

REGPEP 01300

Neurohypophyseal peptides and psychiatric diseases

Jean-Jacques Legros^a, Marc Ansseau^b and Martine Timsit-Berthier^c

^aPsychoneuroendocrine Unit, ^bPsychiatry Unit and ^cLaboratory of Applied Cognitive Psychophysiology, University of Liege – Sart Tilman, Liege (Belgium)

Key words: Neuropsychiatry; Neurophysin; Vasopressin; Oxytocin; Clinical

Summary

The study of neurohypophyseal function in various neuropsychiatric diseases is interesting because:

- (1) The main neurohypophyseal peptides vasopressin (AVP) and oxytocin (OT) share by themselves modulatory influence on behavior.
- (2) Hypothalamo-posterior pituitary axis is directly influenced by modifications of central neurotransmitter metabolism involved in behavior control.

Influence of neurohypophyseal peptides on human behavior

Following the pioneering work of David de Wied (1965) [1] in the rat, many studies have been devoted to the effects of AVP, OT and their analogues or antagonists on animal behavior. AVP and OT seem to modulate in opposite direction memory and learning processes: VP facilitates passive avoidance behavior and increases resistance to extinction of active avoidance behavior while OT induces opposite effects [2]. Our studies in normal middle-aged men [3] and in four patients suffering from post-traumatic

amnesia [4] confirmed this stimulating effect of AVP in humans and initiated many clinical studies regarding the stimulatory influence of AVP or its structural analogues on various cognitive parameters [5,6]. In general, this stimulatory action has been confirmed in the absence of major psychological or neuronal deterioration and in the presence of 'average' baseline memory performance, leaving room for a significant improvement in psychometric test scores. This action on memory could be due to better focusing of attention, as has recently been shown for normal middle-aged men [7]. It can be also related to mood improvement, and increase of 'sociability' [6]. Thus, unexpected hypomanic episodes, consistent with the stimulatory effect of this peptide, have also been observed in two women by one of us (M.T.B.). Fur-

Correspondence to: J.J. Legros, Psychoneuroendocrine Unit, CHU, University of Liege – Sart Tilman, B-4000 Liège, Belgium.

thermore, the stimulatory influence of AVP has been confirmed in studies using the paradigm of endogenous, 'cognitive' cerebral evoked potentials, and more specifically the Contingent Negative Variation (CNV) an electrophysiological phenomenon which is related to anticipation, motivation and regulation of complex behaviors. AVP infusion prevented the spontaneous diminution of CNV amplitude during the testing session [8].

The influence of OT was studied several years after that of AVP. The positive effect of OT on maternal behavior [9] and social affiliation [10] and its inhibitory action on cognitive parameters (the opposite of that of AVP) [11] were already well demonstrated in the rodents. In the human, this inhibitory action on memory was confirmed by Ferrier et al. [12] and by our team who found a modest but significant effect in certain psychometric tests in normal men [13]. The same study showed that OT infusion induced a decrease in CNV amplitude and an increase in the post-imperative positivity, which persisted one week after the day of infusion [12]. This action was the basis of various attempts at treatment of obsessive compulsive disorder by OT [14,15]. Temporary objective and subjective memory impairment has been observed during pregnancy [16] and post partum period [17]: although the role of increased endogenous OT has been suspected, no significant correlation was however found between OT levels and the intensity of cognitive deficits [17]. Interestingly, the central action of some steroids, particularly progesterone, could involve a step of modification of central OT release [18] and modulation of brain receptors [19] for whom homologous regulation has been recently described [20].

Neurohypophyseal hormones in psychopathology

Therapeutic attempts

These psycho-physiological properties of AVP and OT have been applied in the treatment of amnesic and 'hypermnestic' syndromes. Thus, exogenous AVP

was tested in patients with memory problems (Alzheimer's disease, post-traumatic amnesia, Korsakoff's syndrome, schizophrenia, aging) with a number of positive results [6]. Previously, exogenous OT which is hypothesized to have amnesic-like properties, have been applied in the treatment of a patient with severe obsessive-compulsive disorder (see above) – which may be seen as an 'hypermnestic' dysfunction. Although encouraging, such results did not yet allow a strict therapeutic strategy for managing dysmnestic problems.

Physio-pathological approach

In numerous mental disorders, dysfunctions of AVP/OT balance were discovered.

