Antihypertensive Effect of Transplant of Rat Kidney or Its Unclipping
Hemodynamic Effects and Control Mechanisms

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SUMMARY The acute transplantation of a normal kidney into a recipient rat with Goldblatt one-kidney, one clip hypertension (1K1C) results in a blood pressure (BP) fall toward but not below normal levels within 1 hour. Removal of the clip in a 1K1C hypertensive rat also normalizes the BP rapidly. These changes are not mediated by external fluid loss and occur after indomethacin pretreatment, but are associated with a fall in cardiac output. The mechanism of release of a depressor secretion from the kidney transplant appears to be under barostatic control. Thus, transplanting a kidney into a hypertensive recipient caused a prompt BP decline, whereas transplanting an SHR kidney into a hypertensive recipient did not lower the BP. The prompt BP fall seen after unclipping also indicates that abrupt exposure of the kidney to a high perfusion pressure initiates the release of some depressor agent. When the recipient rat was made hypertensive by injecting renin, the kidney transplant did not lower the BP. When angiotensin in subpressor dose was infused into the renal artery of the kidney transplant, the BP of the recipient did not fall, whereas infusion of norepinephrine in equiconstrictor doses did not prevent the depressor response. These experiments suggest that, in addition to a barostatic stimulus for depressor release, angiotensin acts as a specific inhibitor.

Key Words • experimental renal hypertension • cardiac output • spontaneously hypertensive rat

It is well established that acute transplantation of a normal kidney into a renal hypertensive rat induces a decrease in BP within 1 or 2 hours, except when the hypertension is induced by renin infusion. Some studies indicated that the hemodynamic mechanism was a primary reduction in cardiac output, but since the period of anesthesia was extensive the possibility of a nonspecific influence of the anesthetic could not be excluded.

This work was undertaken to study in further detail the mechanisms governing the antihypertensive action of the kidney transplant. To avoid the problem of prolonged anesthesia, we turned to the unclipping experiments, measuring cardiac output in the conscious 1K1C hypertensive rat before and after unclipping. In this way it was hoped to define more precisely the hemodynamic change associated with the decline in BP.

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Methods

Transplant Experiment

Rats (200–300 g of body weight), used as recipients, were of four types: 1) SHR aged 12 to 15 weeks; 2) 1K1C hypertensive Sprague Dawley (SD) rats, with BP in excess of 180 mm Hg, 3 to 4 weeks after nephrectomy and 4 to 5 weeks after left renal artery clipping; 3) renoprival rats with acute renin infusion hypertension, and binephrectomized rats receiving 18 hours later 1.0 Goldblatt unit of renin intraperitoneally (i.p.) followed in 5 min by 0.5 units intravenously (i.v.); 4) normotensive SD and Wistar (WI) rats. Donor kidneys were taken from either normotensive SD or WI rats, or SHR (12–15 weeks) with BP in the range of 180–200 mm Hg.

Preparation of donor of the kidney transplant resembled the procedures described by Omae et al. In the donor rat, a PE 90 cannula (internal diameter, I.D. = 0.86 mm) was passed up the aorta to the orifice of the left renal artery while a PE 190 (I.D. 1.119 mm) cannula was inserted into the vena cava to a point just below the left renal vein. Both cannulas were clamped.
after filling with saline solution containing heparin 100 μ/ml. Attention was then directed to the tracheotomized recipient anesthetized with 40–50 mg/kg pentobarbital sodium and 0.15 mg atropine intraperitoneally. The femoral artery and vein of this rat were cannulated with PE 50 and 90 cannulas respectively. After ligating the ureter of the donor's kidney and injecting 500 units of heparin into the donor and 250 units into the recipient, the donor's tubing was connected to recipient's. Donor's aorta above the left renal artery and vena cava below the left renal vein were ligated and the clamps released. In this way it was possible to establish immediate perfusion of the donor kidney by the recipient's blood. Anesthesia was maintained by giving 10 mg/kg pentobarbital subcutaneously every 15 min into the recipient.

For infusion directly into the donor kidney, a T-tube was inserted at the arterial connection, and the side arm pump-perfused with the desired solution at a rate of 0.02 ml/min. For renal blood flow measurements a similar T-tube was introduced into the venous side. This possessed a long side arm so that the rate of inflow of venous blood into it after distal clamping could be measured with a stop-watch. After releasing the clamp, blood was injected back into the circulation.

