Chronic hypernatremia due to impaired osmoregulated thirst
and vasopressin secretion

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Abstract. We report the case of a young man who became adipsic following a subarachnoid hemorrhage and subsequently had two episodes of life-threatening hypernatremia. Investigations demonstrated that he had defective osmoregulated thirst and AVP release, but normal AVP responses to hypotension and nausea. There is also evidence that he had intact baroregulated thirst. We discuss the results of our investigations in the context of current models of hypothalamic-neurohypophysial function.

In health, plasma osmolality is maintained within strict limits by variation in both fluid intake and output. With rising plasma osmolality arginine vasopressin (AVP, antidiuretic hormone) is released from the posterior pituitary under the influence of a putative hypothalamic osmoreceptor (1,2). This causes increased absorption of water from the renal collecting system and high urinary osmolality, conserving body water. As plasma osmolality rises, thirst intensity also increases causing increased fluid intake (3,4). Osmotically stimulated thirst is also mediated via a hypothalamic centre which is intimately related, if not identical to the osmoreceptor (1,5). Non-osmotic stimuli to AVP release include hypotension, hypovolemia, hypoglycemia, and nausea and vomiting (6,7). Weiss et al. (8) have demonstrated that hypovolemia also stimulates thirst, but little is known about the pathophysiology of this response. Rare patients manifest lesions involving the osmoreceptor (9-12) and are characterized by chronic hypernatremia from both lack of thirst and lack of osmoregulated AVP (although baroregulated AVP secretion is intact). We report the case of a young man with chronic hypernatremia owing to defective osmoregulated thirst and AVP release but with a normal AVP response to an emetic stimulus and hypotension and evidence of normal baroregulated thirst.

Case report

The patient was a Caucasian male referred to our unit at the age of 28 years. He had been well until two and a half years earlier when he collapsed at his work as a joiner. Subarachnoid hemorrhage was diagnosed and cerebral arteriography revealed a 10 by 15 mm aneurysm of the anterior communicating artery. Seven days later the aneurysm was successfully clipped through a left frontal craniotomy in a 3½ h procedure. Postoperatively he had anterior cerebral artery spasm, a left frontotemporal hematoma and marked hypoxia, requiring assisted ventilation for 36 h. He was left with memory impairment, severe dysphasia, and a right hemiparesis. One month after admission he was transferred to an inpatient rehabilitation centre where he remained for a further 5 months. Throughout this time his serum sodium ranged from 150-160 mmol/l and he needed frequent encouragement to drink. Desmopressin (dDAVP) was administered on several occasions despite oliguria. After the 5 months he developed a communicating hydrocephalus for which a ventriculo-peritoneal shunt was inserted. Subsequently he became pyrexial with a urinary infection related to an indwelling catheter. His serum sodium rose to 171 mmol/l and his urine osmolality was 1150 mOsm/kg. He was treated with vigorous rehydration and antibiotics and eventually was discharged back to the rehabilitation unit where he re-
mained for a further 3 months. After this time he was allowed home and his wife given advice to encourage his fluid intake. He remained well for 20 months until he developed a trivial pyrexial illness in the hot June weather. On admission he was obtunded and responding only to deep pain, his temperature was 38°C and his serum sodium 191 mmol/l. He was again successfully resuscitated and subsequently was referred for further inves-

stigation.

He was thin, 180 cm tall and 62 kg in weight. He was not clinically dehydrated and had no signs of overt en-
docrine dysfunction. He had a poor short-term memory and was disorientated in both time and place. He was often inappropriately cheerful and was not distressed by his lack of memory. He was anosmic but could distinguish between a salty, sweet and sour taste. He had a mild spas-
tic right hemiparesis which spared his face, and a minimal expressive dysphasia. Coarse intention tremor was present in his right arm. His gait was hemiparetic with circumsoduction of his right leg and slightly broad based. He had myoclonic jerking episodes affecting his right arm and trunk after eating food associated with an intense subjective feeling of cold, and occasional short-lived ab-

sence attacks. His body temperature normally ranged from 35.5 to 36°C. He never drank spontaneously, and needed constant prompting to maintain his fluid intake. He complained of hunger on occasions and had normal volition for other actions such as getting dressed or shaved.

A full blood count, Westergren sedimentation rate, blood glucose, ionised calcium and T₄ were normal. Fast-

ing serum cholesterol was 7.5 mmol/l and triglyceride 2.26 mmol/l. Tests of anterior pituitary function including resting prolactin and hormonal responses to insulin induced hypoglycemia, TRH and GnRH were normal (Table 1). While at home his creatinine clearances were 82 and 97 ml/min on two separate 24-h collections. On ad-

mission his serum sodium ranged from 145 to 156 mmol/l, the plasma aldosterone was 222 pmol/l (normal

111-859 pmol/l) and the plasma renin activity was 114.6 pmol · 1⁻¹ · min⁻¹ (normal 1.1-42.2 pmol · 1⁻¹ · min⁻¹). The maximum urinary osmolality recorded was 1249 mOsm/kg corresponding to a serum osmolality of 329 mOsm/kg and a serum creatinine of 100 µmol/l.

