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Effects of Dietary Sodium on Renin Content during Renal Hypertrophy in Uninephrectomized Rats[1] (38441)

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The relationship between renin and compensatory renal hypertrophy after unilateral nephrectomy has been studied by several investigators (1–3). It is generally agreed that injection of renin has no significant effect on compensatory hypertrophy at doses sufficient to cause an increase in heart weight (3). However, the doses used in such experiments were far above physiological levels; therefore, any physiological role that renin might play in the process of compensatory renal growth is questionable. The purpose of this experiment is to separate, if possible, the renal hypertrophy from renal renin synthesis and to prove that these two processes can be independent of each other or that the renin system, which may respond parallel with hypertrophy, may be specifically influenced to respond to another stimulus during the process of renal hypertrophy.

Method. One-hundred-and-five adult male rats of Sprague–Dawley strain, weighing approximately 250 g each were used in this experiment. They were divided into three groups: group 1 was fed with standard laboratory rat chow (General Biochem. TD 68503 Diet #2), group 2 was fed with sodium free diet (same as group 1, but without sodium), and group 3 was fed with high sodium diet (Na 3.3% by total weight with other compositions similar to the control diet). Distilled water was given *ad libitum*. Right nephrectomy of all animals was performed at 0 day (the day the rats were placed in their special diets), and five in each group were sacrificed on the 2nd, 4th, 7th, 10th, 20th, 30th and 50th postoperative day. The rats were anesthetized with ether, weighed, and the remaining left kidneys, both adrenal glands, thyroids and pituitaries were removed, trimmed properly and weighed. The kidneys were stored in −20°, then later homogenized for protein, enzyme and renin analyses. Since the enzymes alkaline phosphatase and glutamic pyruvic transaminase are not known to be specifically involved in the renin mechanism, their concentrations per gram of kidney protein were followed as a basis for comparison of changes in renin concentration during the period of renal hypertrophy in the uninephrectomized rats on the three dietary regimens. The analyses of total protein, alkaline phosphatase, and glutamic pyruvic transaminase (GPT) were performed according to Lowry (4), Kind and Armstrong (5) and Reitman and Frankel (6), respectively, by using a Technicon Autoanalyzer. Renal renin activity was assayed according to the method of Braverman *et al.* (7).

Results. The wet weight per gram of body weight of the remaining left kidneys increases in all three groups and reached a maximum between the 7th and 10th postoperative day (Fig. 1). This increase in weight was not due to an increase in water content, indicated by the rather constant protein concentration of the kidneys in all rats (Fig. 2). The absolute kidney weights (unlisted data) in group 1 (control diet) and in group 3 (high Na diet) were greater than that in group 2 (low Na diet) after 30 days postoperatively. However since the body weight was also greater in these two groups, the kidney weight per body ratios were not different in the three groups of animals used. In other words, varying sodium content in the diet did not have any effect on compensatory renal growth based on kidney weight per body weight ratio.

On the other hand, the renin activity in the hypertrophied kidneys of these three groups dif-

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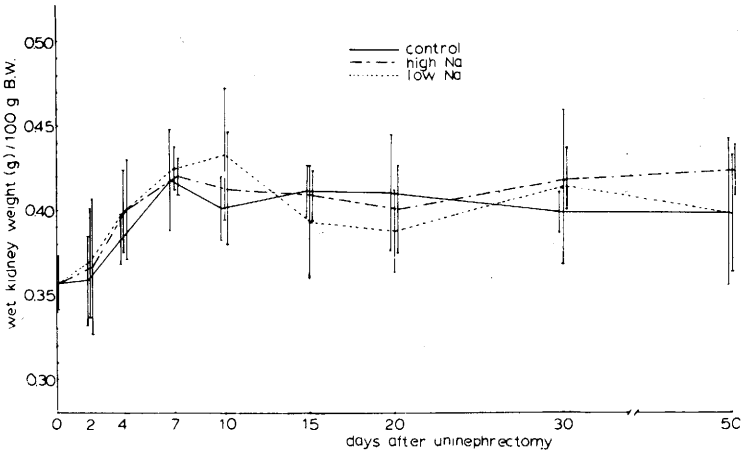

FIG. 1. Changes in the ratio, wet wt of left kidney per 100 g of body wt, following right unilateral nephrectomy at zero time. The rats were placed on a normal (control), high sodium or sodium-free diet on the day of nephrectomy. Five rats in each group were sacrificed following nephrectomy on the days indicated.

fered considerably (Fig. 3). The renal renin activity was significantly higher in the low Na diet group starting from the 7th day and remained high throughout the entire experimental period. The high Na diet group showed a lower renin activity than the control group after the 20th postoperative day. In fact by the 50th day renin activity/g protein appears to be inversely related to the dietary level of Na. The other two enzymes monitored, alkaline phosphatase and glutamic pyruvic transaminase, showed no significant difference among the different groups (Figs. 4 and 5).

