Regulation of vasopressin secretion in a patient with chronic hypernatraemia

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Abstract. A patient with the chronic hypernatraemia syndrome is described. Using a sensitive and specific radioimmunoassay, the plasma arginine-vasopressin (AVP) level was measured under various conditions. With an unrestricted diet, the plasma AVP level was inappropriately low for the degree of plasma hyperosmolality (0.9 pmol/l and 302 mOsm/kg, respectively). After chronic water loading, plasma osmolality was 271 mOsm/kg, plasma AVP level 1.5 pmol/l, and the urine remained hypertonic with respect to the plasma. During hypertonic saline infusion, plasma osmolality increased from 271 to 294 mOsm/kg without a concomitant increase in the plasma AVP concentration. After sc injection of apomorphine and after haemodynamic stimulation, the plasma AVP concentration increased from 0.8 to 36 pmol/l and from 1.2 to 6.3 pmol/l, respectively. These data demonstrate a selective deficiency in the osmoregulation of the AVP secretion. The observed neuroendocrine abnormalities may be linked to a congenital malformation of the brain.

The syndrome of chronic hypernatraemia is a rare disorder of the water metabolism characterized by a chronic fluctuating elevation of the serum sodium level, a decrease of the perception of thirst, a normal renal function, and the absence of clinical signs of dehydration (Welt 1962). The affected patients often present organic lesions of the hypothalamus that can interfere with the normal functioning of diencephalic osmoregulator centres (Sridhar et al. 1974; De Rubertis et al. 1974; Halter et al. 1977). Although abnormalities of arginine vasopressin (AVP) release have been implicated in the physiopathology of hypernatraemia, the direct study of AVP secretion has been reported in only some patients (Shelton & Robertson 1976; Halter et al. 1977; Kimura et al. 1979; Schaff-Blass et al. 1983).

We had the opportunity to study a patient who presented this syndrome. In a preliminary study concerning this patient, we showed a release of hNPI (vasopressin-neurophysin) after non-osmotic stimulations, but not after osmotic stimulation (Smitz & Legros 1981). In the present work, we report the results of a more complete and more specific study of the neurohypophysial secretion based on the use of a sensitive and specific radioimmunoassay for plasma AVP.

Case Report

A 22-year-old male was admitted to the hospital in May 1981 in order to complete the exploration of a chronic hypernatraemia. This patient was born after a normal pregnancy and labour. During his first years, a moderate psychomotor slowness was observed. However, pubescent growth and development were normal. At the age of 4 years, he was hospitalized for treatment of a severe dehydration with hypernatraemia (serum sodium: 164 mmol/l) attributed to an insufficient intake of fluids. Despite plasma hyperosmolality the patient did not complain of thirst.

During the course of a hospitalization in 1976, a study of the water metabolism was performed, based on radioimmunoassay of serum neurophysins concentrations and on indirect methods. This study showed an adipasia and a partial cranial diabetes insipidus. However, a release of
hNPI (vasopressin-neurophysin) was observed after two successive non-osmotic stimulations (Smitz & Legros 1981).

At the physical examination, he appeared to be a normal young man (height: 181 cm; weight: 70 kg). No signs of dehydration were observed. The temperature was normal. The arterial pressure 130/80 mmHg; the pulse regular, 80/min. The cardio-pulmonary examination was normal, as were the pilosity and sexual development. ECG and radiographic examination of the head and thorax were normal. The neuropsychological examination showed evidence of a moderate intellectual slowness, a poor spatiotemporal orientation, and a slight memory dysfunction.

The ophthalmological examination showed a left retinal and choroidal coloboma without visual field abnormalities. Olfactory testing performed by presenting the patient with bottles containing volatile chemical substances, revealed no olfactory disturbance.

With an ad lib. diet, there was a chronic and fluctuating elevation of the serum sodium concentration (144 to 170 mmol/l), the serum chloride concentration (105 to 124 mmol/l), and the plasma osmolality (292 to 345 mOsm/kg). Serum potassium was at the lower limit of the normal (3 to 4 mmol/l), urine osmolality was 739 ± 154 mOsm/kg (n = 18). The routine biological examinations were within the normal range. A serological test for syphilis was negative.

The endocrine examinations showed normal values for adeno-hypophysial hormones with preservation of the diurnal rhythms of cortisol, prolactin and growth hormone. Additional results included serum testosterone and thyroid function tests in the normal range (Table 1). In August 1983, the plasma osmolality and the baseline plasma AVP were 302 mOsm/kg and 0.9 pmol/l, respectively.

