Interrelationships Between Angiotensin, Norepinephrine, Epinephrine, Aldosterone Secretion, and Electrolyte Metabolism in Man

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I SHOULD LIKE to summarize for you some of our studies in man which suggest an interaction between the amide of synthetic valyl-5-angiotensin II, norepinephrine, aldosterone secretion, and sodium and potassium excretion by the kidney.

The studies which I shall report were carried out in normal volunteers and in patients with hypertension or with cirrhosis and ascites. All studies were conducted under conditions of controlled metabolism balance.

Our interest in angiotensin developed as an outgrowth of a long-standing interest in aldosterone metabolism and in the factors concerned with the regulation of the rate of secretion of this hormone. Therefore, I should like first to review briefly some of our work on aldosterone secretion which resulted in our investigation of the relation of angiotensin to aldosterone and to electrolyte balance.

Aldosterone Oversecretion in Man

Many studies of aldosterone have been based on quantitation of the small fraction of hormone excreted unchanged in the urine. By contrast, our work has employed a technic of isotope dilution, which measures with precision the amount of the hormone actually secreted by the adrenal cortex. Details of this method have been previously described.

We have found marked oversecretion of aldosterone in the edematous states of cirrhosis and nephrosis. Of interest was the finding that in advanced heart failure, aldosterone secretion may not be much elevated, pointing again to the fact that hemodynamic rather than hormonal factors may be more important in the sodium retention accompanying this condition.

An increased mean urinary excretion of aldosterone has been reported in patients with benign hypertension with the suggestion that this condition represents mild, chronic hyperaldosteronism. Results from our laboratory do not support this opinion. In our hands, the secretory rate of aldosterone was normal in the frequently occurring forms of hypertension, and there was no indication that aldosterone was involved in the pathogenesis of primary (benign essential) hypertension. On the other hand, in the much less common syndrome of malignant hypertension, oversecretion of aldosterone was a most consistent finding. It is possible that aldosterone hypersecretion is itself a cause of malignant hypertension, but for a number of reasons we have felt that it is an associated phenomenon or even a consequence of the disease process.

I am pleased that Davis and his group have graciously allowed me to report their as yet unpublished data in hypertensive dogs. These studies, in a well-controlled experimental model, seem to agree entirely with our concept of the relation of aldosterone to hypertension in man. These workers found no increase in aldosterone secretion after production of a sustained hypertension by the Goldblatt technic. However, when the clamps were tightened so that a malignant stage (with a hastened demise) was produced, aldosterone secretion then increased markedly.

Problem of the Control of Aldosterone Secretion

Abnormalities in aldosterone secretion, which occur in these various diseases, may provide additional clues, not only for understanding the disease in question, but also for
studying the basic problem of the factors involved in the physiologic control of aldosterone release. In this latter regard, it is known, for example, that aldosterone secretion is largely independent of ACTH. Rather, it fluctuates widely according to the state of sodium and potassium balance or according to the volume or distribution of fluid in the vascular bed. Bleeding and thoracic caval occlusion are potent stimuli for aldosterone secretion in dogs. How these stimuli are mediated is poorly understood. What these various stimuli for aldosterone secretion have in common also remains obscure. Our approach has been that there is probably 1 main efferent pathway for the control of aldosterone secretion which, if exposed, might account for most of the situations in which oversecretion occurs.

More recently, our investigations of this problem have followed 3 rather parallel avenues. First, we studied the effect on aldosterone secretion resulting from altering the arterial pressure itself by various means. Secondly, we investigated the specific effects of norepinephrine and of epinephrine on aldosterone secretion because of the possibility that the autonomic nervous system might mediate control to the adrenal cortex. Thirdly, because of our observations in malignant hypertension, where there is always renal damage, and because of the enormous literature relating the adrenal cortex and the kidneys to experimental hypertension, we investigated the possible trophic effects of a pressor substance of renal origin, angiotensin, on aldosterone secretion. Because angiotensin and norepinephrine were given in equipressor dosage, it seemed possible that any difference in their effect on aldosterone release might reveal a chemotrophic rather than a pressor action.

Problems in the Study of the Relation of Pressor Substances to Aldosterone Secretion and to Sodium Balance

At the outset, I would like to emphasize that certain controls seem essential to proper study of the possible specific influences of any pressor substance on aldosterone secretion and on electrolyte balance. Three of these will be mentioned.

First, it is important to control the non-specific influences of the induced hemodynamic changes. Changes in vascular pressure and flow produced by vasoactive drugs might well affect aldosterone and sodium metabolism. Therefore, one must try to establish that an observed change is not just a consequence of the altered circulation but is rather a unique chemotrophic effect of the particular agent. Different pressor agents must be compared under similar circumstances to see whether an observed effect on aldosterone or on sodium excretion occurs with all of them. This vital control has not always been provided. We have tried to compare systematically the effects of angiotensin with those of norepinephrine and epinephrine, among others, but even this collation may not be entirely adequate because differences do exist in the hemodynamic actions of these agents.

