The Signal Perceived by the Macula Densa during Changes in Renin Release

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ABSTRACT

Renin secretion was studied in acute experiments in dogs during occlusion of the ureter alone (experiment 1), ureteral occlusion with a superimposed intrarenal infusion of papaverine (experiment 2), or ureteral occlusion with a superimposed intravenous ethacrynic acid injection (experiment 3) and following release of the ureteral occlusion (all three experiments). In all three experiments, ureteral occlusion increased renin secretion four- to fivefold. In experiment 2, papaverine, an inhibitor of smooth muscle contractility, was infused intrarenally during the last 20 minutes of ureteral occlusion, but renin secretion was unchanged by the infusion. Renin secretion decreased rapidly and was at the control level 5, 12 1/2, and 27 1/2 minutes after release of the occlusion, but urinary sodium concentration and excretion rate increased markedly during this period. In experiment 3, a superimposed injection of ethacrynic acid failed to alter renin secretion during ureteral occlusion. After release of the ureter, renin secretion remained unchanged for the first 5 minutes. Although renin secretion had decreased 12 1/2 and 27 1/2 minutes after release of the occlusion, it was still elevated twofold above the control level. Again, sodium excretion increased markedly and urinary sodium concentration was high after ureteral release. These findings support the hypothesis that the rate of renin release is inversely related to the rate of sodium transport by the macula densa cells.

KEY WORDS

- renin secretion in the dog
- renal venous plasma renin activity
- papaverine
- ethacrynic acid
- ureteral occlusion
- macula densa receptor

Over the years, evidence has accumulated to support the idea that two wholly intrarenal mechanisms control renin release (1-3); these mechanisms involve an intrarenal vascular receptor in the renal afferent arteriole and the macula densa. The concept of an intrarenal vascular receptor originated with Tobian et al. (4), and early support for the proposed vascular receptor was provided by the experiments of Skinner et al. (5). Vander and Miller (6) and Thurau et al. (7) have championed the macula densa hypothesis. The precise signal perceived by the macula densa is unknown, but it might be related to changes in the renal tubular sodium load (6) or concentration (7). In addition to these two intrarenal mechanisms, studies have implicated the sympathetic nervous system and circulating catecholamines, sodium and potassium ions, angiotensin II, and antiuretic hormone (ADH) in the control of renin secretion (1-3).

Recent observations (8-11) on renin release in the nonfiltering kidney model in which the macula densa is rendered nonfunctional have provided strong support for the existence and the autonomy of the renal vascular receptor, but much less is known about the proposed macula densa receptor. Several investigators (12-14) have studied renin release during ureteral occlusion in an attempt to evaluate the role of the macula densa in renin release. In these studies, an increase in renin secretion or renal venous renin activity has been reported during this maneuver (12-14). Whether the response resulted from activation of the macula densa, the renal vascular receptor, or both cannot be deduced from available evidence, because sodium delivery to the distal tubule, renal hemodynamics, and interstitial pressure are all altered by ureteral occlusion.

The present experiments were designed to provide new information concerning both the autonomy of the proposed macula densa receptor and the nature of the signal perceived by it. Previous studies from this laboratory (10, 11) on renin release in the nonfiltering kidney model have demonstrated that intrarenally administered papaverine, which is known to abolish autoregulation (15), blocks the intrarenal vascular receptor controlling renin release. Therefore, papaverine was...
infused intrarenally during ureteral occlusion in an attempt to block the renal vascular receptor mechanism. Lack of a significant fall in renin secretion in response to intrarenally administered papaverine would suggest a possible role for the macula densa. More important, however, it was reasoned that these experiments might provide data which would have a direct bearing on the signal perceived by the macula densa. Since it has been hypothesized (7) that an increase in sodium concentration at the macula densa produces an increase in local renin activity, the response to ethacrynic acid was studied because there is evidence (16–18) that increased acid in conjunction with ureteral occlusion in their concentration. Cooke et al. (12) used ethacrynic sodium and, possibly, to an increased sodium exposure the macula densa to an increased load of sodium and, possibly, to an increased sodium concentration. Cooke et al. (12) used ethacrynic acid in conjunction with ureteral occlusion in their study which supports the idea that increased sodium concentration at the macula densa is a stimulus for renin release.

