CASE REPORT

Vasopressin–Neurophysin and Bipolar Depression

Jean-Jacques Legros and Marc Ansseau

Introduction

Vasopressin–neurophysin is a part of the precursor molecule for the active nonapeptide vasopressin (antidiuretic hormone, AVP). In humans, this neurophysin has a marked anodal electrophoretic migration and is therefore named neurophysin-I (hN_PI) (Legros and Louis 1973) (see review of the precursor in Ivell et al. 1983).

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 Legros 1975).

Since the pioneer work of de Wied (1965), there has arisen a growing evidence that vasopressin has a central activating action (mood, memory, selective attention) in animals and humans (de Wied 1977; Legros et al. 1978; Kovaks et al. 1979; Weingartner et al. 1981; Legros and Lancranjan 1984). 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 vasopressin analogs or derivatives (Audigier and Barberis 1985) reinforce the psychophysiological meaning of this peptide action on the brain. Based on this activity, Gold et al. (1978) postulated that vasopressin 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 (Gold et al. 1983a). We have also previously described an increase of CSF neurophysins in bipolar as compared to unipolar depressed patients (Legros et al. 1983; Linkowski et al. 1984). We therefore decided to investigate basal and apomorphine-stimulated neurophysin serum levels in different psychopathological conditions. In the course of that study, we recently had an opportunity to test one bipolar patient who had never been treated with lithium, during consecutive depressive and manic episodes while remaining completely unmedicated.

From the Psychoneuroendocrinology Unit and the Biological Psychiatry and Psychopharmacology Unit, University of Liège Medical School, Liège–Sart Tilman, Belgium.
Address reprint requests to Dr. J.-J. Legros, Psychoneuroendocrinology Unit, Centre Hospitalier Universitaire ((B 23), B-4000 Liège–Sart Tilman, Belgium.
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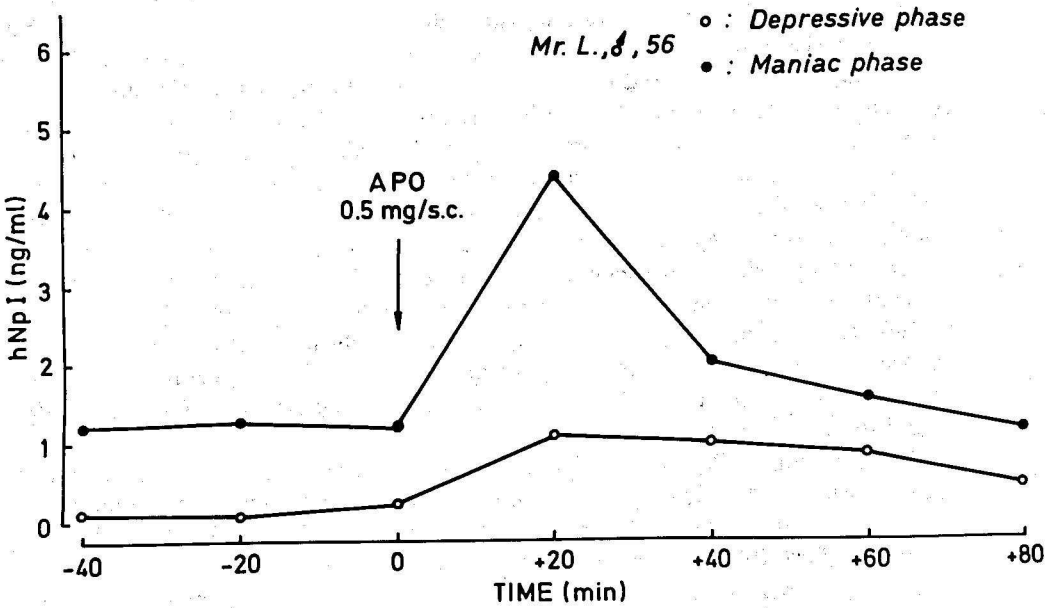
Case Report