All studies were carried out on separate days, after an overnight fast with free access to water. Plasma AVP was measured using a sensitive and specific radioimmunoasay (intra-assay coefficient of variation 9.7% at 2 pmol/l, 13), with limit of detection 0.3 pmol/l. Osmolality was deter-

mined by the depression of freezing point method (Ad-

vanced Instruments Osmometer, model AD 3R; coeffi-
cient of variation 0.3% at osmolality 276 mOsm/kg).

Osmotic stimuli

5% saline was infused at a rate of 0.06 ml · kg⁻¹ · min⁻¹ for 120 min during which time thirst was assessed and blood was sampled every 30 min to measure plasma osmo-
lality and AVP (14). After the infusion the patient was given free access to water and tea, but was not actively prompted to drink. His fluid intake was then carefully monitored for 2 h.

An oral water load test was attempted with 20 ml of tap water per kg taken over 15 min. After 9 min, when he had drunk 1000 ml of water, the patient vomited approxi-

mately 250 ml of clear fluid, but did not feel nauseated. Blood and urine were collected prior to the water load and at hourly intervals for 4 h from its start. Measure-

ments of urine volume and osmolality were made along with plasma osmolality and AVP. An iv load of 5% dext-

rose (20 ml/kg) was given over 30 min. Blood and urine were collected prior to the dextrose load and at hourly intervals for 4 h from its start. Measurements of urine volume, osmolality and glucose content were made along with plasma osmolality and AVP.

Hypotensive stimulus

After a 15-min resting period, the ganglion blocking drug trimethaphan was infused at a rate of 1 mg/min for 10

<table>
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<tr>
<th>Stimulus</th>
<th>Insulin (O.15 IU/kg)</th>
<th>Glucose (mmol/l)</th>
<th>Cortisol (nmol/l)</th>
<th>hGH (mU/l)</th>
<th>PRL (mU/l)</th>
<th>TRH (200 µg)</th>
<th>TSH (mU/l)</th>
<th>GnRH (100 µg)</th>
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min, then increased to a rate of 2 mg/min until hypotension ensued. Blood pressure was recorded each minute for the duration of the infusion. Blood was sampled 15 min before the infusion and as the infusion started, then at regular intervals throughout the next 30 min. Basal osmolality and plasma AVP during the infusion and after hypotension were measured.

**Emetic stimulus**
After a 15-min resting period, a sc injection of apomorphine (0.02 mg/kg) was given. Blood pressure was monitored each 5 min throughout the test. Blood was sampled before the injection and at 5-min intervals for 20 min and then at 30 min. Basal osmolality was measured and plasma AVP before and after the injection.

All studies were carried out in the spirit of the Declaration of Helsinki, and have been approved by the Joint Ethics Committee of the Newcastle Area Health Authority. For the trimethaphan infusion and the apomorphine test explicit written consent was obtained from the patient’s wife after full explanation of the potential benefits and hazards of the procedures to both the patient and his wife.

**Results**

The response of plasma AVP to hypertonic saline infusion, oral water load, and 5% dextrose load is shown in Fig. 1. The maximum plasma AVP (0.7 pmol/l) occurred at a plasma osmolality of 305 mOsm/kg, prior to the beginning of the 5% saline infusion. During this infusion, the plasma osmolality rose to 328 mOsm/kg at which time the plasma AVP was 0.6 pmol/l (normal >12 pmol/l, 4,14). The hematocrit fell from 42.5 to 39.3%. At no point during the infusion did the patient complain of thirst and in the 2 h after the infusion, when the patient was given free access to fluids, only 40 ml of water was drunk (normal 1900 ± 240 ml, 4).

One hour prior to the ingestion of the oral water load the plasma osmolality was 284 mOsm/kg and the plasma AVP 0.3 pmol/l. The plasma AVP remained detectable at 0.3 pmol/l throughout the test even when the plasma osmolality was at a nadir (274 mOsm/kg) one hour after the patient started to drink. The urinary osmolality fell from a basal of 518 mOsm/kg to a minimum of 142 mOsm/kg 3 h after the load was drunk. The free water clearance was maximal at 0.81 ml/min, 3 h after drinking commenced. Data concerning the fractional load excretion are invalid as the amount of water retained by the patient after vomiting could not be precisely assessed.

Prior to the start of the iv 5% dextrose load the plasma and urine osmolalities were 282 mOsm/kg and 569 mOsm/kg, respectively, and the plasma AVP was 0.4 pmol/l. Three h after the beginning of the load the plasma AVP was detectable (0.4 pmol/l) when the plasma osmolality was at a minimum (273 mOsm/kg). The fractional load excretion at 4 h was 54% (normal >90%). The maximal free water clearance was 1.52 ml/min, which is markedly subnormal.

