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# INTERACTION OF THE RENIN–ANGIOTENSIN SYSTEM AND THE RENAL NERVES IN THE REGULATION OF RAT KIDNEY FUNCTION

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SUMMARY

1. Stimulation of the renal sympathetic nerves in pentobarbitone anaesthetized rats achieved a 13% reduction in renal blood flow, did not change glomerular filtration rate, but reduced urine flow by 37%, absolute sodium excretion by 37%, and fractional sodium excretion by 34%. Following inhibition of converting enzyme with captopril (0·38 mmol $kg^{-1}$ $h^{-1}$), similar nerve stimulation reduced both renal blood flow and glomerular filtration rate by 16%, and although urine flow and absolute sodium excretion fell by 32 and 31%, respectively, the 18% fall in fractional sodium excretion was significantly less than that observed in the absence of captopril.

2. Renal nerve stimulation at low levels, which did not change either renal blood flow or glomerular filtration rate, reduced urine flow, and absolute and fractional sodium excretions by 25, 26 and 23%, respectively.

3. In animals receiving captopril at 0·38 mmol $kg^{-1}$ $h^{-1}$, low-level nerve stimulation caused small increases in glomerular filtration rate of 7% and urine flow of 12%, but did not change either absolute or fractional sodium excretions. At one-fifth the dose of captopril (0·076 mmol $kg^{-1}$ $h^{-1}$), low-level nerve stimulation did not change renal haemodynamics but decreased urine flow, and absolute and fractional sodium excretions by 10, 10 and 8%, respectively.

4. These results showed that angiotensin II production was necessary for regulation of glomerular filtration rate in the face of modest neurally induced reductions in renal blood flow and was compatible with an intra-renal site of action of angiotensin II preferentially at the efferent arteriole. They also demonstrated that in the rat the action of the renal nerves to decrease sodium excretion was dependent on angiotensin II.

## INTRODUCTION

Angiotensin II has widespread effects throughout the body, causing vasoconstriction of vascular smooth muscle, increasing aldosterone secretion, stimulation of epithelial fluid transport, together with a number of less well defined activities (Peach, 1977). Within the kidney itself, therefore, angiotensin II has the potential of regulating both haemodynamic and tubular function (Levens, Peach & Carey, 1981). One of the major mechanisms causing the release of renin, and hence the

production of angiotensin II, is activation of the renal sympathetic nerves (Reid, Morris & Ganong, 1978; Keeton & Campbell, 1980). It is recognized that the renin-containing cells of the juxtaglomerular apparatus are innervated and that activity in the nerves can directly cause renin release even when there are no changes in total renal blood flow (DiBona, 1982).

There is good evidence to show that local production of angiotensin II is essential for the appropriate regulation of glomerular filtration rate when renal blood flow is reduced modestly as a result of renal nerve activation (Johns, 1979, 1980) and this is consistent with the viewpoint that angiotensin II preferentially vasoconstricts the efferent arteriole in order to preserve glomerular filtration pressure.

One further property exhibited by angiotensin II, which impinges more directly on the sympathetic nervous system, is that it has the ability to modulate noradrenergic transmission. This appears to be a presynaptic action whereby the amount of transmitter released at neurovascular junctions is enhanced in the presence of angiotensin II (Starke, 1977; Vanhoutte, Verbeuren & Webb, 1981) and is a phenomenon which has been described in a wide variety of tissues (Zimmerman, 1981). Because of the extensive innervation of the kidney, the possibility arises that the level of angiotensin II could change the effectiveness of the sympathetic regulation of renal function itself.

At the tubular level the renal nerves have been shown to end in close proximity to the epithelial cells (Barajas, Powers & Wang, 1984) and functionally they have been shown to directly increase tubular sodium reabsorption by the cells of the proximal tubules and the thick ascending limb of the loop of Henlé (Pelayo, Ziegler, Jose & Blantz, 1983; DiBona & Sawin, 1982). The question arises as to whether this particular end-point of renal nerve activity could be dependent on the level of angiotensin II present at the neuro-epithelial junction. This issue was addressed in the present study by determining whether a reduction in the circulating level of angiotensin II, consequent on the inhibition of angiotensin-converting enzyme, would change the effectiveness of the renal nerves in causing a decrease in sodium excretion.

