Control of sodium excretion in patients with cranial diabetes insipidus maintained on desamino-[8-d-arginine]vasopressin

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1. We have studied the response of six patients with cranial diabetes insipidus and six age-matched control subjects to dietary sodium restriction during constant administration of the synthetic vasopressin analogue desamino-[8-d-arginine]vasopressin.

2. Urine flow increased on the first low salt day in the normal control subjects but not in the patients with cranial diabetes insipidus. Body weight fell 1.35 kg in the control subjects but was constant in the patients with cranial diabetes insipidus.

3. Urinary sodium excretion fell at the same rate in both groups. Diurnal variation of urinary sodium excretion and creatinine clearance was present in the control subjects but not in the patients with cranial diabetes insipidus.

4. Changes in plasma sodium concentration and osmolality were similar. Plasma protein concentration increased more in the control subjects (from 69.1 ± 1.5 to 73 ± 1.2 versus from 71.7 ± 1.1 to 73.2 ± 1.1 g/l). The responses of plasma atrial natriuretic peptide, plasma renin activity and salivary aldosterone concentration were similar between the two groups. Salivary aldosterone concentration levels were consistently higher in the patients with cranial diabetes insipidus.

5. We confirm that the low salt diuresis is triggered by release from the antidiuretic activity of arginine vasopressin. In the patients with cranial diabetes insipidus extracellular fluid osmoregulation appeared to be achieved by the movement of water out of and sodium into the extracellular fluid.

6. Absent posterior pituitary function and hypothalamic disturbances did not alter renal sodium conservation. Total extracellular fluid sodium appeared to be lower in the patients with cranial diabetes insipidus than in the control subjects. Disturbances of hypothalamic and pituitary function may have caused resetting of overall sodium balance and altered diurnal cycles of urinary sodium excretion and creatinine clearance.

INTRODUCTION

Near constancy of extracellular fluid (ECF) osmolality during dietary sodium restriction is ensured by a water diuresis in the first 48 h of adaptation. This diuresis is triggered by a fall in plasma vasopressin (AVP) concentration [1]. The stimulus responsible for the fall in plasma AVP concentration is almost certainly an early, but small, fall in plasma sodium concentration. It is also possible that such changes in plasma sodium concentration could influence sodium excretion, perhaps through sodium receptors within the central nervous system [2-9]. If this were the case, then there would be the potential for central nervous system integration of the regulation of both ECF volume and sodium concentration. AVP itself is unlikely to be the common link as, despite reports that it may be natriuretic [10-12], we have demonstrated that AVP infusion during the first 36 h of salt restriction, sufficient to prevent the diuresis, has no effect on renal sodium conservation [1]. In addition, the natriuresis that results from elevation of cerebrospinal fluid sodium concentration has been demonstrated to be independent of changes in plasma AVP concentration [13]. Hence it has been postulated that there is a central sodium receptor in the anterior hypothalamus with the potential to alter renal sodium excretion through as yet unidentified pathways [14, 15].

For the full syndrome of diabetes insipidus to develop after hypophysectomy, the capacity of the anterior hypothalamus to synthesize and secrete AVP must be lost [16]. Hence patients with com-
plete cranial diabetes insipidus (CDI) secondary to pituitary tumours with hypothalamic extension or to hypothalamic surgery almost certainly have associated disturbance of anterior hypothalamic function. If this region of the hypothalamus was important in regulation of sodium excretion, such patients might exhibit abnormal responses to sodium restriction. To examine this question we studied the response of six patients with CDI and 6 age-matched control subjects to dietary sodium restriction.

