

Thyroid Hormones Are Associated with Poorer Cognition in Mild Cognitive Impairment

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Key Words

Mild cognitive impairment • Neuropsychology • Cortisol • Thyroid hormones • Insulin-like growth factor 1 • Sex steroids

Abstract

Background: Alterations in interrelated endocrine axes may be related to the pathogenesis of mild cognitive impairment (MCI) and dementia. **Methods:** Salivary cortisol before and after a 0.5-mg dexamethasone test, and serum levels of thyroid-stimulating hormone, total thyroxine (T₄), free T₄, total triiodothyronine (TT₃), estradiol, testosterone and insulin-like growth factor 1 were measured in 43 MCI cases and 26 healthy controls. All participants underwent a comprehensive neuropsychological test battery covering the cognitive domains of speed/attention, memory, visuospatial functions, language and executive functions. **Results:** The MCI group did not differ in basal levels of endocrine markers compared to controls. Among those with MCI, TT₃ levels were inversely associated with cognitive performance across all domains. After stratifying MCI cases according to TT₃ levels, those with relatively high TT₃ levels showed impairment in memory as well as in visuospatial and executive functions. Those with TT₃ levels at or below the lower boundary of the normal range performed comparably to healthy controls. Other endocrine markers were not related to cognitive per-

formance. **Conclusions:** Among those with MCI, TT₃ was associated with a neuropsychological profile typical of prodromal Alzheimer's disease. While the mechanisms remain unclear, optimal levels of thyroid hormone under a compromising condition such as MCI and related neuropathology need reconsideration.

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Introduction

Age-associated cognitive decline is paralleled by declines in hormones comprising the major endocrine axes, which include the somatotropic, gonadotropic and thyrotropic axes [1–5]. Data suggest that these declines may be more accentuated or accelerated in individuals who develop dementia. Subsequently, individuals with dementia tend to exhibit lower levels of insulin-like growth factor 1 (IGF-1), estrogen, testosterone and thyroid hormone (TH) compared to those without dementia [6–8]. Lower levels of these hormones have also been associated with future dementia risk [9, 10]. Further complicating the picture is that while this general decline is observed across most endocrine axes, hypothalamic-pituitary-adrenal axis activity tends to increase [11]. In Alzheimer's disease (AD) and mild cognitive impairment (MCI), higher levels of cortisol have been reported

and associated with cognitive impairment and progression of the disease [12–14].

Experimental evidence relating endocrine axes to AD pathology is supportive of the aforementioned observations. IGF-1 and sex steroid hormones increase clearance of the neurotoxic β -amyloid ($A\beta$) protein [15, 16] and may slow down disease progression. They also decrease hyperphosphorylation of the tau protein, which accumulates in neurofibrillary tangles [17, 18] and is associated with cognitive impairment [19]. TH have been observed to decrease amyloid precursor protein expression [20], and estrogen may prevent $A\beta$ accumulation through effects on amyloid precursor protein processing [21]. Cortisol, in contrast, has been shown to increase levels of $A\beta_{40}$ and $A\beta_{42}$ and accelerate the development of neurofibrillary tangles in the brain [22]. Additionally, cortisol generates oxidative stress and excitotoxicity and may thereby accelerate atrophy in dementia [23].

While experimental models are useful to explore underlying mechanisms of hormonal action, they are limited for understanding the efficacy of specific hormone levels and the timing of hormonal exposures, whether endogenous or exogenous. In humans, higher free thyroxine (fT_4) levels within the normal range have been linked to increased risk of dementia and higher count of neurofibrillary tangles and neuritic plaques 4 years before dementia diagnosis [24]. In addition, despite potentially beneficial and protective effects of sex steroid hormone substitution [25–27], major clinical trials have suggested an increased risk for dementia and MCI for women on hormone replacement therapy [28]. Clinical trials and epidemiological findings may be contradictory because beneficial versus adverse effects may depend on the age and/or stage of disease, as well as on the temporal relationship between hormone measurements and the clinical course of the disease.

