Cerebrospinal fluid arginine vasopressin in degenerative disorders and other neurological diseases

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SUMMARY Arginine vasopressin (AVP) was determined in plasma and lumbar CSF from 46 patients with Parkinson's disease, dementia, cerebrovascular disease, multiple sclerosis and other, mostly peripheral neurological disorders. The mean plasma concentration of AVP was 1.62 μ U/ml, the CSF concentration 1.14 μ U/ml and the gradient CSF/plasma 0.72. There was a good correlation between the plasma and the CSF values in most patients. No sex difference could be found. A slight decrease of the CSF values could be found with increasing age. Significantly higher CSF-AVP values were found in patients with cerebrovascular disease, whereas lower CSF values were found in patients with dementia and Parkinson's disease. However there were decreased CSF/plasma gradients in patients with dementia and Parkinson's disease to about 0.30 compared to 0.98 in patients with peripheral neurological disorders. Patients with multiple sclerosis had an increased IgG index indicating an intrathecal IgG production but there was no obvious correlation between this and the AVP concentrations in plasma and CSF, nor with the total CSF protein content, nor with the albumin and IgG concentrations in plasma and CSF.

Arginine vasopressin (AVP) was purified from the posterior lobe of the pituitary gland 30 years ago and has mainly been studied in relation to its peripheral action as an antidiuretic hormone. Over the past few years other effects of this hormone have attracted interest, for example the role of AVP in dysmenorrhoea.¹ There is also evidence for a direct nervous influence through facilitation of learning and memory.^{2,3} With bioassay methods AVP could be demonstrated in human cerebrospinal fluid (CSF) 15 years ago,^{4,5} but not until recently, have quantitative determinations of AVP in CSF been performed with radioimmunoassay (RIA) in patients, with various results.⁶⁻¹¹ In the present study we have analysed plasma and CSF concentrations of AVP in patients with various neurological disorders, especially dementia and Parkinson's disease.

Materials and methods

Plasma and CSF samples were obtained from 46 patients:

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four with cerebrovascular disorders, five with multiple sclerosis, 21 with other neurological diseases, five with organic dementia and 11 with Parkinson's disease. The multiple sclerosis patients were diagnosed according to the criteria of Schumacher *et al.*¹² The other neurological disease group consisted of patients with symptoms such as headache and dizziness which were later found to have a psychoneurotic genesis. The group also consisted of patients with low back pain and peripheral neurological symptoms. The diagnosis of the dementia group was made by patient history, neurological examination, metabolic screening and CT scan. The mean age of the patients was 56 years (range 17-81 years) (table 1). Samples of CSF (15 ml) were obtained by lumbar puncture under standardised conditions. Blood contamination of the CSF was avoided. Plasma samples (5 ml) were collected at the same time and examined in a similar way. All samples were taken at noon to exclude the daily variations in plasma and CSF levels of AVP.¹³ Standard methods were used to examine CSF for cells and for total protein content. The samples were stored at -20°C until determination. Quantitations of albumin and immunoglobulin G (IgG) were performed by rocket electrophoresis as described by Laurell.¹⁴ Albumin, IgG and IgG-index were used to eliminate the influence of blood-brain barrier dysfunction and to detect an intrathecal IgG production.¹⁵ Vasopressin was determined by RIA employing extracted plasma as described by Strömberg *et al.*¹⁶ (1 μ U = 2.5 pg).

Results

The mean concentration of AVP for all 46 patients was 1.62 ± 0.20 μ U/ml in plasma and 1.14 ± 0.27 μ U/ml in CSF and the mean ratio CSF/plasma of AVP was 0.72 ± 0.15 (mean $\pm$ SEM). Statistical variation-analysis did not show any correlation between age and AVP plasma values. The CSF values of AVP decreased slightly with increasing age ($r = 0.20$). Plasma AVP did not significantly differ between the patient groups, whereas AVP in CSF was slightly increased in the patients with cerebrovascular diseases and decreased in patients with dementia and Parkinson's disease (table 2). There was a significant ($0.01 < p < 0.05$) difference between the mean values of these groups. However the CSF/plasma gradients were significantly ($p < 0.05$) decreased in both the groups of patients with dementia and Parkinson's disease compared with the total patient material and the other neurological diseased group (table 2). The other CSF parameters indicating either a damaged blood-brain barrier (increased CSF-total protein, CSF/plasma albumin gradient) or an intrathecal IgG

synthesis (increased CSF-total protein, CSF/plasma IgG gradient, IgG index) were within normal limits except in the multiple sclerosis group where there were significant findings of an intrathecal IgG synthesis (table 3). The patients with cerebrovascular disorders had some evidence (increased albumin CSF/plasma gradients) of blood-brain barrier damage compared to the age-comparable patients with Parkinson's disease. There was no correlation between the CSF-total protein content, the albumin or IgG parameters and the AVP values in either plasma or CSF.

