Contribution of the Adrenal Cortex to Renal and Renoprival Hypertension

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Association of the adrenal cortex with renal hypertension lead to the conclusion that several mechanisms are operating. First, hypertension is not, or is poorly, sustained in true adrenal failure, and mild failure seems to impair vascular responsiveness. This indicates a permissive function of the adrenal in renal hypertension. Furthermore, degrees of renal injury or of hypercorticosidism which are not of themselves very pressor may cause severe hypertension when they are added together. This additive aspect is probably closely related to the sensitizing effect of adrenal steroids on renal pressor activity and underlies the so-called renin-DCA syndrome. It may involve not only an enhanced pressor responsiveness but also a weakening of vessel walls. Lastly, the effects of renin and renal hypertension on the zona glomerulosa suggest that the renal pressor system has a direct effect on the adrenal cortex which would tend to add cortical pressor to existing renal pressor activity and thus sustain renal hypertension.

Repeated experiments have demonstrated that the adrenal cortex has an important role in the maintenance of renoprival as well as of renal hypertension. These experiments have studied the effect on hypertension of adrenalectomy with and without adequate substitution therapy, the influence of adrenal cortical insufficiency and of cortical hormones on the formation of renin substrate (hypertensinogen), the hypertensive vascular disease produced by excess adrenal steroids, the intense arteriolar necrosis produced by renin in animals pretreated with DCA, the effects of adrenal failure on vascular reactivity, and the influence of experimental renal hypertension and of renin on the morphology of the adrenal cortex. The variety of experimental situations in which an adrenal-renal interplay can be demonstrated suggests that these associations of renal and adrenal function in hypertension are probably multiple in their mechanisms. Accordingly we propose that these associations be grouped by their apparent mechanisms as permissive, additive, sensitizing, and reciprocal.

Permissive. That hypertension cannot be fully maintained in the face of inadequately treated adrenal failure was observed by Goldblatt1 and by Page2 in experiments with renal hypertensive dogs and by dell'Oro and Braun-Menéndez3 in rats; later Page and Lewis4 found that such hypertension could be maintained if adequate substitution therapy were given. The antihypertensive effect of hypophysectomy, described by Page and Sweet,5 was widely confirmed and, with availability of corticotrophin,6 shown to be dependent primarily on subtotal adrenal insufficiency. Insofar as severe adrenal insufficiency leads to a decrease in blood volume and cardiac output, it will, inevitably, reduce existing levels of arterial pressure. However, these gross hemodynamic changes do not explain the blood pressure falls that may occur in partial adrenal failure unassociated with hypotension or hemoconcentration. These latter observations suggest that the adrenal cortex may influence the formation of pressor substances and perhaps also diminish vascular responsiveness. The first of these suggestions finds support in the demonstration of Lewis and Goldblatt7 that renin substrate

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(hypertensinogen) formation is deficient in adrenal cortical failure and in Helmer's and Griffith's observation that DCA stimulates the formation of renin substrate in the rat. The second suggestion is borne out by the finding of Salmoiraghi and McCubbin that vascular reactivity is depressed in adrenalectomized dogs.

Thus, the permissive association of the adrenal cortex depends on the influence of cortical hormones on such gross functions as blood volume and cardiac output and on such less well-defined functions as vascular tone and responsiveness. Further, as concerns renal hypertension, the adrenal glands seem to influence the accumulation of pressor agents by their effect on the formation of renin substrate.

Additive. Some of the various technics for the production of experimental hypertension are effective because they combine procedures which, singly, are not sufficient to produce large increases in blood pressure. Thus, uninephrectomized, salt-fed rats show a slight hypertension; administration of DCA causes this to become severe. Uninephrectomy also increases the hypertension that follows adrenal enucleation. From another aspect, Knowlton et al. have reported that doses of DCA which were not pressor in normal rats produced marked hypertension in rats with nephrotoxic serum nephritis.

The association of renal and adrenal influence, here, seems to be additive in that severe hypertension depends on the concurrence of renal and adrenal changes which, in themselves, are only slightly hypertensive.

Sensitizing. Renin is, by definition, pressor, but in the usual short-term experiments does not cause vascular disease. However, if renin is given subcutaneously to rats with mild DCA-salt hypertension, it produces a syndrome resembling toxemia of pregnancy. This condition is characterized by oliguria, edema, intense hypertension, convulsions, hemorrhages, and acute, diffuse vascular and glomerular lesions. Pretreatment with cortisol, likewise sensitizes the rat to the effects of renin. In this instance, there are fewer hemorrhages although the vascular damage is somewhat more intense than with DCA. When hydrocortisone is used as the sensitizing steroid, renin does not cause edema—presumably because the urine flow is well maintained—but does cause lesions similar to those seen in animals given DCA or cortisone. That this is a specific effect of renin is shown by the fact that the DCA-renin syndrome can be reproduced in DCA-treated rats given angiotensin.

The mechanism of the acute vascular disease produced by renin in animals pretreated with adrenal steroids is not apparent; the hypertension, as such, may be an adequate explanation. In uninephrectomized rats maintained on water, single, subcutaneous injections of renin (14 dog units) cause only a slight, transient rise in blood pressure which appears by the first hour and practically disappears by the sixth hour. The uninephrectomized rats maintained on saline have a slightly higher basal blood pressure and show no greater response to the same dose of renin. However, if this same amount of renin is given to bilaterally nephrectomized rats there are large increases in blood pressure which are maximal by the second hour but have practically disappeared by the sixth. A greater degree of sensitization to renin is seen in the DCA-salt hypertensive rats, but in these animals the pressor response persists beyond the sixth hour and, in some, lasts for as long as 24 hours.

Thus, the acute vascular damage caused by renin in uninephrectomized DCA-pretreated rats may result wholly from an enhanced and prolonged increase of arterial pressure. It may be that other factors sensitize the blood vessels to damage. In this instance, steroids, by altering the composition of the vessel walls, may increase the damaging effects of increased arterial pressure.

Reciprocal. Up to this point we have drawn attention to the effects of hypo- or hypercorticism on renal and renoprival hypertension and on the effects of renin, but what of the effects of renal hypertension and renin on the adrenal cortex itself?
son explored this by studying the morphology of the adrenal cortex in rats given renin and in rats with perinephritic hypertension which were maintained on water. In both instances, they found an increase in the width of the zona glomerulosa that seemed to be proportional to the height of the blood pressure. This increase in width of the zona glomerulosa was found even when the rats with wrapped kidneys were maintained on saline. This bears particular mention since, in intact rats, sodium deprivation alone will cause an increase in glomerulosa width, and “sodium flooding” causes a narrowing of this zone. It may well be that the effect of renin and of renal hypertension on the zona glomerulosa reflects the degree of renal pressor activity. This adrenal morphologic change, associated with renal pressor activity, suggested a reciprocal relationship between the adrenal cortex and the kidney in renal hypertension. Renin released as the result of renal artery narrowing or perinephritis would act on the kidney to promote salt loss; renin also acts on the zona glomerulosa stimulating the secretion of DCA-like substances which would promote increased salt reabsorption and be, of themselves pressor. Such a system would result in normal plasma electrolytes and reciprocally sustained renal-adrenal hypertension.

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