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A CENTRAL OSMOSENSITIVE RECEPTOR FOR RENAL SODIUM EXCRETION

BY E. H. BLAINE,* D. A. DENTON, M. J. McKINLEY AND SIGRID WELLER

From the Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Parkville, Victoria 3052, Australia

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SUMMARY

1. The effect on renal Na and water excretion of increasing the NaCl concentration of blood supplying the brain was investigated in conscious water-loaded sheep. Intracarotid infusion of 4 M-NaCl at 0·8 ml./min for 60 min was compared with equivalent intrajugular infusion.

2. A more rapid increase in renal Na excretion and urine osmolality occurred with the intracarotid infusions than with intrajugular infusions.

3. Intracarotid infusions of 2 M sucrose or fructose at 1·6 ml./min for 30 min compared with equivalent intrajugular infusions also caused a greater increase in renal Na excretion, urine osmolality and a decrease in urine flow rate.

4. The results suggest that there are receptors in the brain sensitive to changes in extracellular tonicity which influence renal Na excretion. It is possible that changes in ADH secretion alone mediate the early natriuresis seen with intracarotid hypertonic infusions although an alternative concurrent mechanism cannot be ruled out.

INTRODUCTION

There are data suggesting a direct central nervous system involvement in the control of Na excretion. These include decreased renal Na excretion associated with ventriculocisternal perfusion of artificial c.s.f. with low Na concentration in anaesthetized dogs (Mouw & Vander, 1970), and conscious sheep (Mouw, Abraham, Blair-West, Coghlan, Denton, McKenzie, McKinley & Scoggins, 1974), hypernatremia associated with cerebral disorders in man and dogs (Kastin, Lipsett, Ommaya & Moser, 1965; Pleasure & Goldberg, 1966; Dorn & Rothballer, 1973) and changes

* Present address: Department of Physiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, U.S.A.

in renal sodium excretion resulting from hypothalamic lesions (Keeler, 1959; Novakova & Stevenson, 1971). Furthermore, natriuresis stimulated by a local increase in sodium concentration of CSF in the third cerebral ventricle of goats, dogs, rats and sheep (Andersson, Jobin & Olsson, 1967; Dorn, Levine, Kaley & Rothballer, 1969; Dorn & Porter, 1970; McKinley, Blaine & Denton, 1973) indicates the possibility of a hypothalamic Na sensor. The mechanisms underlying these natriuretic responses are not clear.

In preliminary experiments in this laboratory, intracarotid infusions of hypertonic NaCl caused only a transient antidiuresis in water-loaded sheep, contrasting with the sustained antidiuresis observed by Verney (1947) with intracarotid hypertonic infusions in water-loaded dogs. The 'escape' from the antidiuresis was associated with an increase in renal Na excretion.

The aim of the present experiments was to investigate in the conscious, undisturbed sheep the possibility that there exists a specific receptor in the brain responding to physiological changes in sodium concentration and influencing renal sodium excretion. Using the technique of Verney (1947), who compared the urinary effects of intracarotid with intravenous hypertonic infusions in water-loaded dogs, two questions have been asked. Does a selective increase within physiological limits of the Na concentration of the blood supplying the brain cause an increase in renal Na excretion? If so, could the effects be due to an increase in osmolality of the blood supplying the brain, rather than a specific Na effect?

METHODS

Animals

Experiments were performed on seven conscious ewes weighing 25–40 kg. Animals were housed in metabolism cages and maintained on a daily diet of 0·9 kg oaten-lucerne chaff. Free access to water was provided. Each animal was prepared with both carotid arteries surgically exteriorized in skin loops. Animals were allowed at least 1 month recovery period from this operation, and became accustomed to laboratory personnel and procedure. On the morning of an infusion, two polyethylene cannulae were placed in a single carotid artery and one in the ipsilateral jugular vein. The jugular vein cannula was used for the sampling of blood or for the infusion. Of the carotid cannulae one was used for making the infusion and a more caudal one for the direct measurement of arterial blood pressure with a Statham transducer (P23DB) fastened to the sheep's neck and coupled to an Offner type RS dynograph. Urine was collected throughout all experiments from a Foley retention catheter inserted in the urinary bladder on the morning of the experiment. During the infusions, urine collection periods were 8–10 min. Because of the high urine flow rates and short collection periods, bladder rinses were not made. All solutions were autoclaved before being infused.