Methods

Twenty-two female mongrel dogs weighing 15–26 kg were used in this study. All of the dogs were maintained on a diet that provided approximately 65 mEq of sodium and 55 mEq of potassium daily for at least 4 days prior to the day of the acute experiment. Water was available ad libitum. The dogs were fed in the late afternoon; all experiments were performed with the dogs in the postabsorptive state. Four different experimental protocols were used.

EXPERIMENT 1: EFFECTS OF URETERAL OCCLUSION

On the morning of the acute study, five dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv), and a right unilateral nephrectomy was performed on each dog after the left kidney had been examined to establish that only one renal artery was present and, therefore, that it was suitable for the experiment. If the left kidney was not suitable, then the right kidney was used and a left nephrectomy was done. Nephrectomy was necessary so that observable responses could be related to the kidney being studied. A catheter (Fr 8 polyvinyl) was placed in the right femoral artery, and the tip was advanced into the abdominal aorta for the continuous measurement of arterial blood pressure via a Statham pressure transducer (model P23Db) and a Sanborn recorder (model 7700). Arterial blood for renin determination was also taken from this catheter. Renal venous blood for renin determination was obtained from a catheter attached to an 18-gauge hypodermic needle inserted into the renal vein. Another catheter (Fr 8 polyvinyl) was placed in a femoral vein for the replacement of all blood taken for renin determination. The ureter was catheterized with PE 160 tubing for collection of urine. Renal blood flow was determined with an electromagnetic flowmeter (Carolina Electronic Instruments) via a noncannulating flow probe placed on the renal artery. A 22-gauge hypodermic needle was inserted into the renal artery distal to the flow probe, and an infusion with 0.9% saline was begun at 0.6 ml/min and maintained for the duration of the experiment. The dog was allowed to recover from surgery for approximately 1 hour before the experiment was started.

After two 20-minute observation periods to establish the control levels of renin secretion, renal blood flow, arterial blood pressure, and excreted sodium, ureteral pressure was abruptly elevated to 60–80 mm Hg by the retrograde infusion of a small volume (3–4 ml) of previously collected urine. The ureter was then occluded by attaching it to a Statham pressure transducer (model P23Db). The rates of renin secretion, renal blood flow, and arterial blood pressure were measured at 10, 20, 30, and 40 minutes following ureteral occlusion. After 40 minutes, ureteral occlusion was released to reestablish urine flow, and observations were again made to measure renin secretion, renal blood flow, and arterial blood pressure 5, 12, and 27 minutes later. During the first 5 minutes after release of ureteral occlusion, the urine was collected serially in 1-ml samples which were later analyzed for sodium concentration. After the first 5 minutes, urine was collected over two 15-minute periods, i.e., at 20 and 35 minutes after ureteral occlusion had been released. Following these initial observations, a recovery period of 1 hour was allowed before recovery levels of renin secretion, renal blood flow, arterial blood pressure, and sodium excretion were determined.

EXPERIMENT 2: EFFECTS OF URETERAL OCCLUSION WITH SIMULTANEOUS INTRARENAL INFUSION OF PAPAVERINE

To evaluate the effects of papaverine infusion, a protocol identical to that in experiment 1 with one important exception was followed in six dogs. After the first 20 minutes of ureteral occlusion, the 0.9% saline infusion into the renal artery was discontinued and papaverine infusion was begun in normal saline at 0.6 ml/min at a rate of 3–7 mg/min for the papaverine; this rate of papaverine infusion had previously been found to cause maximal renal blood flow with minimal effects on arterial blood pressure. Infusion of papaverine was continued for the duration of the ureteral occlusion and the 35 minutes immediately following release of ureteral occlusion, i.e., it was continued until the 1-hour recovery period was begun. At this time, saline infusion was reestablished.

EXPERIMENT 3: EFFECTS OF URETERAL OCCLUSION WITH ETHACRYNIC ACID ADMINISTRATION

To evaluate the effects of ethacrynic acid administration, a protocol identical to that in experiment 1 was followed in six dogs with the following exception: 50 mg of ethacrynic acid was given intravenously as a single injection after the first 20 minutes of ureteral occlusion.

