RENAL-ADRENAL RELATIONSHIPS IN HYPERTENSION

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FOLLOWING my training with Dr. Hans Selye, when I became associated with Doctors Page and Corcoran in 1948, my interest understandably was directed to the renal pressor system and the adrenal cortex. At that time the renal pressor system had been identified and was believed by many to be the main pathogenic factor in renal and clinical hypertension. Desoxycorticosterone acetate (DCA), then a hypothetic hormone, was known to elicit hypertension when given to salt-treated rats. Although renal hypertension and DCA hypertension were considered different entities, there were indications they might have some mechanisms in common. Renal hypertension was associated with an increase in adrenal weight, and DCA hypertension, according to some investigators, with an activation of the renal pressor system, because of the presence of nephrosclerosis. With this background, I shall summarize the experiments that have led us to a new concept of renal-adrenal relationships in hypertension, which has proved useful as a working hypothesis.

Our first experiment was based on the assumption that the renal pressor system, not stress, was responsible for adrenal stimulation noted during renal hypertension. In spite of the belief that renin formed antibodies and was active only when administered intravenously, we injected various renal extracts subcutaneously into rats over a period of several weeks. Only extracts possessing pressor activity caused diuresis and proteinuria, effects previously recognized in acute experiments. Animals lost weight as had been noted in malignant hypertension, and their adrenals showed hypertrophy of the zona glomerulosa, which is considered the site of formation of desoxycorticosterone (DC)-like steroids. Similar adrenal changes were noted in rats with renal hypertension. At that time, it was known that the activity of the zona glomerulosa was dependent not on the pituitary gland but on changes in the sodium-potassium ratio of body fluids, and that renin caused sodium loss and that DCA caused sodium retention.

From these observations, we viewed the adrenotrophic effect of renin as a corrective mechanism to conserve sodium, and postulated during hypertension an interplay between kidneys and adrenals: renal hypertension could proceed in two phases. The first phase is renal damage similar to that produced by encapsulation of the kidney, which increases liberation of renin thus causing hypertension and sodium loss. The second phase, because of sodium depletion, is the homeostatic release of DC-like steroids that results not only in sodium retention but also in increased hypertension and hypertensive vascular disease including nephrosclerosis. Such increased effects had been demonstrated in renal hypertensive rats treated with DCA. Thus, this vicious cycle may provide an explanation of the sustained hyper-

tension after removal of the "touched" kidney in renal hypertension or after cessation of DCA treatment. Although this theory had the advantage of unifying some then current theories, its weakness was that it was based on morphologic observations, and on the assumption that DCA or a like compound was secreted by the zona glomerulosa. No direct evidence could then be provided because of the inadequacies of methods used in steroid analysis. However, in later years it was established that aldosterone is the principal salt-active corticosteroid present in adrenal secretions, and is secreted predominantly by the zona glomerulosa after administration of angiotensin, a hormone with a specific adrenotrophic effect.

We have seen that the whole concept was centered on the renal pressor system, which determines adrenal participation. The effects of renin administration should then reproduce all the manifestations of renal hypertension. Infusion of renin into rabbits caused mild hypertension, which disappeared as soon as treatment was discontinued. In rats, subcutaneous renin caused some elevation in blood pressure, but nothing similar to that occurring during renal hypertension. It should be emphasized that we have never observed any vascular lesions, such as nephrosclerosis or periarteritis nodosa, in normal rats treated with renin, even in the presence of excess salt.

Since renin infusion appeared unsuccessful, we decided to modify experimental conditions. Impressed by the fact that renin effects were potentiated by salt, we exaggerated such a situation by treating rats with DCA before administering renin. To our surprise, renin injections were promptly followed by the development of acute signs of thirst, oliguria, often hematuria, water retention, increase in body weight, and occasionally nervous tics or convulsions. These signs were accompanied by a prolonged significant increase in arterial pressure. The majority of animals died within four days. At autopsy, generalized edema and hemorrhages in kidneys, brain, heart, and gastrointestinal tract were found. On microscopic examination, the kidneys were found to be severely damaged: glomeruli were occluded with thrombi, and tubules were degenerated and were filled with casts. Vascular lesions present in arterioles and capillaries seemed to be basically due to an increased permeability of endothelial membranes, and to necrosis of muscle. Although this syndrome had been called eclampsia-like because of impressive water retention, the lesions were characteristic of acute vascular disease, such as in malignant hypertension. Subsequently we showed that, like DCA, cortisone, cortisol, and adrenal-regeneration hypertension will condition the saline-fed rats to the vasculotoxic effects of renin, and that angiotensin can be effectively substituted for renin. Significantly, aldosterone also has the same sensitizing properties as DCA.

Having noted that renal failure was a constant feature, and knowing that nephrectomy enhances the pressor effects of renin, we studied the effects of subcutaneous injections of renin in bilaterally nephrectomized dogs given 1 per cent salt in drinking water. The findings were similar to those reported in DCA-renin

treated rats: symptoms of thirst, edema, increase in weight, hypertension, and convulsions; pathologic changes consisting of hemorrhage and necrosis of vascular muscle fibers. These lesions resembled those of malignant renal hypertension or those found in nephrectomized dogs maintained by vividialysis. It is significant that when renin was given to adrenalectomized and nephrectomized dogs, hypertension was equally severe, but the incidence and severity of vascular lesions were definitely decreased.

