J Neurol (1985) 232:346–351

Journal of
Neurology

Somatostatin-like immunoreactivity and substance-P-like immunoreactivity in the CSF of patients with senile dementia of Alzheimer type, multi-infarct syndrome and communicating hydrocephalus

H. Cramer[1]*, D. Schaudt[2], K. Rissler[1], D. Strubel[2], J.-M. Warter[3], and F. Kuntzmann[2]

[1] Department of Neurology and Clinical Neurophysiology, University of Freiburg, Hansastr. 9, D-7800 Freiburg, Federal Republic of Germany
[2] Department of Geriatrics, University of Strasbourg, France
[3] Department of Neurology, University of Strasbourg, France

Summary. The concentrations of somatostatin-like immunoreactivity (SLI) and substance-P-like immunoreactivity (SPLI) in lumbar spinal fluid of patients with senile dementia of the Alzheimer type (SDAT), multi-infarct syndrome, communicating hydrocephalus and control patients were determined by specific radio-immunoassay. Mean SLI and SPLI levels were significantly lower in an aged control patient group (mean age 83.5 ± 5.6 years) than in an adult control patient group (mean age 30.8 ± 10 years). In the latter group SPLI levels correlated negatively with age. Mean SLI levels decreased with deterioration in SDAT patients by up to 33% in late dementia. SPLI correlated with SLI in SDAT patients but was decreased significantly only in late dementia patients. Moderate and insignificant decreases of SLI were observed in patients with multi-infarct syndrome or communicating hydrocephalus. Analysis of SLI by gel-permeation chromatography revealed molecular heterogeneity of SLI. At least four peaks of SLI were eluted, two of which had apparent molecular weights of about 10,000 and 15,500, possibly representing somatostatin precursors. The ratio of SRIF to SLI of higher molecular weight was increased in patients with dementia compared to control patients.

Key words: Somatostatin – Substance P – Senile dementia, Alzheimer type – Cerebrospinal fluid

Introduction

Alzheimer disease (presenile dementia; AD) and senile dementia of the Alzheimer type (SDAT) are two forms of a degenerative brain disease, characterized by numerous senile plaques and fibrillary tangles in the cerebral cortex and hippocampus [37] and by progressive intellectual deterioration, including language disorders and dementia. Markedly decreased levels of choline acetyltransferase in the neocortex and hippocampus [9] and less consistent changes in other neurotransmitter system [7, 15, 34, 36] have been described.

Post-mortem studies of neuropeptides have shown no changes in the levels of vasoactive intestinal peptide (VIP) and cholecystokinin (CCK) [32] or vasopressin [32] in brains of AD/SDAT patients. In contrast, concentrations of somatostatin-like immunoreactivity (SLI) have been found to be markedly decreased in the cerebral cortex [2, 10, 28, 33] and in the CSF [20, 25, 38].

A loss of cholinergic cells in the forebrain appears to be a prominent biochemical marker for SDAT [21]. However, in the CSF no reliable marker for the metabolism of acetylcholine is available [9,33]. On the other hand, the CSF concentrations of neuropeptides, such as somatostatin and substance P,seem to reflect partially their passage into the extracellular space and hence their synthesis and release from brain cells.

The purpose of this study was to determine SLI and substance-P-like immunoreactivity (SPLI) in the CSF of patients with SDAT. In view of the possible bearing of normal aging on peptide concentrations and of volume effects of brain tissue losses, we compared findings in patients with SDAT to findings in age-matched controls, in normal adult control patients and in patients with symptomatic dementia of vascular or CSF circulatory origin.

Patients and methods

We examined 68 hospitalized geriatric patients (63 females, 14 males), aged 62–89 years (Table 1). The high-age control group consisted of inmates of the Geriatric Department (14 females, 1 male; mean age 83.5 ± 5 years). They were selected because of absence of central nervous disease, intellectual deterioration or major psychiatric disturbances. Four patients showed a slight degree of depression responding to minor drug treatment. Four patients had mild peripheral nervous disease (two diabetic polyneuropathy, two plexus neuritis). The main pathology of these patients was skeletal disease (arthrosis and bone fractures) and moderate cardiorespiratory insufficiency. The lumbar punctures were performed either for diagnostic purposes in order to exclude a central nervous disease, or when informed consent was obtained after the nature of the study had been fully explained.

