REVIEW

Synthesis of endocrine control in hypertension


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In a series of experiments we have attempted to develop a quantitative synthesis of the roles of angiotensin, aldosterone and antidiuretic hormone in the genesis of hypertension. We have come to the conclusion that all of these hormones can increase the arterial pressure under appropriate conditions by their effects on renal function.

Observations

Retention of water and salt caused by sub-pressor infusions of angiotensin into the renal artery

In seven dogs, sub-pressor infusions of angiotensin into the renal artery caused up to 40-50% decrease in sodium and water excretion by the kidneys. The renal blood flow decreased considerably more than the glomerular filtration decreased. Therefore the calculated effect of the angiotensin was to increase efferent arteriolar constriction more than afferent constriction. The importance of these studies is that they demonstrate a direct effect of angiotensin on the kidneys that can lead to volume-loading hypertension.

Possible role of an intrarenal angiotensin suppression mechanism to increased sodium excretion during salt loading

Eight normal dogs were loaded with progressively more and more salt intake over a 2 week period, thereby increasing the rate of sodium excretion up to seven times the initial level. The arterial pressure rose only 6 mmHg, while renin secretion fell to less than one-tenth of normal. In four additional dogs, the blood angiotensin was prevented from falling by infusing angiotensin at a very low rate (5 ng min\(^{-1}\) kg\(^{-1}\)) during the same salt-infusion regimen. Under these conditions the massive increase in excretion of sodium and water did not occur until the arterial pressure rose to 35 mmHg above the control value, a pressure rise six times that in normal animals. Therefore it seems clear that minute amounts of angiotensin can cause sodium and water retention, which can be overcome only by elevated arterial pressure. These studies also suggest that an intrarenal mechanism might exist whereby decreased angiotensin formation is one of the important mechanisms for natriuresis when an animal is sodium loaded or when the arterial pressure increases.

Effect of chronic angiotensin II infusion on aldosterone secretion

Angiotensin II was infused into dogs for more than 2 weeks in over sixty experiments at both low and high concentrations and also in salt-depleted, normal and salt-replete dogs. In all of these dogs except the salt-replete dogs, plasma aldosterone concentration increased two to five times the control value during the first few hours after onset of the infusion. However, within 24 h, the plasma aldosterone concentration had returned all or most of the way to the control value. In the dogs with normal salt intake, the sustained increase in plasma aldosterone was about 30% above the control value when small amounts of angiotensin were infused (5 ng min\(^{-1}\) kg\(^{-1}\)). On the other hand, when very large amounts were infused (22 g min\(^{-1}\) kg\(^{-1}\)), the sustained plasma aldosterone concentration rose as much as twofold but never to the high values caused by potassium infusion or sodium restriction. In six additional dogs, aldosterone was infused for over 3 weeks at a level 100% above the control value, an amount equal to that caused by the maximal effect of angiotensin infusion. This rate of aldosterone infusion increased the arterial pressure an average of 5 mmHg. Therefore, quantitatively, these results cast doubt on the importance of angiotensin stimulation of aldosterone secretion as a chronic hypertensive mechanism.
Hypertensive effect of antidiuretic hormone

Seven 70% nephrectomized dogs were infused with 3 litres of hypotonic sodium chloride solution (90 mmol/l) per day, which caused an average rise in arterial pressure of only 5 mmHg. However, infusion of the same solution along with ADH at a rate equal to three times the animal’s normal calculated secretory rate caused the arterial pressure to rise an average of 35 mmHg.

Therefore, under appropriate conditions, even moderate amounts of ADH can be hypertensive. These experiments suggest especially that ADH might be an important factor in the causation of hypertension in patients with marked renal pathology.

Quantitative studies on the control of potassium ion concentration by an aldosterone feedback mechanism

In eight dogs the adrenal glands were removed and aldosterone and a glucocorticoid were substituted by continuous infusion. The intake of potassium was changed over a range of sevenfold, while the effect on plasma potassium ion concentration was measured. A similar study was performed in a comparable series of normal control dogs. In the adrenalectomized animals the potassium ion concentration increased five times as much as it did in the normal animals.

In another series of four adrenalectomized animals, the aldosterone-potassium ion response curve was determined by infusing aldosterone at different rates, at each rate for 2 weeks or more. Twelvefold increases in infusion rates, from one-third of the animal’s normal secretion rate to four times normal, decreased potassium concentration approximately twofold.

Putting the above two studies together, it can be demonstrated that an increase in potassium ion concentration causes increased aldosterone secretion and this in turn causes a feedback effect to decrease the potassium ion concentration. The minimum overall loop gain of this feedback control mechanism is calculated to be approximately −3, which makes the system a very important controller of potassium ion concentration.

Control of extracellular fluid sodium ion concentration by the ADH–thirst feedback control mechanism

In the adrenalectomized animals discussed above for the potassium ion studies, the sodium intake was changed from a very low value to a very high value, giving a change in sodium load of twentyfold. Despite the inability of the aldosterone mechanism to respond in these animals to the sodium loading, the extracellular fluid sodium ion concentration changed only 2%, which also was equal to the change in sodium concentration that was found in the control animals. Therefore, the aldosterone mechanism did not seem to be of real significance in the control of extracellular fluid sodium ion concentration.

On the other hand, in six dogs in which ADH was infused at six times the normal bodily rate of ADH secretion and in which the fluid intake of the animals was fixed, the extracellular fluid sodium concentration became comparatively uncontrolled. In these animals the extracellular fluid sodium concentration increased six times as much upon sodium loading as occurred in normal control animals. This suggests that the sodium ion concentration in the body fluids is normally controlled by hydrating or dehydrating the body rather than by controlling sodium reabsorption by the renal tubules. The experiments also suggest that the ADH and thirst mechanisms for control of body water are perhaps the major feedback system for control of extracellular fluid sodium ion concentration.

Comments

In the past, many qualitative studies have suggested that one of the mechanisms of hypertension is the following: increased renin secretion causes increased formation of angiotensin, which causes increased aldosterone secretion, which in turn causes aldosterone-induced hypertension presumably as a result of water and salt retention by the kidneys. However, the present studies indicated that the quantitative steps of this mechanism are not potent enough to cause even a measurable hypertension.

On the other hand, other quantitative experiments showed that angiotensin has a direct effect on renal retention of water and salt that is potent enough to cause chronic volume-loading hypertension.

Finally, quantitative studies on the effects of aldosterone and ADH on extracellular fluid sodium and potassium ion concentrations showed that an aldosterone feedback mechanism is probably the major mechanism for control of extracellular fluid potassium ion concentration, while an ADH–thirst feedback control system plays by far the major role in the control of sodium ion concentration.