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INTER-RELATIONSHIPS BETWEEN PLASMA ANGIOTENSIN II, ARTERIAL PRESSURE, ALDOSTERONE AND EXCHANGEABLE SODIUM IN NORMOTENSIVE AND HYPERTENSIVE MAN

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SUMMARY

1. Evidence bearing on the importance of the renin/angiotensin system in the regulation of aldosterone secretion in man is reviewed.
2. Elevation of plasma angiotensin II concentration in simple dietary sodium deprivation has been confirmed.
3. In primary renin deficiency, both angiotensin II and aldosterone are deficient. In these circumstances plasma aldosterone can remain unresponsive to very large rises in plasma potassium, but increase promptly on infusion of angiotensin II.
4. Sodium depletion in normal man increases the adrenocortical sensitivity to angiotensin II, while diminishing the pressor effect.
5. The Na_E/renin and Na_E/angiotensin II interrelations are normal in primary hyper-aldosteronism both before and after treatment, and also in untreated essential hypertension with normal renin levels.
6. These relationships are depressed in low-renin essential hypertension.
7. In renal and malignant hypertension the relationships are enhanced.
8. In renal and malignant hypertension the angiotensin II–pressor relationship is enhanced, and the angiotensin II–aldosterone relationship steepened as compared with normal subjects acutely infused with angiotensin.
9. A hypothetical mechanism for the suppression of renin in essential hypertension is outlined.

INTRODUCTION

A concept central to the inter-relationship between electrolyte status, the renin–angiotensin system and aldosterone in clinical hypertension is that the peptide angiotensin II is a physiological stimulus to aldosterone secretion. This notion derived initially from the work of Gross[1, 2] and Davis[3], and was soon supported by studies in man which showed that the intravenous infusion of angiotensin II increased the excretion [4, 5], secretion rate [6] and plasma concentration [7] of aldosterone. The hypothesis was strengthened with the development of methods sufficiently sensitive to estimate renin concentration in peripheral plasma, when it was shown that simple dietary sodium restriction consistently elevated plasma renin concentration [8, 9]. Conversely, plasma renin was depressed, in all subjects tested, by dietary sodium loading [8, 9]. In recent years the use of radioimmunoassay for estimation of circulating angiotensin II has permitted more detailed, quantitative analysis of angiotensin II: aldosterone relationships [10, 11].

PRIMARY RENIN DEFICIENCY

The central importance of the renin–angiotensin system in governing aldosterone secretion is emphasized by studies of patients with apparently acquired deficiency of renin and hence also of angiotensin II. We recently studied one such case [12], in whom plasma aldosterone was persistently undetectable and remained so despite, on occasion, very marked increases in plasma potassium concentration (up to 8 m-equiv/l). The intravenous infusion of angiotensin II however caused a prompt rise of plasma aldosterone well into the normal range. Since potassium is normally a potent stimulus to aldosterone, the absence of such effect in angiotensin II deficiency argues for a crucial role of angiotensin in regulating aldosterone secretion.

However, despite these several apparently strong lines of evidence, a number of workers have, in recent

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years, questioned the importance of the renin–angiotensin system in the regulation of aldosterone secretion in man.

CIRCULATING ANGIOTENSIN II IN DIETARY SODIUM DEPRIVATION

Firstly, several groups, employing radioimmunoassay methods, reported failure to demonstrate an increase in circulating angiotensin II during simple dietary sodium deprivation in man [13–16]. These were somewhat surprising findings in view of the earlier demonstration of increased plasma renin concentration [8, 9] and also, by techniques of chemical extraction, angiotensin [7], in such circumstances. We therefore re-examined the problem employing the radioimmunoassay method developed in this laboratory by Düsterdieck and McElwee [18] for plasma angiotensin II estimation. Our studies showed a prompt and consistent elevation in plasma angiotensin II during dietary sodium restriction; the increase was highly significant after only 48 h, and increased further on days 4 and 5. Very similar angiotensin II values were obtained in concurrent arterial and venous plasma samples. There was also a close correlation between plasma angiotensin II and aldosterone concentrations [19, 20]. We are not able readily to explain the contrary findings of other workers, but clearly our own results are consistent with the concept of angiotensin II having an important role in aldosterone regulation.