Discussion

While AVP has been measured in the CSF of a number of animal species,^{6,13} only a few studies have been performed on the CSF content of AVP in man.⁶⁻¹¹ The CSF concentrations have been found to be in the same range as those seen in plasma, but values for plasma and CSF were not always similar in the different studies (table 4). Thus Dogterom *et al*⁶ found a mean CSF AVP concentration of 11.5 pg/ml

Table 1 Age and sex in the different patients groups

	n	Age		Sex	
		mean	range	male	female
Cerebrovascular disease	4	60.5	49-68	2	2
Multiple sclerosis	5	44.0	17-64	2	3
Other neurological disease	21	52.2	28-81	11	10
Dementia	5	68.2	63-75	2	3
Parkinson's disease	11	59.9	42-68	5	6

Table 2 AVP in CSF and plasma

	n	AVP CSF μ U/ml	AVP plasma μ U/ml	Ratio CSF/plasma
All patients	46	1.14 ± 0.27	1.62 ± 0.20	0.71 ± 0.15
Cerebrovascular disease	4	3.63 ± 1.77	2.98 ± 1.45	1.27 ± 0.09
Multiple sclerosis	5	1.64 ± 1.59	1.06 ± 0.61	0.55 ± 0.43
Other neurological disease	21	1.10 ± 0.22	1.64 ± 0.26	0.98 ± 0.28
Dementia	5	0.59 ± 0.28	2.04 ± 0.35	0.28 ± 0.10
Parkinson's disease	11	0.35 ± 0.12	1.17 ± 0.21	0.28 ± 0.06

Values are given as means $\pm$ SEM.

Table 3 Albumin, IgG gradients and IgG-index in the different patients

	n	IgG CSF/plasma gradient $\times 10^{-4}$	Albumin CSF/plasma gradient $\times 10^{-4}$	CSF-IgG-index
All patients	46	43.85 ± 4.67	88.57 ± 7.36	0.49 ± 0.03
Cerebrovascular disease	4	43.25 ± 7.81	94.00 ± 11.23	0.45 ± 0.04
Multiple sclerosis	5	70.20 ± 21.70	80.60 ± 22.19	0.85 ± 0.09
Other neurological disease	21	41.62 ± 6.39	99.48 ± 12.61	0.42 ± 0.02
Dementia	5	50.20 ± 19.30	88.80 ± 26.26	0.50 ± 0.11
Parkinson's disease	11	33.45 ± 7.00	69.27 ± 10.89	0.47 ± 0.30

Values are given as mean $\pm$ SEM.

Table 4 AVP plasma and CSF in previously published studies

Authors	Patients and subjects	Plasma values	CSF values	CSF/plasma ratio
Dogterom <i>et al</i> ⁶	21 neurological patients with hernia	<0.5 pg/ml (n = 5)	11.5 ± 2.5 pg/ml (range 1.4–34.9)	>20
Jenkins <i>et al</i> ⁷	12 "controls"	2.8 ± 0.7 pg/ml (range 1.9–3.9)	2.4 ± 0.7 pg/ml (range 1.4–3.6)	0.8
	50 with different neurological diseases	1–4 pg/ml (n = 41)	1–4 pg/ml (n = 36)	
Garcia <i>et al</i> ⁸ (1 µU = 2.5 pg/ml)	40 children with fever and headache	0.92 ± 1.3 µU/ml (range ND – 4.0)	0.14 ± 0.22 µU/ml (range ND – 0.6)	0.2
	14 children with bacterial meningitis	3.9 ± 3.7 µU/ml (range ND – 13.7)	0.6 ± 0.8 µU/ml (range ND – 2.3)	0.2
Mather <i>et al</i> ⁹	42 patients with subarachnoid bleeding (controls see Jenkins <i>et al</i> 1980)	increased in 10 patients (1.5–35.0 pg/ml)	(normal in 32 patients) (1.3–24.0 pg/ml)	
Tsuji <i>et al</i> ¹⁰ (1 µU = 2.5 pg/ml)	8 controls (age 42–47 yr)	not determined	<0.5 µU/ml	
	6 presenile dementia (63–72 yr)		0.78 ± 0.32 µU/ml (range <0.5–1.4 µU/ml)	
	10 senile dementia (65–81 yr)			
Reid, Morton ¹¹	15 "controls"	2.8 ± 0.5 pg/ml (mean ± SEM)	0.49 ± 0.06 pg/ml	0.2
	32 different neurological diseases	2.5 ± 0.25 pg/ml	0.61 ± 0.04 pg/ml	0.3
	11 i.c. hypertension	2.53 ± 0.4 pg/ml	0.64 ± 0.05 pg/ml	0.3

ND = not detectable.

in 21 neurologically healthy patients. The corresponding plasma levels were all below the lower detectable limit (0.5 pg/ml) and thus in that study the relation between the CSF/plasma had to be at least 20:1.

