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CSF Neuropeptides in Euthymic Bipolar Patients and Controls

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Levels of vasopressin, somatostatin, neurotensin, vasoactive intestinal peptide, corticotrophin-releasing factor and adrenocorticotrophin in CSF were determined in lithium-treated and unmedicated euthymic bipolar patients and controls, in a search for a trait marker in affective disorder. No group differences in levels of these peptides were found. Highly significant positive correlations were found among these peptides (with the exception of neurotensin), suggesting that their presence in CSF is functionally significant, as opposed to the result of random diffusion from the interstitial space of the brain.

Bipolar affective (manic-depressive) illness is a cyclic mood disorder of unknown aetiology, in which genetic factors play an important role in pathogenesis (for review, see Berrettini *et al*, 1984). Manic-depressives characteristically have cyclic episodes of markedly sad or euphoric mood, associated with other symptoms, but are well between episodes of mood disturbance. Theoretically, the underlying genetic factors, which increase one's vulnerability to develop affective illness, should be detectable independently of mood state. The study of well-state (euthymic) patients avoids the difficulty of separating state-related abnormalities (associated with acutely ill manic or depressed patients) from trait abnormalities (which may be genetic vulnerability markers). A strategy of studying euthymic patients has been delineated previously (Rieder & Gershon, 1978).

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis has been observed in actively ill manic-depressive patients (Sachar *et al*, 1973; Greden *et al*, 1983). Both the abnormal dexamethasone suppression test results (Greden *et al*, 1983) and the hypercortisolaemia (Sachar *et al*, 1973), seen among actively ill manic-depressive patients, are thought to disappear after remission of the depression or mania (Greden *et al*, 1983). Abnormalities of pituitary adrenocorticotrophin (ACTH) response to corticotrophin-releasing factor (CRF) may accompany the dysregulation of cortisol in these patients (Gold *et al*, 1984). These observations led to the conclusion that there is some state-dependent dysfunction of the HPA axis in some patients with affective illness.

The HPA axis is regulated in part by hypothalamic neurons which release CRF, ACTH, vasopressin (AVP), somatostatin (SRIF), vasoactive intestinal peptide (VIP) or other neuropeptide transmitters and/or hormones (Axelrod & Reisine, 1984). For these five peptides, much evidence suggests that brain is the source of the CSF levels, which are regulated independently of the plasma levels (Wood, 1982; Post *et al*, 1982). In the light of the evidence that the HPA axis is regulated abnormally in the actively ill manic-depressive patient, we reasoned that evidence of a state-independent (genetic) abnormality might be found by examination of some HPA-axis-related peptides in CSF. While plasma evidence of HPA axis dysregulation may not be evident in the euthymic patients, CSF levels of HPA-axis-related peptides may be abnormal, representing a biological genetic vulnerability marker. Abnormalities in CSF levels of HPA-axis-related peptides have been reported among acutely ill patients. Significantly lower CSF levels of CRF (Nemeroff *et al*, 1984), VIP (Gjerris *et al*, 1984), AVP (Gold *et al*, in press; Gjerris *et al*, 1985) and SRIF (Gerner & Yamada, 1982; Rubinow *et al*, 1983) were found among actively depressed subjects, suggesting that CSF levels of these peptides should be evaluated as possible trait markers for vulnerability to affective illness.

Recently, it has been reported that VIP is contained and secreted with acetylcholine from some cholinergic neurons (Lundberg *et al*, 1980). VIP may be released into CSF after cholinergic stimuli (Kaji *et al*, 1983). Neurotensin (NT) has been reported to stimulate cholinergic function in guinea-pig enteric neurons (Yau *et al*, 1983); this stimulation is thought to be secondary to increased presynaptic release of acetylcholine and is blocked by SRIF. These observations (that NT and VIP may be modulators of cholinergic function) prompted us to measure CSF levels of these neuropeptides in euthymic bipolar patients to determine whether the reported cholinergic supersensitivity in affective disorder (Sitaram *et al*, 1980; Nadi *et al*, 1984) is associated with abnormalities in the CSF levels of peptidergic modulators of cholinergic function.

