CASE REPORT

Vasopressin, Major Depression, and Hypothalamic–Pituitary–Adrenocortical Desensitization

Marianne B. Müller, Rainer Landgraf, and Martin E. Keck

Background: The hypothalamic neuropeptide arginine vasopressin is thought to play an important role in the pathophysiology of affective disorders and the hyperactivity of the hypothalamic–pituitary–adrenocortical system that frequently accompanies them. Postmortem studies as well as clinical investigations have described elevated levels of vasopressin in the brain and plasma of depressed patients, and this finding has been suggested to contribute to depressive symptomatology.

Methods: The case of a 47-year-old patient displaying chronically elevated plasma vasopressin levels due to paraneoplastic vasopressin secretion by an olfactory neuroblastoma and the first episode of major depression is presented.

Results: Depressive symptoms improved markedly after surgical resection of the tumor and subsequent normalization of plasma vasopressin levels. Unexpectedly, neither corticotropin nor cortisol secretion could be stimulated by an intravenous corticotropin-releasing hormone challenge under the condition of chronically elevated plasma vasopressin levels in this patient.

Conclusions: Chronically elevated plasma vasopressin levels may induce depressive symptomatology, and—in contrast to the potent corticotropin secretagogue effects of acute vasopressin administration—lead to a marked desensitization of the hypothalamic–pituitary–adrenocortical system.


Key Words: Anxiety, CRH, esthesioneuroblastoma, HPA system, major depression, vasopressin

Introduction

The hypothalamic–neurohypophysial neuropeptide arginine vasopressin (AVP) is thought to play a crucial role in the pathophysiology of affective disorders and their underlying neuroendocrine dysregulation (Holsboer and Barden 1996). After the first observation of hypothalamic–pituitary–adrenocortical (HPA) system hyperactivity in depression, an increase not only in hypothalamic corticotropin-releasing hormone (CRH) but also in hypothalamic AVP had been hypothesized, which was later confirmed in postmortem studies of depressed patients (Purba et al 1996; Raadsheer et al 1994, 1995). In accordance with the latter finding, elevated AVP plasma levels have recently been observed in major depression (van Londen et al 1997). Here we report the case of rare esthesioneuroblastoma with paraneoplastic secretion of AVP that was associated with the onset of the first episode of major depression. In addition, we observed an unexpected dysregulation of the HPA system, indicating that in the condition of chronically elevated plasma AVP concentrations a desensitization of the HPA system may occur.

Case Report

A 47-year-old man was admitted to our psychiatric hospital because of a first major depressive episode. Fifteen months before he had suffered from acute hyponatraemia (serum sodium: 110 mmol/L). Adrenal insufficiency had been excluded and a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) of unknown origin had been hypothesized. The patient had been discharged and recommended to undergo frequent control examinations of serum electrolytes.

At admission to our psychiatric hospital, psychopathologic examination revealed a severe episode of major depression (DSM-IV) with depressed mood, loss of interest and pleasure, sleep disturbances, and an increased level of anxiety (Hamilton depression [HAM-D] score at the day of admission: 33). Physical and neurologic examinations were normal. Serum sodium (125 mmol/L), osmolality (275 mosm/kg), hemoglobin (13.1 g/dL), hematocrit (38.7%), and uric acid (2.7 mg/dL) were decreased. Basal cortisol was normal (509 nmol/L), but basal corticotropin plasma levels were slightly elevated (8.36 pmol/L). Three days after admission and still medication free, the patient underwent a combined dexamethasone–CRH stimulation test; unexpectedly neither corticotropin nor cortisol secretion could be stimulated by an intravenous (IV) CRH challenge (Figure 1B). Magnetic resonance imaging of the skull revealed a large, polypoid mass in the right nasal cavity, extending towards the frontobasis and strongly suggestive of a neoplasm (Figure 2). Biopsy of this mass lesion revealed the typical histopathologic features of an
olfactory neuroblastoma. Four and a half weeks after admission the patient was referred to surgery.

Arginine vasopressin concentrations were measured in extracted plasma samples by a highly sensitive and selective radioimmunoassay (detection limit: 0.1 pg/sample; cross-reactivity of the antisera with other related peptides, including oxytocin: <0.7%; for a more detailed description see Landgraf et al 1995a). All plasma samples were analyzed in the same assay.

Plasma AVP concentrations were found to be increased up to sixfold before surgery, but returned to normal values after complete removal of the tumor, as did serum osmolality and sodium concentrations (Figure 1A). Twelve weeks after admission, and under antidepressant treatment with trimipramine (300 mg/day), the patient experienced a more than 50% reduction of depressive symptoms (HAM-D score: 10; Figure 1A) and was discharged from our hospital.