Major depression. Infusion of hypertonic saline is accompanied by AVP release into the blood: this secretion is diminished in depressed patients as compared with controls, although the basal peptide levels are similar [21]. At variance, we have recently been able to show that the basal level of AVP-neurophysin was significantly lower in a group of major depressive patients than in a group of age-matched controls [22]. Moreover, in a recent study comparing 12 male depressed patients to 14 normal males, we not only confirmed a lower basal AVP-neurophysin level but also a reduced response to apomorphine [23].

Studies performed on the CSF confirmed this diminution of AVP levels in depressed patients, although no correlation existed between the intensity of the depressive symptomatology and the reduction in AVP levels [24].

We have also been able to confirm a reduction in the CSF concentration of AVP-neurophysin in a group of eight patients with unipolar depression (aged 37–50) as compared with a group of 12 patients without neuropsychiatric disorders (aged 29–61) [25].

Mania. In contrast to observations in depression, the first studies of Gold [21] showed hyperreactivity of AVP secretion into the blood in manic patients. We also found an elevation in the concentration of

neurophysins in the CSF in patients with bipolar affective disorder as compared with patients with unipolar depression and controls [26]. Later, we were able to test a patient during a major depressive episode and subsequently during his first manic episode, both basally and during a test of neurohypophyseal activation by apomorphine. The basal plasma level of AVP-neurophysin as well as the response to apomorphine were much higher when this patient was in the manic phase [27]. This increase in basal AVP-neurophysin was confirmed in a larger study of 50 psychiatric patients including five manic patients [28].

Schizophrenia. There is no consensus concerning AVP secretion in schizophrenia. Van Kammen et al. [29] found reduced levels in the CSF while Beckmann et al. [30] found normal levels; we ourselves found reduced levels of AVP-neurophysin [25] in agreement with the former authors. By contrast, other studies have shown that psychotic schizophrenic patients excrete less urine following water loading than controls, which could be secondary to AVP hypersecretion [31–33].

OT concentrations in the CSF have been studied by Beckmann et al. [30], who showed elevated levels in schizophrenic patients, regardless of neuroleptic treatment, as compared with controls. The previous year, we had also shown an elevation in the levels of OT-neurophysin in the CSF as compared with a control group [25].

We recently confirmed the CSF findings at the peripheral plasma level. Nine schizophrenic males (age 28.4 ± 3.5 years) showed a definite elevation in plasma OT-neurophysin as compared with 14 age (24.3 ± 0.9 years) and sex-matched volunteers: 2.8 ± 0.7 ng/ml and 1.1 ± 0.2 ng/ml, respectively. By contrast, apomorphine stimulation, which significantly elevated both types of neurophysins in the controls, was ineffective in the patient group [34].

Thus, in contrast to the results regarding AVP, there seems to be a consensus regarding hypertonicity of the OT system in schizophrenic patients.

Anorexia nervosa. Work by Gold and Robert-

son's group [35,36] has shown that there may be a central dysregulation of AVP secretion, since the normal positive correlation between plasma osmolality and AVP concentration was not observed in the anorectic. This anomaly might also be attributed to a disturbance in effective intravascular volume due to weight loss. However, in the same study, the authors showed that the same patients, having normalized their weight but conserving their psychopathology, showed the same absence of correlation and thus the same disturbance. By contrast, in patients cured psychiatrically and having returned to normal weight, this significant correlation returned, reflecting the fact that the equilibrium between the hypothalamo-neurohypophyseal system and the state of hydration of the organism had been re-established. Thus, this study suggests a link between dysfunction of AVP secretion and a psychiatric disturbance in these cases.

The concentration of OT in the cerebrospinal fluid (CSF) is reduced in anorectics as compared with controls, while the opposite is found in bulimia [37]. Since OT is released after feeding in normal individuals and since 'normal' OT central function is necessary to impair consolidation of aversely condition behavior, the low CSF OT levels in those patients may reflect their persistently low food intake and could exacerbate their tendency for perseverative preoccupation with adverse consequence as postulated by Demitrack et al. [37].

Obsessive-compulsive disorder. Recent studies by Gold's group [38] showed increase AVP secretion in patients with obsessive-compulsive disorder which may be related to their obsessional preoccupation [39] since in adolescents and children with obsessive-compulsive disorders, AVP CSF levels were significantly, negatively correlated with several ratings of obsessive-compulsive symptoms severity while OT was positively correlated with depressive symptoms [40]. Interestingly, we have previously shown an increase in OT-neurophysin in obese [41] and in alcoholics [42] patients: two conditions known to be often associated to depression.