There is insufficient knowledge regarding the relationship between hormones and cognitive function in MCI, the classically defined prodromal stage of dementia. MCI is a state of risk for clinical dementia defined by cognitive decline greater than expected for ‘normal’ aging but preserved activities of daily life [29]. Understanding hormonal interrelationships in MCI provides opportunities for earlier interventions in dementia. Since the endocrine axes form a closely related, functional system, this study aims to examine cortisol, IGF-1, sex steroid hormones and TH (i) in MCI subjects compared to healthy controls, (ii) in relationship to each other, and (iii) in relationship to cognitive function in MCI utilizing a comprehensive neuropsychological test battery. The Gothenburg MCI study [30] forms the basis for these analyses.

Subjects and Methods

Participants

MCI cases and healthy controls participating in the Gothenburg MCI study [30] comprise the sample for these analyses. Data were obtained from the first visit of the participants to the memory clinic at Sahlgrenska University Hospital, Mölndal, Sweden. In total, 43 cases with MCI and 26 healthy controls were included. MCI cases included in these analyses had a higher mean MMSE score (28.1) compared to all cases included in the Gothenburg MCI study (26.6), but did not differ in terms of age or education.

All participants underwent a thorough clinical investigation including medical history, and physical, neurological and psychiatric examinations. Additionally, a neuropsychological examination was carried out by psychologists. Exclusion criteria for this study included psychiatric diseases (major depressive disorder according to the DSM-III-R criteria, psychotic disorder, bipolar affective disorder), chronic alcoholism, cerebral tumor, infection of the central nervous system, systemic diseases and diabetes mellitus. No participants on corticosteroid therapy were included. Reported use of medications potentially affecting hormone levels included oral estrogens (MCI: $n = 5$; controls: $n = 7$), L-thyroxine (MCI: $n = 3$; controls: $n = 2$) and β -blockers (MCI: $n = 2$; controls: $n = 3$). The controls were members of senior citizen organizations or spouses of cognitively impaired subjects who had been assessed at the clinic. This is an extended sample from that reported on by Lind et al. [14]. All participants gave their informed consent to participate. The study was approved by the ethics committee for medical research at the University of Gothenburg.

Diagnostic Procedure

The diagnosis of MCI was made in accordance with recommendations by the International Working Group on Mild Cognitive Impairment [31]. The diagnostic procedure included a medical history (self-reported and medical record review) and assessment of cognitive symptoms including: the cognitive variables 13–20 of the Stepwise Comparative Status Analysis (STEP) covering memory disturbance, disorientation, impaired abstract thinking, impaired spatial functioning, poverty of language, agnosia and apraxia [32]; I-Flex, a short form of the Executive Interview [33]; the MMSE [34], and the Clinical Dementia Rating (CDR) scale [35]. The CDR was based on information provided by the participant and a key informant. Basic criteria for the MCI diagnosis were subjective and objective anamnestic evidence of a progressive cognitive impairment for more than 6 months. In addition, cognitive symptoms according to STEP, I-Flex, MMSE or CDR protocols were required. Participants with more than 2 symptoms on the STEP and/or a score below 24 on the MMSE were considered to fulfill the criteria for dementia and were therefore not included.

Neuropsychological Assessment

The neuropsychological battery included tests of speed and attention, learning and episodic memory, and visuospatial, language and executive functions in agreement with the recommendations by the American Academy of Neurology [36]. The neuropsychological test battery has been described in detail [30]. The tests were administered in a standardized sequence and conducted in 2 sessions of 1–2 h. Verbal tests and nonverbal tests were alternated in each session. The test sequence was designed to min-

imize contamination on the memory tests. Thus, no test with content that could affect performance on a memory test was administered between immediate and delayed recall.

