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RENAL BLOOD-FLOW CHANGES DURING RENAL NERVE STIMULATION IN RATS TREATED WITH α-ADRENERGIC AND DOPAMINERGIC BLOCKERS

BY B. J. CHAPMAN, N. M. HORN AND M. J. ROBERTSON

From the Department of Physiology and Pharmacology, School of Biochemical and Physiological Sciences, University of Southampton, Southampton SO9 3TU

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SUMMARY

1. Blood flow through the inner cortex and outer medulla of the rat kidney was measured by the hydrogen wash-out technique.

2. Renal nerve stimulation caused vasoconstriction in both cortex and medulla. This constriction was abolished or reduced by phenoxybenzamine (9 μmole/kg I.V.), phentolamine (100 n-mole/kg) or prazosin (1·5 μmole/kg).

3. After prazosin (6 μmole/kg I.V.), renal nerve stimulation caused small but significant renal cortical vasodilatation. This vasodilatation was reversed by sulpiride (0·7 μmole kg^{-1} min^{-1}), but was unaffected by propranolol (10 μmole/kg) or atropine (4·3 μmole/kg).

4. These results indicate the existence of dopaminergic vasodilator nerves to the renal cortex of the rat.

INTRODUCTION

Much evidence now suggests that dopamine may play an important role in the normal control of renal function (Dinerstein, Henderson, Goldberg & Hoffman, 1978; Dinerstein, Vannice, Henderson, Roth, Goldberg & Hoffman, 1979; Bell, Lang & Laska, 1978; Chapman, Horn, Munday & Robertson, 1980*a*). Dopamine receptors are present in the renal vasculature of man and dog (Goldberg, Kohli, Kotake & Volkman, 1978) and rat (Chapman *et al.* 1980*a*), and exogenous dopamine can cause renal vasodilatation, diuresis and natriuresis (McDonald, Goldberg, McNay & Tuttle, 1964; Chapman, Lush & Munday, 1980*b*). Anton & Sayre (1964) and Bell, Lang & Laska, (1978) found levels of dopamine in the renal cortex of the dog which were considerably higher than would be expected if dopamine were present only as a precursor of noradrenaline, suggesting some source other than noradrenergic sympathetic neurones. Recent work with histofluorometric techniques has now provided evidence for the existence of exclusively dopaminergic neurones in the renal cortex of the dog. It has been suggested that these fibres represent the physiological prejunctional counterpart of the specific dopamine receptors present within the kidney (Dinerstein *et al.* 1979; Bell *et al.* 1978).

Functional roles for the renal dopamine and for the renal receptors for dopamine,

have been suggested by several groups. Bell & Lang (1973) reported the existence of a neural dopaminergic vasodilator pathway to the kidney and Chapman *et al.* (1980*a*) found that renal dopamine may be involved in the reflex control of renal blood flow in the rat. Further evidence has been provided by Imbs, Schmidt, Erhardt & Schwartz (1979) who found large quantities of dopamine in renal blood during renal nerve stimulation.

There is also evidence that dopamine is involved in the normal control of urinary Na^+ and water excretion. Urinary dopamine excretion parallels normal changes in salt and water excretion (Cuche, Kuchel, Barbeau, Boucher & Genest, 1972; Alexander, Gill, Yamabe, Lovenberg & Keiser, 1974; Oates, Ball, Perkins & Lee, 1979). Conversely, Ball & Lee (1977) found that urinary Na^+ excretion decreases when the synthesis of endogenous dopamine is inhibited. Also, Chapman *et al.* (1980*b*) measured changes in urine composition following expansion of the extracellular fluid volume of the rat and found that the renal response was significantly reduced by pre-treatment with the neuroleptics, sulpiride or haloperidol. In the present study we describe experiments showing that renal nerve stimulation in the rat can cause a dopamine-mediated vasodilatation.

