On the Hemodynamic Regulation of the Secretion of Aldosterone

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Evidence is presented that the secretion of aldosterone in dogs may be considerably influenced by hemodynamic factors. The experiments indicate that secretion of aldosterone may be decreased by expanding the "low pressure" system, and may be increased by reducing the amplitude of the pulse pressure in the carotid arteries. The decrease may be prevented by prior section of the vagi, the increase by prior denervation of the thyro-carotid arterial junctions.

Previous experiments have pointed to some function of blood volume as a major factor in the control of the secretion of aldosterone. In the present studies, we have proceeded on the assumption that the secretion of aldosterone involves a neurohumoral final common pathway, with a mechanism within the central nervous system which integrates signals generated by hemodynamic stimuli. The experiments described here are attempts to delineate the afferent pathways of these stimuli and the essential nature of the hemodynamic stimuli themselves. Some of the work discussed here has been presented elsewhere.

The experiments were performed on healthy mongrel dogs which had been anesthetized with sodium pentobarbital. Adrenal venous blood was collected intermittently by the method of Hume and Nelson. The secretion rate of aldosterone was determined either by Mills' modification of the method of Neher and Wettstein or by the method of Kliman and Peterson. Constriction of the thoracic inferior vena cava (caval constriction) was effected through a closed chest by means of an inflatable cuff passed about the vessel and led out through the thoracic incision. Bilateral constriction of the common carotid arteries was effected by means of silk strings passed about the carotid arteries and led through double-lumen plastic cannulas, held rigid to prevent pull on the arteries. Pressures were measured in the brachial and lingual arteries, right atrium, femoral vein and esophagus by means of Statham pressure transducers and recorded continuously on a Sanborn 8-channel recorder. All acute experiments were designed so that a control collection of adrenal blood for measuring the concentration of

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aldosterone was obtained before application of the specific stimulus. Blood lost, or withdrawn for assay, was replaced by homologous transfusion.

Constriction of the supradiaphragmatic inferior vena cava traps blood "below" the constriction, with a resultant depletion of blood "above" the constriction. Such a constriction is consistently effective in increasing the secretion of aldosterone; this effect can be measured, reproducibly, within 1 hour of the application of the constriction. Upon release of the constriction, there is, also reproducibly, a fall in the secretion of aldosterone which occurs within an hour and a half.² The constriction can then be reapplied and, within an hour, there is again an increase in the secretion of aldosterone. An experiment of this type is illustrated in figure 1a.

It has been suggested by Davis and co-workers⁶ that caval constriction stimulates an increase in the secretion of aldosterone in some way other than by modifying a function of the blood volume. In their experiments, the increase in the secretion of aldosterone, which ordinarily follows caval constriction, could not be prevented by infusion of a quantity of dextran which was calculated to compensate for the blood sequestered or lost by application of the constriction. However, the extent of hemodynamic changes evidently depends on the degree of the constriction, and the susceptibility of these changes to reversal by infusion depends upon the rate of infusion as well as upon its volume. Figure 2 shows 2 experiments in which an increase in the secretion of aldosterone was first produced by caval constriction, and the effect then nullified while
the constriction was maintained, by rapid infusion of blood above the constriction. This evidence suggests that caval constriction is, in fact, a hemodynamic stimulus.

Bilateral section of the vagus nerves in the neck does not prevent the rise in the secretion of aldosterone which follows caval constriction, but it does prevent the fall which follows release of the constriction.² An experiment of this type is shown in figure 1b. As shown in figure 1c,² vagotomy per se has no effect upon the secretion of aldosterone. Both the increase in the secretion of aldosterone which follows caval constriction despite vagotomy, and the absence of the fall in the secretion of aldosterone in the vagotomized animal after the constriction is released are reproducible phenomena. This evidence is consistent with the hypothesis that impulses leading to decreases in the secretion of aldosterone may arise in the atria or great vessels and be conveyed to the central nervous system via the vagus nerves. It also suggests that stimuli leading to increases in the secretion of aldosterone are mediated by some other pathway.

Bilateral constriction of the common carotid arteries low in the neck (carotid constriction) produces an increase in the rate of secretion of aldosterone. In the intact animal, it also gives rise to an increase in systemic (extra-carotid) arterial blood pressure. Prior stripping of the carotid arteries of their nerve supply—from above the carotid sinuses to low in the neck—abolished the increased secretion of aldosterone and the increase in blood pressure which otherwise follow carotid constriction.

