Evidence for Hemodynamic Autoregulation of Renin Release

By Ivar Eide, Einar Løyning, and Fredrik Kiil

ABSTRACT

To examine the relationship between renal arteriolar dilatation and renin release, arterial perfusion pressure in anesthetized dogs was lowered in steps within and below the range of autoregulation of renal blood flow. Renin release, determined by both bioassay and radioimmunoassay, averaged $2.7 \pm 0.9$ (SE) μg/min at control pressure and increased to $20.0 \pm 4.1$ (SE) μg/min at the lowest autoregulating pressure, which averaged $66.4 \pm 2.9$ (SD) mm Hg. However, renin release then remained constant during further lowering of arterial perfusion pressure despite reductions in renal blood flow. This response was not significantly changed when sodium excretion was increased by intravenous infusion of mannitol. In another series of experiments, renin release was raised by reducing arterial perfusion pressure below the range of autoregulation, and control sodium excretion was reestablished by mannitol or saline infusion; renin release remained high. Therefore, renin release appears to be related to autoregulated dilatation of the renal arterioles, and it becomes maximal when the arterioles are completely dilated at the lowest pressure of autoregulation of renal blood flow. This mechanism is different from release mechanisms dependent on sodium delivery to the distal nephron.

KEY WORDS

afferent arterioles  macula densa  angiotensin
juxtaglomerular apparatus  urinary sodium excretion  dog  tubular sodium load  kidney hormones

Two distinct renal mechanisms have been postulated for the release of renin. According to the baroreceptor hypothesis proposed by Tobian (1, 2), blood pressure stretches the afferent arteriolar wall where the renin granules are located, and a reduction in renal arterial perfusion pressure is associated with the release of renin. Therefore, reduced distention of the arteriolar wall is assumed to promote renin release, and stretching of the arteriolar wall is assumed to prevent release. However, Vander and Miller (3) have attributed the rise in renin release during a reduction in arterial pressure to the reduced delivery of sodium to the macula densa region of the distal tubules. The main evidence is that various diuretics responsible for increasing delivery to the distal tubules—the most potent being mannitol—blunt the renin release response to a reduction in arterial perfusion pressure. Considerable evidence has since accumulated for a close relationship between renin release and sodium metabolism (4). The question therefore arises whether the hemodynamic baroreceptor hypothesis is obsolete.

During lowering of the arterial perfusion pressure, renal blood flow is maintained to 65–70 mm Hg because of autoregulated vasodilatation of the arterioles. Tobian's hypothesis therefore requires the modification that dilatation rather than reduced distention of the arteriolar wall is the stimulus for renin release (5). At least two conditions must be fulfilled, however, before a hemodynamic release hypothesis can be accepted. First, if release is a consequence of arteriolar dilatation, renin release should become maximal with complete dilatation of the arterioles, i.e., at the lowest autoregulating pressure before renal blood flow declines. Further reductions in arterial perfusion pressure should cause renal blood flow to fall proportionately, signifying complete arteriolar dilatation, which, according to the hypothesis, should be associated with no further change in renin release. The second condition is that renin release should not be normalized during reduced arterial perfusion pressure by reestablishing control sodium delivery to the macula densa region.
These two conditions were examined in anesthetized dogs during mechanical constriction of the renal artery at several steps within and below the range of autoregulation. Sodium delivery to the distal tubules was maintained by infusion of mannitol or hypertonic saline.

