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PITUITARY HORMONES IN HUMAN CEREBROSPINAL FLUID

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Abstract

Introduction. The blood brain barrier (BBB) restricts the transport of hydrophilic molecules such as peptidic pituitary hormones into the brain tissue. The blood-cerebrospinal fluid (CSF) is a part of the BBB.

Aim To compare the pituitary hormone levels on the two sides of the BBB in a group of subjects without endocrine diseases.

Patients and methods. We investigated, with the approval of the local ethics committee, 78 subjects without endocrine diseases. Growth hormone (GH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and thyroid stimulating hormone (TSH) were measured by rapid fluoroimmunoassay with Europium in the blood and cerebrospinal fluid (CSF) sampled simultaneously before rachianestesia for minor surgery.

Results. CSF concentrations are significantly lower than the corresponding serum ones for all hormones studied: 0.04 ± 0.009 mU/mL *vs* 2.29 ± 0.57 mU/mL for GH, 1.49 ± 0.078 ng/mL *vs* 10.07 ± 1.42 ng/mL for PRL, 0.57 ± 0.078 U/L *vs* 22.71 ± 3.65 U/L for FSH, 0.39 ± 0.038 U/L *vs* 11.11 ± 1.55 U/L for LH and 0.01 ± 0.003 µU/mL *vs* 1.36 ± 0.17µU/mL for TSH (mean ± SEM; $p<0.001$). The CSF/serum ratio was below 1 in the vast majority of cases (from all subjects studied we only found 3 cases with supraunitary CSF/serum ratio). The serum and CSF levels were not significantly correlated for any of the pituitary hormones. Comparing pre- and postmenopausal women the CSF gonadotropin levels were slightly but nonsignificantly increased after menopause, despite marked differences in the serum concentrations: CSF FSH 1.21 ±0.17U/L after *vs* 0.84± 0.4U/L before menopause, CSF LH 0.60± 0.047U/L after *vs* 0.43± 0.14U/L before menopause. The CSF/ serum ratio for FSH markedly decreased after menopause (0.02±0.003 *vs* 0.22±0.11) although the effect did not reach statistical significance. The same was true for CSF/serum LH ratio (0.026±0.005 *vs* 0.09±0.002). For none of the hormones studied the CSF levels correlated with age.

Conclusion. Pituitary hormones are normally found in the CSF at much lower levels than in the serum. The CSF hormonal concentrations do not significantly correlate with the serum ones.

Key words: cerebrospinal fluid, pituitary, hormones.

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INTRODUCTION

The blood-brain barrier (BBB) functions to maintain the homeostasis of neural microenvironment, in order to preserve the normal function of the brain, mainly by preventing toxic substances to gain access to cerebral structures. This barrier consists of a system of specialized semipermeable capillaries which are different from other vessels by the presence of distinct anatomical characteristics such as tight junctions and the absence of fenestrae (1).

The BBB is permeable for hydrophobic molecules (permeability increases proportional to the lipophilic character and decreases with the size of the molecule), but restricts the transport of circulating peptides from the blood into brain parenchyma. Substances may cross the blood-brain barrier by several mechanisms such as penetration through the membrane, *via* pinocytosis or transport *via* saturable carrier mechanisms (2,3). Literature data as early as 1970 show that pituitary peptidic hormones are normally found in the cerebrospinal fluid (CSF) (4,5).

In pituitary adenomas most of the studies reported higher CSF concentration of hormones than in control groups (4,6-8). The CSF levels of pituitary hormones are investigated as potential markers in the diagnosis of the pituitary adenomas and, possibly, in the future, to better appreciate the evolution and to choose the most appropriate therapeutic method.

Besides, in the past years a growing number of studies have begun to address the possible behavioural effects of various hormones that come in contact with cerebral structures.

As this research field is growing, studies of the CSF hormonal distribution in the general population are even more needed in order to provide a valid reference for further studies (when using a commercial kit for CSF samples it is strongly recommended to first obtain an appropriate range from a reference control group).

The aim of the present study is to assess the CSF concentrations of pituitary hormones in a control group and to describe the relation between serum and CSF concentrations in the study group.

