Short- and long-term enalapril affect renal medullary hemodynamics in the spontaneously hypertensive rat

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Dukacz, Stephen A. W., Michael A. Adams, and Robert L. Kline. Short- and long-term enalapril affect renal medullary hemodynamics in the spontaneously hypertensive rat. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R10–R16, 1999.—Long-term angiotensin-converting enzyme (ACE) inhibition in the spontaneously hypertensive rat (SHR) resets pressure natriuresis and shifts the relationship between renal arterial pressure (RAP) and renal interstitial hydrostatic pressure (RIHP) to lower levels of arterial pressure. These effects persist after withdrawal of treatment. The purpose of this study was to determine the effect of short- and long-term ACE inhibition on medullary blood flow (MBF). Enalapril (25 mg·kg−1·day−1 in drinking water) was given to male SHR from 4 to 14 wk of age. Four weeks after stopping treatment, we measured MBF over a wide range of RAP using laser-Doppler flowmetry in anesthetized rats. Additional rats, either untreated or previously treated for 10 wk, received 3-day enalapril treatment just before the experiment. RAP (mmHg ± SE) was 178 ± 6 (n = 8), 134 ± 6 (n = 8), 138 ± 5 (n = 9), and 111 ± 6 mmHg (n = 9) for the untreated, 3 day, 10 wk, and 10 wk + 3 day groups, respectively. Total renal blood flow for the groups receiving 3-day treatment was significantly higher when compared with that in rats with an intact renin-angiotensin system. Three-day treatment had no effect on the relationship between RAP and RIHP, whereas that in rats receiving 10-wk treatment was shifted to lower levels of RAP by −30 mmHg. Both 10-wk and 3-day treatment independently increased the slope of the RAP versus MBF relationship at values of RAP > 100 mmHg. The slopes in perfusion units/mmHg were 0.12 ± 0.01 (n = 8), 0.26 ± 0.01 (n = 8), 0.27 ± 0.01 (n = 9), and 0.30 ± 0.02 (n = 9) for the untreated, 3 day, 10 wk, and 10 wk + 3 day groups, respectively. These results indicate that the effect of short-term and the persistent effect of long-term enalapril alter renal medullary hemodynamics in a way that may contribute to the resetting of the pressure-natriuresis relationship in treated rats.

renal medulla; renal interstitial hydrostatic pressure; renal medullary blood flow; laser-Doppler; renal blood flow; pressure natriuresis

Previous studies have demonstrated that the pressure-natriuresis relationship in spontaneously hypertensive rats (SHR) is shifted to higher levels of renal arterial pressure (RAP) when compared with that in normotensive Wistar-Kyoto (WKY) rats (27). The exact mechanism by which increases in RAP result in increases in sodium excretion remains to be fully elucidated; however, changes in blood flow to the medullary region of the kidney have been implicated (4, 5). Unlike glomerular filtration rate (GFR) and total renal blood flow (RBF), which are well autoregulated, medullary blood flow (MBF) appears to be poorly autoregulated, and thus increases in RAP are accompanied by increases in MBF (5). An increase in MBF results in an increase in renal interstitial hydrostatic pressure (RIHP), which, by inhibiting sodium reabsorption, ultimately leads to an increased excretion of sodium (4, 11, 13). It is interesting to note that the MBF response to a given increase in RAP is significantly attenuated in the SHR when compared with that of normotensive rats over an RAP of 80 mmHg (29). Furthermore, it has been shown that the RIHP of SHR is less than that of normotensive rats at a given level of RAP (17). Thus alterations in the medullary circulation may be responsible in part for the shift of the pressure-natriuresis relationship and thereby contribute to the pathogenesis of hypertension in this strain of rat.