Methods

Surgical Procedures

Experiments were performed in mongrel dogs of either sex (15-28 kg). The dogs were fasted overnight, but they had free access to water. Anesthesia was induced by sodium pentobarbital (25 mg/kg, iv) and maintained with subsequent doses (1-3 mg/kg, iv). Polyethylene catheters were inserted into the aorta for recording systemic blood pressure and for blood sampling and into the femoral vein into the renal vein for blood sampling. The left renal artery close to the aorta was approached through a flank incision, and an electromagnetic flow probe was placed on the artery. The flowmeter had been directly calibrated on renal and femoral arteries of the same caliber. A polyvinyl catheter was inserted into the renal artery peripheral to the flow probe, according to the method of Herd and Barger (6), with the tip directed upstream. Pressure was measured through this catheter with a Statham transducer and recorded on a Sanborn recorder. The renal artery was constricted with a plastic clamp, adjustable from outside the body; the clamp was placed between the flow probe and the polyvinyl catheter. Renal arterial pressure was reduced in three steps within the range of autoregulation of renal blood flow and in two to four steps below that range. Seven minutes after each blood pressure reduction, samples were taken of aortic and renal venous blood, with the addition of 5 units heparin/ml. In other experiments, renal arterial pressure was reduced below the range of autoregulation of renal blood flow and 5% mannitol (in hypotonic saline) or hypertonic saline (2.9% NaCl) was infused to reestablish sodium excretion. The blood samples were kept on ice and centrifuged at 4°C, and the plasmas were frozen for later renin determinations.

In all experiments, the ureter was cannulated with a polyethylene catheter for urine collection.

Renin Determinations

Preparation of Renin Substrate.—Angiotensinogen was prepared by exsanguinating pigs 48 hours after nephrectomy, and plasma proteins were salted out according to Dahlheim et al. (7). The precipitated fractions containing the angiotensinogen were emulsified in a minimum of distilled water and dialyzed against ethylenediaminetetraacetic acid (EDTA), 0.003 M in saline, at pH 7.0. Dialysis for 24 hours completely dissolved the precipitate, which was then frozen in small aliquots that were thawed before use. When the aliquots were buffered at pH 7.4 with 100 µliters of 1.0 M phosphate, made up to 1 ml with saline containing 0.002% neomycin, and incubated for 16 hours at 37°C with an excess of pig renin (2.5 Goldblatt units), 200 µliters of substrate formed an average of 5.75 µg/ml of angiotensin (bioassay). In nine determinations of three substrate pools, the average recovery was 98.3 ± 3.3% (SD) when 60-100 ng of angiotensin II was buffered and incubated for 16 hours with 300 µliters of substrate, indicating virtually complete inhibition of angiotensinases.

The relative velocity of angiotensin formation when dog renin was incubated with increasing amounts of pig substrate is shown in Figure 1. The reaction proceeded with zero-order kinetics at 1,725 ng (300 µliters), which was therefore used in the standard procedure. By incubating standard dog renin1 with this amount of substrate, a proportional relationship was found between added renin and generated angiotensin (bioassay) (Fig. 2). Plasma samples measured subsequently with high renin concentrations were always diluted to fall within this rectilinear curve. The renin substrates were stable for more than 1 year after preparation and generated no pressor activity when incubated alone.

Bioassay.—Renin bioassays were performed as described by Gould et al. (8), but with 300 µliters of substrate and with 0.002% neomycin (final concentration) as a bacteriostatic agent during a 16-hour incubation.

In paired incubations, each incubate was tested against angiotensin II (Hypertensin, Ciba) in at least two rats, and the coefficient of variation was 9.9%; 94.2 ± 3.2% (SD) was recovered when angiotensin II was added to plasmas before incubation.

Radioimmunoassay.—Radioimmunoassays of angiotensin I were performed according to Haber et al. (9). The plasma samples were incubated with substrate as they were for bioassay but with added EDTA, dimercaprol, and 8-hydroxyquinoline; radioimmunoassay of the incubates was performed without acidification or boiling. A standard curve was prepared for each

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1Provided by Dr. Erwin Haas, Mt. Sinai Hospital, Cleveland, Ohio.