Electrical stimulation of the renal nerves normally leads to vasoconstriction of the renal blood vessels. This vasoconstriction is maximal at a stimulation frequency of 10–16 Hz (Coote, Johns, Macleod & Singer, 1972) and decreases at higher frequencies (DiSalvo & Fell, 1971). This neurally induced vasoconstriction can be almost abolished by pre-treatment with many blockers of the α-adrenergic pathway, such as phenoxybenzamine, bretylium, reserpine or guanethidine (Goodman & Gilman, 1979). This suggests that the over-riding contribution to the vasoconstriction is made by noradrenaline released from sympathetic nerve endings acting on α-adrenergic receptors (Gomer & Zimmerman, 1972).

Earlier workers have not reported vasodilator responses to renal nerve stimulation during α-adrenergic blockade (Gomer & Zimmerman, 1972) and this has been taken to indicate the absence of neural vasodilator influences acting on the kidney. Furthermore, β-adrenergic receptor blockade with propranolol does not modify the response to renal nerve stimulation (DiSalvo & Fell, 1971; Gomer & Zimmerman, 1972) which is evidence against any neural vasodilator effect mediated by β-adrenergic receptors. Atropine, however, slightly reduced the vasoconstrictor response to renal nerve stimulation (DiSalvo & Fell, 1971), which is a surprising observation since injected acetylcholine leads to renal vasodilatation, and atropine might therefore be expected to promote vasoconstriction by antagonizing any dilator actions of endogenous acetycholine. McGiff, Burns & Blumenthal (1967) have suggested that acetylcholine can facilitate noradrenaline release during renal nerve stimulation, but attempts to alter the vasoconstrictor response by hemicholinium or neostigmine (which change the amount of endogeneous acetylcholine present in the junctional region) have given contradictory results (McGiff *et al.* 1967; Takeuchi, Aoki, Nomura, Mizumura, Shimizu and Kubo, 1971). Lyrdal & Staubitz (1972) stimulated the distal end of the cut vagus nerve and found that this had no effect on renal blood flow. This clearly suggests that parasympathetic nerves are not important in the control of renal blood flow.

We therefore decided to stimulate the renal nerve of the rat before and after

treatment with prazosin (a selective α_1-adrenergic blocker) and then with sulpiride (a selective antagonist of dopamine receptors). This work has been briefly reported elsewhere (Chapman, Horn, Munday & Robertson, 1979).

METHODS

Male Wistar albino rats weighing 250–400 g were anaesthetized with sodium pentobarbitone (60 mg kg^{-1} I.P.). Mean arterial blood pressure was measured from a cannula in a femoral artery using an Elcomatic transducer, and recorded on a Servoscribe potentiometric recorder. Solutions were injected or infused via a cannula in a femoral vein.

The peritoneum was opened and tissues overlying the left kidney carefully displaced. Two H_2-sensitive platinum electrodes were inserted to different depths within the parenchyma of the left kidney. These two electrodes were used to measure H_2 concentrations polarographically (Chapman *et al.* 1980*a*), so that blood flows could be calculated for two highly localized regions of the kidney. Calibration marks were painted on to each electrode to facilitate insertion of the electrodes to known depths. One electrode was inserted to a depth of 1 mm to measure inner cortical blood flow, the other to a depth of 3 mm to measure outer medullary blood flow. A single calomel–KCl bridge, held against the exposed tissues of the leg, completed the two circuits. The preparation was then left for 30 min for renal function to stabilize.

Small volumes of H_2 gas were then introduced into the tracheal cannula for one or two inspirations and distributed via the blood supply to the tissues of the body. Dissolved H_2, detected by the electrodes in the kidney, caused a change in electrical current through the electrodes and recording system; this current was recorded on a Vitatron logarithmic recorder (Vitatron U.K. Ltd., Maidenhead). The blood flow rate around the tip of the electrode (in ml. min^{-1} 100 g $tissue^{-1}$) was determined from the rate constant for the exponential disappearance of H_2 from the kidney.

In all cases, the blood flow was calculated as the mean of two to four consecutive recordings, made at intervals of 3–5 min. The recordings obtained by this method were analysed independently by two people and were analysed 'blind', i.e. the recordings were coded and assorted to prevent the person analysing from knowing what treatment had been applied. There was good correlation between these two analyses ($r^2 = 0{\cdot}98$). The experimental preparation and evidence validating this method of measuring renal blood flow have been described by Chapman *et al.* (1980*a*).