Secondly, it seems important to control the state of sodium balance during administration of pressor agents because, as I will show you, the effect of these agents on salt excretion and on the rate of aldosterone secretion may at times be different after sodium depletion. This factor too has not always been controlled in reported studies.
Thirdly, I would like to say a word about the differing sensitivity of various patients to dosages of pressor agents. Recently, the provocative studies of Wood\textsuperscript{10} demonstrated that hypertensive subjects may be more sensitive to angiotensin. Some time ago, Goldenberg demonstrated that hypertensive subjects are also more sensitive to norepinephrine,\textsuperscript{11} so that less drug is necessary to produce a rise in blood pressure. It seems uncertain, therefore, whether this phenomenon of increased sensitivity is unique or whether it is just a nonspecific reflection of an increased vascular reactivity of hypertensive subjects. On the other hand, patients with cirrhosis and ascites appear to have a reduced sensitivity to pressor drugs. In table 1, data are shown which indicate that more angiotensin or more norepinephrine must be given to produce rises in blood pressure similar to those of normal controls. Again, the specificity of such phenomena remains to be established, and the altered sensitivity to various pressor agents in these diseases could be the result of the altered circulatory dynamics associated with the disease.

Relation of Norepinephrine, Epinephrine, and Angiotensin to Aldosterone Secretion and to Electrolyte Balance

Let us now consider the effects of infusion of these pressor substances on aldosterone secretion under different conditions of sodium balance.

The medullary hormones have a variable effect on aldosterone secretion. In a previously reported study,\textsuperscript{9} it appeared that the effect of norepinephrine or of epinephrine on aldosterone secretion might be determined by the pre-existing state of sodium balance. Thus, in subjects in a normal state of sodium balance with an initially normal rate of aldosterone secretion, no consistent changes were produced by norepinephrine or epinephrine infusions. However, in sodium-depleted subjects with an initially high rate of secretion of aldosterone, these hormones often produced a profound reduction in aldosterone secretion with natriuresis. This suppressive effect of the medullary hormones on aldosterone secretion may, at times, be of clinical significance; it seems possible that activity of the autonomic nervous system plays some balancing role in regulation of aldosterone secretion. For example, we have studied a patient in whom oral administration of sympathomimetic drugs has led to sustained correction of excess aldosterone secretion and to complete diuresis of edema fluid. These agents were more effective than conventional diuretic agents in this patient.\textsuperscript{12}

We compared the effects of angiotensin with those of norepinephrine. Angiotensin was given in amounts sufficient to produce pressure changes similar to those following norepinephrine administration. The effects of angiotensin on aldosterone secretion differed sharply from those of norepinephrine. Angiotensin consistently produced an increase in aldosterone secretion to levels of from 35 to 250 per cent above the control values.\textsuperscript{6} Also, in contrast to epinephrine and norepinephrine, this action of angiotensin was independent of the state of sodium balance. It occurred in subjects ingesting normal amounts of sodium as well as in sodium-depleted subjects.

In figure 1, additional data are presented which point up the possible influence of sodium depletion on the action of these pressor substances. Normal subjects on constant, but unrestricted, intake of sodium are compared with normal subjects studied in a similar manner after sodium depletion. The open boxes represent the control study, during which a dextrose infusion without pressor agent was administered. Angiotensin infusion always produced an increased aldosterone secretion. In contrast, the hormones of the autonomic nervous system had a variable effect on aldosterone but often appeared to reduce the rate of steroid secretion in the sodium-depleted group.

Also, I call your attention to the effect of infusion of these pressor agents on sodium excretion by the kidney. In this particular group, before sodium depletion, all of them caused a reduced sodium excretion. But after sodium depletion, all tended to cause an increased urinary sodium content, regardless of their influence on aldosterone secretion.

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The effect of intravenous infusion of pressor substances is compared before and after sodium depletion in normal subjects on a metabolism ward constant dietary regimen. The pressor agents were given in 5 per cent dextrose solution with a constant infusion pump for periods of from 5 to 24 hours. The average increment in blood pressure produced by the infusion is shown. The open boxes represent control values for each experiment, during which glucose infusion was given without a pressor agent. It can be seen that angiotensin always produced an increase in the secretory rate of aldosterone. By contrast, medullary hormones had a variable effect but tended to suppress the elevated aldosterone secretion of sodium depletion. Infusion of all of these agents tended to produce sodium retention before sodium depletion. However, after sodium depletion, all tended to be natriuretic, regardless of their effect on aldosterone.