Material and Methods

Informed consent was obtained before each diagnostic procedure that represented a risk or possible discomfort for the patient. All blood samples were collected in plastic syringes containing heparin (NOVO, 10 IU/ml of blood) and then transferred to chilled plastic tubes. The plasma, separated by centrifugation at 4°C, was used for determining the osmolality and was stored at −20°C before the extraction.

RIA of plasma AVP was performed using an antiserum prepared according to the method described by Skowsky & Fisher (1972). This antiserum was used at a final dilution of 1/600000 and it displayed the following cross-reactivity with other peptides: 8-lysine-vasopressin (Ferring) 100%; desglycinamide-8-arginine-vasopressin (Organon) 160%; pressinoic acid (Peninsula Laborato-

<table>
<thead>
<tr>
<th>Hormone measured</th>
<th>Results</th>
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<tr>
<td>T₃</td>
<td>3.25 nmol/l (NI 1.8–3.4)</td>
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<tr>
<td>T₄</td>
<td>181 nmol/l (NI 65–194)</td>
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<tr>
<td>TSH</td>
<td>Basal = 1.5 mIU/l (NI &lt; 6) Stimulated (200 µg TRH) = 6.6 mIU/ml</td>
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<tr>
<td>Testosterone</td>
<td>13 nmol/l (NI 8.7–35.0)</td>
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<tr>
<td>LH</td>
<td>Basal = 4.1 mIU/l (NI 5–9) Stimulated (50 µg LRH) = 21.1 IU/l</td>
</tr>
<tr>
<td>FSH</td>
<td>Basal = 2.7 IU/l (NI 2–7) Stimulated (50 µg LRH) = 3.6 IU/l</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Basal = 250 nmol/l (NI 250–558) Stimulated* = 510 nmol/l</td>
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<tr>
<td>Growth hormone</td>
<td>Basal = 5 µg/l (NI 0.2–6.0) Stimulated* = 29.3 µg/l</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Basal = 247 mIU/l (NI 100–400) Stimulated (200 µg TRH) = 665 mIU/l</td>
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NI: Range of normal values.
* Insulin induced hypoglycaemia (decrease of serum glucose from 3.56 to 1.6 mmol/l).
ries) 16%; 8-arginine-vasotocin (Ferring) 0.03%; oxytocin (Sandoz) < 0.01%; somatostatin (Ferring) < 0.01%; human neurophysins (kindly provided by Professor C. Johnston, Australia) < 0.01%. The antiserum appeared to be directed towards the ring moiety of the vasopressin molecule.

AVP (Ferring, 390 IU/mg) was used as standard and for preparing the tracer. Radioiodination (1 mCi carrier-free $[^{125}\text{I}]\text{Na}$, Amersham, England), purification of the tracer, and dosage were performed according to the general method described by Robertson et al. (1973). The limit of detection was from 0.2 to 0.4 pmol/tube with a 50% displacement of the tracer (1500 CP) for 1.6 to 2.0 pmol/tube.

Plasma AVP assay was performed after extraction of 3 ml of plasma by means of C18 cartridges (Waters). The product resulting from extraction of 3 ml of plasma was divided into two parts for duplicate assay. When physiological amounts of synthetic AVP were added to 3 ml of fresh plasma, in order to obtain concentrations 2.5, 5.0 and 33.3 pg/ml above the endogenous AVP concentration, the recoveries were 87 ± 14% (n = 6), 89 ± 13% (n = 6) and 94 ± 8% (n = 7), respectively. The intra- and the inter-assay coefficient of variation were 8 and 19%. The smallest AVP levels detected were 0.2 to 0.3 pg/ml of plasma.

The urine and plasma osmolality were measured in duplicate by freezing point osmometry (Advanced Instruments Inc., Needham Heights, Mass., Osmometer model 3 C 11).

In 9 healthy recumbent subjects who had an unrestricted diet, the osmolality and the plasma AVP levels were 283.6 ± 2.5 mOsm/kg and 2.8 ± 1.8 pmol/l (mean ± sd), respectively.

**Chronic water loading**

For the entire duration of the test (2 weeks), the patient had a supplement of fluids (2 to 31/24 h) and his activities were unrestricted. Each day, a urine sample was taken in the morning and evening for measurement of osmolality. The serum sodium concentration, the plasma osmolality, and the plasma AVP level were determined at the end of the test.