Another control group consisted of 15 normal adult patients (10 females, 5 males; mean age 30.8 ± 10 years) who had lumbar puncture performed for diagnostic purposes. These patients were admitted with complaints of headache,

* Corresponding author

lumbalgia, dysaesthesia or general asthenia. Thorough clinical and laboratory examinations revealed no organic central nervous or meningeal pathology. The total protein concentration of CSF was 29.0 ± 8.0 mg/dl.

A total of 32 patients (31 females, 1 male; mean age 84 ± 7 years) were diagnosed as having SDAT, the diagnosis being based on clinical criteria. All these patients had progressive deterioration of intellectual functions, including language, memory and personality. Symptomatic causes of dementia were excluded by the absence of strokes, focalized neurological deficits, and by laboratory examinations, including EEG and vascular status.

The intellectual status of patients and the degree of deterioration were estimated by a neuropsychological examination based on the Brief Cognitive Rating Scale (BCRS) of Reisberg et al. [30]. The diagnosis of SDAT was made when there was a uniform profile of intellectual deterioration for all eight criteria (concentration, recent memory, old memory, orientation, functioning and self control, speech and language, motor performance, personality and behaviour). Of the seven degrees of deterioration, only the last three (early dementia, middle dementia and late dementia) corresponded to the patients selected for our study. Particular care was taken in establishing the diagnosis of degree I of SDAT because of the difficulty involved. Only five patients were selected for the study; in four of them, the diagnosis was confirmed by re-examination at least 6 months after the lumbar puncture had been performed.

The group of patients with vascular disease (9 females and 8 males; mean age 79 ± 7 years) was characterized by a history of strokes and presence of hemiplegia and unilateral or bilateral Babinski signs. Six patients had a pseudo-bulbar syndrome, one patient had in addition aphasia, one rigidity, and another patient had cerebellar ataxia. Only three patients showed no evidence of dementia; eight patients had marked dementia of the multi-infarct type. Other signs of vascular disease (arteriosclerosis, hypertension) were present. In all patients the Hachinski ischaemia score [18] was above 12. In the absence of systematic CT scans and of neuropathological examinations no attempt was made to further classify this group.

Five patients (4 females, 1 male; mean age 71 ± 6 years) were diagnosed as having communicating hydrocephalus (normal pressure hydrocephalus) [1] as the cause of dementia. The diagnosis was established by a progressive appearance of gait disturbance, loss of sphincter control and mild mental deterioration. In all these cases the diagnosis was confirmed by functional tests and by brain CT scans, which showed marked ventricular dilatation and absence or only a moderate degree of cortical atrophy.

Almost all the geriatric patients received drug treatment, at least for diseases other than neurological ones (cardiovascular, diabetes, "rheumatism"). Noteworthy was the use of neuroleptics, which was mandatory in agitated demented patients and consisted of low doses of haloperidol or thioridazine. Dependent upon the degree of dementia, the proportion of patients treated in this way was 40%–62%. A considerable number of patients received low doses of benzodiazepines; four control subjects and two patients with vascular disease were treated with antidepressants (amitryptilin, clomipramin).

The night before the lumbar puncture the patients had 12 h of bedrest. The lumbar punctures were performed in the morning. First, 9 ml of CSF was withdrawn without fractionation, immediately frozen on dry ice and then kept at −30°C for further analysis. CSF contaminated by blood was excluded from the study. Finally, 1 ml of CSF was subtracted for routine laboratory examinations of cell count, total protein, albumin and glucose content.

Radio-immunoassay for somatostatin

Tyrosine^{O}-somatostatin (Serono Co., Freiburg, FRG) was iodinated starting with $Na^{125}J$ (purchased from Amersham-Buchler, Braunschweig, FRG) according to the method of Greenwood et al. [16]. The radio-iodinated peptide was purified by column chromatography on a 90 × 1 cm Sephadex G-25 fine column (Pharmacia, Uppsala, Sweden). Fractions were pooled and stored at −40°C. A tracer prepared in this manner was storeable for 2–3 months without significant degradation.