CHANGES IN ADRENOCORTICAL SENSITIVITY TO ANGIOTENSIN II IN SODIUM DEPLETION

A second serious doubt was raised by the observation that, in sodium-depleted man, plasma aldosterone concentration was disproportionately high for a given plasma angiotensin II level as compared with the relationship in the sodium-replete state [16, 21]. This finding would be explicable if the sensitivity of the adrenal cortex to angiotensin II was enhanced in sodium depletion, but neither Boyd *et al.*[21] nor Mendelsohn *et al.*[16] were able to find evidence of such enhancement. However, in their experiments possible changes in sensitivity were assessed in sodium depletion by the administration of angiotensin II at a single dose, a procedure which might well be insufficient to unmask changes in dose–response curves. We therefore pursued this further by administering a series of incremental doses of angiotensin II before and after sodium depletion in normal subjects, and plotting the resultant angiotensin II–aldosterone dose–response curves. These procedures revealed a distinct steepening of the curve in sodium depletion, while the angiotensin II–pressor dose–response curve was concurrently moved in parallel to the right [20, 22]. These results have been confirmed in a recent study by Hollenberg *et al.*[23]. The mechanism of the enhanced response of aldosterone to angiotensin II in sodium depletion remains to be determined. The converse changes in the aldosterone and pressor dose–response curves would both favour sodium conservation in these circumstances, and the findings strongly suggest an important role of the renin–angiotensin system in aldosterone regulation, despite the previous arguments against this proposition.

SODIUM, RENIN, ANGIOTENSIN II AND ALDOSTERONE IN HYPERTENSION

These various observations emphasize the importance of concurrent quantitative evaluation of the renin–angiotensin system, aldosterone and sodium status in elucidating the pathogenesis of different forms of hypertension.

(*i*) *Assessment of sodium status*

Assessment of sodium status has been attempted in various ways. Laragh and his colleagues [24] approached the problem by relating estimates of renin and aldosterone to the concurrent 24-h urinary sodium output. However, sodium excretion rate is a somewhat uncertain indicator of dietary sodium intake, there being not rarely a time lag of more than a day before changes in dietary sodium intake are reflected in the urinary sodium excretion.

Our own routine procedure in the assessment of hypertensive subjects is to fix the dietary sodium and potassium intake at points within the normal range (between 120 and 140 m-equiv Na and 40–70 K daily) for 3 days, and then to draw blood samples for renin, angiotensin II and aldosterone assay between 0830 and 0930 h after overnight recumbency and fasting. Such manoeuvres however provide essentially limited information, in that estimates of renin, angiotensin and aldosterone are related only to dietary intake.

A potentially more relevant assessment of sodium status is made by estimating total exchangeable sodium (Na_E), which can vary quite independently of changes in sodium intake. A subject may be in sodium balance in that daily output equals intake, but with variously normal, high or low Na_E.

In the studies reported here, Na_E was measured by the method of Davies and Robertson[25], and expressed as a percentage of Na_E in mEq per Kg expected for a normal individual of the same "leanness index" (ratio of height^3/weight) [26].

(*ii*) *Renin, angiotensin II and aldosterone assay methods*

Plasma renin concentration was measured by an enzyme kinetic technique [27], plasma angiotensin II by radioimmunoassay [18], and plasma aldosterone either by a double isotope dilution derivative method or by radioimmunoassay [28, 29].

(*iii*) *Results: normotensive subjects*

In normotensive subjects, a highly significant inverse relationship was established between Na_E and both the concurrent plasma renin concentration ($r = -0{\cdot}62$, $P < 0{\cdot}001$) and the concurrent plasma angio-

tensin II concentration ($r = -0{\cdot}68$, $P < 0{\cdot}001$) [26, 30]. Estimates in the various groups of hypertensive subjects were then related to these respective ranges.