Unclipping Experiments

Rats weighing 150 g were operated on to create 1K1C animals with post nephrectomy hypertension of 4 weeks' duration. On the day of unclipping, under halothane anesthesia, PE 50 canulas were implanted into the carotid artery and jugular vein. Thirty minutes after withdrawal of anesthesia, two baseline cardiac output determinations were made 1 hour apart. The rats were then reanesthetized and clips were removed or a sham removal performed. Cardiac output determinations were repeated at 60 and 120 minutes after the anesthetic withdrawal. Cardiac output was measured by injecting 1 mg of cardiogreen dye using a specially prepared injection device. Blood was simultaneously withdrawn from the carotid artery, passed through a specially designed cuvette, and returned to the rat after each measurement. Cardiac output was calculated from dye dilution curves in the usual manner; BP was determined continuously from the carotid cannula by a strain gauge.

Results

Transplant Experiments

Response of Blood Pressure of Chronic Hypertensive Recipients to Kidney Transplantation

Figure 1 left shows that only a kidney from a normotensive rat will lower the BP of a 1K1C hypertensive recipient. Figure 1 right indicates that the BP of an SHR rat undergoes a major reduction only when connected to the kidney from a normotensive donor. Kidney from donors with hypertension equal to that in the recipient did not lower the BP; similarly normotensive-normotensive connections did not change the recipient’s BP.

Renal blood flow (RBF) was determined in six experiments, each where a donor kidney had been connected for 45–50 minutes to various recipients. The mean RBF was as follows: normal recipient + normal donor 2.5 ± 0.4; SHR + WI 3.0 ± 0.2; SHR-SHR 2.9 ± 0.2; 1K1C + normal donor 3.0 ± 0.2; 1K1C + SHR 3.0 ± 0.2 ml/min. It is apparent that variations in RBF were not related to the antihypertensive effects of the procedure.

Response to Kidney Transplant of Blood Pressure of Recipients Acutely Hypertensive from Renin Injection

Sustained hypertension (150–160 mm Hg) was created by injecting hog renin into 12 uni- or binephrectomized recipients. The course of the BP was unchanged in the six rats in which the transplant was opened to the recipient’s circulation.

Intrarenal Administration of Angiotensin II (A11) and Norepinephrine (NE)

The BP change of the SHR at 15 minutes after the transplant of a WI kidney receiving an intrarenal A11 infusion (5 ng/kg/min), a NE infusion (10 ng/kg/min), or a saline infusion (0.02 ml/min) was −4 ± 0.8, −19 ± 1.9 or −21 ± 2.7 mm Hg, respectively (figure 2). The BP fall in the A11 group was significantly less than in the other two groups (p < 0.001) vs each group. The RBF at 15 minutes after the transplant was 3.2 ± 0.2 ml/min for the A11 group, 3.3 ± 0.2 for the NE group, and 3.7 ± 0.2 for the saline group. Infusions of these doses for 15 minutes into the WI kidney connected to a WI recipient did not change the latter’s BP. The reduction in RBF in the A11 group was not significantly different from that in the NE group, but was significantly reduced when compared to that in the saline group (p < 0.05). Thus, despite an equal reduction in RBF, the depressor effect of the kidney transplantation was inhibited by A11 and not by NE.

Changes in Vascular Reactivity of the Recipient

Average of mean BP of the six recipient SHR just before the A11 injection was 184 ± 2 mm Hg. The pressor response to a bolus dose of 50 ng/kg of A11 given i.v. was 16 ± 1 mm Hg. When the average mean BP of the recipient had fallen to 165 ± 4 mm Hg 45–60 minutes after the transplant, the pressor response to the same dose of A11 was 16 ± 1 mm Hg. Likewise NE responsiveness was unaffected: 0.25 μg/kg caused a BP rise of 18 ± 1 mm Hg before transplant (BP 182 ± 2 mm Hg) and 20 ± 2 mm Hg afterward when the BP had fallen to 163 ± 3 mm Hg.

Indomethacin Blockade

Six SHR recipients and WI normotensive kidney donors were pretreated i.v. with indomethacin 2
mg/kg in 0.2 ml Trizma base (Sigma Chemicals, St. Louis, Missouri). This dose had been shown to be effective in blocking the depressor response to i.v. arachidonic acid (5 mg/kg in Trizma base) for a period of 90 minutes. The depressor effect of the kidney transplant was unmodified.

