies may account for this difference in results. Nevertheless, we found no evidence of increased sympathetic tone in the two-kidney, one clip Goldblatt hypertensive dog in the chronic phase through the use of α-blocking agents. Although we have employed a maximally effective hypotensive dose of prazosin and urapidil (unpublished results), it is possible that the sympathetic tone in the hypertensive dogs may not have been completely eliminated by the doses we used. Alternatively, this group of hypertensive dogs may have had a negligible increase in sympathetic tone compared to those observed in our previous study.

Urapidil appears to be similar in its peripheral α-receptor blocking action to prazosin, because, like prazosin, it blocks α1-adrenergic receptor sites in the kidney. The ability of these agents to lower renal vascular resistance is attributable in part to an autoregulatory response to the fall in blood pressures. However, in the normotensive subjects a significant increase in renal blood flow with urapidil, when the blood pressure falls, is a better indicator of renal vasodilatation than a decrease in renal vascular resistance. Urapidil also blocked at α2-receptor sites, as suggested by our results with B-HT 933; however, as indicated above, at least in renal vessels, a specific α2-agonist is not yet on hand. Horn et al. reported relatively fewer vascular α1-receptors in the canine renal than femoral bed based on the response to clonidine administered intraarterially. Clonidine, however, acts on both α1 and α2 post-synaptic receptors and is thus not an ideal α agonist.

In the present investigation we have explored only the peripheral α-receptor interactions of urapidil; we have not considered its potential central α-receptor interaction(s). Conceivably, a central α1-receptor agonist action of this agent may contribute to its hypotensive effect.

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