## METHODS

Male Sprague–Dawley rats, in the weight range 340–400 g, were anaesthetized with sodium pentobarbitone (240 $\mu$mol kg$^{-1}$, I.P.) and maintained with supplemental intravenous doses as required. Following tracheostomy, the left carotid artery was cannulated to allow blood pressure measurements (Statham P23Db pressure transducer linked to a Grass model 5 or 7 polygraph) and removal of blood samples. The left jugular vein was cannulated and an infusion of saline (150 mM-NaCl) was begun at 6 ml h$^{-1}$ (Braun Unita I infusion pump) and continued at the same rate throughout the experiment. The left kidney was exposed via a ventral mid-line incision, its ureter cannulated for collection of urine and the renal artery cleared to allow fitting of an electromagnetic flow probe (Carolina EP 100 series) for direct measurement of renal blood flow (Carolina FM 501 flowmeter linked to the Grass polygraph). Renal nerve fibres were isolated distal to the coeliac ganglion and prepared for stimulation.

*Renal function measurements.* On completion of all surgery a primer solution of 1 ml saline containing inulin (20 mg ml$^{-1}$) was administered I.V. over a 2 min period and the saline infusion changed to one containing inulin at 8 mg ml$^{-1}$. Measurements were begun 2 h later. Arterial blood samples (0·35 ml) were collected into cooled syringes, immediately centrifuged, the plasma stored (deep frozen) and the erythrocytes resuspended in an equal volume of saline and infused back into the animal after removal of the subsequent blood sample.

The experimental protocol consisted of five clearance periods: two 30 min control clearance periods, followed by a 20 min clearance period during which the renal nerves were stimulated, and a further pair of 30 min recovery clearance periods. At least 5 min was allowed from the start and cessation of the renal nerve stimulation before urine collection was begun in order to take account of dead space in the collection system.

Inulin in plasma and urine was assayed as previously described (Johns, Lewis & Singer, 1976) and plasma inulin levels were measured at the beginning and end of the control and recovery pair of clearance periods. Glomerular filtration rate was calculated as the clearance of inulin (Arundell & Johns, 1982) and renal blood flow was measured from the calibrated paper trace obtained from the Grass polygraph at 3 min intervals throughout each clearance period. At the end of each experiment an *in vivo* calibration of the flow probe was undertaken, using the femoral artery and collecting timed blood samples. Plasma and urinary sodium concentrations were measured using a Beckman flame photometer.

*Renal nerve stimulation.* The renal nerves were placed on bipolar silver wire electrodes and square-wave stimuli were delivered at 15 V, for 0·2 ms duration (Grass S8 stimulator). Stimulation frequencies ranged between 2 and 4 Hz to reduce renal blood flow by approximately 15%, and between 0·5 and 1·5 Hz, for subthreshold effects on renal blood flow. The frequency of stimulation was adjusted as necessary through the course of the clearance period to ensure that the required flow reduction was maintained.

*Captopril infusions.* The angiotensin-converting enzyme inhibitor, captopril, was dissolved in saline containing inulin (8 mg $ml^{-1}$) at a concentration such that it was delivered into the animals at a rate of either 0·38 or 0·076 mmol $kg^{-1}$ $h^{-1}$. 1 h after completion of surgery the vasopressor and renal vasoconstrictor effects of a bolus dose of 77 pmol angiotensin I were measured. The infusion was then switched to one containing the captopril, and 40 min later and at the end of the experiment further doses of 77 pmol angiotensin I were given to assess the degree of blockade of the renin–angiotensin system.

*Statistics.* A mean value of the two clearances before and the two clearances after the period of renal nerve stimulation was calculated, and termed the basal value, which was compared to the value obtained during the period of nerve stimulation. The absolute and percentage changes quoted in the text represent the mean of the individual changes recorded in each animal. Mean values ± S.E. of mean are used. Paired and unpaired Student's *t* tests were performed for analysis of significance. Differences were taken to be statistically significant when $P < 0·05$.

## RESULTS

### *High-level renal nerve stimulation*

The initial study was aimed at defining the effects of high rates of renal nerve stimulation, to cause an approximate 15% reduction in renal blood flow, on kidney function under normal conditions and following blockade of the renin–angiotensin system with captopril. The findings are presented in Table 1. In a group of animals infused with saline, blood pressure remained constant throughout the period of renal nerve stimulation at rates which significantly ($P < 0·001$) reduced renal blood flow by 13%. During this nerve stimulation glomerular filtration rate did not change significantly but there were significant reductions in urine flow of 37% ($P < 0·01$), absolute sodium excretion of 37% ($P < 0·02$), and fractional sodium excretion of 34% ($P < 0·02$).