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Method

Subjects

All individuals participating in this study were out-patients at the National Institute of Mental Health, Bethesda, Maryland. All provided informed consent. The bipolar patients and normal subjects (as well as the clinical details of the lumbar puncture) have been previously described (Berrettini *et al*, 1985*b*). Briefly, euthymic bipolar patients (who were treated solely with lithium for at least 1 month prior to study) and normal volunteers underwent a lumbar puncture as an out-patient procedure after 2 h of bedrest. In addition, 15 of the lithium-treated patients discontinued lithium for at least 2 weeks to provide a second CSF sample in the unmedicated state. Thus, for these patients, paired CSF samples, on and off lithium, were obtained.

Peptide radioimmunoassay

CSF concentrations of immunoreactive human CRF were measured as previously described (Roy *et al*, in press), except that unextracted CSF was used.

VIP radioimmunoassay kits were obtained from Immunoclear Corporation (Stillwater, Minnesota). VIP was determined in duplicate 0.450-ml aliquots of CSF. Recovery of added standard was 90%. Final volume was 0.650 ml. The limit of detection was 4 pg/tube.

A volume of 0.200 ml of unextracted CSF was used to make each AVP determination, as previously described (Zerbe *et al*, 1982).

SRIF was determined on 1.00 ml of lyophilised CSF, as described previously (Patel & Reichlin, 1979; Rubinow *et al*, 1983), and levels were corrected by indexing to chloride concentration.

NT radioimmunoassay kits were purchased from Immunoclear Corporation (Stillwater, Minnesota). NT was determined in duplicate 0.400-ml samples of CSF collected from a 1-ml fraction to which 0.020 ml of concentrated perchloric acid was added. Samples were adjusted to neutral pH with 10-M NaOH before assay. Recovery of added standard was 90%, and the limit of detection was 35 pg/ml.

For the ACTH radioimmunoassay, Sep-Pak cartridges were washed with 10 ml of methanol followed by 10 ml of distilled water. Aliquots of 0.6 ml of CSF were applied to the cartridges which were then washed with 10 ml of distilled water. Immunoreactive ACTH was eluted with a mixture of TEAF buffer (1% formic acid, pH 3.2 with addition of triethylamine) and acetonitrile (4 : 6, v/v). The eluent was lyophilised and the residue taken up in assay buffer (0.63-M Na_2HPO_4 and 0.13-M Na_2EDTA, pH 7.4), containing 0.02% Na_2NO_2, 0.1% triton X-100 and 250 KIU of aprotinin/ml. The recovery of ACTH by this procedure is 85–95%. The antibody was obtained from IgG Corporation (Nashville, Tennessee, ACTH-1). Both standard and trace were $ACTH_{1-39}$. ACTH labelled with ^{125}I was prepared using the chloramine-T method (Greenwood *et al*, 1963). The specific activity was approximately 450 Ci/g. The methods of the radioimmunassay have been previously described (Orth, 1979). The detection limit is 3–5 pg/ml.

Analysis of data

A general linear models procedure was used to assess the effects of age, height, weight and sex on CSF peptide levels. ACTH levels in CSF were corrected for a sex effect. Males ($n=33$, $\bar{x}=22.2\pm5.7$ pg/ml) had significantly higher ($P<0.005$) values than did females ($n=34$, $\bar{x}=18.4\pm4.7$ pg/ml). No other peptide was altered significantly by age, sex, height or weight.

Group *t*-tests were performed to compare euthymic bipolar patients and controls. Paired *t*-tests were used to study the effect of lithium, using those patients from whom paired CSF samples were obtained. Pearson correlation coefficients were calculated for the three separate groups of data (and on all individuals combined) to examine the relationships between these CSF neuropeptides. Z transformation of the correlation coefficients was done to evaluate possible significant differences in correlation coefficients between groups.

All ACTH, CRF, VIP and NT levels were measured in one assay. The coefficient of variation within an assay was less than 15% for all assays. SRIF and AVP levels were measured in two separate assays.

Results

The levels of the six neuropeptides are shown in Table I. No group differences (*t*-tests) or effects of lithium (paired *t*-test) were found, except a trend ($P=0.05$) for CSF VIP to be lower during lithium treatment.

As shown in Table II, a number of significant positive correlations were found among AVP, ACTH, CRF, SRIF and VIP. The correlation coefficients were similar for the three subject groups, with the exception of the correlation coefficient for CRF and VIP (see Table II). The strongly positive correlation between CRF and VIP in controls was not present among the bipolar patients, suggesting that the patients may have had a dysfunction of whatever regulatory mechanisms determine the levels of these two peptides in CSF. No significant correlations (defined as $P\leqslant0.05$) were found between CSF NT levels and any other peptide (data not shown).