The position of the renal nerves was revealed by staining with Methylene Blue (5 % solution) which was applied to the tissues near the left kidney. Some of the renal nerves of the rat were found to enter the kidney not in a discrete bundle, but in the form of two or more plexi located between the renal and adrenal veins. These plexi would lie midway along a hypotenuse drawn from the inferior vena cava to meet the left renal vein just medial to the adrenal vein. Dissection was kept to a minimum, and the nerves were not separated from adjacent fat and connective tissue. Fine bipolar platinum electrodes were manoeuvred under a flap of connective tissue containing some of these nerves and stimuli applied (using a CFP simulator, model 8048) at 10–17 V at 10–15 Hz with a pulse duration of 0·05 msec. One or two drops of mineral oil were applied to the nerves to prevent desiccation.

The following drugs were dissolved in 0·9 % saline and injected or infused intravenously (I.V.) by means of a Braun (Melsungen) infusion pump: prazosin (Pfizer), phenoxybenzamine (Smith, Kline & French), phentolamine (CIBA), (R-S)-sulpiride (Delegrange Laboratories, France), noradrenaline (Koch-light), propranolol (Sigma), acetylcholine and atropine (B.D.H.).

All experimental results are quoted as the mean $\pm$ S.E. of the mean and any differences between means were evaluated statistically using Student's t test. The statistical methods used were those described by Colqhoun (1971).

RESULTS

Changes in blood flow through the cortex and the medulla of the kidney were measured in experiments where the renal nerves were stimulated before or during pharmacological blockade of the α-adrenergic receptors in three groups of rats; renal

vascular resistance changes in these animals are described below (Fig. 1). In the absence of renal nerve stimulation and before drug treatment, the mean blood flow through the cortex was 310 ± 13 ml. min^{-1} 100 g tissue^{-1} ($n = 17$ observations) with no significant difference between these control measurements in the three groups. Similarly, in the absence of renal nerve stimulation and before pharmacological blockade, the mean blood flow through the renal medulla was 144 ± 8 ml. min^{-1} 100 g tissue^{-1} ($n = 17$ observations), and again there were no significant differences between the control measurements of the three groups of experiments. Stimulation of the renal nerves caused the blood flow through the renal cortex to decrease by about 40 % in each of these three groups of experiments and caused the blood flow through the medulla to decrease by 40–60 %.

Treatment of the animals with α-adrenergic blocking agents caused the cortical blood flow to decrease to 229 ± 20 ml. min^{-1} 100 g tissue^{-1} after phenoxybenzamine; to 242 ± 9 ml. min^{-1} 100 g tissue^{-1} after phentolamine; and to 223 ± 13 ml. min^{-1} 100 g tissue^{-1} after prazosin. These falls in blood flow were proportional to the falls in arterial blood pressure (see below) indicating that there was no change in the vascular resistance to blood flow, i.e. the α-blockers did not cause vasoconstriction. The renal nerves were then re-stimulated in these α-blocked rats, and the changes in blood flow recorded. The renal response to nerve stimulation was abolished by phenoxybenzamine, was slightly reduced by phentolamine, and was almost abolished by prazosin. These results are in agreement with the well established concept that renal nerve stimulation leads to renal vasoconstriction, mediated by the release of noradrenaline from sympathetic nerve endings within the kidney, and noradrenaline action on α-adrenergic receptors (Ahlquist, 1948; Green & Kepchar, 1959).