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![Figure 1](http://circres.ahajournals.org/)

**Figure 1**

Relationship between generation of angiotensin (relative activity) and concentration of renin substrate. Data obtained from four experiments on two different substrate pools using 2.5 X 10⁻⁴ and 4.0 X 10⁻⁴ units of dog renin. Open circles indicate the mean. Bioassay.
experiment in the dog, and the complete experiment was always processed in one series. Standards (1-Asp-
5-Ile-angiotensin I [Schwarz BioResearch]) or samples were always run in duplicate. As a correction for
nonspecific effects of plasma proteins and for possible cross-reactions with substrate, one plasma from each
experiment in the dog was incubated at 4°C and then included with each of the standards. Incubating
substrate alone at 37°C generated no detectable amounts of immunoreactive substances.

Antiangiotensin I antiserum was raised according to Goodfriend et al. (10) and bound 40-60% of the labeled
angiotensin added (4,000 counts/min, i.e., 48.5 pg) at a final dilution of 1:8,000; no cross-reactions with 5-
Val- or 5-Ile-angiotensin II could be detected. Angioten-
sin I was labeled according to Greenwood et al. (11),
using 2 mc 125I and 10 µg of angiotensin I, and
separated from free 125I on a Sephadex G-10 column
(8 X 1.5 cm), emerging with an average specific
activity of 75 µCi/µg according to the method of Gocke
et al. (12).

In this radioimmunoassay system, 20 pg of angioten-
sin I would be significantly different from zero at the 5%
level (modified Student's t-test [13]). The recovery of
angiotensin I added to one or two plasmas from each of
the dog experiments was 104 ± 7.7% (sd). For different
renin concentrations in plasma, the coefficients of
variation were 4.8% within day and 6.7% between days.
Renin concentrations were given as the amount of
angiotensin generated per milliliter plasma during a 16-
hour incubation, and secretion rates were calculated by
multiplying the difference between venous and arterial
renin concentrations by the renal plasma flow. For 30
paired determinations of 30 venous-arterial sets, the
coefficient of variation was 10.9%. In single incubations
of 40 different plasmas, a close correlation was found
between radioimmunoassay and bioassay (r = 0.96)
(Fig. 3).

Wilcoxon's signed rank test (13) was used for paired
comparisons of renin release.

OTHER LABORATORY PROCEDURES
Glomerular filtration rate was measured as the
plasma clearance of 51Cr-EDTA (14), multiplying its
renal extraction by renal plasma flow. 51Cr-EDTA in a
priming dose of 75 µc and a sustaining infusion of 1
µc/min gave suitable counting statistics in all dogs
examined. Sodium concentrations in urine were mea-
sured with an EEL direct-flame photometer.

Results
Whether bioassay or radioimmunoassay was used
for renin determination, in all eight dogs similar
patterns of renin release during step reductions in
renal perfusion pressure were obtained. From a
mean control level of 2.7 ± 0.95 (se) µg/min, renin
release increased during lowering of perfusion
pressure to an average of 20.0 ± 4.1 (se) µg/min at
the lowest autoregulating pressure, which averaged
66.4 ± 2.9 (sd) mm Hg. Further lowering of the
arterial perfusion pressure to an average of 41 ± 11

FIGURE 2
Generation of angiotensin with increasing concentrations of
standard renin. Substrate concentration was 1,725 ng/ml. Bioassay.
(SD) mm Hg caused a renin release which averaged 19.8 ± 3.8 (SE) μg/min. No significant (P > 0.05) increment in renin release occurred, despite large reductions in renal blood flow and a marked increase in renal venous renin concentration. The 95% confidence interval indicated that at perfusion pressures below autoregulation renin release deviated less than ±15.5% from release obtained at the lowest step of autoregulation. Renin release remained essentially constant during constrictions lasting up to 35 minutes, although arterial concentrations of renin continued to rise. Table 1 shows results of experiments in dogs receiving no intravenous infusions. Figure 4 shows an experiment in a dog subjected to both mannitol infusion and lowering of arterial perfusion pressure, and Table 2 summarizes the other experiments of this type. Renal blood flow was maintained at a perfusion pressure averaging 66.4 ± 2.9 (SD) mm Hg for all experiments. Glomerular filtration rate was not significantly reduced at a perfusion pressure averaging 72.2 ± 8.6 (SD) mm Hg, but the lowest autoregulating pressure seemed to be higher for glomerular filtration rate than for renal blood flow. Sodium excretion was raised by mannitol infusion but fell during lowering of arterial perfusion both within and below the range of autoregulation of renal blood flow. On an average, arterial perfusion pressure was reduced to 72.5 mm Hg before sodium excretion was reduced to the control level that existed before the administration of mannitol. At this perfusion pressure, the average renin release was eight times larger than it was in the control periods.

