
CSF Monoamine Metabolites and Somatostatin in Alzheimer's Disease and Major Depression

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Decreased cerebrospinal fluid (CSF), somatostatinlike immunoreactivity (SLI) and alterations in the CSF monoamine metabolites 3-methoxy-4-hydroxyphenylethylglycol (MHPG), 5-hydroxyindoleacetic acid (5-HIAA), and homovanillic acid (HVA) have been reported in patients with probable Alzheimer's disease (AD) and in patients with major depression. In this study, we found CSF SLI to be significantly lower in a large group of AD patients (n = 60) and in a group of age-matched patients with major depression (n = 18) as compared with normal controls (n = 12). Mean CSF, MHPG, 5-HIAA, and HVA levels were not significantly different among diagnostic groups. Within a group of "depressed" AD patients, CSF levels of 5-HIAA showed a significant positive correlation (p = 0.03) with CSF SLI; a similar relationship was found within the group of patients with major depression. Further exploration of the relationship between the somatostatin and serotonin systems may provide clues as to how neuropeptides interact with monoamine neurotransmitters and what role they have in depression.

Introduction

Decreased somatostatinlike immunoreactivity (SLI) has been a consistent finding in many studies of the cerebrospinal fluid (CSF) and brains of patients with Alzheimer's disease (AD) (Davies et al 1980; Francis et al 1984; Sunderland et al 1987; Davis et al 1988), as well as in the CSF of patients with major depression (Rubinow et al 1983; Bissette et al 1986). In normal brain the highest concentrations of the tetradecapeptide, somatostatin, exist in the hypothalamus and limbic system, including the amygdala and hippocampus, those areas of the brain thought to be especially involved in affective and cognitive functions. In the central nervous system (CNS), somatostatin functions as a neuromodulator, if not a neurotransmitter (Rubinow et al 1983). CSF SLI is thought to reflect brain SLI as reviewed by Rubinow (1986).

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Many interactions between somatostatin and the monoamine neurotransmitters have been documented (see Rubinow 1986 for review). While most discussions of AD focus on the cholinergic system deficits (Davies and Maloney 1976; Whitehouse et al 1982), alterations have been reported in other neurotransmitter systems (Gottfries 1985), especially the noradrenergic (Bondareff et al 1982; Zweig et al 1988) and serotonergic systems (Mann and Yates 1982; Cross et al 1984; Crow et al 1984; Yamamoto and Hirano 1985; Baker and Reynolds 1989; Sparks 1989); the data have been less consistent for the dopaminergic system (Soizinen et al 1981; Gottfries 1985). Alterations in these monoamine neurotransmitter systems have also been documented in the brains and CSF of patients with major depression (Asberg et al 1984; Roy et al 1985; Mann et al 1986; Yates et al 1990), and the monoaminergic theory remains one of the prime etiological theories of depression (Rothschild 1988).

Depressed mood is increasingly recognized to be an important symptom in AD patients; most studies estimate that from 17% to 50% of these patients have significant depression at some time during the course of the disease (Reding et al 1985; Reifler et al 1986). AD patients with major depression have been found to have significantly more degeneration in the locus ceruleus and substantia nigra than nondepressed AD patients (Zubenko and Moosy 1988). Similar findings in the locus ceruleus were found in another study (Zweig et al 1988), which also found that AD patients with major depression had significantly fewer neurons in the central superior (raphe) nucleus, and a trend for such a loss in the dorsal raphe nucleus. Zubenko and coworkers (1990) recently reported that demented patients with major depression had a ten-fold decrease of cortical norepinephrine, an increase in dopamine levels in entorhinal cortex, and a decrease in serotonin that approached significance in frontal cortex.

Studies in animals have shown that somatostatin affects many behavioral functions, including sleep, appetite, circadian rhythm, motor activity, and pain sensitivity (functions that are commonly disrupted in depression) (Reichlin 1982; Rubinow et al 1983). Because of the overlapping cognitive and behavioral symptoms and abnormal biological measures in AD and major depression and earlier work showing alterations in CSF SLI and monoamine levels in both AD and elderly depression (Sunderland et al 1987; Davis et al 1988), we sought to determine the relationship between CSF SLI, CSF monoamines, measures of depression, and measures of dementia severity in these populations.

