Subpressor Angiotensin Infusion, Renal Sodium Handling, and Salt-Induced Hypertension in the Dog

JAMES W. DEClue, ARTHUR C. GUYTON, ALLEN W. COWLEY, JR., THOMAS G. COLEMAN, ROGER A. NORMAN, JR., AND ROBERT E. MCCAA

SUMMARY We studied the combined effect of subpressor amounts of angiotensin and long-term sodium chloride infusion on arterial pressure in 16 dogs for periods of 2-8 weeks. In dogs receiving 3.5 liters of isotonic NaCl daily, but no angiotensin, the arterial pressure increased an average of only 3 mm Hg. When angiotensin was infused continuously at a rate of 5 ng/kg per min (a rate too small to cause an observable immediate increase in pressure), subsequent infusion of 3.5 liters of saline daily then increased the pressure by 39 mm Hg. The urinary output of sodium increased to the same extent.

Sodium and water output. This effect occurs within hours. We observed that the level to which the pressure rises is highly dependent on salt intake. In another type of study, Yeyati et al.,3 Waugh,6 and Fagard et al.7 demonstrated that infusion of nonpressor doses of angiotensin either intravenously or into the renal artery can cause a 50% decrease in renal sodium and water output. This effect occurs within minutes, presumably before the angiotensin can cause aldosterone secretion. More recently, Hall et al.,8 Lohmeier et al.9 and Trippodo et al.10 have shown that salt-depleted dogs given appropriate amounts of angiotensin antagonists may in-
crease their sodium output as much as several hundred percent, indicating that intrinsic angiotensin, before its action was blocked, prevented the kidneys from excreting sodium. Lohmeier's experiments were performed in adrenalectomized dogs that had been given substitute steroids on a chronic basis. Therefore, these studies indicated that block of the angiotensin action increased the sodium output in some way other than by acting through the aldosterone salt-retaining mechanism.

Thus, there is, on the one hand, an accumulating body of evidence which suggests that angiotensin plays an important intrarenal role, causing sodium and water retention and, on the other hand, another body of evidence which suggests that minute amounts of angiotensin infused over a period of days can cause hypertension, but a hypertension that is highly dependent on salt intake. Putting this information together, one could suggest that, in addition to the function of angiotensin to cause hypertension by its direct vasoconstrictor effect and its effect to increase the secretion of aldosterone, it also might contribute significantly to the hypertension by its direct effect on the kidneys to promote sodium retention. In the experiments to be described, we have examined this hypothesis.

Methods

All of these experiments required long-term infusion of angiotensin and/or sodium chloride solution and long-term continuous recording of arterial pressure. Sixteen mongrel dogs, 18-25 kg, were studied using five separate protocols. Each protocol involved two to seven different steady states of sodium or volume intake. The infusions and pressure recording periods lasted 2-8 weeks. The infusions and recording systems were similar to those described by Cowley and DeClue. Briefly, an infusion catheter was inserted into the femoral vein, and a catheter to record arterial pressure was inserted into the femoral artery. Each catheter was looped in the femoral triangle and then brought subcutaneously to the posterior thoracic region where it was exteriorized. The arterial pressure catheter then was attached to a Statham pressure transducer (model P23Db) mounted at heart level in a plaster and canvas jacket around the dog's thorax. The infusion catheter and electrical connections to the transducer were brought from the jacket through a flexible tube to the top of the cage. Infusion of angiotensin was provided by a Harvard infusion pump (model 944), and a calibrated tubing pump (Sage model 375A) was used to infuse the large quantities of saline solution. The arterial catheter was refilled with heparinized saline solution (1000 U/ml) each day.

The solutions that were infused in different protocols were the following: (1) Angiotensin II solution was prepared fresh daily, using Ciba Hypertensin (Asp²,Val⁵)angiotensin II amide, and was injected at rates from 0.25 to 5 ng/kg per min at concentrations between 0.2 and 6 μg/ml dissolved in 0.154 M sodium chloride solution (the concentration was adjusted so that a volume of exactly 24 ml was infused each day). (2) Sodium chloride solution was prepared at a concentration of 0.154 M. (3) Furosemide solution (Lasix, Hoechst Pharmaceuticals, Inc.) was infused at a concentration of 2 mg/ml in 0.154 M sodium chloride solution at rates of 26 to 83 mg/day. Also, in two experiments, spironolactone was administered orally in capsules in doses of 100 mg every 6 hours for 6 days.

