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Somatostatin-Like Immunoreactivity in the Cerebrospinal Fluid of Neurological Patients

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Abstract. Using a specific radioimmunoassay we have measured somatostatin-like immunoreactivity (SLIR) of CSF in patients with brain atrophy, spinal spasticity, seizures, brain tumors and inflammatory disorders.

Patients with marked brain atrophy had significantly decreased somatostatin levels in CSF. In patients with spinal spasticity significantly higher levels were observed. Seizure patients had reduced levels but the difference was not significant. In patients with inflammatory disorders and malignant brain tumors SLIR levels were significantly elevated but not in patients with benign brain tumors. A possible pathophysiologic meaning of SLIR in spasticity and seizures is discussed. The altered levels in brain atrophy, tumors and inflammatory disorders are probably indirect signs of altered somatostatin turnover or increased somatostatin leakage from damaged CNS.

Key words: Somatostatin – Cerebrospinal fluid – Human – Brain atrophy – Spasticity – Tumor – Inflammation – Epilepsy

Zusammenfassung. Bei neurologischen Patienten wurde die Immunreaktivität für Somatostatin (SLIR) im Liquor cerebrospinalis mit einem spezifischen Radioimmuntest gemessen. Patienten mit Hirnatrophie hatten signifikant verminderte, Patienten mit spinaler Spastik signifikant erhöhte SLIR-Werte. Auch bei Patienten mit malignen Hirntumoren und mit entzündlichen Prozessen fanden sich erhöhte Werte, während Patienten mit Epilepsie gering und nicht signifikant erniedrigte SLIR-Spiegel hatten. Die mögliche pathophysiologische Bedeutung einer erhöhten Aktivität spinaler somatostatinerger Neurone bei Spastik und Ursachen der Änderungen bei cerebralen Prozessen werden diskutiert.

Introduction

Somatostatin, a cyclic tetradecapeptide, was first isolated by Brazeau and coworkers in 1973 from hypothalamus as a hypophysiotropic hormone that inhibits the secretion of growth hormone.

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Several studies over the past few years have shown a widespread distribution in hypothalamus, extrahypothalamic brain, spinal cord and gastrointestinal tract (Patel and Reichlin 1978; Vale et al. 1975). Somatostatin has a depressant action on neuronal activity in brain and spinal cord (Koranyi et al. 1977; Randic and Miletic 1978; Renaud et al. 1975). The presence of somatostatin in synaptic terminals (Petrusz et al. 1977), the calcium-dependent release (Berelowitz et al. 1978) and the interaction with other putative neurotransmitter (Göthert 1981; Guillemin 1976; Negro-Vilar et al. 1978; Richardson et al. 1980) suggest that somatostatin may be a transmitter or modulator of neuronal function in CNS. In previous studies we have found increased levels of somatostatin-like immunoreactivity (SLIR) in patients with spinal cord compression (Cramer et al. 1981) and markedly decreased levels in patients with Huntington's chorea (Cramer et al. 1981).

In the present study we have investigated SLIR in degenerative and atrophying brain and spinal cord diseases and, additionally, in patients with epilepsy, brain tumors and inflammatory disorders of the CNS.

Patients and Methods

In total 59 patients with CNS disease were investigated. For control purposes 18 non-medicated neurologically normal patients were also studied.

Group 1. Nine patients (3 women, 6 men, mean age 57 years, range 29–79 years) with degenerative and related diseases of the brain characterized by marked brain atrophy were studied; 4 patients had a normal pressure hydrocephalus, 1 a presenile dementia of the Alzheimer type, 1 a diffuse atrophy of the brain following alcohol abuse and 3 patients had a Wernicke encephalopathy following alcohol abuse. Cell count and CSF protein of all patients were normal, and 3 patients were receiving digitalis and diuretics.

Group 2. Nine patients (3 women, 6 men, mean age 53 years, range 35–83 years) with disorders of the spinal cord and spaticity were studied; 4 patients had an amyotrophic lateral sclerosis (ALS), 4 a spastic spinal paralysis and 1 a tetraparesis due to cervical disk protrusion. Of these patients 3 had antispastic medication with baclofen. Cell count and CSF protein were normal.

Group 3. Eleven seizure patients were studied (5 women, 6 men, mean age 42 years, range 12–67 years); 6 patients had generalized tonic-clonic seizures, 3 of them as a symptomatic form, 4 patients had complex partial seizures and 1 had a myoclonic seizure type. Regular anticonvulsive medication (phenytoin, valproic acid, carbamazepine, clonazepam) was used in 9 of these patients. Cell count and CSF protein were normal.

Group 4. Thirteen patients with brain tumors were investigated (5 women, 8 men, mean age 54 years, range 19–72 years). The diagnoses were: glioblastoma (2×), astrocytoma (2×), cerebral metastasis (2×), oligodendroglioma (1×) and meningeoma (4×) according to the UICC classification of brain tumors. All patients were seizure-free and 5 had anticonvulsive medication. In this group cell count and CSF protein were elevated. The mean protein content ± SEM was 91.7 ± 23.1 mg/dl.