Although corticosteroids, renin, and salt were known to participate in experimental renal hypertension, the implications of the results reported did not seem obvious, possibly because of lack of accurate and reliable data on the endocrine activity of kidneys and adrenals. Recently attention was again focused on the adrenals by many of the studies relating to aldosterone. Aldosterone is a mildly hypertensive agent as compared with DCA; such hypertension is moderate, and is not accompanied by vascular disease. These observations agree with clinical observations on patients with primary aldosteronism. When aldosterone-treated rats are injected with renin the same acute and severe symptoms and vascular lesions develop as with DCA plus renin. Aldosterone secretion determined by direct analysis of adrenal venous blood or by an isotope-dilution technic is increased during the malignant but not during the benign phase of experimental and clinical hypertension. There is evidence that concentrations of blood renin and angiotensin are increased during malignant hypertension. From these observations, aldosterone-renin disease can be postulated as the experimental equivalent of malignant hypertension, and aldosterone and renin as the causative agents of malignant hypertension.

The concept of the renal-adrenal interplay was originally formulated to interpret a pathologic situation. Later on, when attempts were made to prove its validity, it appeared to reflect a physiologic relationship concerned with the regulation of blood pressure and sodium metabolism. Now, emphasis is again placed on its participation in hypertension. One may wonder what the real significance is of this concept. Does it represent a physiologic homeostatic mechanism? Is malignant hypertension an exaggeration or a dysfunction of a physiologic situation? The best way to answer these questions is to summarize the present evidence, thus delineating facts from speculation.

Renin is secreted by the juxtaglomerular cells of the kidney; renin stimulates the zona glomerulosa; stimulation of renin secretions by a low-sodium diet is accompanied by hypertrophy of the zona glomerulosa, whereas a high-sodium diet has the opposite effects; hypertrophy of the zona glomerulosa is associated with an increased secretion of aldosterone; administration of aldosterone or DCA causes atrophy of the juxtaglomerular cells and inhibits renin secretion; administration of nonpressor doses of angiotensin causes release of aldosterone; and finally, stimulation of aldosterone secretion by hemorrhagic hypotension is prevented by nephrectomy. These data constitute ample evidence of a specific endocrine system with its

own feedback mechanism, where angiotensin is the trophic hormone, the zona glomerulosa the target organ, and aldosterone the end effector agent. The system is influenced by changes in arterial pressure and in the sodium-potassium ratio of body fluids. It has been suggested that the juxtaglomerular cells that produce renin are stretch or volume receptors responsive to the degree of filling of the afferent arterioles; decreased stretch would stimulate renin secretion and vice versa. Present evidence supports such a hypothesis; the factors known to regulate renin secretion also affect blood volume. Thus the renin-angiotensin system would have a dual homeostatic role: one of regulating blood pressure by a direct effect of angiotensin on blood vessels, and the other of regulating sodium and water through aldosterone.

In contrast with this apparently well-defined physiologic mechanism, our knowledge concerning the role of renin and aldosterone during hypertension remains mostly theoretic. The concepts as originally formulated assumed that renin and a DC-like compound, which is aldosterone, were increased during hypertension. Subsequent results with few exceptions did not support that hypothesis. Recently, various methods have been used to evaluate the pressor function of kidneys: estimation of the degree of activity of the juxtaglomerular cells, and determination of pressor substances in kidneys and in renal venous blood. The results can be briefly summarized.

Renin content and renin secretions are normal or increased only during hypertension caused by constriction of the renal artery, no distinction being made between the benign and the malignant form. When malignant hypertension was purposely elicited, the renin content of kidneys and the amount of blood angiotensin were definitely increased. In renal hypertension caused by renal encapsulation and renal infarction, renin secretions are decreased or absent. Also, hormonal hypertension and salt hypertension are associated with inactivation of the renal pressor system. Comparison of renin secretion and incidence of nephrosclerosis shows an inverse relationship: kidneys that are depleted of renin are susceptible to vascular disease; whereas, those with normal or increased secretions, such as occur after clamping of the renal artery, are free of lesions. Thus, a nephrosclerotic kidney is hypoactive, not hyperactive. This observation therefore refutes our original view that a DC-like compound enhances renal hypertension by contributing to the development of nephrosclerosis, which in turn increases renin release.

In contrast with renin, aldosterone is a well-defined compound that can be determined with a high degree of accuracy in body fluids. We have seen that aldosterone secretions are increased during experimental and clinical malignant hypertension, but not during benign hypertension. In our opinion, this last observation is important because of the conditions under which this experiment was carried out, and also because it bears indirectly on the matter of renin secretion. Benign hypertension was elicited in dogs by clamping of both renal arteries. Blood pressure reached values between 180 and 200 mm. of Hg. Aldosterone determinations were performed between the third and the sixth days, therefore eliminating the

immediately postclamping period when renin is likely to be released, and the period of chronic hypertension. Finally, under conditions that differed only by a more severe constriction of the renal artery, leading to malignant hypertension, aldosterone secretions were greatly increased. Thus these experiments suggest that in benign hypertension, aldosterone, and presumably also renin, have a limited role, if any. This would also agree with some observations on renin content in kidneys and in renal venous blood, which was found to be normal in some animals with partial constriction of the renal artery. It may be that these animals had only benign hypertension. If the absence of hypersecretion of aldosterone and renin in benign hypertension were confirmed, this would clear the way for a more concentrated positive approach to the problem of hypertension.

In summary, the concept of renal-adrenal relationships formulated many years ago has been useful as a working hypothesis. Although its purpose was to explain a pathologic situation, further investigations proved that the interplay represents primarily a homeostatic mechanism for the regulation of blood pressure and sodium metabolism. Its value for the interpretation of pathogenic mechanisms in hypertension is not obvious, in spite of the demonstration that renin and aldosterone secretions are increased in malignant hypertension. The production of a syndrome of accelerated malignant hypertension by the administration of renin to aldosterone-treated rats fed salt, strongly suggests that renin and aldosterone may have a primary role in experimental and clinical malignant hypertension.

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