The pressures were recorded continuously either on a slow speed Grass model 7 recorder or on a slow speed multiplexed Leeds and Northrup recorder, and the reported pressure values represent average values for the last 48 hours of pressure levels at each steady state.

Plasma renin activities were measured using a modified Haber radioimmunoassay technique. Plasma aldosterone concentration was measured using the method of McCaa and McCaa as modified from Mayes. Plasma [Na⁺] and [K⁺] were measured by flame photometry, and ²²Na space by standard radioisotope-counting procedures.

The statistical probabilities were calculated by paired t-test, comparing the experimental data of each group with the control data. Statistical significance was considered to be P < 0.05. All data are expressed as means ± SE.

Results

Long-Term Infusion of Sodium Chloride Solution at Progressively Increasing Rates into Awake Dogs, First, under Normal Conditions and, Second, while Infusing Angiotensin II at a Low Rate

In six conscious dogs, the effects on arterial pressure, renin secretion, aldosterone secretion, and other variables related to circulatory function were determined at different levels of chronic intravenous infusion of sodium chloride. These studies were done, first, in normal dogs and again several weeks later in the same dogs while angiotensin II (A II) was infused at a low rate. The circulatory effects of the infused sodium chloride were markedly different when angiotensin was infused, as will be described below.

Initially, the dogs were depleted of sodium by maintaining them for a period of 2 weeks on a sodium-deficient diet containing approximately 5 mEq Na⁺ and 30 mEq K⁺ (H-d Prescription Diet, Riviana Foods, Inc.). Drinking water was limited to 150 ml/day, although in many instances this amount was not drunk. Continuous recordings of arterial pressure were begun on the 7th day of the sodium-deficient diet. After 14 days, all drinking water was removed and a consecutive series of intravenous isotonic sodium chloride infusions was initiated beginning at a rate of 0.7 liter/day for 3 days, increasing to 2 liters/day for 3 days, and then
increasing to 4 liters/day for 4 days. The protocol then was reversed, lowering the rate of isotonic sodium chloride infusion to 2 liters/day and 0.7 liters/day for 3 days each and back to no intravenous infusion for 2 weeks on the original sodium-deficient and limited water intake. Blood specimens were taken on each of the last 2 days at the lowest and highest levels of sodium intake and at the end of the 3rd day of each of the intermediate levels of sodium intake. Thus, a total of 10 blood-sampling periods was included during a 44-day period of study.

In the same six dogs, the same protocol was pursued several weeks later except that A II was infused continuously intravenously at a rate of 5 ng/kg per min. Infusion of A II was begun 7 days after the dogs were first placed on the sodium-deficient diet, and the infusion was continued thereafter until the termination of the experimental protocol. This rate of A II infusion was approximately 2.5 times the normal rate of A II formation in the normal dog, based on previous studies by Cowley and Guyton.14 The infusion did not cause a noticeable immediate increase in arterial pressure even though the pressure did rise during the succeeding several days; the magnitude of the increase depended on the simultaneous rate of salt intake.

Changes in Mean Arterial Pressure Caused by Changing Levels of Sodium Intake in Normal and in Angiotensin-Sensitized Dogs

Figure 1 illustrates the changes in arterial pressure at the different levels of sodium intake during both the increasing and decreasing steps. Note that in the normal dogs, the massive changes in sodium intake caused a maximum increase in pressure of only 3 ± 1.2 mm Hg at the highest level of intake. On the other hand, in dogs receiving the low rate of infusion of angiotensin (5 ng/kg per min), arterial pressure increased by 6 ± 2.0 mm Hg at the lowest sodium intake level as a result of angiotensin infusion alone and by 45 ± 3.8 mm Hg at the highest sodium intake, a 39-mm Hg increase in pressure from the lowest to the highest sodium intake level. This was 13 times as much increase in pressure as occurred in response to the salt loading in the dogs that did not receive an angiotensin infusion.