Group 5. Seventeen patients with inflammatory diseases of the CNS (9 women, 8 men, mean age 38 years, range 19–59 years) were studied; 10 patients had meningoencephalitis or meningomyelitis, 3 had meningitis, 2 encephalitis and 2 had polyradiculitis. Of these patients 3 were receiving cortisone. Cell counts and CSF protein were elevated. The mean protein level ± SEM was 117.5 ± 23.6 mg/dl.

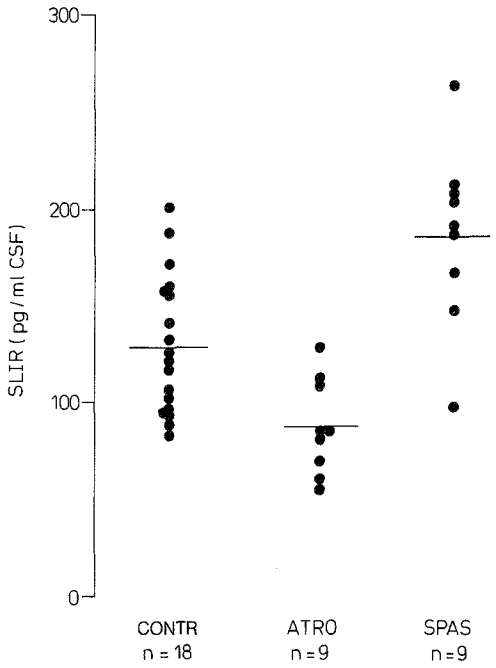

Fig. 1. Cerebrospinal fluid *(CSF)* somatostatin-like immunoreactivity *(SLIR)* in neurologically normal subjects *(CONTR)* and patients with brain atrophy *(ATRO)* and spinal spasticity *(SPAS)*

Group 6. Eighteen non-medicated patients without proven cerebral or spinal disorders were used as controls (11 women, 7 men, mean age 35 years, range 17–55 years). These patients consulted for headache (5×), ischialgia (5×), "giddiness"(2×), brachial plexus lesion (1×), hypotension (1×), descensus uteri (1×), hypoglycemia (1×), peripheral trauma without involvement of CNS (1×) and myalgia (1×).

Neurological status, cell counts and CSF protein concentrations were normal.

The CSF samples for SLIR determination were frozen at −40°C immediately after collection. An aliquot was used for determination of total protein and cell count.

SLIR was measured by radioimmunoassay with antibody 101 (Arimura et al. 1975). N-tyrosyl-somatostatin as a tracer (Serono) was iodinated by the method of McIntosh et al., and maximal antibody binding ranged from 25.1% to 32.5%. Standard solutions were prepared with synthetic cyclic somatostatin (Serono). The non-specific binding ranged from 3.6% to 6.5%. The intra-assay variance was 4.0% the inter-assay variance 15.9%, and the recovers of synthetic somatostatin added to native CSF ranged from 96% to 107%. For statistical analysis Student's *t*-test was used.

Results

The results are shown in Figs. 1 and 2. The CSF of 18 neurological control patients contained SLIR in concentrations ranging from 82.4 to 201.7 pg/ml with a mean level ± SEM of 128.7 ± 8.6 pg/ml.

In patients with degenerative disorders of the brain and marked brain atrophy SLIR levels were significantly reduced. The mean ± SEM was 88.4 ± 8.4 pg/ml ($P \leqq 0.01$). The lowest level was found in the patient with Alzheimer type dementia.

In contrast, patients with disorders of the spinal cord characterized by marked spasticity had significantly elevated levels ($P \leqq 0.01$). The mean ± SEM was 186.6 ± 14.6 pg/ml. There were no significant differences in the mean levels