In a previous paper (6), we confirmed that long-term inhibition of the renin-angiotensin system (RAS) in young SHR (angiotensin-converting enzyme (ACE) inhibition from 4 to 14 wk of age) results in an antihypertensive effect that persists after cessation of treatment (22). In addition, we showed that the “persistent” effect of long-term treatment (10 wk) with enalapril on arterial pressure was associated with a shift in the pressure-natriuresis relationship as well as a shift in the relationship between RAP and RIHP to lower levels of RAP (6). On the other hand, short-term treatment (3 day) with enalapril decreased arterial pressure and shifted the pressure-natriuresis curve but did not alter the relationship between RAP and RIHP (6). Because MBF has been suggested to play a major role in the production of RIFP and in the mechanism of pressure natriuresis (4, 5), the present study was designed to determine the effect of 10-wk and 3-day enalapril treatment on MBF in SHR.

Methods

Experimental design and treatment. Male SHR (Harlan, Minneapolis, MN) were purchased at 3–4 wk of age. The rats were individually housed in suspended wire mesh steel cages. Temperature in the housing facility was maintained at 21°C, and a 12:12-h light-dark cycle was used. All experimental protocols followed guidelines of the Canadian Council on Animal Care and were approved by the University of Western Ontario Council on Animal Care.

Four treatment groups were used for this study, and all experiments were done when rats were 18 wk of age. The experiment was designed to allow comparisons between short- and long-term effects of enalapril as well as to determine if there were interactions between short- and long-term effects. Group 1 (untreated group) received no treatment,
group 2 (3 day group) received no long-term treatment but did receive treatment for the 3 days immediately before the experiment, group 3 (10 wk group) received enalapril from 4 until 14 wk of age, and group 4 (10 wk + 3 day group) received enalapril from 4 to 14 wk of age and then again for the 3 days immediately before the experiment, at 18 wk of age. Therefore, the untreated group and the 10 wk group had an intact RAS, whereas the 3 day and the 10 wk + 3 day groups had a blocked RAS at the time of the experiment. Thus the persistent effect of long-term ACE inhibition would be seen when comparing the 10 wk group and the untreated group and also when comparing the 10 wk + 3 day group and the 3 day group. The effect of short-term ACE inhibitor treatment would be seen by comparing the 10 wk group and the 3 day group and also by comparing the untreated and 3 day groups.

All groups were provided with standard rat chow (Pro Lab RMH 3000; Agway, St. Mary’s, OH) and tap water ad libitum. For all treatment groups, the water served as the medium for drug administration. The ACE inhibitor enalapril maleate was dissolved in sufficient water to provide a dose of 25 mg·kg$^{-1}$·day$^{-1}$. The drug concentration was adjusted two times weekly for each rat to account for changes in body weight and water intake. This dose of enalapril, given long term, has been shown to produce the persistent effect of ACE inhibitor treatment on arterial pressure and pressure natriuresis (6). Given for 3 days, this dose of enalapril has been shown to effectively block the pressor response to acute administration of ANG I and to shift the pressure-natriuresis curve (6).