Experimental protocols

Two groups of experiments were carried out:

(i) intracarotid 4M-NaCl infusions were compared with equivalent 4 M-NaCl intrajugular infusions (Group I);

(ii) intracarotid 2 M sucrose or fructose infusions were compared with intrajugular infusions (Group II).

NaCl infusions

The carotid artery contralateral to the infusion was occluded to provide essentially bilateral distribution of the infusate in the brain (Baldwin & Bell, 1963; Beilharz, Bott, Denton & Sabine, 1965) and animals were given a water load (100 ml./kg body wt. of tepid water by rumen tube), which after 60–90 min in preliminary experiments, caused an increase in the urine flow rate to 7–10 ml/min which persisted at least 4 hr. When the urine flow had reached 6–8 ml./min, 4 M-NaCl was infused at 0·8 ml./min into the carotid artery for 60 min. Observations were continued for a further 2 hr after stopping the infusion. To match these infusions, intrajugular 4 M-NaCl infusions were made on a different day. The same protocol was followed, the animal being hydrated and a carotid artery occluded. Five experiments of each type were carried out, each sheep tested being used for both types of infusion. Blood was sampled (8 ml.) from the jugular vein before making the infusion, 2 min after the end of infusion, and 2 hr after finishing the infusion.

Sucrose and fructose infusions

Infusions of 2 M sucrose or fructose were made into similarly water-loaded sheep via the carotid artery or jugular vein for periods of 30 min at 1·6 ml./min. Both the intrajugular and intracarotid infusions were done on the same day, at least 2 hr being allowed to elapse from the end of the first infusions to allow the re-establishment of a water diuresis before commencing the second infusion. The order of infusions was random, a total of twenty-two infusions, eleven via each route, were carried out. The results with both of the saccharides were similar and have been combined for statistical analysis.

Analytical procedures

Urine and plasma samples were analysed for Na and K concentration on a Technicon auto-analyser and osmolality on an advanced osmometer or Knauer Halbmikro osmometer.

Statistical methods

For each group, data are expressed as mean ± S.E. of the mean. For any one route of infusion, changes were measured as the difference between the final pre-infusion value and the value at a particular time period after commencement of infusion; whether each mean change was significantly different from zero was assessed by paired t test. For both Group I (4 M-NaCl infusions) and II (2 M saccharide infusions) the mean changes caused by intracarotid infusion were compared with those caused by intrajugular infusion (Student's t test).

RESULTS

Group I: infusions of 4 M-NaCl at 0·8 ml./min for 60 min

Consistent differences between the intracarotid and the intrajugular infusions were obtained with each sheep. The intracarotid infusions caused a significant reduction in the urine flow rate 8–16 min after the commencement of the infusion (6·63 ± 0·99 ml./min to 4·53 ± 0·95 ml./min, $P < 0·05$, $n = 5$ paired t test). This reduction in the urine flow rate was transient and 16–24 min after starting the infusion it began to increase again reaching its maximum level at the end of the infusion (Fig. 1). In contrast,