Mr. L., born in 1928, was admitted to the Biological Psychiatry and Psychopharmacology Unit of the University Hospital of Liège (Belgium) in March 1984 with a Research Diagnostic Criteria diagnosis of major depression. He had had two previous psychiatric hospitalizations with the same diagnosis, in June 1981 and March 1983, respectively, when he had been treated with electroconvulsive therapy (ECT) and monoamine oxidase inhibitors (MAOI) with good therapeutic response. At the time of his admission, Mr. L. had stopped all psychotropic medication for 4 months. Physical examination, electrocardiogram (EKG), chest x-ray, and routine laboratory tests were normal. The patient fulfilled Research Diagnostic Criteria for major depressive disorder, subtyped as primary, recurrent, incapacitating, endogenous, retarded, and simple; the predominent mood was apathy, with loss of both interest and pleasure. The patient also fulfilled DSM-III criteria for major depression with melancholia and had a score of 31 on the 24-item Hamilton Depression Scale and 8 on the Newcastle Index for Endogenous Depression (Carney et al. 1965). After informed consent had been obtained, and before any drug therapy was initiated, Mr. L. had a biological evaluation that included an apomorphine test performed according to a procedure previously described (Ansseau et al. 1984). Briefly, at 7:00 AM, after an overnight fast, an indwelling catheter was inserted in a forearm vein and blood samples of 10 ml were collected every 20 min for 40 min before and 80 min after subcutaneous injection at 8:00 AM of 0.5 mg apomorphine. hN_PI was assayed by radioimmunoassay (RIA) using the system developed by Dax et al. (1979) with intra- and interassay variability of 6.1% and 7%, respectively. The normal hN_PI value is 0.44 ± 0.02 (SEM) ng/ml.

Changes over time in hN_PI level during the test are displayed in Figure 1. T_0 level

Figure 1. Changes over time in the vasopressin–neurophysin plasma level following a subcutaneous injection of 0.5 mg apomorphine in a bipolar depressive during consecutive depressive and manic episodes.



was 0.15 ng/ml, increasing to a peak level of 1.1 ng/ml 40 min following apomorphine. Mr. L. did not exhibit sedative or digestive side effects.

After biological evaluation had been completed, the patient was treated with zimelidine, a specific 5-hydroxytryptophan (5-HT) reuptake inhibitor, with an excellent therapeutic response, and was discharged 4 weeks later. Mr. L. was then followed on an outpatient basis, and all psychotropic treatment was stopped in December 1984.

In March 1985, Mr. L. was readmitted to our department because of an acute manic episode. At that time, he fulfilled all Research Diagnostic and DSM-III criteria for a definite manic disorder with elevated mood, increased activity and talk, flight of ideas, inflated self-esteem, decreased need for sleep, distractibility, and excessive involvement in dangerous activities, all lasting for 2 weeks. Again, physical assessments were normal and with the informed consent of both the patient and his wife, the same biological evaluations were performed before initiation of any treatment. Changes over time in hN_PI levels are displayed in Figure 1. Baseline level was 1.25 ng/ml, increasing to a peak value of 4.60 ng/ml 40 min following apomorphine. No side effects were noted during the test.

Discussion

As plasma neurophysin levels are quite stable in normal individuals (Legros 1975), the major finding in this patient is the normal basal hN_PI concentration measured during the depressive phase, which increased to higher than normal levels during the manic phase of the disease. The importance of this observation is strengthened by the absence of any previous treatment that might have affected neuropituitary function, especially lithium. Indeed, we could observe this patient during his initial manic episode.

To our knowledge, this is the first report of an increase in the *basal* blood level of a vasopressin-related peptide in a drug-free manic patient. This difference from previous studies might be due to the fact that plasma neurophysin concentrations better reflect chronic "vasopressingergic" function than the isolated AVP assay itself (see above).

The increase of vasopressinergic activity in the manic compared to the depressed phase is fully consistent with the hypothesis of Gold et al. (1978) and with recent clinical studies that show either an increased plasma AVP *release* following hypertonic saline infusion in manic compared to depressed patients (Gold et al. 1980) and increased CSF AVP levels in manics compared to controls (Sorensen et al. 1985) or to depressed patients (Gold et al. 1983a). In our patient, we not only found elevated basal serum levels of hN_PI, but we also could confirm the presence of an increased readily releasable pool of vasopressin-related peptide during a challenge test (Gold et al. 1980).

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 (Gold et al. 1978; Timsit-Berthier, personal communication).

The mechanism of action that may cause AVP to induce manic symptomatology should be discussed. As AVP has been shown to potentiate catecholaminergic neurotransmission (Buijs 1983), and as catecholamine overactivity could be implicated in the pathogenesis of mania (Post 1980), an increased vasopressin 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 (Gold et al. 1983b) and could share its antimanic properties through a similar action at the central AVP receptor system, as suggested previously by Gold et al. (1978).

The neuropsychological, neuroendocrinological, and neuropharmacological data are thus consistent with the hypothesis that an increase in vasopressin synthesis and/or release can occur in manic patients and could initiate, or participate in, the genesis of the symptoms. Obviously, the opportunistic observation of this patient must be confirmed in a larger study of bipolar depressive subjects.

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