Experimental preparation. On the day of the experiment, rats were anesthetized with Inactin (100 mg·kg body wt ip; Research Biochemicals International, Natick, MA) and ketamine (30 mg/kg body wt im; MTC Pharmaceuticals, Cambridge, Ontario, Canada). Body temperature was monitored using a thermistor (model 402; Yellow Springs Instruments, Yellow Springs, OH) and maintained at 37 ± 0.5°C using a controller (model 73A; Yellow Springs Instruments), a heat lamp, and a warming pad (model K-1-3; Gorman Rapp Industries, Belville, OH). A tracheotomy (PE-240 tubing) was done to facilitate breathing. The femoral artery was cannulated (pulled PE-50 tubing) to allow for the continuous measurement of arterial pressure and for the collection of arterial blood samples. The tip of the cannula was advanced to just below the level of the left renal artery. Arterial pressure was recorded for 10 min to obtain an initial level of arterial pressure. The left internal jugular vein was cannulated with two catheters of pulled PE-50 tubing. One catheter was used for bolus injections (0.1–0.2 ml) of ANG I (250 ng/kg iv) or 0.9% NaCl to estimate the extent of ACE inhibition in 3-day-treated rats. The catheters were then used for the infusion of 5% albumin (bovine, fraction V; Sigma, St. Louis, MO) in 0.9% NaCl for 30 min during the surgery to compensate for fluid losses and for the infusion of a hormone cocktail for the full duration of the experiment. The hormone cocktail was used to minimize the hormonal influences on the kidney that may be caused by experimental manipulation of RAP (27). The infusions were started at the same time, both at a rate of 33 μl·min$^{-1}$·100 g body wt$^{-1}$ via a syringe pump (model 355; Sage Instruments). The hormone cocktail contained arginine vasopressin (0.17 ng·kg$^{-1}$·min$^{-1}$), norepinephrine (333 ng·kg$^{-1}$·min$^{-1}$) and hydrocortisone (3 μg·kg$^{-1}$·min$^{-1}$) dissolved in 0.9% NaCl containing 1% albumin and 1.3% inulin (Eastern Chemical, Smithtown, NY). Inulin was included for estimation of GFR.

A midline abdominal incision was made, and the right kidney was removed. To remove the neural influences, we denervated the left kidney by separating the renal artery and vein and by stripping away the nerve fibers and adventitia. A 10% phenol in alcohol solution was then applied to the renal artery and vein to ensure complete destruction of any remaining fibers.

A Silastic balloon cuff was placed around the aorta between the celiac and superior mesenteric arteries. In addition, snare clamps were placed around the aorta distal to the left renal artery and around the celiac and superior mesenteric arteries. A balloon cuff and clamps allowed for the manipulation and control of RAP over a wide range of pressures.

The left kidney was freed from the surrounding tissue and placed in a stainless steel cup lined with saline-soaked gauze. An RIHP catheter was inserted into the kidney parenchyma at approximately the level of the corticomедullary junction, as described previously (6, 11). The catheter was made by inserting a cylinder of polyethylene matrix (35-μm pore size; Bel-Art Products, Pequannock, NJ) into a polyvinyl catheter. Using an electrocautery needle (23 gauge), we made a 3-mm deep hole in the kidney. The catheter was placed in the hole, flushed with heparinized saline, and sealed to the capsule using cyanoacrylate adhesive (Krazy Glue; Borden, Willowdale, Ontario, Canada). Brief occlusion of the renal vein was used as a test of the catheter: a rapid rise in RIHP followed by a rapid return to baseline indicated a good seal and a sensitive catheter. Both RAP and RIHP were monitored on a polygraph (Grass, Quincy, MA) via pressure transducers (model CDX3; Cobe, Lakewood, CO).

A fiber-optic strand (500-μm diameter; Perimed) was passed through a 5-mm polypropylene mesh square (Small Parts, Miami, FL) which was glued perpendicular to the length of the strand 7 mm from the tip. The fiber-optic strand was inserted into the lower pole of the kidney through a hole in the capsule made by a 26-gauge needle and was advanced 7 mm, parallel to the aorta, to the medulla of the kidney, as described previously (21). The fiber was then fixed in place by cyanoacrylate adhesive, with the mesh providing a good bond with the renal capsule. The fiber-optic strand was connected via a master probe coupler (probe 318; Perimed) to a Laser-Doppler perfusion monitor (model PF3; Perimed). Fused silica-matching liquid (Carigle Laboratories, Cedar Grove, NJ) was used for the connection between the fiber-optic strand and the probe to ensure a good optical connection. The flow probe and strand were calibrated before the experiment using a motility standard (Perimed). Random motion of this colloidal suspension of latex particles gives a reading of 250 perfusion units when the master probe is inserted into the solution. To check the fiber-optic strands, we used a diluted standard. Fibers were rejected if the value of 100 perfusion units (100 perfusion units = 1 V) was not attained when the fiber was immersed in the suspension.