Modifications of Intravascular Fluid Volumes

Percent change in hematocrit (Hct) and in MAP at 15 minutes after 7 WI-W1 transplants was +3.5 ± 1.0% (p < 0.02) and −2.0 ± 1.1% (NS) respectively, using paired t tests. In 6 SHR-W1 transplants, Hct change was comparable (+4.3 ± 1.5%), but % fall in MAP was significantly larger (−11.4 ± 1.2%, p < 0.001). When saline was infused at a rate of 0.10 ml/min into six SHR transplant recipients, Hct did not change (−0.3% ± 1.5%), but % MAP fell significantly (−8.6 ± 0.74%, p < 0.001). However, the MAP fall was slightly, but significantly less when compared to that in SHR-W1 transplant in which no fluid was given.

Unclipping Experiments

The clip was successfully removed in 13 animals; in six cases the BP did not fall. In these latter the hemodynamic changes resembled those of 6 sham control experiments. In the seven in which the BP fell, the change was due entirely to a fall in cardiac output (figs. 3 and 4).

Discussion

This work confirms reports of others that the animal with experimental hypertension has a decline in BP when exposed to a kidney transplant whether such hypertension is initiated by renal artery clipping or Figure 8 ligation and nephrectomy,1,4 binephrectomy,5,7 DOC-salt administration,1,8 carotid denervation.8 In reviewing acute renal transplants into rats, the vasodepressor mechanisms appears to be primarily through a reduction in cardiac output.2 Since we consider the acute depressor effect of removing the renal artery clip in 1K1C hypertensive rats is mediated by a comparable mechanism, and since this experiment can be done in stages so as to avoid the cardiodepressor effect of anesthesia, cardiac output determinations were performed in conscious rats before and after unclipping. The results are consistent with the conclusion of others, studying both conscious and anesthetized animals10 that the primary effect of un-
clipping is a decline in cardiac output. That the abrupt offset of hypertension does not involve a decline in total peripheral resistance at first seems paradoxical. It is possible that there is a later, secondary readjustment (autoregulation) which follows the decline in cardiac output.

There are a few known mechanisms for initiating a BP fall by an initial primary decline in cardiac output. DuCharme and McCandlis have described a venoconstrictor originating in the kidney. If this agent were augmented in hypertension and its release inhibited by...
exposure of a kidney to high perfusion pressure it could be a candidate for the unknown depressor secretion. A neural inhibitory mechanism could also be postulated which would act primarily on venous return and cardiac output, in the manner of ganglionic blocking agents. However, the carotid sinus reflex appears to be active in attempting to oppose the BP fall, at least in the unclipping experiment. Another possibility is the hormone postulated by Lucas and Floyer which is secreted by the kidney, and which facilitates the transfer of fluid into the interstitial space. This agent, if released by the perfused transplant or the unclipped kidney, would result in a decline in cardiac output and an increase in hematocrit. In the experiments reported above a small rise in the latter occurred but it was no less in the situations in which the BP did not fall and when the decline was prevented by infusion of saline the BP fall still occurred.

Despite the hemodynamic evidence against an immediate arterial dilator action, it seemed advisable to exclude as many known agents as possible. Indomethacin pretreatment excluded prostaglandin as mediator of transplant effect. The renal depressor lipid described by Muirhead's group seems to be an unlikely candidate since it is reported to be an acute arterial dilator.

The 1K1C hypertensive animal is said to have "volume" hypertension and external loss of fluid is said to be a factor in the reversal. However, the BP fall after unclipping is noted when urinary loss of fluid is replaced. In this and previous work on the depressor effect of renal transplants external fluid loss by the donor kidney has been prevented without altering the depressor effect. Since an increased urinary loss by the recipient's kidney (1K1C or SHR) has not been excluded and is hard to measure, we provided an infusion of saline of 1.5 ml over a 15-minute period to compensate for any hypothetical urinary fluid loss through the recipient's kidneys, but a depressor effect of the procedure was still observed.

Evidence that a low concentration of angiotensin may inhibit the antihypertensive effect of the kidney has at least two logical consequences. It explains the failure of the normal kidney to lower the BP of an animal with acute renin-induced hypertension. It also may be the factor which keeps the "untouched kidney" in the two-kidney one clip hypertensive model from preventing the hypertension. Although such a kidney is exposed to a high perfusion pressure, its antihypertensive function is nevertheless inhibited by the rise in circulating angiotensin coming from the opposite, ischemic kidney.

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**References**

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