Moreover, preliminary findings suggest that the clinical effectiveness of fluoxetine (a blocker of serotonin reuptake) for treatment of obsessive-compulsive disorders involves a decrease of central vasopressin synthesis [43].

Conclusions and perspectives

Various neuropsychiatric disorders are accompanied by modification in the central or peripheral secretion of these AVP and OT neuropeptide systems.

It is possible that this represents merely one of the numerous neuroendocrine consequences of the biochemical perturbations underlying psychiatric illness. According to this hypothesis, the study of neurohypophyseal function is interesting, on the one hand, as a marker of these anomalies (a 'window to the brain') and, on the other hand, to understand certain anomalies of electrolyte and water balance observed in patients.

It is also possible that the perturbations observed peripherally may be an indirect reflection of certain states of central hyper- or hypo-secretion of neuropeptides which might, then, be closely linked to the genesis of the behavioral abnormality. It is, in fact, interesting to note that the anomalies of endogenous function described here are generally in agreement with our knowledge of the actions of the exogenous peptides on behavior, i.e., global stimulant effect of AVP and global inhibitory effect of OT.

We are currently developing a conceptual framework which tries to integrate the various changes in AVP and OT levels observed in several psychopathological conditions. According to this model, AVP and OT could act on two different psychological dimensions. Vasopressin levels could relate to a general concept of stimulation, particularly of mood and cognition, and OT levels to a general concept of dissociation, with delusions, hallucinations, incoherence or loosening of associations as particular symptoms.

The study of those perturbations could form part

of an avenue of research devoted to the possibility of modulating the endogenous release, perhaps even of blocking the central action of these neuropeptides by the use of peptide antagonists or by intervening at the level of biodegradation using enzyme antagonists.

References

- 1 De Wied, D., The influence of the posterior and intermediate lobe of the pituitary and pituitary peptides on the maintenance of a conditioned avoidance response, *Int. J. Neuropharmacol.*, 4 (1965) 157-167.
- 2 De Wied, D. and Versteeg, V., Neurohypophyseal principles and memory, *Fed. Proc.*, 38 (1979) 2348-2354.
- 3 Legros, J.J., Gilot, P., Seron, X., Claessens, J., Adam, A., Moeglen, J.M., Audibert, A. and Berchier, P., Influence of vasopressin on learning and memory, *Lancet*, 1 (1978) 41-42.
- 4 Oliveros, J.C., Jandali, M.K., Timsit-Berthier, M., Remy, R., Benghezal, A., Audibert, A. and Moeglen, J.M., Vasopressin in amnesia, *Lancet*, 1 (1978) 42.
- 5 Jolles, J., Neuropeptides and the treatment of cognitive deficits in aging and dementia. In D.F. Swaab, E. Fliers, M. Mirmiran, W.A. Van Gool and F. Van Haaren (Eds.), *Progress in Brain Research*, Elsevier, Amsterdam, Vol. 70, 1986, 429-441.
- 6 Legros, J.J. and Timsit-Berthier, M., Vasopressin and vasopressin analogues for treatment of memory disorders in clinical practice, *Progr. Neuro-Psychopharmacol. Biol. Psychiat.*, 12 (1988) S71-S86.
- 7 Jennings, J.R., Nebes, R.D. and Reynolds, C.F., III Vasopressin peptide (DDAVP) may narrow the focus of attention in normal elderly, *Psychiat. Res.*, 17 (1986) 31-39.
- 8 Timsit-Berthier, M., Mantanus, H., Devos, J.E. and Spiegel, R., Action of lysin vasopressin on human electrophysiological activity: night-sleep pattern, auditory evoked potential, contingent negative variations, *Neuropsychobiology*, 8 (1982) 248-258.
- 9 Pederson, C.A. and Prange, A.J. Jr., Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin, *Proc. Natl. Acad. Sci. USA*, 76 (12) (1979) 6661-6665.
- 10 Insel, T.R., Oxytocin - a neuropeptide for affiliation: evidence from behavioral, receptor autoradiographic, and comparative studies, *Psychoneuroendocrinology*, 17 (1992), 3-35.
- 11 Bohus, B., Kovacs, G.L. and De Wied, D., Oxytocin, vasopressin and memory: opposite effects on consolidation, *Brain Res.*, 157 (1978) 414-417.
- 12 Ferrier, B.M., Kenett D.J. and Devlin, M.C., Influence of