Prior to captopril administration, bolus injection of 77 pmol angiotensin I increased blood pressure by 43 mmHg and decreased renal blood flow by 12·3 ml $min^{-1}$ $kg^{-1}$. 40 min after the start of the captopril infusion at 0·38 mmol $kg^{-1}$ $h^{-1}$ the vasopressor and renal vasoconstrictor actions of a further dose of angiotensin I were blocked by 90%, and a similar degree of inhibition of angiotensin I was obtained at the end of the experiment. Infusion of captopril at

0·38 mmol $kg^{-1}$ $h^{-1}$ did not change blood pressure but significantly increased renal blood flow and glomerular filtration rate (for both $P < 0.05$) when compared to animals receiving saline, whereas basal rates of urine flow, and absolute and fractional sodium excretions were unchanged. Stimulation of the renal nerves in the captopril-infused animals did not affect systemic blood pressure but reduced renal

TABLE 1. Blood pressure and kidney responses to high-level renal nerve stimulation during infusion of saline or captopril (0·38 mmol $kg^{-1}$ $h^{-1}$)

| | Saline ($n = 6$) | | Captopril ($n = 7$) | |
|---|---|---|---|---|
| | Basal | Stimulation | Basal | Stimulation |
| Systemic blood pressure (mmHg) | 126±4 | 127±3 | 124±3 | 125±4 |
| Renal blood flow (ml $min^{-1}$ $kg^{-1}$) | 17·0±1·1 | 14·8±1·2† | 24·1±1·5 | 20·2±1·2† |
| Glomerular filtration rate (ml $min^{-1}$ $kg^{-1}$) | 3·90±0·30 | 3·80±0·30 | 5·20±0·20 | 4·40±0·20† |
| Urine flow ($\mu$l $min^{-1}$ $kg^{-1}$) | 62·1±7·6 | 38·7±6·8*** | 71·5±3·9 | 48·6±3·5† |
| Absolute sodium excretion ($\mu$mol $min^{-1}$ $kg^{-1}$) | 16·0±2·7 | 9·8±1·4** | 19·1±1·7 | 13·2±1·4† |
| Fractional sodium excretion (%) | 2·49±0·50 | 1·58±0·31** | 2·07±0·12 | 1·71±0·17** |

** $P < 0.02$; *** $P < 0.01$; † $P < 0.001$.

The $t$ test was undertaken using a mean of the absolute values of the two clearances before and the two after stimulation (basal) and comparing it with the value obtained during stimulation. $n$ = number of animals.

blood flow significantly ($P < 0.001$) by 16%. This was associated with a significant ($P < 0.001$) reduction in glomerular filtration rate of 16%, which was a response significantly ($P < 0.02$) different from that obtained in the saline-infused animals. These high rates of renal nerve stimulation in the presence of captopril resulted in significant falls in urine flow of 32% ($P < 0.001$), and absolute sodium excretion of 31% ($P < 0.001$), which were responses similar in magnitude to those in animals given saline; however, fractional sodium excretion was reduced by only 18% ($P < 0.005$) which was significantly ($P < 0.05$) less than the reduction obtained in the animals given saline. Fig. 1. presents a comparison of the percentage changes in each of the renal function variables to renal nerve stimulation in the saline- and captopril-infused animals.

*Low-level renal nerve stimulation*

In this study the renal nerves were stimulated at rates which were subthreshold for changes in renal blood flow such that the direct effects of the nerves on tubular sodium reabsorption could be more clearly examined. The results are given in Table 2. In the group of animals given a saline infusion blood pressure remained unchanged throughout the experiment. Stimulation of the renal nerves at these low rates did not change either renal blood flow or glomerular filtration rate but induced significant reductions in urine flow of 25% ($P < 0.01$), absolute sodium excretion of 26% ($P < 0.01$), and fractional sodium excretion of 23% ($P < 0.05$).

Infusion of captopril at 0·38 mmol $kg^{-1}$ $h^{-1}$ again resulted in significantly greater basal rates of renal blood flow ($P < 0.02$) and glomerular filtration ($P < 0.025$) but did not change either blood pressure or the level of water and sodium output.