METHODS

Subjects

The patients with CDI were all well at the time of the study and on long-term medication. All had been investigated and none was able to concentrate urine off medication. Their ages ranged from 37 to 52 years, and three were male. Three had had hypophysectomies; the other three had had craniopharyngiomas removed. All operations had been performed by the transfrontal route. No patient with CDI had detectable plasma levels of AVP. All patients were on desamino-[8-D-arginine]vasoressin (DDAVP) taken either orally or via the nasal mucosa. DDAVP is an analogue of AVP created by desamination of the N-terminal and replacement of 8-L-arginine by 8-D-arginine. Thus modified, antidiuretic (V2) activity is increased,pressor (V1) activity is almost absent and the duration of action is prolonged [17]. Doses of DDAVP had been previously tailored to control urine volumes and ranged from 200 µg three times a day taken orally to 10 µg twice a day by nasal spray. All patients with CDI remained on a constant dose throughout the 5 day study period. Five out of six were on thyroxine (150 µg/day). The need for corticosteroid replacement was determined by the response to insulin-induced hypoglycaemia stress testing and was given as hydrocortisone, 15 mg in the morning and 5 mg in the evening, in four patients, and prednisolone, 5 mg in the morning, in one patient. Two of the female patients, aged 37 and 44 years, were receiving combined oestrogen/progestogen replacement. One of the male subjects, aged 49 years, was on testosterone replacement. All medications were chronic and were continued throughout the experimental period.

The control subjects comprised five males aged between 23 and 52 years and one female aged 57 years. They were on no medication and none had a history of serious illness or any evidence of abnormal renal function or hypertension. All subjects gave their fully informed, written consent, and local ethical committee approval for the study was obtained.

A controlled sodium diet was given throughout the study period. This contained 11715 kJ/day as 90 g of protein, 80 g of fat, 300 g of carbohydrate, 90 mmol of potassium and 50 mmol of sodium. For the first 3 days sodium intake was raised to 290 mmol/day (days 1, 2 and 3) by adding eight sodium chloride tablets ("Slow Sodium"; Ciba, 10 mmol/tablet) to each meal. The 48 h period of sodium restriction began with the withdrawal of these tablets on the morning of the fourth day (days 4 and 5). None of the subjects experienced any adverse effects. Daily fluid intake was held constant according to individual preference established on the first day of the first study (mean 3.2 litres in the patients with CDI and 1.9 litres in the control subjects).

Samples

Venous blood was sampled via an indwelling Teflon cannula introduced under lignocaine local anaesthesia into a forearm vein on the morning of day 3. Blood samples were taken after 30 min recumbency at 08.00, 12.00, 16.00 and 22.00 hours on days 3, 4 and 5 for the measurement of plasma electrolyte, protein and creatinine concentrations, osmolality, packed cell volume, plasma renin activity and atrial natriuretic peptide (ANP) concentration. Samples for ANP were taken into chilled tubes containing aprotonin for plasma separation and were stored at −70°C before analysis. Plasma electrolyte concentrations and osmolality were measured immediately, and the remaining plasma was stored at −20°C.

Saliva samples were taken every 2 h from 08.00 hours to 24.00 hours on every day and were stored at −20°C for measurement of aldosterone concentration. Salivary aldosterone concentration is linearly related to plasma aldosterone concentration [18], hence frequent samples were possible while minimizing the amount of blood samples taken from our subjects.

Urine was collected every 12 h on days 1 and 2 and every 4 h from 08.00 to 24.00 hours and 8 h overnight on days 3, 4, and 5. Urine was analysed for electrolyte and creatinine concentrations and osmolality.

Subjects were weighed and lying and standing blood pressure was measured at 08.00 hours and 18.00 hours each day using a standard sphygmomanometer.

Laboratory analyses

Sodium and potassium concentrations in plasma and urine were measured by flame photometry (Corning Flame Photometer 430). Osmolality was measured cryoscopically (Gonotec Osmomat 030). Plasma was analysed before freezing to avoid artefactual changes in osmolality. Creatinine in urine and plasma was measured colorimetrically as creatinine alkaline picrate (Chemlab Auto Analyser), and total plasma protein concentration was determined by the Biuret method (Chemlab Auto Analyser).