Before injection of α-adrenergic blocking agents, the mean arterial blood pressure was 114 ± 3 mmHg in these animals (there was no statistically significant difference between the three groups of animals studied). Renal nerve stimulation caused the systemic arterial pressure to increase on average by $1{\cdot}6 \pm 1{\cdot}0$ mmHg ($n = 33$; Student's $t = 1{\cdot}60$; n.s.). The mean blood pressure decreased to 79 ± 2 mmHg after injection of phenoxybenzamine, to 107 ± 6 after injection of phentolamine, and to 84 ± 2 after injection of prazosin. Nerve stimulation had no consistent effect on the arterial blood pressure after the injection of any α-blocker: the mean change in blood pressure during nerve stimulation was $+0{\cdot}4 \pm 1{\cdot}5$ mmHg ($n = 33$; Student's paired $t = 0{\cdot}27$; n.s.). Thus renal nerve stimulation did not alter the systemic arterial pressure in these rats, which makes interpretation of the results easier since pressure-induced changes do not have to be taken into account.

Fig. 1 *A* and *B* shows the changes in renal vascular resistance to blood flow in these same groups of animals treated with the α-adrenergic blocking agents. Before α-adrenergic blockade, renal nerve stimulation caused increases in resistances to blood flow in all three groups of animals, in both cortex and medulla. In groups *A* and *B* the medullary response to nerve stimulation was greater than the cortical response, while in group *C* the reverse was true; these differences do not influence any of the conclusions to be drawn below.

These responses to renal nerve stimulation were abolished by phenoxybenzamine, attenuated by phentolamine, and almost abolished by prazosin at the doses used. As stated above, these results agree with existing concepts that the vasoconstrictor

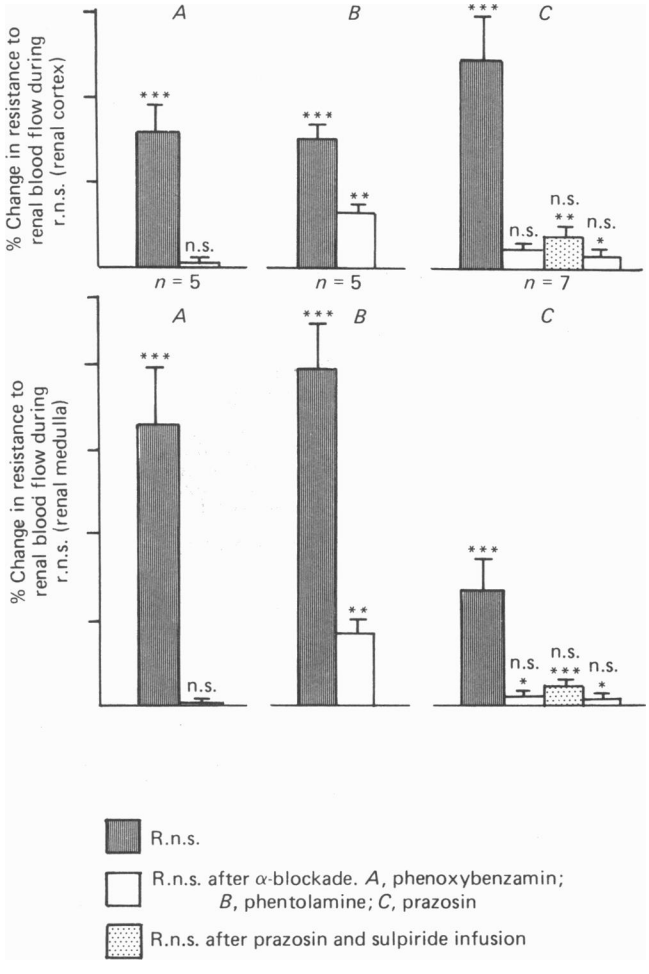

Fig. 1. The effects of renal nerve stimulation (r.n.s.) on the resistances to cortical and medullary blood flow before (hatched histograms) and after (unshaded histograms) treatment with various α-adrenergic blockers: *A*, before and after phenoxybenzamine, 9 μmole kg^{-1} I.V.; *B*, before and after phentolamine, 100 n-mole kg^{-1} I.V.; and *C*, before and after prazosin, 1·5 μmole kg^{-1} I.V. The animals in *C* were also treated with sulpiride (0·7 μmole kg^{-1} min^{-1} I.V.; stipplied histograms) for part of the experiment. Values are shown as means ± S.E. of means. The changes due to nerve stimulation were evaluated by paired *t* test; differences due to sulpiride were also evaluated by *t* test; *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$. n.s. = not significant.

effects of renal nerve stimulation are mediated by the release of noradrenaline from sympathetic nerve endings. Furthermore, these results agree with the findings of Gomer & Zimmerman (1972), that renal vasodilatation is not seen during renal nerve stimulation after application of α-adrenergic blockers. Such experiments have been interpreted as indicating that there are no renal vasodilator nerves.

