Control of Renin Secretion

By Sandford L. Skinner, M.D., James W. McCubbin, M.D., and Irvine H. Page, M.D.

The nature of the stimulus that causes kidneys to release renin has not been established with certainty. It has been assumed by many that ischemia is a logical cause, while others have concluded that a hemodynamic change is responsible. Several hypotheses have been based on a suggestive, but unproven, correlation between degree of granulation of the juxtaglomerular apparatus and rate of secretion of renin. (For review see Braun-Menendez et al., Tobian, and Page and McCubbin.)

During experiments which demonstrated that renin is released primarily into renal venous blood rather than renal lymph, it was noted that renin secretion increased during rather small reductions in renal perfusion pressure that were not likely to cause renal ischemia. This observation was pursued and preliminary experiments indicated that renin could be released during reduction in renal perfusion pressure without change in total renal blood flow. A renal baroreceptor mechanism was postulated to control renin secretion. The present experiments examine the behavior of this baroreceptor more fully and investigate the effects of a variety of other stimuli on renin secretion.

Methods

Thirty fasting mongrel dogs weighing 10 to 20 kg were anesthetized with morphine sulphate (2 mg/kg sc) and sodium pentobarbital (15 mg/kg iv). Through a flank incision the left renal pedicle was exposed and a noncannulating square-wave electromagnetic flowmeter* applied to the renal artery, leaving renal nerves intact. The flowmeter was calibrated using whole blood with different hematocrit values; the response was linear over a range of 40 to 400 ml/min. Once balanced, the instrument did not drift significantly during the experiment; both mechanical zero and sensitivity remained essentially unchanged. Five per cent was the threshold for accurate detection of change in flow in the range 100 to 300 ml/min. In determining absolute flows, correction was made for the hematocrit in all experiments. Renal venous blood was collected as required through a polyethylene catheter (1.5 mm outside diameter) threaded into the left renal vein via the left testicular or ovarian vein and passed peripherally into the hilum. Pressure in the aorta at the level of the renal arteries was recorded continuously with a strain gauge manometer, via a polyethylene catheter passed from a femoral artery. Intermittent positive pressure respiration was used in all experiments. Five per cent dextrose in physiological saline was given by slow intravenous drip. In some experiments, oxygen saturation was determined on 2 ml samples of arterial and renal venous blood using a light reflection oximeter.

PLASMA PESSOR ASSAY

Samples of arterial and renal venous blood (3 to 5 ml) were collected simultaneously into 5 × 10⁻⁸ molar disodium ethylenediaminetetraacetic acid (EDTA) which acted as an anticoagulant and also inhibited plasma angiotensinase A. All blood samples were treated in an identical manner, centrifuged at 7,000 rev/min for 5 minutes at 20°C, the plasma separated, divided into two portions, and then frozen within 10 minutes of collection. At a later time, one portion of each plasma sample was incubated for 60 minutes at 37°C and again frozen. The pH of plasma remained at 7.4 ± 0.05.

Assay of pressor activity in incubated and unincubated plasma was performed on rats of either sex and weighing 150 to 200 g. They were anesthetized with sodium amobarbital (10 mg/100 g iv), treated with pentolinium tartrate (4 mg/100 g sc), a tracheal cannula inserted, and

* Carolina Medical Electronics.
† American Optical Company.
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vagotomy performed. Plasma samples, kept cold throughout the assay, were brought to body temperature one minute before slow injection of 0.1 to 0.2 ml into a cannulated jugular vein. The subsequent pressor response was recorded from a carotid artery with a strain gauge manometer on slow moving paper. During all assays, angiotensin (aspartyP, isoleucyl'octapeptide) was injected at frequent intervals to determine the sensitivity of the preparation. Rats were discarded unless a consistent response of 15 mm Hg or more was obtained to a dose of 2 nanograms of angiotensin.