Serum Samples

Fasting serum samples were drawn between 8 a.m. and 10 a.m. for measurement of total testosterone (TT), estradiol, IGF-1 and sex-hormone-binding globulin (SHBG). Nonfasting serum samples were drawn for measurements of thyroid-stimulating hormone (TSH), total T₄ (TT₄), fT₄ and total triiodothyronine (TT₃). All samples were transported immediately to the laboratory for biochemical analyses. TSH, TT₄, fT₄ and TT₃ were analyzed using electrochemiluminescent immunoassays. TT and IGF-1 were determined using immunochemical assays. Estradiol was determined using a radioimmunoassay, and for SHBG, a carbonylmet-alloimmunoassay was used. All hormonal analyses were conducted at accredited hospital laboratories in Gothenburg, Sweden.

Saliva Samples

Saliva was collected by the participants at home, using Salivette® (Sarstedt Rommelsdorf, Germany) [37] over the course of 2 days. The participants received oral and written instructions including noting times of awakening, intake of lunch and saliva collection. The participants were asked to refrain from eating, brushing teeth, smoking or rinsing their mouths for at least 30 min prior to sample collection (for a more detailed description, see Lind et al. [14]). On day 1, saliva samples were collected in the morning upon awakening, 15 min after awakening, and at noon, 4 p.m. and 8 p.m. At 10 p.m., 0.5 mg dexamethasone was administered orally. On day 2, saliva was collected according to the same protocol. Salivary cortisol levels were determined using SPECTRIA®.

Statistical Analyses

Means and SD were determined for continuous variables. Skewed variables were log transformed to approximate normal distributions. Continuous variables were compared using independent sample t tests, and for skewed variables that could not be transformed, the nonparametric Mann-Whitney U test was utilized. Logistic regression analyses estimating the odds of MCI were performed separately for each hormone: cortisol, testosterone, estradiol, IGF-1 and TH. Hierarchical multiple regression analyses were employed to evaluate multiple endocrine predictors of cognition. All regression models were adjusted for age, sex, body mass index, total cholesterol, high-density lipoprotein, low-density lipoprotein, systolic and diastolic blood pressure, and use of medications such as L-thyroxine, β-blockers and estrogens.

Principal component analysis (PCA; SIMCA-P 10.0) was performed on the data from the neuropsychological test battery presented in Eriksson et al. [38]. The significance of the model was determined by cross-validation. The PCA resulted in one significant latent variable that summarized the constituent neuropsychological test variables. The composite score of each subject was considered to express the general level of neuropsychological performance. Group comparisons for the subsequent analysis were carried out by univariate ANOVA. For post hoc analyses, Tukey's honestly significant difference was used. Results were considered significant at $p < 0.05$. Correction for multiple comparisons has not been applied due to the preliminary nature of the data. SPSS version 13.0 was used for all statistical analyses.

For further evaluation of cortisol, areas under the curve (AUC) with reference to 0 for each day were calculated to estimate the total cortisol secreted over the day (AUC_G). The formula for the AUC was derived from the trapezoid formula [39]. Additionally, mean values for both days were calculated, as well as mean values only for the wake-up response (wake-up + 15 min after wake-up divided by 2). The free androgen index (FAI) was computed (TT/SHBG × 100) as an indicator of testosterone not bound to SHBG [9]. TT₃/fT₄ × 100 ratios were calculated to estimate the conversion of fT₄ to TT₃ [40].

Results

Demographics and Neuropsychological Assessment

Data from all 43 MCI cases and 26 healthy controls were analyzed. As presented in table 1, the controls were significantly older than the MCI group ($p = 0.001$). However, no significant differences were observed regarding years of education ($p = 0.128$) or general intellectual capacity ($p = 0.538$), as assessed by Raven's Coloured Progressive Matrices. As indicated in table 2, the control group performed significantly better than the MCI group on 10 neuropsychological tests.

Of the MCI cases, 2 were considered pure amnesic MCI, 12 amnesic MCI multiple domain, 11 nonamnesic MCI multiple domain, and 17 nonamnesic MCI single domain. The PCA yielded one component accounting for 34.2% of the variance, and the weighted average scores (PCA) of the MCI group were significantly lower compared to the controls.

