Renal Inhibition of Pressor Responses to Drugs

By J. W. McCubbin and Irvine H. Page

Bilateral nephrectomy selectively augments reactivity to pressor drugs and affects that to angiotensin the most prominently. This change is not mediated through the central nervous system, does not depend upon mechanical exclusion of the renal vascular bed, and is not modified by change in sodium intake. The inhibitory action on pressor responsiveness is independent of renal excretory function.

FIFTY-FIVE years ago Tigerstedt and Bergman found the pressor response to intravenously injected renin increased after bilateral nephrectomy; more recently, Page and Helmer showed similar augmentation of response to injection of angiotensin, the reaction product of renin and substrate.

Consistent with an apparent inhibitory influence of functioning renal tissue on responses to injected renin and angiotensin are studies which show that presence of normal kidney tissue reduces the severity of experimental renal hypertension and protects against the acute vascular lesions elicited by injection of renin-containing kidney extracts.

The nature and mechanism of action of this renal inhibitory or protective influence are not known. It is known, however, that certain kidney extracts are effective in the treatment of experimental renal and clinical essential hypertension; the efficacy of these extracts might depend upon the presence in them of a substance inhibitory to renin and angiotensin.

Should such a substance occur in nature, its identification and preparation would be of clinical importance. But before confidently postulating its existence and again undertaking a search for it, it is prudent to determine whether or not the renal inhibitory and/or protective influence depends upon other identifiable mechanisms, to characterize its action further, and to determine its relationship to excretory renal function. These were the purposes of this study.

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Methods

Normal adult mongrel dogs were anesthetized with intravenous sodium pentobarbital (30 mg. per kilogram). Arterial pressure was recorded from a cannulated femoral artery by a mercury manometer. Test drugs were given through a needle inserted into a femoral vein in the following order and dosage: angiotensin (amount eliciting an average response of 10 mm. Hg in 10 normal pentobarbitalized dogs); noradrenaline (0.01 mg.); serotonin creatinine sulfate (0.06 or 0.12 mg. of 5-hydroxytryptamine); tryptamine (1 to 4 mg.); barium chloride (5 mg.); Pitressin (0.25 U.); renin (amount eliciting an average response of 17 mm. Hg in 10 normal pentobarbitalized dogs).

Surgical procedures were sterile and penicillin was used prophylactically. One stage bilateral nephrectomy was done through flank incisions. To drain the ureter into the vena cava, the abdomen was entered in a lower quadrant and the ureter sectioned between ties near its entrance into the bladder. The central end was cannulated with small polyvinyl tubing and the other end of the tubing was passed through a nick in the external iliac vein and then well into the vena cava. A tie was placed around the external iliac vein and tubing to prevent bleeding and to secure the position of the catheter; despite complete occlusion of the vein, no edema of the legs or venous congestion was noted. Care was taken to prevent kinking of ureter and polyvinyl tubing.

Results

Effect of Nephrectomy on Pressor Responses in Normal Dogs (fig. 1). Pressor responses to angiotensin and renin were increased 48 hours after nephrectomy in all experiments; the average reaction to both agents was slightly more than doubled. Noradrenaline usually gave greater rises in pressure after nephrectomy, but this was not invariably; the increase, when it occurred, was commonly less than with angiotensin or renin. Tryptamine and serotonin were
usually more pressor, but the increase was not comparable with that to angiotonin and renin. Responses to Pitressin increased irregularly, those to barium chloride decreased after nephrectomy in five of six experiments.

Pressor reactivity was increased more at 48 than at 24 hours after nephrectomy, but diminished somewhat at 72 hours, possibly due to deterioration of the dog's general condition.

To determine whether the effect of nephrectomy is simply mechanical, responsiveness was measured immediately before and after exclusion of the renal circulation. Arterial pressure rises to angiotonin, noradrenaline, barium, tryptamine and renin were all unchanged. As the experiments were continued, slight but definite increase in response to angiotonin was observed after four and one-half hours in one experiment, but they were commonly still unchanged after six or eight hours.

