Clinical Reports

Chronic hypernatraemia and hypothermia following subarachnoid haemorrhage

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Summary: We describe a 30 year old man who developed chronic adipsic hypernatraemia and hypothermia following a subarachnoid haemorrhage from an anterior communicating artery aneurysm. Anterior pituitary function tests were normal. Hypothermia was demonstrated over 4 years with loss of the ability to control heat conservation despite body temperatures as low as 30°C. He failed to experience thirst despite plasma sodium concentrations of up to 187 nmol/l and plasma osmolalities of up to 397 mOsm/kg. The slope of the plasma vasopressin-plasma osmolality curve indicated loss of the osmoreceptor. There was an absent vasopressin response to insulin-induced hypoglycaemia but a normal response to apomorphine. The apomorphine-stimulated immunoreactive vasopressin was shown to behave identically to the synthetic peptide on HPLC and was bioactive.

Introduction

The hypothalamus is intimately involved in the regulation of both temperature and fluid balance (Plum & Van Uitert, 1978). It lies close to the circle of Willis and receives its blood supply from many small branches of vessels forming this circle (Crompton, 1963). It is frequently damaged by ruptured aneurysms particularly of the anterior and posterior communicating arteries (Crompton, 1963). Hypernatraemia following rupture of an aneurysm is associated with a high mortality (Takaku *et al.*, 1979). Chronic hypernatraemia is unusual and, when present, is characterized by normal renal function, absence of clinical hypovolaemia and decreased perception of thirst (Halter *et al.*, 1977). Direct assay of plasma arginine vasopressin (AVP) in response to independent stimulation of both osmoreceptor and baroreceptor mechanisms suggested selective osmoreceptor dysfunction as a cause of this syndrome (Halter *et al.*, 1977; Robertson, 1983). However, in these studies the AVP was not characterized beyond immunoreactivity with the antiserum.

We report a patient who developed chronic hypernatraemia and hypothermia following a subarachnoid haemorrhage from an anterior communicating artery aneurysm which was surgically clipped. AVP concentration in the plasma was monitored following in-

dependent stimulation of both osmoreceptor and non-osmoreceptor (hypoglycaemia and apomorphine) mechanisms for AVP release. In view of recent data illustrating the importance of characterizing immunoreactive neurohypophysial peptides (Amico *et al.*, 1985), we characterized the secreted AVP by HPLC.

Case report

A 30 year old man with no previous history of hypertension suffered a subarachnoid haemorrhage in April 1981. Computed tomographic (CT) scan and angiography demonstrated an anterior communicating aneurysm and a hypoplastic right anterior cerebral artery. He underwent right frontal craniotomy and clipping of the aneurysm. Postoperatively he was noted to be hypothermic (oral/rectal temperature 34.5–35.5°C) and hypernatraemic (plasma sodium 156 ± 6.6 mmol/l; mean $\pm$ s.d., $n = 19$; range 147–173 mmol/l). Although he ate spontaneously and with normal appetite, he needed encouragement to drink and exhibited little spontaneous thirst even though his plasma sodium and osmolality had risen significantly. Daily urine output when encouraged to drink was 1–2 litres. On occasion he was noted to sweat profusely and to become discomforted in a warm room despite an oral temperature of around 35°C and a cool skin. He was a barrister by profession

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but following his recovery from the subarachnoid haemorrhage he behaved childishly and exhibited defects in memory and learning. Psychometric tests were interpreted as showing evidence of frontal lobe damage. Two months after the subarachnoid haemorrhage his plasma thyroxine, diurnal plasma cortisol variation and metyrapone tests were normal. Over the following 3 years he had several admissions to hospital with recurrent hyponatraemia. In 1983 he suffered an episode of muscle weakness associated with hyponatraemia (plasma sodium 187 mmol/l, plasma osmolality 397 mOsm/kg and urine osmolality 949 mOsm/kg) and markedly elevated plasma creatine phosphokinase (4434 IU/l; normal < 270 IU/l). Despite the marked elevation of plasma sodium and osmolality he failed to complain of thirst. Plasma lipids were normal on several occasions.

