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Dietary and pharmacological alterations in endogenous angiotensin II: effect on noradrenaline pressor responsiveness in the rat

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1 Rats were placed on either a low sodium intake (low sodium diet 0.025% dry weight, tap water for drinking) or a high sodium intake (normal sodium diet 0.45% dry weight, 0.9% saline for drinking) for 10 days. The pressor-response curve to angiotensin II in rats previously on a high sodium intake was shifted to the left of that found in rats previously on a low sodium intake.

2 Suppression of endogenous angiotensin II formation with captopril (0.3 mg kg^{-1}) or acute volume repletion (3% body wt per 30 min) resulted in a significant parallel shift of the pressor-response curve for angiotensin II to the left in the low salt group. In the high salt group captopril produced a similar but smaller parallel shift of the dose-response curve to the left.

3 Similar manipulation of endogenous angiotensin II concentrations with high and low salt intake plus captopril treatment or acute volume repletion, produced no alterations in the pressor response for noradrenaline.

4 The attenuated *in vivo* response to angiotensin II in the low salt intake group may be explained in part by the suppressed vascular sensitivity to angiotensin II in this group, as measured in the isolated perfused kidney of the rat. In kidneys from rats previously on a low sodium intake, an enhanced maximal vasoconstrictor response to noradrenaline was observed as compared to kidneys from high sodium intake rats.

5 These results indicate that, whereas alterations in endogenous angiotensin II concentrations within physiological limits affects the response to exogenous angiotensin, there is little if any effect on the pressor response to noradrenaline.

Introduction

Previous studies have demonstrated that changes in angiotensin II receptor occupancy, following alterations in endogenous angiotensin II concentrations, were responsible for changes in response to this peptide (Thurston & Laragh, 1975; Oliver & Cannon, 1978). Thus, reduction of endogenous angiotensin II levels either by increased sodium intake (Reid & Laragh, 1965; Slack & Ledingham, 1976), converting enzyme inhibition (Thurston & Laragh, 1975), bilateral nephrectomy (Swales *et al.*, 1975) or prostaglandin synthetase inhibition (Smyth & Fung, 1984) would be expected to enhance the pressor responsiveness to exogenously administered angiotensin. The effect on the noradrenaline pressor response has been less clear. Previous studies have shown an enhanced renovascular response to noradrenaline in dogs (Kilcoyne & Cannon, 1971) and man (Hollenberg *et al.*, 1972) following sodium deprivation. However, others have found no change in the renovascular response in dogs (Oliver & Cannon, 1978) or the pressor response in rats (Smyth & Fung, 1984) following a sodium deprived diet.

Recent studies in the pithed rat, however, have suggested that endogenous angiotensin II concentrations may also be an important determinant of the pressor response to adrenoceptor agonists such as noradrenaline (de Jonge *et al.*, 1981; 1982; Hatton & Clough, 1982; Tobian *et al.*, 1984).

We evaluated, therefore, the importance of endogenous angiotensin in regulating the pressor response to noradrenaline in the presence of intact cardiovascular reflexes. This was achieved by manipulating the endogenous concentration of angiotensin, within physiological limits, through the regulation

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of sodium intake (high vs. low) and converting enzyme inhibition with captopril. Since vascular sensitivity is an important factor in determining pressor activity, we used the isolated perfused kidney to determine whether or not sodium intake altered this parameter. The present results suggest that, whereas physiological alteration of endogenous angiotensin concentrations alters the pressor response to exogenous angiotensin II, there is little if any effect on noradrenaline responsiveness. In addition, changes in vascular sensitivity may contribute to alterations of angiotensin II pressor responsiveness.

A preliminary account of this work was presented at the 69th Annual Meeting of the Federation of American Societies for Experimental Biology (Penner *et al.*, 1985).

Methods

Animal pretreatments

Male Wistar rats weighing 300–400 g were used. Animals were weighed and placed on a high or low sodium diet for 10 days. The low sodium diet consisted of a low sodium chow, 0.025% dry weight (ICN Nutritional Biochemicals). These animals had free access to tap water for drinking. Frusemide (Lasix, Hoechst; 3 mg kg^{-1}) was administered intraperitoneally on the first and second day of the low salt diet. The high sodium group received normal rat diet (0.45% dry weight) with 0.9% saline for drinking water. This was supplemented with 0.5 mg kg^{-1} of deoxycorticosterone acetate (DOCA; Percorten, CIBA) given intraperitoneally on the last 3 days of the diet. This dosage of DOCA was much lower than that used by others to increase blood pressure (Berecek *et al.*, 1980). Animals were placed in individual metabolic cages where urine was collected for 24 h before the day of the experiment.