EXPERIMENT 4: EFFECTS OF ETHACRYNIC ACID ADMINISTRATION WITHOUT URETERAL OCCLUSION

To evaluate the effects of ethacrynic acid administration without ureteral occlusion, a protocol very similar to the preceding protocols was used. Five dogs were prepared as the dogs had been in experiment 1, and
observations were made to establish control levels of renin secretion, renal blood flow, arterial blood pressure, and excreted sodium. Then 50 mg of ethacrynic acid was given intravenously, and renin secretion, renal blood flow, and arterial blood pressure were determined 5, 12, and 27 minutes later. Renal sodium excretion was determined 5, 20, and 35 minutes after administration of the ethacrynic acid. A period of 1 hour was allowed for recovery, and then additional observations were made.

ANALYTICAL METHODS
The techniques for measurement of plasma renin activity have been reported previously (19). Briefly, 10-ml samples of arterial and renal venous blood were collected in 0.1 ml of 10% ethylenediaminetetraacetic acid (EDTA) during each control, experimental, and recovery period. The samples were cooled to 4°C, and the plasma was removed after centrifugation. After the samples had been prepared for assay of renin by the method of Schneider et al. (19), they were assayed by the pressor response in the pentobarbital-anesthetized, pen tolinium-blocked rat; angiotensin II (Hypertensin, CIBA) was used as the standard. Plasma renin activity is expressed as nanograms of angiotensin II per milliliter per 3 hours of incubation. Renin secretion was calculated by multiplying the renal plasma flow by the difference in renal vein plasma renin activity and arterial plasma renin activity. Urinary sodium was measured by flame photometry, and hematocrit was determined by the capillary tube method.

Student's t-test for paired observations was used for statistical analysis of the data. Values are presented as means ± SE.

Results

EXPERIMENT 1
The results of experiment 1 are presented in Figures 1 and 2. Ureteral occlusion increased renin secretion significantly \( (P < 0.05) \) from a mean control level of 625 ± 251 ng angiotensin II/min to a mean of 958 ± 994 ng/min during the first 20 minutes of occlusion and a mean of 2255 ± 1024 ng/min during the last 20 minutes of occlusion. Immediately following release of ureteral occlusion, renin secretion fell quickly to levels not significantly different from the control level \( (P > 0.1) \). Renin secretion did not change during the recovery period \( (P > 0.1) \). Although it is not shown in either Figure 1 or Figure 2, renal venous renin activity also increased significantly \( (P < 0.05) \) from a control level of 10.6 ± 3.7 ng angiotensin II/ml to means of 24 ± 9.0 and 26.4 ± 9.4 ng/ml during the first and last 20 minutes of occlusion, respectively. Renal venous renin activity decreased in parallel with renin secretion following the release of ureteral occlusion. Renal blood flow during ureteral occlusion was not significantly different from the control flow \( (P > 0.1) \), but it fell approximately

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

Changes in renin secretion, sodium excretion, arterial blood pressure (BP), and renal blood flow (RBF) in five dogs before, during, and after ureteral occlusion. In this figure and all subsequent figures, the asterisks indicate \( P \) values for the noted period compared with the control period. Values are means ± SE.

![FIGURE 2](http://circres.ahajournals.org/)

Changes in the urinary sodium concentration in 1.0-ml serial urine samples collected during the first 5 minutes following the release of ureteral occlusion in experiment 1 (n = 5).
40–50 ml/min following release of the occlusion; this fall was not quite statistically significant at the 5% level. Renal sodium excretion increased significantly \( (P < 0.025) \) following release of the occlusion and returned to the control level during the recovery period \( (P > 0.2) \). Serial analysis (Fig. 2) of urinary sodium concentration during the first 5 minutes following the release of ureteral occlusion revealed a brief transient increase in sodium concentration followed by a decrease. Neither arterial blood pressure nor hematocrit changed throughout the duration of the experiment.