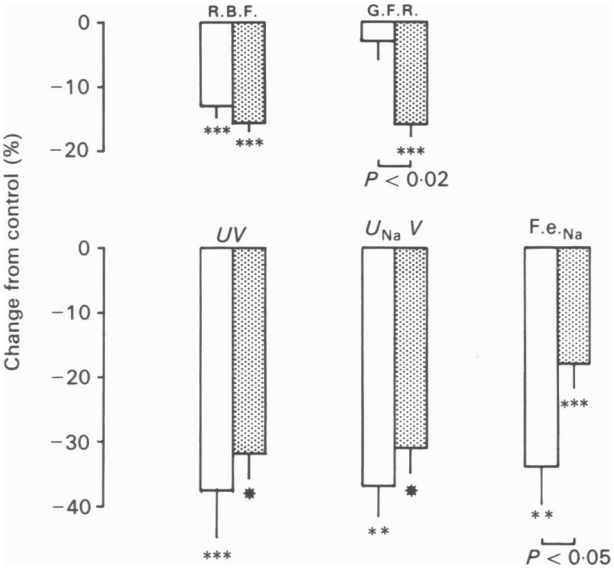


Fig. 1. A comparison of the responses, presented as percentage changes, in renal blood flow (R.B.F.), glomerular filtration rate (G.F.R.), urine flow ($UV$), absolute sodium excretion ($U_{Na}V$), and fractional sodium excretion ($F.e._{Na}$) to high-level renal nerve stimulation in the absence (open histograms) and during captopril at 0·38 mmol $kg^{-1}$ $h^{-1}$ (stippled histograms). The numbers of animals in each group are as given in Table 1. ** $P < 0·02$; *** $P < 0·01$; * $P < 0·001$.

Stimulation of the renal nerves at these low levels, which did not change renal blood flow or affect blood pressure, was associated with a small, but significant ($P < 0·005$) 7% rise in glomerular filtration rate, a 12% ($P < 0·05$) increase in urine flow, but no change in either absolute or fractional sodium excretions. These latter three responses were all significantly ($P < 0·001$, $P < 0·005$, $P < 0·01$, respectively) smaller than those obtained during low-level renal nerve stimulation in the animals infused with saline, as seen by the percentage changes compared in Fig. 2.

In a third group of animals captopril was administered at a rate of 0·076 mmol $kg^{-1}$ $h^{-1}$ and neither blood pressure nor any of the renal functional variables were different from those observed in animals given a saline infusion. The vasopressor and renal vasoconstrictor effects of 77 pmol angiotensin I were reduced by approximately 60% 40 min after the start of the captopril infusion, and a similar degree of inhibition of angiotensin I responses was observed at the end of the experiment. Stimulation of the renal nerves at low levels in these animals caused a small but significant ($P < 0·02$) increase (3 mmHg) in systematic blood pressure, did not change either renal blood flow or glomerular filtration rate, but significantly ($P$ in all cases $< 0·05$) reduced urine flow by 10%, absolute sodium excretion by 10%, and fractional sodium excretion by 8%. The magnitude of these responses in urine flow, absolute and fractional sodium excretions were significantly less ($P < 0·005$, $P < 0·005$, $P < 0·001$, respectively) than those obtained in animals only given saline, but were significantly greater ($P < 0·005$, $P < 0·05$, $P < 0·05$,

TABLE 2. Blood pressure and kidney responses to low-level renal nerve stimulation during infusion of saline or captopril (0·38 or 0·076 mmol $kg^{-1}$ $h^{-1}$)