Experimental procedure

On the day of the experiment, rats were anaesthetized with pentobarbitone (Nembutal, BDH; 60 mg kg^{-1}, i.p.). Further anaesthetic was administered in bolus doses of 3 mg kg^{-1} intravenously as required throughout the experiment. A tracheostomy was performed and animals were allowed to breathe spontaneously. A polyethylene catheter (PE60) was placed in the right carotid artery for monitoring of blood pressure with a Statham pressure transducer (Model P23Dc), recorded on a Grass polygraph Model V. Two other polyethylene catheters (PE20) were placed in the left jugular vein. One catheter was used for the infusion of angiotensin II (AII) or noradrenaline (NA) with a Harvard constant infusion pump. The other catheter was used for the intravenous administration of anaesthetic agent, 0.9% saline or captopril (Capoten, Squibb). Body temperature was not recorded; however, an overhead lamp was used to help prevent the animal from becoming hypothermic. The preparation was then allowed to stabilize for approximately 30 min.

In vivo *pressor responses*

Following stabilization, the pressor responses to incremental rates of infusions of AII (0.03, 0.1, 0.3, 1.0, 3.0 $\mu g\ kg^{-1}\ min^{-1}$) or NA (0.3, 1.0. 3.0, 10.0 and 30.0 $\mu g\ kg^{-1}\ min^{-1}$) were recorded. Each infusion rate was maintained until a steady state in blood pressure had been achieved. Except for the lowest infusion rate, the duration of each infusion did not exceed 5 min. The rate of volume delivery ranged from 0.0010 ml min^{-1} to 0.102 ml min^{-1}. Preliminary experiments demonstrated that following a dose-response curve, randomly selected infusion rates produced similar changes in blood pressure. This eliminated the necessity of random administration of our study infusion rates.

Angiotensin II (Hypertensin, CIBA) was dissolved in 0.9% saline at a concentration of 100 $\mu g\ ml^{-1}$. Noradrenaline HCl (CalBiochem) was dissolved in acidified 0.9% saline (0.05N HCl) at a concentration of 1 mg ml^{-1}.

Effect of converting enzyme inhibition with captopril

The effect of converting enzyme inhibition on the pressor response to AII or NA was studied in both high salt and low salt intake rats. Captopril (0.3 mg kg^{-1}) dissolved in 0.9% saline (1 mg kg^{-1}) was administered intravenously in a bolus. Approximately 15 min after the captopril administration, the first dose-response curve was repeated (i.e. AII or NA). Preliminary experiments demonstrated that the steady state blood pressure following captopril did not change significantly for a period of time equal to that required to complete the second dose-response curve. Converting enzyme inhibition was assessed by measuring the pressor response to a 200 ng bolus i.v. injection of angiotensin I (Peninsula Laboratories) dissolved in 0.9% saline. This angiotensin I was administered just prior to the captopril and at the end of the experiment. In all rats studied, the pressor response to AI was decreased by 75–85% indicating converting enzyme inhibition in all animals studied.

Effect of acute volume repletion

The effect of acute volume repletion on the pressor response to AII or noradrenaline was studied in rats on a low sodium intake. Again, two consecutive dose-response curves to AII or noradrenaline were done in

each rat. Following the first dose-response curve (control), the blood pressure was allowed to stabilize for 10 to 15 min. At this time, 0.9% saline was infused at a rate of 6% of the animals' body weight per hour for 30 min (i.e. 3% body weight per 30 min). Then the rate of infusion was decreased to 3% of the body weight per hour. During this final infusion rate the second dose-response curve was obtained. Preliminary experiments had shown that mean blood pressures were unaffected by this rate of saline infusion.