Methods

Subjects

Sixty patients with AD (mean \pm SD age = 66.2 \pm 8.7 years; 32 women, 28 men), 18 patients with major depression (64.6 \pm 9.9 years; 12 women, 6 men), and 12 normal controls (65.8 \pm 10.7 years; 4 women and 8 men) were included in the study. All patients and controls were studied as inpatients at the National Institute of Mental Health (NIMH). Primary degenerative dementia of the Alzheimer type and major depression were diagnosed according to DSM-III-R criteria (American Psychiatric Association 1987). Some AD patients had significant depressive symptoms and may have had a prior history of depression. Symptoms of depression in these patients were considered a secondary phenomenon, with dementia being the primary diagnosis. Patients with serious medical problems were excluded from the study. Normal controls were screened to exclude those with a personal or family history of any significant medical, cognitive, or psychiatric

disorder. Normal controls were recruited from the community and were paid for their participation. All subjects were free of centrally active drugs for at least 3 weeks before the study. All subjects gave written informed consent. For AD patients, a relative also signed the consent form.

Rating Scales

Patients with AD were evaluated with the Dementia Mood Assessment Scale (DMAS) (Sunderland et al 1988a, 1988b), a 24-item scale in which the first 17 items are designed to measure depression in dementia (DMAS-17) and the last 7 items to measure cognitive and functional impairment. The DMAS-17 has some questions that are similar to those on the Hamilton Depression Scale (Hamilton 1960), but the two scales are not equivalent (Sunderland et al 1988a). AD patients were also evaluated with the modified Bunney-Hamburg Global Behavioral Rating Scales (Bunney and Hamburg 1963; Sunderland et al 1988a) to rate different aspects of behavior, mood, and impairment, with scores ranging from 0 (no impairment) to 13-15 (very severe). Patients diagnosed with major depression were rated with the Hamilton Depression Scale as well as the Bunney-Hamburg Global Behavioral Rating Scales. Dementia severity was rated using the Global Deterioration Scale (GDS) (Reisberg et al 1982) and the Clinical Dementia Rating Scale (CDR) (Hughes et al 1982).

CSF Measures

Lumbar punctures (LPs) were done between 8:00-9:00 AM on subjects in the lateral decubitus position, after an overnight fast, and after at least 3 days on a low monoamine diet. Subjects were on bed-rest prior to the LP, except for voiding. The 26th ml of collected CSF was immediately frozen without preservatives on dry ice and then stored at -70°C for later measurement of SLI. The 10th through 15th mls of each CSF sample were frozen at -70°C and used to measure the neurotransmitter metabolites 3-methoxy-4-hydroxyphenylethylglycol (MHPG), 5-hydroxyindoleacetic acid (5-HIAA), and homovanillic acid (HVA) as described elsewhere (Scheinin et al 1983). All monoamines were assayed in the Laboratory of Clinical Science, NIMH. The SLI radioimmunoassay was done by the Section on Behavioral Endocrinology, NIMH and used ^{125}I -tyrosine-1-somatostatin, rabbit antisomatostatin antiserum (kindly provided by Dr. Seymour Reichlin, Tufts University), synthetic cyclic somatostatin standards, and charcoal separation, and was performed using procedures described elsewhere (Patel et al 1977). Assay sensitivity is 1 pg/tube, with an ED_{50} of 8.6 pg/tube. The antisomatostatin antibody used is directed toward the midportion of the tetradecapeptide, so it recognizes N-terminal extensions of somatostatin-14, such as somatostatin-28. Samples from AD, depressed, and normal subjects were run in the same assays. The intraassay coefficient of variation was about 6%; the interassay coefficient of variation for this assay is 12%-15%.

Data Analysis

CSF SLI and monoamine levels were compared between diagnostic groups by one-way ANOVA and post hoc Bonferroni *t*-tests. Pearson's product-moment correlations were used to explore potential relationships among measures of mood, dementia severity, CSF

Table 1. Demographic and Clinical Data^a

Parameter	Alzheimer patients ^b (n = 60)	Depressed patients (n = 18)	Normal controls (n = 12)
Age (years)	66.2 ± 8.7	64.6 ± 9.9	65.8 ± 10.7
Gender	32F, 28M	12F, 6M	4F, 8M
Illness duration (years)	3.8 ± 2.6		
Age of onset (years)	62.2 ± 9.0		
Dementia severity			
Global Deterioration Scale	4.5 ± 1.0		
Clinical Dementia Rating Scale	1.7 ± 0.6		
Dementia Mood Assessment Scale			
17-item	23.0 ± 9.9		
Hamilton Depression Scale			
17-item		22.4 ± 7.1	
24-item		30.0 ± 8.6	
Bunney-Hamburg Global Scales			
Depression	4.3 ± 1.8	6.9 ± 2.1	
Sadness	5.2 ± 2.2	1.9 ± 2.2	
Anxiety	4.8 ± 1.6	6.6 ± 1.4	

^aValues are mean ± SD.^bNot all patients had all ratings.

monoamine metabolites, and CSF SLI. To explore the relationship between CSF SLI and CSF monoamines in AD patients with affective symptoms, the AD group was divided a priori into "depressed" and "nondepressed," and "anxious" and "nonanxious" groups based on scores from the DMAS-17 and the Global Depression and Global Anxiety Scales. The scores differentiating "depressed" and "nondepressed" patients were based on the mean scores of those scales in a prior publication which established the validity of the use of those scales in AD patients (Sunderland, et al 1988a). Patients with scores greater than or equal to the mean in that prior study (scores of ≥ 25 on the DMAS-17 and ≥ 5 on the Global Depression and Anxiety Scales) were considered to have significantly more depressive or anxious symptoms than those with scores that were less than the mean. Data are presented as the mean \pm SD.

