Evidence for a Renomedullary Vasodepressor System in Rabbits and Dogs

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Renal perfusion was increased in anesthetized rabbits and dogs by using an extracorporeal circuit. When left kidney perfusion pressure was raised in rabbits (145–240 mm Hg), arterial pressure fell by 1.34±0.20 mm Hg/min. Pretreatment of the rabbits with 2-bromoethylamine hydrobromide, which destroyed the renal medulla, abolished the fall in arterial pressure (−0.08±0.08 mm Hg/min) in response to increased renal perfusion pressure. In dogs (with blockade of autonomic ganglia by pentolinium, converting enzyme inhibition [captopril/enalaprilat], and surgical renal denervation), increasing renal perfusion pressure to 170–220 mm Hg resulted in a fall in arterial pressure by 0.32±0.03 mm Hg/min (or by 28.9±3.1 mm Hg over a 90-minute period). Mean arterial pressure did not change significantly in identically prepared dogs not subjected to increased renal perfusion pressure, whereas pretreatment of dogs with bromoethylamine abolished the hypotensive response to increased renal perfusion pressure. Thus, the hypotensive response to increased renal perfusion was dependent on the presence of an intact renal medulla, but hypotension still occurred in the presence of converting enzyme inhibition, autonomic ganglion blockade, and renal denervation. The results provide in vivo evidence in two species that a vasodepressor factor from the renal medulla is released in response to increased renal perfusion. (Hypertension 1991;18:325–333)

The existence of a vasodepressor system in the renal medulla has been postulated for over a decade. Muirhead et al1 first suggested that the medulla was a possible source of an antihypertensive substance by showing that transplants of cultured medullary interstitial cells reversed renoprival hypertension. Swales and colleagues2 then showed that destruction of the renal medulla retarded the fall in blood pressure after the removal of a renal artery clip from Goldblatt hypertensive rats. The possibility that increased renal perfusion may release one or more medullary depressor hormones received strong support recently from Karlstrom and colleagues,3 who demonstrated that increasing the perfusion pressure of isolated kidneys released a depressor substance in the venous effluent that when infused into conscious rats, produced profound hypotension.

The evidence that increased renal perfusion pressure releases a medullary vasodepressor hormone has been confined to the rat. We have now studied whether evidence for renal medullary vasodepressor hormones can be found in other mammalian species, namely, rabbits and dogs. The experiments use an approach similar to that of Karlström and colleagues,3 but allow alteration of renal perfusion pressure in situ. In rabbits, we studied whether increased renal perfusion pressure caused systemic hypotension and whether chemical renal medullectomy abolished this response. We then studied whether the response to increased renal perfusion pressure occurred in dogs with autonomic ganglion blockade, angiotensin converting enzyme inhibition, and renal denervation. The aim of these dog studies was to create an "open loop" preparation, avoiding the confounding influences of cardiovascular reflexes on the arterial blood pressure response to increased renal perfusion.

Methods

Animals and Experimental Groups

The experiments were performed in anesthetized rabbits (2.33±0.09 kg) from a colony of English multicolored stock maintained at the Baker Medical Research Institute and in anesthetized greyhound dogs (31.8±0.7 kg). An extracorporeal circuit was established in both species to allow alterations in left renal perfusion without direct effects on systemic
hemodynamics. The animal experiments were approved by the Alfred Hospital/Baker Institute Animal Experimentation Committee.

The systemic blood pressure and heart rate responses to increased renal perfusion pressure were first studied in five rabbits. After establishing a model in which increasing renal perfusion pressure led to a consistent hypotensive response, we studied the responses in five rabbits with chemical medullectomy to increased renal pressure and compared these responses with those in six normal rabbits. In seven dogs, the responses to increasing renal perfusion pressure were studied with converting enzyme inhibition and autonomic ganglion blockade. Five dogs, alternating with the above and also with converting enzyme inhibition and ganglion blockade, were studied as "time" controls in which observations were made over the same period of time without increases in perfusion pressure. In another two dogs, again with converting enzyme inhibition and ganglion blockade, the responses to increased renal perfusion pressure were studied after chemical medullectomy. The experiments involving pharmacological blockade of autonomic and hormonal responses were performed in dogs rather than rabbits because of the marked hypotension that such blockade produces in anesthetized rabbits.