DETECTION OF CHANGES IN THE RATE OF RENIN SECRETION

Changes in the rate of renin secretion were detected by comparing the pressor activity of incubated renal venous plasma with that of simultaneously sampled incubated arterial plasma and then comparing each with their unincubated counterparts. Before an increase in pressor activity of incubated renal venous plasma could be accepted as indicating an increase in renin secretion, the following criteria had to be applicable:

1. Incubated renal venous plasma collected during an experimental period demonstrated greater increase in pressor activity over control samples than did incubated arterial plasma, i.e., an increased veno-arterial difference in plasma pressor activity across the kidney.
2. Incubated renal venous and arterial plasma displayed greater pressor activity than their unincubated counterparts.
3. When normal renal perfusion was reinstated, the pressor activity of incubated renal venous plasma reverted to control values.
4. The pressor material in incubated plasma displayed the properties of angiotensin, being unaffected by norepinephrine or serotonin blocking drugs, being stable during heat precipitation of protein, but being destroyed by chymotrypsin. The details of these procedures have been described elsewhere.
5. Change in pressor activity of incubated renal venous plasma could not be accounted for on the basis of a change in renal blood flow either concentrating or diluting renin leaving the kidney into a smaller or larger volume of blood.

Results

The kidneys were subjected to the following altered arterial perfusion characteristics.

1. REDUCTION IN RENAL ARTERIAL MEAN PRESSURE WITHOUT CHANGE IN MEAN BLOOD FLOW

In 18 dogs, the aorta was constricted by means of a tape introduced through the left flank incision and placed above the renal arteries. The ends of the tape were passed through a short polyethylene tube to provide a sliding noose with which constriction could be adjusted to produce any desired level of mean pressure at the renal arteries. At the end of each experiment the position of the tape was examined and found to be at least half an inch above the right renal artery. The flowmeter was applied to the left renal artery only, it being assumed that both kidneys would be affected similarly by aortic constriction.

Figure 1 illustrates a typical experiment, similar results being obtained in 15 of the 18 dogs. The upper tracings show the renal arterial perfusion characteristics before, during, and after two short periods of aortic constriction. The lower tracing is the corresponding assay of pressor activity in incubated arterial and renal venous plasma collected at the time indicated. The pressor responses to incubated renal venous plasma have been traced across the bottom of the mean pressure channel at their respective times of sampling.

Each period of aortic constriction was associated with a reduction in the pulsatile portion of renal blood flow, reduction in pulse pressure, and a fall in mean pressure, but without fall in mean blood flow. The first period of constriction (23 minutes) caused a fall of 10 mm Hg mean pressure, from 95 to 85 mm Hg. During this period there was an increase in the pressor activity of incubated renal venous plasma (sample 2v) and little change in arterial plasma (sample 2a). Release of the aortic constriction caused the pressor activity of venous plasma to revert to the control level (sample 3v). Renewed constriction so as to drop mean pressure to 75 mm Hg without reduction in mean blood flow caused reappearance of pressor activity in incubated renal venous plasma (sample 4v) and considerable activity also appeared in arterial plasma (sample 4a). This second period of aortic constriction was maintained for only 17 minutes and yet it is apparent that a greater amount of pressor material appeared in incubated renal venous and arterial plasma than during the earlier, longer period of constriction at a higher mean renal perfusion pressure, but at the same level of renal blood flow. Again on release of aortic
constriction, pressor activity in incubated plasma decreased.

The changes in plasma pressor activity that occurred during aortic constriction fulfilled all the criteria designated in Methods and, therefore, reflected an increased rate of renin se-

![Graph](image)

**FIGURE 1**

From top down, changes in pulsatile renal blood flow, mean renal blood flow, pulsatile renal perfusion pressure, and mean renal perfusion pressure during graded constrictions of aorta above renal arteries. Flow measurements are from left renal artery and pressure from aorta at level of renal arteries. Numbers refer to time of sampling of arterial and renal venous blood. Pressor responses to incubated renal venous plasma are traced beneath the mean pressure record. Lower record is assay of pressor activity in incubated plasma using rat blood pressure. A: angiotensin 2 nanograms (0.1 ml); a: arterial plasma (0.1 ml); v: renal venous plasma (0.1 ml). Dog 16.8 kg.
cretion. In 15 of the 18 experiments, increased renin secretion occurred with reduction in mean pressure of 10 to 40 mm Hg from resting control levels, without change in total renal blood flow, and in any one experiment, greater secretion occurred as the pressure drop increased. Lack of change in renal blood flow with reductions in perfusion pressure of the magnitude employed in these experiments is consistent with the observation of Schmid and Spencer who, also using a noncannulating electromagnetic flow probe, frequently observed complete autoregulation of flow down to 70 mm Hg. It was difficult, when using this