The weights of the thyroid glands, pituitaries, and the adrenal glands were also recorded. The weights of the thyroids, as well as that of the pituitaries in all rats, showed no significant difference (unlisted data), while the adrenal glands of the low Na diet group were enlarged after the 30th postoperative day (Fig. 6).

Discussion. Virtually nothing is known about the mechanism by which renal hypertrophy is initiated following unilateral nephrectomy. Due to the complexity of the function and the heterogenicity of the cell types of the kidney, a simple work load hypothesis which has been applied to hypertrophic phenomena of other organs could not be successfully evaluated in the kidney by experimental methods. It is known that severence of one ureter (8, 9), implanting the ureter into gut (10) or peritoneum (11) to double the excretory load failed to induce the growth response in the kidneys. High urea diet was proved equally ineffective (12). One could argue the excretion is only 1% of all the work of the kidneys, and since the sodium ion is the main electrolyte that is actively transported and roughly 80% of the O_2 consumed by the kidney is believed to be used in electrolyte transport (13), it may be the sodium ion transport, not the

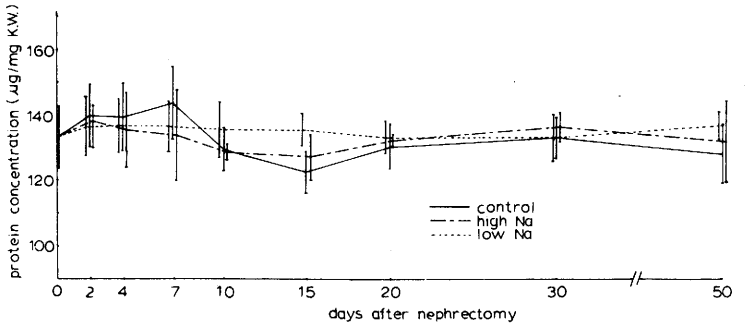

FIG. 2. Changes in renal protein concentration (μg/mg KW) in the left kidney in the rats treated as described in Fig. 1.

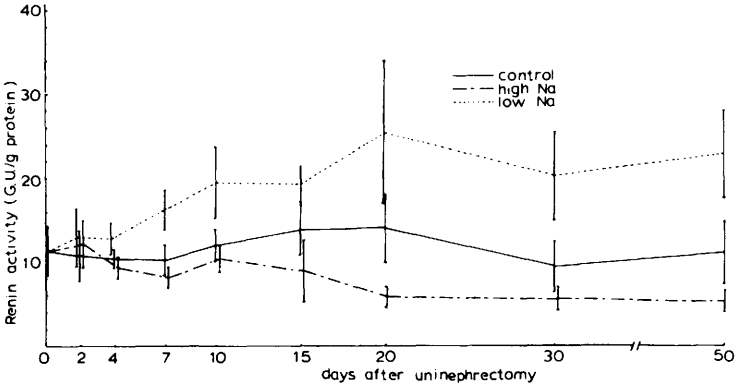

FIG. 3. Changes in renal renin content (GU/g protein) in the left kidney of the rats treated as described in Fig. 1.

excretory load, that determines the excessive work of the remaining kidney after uninephrectomy. However, high sodium diet has been shown to have no influence upon kidney growth, unless the sodium was given in drinking water (14, 15). This is also proved in the present experiment.

Besides being an excretory organ, the kidney also serves as an endocrine gland, secreting renin and erythropoietin. But unlike many other endocrine organs, the growth of the kidney is not affected by the feedback signals exerted on the controlling system by the final product of the gland. It is shown in the present experiment that renal renin activity can be separated from the process of renal hypertrophy. Presumably renin secretion keeps a parallel relationship to the renal activity in rats treated with various salt containing diets (16). Although hypertrophy of the kidney and renin synthesis must involve DNA and RNA processes, only those governing the latter appear to be specifically influenced in some unknown manner by dietary sodium. In other words, the renin system can be independently influenced during the occurrence of renal hypertrophy following uninephrectomy although renin activity, in the absence of a "separate" stimulus such as dietary sodium, does parallel the general hypertrophy.