A slightly different approach was chosen for studies in seven other dogs. The results of all experiments are summarized in Table 3. After a

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td><strong>Effect of Step Reductions in Blood Pressure on Renal Blood Flow and Renin Release</strong></td>
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<tr>
<td>Minutes</td>
</tr>
<tr>
<td>Dog 1 (5 kg)*</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>32</td>
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<tr>
<td>Dog 2 (18.5 kg)*</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>33</td>
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<tr>
<td>Dog 3 (21 kg)*</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>29</td>
</tr>
<tr>
<td>48</td>
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<tr>
<td>Dog 4 (27 kg)*</td>
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<tr>
<td>10</td>
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<tr>
<td>20</td>
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RPP = renal perfusion pressure, RBF = renal blood flow, RPF = renal plasma flow, GFR = glomerular filtration rate, UN.V = urinary sodium excretion, AP = mean aortic blood pressure, a = mean aortic renin concentration measured as the amount of angiotensin liberated per milliliter of plasma during the 16-hour incubation period (ng/ml), v = mean renal venous concentration, and RR = (v - a) X RPF, i.e., the venoarterial difference of angiotensin generated in 1 minute of plasma flow (μg/min) during the 16-hour incubation period.

*Renin determined by bioassay.
†Renin artery constricted.
‡Renin determined by radioimmunoassay.
Effect of Step Reductions in Blood Pressure and Mannitol Infusion on Renal Blood Flow, Sodium Excretion, and Renin Release

Control period, renin release was maximally raised by lowering arterial perfusion pressure below the range of autoregulation of renal blood flow. This low perfusion pressure was maintained during infusion of either mannitol (in hypotonic saline) or hypertonic saline, and plasma was sampled for determination of renin release when immediate examinations of sodium excretion showed that control levels had been reached or exceeded. In these experiments, renin release rose from 3.5 ± 3.1 (SD) μg/min in control periods to 24.2 ± 9.5 (SD) μg/min during a lowering of arterial perfusion pressure. During combined reduction of perfusion pressure and infusion of mannitol or saline, renin release averaged 25.0 ± 9.0 (SD) μg/min. Despite normalization of sodium excretion, renin release was not significantly different from release during reduced perfusion pressure alone.

See Table 1 for abbreviations. All measurements except those at zero time were made during a 5% mannitol infusion at a rate of 5 ml/min.

*Renin determined by bioassay.
†Renal artery constricted.
‡Renin determined by radioimmunoassay.
**TABLE 3**

Renin Release during Reduced Renal Perfusion Pressure and Maintained Sodium Excretion