(*iv*) *Results: renal and malignant hypertension*

(*a*) Na_E–*renin and* Na_E–*angiotensin II relationships.* In a series of hypertensive patients with renal disease or in the malignant phase, the inter-relation of plasma renin concentration with Na_E and of plasma angiotensin II concentration with Na_E were both shown to be abnormally high in comparison with the relationships established in normotensive subjects [26, 30] (Fig. 1). These abnormal relationships were apparent in both untreated and treated (but still hypertensive) patients. In subjects with chronic renal failure the disproportion was due mainly to an increase in Na_E, whereas in the malignant phase, excessive elevation of renin and angiotensin II was mainly responsible. In those patients with chronic renal failure in whom blood pressure reverted to normal with regular dialysis therapy or following bilateral nephrectomy, the abnormal relationship between the renin–angiotensin system and Na_E was also corrected by the therapeutic manoeuvres. As it is well-established that the pressor effect of a given plasma angiotensin II or renin concentration various directly with sodium status [11, 22, 23], the findings strongly suggest that the elevated arterial pressures in these patients were at least partly a consequence of the disordered relationship. The disproportion appears likely to be the immediate result of inappropriate renin release, due in turn to the intrarenal lesions of the primary renal disorder or of the malignant phase. We have discussed these aspects in more detail elsewhere [26, 30, 31].

(*b*) *Angiotensin II relationships with arterial pressure and plasma aldosterone.* Examination of the quantitative relationships between plasma angiotensin II concentration and the concurrent arterial pressure and plasma aldosterone concentration in renal and malignant hypertension reveals further striking differences from normal. In studies previously quoted [20, 22], in which incremental angiotensin II infusions were given to normal subjects on controlled diets, the relationship between plasma angiotensin II, aldosterone and arterial pressure was established for both the sodium-replete and sodium-deplete state. As mentioned, sodium depletion enhanced the aldosterone response, while diminishing the pressor response, to a given plasma angiotensin II concentration.

Figure 2 shows the relationship of plasma angiotensin II concentration to the concurrent mean arterial pressure (diastolic plus one-third of pulse pressure) in a series of patients with untreated renal and/or malignant phase hypertension. Blood samples were obtained under closely similar conditions in both patients and controls, i.e. in the metabolic ward, after overnight recumbency and fasting, and between 0830 and 0930 h. In the hypertensive patients, the plasma angiotensin II concentrations encompassed a very similar range to that seen in the normal subjects before and during angiotensin II infusion and, also, as in the normal subjects, there was a statistically significant positive correlation between the angiotensin II and arterial blood pressure levels ($r = +0{\cdot}36$, $P < 0{\cdot}02$). However, the blood pressures in all the hypertensive subjects were clearly much higher in relation to the concurrent plasma angiotensin II concentration than in any of the infused normal subjects (Fig. 2). Thus, factors other than simple elevation of plasma angiotensin II concentration require to be invoked to explain the elevated arterial pressure of renal or malignant hypertension. This point is emphasized by data from a patient with a renin-secreting

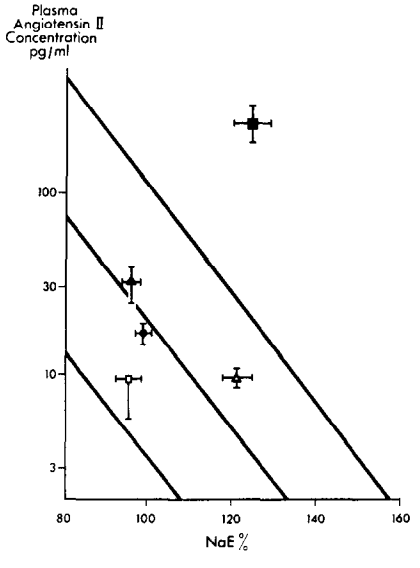

Fig. 1. Inter-relationship between plasma angiotensin II concentration and Na_E in various forms of hypertension. For expression of Na_E see text and reference [26]. Diagonal lines indicate mean ± 2 S.D. for normotensive subjects [26]. For each hypertensive group mean ± S.E.M. plotted thus: renal and malignant ■; primary aldosterone excess before (△) and after (▲) treatment; normal-renin ● and low-renin □ essential hypertension. Log. ordinate.