**Extracorporeal Circuit**

The extracorporeal circuit was constructed from Silastic tubing (Dow Corning, Midland, Mich.) with a total volume for rabbits and dogs of approximately 30 and 200 ml, respectively. A roller pump (in the rabbit, Masterflex, Cole Parmer Instrument Co., Barrington, Ill.; in the dog, Drake Willock, Portland, Ore.) was used to circulate blood through the circuit. For the rabbit and dog, blood was drawn from the distal aorta and iliac artery, respectively, passed through the roller pump, and returned to the animal by two routes: to the renal artery and directly into the venous circulation (vena cava and iliac vein, respectively) (Figure 1). For the rabbits, the renal artery limb contained a windkessel to normalize the pulse pressure. The circuit tubing was primed with 10% (vol/vol) dextran solution (Rheomacrodex, Pharmacia, Melbourne, Australia) in normal saline solution, or 10% (vol/vol) polygeline (Haemaccel, Hoechst, Melbourne, Australia) in some dogs. In both species the pressure in the renal limb of the circuit was measured via a side arm catheter proximal to the cannula inserted into the renal artery. Pressure measured directly by renal artery puncture at the end of some experiments gave values around 15 mm Hg lower than pressures measured from the side arm catheter. A Starling resistor was incorporated into the venous limb of the circuit to enable finely graded reductions in blood flow through this limb, thereby increasing the rate of flow and the pressure in the renal limb of the circuit.

**Rabbit Experiments**

**Surgery.** Ear artery and vein catheters were inserted while the animals were under local anesthesia (Xylocaine, 0.5%, Astra, North Ryde, Australia). The rabbits were anesthetized with pentobarbitone (Boehringer Ingelheim, Artarmon, Australia), which was infused at 360 mg/hr i.v. until endotracheal intubation was possible and then at 30–60 mg/hr i.v. Surgery was performed on a heated table, and rectal temperature was monitored. Bilateral ureter catheters were inserted via a suprapubic midline incision. The rabbits were then placed in an upright position that has been found previously to result in the maintenance of cardiovascular and renal variables close to those of conscious animals. The left kidney, abdominal aorta, and inferior vena cava were exposed via a retroperitoneal flank incision. A large bore cannula (3 mm o.d., 2 mm i.d.) was inserted into the abdominal aorta below the level of the inferior mesenteric artery, another cannula (1.2 mm i.d.) was inserted into the inferior vena cava, the renal artery was cannulated (1.2 mm i.d.) (flow was arrested for 2–3 minutes in all rabbits), and perfusion of the kidney via the extracorporeal circulation was commenced.

**Infusions.** Normal saline (Baxter, Melbourne, Australia) was infused at 10 ml/kg/hr until the end of the surgical preparation of the rabbit. Sodium heparin (2,000 IU bolus i.v., Fisons, Sydney, Australia) was given before the establishment of the extracorporeal circuit, and then polygeline (Haemaccel) containing 200 IU heparin/ml was infused at 10 ml/kg/hr throughout. In the study comparing responses in untreated and 2-bromoethylamine hydrobromide (BEA)–treated rabbits, an infusion of whole rabbit blood was commenced before completion of surgery and maintained throughout the experiment at a rate of 6–7 ml/hr to offset blood losses from the wound after heparinization.