- oxytocin on human memory processes, *Life Sci.*, 27 (1980) 2311–2317.
- 13 Geenen, V., Adam, F., Baro, V., Mantanus, H., Anseau, M., Timsit-Berthier, M. and Legros, J.J., Inhibitory influence of oxytocin infusion on contingent negative variation and some memory tasks in normal men, *Psychoneuroendocrinology*, 13 (1988) 367–375.
 - 14 Anseau, M., Legros, J.J., Mormont, C., Cerfontaine, J.L., Papart, P., Geenen, V., Adam, F. and Franck, G., Intranasal oxytocin in obsessive-compulsive disorder, *Psychoneuroendocrinology*, 12 (1987) 231–236.
 - 15 Charles, G., Guillaume, R., Schittecatte, M., Pholien, P., Van Wettere, J.P. and Wilmotte, J., L'ocytocine dans le traitement du trouble obsessionnel: un rapport négatif à propos de deux cas, *Psychiatrie et Psychobiologie*, 4 (1989) 111–115.
 - 16 Brindle, P.M., Brown, M.W., Griffith, H.B. and Turner, G.M., Objective and subjective memory impairment in pregnancy, *Psychol. Med.*, 21 (1991), 647–653.
 - 17 Silber, M., Almkvist, O., Larsson, B. and Unnas-Moberg, K., Temporary peripartal impairment in memory and attention and its possible relations to oxytocin concentration, *Life Sci.*, 47 (1990), 57–65.
 - 18 Schumacher, M., Coirini, H., Frankfurt, M. and McEwen, B.S., Localized actions of progesterone in hypothalamus involve oxytocin, *Proc. Natl. Acad. Sci. USA*, 86 (1989) 6798–6801.
 - 19 Schumacher, M., Coirini, H., Pfaff, D.W. and McEwen, B.S., Behavioral modification of progesterone associated with rapid modulation of oxytocin receptors, *Science*, 250 (1990) 691–694.
 - 20 Insel, T.R., Winslow, J.T. and Witt, D., Homologous regulation of brain oxytocin-receptor, *Endocrinology*, 130 (1992) 2602–2608.
 - 21 Gold, P.W., Goddwin, F.K., Post, R.M. and Robertson, G.L., Vasopressin function in depression and manic, *Psychopharmacol. Bull.*, 17 (1981) 7–9.
 - 22 Laruelle, M., Seghers, A., Goffinet, S., Bouchez, S. and Legros, J.J., Plasmatic vasopressin neurophysin in depression: basic levels and relations with HPA axis, *Biol. Psychiat.*, 27 (1990) 1249–1263.
 - 23 Legros, J.J. and Anseau, M., Neurohypophyseal peptides and psychopathology, In D.F. Swaab, M.A. Hofman, M. Mirmiran, R. Ravid, F.W. van Leeuwen (Eds.), *Progress in Brain Research*, Elsevier, Amsterdam, Vol. 93, 1992, pp. 455–461.
 - 24 Gjerris, A., Hummer, M., Vendsborg, P., Christensen, N.J. and Rafaelson, D.J., Cerebrospinal fluid vasopressin changes in depression, *Br. J. Psychiat.*, 147 (1985) 696–701.
 - 25 Linkowski, P., Geenen, V., Kerkhofs, M., Mendlewicz J. and Legros, J.J., Cerebrospinal fluid neurophysins in affective illness and in schizophrenia, *Eur. Arch. Psychiat. Neurol. Sci.*, 234 (1984) 162–165.
 - 26 Legros, J.J., Geenen, V., Linkowski, P. and Mendlewicz, J., Increased neurophysins I and II cerebrospinal fluid concentration from bipolar versus unipolar depressed patients, *Neuroendocrinol. Lett.*, 5 (1983b) 201–205.
 - 27 Legros, J.J. and Anseau, M., Vasopressin-neurophysin and bipolar depression: a case report, *Biol. Psychiat.* 21 (1986) 1212–1216.
 - 28 Legros, J.J. and Anseau, M., Increased basal plasma vasopressin-neurophysin in mania, *Hormone Res.*, 31 (1989) 81–84.
 - 29 Van Kammen, D.P., Waters, R.N. and Gold, P., Spinal fluid vasopressin, angiotensin I and II, beta-endorphin and opioid activity in schizophrenic: a preliminary evaluation. In C. Peris, G. Strume and B. Jansson (Eds.), *Biological Psychiatry*, Elsevier North Holland, Amsterdam, 1981, pp. 339–344.
 - 30 Beckmann M., Lang, R.E. and Gattaz W.F., Vasopressin-oxytocin in cerebrospinal fluid of schizophrenic patients and normal controls, *Psychoneuroendocrinology*, 10 (1985) 187–191.
 - 31 Raskind, M.A., Courtney, N. and Murberg, M.M., Antipsychotic drugs and plasma vasopressin in normal and acute schizophrenic patients, *Biol. Psychiat.*, 22 (1987) 453–462.
 - 32 Goldman, M.B., Luchins, D.J. and Robertson, G.L., Mechanism of altered water metabolism in psychotic patients with polydipsia and hyponatremia, *N. Engl. J. Med.*, 318 (1988) 397–403.
 - 33 Emsley R., Potgieter, A., Takjaard, F., Joubert, G. and Gledhill, R., Water excretion and plasma vasopressin in psychiatric disorders, *Am. J. Psychiat.*, 146 (1989) 250–253.
 - 34 Legros, J.J., Gazotti, C., Carvelli, T., Franchimont, P., Timsit-Berthier, M., Von Frenckell, R. and Anseau, M., Apomorphine stimulation of vasopressin- and oxytocin-neurophysics. Evidence for increased oxytocinergic and decreased vasopressinergic function in schizophrenics, *Psychoneuroendocrinology*, 17 (1992) 611–617.
 - 35 Gold, P.W., Kaye, W., Robertson, G.L. and Ebert, M., Abnormalities in plasma and cerebrospinal fluid arginine vasopressin in patients with anorexia nervosa, *N. Engl. J. Med.*, 308 (1983) 1117–1123.
 - 36 Demitrack, M.A. and Gold, P.W., Oxytocin: neurobiologic considerations and their implications for affective illness, *Progr. Neurol. Psychopharmacol.*, 12 (1988) S23–S51.
 - 37 Demitrack, M.A., Lesem, M.D., Listwak, S.J., Brandt, H.A., Jimerson, D.C. and Gold, P.W., Cerebrospinal fluid oxytocin in anorexia nervosa and bulimia nervosa: clinical and pathophysiological considerations, *Am. J. Psychiat.*, 147 (1990) 882–886.
 - 38 Altemus, M., Pigott, T., Kalogeras, K.T., Demitrack, M., Dubbert, B., Murphy, D.L. and Gold, P.W., Abnormalities in the regulation of vasopressin and corticotropin releasing factor secretion in obsessive-compulsive disorder, *Arch. Gen. Psychiat.*, 49 (1992a) 9–20.