Results

Demographic and clinical characteristics of the subjects are summarized in Table 1. The CSF SLI levels of 60 patients with probable AD and the group of 18 elderly depressives was decreased significantly from that of the age-matched controls ($df = 2,87$, $F = 11.42$, $p < 0.001$) (see Table 2). CSF SLI levels differed significantly between the "depressed" and "nondepressed" AD patients (Table 2). CSF 5-HIAA did not differ significantly between diagnostic groups ($df = 2,85$, $F = 2.41$, $p < 0.10$) (Table 2), nor did CSF MHPG or HVA levels ($df = 2,84$, $F = 2.24$, $p < 0.11$ and $df = 2,85$, $F = 0.14$, $p < 0.87$, respectively) (Table 2). The CSF 5-HIAA levels among the major depression patients, the "depressed" AD patients and the "nondepressed" AD patients did not differ significantly ($df = 2,59$, $F = 2.353$, $p < 0.20$) (Table 2). Mean CSF MHPG and HVA levels also did not differ significantly among these 3 groups ($df = 2,59$, $F = 2.35$, $p < 0.10$ and $df = 2,59$, $F = 2.28$, $p < 0.11$, respectively).

In the overall group of AD patients, there was no significant correlation between any

Table 2. Mean Levels (\pm SD) of CSF Somatostatinlike Immunoreactivity and CSF Monoamine Metabolites

Group (n)	SLI (pg/ml)	5-HIAA (pmol/ml)	MHPG (pmol/ml)	HVA (pmol/ml)
Alzheimer's (60)	37.2 \pm 15.5 ^a	93.0 \pm 30.9	51.3 \pm 16.0	187.9 \pm 74.1
"Depressed" (18)*	32.4 \pm 15.5 ^b	92.0 \pm 36.0	50.1 \pm 14.6	166.3 \pm 65.8
"Nondepressed" (26)*	42.0 \pm 15.6	100.2 \pm 28.5	50.3 \pm 16.4	213.7 \pm 69.0
Major Depression (18)	45.1 \pm 15.5 ^{a,c}	112.1 \pm 37.0	60.8 \pm 20.9	190.2 \pm 83.5
Controls (12)	60.2 \pm 16.1	94.5 \pm 34.3	51.1 \pm 14.7	201.6 \pm 66.4

^aDifferent from controls, $p < 0.001$.

^bDifferent from "nondepressed" AD patients, $p < 0.03$.

^cDifferent from "depressed" AD patients, $p < 0.01$.

*44/60 AD patients were evaluated with depression ratings.

of the CSF monoamine metabolites and SLI. When the AD group was divided into "depressed" and "nondepressed" 5-HIAA was the only metabolite to correlate significantly with SLI in the group of "depressed" AD patients as well as in the group of patients with major depression ($r = 0.49$, $p < 0.03$, $n = 20$ and $r = 0.55$, $p < 0.02$, $n = 18$, respectively) (Figures 1 and 2). A similar relationship was found between SLI and 5-HIAA ($r = 0.40$, $p < 0.04$, $n = 26$) (and not MHPG and HVA) in the group of "anxious" AD patients, and also in "anxious" patients with major depression ($r = 0.54$, $p < 0.04$, $n = 12$). Neither CSF SLI nor 5-HIAA correlated with measures of dementia severity.

Comment

In our study, a significant positive relationship between CSF SLI and CSF 5-HIAA was found within a group of depressed AD patients and within a group of patients with major depression; this relationship was consistent across the different scales used to assess mood. The other monoamine metabolites examined, MHPG and HVA, showed no such relationship with SLI. These results suggest an interaction between serotonin and so-

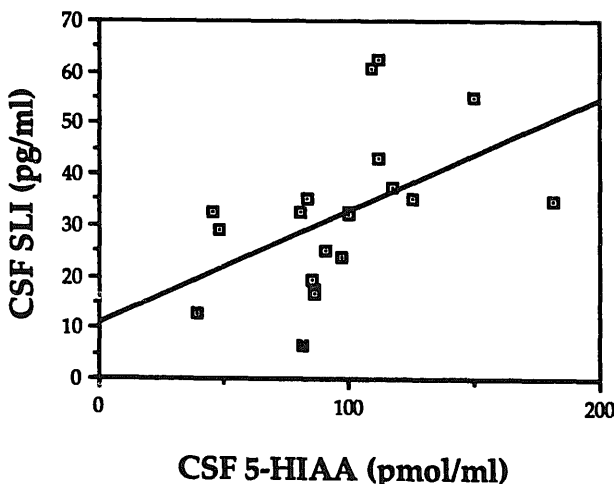


Figure 1. Correlation between CSF SLI and CSF 5-HIAA in "depressed" AD patients ($r = 0.49$; $p < 0.03$; $n = 20$).