Effect of Angiotensin and Increasing Levels of Sodium Intake on Plasma Renin Activity

Figure 2B illustrates for four normal dogs and for four angiotensin-infused dogs the effect on plasma renin activity of different levels of sodium intake. When angiotensin was infused, the plasma renin activity was greatly reduced at all levels. Only at the lowest sodium intake in the angiotensin-infused dogs was a significant amount of renin activity detected. At the higher levels of sodium intake, the renin activities were below the sensitivity level of the method, or less than one-tenth the normal control level.

Note also in Figure 2B that in the normal dogs the plasma renin activity fell from a peak value of 3.7 ± 1.3 ng of angiotensin I (A I)/ml per hour in the sodium-depleted dogs to an undetectable level at the highest rate of sodium intake. Subsequently, during the descending sodium intake steps, renin activity increased from this undetectable level back to 2.2 ± 0.26 ng of A I/ml per hour. As illustrated in the figure, the curve was much higher in the normal dogs than in the angiotensin-infused dogs.

Effect of Angiotensin and Different Levels of Sodium Intake on Plasma Aldosterone Concentration

Figure 2C illustrates the plasma aldosterone concentrations measured in four dogs at each sodium intake level for both normal dogs and those receiving angiotensin infusion. (The normal range for plasma aldosterone concentration by the method
used in our laboratory is illustrated by the horizontal shaded bar.) The aldosterone concentrations were high in both groups of dogs at the lowest sodium intake level. However, at all of the higher levels of sodium intake, the aldosterone concentrations were slightly below the normal range. Note especially that the presence or absence of angiotensin infusion did not cause a significant difference between the aldosterone concentrations at any level of sodium intake.
Effect of Angiotensin and of Increasing Levels of Sodium Intake on Sodium Space.

Figure 2D illustrates the changes in $^{22}$Na space at each consecutive level of sodium intake in the normal dogs and in the dogs infused with A II. There was a general increase in sodium space with increasing sodium intake. The increase in sodium space at the highest values of sodium intake was significantly greater ($P < 0.05$) than that at the lowest values of sodium intake. However, it is equally clear from the figure that there were no distinguishable differences between the sodium space values in the normal dogs vs. those in dogs receiving the A II infusion.

Effect of Angiotensin and Sodium Intake on Plasma Sodium Concentration, Plasma Potassium Concentration, and Hematocrit.

Figure 2E illustrates the progressive changes in plasma sodium concentration, plasma potassium concentration, and hematocrit at the different levels of sodium intake in both the normal and angiotensin-infused dogs. None of these factors changed remarkably. However, there was a small but statistically significant ($P < 0.05$) decrease in plasma potassium concentration in the dogs receiving angiotensin when they were at the highest level of sodium intake as compared with the lowest level of sodium intake.

Increase in Mean Arterial Pressure Caused by Progressive Increases in Rate of Angiotensin II Infusion in Dogs on a High Sodium Intake

In two dogs, the sodium intake was first increased to a level of 544 mEq/day, and the dogs were maintained at this level for 5 days of control observations. This sodium intake was similar to the highest intake given to the dogs in the experiment described above, and it represented a level approximately 13 times that of the dogs’ average daily normal intake. At the end of the control period, A II infusion was begun at a rate of 0.25 ng/kg per min, and increased successively to three other steps, 1 ng/kg per min, 2.5 ng/kg per min, and, finally, 5 ng/kg per min. Each of these levels of angiotensin infusion was maintained for 5-6 days. Figure 3 illustrates the progressive rise in mean arterial pressure, expressed as percent increase above control values, as the rate of angiotensin infusion was increased. The initial control level (at the high salt intake) averaged 110 mm Hg. This figure shows an almost linear increase in mean arterial pressure in relation to the angiotensin infusion rate.

