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RENAL FUNCTION IMMEDIATELY AFTER CONTRALATERAL NEPHRECTOMY: RELATION TO THE MECHANISM OF COMPENSATORY KIDNEY GROWTH**

After one kidney is removed, its mate enlarges and gradually increases in function to approach the combined capacity of both kidneys prior to nephrectomy. To date, substantial information on the chemical and morphological changes that follow reduction of renal mass has been accumulated.[1-5] By contrast, the nature of the mechanisms that initiate and sustain compensatory kidney growth remains unknown. Two hypotheses are usually invoked to explain this phenomenon. The first, for which there is growing supporting evidence, attributes the compensatory growth of the kidneys to changes in the concentration of an organ-specific humoral substance that controls renal mass.[6-10] According to the alternative theory, enlargement of the remaining kidney is due to the increased work load the smaller renal mass is now called upon to perform.[11-13]

Since the major part of renal energy expenditure is invested in the reabsorption of sodium from the glomerular filtrate, the role of the renal work load in compensatory kidney hypertrophy can be tested by evaluating the relationship between sodium reabsorption and growth of the remaining kidney after partial nephrectomy. Previously, we found no correlation between changes in tubular reabsorption of sodium and kidney weight between 24 hours and 21 days after unilateral nephrectomy in the rat.[14] These results, and in particular the observation that the increase in kidney mass preceded the rise in sodium reabsorption, suggested that enhanced reabsorptive work load was not the primary cause of the observed kidney growth in the time-interval studied. However, the earliest phase of compensatory hypertrophy was not included in these experiments.

Increased renal RNA and protein synthesis begin within hours,[1,2] and fine structural changes at the subcellular level may be detected in the remaining kidney as early as 15 minutes after nephrectomy.[5] In order to evaluate the possible role of altered sodium reabsorption in causing these early changes of compensatory kidney growth, the present report extends our observations to the first hours following unilateral nephrectomy. The results indicate that the renal handling of sodium does not change during this period and there-

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fore do not support the concept that an early increase in reabsorptive work load is the initiating event of compensatory kidney growth.

METHODS

Male albino Sprague-Dawley rats (Charles River C.D.®) had free access to Purina rat chow and water until surgery. Rats weighing 182-430 g. were anesthetized with Inactin, 100-120 mg/kg. intraperitoneally, a tracheostomy was performed, the bladder and a jugular vein were cannulated with polyethylene PE 50 tubing and the animals placed on a heated board. Rectal temperature, monitored by a thermocouple (Tele-Thermometer, Yellow Springs Instrument Co., Yellow Springs, Ohio), was maintained between 36° and 38°C. throughout the experiments. During surgery, isotonic saline equal to 0.5-1 percent of the body weight was infused intravenously in amounts calculated to replace estimated surgical losses.

Glomerular filtration rate (GFR) was calculated from the clearance of inulin. Following a priming dose of 15-20 mg., a sustaining infusion of inulin in isotonic saline was administered at the rate of 1.25 ml./hour with a Harvard constant infusion pump (Model 975) to maintain plasma inulin levels between 50-100 mg/100 ml. After an equilibration period of 60 minutes, urine was collected under mineral oil and the volume measured with calibrated glass micropipettes. Blood from the cut end of the tail was collected in capillary tubes at the beginning and end of each collection period and plasma concentrations calculated as the average of the two determinations. At the end of three consecutive 30-minute collection periods, the left or the right kidney, alternately,* was removed through a midline incision, after ligating the renal pedicle close to the hilus. After another 60-minute period, in which the animals were allowed to return to a steady-state condition, urine and blood were obtained as described above for four consecutive 30-minute collection periods before the experiment was terminated. Results from the three collection periods preceding nephrectomy calculated for one kidney were averaged and compared to the average of the four collection periods following nephrectomy. Inulin was determined by a modification of the anthrone method[16] and sodium by flame photometry with lithium as internal standard. All determinations were carried out in duplicate. The kidneys were blotted on filter paper and weighed on a Mettler analytical balance immediately (wet weight) and after desiccation for 48 hours at 105°C. (dry weight). Since both the control and post-nephrectomy determinations were done in the same animal, they were not corrected for body weight. Statistical significance was assessed by analysis of paired differences with standard methods.