**Experimental protocol.** After the rabbits had achieved stable urine flow and blood pressure and at
least 1 hour after completion of preparation, two 15-minute collections of urine and measurements of blood pressure and heart rate were performed. In a total of 11 rabbits, renal artery perfusion pressure was then increased to 145-240 mm Hg and was maintained at this level for 30 minutes or until systemic blood pressure fell to 45 mm Hg. Timed urine collections were made. After returning the renal perfusion pressure to normal, there was a recovery period of 30 minutes, with 15-minute urine collections. Renal artery perfusion pressure was then raised a second time in four rabbits.

Two rabbits were studied as time controls in which extracorporeal circulation was established as described above, but renal perfusion was not increased.

**Chemical medullectomy with 2-bromoethylamine hydrobromide.** Five rabbits were pretreated with a single dose of BEA (75 mg/kg i.v., Sigma, Sydney, Australia) 3 days before experimentation. The dose of BEA was determined from pilot studies and histological examination of resulting medullary damage. The BEA-treated rabbits had high urine outputs, and although they ate normally, they did not always drink sufficiently to maintain fluid balance. They were therefore given 30 ml saline subcutaneously at the time of BEA treatment and then saline intravenously during the 2 days before the experiment. The volume of saline given daily was matched to the rabbits' weight loss over the previous 24 hours and averaged approximately 100 ml. There was an interval of about 24 hours between the last intravenous fluid replacement and the experiment.

**Dog Experiments**

**Surgery.** Captopril (100 mg orally twice daily, E. R. Squibb & Sons, Inc., Princeton, N.J.) was administered to all dogs for 2 days before surgery. The greyhounds were anesthetized (45-60 mg/kg pentobarbital) and were ventilated with a respirator (Harvard Apparatus, South Natick, Mass.). The left renal artery was exposed through a retroperitoneal incision, the kidney was denervated by stripping all visible nerves from the renal vessels, and the left ureter was cannulated. The dogs were then heparinized (15,000 IU), and catheters for the extracorporeal circuit were inserted (renal blood flow was arrested for about 5 minutes). Flow rate within the circuit and resistance in the venous limb were adjusted to maintain pressure in the renal limb between 50 and 75 mm Hg; pump flow rate was 450-500 ml/min depending on the size of the dog. A bladder catheter was inserted.

Saline (0.5 l, Baxter) was administered over the first 30 minutes after induction of anesthesia and was then infused at 200 ml/hr until the end of the surgical preparation. At this time, an infusion of glucose (4%) solution in saline (Baxter) or dextran (Rheomacrodex, Pharmacia) or polygeline (Haemaccel, Hoechst) 4:1 vol/vol with glucose/saline solution was infused at 9 ml/min for 40 minutes and thereafter at 5 ml/min.

**Experimental protocol.** After surgery, a period of at least 1 hour was allowed for equilibration. During this time pentolinium (6 mg/kg bolus and 3 mg/kg/hr infusion, I.D.T., Melbourne, Australia) and enalaprilat (0.75 mg/kg i.v., Merck Sharp & Dohme, West Point, Pa.) were administered. When steady-state hemodynamics and urinary flows had been achieved, two control periods (15 minutes each) were performed. The Starling resistor on the venous limb was then inflated to raise perfusion pressure in the renal artery limb to 170-220 mm Hg, and this pressure was maintained for 90 minutes. In the dogs studied as time controls, the protocol was identical to the above procedure except that the renal perfusion pressure was not increased. Arterial blood pressure, pressure in the renal artery cannula upstream to the site of insertion into the renal artery, and heart rate were measured throughout, and timed collections of urine were made.

**2-Bromoethylamine hydrobromide treatment.** In two dogs, BEA (30 and 40 mg/kg, Sigma) was administered intravenously 5 days before the experiment. These dogs were placed in metabolic cages to measure the effects of BEA on fluid balance. Their water intake and urine output increased by about fourfold to 3.5 and 4.8 l and 3.4 and 4.2 l, respectively. The dog given 40 mg/kg BEA required fluid administration (Hartmann's solution intravenously) to maintain body fluid balance over the fourth and fifth days after BEA was administered. On the experimental day, these dogs were studied in the same manner as the dogs described above, including autonomic blockade and converting enzyme inhibition.