**FIGURE 2**
Characteristics of left renal arterial perfusion before, during, and after a 90 second period of aortic constriction above renal arteries. Numbers indicate times of sampling of arterial and renal venous blood. Pressor responses to incubated renal venous plasma are traced beneath the mean pressure record. Lower record is assay of incubated renal venous plasma (0.15 ml) using rat blood pressure. A: angioten旨2 nanograms. Dog 17.1 kg.
aortic constriction technique, to produce sustained falls in mean pressure smaller than 10 mm Hg (fig. 1), but in one experiment there was clearly an increased rate of renin secretion with a fall of only 5 mm Hg.

Unincubated arterial and renal venous plasma taken under resting conditions usually showed a small amount of pressor activity as described previously, and in most experiments, incubation caused the appearance of slightly greater activity that was angiotensin-like. The increase was usually greater in renal venous plasma than in arterial plasma, indicating renal origin. Unincubated control plasmas did not show differences in pressor activity between arterial and renal venous samples. During periods of reduced renal perfusion pressure, however, unincubated samples showed small increases in pressor activity that were qualitatively similar to the incubated samples but quantitatively much less.

In three experiments an attempt was made to determine how quickly increased renin secretion occurs following aortic constriction. One of these experiments is shown in figure 2 and all three provided similar findings. The paper was run at fast speed, and renal vein blood sampled as soon as possible after applying aortic constriction. Incubated renal venous plasma collected 60 to 90 seconds after aortic constriction contained increased pressor material. Response to arterial plasma is not shown in the assay, but greater activity of renal venous over arterial plasma was confirmed, as were the other criteria indicating increased rate of renin secretion. Reduction in renal blood flow during aortic constriction in this experiment cannot account for the increase in pressor material on the basis of a concentration effect since blood flow was reduced only 25% while plasma pressor activity more than doubled.

II. REDUCTION IN RENAL ARTERIAL PULSE PRESSURE AND PULSATILE FLOW WITHOUT CHANGE IN MEAN PRESSURE OR MEAN FLOW

Using the technique of aortic constriction it was possible to reduce pulse pressure at the renal arteries up to 50% without affecting mean pressure. In seven dogs this procedure did not increase the rate of renin secretion. In six of the seven experiments, further aortic constriction, so as to reduce mean pressure by 10 to 40 mm Hg, caused increased renin secretion. One such experiment has been illustrated in a preliminary report.
Using aortic constriction it was not possible to abolish pulse pressure and yet maintain a constant mean pressure, but this was accomplished with a modified technique in a second group of five experiments, one of which is illustrated in figure 3. Bilateral vagotomy, by releasing vagal tone to the heart, caused tachycardia, rise in mean arterial pressure, and narrowing of pulse pressure. Following this procedure the aorta was constricted until the level of mean pressure at the renal arteries was equal to the level before vagotomy. Virtually complete abolition of pulse pressure was thereby accomplished, but no increase in

\[ \text{FIGURE 4} \]

Stimulation of peripheral end of cut right vagus and associated changes in aortic pressure and the pressor activity in arterial and renal venous plasma. Pressor responses to incubated renal venous plasma are traced above mean pressure record at respective times of sampling. Lower trace is assay of pressor activity in incubated plasma. A: angiotensin 2 nanograms; a: arterial plasma (0.1 ml); v: renal venous plasma (0.1 ml). Dog 16.5 kg.
pressor activity of incubated renal venous plasma was detectable. More severe aortic constriction so as to reduce mean pressure to a level slightly above the original diastolic pressure initiated considerable increase in plasma pressor activity. Release of constriction was followed by disappearance of the pressor material. Again in these experiments the criteria which indicate changes in the rate of renin secretion were fulfilled. Four of the five experiments provided identical results, but in one a slight increase in the rate of renin secretion was detected during abolition of the pulse pressure at a constant mean pressure. In this experiment, however, as in the others, a reduction in mean pressure was associated with a greatly increased rate of secretion.

