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Cerebrospinal Fluid Neurophysins in Affective Illness and in Schizophrenia

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Summary. We studied the concentration of neurophysin I (hNPI) and II (hNPII), the hypothalamo-pituitary carriers of vasopressin and oxytocin, in CSF of depressed and schizophrenic patients and age matched controls. Mean hNPI values were lower and mean hNPII values greater in schizophrenics than in controls. Lower hNPI values were observed in unipolar patients than in controls. In bipolar patients however, higher hNPI values were present. Significantly higher hNPII values were observed in bipolar patients than in controls; no difference was present between unipolars and controls. A positive correlation was observed with age in controls and bipolars for hNPII. These data emphasize the interest of studying the neurohypophysal function in affective illness and in schizophrenia.

Key words: Neurophysins – Vasopressin – Oxytocin – Schizophrenia – Depressive disorders – CSF

Introduction

Until recently biological correlates of cognitive dysfunction have been poorly studied in depressive disorders and in schizophrenia. Memory, attention and learning disturbances have been reported in affective illness (Calne et al. 1977) and schizophrenia (Abrams et al. 1981). There is growing evidence that the neurohypophysal hormones, vasopressin (AVP) and oxytocin (OXY) have important behavioral influences within the CNS through their action on memory (AVP improving and OXY decreasing memory function) in animals and in humans (De Wied 1976; Legros et al. 1978; Kovacks et al. 1979; Ferrier et al. 1980; Weingartner et al. 1981). Others failed to observe any reliable behavioral effect with AVP in man (Blake et al. 1978; Jenkins et al. 1979) or in rodents (Hostetter et al. 1980; Sahgel et al. 1982). Ettenberg et al. (1983) also suggested that in rat the memory enhancing properties of peripherally administered AVP may partially depend on its aversive and consequently arousing actions. Vasopressin analogues have been further reported to improve mood in some depressed patients (Gold et al. 1981). Neurophysins are the hypothalamo-hypophysal carriers of AVP and OXY; in the human, neurophysin I (hNPI) is associated with AVP and neurophysin II (hNPII) with OXY (Legros and Louis 1973), both neurophysins being released simultaneously with the active peptides (Pullan et al. 1979). Although they correlate weakly with AVP and OXY in basal CSF samples, neurophysins might reflect long term oxytocinergic and vasopressinergic function as they are more stable than active peptides in the CSF and are released simultaneously at the synaptic level (Robinson and Jones 1982).

In a preliminary study, we described higher hNPII CSF concentrations in bipolar versus unipolar depressed patients (Legros et al. 1983). In the present investigation we performed radioimmunoassay determinations of hNPI and hNPII in CSF samples of affectively ill and schizophernic patients, in comparison to age matched nonpsychiatrical neurological controls.

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Material and Methods

We investigated 28 patients admitted to the metabolic ward of the psychiatric department of Erasme Hospital, University of Brussels. Patients were diagnosed according to the Research Diagnostic Criteria (Spitzer et al. 1978) as major depressives (8 unipolars: 5 males and 3 females aged 37–59 years; mean $\pm$SD = 47.2 ± 11.7; 8 bipolars: 4 males and 4 females aged 32–60 years; mean 43.3 ± 9.6) and 12 schizophrenics (9 males and 3 females, aged 29–61 years; mean 46.8 ± 11.2). Controls were 12 age matched nondepressed neurological controls (8 with hydrocephalus 1 with acoustic neurinoma and 3 with cerebral atrophy) (8 males and 4 females aged 33–65 years, mean 46.8 ± 11.2). All depressed patients were studied after a drug washout period of at least 8 days (15 days for the schizophrenics). CSF samples were collected between 8 and 9 a.m. after an overnight fast and kept frozen at $-20°C$ until the time of assay.

Assay Method

The neurophysins hNPI and hNPII were measured by a radioimmunoassay method as described previously (Pullan et al. 1979). Cross reaction of hNPI in the hNPII system was $<1\%$ and of hNPII in the hNPI system $<2\%$.

Statistics

Pearson's product-moment correlation was used to describe the relations between two variables. Comparison of the correlation coefficients was done using z transformations and χ^2 tests (Snedecor and Cochran 1967). One-way analysis of variance and Student's *t*-test were performed to assess differences between groups. The analysis of contrasts used Bonferroni's t statistics (Winer 1972). Computation on the hNPI data was done after log transformation which normalized the distribution of this parameter.