| | Basal | Stimulation |
|---|---|---|
| Saline ($n = 6$) | | |
| Systemic blood pressure (mmHg) | 115±2 | 115±3 |
| Renal blood flow (ml $min^{-1}$ $kg^{-1}$) | 15·8±1·0 | 15·8±0·9 |
| Glomerular filtration rate (ml $min^{-1}$ $kg^{-1}$) | 3·70±0·30 | 3·50±0·20 |
| Urine flow ($\mu$l $min^{-1}$ $kg^{-1}$) | 48·1±8·3 | 36·1±6·3*** |
| Absolute sodium excretion ($\mu$mol $min^{-1}$ $kg^{-1}$) | 12·5±2·4 | 9·3±1·8*** |
| Fractional sodium excretion (%) | 2·11±0·47 | 1·62±0·34* |
| Captopril (0·38 mmol $kg^{-1}$ $h^{-1}$) ($n = 8$) | | |
| Systemic blood pressure (mmHg) | 114±1 | 118±3 |
| Renal blood flow (ml $min^{-1}$ $kg^{-1}$) | 22·8±1·9 | 22·5±1·9 |
| Glomerular filtration rate (ml $min^{-1}$ $kg^{-1}$) | 4·60±0·20 | 4·90±0·20*** |
| Urine flow ($\mu$l $min^{-1}$ $kg^{-1}$) | 64·8±9·5 | 71·4±9·3* |
| Absolute sodium excretion ($\mu$mol $min^{-1}$ $kg^{-1}$) | 16·7±2·6 | 18·5±2·6 |
| Fractional sodium excretion (%) | 2·33±0·34 | 2·42±0·34 |
| Captopril (0·076 mmol $kg^{-1}$ $h^{-1}$) ($n = 6$) | | |
| Systemic blood pressure (mmHg) | 114±1 | 117±1** |
| Renal blood flow (ml $min^{-1}$ $kg^{-1}$) | 16·2±1·9 | 15·4±1·6 |
| Glomerular filtration rate (ml $min^{-1}$ $kg^{-1}$) | 3·30±0·10 | 3·20±0·20 |
| Urine flow ($\mu$l $min^{-1}$ $kg^{-1}$) | 78·0±9·8 | 69·8±8·4* |
| Absolute sodium excretion ($\mu$mol $min^{-1}$ $kg^{-1}$) | 16·3±2·3 | 14·7±2·1* |
| Fractional sodium excretion (%) | 3·32±0·39 | 3·05±0·37* |

* $P < 0·05$; ** $P < 0·02$; *** $P < 0·01$.

The $t$ test was undertaken using a mean of the absolute values of the two clearance periods before and the two following stimulation (basal) and comparing it with the value obtained during stimulation. $n$ = number of animals.

respectively), than those observed during infusion of captopril at 0·38 mmol $kg^{-1}$ $h^{-1}$. A comparison of the percentage changes obtained in these groups of animals is shown in Fig. 2.

## DISCUSSION

The aim of this investigation was to determine whether the ability of the renal sympathetic nerves to regulate sodium and water excretion was modulated in any way by the presence of angiotensin II. This was done by stimulating the renal nerves electrically at two different levels, to cause modest reductions in renal blood flow or just subthreshold changes in renal haemodynamics.

Stimulation of the renal nerves at high rates resulted in a reduction in renal blood flow of approximately 13%; this did not change the level of glomerular filtration rate. Clearly, regulation of glomerular filtration rate was dependent on the production of angiotensin II, since following administration of the converting enzyme inhibitor filtration rate could not be maintained during the period of neurally induced reduction in blood flow. This dependency of filtration rate regulation on the generation of angiotensin II was similar to that previously reported in the cat (Johns, 1979, 1980) and rat (Arundell & Johns, 1982; Ball & Johns, 1982) during adrenergic stimulation, and is consistent with the contention that within the kidney locally produced angiotensin II causes a preferential vasoconstriction of the efferent

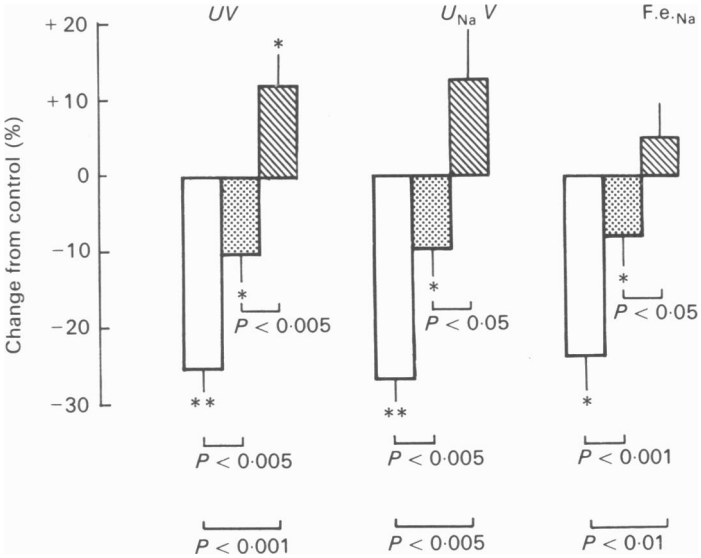


Fig. 2. A comparison of the responses, presented as percentage changes, in urine flow ($UV$), absolute sodium excretion ($U_{Na}V$) and fractional sodium excretion (F.e.$_{Na}$) to low-level stimulation during saline infusion (open histograms) or following administration of captopril at 0·38 mmol kg$^{-1}$ h$^{-1}$ (hatched histograms) or 0·076 mmol kg$^{-1}$ h$^{-1}$ (stippled histograms). The numbers of animals given in each group are as given in Table 2. * $P < 0·05$; ** $P < 0·02$.

