Augmented Vascular Response of the Nephrectomized Rat to Angiotensin (36819)

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It has been shown that nephrectomized animals, in general, are more reactive to angiotensin and renin than are control animals (1, 2). Potentiation of the responses has been noted not to appear until some hours postnephrectomy (3–5). Also, lower base line blood pressures have been noted in nephrectomized rats some hours postnephrectomy (5).

Pressor responses in dogs have been shown to be somewhat related to serum K levels. For instance, insulin administration to lower serum K in normal dogs decreased pressor responsiveness. The insulin effects were reversed by KCl administration. A corollary was the finding that hypokalemia induced by peritoneal dialysis in a nephrectomized dog decreased vascular responsiveness to pressors. Nephrectomized dogs with hyperkalemia showed increased responsiveness to pressors (6).

In view of the above findings, studies were undertaken to determine if there was any correlation between pressor responsiveness and serum K changes in bilaterally ureterally ligated or nephrectomized rats at a time postoperatively when the experimental groups showed increased sensitivity to intravenous angiotensin injections.

Method. The rats used for the following experiments were males and weighed 280–380 g. The rats were designated as follows: M = mock operated, N = bilateral nephrectomy and UL = bilateral ureteral ligation. All operations were carried out using ether anesthesia. The mock operation consisted of exposing both kidneys by retroperitoneal incisions followed by appropriate suturing. In addition, some M rats were etherized but not operated. All animals were kept fasting after the operative procedures until the time of the sensitivity experiments or until measurement of serum Na and K.

At the time of the sensitivity experiments (2–20 hr postoperatively), the rats were anesthetized with Nembutal (33 mg/kg). The blood pressure was obtained from the carotid artery via pressure transducer recording on a Grass polygraph. The jugular vein was used for the site of injections. The injections consisted of saline followed by different doses of angiotensin II followed again by injections of saline. The peak pressure responses were measured. The responses to saline injection alone, if any, were then subtracted from the responses to angiotensin II.

The plasma ion studies were carried out separately from the sensitivity studies on different groups of animals but the operative manipulations were the same as those used for the rats in the sensitivity experiments. There were 5 rats used in each group at different hours postoperatively. Plasma Na and K were measured by standard flame photometry techniques.

The angiotensins used in these experiments were: (a) naturally occurring hog angiotensin II,[1] and (b) synthetic angiotensin II amide (5-valyl aspartyl amide angiotensin II) purchased from Ciba.

Results. The characteristic response to iv injections of angiotensin II is a sharp rise in systemic arterial pressure. Pressure begins to rise within 15–25 sec and reaches a peak in 1–2 min; 3–5 min later it returns approximately to the initial base line level. Experimental groups showed both an increase in the peak pressure as well as an increase in the

[1] Kindly supplied by Dr. O. M. Helmer, I.U.M.C., Indianapolis, IN.

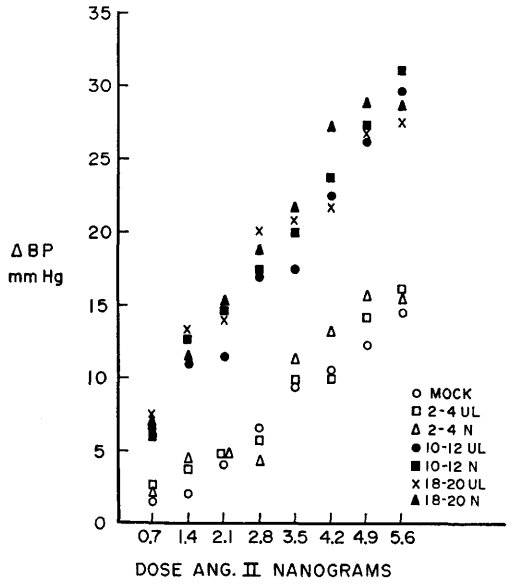

FIG. 1. A comparison of the mean blood pressure responses to iv injection of angiotensin in two groups of rats. The open symbols represent mean data from mock operated rats injected from 0 to 20 hr postoperatively (PO), and ureteral ligated (UL) and nephrectomized (N) injected between 2 and 4 hr PO. The solid symbols represent data for UL and N rats injected with angiotensin between 10 and 20 hr PO. Analysis of the regressions give r values of .96 and .98 with slopes of 2.9 and 4.2, respectively.

duration of pressor response when compared to the control animals.

It was found that M rats showed about the same responsiveness to angiotensin II regardless of the times post-mock operation. Therefore, the averages for this group are from the 2–20 hr period inclusive. There were 6–10 rats in each series and each dosage of angiotensin II was tested 1–2 times/rat. Average response was determined, therefore, from the total numbers of injections.

The dose of angiotensin II versus change in blood pressure (mm Hg) is shown in Fig. 1. It can be seen that the N and UL rats at both 18–20 and 10–12 hr postoperatively showed about the same increased sensitivity to angiotensin ($p > .5$). When compared to the 2–4 hr N and UL rats or to the M group of rats, the 18–20 and 10–12 hr UL and N were collectively significantly different ($p < .01$).