Somatostatin-like immunoreactivity (SLI) was determined by radio-immunoassay according to the method of Arimura et al. [3], using a specific antibody (K 18, obtained from Ferring Co., Kiel, FRG) raised in rabbits, which recognizes the somatostatin molecule at the ring structure. Cyclic synthetic SST-14 (SRIF) and synthetic SST-28 are detected on an equimolar basis by this antibody. Standard solutions were prepared with synthetic SRIF (Serono Co.). The incubation period was 60 h. The incubation medium consisted of a phosphate buffer system mimicking the conditions of somatostatin in CSF (pH 7.4). The final antibody dilution ws 1:700,000. Free SLI was separated from the antibody-bound species by using the charcoal separating technique. Incubation damage, checked in each assay by omitting the antibody, showed negligible denaturation of the tracer.

Determinations were done in duplicate. The detection limit was 10 pg/ml. Intra-assay and interassay variation coefficients were 5% and 12% respectively. For proof of identical immunological reactivity between SRIF and CSF-SLI a dilution series was prepared from synthetic SRIF and SLI originating from CSF and the content of somatostatin measured by radio-immunoassay. Immunological identity was indicated if the resulting curves were parallel. The recovery of synthetic SRIF added to CSF was greater than 90% (range 90%–96%).

For peptide characterization the following procedure was chosen. About 300–600 fmol/ml SLI containing CSF (corresponding to about 10–20 ml native CSF) was concentrated on an octadecasilyl-silicagel cartridge and then eluted by 90% aqueous acetic acid (vol/vol). This method affords 90% recovery for synthetic SRIF and a 60% recovery for SST-28. The recovery of a CSF sample treated in this manner was 60%.

The acetic acid eluate was lyophilized, reconstituted in 1 ml of 0.1 *M* acetic acid containing 0.05% bovine serum albumin and subjected to gel-permeation chromatography (GPC) on a 40 × 1 cm Sephadex G-25 superfine column. Thirty fractions each containing 2 ml of eluate were collected and lyophilized. After reconstitution with assay buffer the SLI content of each fraction was measured by radio-immunoassay. In this way, it was shown that synthetic SRIF and synthetic SST-28 do not undergo chemical modification and retained their full immunoreactivity during the adsorption-desorption procedure. No reaction products other than the synthetic reference peptides could be detected. The elution profile of CSF pooled from 3–5 patients revealed three peaks of SLI. One peak co-eluted with synthetic SRIF and one peak eluted with the void volume. The third peak consistently appeared be-

Table 1. Clinical data and CSF levels of somatostatin-like immunoreactivity (SLI) and substance-P-like immunoreactivity (SPLI) in control patients and in patients with senile dementia of the Alzheimer type, vascular disease and communicating hydrocephalus

Patient group		Number (sex F/M)		Mean age	SLI (fmol/ml)	SPLI (fmol/ml)
Control I		15	(10/5)	30.8 ± 10.0	49.0 ± 11.2	11.3 ± 3.3
Control II		15	(14/1)	83.5 ± 5.6	32.5 ± 12.0*	8.1 ± 2.0*
SDAT	Deterioration stage I	5	(4/1)	80.2 ± 4.4	32.3 ± 6.0	8.1 ± 0.4
	Deterioration stage II	13	(13/0)	82.8 ± 8.4	23.7 ± 8.0**	8.0 ± 2.4
	Deterioration stage III	13	(13/0)	86.7 ± 6.1	22.0 ± 10.2***	6.0 ± 2.0***
	Total	31	(30/1)	84.0 ± 7.2	24.3 ± 9.2***	7.2 ± 2.3
Vascular disease		17	(9/8)	78.9 ± 6.7	26.6 ± 9.3	6.9 ± 2.1
Communicating hydrocephalus		5	(4/1)	70.8 ± 5.9	22.6 ± 5.9	9.1 ± 4.3

* $P < 0.01$ vs. control I
** $P < 0.05$ vs. control II
*** $P < 0.02$ vs. control II

tween the other two, corresponding to neither SST-28 nor to SST- 14 (SRIF) nor SST-25.

For molecular weight determinations of SLI arising from the Sephadex G-25 superfine void volume, the corresponding fractions were subjected to chromatography on 84 × 1 cm columns of Sephadex G-25 superfine and G-50 superfine, using a set of appropriate molecular weight markers: myoglobin (18,000), cytochrome-C (13,000), aprotinin (6,500), somatostatin-28 (3,200) and somatostatin-14 (1,600). Prior to chromatography the G-25 superfine void volume samples were incubated with 8 *M* urea-containing phosphate buffer (0.05 *M*, pH 7.5) for 24 h.

