The Role of Angiotensin in the Control of Blood Pressure During Sodium Depletion

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SUMMARY Sodium depletion was induced in dogs to raise plasma renin activity (PRA) from 1.11 to 26.48 ng/ml/hr. Little overall change in blood pressure (BP) occurred, but cardiac output (CO) and central venous pressure fell, while total peripheral resistance and heart rate (HR) increased.

A nonapeptide converting enzyme inhibitor (CEI) produced a fall in BP which was linearly related to log. PRA; the intercept with PRA was at 1.05 ng/ml/hr, close to the average value for dogs on a normal diet. The fall in BP with this agent was not accompanied by an increase in HR or CO.

When Sar'-Ala' angiotensin II was used to antagonize the action of angiotensin, the fall in BP was also linearly related to log. PRA. However, for a given level of PRA this fall in BP was less than that achieved with CEI and the intercept of BP fall with PRA was 2.6 ng/ml/hr. Again with this agent there was little change in HR or CO as BP was reduced.

Thus, both antagonists lowered peripheral resistance without exciting the homeostatic reflexes indicating that, as PRA rose above the normal resting level, the angiotensin generated had both a direct and indirect effect in maintaining BP. (Hypertension 1: 402-409, 1979)

KEY WORDS • converting enzyme inhibitor • Sar'-Ala' angiotensin II • graded sodium depletion • plasma renin activity • angiotensin II • hemodynamics

THE direct involvement of angiotensin in the control of blood pressure can be demonstrated by the interference with its action following the administration of a competitive antagonist or by inhibition of the generation of angiotensin II (AII) by a converting enzyme inhibitor. A fall in blood pressure can then be observed both in man and in animals, but this is usually seen when plasma renin activity (PRA) is abnormally high or after stimulation by sodium depletion, upright posture, heart failure or constriction of a renal artery.

Studies have also been made which relate the hypotensive effect produced by one or other of these antagonists to the prevailing level of PRA. The results differ from one study to another, probably because of the antagonist chosen, the range of PRA examined, the assay procedure and the methods used to stimulate renin release.

In order to gain a closer insight into the role of angiotensin in the control of blood pressure it seemed important to establish, as precisely as possible, the minimal level of PRA at which a hypotensive response can be detected by removing the constrictor effect of AII and to determine the hypotensive response of the antagonists over a wide range of PRA.

It also seemed important to measure the hemodynamic changes, since AII has been shown to activate the sympathetic nervous system by effects within the central nervous system and to enhance norepinephrine release from sympathetic nerve endings. Since the angiotensin antagonists themselves possess properties other than those due to antagonism of the polypeptide, studies have been undertaken in which the response to two different types of antagonists, a converting enzyme inhibitor (CEI) and the competitive antagonist Sar'-Ala' angiotensin II (SAR), was measured as renin levels were varied over a wide range in dogs by sodium depletion.

Methods

Under thiopentone/halothane anaesthesia, vinyl catheters were surgically implanted in the left common carotid artery and external jugular vein of male beagle dogs weighing between 11.5 and 14.5 kg. These catheters were exteriorized at the back of the neck and
Experimental Protocol

The dogs were maintained on a cereal-based diet (Ralston Purina) providing 70 mEq sodium per day. After two to three control measurements had been made over a period of 1 week the animals were given a low-sodium diet (Riviana Foods Inc.), providing 5 mEq of sodium per day, for 8 days. Tap water containing 1.0 mEq/litre of sodium was provided ad libitum. On alternate Days 1, 3, 5 and 7 a diuretic containing hydrochlorothiazide and 1% amiloride (Moduretic) was administered in total doses of 50, 50, 100 and 100 mg. On Days 2, 4, 6 and 8 of sodium restriction the hemodynamic response to either inhibitor was measured at the same time each day before feeding.

The animals were divided into three groups. Group 1, consisting of six animals, received the nonapeptide angiotensin converting enzyme inhibitor SQ20881, Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro-OH, 0.5 mg/kg I.V. (Beckman Laboratories). This dose of the inhibitor reduced the pressor response to AI (1 μg/kg I.V.) by 80%. The hemodynamic response to the inhibitor was recorded for 30 minutes following each dose. Arterial blood samples were taken immediately before administration of the inhibitor for measurement of PRA. The seven animals in Group 2 were given the inhibitor while on a high sodium intake (> 70 mEq/day). In three of these, AlI levels were measured in the replete state and after 2 and 4 days of sodium depletion without diuretic treatment.