**Histology**

At the end of the experiment, slices from the right kidneys of both the rabbits and dogs were fixed (formalin 4% in buffered saline solution) and were stained with hematoxylin and eosin.

**Statistical Analysis**

Unless otherwise specified, paired or unpaired t test (as appropriate) was used to analyze the results, except for urinary data where "two-way" analysis of variance was used.

**Results**

**Experiments in Rabbits**

Increasing renal perfusion pressure from an average level of 62.8±3.7 mm Hg to an average of 184.6±9.6 mm Hg produced a rapid and progressive fall in mean arterial pressure (from an average resting value of 72.1±2.5 mm Hg, n=11), which continued throughout the period of increased renal perfusion pressure. The increased renal perfusion pressure was maintained for 30 minutes or until mean arterial pressure fell to 45 mm Hg and the average rate of fall in mean arterial pressure was 1.35±0.28 mm Hg/min (range 0.5-3.42 mm Hg/min, p<0.05, n=11) (Figure 2). In each rabbit, mean
arterial pressure began to recover as soon as renal perfusion pressure was returned to normal, but the rate of recovery was slower than the rate of fall (Figure 3). In four of these rabbits, the effects of raising the perfusion pressure a second time 1–2 hours later were examined. The rate of fall of systemic arterial pressure was 1.11±0.11 mm Hg/min on the first occasion in these four rabbits, significantly less than the rate of 1.79±0.21 mm Hg/min on the second occasion (p=0.051, paired t test) (Figure 2).

Despite the progressive fall in arterial pressure during elevation of renal perfusion pressure, heart rate did not change significantly. In the 11 rabbits, heart rate averaged 203.8±7.7 systoles/min before elevation of renal perfusion pressure and 205±9 systoles/min at the end of the period of elevated renal perfusion pressure when systemic arterial pressure had fallen to 45–50 mm Hg.

In two rabbits studied over the same time course, but without increases in renal perfusion pressure, arterial pressure did not change significantly over the equivalent 30-minute period (−0.17 and 0.0 mm Hg/min, respectively).

The effects of BEA pretreatment were studied in five rabbits; these experiments were alternated with experiments in six rabbits with no pretreatment (Figure 3). On the day of the experiment body weight averaged 310±60 g (p<0.01) less than 3 days earlier before BEA treatment. Before anesthesia, mean arterial pressure was significantly lower in BEA-treated rabbits than in the untreated rabbits (66.4±1.9 and 74.0±3.8 mm Hg, respectively; p<0.05, unpaired t test). Heart rate was not significantly different between the BEA-treated (251±1 systoles/min) and untreated rabbits (232±9 systoles/min), and hematocrit was 36.8±5.0% and 35.4±2.8%, respectively (NS, unpaired t test).

Increasing renal perfusion pressure did not produce a fall in systemic arterial pressure in any BEA-treated rabbit (Figure 3). The average change in mean arterial pressure was −0.08±0.08 mm Hg/min (NS, n=5). In contrast, mean arterial pressure fell in all the untreated rabbits in response to increased renal perfusion pressure, average rate of fall being 1.34±0.21 mm Hg/min (p<0.001, n=6) (Figure 3). Heart rate fell significantly in BEA-treated rabbits from 188±15 to 177±17 systoles/min during the period of increased renal perfusion pressure (p<0.05).

**Urinary changes.** Elevation of renal perfusion pressure produced a rapid rise of urine flow (from 0.08±0.05 to 1.98±0.20 ml/min, p<0.001) and urinary sodium excretion (from 8.9±5.9 to 267.6±23.4 μmol/min, p<0.001) from the perfused kidney. In the BEA-treated rabbits, both urine flow and sodium excretion from the perfused kidney also rose with increased perfusion pressure (0.02±0.01 to 0.50±0.08 ml/min, p<0.001 and 3.0±1.0 to 68.6±10.0 μmol/min, respectively; p<0.001). These rises were significantly smaller than in untreated rabbits (p<0.001), but expressed as percentage increase from control values, the changes in the untreated and BEA-treated groups were not significantly different (t=0.008, unpaired t test).

