Acute renal effects of doxazosin in man

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1 To evaluate the role of α_1 -adrenoceptors in the regulation of renal blood flow and renin secretion, we infused doxazosin in incremental doses (group I, $n = 5$) or at a fixed rate of $1 \mu\text{g kg}^{-1} \text{min}^{-1}$ (group II, $n = 6$) into the renal artery of hypertensive patients just prior to diagnostic renal angiography.

2 In group I, stepwise increasing doses of doxazosin were associated with increases in renal perfusion and, at doses above $1 \mu\text{g kg}^{-1} \text{min}^{-1}$, also with a fall in blood pressure.

3 Compared with observations in control subjects, doxazosin enhanced renal renin release at rest but did not modify the renin response to isometric exercise in group II.

4 α_1 -Adrenoceptors are involved in causing renal vasoconstriction and inhibition of renin secretion. However, the latter is only of importance in resting subjects.

Keywords α -adrenoceptors doxazosin renal blood flow renin

Introduction

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. One of the products of the intensified research in this area is the notion that, in several animal models, renal sympathetic nerves play a major role in the development and maintenance of hypertension (Diz *et al.*, 1982; Katholi *et al.*, 1981; Winternitz *et al.*, 1982).

Given that the kidney is a highly vascularized and densely innervated organ, it is possible that renal adrenergic activity is also of importance in human essential hypertension. Unfortunately, it has been difficult to assess sympathetic activity in man directly, and this applies in particular to local (e.g. intrarenal) events. Nevertheless, the development of specific agonists and antagonists acting on adrenoceptors has made it possible to use pharmacological probes to elucidate physiological processes. One such agent is doxazosin, an α_1 -adrenoceptor antagonist which can be administered parenterally. When this drug is infused into the renal artery in low doses which do not affect blood pressure, one may be able to evaluate the impact of intrarenal processes involving α_1 -adrenoceptors. Therefore we set up a study to investigate whether α_1 -adrenoceptors play

a role in the regulation of renal blood flow and renin release in patients with high blood pressure.

Methods

The invasive nature of the study meant that only patients who needed to undergo diagnostic renal arteriography could qualify for inclusion in the study. In this report we will describe the results obtained in a subgroup of 11 patients, in whom, retrospectively, the arteriogram failed to disclose abnormalities and who subsequently were classified as essential hypertensives. There were seven men and four women, aged 34–59 years (mean age 47 years). The study was approved by the local Ethics Committee.

All patients had been hospitalized and put on a diet containing 55 mmol of sodium per day; none of them had used antihypertensive medications for at least 3 weeks before the study.

On the morning of the fifth hospital day, after an overnight fast and complete bed rest for about 10 h, percutaneous catheterization of the right renal artery and vein was performed. Following a brief stabilization period, blood samples were drawn simultaneously from both catheters for determination of active plasma renin concentration. In addition, intra-arterial blood pressure was measured through the arterial line and renal blood

flow was assessed by means of the ^{133}Xe -washout technique. A control infusion of glucose 5% was started through the arterial catheter and 10 min later all variables were measured again. Subsequently, the glucose was replaced by doxazosin which was infused either at incremental doses (group I, $n = 5$) or at a fixed rate (group II, $n = 6$). Five patients continued to receive glucose alone and acted as a control group.

In group I, doses of 0.1, 0.3, 1, 3 and $10 \mu\text{g kg}^{-1} \text{min}^{-1}$ were infused, each dose lasting for 10 min. Blood pressure and renal blood flow were determined at the end of each infusion. In group II, doxazosin was given at a rate of $1 \mu\text{g kg}^{-1} \text{min}^{-1}$ for 15 min; blood pressure and renal blood flow were measured at 10 min, immediately followed by sampling of blood for assay of active renin. While the infusion continued, patients were then asked to perform isometric exercise by squeezing a balloon at 25% of maximal strength for 3 min. At the end of this manoeuvre the final assessment of blood pressure, renal blood flow and renin took place. Results obtained in this group of patients were compared with those of the five control patients, who also performed the handgrip exercise.

Mean renal blood flow was calculated by computer analysis of the washout curves (Dell *et al.*, 1973), where the mean represents the arithmetic mean of the various components (Ladefoged, 1966). Active renin was measured by radioimmunoassay for angiotensin I (Skinner *et al.*, 1975). Renin secretion expressed as $\text{mU min}^{-1} (100 \text{ g})^{-1}$ was calculated as the product of active renin and renal blood flow. Data were evaluated statistically by analysis of variance; results are expressed as means $\pm$ s.e. mean.

Results

In doses of 0.1 and $0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$, doxazosin had no effect whatsoever on blood pressure or renal blood flow in patients from group I. However, at a dose of $1 \mu\text{g kg}^{-1} \text{min}^{-1}$ flow rates increased from 338 ± 30 to $374 \pm 36 \text{ ml min}^{-1} (100 \text{ g})^{-1}$; this change in flow was statistically significant ($P < 0.05$) but was not accompanied by alterations in blood pressure. At higher doses renal blood flow rose further but this time in the face of a progressive fall in blood pressure.

In patients from group II, renal blood flow rose from 360 ± 28 to $400 \pm 31 \text{ ml min}^{-1} (100 \text{ g})^{-1}$ during the first 10 min of doxazosin infusion. This was associated with a small rise in renin secretion from 580 ± 170 to $642 \pm 225 \text{ mU min}^{-1} (100 \text{ g})^{-1}$

($P < 0.05$). Handgrip exercise significantly increased mean blood pressure by $19 \pm 3 \text{ mmHg}$, ($P < 0.05$) while reducing renal blood flow (not significant) from 400 ± 31 to $372 \pm 46 \text{ ml min}^{-1} (100 \text{ g})^{-1}$. In the control subjects who performed isometric exercise while receiving an intrarenal infusion of glucose, mean blood pressure rose by $20 \pm 4 \text{ mmHg}$ ($P < 0.05$), while renal blood flow fell from 320 ± 16 to $265 \pm 24 \text{ ml min}^{-1} (100 \text{ g})^{-1}$ ($P < 0.05$). When compared with the control group, the doxazosin patients exhibited a similar rise in blood pressure (NS) during handgrip exercise but a lesser fall in renal perfusion ($0.05 < P < 0.10$).