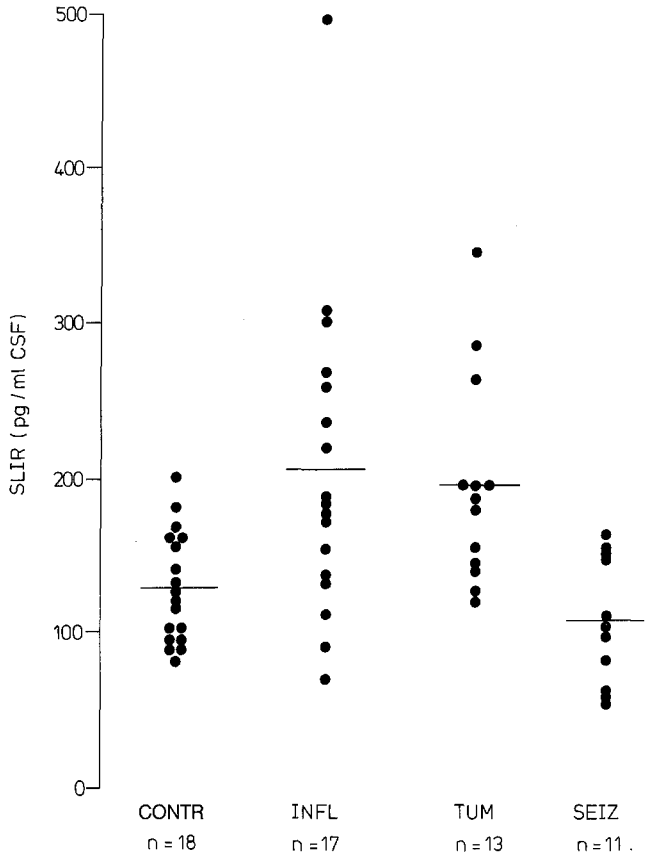

Fig. 2. Cerebrospinal fluid *(CSF)* somatostatin-like immunoreactivity *(SLIR)* in neurologically normal subjects *(CONTR)*, patients with inflammations of CNS *(INFL)*, brain tumors *(TUM)* and epilepsy *(SEIZ)*

among the subgroups with ALS and spastic spinal paralysis and between medicated and non-medicated patients.

In the seizure group we measured slightly reduced levels (109.8 ± 12.5 pg/ml), which were not statistically significant. In the patient groups with brain tumors and inflammatory diseases of the CNS we found significantly increased SLIR levels. The mean $\pm$ SEM of the tumor group was 195.4 ± 18.3 pg/ml. In the subgroup with malignant tumors the level was 229.9 ± 26.5 pg/ml ($P \leqq 0.001$) while the subgroup with benign tumors (meningeoma) showed a normal level (155.2 ± 12.5 pg/ml).

The mean $\pm$SEM of the group with inflammatory diseases was 207.0 ± 25.0 pg/ml ($P \leqq 0.01$). There was no correlation between SLIR and protein concentrations in either group of patients ($r = 0.580$).

Discussion

Our findings demonstrate reduced SLIR levels in the lumbar CSF of patients with brain atrophy (Fig. 1).

Davies et al. (1980) found reduced somatostatin levels in the cerebral cortex of patients with presenile and senile dementia of Alzheimer's type. CSF content of somatostatin may reflect a reduction of the somatostatin pool and turnover in atrophic brain. A specific alteration of somatostatinergic pathways in these cases is improbable. Also in patients with decreased oxygen availability due to cerebrovascular diseases reduced SLIR levels occur (unpublished observation).

Somatostatin and somatostatinergic neurons and fibers are present in spinal cord (Forssmann 1978; Forssmann et al. 1979; Hökfelt et al. 1975) and release of somatostatin from spinal cord has been shown in vitro (Sheppard et al. 1979). We observed increased SLIR levels in CSF of patients with spinal cord compression by extramedullary tumors and myelitis (Cramer et al. 1981). This indicates that somatostatin can be released from spinal cord in vivo and that enhanced release may occur from damaged tissue. The function of spinal somatostatinergic systems is still unknown. SLIR has been found mainly in the dorsal horn where it possibly acts as a modulator of synaptic transmission. Since in spasticity the pattern of afferences to the dorsal horn is markedly altered (Hagbarth et al. 1973) the increased levels of SLIR which we observed in patients with spinal spasticity are compatible with an enhanced activity of somatostatinergic afferences in this condition. Normal levels of SLIR were found in patients with spinal atrophy without spasticity (unpublished observation).

Increased levels of SLIR were also observed in patients with brain tumors and inflammatory diseases of the CNS (Fig. 2). This is comparable with findings of other authors (Patel et al. 1977). The subgroup with malignant tumors had highly significant increased levels (229.9 ± 26.5 pg/ml, $P \leqq 0.001$). Patients with benign tumors (meningeoma) had normal SLIR levels (155.2 ± 12.5 pg/ml). Under such severe conditions as intracranial mass lesion and inflammation rather nonspecific leakage of somatostatin from CNS tissue into the CSF may occur. In these cases the CSF protein was also elevated and we cannot exclude the concept that somatostatin may enter from peripheral blood. There was, however, no correlation between CSF SLIR and protein concentration.

In our preliminary study we found a reduction of CSF SLIR in patients with seizures. The lowest levels were measured in patients with tonic-clonic and complex partial seizures with high frequency and protracted anticonvulsive medication (94.3 pg/ml). Patients with symptomatic epilepsy of short duration had normal values. Although it is tempting to relate the inhibitory modulator somatostatin to antiepileptogenic mechanisms there is as yet no basis for such an association. Interactions between seizure type and frequency or between anticonvulsive medication and somatostatin content in CSF are possible and further studies are necessary to clarify the meaning of somatostatin in epilepsy.

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