<table>
<thead>
<tr>
<th>Minutes</th>
<th>RPP (mm Hg)</th>
<th>RBF (ml/min)</th>
<th>RPP (ml/min)</th>
<th>GFR (ml/min)</th>
<th>Uptake (uEq/min)</th>
<th>AP (mm Hg)</th>
<th>Renin (ng/ml)</th>
<th>RR (ng/min)</th>
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</thead>
<tbody>
<tr>
<td>Dog 0 (12 kg)</td>
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<td>138</td>
<td>132</td>
<td>74</td>
<td>23.7</td>
<td>28</td>
<td>145</td>
<td>164</td>
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<td></td>
<td>31</td>
<td>80*</td>
<td>117</td>
<td>75</td>
<td>19.9</td>
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<td>153</td>
<td>493</td>
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<tr>
<td></td>
<td>43</td>
<td>Infusion of 5% mannitol in 0.3% saline (5 ml/min)</td>
<td>87</td>
<td>75*</td>
<td>121</td>
<td>80</td>
<td>18.8</td>
<td>29</td>
</tr>
<tr>
<td>Dog 10 (16 kg)</td>
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<td>110</td>
<td>156</td>
<td>97</td>
<td>26.5</td>
<td>30</td>
<td>110</td>
<td>0</td>
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<tr>
<td></td>
<td>22</td>
<td>70*</td>
<td>136</td>
<td>84</td>
<td>23.7</td>
<td>4</td>
<td>125</td>
<td>100</td>
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<tr>
<td></td>
<td>33</td>
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<td>75*</td>
<td>124</td>
<td>81</td>
<td>21.0</td>
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<td>61</td>
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<td>128</td>
<td>88</td>
<td>23.4</td>
<td>52</td>
<td>110</td>
<td>40</td>
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<tr>
<td>Dog 11 (24 kg)</td>
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<td>115</td>
<td>160</td>
<td>90</td>
<td>25.2</td>
<td>17</td>
<td>128</td>
<td>69</td>
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<tr>
<td></td>
<td>20</td>
<td>72*</td>
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<td>80</td>
<td>16.4</td>
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<tr>
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<td>Infusion of 10% mannitol in 0.3% saline (7.5 ml/min)</td>
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<td>70*</td>
<td>259</td>
<td>176</td>
<td>22.9</td>
<td>234</td>
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<tr>
<td></td>
<td>183</td>
<td>70*</td>
<td>115</td>
<td>71</td>
<td>7.2</td>
<td>28</td>
<td>135</td>
<td>12</td>
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<tr>
<td>Dog 12 (23 kg)</td>
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<td>115</td>
<td>315</td>
<td>189</td>
<td>39.7</td>
<td>120</td>
<td>125</td>
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<td>Infusion of 2.9% NaCl (7.5 ml/min)</td>
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<td>70*</td>
<td>259</td>
<td>176</td>
<td>22.9</td>
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<td>75*</td>
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<td>135</td>
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<td>Dog 15 (25 kg)</td>
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<td>152</td>
<td>97</td>
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<td>14</td>
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<td>Infusion of 2.9% NaCl (7.5 ml/min)</td>
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<td>10.8</td>
<td>74</td>
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<td>115</td>
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See Table 1 for abbreviations. Renin was determined by radioimmunoassay. RR is the mean of 1–3 determinations obtained at 2-minute intervals.

*Renal artery was constricted until renal blood flow decreased.

**Discussion**

Since the renin granules are located in the walls of the afferent arterioles, renin release might vary with the degree of arteriolar dilatation. In support of this concept, this study showed that renin release reached a high and constant rate when arterioles were maximally dilated at the lowest autoregulating pressure and during further reductions in perfusion pressure. There was no relationship between renin release and renal blood flow. By the same argument, renin release was shown to be independent of glomerular filtration rate, since glomerular filtration rate continued to fall when renin release had stabilized during step reductions in arterial perfusion pressure. In the lowest autoregulating range, a reduction in glomerular filtration rate despite the maintenance of renal blood flow may reflect a decrease in postglomerular vascular...
FIGURE 4

Renin release during step reductions in renal perfusion pressure, showing that the increase in renin release is confined to the autoregulating range of renal blood flow. Solid circles indicate renal blood flow, and open circles indicate urinary sodium excretion.