In both groups, handgrip exercise caused a small but insignificant increase in renin secretion which did not differ between the groups (22 ± 18 and $28 \pm 12 \text{ mU min}^{-1} (100 \text{ g})^{-1}$ in the control and doxazosin groups respectively).

Discussion

The extent to which α -adrenoceptors play a role in the human hypertensive kidney is at present unknown. Therefore, in this study we evaluated the effects of the selective α_1 -adrenoceptor blocking drug doxazosin on renal blood flow and renin secretion. The drug was infused intrarenally in order to avoid reflex mechanisms due to systemic effects. Our data show that when doxazosin was administered at a dose of $1 \mu\text{g kg}^{-1} \text{min}^{-1}$, a small rise in renal blood flow ensued. At higher infusion rates blood pressure progressively fell, suggesting blockade of α -adrenoceptors in the systemic circulation at these higher doses. The increase in renal perfusion following doxazosin infusion points to a role of α_1 -adrenoceptors in the mediation of renal vasoconstriction. Although the relative importance of these receptors cannot be assessed from our study, previous experiments in our laboratory indicated that the effect on renal blood flow was quantitatively greater when the non-selective drug phentolamine was infused (de Leeuw *et al.*, 1985). Thus, it may be that α_2 -adrenoceptors have an even greater impact than do α_1 -adrenoceptors on the regulation of renal blood flow. However, the renal vasoconstriction which accompanies isometric exercise is at least partly accomplished through α_1 -adrenoceptors, as doxazosin was able to blunt the vascular response.

Several studies have suggested that α -adrenoceptors are also involved in the regulation of renin release and, although their precise role is still obscure, most authors now seem to agree that their stimulation causes inhibition of renin secretion

(Pedrinelli *et al.*, 1981; VanDongen *et al.*, 1979). Whether this is an α_1 - or an α_2 -effect remains a matter of speculation. The results of the present study show that under resting conditions doxazosin enhanced renal renin release. However, when the sympathetic nervous system was activated by isometric exercise, renin secretion during doxazosin infusion was similar to that during saline infusion. Therefore, one may infer that α_1 -adrenoceptors exert a tonic inhibitory effect on renin secretion at rest, but apparently this mechanism is of lesser importance during activation of the adrenergic system. Again, this contrasts to our previous results where we found that phentolamine significantly enhanced renin release, not only at rest but also during handgrip exercise (de Leeuw *et al.*, 1985). Thus, further studies with more specific antagonists are necessary to elucidate whether α_2 -receptors are more important than α_1 -receptors in this respect. Also, it remains to be established whether the α -adrenergic effects are accomplished through receptors located on the juxtaglomerular cell or indirectly through changes in flow and/or resistance.

In conclusion, our results suggest that α_1 -adrenoceptors in the human hypertensive kidney are involved in renal vasoconstriction and inhibition of renin release, the latter being more pronounced at rest than during sympathetic activation. Quantitatively, however, the impact of these receptors seems rather small.

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References

- de Leeuw, P.W., De Bos, R., Van Es, P.N. & Birkenhäger, W.H. (1985). Effect of sympathetic stimulation and intrarenal alpha-blockade on the secretion of renin by the human kidney. *Eur. J. clin. Invest.*, **15**, 166–170.
- Dell, R.G., Sciacca, R., Lieberman, K., Case, D.B. & Cannon, P.J. (1973). A weighted least squares technique for analysis of kinetic data and its application to the study of renal ^{133}Xe -washout in dogs and man. *Circ. Res.*, **32**, 71–84.
- Diz, D.I., Nasjletti, A. & Baer, P.G. (1982). Renal denervation at weaning retards development of hypertension in New Zealand genetically hypertensive rats. *Hypertension*, **4**, 361–368.
- Katholi, R.E., Winternitz, S.R. & Oparil, S. (1981). Role of the renal nerves in the pathogenesis of one-kidney renal hypertension in the rat. *Hypertension*, **3**, 404–409.
- Ladefoged, J. (1966). Measurement of the renal blood flow in man with the ^{133}Xe washout-technique; a description of the method. *Scand J. clin. lab. Invest.*, **18**, 299–315.
- Pedrinelli, R., Sassano, P., Arzilli, F., Magagna, A. & Salvetti, A. (1981). Mediation of renin release in essential hypertension by alpha-adrenoceptors. *J. cardiovasc. Pharmac.*, **3**, 153–161.
- Skinner, S.L., Cran, E.J., Gibson, R., Taylor, R., Walters, W.A.W. & Catt, K.J. (1975). Angiotensin I and II, active and inactive renin, renin substrate, renin activity and angiotensinase in human liquor amnii and plasma. *Am. J. Obstet. Gynecol.*, **121**, 626–630.
- VanDongen, R., Strang, K.D., Poessé, M.H. & Birkenhäger, W.H. (1979). Suppression of renin secretion in the rat kidney by a nonvascular alpha-adrenergic mechanism. *Circ. Res.*, **45**, 435–439.
- Winternitz, S.R., Katholi, R.E. & Oparil, S. (1982). Decrease in hypothalamic norepinephrine content following renal denervation in the one-kidney, one clip Goldblatt hypertensive rat. *Hypertension*, **4**, 369–373.