PATIENTS AND METHODS

Seventy eight individuals (45 males, 33 females) without endocrine diseases or major chronic ilnesses were included in the study; they were recruited in the Surgery Department of "Sf. Maria" Hospital in Bucharest, Romania. All patients were subjected to minor surgery performed under spinal anesthesia and during this procedure lumbar puncture was carried out and 1 ml of cerebrospinal fluid (CSF) was extracted for analysis. Venous blood was obtained by venipuncture at the time of the lumbar puncture. All patients had previously signed an informed consent. The samples were centrifuged and both CSF and plasma samples were frozen at -20°C for storing. The study was approved by the local Ethics Committee.

Hormonal measurements

The plasma and CSF levels of growth hormone (GH), prolactin (PRL), follicle-

Table 1. Analytical performance characteristics of the kits used

Hormone	Analytical sensitivity	CV% intra-assay	CV% inter-assay
GH (mIU/mL)	0.03	2.1-5	3.7-6.3
PRL (ng/mL)	0.04	1.4-2.0	1.8-3.4
FSH (U/L)	0.05	2.0-2.8%	1.8-2.0%
LH (U/L)	0.05	2.0-2.4 %	3.1-4.2 %
TSH (μU/mL)	0.005	1.7-7.7 %	2.6-3.1%

Analytical sensitivity = 2SD above mean of zero standard (mean value + 2 SD)

stimulating hormone (FSH), luteinizing hormone (LH) and thyrotropin (TSH) were determined by fluoroimmunoassay using Europium (Dissociation- Enhanced Lanthanide Fluorescent Immunoassay DELFIA). Commercial hits for hFSH, hLH, hPRL, hGH, hTSH, Pharmacia Wallac, Finland were used.

The intra-assay, inter-assay variations and sensitivities of the DELFIA kits were as follows (see Table 1).

In order to obtain results that can be compared and interpreted inside the study group we used the same immunometric method both for measurements in serum and in CSF, thus ensuring the uniformity of the results and making it possible to assess the integrity of the blood-brain barrier by interpreting the CSF/serum ratio. Albumin was measured in the serum and CSF samples by rate nephelometry using IMMAGE Immunochemistry Systems for Albumin (Beckman-Coulter). The reference range was 3660-5100 mg/dL for serum and 13.9-24.6 mg/dL for CSF.

The CSF/serum albumin index was calculated as follows: CSF/serum albumin Index = (CSF albumin/serum albumin) x 1000 (concentrations in mg/L). Impairment of the blood-CSF barrier was estimated by interpreting this index with the criteria of Schliep and Felgenhauer (9): less than 9, no significant impairment; 9-14.3, slight impairment; 14.3- 33.3, moderate impairment; 33.3-100, severe impairment; greater than 100, total breakdown.

Statistical methods

For the statistical analyses we used the SPSS version 9.0 for Windows. Normal variables were expressed as mean ± standard deviation. We performed Spearman correlation tests to explore the correlation between the serum and CSF levels. Mann Whitney rank test was used to check for differences between groups. The level of significance <0.05 was accepted as indicative of a significant relationship between the variables.

RESULTS

Demography of subjects is summarised in Table 2. From the 33 females included in the study, 14 (42.4%) were premenopausal and 19 (57.6%) were postmenopausal (without current hormone replacement therapy). The most common reasons for surgery were various types of abdominal hernias (29 cases,

Table 2. Demography of subjects

Patient Data	Number	%
Gender		
Male	33	42.3
Female	45	57.7
Age (yrs)		
15-29	10	12.8
30-39	10	12.8
40-49	13	16.6
50-59	17	21.79
60-69	15	19.23
70-79	11	14.1
>80	2	2.5

representing 37.17%), fistulas (15 cases, representing 19.23%) or appendicectomy (7 cases, representing 8.9 %). The mean age was 51.23 years with a wide range (19-85 years)- see Table 2.

The mean hormonal levels in the serum and CSF samples are presented in Table 3 (expressed as mean and standard error of the mean, SEM): CSF concentrations are much lower than the corresponding serum ones for all hormones studied. The CSF/serum ratio is well below 1 (from all subjects studied we only found three cases with a CSF/serum ratio over 1, two for GH and one for FSH).

The serum and CSF levels seemed to be correlated only for FSH and LH: correlation coefficients of 0.415 and 0.340 with p values <0.001 (see Table 4). If we restricted the range of the serum concentrations by excluding from the study group the postmenopausal women (in order to have a more homogeneous group and to minimize the risk of biasing the correlation) the correlation did not persist: correlation coefficient 0.11 for LH ($p = 0.21$) and -0.02 for FSH ($p = 0.86$).