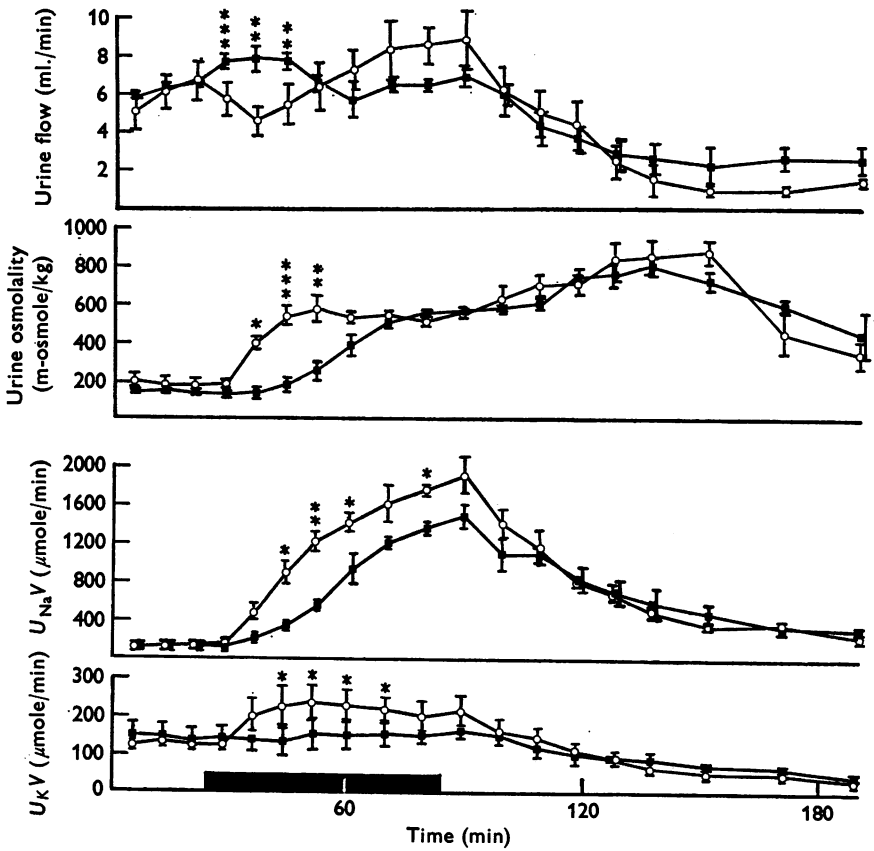

Fig. 1. The effect of intracarotid (○) and intrajugular (■) infusions of 4M-NaCl at 0·8 ml./min for 60 min on urine flow rate, urine osmolality, renal Na excretion and renal K excretion. The black bar denotes the period of infusion. Mean values ± S.E. are given. A statistical difference in change from final pre-infusion control values between the intracarotid and intrajugular infusions is denoted by * = $P < 0·05$, ** = $P < 0·01$, *** = $P < 0·001$ (Student's t test).

urine flow rate increased for the first 24 min, then returned towards pre-infusion levels with intrajugular infusions (Fig. 1). Renal sodium excretion rate ($U_{Na}V$) increased with both carotid and jugular 4 M-NaCl infusions. However, the increase over control in $U_{Na}V$ was significantly greater for the intracarotid than the intrajugular infusion and the natriuresis occurred earlier (Fig. 1) even though the Na load was the same in both instances. The urine osmolality also increased more rapidly in the intracarotid experiments, where it reached a maximum 30 min after the commencement of an infusion and remained high during the final 30 min. Potassium excretion (U_KV) increased with intracarotid, but not with intrajugular infusion (Fig. 1). On stopping either type of infusion, the urine flow rate and $U_{Na}V$ decreased within 10–20 min and urine osmolality increased above levels seen during the infusions. 2–2½ hr after the end of the infusions, urine flow rate and urine osmolality returned towards pre-infusion levels, indicative of a water diuresis. A gradual increase in systolic blood pressure of approximately 15 mmHg during the infusion period was observed in all five intrajugular and two intracarotid infusions. In the other three intracarotid infusions, blood pressure increased 20–30 mmHg within 5 min and remained elevated.

With the intracarotid infusions, plasma Na concentration increased from $144 \pm 0{\cdot}8$ (mean ± S.E. of mean) to $153 \pm 1{\cdot}0$ mM just after ending the infusion, and with intrajugular infusions from $145 \pm 1{\cdot}0$ mM before infusion to 152, 152 and 154 mM, the other two samples were lost. 2 hr after ending the infusions plasma sodium had decreased to $145 \pm 0{\cdot}9$ mM for the carotid infusions and $146 \pm 0{\cdot}6$ mM for the jugular infusions.