Adrenalectomy has been shown to inhibit the compensatory renal growth provided that no high sodium diet or saline was given to the animal postoperatively (17). It was suggested that the adrenalectomy prevents compensatory renal growth by means of sodium depletion. The present experiment has ruled out this possibility, which is indicated by the lack of effect of sodium free diet on the process of renal hypertrophy (expressed as a ratio of renal weight/body weight). However in view of the increase in adrenal weights and the increase in renal renin content in the unilaterally nephrectomized rats

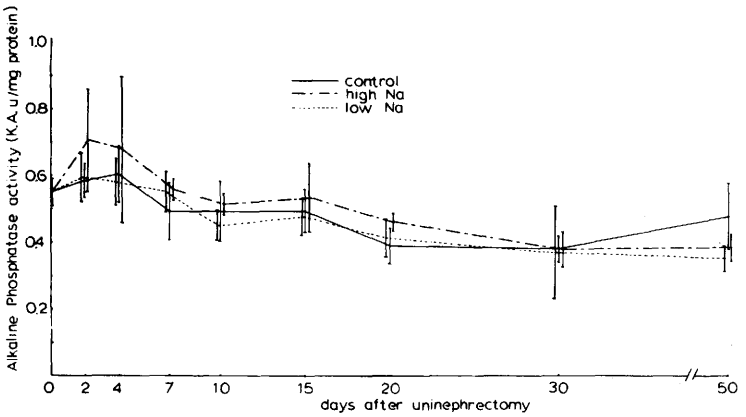

FIG. 4. Changes in renal alkaline phosphatase activity (KA μm/mg protein) in the rats treated as described in Fig. 1.

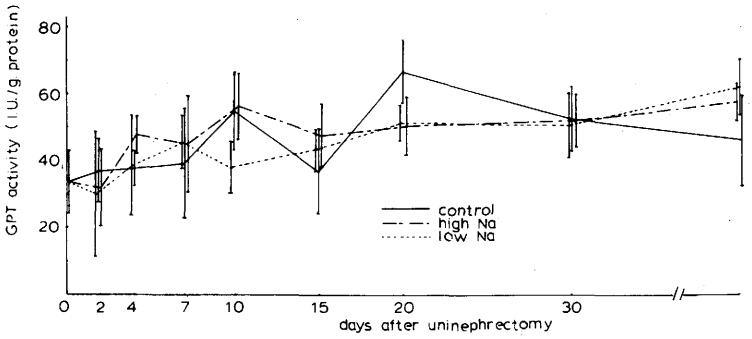

FIG. 5. Changes in renal glutamic pyruvic transaminase (GPT) activity (IU/g protein) in the rats treated as described in Fig. 1.

maintained on a sodium free diet, the possibility exists that the adrenal hypertrophy was in part related to the rise in renal renin content. Although plasma renin concentrations were not measured, it is probable there was a higher plasma renin level due to a greater renin release from the higher renin content of the kidney in the uninephrectomized rats maintained on a low sodium diet. This could, in part, account for the observed adrenal hypertrophy in this group. Indeed a cursory examination of the hypertrophic adrenals did apparently indicated a widening of the zona glomerulosa.

Summary. The effects of dietary sodium levels on renal hypertrophy following unilateral nephrectomy and on renal renin content of the hypertrophic kidney were investigated in the rat. Renal hypertrophy occurred at the same rate in rats on all sodium diets when expressed in g kidney weight/100 g body weight. However, renal renin content of the hypertrophic kidneys was inversely related to the dietary sodium chloride intake by the 7th day following unilateral nephrectomy and the beginning of the dietary regimen. It is suggested that although renin content increases as hypertrophy occurs in the normal animal, it plays no role in hypertrophy, but is subject to a separate control, on some unknown manner, via dietary intake of sodium chloride. This control occurs even in the presence of the general stimulus for renal hypertrophy in the uninephrectomized animal. The increase in renal renin probably affected the adrenal cortex which was hypertrophic in the uni-

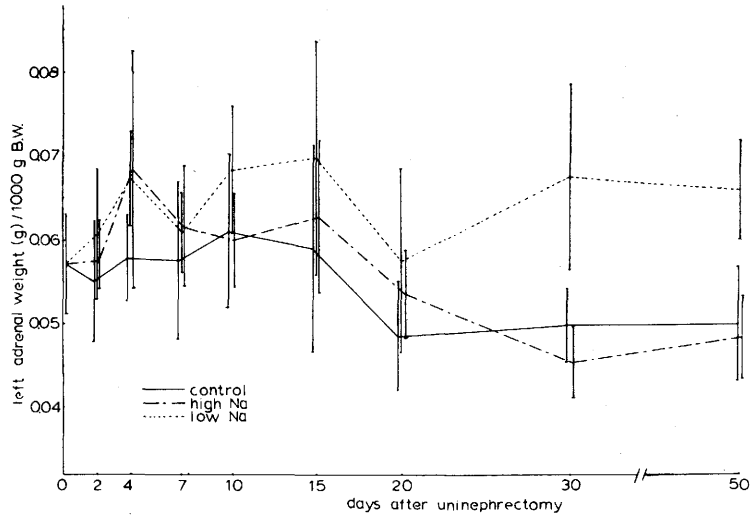

FIG. 6. Changes in left adrenal weight (g/100 g BW) in the rats treated as described in Fig. 1.

nephrectomized animals on a low sodium diet.

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