**Hypertonic saline infusion**

This test was performed immediately after the preceding test. Twenty min before the beginning of the hypertonic infusion, the patient was placed in a recumbent position. The infusion (NaCl 5%) was performed via the antecubital vein with a flow of 0.1 ml/kg/min during 120 min. The blood samples for measurement of plasma AVP and osmolality were drawn from the antecubital vein of the other arm at regular intervals.

**Apomorphine injection**

Ten min after the end of the hypertonic saline infusion 0.25 mg of apomorphine was injected sc. The injection was repeated two times at 5-min intervals. The samples were taken 2.5 and 20 min after the first injection for dosing plasma AVP.

**Haemodynamic stimulation test**

Ten min before its beginning and during the entire test, the patient was placed in a recumbent position (clinostratism). Haemodynamic stimulation was performed by infusing a vasodilator, sodium nitroprusside (SNP, Nipride, Roche). The flow of the SNP infusion was progressively increased (from 0.5 to 6.0 µg/kg/min). The measurements of the blood pressure, the heart rate, and the blood samples were performed as indicated in Fig. 2. While he was undergoing the test, the patient did not smoke or drink alcoholic beverages, and all therapy was stopped.

**Results**

During the period of water loading the urine osmolality was 510 ± 158 mOsm/kg. The plasma osmolality, serum sodium and plasma AVP at the end of this period was 271 mOsm/kg, 140 mmol/l and 1.5 pmol/l, respectively.

The hypertonic saline infusion was performed after the chronic water loading thus permitting the study of the AVP secretion when the patient was well hydrated. The patient remained recumbent during the entire time of testing, except at 55 min (Fig. 1) when he stood up to urinate. Twenty min before the beginning of the saline infusion, the plasma osmolality was 271 mOsm/kg, plasma AVP 1.7 pmol/l, and urine osmolality 320 mOsm/kg. After 20 min of recumbency (clinostratism), the plasma AVP was 0.8 pmol/l. Under the effect of the hypertonic saline infusion, the plasma osmolality progressively increased from 271 to 294 mOsm/kg. The plasma AVP concentration did not increase during this infusion except 4 min after standing (orthostatism) when it reached 1.4 pmol/l. Heart rate and blood pressure remained stable during the test. Forty min after the beginning of the hypertonic infusion, the patient asked for a drink and we observed at this time a dryness of the buccal mucosa. After drinking 100 ml of water, his thirst disappeared (60th min of the test) and never reappeared.

After the injections of apomorphine, the AVP concentration rose markedly (Fig. 1). This elevation began 2 min after the first injection, and plasma AVP concentrations higher than 20 pmol/l were observed for more than 15 min. The patient complained of a slight nausea after the first injection.
Course of the plasma AVP concentration and of the plasma osmolality during hypertonic saline infusion and after injection of apomorphine. In spite of the important increase in osmolality, the plasma AVP concentration did not increase during the infusion. A slight increase was observed at 60 min, 5 min after a transitory orthostatism. Two min after the first sc injection of apomorphine (0.25 mg), an important increase in plasma AVP was observed. The detection limit of the assay for plasma AVP is indicated by the horizontal broken line.

Effect of an acute haemodynamic stimulation on the plasma AVP concentration. The plasma AVP levels and the blood pressure were measured before, during and after iv infusion of vasodilator (SNP, Sodium Nitroprusside), SAP: systolic arterial pressure. DAP: diastolic arterial pressure. The plasma osmolality remained stable at 302 mOsm/kg during the entire procedure.
Under the effect of the SNP infusion, the blood pressure progressively decreased from 120/70 to 100/50 mmHg and the heart rate increased from 64 to 84 beats/min. The plasma AVP level was 2.8 pmol/l at the beginning of the infusion and progressively decreased to 1.2 pmol/l at 40 min (Fig. 2). The plasma AVP then increased to 6.3 pmol/l at 60 min. At this time the mean blood pressure was reduced by about 30%. The plasma osmolality remained constant at 302 mOsm/kg throughout the entire test.