III. REDUCTION IN MEAN PRESSURE ACCOMPANIED BY INCREASED PULSE PRESSURE

This set of renal perfusion characteristics was accomplished by stimulating the peripheral end of the cut right vagus in dogs treated with guanethidine or bretylium. Two dogs were treated with 3 mg/kg guanethidine sulphate orally daily for three days and then the same dose intramuscularly one hour before the experiment. Two other dogs were treated with bretylium tosylate, 3 mg/kg IM, the night before and again on the morning of the experiment. These treatments were given to block sympathetic reflexes but to leave vagal transmission intact. After preparing the dog in the manner described in Methods, the right vagus was divided in the neck and the peripheral end stimulated with biphasic square waves of 3 to 12 volts at a frequency of 10 to 20/seconds with a duration of 1 to 2 milliseconds. During stimulation, heart rate slowed and mean pressure fell, while stroke volume and pulse pressure slowly increased. By gradually increasing the voltage of stimulation a reduced mean pressure could be maintained for periods of five to ten minutes.

Figure 4 illustrates a typical experiment in which increased pressor material appeared in incubated renal venous plasma during vagal stimulation and disappeared afterwards. All experiments provided similar findings of increased renin secretion during a period of renal perfusion at reduced mean pressure and increased pulse pressure.

IV. REDUCTION IN MEAN BLOOD FLOW AT A CONSTANT MEAN PRESSURE AND PULSE PRESSURE

The right kidney was removed from seven dogs and the left kidney prepared as pre-

![Figure 5](image-url)

**FIGURE 5**

Effect of bilateral carotid occlusion on the pressor activity of incubated renal venous plasma during constriction of the aorta above the renal arteries. Schematic, symbols, and drug doses are same as in figure 3. Dog 18.1 kg.

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RENAL COMPRESSION (20 mm Hg)

![Graph showing renal arterial perfusion and changes in pressor activity of renal venous plasma during renal parenchymal compression with 20 mm Hg. Schematic symbols and drug doses are same as in figure 1. Dog 17.8 kg.]

Characteristics of left renal arterial perfusion and changes in pressor activity of renal venous plasma during a period of renal parenchymal compression with 20 mm Hg. Schemata, symbols, and drug doses are same as in figure 1. Dog 17.8 kg.

Previously described, but in addition a length of tape was passed loosely around the left renal vein and made into a sliding noose. By careful manipulation the renal vein could be compressed with this tape to reduce renal blood flow to any desired level, at which it was maintained for periods of 10 to 20 minutes.

In seven experiments, reductions in mean renal blood flow of up to 50% did not increase the rate of renin secretion. In three experiments an increase in pressor activity of incubated renal venous plasma appeared but was not paralleled by any change in arterial plasma activity. The increase was probably due to concentration of a constant amount of normally secreted renin into a smaller volume of blood. In all experiments aortic constriction, to a degree that lowered blood flow to the same extent as the venous constriction, caused a large increase in the rate of renin secretion.

V. CAROTID ARTERY OCCLUSION

In three bilaterally vagotomized dogs the rate of renin secretion was determined before, during, and after bilateral carotid occlusion. In none of these dogs was any increase detectable.

In an additional five vagotomized dogs, the aorta was constricted so as to reduce renal perfusion pressure and increase the rate of renin secretion. During this procedure bilateral carotid occlusion uniformly reduced the rate of renin secretion. Figure 5 illustrates this effect. Aortic constriction in order to reduce renal perfusion pressure by 15 mm Hg without change in mean blood flow caused increased pressor material to appear in incubated renal venous plasma. The plasma pressor activity reverted to control levels during the rise in pressure induced by the sympathetic discharge during carotid occlusion, again without change in total renal blood flow. Release of carotid occlusion caused the pressor activity to reappear and upon release of aortic constriction it reverted to the control level once again. All five dogs provided identical results.