Effect of nitroprusside-induced hypotension

In rats previously on a low sodium intake, two consecutive dose-response curves to AII were done, separated by an infusion of nitroprusside which was maintained during the second dose-response curve. Nitroprusside was infused into the right jugular vein at a rate of $5\,\mu g\,kg^{-1}\,min^{-1}$. The rate of volume delivery was $0.017\,ml\,min^{-1}$. Ten to fifteen minutes after the start of the nitroprusside infusion, the second dose-response curve for AII was done in the presence of the nitroprusside-induced hypotension. Preliminary experiments had shown that this dose of nitroprusside produced a sustained drop in blood pressure of 15 to 25 mmHg that was maintained for at least 30 min (i.e. the time to complete the second curve).

In vitro *vascular sensitivity*

The *in vitro* isolated perfused kidney was used to assess the effect of sodium balance on vascular sensitivity to AII or NA where the effects of endogenous circulating angiotensin II as well as other systemic factors were largely eliminated. Male Wistar rats weighing 300–400 g previously placed on a high or low sodium diet were used. Following anaesthesia and a tracheostomy, an abdominal cruciate incision was made and the abdominal viscera reflected to the right, exposing the aorta. The aorta distal to the renal arteries was cannulated with a PE60 catheter. This catheter was used for continuous pressure monitoring with a pressure transducer as described. The superior mesenteric artery was cannulated in the retrograde direction with a PE20 catheter. This was connected to a Cole-C Palmer peristaltic pump, which was used to perfuse an oxygenated (95% O_2, 5% CO_2) Krebs-Henseleit solution (composition, mM: NaCl 118.0, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 26.0, dextrose 11.0) with $3.6\,g\,l^{-1}$ mannitol added. After the perfusion had begun, the aorta above the superior mesenteric artery was ligated, thus isolating the renal circulation. The superior vena cava was then severed, the left renal artery ligated, and the animal killed. The bladder was then cannulated for urine collection. This preparation allowed the isolated perfusion of the right kidney without manipulation of the kidney itself or interruption of flow to this kidney. The effectiveness of isolation could be confirmed at the end of the experiment by the addition of ink to the perfusate. The perfusion rate was adjusted to produce a perfusion pressure at the level of the renal artery of about 100 mmHg. The preparation was allowed to stabilize for 30 min. The dose-response relationship to angiotensin II or to noradrenaline was then examined by the addition of the appropriate amounts of drug to the perfusion solution. The perfusion rates necessary to produce a perfusion pressure of 100 mmHg were similar in the kidneys from rats on a low sodium ($13.6 \pm 1.1\,ml\,min^{-1}$) and high sodium ($12.8 \pm 0.9\,ml\,min^{-1}$) intake. Thus, at a constant perfusion rate, any changes in perfusion pressure would reflect a change in renal vascular resistance. Preliminary experiments have shown that this preparation was stable over 2 h. Experiments described here were performed at room temperature.

Plasma renin activity was measured by radioimmunoassay in plasma obtained from high and low salt intake rats with a modification of the Haber method (Haber *et al.*, 1969). The only significant modification from this method was the use of a second stage antibody instead of a dextran-coated charcoal to separate the bound antibody from the free peptide.

Plasma and urine Na^+ and K^+ concentrations were determined with a Beckman Model Klina Flame photometer. Creatinine concentrations were determined by a modified Jaffee method using a Beckman Creatinine Analyzer Model 2.

Statistical analysis of the sigmoid shaped curves obtained from the *in vitro* studies (isolated perfused kidney) was with the ALLFIT computer programme (Delean *et al.*, 1978). This programme fits the curve to the standard formula:

$$y = \frac{a - d}{1 + (x/c)b} + d$$

The model used was the four parameter logistic equation where y and x were response and dose, and a, b, c and d were the four derived parameters where a = response at dose zero, b = slope factor, c = dose causing half maximal response ($ED_{50\%}$) and d = infinite dose or maximal response. In these analyses, a was set to zero since no change in perfusion pressure was observed at zero drug levels.

In the *in vivo* studies, since maximal responses were not obtained, a REGRESS programme (Medical Computer Resources Center, University of Texas, Health Science Center at Dallas) was used to evaluate whether or not the dose-effect relationship between groups was parallel. If the lines were parallel, then a test of equality of intercepts (coincidence) was done as described by Zar (1974). For other parameters

Student's t test was used. In addition, the dose infusion rate required to increase blood pressure by 50 mmHg ($Ed_{50\,mmHg}$) could be calculated for each individual experiment. All data in the figures are expressed as mean ± standard error of the mean.