For the contralateral right kidney, urine flow fell from 0.20±0.13 to 0.02±0.01 ml/min during the period of increased perfusion of the left kidney. For BEA-treated rabbits, these values were 0.07±0.03 to 0.07±0.02 ml/min, respectively.

**Experiments in Dogs.** All dogs were studied throughout the experiment with blockade of the renin-angiotensin and autonomic nervous systems to avoid confounding influences of neural and humoral reflex responses to the falling arterial pressure and the increased renal perfusion pressure. Increasing the renal perfusion pressure to 170–220 mm Hg resulted in progressive falls in mean arterial pressure (Figures 4 and 5). The fall in arterial pressure averaged 0.32±0.03 mm Hg/min over the 90 minutes of increased left renal perfusion pressure; a total of 28.9±2.7 mm Hg. Mean arterial pressure had fallen by 11.6±3.1 mm Hg 30 minutes after the increase in renal perfusion pressure and by 23.0±3.4 mm Hg after 60 minutes (Figure 4). There were no significant changes in heart rate during the fall in mean arterial pressure (0±1 systoles/min).

Another group of dogs served as “time controls” (i.e., the extracorporeal circuit was established but perfusion pressure was not raised) (Figure 5). In these dogs, the blood pressure remained near preperfusion levels (the average rate of change of mean arterial pressure was −0.07±0.03 mm Hg/min). In one dog with two renal arteries supplying the left
BEA PRETREATMENT

![Graph showing mean arterial pressure responses to increased renal perfusion pressure in untreated and BEA-pretreated rabbits.]

NO PRETREATMENT

![Graph showing mean arterial pressure responses to increased renal perfusion pressure in untreated rabbits.]

Figure 3. Line graphs show comparison of mean arterial pressure responses to increased renal perfusion pressure in untreated (bottom panel) and 2-bromoethylamine hydrobromide (BEA)-pretreated (top panel) rabbits. Responses in each rabbit are shown. Pressure was measured every 5 minutes except during the period of increased renal perfusion pressure in untreated rabbits when values were plotted every minute.

kidney, the left hind limb was perfused rather than the kidney, and mean arterial pressure rose by 8 mm Hg over the 90-minute period of increased hind limb perfusion in this dog. In two BEA-treated dogs, mean arterial pressure changed from 88.9 to 90.0 and from 81.6 to 75.0 mm Hg, respectively, in response to 90 minutes of increased renal perfusion pressure. These responses were indistinguishable from the responses in control (no increase in perfusion pressure) dogs.

Urinary changes. Increasing left renal perfusion pressure resulted in an immediate diuresis from that kidney. Urine flow increased from 0.26±0.10 to 2.69±0.77 ml/min after 15 minutes and then to 2.91±0.93 ml/min after 90 minutes (Figure 4). Sodium excretion rose initially from 4.0±0.8 to 187.6±76.0 μmol/min over the first 15 minutes and then progressively increased to 391.0±155.7 μmol/min by 75–90 minutes (Figure 4). In the BEA-treated dogs, increasing renal perfusion pressure also produced a marked diuresis and natriuresis from the perfused kidney, but these were not progressive. In the dogs studied as time controls with no increase in renal perfusion pressure, urine flow and sodium excretion from the perfused kidney did not change significantly over the duration of the experimental period (urine flow was 0.02±0.01 ml/min in the control period and 0.06±0.02 ml/min 75–90 minutes later; respective values for Na+ excretion were 4.2±2.3 and 1.3±0.03 μmol/min).