Discussion

The most interesting finding in this study is the significant correlations among CSF neuropeptides. This deserves a comment on the origins of CSF neuropeptides.

Some hypothalamic neurons (that contain SRIF) have nerve endings at the wall of the third ventricle (Pollay M., 1979; Knigge *et al*, 1980). Several investigators have hypothesised that neuropeptides may be released into CSF from such periventricular neurons, to be transported to distant CNS sites of action (Pollay, 1979; Knigge *et al*, 1980; Post *et al*, 1982). As indicated in the review by Jackson (1981), peptides may gain access to CSF via diffusion from CNS interstitial fluid, from the periphery at sites

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TABLE I
CSF neuropeptide levels[1] in euthymic bipolar patients and controls

Peptide	*Controls*	*Lithium-treated bipolar patients*	*Unmedicated bipolar patients*
Neurotensin	58.6±13 (25)	65.2±6.8 (19)	56.0±13 (11)
Vasopressin	4.4±1.0 (30)	4.6±1.0 (25)	4.6±1.7 (14)
VIP	18.0±7.4 (32)	15.7±6.0 (21)	20.0±6.5 (13)
ACTH	22.6±5.8 (29)	21.4±5.8 (25)	22.3±5.4 (13)
SRIF	36.3±16.4 (31)	32.3±15.6 (27)	39.8±15.1 (16)
CRF	33.0±11.9 (31)	29.8±12.9 (26)	31.8±13.7 (15)

1. Values are mean (pg/ml)±standard deviation. The number of observations is given in parentheses.

where the blood–brain barrier does not exist or by transport from the tanycyte median eminence, as well as by direct release from neurons into CSF. However, Wood's (1982) review states that peripheral sources of CSF peptides are unlikely. Thus, it seems more probable that peptides reach CSF either through random diffusion or direct neuronal release.

Do the observed significant correlations favour direct release or random diffusions as the point of entry of neuropeptides into CSF? These correlations do not provide strong evidence favouring either hypothesis. However, these significant correlations are more congruous with the hypothesis that the concentrations of CRF, SRIF, AVP, VIP and ACTH in CSF are not the result of random simple diffusion from the interstitial space of the neurons of origin, because differences in number and activity of the various peptidergic neurons and their distance from the ventricular space would affect the process of random diffusion, and one would be less likely to observe significant correlations between numerous peptides (Berrettini *et al*, 1985*a*).

One possible explanation for the correlations between SRIF, AVP, VIP, CRF and ACTH in CSF may be that they are released from neurons into CSF in response to a stimulus. From their sites of release, they may be transported to distant CNS sites where each of them may mediate some aspect of the response to that stimulus. What evidence exists for stimulus-induced changes in these CSF peptides? Koob & Britton (1984) have shown that random inescapable footshock causes a doubling in rat CSF CRF, a response which is attenuated by diazepam. CSF, ACTH and β-endorphin levels increase several-fold following periaqueductal grey (but not internal capsule) self-stimulation for analgesia (Hosobuchi & Bloom, 1983). These studies suggest that certain stimuli can increase CSF levels of these peptides. Shared mechanisms of release into CSF may account for these correlations.

Other possible explanations for these correlations include shared catabolism by peptidases in CSF and shared transport out of CSF, but no evidence exists to support either of these possibilities.

Rubinow *et al* (1985) have reported that carbamazepine, which is an effective acute and prophylactic treatment for manic-depressive illness (Okuma *et al*, 1973; Post *et al*, 1983), decreases CSF SRIF levels. Because carbamazepine seems to have a therapeutic effect in the treatment of manic-depressive illness which is similar to that of lithium, we hypothesised that lithium might have a similar effect on CSF SRIF. This was clearly not the case in our data. Our results support those of Rubinow *et al* (1983), who reported that recovered patients did not show significantly decreased CSF SRIF levels, as was found among the acutely depressed patients. Thus, the lower CSF SRIF level is a state-dependent marker for depression.

Given that lithium antagonises the effects of AVP (Forrest, 1979) at a post-receptor site in the kidney, we hypothesised that lithium might cause increased presynaptic release of AVP in the CNS, yielding a higher CSF AVP level. There was no effect of lithium on CSF AVP, but we cannot exclude the possibility that lithium may alter CNS AVP activity without affecting CSF AVP levels.