Captopril (Capoten, Squibb) used in the whole animal preparations was a gift from the E.R. Squibb & Sons Ltd. through the courtesy of Dr Z. Horovitz.

Results

Effects of sodium balance on pressor responsiveness

Rats placed on a high sodium intake ($n = 14$) had a mean sodium excretion of 1.50 ± 0.07 mEq per day. Animals placed on a low sodium intake showed a markedly reduced sodium excretion of 0.011 ± 0.004 mEq per day, ($n = 33$), ($P < 0.001$). In our laboratory, rats on a normal Purina rat diet with tap water for drinking, had a sodium excretion of 0.33 ± 0.13 mEq per day. The plasma renin activity was significantly greater in the low sodium group as compared to the high sodium group (28.0 ± 3.7 vs. 2.18 ± 0.81 ng AI ml^{-1} h^{-1}; $P < 0.001$). Thus, these represented high and low states of sodium intake.

The dose-response curves to angiotensin II (Figure 1) in the high and low sodium groups were parallel (i.e. same slope). However, the intercept for the high sodium group was significantly less ($P < 0.001$) than that of the low sodium group. This indicated a leftward shift of the dose-response curve for the high sodium group relative to the low sodium group. As well, the infusion rate of AII ($\mu g\,kg^{-1}\,min^{-1}$) required to increase blood pressure by 50 mmHg ($ED_{50\,mmHg}$) was significantly less ($P < 0.001$) in the high sodium group (0.280 ± 0.037) as compared to the low sodium group (0.617 ± 0.064). The level of sodium intake had no effect on the dose-response curves for noradrenaline (Figure 1).

Effect of converting enzyme inhibition

The mean arterial blood pressure was 92.2 ± 3.7 mmHg in high sodium and 110.0 ± 5.1 mmHg in low sodium rats. The maximal decrease in blood pressure, observed 3 min following the captopril administration, was greater in the low sodium group (−31.6 ± 6.6 mmHg, $n = 11$), as compared to the high sodium rats (−16.3 ± 5.6 mmHg, $n = 12$). After a period of approximately 10 min, the blood pressure returned to pre-captopril levels in the high sodium group but remained slightly reduced (−7.9 ± 2.5 mmHg) in the low sodium group. In the low sodium group, following converting enzyme inhibition, there was a parallel shift of the dose-response curve for AII to the left (Figure 2a). This was indicated by the same slope of both curves, however, the intercept was less ($P < 0.005$) for the dose-response curve following captopril treatment. In addition, captopril treatment decreased ($P < 0.005$) the $ED_{50\,mmHg}$ for AII (0.617 ± 0.064 to 0.289 ± 0.061 $\mu g\,kg^{-1}\,min^{-1}$).

In the rats on a high sodium intake, there was again a significant ($P < 0.05$) but modest parallel shift of the dose-response curve for AII to the right. The $ED_{50\,mmHg}$ for AII decreased following converting enzyme inhibition (0.277 ± 0.032 to 0.195 ± 0.018 $\mu g\,kg^{-1}\,min^{-1}$; $P < 0.05$) in the high sodium intake rats.

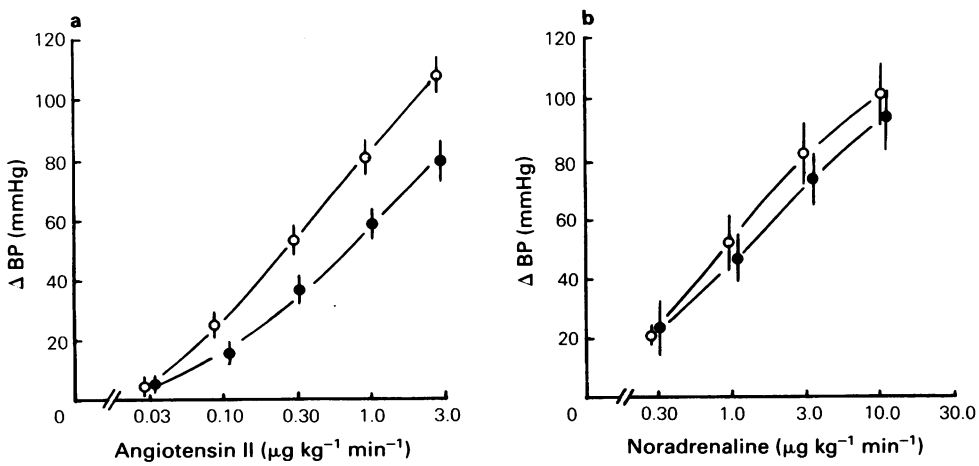

Figure 1 Effect of low (●) and high (○) sodium intake on the pressor responsiveness to angiotensin II or noradrenaline. Values represent mean with s.e.mean indicated by vertical lines.

