Enhanced adrenocorticotropic hormone and cortisol responses to corticotrophin-releasing hormone in central idiopathic diabetes insipidus

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It is well known that arginine vasopressin (AVP) exerts a stimulatory effect on adrenocorticotropic hormone (ACTH) secretion. Moreover, there is consistent evidence that the hypothalamic AVP-secreting neurons are involved in the neuroregulation of ACTH secretion. With the aim to throw further light on the interaction between AVP and corticotrophin-releasing hormone (CRH) in the neuroregulation of ACTH secretion, in this study we compared the ACTH and cortisol responses to human CRH (100 μg iv as a bolus) in 18 normal subjects (15 females and three males, age 22-35 years) and seven patients with central isolated diabetes insipidus (six females and one male, age 16-40 years). Two patients were newly diagnosed and five had discontinued substitution therapy with desamino-D-AVP 24 h before testing. All had free access to water before and during the test period. The ACTH and cortisol responses to CRH were higher in subjects with diabetes insipidus than in controls, either when evaluated as peak values (ACTH, mean ± SEM: 17.0 ± 1.2 vs 7.7 ± 0.7 pmol/l, p = 0.0003; cortisol: 611.3 ± 59.4 vs 450.7 ± 21.2 nmol/l, p = 0.01) or area under curve values (ACTH: 672.5 ± 75.7 vs 364.0 ± 33.6 pmol.l⁻¹.h⁻¹, p = 0.002; cortisol: 29158.0 ± 2937.0 vs 232276.7 ± 1052.1 nmol.l⁻¹.h⁻¹, p = 0.03). These results show that patients with diabetes insipidus have an exaggerated pituitary-adrenal response to CRH. This may be due to the fact that in diabetes insipidus AVP secretion from parvocellular neurons of the paraventricular nucleus in the hypothypophysial portal system is not impaired. Alternatively, AVP secretion may be defective in both magnocellular and parvocellular hypothalamic AVP-secreting neurons. In this case, it could be hypothesized that adjustment is made to the feedback regulatory mechanisms of the hypothalamic-pituitary-adrenal axis, so that the CRH-ACTH axis assumes a main role with respect to the AVP-ACTH axis.

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It is well known that arginine vasopressin (AVP), in addition to its role as an antidiuretic hormone, exerts a stimulatory effect on adrenocorticotropic hormone (ACTH) secretion both in animals and man. Both AVP and corticotrophin-releasing hormone (CRH) exert a synergistic stimulatory effect on ACTH secretion by pituitary cells in vitro (see Refs. 1 and 2 for a review) and acute administration of AVP potentiates CRH-induced ACTH secretion in humans (3-5). On the other hand, many clinical and experimental observations indicate a primary physiological role for AVP in the neuroregulation of ACTH secretion (6-16). Immunohistochemical studies showed that two subpopulations of hypothalamic AVP-secreting neurons exist. Magnocellular neurons of the supraoptic nucleus (SON) and of the paraventricular nucleus (PVN) regulate water balance and project directly to the posterior pituitary. Conversely, neurons of the parvocellular division of the PVN project into the zona externa of the median eminence, where the hormone is secreted into the hypophyseal-portal vascular system. These neurons are involved in the neuroregulation of ACTH secretion and may secrete CRH and AVP (2, 17-20).

With the aim of elucidating further the interaction between AVP and CRH in the neuroregulation of ACTH secretion, in this study we have compared the ACTH and cortisol responses to exogenous CRH in normal subjects and in patients with central isolated diabetes insipidus.

Subjects and methods

Subjects

Seven subjects with central diabetes insipidus (six females and one male, age 16-40 years) and 18 normal volunteers (15 females and three males, age 22-35 years) were studied after informed consent was obtained. The procedures followed were in accordance with the
ethical methods of our institutional committee on human experimentation. All subjects were within ± 10% of their ideal body weight; all females had regular menses and were tested during the follicular phase of the cycle.

In all patients the diagnosis of diabetes insipidus was established during the last 3 years. Two were newly diagnosed and five discontinued antidiuretic hormone substitution therapy with desamino-D-Arg8-vasopressin (DDAVP) 24 h before testing. In the newly diagnosed subjects symptoms persisted for at least 2 months before the diagnosis. At the time of diagnosis, diuresis ranged from 6.8 to 15.0 l/24 h and urinary osmolality ranged from 30 to 89 mOsm/kg. Plasma osmolality on the day of CRH testing ranged from 271 to 297 mOsm/kg (mean ± SEM: 284.3 ± 3.3 mOsm/kg). In the subjects who discontinued DDAVP, the diuresis in the 12 h preceding testing was higher than 4 l.

The diagnosis of central diabetes insipidus was established according to Thompson (21) and Baylis (22): a dehydration test was performed, with hourly evaluation of plasma and urine osmolality until a steady-state urinary osmolality was achieved (a variation in urine osmolality of less than 30 mOsm/kg in three consecutive hourly urine samples) or until a decrease in absolute weight of more than 5% was observed. At the end of the dehydration period the patients underwent sc administration of 1 μg of DDAVP, with evaluation of urinary osmolality every 30 min for 2 h. An increase of 10% in this parameter in the presence of a urinary osmolality/plasma osmolality ratio of > 1 was considered to be diagnostic for central diabetes insipidus. The duration of the dehydration period ranged from 5 to 15 h. An organic cause of central diabetes insipidus was excluded by radiological examination of the hypothalamic–pituitary area with high-resolution computed tomography or magnetic resonance imaging. The results of laboratory evaluation of anterior pituitary function were normal in all patients.