Discussion

Esthesioneuroblastoma (olfactory neuroblastoma) is a rare malignant neuroectodermal tumor originating from neurosensory receptor cells in the nasal mucosa and rarely presenting with neuroendocrine activity (Broich et al 1997). In this case the clinical diagnosis of SIADH, which is defined by an excess in AVP secretion in the presence of serum hypo-osmolality, pointed towards paraneoplastic vasopressin secretion. After tumor resection, plasma AVP concentrations returned to normal values (Figure 1A), and

Figure 1. (A) Clinical course in a patient with vasopressin-secreting esthesioneuroblastoma. The vertical line indicates the day of surgery. Top: Hamilton depression score and vasopressin plasma concentrations. The grey horizontal bar indicates the range for vasopressin plasma concentrations appropriate for normal serum osmolality. Bottom: Serum sodium concentration and serum osmolality. (B) Results of the combined dexamethasone–corticotropin-releasing hormone (CRH) challenge test (Holsboer and Barden 1996): corticotropin (ACTH) and cortisol plasma concentrations in our patient with paraneoplastic vasopressin secretion (■). For comparison (dashed lines): the results of this neuroendocrine challenge test in healthy control subjects (n = 20, △) and patients with a current episode of major depression (n = 18, ○). (Modeled after Holsboer and Barden 1996.)
depressive as well as anxiety symptoms were markedly reduced.

Considering the well-characterized behavioral effects of AVP, such as increased avoidance behavior after central administration of AVP and reduced anxiety following treatment with a vasopressin V₁ receptor antagonist or antisense targeting (Landgraf et al 1995b), we could argue that in our case the first depressive episode was triggered by an excess in circulating AVP. Symptoms of a major depressive episode usually develop over several weeks, and there is convincing evidence that in our patient the depressive episode had already developed several months before admission to our hospital. He reported having experienced an increased level of anxiety at least 6 months before; further, anxiety and worry were accompanied by increasing difficulties in concentrating, the feeling of being easily fatigued, and sleep disturbances. Therefore, it is most likely that in this patient the prodromal period lasted for several weeks or even months before full onset of the major depressive episode.

After tumor resection and subsequent normalization of plasma AVP levels, depressive as well as anxiety symptoms improved by more than 50%; however, at this time the patient was already under treatment with trimipramine.

Tumors of neuroectodermal origin, such as olfactory neuroblastoma, may present with ectopic expression of a variety of hormones, hormone precursors, or biologically active peptides (e.g., somatostatin, vasoactive polypeptide, calcitonin). Therefore, we cannot completely rule out the possibility that other and as yet unidentified compounds produced by the tumor might have contributed to elevating AVP secretion in our patient.

The dexamethasone–CRH challenge test yielded unexpected results (viz., a lack of increase in both plasma cortisol and corticotropin concentrations after an IV CRH challenge). Several investigations have shown not only baseline alterations in corticotropin and cortisol secretion in 20–50% of depressed patients, but also characteristic alterations in specific HPA system function tests such as the combined dexamethasone–CRH challenge test. These findings are consistently suggestive of HPA system overactivity in up to 90% of all investigated patients with major depression (Heuser et al 1994).

Since the discovery of CRH in 1981, it was rapidly established that AVP potently synergizes with CRH to stimulate pituitary ACTH release: when CRH and AVP are administered together, hormone output is well above the added effects of the two peptides alone (for review, see Antoni 1993). This CRH/AVP synergism is known to be functionally relevant under both physiologic and pathophysiologic conditions such as stress or glucocorticoid deficiency (de Goeij et al 1992; Kiss et al 1984); however, the differential contribution of magnocellular and parvicellular hypothalamic vasopressinergic neurons to the regulation of HPA system activity as well as the synergistic or even opposing effects of AVP released within distinct brain areas and/or into the systemic circulation are still discussed controversially (Kalsbeek et al 1992; Wotjak et al 1996).

An escape of both corticotropin and cortisol response from dexamethasone suppression has been described in healthy subjects after combined AVP/CRH infusion (von Bardeleben et al 1985). In contrast to this clear stimulatory effect of an acute AVP coadministration, our results provide the first clinical evidence that a marked desensitization of the HPA system may occur under conditions of chronically elevated plasma AVP concentrations. A similar observation has been previously made in rodents, where chronic AVP/CRH coadministration led to a desensitization of the HPA system and downregulation of pituitary CRH receptor expression (Tizabi and Aguilera 1992).

The authors thank Dr. Nicola Toschi for critically reviewing the manuscript.

References


Broich G, Pagliari A, Ottaviani F (1997): Esthesioneuroblastoma: A general review of the cases published since the


Purba JS, Hoogendijk WJG, Hofman MA, Swaab DF (1996): Increased number of vasopressin- and oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depression. *Arch Gen Psychiatry* 53:137–143.