Radio-immunoassay of substance P

8-Tyrosyl-substance P (Peninsula Laboratories, Belmont, Calif.) was iodinated according to the method of Greenwood et al. [16] with $Na^{125}J$. The tracer was purified by ion-exchange chromatography on a 6 × 1 cm sulfopropyl-Sephadex column (Pharmacia), using gradient elution starting with 10 ml of 0.006 *M* ammonium acetate solution (pH 4.6), followed by 0.6 *M* ammonium acetate solution (pH 4.6). Fractions exhibiting maximal antibody binding were pooled and stored at −40°C. The storage does not alter the tracer quality for at least 3 months.

Substance-P-like immunoreactivity (SPLI) was determined in 1:10 concentrated CSF by radio-immunoassay. In spite of the elevated salt concentrations due to the concentration procedure, there was no interference with the assay by antibody precipitation. The final antibody dilution in the assay was 1:1,400,000. We used an antiserum raised in rabbits (kindly donated by the Department of Pharmacology, University of Freiburg, FRG), which shows little cross-reaction with the closely related undeca-peptide physalaemine (15%), whereas cross-reactions with eledoisin, bombesin and somatostatin can be neglected (< 1%). Standard solutions were prepared with synthetic substance P (Peninsula Laboratories, Belmont, Calif., USA). The incubation period was 72 h in phosphate buffer of pH 7.5. Separation of free SPLI from the antibody-bound species was performed by the charcoal technique. Incubation damage checked by omitting the antibody showed negligible denaturation of the tracer. Determinations were done in duplicate. The detection limit of the assay was 15 pg/ml. Intra-assay and interassay variation coefficients were 5%

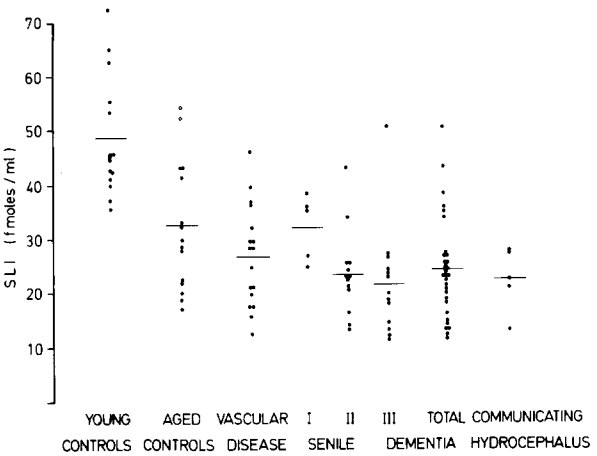

Fig. 1. Scattergram of individual concentrations of somatostatin-like immunoreactivity (SPLI) in CSF of control patients and patients with dementia, vascular disease and communicating hydrocephalus

and 11% respectively. The recovery of synthetic substance P added to CSF ranged from 92% to 104%.

For statistical analysis Student's *t*-test was employed to determine significance indicated by *P* values. Correlations were established by linear regression on a Hewlett-Packard HP 9825 A.

Results

The mean SLI concentration in control group I (mean age 30.8 ± 10 years) was 49.0 ± 11.2 and in control group II (mean age 83.5 ± 5.6 years) was 32.5 ± 12.0 fmol/ml (Table 1). The corresponding SPLI values were 11.3 ± 3.3 for control group I and 8.1 ± 2.0 fmol/ml for control group II. The difference in SLI concentrations between control group I and control group II was significant ($P < 0.05$). The individual values are shown in Figs. 1–2. There was no significant correlation between age and peptide levels with the exception of control group I, which showed age and SPLI to be negatively correlated ($r = -0.619$). A small positive correlation of SLI and SPLI was apparent in control group II ($r = +0.392$).