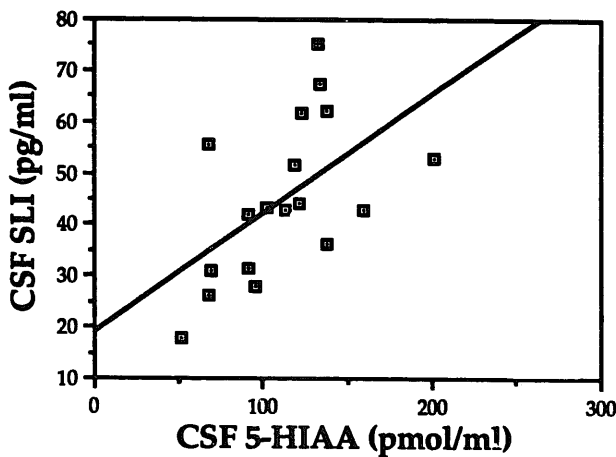


Figure 2. Correlation between CSF SLI and CSF 5-HIAA in patients with major depression ($r = 0.55$; $p < 0.022$; $n = 18$).

matostatin related to depressed and anxious mood in both these patient groups. The finding of this relationship on rating scales designed to measure depressed mood (the DMAS 17-item and the Global Depression Scale) and anxiety (Global Anxiety Scale) is consistent with the frequent coexistence of these symptoms in patients with major depression, especially in the elderly (Salzman 1990).

Prior studies of the CSF and brains of AD patients have also suggested a relationship between serotonin and somatostatin, though in none of these studies was depressed mood or the presence of major depression evaluated. In one study, decreased numbers of serotonin receptors correlated with decreased SLI concentrations in the cortices of AD patients (Beal et al 1985). A significant correlation between decreased 5-HT₂ (serotonin) receptor binding and SLI in temporal and frontal cortices of AD patients has also been reported (Cross et al 1984). In another study, decreased CSF SLI concentrations in AD patients paralleled decreased CSF 5-HIAA and HVA concentrations (Francis et al 1984).

In depressed patients, the relationship between decreased SLI levels and CSF monoamines has been inconsistent. In a study of patients with major depression, Rubinow and coworkers found a significant positive correlation between CSF SLI and CSF 5-HIAA in seven patients, a positive correlation with MHPG in a small number of patients, and a significant negative correlation between SLI and norepinephrine in 16 patients (Rubinow et al 1983). In a previous study, we found no such relationship in 20 older patients diagnosed with major depression (Sunderland et al 1987). In a study of 85 patients with major depression, Agren and Lundqvist found that SLI correlated negatively with MHPG/HVA (Agren and Lundqvist 1984). Bissette et al (1986) found no correlation between CSF SLI and monoamines in 29 patients with major depression. Small numbers of subjects, different diagnostic criteria, different symptom and demographic profiles, different rating scales, and different assay methods may have contributed to these different findings and the lack of a clear relationship between CSF monoamines and CSF SLI.

In AD, loss of 5-HT₂ receptors may be an early change in the pathological process (Cross et al 1984). Studies of SLI indicate that changes in the somatostatin system also appear to occur early (Roberts et al 1985; Nakamura and Vincent 1986). Our data support that changes in these systems occur early, in that neither SLI or 5-HIAA correlated with age, dementia severity, or duration of dementia symptoms. Depression can occur early

in the course of AD and can even be an initial symptom (Reding et al 1985; Reifler et al 1986). Whether there is a relationship between early depressive symptoms (some of our "depressed" patients were not just beginning the course of their illness) and deficits in the somatostatin and/or serotonin systems is open for future studies. The study of cortical somatostatin and 5-HT₂ receptors may also provide clues as to which neurons are susceptible to the pathological processes in AD and why, in that both are thought to be located predominantly on intrinsic neurons. The primary damage in these systems is thought to be in the terminal fields, especially in the temporal cortex and hippocampus, areas of the brain that are known to be affected early in AD (Cross et al 1984; Roberts et al 1985; Nakamura and Vincent 1986). Further studies of the relationship between the somatostatin and serotonin systems may provide clues as to how neuropeptides interact with monoamine neurotransmitters and what role those interactions have in AD and in depression.

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