Comparison of the Effect of Sodium Chloride Infusion vs. Water Infusion

To determine whether or not similar increases in arterial pressure could be achieved by infusing large quantities of water in place of sodium chloride solution, two dogs infused with angiotensin at 5 ng/kg per min were first given a low sodium intake (8 mEq/day) for 14 days and then a high sodium intake (544 mEq/day) in the form of isotonic saline solution for 5 days. An additional two dogs receiving the same amount of A II were given a low sodium intake (8 mEq/day) and low volume (0.6 liter of water in the food plus 0.1 liter drinking water) for 14 days followed by high water intake (4.1 liters/day administered as 3.5 liters of sterile water intravenously and 0.6 liter of water in the food for 5 days). In this instance, sodium intake was held constant at 8 mEq/day. The increase in volume intake each day was the same in these experiments as in the sodium-loading experiments; that is, we substituted water for sodium chloride solution. The results of the two studies are compared in Figure 4. The most remarkable difference between the effects of the two different types of infusion was a very marked increase (40 mm Hg) in arterial pressure when the intake was isotonic saline solution, but only a 4-mm Hg increase when the intake was increased by an equal volume of water. Thus, there was a 10 times greater rise in pressure with the sodium chloride solution. A possible cause of this difference could have been hemolysis of red blood cells caused by contact of pure water with the cells. However, to prevent this, the tip of the infusion catheter was positioned in an area of fast-flowing blood in the vena cava, and careful inspection of the centrifuged blood samples from the water-infused dogs did not demonstrate hemolysis. The results also showed four times as great an increase in sodium space when sodium chloride solution was infused as when water was infused. However, sodium chloride infusion reduced both plasma renin activity and aldosterone concentration markedly, as illustrated in the figure, whereas water infusion had little effect on
LONG-TERM EFFECTS OF A CONTINUOUS INTRAVENOUS INFUSION OF ANGIOTENSIN II IN SODIUM DEPLETED AND SODIUM LOADED STATE

Blood Pressure

Angiotensin II 5 ng/kg/min
Dog A-73 *
Dog A-74 *

Plasma [Na+]

Plasma [K+]

Hematocrit

Vol.

SODIUM INTAKE AND OUTPUT (mEq/day)

LONG-TERM EFFECTS OF INCREASING WATER TURNOVER IN ANGIOTENSIN INFUSED DOGS WITH A CONTRACTED EXTRACELLULAR FLUID VOLUME

Blood Pressure

Angiotensin II 5 ng/kg/min, i.V.
Sodium intake 8 mEq/day
Dog A-75 *
Dog A-76 *

Plasma [Na+]

Plasma [K+]

Hematocrit

Vol.

WATER INTAKE AND OUTPUT (L/day)

Effect of Furosemide or Spironolactone on Salt-Induced Hypertension during Angiotensin Infusion

We studied the effect of furosemide on hypertension in two dogs made hypertensive by infusing sodium chloride solution at a salt intake level of approximately 13 times normal and angiotensin at the rate of 5 ng/kg per min. In two additional dogs receiving the same regimen, the effect of spironolactone was determined. These results are illustrated in Figure 5.

Furosemide in a sufficient dose reduced the mean arterial pressure to near to the normal level (Fig. 5A). On the other hand, spironolactone, even

plasma renin activity and did not reduce plasma aldosterone concentration.

FIGURE 4 Comparison of effects of long-term continuous intravenous infusion of A II on several variables in two dogs when the volume of intake was increased from plasma renin activity and did not reduce plasma aldosterone concentration.

Effect of Furosemide or Spironolactone on Salt-Induced Hypertension during Angiotensin Infusion

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a very low to a very high level. In A, the fluid infused was isotonic sodium chloride solution. In B, the fluid infused was a volume equal to that of the isotonic saline solution but containing only distilled water.
though given in a dose that blocks either fully or almost fully the action of aldosterone, did not reduce the pressure significantly (Fig. 5B). The $^{22}\text{Na}$ space measurements show that the decrease in pressure with furosemide was associated with a decrease in sodium space.

Discussion

Most of the implications of these studies are self-evident from the results. Therefore, we will only briefly review some of these and then discuss another aspect of the study that is not quite as evident but that may have been important, namely, the role of the kidneys in causing the different results between normal animals and those receiving low levels of angiotensin infusion.

First, it is clear that angiotensin sensitizes an animal to the development of salt-loading hypertension. This is not a new observation, but our data add important quantitative documentation of the effect. The data demonstrate that even the small rate of angiotensin infusion employed in these studies, 5 ng/kg per min, will increase the effect of salt loading on the arterial pressure by 13-fold. That is, in the presence of angiotensin, increasing salt intake has the result of increasing pressure 13 times as effectively as in the absence of angiotensin.