**EXPERIMENT 2**

The results of experiment 2 are presented in Figures 3 and 4. As in experiment 1, ureteral occlusion increased renin secretion significantly \( (P < 0.025) \) from a mean control level of 460 ± 152 ng angiotensin II/min to a mean of 2173 ± 519 ng/min during the first 20 minutes of occlusion and a mean of 2473 ± 457 ng/min during the last 20 minutes of occlusion when a simultaneous intrarenal infusion of papaverine was being given at 3–7 mg/min. The response of renin secretion to ureteral occlusion was not significantly altered by the papaverine infusion \( (P > 0.15) \). Immediately following release of ureteral occlusion and with continued infusion of papaverine, renin secretion fell very quickly to levels below the control level \( (P < 0.05) \) and remained depressed during the recovery period; however, only the 5-minute postocclusion renin secretion value of −203 ± 210 ng/min was significantly less than the control level of 460 ± 152 ng/min \( (P < 0.05) \). Renal venous renin activity also increased significantly \( (P < 0.025) \) from a mean control level of 15.6 ± 3.7 ng angiotensin II/ml to mean values of 37.3 ± 4.9 and 44.4 ± 7.1 ng/ml during the first and last 20 minutes of occlusion, respectively. Renal venous renin activity was not significantly altered by infusion of papaverine during ureteral occlusion \( (P > 0.15) \). Renal venous renin activity decreased rapidly toward the control level to values ranging from 19.6 ± 6.0 ng/ml to 22.3 ± 5.6 ng/ml following the release of ureteral occlusion; these decreased levels were significantly different from the occlusion levels \( (P < 0.05) \). Renal blood flow was 250 ± 36 ml/min during the control period and 279 ± 38 and 279 ± 36 ml/min during the first 20 minutes of ureteral occlusion; renal blood flow increased to 287 ± 36 and 284 ± 35 ml/min during the last 20 minutes of ureteral occlusion with simultaneous papaverine infusion \( (P < 0.05) \). Following release of the ureteral occlusion and with continued infusion of papaverine, renal blood flow returned toward or to...
the control level; however, it declined significantly from the control of 250 ± 36 ml/min to 215 ± 34 ml/min (P < 0.025) during the recovery period. Renal sodium excretion increased significantly (P < 0.01) immediately following release of the occlusion but returned to the control level (P > 0.2) during the recovery period. Arterial blood pressure increased slightly during the entire period of ureteral occlusion and decreased slightly after release of the occlusion; however, none of the changes were statistically significant (P > 0.1). The hematocrit was 41% during the control period and 43% during the recovery period (P > 0.1). Serial analysis (Fig. 4) of urinary sodium concentration during the first 5 minutes following release of ureteral occlusion revealed a rapid increase to a plateau; thus, urinary sodium concentration was markedly elevated at the time when renin secretion was significantly depressed below both control and occlusion levels (Fig. 3).

EXPERIMENT 3

The results of this experiment are presented in Figures 5 and 6. Again, ureteral occlusion increased renin secretion significantly (P < 0.025) from a mean control value of 309 ± 72 ng angiotensin II/min to a mean of 1455 ± 318 ng/min during the first 20 minutes of ureteral occlusion and a mean of 1677 ± 351 ng/min during the last 20 minutes of occlusion with simultaneous ethacrynic acid administration (50 mg, iv). The response to ureteral occlusion alone appeared to be slightly less than that in experiments 1 and 2, but the difference in response was not significant (P > 0.05). Renin secretion was not significantly altered during ureteral occlusion by ethacrynic acid administration (P > 0.15), and it did not change significantly (P > 0.25) during the first 5 minutes following release of the ureteral occlusion. Renin secretion had declined significantly (P < 0.05) from the occlusion rates of secretion 12½ and 27½ minutes after release of the occlusion, but it was still elevated approximately twofold (P < 0.05 for the 27½-minute value) over the control level. Renin secretion returned to the control level (P > 0.4) during the recovery period. Renal venous renin activity increased significantly (P < 0.025) from a mean control level of 14.1 ± 2.0 ng angiotensin II/ml to a mean of 31.1 ± 5.2 ng/ml during the first 20 minutes of ureteral occlusion and a mean of 34.7 ± 5.5 ng/ml during the last 20 minutes of the occlusion with simultaneous administration of ethacrynic acid. Renal venous renin activity remained elevated approximately twofold above the control level during the entire first 27½ minutes after the release of ureteral occlusion (P < 0.05 for all three

FIGURE 5

Changes in renin secretion, sodium excretion, arterial blood pressure (BP), and renal blood flow (RBF) in six dogs before, during, and after ureteral occlusion with ethacrynic acid administration (50 mg, iv). Values are means ± SE.

