1. Thyroxine treatment and neurotransmitter levels in the cerebrospinal fluid of hypothyroid patients: a pilot study

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Abstract

Monoamine precursors, neurotransmitters and their metabolites were studied in cerebrospinal fluid (CSF) obtained from nine newly diagnosed hypothyroid patients.

Before treatment, the serum TSH correlated positively with the CSF concentrations of tyrosine and phenylalanine.

During treatment, the levels of the precursors tryptophan, phenylalanine and tyrosine decreased significantly, as was also the case with dopamine and the noradrenaline metabolite 4-hydroxy-3-methoxyphenylglycol (HMPG), but not with serotonin, noradrenaline and the serotonin metabolite 5-hydroxyindoleacetic acid, nor the dopamine metabolites homovanillic acid and dihydroxyphenylacetic acid. The study provided some indication that the CSF levels of phenylalanine and tyrosine are related to thyroid function. Furthermore, we have found an indication that l-thyroxine treatment affects the CSF levels of the precursors as well as dopamine and HMPG. Our results support the notion that there is an interaction between thyroid function and CSF disposition of monoamine compounds.

European Journal of Endocrinology 139 493–497

Introduction

Hypothyroidism may be associated with mental disturbances, ranging from irritability and agoraphobia to melancholia and dementia (1). In adults, these states are reversible and psychological testing of hypothyroid patients has consistently revealed that intellectual impairment subsides with thyroxine treatment (2, 3).

A specific state of depression has been described in hypothyroid patients (4, 5) and a connection between hypothyreosis and depression is indicated by the observation that the thyroid hormone triiodothyronine (T3), administered as an adjunct to a tricyclic antidepressant drug, speeds up recovery in some patients with depression (6). It has recently been reported that dysphoric mood disturbances were common after withdrawal of thyroxine in patients on regular therapy (7).

The concentrations of neurotransmitter metabolites in the cerebrospinal fluid (CSF) have been investigated in depression (8, 9), but not, to our knowledge, in the hypothyroid state before and after treatment with thyroxine.

The present study was therefore undertaken to elucidate whether monoamine precursors, transmitters and their metabolites in the CSF of hypothyroid patients change during thyroxine therapy. Our project is a pilot study and the design is hypothesis generating.

Subjects and methods

Nine recently diagnosed hypothyroid outpatients (Table 1) participated after giving their informed consent. All of them showed increased concentrations of thyroid stimulating hormone (TSH), with or without decreased serum concentrations of free T3 and/or thyroxine (Table 2). TSH, free T3 and free thyroxine were analysed by a commercially available dissociation-enhanced lanthanide fluoroimmunoassay (Auto DELFIA, Wallac Oy, Turku, Abo, Finland). The intra-assay coefficient for TSH levels >11 mU/l was <4.4% and the interassay coefficient <3.9%. The intra-assay coefficient was <13% and the interassay coefficient was <13% for free T3. The intra-assay coefficient was <13% and the interassay coefficient was <13% for free T4. The intra-assay coefficient was <6.8% and the interassay coefficient was <7.3% for free thyroxine. All patients were free from medication and, apart from their hypothyroid disorder, were healthy, according to their medical history, physical examination and blood laboratory tests.