Plasma renin activity was measured by the radioimmunoassay of angiotensin I (ANG I) generated from its endogenous substrate on incubation of
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Fig. 1. Renal response of patients with CDI to 2 days of dietary sodium restriction compared with that of control subjects (a), and daytime and night-time urinary excretion rates in patients with CDI compared with those of the control group (b). Control subjects: [], patients with CDI. Values are means ± SEM. Statistical significance: *P < 0.05 compared with day 3 (a) or with daytime (b).

plasma and expressed as pmol of ANG h⁻¹ ml⁻¹ [19].

Salivary aldosterone was measured directly by radioimmunoassay of unextracted samples [18].

Plasma levels of ANP were assayed, after extraction, by radioimmunoassay with a lower limit of detection of 3.5 pmol/l [20].

Each subject's samples were run in one assay to avoid inter-assay variability.

Data analysis

Data from the first 2 days of each study were excluded from the analysis as this was the time necessary to allow equilibration from varying pre-study sodium intakes.

Plasma renin activity, salivary aldosterone concentration, plasma ANP concentration and urinary data were log-normally distributed and consequently were analysed after log-transformation. These results are expressed as the geometric means and SEM on analog scales. The remaining plasma data, fractional sodium excretion and creatinine clearance were normally distributed. These results are expressed as means ± SEM. The significance of differences between days 3–4 and days 3–5 within each group and between corresponding days between groups were assessed by analysis of variance and t test using the Bonferroni correction for repeated comparisons.

In a separate analysis, the patients with CDI who had had hypophysectomies were compared with those who had had craniopharyngiomas resected.

RESULTS

Effect of salt restriction on urinary excretion (Fig. 1)

Urine flow was greater in the patients with CDI on day 3 but remained constant in this group, increasing from day 3 to day 4 only in the control subjects. Body weight fell by 1.35 ± 0.16 kg in the control subjects, but only by 0.25 ± 0.21 kg in the patients with CDI (P = 0.0004 between groups by t-test). Urinary sodium excretion decreased at the same rate on days 4 and 5 in both groups. Creatinine clearance was the same on day 3 in both groups, tending to fall in the control subjects only. Because of this divergence creatinine clearance was significantly greater in the patients with CDI on day 4 (P < 0.05). Pooling days 3, 4 and 5 and comparing the daytime collections with the overnight collection, there was a nocturnal fall in creatinine clearance in control subjects (day, 134.1 ± 5.2 versus night 107.8 ± 6.9 ml/min, P = 0.2 by t-test) that was not seen in the patients with CDI (day, 140.1 ± 5.6 versus night, 148.1 ± 9.5 ml/min, not significant). The diurnal pattern of sodium excretion followed the same pattern, being greater during the day in control subjects (day 9.18 ± 0.56, night 6.69 ± 1 mmol/l, P = 0.03 by t-test) but constant through day and night in CDI (day 7.94 ± 0.57, night 9.38 ± 1.21 mmol/l, not significant). The diurnal variation in renal potassium excretion was the same in both groups (control subjects: day 5.51 ± 0.23, night 3.2 ± 0.37 mmol/l, P < 0.001, patients with CDI: day 5.09 ± 0.39, night 3.5 ± 0.41 mmol/l, P = 0.007 by t-test).

Effect of salt restriction on blood pressure and heart rate (Fig. 2)

Mean arterial pressure, standing and lying, was the same in both groups throughout salt restriction.
Neither mean arterial pressure nor heart rate, standing or lying, was affected by salt restriction. Further comparisons refer to data pooled from days 3, 4 and 5. Standing heart rate was always higher in the patients with CDI. Mean arterial pressure and heart rate increased on standing in both groups, but the orthostatic increase in heart rate in the patients with CDI was greater than in the control subjects. In the control subjects, irrespective of posture, mean arterial pressure was greater at 08.00 than at 22.00 hours over days 3–5, but time of day had no influence on heart rate. In patients with CDI this pattern was reversed as mean arterial pressure was unaffected by time of day and heart rate was greater at 22.00 than at 08.00 hours.