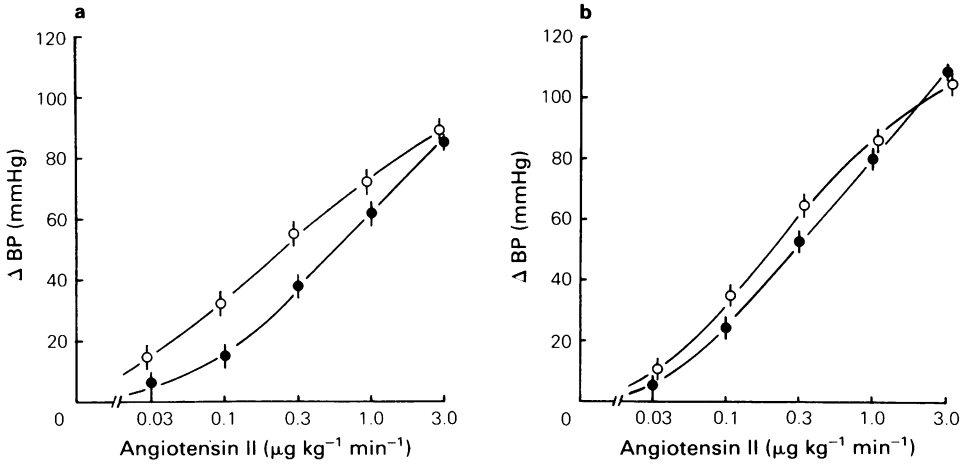

Figure 2 Effect of low (a; $n = 6$) and high (b; $n = 6$) sodium intake on the pressor response to angiotensin II before (●) and after (○) captopril (0.3 mg kg^{-1}) administration. Values represent mean with s.e.mean indicated by vertical lines.

In contrast, there was no shift in the dose-response relationship to noradrenaline in the low sodium group following converting enzyme inhibition (Figure 3) while, captopril had no effect on the pressor response for noradrenaline in the high sodium group (Figure 3).

In the above experiments the degree of converting enzyme inhibition as determined by the percentage inhibition of the angiotensin I pressor response in the high sodium and low sodium groups was 74.6 ± 5.4% and 81.3 ± 4.5% respectively.

Effect of acute volume repletion

In rats on a low sodium intake, acute volume repletion with saline produced a significant increase in the pressor response to AII (Figure 4). Following volume repletion, there was significant parallel shift ($P < 0.05$) of the dose-response curve for AII to the left of the control curve (pretreatment). There was also a significant decrease in the $ED_{50\,mmHg}$ for AII following the saline infusion (0.399 ± 0.097 to

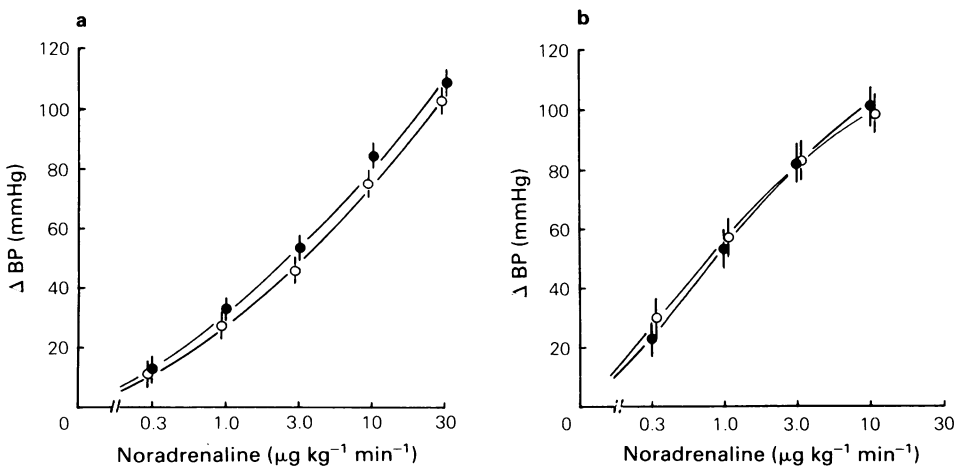

Figure 3 Effect of low (a; $n = 7$) and high (b; $n = 6$) sodium intake on the pressor response to noradrenaline before (●) and after (○) captopril (0.3 mg kg^{-1}) administration. Values represent mean ± s.e.mean.