Second, angiotensin does not sensitize an animal to the development of hypertension caused by volume loading with water even though it does sensitize the animal to the development of hypertension caused by loading with saline solution. Massive water loading caused only a 7% increase in sodium space, whereas the same volume loading with saline solution increased the sodium space more than 30%. This is evidence that the increase in pressure was related at least partly to an increase in retained fluid volume when there was a combination of both angiotensin and saline loading.

Third, both angiotensin infusion and increased sodium intake decreased the plasma renin activity, and the combination of both of these had an additive effect. These were the effects to be expected from studies reported by others.15

Fourth, in contrast to the marked effect of angiotensin infusion on renin secretion by the kidneys, we were not able to show in the present experiments that angiotensin infusion caused a significant difference in the rate of aldosterone secretion at any of the levels of sodium intake employed. This was disconcerting in view of the literature that suggests that angiotensin is a potent stimulator of aldosterone secretion.16-18 However, other studies have shown that, under some conditions at least, angiotensin has most of its effect on aldosterone secretion only during the first 6-8 hours after angiotensin infusion begins, and the rate of aldosterone secretion then decreases toward control levels under chronic conditions.19, 20 This secondary decrease might be caused either entirely or partly by a simultaneous decrease in plasma potassium concentration. In fact, in the present experiments, the plasma potassium concentration in the dogs receiving an A II infusion decreased by several tenths of a milliequivalent per liter when the sodium intake was increased to the high levels. The important aspect of these findings is that we found no evidence to support the belief that increased aldosterone secretion was one of the mechanisms for the marked pressure response observed in the dogs receiving a combination of angiotensin infusion and a high intake of sodium chloride. This conclusion was supported further by the fact that spironolactone given in very large quantities to the dogs with marked hypertension caused essentially no decrease in pressure even though furosemide did reduce the pressure.

Effect of Angiotensin on the Relationship between Arterial Pressure and Renal Sodium Output

One also can derive from the data in these experiments some idea of the effect of angiotensin on the ability of the kidneys to excrete sodium. This can be done by replotting the data of Figure 1 in the form presented in Figure 6. Let us explain the way in which this has been done:

First, it should be remembered that the data of Figure 1 were obtained from dogs only after they had attained steady state conditions. Thus, they were in the so-called "isorrheic state" in which there was essential equality between input and output. Therefore, the data are plotted in Figure 6 in terms of sodium output rather than sodium intake. The mathematical justification and the logical basis for this procedure were presented in a previous publication.21 The solid points of this figure represent the urinary sodium output calculated in case all of the intake of sodium appeared in the urine. The crosses represent the data points if we assume

**Figure 6** Curves representing the relationship between mean arterial pressure and urinary sodium output in normal and in angiotensin-infused dogs when the sodium intake was increased from a sodium-deficient level to a very high sodium intake level. The numbers in parentheses represent the calculated relative levels of circulating angiotensin, considering the original control level to be 1.0. See text for further explanation.
that the fluid of the feces contained sodium at a concentration equal to that of plasma, a value that is the theoretical maximum. It is clear from the two sets of points that the final curves would hardly be affected from a conceptual point of view by this possible maximum loss of sodium in the feces.

Therefore, in Figure 6, what are shown are two separate curves that show the relationship (but not necessarily a cause and effect relationship) between mean arterial pressure and urinary sodium output under the two separate conditions of these experiments: (1) under normal conditions, and (2) while the dogs were receiving a continuous but low level of angiotensin infusion. There are two questions that need to be answered about these curves: (1) what is the meaning of the differences between the shapes of the two curves? and (2) what is the cause of the differences between the two curves?

It is clear from Figure 6 that the curve labeled "angiotensin" is displaced far to the right of the "normal" curve and also has less than one-tenth as steep a slope. That is, the curve is displaced toward higher pressure values. This means that for each level of sodium output, a much higher level of arterial pressure is attained for the same sodium output than is true in the normal dog not infused with angiotensin. Also, the "angiotensin" curve resembles the pressure-output curve for sodium recorded in many laboratories in acute experiments on isolated, perfused kidneys. The collective results of all these studies have contributed to the quantitative understanding of the well-known mechanism of pressure natriuresis. That is, in acute experiments on perfused kidney preparations, an increase in renal arterial perfusion pressure is always accompanied by a drastic increase in urinary sodium output—for instance, a 6- to 8-fold increase when the pressure is increased to double normal.