Recent data show that CSF ACTH and CSF CRF levels are not abnormal in acutely depressed patients (Davis *et al*, 1984; Roy *et al*, in press), although Nemeroff *et al* (1984) found higher CSF CRF in acutely depressed patients. Thus, although evidence for abnormal pituitary ACTH regulation in acutely depressed patients has been reported by Gold *et al* (1984), CRF or ACTH levels in CSF do not appear to be affected. These observations are consistent with the hypothesis that CSF levels of these HPA-axis-related peptides are regulated independently of HPA axis function.

CSF levels of VIP and NT do not provide evidence for a trait disturbance of cholinergic function in affective illness. The fact that the bipolar group does not show a significant positive correlation between

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TABLE II
CSF neuropeptide correlations[1]

		ACTH	*VIP*	*AVP*	*SRIF*
Controls					
CRF	*r*	0.62	0.63	0.24	0.28
	P	0.0005	0.0002	0.19	0.14
	n	28	30	30	29
ACTH	*r*		0.56	0.39	0.37
	P		0.0024	0.050	0.060
	n		27	26	27
VIP	*r*			0.22	0.50
	P			0.24	0.0057
	n			29	29
AVP	*r*				0.34
	P				0.07
	n				28
Lithium-treated euthymic bipolar patients					
CRF	*r*	0.41	0.075**	0.42	0.17
	P	0.045	0.75	0.040	0.41
	n	24	20	24	26
ACTH	*r*		0.42	0.57	0.028
	P		0.064	0.0038	0.89
	n		20	24	25
VIP	*r*			0.58	0.27
	P			0.0071	0.24
	n			*20*	*21*
AVP	*r*				0.11
	P				0.60
	n				25
Unmedicated euthymic bipolar patients					
CRF	*r*	0.38	0.18*	−0.056	0.58
	P	0.21	0.58	0.86	0.023
	n	12	12	12	12
ACTH	*r*	0.67	0.22	0.64	
	P		0.024	0.51	0.019
	n		11	11	13
VIP	*r*			0.58	0.36
	P			0.062	0.23
	n			11	12
	r				0.13
	P				0.63
	n				12

1. *r* = correlation coefficient; *P* = probability; *n* = number of observations. Significant differences from control correlation: **P*<0.05; ***P*<0.01.

CRF and VIP may reflect a disturbance of some regulatory factor that controls the release of CRF and VIP into CSF. Whether this is related to a trait disturbance of central cholinergic neurons in affective disorder must await further study. This connection seems possible in light of recent evidence that cholinergic agonists increase CSF VIP (Kaji *et al*, 1983).

Gjerris *et al* (1984) reported decreased CSF VIP levels in atypically depressed patients. They rated their patients atypical, using the Newcastle Rating Scale. While our patients were not rated with this scale, we believe that they are not atypical. Thus, our results in a euthymic population may be in agreement with those of Gjerris *et al* (1984), who found normal CSF VIP levels in their endogenously depressed patients.

The trend for lithium to reduce CSF VIP levels must be interpreted with caution, as it is of borderline significance. We have reported elsewhere similar results in plasma and an effect of lithium to increase the affinity of a lymphocyte VIP receptor for its ligand (Berrettini *et al*, 1985*b*). Whether this effect of lithium on VIP function is related to the efficacy of that ion in affective illness must await further study. The levels reported here for CSF VIP are somewhat lower than previously reported by us (Berrettini *et al*, 1985*b*). This may represent slight changes in antibody specificity. (The antibody is from a commercial source.)

That CSF NT levels are not correlated with those of any other CSF peptide suggests that CSF NT levels are relatively independent of whatever factors generate the correlations between the CSF levels of CRF, ACTH, VIP, SRIF and AVP. This statement is limited by the difficulty in drawing conclusions about the absence of a significant correlation.

In summary, we find no evidence in bipolar affective illness for a trait disturbance of CSF, SRIF, ACTH, CRF, AVP, VIP or NT. It is unknown to what extent CSF levels of these neuropeptides reflect CNS activity of the peptidergic neurons in question. CSF levels of ACTH, CRF, SRIF, AVP and VIP are positively correlated with one another, suggesting that they share a common regulatory factor which determines CSF levels. Lastly, some evidence has been obtained suggesting that the functional relationship of CRF and VIP in CSF is disturbed in euthymic bipolar patients.

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