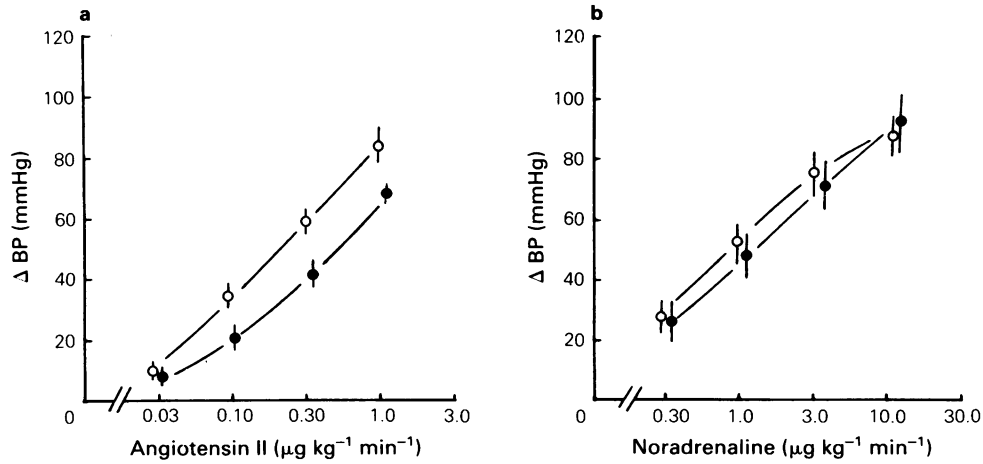

Figure 4 Pressor responsiveness to angiotensin II (a; $n = 6$) and noradrenaline (b; $n = 6$) before (●) and after (○) acute volume repletion (3% body wt per 30 min) in low sodium intake rats. Values represent mean with s.e.mean indicated by vertical lines.

$0.207 \pm 0.033\ \mu g\ kg^{-1}\ min^{-1}$; $P < 0.05$).

However, the dose-response curve for noradrenaline was unaltered by the volume repletion in the low sodium intake rats (Figure 4).

Effect of nitroprusside-induced hypotension

Nitroprusside infusion ($5\ \mu g\ kg^{-1}\ min^{-1}$) in low sodium intake rats decreased blood pressure from a baseline of 90.3 ± 7.8 mmHg to a new steady state of 64.5 ± 9.4 mmHg. This represented a mean decrease of 25.8 ± 7.3 mmHg. In the presence of this decrease in blood pressure, the dose-response curve for AII was unaltered (Figure 5).

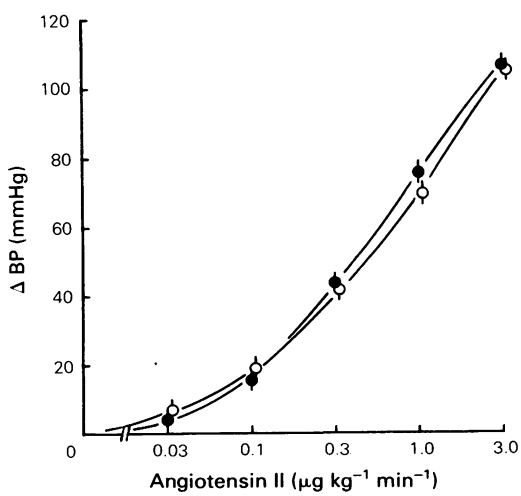

Figure 5 Pressor responsiveness to angiotensin II in low sodium intake rats before (●) and during (○) nitroprusside infusion ($n = 6$). Values represent mean with s.e.mean indicated by vertical lines.