**Effect of salt restriction on plasma variables (Fig. 3)**

Plasma sodium concentration was greater in the control subjects than in the patients with CDI throughout days 3–5 but fell equally in both groups. Plasma osmolality was lower in the control group on day 3 and also fell equally in both groups during salt restriction. Plasma potassium concentration was the same in both groups throughout the last 3 days (control subjects: 3.96 ± 0.03, 3.99 ± 0.03 and 4.03 ± 0.04 mmol/l, patients with CDI: 4.01 ± 0.06, 3.94 ± 0.05 and 4.11 ± 0.06 mmol/l). Packed cell volume and plasma protein concentration were both greater on day 3 in the patients with CDI. The increase in packed cell volume during salt restriction was the same in both groups, but by day 5, plasma protein concentration had increased more in the control subjects than in the patients with CDI (control subjects up by 6.1 ± 1.4%, patients with CDI up by 2.1 ± 1.2%, *P* < 0.05). The rise in plasma renin activity in response to salt restriction was similar in both groups. Salivary aldosterone concentration was almost three times higher in the patients with CDI throughout the study but increased in similar fashion by day 5 in both groups. Baseline plasma levels of ANP and degree of fall during salt restriction were the same in both groups.

**Comparison between patients with previous pituitary tumours and those with previous craniopharyngiomas (Fig. 4)**

In a direct comparison between the patients undergoing surgery for craniopharyngiomas with those having transfrontal hypophysectomies, the three patients with craniopharyngiomas showed a more rapid fall in urinary sodium excretion and had an antidiuresis during salt restriction. In the craniopharyngioma group, salivary aldosterone concentration was higher but failed to increase significantly during salt restriction, whereas plasma renin activity was consistently lower. Plasma protein concentration was higher and did not increase during salt restriction. Similarly, packed cell volume failed to increase. Plasma ANP level was lower on days 3 and 4. As the fall in plasma ANP level was not sustained in the craniopharyngioma group, there was no difference between patient groups on day 5.

**DISCUSSION**

**Low salt diuresis**

The diuresis that occurs during adaptation to a reduction in sodium intake is most probably trig-
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Gerard by a fall in AVP secretion [1]. The possibility that this diuresis results from a reduction in renal sensitivity to AVP is not supported by our findings, as no low salt diuresis occurred in the patients with CDI on constant doses of DDAVP.

Control of osmolality and plasma volume during salt restriction

Baseline plasma volume appeared to be lower in the patients with CDI as both packed cell volume and plasma protein concentration were higher than in the control subjects. This may have been due to difficulty in adjusting the dose of DDAVP to individual requirements, illustrated by the nocturnal diuresis in the patients with CDI which was almost certainly a consequence of the lack of DDAVP overnight. The relative contraction of plasma volume in the patients with CDI might explain the greater increase in heart rate on change from lying to standing in this group, resulting from increased activation of the sympathetic nervous system. To some extent, a direct effect of DDAVP may have caused some increase in heart rate. This effect has, however, only been demonstrated with relatively large intravenous doses given as a bolus [21] and is thought to occur as a result of vasodilatation rather than plasma volume contraction. If volume contraction was the consequence of dehydration alone, plasma sodium concentration might have been expected to be higher in the patients with CDI; we found it to be lower. This suggests that the patients with CDI were relatively sodium-depleted compared with the control subjects. Central nervous system 'salt-wasting' lesions have been described [22] and the lesions in the patients with CDI may have resulted in such a salt-wasting state. Our observation that salivary aldosterone concentration was higher in the patients with CDI is consistent with this interpretation, suggesting that overall sodium balance was achieved by increased aldosterone secretion whatever the level of sodium intake.

It is conceivable that lesions distant to the hypothalamus, resulting from surgery, could have had some influence on body fluid homeostasis in our patients. It would, however, seem most likely that the altered responses of the patients with CDI resulted from documented lesions in that area of the brain known to be of central importance in body fluid regulation and circulatory control.

We cannot explain the differences in baseline plasma sodium concentration and plasma osmolality between groups. It appeared that some osmotically active component of plasma, other than sodium, must have been elevated in the patients with CDI.