Patients with SDAT had a significantly decreased mean concentration of SLI in comparison to control group II (Table

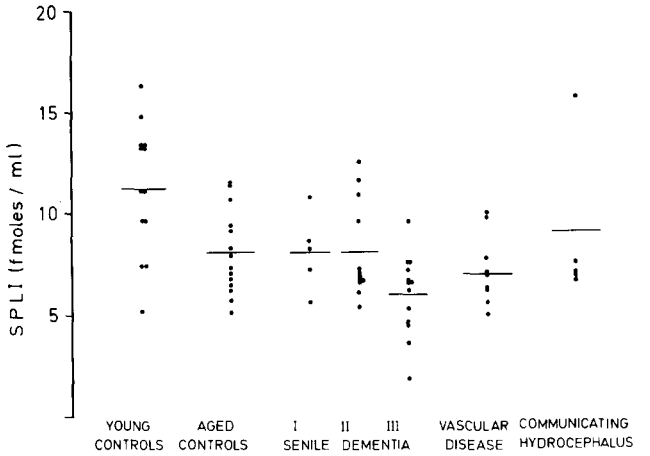

Fig. 2. Scattergram of SPLI in CSF of control patients with senile dementia, vascular disease, and communicating hydrocephalus

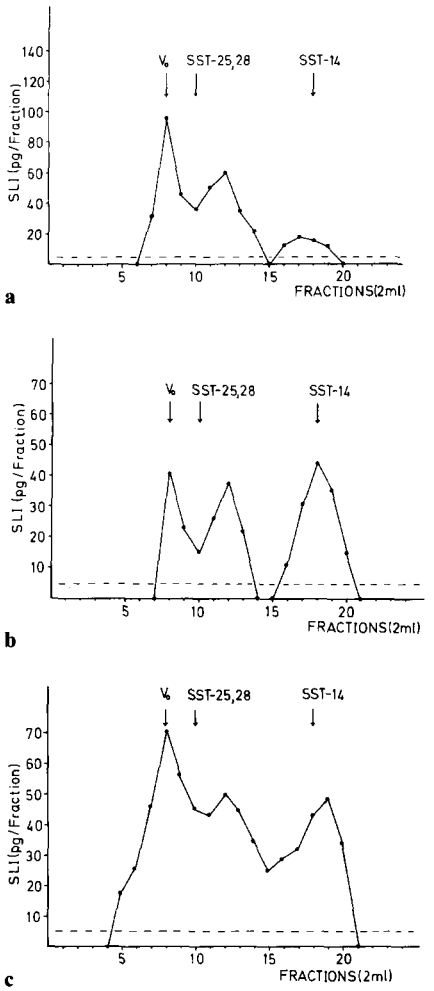

Fig. 3a–c. Pattern of molecular size of immunoreactive somatostatin in the CSF. Gel-permeation chromatography on Sephadex G-25 of identically treated pooled CSF samples. **a** High-age control group II; **b** senile dementia of the Alzheimer type; **c** vascular disease

1). When classified according to the stage of deterioration, patients in the early dementia phase (stage I) showed no decrease of SLI compared with the age-matched controls, while a significant decrease was observed in stage II (mid-dementia; $P < 0.05$) and in stage III patients (late dementia; $P < 0.02$; Table 1; Fig. 1). SPLI was significantly decreased only in stage III patients. The decrease of SPLI correlated with that of SLI in stage III ($r = +0.669$) and less so in the total SDAT group ($r = +0.533$).

Our patients with vascular disease and dementia exhibited a slight and non-significant decrease of SLI (Table 1; Fig. 1) and SPLI (Fig. 2). These decreases were correlated ($r = +0.486$). In patients with communicating hydrocephalus only SLI was non-significantly decreased (Table 1; Fig. 1).

GPC of pooled CSF samples of control group II showed only a small peak co-eluting with synthetic SST-14 (SRIF) and no peak co-eluting with synthetic SST-28. Two major peaks were observed, one eluting with the void volume of the column, and a second peak showing a molecular weight between the two synthetic species. In patients with SDAT as well as in patients with vascular disease, the peak corresponding to SST-14 became much more pronounced and was the preponderant peak in the CSF of DSAT patients (Fig. 3). In patients with communicating hydrocephalus the pattern was similar to that of high-age control patients.

On Sephadex G-50 superfine the void volume fraction yielded two peaks with apparent molecular weights of about 10,000 and 15,500. A 24-h incubation under denaturating conditions did not afford smaller peptides related to somatostatin in significant amounts, indicating that these putative precursor molecules do not represent species aggregated by hydrogen bonding. The second peak from G-25 columns exhibited an apparent molecular weight close to that of synthetic SST-25 and might represent a short-chain N-terminally extended SST-14 molecule.