Group 3 consisted of seven dogs. Each was subjected to sodium restriction and diuretic treatment. The response to the administration of the AI inhibitor Sar'-Ala' angiotensin II (Saralasin, Beckman Laboratories) was then studied as PRA increased. An initial dose of the antagonist (25 μg/kg I.V.) was followed by a second dose of 25 μg/kg after 15 minutes. The hemodynamic response was recorded 15 minutes after the second dose.

Mean data are given with the standard error and the paired t test has been used to determine the effects of the antagonists over the control state. Linear regression analysis was used to establish the relationship between the initial PRA levels and the changes in blood pressure.

Results

Hemodynamic Changes due to Sodium Depletion

Sodium depletion induced a progressive increase in PRA from the normal level of 1.11 ±0.15 ng/ml/hr to 26.48 ± 3.77 ng/ml/hr (p < 0.001) by Day 8. Mean arterial pressure showed little overall change. There was a progressive reduction in cardiac output from 2.66 ± 0.17 to 2.01 ± 0.13 litres/min (p < 0.005). Central venous pressure was reduced from +2.3 ± 0.8 to -4.2 ± 0.6 cm H₂O (p < 0.001). Heart rate increased from 84 ± 5.4 to 110 ± 4.3 beats/min on Day 8 (p < 0.005). Similarly, total peripheral resistance increased progressively from 3300 ± 231 to 4472 ± 282 dynes · sec · cm⁻⁸ (p <
The hemodynamic effects of converting enzyme inhibitor (CEI) in dogs as plasma renin activity was progressively raised by means of dietary sodium restriction and the intermittent use of a diuretic (D). The first set of shaded columns on the left represents the findings in a separate group of seven sodium-replete dogs. In this figure and in figure 3, significant difference from the pretreatment values is given by * = p < 0.05; ** = p < 0.01; and *** = p < 0.001.

0.005) over the same period. These changes are illustrated as the control measurements in figures 1 and 3.

Response to Converting Enzyme Inhibitor

A fall in blood pressure occurred within 10 minutes of the administration of inhibitor and lasted for approximately 20 minutes. This provided steady-state conditions for the measurement of cardiac output. The magnitude of the fall increased progressively as sodium depletion became more severe, (fig. 1). Thus on Day 2, mean arterial pressure fell from 103 ± 3.1 to 82 ± 3.5 mm Hg (p < 0.005) and by Day 8 from 111 ± 3.4 to 75 ± 5.9 mm Hg (p < 0.005). The main determinant of blood pressure fall was a reduction in total peripheral resistance, which became progressively larger as sodium depletion developed and
finally on Day 8 it fell from 4635 ± 470 to 3337 ± 378 dynes • sec • cm⁻² (p < 0.001).

Heart rate showed little change except when depletion was severe (Day 8) when it increased from 116 ± 8.4 to 137 ± 17.8 beats/min. This change, however, was not statistically significant. Both cardiac output and central venous pressure remained unaffected by CEI throughout sodium depletion.

Plasma Renin Activity and BP Fall to CEI

There was a linear relationship between the logarithm of the level of PRA and the fall in mean arterial pressure produced by CEI (fig. 2). The coefficient of correlation was −0.76 (p < 0.001) and the level of PRA above which the fall in mean arterial pressure became dependent on the generation of AII was 1.05 ng/ml/hr. Also shown in figure 2 are values obtained in Group 2 animals in the sodium-replete state, which showed that a fall in pressure of the order of 5 to 10 mm Hg was not uncommon. The data from these animals have not been included in determining the regression line. In Group 2 dogs studied in the sodium-replete state, CEI produced a small fall in mean arterial pressure from 109 ± 2.0 to 102 ± 2.0 mm Hg (p < 0.005) with no significant change in cardiac output or heart rate (fig. 1). To obtain an estimate of the plasma level at which AII affected the circulation, plasma levels were measured in three of these dogs with mild sodium depletion induced by diet alone. The changes observed were essentially the same as those in the last group. The PRA rose from 0.61 ± 0.25 to 1.57 ± 0.49 ng/ml/hr at Day 2 and 3.52 ± 0.68 ng/ml/hr by Day 4 (p < 0.05). The AII levels then rose from 14.7 ± 4.3 to 24.3 ± 7.9 pg/ml by Day 2 and 56.7 ± 11.4 pg/ml by Day 4 (p < 0.05).