Lumbar puncture was performed before starting oral l-thyroxine treatment (n = 9) and after (n = 7), reaching a clinically adequate dosage 1–12 months later with normalisation of TSH. A standardised technique was used (10) comprising puncture at the L 4–5 level at 0800 h after a minimum of 8 h in the fasting state, along with strict bed rest. With the patient in a sitting
position. CSF was drawn in two consecutive 6 ml fractions with a disposable needle (Becton-Dickinson, Oxford, UK: 0.70 × 75 mm), from which the CSF was allowed to drip into a test tube. Tapping-time was recorded using a stop-watch. CSF was immediately protected from light, centrifuged and stored at −70°C until analysed. All samples were analysed in the same assay run. Precursors (tryptophan, phenylalanine and tyrosine), transmitters (serotonin (5-HT), dopamine (DA) and noradrenaline (NA)) and transmitter metabolites (5-hydroxyindoleacetic acid (5-HIAA), 4-hydroxy-3-methoxyphenylglycol (HMPG), dihydroxyphenylacetic acid (DOP AC) and homovanillic acid (HVA)) were determined using HPLC. Electrochemical detection was used for DA, NA (11) tryptophan, 5-HT, 5-HIAA, HMPG, DOPAC and HVA (12), while fluorescence detection was used for phenylalanine and tyrosine (13). The inter- and intra-assay coefficients of variation were <2 and <1% (11, 12), and >2 and 0.4% respectively (13). In one patient, only the first (0–6 ml) CSF fraction was obtained before treatment. Concentrations in the second (7–12 ml) fraction were estimated using linear regression analysis. Some attention was paid to previously described factors that are known to influence the levels of monoamine compounds in the CSF (14). The Stat View II programs (Abacus Concepts, Inc., Berkeley, CA, USA) were used for statistical analysis. The study was approved by the Ethics Committee of Huddinge University Hospital.

Results

Clinical data on the patients are presented in Table 1.

During thyroxine therapy, the levels of the precursors tryptophan, phenylalanine and tyrosine in the standardised amount of 12 ml CSF (10) decreased significantly, which was also the case with DA and the NA metabolite HMPG, but not with 5-HT, NA and the 5-HT metabolite 5-HIAA or the DA metabolites HVA and DOPAC (Table 2).

Before treatment, significant positive correlations were found between TSH in serum and tyrosine in 12 ml CSF (n = 9, r = 0.75, P = 0.0349, Fig. 1), and between TSH in serum and phenylalanine in 12 ml CSF (n = 9, r = 0.71, P = 0.044). No correlation was found between TSH in serum and tryptophan in 12 ml CSF (n = 9, r = −0.32, NS). After treatment, no relationships were found.

Since the data presented in Fig. 1 might indicate the existence of two distinct groups, this hypothesis was tested as to the percentage change in levels of the different CSF constituents. However, using the Mann–Whitney U test, we found no difference for any of the precursors, transmitters and transmitter metabolites.

On comparing CSF levels before and after treatment (n = 7), significant (P < 0.05) positive correlations were found for tryptophan, phenylalanine, tyrosine, 5-HT,
DA, DOPAC and 5-HIAA and HMPG, but not for HVA and NA.

Tapping-time for the first 6 ml fraction was significantly reduced during treatment (Table 3).

On correlating the levels of compounds in 12 ml CSF with age, height, body weight, neuraxis distances (from the external occipital protuberance to the site of puncture in the lying and sitting positions), tapping-time and atmospheric pressure factors that are known to influence CSF levels of precursors, transmitters and transmitter metabolites (15), we were not able to find correlations with age, body weight or tapping-time. Height correlated, however, with DA (\(r_s = 0.74, P = 0.0352\)). In the seven female patients (but not in the whole group of patients), the neuraxis distance in the supine position correlated significantly with HMPG (\(r_s = 0.96, P = 0.0182\), Fig. 2) and DA (\(r_s = 0.93, P = 0.0229\)), while neuraxis distance in the sitting position displayed a correlation only with HMPG (\(r_s = -0.85, P = 0.038\)). Bonferroni corrections were not used in order not to increase the risk of false negative results.

**Discussion**

Treatment with L-thyroxine caused a significant reduction in the CSF levels of tryptophan, phenylalanine, tyrosine, DA and HMPG (Table 2). These changes might mirror an effect of thyroxine on at least the metabolic pathway from phenylalanine to tyrosine and further on to DA. Since we found significant correlations between TSH and phenylalanine and tyrosine respectively, the hypothyroid disease might induce a blockage located at the beginning of at least one of the three pathways by which tyrosine is further metabolised. One metabolic step is the transformation of tyrosine by tyrosine hydroxylase to dihydroxyphenylalanine (DOPA) (16).