Discussion

Somatostatin-like immunoreactivity was significantly reduced in the CSF of patients with SDAT in accordance with earlier reports [20, 25, 35, 38]. These findings agree with observations of reduced cerebrocortical SLI in AD/SDAT [10, 33]. The loss of SLI appeared to increase with progression of dementia, reaching 33% in patients with severe deterioration. A more marked decrease of SLI in 42% of control patients was reported previously by Wood et al. [38]. These authors, however, did not use an age-matched control group.

Age has generally not been found to correlate with CSF SLI changes. Yet, our control group II, which consisted of high-age patients free of abnormal neurological signs or dementia, showed a significantly reduced SLI level when compared with a young adult control group (mean age 30.8 years), which had a mean SLI level identical to that of a group of schizophrenics, matching with respect to age [14]. Age-related decrease has also been observed in the number of cholinergic cells of the basal forebrain [21]. Aging per se may affect somatostatin producing and substance P-ergic cells, which may be a slow process, easily escaping detection except when comparing young adults with very old subjects. This is supported by the negative correlation between age and SPLI in control group I.

Patients with vascular disease showed a non-significant decrease of CSF SLI. Although most of these patients exhibited various degrees of dementia, there was no correlation between SLI and dementia within this group. Probably extensive brain damage in multi-infarct dementia will reduce the extra-

cellular pool of SLI, similar to brain atrophy of other origins [20]. Moreover, a volume effect should result in a decrease of CSF SLI concentration in cases of hydrocephalus. Decreased SLI concentrations in normal pressure hydrocephalus were also found by Kohler et al. [20]. Drug effects are unlikely to be responsible for the decrease of SLI in dementia. Treatment with neuroleptics would more likely increase than decrease SLI in the CSF, according to Gattaz et al. [14].

Extrahypothalamic somatostatin has been detected in numerous areas of the brainstem [5], but the bulk of the peptide occurs in the cerebral hemispheres [29]. Studies based on animal experiments suggest that somatostatin has important physiological functions [31]. Electrophysiological studies in the cerebral cortex [19] and in the hippocampus [12] have shown an excitatory effect like that of acetylcholine. In peripheral autonomic neurons, somatostatin has been reported to inhibit the release of acetylcholine [17]. Co-existence of somatostatin and acetylcholine has not been demonstrated in the forebrain, but the striking decrease of cerebral cholinergic cells and somatostatin concentrations both in the cortex and in the CSF is compatible with a pathophysiological link occurring in SDAT.

The presence of multiple forms of SLI in the CSF is in accordance with recent studies (e.g. [29]). The origin of various somatostatin species is at present unclear; both spinal cord and brain apparently contribute to the SLI in lumbar CSF. Most of the molecular forms of somatostatin recovered from CSF still require further characterization, including the high-molecular-weight forms which may represent somatostatin precursors [29]. Surprisingly, little SRIF was detected in the CSF of our control patients. This, however, was also observed by Penman and Wass [27], who found about 80% high-molecular-weight forms of SLI and about 20% in the region of SST-28. Reichlin et al. [29] also reported a preponderance of high-molecular-weight SLI and only little SST-25,28.

Our finding of an altered GPC pattern of SLI in demented patients needs further classification. Qualitative alterations of somatostatins in neurological diseases have been neglected until now, unlike estimations of total SLI. In this preliminary study, a discrete peak of SST-28 could not be detected, but the resolution of GPC is not optimal for the distinction of this and closely related forms of SLI. Besides SST-14 (SRIF) at least SST-28 and SST-25 have been proved to possess biological activity [4, 22]. Recently, SST-28 [1–12] has been detected in the cerebral cortex with the suggestion that it may be a neuromodulator within the cortico-cortical intrinsic system [23]. Interestingly, SLI has also been observed in neuritic plaques of AD [24]. It has been suggested that somatostatin is one of several peptides located in cerebral cortical interneurons [11, 24], the failure and destruction of which might represent a crucial event in the pathophysiology of AD-SDAT, notwithstanding the importance of failure of cholinergic projections from the nucleus basalis [21].