FIGURE 6

Effect of ethacrynic acid on the changes in sodium concentration in 1.0-ml serial urine samples collected during the first 5 minutes following the release of ureteral occlusion in experiment 3 (n = 6).
values). Moreover, unlike renin secretion, renal venous renin activity did not decrease significantly from occlusion levels until 27½ minutes after release of the occlusion and remained significantly elevated ($P < 0.05$) above the control level at 20.7 ± 2.2 ng/ml during the recovery period. Renal blood flow increased slightly during the duration of ureteral occlusion, but this change was not significant ($P > 0.05$). However, renal blood flow did increase significantly ($P < 0.025$) from the mean control level of 302 ± 41 ml/min to a mean of 380 ± 22 ml/min within 5 minutes after release of the occlusion; it then declined and was significantly depressed to a mean of 224 ± 18 ml/min during the recovery period ($P < 0.025$). Urinary sodium excretion increased markedly ($P < 0.01$ for all three periods) during the first 35 minutes following release of ureteral occlusion and was still elevated approximately threefold above the control level ($P < 0.025$) during the recovery period. Mean arterial blood pressure did not change significantly throughout the course of the experiment, but hematocrit was elevated from a control of 42 ± 1% to a mean of 50 ± 2% during the recovery period ($P < 0.01$). Serial analysis (Fig. 6) of urinary sodium concentration during the first 5 minutes following the release of ureteral occlusion revealed that it increased rapidly and then reached a plateau; thus, urinary sodium concentration was markedly elevated at the time when renin secretion and renal venous renin activity were unchanged from occlusion levels.

**EXPERIMENT 4**

The results of this experiment are presented in Figure 7. Ethacrynic acid administration (50 mg, iv) resulted in an increase in renin secretion from a control level of 480 ± 165 ng angiotensin II/min to means of 1437 ± 200, 1603 ± 222, and 1312 ± 89 ng/min 5, 12½, and 27½ minutes later, respectively ($P < 0.05$ for all three values); renin secretion returned to near the control value during recovery ($P > 0.2$). Renal venous renin activity also increased after ethacrynic acid administration from a mean control level of 9.3 ± 1.8 ng/ml to 18.6 ± 2.8, 23.0 ± 3.4, and 24.3 ± 3.9 ng/ml 5, 12½, and 27½ minutes later, respectively ($P < 0.05$ for all three values); it returned to 13.9 ± 2.3 ng/ml during the recovery period ($P > 0.05$ compared with the control of 9.3 ± 1.8 ng/ml). Renal blood flow increased from a mean control level of 254 ± 54 ml/min to 277 ± 57, 282 ± 56, and 279 ± 57 ml/min 5, 12½, and 27½ minutes after ethacrynic acid administration ($P < 0.05$ for all three values); although it then declined to a mean of 237 ± 45 ml/min during the recovery period, this level was not significantly less than the control level of 254 ± 54 ml/min ($P > 0.15$). Renal sodium excretion increased more than tenfold during the 35 minutes following ethacrynic acid administration ($P < 0.01$ for all three values) and was still elevated from the control value of 33 ± 11 μEq/min to 251 ± 21 μEq/min during the recovery period ($P < 0.01$). Arterial blood pressure did not change significantly during the course of the experiment. However, the hematocrit was significantly changed from its control value of 44 ± 1% to 48 ± 2% at 27½ minutes after ethacrynic acid administration ($P < 0.025$) and 52 ± 2% during the recovery period ($P < 0.025$).

**Discussion**

According to current theory, two intrarenal receptors—the intrarenal vascular receptor in the renal afferent arteriole and the macula densa—are
the primary regulators of renin release (1–3). Convincing evidence has been obtained for both the existence and the autonomy of the intrarenal vascular receptor (8–11), but less is known about the macula densa. One reason for the lack of evidence about the macula densa is that no one has identified a forcing which affects renin release via a macula densa input only; most experimental forcings could conceivably influence the renin release mechanisms by activation of both the renal vascular receptor and the macula densa.