*Effect of Sodium Intake on Change in Pressor Responses after Nephrectomy* (fig. 2). To determine whether increased sodium intake before and after nephrectomy would modify the change in pressor reactivity, one group of eight dogs was offered salt-free bread and tap-water for 48 hours before operation; another group of 11 dogs was placed on salt-free bread, but 0.9 per cent saline was substituted for tap-water. Animals in the first group were given 50 ml. per kilogram of 5 per cent glucose in water intravenously the day of and the day after nephrectomy; animals in the second group were given 50 ml. per kilogram of 0.9 per cent saline instead. After nephrectomy neither group received anything by mouth.

Change in pressor responsiveness was essentially the same in the two groups 48 hours after nephrectomy; reactivity to angiotonin and renin was slightly more than doubled, as in dogs on the usual kennel diet. Noradrenaline more consistently caused greater rises in pressure in both groups of dogs given fluid by infusion after nephrectomy than in the control group, but the magnitude of the increased response, when it occurred, was not greater. There was no significant difference between change in reaction to noradrenaline in the group given glucose in water and the group given saline. The hypotensive action of tetraethyl ammonium chloride (TEAC 2.5 mg. per kilogram) was diminished in both groups.

Animals given saline by vein after nephrectomy showed slight gain in weight more often than those given glucose in water, but, in most experiments, body weight was substantially unchanged 48 hours after nephrectomy.

*Effect of Prior Cord Transection on Change in Pressor Responsiveness after Nephrectomy* (fig. 3). Twenty-four hours after section of the spinal
cord at C-6, arterial pressures had recovered
to levels ranging from 80 to 100 mm. Hg, and
the dogs ate and drank with assistance. They
were tested at this time under very light pento-
barbital anesthesia. Atropine (0.05 or 0.2 mg.
per kilogram) was given to abolish the in-
creased cardio-inhibitory reflexes that appear
after section of the spinal cord, since they tend
to mask the action of pressor drugs. The ac-
tions of angiotonin, renin, Pitressin and barium
showed moderate increase and that of nor-
adrenaline a great increase over normal. Ne-
phrectomy was done immediately after testing;
during the next 48 hours the dogs were offered
food and water several times daily and in three
of four experiments were given one infusion of
25 ml. per kilogram of 5 per cent glucose in
normal saline. Responsiveness was measured
48 hours after nephrectomy and after adminis-
tration of the same amounts of atropine and
anesthetic as during the respective control tests. Although cord section as such had already enhanced responses, nephrectomy further augmented those to renin, angiotonin, noradrenaline and Pitressin, while that to barium was not changed significantly (fig. 4).

**Effect of Ligation of the Ureters on Pressor Responsiveness.** Ligation of both ureters was substituted for nephrectomy in five experiments. Forty-eight hours later, the pressor effect of drugs was modified similarly, and often to the same extent as by nephrectomy. Gross examination of the kidneys revealed extreme damage from hydrenephrosis and large venous infarcts. Unfortunately, the experiment was not clear-cut: the animals were neither nephrectomized nor had they normal kidney tissue; they were sick, did not eat and drink freely and vomited often.

**Effect on Pressor Responsiveness of Unilateral Nephrectomy and Transplantation of the Opposite Ureter into the Vena Cava** (fig. 3). Control measurements were made two or more weeks after unilateral nephrectomy, and retesting was done 48 hours after the opposite ureter was made to drain into the vena cava. Comparison with figure 1 shows the striking difference between the effect of this procedure and of bilateral nephrectomy. Responses to angiotonin, renin, noradrenaline, Pitressin and barium were all substantially unchanged after ureter transplant, though renal excretory function was abolished as completely as by nephrectomy.

In three experiments, a clot formed in the catheter draining the ureter, and hydrenephrosis developed. Responses were increased in these dogs as after ligation of the ureters; the data are not included in figure 3. In the others, slight dilation of the ureters and slight hydrenephrosis sometimes appeared but no other abnormality was observed. These animals, like the nephrectomized groups, appeared in good condition during the 48 hour course of the experiments. Kidney tissue was examined microscopically through the courtesy of Dr. J. B. Hazard of the Cleveland Clinic, and sometimes revealed slight dilation of the tubules but, in most cases, no pathologic change was found.