Fojas and Schmid (16) and Schmid (17) showed no evidence that autoregulation was completed at 80 mm Hg. It is in conformity with the present findings that renin release is higher at 50 than at 80 mm Hg, but this finding does not imply that renin release continues to increase at perfusion pressures below the range of autoregulation. In a recent study on nine areflexic dogs, Cowley and Guyton (18) found that renin release was not significantly different at perfusion pressures ranging between 65-70 and 50-55 mm Hg. To maintain blood pressure, these dogs received large quantities of norepinephrine at a constant rate. Other studies have shown that norepinephrine infused at a constant rate has little or no effect on the range of autoregulation (19). These findings are therefore compatible with a hemodynamic mechanism for renin release. Imbs et al. (20) found declining renin release at pressures below the range of autoregulation, but these investigators used the method of Boucher et al. (21), which underestimates renin concentrations.
in one-third of human plasmas due to a shortage of substrate (22). This methodological shortcoming may have even more serious implications in studies on dog plasma because of the lower substrate concentration in this species. The method might therefore fail to reveal a further increase in already high renin concentrations in renal venous blood when renal blood flow is markedly reduced. During a severe reduction in renal blood flow, a redistribution of renin between renal venous blood, urine, and lymph might occur, but such a redistribution may not affect estimates of renin release significantly, since lymph and urine flow are low during arterial constriction and renin concentrations in these fluids almost equal those in renal venous blood (23-25).

As shown in Tables 1 and 2, arterial renin concentrations continued to rise despite the constancy of renin release. Such a rise would be expected until the rate of elimination of renin equaled the rate of release. With a half-time of elimination of about 30 minutes (26), it is clear that arterial concentrations of renin are a poor indicator of changes in renin release in acute experiments.

The second main argument for hemodynamic regulation is that the observed changes in renin release could not be attributed to changes in sodium delivery to the macula densa region of the distal tubules. Sodium delivery to the distal tubules is reduced during lowering of arterial perfusion pressure both within and below the range of autoregulation of renal blood flow, and sodium excretion reflects these changes. As illustrated in Figure 4 and Table 2, no relationship exists between renin release and sodium excretion. Furthermore, it was possible to maintain sodium excretion by mannitol or saline infusion during lowering of arterial perfusion pressure without normalization of renin release. Mannitol inhibits proximal sodium reabsorption (27) and possibly reabsorption in the ascending limb of the loop of Henle (28). Increased sodium excretion therefore reflects increased delivery to the macula densa region, but sodium reabsorption from the lumen through the macula densa into the interstitial area may not be increased, although mannitol is the most efficient inhibitor of renin release during constriction of the renal artery (3). Saline infusion increases glomerular filtration rate and inhibits proximal reabsorption (29). The increased delivery from the proximal tubules is partly compensated for by increased reabsorption in the ascending limb (30) associated with a rise in the energy requirement (31). Because there is no indication of distal inhibition of sodium reabsorption (32), it may safely be assumed that both the delivery to the macula densa region and the sodium reabsorption at the macula densa were raised during saline infusion. Nevertheless, renin release was not inhibited.

Apart from a single difference, the general design for the last part of the present study was the same as that used by Vander and Miller (3). In the present study care was taken to reduce arterial perfusion pressure until maximal secretion rates of renin were obtained before administration of solutes. In contrast, Vander and Miller (3) reduced arterial perfusion pressure to only 90 mm Hg. At this pressure, renin release is labile and far from maximal. This difference in design may account for the minimal effect of mannitol and saline infusion on renin release in the present study.

In a nonfiltering kidney preparation, Blaine et al. (33) found that renin release varied with perfusion pressure; variations in delivery to the macula densa region could thus be excluded as a factor regulating renin release. The results of the present investigation more specifically favor a hemodynamic regulation and strongly support the baroreceptor hypothesis, although in a modified version. It should be emphasized, however, that these studies do not rule out the macula densa hypothesis: at high infusion rates of saline and mannitol when control excretion rates of sodium were greatly exceeded renin release declined. Speculation may therefore be made as to the existence of both a production mechanism dependent on stimuli from the macula densa region and a release mechanism affected by the degree of arteriolar dilatation.

Because most of the change in renin release occurred by variations in perfusion pressure within the lowest 15 mm Hg of the range of autoregulation, hemodynamically induced release may be the main mechanism under pathological conditions of arterial or arteriolar obstructions. But such a mechanism is probably of less significance in the regulation of renin release during variations in sodium load to macula densa at normal blood pressure.

Acknowledgment

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