To test in a different way whether dopamine might be involved in the renal

responses to nerve stimulation, the following experiment was performed. After application of an α-blocker (viz. prazosin; for the reasons behind this choice, see the Discussion) the renal nerves were stimulated with and without the application of sulpiride (unshaded histograms and hatched histograms respectively in Fig. 1). Sulpiride is the most potent inhibitor known for peripheral dopamine receptors

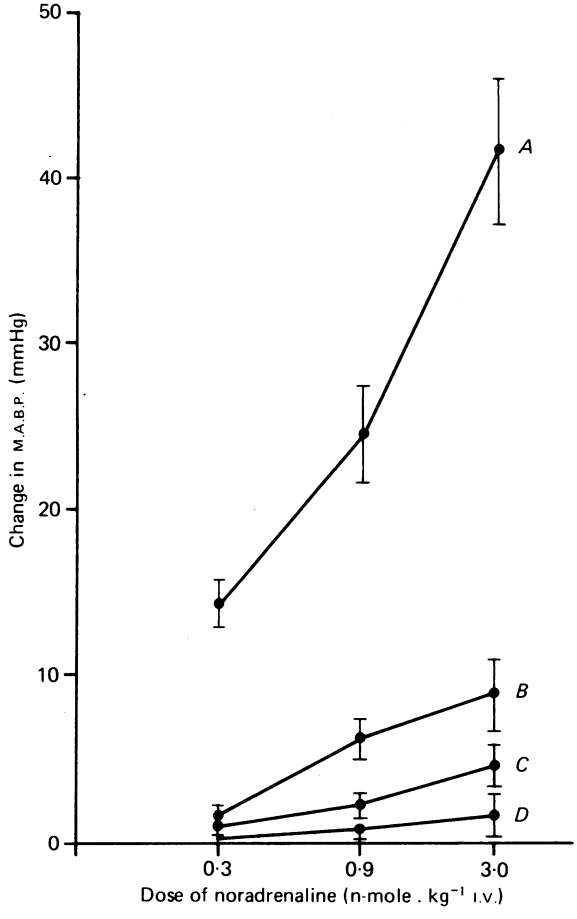

Fig. 2. The effect of noradrenaline (0·3, 0·9 and 3·0 n-mole kg^{-1} I.V.) on the mean arterial blood pressure (M.A.B.P.); *A*, in the absence and *B–D*, in the presence of prazosin at doses of 1·5 (*B*), 3 (*C*) or 6 μmole kg^{-1} (*D*) I.V. ($n = 5$ rats).

(Kohli, Volkman, Glock & Goldberg, 1978), and we have shown in experiments similar to those described here, that dopamine is a vasodilator in the renal cortex and renal medulla of the rat and that this vasodilator activity is blocked by sulpiride in the same dose as used in the present study (Chapman *et al.* 1980*a*); furthermore, we found that sulpiride is a selective blocker of dopamine vasodilator activity and does not block responses to noradrenaline, acetylcholine, 5-hydroxytryptamine, histamine or isoprenaline. In the present study, sulpiride (0·7 μmole kg^{-1} min^{-1}) was infused intravenously and the renal vasoconstrictor response to nerve stimulation was

partially restored; this effect was statistically significant in the renal cortex, but not in the renal medulla (Fig. 1*C*). One possible interpretation of these results is as follows: during nerve stimulation both noradrenaline and dopamine are released (from different populations of neurones); due to incomplete α-adrenergic blockade the noradrenaline can exert a weak residual vasoconstrictor activity sufficient to cancel out the vasodilator activity of the released dopamine in Fig. 1*C* (unshaded histograms) and sufficient to completely obscure any such vasodilator activity in Fig. 1*B*; when the actions of dopamine are selectively inhibited with sulpiride, the (weak, vasoconstrictor) activity of the noradrenaline is revealed, as in Fig. 1*C* (stippled histogram).