The natriuretic action of these pressor agents in sodium-depleted subjects seemed worthy of further investigation. We have now studied over 20 subjects and have also examined the effects of various other sympathomimetic agents. At the present time, it is fair to say that frequently, but certainly not always, significant natriuresis can be induced in sodium-depleted subjects by the administration of pressor drugs, either orally or intravenously.

This point is amplified in figure 2, where the effect of the infusion of various pressor substances given before and again after sodium depletion to 2 normal subjects and to 1 subject with uncomplicated hypertension is illustrated. The natriuretic action of these pressor agents only occurred after sodium depletion; the effect, well demonstrated in the normal subject, was not so marked in this particular patient with hypertension. Thus far, it has been impossible to determine which of the various pressor agents is most natriuretic because the results have not revealed a consistent pattern among different subjects. The slight natriuresis of this hypertensive subject is perhaps of less magnitude than has been reported. I would like to suggest, however, that possibly the natriuresis reported by several groups in hypertensive subjects after angiotensin is not altogether unique for this group of patients; also, it may not be entirely specific for angiotensin. Further studies which control sodium balance and which compare various pressor agents may be necessary.

In a number of previous studies of pressor substances, different effects on electrolyte and water excretion have been observed. Some of these differences may be explained by differences in experimental conditions, particularly in the duration of the studies.
After sodium depletion, sympathomimetic agents tended to increase sodium depletion, whereas before depletion, variable effects on sodium excretion were observed. Angiotensin also increased sodium excretion after sodium depletion but only very slightly. Responses similar to normal subjects were encountered in a patient with benign essential hypertension.

Acute clearance studies, Smythe, Nickel, and Bradley demonstrated a diminished sodium and potassium excretion and a tendency to loss of water during the pressor action of adrenal medullary hormones. Subsequently, this group showed that these effects could occur with dosages which did not change the pulse or arterial pressure. Angiotensin and ephedrine produced different effects on electrolyte excretion. It was suggested that the effects of pressor agents on sodium and potassium excretion might be an indirect result of alterations in renal hemodynamics. Other clearance studies have indicated that renin differs from norepinephrine because renin, at times, produced a diuresis and natriuresis while inducing changes in renal blood flow and glomerular filtration which appeared similar to norepinephrine.

The studies reported in this communication are of a more prolonged nature, with the infusions of pressor substances having been carried out for from 5 to 24 hours. Therefore, the different effects on electrolyte and water excretion from those noted during acute clearance studies may be a reflection of addi-
The effect of angiotensin and of norepinephrine infusion on sodium excretion and aldosterone secretion in 2 patients with cirrhosis and ascites. The patient shown above (M.L.) exhibited a pressor response to relatively low dosages given over an 8-hour period in isotonic glucose by constant infusion pump. In contrast, the patient shown below (P.S.) required very large dosages of both agents to elevate the blood pressure. Marked natriuresis was produced in the second patient when larger doses of angiotensin were given. In both patients, in marked contrast to what is found in normal subjects, angiotensin failed to augment aldosterone secretion. The reduced pressor sensitivity and the failure to augment aldosterone with angiotensin perhaps may be taken as evidence for an endogenous excess of renin and angiotensin in this disorder.

Is Angiotensin the Trophic Hormone for Aldosterone?—Studies in Cirrhosis

Because angiotensin consistently stimulates aldosterone secretion, the question is raised as to whether this peptide is the principal trophic hormone for aldosterone. This action of angiotensin fits well with the finding of oversecretion of aldosterone in malignant hypertension. However, in malignant hypertension, there is severe renal damage, which might cause inappropriate release of renin. You will recall that neither renin nor angiotensin has been incontrovertibly demonstrated in normal plasma, and it thus remains possible that the effect of angiotensin on aldosterone is pharmacologic rather than physiologic. On the other hand, these findings may mean that a renal-adrenal mechanism exists which operates for normal control of sodium balance. There is already considerable indirect evidence for the existence of such a system, implicating renin release by the juxtaglomerular cells and aldosterone secretion by the adrenal cortex.20, 21

Finally, I would like to consider briefly the effects of pressor agents in patients with cirrhosis and ascites (fig. 3). These patients characteristically excrete virtually no sodium (often less than 1 mEq./day), and, in our hands, their rate of aldosterone secretion is usually higher than in any other disorder. Aldosterone seems especially important in the pathogenesis of this edema since complete diuresis may follow adrenalectomy and since the aldosterone antagonists (spiroloactones) are especially effective in these patients. Patients with cirrhosis and ascites may therefore represent a particularly useful model for study of the factors concerned in the normal regulation of aldosterone secretion.