X-rays of the skull and the sella turcica performed in 1981 revealed no abnormalities. CT scan of the head revealed that the third ventricle was slightly displaced towards the rear and so was the frontal cornua apparently. Right carotid arteriography showed no signs of any expansive lesions. Pneumoencephalography showed an extension of the aperture of the third ventricle towards the top, in the region corresponding to the topography of the septum lucidum, suggesting an agenesia of the septum lucidum.

Discussion

In this patient, who presented characteristics of the chronic hypernatraemia syndrome, investigations were performed in order to determine neuroendocrine abnormalities. The clinical data and the results of the endocrine tests revealed no abnormalities in the anterior pituitary function. The hypothalamic control of the adenohypophysial function was also normal as evidenced by the preservation of diurnal rhythms.

Since the clinical history suggested a disturbance of the water metabolism, a thorough study of the AVP secretion and of thirst was performed during the course of several dynamic tests. The deficiency of the mechanism of thirst perception was particularly well demonstrated during the test of water deprivation. In the course of this test, the sensation of thirst did not appear at any time in spite of the marked elevation of the plasma osmolality (340 mOsm/kg) (Smitz & Legros 1981). Contrary to what was observed during the test of water deprivation, the need to drink appeared transitory during the hypertonic infusion and seems to be associated with the desiccation of the buccal mucosa that was induced by the hypertonic charge. In this patient, the principal mechanism implicated in the control of the sensation of thirst was deficient, but the need to drink, however, did not totally disappear since it could be provoked by stimuli originating from the buccal mucosa.

A characterization of the neurohypophysial secretion was performed by measuring circulating levels of AVP with a sensitive and specific radioimmunoassay. Contrary to what is observed in the normal subject (Robertson 1977), the results indicate that the secretion of AVP was not modulated by variations in the plasma osmolality. This was strongly suggested by

1. an inappropriately low plasma AVP concentration (0.9 pmol/l) for the degree of plasma hyperosmolality (302 mOsm/kg). Expected plasma AVP concentration for such a hyperosmolality is above 5 pmol/l (Robertson 1977);

2. the persistence of circulating levels of AVP (1.5 pmol/l) with the absence of dilution of urine when the plasma was slightly hypotonic;

3. the absence of an increase in the plasma AVP concentration during the course of hypertonic saline infusion. On the other hand, a release of AVP was observed after a haemodynamic stimulation (arterial hypotension) and after the induction of nausea by apomorphine. An increase in the serum hNPI concentration had also been observed in this patient after two successive non-osmotic stimulations (hypovolaemia and nicotine) (Smitz & Legros 1981). These results demonstrate the capacity of the hypothalamo-neurohypophysial system to synthesize and release AVP and hNPI and the integrity of its connections with the cardiovascular receptors and the emetic center.

Quantitative evaluation of the AVP secretion by measurement of the plasma AVP concentrations has been performed in some patients with the hypernatraemia syndrome and showed a partial or total loss of osmotic regulation of AVP secretion (Shelton & Robertson 1976; Halter et al. 1977; Schaff-Blass et al. 1983). Patients with adipsia and complete absence of osmotic regulation of the AVP secretion lack an effective defense against over- as well as underhydration. If they are given fluids injudiciously, they may go from hypertonic dehydration to a syndrome of water intoxication indistinguishable from the syndrome of inappropriate secretion of antidiuretic hormone (Robertson et al. 1982). The defect in osmoregulation observed in our patient and in the patient described by Shelton & Robertson (1976) can be explained by the persistence of a tonic secretion of AVP, without stimulation or inhibition by the osmoreceptors (Robertson et al. 1982).
Clinical observations and experimental studies have shown that the region of the third ventricle plays a key role in the control of thirst and AVP secretion (Fitzsimons 1976; Robertson 1977; Buggy & Johnson 1977). In animals, lesions of the anterior wall of the third ventricle reproduce the syndrome of chronic hypernatraemia with adipsia (Buggy & Johnson 1977). In patients who present this syndrome, one frequently discovers hypothalamic lesions (tumoural, vascular, congenital, traumatic, inflammatory or granulomatous (Sridhar et al. 1974; De Rubertis et al. 1974; Halter et al. 1977).

The congenital abnormalities that are observed in association with this syndrome are microcephaly and dysplasia of the septum lucidum and medial structures (Segar 1966; Schaff-Blass et al. 1983). With the absence of tumoral lesions and the existence of hypothalamic abnormalities as demonstrated by radiological examination, the deficiency in osmoregulation in our patient may result from a congenital malformation of the brain.

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References


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