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Increased Basal Plasma Vasopressin-Neurophysin in Mania

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Abstract. Basal plasma vasopressin-neurophysin (hN_pI) was estimated in 50 drug-free neuropsychiatric patients classified according to the Research Diagnostic Criteria. The hN_pI concentration was higher in the 5 manics (0.76 ± 0.15 ng/ml) than in the 16 schizophrenics (0.53 ± 0.08), 12 minor depressed (0.54 ± 0.06) and 17 major depressed (0.48 ± 0.10; $p < 0.05$). Thus, those results confirm our initial observation of an increased vasopressinergic function in the manic compared to the depressed phase in one bipolar patient. Whether this increase in the vasopressin release is a consequence of the neuropsychiatric disorders or initiates and/or participates in their pathophysiology remains to be elucidated. The hypothetic consequence on water metabolism of such an increase remains also to be defined.

Introduction

Vasopressin-neurophysin is a part of the precursor molecule for the active nonapeptide vasopressin (antidiuretic hormone, AVP) [1]. In humans, this neurophysin has a marked anodal electrophoretic migration and is therefore named neurophysin-I (hN_pI) [2].

AVP and hN_pI are released simultaneously by exocytosis of neurosecretory granules in the peripheral circulation and in the cerebrospinal fluid (CSF): modifications of hN_pI concentrations therefore reflect the fluctuations of AVP release in different physiological and pathological conditions. Moreover, as hN_pI is more stable than AVP, its blood and CSF levels might better reflect long-term vasopressinergic function than isolated AVP assays [see discussion in ref. 3].

Since the pioneer work of the Wied [4], there has arisen a growing evidence that AVP has a central activating action (mood, memory, selective attention) in animals and humans [5–8]. The recent discovery of hippocampal receptors for AVP and the close correlation between the in vitro binding affinity and the in vivo behavioral power of different AVP analogues or derivatives [9] reinforce the psychophysiological meaning of this peptide action on the brain. Based on this activity, Gold et al. [10] postulated that AVP release can be altered in some psychopathological conditions, and more particularly in depression and mania. However, basal plasma levels did not differ in the different groups of patients, whereas sophisticated challenge tests (hypertonic saline infusion) revealed decreased release during the depressive phase and increased response during the manic phase [11]. We have also previously described an increase in CSF neurophysins in bipolar as compared to unipolar depressed patients [12, 13].

Moreover, in one privileged observation, we recently described a bipolar depressed patient in a depressive and in his initial manic phase, and we demonstrated an increase in basal as well as in apomorphine-stimulated plasma hN_pI levels [14]. Therefore, in the present study, we decided to investigate systematically hN_pI levels in drug-free, hospitalized neuropsychiatric patients.

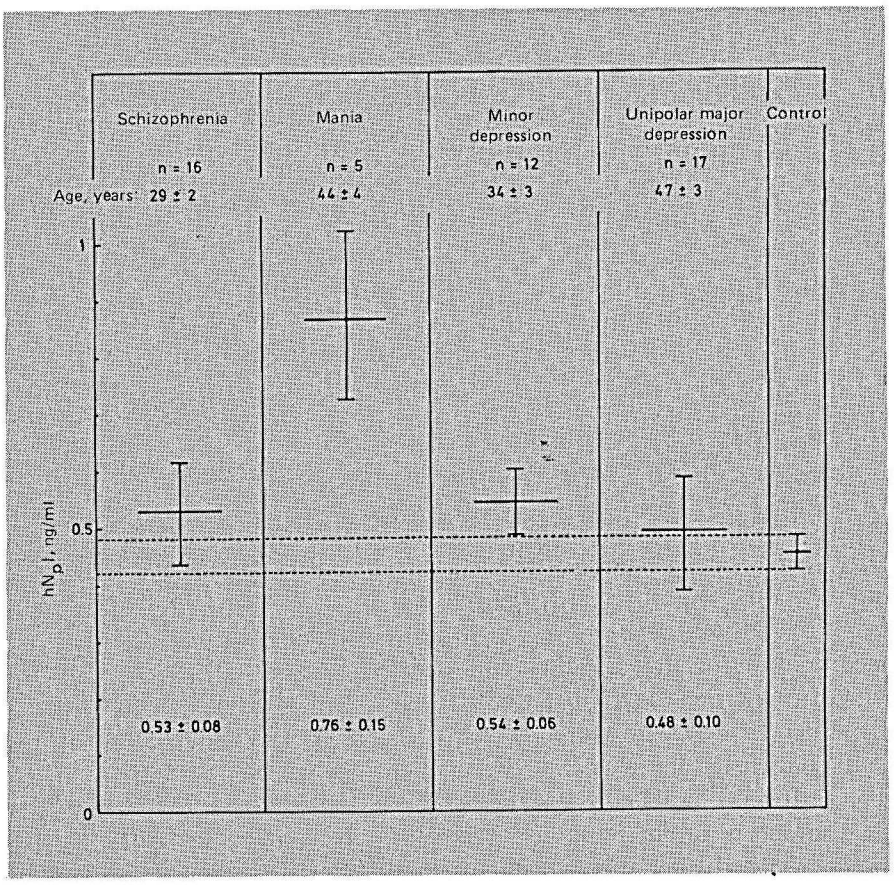

Fig. 1. Basal plasma hN_pI levels in a group of 50 drug-free psychiatric inpatients classified according to the RDC.