arteriole to maintain filtration pressure and hence filtration rate. It is evident that this particular action of angiotensin II, to regulate glomerular filtration rate, is also involved when renin release is increased during renal perfusion pressure reduction within the autoregulatory range (Hall, Guyton & Cowley, 1977; Hall, Guyton, Jackson, Coleman, Lohmeirer & Trippodo, 1977; Johns, 1979, 1980; Kastner, Hall & Guyton, 1984).

The reduction in water and sodium output during the high level of renal nerve stimulation was similar to that observed in other studies utilizing such high rates of nerve stimulation (Johns, Lewis & Singer, 1976; Hesse & Johns, 1984*a*) and could arise from a number of mechanisms. First, the reduction in renal blood flow together with an unchanged glomerular filtration rate would raise filtration fraction and hence the effectiveness of Starling's forces contributing to sodium reabsorption. Secondly, there would be a possibility of redistribution of blood flow to nephrons with greater glomerular filtration and higher rates of sodium reabsorption. Thirdly, there would be a contribution from the renal nerves directly stimulating the sodium reabsorptive processes of the tubular cells (DiBona, 1982). The importance of the first two mechanisms appears minor, as a previous report (Hesse & Johns, 1984*a*) showed that the magnitude of the nerve-induced reductions in sodium excretion was relatively independent of reductions in renal blood flow of less than 15%. Furthermore, in the presence of the $\alpha_1$-adrenoceptor antagonist, prazosin, stimulation of the renal nerves to cause the same reduction in renal blood flow completely blocked the falls in sodium excretion in both the rabbit (Hess & Johns, 1984*b*) and rat (E. J. Johns, unpublished

observations), suggesting a minimum influence of renal haemodynamics over this range. This evidence would strongly indicate that the major contribution of the reduction in sodium excretion during renal nerve stimulation most probably resulted from a direct action of the tubules themselves.

Administration of captopril, a potent inhibitor of angiotensin-converting enzyme (Rubin, Laffan, Kotler, O'Keefe, Demaio & Goldberg, 1978), effectively blocked conversion of angiotensin I to angiotensin II and caused an increase in both renal blood flow and glomerular filtration rate. Similar changes in renal haemodynamics have been reported widely and appear to be related to the decrease in circulating levels of angiotensin II caused by inhibition of the converting enzyme (Arendshorst & Finn, 1977). Stimulation of the renal nerves in the presence of the high dose of captopril caused reductions in renal blood flow, urine flow and absolute sodium excretion comparable to those observed when the captopril was not present. There was, however, a much smaller fall in fractional sodium excretion because of the concomitant reduction in glomerular filtration rate and therefore filtered load. Fractional sodium excretion more clearly reflects changes in the tubular handling of sodium. The smaller response in the presence of captopril indicated that the nerve-induced reductions in sodium excretion had been blunted, suggesting that angiotensin II was important and necessary to allow the full expression of the renal nerves on the tubular cells.

To investigate this phenomenon more fully, the renal nerves were stimulated at low rates in order to minimize any complications due to changes in renal haemodynamics. This degree of nerve stimulation caused reductions in water and sodium output comparable to those observed using such low levels of stimulation in the rat (Bello-Reuss, Trevino & Gottschalk, 1976), dog (Zambraski & DiBona, 1976) and rabbit (Hess & Johns, 1984*a*). It has been widely accepted as representing a direct action of the nerves on the sodium reabsorptive processes of the cells of the proximal tubule and the thick ascending limb of the loop of Henlé (DiBona, 1982; DiBona & Sawin, 1982). The results clearly showed that the infusion of the high dose of captopril completely abolished the ability of the renal nerves to decrease sodium excretion, while the lower dose of captopril partially blocked this particular nerve-mediated response. The action of captopril appeared to be related to its ability to inhibit angiotensin II production, with the higher dose blocking approximately 90% and the lower dose over 60% of the vasopressor and renal vasoconstrictor activity of exogenously administered angiotensin I. The question arises as to what aspect of angiotensin physiology could interfere with the neural regulation of the tubules.