Group II: Infusion of 2 M sucrose or fructose at 1·6 ml./min for 30 min

Of the eleven experiments performed, five were associated with adverse behavioural effects (see below), and these experiments (ten infusions) have been omitted from the group data. Of the six experiments reported, the intracarotid infusion was given first in three of these. Comparison of the results of the intracarotid with the intrajugular infusions (Fig. 2) shows a significantly decreased urine flow rate, and increased urine osmolality with the intracarotid infusions compared to the intrajugular. In all six experiments, $U_{Na}V$ increased with the intracarotid infusion, this increment being at least twice as great as that observed with the corresponding jugular vein infusion. In the final urine collection period during the infusion, the increase in $U_{Na}V$ over the final control value was significantly greater ($P < 0{\cdot}05$) for the intracarotid experiment compared with the intrajugular experiment. U_KV was not affected. The mean pre-infusion control values of $U_{Na}V$ were not significantly different between intracarotid and intrajugular infusion trials.

The plasma concentration of Na before the infusion was not significantly different between the intracarotid and intrajugular trials being 142 ± 0·9 mM and 140 ± 0·9 respectively. Both groups showed a decrease in plasma Na concentration just after ending the infusion. Values were 136 ± 1·4 for carotid infusions and 138 ± 2·2 mM for jugular infusions. Two hours after ending the infusions, values were 141 ± 1·4 and 143 ± 0·9 mM

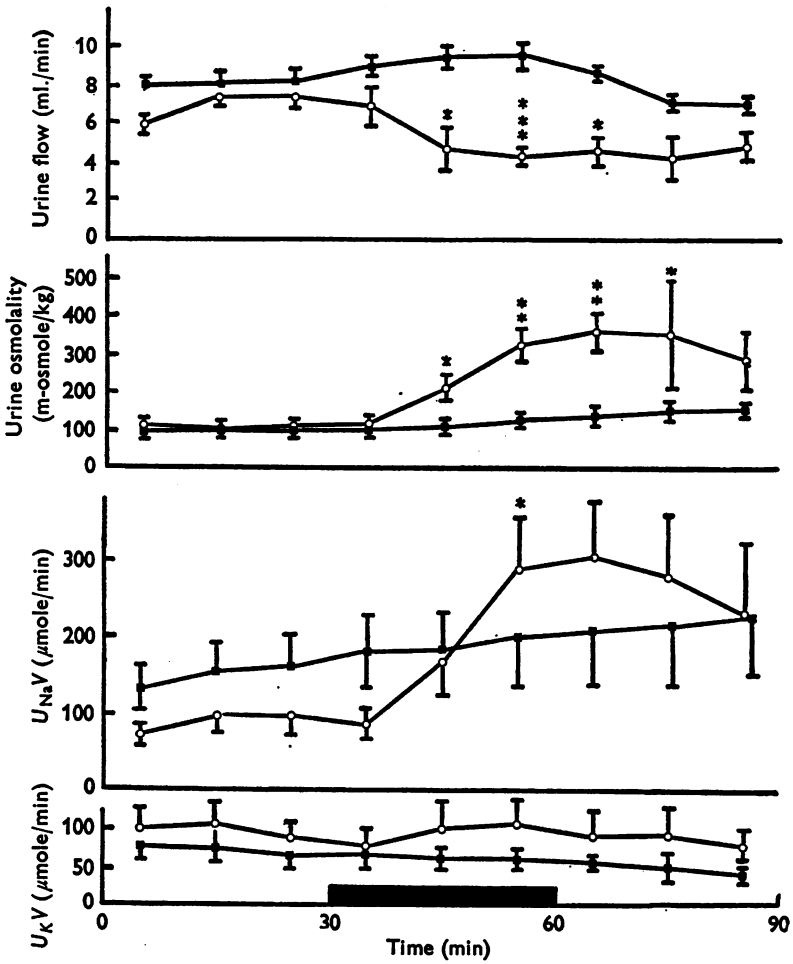

Fig. 2. The effect of intracarotid (○) and intrajugular (■) infusions of 2 M sucrose or fructose at 1·6 ml./min for 30 min on urine flow rate, urine osmolality, renal Na excretion and renal potassium excretion. The black bar denotes the period of infusion. Mean values ± S.E. A statistical difference in change from final pre-infusion control values between the intracarotid and intrajugular infusions is denoted by * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$ (Student's t test).

respectively. Arterial blood pressure was unchanged in all but one intracarotid infusion, in which it increased 20 mmHg within 3 min of commencing the infusion, and remained at this level till approximately 30 min post-infusion.