RBF was determined with a transit-time ultrasound flowmeter (model 206T; Transonic Systems, Ithaca, NY) coupled to a flow probe (1-mm RB series; Transonic Systems) that was placed around the renal artery. H-R lubricating jelly (Mohawk Medical Supply, Utica, NY) was used as an acoustic coupler around the flow probe. MBF and RBF were recorded on the polygraph.

To complete the surgery, we placed a catheter (PE-190) in the bladder for the collection of urine. A 1-h period was given for equilibration after the completion of the surgery.

Experimental protocol. After equilibration, urine was collected for 30 min and an arterial blood sample (300 μl) was taken at the midpoint of the clearance period. MBF, RBF, mean arterial pressure (MAP), and RIHP were measured every minute during the clearance period and averaged. After the clearance period, the RAP was increased by tying off the
RESULTS

The initial values for MAP taken under Inactin anesthesia and before starting the infusions were 178 ± 6 (n = 8), 134 ± 6 (n = 8), 138 ± 5 (n = 9), and 111 ± 6 mmHg (n = 9) for the untreated, 3 day, 10 wk, and 10 wk + 3 day groups, respectively. Both short- and long-term treatment had a statistically significant effect on MAP, but there was no interaction between these two treatments. Adding short-term treatment to rats previously treated with enalapril resulted in arterial pressures that were on average almost 70 mmHg lower when compared with those in untreated SHR. A bolus of ANG I increased MAP by 32 ± 9 (n = 8) and 31 ± 6 mmHg (n = 9) for the untreated and 10 wk groups, respectively. These responses were significantly greater than the responses for a bolus of saline of the same volume (7 ± 5 and 8 ± 3 mmHg for same groups, respectively). Bolus doses of ANG I increased MAP by 13 ± 8 (n = 9) and 6 ± 6 mmHg (n = 8) for the 10 wk + 3 day and 3 day groups, respectively. These responses were not significantly different from those elicited from saline administration (7 ± 5 and 6 ± 4 mmHg for same groups, respectively).

Effect of short- and long-term enalapril on resting levels of MAP, renal hemodynamics, and indexes of renal function. Hemodynamic and renal function measurements were made after a 1-h equilibration period during infusion of the hormone cocktail. Both 3-day- and 10-wk-treated SHR had significantly (P < 0.05) lower MAP when compared with that in untreated SHR (Fig. 1A). The 10-wk effect and the 3-day effect were additive.

The 10-wk treatment had no significant effect on the MAP, whereas RBF in rats with the 3-day treatment, with or without the previous 10-wk treatment, was significantly higher when compared with that of rats not receiving the 3-day treatment (Fig. 1B). Similarly, 10-wk treatment had no significant effect on the resting level of MBF, whereas rats receiving the 3-day treatment had a significantly higher MBF, whether or not they received previous treatment with enalapril (Fig. 1C). There was no significant effect of the 10-wk treatment on the resting level of RIHP; however, 3-day treatment resulted in a significantly lower resting level of RIHP (Fig. 1D). It is important to note that the observed differences in these variables (Fig. 1) existed at significantly different levels of MAP; e.g., RBF, MBF, and RIHP in rats previously treated for 10 wk with enalapril were not significantly different when compared with values seen in untreated SHR, but the resting levels of MAP were 25 mmHg lower in the 10 wk group.

No significant effects of 10-wk or 3-day treatment were found on GFR, urine flow, or fractional excretion of sodium, although SHR treated previously for 10 wk had a significantly lower sodium excretion compared with that of the other groups (Table 1). Again, it should be noted that renal function was similar in all groups despite large differences in MAP among the groups.