Effect of sodium balance on in vitro *renovascular responsiveness*

The vascular sensitivity to AII was found to be greater in kidneys obtained from rats previously on a high sodium intake as compared to those on a low sodium intake (Figure 6). In both groups, the slope of the curves and the maximum responses were similar. However, the concentration of AII necessary to produce 50% of the maximum response ($ED_{50\%}$) was significantly ($P < 0.005$) less in the kidneys from high sodium rats (5.23 ± 0.93 nM) as compared to those from low sodium rats (12.19 ± 1.68 nM). Thus, the dose-response curve for AII in the kidneys from high sodium rats was shifted parallel and to the left as compared to the low sodium group.

The vascular sensitivity to noradrenaline was altered but in a different fashion (Figure 6). The slopes of the dose-response curves for noradrenaline and the $ED_{50\%}$ were similar in kidneys obtained from rats previously on a high or low sodium intake. However, the maximal response to noradrenaline was greater ($P < 0.05$) in kidneys from low sodium intake rats (220.8 ± 5.7 mmHg) than in those from high sodium intake rats (190.5 ± 11.0 mmHg).

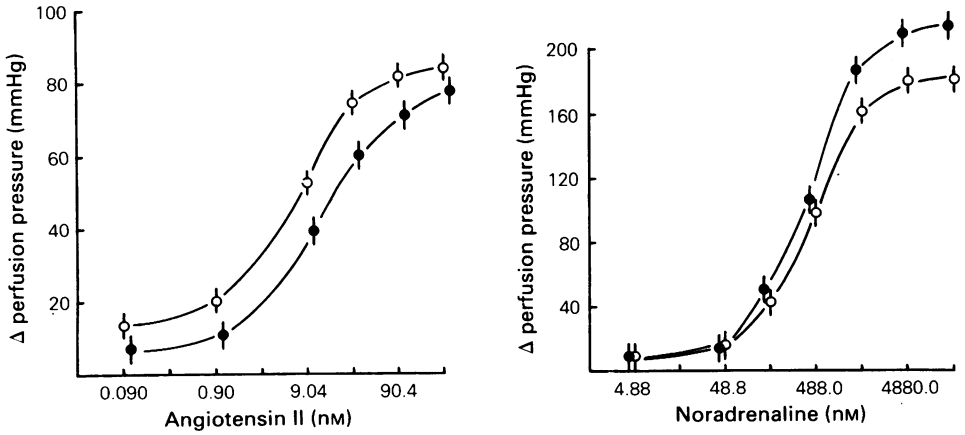

Figure 6 Renovascular sensitivity to angiotensin II (a) and noradrenaline (b) in isolated perfused kidneys obtained from rats previously on a low (●) or high (○) sodium intake.

Discussion

Angiotensin II, at subpressor doses, potentiates noradrenaline and nerve stimulation-induced vasoconstriction in the rat (de Jonge *et al.*, 1982; Hatton & Clough, 1982). This may be related to the ability of angiotensin II to modulate noradrenaline release from nerve endings (Zimmerman, 1981) and/or potentiate the postjunctional effects of noradrenaline (Malik & Nasjletti, 1976; Campbell & Jackson, 1979). Recent studies have used a converting enzyme inhibitor, captopril, to demonstrate the dependency of noradrenaline-induced vasoconstriction on endogenous angiotensin II (de Jonge *et al.*, 1982; Hatton & Clough, 1982). These studies were conducted in pithed rats where converting enzyme inhibition would result in a major decrease in vascular tone. In fact, de Jonge *et al.* (1982) concluded that a maintained vascular tone was the mechanism by which angiotensin worked since vasopressin and angiotensin were equally effective. Thus, in the non-pithed, intact rat, suppressed endogenous angiotensin formation by converting enzyme inhibition may fail to alter the response to noradrenaline since cardiovascular reflexes would largely maintain vascular tone.

In the present study, increasing dietary sodium intake significantly lowered plasma renin activity and enhanced the pressor response to angiotensin II. Lowering endogenous angiotensin II levels by converting enzyme inhibition with captopril significantly enhanced the pressor response to angiotensin II in rats previously on a low sodium diet but had little effect in rats previously on a high sodium diet. Lowering endogenous AII levels with acute volume repletion (Oliver & Cannon, 1978) also enhanced the pressor response to AII in rats with a low sodium intake. These results are consistent with the postulate that elevations in endogenous angiotensin II levels result in an attenuated response to this peptide as has been reported previously (Thurston & Laragh, 1975; Oliver & Cannon, 1978; Smyth & Fung, 1984). These results substantiated the sensitivity of our system for detecting differences in pressor responsiveness.