Results

A. Schizophrenia (Table 1)

A negative nonsignificant correlation ($r = -0.41$, P = NS) with age was observed in schizophrenic patients for hNPI, indicating that the amount of hNPI diminished as age increased. An inverse trend was observed for controls showing an age related increase ($r = 0.46$, P = NS). Mean values for schizophrenics (0.23 ± 0.11 ng/ml) were signigicantly lower than in controls (0.34 ± 0.19 ng/ml) ($t = 1.88$, $P < 0.05$). No correlation was observed between age and hNPII in schizophrenics ($r = 0.001$, P = NS) whereas a significant correlation with age was observed in controls ($r = 0.64$, $P < 0.05$). In schizophrenics hNPII was greater (4.5 ± 1.2 ng/ml) when compared to age matched controls (3.05 ± 1.4 ng/ml) ($t = 2.82$, $P < 0.01$).

B. Depressed patients (Table 1, Figs. 1 and 2)

Values of hNPI for unipolars, bipolars and controls, in relation to age are illustrated in Fig. 1. A positive nonsignificant correlation was observed between age and hNPI for controls ($r = 0.46$, P = NS) unipolars ($r = 0.56$, P = NS) and bipolar ($r = 0.46$, P = NS). These three correlation coefficients are not significantly different ($\chi^2 = 0.26$, P = NS). A one-way analysis of variance on log transformed data showed a significant difference between the three groups ($F_{2.25} = 13.75$, $P < 0.001$). Significantly lower hNPI values were observed in unipolars when compared to controls ($t = 13.0$, $P < 0.001$) as well as in controls when compared to bipolars ($t = 26.25$, $P < 0.001$). The values of hNPII for unipolar and bipolar patients and controls are shown in Fig. 2. A significant correlation was observed between age and hNPII for controls ($r = 0.64$, $P < 0.05$) and bipolars ($r = 0.75$, $P < 0.001$) but not for unipolars ($r = 0.21$, P = NS) These three correlation coefficients were not significantly different ($\chi^2 = 1.57$, P = NS). A significant difference was however observed between the three groups ($F_{2.25} = 33.9$, $P < 0.001$). Analysis of contrasts was performed to compare unipolar and bipolar patients to controls. No significant difference was observed between unipolars and controls ($t = 0.37$) whereas bipolar patients did had significantly higher hNPII levels than their age matched controls ($t = 3.19$, $P < 0.005$).

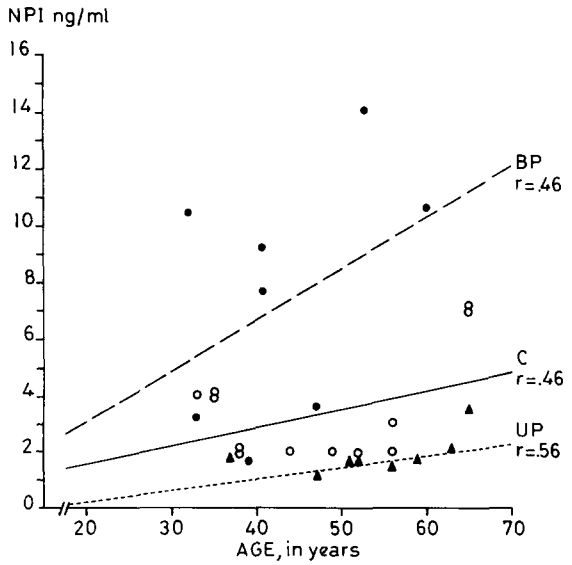

Fig. 1. hNPI values in unipolars, bipolars and controls in relationship with age. (●) bipolars; (○) controls (▲) unipolars

Table 1. CSF hNPI and hNPII values in patients and controls

	Schizophrenia ($n = 12$)	Unipolar depression ($n = 8$)	Bipolar depression ($n = 8$)	Controls ($n = 12$)
hNPI (ng/ml) ($\bar{x} \pm SD$)	0.23 ± 0.11	0.19 ± 0.07	0.75 ± 0.43	0.34 ± 0.19
hNPII (ng/ml) ($\bar{x} \pm SD$)	4.5 ± 1.2	3.7 ± 0.53	7.2 ± 1.5	3.05 ± 1.4