Comparing pre- and postmenopausal women we only found significant differences between serum prolactin (higher in premenopause) and, as expected, serum gonadotropins. The CSF hormonal levels were comparable for all pituitary hormones including the gonadotropins. The mean CSF FSH was 1.21 U/L post- and 0.84 U/L premenopause, CSF LH 0.60 U/L post *vs* 0.43 U/L premenopause (see Fig.1).

The CSF/ serum ratio for FSH has a marked decrease after menopause (0.02 vs 0.22) although the effect does not reach statistical significance (due, most probably, to the small numbers of cases subjected to comparison). The same is true for CSF/serum LH ratio (0.026 vs 0.09). This confirms the previous findings indicating that although at menopause the serum gonadotropin levels significantly increase, the brain seems to be protected against these rising blood peptides by a specific decrease in the BBB permeability (10).

For none of the hormones studied, the CSF levels correlated with age; the serum concentration was significantly

Table 3. Mean hormonal levels in serum (s) and CSF (c) and the CSF/serum ratio

	Mean	SEM	Range	N
s-GH(mU/mL)	2.2941	.5718	0-32.15	68
c-GH(mU/mL)	0.0421	0.0099	0-0.55	68
c/s-GH	0.2365	.1214	0-7.86	66
s-PRL (ng/mL)	10.0756	1.4265	1.30-90.93	75
c-PRL(ng/mL)	1.4904	0.0784	0-3.99	75
c/s-PRL	0.2447	0.018	0-1	75
s-LH(U/L)	11.1168	1.5586	.97-65.05	73
c-LH(U/L)	0.3904	0.0381	0-1.86	73
c/s-LH	0.0788	0.0144	0-0.88	73
s-FSH(U/L)	24.5053	4.1011	1.24-122.3	72
c-FSH(U/L)	.5780	0.0785	0-2.95	64
c/s-FSH	0.0899	0.0262	0-1.29	72
sTSH(μU/mL)	1.3610	0.1798	0.16-8.11	48
cTSH(μU/mL)	0.0116	0.00399	0-0.14	46
c/s-TSH	0.077	0.00219	0-0.08	46

correlated with age only for FSH ($r=0.313$, $p=0.007$).

The only significant differences between men and women are found in the serum and CSF concentrations of gonadotropins. For subjects below 50 years old there were no differences between the serum and CSF levels for all studied hormones. In older individuals (over 50 years), because the female group exhibited postmenopausal concentrations of gonadotropins, their serum but also corresponding CSF concentrations differed significantly from those found in males (see Fig. 2).

CSF albumin did not show any impairment of the blood-brain barrier according to the albumin index by the criteria designed by Schliep and Felgenhauer (9): albumin index was 6.432 ± 1.859 (range 4.24-9.8).

DISCUSSION

Pituitary hormones are large hydrophilic peptides once assumed not to cross the BBB. Our study confirms that pituitary hormones are a normal constituent of the CSF and that the levels of all studied hormones are significantly lower in the CSF compartment (situated on the other side of the BBB) as compared to serum. Although passage mechanisms are still incompletely clarified it seems that they do not involve passive crossing of the BBB but mostly specific, saturable carrier mechanisms.

In support of this view comes the fact that minor changes of the natural molecules abolish this transmembranary crossing (i.e. antagonists of the GH

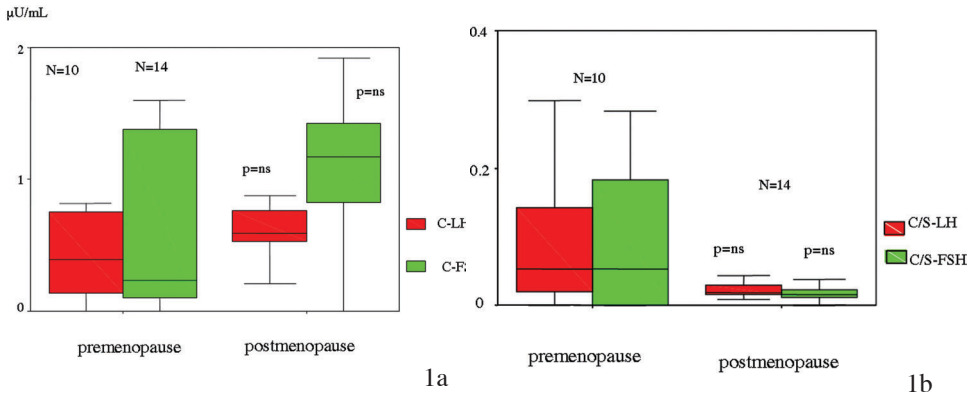

Figure 1. 1a. CSF gonadotropins in women before and after menopause.
1b. CSF/serum (C/S) ratio for gonadotropins in women before and after menopause

receptor, pegvisomant, very similar in structure to the natural GH does not cross the BBB)(11).