Endocrine Profile in MCI Cases versus Controls

The average levels of testosterone, FAI, estradiol, IGF-1, TSH, TT₄, fT₄ and TT₃ did not differ between MCI cases and controls, and between men and women. A multivariate logistic regression model estimating the odds of MCI by all 7 endocrine variables showed no relationships. The pre- and postdexamethasone cortisol awakening response, including cortisol levels at awakening and 15 min after awakening, distinguished between MCI and controls ($\chi^2 = 12.4$; d.f. = 4; $p = 0.015$) with an overall correct prediction of 71.6%. An independent contribution was found for cortisol levels at 15 min after awakening on day 2 after the dexamethasone test (Wald = 4.126; $p = 0.041$; OR = 4.538; 95% CI: 1.05–19.53).

Relationship of Cortisol to Other Endocrine Axes

In the MCI group, positive correlations were found between fT₄ and basal mean salivary cortisol ($r = 0.514$; $p = 0.001$), cortisol awakening response ($r = 0.556$; $p < 0.001$),

Table 1. Characteristics of MCI cases and controls: the Gothenburg MCI study

	Controls			MCI		
	male (n = 8)	female (n = 18)	total (n = 26)	male (n = 18)	female (n = 25)	total (n = 43)
Age, years	66.8 ± 6.9	66.3 ± 6.2	66.5 ± 6.2	60.9 ± 3.9	61.1 ± 6.3	61.1 ± 5.4
Education, years	11.5 ± 2.1	11.1 ± 2.4	11.2 ± 2.3	12.4 ± 3.6	12.6 ± 3.7	12.6 ± 3.7
MMSE score (0–30 points)	29.6 ± 0.5	29.2 ± 1.1	29.4 ± 1.0	28.2 ± 1.6	27.9 ± 1.6	28.1 ± 1.5
Raven's CPM	30.3 ± 3.1	32.1 ± 2.7	31.0 ± 3.5	32.3 ± 3.3	30.4 ± 3.5	31.6 ± 2.9
<i>Endocrine variables</i>						
Testosterone, nmol/l	14.2 ± 3.0	1.1 ± 0.6	5.3 ± 6.5	16.5 ± 5.3	1.0 ± 0.6	7.5 ± 8.5
FAI	41.5 ± 9.7	2.3 ± 1.6	14.9 ± 19.4	46.3 ± 16.1	1.0 ± 2.3	20.7 ± 24.3
Estradiol, nmol/l	0.06 ± 0.02	0.06 ± 0.05	0.06 ± 0.04	0.07 ± 0.02	0.05 ± 0.02	0.05 ± 0.02
IGF-1, µg/l	160.6 ± 39.5	147.2 ± 64.8	151.3 ± 57.7	157.2 ± 46.7	154.2 ± 55.9	155.7 ± 51.8
TSH, mIU/l	1.5 ± 0.7	1.6 ± 1.5	1.6 ± 1.3	1.9 ± 0.9	1.5 ± 0.5	1.7 ± 0.7
TT ₄ , nmol/l	84.5 ± 14.4	92.2 ± 17.5	89.7 ± 16.7	81.8 ± 16.6	91.7 ± 17.3	87.6 ± 17.5
fT ₄ , pmol/l	12.9 ± 2.0	14.3 ± 2.6	13.8 ± 2.5	13.2 ± 2.0	13.7 ± 2.2	13.5 ± 2.1
TT ₃ , nmol/l	1.5 ± 0.3	1.6 ± 0.3	1.5 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	1.5 ± 0.2
<i>Cortisol</i>						
AUC _G day 1	6,938.1 ± 1,864.9	6,519.1 ± 3,582.3	6,648.0 ± 3,120.7	6,159.4 ± 3,427.1	6,755.5 ± 2,589.4	6,508.3 ± 2,939.7
AUC _G day 2	2,052.6 ± 2,119.54	1,409.3 ± 877.7	1,596.9 ± 1,340.7	1,514.5 ± 885.4	1,629.5 ± 1,179.3	1,580.6 ± 1,053.3
Awakening day 1, nmol/l	12.5 ± 5.8	13.6 ± 5.8	13.3 ± 5.7	10.5 ± 4.7	14.9 ± 10.3	13.1 ± 8.5
Awakening 15 min day 1, nmol/l	16.5 ± 6.2	18.4 ± 5.8	17.8 ± 5.9	15.5 ± 7.1	21.4 ± 10.9	19.0 ± 9.8
Awakening day 2, nmol/l	2.3 ± 1.9	1.6 ± 0.9	1.8 ± 1.3	1.4 ± 0.9	2.2 ± 2.4	1.9 ± 1.9
Awakening 15 min day 2, nmol/l	2.0 ± 1.7	1.3 ± 0.5	1.5 ± 1.0	2.2 ± 2.5	2.9 ± 3.9	2.5 ± 3.4
<i>Somatic variables</i>						
BMI score	26.9 ± 2.9	25.1 ± 3.0	25.7 ± 3.0	24.7 ± 3.1	24.3 ± 3.8	24.4 ± 3.5
Total cholesterol, mmol/l	6.0 ± 1.9	5.6 ± 1.2	5.7 ± 1.4	5.2 ± 0.7	6.1 ± 1.2	5.7 ± 1.1
HDL, mmol/l	1.5 ± 0.4	2.0 ± 0.5	1.8 ± 0.5	1.6 ± 0.4	2.0 ± 0.5	1.8 ± 0.6
LDL, mmol/l	4.4 ± 2.1	2.9 ± 1.1	3.3 ± 1.5	3.0 ± 0.7	3.6 ± 1.3	3.4 ± 1.1
Systolic blood pressure, mm Hg	140.6 ± 16.8	137.0 ± 21.3	138.2 ± 19.7	131.7 ± 17.7	142.6 ± 23.6	138.1 ± 21.8
Diastolic blood pressure, mm Hg	78.5 ± 13.1	77.2 ± 8.7	77.6 ± 10.0	79.3 ± 10.6	82.5 ± 9.5	81.2 ± 10.0