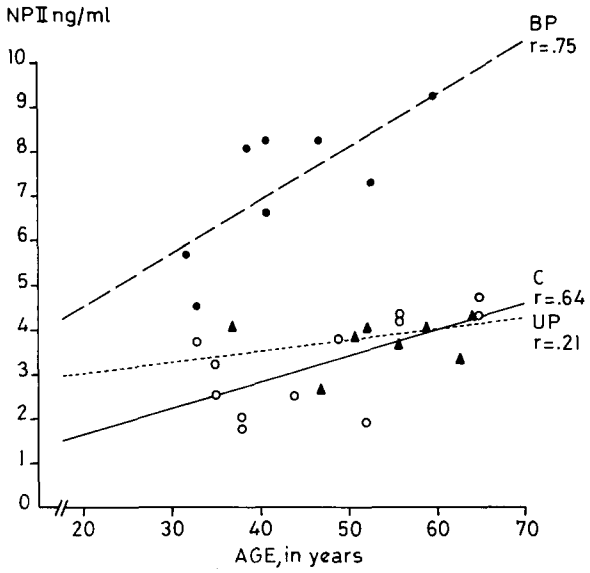

Fig. 2. hNPII values in unipolars, bipolars and controls in relationship with age. (●) bipolars; (○) controls; (▲) unipolars

Comment

Our report of differences in CSF levels of hNPI and hNPII in patients with affective illness and schizophrenia adds to previous observations of abnormal levels of neurohypophyseal hormones in the CSF of depressed patients (Gold et al. 1981; Legros et al. 1983). We have shown a significant positive correlation between age and CSF hNPII in controls and bipolars but not for unipolars and schizophrenics. Furthermore, using carefully age controlled samples, we have shown bipolar patients to have higher CSF hNPI and hNPII values when compared to both unipolars and controls, while unipolar

patients showed lower CSF values of hNPI in comparison to normal controls. Schizophrenics showed lower hNPI and higher hNPII values than their controls. Gold et al. (1981) found that nonpsychotically depressed patients had significantly lower levels of CSF AVP when compared to manic patients while two psychotic depressed patients had extremely elevated levels of CSF AVP. Gjerris et al. (1980) found no difference for CSF AVP between depressed patients (as a group) and normal controls. In addition, no significant difference was found between euthymic bipolar patients and normal volunteers when determinations of the affinity constant (K_d) and number of binding sites (B_{max}) were considered (Berettini et al. 1982). In a case report, Whalley et al. (1982) mentioned a high hNPII plasma level in a manic female patient. Until now no observations have been reported on neurohypophysal hormones or neurophysins in CSF of schizophrenic patients. Raskind et al. (1978) noted elevated baseline plasma AVP levels in acute psychiatric patients. It is further well recognized that patients suffering from major depressive illness show significant disturbances in cognitive function as well as memory processes (Stömgren 1977). The effect of AVP in reinforcing memory suggested to Gold et al. (1978) that AVP may play a role in affective disorders. Oxytocin also presents behavioral and cognitive correlates which are poorly understood but could have opposite effects to those of AVP in man (Bohus et al. 1978; Ferrier et al. 1980). A diurnal variation of CSF AVP and OXY but not hNPII has been demonstrated in man (Reppert et al. 1981; Amico et al. 1983). Our data studying parent compounds to AVP and OXY are partly at variance with those of Gold et al. (1981) and those of Gjerris et al. (1980). These differences could be attributed to heterogeneity in patient sampling as well as age differences (which were carefully controlled in our study). In the study of Gold et al. (1983), there was however no difference between CSF AVP values in normal males and females nor was there any correlation with age. Interpretation of our results on this point remains largely speculative. Putative relationships have been described between AVP, OXY and monoamine metabolism in the CNS; AVP and OXY could act as neuromodulators, modifying noradrenergic (Bondareff et al. 1981) and dopaminergic systems (Courtney and Raskind 1983). Dopamine further appears to be extensively involved in the control of OXY secretion (Clarke et al. 1979). Another finding of interest is the observation that AVP is an important constituent of the suprachiasmatic nucleus, the putative site of the endogenous circadian biological clock (Stetson and Watson-Whitmyre 1976) suggesting a possible role for this substance in regulating abnormal rhythms in recurrent affective disorders. The psychophysiological significance of the abnormal AVP and OXY peptidergic activity as well as neurophysin disturbances remains to be determined keeping in mind that neurophysins are dose related to AVP and OXY in the physiological process of release at the synaptic level. Further studies should also compare AVP, OXY, neurophysins and other cerebrospinal components in longitudinal investigations of mentally ill patients.

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