Glycoprotein hormones have a significantly lower CSF/serum ratio compared to GH and PRL which could be explained by a different kinetics through the BBB (due to different molecular weight and hydrophobicity).

In the past years many studies began to explore possible brain effects of hormones. For example, for GH a specific neurotrophic effect upon injured neurones and glia in the frontoparietal cortex, hippocampus and dorsolateral thalamus after hypoxic-ischaemic brain injury was described (12). High prolactin in pregnancy and lactation exerts many behavioural effects upon appetite, stress system and maternal behaviour (13). Recently gonadotropins have been actively studied for their potential implication in neurodegenerative disorders, as discussed below.

Although the mechanisms of crossing the BBB are mostly unclarified, and so is the source of the pituitary hormones (i.e. originating not only from the pituitary but also from other brain areas), it is of great importance to perform detailed studies of the CSF hormonal distribution in the general population in order to provide a valid reference for further studies exploring their cerebral effects.

The high sensitivity of the DELFIA assay, with femtogram level of detection, makes it ideal for complex sample matrices as it detects very low concentration targets that would be missed by less sensitive methods. Even though the serum and the CSF are different with respect to the protein content we consider that using ultrasensitive immunometric assays the results obtained in CSF are correct (as proved previously after the validation of IRMA method (14) and RIA on CSF samples (15)).

In older studies the mean CSF GH in controls, measured by radioimmunoassay (RIA) was 0.35 ng/mL ± 0.03 ng/mL (higher than what we found in our group), with a CSF/serum ratio of 0.17 (5).

Similar results were obtained in 57 neurological patients without hypothalamic or pituitary involvement and the CSF GH concentration was correlated to the serum one ($r = 0.52$, $p < 0.05$) (16). In more recent

Table 4. Correlation between serum and CSF hormonal levels

Hormone	Spearman correlation coefficient between serum and CSF concentration	p
GH	0.146	0.23
PRL	0.159	0.173
FSH		
entire group	0.415	0.000*
postmenopausal women	0.262	0.327
all subjects except for postmenopausal women	-0.024	0.869
LH		
entire group	0.340	0.006*
postmenopausal women	0.229	0.412
all subjects except for postmenopausal women	0.110	0.214
TSH	0.209	0.164

studies, using ultrasensitive ELISA immunoassay the mean CSF GH was 0.02 ± 0.011 ng/mL (mean ± SD)(17), a value very similar to our results (if we apply a conversion factor of 2). The same authors demonstrated that the CSF GH level decreases with advancing age as opposed to IGF I and IGF binding proteins, finding that was not confirmed in our study.

Our results concerning prolactin are very similar to another study using Romanian female population, study that found a mean CSF PRL of 1.65 ± 0.77 ng/mL (range 0.53 – 3.24) in non-pregnant women aged 21-43 years and a CSF/serum ratio of 0.22 ± 0.03 (18)**.** The prolactin level in CSF was 1.1 ± 0.5 after menopause (significantly higher) but with similar CSF/serum ratios (18).

The effect of menopause upon the CSF gonadotropins was intensely explored in previous studies. One study done on Romanian female population found significantly higher CSF levels in postmenopause as compared to fertile women in the early follicular phase: for FSH 2.7 mU/mL (0.4-5.9) *vs* 0.7 mU/mL (0.3-1) and for LH 1.6 mU/mL (0.7-2.6) *vs* 0.4 mU/mL (0.1-1). The same was observed by other authors who obtained a mean FSH ± SD of 2.9 ± 2.1 U/L and a mean LH ± SD of 3.7± 2.4 U/L postmenopause as compared to 1.1 ± 0.9 U/L for FSH and 1.8± 2.0 U/L for LH before menopause ($p < 0.01$) using radioimmunoassay (19). Despite these differences, the CSF /serum ratio for gonadotropins was significantly lower at menopause (10).