RESULTS

Results are summarized in Table 1. Dry and wet kidney weight remained unchanged three hours after removal of the contralateral organ. Dry weight was not expected to change within this time interval, since in the rat only a minute increase in dry kidney mass of approximately 3% is found after

* Since in rodents the two kidneys are unequal in size[8,5] and perhaps in function,[15] the possibility of introducing fortuitous bias was avoided by alternating the nephrectomy side. This procedure also justifies calculation of kidney function prior to nephrectomy as one-half of the combined value for both kidneys during this period.

TABLE 1. THE SHORT-TERM EFFECT OF UNINEPHRECTOMY ON KIDNEY WEIGHT, GFR, URINE VOLUME, AND RENAL HANDLING OF SODIUM IN THE REMAINING KIDNEY

	Kidney weight (Wet) (mg.)		*Kidney weight (Dry) (mg.)*		*GFR (ml/min.)*		*Tubular sodium reabsorption a. Net (μEq/min.)*		*b. Fractional (% of filtered load)*		*Urine volume (μl/min.)*		*Urine sodium excretion (mμEq/min.)*	
	*B**	*A***	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*
a. Young animals (182-216 g. body weight) (n = 10)														
Mean	775.8	777.6	177.8	174.3	0.88	0.89	128.8	129.9	99.80	99.86	2.8	2.7	220	189
±SE	±24.7	±25.9	±5.2	±5.2	±0.03	±0.04	±4.4	±6.4	±0.03	±0.04	±0.3	±0.3	±42	±74
P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	
b. Adult animals (268-430 g. body weight) (n = 14)														
Mean	1196.8	1201.0	277.4	274.0	1.54	1.55	232.4	235.3	99.70	99.76	7.7	4.2	720	560
±SE	±62.2	±64.9	±12.9	±14.8	±0.09	±0.10	±14.6	±15.5	±0.07	±0.05	±1.8	±0.2	±161	±129
P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	
c. All animals (n = 24)														
Mean	962.9	965.8	222.1	218.6	1.27	1.28	189.3	191.4	99.74	99.80	5.7	3.6	512	406
±SE	±58.9	±60.0	±13.5	±13.9	±0.09	±0.09	±14.0	±14.6	±0.05	±0.04	±1.2	±0.2	±109	±90
P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

* B = before nephrectomy; values calculated for one kidney.

** A = after nephrectomy.

24 hours,[8] and in the experience of others, the first detectable increase in kidney weight occurs only 30-36 hours after uninephrectomy.[17] The absence of wet weight change, coupled with the unchanged gross appearance of the kidneys, indicates that the early, transitory engorgement occasionally seen after nephrectomy in some species,[8] did not occur in these experiments.

There was a slight decrease in urine volume and sodium excretion following nephrectomy, which was not statistically significant. Glomerular filtration rate, plasma sodium and tubular reabsorption of sodium by the remaining kidney did not change during the first hours after removal of its mate. Since the results were identical in young (182-216 g. body weight) and adult (268-430 g. body weight) animals, the absence of renal functional changes was not due to decreased compensatory ability caused by advanced age.[17,18]

DISCUSSION

The concept that increased renal work underlies the phenomenon of compensatory kidney growth, first proposed in the latter part of the nineteenth century,[19] was derived largely from studies showing accelerated kidney growth of both intact and uninephrectomized animals when fed diets rich in protein and urea.[20,21] Proponents of the "work hypertrophy" theory attributed compensatory kidney growth to the increased excretory loads of urea and other solutes placed on the reduced renal mass after partial nephrectomy, and made the assumption that the size of the kidney is determined by the amount of material it has to excrete.[11-13,22,23] The "work hypertrophy" theory, based on the misconception that excretion of nitrogenous end-products of metabolism requires work, is obviously incongruous with modern renal physiology. However, even separated from the concept of work, the role of the augmented excretory load in compensatory kidney hypertrophy is not substantiated by more recent studies which cast considerable doubt on the validity of its supportive evidence.[8,24-26]