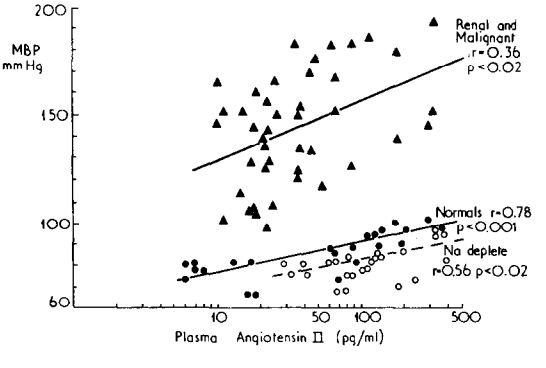

Fig. 2. Inter-relationship between plasma angiotensin II and mean blood-pressure (diastolic plus ⅓ pulse pressure) in Na-replete (●) and Na-deplete normals (○) before and during angiotensin II infusions [22] compared with untreated renal and malignant hypertensives (▲). Only one point plotted for each hypertensive patient apart from three highest angiotensin II values, all obtained in a patient with renin-secreting tumour [32]. Log. abscissa.

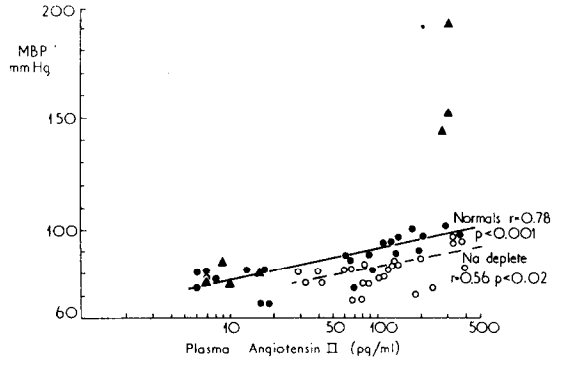

Fig. 3. As for Fig. 2, to emphasize changes in angiotensin II/MBP relationship after operation in patient with renin-secreting tumour (▲) [32]. Lowest four points in patient show normal Na-replete values after operation.

renal tumour in whom severe hypertension was completely corrected by excision of the kidney containing the abnormality [32]. Before treatment, arterial blood pressure was disproportionately high in relation to peripheral plasma angiotensin II levels as compared with normal subjects acutely infused with angiotensin II (Fig. 3). After removal of the tumour and correction of the hypertension, the angiotensin II–blood pressure relationship reverted to the normal sodium-replete range (Fig. 3).

These findings are consistent with those obtained by Bianchi and his colleagues in the conscious dog [33, 34] in which, in experimental renal hypertension, the relationship between arterial pressure and plasma renin concentration was initially similar to that in dogs made hypertensive by infusing renin. Later in the course of renal hypertension, blood pressure became disproportionately high in relation to the plasma renin level. One possibility which has been considered in explaining progressively enhanced pressor sensitivity to angiotensin II in experimental hypertension is a stimulant effect of angiotensin on the sympathetic nervous system [35].

