Role of $\alpha_1$- and $\alpha_2$-Adrenergic Receptors in the Human Hypertensive Kidney

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SUMMARY Since it is not known for certain which $\alpha$-adrenergic receptors mediate renal vasoconstriction in human essential hypertension, we infused either doxazosin ($n = 7$) or yohimbine ($n = 7$) into the renal arteries of hypertensive subjects immediately prior to diagnostic angiography. Both agents caused an increment in renal blood flow as assessed with the xenon-washout technique. Doxazosin increased renal flow from $342 \pm 36$ to $360 \pm 55$ ml/min per 100 g ($0.05 < p < 0.10$). Yohimbine enhanced flow from $380 \pm 41$ to $485 \pm 63$ ml/min per 100 g ($p < 0.01$). The effect of yohimbine was significantly greater than that of doxazosin. In a control group ($n = 7$) receiving only saline, no changes in renal blood flow occurred. Doxazosin enhanced renin secretion in the kidney by $10 \pm 4\%$ over levels in controls ($0.05 < p < 0.10$), whereas yohimbine increased renin release by $80 \pm 23\%$ ($p < 0.01$). The latter increase was apparently not due to alterations in flow alone, since the arteriovenous gradient for renin also widened. We conclude that in resting conditions, neurogenic vascular tone in the kidney depends mainly upon activation of $\alpha_2$-adrenergic receptors. Moreover, these receptors exert a tonic inhibitory influence on renin release. (Hypertension 9 [Suppl III]: III-210-III-212, 1987)

Key Words • $\alpha$-adrenergic receptors • renal blood flow • hypertension • renin secretion • doxazosin • yohimbine

Enhanced activity of efferent renal sympathetic nerves may lead to a variety of abnormalities, including a rise in renal vascular resistance, alterations in renin secretion, and augmented reabsorption of salt and water. Since some of these features have also been observed in essential hypertension, it may be hypothesized that the sympathetic nervous system is involved in the elaboration of renal changes in this disease.

Functional responses to an increase in sympathetic activity in the kidney or to circulating catecholamines are mediated by two types of adrenergic receptors: $\alpha_1$ and $\alpha_2$. Since it is not known which type of receptor is involved in human hypertension, we infused two receptor-specific antagonists into the renal arteries of hypertensive subjects and studied the effects of these agents on renal blood flow and renin secretion.

Patients and Methods

The invasive nature of our investigations meant that only patients who had been admitted to the hospital for diagnostic renal arteriography could qualify for inclusion in the study. In this report, we will describe our findings in a group of 21 patients, aged 26 to 64 years, in whom the arteriogram failed to disclose abnormalities and who subsequently were diagnosed as having essential hypertension.

All subjects had been patients for at least 4 days in a metabolic ward where sodium intake was fixed at 55 mmol/day and checked by 24-hour urine collections. Antihypertensive medication, if any, was discontinued 3 weeks prior to hospitalization.

On the morning of the fifth hospital day, after an overnight fast and complete bed rest for about 10 hours, percutaneous selective catheterization of the renal artery and vein was carried out by the method of Seldinger. For the studies described here, only the right kidney was used. Intraarterial pressure was monitored through the arterial line with a Statham transducer (Oxnard, CA, USA). When blood pressure and heart rate had been stable for 10 minutes, blood samples for determination of active renin concentration were drawn simultaneously from the renal artery and vein. Subsequently, renal blood flow was measured by means of the $^{133}$Xe-washout technique as described previously. After baseline characteristics were obtained, an intrarenal infusion of 5% glucose was started through the arterial catheter, and 10 minutes later all
variables were measured again. Subsequently, the glucose was replaced by either the \( \alpha \)-antagonist doxazosin \((n = 7) \) or the \( \alpha \)-antagonist yohimbine \((n = 7) \). In a third group of patients, who served as controls \((n = 7) \), saline was infused instead. Doxazosin was administered at a dose of 1 \( \mu g/kg/min \), and yohimbine at a dose of 3 \( \mu g/kg/min \). These doses were given for 10 minutes. In the control group receiving only saline, the rate of infusion was adjusted so as to match infusion rates in the other two groups. Before the infusions and at the end, intraarterial blood pressure and renal blood flow were measured. Following the infusions blood samples were taken again for assessment of renin levels. The study was approved by the local Ethical Committee, and all patients gave their informed consent.