Despite the lack of diuresis during salt restriction in the patients with CDI, plasma sodium concentration fell to the same extent as in the control subjects. Given the negative sodium balance over days 4 and 5 of approximately 200 mmol and assuming an ECF volume of 14 litres and a day 3 plasma sodium concentration of 142 mmol/l, a drop in plasma sodium of 14 mmol/l might have been expected. This fall in plasma sodium concentration would have been prevented by the loss of 1.41 litres of water from the ECF, a volume consistent with the weight loss observed in the control subjects of 1.35 kg. As changes in plasma sodium concentration could not be regulated by renal water loss in the patients with CDI, it is possible that the movement of water was from ECF to intracellular fluid (ICF). If this were the case, plasma volume contraction would have been the same in both groups. If, for the sake of argument, water loss were 1.4 litres, total ECF volume 14 litres and plasma volume 3 litres, then a contraction in plasma volume of 10% or some 300 ml would be expected as a result of the homoeostatic low salt diuresis in response to the loss of 200 mmol of sodium. Plasma protein concentration had increased on day 5 by 6.1 ± 1.4% in the control subjects, but by only 2.1 ± 1.2% in the patients with CDI (P < 0.05). Although the rise in packed cell volume was similar in the two groups, there were clear differences in weight between the groups by day 5. The balance of evidence therefore suggested that plasma volume contraction during
salt restriction was less in the patients with CDI. Thus in the patients with CDI, some buffering of plasma sodium concentration may have occurred from movement of sodium into the ECF as well as from movement of water into the ICF. A potential source of sodium in such a process has been suggested by a study in rats, where sodium was mobilized from bone during salt depletion [23].

Regulation of sodium excretion and diurnal variation in renal function

The ability to conserve sodium in response to dietary salt restriction was not affected by the pituitary and hypothalamic lesions present in the patients with CDI we studied. Constant doses of DDAVP also had no effect on sodium excretion. There were, however, marked differences between patients with CDI and control subjects in the diurnal pattern of urinary sodium excretion, creatinine clearance and systemic hemodynamics. In our control study, as has been well described in the past in normal man [24–29], urinary sodium excretion and creatinine clearance were both lower at night than during the day. By contrast, in the patients with CDI, there were no differences in these variables between night and day. These disturbances of the usual diurnal changes in renal function may have resulted from abnormal hypothalamic function, from hormone replacement, or from other differences between the groups such as in 24h blood pressure patterns.

All the patients with CDI were on constant doses of glucocorticoid, divided throughout the day so as to mimic the endogenous rhythms of steroid hormone secretion seen in intact man. Evidence in man suggests that glucocorticoids, although causing sodium retention, do not alter the diurnal pattern of sodium excretion [24]. A study in renal transplant recipients demonstrated early reversal of day–night patterns of sodium excretion that reverted to normal some 6 months after transplantation despite constant glucocorticoid administration [30].

The possibility that administration of DDAVP during the day in the patients with CDI could have altered sodium excretion or creatinine clearance is not supported by an earlier study in ileostomy patients in whom the usual nocturnal fall in urinary sodium excretion and creatinine clearance was not affected by administration of DDAVP (M. Sutters et al., unpublished work).

Mean arterial pressure was higher in the morning than at night in the control subjects, as previously described in man [31]. There was no such diurnal variation of blood pressure in the patients with CDI. As renal perfusion pressure may directly influence renal sodium excretion and glomerular filtration rate [32, 33] it is possible that the lack of fall in urinary sodium excretion and creatinine clearance overnight in the patients with CDI resulted from the absence of the usual nocturnal fall in mean arterial pressure.

Finally, the suprachiasmatic nuclei within the hypothalamus have been implicated in the generation of mammalian endocrine rhythms [34]. The suprachiasmatic nuclei are closely related to the paraventricular and supraoptic nuclei, both of which synthesize AVP and lie in the anterior hypothalamus. The lesions in the patients with CDI may therefore have directly affected the generation of cycles of urinary sodium excretion and creatinine clearance.