Values denote means ± SD. Between the groups, there were differences in age and MMSE scores ($p < 0.001$). No differences in endocrine and somatic variables were observed ($p < 0.05$).

Raven's CPM = Raven's Coloured Progressive Matrices; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

AUC_G ($r = 0.361$; $p = 0.021$) and cortisol awakening response after the dexamethasone test ($p = 0.359$; $p = 0.021$) and AUC_{G_{Dex}} ($r = 0.355$; $p = 0.024$). Similar associations were found for TT₄ levels ($p < 0.05$). No associations between cortisol and other hormones were found in the control group.

Endocrine Variables and Cognition

TT₃ levels were inversely associated with neuropsychological tests of episodic memory, and of language, visuospatial and executive function. Performance on neuropsychological tests declined with TT₃ levels as displayed in table 3. TT₃ levels predicted 26% of the variance in the cognitive composite scores. No associations between TT₃ and cognitive variables were found in the control group. After exclusion of 3 MCI cases on L-thyroxine treatment with TT₃ levels below the normal range, Rey Auditory Verbal Learning Test delayed recall ($p = 0.062$), the Boston Naming Test ($p = 0.092$), FAS word fluency

($p = 0.134$) and similarities ($p = 0.100$) did not reach significance. The inverse association for these tests with TT₃ remained. The inclusion of other endocrine variables did not improve the model to predict cognitive performance.

Stratification of the MCI cases by tertile of TT₃ levels (reference range: 1.3–3.1 nmol/l) revealed differences ($p > 0.05$) between the TT₃ groups in parallel serial mental operations, Block design, FAS word fluency, and Assessment of Subtle Language Deficits repetition. Differences were also observed for the episodic memory test, Rey Auditory Verbal Learning Test delayed recall, learning, maximum number of words learned, and recognition. The high-TT₃ group (TT₃ >1.6 nmol/l) had a 44.3% rate of forgetting between the maximum number of words and delayed recall, compared to 29.7% in the normal-TT₃ group (TT₃ = 1.4–1.6 nmol/l) and 23.1% in the low-TT₃ group (TT₃ <1.4 nmol/l). No mean difference in cognitive function could be found comparing MCI cases with low TT₃ levels to normal controls (data not presented).