Histology

Damage to the renal medulla of both the rabbits and dogs treated with BEA was confirmed with light microscopy. BEA produced extensive medullary damage in both rabbits and dogs as has been previously documented in rats.6 Damage was most marked in the papilla where the collecting ducts and their epithelium were destroyed. The middle and outer medulla showed loss of ductal epithelium and a hemorrhagic infiltrate.
into the interstitium. Medullary interstitial cells were not discernible. There was no evidence of cortical damage in any of the BEA-treated kidneys.

**Discussion**

The findings reported here in the rabbit and dog indicate that a renal hypotensive, or “vasodepressor,” hormone is present in other mammalian species in addition to the rat. In both rabbits and dogs, increasing the renal perfusion pressure to one kidney in situ elicited a fall in systemic blood pressure, which began soon after the elevation of renal perfusion pressure and continued progressively over the entire period of renal pressure elevation. Experiments in dogs showed that the renal factor exerted its effects even when there was blockade of the autonomic nervous and renin-angiotensin systems. The hypotension was completely abolished by BEA-induced renal medullary damage, indicating that the renal medulla was the source of the hypotensive factor.

The experiments in dogs were designed to test whether hypotension still occurred when homeostatic cardiovascular reflexes were blocked. We found that arterial pressure still fell in response to increased renal perfusion pressure in dogs with converting enzyme inhibition, autonomic ganglion blockade, and renal denervation. The fall was abolished by BEA treatment, and these results strongly suggest that the hypotension was humorally mediated and the substance was of medullary origin. These dog studies were not designed to quantify the magnitude of the contributions of suppression of the renin-angiotensin and autonomic nervous systems in the hypotensive response. The reasons for the more rapid fall in blood pressure in rabbits than in dogs are not known, but it could be that there was some involvement of
the renin-angiotensin or autonomic nervous systems in the rabbit.

Previous work using rats has suggested a role for the autonomic nervous system in the response to increased renal perfusion (e.g., Gothberg and colleagues concluded that the autonomic nervous system responded to a role in the hypotension following renal artery unclipping in Goldblatt hypertension). Similarly, infusion of medullipin extracted from renal medullae has also been reported to suppress the sympathetic nervous system. In the rabbits of the current experiments, no change in heart rate was seen during the hypotensive response, even when this was rapid. However, it is likely that the pentobarbital anesthesia inhibited the autonomic nervous activity in these animals, and thus it cannot be concluded that the renal medullary substance inhibited arterial baroreceptor reflexes. In the ganglion-blocked dogs, the absence of any heart rate changes indicated that the hypotensive substance had no direct chronotropic activity.

One possible contributor to the fall in systemic pressure following increased renal perfusion pressure could have been volume depletion, caused by the increased urinary output from this kidney. However, the BEA-treated animals did not show a fall in systemic pressure even though they also had an increased urinary output. Furthermore, both the rabbits and dogs were in positive fluid balance throughout the experiment.

In all the present experiments, increasing the perfusion pressure of the kidney produced a marked diuresis and natriuresis from the kidney. Part or most of this may have been due to the "pressure-natriuresis" mechanism. Karlström et al suggested that the renal medullary system is natriuretic and some of the data from the present study supports this. The natriuresis was significantly less in BEA-treated rabbits than in untreated rabbits even though renal perfusion pressure was similar, but this may be explained by altered fluid balance status in these rabbits. Preperfusion urine flow and sodium excretions were lower in BEA-treated rabbits compared with untreated rabbits, and the BEA-treated rabbits had reduced body weight relative to their pretreatment weights, suggesting dehydration. The data in the dog is also consistent with the substance being natriuretic since natriuresis increased progressively in the face of constant renal perfusion pressure, but this phenomenon may also have been due to intrarenal redistribution of blood flow. Against this, the right kidney of both the dogs and rabbits had an antidiuretic and antinatriuretic response to increased contralateral pressure. This did not occur in BEA-treated rabbits and may be explained by the fall in systemic arterial pressure, which is the perfusion pressure for this kidney. Caution therefore must be exercised in interpreting these urinary results, and further studies are needed to clarify whether the renal medullary system is natriuretic.