Endocrine response to salt restriction

As a group, there were no differences in plasma renin activity between the patients with CDI and the control subjects either at baseline or in response to salt restriction. When the patients with craniopharyngiomas and hypophysectomies were analysed separately, it became clear that plasma renin activity in the latter exceeded levels in control subjects or patients with craniopharyngioma. Values for plasma protein concentration suggested that the patients with craniopharyngiomas were relatively plasma volume contracted compared with the patients with hypophysectomy and the control subjects. Hence, the elevated plasma renin activity in the patients with hypophysectomy could not be explained on the basis of differences in drug treatment or degree of plasma volume depletion. In patients with CDI, differences in plasma renin activity thus appear to depend on the anatomical site or nature of the lesion.

The increased salivary aldosterone concentration in the patients with CDI could not be explained on the basis of differences in plasma renin activity between the groups. Increased sensitivity of aldosterone release may have been important. This is suggested by the elevation of salivary aldosterone concentration in the craniopharyngioma group above the levels seen in either the hypophysectomy or control groups, in whom plasma renin activity was either elevated or similar, respectively. In a previous study by other workers, plasma aldosterone concentration failed to rise during salt restriction in a group of patients with absent anterior pituitary function [35]. The disagreement between their findings and those in the hypophysectomized patients in the present study may have arisen out of differences in patient type and experimental protocol. Our hypophysectomized patients had, in addition to loss of anterior pituitary function, disturbance of posterior pituitary and hypothalamic function. In addition, aware of the episodic nature of aldosterone release [36] we measured salivary aldosterone concentration every 2h throughout each study day. In the study of McCaa et al. [35], plasma aldosterone concentration was measured over a 1h period only.

Despite differences in body weight and indices of
plasma volume at baseline and in response to salt restriction between the CDI and control groups, ANP levels were similar. A clear relationship between plasma volume and heart rate has been described in other experimental situations [20, 37, 38] but this relationship appeared to be less certain in the patients with CDI.

Comparisons between patient groups

The data presented in Fig. 4 suggest that in those patients from whom craniopharyngiomas were resected, there was a combination of relatively greater basal plasma volume contraction and more avid sodium retention than in those receiving hypophysectomies. This impression receives further support from the haemodynamic data, where standing heart rate was higher on day 3 and day 4 in the craniopharyngioma group. Perhaps as a consequence of the swifter fall in urinary sodium excretion during days 4 and 5, there was no increase in urine flow, standing heart rate, plasma protein concentration or packed cell volume during salt restriction in the craniopharyngioma group.

The craniopharyngioma group probably made a greater contribution than did the hypophysectomy group to the relative plasma volume contraction, lack of diuresis and greater levels of salivary aldosterone seen in the CDI group as a whole. Nonetheless, no diuresis occurred in either of the CDI subgroups and packed cell volume, plasma protein concentration and salivary aldosterone concentration in each of the sub-groups exceeded the corresponding values in the control group.

Conclusion

We have found no evidence that large suprasellar lesions of the pituitary gland or craniopharyngiomas of the anterior hypothalamus result in impaired sodium conservation in response to dietary sodium restriction in man. Our data do, however, suggest that the lesions present in the patients with CDI resulted in resetting of sodium homeostasis, particularly in the craniopharyngioma group, with the result that total ECF sodium content was lower in the patients with CDI irrespective of sodium intake. We provide evidence that the effects of lesions in the vicinity of the hypothalamus upon the control of the secretion of renin and aldosterone vary with their nature and location.

Our findings provide further evidence that the low salt diuresis is triggered by a fall in AVP secretion and raise the possibility that falls in plasma sodium concentration may be buffered by movement of sodium into the ECF from some sequestered source.

The patients with CDI had an altered diurnal cycle of blood pressure, creatinine clearance and sodium excretion. It is likely that central nervous integration of circadian rhythms had been disturbed in the patients with CDI as a result of damage to the anterior hypothalamus.

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REFERENCES