Response to Sar⁺-Ala⁻ Angiotensin II

The response of blood pressure to SAR, 25 µg/kg I.V., was characterized by a small initial pressor response and this was more pronounced when sodium intake was normal. A fall in blood pressure, which was maximal within 10 minutes, was sustained for 20 minutes. The second dose of 25 µg/kg I.V. was then without a pressor effect. The maximal fall in pressure was taken as the response to the antagonist. The fall in mean arterial pressure on Day 2 was from 97 ± 1.9 to 89 ± 1.4 mm Hg (p < 0.01) and it progressively increased until Day 8 when a reduction from 108 ± 3.5 to 83 ± 3.0 mm Hg (p < 0.001) was observed (fig. 3). The main determinant of the fall in blood pressure was again a reduction in total peripheral resistance. Thus, on Day 8, it fell from 4333 ± 360 to 3303 ± 368 dynes • sec • cm⁻² (p < 0.005). There was then a small increase in heart rate from 104 ± 2.8 to 133 ± 6.7 beats/min (p < 0.01). At no time during salt depletion was a significant change in cardiac output observed. A small but significant reduction in central venous pressure −3.8 ± 0.9 to −6.0 ± 1.1 cm H₂O (p < 0.01) was evident at Day 8. In preliminary experiments a large dose of SAR (50 µg/kg) produced no greater effect on blood pressure than that chosen for this study.

Plasma Renin Activity and BP Fall to SAR

There was a linear relationship between the fall in mean arterial pressure produced by SAR and logarithm of the prevailing PRA level with a coefficient of correlation of −0.65 (p < 0.001) (fig. 4). The line was shifted to the right of that seen with CEI, and the level of PRA above which the fall in mean arterial pressure became dependent on angiotensin was 2.6 ng/ml/hr. SAR was, therefore, less effective than CEI in lowering blood pressure for a given level of PRA, but the slope of the regression line was not significantly different.

Discussion

Sodium depletion has been used to study the role of angiotensin in the direct control of blood pressure, since it is an effective physiological stimulus for renin release. A progressive rise in the level of renin over a wide range could be achieved by the judicious use of diet and a diuretic, while a relatively stable state was maintained for the measurement of cardiovascular changes. It must be said, however, that the importance of angiotensin in the regulation of blood pressure during sodium depletion does not reflect its role in other circumstances, since it is known that the sensitivity of the vasculature to angiotensin is diminished by sodium depletion.²⁵⁻²⁹

The regimen of sodium depletion led to a progressive increase in PRA, but the blood pressure itself changed little, although cardiac output and central venous pressure fell and heart rate increased. Consequently, calculated total peripheral resistance increased substantially as the sodium depletion
progressed. These findings are in contrast to those in the rat\(^8\) where blood pressure was maintained with a normal cardiac output and total peripheral resistance, but resemble those seen in man after sodium depletion.\(^9\) It has been suggested that in the rat normal cardiac output was maintained during sodium depletion by a decrease in venous compliance, thus increasing venous return.\(^9\) Since in our experiments cardiac output was reduced, it may be that this adaptation is less effective or even absent in the dog, particularly since central venous pressure showed little change after antagonism of angiotensin.

**FIGURE 3.** The hemodynamic effects of the angiotensin antagonist, Saralasin, in dogs as plasma renin activity was raised by dietary sodium depletion and the use of a diuretic (D).
The administration of either the CEI or the angiotensin antagonist resulted in a fall in pressure with insignificant changes in cardiac output. This revealed that the component of resistance sustained by angiotensin increased as sodium depletion progressed. It was noteworthy that the level to which peripheral resistance fell after CEI was the same throughout the progressive sodium-depletion experiments, demonstrating that blood pressure was supported by angiotensin alone. This pattern was not seen quite so clearly with SAR. Under conditions of mild sodium depletion, the level of resistance achieved by the drug was higher than that seen with more severe depletion. This may reflect partial agonist activity. The hemodynamic response to both compounds was broadly similar and at no level of PRA did we observe the fall in cardiac output seen by others with a different antagonist.