Thus, one reason why renal nerve stimulation did not lead to vasodilatation after α-adrenergic blockade might be because the dose of prazosin (1·5 μmole kg^{-1} I.V.) produced incomplete blockade of the α-adrenergic receptors.

The following experiment was therefore performed to test the extent of α-adrenergic receptor blockade produced by this dose of prazosin. Three doses of noradrenaline (0·3, 0·9 and 3·0 n-mole kg^{-1}) were injected intravenously into five animals before the injection of prazosin (Fig. 2*A*) and after the injection of prazosin (1·5, 3·0 and 6·0 μmole kg^{-1} I.V.; Fig. 2*B*, *C* and *D*). This graph confirms that the 1·5 μmole kg^{-1} dose of prazosin provides incomplete blockade of the renal α-adrenergic receptors. The highest dose of prazosin (6 μmole kg^{-1}) almost abolished the pressor responses to noradrenaline and it was decided to re-test the effect of renal nerve stimulation on renal blood flow after application of this dose.

Figure 3 shows changes in blood flow in the renal cortex and the renal medulla in another three groups of animals using the highest dose of prazosin (6 μmole kg^{-1}) injected intravenously. Before prazosin injection, the cortical blood flow was 316 ± 12 ml. min^{-1} 100 g tissue^{-1} (mean of sixteen rats from all three groups; the slight differences between the three groups of animals were not statistically significant), and the medullary blood flow was 152 ± 12 ml. min^{-1} 100 g tissue^{-1} ($n = 16$; the three groups were not statistically different). Before prazosin injection, renal nerve stimulation caused the cortical blood flow to decrease by 62 ± 5 % and the medullary blood flow to decrease by 55 ± 11 % ($n = 7$–16 observations, with no significant differences between the three groups of animals). After prazosin injection, nerve stimulation caused the blood flow through the renal cortex to increase by $4{\cdot}1 \pm 1{\cdot}5$ % (Fig. 3*A*; $t = 2{\cdot}75$; $P < 0{\cdot}05$) in the first groups of seven animals; the increase in cortical blood flow was similarly $6{\cdot}6 \pm 0{\cdot}8$ % ($t = 7{\cdot}51$; $P < 0{\cdot}01$) in five different animals which were treated with prazosin and with the β-adrenergic blocking agent, propranolol, 10 μmole kg^{-1} I.V. (Fig. 3*B*); and the increase in cortical blood flow was $6{\cdot}1 \pm 3{\cdot}7$ % ($t = 1{\cdot}65$; n.s.) in four rats treated with prazosin plus atropine, 4·3 μmole kg^{-1} I.V. (Fig. 3*C*). The average increase in cortical blood flow during nerve stimulation, in the presence of prazosin alone was $6{\cdot}1 \pm 1{\cdot}4$ % ($t = 4{\cdot}27$; $P < 0{\cdot}001$) which is the average of the three experiments just described (Fig. 3*E*). In all of these three experiments the renal nerves were re-stimulated during infusion of sulpiride; in all cases the response to nerve stimulation was reversed, and in all three experiments the vasoconstrictor response to nerve stimulation was then statistically significant (stippled histograms in Fig. 3).

The blood flow through the renal medulla was also measured in some of these

experiments. Nerve stimulation caused a slight vasoconstriction, and during sulpiride infusion the vasoconstrictor response was slightly but not significantly enhanced (Fig. 3*D*).