The serum Na and K changes occurring in the various groups at different times postoperatively are displayed as bar graphs (Fig. 2) as a percentage of the control with the control (M) regarded as 100%. The serum Na tends to decrease and the serum K does indeed increase in the UL and N rats with an overall maximum decrease in serum Na/K at least by 10–12 hr postoperative. The Na/K at 2–4 hr in the N and UL rats approached 100% of control. The same statistical significance applies to the K and Na/K data as to the blood pressure response above.

Finally, the base line blood pressures in the experimental groups are shown in Table I. The findings are consistent with the observation of others in that the base line blood pressure tends to be lower ($p = .01$) in the experimental groups of animals some hours postoperatively in comparison with M and 2–4 hr UL and N groups.

These data indicate that at the time the UL and N groups exhibit increased sensitivity to angiotensin injections there is a significant decrease in the Na/K in the serum with most of the change occurring in the serum K.

Discussion. Bilateral nephrectomy augments the vascular response to both angiotensin and renin. The mechanism for this response remains debatable. Studies in rats suggest that persistence of angiotensin in the blood of nephrectomized animals, involvement of the neurogenic buffer system, changes of blood viscosity and hematocrit values, and the increase in cardiac output

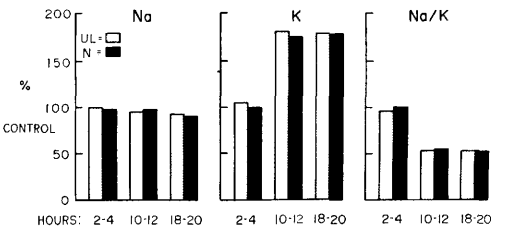

FIG. 2. A comparison of the percent change in the plasma concentrations of Na, K and in the Na/K ratio in rats at different postoperative times following ureteral ligation (UL) or nephrectomy (N). The real values at 100% are [Na] = 142.1 ± 1.5 mEq/liter [K] = 4.2 ± 0.1 mEq/liter and [Na]/[K] = 31.7 ± 1.9.

TABLE I. Base Line Blood Pressures at Different Times Postoperatively.

Group	0–20	2–4	10–12	18–20
M	137 ± 3.6			
UL		127.4 ± 5.9	106.3 ± 5.1	106.3 ± 7.6
N		125.2 ± 7.3	97.6 ± 6.2	101.2 ± 4.5

probably are not involved. A reduction in total peripheral resistance (lower base line blood pressure) as well as a general change in vascular responsiveness seems likely and has been suggested (5). Also, any explanation of this change must take into account the time interval between nephrectomy and the development of increased responsiveness to angiotensin. This required time interval observed by us has been noted, likewise, by other workers (4).

Electrolyte changes have been observed to affect vascular reactivity. Krieger and Hamilton (6) found that a decrease in serum potassium in a peritoneally dialyzed, bilaterally nephrectomized dog decreased the pressor responses to epinephrine, norepinephrine, and angiotensin. Also lowering of the serum K resulted in an increased resting blood pressure due to an increase in peripheral resistance despite a reduction in cardiac output in normal dogs. These investigators suggested that the increased K in the renoprival state might be causally related to the increase in reactivity to pressor substances (6).

Friedman and Friedman (7) found that infusion of a small amount of K, sufficient to raise the plasma level only a few milliequivalents per liter, produced a generalized fall in peripheral vascular resistance. Emanuel, Scott and Haddy, (8) found that (a) infusion of K into the arterial supply of dog forelimb, kidney, heart muscle or ileum, raising K by about 4–8 mEq/liter, reduced resistance to flow by inducing active vasodilatation, (b) a reduction of K concentration to about 2 mEq/liter may produce active vasoconstriction, and finally, Burks, Spalding and Jones (9) have presented evidence that arterial tissue may be hyperresponsive to pressor stimuli if the artery contains relatively minimal levels of K and an excess of Na in its cellular phase.

Ionic shifts have also been noted during the action of some pressors. For example, the contractile response to angiotensin is characterized by a shift of Na into the cellular phase. A converse movement of K (10) seems to be associated.

The data presented here are in accord with many of the above findings. The Na/K changes in the experimental groups of rats at different times postoperatively would help explain (a) the time lapse between bilateral nephrectomy or ureteral ligation and the development of increased sensitivity to angiotensin injections, (b) the lower base line blood pressures noted in the UL and N groups of rats at both 10–12 and 18–20 hr postoperatively. It should be noted that hydrogen ion would change in these groups as well and the effect of this is unknown in the present studies.

In the absence of renal function over a period of hours postoperatively in rats, it appears that Na moves from the extracellular phase to the intracellular phase while K moves conversely in some tissues. Angiotensin, in inducing its constrictive action on blood vessels, apparently tends to shift these ions in like manner. It is suggested that this ionic situation preexisting in the experimental animals may increase the response to angiotensin while at the same time accounting for the lower base line blood pressure. The presence of renal tissue (ureterally ligated animals) does not negate this response since the Na/K changes and the increased sensitivity paralleled each other in both the N and UL groups 10–12 and 18–20 hr postoperatively.

Summary. An increased response to iv angiotensin occurs in rats from 10 to 20 hr after ureteral ligations or nephrectomy. During this time there is also a rise in plasma K and a marked fall in Na/K ratio. It is suggested

that the vascular bed is more sensitive to the action of angiotensin when the ionic shift has taken place in the plasma.

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