Patients and Methods

Patients

A total of 50 patients were included in this study; the diagnoses defined according to the Research Diagnostic Criteria (RDC) [15] were: schizophrenia (n = 16, age 29 ± 2, SE, years); mania (n = 5, age 44 ± 4 years); minor depression (n = 12, age 34 ± 3 years), and unipolar major depression (n = 17, age 17 ± 3 years). All patients were free of medical illness and tested after a drug-free period of at least 2 weeks.

Plasma Assays

Basal blood samples (± 10 ml) were taken by venipuncture in fasting, recumbent individuals at ± 8 a.m. as part of a larger neuroendocrine testing described previously [16, 17].

Since the original hN_pI assay used previously [18] was no more available, we developed a personal hN_pI assay. In summary, hN_pI was purified according to a previously described method [19] followed by a high-performance liquid chromatography step. The labeling of hN_pI was realized as described previously for bovine and human neurophysins [20], the specific activity being 225 ± 25 μCi/μg. Anti-hN_pI antiserum was used at the initial dilution of 1/10,000. Separation of free from bound hormones was achieved by double-antibody techniques. At this dilution, ± 30% of the tracer (± 9,000 cpm) was bound, the limit of detection being 0.02 ng/tube, and the sensitivity (50% inhibition binding) being 0.2 ng/tube. The volume of known or unknown samples was usually 100 μl. Cross-reaction of oxytocin-neurophysin (hN_pII) was detectable at the 0.01% level; no cross-reactivity was detected using synthetic nonapeptide (oxytocin or AVP) or purified extracted human antehypophyseal hormone. Intraassay variability was 6.5% and interassay variability was 10.7%; all the samples of 1 individual were assayed in the same run.

Using this assay technique, the mean level calculated in 120 samples from healthy blood donors but without psychiatric control was 0.44 ± 0.05 ng/ml, a value in accordance with the results obtained using a previously reported radioimmunoassay [18].

Since at the present time we have no matched, psychologically controlled group, we compared only the different psychiatric groups using the Student t test for unpaired samples.

Results

The basal plasma hN_pI values are shown in figure 1. Patients suffering from unipolar major depression and mania were significantly older than the schizophrenic ones ($p < 0.02$). However, only manic patients signifi-

cantly differed (0.76 ± 0.15 ng/ml) from the 3 other groups (schizophrenia: 0.53 ± 0.08 ng/ml; minor depression: 0.54 ± 0.06 ng/ml; unipolar major depression: 0.48 ± 0.10 ng/ml; $p < 0.05$ for each comparison).

Discussion

These data confirmed our initial one-case study of a bipolar depressed patient [14]. To our knowledge, this is the first demonstration of an increase in *basal* blood level of an AVP-related peptide in a group of drug-free manic patients compared to depressed and schizophrenic ones.

The increase in vasopressinergic activity in mania is fully consistent with the hypothesis of Gold et al. [10] and with recent clinical studies showing either an increased plasma AVP release following hypertonic saline infusion in manic compared to depressed patients [21] or increased CSF AVP levels in manic patients compared to controls [22].

The pathophysiological meaning of this increased vasopressinergic activity in manic patients is still uncertain; it may be either a nonspecific consequence of the gross behavioral disturbances in mania or part of the specific central mechanisms leading to mania. In that respect, it is of interest to note that exogenous AVP given as a treatment for memory disturbances has been reported to sometimes induce manic symptoms [10; Timsit-Berthier, pers. commun.].

The mechanism of action that may cause AVP to induce manic symptomatology should be discussed. As AVP has been shown to potentiate catecholaminergic neurotransmission [23], and as catecholamine overactivity could be implicated in the pathogenesis of mania [24], an increased AVP neuromodulatory action might be responsible for an increased catecholamine activity. In that hypothesis, lithium, which could act as an antagonist to AVP at the peripheral receptor level, may increase the sensitivity of the plasma AVP response to osmotic stimuli [25] and could share its antimanic properties through a similar action at the central AVP receptor system, as suggested previously by Gold et al. [10].

Another question arises to the endocrinologists: i.e. does this central oversecretion of AVP induce any perturbation in the water regulation in manic patients?

In the present study, we have no documented data on the water metabolism in our patients; however, a syndrome of hyponatremia due to water retention, very similar to the syndrome of inappropriate antidiuretic hormone (ADH) secretion, has been described in psychiatric patients (PIP syndrome) [26].

Lastly, in this study, we failed to find any decrease in plasma vasopressinergic activity as tested by hN_pI assay in depressed patients compared to our healthy group. However, the controls were not adequate since they were not age-matched, nor psychologically tested. In one preliminary study we indeed have found decreased plasma neurophysin levels in depressed patients when they were compared to carefully age-matched psychologically healthy controls [27].

Thus, it appears that the secretion of neuropituitary peptides is modified in various neuropsychiatric diseases: as fas as AVP is concerned, a large body of evidence suggests an increased release during mania and a decreased release during depression.

Whether these modifications are only a consequence of the central disturbances or whether those peptides could participate in the pathogenesis of the affection remains to be elucidated. The hypothetic peripheral metabolic consequences of such modifications (dehydration, water intoxication) must alos be studied using carefully controlled psychoendocrine paradigms.

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