Jenkins, Mather and co-workers^{7,9} have measured AVP levels in plasma and CSF in control patients and patients with different neurological diseases, especially those with subarachnoid bleeding. In these studies the CSF/plasma relation of AVP were around 0.8 with CSF concentrations between 1–4 pg/ml, except increased values up to 24 pg/ml in some patients with subarachnoid bleeding and disturbed consciousness.⁹ In a study of 54 children with fever and headache, 14 children with proved bacterial meningitis had increased AVP levels in both plasma and CSF to 3.9 ± 3.7 µU/ml and 0.6 ± 0.8 µU/ml (mean ± SD) respectively.⁸ The patients with meningitis also had increased CSF total protein content and a decreased glucose concentration. After antibiotic treatment, both plasma and CSF AVP values decreased to "normal" levels around 1 µU/ml and 0.1 µU/ml respectively. In that study the CSF/plasma ratio was about 1:10. About the same proportions of the CSF and plasma AVP values were found in 58 patients studied by Reid and Morton,¹¹ who found plasma AVP around 2.5 pg/ml and CSF-AVP around 0.5 pg/ml both in controls and patients with neurological diseases, except increased values in some patients with intracranial hypertension. In the present study the plasma and the CSF values were usually correlated, but with slightly lower CSF than plasma concentrations. The mean plasma values were about twice those found in normal subjects with the assay employed by Jenkins *et al*,⁷ whereas the individual plasma and CSF values lay within the same

range. However, the CSF/plasma ratios in the patients with different neurological diseases were around 0.8 in both studies. No children were investigated in the present study, but it was noted that AVP concentrations fell with age, an observation consistent with studies in animals.¹⁷ The high age in some groups of patients, that is those with cerebrovascular disorders, dementia and Parkinson's disease, may partly explain the low CSF/plasma gradients of AVP in those groups of patients. However, the fact that plasma and CSF AVP concentrations were not identical and that the ratio of the two concentrations showed some variations, suggests that AVP may be released directly into the CSF. Indeed many authors have demonstrated AVP pathways other than those in the neurohypophysis, some of which lead to the lateral ventricle.¹⁸

Recently Tsuji and co-workers¹⁰ studied CSF AVP values from 24 elderly patients of whom 16 had presenile-senile dementia. The dementia patients had higher CSF AVP values, 0.78 ± 0.32 µU/ml (mean ± SD) than the control patients, who all had CSF concentrations between 0.5 µU/ml (1 µU = 2.5 pg). Plasma samples were not analysed. We found in the present study that patients with dementia and Parkinson's disease had CSF AVP concentrations of about the same levels as in the study of Tsuji *et al*.¹⁰ However the other groups of patients had higher CSF AVP values and the CSF/plasma gradients were decreased in patients with dementia and Parkinson's disease. Therefore we conclude that the AVP values are decreased in the CSF from these patients. This would be consistent with the concept of AVP deficiency and AVP treatment in patients with defect memory.

All the patients in this study with Parkinson's

disease were on levodopa treatment, which influences the plasma and CSF AVP values, as dopamine may decrease AVP release.¹⁹ Intranasal AVP treatment in Parkinson's disease has not been found effective in a double-blind study,²⁰ which may also be due to the inability of AVP to pass the blood-brain barrier after intranasal or intravenous administration.²¹ For beneficial therapeutic results with AVP in, for example dementia, it may be necessary that either a precursor is given or that intrathecal administration is employed. Increased plasma AVP concentrations have been found in patients with pain syndromes especially primary dysmenorrhoea.¹ Only a few patients examined in this study had a pain syndrome. One of these, a 38-yr-old man with chronic lumbar pain, without neurological symptoms, had quite normal plasma and CSF AVP values, 0.26 and 0.80 $\mu\text{U/ml}$ respectively, but a marked increased CSF/plasma gradient of 3.1. The AVP analogue tested in dysmenorrhoea²² may therefore be valuable also in other chronic pain syndromes, especially those with a disturbed CSF/plasma gradient. However further studies of plasma and CSF AVP concentrations in chronic pain patients are required.

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