The changes in vascular resistance to blood flow in these experiments paralleled those in renal blood flow because the changes in arterial blood pressure were small. Before α-blockade, renal nerve stimulation increased the vascular resistance to blood flow through the cortex by 205 ± 4 % and the vascular resistance to blood flow through

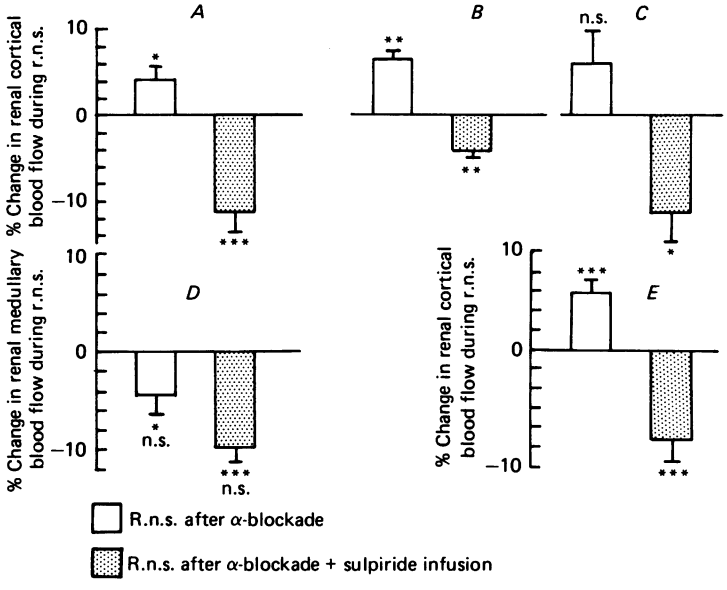

Fig. 3. The effect of renal nerve stimulation (r.n.s.) on renal cortical and renal medullary blood flows in the absence (unshaded histograms) or presence (stippled histograms) of sulpiride (0·7 μmole kg^{-1} min^{-1} I.V.). All animals were pre-treated with the α-adrenergic blocker prazosin (6 μmole kg^{-1} I.V.). *A* and *D*, seven rats given no extra treatment; *B*, five animals given β-adrenergic blocker (propranolol, 10 μmole kg^{-1} followed by 12 μmole kg^{-1} hr^{-1} I.V.); *C*, four rats given cholinergic blocker (atropine, 4·3 μmole kg^{-1} I.V.); *E*, summary of results from sixteen animals shown in *A*, *B* and *C*. All results shown as the means ± S.E. of means; differences were evaluated by paired *t* test; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

the medulla by 103 ± 23 %. After α-blockade, nerve stimulation caused a small but highly significant decrease of 5·3 ± 1·1 % in resistance to flow through the cortex ($t = 4.66$; $P < 0.01$) and caused an increase of 2·3 ± 1·0 % in the resistance to flow through the medulla ($t = 2.3$; n.s.). Sulpiride was infused and renal nerve stimulation then caused an 11·1 ± 3·9 % increase in the cortical resistance to blood flow and a 9·0 ± 4 % increase in the medullary resistance to blood flow (see Fig. 3*A* and *D*). The change in response due to the presence of sulpiride was 16·4 ± 3·6 % ($t = 4.5$; $P < 0.01$) in the cortex and 6·9 ± 1·5 % ($t = 4.6$; $P < 0.01$) in the medulla. All studies of the effect of renal nerve stimulation on the renal cortical resistance to blood flow after α-blockade with the higher dose of prazosin were pooled to give the mean values from the total

of sixteen rats: in the absence of sulpiride, nerve stimulation caused a statistically significant $5{\cdot}9 \pm 0{\cdot}8\,\%$ decrease in the renal cortical resistance to blood flow ($t = 7{\cdot}04$; $P < 0{\cdot}001$). In the presence of sulpiride (0·7 μmole kg^{-1} I.V.), nerve simulation caused an increase of $11{\cdot}0 \pm 2{\cdot}1\,\%$ in the renal cortical resistance to blood flow; again this change was statistically significant ($t = 5{\cdot}35$; $P < 0{\cdot}001$). The difference between these two values was also highly significant ($t = 7{\cdot}71$; $P < 0{\cdot}001$).