Since the major component of renal energy expenditure is invested in the reabsorption of sodium from the glomerular filtrate,[27] a more rational approach to elucidate the role played by increased renal work in compensatory kidney growth is to evaluate the relation between tubular sodium reabsorption and kidney mass after partial nephrectomy. Bugge-Asperheim and Kiil[26] found increased GFR and tubular sodium reabsorption in dogs 5-30 days after either unilateral ureteroperitoneostomy or nephrectomy, whereas mitotic activity increased only in the remaining kidney of nephrectomized animals. Since ureteroperitoneostomy produced large changes in sodium reabsorption without effect on kidney growth, these authors concluded that

demands for increased oxidative metabolism were not important stimuli to hypertrophy and hyperplasia, and that renal growth is related only to the number of functioning nephrons. In a previous study,[14] we found no correlation between changes in tubular reabsorption of sodium and kidney mass between 24 hours and 21 days after uninephrectomy in the rat, and concluded that during this period increased reabsorptive work load was not the primary cause of the observed kidney growth. However, the possible role of altered tubular sodium reabsorption in compensatory kidney growth could not be fully evaluated in these experiments since they did not cover the earliest phases of this phenomenon.

Structural and biochemical changes of compensatory kidney growth occur promptly after removal of the contralateral organ. Protein synthesis by the remaining kidney increases within 3 hours, and augmented RNA synthesis, detectable as soon as one hour after nephrectomy, is fully developed by 24 hours.[1,20] Ribonuclease activity of rat kidney homogenates is significantly increased 4 hours after nephrectomy.[20] Presumably associated with the early changes in RNA metabolism, an increase in free ribosomes was found 15 minutes after contralateral nephrectomy in the mouse,[5] and within 6 hours in the rat.[21] Whatever the events initiating compensatory kidney growth, they obviously operate soon after renal mass is reduced. In the present study, we tested the hypothesis that an early increase in reabsorptive work load might trigger renal growth by measuring net tubular reabsorption of sodium immediately before and after unilateral nephrectomy in the same animals.

Glomerular filtration rate and net tubular reabsorption of sodium by the remaining kidney were the same during the 3 hours following nephrectomy, as in the 1½ hours preceding it. Sodium reabsorption in each of the four collection periods after nephrectomy was not significantly different from the prenephrectomy values calculated for one kidney (Fig. 1). It is doubtful that anesthesia or surgery influenced these results substantially, since our mean inulin clearance was 146% of that measured by Kleinman, *et al.*[22] and 90% of that found by Peters[23] in unanesthetized animals. Furthermore, in rats receiving identical doses of the same anesthetic employed by us, Barenberg and associates found no significant change in GFR and sodium reabsorption for up to 510 minutes after its administration.[24] The extent of the surgical procedures and the volume of isotonic saline infused in these experiments[24] were also very similar to ours. Progressive dehydration could not have influenced our results since the maintenance infusion of 1.25 ml/hr. amply exceeded the sum of the urine volume (*ca.* 300 μl/hr.) and the blood drawn for chemical analyses (*ca.* 500 μl/hr.). While the anesthesia em-