Table 2. Selected neuropsychological test scores for MCI cases and controls: the Gothenburg MCI study

	Controls	MCI	p
Speed and attention			
Trail Making Test A, s	34.4 ± 8.3	40.8 ± 12.6	0.026
Digit Symbol	50.5 ± 7.7	43.9 ± 10.2	0.007
Memory			
RAVLT delayed recall	9.3 ± 2.3	7.5 ± 2.8	0.018
WLM delayed recall	21.9 ± 4.8	17.9 ± 7.9	0.013
Visuospatial function			
VOSP silhouettes	22.0 ± 2.6	21.1 ± 3.7	0.264
Block design	27.48 ± 7.9	25.7 ± 10.2	0.455
Language			
Token Test	21.1 ± 1.0	20.2 ± 1.6	0.014
Boston Naming Test	54.9 ± 4.8	53.1 ± 4.1	0.032
Executive function			
Stroop test, s	24.5 ± 5.3	31.5 ± 10.8	0.001
PaSMO, s	61.8 ± 23.2	84.0 ± 31.1	0.002
Cognitive estimation test	3.0 ± 1.6	4.0 ± 1.9	0.047
Cognitive weighted averages (PCA)	1.2 ± 1.5	-0.5 ± 2.5	0.001

Values denote means ± SD unless specified otherwise.
RAVLT = Rey Auditory Verbal Learning Test; WLM = Wechsler logical memory; VOSP = Visual Object and Space Perception; PaSMO = parallel serial mental operations.

Discussion

To our knowledge this is the first study to report an inverse association of serum TT₃ levels with cognitive function in MCI. While MCI cases with high TT₃ levels within the normal range showed more cognitive impairment in episodic memory, language and executive function, MCI cases with TT₃ levels at or below the lower boundary of the normal range were comparable with healthy controls. No association between TT₃ and cognition was found in the control group. It may be that circulating TT₃ is related to cognitive impairment under the compromising condition of MCI. Compared to healthy controls, higher measurements of AD pathology [41] and brain atrophy [42] have been observed in MCI, which may, in combination with higher TT₃, decrease cognitive function. This may explain why the association was specific to the MCI group. The lack of differences in TH between MCI and controls suggests that cognitive impairment is not due to thyroid disease or reduced levels of TH. Conversely, optimal TH levels may shift in MCI to lower ranges.

Potential direct action of T₃ on cognition and dementia pathology has been discussed. Aggravation of the cho-

Table 3. Univariate linear regression models predicting cognitive test scores by TT₃: the Gothenburg MCI study

	β	p	95% CI
Speed and attention			
Digit Symbol	-0.220	0.157	-26.5; 4.4
Trail Making Test A, s	0.254	0.100	-3.2; 35.7
Trail Making Test B, s	0.381	0.012	22.2; 167.6
Digit span forward	-0.189	0.225	-2.7; 0.7
Digit span backward	-0.356	0.019	-3.5; -0.3
Memory and learning			
RAVLT delayed recall	-0.397	0.008	-12.7; -2.0
RAVLT recognition	-0.342	0.029	-5.1; -0.3
RAVLT max	-0.437	0.004	-8.5; -1.7
WLM delayed recall	-0.055	0.734	-14.7; 10.4
RCF delayed recall	-0.219	0.158	-17.2; 2.9
Visuospatial function			
RCF copy	-0.271	0.079	-10.9; 0.6
VOSP silhouettes	-0.165	0.291	-8.3; 2.5
Block design	-0.494	0.001	-37.2; -10.6
Language			
Token Test	-0.231	0.136	-4.3; 0.6
Boston Naming Test	-0.318	0.038	-11.9; -0.3
FAS word fluency	-0.385	0.011	-51.5; -7.1
Similarities	-0.358	0.019	-10.6; -1.0
ASLD repetition	-0.500	0.001	-22.0; -6.3
Executive function			
PaSMO, s	0.384	0.012	16.2; 124.5
Dual Task (t-score)	-0.097	0.540	-17.3; 9.2
WCST	-0.352	0.052	-39.5; 0.2
Stroop test, s	0.164	0.306	-8.6; 26.6
Cognitive estimation task	0.216	0.174	-0.9; 4.8
Cognitive weighted averages (PCA)	-0.509	0.001	-10.5; -3.1