We have reasoned that if angiotensin is the trophic hormone for aldosterone, one might expect patients with cirrhosis and ascites to manifest arterial hypertension unless some sort of tolerance or tachyphylaxis to angiotensin has developed. In figure 3, it can be seen that, in fact, patients with cirrhosis may be relatively resistant to the pressor effects of synthetic angiotensin. At times (patient P.S.), much larger doses are required to produce a blood pressure elevation; however, to date, whenever this situation has been encountered, much more norepinephrine has also...
been required. There is, therefore, no evidence as yet that the reduced pressor responsiveness of these patients is unique for angiotensin.

One might deduce from these findings that patients with cirrhosis are secreting excessive, but subpressor, amounts of renin to account for the increased aldosterone output. The failure of exogenous angiotensin to augment aldosterone secretion might thus mean that these patients are already maximally stimulated.

Alternatively, one may interpret the findings in cirrhosis to mean that angiotensin is really not the trophic hormone for regulating aldosterone secretion. The reduced pressor sensitivity could be nonspecific, and the failure of angiotensin to stimulate further aldosterone secretion might mean that the adrenal cortex is preferentially receptive to a stimulus other than angiotensin, perhaps the trophic hormone, which is present in great excess in these patients. Because of the nature or the degree of such a stimulus, the adrenal cortex is preclusively engaged.

Despite these reservations, it is the author's view that the renin-angiotensin system could well be the main trophic hormonal system for regulation of aldosterone secretion. Hyperactivity of such a system would explain the oversecretion of aldosterone in malignant hypertension and might account for other instances of physiologic and pathologic aldosteronism. But a critical experiment remains to be done, i.e., the demonstration of renin or of angiotensin in increased amounts in the circulation of sodium-depleted normal subjects or of patients with edema who have increased aldosterone secretion.

In closing, consider the striking natriuresis which can also be produced in patients with cirrhosis and ascites by various pressor agents, including both norepinephrine and angiotensin. In 8 studies, we have found that the angiotensin produces a much more marked natriuresis in these patients than does norepinephrine. This finding raises the question once more as to whether there is anything unique about the natriuretic effects of angiotensin reported in patients with arterial hypertension.13-15 Further studies of this phenomenon which utilize more precise technics of renal clearance are necessary.

**Summary**

Oversecretion of aldosterone is a consistent finding in the syndrome of malignant hypertension. Infusion of angiotensin has been consistently shown to induce an increased secretion of aldosterone by the adrenal cortex in normal human subjects. Because renal damage is so prominent in malignant hypertension, it seems possible that renin release and then aldosterone oversecretion by the adrenal cortex are involved in the pathogenesis of this disorder.

These findings support the possibility that there is a renal-adrenal system which operates for the normal regulation of electrolyte balance. This system might function to maintain and protect renal perfusion by promoting sodium retention via stimulation of the adrenal cortex.

Our recent work has been predicated on the possibility that aldosterone secretion is chiefly regulated by 1 specific trophic hormone (possibly angiotensin), oversecretion of which accounts for the increased secretion of aldosterone observed in various other conditions.

Preliminary studies designed to investigate the possible role of angiotensin in the marked oversecretion of aldosterone found in cirrhosis have been reported. It has been observed that patients with cirrhosis and ascites may be less sensitive to both angiotensin and norepinephrine so that more drug is required to produce a given pressor response. Furthermore, aldosterone secretion could not be augmented by administering angiotensin in these patients. While several interpretations are possible, these findings are consistent with the view that the adrenal cortex is already maximally stimulated by circulating endogenous angiotensin.

Because of reduced pressor responsiveness, increased amounts of angiotensin could circulate without causing hypertension. This hypothesis awaits actual demonstration of increased amounts of circulating renin or...
angiotensin in this condition (and others) associated with aldosteronism.

Proper study of the interrelationships between pressor substances, aldosterone secretion, and sodium balance requires that effects of the different types of pressor agents be compared under similar circumstances. Thus, both norepinephrine and angiotensin affect the renal excretion of electrolytes. Both can cause a natriuresis in normal or hypertensive subjects. In normal subjects, the natriuresis occurs inconsistently but seems more readily induced after sodium depletion.

Angiotensin has been found to produce a marked increase in sodium excretion in patients with cirrhosis and ascites who have increased aldosterone secretion. In equipressor doses, the natriuresis of angiotensin is of strikingly greater magnitude than that of norepinephrine, possibly indicating that the peptide affects tubular transport of sodium. The natriuresis effected by these pressor agents seems independent of their effect on aldosterone secretion because medullary hormones often suppress aldosterone output, whereas angiotensin increases it.

Further study is necessary to define more specifically the conditions which determine these responses and interrelationships. The results to date support the view that an aldosterone-regulating hormone (possibly angiotensin) could be elaborated as a result of a critical change in intrarenal pressure.

References
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