He was admitted to this hospital in January 1985 in a marked hypothermic state (rectal temperature = 30°C) despite living in modern and well-heated accommodation. Despite his low body temperature he was noted neither to shiver nor to seek a warm place or clothing. His baseline biochemistry was normal but he had a marked thrombocytopenia (platelet count $95 \times 10^9/l$). He responded well to rewarming and his platelet count returned to normal over 10 days. However, he was, again, noted to sweat profusely in a warm room despite a core temperature of around 35°C. When recovered from his hypothermia and running a temperature of around 35°C he underwent a combined intravenous insulin stress test (0.15 U/kg), thyrotrophin releasing hormone (TRH) test and gonadotrophin releasing hormone (GnRH) test; hypertonic saline infusion and apomorphine test.

Methods

Anterior pituitary function

An indwelling needle was inserted into an antecubital vein and 30 minutes later baseline blood samples

removed. The line was flushed with small volumes of isotonic saline. After baseline samples had been taken, soluble insulin (0.15 U/kg body weight), TRH 200 µg and GnRH 100 µg were injected and flushed through with isotonic saline. Further samples of blood were taken at 30 minute intervals via the indwelling line.

Hypertonic saline infusion

The procedure for obtaining blood samples was similar to that for insulin-induced hypoglycaemia except that an additional indwelling needle was inserted into the opposite antecubital vein to infuse hypertonic saline (3% w/v). After baseline samples of blood had been taken saline was infused at 0.1 ml/kg/min via an Imed pump (Model 960, Imed, Milton Trading Estate, Abingdon, Oxford).

Apomorphine test

The procedure for taking blood samples was identical to that for the tests of anterior pituitary function. After the baseline samples had been taken 16 µg of apomorphine was injected subcutaneously and further samples of blood taken at 5 minute intervals.

Analyses

All blood samples were collected into chilled plastic containers containing lithium heparin or fluoride for glucose only. After mixing, samples were centrifuged at 4°C for 10 minutes at 2000 g. Aliquots of fresh plasma were removed for estimation of sodium and glucose concentrations. Osmolality was measured by freezing point depression using an Advanced Digimatic Osmometer Model 3D. The remainder was frozen for hormone assays. AVP was extracted and assayed as previously described (Jenkins *et al.*, 1984). Cortisol was measured by RIA using an Amerlex kit (Amer-sham). Glucose was estimated using a glucose oxidase method.

Table 1 Combined pituitary function test

Time (min)	Glucose (mmol/l)	TSH (mU/l)	FSH (mU/ml)	LH (mU/ml)	GH (mU/l)	PRL (mU/l)	Cortisol (nmol/l)
0	3.3	2.5	3.5	5.0	2.2	115	577
30	1.3	9.7	4.0	10.0	2.4	420	498
60	3.4	8.5	4.5	9.5	32.0	250	1072
90	4.0				7.0	150	916
120	4.0				5.0		657

T4 = 78 nmol/l; testosterone = 14 nmol/l. After time 0 samples, 0.15 U soluble insulin/kg, 200 µg TRH and 100 µg GnRH were given i.v. TSH = thyroid stimulating hormone; FSH = follicle stimulating hormone; LH = luteinizing hormone; GH = growth hormone; PRL = prolactin.

Figure 1 The relationship between plasma AVP and plasma osmolality during hypertonic saline infusion in the patient (○) compared with that for control subjects (●) (mean $\pm$ s.e.). For the normal subjects ($n = 10$) the regression line is given by the equation $y = 0.36(x - 283)$; $r = 0.74$, $P < 0.001$. For the patient the equation is $y = 0.005(x - 108)$; $r = 0.2$, P not significant.

Human growth hormone (HGH) RIA utilized MRC hGH 69/46 iodinated by the iodogen method, 1st IRP 66/217 as standard and MRC antiserum at a final concentration of 1:180,000.

Human prolactin (HPRL) RIA was performed using materials supplied by NIADDK, iodination by the lactoperoxidase method and WHO 75/504 as standard.

Figure 2 Response of plasma AVP to insulin-induced hypoglycaemia in the patient (○—○) compared with control subjects (●—●; $n = 10$ mean $\pm$ s.e.m.).

Figure 3 Response of plasma AVP to apomorphine.