The nature of the renal medullary factors responsible for the hypotension remains to be determined, but evidence has been accumulating over the last decade that the kidney possesses a vasodepressor endocrine substance, a lipid hormone whose chemical structure is unknown but which can cause a profound hypotension. It is known that extracts of the renal medulla protect against renopirival hypertension, and that chemical medullectomy of the kidney retards the normalization of blood pressure after the removal of renal artery clip, and that isolated kidneys release a depressor substance when their perfusion pressure is increased. These latter experiments, in which the blood to perfuse the kidney came from and the renal venous effluent was returned to conscious rats, have been the most convincing to date that a renal medullary lipid might be involved in the regulation of blood pressure.

Attempts have been made to isolate vasodepressor substances from the renal medulla. Daniels et al isolated prostaglandin E, in the venous effluent of unclipped kidneys and Muirhead et al later isolated
two other lipids, which they named APRL (now believed to be platelet activating factor) and ANRL (now termed "medullipin"). Attempts to identify the chemical nature of medullipin have not yet been successful, although Muirhead has reported recently that the form released from the kidney is inactive and is converted to the active form (medullipin II) in the liver.

Despite the above experimental evidence provided by other laboratories, it was not known whether other species possess a renal medullary vasodepressor system since all these experiments were performed in rats. Our experiments have shown that other mammalian species can also release (one or more) renal medullary factors and have indicated that these can have powerful hypotensive actions in vivo. However, the renal perfusion pressures used in this study were high and the broader physiological significance, particularly whether the medullary factor has a role in the regulation of normal blood pressure, requires further work. Studies using chemical medullectomy have shown that rats develop hypertension after renal medullary damage.

Clinical evidence also suggests that damage to the renal medulla in humans is associated with a high incidence of hypertension. In the present study, the blood pressure in rabbits 3 days after BEA treatment was lower not higher as may have been expected if the renal medullary vasodepressor system was having a tonic effect on blood pressure. However, these BEA-treated rabbits may have been volume depleted; they made large volumes of dilute urine and became dehydrated as illustrated by their body weight loss despite fluid replacement. Furthermore, it is known that hypertension develops over weeks rather than days after chemical medullectomy in rats. Chemical medullectomy using BEA is a technique that has been widely used with well-documented histological and functional effects. The use of BEA has been largely restricted to rats, but the doses chosen in our study for both rabbits and dogs demonstrated histological evidence of medullary damage with no cortical damage.

The nature of the stimulus to release the renal medullary factor also remains to be determined. Although renal perfusion pressure was varied in this study and others, the technique increased renal blood flow and thus factors dependent on blood flow such as local oxygen and metabolite concentrations could be the stimuli. There was also a prompt natriuresis and diuresis that presumably altered medullary osmotic pressure, and this too could be a stimulus for release, especially considering the close apposition of the renal medullary interstitial cells to the collecting ducts and the loops of Henle.

One advantage of the present study was the method used to change renal perfusion pressure. It allowed the kidney to be studied in situ, allowed alterations in renal perfusion pressure without changes in total circuit flow or direct systemic circulatory effects, and avoided catheterization of the renal vein with the possibility of raising renal venous and renal interstitial pressure.

In summary, this study provides evidence in two species other than the rat that a vasodepressor substance of renal medullary origin is released by an increase in renal perfusion pressure. Furthermore, the hypotensive response to increased renal perfusion pressure occurred despite converting enzyme inhibition and blockade of the autonomic nervous system. Further research is needed into the factors stimulating release of the medullary substance, the mechanisms by which it lowers blood pressure, including the roles of the renin-angiotensin and autonomic nervous systems, the chemical nature of the substance, and its physiological significance.

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References

14. Bing RF, Russell GI, Swales JD, Thurston H, Fletcher A: Chemical renal medullectomy: Effect upon reversal of two-

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