Effect of short- and long-term enalapril on the relationship between RAP and renal hemodynamics. RBF for all groups was well autoregulated at levels of RAP > 100 mmHg (Fig. 2A). Ten-week treatment resulted in a statistically significant decrease in the estimated lower limit of autoregulation, whereas 3-day treatment had no significant effect on this value [untreated: 111 ± 5 mmHg (n = 8), 3 day: 106 ± 5 mmHg (n = 8), 10 wk: 97 ± 4 mmHg (n = 9), and 10 wk + 3 day: 86 ± 4 mmHg (n = 9)]. Over the autoregulatory range studied, RBF for the groups receiving 3-day treatment was significantly greater than that for the groups not receiving 3-day treatment, whereas 10 wk of treatment with enalapril had no significant effect on total RBF 4 wk after stopping treatment.

At levels of RAP > 100 mmHg, groups receiving 3-day treatment had levels of MBF significantly greater than that in groups not receiving 3-day treatment (Fig. 2B). SHR treated for 10 wk also had a significantly in-
creased MBF at levels of RAP > 100 mmHg when compared with that in untreated SHR. The effects of 10-wk and of 3-day treatment were additive, as shown by the absence of a statistically significant interaction between short- and long-term treatment. Both 10-wk and 3-day treatment alone and combined resulted in a significant increase in the slope of the relationship between RAP and MBF at RAP > 100 mmHg when compared with the slope for the untreated group [slopes in perfusion units/mmHg were determined for each individual rat and averaged to give a value for each group: 0.12 ± 0.01 (n = 8), 0.26 ± 0.01 (n = 8), 0.27 ± 0.01 (n = 9), and 0.30 ± 0.02 (n = 9) for untreated, 3 day, 10 wk, and 10 wk + 3 day groups, respectively]. RIHP varied directly with changes in RAP in all groups; however, 10-wk treatment resulted in a 40- to 50-mmHg shift of the relationship between RAP and RIHP to lower levels of RAP (Fig. 2C). Thus, at RAP of 75 mmHg or over, the RIHP was significantly greater for groups receiving 10-wk treatment compared with groups not receiving 10-wk treatment. Three-day treatment had no significant effect on the relationship between RAP and RIHP. Neither 10-wk nor 3-day treatment had a significant effect on the slope of this relationship.

**DISCUSSION**

In agreement with previous studies (3, 6, 15, 22), our present study showed that chronic treatment of young SHR with an ACE inhibitor prevented the full development of hypertension and that a significant antihypertensive effect persisted 4 wk after the cessation of treatment. This persistent antihypertensive effect occurred in the presence of a normally functioning RAS, as shown by the similar pressor responses to ANG I in the untreated group and the 10-wk group. Three-day treatment with enalapril also had a significant antihypertensive effect on MAP that was similar in magnitude whether the rats received the 10-wk treatment previously or not. This finding suggests that under the conditions of this experiment, the RAS was contributing about equally to the resting level of MAP for both the untreated and 10-wk groups and further supports the conclusion that the persistent effect of 10-wk treatment was not due to an altered RAS. Overall, these data support our previous suggestion (6) that there are two additive components to the antihypertensive effect.
of long-term ACE inhibitor treatment: 1) an effect due to the functional antagonism of the RAS and 2) an effect that persists in the absence of the drug. The former likely involves hemodynamic and direct tubular effects of ACE inhibition (14), whereas the latter has been proposed to involve hemodynamic effects due to the prevention of the development of vascular structural hypertrophy (1, 22). The new information provided by the present study is that both short- and long-term treatment of SHR with enalapril increase MBF and that these effects are also additive.

Effect of short- and long-term enalapril on resting levels of MAP, renal hemodynamics, and indexes of renal function. Hypertension is associated with a shift of the pressure-natriuresis relationship to higher levels of MAP (4), whereas antihypertensive therapy resets the pressure-natriuresis mechanism to a lower level of MAP. In our current study, the various indexes of renal excretory function were similar for all of the groups despite a very large range of MAP for the four groups. These results are consistent with a leftward shift in the pressure-natriuresis relationship in treated SHR, which we have previously shown for both 3-day and 10-wk enalapril treatment (6).