RAVLT = Rey Auditory Verbal Learning Test; WLM = Wechsler logical memory; VOSP = Visual Object and Space Perception; ASLD = Assessment of Subtle Language Deficits repetition; FAS = verbal fluency test (number of words beginning with F, A and S); PaSMO = parallel serial mental operations; WCST = Wisconsin Card Sorting Test (computer version).

linergic deficit and associated cognitive dysfunction observed in AD has been suggested due to TH-induced depletion of acetylcholine [10]. TH-induced oxidative damage and simultaneously reduced antioxidative defense enzyme levels may also increase neurodegeneration [43]. The interpretation of our findings is difficult since serum concentrations of TH do not accurately reflect TH metabolism in the central nervous system. With the occurrence of hippocampal and cortical atrophy in MCI and dementia, a normal concentration of peripheral TH entering the brain may become toxic under the condition

of an altered ratio of TH-sensitive neurons to TH. Increased CSF levels of rT_3 and decreased TT_3 have been observed in AD compared to healthy controls, which may reflect a relative excess of TH in the brain since corresponding serum TH levels were not altered [44]. The hippocampus is remarkably sensitive to T_3 , and relative excess may manifest in aggravated episodic memory impairment.

Despite a higher cortisol awakening response after a dexamethasone load in the MCI group, cortisol was not related to impaired cognitive function in MCI. Other hormones were not related to cognition as well. The effect of cortisol on cognition is well studied. The lack of association in this study may be due to the cross-sectional design. The effect of higher cortisol levels on cognition may be only observable over time in relationship to greater cognitive decline, rather than in cross-sectional associations with neuropsychological test scores [45]. It has also been reported that age-related increases in cortisol levels are not uniformly observed. In some people they increase and in others they remain stable in relationship to age [11], which may obscure a potential association with cortisol in this study. All participants in this study were considered healthy according to endocrine markers. A positive effect on cognition as shown by some hormone supplementation studies [25] may only be detectable in MCI cases with low hormone levels at baseline, followed by pharmacologically increased levels.

While our data point to some new findings relating TH to cognition in MCI, limitations need to be discussed. Our sample size is small and requires replication. The use of a comprehensive neuropsychological test battery and a comprehensive panel of endocrine markers with subse-

quent multiple comparisons may lead to familywise type I error and false-positive findings. Due to the explorative nature of this study, we did not correct for multiple comparisons. Analyses of the association of TT_3 with cognitive function included three MCI cases on L-thyroxine treatment. All three cases had normal TSH and fT_4 , but low TT_3 values. Upon exclusion of these cases, four neuropsychological tests, mainly assessing language, did not reach significance, but the results remained similar in essential aspects. Although this may point to a specific role for circulating TT_3 levels, a potential bias due to thyroid disease and treatment should not be excluded.

In conclusion, serum TT_3 was inversely associated with cognitive function in MCI, such that those cases with TT_3 levels at or below the lower boundary of the reference range performed better on neuropsychological tests. While the mechanisms remain unclear, optimal levels of TH under a compromising and potentially progressive condition such as MCI and related neuropathology need reconsideration.

Acknowledgments

The study was financially supported by the Swedish Research Council (grants No. K2002-21P-14359-01A, 09946 and 2005-8460); Swedish Brain Power; Sahlgrenska University Hospital; the National Institutes of Health/National Institutes on Aging; EU FP7 project LipiDiDiet, Grant Agreement No. 211696; Handlanden Hjalmar Svenssons Forskningsfond, Pfanenstills Forskningsstiftelse, the Alzheimer Research Fund, Axel Linders Stiftelse, Organon Forskningsstiftelse, the Foundation Gamla Tjänarinnor, the Sahlgrenska University Funds; Stiftelsen Psykiatriska Forskningsfonden, and the SUNY-Downstate Research Foundation.

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