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Synergistic Action of Sodium and Angiotensin on Brain Mechanisms controlling Water and Salt Balance

INFUSIONS of hypertonic NaCl into the third brain ventricle of goats have been found to cause drinking[1], release of antidiuretic hormone (ADH)[2] and natriuresis[3] Thirst may also be elicited in the rat by intravenous infusions[4] and intrahypothalamic injections[5] of angiotensin. The effects of angiotensin and hypertonic saline on drinking are additive when both substanees are administered intravenously to nephrectomized rats[4]. For these reasons it seemed of interest to study how infusions into the third ventricle of angiotensin alone, or in combination with moderately hypertonic NaCl, would affect central mechanisms of importance in the regulation of water and salt metabolism.

Slow (10 μl./min) infusions into the cerebrospinal fluid of the third ventricle were made for 30 min periods in five goats, and for repeated 5 min periods in two of these animals. The infusion technique has been described earlier[1]. The goats were either in normal water balance or were hydrated by giving 100 ml. of water/kg body weight by stomach tube into the rumen 90 min before the infusions were started. Angiotensin (Hypertensin, Ciba) was dissolved either in slightly hypotonic (0·12 M) NaCl, or in hypertonic (0·33 M) NaCl, and was infused at a rate of 1–2 ng/kg/min. For comparison infusions of 0·33 M NaCl without angiotensin were also made.

When the goats were in normal water balance, 30 min infusions of 0·33 M NaCl or of angiotensin dissolved in hypotonic saline caused cumulative drinking of a total of 1–2 l. of water. These infusions also resulted in a two to five-fold increase in renal sodium excretion. The infusions of angiotensin together with hypertonic NaCl induced much more conspicuous polydipsia and more pronounced natriuresis. The animals drank 4 to 6 l. of water and renal Na^+ excretion rose to levels about 1 mequiv/min (= ten times control excretion).

During hydration, 30 min infusions of 0·33 M NaCl or of angiotensin dissolved in hypotonic saline caused little or no drinking. A moderate inhibition of the water diuresis became apparent towards the end of the infusion period and lasted for about 40 min. Renal sodium excretion became moderately elevated (two to three times control level). Also in the hydrated goat, however, the combination of angiotensin and hypertonic NaCl acted as a powerful thirst stimulus, and water had to be withheld in order to prevent fatal overhydration. Conspicuous natriuresis developed during the 30 min infusions (peak level >ten times above control Na^+ excretion). The natriuresis was succeeded by a long-lasting (2 h), profound inhibition of the water diuresis with high urine osmolality.

In two of the goats 5 min intraventricular infusions of 0·33 M NaCl, of angiotensin dissolved in hypotonic saline, and of angiotensin together with 0·33 M NaCl were made alternately during hydration. The brief infusions of 0·33 M NaCl and of angiotensin dissolved in hypotonic saline did not inhibit the water diuresis of the animals. Five minute infusions of angiotensin dissolved in 0·33 M NaCl, however, effectively inhibited the water diuresis for 40 to 60 min. During this antidiuresis urine osmolality rose four to five times, implying that the inhibition was due to release of ADH.

The observation that injections of minute amounts of hypertonic NaCl into the anterior hypothalamus may elicit polydipsia[6] has led to the suggestion that a hypothalamic "osmoreceptor" mechanism in Verney's[7] sense regulates not only the release of ADH but also the urge to drink. Infusions of hypertonic glucose or saccharose into the third ventricle, however, apparently do not elicit thirst or release ADH in the goat[1,8]. This indicates that an elevated Na^+ concentration is a more efficient stimulus to the thirst eliciting and ADH releasing mechanisms than is a rise in extracellular os moticepressure as such. The present study shows that all the effects on water and salt metabolism that are obtained in the goat by infusions of hypertonic NaCl into the third ventricle may be reproduced to a certain extent by similar infusions of angiotensin. It is also obvious that angiotensin markedly potentiates the effects of hypertonic NaCl infused into the ventricle. A possible explanation might be that angiotensin mimics the effect of an elevated extracellular Na^+ concentration by changing (increasing ?) the transport of Na^+ into brain cells which are involved in the regulation of water and salt metabolism. This would mean that the intracellular, rather than the extracellular, Na^+ concentration may determine the activity of these neurones.

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BENGT ANDERSSON
OLA WESTBYE

Department of Physiology,
Veterinärhögskolan,
104 05 Stockholm 50.

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Antagonism of Pressure and Anaesthesia

THE increase in ion permeability of 4 per cent phosphatidic acid–96 per cent phosphatidyl choline liposomes when exposed to liquid anaesthetics has been reported[1,2], and it was deduced that this increase was caused by increased freedom of movement of the lipid molecules, especially at the aqueous-lipid interface.

In 1950, Johnson and Flagler[3] reported that the spontaneous swimming motion of tadpoles disappeared when