**DISCUSSION**

The data show that presence of normal kidney tissue inhibits pressor responsiveness and that this inhibitory influence is independent of excretory function. Although the inhibition extends to other pressor drugs in some degree, it is greater and more consistently exercised on reactivity to renin and angiotonin. Thus the kidneys seem to moderate cardiovascular responses to the renin they secrete.

The mechanism of the renal inhibitory influence is obscure. It does not depend on the recognized ability of the kidneys to inactivate angiotonin and/or renin as it passes through
the renal circulation, since inhibition is still present immediately after exclusion of the kidneys from the circulation. Increased pressor effects after nephrectomy are not dependent on a possible increase in blood or extracellular fluid volume, since responsiveness does not change after ureter-transplantation. Conceivably, the inhibitory influence may be attributable to the inactivation of a substance in normal blood which augments pressor responsiveness, and which slowly accumulates after nephrectomy. Alternatively, normal kidney tissue may liberate an inhibitory substance into the blood. Page and Helmer have shown that this possibility is the more likely, since transfusions of large amounts of blood from normal into nephrectomized dogs transiently reduced the enhanced pressor reactivity of the recipients. Also favoring the latter possibility are experiments of Collins and Harakal, which indicate that plasma angiotonase concentration is diminished when it is measured in the same dogs after nephrectomy.

The supposition that the kidney liberates a substance inhibiting pressor responsiveness accords with Grollman's view that the kidney normally secretes a principle which suppresses arterial pressure; he suggests, however, that the absence of this secretion is the primary pathogenetic mechanism in renal hypertension, to the exclusion of the renal pressor system. Our data, on the other hand, suggest that the renal inhibitory principle acts only indirectly on arterial pressure, and that both concepts of the mechanisms of renal hypertension may be valid.

The concentrations of angiotonin and renin so far demonstrated in the blood of either experimental animal or man are insufficient of themselves to account for the hypertension, assuming a normal cardiovascular response. But with the progressive renal damage that occurs during a long course of "benign" renal hypertension, the renal inhibitory, or regulatory, function of the kidney might be diminished so that response to circulating angiotonin becomes more severe. More destruction of renal tissue would further augment response and result in the vicious cycle leading to fulminant, malignant hypertension.

There is other evidence to support this concept of dual renal mechanisms in the malignant phase of hypertension. Pressor reactivity is not abnormally increased in the more benign phase of experimental hypertension, but it may increase in the malignant phase. And the malignant phase appears to be more predominantly humoral than the benign, as judged by estimates of neurogenic vasomotor tone with TEAC.

A similar dual mechanism might also prevail in the hypertension that develops after nephrectomy when dogs are kept alive with an artificial kidney or by peritoneal lavage. Increased responsiveness to small amounts of extrarenal renin should exist, might be an integral mechanism. Consistent with this concept is the fact that ureter-transplanted dogs do not develop hypertension, as nephrectomized dogs do and the fact that such dogs also fail to manifest enhanced reactivity to renin and angiotonin.

SUMMARY

Bilateral nephrectomy augments selectively the action of injected pressor agents: responses to angiotonin and renin are increased more regularly and more prominently than are those to noradrenaline, serotonin, tryptamine and Pitressin; that to barium chloride is not increased.

Change in pressor responsiveness after nephrectomy is not mediated through the central nervous system and does not depend upon denervation of a portion of the splanchnic bed. Acute exclusion of the renal vascular bed does not alter reactivity; increase occurs only after several hours.

Increase or decrease in sodium intake does not modify the effect of nephrectomy on pressor reactivity.

Elimination of only the excretory function of the kidneys by unilateral nephrectomy and transplantation of the other ureter into the vena cava does not alter pressor responsiveness.

It is suggested that the nonexcretory renal
function that inhibits, or regulates, response to angiotonin and renin may participate in the genesis of the malignant phase of hypertensive disease and in postnephrectomy hypertension.

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