- 39 Demitrack, M.A., Kalogeras, K.T., Altemus, M., Pigott, T.A., Listwak, S.J. and Gold, P., Plasma and cerebrospinal fluid measures of arginine vasopressin secretion in patients with bulimia nervosa and in healthy subjects, *J. Clin. Endocr. Metab.*, 74 (1992) 1277-1283.
- 40 Swedo, S.E., Leonard, H.L., Kruesi, M.J.P., Rettew, D.C., Listwak, S.J., Berrettini, W., Stipetic, M., Hamburger, S., Gold, P.W., Potter, W.Z. and Rapoport, J.L., Cerebrospinal fluid neurochemistry in Children and adolescents with obsessive-compulsive disorder, *Arch. Gen. Psychiat.*, 49 (1992) 29-36.
- 41 Legros, J.J. and Franchimont, P., Human neurophysin blood level under normal, experimental and pathological conditions, *Clin. Endocrinol.*, 1 (1972) 99-113.
- 42 Legros, J.J., Deconinck, I., Willems, D., Roth, B., Pelc, O., Brauman, J. and Verbanck, M., Increase of neurophysin II serum levels in chronic alcoholic patients: relationship with alcohol consumption and alcoholism blood markers during withdrawal therapy, *J. Clin. Endocr. Metab.*, 56 (1983) 871-875.
- 43 Altemus, M., Brady, L., Cizza, G., Kennedy, B. and Gold, P.W., Unique effects of fluoxetine on AVP synthesis and secretion (Abstract). In *The neurohypophyse: a window to brain function*, Dartmouth, July 16-20, 1992.