**Table 3** Tapping-time (means ± s.d.) before and during treatment.

<table>
<thead>
<tr>
<th>CSF fraction</th>
<th>Before treatment</th>
<th>During treatment</th>
<th>z value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 ml</td>
<td>5.7 ± 3.4</td>
<td>2.7 ± 1.1</td>
<td>-2.2, (P = 0.0277)</td>
</tr>
<tr>
<td>7–12 ml</td>
<td>4.7 ± 3.3</td>
<td>3.9 ± 3.2</td>
<td>0, NS</td>
</tr>
<tr>
<td>0–12 ml</td>
<td>10.3 ± 6.5</td>
<td>6.6 ± 4.3</td>
<td>-1.18, NS</td>
</tr>
<tr>
<td>Atmospheric pressure (hPa)</td>
<td>1013.2</td>
<td>1010.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Wilcoxon matched pairs signed rank test.
(which was not measured in this study), the next step being a biotransformation from DOPA into DA by aromatic amino acid decarboxylase (16). Since DA was reduced during l-thyroxine treatment, this might indicate that the pathway to DA remains unaffected, at least to a major extent, thus suggesting in turn that the increase in tyrosine (and phenylalanine) with increasing TSH is caused by a blockage involving one or two other metabolic pathways from tyrosine, viz. the conversion into either thyrine and p-hydroxyphenylpyruvate or into dihydroxyphenylalanine (and further on to melatonin) by the action of tyrosinase (16).

Despite the reduction in DA during treatment, we could not detect any effect on consecutive metabolic pathways from DA, viz. NA, DOPAC and HVA. If the CSF levels are dependent only on brain metabolism, this absence of reduction is difficult to explain. However, if l-thyroxine treatment exerts an influence on the CSF circulation and/or the elimination of compounds from the CSF, deviations from what might be expected, from a strictly metabolic point of view, would be more understandable. Differences in the CSF circulation have previously been suggested to influence the CSF levels of, for instance, monoamine compounds (15). The fact that catecholamines in the CSF are largely derived from the periphery (17) is another confusing factor. Whether l-thyroxine treatment influences the exchange of catecholamines between the periphery and the CSF is an intriguing question.

In the seven female patients (but not in the whole group), we found a significant negative correlation between neuraxis distance in the supine position and HMPG (Fig. 2) and DA. The length of the spine has been addressed in earlier studies of CSF monoamine metabolites (15, 18, 19) and in the case of HMPG, a positive influence of neuraxis distance has been reported in healthy males (18). Previously, height has been assumed to mirror the length of the spinal canal (20) but, in males, we found no correlation between height and neuraxis distance, thus making that assumption questionable in the present group (18). We concluded that neuraxis distance is a better estimate of the length of the spinal canal and that, consequently, the positive influence on HMPG reflects the process of CSF circulation (18). If this holds true for the present female patients, the negative correlation between neuraxis distance and HMPG might be an effect of a disturbed CSF circulation, associated with generally reduced physiological functions owing to the hypothroid disease. This conclusion might be in keeping with the observation that neuraxis distance has no influence whatsoever on HMPG in healthy female volunteers (14).

An unexpected finding is the change in tapping-time. Unpublished data indicate that tapping-time might be dependent on the intraspinal pressure and, if this is true, it is reasonable to investigate the role of thyroxine and thyroid function in relation to the intraspinal pressure.

In conclusion, our hypotheses are that: (a) hypothyroidism affects the CSF levels of tyrosine and phenylalanine; (b) treatment with l-thyroxine reduces the levels of tryptophan, phenylalanine, tyrosine, DA, and HMPG in lumbar CSF; and (c) the plausibility of an interaction between CNS and thyroid function is strengthened by their common use of the amino acid tyrosine.

Acknowledgements

This study was supported by grants from the Karolinska Institute. We thank Dr Ali Qureshi for the measurements of CSF compounds, and our research nurse, Mrs Catharina Sjöberg, for her excellent assistance.

References


Received 9 April 1998
Accepted 23 June 1998