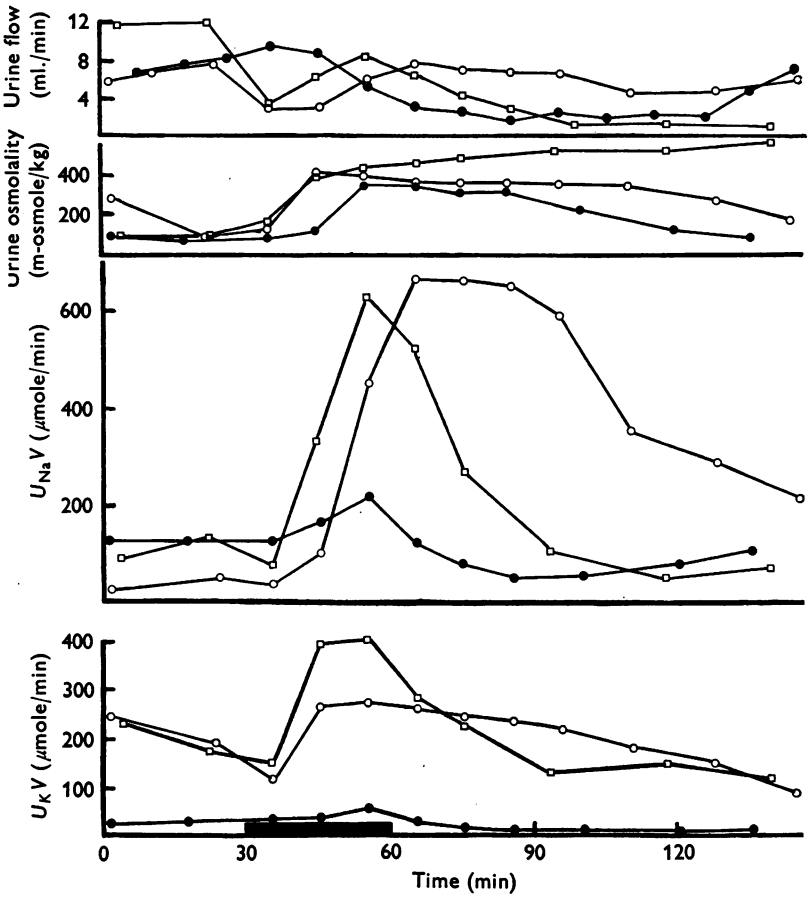

Fig. 3. The effects of hypertonic infusions causing adverse behavioural patterns on urine flow rate, urine osmolality, renal sodium excretion and renal potassium excretion. An intracarotid infusion of 2 M sucrose at 1·6 ml./min which caused a coughing bout (○), an intrajugular infusion of 2 M sucrose at 1·6 ml./min which caused the animal to collapse (□), and for comparison in the same animal an intracarotid infusion of 2 M sucrose at 1·6 ml./min in which no adverse behavioural patterns were observed (●) are shown. The black bar represents the period of infusion.

Adverse effects of saccharide infusions

In one sheep which was tested twice, a 2 M sucrose intrajugular infusion resulted in a large decrease in arterial blood pressure and the animal

collapsed. The animal recovered after interruption of the infusion for 1–2 min. A second sheep showed panting, tachycardia and head-shaking with an intrajugular 2 M sucrose infusion. Another animal exhibited coughing spasms with intracarotid infusions of 2 M sucrose or fructose, which ceased when the infusion was stopped for 1–2 min. In each of these experiments, rapid antidiuresis and large increases in urine osmolality and $U_{Na}V$ occurred. Two experiments in which adverse effects occurred are compared with an uncomplicated infusion in Fig. 3.