Renal arterial levels of active renin were similar before and during infusion of saline as well as during infusion of doxazosin. However, when yohimbine was infused, active renin in arterial blood was increased mean renal blood flow. Renal blood flow rose from 324 \( \pm \) 36 to 360 \( \pm \) 55 ml/min per 100 g \((0.05 < p < 0.10) \) when doxazosin was infused and from 380 \( \pm \) 41 to 485 \( \pm \) 63 ml/min per 100 g \((p < 0.01) \) when yohimbine was administered.

Effect of Intrarenal \( \alpha \)-Adrenergic Blockade on Renal Blood Flow

Before the infusions were started, only minor, statistically insignificant differences in blood pressure and renal blood flow existed. In all three groups blood pressure and heart rate remained constant during the intrarenal infusion, indicating that the drugs had negligible systemic effects. However, while saline did not affect renal perfusion, both doxazosin and yohimbine increased mean renal blood flow. Renal blood flow rose from 324 \( \pm \) 36 to 360 \( \pm \) 55 ml/min per 100 g \((0.05 < p < 0.10) \) when doxazosin was infused and from 380 \( \pm \) 41 to 485 \( \pm \) 63 ml/min per 100 g \((p < 0.01) \) when yohimbine was administered.

Effect of Intrarenal \( \alpha \)-Adrenergic Blockade on Renin Secretion

Renal arterial levels of active renin were similar before and during infusion of saline as well as during infusion of doxazosin. However, when yohimbine was infused, active renin in arterial blood was increased from 27 \( \pm \) 4 to 32 \( \pm \) 3 mU/L \((p < 0.05) \). In renal venous blood, active renin levels were unchanged during infusion of saline. When doxazosin was given, renal venous renin rose only insignificantly, but yohimbine infusion caused renin levels to rise from 30 \( \pm \) 4 to 39 \( \pm \) 5 mU/L \((p < 0.05) \). Thus, the arteriovenous concentration gradient for renin widened during the infusion of yohimbine. When renin secretion rates were compared, no effect of saline was demonstrable, but doxazosin enhanced secretion by 10 \( \pm \) 4% \((0.05 < p < 0.10) \) and yohimbine by 80 \( \pm \) 23% \((p < 0.01) \).

Discussion

Over the past decade, considerable interest has arisen in the role of the sympathetic nervous system in the regulation of blood pressure and vascular resistance, especially in patients with essential hypertension. In several animal models, renal sympathetic nerves appear to be of paramount importance in the development and maintenance of hypertension, and, in view of the dense innervation of the kidney, it seems possible that renal adrenergic activity contributes to hypertension in humans as well. In order to clarify whether the efferent sympathetic system causes renal vasoconstriction through activation of vascular \( \alpha \)-adrenergic receptors, we evaluated responses to an intrarenal infusion of doxazosin, an antagonist at \( \alpha \) receptors, or yohimbine, an antagonist at \( \alpha \) receptors. By infusing doses that had no systemic effects, we were able to assess the impact of local processes involving \( \alpha \)-adrenergic receptors.

Our data showed that when doxazosin is infused intrarenally at a dose of 1 \( \mu g/kg/min \), a small rise in renal blood flow ensues. This observation points to a modest role for \( \alpha \)-adrenergic receptors in the regulation of renal vascular tone. On the other hand, yohimbine infused at a rate of 3 \( \mu g/kg/min \) induced a far greater increase in renal perfusion. Insomuch as the dosages used can be considered equipotent (admittedly this has not been proven, although higher doses of both substances invariably caused systemic effects), the data support the conclusion that \( \alpha \)-adrenergic receptors have a greater impact than \( \alpha \)-adrenergic receptors in mediating adrenergic activity in the renal arterioles.