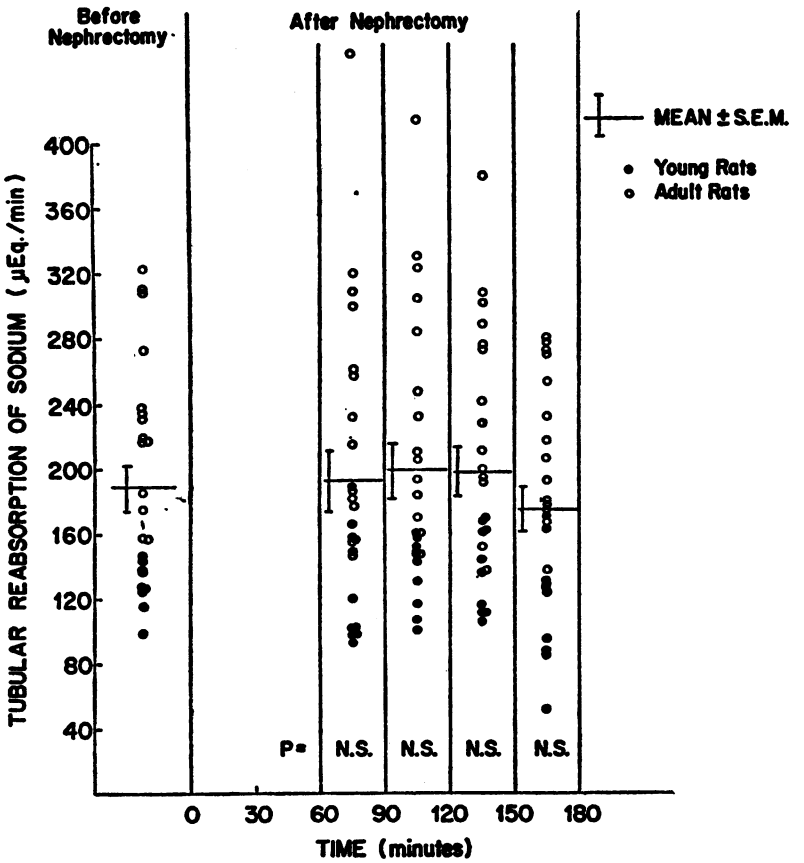

FIG. 1. Absolute tubular reabsorption of sodium before and after unilateral nephrectomy. Points represent individual animals.

ployed in these experiments does not appear to have influenced renal function, its possible effect on the early chemical and morphological changes of compensatory growth—usually observed in animals briefly anesthetized with ether—cannot be ruled out. Although there is no obvious reason to believe that more prolonged anesthesia would interfere with its expression, it should be emphasized that the occurrence of compensatory kidney growth under these experimental conditions has not been established.

Information on renal function immediately after nephrectomy is sparse and inconclusive. No change in GFR and sodium reabsorption is apparent two hours after nephrectomy in the rabbit.[35] In the dog, GFR decreases[36] or remains unchanged[37] immediately after one kidney is removed or its blood

supply interrupted. In the unanesthetized rat, Peters found no change in GFR of the remaining kidney within the first 18 hours after removal of its partner.[38] On the other hand, Potter and colleagues noted a mean increase of approximately 10% in GFR and tubular reabsorption of sodium in the first 2½ hours after nephrectomy in the rat, and suggested that this early change is the initiating event of compensatory kidney hypertrophy.[38] In a separate communication,[39] the same authors found no significant change in GFR 4 and 5 hours after uninephrectomy, while tubular sodium reabsorption increased slightly after 5 hours. Fractional sodium reabsorption after nephrectomy increased in one study[39] and decreased in the other.[38] Since both latter studies have been published in abstract form and details of the experimental protocols are not available, the cause of the apparent discrepancy between them is not clear. For the same reason it is difficult to explain the difference between the results reported therein and those presented in this paper. The average fractional sodium reabsorption of 97.8% found in one of these studies[38] is unusually low for the antidiuretic rat, and suggests that differences in the volume of fluid infused during the experiments may be involved.

Despite intensive investigation for nearly a century, the mechanism responsible for compensatory kidney growth remains unknown. The results of this study, coupled with the previously reported[14] lack of temporal correlation between changes in tubular sodium reabsorption and kidney weight later after nephrectomy, suggest that increased reabsorptive sodium load is neither the initiating, nor the primary controlling factor of the compensatory growth of the kidney that follows unilateral nephrectomy in the rat.

SUMMARY

Chemical and morphological correlates of compensatory kidney growth begin shortly after renal mass is reduced by partial nephrectomy. In order to evaluate the possible role of increased reabsorptive work load in initiating the early changes of compensatory kidney growth, renal function was examined before and for 3 hours after unilateral nephrectomy in the rat. Absolute tubular sodium reabsorption after nephrectomy was not significantly different from the value measured in one kidney of the same animals in the period immediately preceding it. Likewise, glomerular filtration rate, urine volume, urine sodium excretion and fractional tubular sodium reabsorption did not change after contralateral nephrectomy. The same results were obtained in young (182-216 gram) and adult (268-430 gram) animals. The results of this study, coupled with the previously reported lack of temporal correlation between changes in tubular sodium reabsorption and kidney

weight later after nephrectomy, suggest that increased reabsorptive work load is neither the initiating, nor the primary controlling factor of the compensatory growth of the kidney that follows unilateral nephrectomy in the rat.

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