VI. RENAL COMPRESSION

In seven dogs with vagi intact, the right kidney was removed and the left prepared as previously described, but in addition the kidney was dissected free from surrounding tissue and placed inside a kidney shaped metal oncometer. A thin-walled latex balloon the size of a 50 g kidney was placed inside one wall
of the oncometer. The volume of the oncometer was just sufficient to house both the kidney and the collapsed balloon without renal compression. This insured that when water was introduced into the balloon under pressure and the kidney compressed against the opposite wall, the balloon was still in a state of partial collapse and the head of water was a genuine measure of force applied against the kidney.

Renal blood flow was monitored continuously to detect any interference with arterial inflow. Interference with the main renal artery or its branches could be detected immediately by a reduction in pulsatile blood flow; this did not occur in any experiment.

Figure 6 illustrates that balloon inflation at a pressure of 20 mm Hg resulted in an increased rate of renin secretion as demonstrated by the changes in pressor activity in incubated renal venous plasma which fulfilled the criteria discussed in Methods. All experiments provided similar results, renin secretion being increased by balloon pressures of 15 to 40 mm Hg without change in renal blood flow. Increased compression caused increased secretion and bilateral carotid occlusion, with associated rise in arterial pressure, reduced the rate of secretion (fig. 7) in an identical manner, as described above during aortic constriction.

VII. REDUCTION IN OXYGEN SATURATION OF ARTERIAL BLOOD

Three dogs were prepared as described in Methods. Nitrogen was run into the open inlet valve of a piston type respirator at rates sufficient to drop arterial oxygen saturation to between 50 and 70 per cent from control levels of 96 to 97 per cent. Renal venous oxygen saturation was determined in two of the dogs and renal blood flow was monitored continuously. With a knowledge of the arteriovenous difference in oxygen saturation across the kidney, the hemoglobin content, and the renal blood flow, renal oxygen consumption could be determined, assuming the oxygen capacity of hemoglobin to be 1.36 ml/g.

In these experiments, one of which is illustrated in table 1, incubated renal venous plasma did not display any changes in pressor activity before, at different intervals during, or after 30 to 60 minutes of reduced arterial oxygen saturation. This period of anoxia was accompanied by a slow rise in systemic pressure of 10 to 20 mm Hg, without significant change in renal blood flow. Despite the very low oxygen saturation of arterial blood, renal venous saturation fell proportionately in both dogs in which it was measured, so that total

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**FIGURE 6**

Effect of carotid occlusion on the pressor activity of incubated renal venous plasma during renal parenchymal compression with 35 mm Hg. Schemata, symbols, and drug doses are same as in figure 5. Dog 17.8 kg.

**FIGURE 7**

Effect of bilateral carotid occlusion on the pressor activity of incubated renal venous plasma during renal parenchymal compression with 35 mm Hg. Schemata, symbols, and drug doses are same as in figure 5. Dog 17.8 kg.
TABLE 1
Renal Oxygen Uptake Before, During, and After Nitrogen Breathing

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial O₂%</td>
<td>96</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>Renal venous O₂%</td>
<td>86</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>Renal blood flow, ml/g/min</td>
<td>2.4</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Oxygen uptake, ml/g/min</td>
<td>0.05</td>
<td>0.05</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Hemoglobin 15.6 g/100 ml.

oxygen extraction remained relatively constant at 0.04 to 0.05 ml/g renal tissue per minute.

Discussion

By a combination of techniques that alter renal perfusion characteristics, it has been possible to show that secretion of renin is controlled by a sensitive pressure-dependent mechanism that responds rapidly and continuously to small changes in mean systemic arterial pressure independently of changes in renal blood flow.

The degree of change in mean perfusion pressure that caused an alteration in renin secretion was unexpectedly small. Decreases, or increases, of as little as 5 or 10 mm Hg caused changes in the amount of renin released into renal venous blood. This suggests that renin secretion is a physiologic event, since the perfusion pressures in these experiments were well within the physiologic range. The control level of arterial pressure in all dogs that were not vagotomized ranged between 80 and 115 mm Hg. It is recognized that the dogs were anesthetized and had undergone operative procedures, but if renin is released in larger amounts in these preparations when arterial pressure is lowered a few mm Hg, it is likely that secretion also increases in the unanesthetized, intact dog when pressure is lowered even further under normal conditions, as during sleep when mean pressure drops to 60 to 80 mm Hg (F. Olmsted, personal communication). Often, incubated renal venous plasma showed slightly greater pressor activity than arterial plasma under resting conditions prior to any change in renal perfusion pressure, again suggesting that secretion of renin may be a physiologic occurrence.