DISCUSSION

Intracarotid infusions of hypertonic NaCl cause an increase in renal Na excretion and urine osmolality and a transient reduction in urine flow rate in water loaded sheep. If a similar hypertonic NaCl infusion is made into the jugular vein, the changes in renal Na excretion and urine osmolality are significantly less. In both instances the Na load to the body is the same, but in the case of the intracarotid infusion, the NaCl concentration of the blood perfusing the head is greater than in the remainder of the body. This indicates that at a site within the distribution of the carotid artery, possibly in the brain, the increased NaCl concentration of the blood stimulates mechanisms which increase sodium excretion. That the brain is involved in the response is strongly supported by the observation that ablation of the subfornical organ abolishes the natriuresis caused by infusion of hypertonic NaCl into the carotid artery (Thornborough, Passo & Rothballer, 1973*a*). Observations in this laboratory (Abraham, Baker, Blaine, Denton & McKinley, 1974) indicate carotid blood flow with the contralateral carotid artery occluded to be in the range of 300–600 ml./min during hypertonic NaCl infusion. This indicates that the initial maximum increase in NaCl concentration in blood perfusing the brain during the intracarotid infusions would be 6–12 m-equiv/l., a physiological change.

Although it may not be necessary to invoke a specific sensor in explanation, these results are consistent with a hypothalamic brain receptor involved in renal Na excretion (Andersson *et al.* 1967; Andersson, Dallman & Olsson, 1969; Dorn *et al.* 1969; Dorn & Porter, 1970; Zucker & Kaley, 1972). However, unlike these experiments our results with saccharide infusions suggest that an osmo-sensing system rather than a specific Na sensing receptor may be involved in renal Na excretion. It could be argued that the increase in $U_{Na}V$ is small with the sugar infusion when compared with the hypertonic NaCl infusion. However, comparison of the changes in $U_{Na}V$ between NaCl infusions and saccharide infusions is not feasible because the hypertonic stimulus provided by the sugar infusion was only half that of the NaCl infusion and even if the hypertonic stimulus were the

same, the large difference in systemic Na load between the two types of infusion would preclude comparison.

Thornborough, Passo & Rothballer (1973*b*) using cats and Olsson (1973) with goats have found that infusion of hypertonic NaCl into the carotid artery produced a larger increase in renal Na excretion than equivalent I.V. infusion, which is consistent with the present results. Thornborough, Passo & Rothballer (1973*b*) however, were unable to show significant increases in $U_{Na}V$ with carotid artery infusions of hypertonic sucrose, a finding which conflicts with the present results in sheep. Olsson (1973) investigated the effects of hypertonic NaCl infusion only. The difference between results in the sheep and cat may possibly be due to the fact that anaesthesia, laparotomy and mineralocorticoid administration were carried out during experiments in the cat. These procedures would tend to have sodium retaining effects, possibly obscuring natriuretic effects of intracarotid, hypertonic sucrose infusions. This possibility is strengthened by the observation that during 90 min of infusion and 60 min post-infusion period, only 23 % of the hypertonic NaCl load infused into the carotid artery was excreted by the cats, while up to 70 % of the NaCl load was excreted by conscious sheep during 60 min of hypertonic infusion, and the 60 min following in the present experiments. These observations suggest that the effectiveness of renal Na excretory mechanisms may have been diminished under the conditions of the experiments in the cat.