Depletion of SLI in CSF is not specific to SDAT and also occurs in degenerative diseases of the basal ganglia which are normally rich in SLI [6, 13]. On the other hand, studies of SDAT have suggested deficiencies in multiple neurotransmitter systems [7, 9, 15, 24, 32]. In this study, the decrease of substance P correlated with the decrease of SLI, but was less marked and significant only in patients with advanced SDAT. This neuropeptide has central nervous distribution different from that of somatostatin, highest concentrations occurring in the substantia nigra and in the dorsal horn of the medulla [26]. Crystal and Davies [8] found significantly decreased SPLI concentrations in five of eight brain regions of patients with SDAT compared with aged control patients. Our finding of a late and rather moderate decrease of SPLI in SDAT, together with a negative correlation of SPLI with age in control patients, suggests that the decrease of lumbar SPLI in SDAT may be a secondary and less specific change compared with the change in SLI.

Acknowledgement. This work was supported by the Deutsche Forschungsgemeinschaft (SFB 70). The expert technical assistance of Miss U. Strittmatter is gratefully acknowledged. We thank Dr. J. Musil, Serono Co, for gifts of SST-14, SST-28 and Tyr^0-SST-14.

References

1. Adams RD, Fisher CM, Hakim S, Ojeman RG, Sweet HW (1965) Symptomatic occult hydrocephalus with 'normal' cerebrospinal fluid pressure. N Engl J Med 273:117–126
2. Allen JM, Ferrier IN, Roberts GW, Gross AJ, Adrian TE, Crow TJ, Bloom SR (1984) Elevation of neuropeptide Y (NPY) in substantia innominata in Alzheimer's type of dementia. J Neurol Sci 64:325–331
3. Arimura A, Sato H, Coy DH, Schally A (1975) Radioimmunoassay for GH-release inhibiting hormone. Proc Soc Exp Biol Med 148:784–789
4. Brazeau P, Ling N, Esch F, Böhlen P, Benoit R, Guillemin R (1981) High biological activity of the synthetic replicates of somatostatin-28 and somatostatin-25. Regul Pept 1:255–264
5. Brownstein M, Arimura A, Sato H, Schally AV, Kizer JS (1975) The regional distribution of somatostatin in the rat brain. Endocrinology 96:1456–1461
6. Cramer H, Wolf A, Rissler K, Weigel K, Ostertag Ch (1985) Ventricular somatostatin-like immunoreactivity in patients with basal ganglia disease. J Neurol 232:219–222
7. Cross AJ, Crow TJ, Perry EK, Perry RH, Blessed G, Tomlinson BE (1981) Reduced dopamine-beta-hydroxylase activity in Alzheimer's disease. Br Med J 282:93–94
8. Crystal HA, Davies P (1982) Cortical substance P-like immunoreactivity in cases of Alzheimer's disease and senile dementia of the Alzheimer type. J Neurochem 38:1781–1784
9. Davies P (1979) Neurotransmitter-related enzymes in senile dementia of Alzheimer's type. Brain Res 171:319–327
10. Davies P, Terry RD (1980) Cortical somatostatin-like immunoreactivity in cases of Alzheimer's disease and senile dementia of the Alzheimer type. Neurobiol Aging 2:9–14
11. Dawbarn D, Emson PC (1985) Neuropeptide Y-like immunoreactivity in neuritic plaques of Alzheimer disease. Biochem Biophys Res Commun 126:298–294
12. Dodd J, Kelly JS (1978) Is somatostatin an excitatory transmitter in the hippocampus? Nature 273:674–675
13. Dupont E, Christensen SE, Hansen AaP, Olivarius BF, Orskov H (1982) Low cerebrospinal fluid somatostatin in Parkinson's disease: an irreversible abnormality. Neurology (NY) 32:312–314
14. Gattaz WF, Rissler K, Gattaz D, Cramer H (1985) Haloperidol increases somatostatin-like immunoreactivity in the CSF of schizophrenic patients. Psychiatry Res (in press)
15. Gottfries CG, Gottfries I, Roos BE (1969) Homovanillic acid and 5-hydroxyindoleacetic acid in the cerebrospinal fluid of patients with senile dementia, presenile dementia and parkinsonism. J Neurochem 16:1341–1345
16. Greenwood FC, Hunter WM, Glover JS (1963) The preparation of ^{131}J-labelled human growth hormone of high specific radioactivity. Biochem J 89:114–120
17. Guillemin R (1976) Somatostatin inhibits the release of acetylcholine induced electrically in the myenteric plexus. Endocrinology 99:1633–1654
18. Hachinski V (1978) Cerebral blood flow: differentiation of Alzheimer's disease from multi-infarct dementia. Aging 7:97–103
19. Ioffe S, Havlicek V, Friesen H, Chernick V (1978) Effect of somatostatin (SRIF) and L-glutamate in neurons of the sen-