The assay technique used was sensitive, reproducible, and had a high degree of specificity. It is unlikely that the pressor material measured is one other than angiotensin made by renin released from the kidney. The criteria listed in Methods, which were satisfied in all experiments, insure that the substance released by the kidney into the circulation is renin, and the pharmacologic procedures described previously indicate that the pressor material assayed is angiotensin. The addition of EDTA to plasma, by protecting angiotensin from destruction by specific angiotensinase, enhanced the sensitivity of the assay. Dr. P. A. Khairallah kindly assayed several plasma samples in the present experiments and confirmed that angiotensinase was inhibited during a 60-minute incubation.

The renal baroreceptor mechanism that initiates release of renin appears to be sensitive only to change in mean perfusion pressure. Unlike carotid sinus baroreceptors, those in the kidneys are not influenced by change in pulse pressure. Further, the diastolic pressure level is not a critical variable controlling the secretion of renin. When pulse pressure was largely dampened and mean pressure lowered slightly, diastolic pressure was above the control resting level, yet there was increased secretion of renin.

This renal pressure-sensitive mechanism has the ability to respond in a quantitative manner. There was a relationship between decrease in mean pressure and amount of renin released; graded reductions in mean pressure provoked progressively larger secretion of renin. Furthermore, release of renin was an almost instantaneous response to lowering of perfusion pressure. Whether increased secretion, once provoked in this manner, will continue indefinitely is not known. It has previously been shown that reduced renal perfusion pressure continues to cause increased renin secretion for at least two hours, but no experiments have been performed beyond this time.
It was observed consistently that renin is released in the absence of any change in renal blood flow. The very sensitive nature of the renal baroreceptor mechanism facilitated this observation. Reduction of mean perfusion pressure by only 10 mm Hg usually caused increased renin secretion, but this small change in pressure was well below the threshold at which blood flow was reduced. It seems unequivocal that ischemia was not the cause of renin release and, also, that ischemia is not an effective stimulus even when present. When renal blood flow was purposely reduced by constricting the renal vein, there was no detectable increase in the rate of renin secretion. In the same experiments a similar reduction in renal blood flow, by arterial constriction with associated fall in perfusion pressure, caused considerable increase in renin release. Severe hypoxia produced in dogs breathing nitrogen also failed to cause release of renin.

It is reasonably well-established, and preliminary observations using the present methods have confirmed, that complete occlusion of the renal artery for several minutes is not followed by release of a measurable amount of renin. This observation is provocative since the procedure produces a definite fall in mean perfusion pressure. It is puzzling that very much smaller reductions in perfusion pressure cause immediate and prominent release of renin by the kidney. The only explanation that occurs to us is that complete occlusion of a renal artery deprives the kidney of an aerobic metabolic function that is essential to the active process of renin release.

Hoff et al. have shown that electric stimulation of central vasomotor centers can cause severe renal vasoconstriction, so severe that cortical necrosis ensues. It would be very interesting if sympathetic vasomotor discharge could be shown to affect secretion of renin. It is known that occlusion of the common carotid arteries increases vasomotor activity in renal nerves. In the present experiments, the effect of carotid occlusion was measured during small reductions in renal perfusion pressure to determine if there was further increase in the rate of renin secretion. The observed suppression is probably due to the associated rise in arterial pressure during carotid occlusion and not to any direct effect of sympathetic impulses on the kidneys. This does not deny that under some circumstances efferent vasomotor discharge may cause release of renin. Greater sympathetic discharge, such as in the experiments of Hoff et al., might induce renin secretion.