Our findings are different only in observing similar CSF gonadotropins levels before and after menopause. This observation, corroborated with the lowering of the CSF/serum ratio at menopause despite a marked increase in serum levels supports the idea that with aging the BBB permeability is selectively altered (decreased) for certain peptides. If

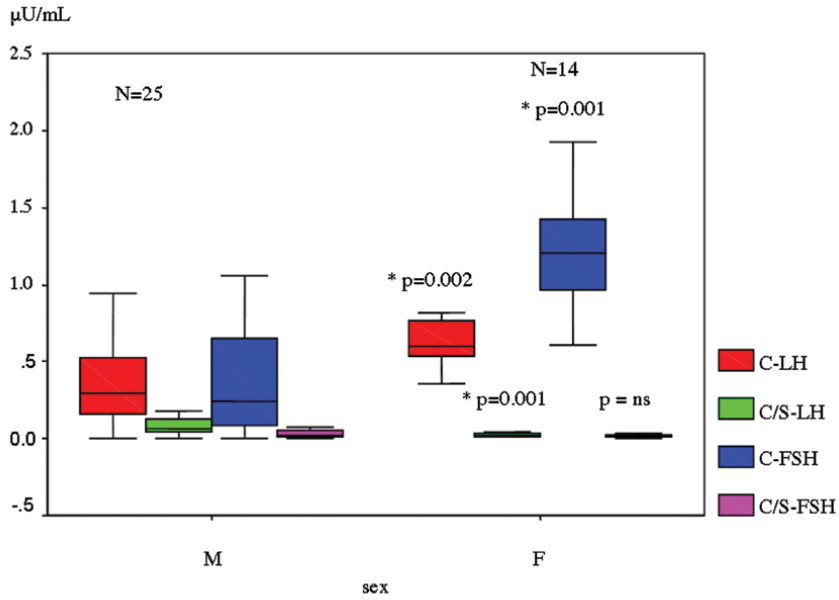

Figure 2. CSF gonadotropins in women and men aged over 50 years.

we take into account that the BBB permeability normally shows a non-specific increase with age (20), it appears that gonadotropins in high concentrations could represent a threat to the good functioning of the brain and so the brain develops a protective mechanism against their rising levels that occur at menopause. As a matter of fact clear links have recently been made between elevated gonadotropins and the development of Alzheimer's disease and potential candidate mechanisms for their putative neurodegenerative effects are currently studied (21). Another study performed by our group showed that CSF FSH and GH correlate with sleep events (i.e. obstructive apnea index and mean duration of central apnea episodes, respectively) in patients with pituitary adenomas (22).

The thyroid-stimulating hormone (TSH) measured by radioimmunoassay (RIA) gave in controls mean basal levels of 2.65 +/- 0.2 µU/mL in CSF and 5.95 +/- 0.3 µU/mL in plasma with a CSF/plasma ratio of 44% (5), again values much higher than our results. In more recent studies using immunochemiluminescence the mean CSF TSH in controls was 0.08 mU/L (range 0.01-0.14), concordant with our findings.

In controls many older studies reported a good correlation between serum and CSF levels of pituitary hormones (5,16,23,24). We did not notice such correlations; in the case of gonadotropins the apparent correlations between the serum and CSF levels were most likely due to the lack of homogeneity in the study group which biased the value of the correlation. This was confirmed by the fact that exploring the postmenopausal women (with high serum gonadotropins) separately from the rest of the subjects no correlation could be found in either group.

In pituitary adenomas, most authors reported a lack of correlation (or a very

weak correlation) between serum and CSF gonadotropins levels, arguing against a mechanism of simple diffusion through the BBB(6,25-27). In support of the same idea comes the fact that after castration of animals the CSF gonadotropins levels do not rise significantly after 6 weeks despite a significant serum concentration rise (28).

CONCLUSION

Our study confirms that pituitary hormones are normal constituents of the CSF in humas without endocrine diseases, where they circulate in concentrations much lower than those found in the serum. There is no significant correlation between the serum and the CSF levels for the studied hormones. The postmenopausal status seems to bring important adaptive changes in the BBB permeability, presumably protecting the brain from neurotoxic effects of rising blood peptides, effects that should still be actively studied.

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