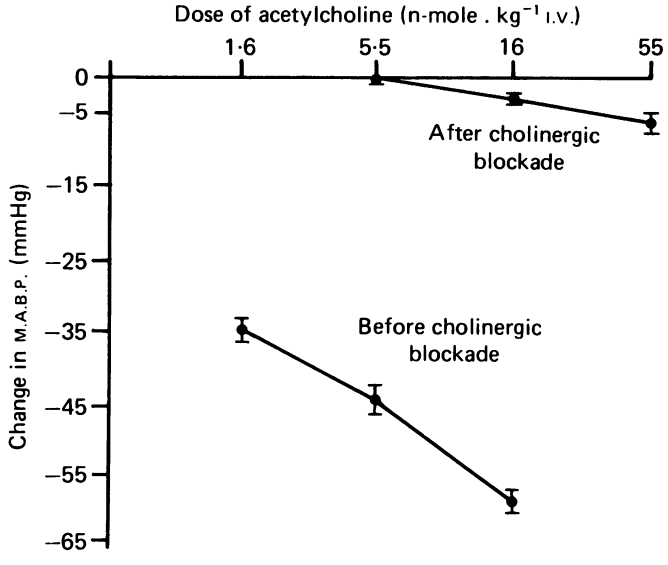

Fig. 4. The effect of injected acetylcholine on the mean arterial blood pressure (M.A.B.P.) in the absence (lower line) or presence (upper line) of atropine (4·3 μmole kg^{-1} I.V.); $n = 5$ rats. Values are shown as means ± S.E. of means.

Neither the presence of a β-adrenergic blocker (propranolol, 10 μmole kg^{-1} I.V.) nor a cholinergic blocker (atropine, 4·3 μmole kg^{-1} I.V.) significantly altered the renal blood-flow changes or renal vascular resistance changes evoked by nerve stimulation in the presence or absence of sulpiride (Fig. 3*B* and *C*).

Of the pharmacological blocking agents used in this study, phenoxybenzamine, propranolol and sulpiride have been previously established as selective antagonists of α-adrenergic, β-adrenergic and dopamine receptors respectively (Chapman *et al.* 1980*a*) and prazosin as a selective antagonist of α_1-receptors (Langer, Massingham & Shepperson, 1981). To test that the dose of atropine used above was sufficient to block cholinergic receptors, the following experiment was performed. Three different doses of acetylcholine (1·6, 5·5 or 16 n-mole kg^{-1} I.V.) were injected into rats and these caused dose-dependent decreases in the mean arterial blood pressure (Fig. 4). Atropine (4·3 μmole kg^{-1} I.V.) was injected and the doses of acetylcholine re-tested. The depressor responses to acetylcholine were severely reduced in the presence of atropine. It can be concluded that the dose of atropine used in these experiments was adequate to effectively antagonize the action of acetylcholine at cholinergic receptors.

DISCUSSION

Dinerstein *et al.* (1979) and Bell *et al.* (1978) have reported the existence of dopaminergic nerves in the renal cortex. The present studies provide strong confirmation of the existence of dopaminergic vasodilator fibres in the renal nerves by showing clear dilator responses to the nerves after α-adrenergic blockade with a high dose of prazosin, and by showing that specific blockade of dopamine receptors with sulpiride blocked this vasodilatation.

Prazosin was employed in the present studies because it is believed to be a more selective blocker of target organ (post-synaptic) α_1-adrenergic receptors (Cambridge, Davey & Massingham, 1977; Langer & Dubocovitch, 1979) than phentolamine or phenoxybenzamine (the blockers widely used by other workers in this field), and it does not stimulate the release of endogenous noradrenaline (Cambridge *et al.* 1977); these factors may have been significant in enabling the demonstration of the neural dilator activity. Imbs *et al.* (1979) have also reported that renal nerve stimulation can produce small increases in renal blood flow in dogs pre-treated with a mixture of α-adrenergic blocking agents (thus achieving a high degree of receptor blockade, while minimizing the side effects of any one blocker).

This demonstration of a dopaminergic renal vasodilator activity is consistent with many studies indicating that dopamine plays a role in the normal control of renal function (see Introduction).

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