The only way that we have been able to explain the displacement of the "angiotensin" curve far to the right of the "normal" curve in Figure 6 is to assume that angiotensin has either an indirect or a direct effect on kidney function to cause sodium retention. Because of the well known relationship between angiotensin and aldosterone, one would first suspect that the angiotensin in these experiments caused increased sodium retention as a result of increased aldosterone secretion. However, the measurements of plasma aldosterone failed to support this hypothesis.

A second indirect way in which angiotensin could have affected renal function in our experiments would have been for the angiotensin to stimulate the nervous system, and this in turn to send sympathetic impulses to the kidneys. In recent reviews, Ferrario et al. and Dickenson and Ferrario have summarized a large number of studies demonstrating a stimulatory effect of angiotensin on the vasomotor center of the brain stem. Also, McCubbin has summarized both his own studies and those of others, showing that angiotensin sensitizes the peripheral vasculature to sympathetic stimuli. Finally, especially important in relation to our experiments have been long-term infusions of angiotensin into the vertebral artery by Fukiyami et al. and Sweet et al., both of whom suggested that angiotensin has a continuing, nonadapting, long-term effect which stimulates the sympathetic vasomotor centers. Therefore, it obviously is possible that central stimulation of the vasomotor center and peripheral sensitization of the sympathetic nerve endings could have played important roles in reducing renal excretion of sodium, as observed in the present experiments when angiotensin was infused chronically. Yet, we feel that final judgment concerning the quantitative importance of these mechanisms probably should be reserved because of recent studies from our laboratory. Most important, Cowley and Guyton showed that decapitated dogs with destroyed spinal cords (by alcohol injection) exhibit considerably increased rather than decreased sensitivity of the arterial pressure response to A II infusion, even though the decapitation and cord destruction presumably eliminated sympathetic stimulation by the central nervous system. When compared with the pressure responses in normal unanesthetized dogs, as presented by Cowley and McCaa in another study, the pressure elevations caused in the decapitated dogs were, on an average, 1.5 to 2 times as great at the different rates of A II infusion.

There still remains the possibility that the A II infused in these experiments had a direct sodium-retaining effect on the kidneys. This fits well with results of previous studies which have shown that intravenous (Yeyati et al.) and renal arterial infusion (Waugh; Fagard et al.) of A II will cause an immediate decrease in sodium excretion by the kidneys, an effect that occurs too rapidly to be mediated through the slowly acting aldosterone system. Also, the rates of infusion into the renal artery in the studies of Waugh and of Fagard were too low (less than 1 ng/kg per min) to raise the systemic arterial pressure a measurable amount. Therefore, it is unlikely that the effect of renal sodium retention in these experiments could have been mediated through the vasomotor centers. Still other studies (Hall et al.; Lohmeier et al.; Trippodo et al.) have shown that angiotensin antagonists cause an immediate increase in sodium excretion if the antagonist is given directly into the renal artery at an infusion rate low enough so that systemic arterial pressure does not fall. In Lohmeier's experiments, the adrenal glands were removed and the animals placed on substitutive steroids; therefore, the effect could not have been mediated through an aldosterone response.

A possible explanation for the very steep slope of the curve in the "normal" dogs can be gleaned from the data of Figure 2B which shows the renin activity at different levels of daily sodium intake and output. In the dogs receiving angiotensin, the renin levels...
either remained extremely low or, in most instances, were undetectable. On the other hand, in the normal dogs, the renin activity rose to high levels at the lower rates of sodium intake and output, whereas they fell to very low levels at the high rates of sodium intake and output. Using this information plus a finding from a previous study that the normal rate of formation of angiotensin in the circulation is about 1.5 ng/kg per min,14 we have calculated the relative levels of circulating angiotensin, based on a control value of 1, to be those shown in parentheses in Figure 6. Note that in the “normal” dogs, the calculated circulating angiotensin decreased markedly as the rate of sodium output increased. However, in the dogs that received angiotensin, the calculated circulating angiotensin remained almost exactly constant except for a slight elevation at the lowest rate of sodium output. If angiotensin shifts the pressure-sodium output curve to the right (a finding previously shown in acute studies on dogs by Fourcade et al.), one would expect the points on the lower portion of the “normal” curve to have been displaced to the right by the excess angiotensin, and the points on the upper portion of the curve to have been displaced to the left by lack of angiotensin. Thus, the “normal” curve would have been markedly steepened in comparison with the “angiotensin” curve.