What is the efferent pathway from the head mediating the greater natriuretic response of intracarotid hypertonic infusions? Brooks & Pickford (1957) reported that production of experimental diabetes insipidus in a dog abolished both the natriuretic and antidiuretic response to an I.V. injection of hypertonic sucrose. Mitrakova (1972) found that hypophysectomy abolished the natriuretic and antidiuretic response to an injection of hypertonic NaCl into the left atria of dogs. This evidence suggests that the natriuretic effects of the hypertonic injections were not due to production of an osmotic diuresis, but were dependent on an intact pituitary, and suggest that the greater renal Na excretion with intracarotid than with intrajugular infusion in the present experiments may be due to a larger secretion of a pituitary hormone. In the present experiments, stimulation of ADH secretion by 4 M-NaCl intracarotid infusion is indicated by the rapid increase in urine osmolality and decrease in urine flow which occurs, and also by the persistent antidiuretic effect seen after ending the infusions. In view of reports that administration of ADH can elicit natriuresis (Sawyer, 1952; Anslow & Wesson, 1955; Brooks & Pickford, 1958; Macfarlane, Kinne, Walmsley, Siebert & Peter, 1967; Humphreys, Friedler & Earley, 1970) possibly dependent on Na balance (Andersson, Denton & Verney, 1957) it is possible that the more rapid and

larger increase in $U_{Na}V$ seen with intracarotid 4 M-NaCl infusions compared to the intrajugular infusions is due to an earlier and larger increase in ADH levels in the intracarotid experiment.

The rapidity of the natriuretic response to the intracarotid hypertonic infusion suggests that reduction of aldosterone level is not the cause of the response. The inconsistency of the changes in arterial blood pressure during the intracarotid NaCl infusions, militates against changes in electrolyte excretion being mediated by alterations of arterial blood pressure. In fact the two experiments showing the largest increase in $U_{Na}V$ were the two experiments in which arterial blood pressure increased the least. A pathway via the renal nerves remains as a possibility.

As with the experiments of Verney (1947) in the dog, the intracarotid hypertonic NaCl infusions rapidly decrease urine flow. Unlike Verney's experiments, however, this effect was transient (Fig. 1). The likely explanation for this phenomenon is stimulation of solute excretion combined with a decreased concentrating action of ADH on the kidney during an osmotic diuresis. This is supported by the reports which indicate ADH to be less effective in concentrating urine during high levels of solute excretion (Orloff, Wagner & Davidson, 1958; Gottschalk, 1964; Rabinowitz & Gunther, 1972) and also by the increase in urine osmolality and antidiuresis which occurs on ending the hypertonic infusions, concomitant with a decrease in $U_{Na}V$.

The role of osmoreceptors controlling ADH release in ruminants has been questioned recently (Eriksson, Fernandez & Olsson, 1971; Olsson, 1972; Eriksson, 1973) and volume receptors in the left atrium have been shown to exert a considerable influence over ADH secretion (Johnson, Zehr & Moore, 1970; Gauer, Henry & Behn, 1970). Olsson & McDonald (1970) were unable to elicit antidiuresis in water loaded sheep with intracarotid hypertonic infusions until a certain fraction of the water load had been excreted. This suggested to them that a factor related to the volume of water retained could override osmotic stimuli. Our experiments have employed a similar water load, but a larger osmotic stimulus in the case of 4 M-NaCl, and an antidiuresis was obtained before the excretion of a significant fraction of the water load, indicating that a sufficiently large osmotic stimulus can overcome the inhibitory effect of increased volume stimulus on ADH secretion if such an effect operates. Stress and bilateral carotid artery occlusion are stimuli to ADH release (O'Connor & Verney, 1942; Smith, 1957; Moran & Zimmermann, 1967; Perlmutt, 1968), and it is likely that in some of the saccharide infusions where adverse effects were noted, the rapid antidiuresis and increase in urine osmolality was caused by ADH secretion resulting from stress or the rapid decrease in arterial pressure. This indicates that these two types of stimuli may overcome any

putative volume influences inhibiting ADH release. The mechanism of the increased electrolyte excretion in these experiments is unknown, but the importance of using unstressed animals in studying salt and water excretion by the kidney is indicated.

In summary, it is probable in the sheep that stimulation of cranial osmoreceptors causes ADH secretion and increased renal Na excretion. The osmo-receptors mediating antidiuresis and Na excretion are not necessarily the same. The pathway by which this effect on electrolyte excretion occurs cannot be stated with certainty from the present experiments, but mediation in whole or part by ADH action is possible. A role for a non-ADH osmo-receptor mediated influence on renal Na excretion is not excluded.

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