sorimotor cortex in awake habituated rabbits. Brain Res 153:414–418
20. Kohler J, Schröter E, Cramer H (1982) Somatostatin-like immunoreactivity in the cerebrospinal fluid of neurological patients. Arch Psychiatr Nervenkr 231:503–508
21. McGeer PL, McGeer EG, Suzuki J, Dolman CE, Nagai T (1984) Aging, Alzheimer's disease and the cholinergic system of the basal forebrain. Neurology (Cleveland) 34:741–745
22. Meyers CA, Murphy WA, Redding TW, Coy DH, Schally AV (1980) Synthesis and biological actions of prosomatostatin. Proc Natl Acad Sci USA 77:6171–6174
23. Morrison JH, Benoit R, Magistretti PJ, Bloom FE (1983) Immunohistochemical distribution of pro-somatostatin-related peptides in cerebral cortex. Brain Res 262:344–351
24. Morrison JH, Rogers J, Scherr St, Benoit R, Bloom FE (1985) Somatostatin immunoreactivity in neuritic plaques of Alzheimer's patients. Nature 314:90–92
25. Oram JJ, Edwardson J, Millard PH (1981) Investigation of cerebrospinal fluid neuropeptides in idiopathic senile dementia. Gerontology 27:216–223
26. Otsuka M, Konishi S (1983) Substance P—the first peptide neurotransmitter? Trends Neurol Sci 6:317–320
27. Penman E, Wass JAH (1981) Radioimmunoassay of somatostatin: methodological problems and physiological investigations. In: Bizollon CA (ed) Physiological peptides and new trends in radioimmunology. Elsevier-North Holland Biomedical Press, The Hague, pp 3–18
28. Perry RH, Dockray GJ, Dimaline R, Perry EK, Blessed G, Tomlinson BE (1981) Neuropeptides in Alzheimer's disease, depression and schizophrenia. J Neurol Sci 51:465–472
29. Reichlin S, Robbins R, Lechan R (1984) Somatostatin and the nervous system. In: Raptis S, Rosenthal J, Gerich JE (eds) Proceedings of the 2nd International Symposium on Somatostatin. Attempto Verlag, Tübingen, pp 21–37
30. Reisberg B, London E, Ferris SH, Borenstein J, Scheier L, de Leon MJ (1983) The brief cognitive rating scale: language, motoric and mood concomitants in primary degenerative dementia. Psychopharmacol Bull 19:702–708
31. Rorstadt OP, Martin JB (1980) Somatostatin and the nervous system. In: Barker JL, Smith TG Jr (eds) The role of peptides in neuronal function. Marcel Dekker, New York, pp 573–613
32. Rossor MN, Emson PC (1982) Neuropeptides in degenerative disease of the central nervous system. Trends Neurol Sci 4:399–401
33. Rossor MN, Emson PC, Mountjay CQ, Roth M, Iversen LL (1980) Reduced amounts of immunoreactive somatostatin in the temporal cortex in senile dementia of Alzheimer type. Neurosci Lett 20:373–377
34. Soininen H, MacDonald E, Rekonen M, Riekkinen PJ (1981) Homovanillic acid 5-hydroxy-indoleacetic acid levels in cerebrospinal fluid of patients with senile dementia of Alzheimer type. Acta Neurol Scand 64:101–107
35. Soininen H, Jolkkonen JT, Keinikainen KJ, Halonen TO, Riekkinen PJ (1984) Reduced cholinesterase activity and somatostatin-like immunoreactivity in the cerebrospinal fluid of patients with dementia of the Alzheimer type. J Neurol Sci 63:167–172
36. Terry RD, Davies P (1980) Dementia of the Alzheimer type. Ann Rev Neurosci 3:77–95
37. Tomlinson BE (1977) Morphological changes and dementias in old age. In: Smith WL, Kinsbourne M (eds) Aeging and dementia. Spectrum, New York, pp 25–56
38. Wood PL, Etienne P, Lal S, Gauthier S, Cajal S, Nair NP (1982) Reduced lumbar CSF somatostatin in Alzheimer's disease. Life Sci 31:2073–2079

Received March 26, 1985 / Received in revised form July 5, 1985
Accepted July 9, 1985