It is possible to dissociate the effects of constriction of the common carotid artery on the secretion of aldosterone from the effects on the blood pressure. Some animals were subjected to a careful denervation of the carotid sinuses alone. In these animals carotid constriction produced normal increases in the secretion of aldosterone even though the usual pressor responses were absent. In another group of dogs, the thyro-carotid arterial junctions were denervated without denervation of the carotid sinuses or of the remainder of the carotid arteries; the region of the thyro-carotid arterial junctions has been shown to be a baroceptor area in both the dog⁵ and the cat.¹⁰ In these dogs, carotid constriction produced no increases in the secretion of aldosterone despite intact pressor responses.⁵ The effects of carotid constriction on the peripheral arterial pressure and on the secretion of aldosterone are shown schematically in figure 3. Statistical evaluation of the data derived from these experiments reveals no significant difference between normal and sinus-denervated animals with respect to increases in the secretion of aldosterone following carotid constriction. However, the responses of the group with denervated thyro-carotid arterial junctions were significantly different (p < .001) from those of the normal group. Denervation
HEMODYNAMICS ON ALDOSTERONE SECRETION

Figure 4

Effects of caval constriction, of denervation of the thyro-carotid arterial junctions ("T") and of administration of desoxycorticosterone (DOC) on urinary sodium and body weight in a dog receiving a daily sodium intake of 50 mEq.

of this region in another group of dogs was also shown to prevent the acute increase in the secretion of aldosterone which ordinarily follows caval constriction. Again, the results were highly significant statistically. These data suggest that the increases in aldosterone secretion following caval or carotid constriction depend on the integrity of the nerves arising at the thyro-carotid arterial junction.

Chronic constriction of the supradiaphragmatic inferior vena cava commonly produces a form of secondary aldosteronism characterized by retention of sodium, ascites and, at times, edema. The retention of fluid in this condition is an exceedingly complex phenomenon, and it seems clear that aldosterone plays only a part in its development or maintenance. An experiment on an animal prepared in this way is shown in figure 4. Following caval constriction, there was retention of sodium with gain in weight and the development of ascites on an intake of approximately 50 mEq. per day of sodium. This animal was then subjected to bilateral denervation of the thyro-carotid arterial junctions. This operation was followed by natriuresis, a loss of
ascites and a reduction in weight. That this response was not due to development of collateral circulation is shown by the response to desoxycorticosterone, which produced retention of sodium and gain in weight. Figure 5 shows a series of values for the secretion of aldosterone in a dog with a chronic adrenal cannula. The animal was first subjected to caval constriction and, later, to denervation of the thyro-carotid arterial junctions. Caval constriction produced an increased secretion of aldosterone which was reversed after the denervation.

Because ascites per se may reduce the ability to retain further amounts of sodium, still another preparation was utilized. Dogs with ascites following caval constriction, receiving a constant sodium intake of 60 mEq. per day, were subjected to paracentesis. After the abdominal fluid had reaccumulated, they were subjected to bilateral denervation of the thyro-carotid arterial junctions. In order to provide a maximal stimulus to sodium retention, a paracentesis was again done. One such experiment is shown in figure 6. It is seen that following the denervation, the ability of the animal to retain sodium on a daily intake of 60 mEq. was impaired. However, an increase in the intake of sodium to more than 200 mEq. per day resulted in retention of sodium and gain in weight, indicating that caval constriction was still present. The fact that this last phenomenon can be demonstrated in bilaterally adrenalectomized animals is further evidence that the retention of sodium in the caval-constricted dog is not
Hemodynamic data derived from acute experiments with caval and carotid constriction have been compared with data from animals which were subjected to blood loss, a stimulus which is known to increase the secretion of aldosterone. Such data are summarized diagrammatically in figure 7. Of the changes measured, only diminished intracarotid pulse pressure was consistently associated with the increase in the secretion of aldosterone. Because of the reflex increase in mean systemic blood pressure as the carotid pulse pressure decreased, it was possible to maintain, or even to increase, intracarotid mean pressure during carotid constriction by using a small amount of constriction.

It is not yet possible to assess the role of pulse pressure in the aldosteronism of cardiac failure in man; we are engaged in such studies at the present time. The published literature on man does contain data consistent with the schema suggested by the results in the dog. Eichna and associates, for example, induced loss of sodium and of weight in patients with "low-output" cardiac failure by rapid digitalization. In each patient, arterial pulse pressure rose promptly with digitalization. In patients with "high-output" failure, the situation is more complex. If hypersecretion of aldosterone is an important element in the disease picture, it is clear that a low absolute value of pulse pressure cannot be a prerequisite, since elevated pulse pressure and edema may certainly coexist in beriberi heart disease. However, one of the earliest responses of patients with beriberi heart disease to thiamine is an increase of pulse pressure which precedes the loss of sodium and of weight. Thus, a relative decrease of pulse pressure may be related even to the aldosteronism of high-output failure.

In summary, figure 8 presents schematically a working hypothesis concerning the hemodynamic control of the secretion of aldosterone. A dual mechanism is illustrated. Secretion of aldosterone may be inhibited by...
expansion of the "low pressure" system; the afferent impulses traverse vagal pathways. Secretion of neurohormone may be increased by constriction of (that is, decrease of pulse pressure in) the common carotid artery; the afferent impulses arise from baroreceptors in the region of the thyro-carotid arterial junctions.  

References

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HEMODYNAMICS ON ALDOSTERONE SECRETION


The Laws of Nature

It is one thing for the human mind to extract from the phenomena of nature the laws which it has itself put into them; it may be a far harder thing to extract laws over which it has no control. It is even possible that laws which have not their origin in the mind may be irrational, and we can never succeed in formulating them.—A. Eddington. The Philosophy of Physical Science. Ann Arbor, University of Michigan Press, 1948, p. 179.
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