In the present experiments, papaverine was given in an attempt to block the renal vascular receptor mechanism. It has been demonstrated previously that the intrarenal infusion of papaverine blocks the increase in renin release in response to hemorrhage in dogs with a nonfiltering kidney (10) and produces a marked decrease in renin release in dogs with thoracic caval constriction and a nonfiltering kidney (11). Papaverine relaxes smooth muscle, and its previously observed (10, 11) blocking action appears to be referable to its inhibition of the vascular smooth muscle in the renal afferent arteriole. Also, Thurau and Kramer (15) have found that papaverine blocks renal autoregulation, which is an afferent arteriolar function. In the present study (experiment 2), papaverine failed to reduce renin secretion elicited by ureteral occlusion; this finding gives no indication of involvement of the vascular receptor. However, if the vascular receptor responds to a decrease in the transmural pressure gradient secondary to an increase in renal interstitial pressure, then it is possible that renal afferent arteriolar dilatation might not prevent the vascular receptor from responding. Thus, the possibility that the renal vascular receptor is involved in the increased renin release induced by ureteral occlusion must still be considered; this interpretation is in agreement with the recent finding of Kaloyanides et al. (20). These workers have demonstrated that raising renal perfusion pressure decreases renin release during ureteral occlusion, a finding that seems to be best explained by an action on the renal vascular receptor.

In regard to the macula densa theory of renin release, there have been two schools of thought. First, Vander and Miller (6), Vander and Carlson (21), and Nasch and co-workers (22) have suggested that renin release is inversely related to either sodium load at the macula densa or some associated function such as sodium transport by the macula densa cells. Second, Thurau et al. (7), Meyer and associates (23), and Cooke et al. (12) have related increased renin release to increased sodium concentration at the macula densa. Since glomerular filtration ceases and movement of fluid down the renal tubule system is slow or absent during ureteral occlusion, it seems likely that the macula densa senses a decrease in sodium load if it is involved in the hypersecretion of renin during ureteral occlusion. More important, perhaps, are the changes in sodium load and sodium concentration following release of the ureteral occlusion. In experiment 1, renal sodium excretion increased strikingly during the first 5 minutes following the release of the occlusion and, in experiment 2, both urinary sodium concentration and the rate of sodium excretion increased; these increases were associated with a striking decrease in renin release. If the macula densa is involved in the increase in renin secretion induced by ureteral occlusion, then the most reasonable interpretation of the data on the response to opening the ureter is that the increased renal tubular sodium load or sodium concentration is associated with the decreased renin secretion. After release of the ureteral occlusion, both renin secretion and renal venous renin activity remained at low preocclusion levels for the remainder of experiments 1 and 2. It should also be pointed out that the rate of renal sodium excretion after release of the ureteral occlusion was considerably higher during papaverine infusion (experiment 2) than it was after reopening of the ureter alone (experiment 1). It has been reported previously (24) that papaverine produces renal tubular rejection of sodium.

In experiment 3, renin secretion and renal venous renin activity were unchanged during the first 5 minutes following release of the ureteral occlusion, although the urinary sodium concentration was high. If the macula densa is involved in this situation, failure of renin secretion to fall might reflect a direct action of ethacrynic acid on the macula densa cells to inhibit sodium transport. This interpretation assumes that renin secretion during ureteral occlusion alone was high enough that ethacrynic acid administration did not increase secretion further. The fall in renin secretion 12½ minutes after release of the ureteral occlusion might reflect an overriding influence of increased sodium load to the macula densa in comparison with a direct action of ethacrynic acid on the macula densa cells. This effect could have occurred alone or in combination with a decrease in renal interstitial pressure and an increase in the pressure gradient across the renal arteriolar wall; either way, the result was a decrease in renin release. Although
renin release continued to remain depressed below the occlusion levels throughout the duration of the experiment, renin secretion was still elevated approximately twofold above the preocclusion levels, and it did not return to control values until the recovery period. Thus, the decrease in renin secretion was slower following release of the occlusion in this experiment with ethacrynic acid than it was in the experiments with ureteral occlusion alone (experiment 1) or ureteral occlusion in conjunction with infusion of papaverine (experiment 2). Moreover, there was a clear dissociation between renin secretion and renal venous renin activity in this experiment, since renal venous renin activity did not decrease significantly from occlusion levels until 27 1/2 minutes after release of the occlusion and, unlike renin secretion, never returned to the control level during the recovery period.