In this same series of untreated patients with renal and malignant hypertension the plasma angiotensin II–aldosterone relationship also showed interesting differences from normal. Overall, the positive correla-

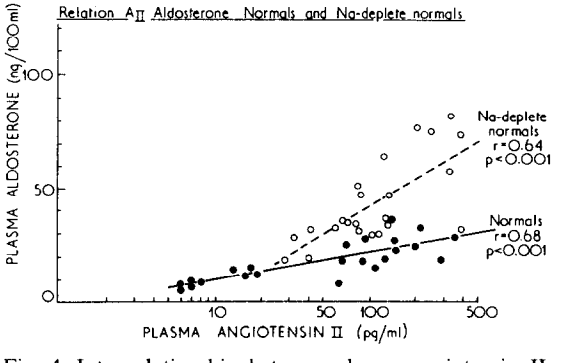

Fig. 4. Inter-relationship between plasma angiotensin II and plasma aldosterone in Na-replete (●) and Na-deplete (○) normals before and during angiotensin II infusion [20, 22]. Log. abscissa.

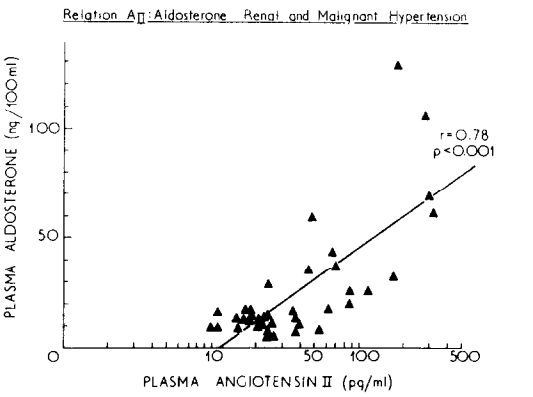

Fig. 5. Inter-relationship between plasma angiotensin II and plasma aldosterone in patients with untreated renal and malignant hypertension. One point only plotted for each patient apart from three highest angiotensin II values, all obtained in patient with renin-secreting tumour [32]. Slope of regression line does not differ significantly from that in Na-deplete normals (Fig. 4).

tion between the two measurements was close ($r = +0{\cdot}78, P < 0{\cdot}001$). The regression line was much steeper than in sodium-replete normal subjects and very similar to that seen in sodium-depleted normals. However, the lowermost points extended lower than in sodium-depleted normals, to overlap with the lower end of the normal sodium-replete range (Figs. 4 and 5). The mechanism of the steepening of the angiotensin II/aldosterone curve in renal and malignant hypertension remains to be determined (as indeed, in sodium-depleted normals also), but the enhanced relationship was again particularly well seen in the patient with a renin-secreting tumour before operation (Fig. 6). After removal of the tumour the relationship was restored to normal (Fig. 6).

(*v*) *Results: primary hyperaldosteronism*

In "primary" hyperaldosteronism, whether associated with a discrete adrenocortical adenoma or diffuse hyperplastic change, the aldosterone excess leads to expansion of Na_E and consequent suppression of the renin/angiotensin system [36–38]. Significant inverse correlations have been demonstrated between concurrent plasma aldosterone and renin concentrations [38, 39]. Examination of both the Na_E/

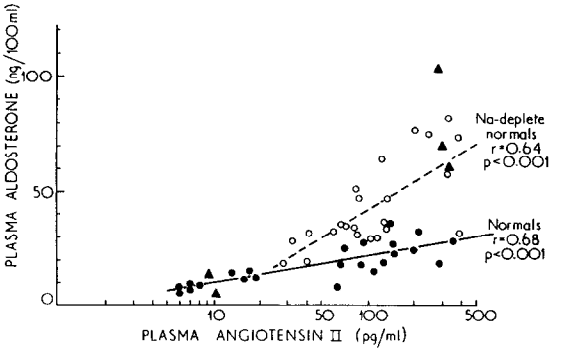

Fig. 6. As Figs. 4 and 5, to show changes in patient with renin-secreting tumour (▲) after operation [32].

renin and Na_E/angiotensin II relationships shows that these lie close to the mean for normotensive control subjects [30, 40] (Fig. 1), confirming that suppression of the renin/angiotensin system is appropriate to the expansion of Na_E. When Na_E is restored to normal by treatment, whether this comprises surgical excision of the abnormal adrenal gland or antagonism of the excess aldosterone with spironolactone, the Na_E/renin and Na_E/angiotensin II relationships remain normal, both plasma renin and angiotensin II concentrations increasing as Na_E (and blood pressure) are lowered [30, 40] (Fig. 1).