That the antagonists did, indeed, produce effective adrenergic blockade may be inferred from our previous experiments, in which we showed that similar doses of the drugs antagonized the renal vasoconstrictor response to isometric exercise. Our present data are therefore in line with our earlier observations on the effects of phenotolamine. However, since phenotolamine is a nonspecific, \( \alpha \)-adrenergic receptor antagonist, we deemed it necessary to explore the renal vascular response to blockade of \( \alpha \)-adrenergic receptors only. Whereas compelling experimental evidence indicates that the kidney contains both \( \alpha \) and \( \alpha \)-adrenergic receptors, there is still uncertainty about their relative importance. Presumably, species differences play some role since rats, cats, and dogs display mainly \( \alpha \)-adrenergic receptor activity in their renal vasculature, while rabbits show a preponderance of \( \alpha \)-adrenergic receptors. Our study suggests that humans are more like rabbits in this respect, although it has to be borne in mind that we included only hypertensive individuals and we cannot exclude the possibility that a different situation exists in individuals without hypertension.

It is well established that the sympathetic nervous system not only regulates vascular tone in the kidney but also modifies renin release. The role of \( \alpha \)-adrenerg-
ergic receptors in this process is still obscure, but most authors seem to agree that their effect is inhibitory.\(^\text{14, 15}\) However, previous studies in humans are difficult to interpret in view of the fact that they have assessed systemic levels of renin, which may not accurately reflect renal release of this enzyme. In the present study, we attempted to overcome this difficulty by sampling directly from the renal artery and vein and by calculating secretion rates for renin. We found doxazosin to have little effect on renin release, although a small rise was demonstrable. Thus it appears that \(\alpha_1\)-adrenergic receptors are only modestly involved in renin secretion. It should be remembered, however, that methodological errors associated with the renin assay may obscure a greater role for these receptors. Calculation of an arteriovenous gradient involves two analytical errors, and calculation of a secretion rate introduces a third one related to the determination of flow. These considerations may explain why we found in a previous study\(^3\) that doxazosin had a somewhat larger effect.

When we compared the results obtained with yohimbine with those obtained with doxazosin, it was clear that yohimbine was profoundly more effective in raising renin secretion. In fact, the changes induced by yohimbine were far greater than could be accounted for by methodological errors. Hence, it seems reasonable to assume that stimulation of \(\alpha_2\)-rather than \(\alpha_1\)-adrenergic receptors in the human kidney inhibits renin secretion by that organ. Our studies did not show whether stimulation is accomplished directly at receptors on the juxtaglomerular cell or indirectly through changes in flow and arteriolar resistance. It might even be possible that we are dealing with actions at prejunctional (\(\alpha_2\)) receptors. It is conceivable, for instance, that reduction of noradrenaline release from nerve terminals as a consequence of stimulation of prejunctional \(\alpha_2\)-adrenergic receptors decreases the activity of postjunctional \(\beta\)-adrenergic receptors. Blockade of the prejunctional receptors by yohimbine could likewise enhance \(\beta\)-receptor-mediated renin secretion. Since increased neuronal noradrenaline release would be expected to cause a reduction in blood flow, it is most likely that the vascular effects of yohimbine are due to blockade of postjunctional receptors. Indeed, there is some evidence that postjunctional \(\alpha_2\)-adrenergic receptors exist in humans.\(^16\)

In conclusion, the present data showed that in human hypertension, renal \(\alpha_2\)-adrenergic receptors are involved in the regulation of both renal blood flow and renin secretion. The vasoconstrictor effects of these receptors are probably related to a postjunctional mechanism, but further studies are required to characterize the location of the receptors causing inhibition of renin secretion.

References

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