Methods

All subjects underwent a test with CRH (human CRH, Novabiochem, Switzerland, 100 μg as an iv bolus) at 09.00 h after overnight fasting. The tests were performed in the same period in patients and controls. An indwelling catheter was inserted in an antecubital vein at least 30 min before the test and kept patent by slow infusion of 0.9% saline (150 ml throughout the test). All subjects had free access to water before and during the test. Blood samples for ACTH and cortisol were drawn every 15 min from −15 to 120 min.

Blood samples for ACTH were collected in EDTA-containing refrigerated tubes and centrifuged immediately at 4°C. Plasma ACTH was measured in duplicate by immunoradiometric assays (Allegro IIS-ACTH, Nichols Institute Diagnostics, CA, USA). The sensitivity of the assay was 0.2 pmol/l. The inter and intra-assay coefficients of variation in our laboratory ranged from 6.9 to 8.9% and from 1.1 to 3.0%, respectively. Serum cortisol was measured in duplicate by radioimmunoassays (CORT-CTK 125, Sorin, Italy). The sensitivity of the assay was 11.0 nmol/l. The inter and intra-assay coefficients of variation in our laboratory ranged from 6.6 to 7.5% and from 3.8 to 6.6% respectively.

Results were expressed as means ± SEM. either of absolute values or area under the response curve (AUC) values calculated by trapezoidal integration. Statistical analysis was performed using non-parametric (Kruskal–Wallis) analysis of variance.

Results

Results are reported in Table 1 and Fig. 1.

Basal ACTH and cortisol levels did not differ significantly in patients with diabetes insipidus and normal subjects.

The ACTH and cortisol responses to CRH were higher in subjects with diabetes insipidus than in controls, either when evaluated as absolute peak values (ACTH: p = 0.0003; cortisol: p = 0.01) or AUC values (ACTH: p = 0.002; cortisol: p = 0.03). The response of the newly diagnosed subjects overlapped with that observed in the patients who discontinued DDAVP.

No side-effects were observed after CRH administration in any of the subjects.

Table 1. Basal adrenocorticotropic hormone (ACTH) and cortisol levels, and ACTH and cortisol responses to corticotrophin-releasing hormone (CRH) in 18 control subjects and seven patients with diabetes insipidus.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Basal levels (± SEM)</th>
<th>Peak (± SEM)</th>
<th>AUC (± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACTH (pmol/l)</td>
<td>Cortisol (nmol/l)</td>
<td>ACTH (pmol/l)</td>
</tr>
<tr>
<td>Controls</td>
<td>3.2 ± 0.3</td>
<td>318.7 ± 17.6</td>
<td>7.7 ± 0.7</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>4.3 ± 0.4</td>
<td>317.9 ± 31.1</td>
<td>17.0 ± 1.2</td>
</tr>
</tbody>
</table>


Discussion

Present findings show an enhanced pituitary–adrenal response to CRH in patients with diabetes insipidus with respect to normal controls.

There is consistent evidence for a physiological stimulatory role of AVP in the neuroregulation of ACTH secretion both in animals and man:

(i) patients with ACTH deficiency can develop a syndrome of inappropriate antidiuretic hormone secretion, reversible after hydrocortisone replacement therapy (6, 7);

(ii) patients with Addison’s disease have plasma AVP levels that are significantly more elevated than normal subjects (8);

(iii) the ACTH response to CRH is enhanced by dehydration or administration of hypertonic saline both in animals (9) and man (10–12);

(iv) the ACTH response to stress is present after pharmacological block of CRH release in normal rats but not in congenitally AVP-deficient Brattleboro rats (13);

(v) hypoglycaemia enhances turnover of both CRH and AVP in rat hypothalamus (14) and increases plasma concentrations of both CRH and AVP in man (15);

(vi) in neurohypophysectomized dogs the ACTH response to insulin-induced hypoglycaemia is defective while the response to CRH is normal (16).

The finding that the pituitary–adrenal response to CRH in central diabetes insipidus is not only preserved but even increased suggests that, in this disease, the synergistic effect of AVP with CRH-induced ACTH release is not lacking. Two hypotheses may be suggested to explain our findings. On the one hand, it could be hypothesized that in central diabetes insipidus AVP secretion is defective only in magnocellular neurons of SON and PVN, which regulate the water balance, but not in the parvocellular neurons of the PVN, which regulate ACTH secretion. In fact, this excessive response may be secondary to elevations of hypophysial portal AVP. This may be expected because a relative hypovolaemia is common in patients with diabetes insipidus (21) and the parvocellular neurons of the PVN are under the control of water balance (9–12). This hypothesis is favoured indirectly by the observations that in the Brattleboro rat there is an impaired pituitary–adrenocortical response to stress (13) or to electrical stimulation of the hypothalamus (23). In fact, in this rat strain AVP secretion is defective not only in the neurohypophysis but also in the hypophysial portal system (24). This hypothesis is favoured also by the few histological observations on the hypothalamus of patients with diabetes insipidus, showing that the lesions of the SON appear to be more marked than those of the PVN, both in the acquired (25) and the congenital variant (26) of the disease.

Alternatively, it could be hypothesized that in patients with diabetes insipidus AVP secretion is defective in both the neurohypophysis and the hypophysial portal system. If this were true, one may speculate that, in the presence of a relative and persistent AVP deficiency the population of corticotroph cells increases its sensitivity to CRH. This hypothesis may be considered because our patients were not dehydrated at the moment of the study. Hypothetically, this augmented sensitivity may be due to an increase in the number and/or activity of CRH receptors or, alternatively, to a relative increase in the number of CRH-sensitive corticotroph cells with respect to AVP-sensitive corticotroph cells. Recently, subpopulations of corticotroph cells with different sensitivities to the two neurohormones have been demonstrated in animals (27).

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