(vi) Results: essential hypertension

The relationship of the renin–angiotensin system to Na_E is of particular interest in essential hypertension. Despite varied diagnostic criteria, it is generally agreed that some 25% of patients with essential hypertension have evidence of suppression of the renin–angiotensin system and it is widely believed that "low renin essential hypertension" is a distinct clinical entity, possibly attributable to excess of a mineralocorticoid other than aldosterone [see 40, 41].

We recently reported [40] a study of a series of 45 patients with untreated essential hypertension, none of whom showed clinical, biochemical or radiological features of aortic coarctation, Cushing's syndrome, renal disease or phaeochromocytoma. Intravenous urography was normal and blood urea below 45 mg/100 ml in each case. Thirty three of these 45 were classified as having "normal-renin essential hypertension", plasma concentrations of renin, aldosterone and potassium being persistently normal in all.

Twelve of the 25 were arbitrarily classified as having "low-renin hypertension", each having a mean plasma renin concentration below 6 units/l (normal range 4–20) and at least one subnormal value. Plasma levels of aldosterone and deoxycorticosterone were normal in all of these, although 4 of the 12 showed hypokalaemia not attributable to previous therapy (mean values ranging from 2·4–3·6 m-equiv/l).

Mean Na_E was found to be close to 100% in both the normal-renin and low-renin groups; consequently the Na_E–renin and Na_E–angiotensin II relationships were normal in the normal-renin essential hypertensives, and abnormally depressed in the low-renin cases (Fig. 1). Thus low-renin essential hypertension contrasts with primary hyperaldosteronism, and the present data provide no evidence supporting the concept that it is due to excess mineralocorticoid activity, unless such activity were having an effect quite distinct from that seen in aldosterone excess.

These findings accord with a parallel study in 38 patients with normal-renin hypertension and 17 with low-renin hypertension, in which plasma and extracellular fluid volumes were normal and similar in both groups [42].

Overall the data strongly suggest that the reduction of renin and of angiotensin II in the bulk of cases of low-renin hypertension is not brought about by sodium retention with volume expansion, a general conclusion which does not, it must be emphasized, exclude the possibility of occasional cases of mineralocorticoid hypertension presenting as "low-renin essential hypertension". Alternative explanations for the suppression of the renin-angiotensin system therefore require to be considered.

(vii) Hypothesis: renal changes in hypertension

We have recently developed the hypothesis [43] that renin decreases and sodium status remains normal in essential hypertension because the pressure-natriuretic mechanism within the kidney is reset by an increase in filtration fraction. It is proposed that pressure-natriuresis results from a reduction of tubular sodium reabsorption following transmission of increased hydrostatic pressure from the renal artery into the peritubular capillary circulation. Resetting of this process in essential hypertension is, it is suggested, due to increased resistance in pre- and post-glomerular vessels, leading to increased filtration fraction. This in turn raises the oncotic pressure of plasma in the peritubular capillaries, thus enhancing sodium reabsorption. Renin release may at the same time be progressively inhibited by increased pressure in blood vessels close to the glomerulus. This latter point is supported by data showing an inverse correlation of plasma-renin with arterial pressure and filtration fraction [44, 45]. It should also be noted that in essential hypertension plasma renin level is inversely related to age [45]. Thus sodium balance and normal Na_E are maintained in essential hypertension because the natriuretic effect of increased arterial pressure is compensated by the sodium-retaining effect of the resetting process.

Intrarenal functional adaptations of this kind could well underly the enhancement of arterial pressure in relation to concurrent plasma angiotensin II seen in renal and malignant hypertension (Fig. 2).

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