Since the observations were made over a range of PRA values it was possible to relate the level of PRA to the fall in blood pressure with both CEI and SAR. The linear relation between log PRA and the fall in pressure with CEI could be projected to the renin axis to show that a level of PRA exceeding 1.05 ng/ml/hr is required before sufficient All can be generated to directly affect blood pressure. This value is close to the average for dogs on a normal sodium diet and corresponds to a plasma level of approximately 20 pg/ml All. With SAR the figure would be 2.6 ng/ml/hr for PRA and approximately 40 pg/ml for All. It is of interest that in human studies similar values are found for both CEI and SAR. With these agents it is not possible to be more precise in determining the PRA level at which angiotensin controls blood pressure since each agent is compromised by nonspecific effects. For CEI, vasodilatation would be expected to occur if plasma bradykinin levels should rise because this inhibitor also influences the breakdown of this polypeptide.

A constrictor effect may also be present due to intrinsic activity of SAR and release of catecholamines. In addition, CEI would be expected to prevent the formation of AIII whereas SAR would not. Nevertheless, the use of the two antagonists permits the range to be established above which plasma renin would be expected to generate sufficient All directly to affect blood pressure. It can be concluded from this study that angiotensin generation appears to be the major mechanism by which blood pressure is maintained with sodium depletion in dogs. In addition, some degree of pressure dependence on All may be present when sodium intake is normal.

The use of the antagonists also made it possible to examine the characteristics of the hypotensive response to the sudden interruption of the action of angiotensin. The reduction in blood pressure they produced, as sodium depletion progressed, became greater, mainly as a result of a reduction in total peripheral resistance. With each agent it was noticed that the tachycardia and the increase in cardiac output that would normally be expected to accompany a fall in blood pressure did not occur. This effect has been observed by others in the dog and in man. In the dog another angiotensin antagonist (Sar-Thr All) has been shown to produce a reduction in heart rate and cardiac output both in sodium-replete and sodium-depleted animals. Therefore, it was not related to sodium status or PRA. A fall in blood pressure and TPR were only observed in severely depleted animals. These cardiac effects appeared to have a large parasympathetic component. The differences between these findings with Sar-Thr All and ours are probably accounted for by the different pharmacological properties, although the possibility of differences due to the strain of animal must also be entertained. In the trained beagle there is high intrinsic parasympathetic activity which could reduce the expression of parasympathetic action of the compound.

In our study, however, the effect of SAR was qualitatively similar to CEI, suggesting an ultimate dependence on the blockade of action of All. Similar results for SAR have also been reported in man. The most likely explanation for the blunted reflex is an interference with the central action of All, since an infusion of All into the vertebral artery leads to tachycardia even in the presence of peripheral All blockade. Since All facilitates the release of norepinephrine from sympathetic nerve endings, an interruption of this effect could also be responsible for the blunted reflex response to the fall in pressure. There is further evidence of a facilitative action of All on the sympathetic nervous system contributing to the maintenance of blood pressure. When sodium-depleted subjects are tilted, All is involved in the hemodynamic adjustment to upright posture or to exercise. In the dog, central administration of All enhances reflex vasoconstriction and reduces reflex vasodilatation to changes in arterial pressure.

The use of the angiotensin antagonists has demonstrated, therefore, that the renin angiotensin system plays a role in the maintenance of blood pressure during sodium depletion and it comes into
play at PRA levels that just exceed the values for resting animals. Approaching this question by measuring the pressor response to infused AII, Chinn and Düsterdieck came to the conclusion that the resting level of AII in man is close to the range capable of affecting blood pressure.

These studies have shown that although angiotensin constricts blood vessels, it also plays a role maintaining the sensitivity of the homeostatic reflexes. The renin angiotensin system appears to be an excellent backup for the sympathetic nervous regulation of the circulation since angiotensin has a dual action; to constrict blood vessels and to augment the sensitivity of the regulatory reflexes. Angiotensin becomes effective when PRA rises above the normal resting value. If the response seen in the dog is found in man it would indicate that the fall in pressure seen with sodium restriction and diuretics is limited by the response of the renin angiotensin system.

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