Because the mechanism of pressure natriuresis is believed to involve changes in MBF and RlHP (4, 5), we measured these variables in treated and untreated SHR. No significant differences were found between the untreated and 10 wk groups at their resting levels of MAP for MBF and RlHP, despite a difference in MAP of \(\sim 25 \text{ mmHg}\). Similarly, no significant differences in MBF and RlHP were observed between the 3 day and the 10 wk + 3 day groups at their resting levels of MAP, which differed by 30 mmHg. These observations are consistent with a resetting of the mechanism of pressure natriuresis by both 3-day and 10-wk treatment (6). However, the mechanism for the shifts in the pressure-natriuresis curves produced by 3-day and 10-wk treatment appears to be different because rats in the two treatment groups had similar resting levels of MAP but significantly different resting levels of RBF, MBF, and RlHP. To further investigate these differences, we examined the relationship between RAP and these variables over a wide range of RAP.

RBF is autoregulated in both SHR and normotensive rats; however, in adult SHR the autoregulatory range is shifted to higher levels of RAP (27). The cause of this shift may involve changes in renal vascular structure (9) as well as altered renal vascular tone (12). In the current study, untreated and 10-wk-treated SHR showed good autoregulation of RBF and rats receiving the 10-wk enalapril treatment had a significantly lower limit of autoregulation when compared with that in untreated SHR. Previously it has been shown that long-term ACE inhibitor treatment of young SHR can prevent the development of vascular hypertrophy (1, 19, 22). Thus a decrease in structurally based renal vascular resistance would allow for a lower limit of autoregulation when compared with that in untreated SHR. Previously it has been shown that long-term ACE inhibitor treatment of young SHR can prevent the development of vascular hypertrophy (1, 19, 22). Thus a decrease in structurally based renal vascular resistance would allow for a lower limit of autoregulation when compared with that in untreated SHR. Not surprisingly, 3-day treatment with enalapril resulted in an increase in RBF but no change in the lower limit of autoregulation. This is consistent with a short-term functional antagonism of the RAS and no change in vascular structure (14).

Unlike total RBF, MBF in normal rats under volume-expanded conditions is not autoregulated (28), and it is
this observation that forms the basis for the proposed mechanism of pressure natriuresis (5). For example, an increase in RAP results in an increase in vasa recta capillary blood flow and pressure. This change in medullary hemodynamics in turn both reduces the medullary solute gradient and increases RIHP, resulting in decreased sodium reabsorption in proximal and distal portions of the nephron (30). That changes in MBF can play an important role in the control of arterial pressure was shown by selective infusion of nitro-l-arginine methyl ester (L-NAME) (25) or captopril (20) into the renal medulla of conscious rats for several days to reduce or increase MBF, respectively. A reduction of MBF during L-NAME infusion was associated with sodium retention and increased arterial pressure, whereas an increase in MBF during captopril delivery was associated with sodium excretion and a decrease in arterial pressure. The latter study using captopril was done using SHR and would presumably correspond to our results obtained with 3-day treatment with enalapril.

It has been reported previously that the relationship between RAP and MBF in SHR is blunted when compared with that in normotensive rats (29). Thus, at a given level of RAP, both capillary blood flow and RIHP are lower in SHR when compared with values in WKY rats (17, 29). The explanation for this may involve vascular hypertrophy and/or increased vascular tone in the juxtamedullary nephrons of SHR (12).

Studies in normotensive rats have suggested that the linear relationship between RAP and MBF is dependent on a functional nitric oxide system, because acute (8) or chronic (7) administration of L-NAME converts the relationship between RAP and MBF from a pressure-dependent to a blunted relationship. It is of interest that administration of L-arginine to SHR restored the blunted capillary blood flow and natriuretic responses to an increase in RAP (18). Similarly, acute administration of nitro-monomethyl-L-arginine shifted the pressure-natriuresis curve to the right in WKY rats but not in SHR (16), suggesting further that the influence of the nitric oxide system on the medullary circulation may be altered in SHR.