The patient’s response to an iv trimethaphan infusion is shown in Fig. 2. Prior to hypotension the mean arterial pressure was 81 mmHg. Symptomatic hypotension (mean arterial pressure 56

![Fig. 1.](image)

Plasma vasopressin response to hypertonic saline infusion (□), iv 5% dextrose (○) and oral water loads (∆). Shaded area represents the normal range.
Fig. 2. Plasma vasopressin response to trimethaphan-induced hypotension. Shaded area represents the normal range.

mmHg) was achieved after 17 min, when the rate of the infusion was 2 mg/min. Subsequently his plasma AVP rose from a basal value of 0.7 to 615.0 pmol/l. Immediately after hypotension the patient admitted to feeling thirsty.

Fig. 3 shows the patient's AVP response to an apomorphine injection. The basal plasma osmolality was 289 mOsm/kg, urine osmolality 729 mOsm/kg, and the basal plasma AVP 0.7 pmol/l. After 7 min the patient first complained of nausea and he vomited several times between 12 and 23 min after the injection. The plasma AVP rose to 1100 pmol/l at 15 and 20 min. The mean arterial pressure dropped from 99 to 78 mmHg at the time when nausea was most intense.

Discussion

Our studies demonstrate that this patient was able to synthesize and secrete AVP in a normal or slightly exaggerated fashion in response to hypo-
tension and apomorphine-induced nausea. This implies that he had intact hypothalamic-neurohypophysial connections. However, his AVP and thirst responses to an osmotic stimulus were severely deranged. It is believed that the osmoreceptor is composed of both inhibitory and stimulatory components, one or the other of which become more active when the plasma osmolality deviates from a "set point" in a given direction (15). When disrupted, either or both of these two components can become defunct. When neither component is intact, AVP is tonically secreted at a variable level close to a baseline which approximates to the amount of AVP secreted at the osmolar "set point". Our patient had a complete osmoreceptor defect and exhibits this phenomenon well, plasma AVP levels ranging from 0.3 to 0.7 pmol/l throughout a range of plasma osmolalities between 273 and 328 mOsm/kg. Osmotic control of thirst was also severely defective, with the patient denying thirst at high plasma osmolalities. Although this was difficult to quantitate owing to his cognitive impairment, the intake of only 40 ml of water in the 2 h after his 5% saline infusion (when his plasma osmolality was 328 mOsm/kg) is highly pathological, normal subjects drinking about 1900 ml (4). Our patient admitted to thirst after trimethaphan-induced hypotension, which leads us to suspect that he may have intact baroregulated thirst. Trimethaphan is a ganglion blocking drug and produces a reduction in salivary flow which might be expected to produce a feeling of thirst; however, this has not been our experience in other subjects after trimethaphan infusions of similar duration (11). Furthermore, our patient failed to drink on other occasions when he had a dry mouth, making it unlikely his thirst following trimethaphan infusion was purely the result of decreased salivation. The observation that our patient experienced thirst after hypotension is unique and suggests that osmoregulated thirst and baroregulated thirst may be mediated by functionally distinct hypothalamic pathways.

Our patient had a supranormal release of AVP in response to hypotension and in particular to apomorphine-induced nausea (Figs. 2 and 3). Plasma AVP levels in excess of 500 pmol/l are rarely seen in healthy subjects even in response to severe hypotension or nausea, but have been noted before in patients with osmoreceptor defects (15). Rowe et al. (6) have demonstrated that there is no correlation between the maximum AVP value and degree of hypotension induced in normal subjects given apomorphine. Thus the hypotension that occurred in our patient during his apomorphine test is insufficient to account for AVP levels of 1100 pmol/l in the absence of another factor. One interpretation of these exaggerated AVP responses, in the light of the two-component model of osmoreceptor function, is that they represent the non-osmotic stimuli to AVP secretion acting upon the neurohypophysis unopposed by the normal inhibitory arm of the osmoreceptor.

 Appropriately concentrated urine was produced by our patient at high plasma osmolalities, despite apparent lack of osmoregulated AVP release during dynamic testing. It is clear that he had a high renal sensitivity of AVP, with urine osmolalities in excess of 500 mOsm/kg commonly occurring with a plasma AVP of less than 0.5 pmol/l. However, maximally concentrated urine (>1000 mOsm/kg) was only found after he had been at home for a period of time and on these occasions the serum urea and creatinine levels were raised, indicative of moderate dehydration and high plasma renin activity suggesting hypovolemia. Furthermore, hypertonic saline infusion causes expansion of the intravascular space and should suppress volume-mediated AVP release, a phenomenon that we observed in our patient (Fig. 1). DeRubertis et al. (9) have postulated that the ability of these patients to produce concentrated urine is due to intact volume regulation of AVP release. Our results would support the hypothesis that a high renal sensitivity to AVP combined with intact volume-regulated AVP release leads to the production of appropriately concentrated urine at high plasma osmolalities.

Reports of a patient with an isolated defect in osmoregulated thirst (5) and of a patient with an intact AVP response to an emetic stimulus despite absent osmoregulated and hypoglycemia-induced AVP release (12) cast light on the hypothalamic control of AVP. Elucidation of hypothalamic-neurohypophyisal function in this patient provides evidence that supports some current theoretical models of osmoreceptor function and gives us a new insight into the hypothalamic regulation of thirst.

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References


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