Increased Basal Plasma Vasopressin-Neurophysin in Mania

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**Abstract.** Basal plasma vasopressin-neurophysin (hN\textsubscript{p}I) was estimated in 50 drug-free neuropsychiatric patients classified according to the Research Diagnostic Criteria. The hN\textsubscript{p}I 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\textsubscript{p}I) \[2\].

AVP and hN\textsubscript{p}I are released simultaneously by exocytosis of neurosecretory granules in the peripheral circulation and in the cerebrospinal fluid (CSF): modifications of hN\textsubscript{p}I concentrations therefore reflect the fluctuations of AVP release in different physiological and pathological conditions. Moreover, as hN\textsubscript{p}I 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\textsubscript{p}I levels \[14\]. Therefore, in the present study, we decided to investigate systematically hN\textsubscript{p}I levels in drug-free, hospitalized neuropsychiatric patients.
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_p,I assay used previously [18] was no more available, we developed a personal hN_p,I assay. In summary, hN_p,I was purified according to a previously described method [19] followed by a high-performance liquid chromatography step. The labeling of hN_p,I was realized as described previously for bovine and human neurophysins [20], the specific activity being 225 ± 25 μCi/μg. Anti-hN_p,I 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-neuropophin (hN_p,II) was detectable at the 0.01% level; no cross-reactivity was detected using synthetic nonapeptide (oxytocin or AVP) or purified extracted human antihypo-phphysial 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_p,I 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 \pm 0.15 \text{ ng/ml}) from the 3 other
groups (schizophrenia: 0.53 \pm 0.08 \text{ ng/ml}; minor depress-
ion: 0.54 \pm 0.06 \text{ ng/ml}; unipolar major depression: 0.48
\pm 0.10 \text{ 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 schizo-
phrenic 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 in-
creased plasma AVP release following hypertonic saline
infusion in manic compared to depressed patients [21]
or increased CSF AVP levels in manic patients com-
pared to controls [22].

The pathophysiological meaning of this increased va-
 sopressinergic activity in manic patients is still uncer-
tain; 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 re-
ported to sometimes induce manic symptoms [10; Tim-
 sit-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 overac-
tivity 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 an-
tagonist 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 prop-
erties through a similar action at the central AVP recep-
tor system, as suggested previously by Gold et al. [10].

Another question arises to the endocrinologists: i.e.
do\thes\ does this central oversecretion of AVP induce any per-
turbation 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 syn-
drome of hyponatremia due to water retention, very sim-
ilar to the syndrome of inappropriate antidiuretic hor-
mone (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 hNP\L 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 pre-
liminary 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 dis-
 ease: as far as AVP is concerned, a large body of evi-
dence 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 (dehydra-
tion, water intoxication) must also be studied using carefully
controlled psychoendocrine paradigms.

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