There is considerable literature suggesting that endothelial function is impaired in hypertension (2, 12, 31) and that ACE inhibitors improve endothelium-dependent vasodilation (2). Clearly, in this study, both 3-day and 10-wk treatment with enalapril improved nonautoregulating characteristics to the medullary circulation of SHR, and these effects of short-term and long-term treatment on the relationship between MBF and RAP were additive. The mechanism for the long-term effect of enalapril on the medullary circulation cannot be determined from this study. It is reasonable to suggest that prevention of vascular structural change is involved (22), although functional changes, such as improvement of endothelial function, may also accompany structural changes. Bennett et al. (2) showed that long-term ACE inhibitor treatment restored endothelium-dependent relaxation responses in vessels from SHR to levels seen in vessels from WKY rats. Whether the presence of the drug after long-term treatment was necessary to demonstrate this effect in their preparation is not known.

Although treatment with enalapril for 3 days alone increased MBF similarly to that seen after 10-wk treatment alone, the 3-day treatment had no effect on the relationship between RAP and RIHP. This difference between the effect of 3-day and 10-wk treatment on RIHP can probably be explained by an involvement of kinins in the short-term effect of enalapril on MBF. Mattson and Cowley (23) found that captopril given acutely increased MBF through kinin- and nitric oxide-dependent mechanisms, which also involved a decrease in venous resistance (24). The combined effect of both pre- and postcapillary vasodilation caused by 3-day treatment with enalapril could explain the seemingly paradoxical observation that MBF but not RIHP was increased at a given RAP when compared with untreated SHR. On the other hand, 10-wk treatment increased both MBF and RIHP, presumably because kinins and venous dilation were not involved in the mechanism responsible for the increase in MBF.

In summary, we have demonstrated that both short- and long-term enalapril treatment of young SHR act to enhance the transduction of changes in RAP to changes in MBF. Furthermore, at a given level of RAP, the effect on MBF of 3-day treatment and of 10-wk treatment are additive, suggesting that the mechanisms for enhancing MBF by the two treatments are different. This conclusion is supported by the fact that RIHP levels are affected differently by short-term and long-term treatment. The mechanism by which 10-wk treatment increases MBF is likely via a reduction of the pre-vasa recta resistance, which would lead to an increased MBF and RIHP at a given level of RAP. We suggest that reduction of this resistance results from the prevention of vascular hypertrophy and/or a reduction in the vascular tone, perhaps by enhancing the activity of the nitric oxide system at a given RAP. The mechanism for the effect of 3-day treatment on MBF likely involves kinin-induced dilation of pre- and post-vasa recta vessels. In this case, at a given RAP, an increase in MBF would not result in a corresponding increase in RIHP.

Perspectives

Theoretical and experimental evidence points strongly to the renal medullary circulation as being an integral component of the long-term regulation of arterial pressure (4). Alterations in renal medullary hemodynamics may play a role in the resetting of pressure natriuresis that is seen in genetic hypertension (5). In the SHR, MBF, RIHP, and sodium excretion all require a higher RAP to give normal values for these variables, consistent with a resetting of the pressure-natriuresis mechanism. The cause of this resetting is still an open question, but it appears that both structural and functional changes in the renal vasculature may be involved. The results of this study and our previous study (6) now show that ACE inhibitors are very effective antihypertensive agents in the SHR, at least in part because both short-term and long-term effects of
these drugs improve renal medullary hemodynamics to reestablish a pressure-natriuresis response more similar to that of normotensive rats. These effects probably involve both functional and structural changes in the renal vasculature that together increase MBF and enhance its response to changes in RAP. Combined with the direct tubular effect of ACE inhibition, these renal medullary hemodynamic changes increase the ability of the kidney to excrete sodium, thereby permitting a lower steady-state level of arterial pressure.

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