HPLC of vasopressin was carried out as previously described (Ang & Jenkins, 1984). Bioassay of extracted peptide was performed in the alcohol-anaesthetized rat (Bisset & Chowdrey 1984).

Results

Anterior pituitary function was normal (Table I) but there was a deficient response of AVP to 3% saline infusion (Figure 1) and insulin (Figure 2). Regression analysis of the plasma AVP-plasma osmolality curves (Figure 1) showed a similar relationship to that found by Halter *et al.* (1977) for the normal subjects but no significant relationship for the patient. There was a rapid and large increase in plasma immunoreactive AVP after the subcutaneous injection of apomorphine (Figure 3). The immunoreactive AVP was shown to behave identically to synthetic AVP on HPLC (Figure 4) and was biologically active (Figure 5).

Figure 4 (a) Elution profile of apomorphine-stimulated AVP on reversed phase HPLC using 10–60% acetonitrile gradient. (b) Elution profile of synthetic AVP (Ferring) under identical conditions.

Figure 5 Bioassay of antidiuretic activity. Antidiuretic activity was assayed in the water-loaded, ethanol-anaesthetized rat. Each vertical line represents the urine output in 1 minute. Intravenous injections were given at the arrows: 1 (100 μ l) and 3 (200 μ l) – extract of HPLC-purified immunoreactive material from plasma collected after apomorphine-induced nausea; 2 (40 μ U) AVP; 4 (20 μ U) AVP.

Discussion

The anterior hypothalamus is intimately involved in the control of water balance (Andersson, 1978), temperature (Cabanac, 1975; Satinoff, 1978) and plasma glucose (Frohman, 1983). Adipsic hypernatraemia may have a variety of pathological causes and has been distinguished from essential hypernatraemia (Robertson *et al.*, 1982) though few studies have utilized dynamic studies of AVP release (Halter *et al.*, 1977; Robertson, 1983). Regression analysis of the hypertonic saline test results suggests destruction of the osmoreceptor (Robertson, 1983). While it may be argued that the osmotic stimulus was not sufficient to exclude resetting of the osmostat (Gill *et al.*, 1985) it may be noted that the patient demonstrated adipsia despite a plasma sodium of 187 mmol/l and plasma osmolality of 397 mOsm/kg in circumstances producing the syndrome of muscle weakness (Maddy & Winternitz, 1971) and rhabdomyolysis (Opas *et al.*, 1977).

Nausea is a potent non-osmotic stimulus to AVP release (Rowe *et al.*, 1979) and a rapid and marked rise in plasma AVP was provoked by the apomorphine test. The physiological importance of this phenomenon is not yet known. It has been proposed that both osmotic and non-osmotic sensory information is

fed into one unit which synthesizes and secretes AVP (Robertson, 1979). The apomorphine test result indicates that the pathway from the emetic centre to this unit was intact.

Of interest is the observation that insulin-induced hypoglycaemia caused a normal rise in GH and ACTH (as measured by plasma cortisol) but failed to stimulate AVP release suggesting a lesion between the glucose sensor and the AVP secretor unit but intact pathways in the regulation of GH and ACTH secretion.

Amico *et al.* (1985) have recently demonstrated the importance of the characterization of immunoreactive neurohypophysial peptides. In view of this we showed that the AVP immunoreactive material secreted in response to apomorphine behaved identically to the synthetic peptide on HPLC and was biologically active.

Chronic hypothermia was documented over a period of 4 years. Formal tests of temperature regulation were not performed but it is evident that the patient demonstrated loss of the ability to control heat conservation by both behavioural (e.g. seeking a warm room or clothing) and physiological mechanisms at least down to a central temperature of 30°C. The available data do not allow us to distinguish between a lesion causing regulation around a lower set-point and one causing failure of mechanisms of heat conservation (Hockaday *et al.*, 1962).

Thrombocytopenia is considered to occur in hypothermia as a result of splenic pooling and is noted in hibernating animals and patients undergoing hypothermic cardiac surgery (Aster, 1983); it may play a role in the pathology of neonatal cold injury (Cohen *et al.*, 1984). After rewarming the thrombocytopenia did not recur and there were no clinical features to suggest another cause.

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