The kidneys also released renin during renal parenchymal compression. Inflation of a balloon within an oncometer containing the kidney to 15 to 40 mm Hg did not reduce renal blood flow but caused an increase in renin secretion as striking as that produced by constriction of the aorta. The postulate that a baroreceptor controls renin secretion is compatible with this finding since increased renal parenchymal pressure may cause the same hemodynamic change that is produced by reduction of perfusion pressure. The renal baroreceptor might sense changes in transmural pressure, which in most instances would amount to an intravascular baroreceptor, but in the case of renal compression the stimulus would be a fall in transmural pressure rather than a fall in intravascular pressure. A less likely explanation is that the renal baroreceptor responds to distortion, as has been shown for carotid sinus baroreceptors. It might be imagined that compression through a direct effect of pressure on renin-containing cells causes renin to be displaced from its intracellular location. If this were so, it is difficult to understand why bilateral carotid occlusion with rise in systemic pressure should decrease the rate of renin secretion during renal compression.

Whatever the mechanism is, both reduced arterial perfusion pressure and renal compression are conditions which in chronic preparations lead to hypertension. The clamp in Goldblatt's method and the perinephritis of Page's method produce situations comparable to those shown here to be associated with increased rates of renin secretion. It is important to determine how the renal baroreceptor is functioning in these two types of experimental hypertension.

A growing body of evidence indicates that
changes in sodium intake influence the concentration of renin in the kidneys and the level in circulating blood. In view of the present findings, these changes in renin levels may occur because of the associated tendency toward a fall in systemic pressure during salt depletion and a rise during salt excess. Furthermore, the control of aldosterone secretion is intimately related to the renin-angiotensin system.

The present experiments prompt the tentative conclusion that the level of mean pressure at the renal baroreceptor is an important variable regulating aldosterone secretion. The experimental techniques used to produce hyperaldosteronism in dogs (inferior vena cava constriction, pulmonary artery stenosis, and aortocaval shunt) all produce slight falls in mean renal perfusion pressure which, on the basis of the experiments reported here, should cause increased renin secretion. That this is probably the case is indicated by the recent findings of Higgins et al. of increased renin in thoracic duct lymph of dogs with inferior vena cava constriction. It seems that experimental hyperaldosteronism due to such procedures is a hemodynamic state in which mean pressure is prevented from rising to the level necessary to reduce the secretion of renin to normal.

The present experiments indicate that the renal baroreceptor, through its control of renin secretion, functions as a barostat mechanism on arterial pressure. This receptor is delicately regulated to the prevailing mean arterial pressure; it is not only controlled by that pressure, and everything that influences pressure, but is in turn also capable of influencing the pressure itself. It is tentatively suggested that under normal resting circumstances the average height of arterial pressure is set in part by the threshold of the renal baroreceptor, pressure tending to stabilize at a level at which renin secretion is minimal.

Summary

Renin secretion was found to be controlled by a renal baroreceptor rather than by ischemia. Development of a sensitive assay technique that detects renin in small quantities of renal venous and peripheral arterial plasma has permitted the demonstration that the rate of renin secretion varies inversely with the level of arterial pressure independently of renal blood flow.

When mean renal perfusion pressure was reduced 5 to 40 mm Hg by a constricting band around the aorta above the level of the renal arteries, increased renin secretion commenced within 60 seconds. Reductions of this magnitude did not necessarily cause mean perfusion pressure to fall below control levels of diastolic perfusion pressure. Rises in perfusion pressure had the reverse effect, reducing the rate of renin secretion again without measurable change in renal blood flow. Compression of the kidney within an oncometer by an applied force of from 15 to 40 mm Hg also caused increases in the rate of renin secretion in the absence of change in total renal blood flow. Reduction of pulse pressure alone did not provoke secretion of renin, nor did reduced oxygen tension, or renal ischemia. Rise in perfusion pressure due to occlusion of the common carotid arteries was associated with reduction in the rate of renin secretion.

A small amount of renin was secreted continuously under the conditions of these experiments; physiologic changes in mean perfusion pressure served to alter the rate. This suggests that a renal baroreceptor mechanism regulates renin secretion under normal circumstances and that arterial pressure tends to stabilize at a level at which renin secretion is minimal.

Acknowledgment

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SANDFORD L. SKINNER, JAMES W. MCCUBBIN and IRVINE H. PAGE

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