Ethacrynic acid administration without ureteral occlusion (experiment 4) increased both renin secretion and renal venous renin activity approximately two- to threefold within 5 minutes; both parameters were maintained at elevated levels until the recovery period. Because renin secretion always decreased after release of the ureteral occlusion in the other three experiments and presumably in association with an increase in sodium load at the macula densa, the results of experiment 4 suggest that ethacrynic acid increases renin secretion by a direct action on the macula densa.

Investigators have suggested that ethacrynic acid (12, 25) and furosemide (23) stimulate renin secretion by increasing the sodium concentration at the macula densa. This interpretation is predicated on the basis of experiments which indicate that these drugs inhibit sodium reabsorption in the ascending limb of the loop of the Henle (16-18).

The present data, however, do not support this macula densa hypothesis of renin release. Although ethacrynic acid administration alone (experiment 4) resulted in an increase in renin secretion, renin secretion decreased significantly (experiment 3) at a time when renal sodium excretion increased and, presumably, sodium concentration and sodium load at the macula densa increased. Therefore, these data are difficult to reconcile with the hypothesis that an increase in sodium concentration per se stimulates renin release. Indeed, other investigators (6, 21, 22) have suggested that renin release is inversely related to net sodium flux into or across the macula densa cells. In this context, Vander and Carlson (21) have suggested that diuretics such as ethacrynic acid and furosemide increase renin release but not by increasing the sodium concentration at the macula densa cells. This hypothesis also explains the current data.

Let us examine the predictions of the hypothesis that macula densa regulation of renin release is inversely related to net sodium flux into or across the macula densa region. Accordingly, ethacrynic acid suppresses net sodium flux enough to result in a two- to threefold increase in renin release (experiment 4), and ureteral occlusion suppresses net sodium flux enough to result in a four- to fivefold increase in renin release (experiments 1-3). Release of ureteral occlusion in the absence of ethacrynic acid (experiment 1) results in the prompt return of renin release back to control levels. The hypothesis predicts, however, that the release of ureteral occlusion in the presence of ethacrynic acid should result in a decrease in renin release from the ureteral occlusion level (four- to fivefold elevation) to the ethacrynic acid level (two- to threefold elevation). This situation is indeed the observed finding in experiment 3 of the present study (Fig. 5). In experiment 3, ureteral occlusion increased renin secretion approximately fivefold. After the release of ureteral occlusion in the presence of ethacrynic acid, however, renin release decreased to a level which was still elevated approximately twofold over the control level; in other words, renin secretion decreased to the ethacrynic acid level observed in experiment 4. Also, after the ureter was released, the drop from a four- to fivefold to a two- to threefold elevation in renin secretion was associated with an increase in urinary sodium concentration and excretion. In addition, there was volume depletion and, presumably, activation of the renal vascular receptor in both experiment 3 and experiment 4.

Cooke and co-workers (12) performed an experiment very similar to experiment 3 of the current study, but they obtained different results. When they administered ethacrynic acid during ureteral occlusion, they too found that no change in renal venous renin activity occurred. However, following release of the ureters, they reported a prompt rise in renal venous renin activity from a mean of 4754 ± 875 to 7488 ± 1306 ng angiotensin II/100 ml plasma at 5-15 minutes after release. This rise occurred in association with an increase in urinary sodium concentration. These data differ from our renal venous renin activity data which showed no significant change from 34.7 ± 5.5 to 29.2 ± 4.4 and 28.7 ± 4.0 ng angiotensin II/ml plasma at 5 and 12½ minutes, respectively, following release of occlusion (P > 0.1 for both values). The cause of this discrepancy is not known, but it should be
nism for the control of renin release. Moreover, the explanation on the basis of a macula densa mechanism provides support for the earlier hypothesis of Vander and Miller (6), Vander and Carlson (21), and Nash et al. (22) that renin release is inversely related to sodium transport into or across the macula densa cells.

In the broader context of renin secretion and its control, available evidence thus provides support for the existence of both a renal vascular receptor (5, 8-11) and a macula densa receptor (6, 21, 22, and present experiments). Superimposed on and interacting with these two more basic mechanisms are the renal sympathetic nerves and various humoral agents including angiotensin II, ADH, sodium and potassium ions, and the catecholamines (1-3). Both intrarenal receptors probably operate together to regulate closely renin secretion and the extent of dominance is probably variable under different conditions.

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References

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