Previous reports on the effect of sodium intake and, presumably, endogenous angiotensin II levels on noradrenaline pressor response have been less clear (Hollenberg *et al.*, 1972; Oliver & Cannon, 1978). In the present study, experimental interventions which significantly altered the response for AII failed to have any effect on the response for noradrenaline. Alteration of plasma renin activity through changes in dietary sodium, in the present study, demonstrated no significant effect on the pressor response to noradrenaline. Suppression of endogenous angiotensin II formation with captopril also failed to alter the response for noradrenaline in both the high and low salt groups. Similarly, acute volume repletion in low sodium intake rats also failed to alter the pressor response to noradrenaline. These results are consistent with our previous observation that prostaglandin synthetase inhibition failed to alter the response to noradrenaline in high and low sodium intake rats (Smyth & Fung, 1984). Thus, alteration of endogenous angiotensin levels within physiological limits, where vascular tone was maintained by intact cardiovascular reflexes, failed to alter the response to noradrenaline.

In the high sodium intake groups studied, the drop in blood pressure following converting enzyme inhibition was only transient. In the low sodium groups, the blood pressure remained significantly suppressed. It may be argued that this reduced blood pressure may have resulted in a non-specific increase in response to

pressor agents in low sodium rats. The failure of the pressor activity of noradrenaline to be enhanced would be evidence against this. To answer this question more specifically, blood pressure was reduced 15–20 mmHg by the nitroprusside infusion. Even at this lowered baseline blood pressure, the response to AII was unaltered. A non-specific action of the moderate captopril-induced hypotension appeared unlikely.

The renovascular response to angiotensin in the isolated perfused kidney preparation was enhanced in kidneys obtained from rats previously on a high sodium diet relative to those on a low sodium diet. This increased activity may have contributed to the differences observed in the intact animal. Strewler *et al.* (1972) also observed a similar change in vascular sensitivity which may be related to an alteration of angiotensin receptor number following changes in endogenous angiotensin II levels (Devynck *et al.*, 1979; Aquilera & Catt, 1981). The failure to observe a difference in pressor response to noradrenaline may have been due to a concomitant alteration of the vascular sensitivity. However, no difference was observed in the renovascular sensitivity to noradrenaline between the high and low sodium intake groups, except at maximal doses studied. The significance of this increased maximal response to noradrenaline in kidneys from low sodium intake rats as compared to those on a high sodium intake is not known.

The present results do not exclude the importance of endogenous angiotensin II on the pressor response for noradrenaline. They do, however, suggest that physiological alterations in endogenous angiotensin II levels do not alter the level of facilitation of the noradrenaline response for which even extremely low levels of angiotensin II have been found to be sufficient. de Jonge *et al.* (1982) reported that one hour following bilateral nephrectomy, the extremely low levels of endogenous angiotensin remaining were still adequate to potentiate the response to noradrenaline. Similarly Tobian *et al.* (1984) have demonstrated that only extremely low levels of endogenous angiotensin were required to potentiate sympathetic induced vasoconstriction.

The present study also demonstrates that noradrenaline responsiveness is unrelated to sodium balance. Physiologically, there may be an explanation as to why sodium intake alters angiotensin II but not noradrenaline responsiveness. In states of low sodium balance, plasma angiotensin II levels may be elevated as much as 20 times that observed in high sodium states. These high levels may be required to ensure adequate release of aldosterone to maintain plasma volume (Hollenberg *et al.*, 1974). This elevation of plasma angiotensin II may be sufficient to result in a down regulation of receptors (Aquilera & Catt, 1981). A down regulation of receptors would ensure that blood pressure did not become inordinately high in the presence of elevated angiotensin II levels. A high sodium intake, however, only decreases the noradrenaline levels by one-half when compared to low salt states (Luft *et al.*, 1979; Rankin *et al.*, 1981). Thus, this small change in noradrenaline concentration may not be sufficent to result in a situation comparable to 'denervation sensitivity'.

In summary, dietary and pharmacological interventions which lower endogenous angiotensin II levels significantly enhance the pressor response to angiotensin II. These alterations of endogenous angiotensin II levels within physiological extremes failed to alter the pressor response to noradrenaline. Changes in vascular sensitivity may also contribute to the response for angiotensin.

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