If this is indeed the explanation for the difference between the slopes of these two curves, it suggests a mechanism by which an intrarenal renin-angiotensin system could help to maintain an almost unchanged arterial pressure day in and day out, despite marked changes in sodium intake. That is, whenever the sodium intake is low, the increased activity of the renin system could cause the kidneys to retain sodium; yet, at high rates of sodium intake, decreased activity of the renin-angiotensin system could then allow the kidneys to excrete the excess sodium with ease. This is a concept also suggested by Leyssac and co-workers on the basis of other data, including micropuncture measurements.13

References

Preferential Distribution of Inhibitory Cardiac Receptors with Vagal Afferents to the Inferoposterior Wall of the Left Ventricle Activated during Coronary Occlusion in the Dog

MARC D. THAMES, HAROLD S. KLOPFENSTEIN, FRANCOIS M. ABBoud, ALLYN L. MARK, AND JOHN L. WALKER

SUMMARY The purpose of this study was to determine the relative magnitudes of the reflex effects mediated by cardiac receptors during anterior as opposed to inferoposterior ischemia of the left ventricle of the dog. Cessation of perfusion (coronary "occlusion") of the circumflex coronary artery (Cx) in 29 chloralose-anesthetized dogs with common carotids ligated (group I) resulted in significant bradycardia and hypotension, but in no significant change in perfusion pressure in the gracilis muscle perfused at constant flow. Occlusion of the left anterior descending coronary artery (LAD) produced less hypotension, no change in heart rate, and vasoconstriction in the gracilis. After vagotomy and aortic nerve section, no significant change in heart rate or gracilis perfusion pressure was observed during LAD or Cx occlusion, and the blood pressure responses to LAD and Cx occlusion were not different. In nine dogs with sinoaortic denervation (group II), brief Cx occlusion resulted in bradycardia, hypotension, and vasodilation in the gracilis muscle. LAD occlusion in group II dogs caused less hypotension and no change in heart rate or gracilis perfusion pressure. After vagotomy, the bradycardia and vasodilation resulting from Cx occlusion were abolished and the blood pressure responses to LAD and Cx occlusion were not different. The weights of left ventricle perfused by each occluded vessel were not different. These data show that left ventricular receptors with vagal afferents which are activated during coronary occlusion and which mediate cardioinhibitory and vasodepressor responses are located mainly in the inferoposterior left ventricle of the dog heart.

PATIENTS with infarction of the inferior wall of the left ventricle have been noted to have more frequent bradycardia and hypotension than do those with anterior wall infarction. Similarly, injection of contrast medium into the coronary arteries supplying the inferior wall of the heart results in bradycardia and hypotension more frequently than does injection into the artery supplying the anterior wall. These effects seen during inferior infarct and coronary arteriography are thought to be reflex in origin and to result principally from activation of cardiac receptors. Further, these observations suggest that cardiac receptors mediating vasodepressor effects are preferentially distributed to the inferior wall of the heart in man.

Myocardial necrosis in dogs and coronary occlusion in cats are known to activate cardiac receptors and to induce reflex responses of bradycardia, hypotension, and vasodilation or vasoconstriction. Vagotomy reduces or abolishes these reflex effects. Costantin has suggested that ventricular receptors are responsible for these effects and are activated by the bulging of the ischemic area; the recent study of Thoren supports this view.

Studies in our laboratories have recently shown that injection of veratridine into the circumflex branch of the left coronary artery in the dog results in significantly greater bradycardia, hypotension,
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J W DeClue, A C Guyton, A W Cowley, Jr, T G Coleman, R A Norman, Jr and R E McCaa

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