Since increased activity within the renal nerves activates the renin–angiotensin system (Ball & Johns, 1982; DiBona, 1982), the attenuated neurally induced anti-natriuresis observed in the present study could, in part, reflect the removal of a direct stimulatory action of angiotensin II on tubular sodium reabsorption (Harris & Young, 1977; Johnson & Malvin, 1977). However, there are reports that adrenergic stimulation promotes sodium and fluid reabsorption by acting solely on tubular $\alpha$-adrenoceptors which appear to be of the $\alpha_1$ subtype (Osborn, Holdaas, Thames & DiBona, 1983; Hesse & Johns, 1984*b*, 1985). Furthermore, these studies in the dog (Osborn *et al.* 1983) and rabbit (Hesse & Johns, 1985) demonstrated that

renal α-adrenoceptor blockade with prazosin could abolish the antinatriuresis to low-level renal nerve stimulation or intra-renal infusion of noradrenaline, without affecting the renin-releasing action of these procedures. Together, all this information indicates that the direct stimulatory action of the angiotensin II on the tubules does not appear to contribute in any major way to the changes in sodium excretion following renal nerve stimulation.

There is now recognition of the fact that angiotensin II can modify the effectiveness of the sympathetic nervous system by facilitating the release of noradrenaline from nerve endings as well as the adrenal medulla during the passage of action potentials (Zimmerman, 1981) and that this is an action of angiotensin II presynaptically (Vanhoutte *et al.* 1981). There is now good evidence that angiotensin II has such an action at the neuro-effector junctions of the renal vasculature, as Böke & Malik (1983) have shown, using the isolated perfused kidney, that both nerve-induced release of tritiated noradrenaline and increased renal vascular resistance was enhanced by angiotensin II infusion but blunted by captopril administration. The results of the present study are compatible with the view that angiotensin II may also interact synergistically with the renal nerves to decrease sodium excretion by facilitating adrenergic transmission at the neuroepithelial junctions. Indirect support for this contention has been provided by studies which have demonstrated that α-adrenoceptor antagonists inhibited the angiotensin II-induced increase in active sodium transport in rat kidney cortical slices (Brunton, Parsons & Poat, 1978) and the angiotensin II-induced antinatriuresis in intact rats (Radhi, Chapman & Munday, 1982), implying that angiotensin II exerted its effect indirectly through the release of noradrenaline from sympathetic nerve endings. Two studies in the dog have also shown that captopril or angiotensin II receptor antagonists attenuated the renal nerve-mediated antinatriuresis during hypercapnic acidosis (Anderson, Henrich, Gross & Dillingham, 1982) or shock avoidance (Koepke & Obrist, 1983), in the absence of changes in renal haemodynamics. Together these data would establish that angiotensin II plays an important role in modulating neurotransmission at the level of the renal tubule comparable to that exhibited at neurovascular junctions within the sympathetic nervous system.

In contrast, there are a number of reports, in the dog using low level nerve stimulation (Zambraski & DiBona, 1976), and in the cat (Johns *et al.* 1976; Johns, 1979, 1980) which showed that blockade of the renin–angiotensin system did not modify the neurally mediated antinatriuretic response. The reasons for this conflict with the present findings are unclear, but could reside in the different surgical preparations having different levels of circulating antiotensin II, or varying effectiveness of the differing methods of inhibiting angiotensin II activity; on the other hand, the differences may reflect a species variation in the dependency of this particular neuro-effector junction on the presence of angiotensin II, or may be related to the degree of nerve stimulation since angiotensin-induced facilitation is most pronounced at low rates of stimulation (Hughes & Roth, 1971; Starke, 1977; Zimmerman, 1978).

The present study has demonstrated that at high rates of renal nerve stimulation the regulation of glomerular filtration rate in the face of small reductions in renal blood flow was dependent on the production of angiotensin II which probably acted locally to preferentially constrict the efferent arteriole. The data also showed that

angiotensin II was necessary to allow the renal nerves to have their maximum effect in decreasing sodium excretion, probably via a mechanism of facilitating transmission at the neuro-epithelial junction. Whether this latter phenomenon is dependent on locally generated or circulating angiotensin II remains to be explored.

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