0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(1):198–202

doi: 10.1210/jc.2004-1083

Increased Cerebrospinal Fluid Levels of 3,3′,5′-Triiodothyronine in Patients with Alzheimer's Disease

Simone Sampaolo, Angel Campos-Barros, Gherardo Mazziotti, Sergio Carlomagno, Vincenzo Sannino, Giovanni Amato, Carlo Carella, and Giuseppe Di Iorio

Department of Neurological Sciences (S.S., V.S., G.D.I.), and Department of Clinical and Experimental Medicine, F. Magrassi and A. Lanzara (G.M., G.A., C.C.), Second University of Naples, 80138 Naples, Italy; Department of Pediatric Endocrinology, Hospital Infantil Universitario Niño Jesús, Universidad Autónoma (A.C.-B.), E-28009 Madrid, Spain; and Department of Psychology, University of Trieste (S.C.), 34100 Trieste, Italy

Cerebrospinal fluid (CSF) levels of rT_3 were evaluated in 21 euthyroid patients with overt Alzheimer's disease (AD) and 18 matched healthy controls. The assessment also included transthyretin and total T_3 and T_4 CSF concentrations. Despite normal circulating thyroid hormone levels, AD subjects showed significantly increased rT_3 levels and an increased rT_3 to T_4 ratio in the face of unchanged CSF total T_4 and transthyretin levels. These results suggest an abnormal intracerebral thyroid hormone metabolism and possibly the occurrence of brain hypothyroidism, either as a secondary consequence of the ongoing process or as a cofactor in the progression of the disease. (*J Clin Endocrinol Metab* 90: 198–202, 2005)

ALZHEIMER'S DISEASE (AD) is a degenerative disorder of the central nervous system (CNS) characterized by loss of neurons in the limbic system, association neocortex, and basal forebrain accompanied by neuritic plaques, neurofibrillary tangles, and neuropil thread formation. Several laboratory and clinical data suggest that thyroid dysfunction might be relevant to the pathogenesis of AD. Evidence exists in both embryonic and adult laboratory mammals showing that thyroid hormones (TH) play a key role in the development and maintenance of basal forebrain cholinergic neurons typically involved in AD (1, 2). A reduction of c-erbAα TH receptor mRNA has been found in AD brains at the level of the hippocampus, another brain structure primarily affected by the disease (3). Furthermore, *in vitro* studies have shown that TH may regulate the gene expression of the amyloid precursor protein from which the Aβ peptide, the main component of β-amyloid that accumulates in the neuritic plaques of AD patients, is derived (4, 5).

Population-based studies also suggest that either hypo- or hyperthyroidism increases the risk of developing AD in the elderly (6–8). However, to date, no evidence of thyroid dysfunction has been found in AD patients. Indeed, available data only relate to the measurement of TH in the serum, where no major alterations have been detected during AD diagnosis (9). Furthermore, circulating TH levels do not properly reflect TH metabolism in the CNS (10–13). Thus, the question of whether cerebral metabolism of these hormones is modified in AD remains to be clarified.

Because most of the solutes from the cerebral extracellular spaces directly flow into the cerebrospinal fluid (CSF), analysis of CSF TH levels might provide better clues for investigating the status of TH metabolism and the role of TH in the brain of AD patients (14). In the CNS, TH metabolism is finely regulated by the activity of two different deiodinases, type 2 (D2) and type 3 (D3) iodothyronine deiodinases (11–13). In fact, D2 and D3 activity balance has been shown to be critical for allowing adequate intraneuronal concentration of the most biologically active form, T_3 (11, 13). D2 is responsible for the conversion of T_4 to T_3 and therefore is considered an activating enzyme. Its localization seems to be mainly glial (26). In contrast to the peripheral tissues, where most of the nuclear-bound T_3 is imported from the plasma pool, the supply of the physiologically active hormone T_3 in the brain depends mainly on the cellular uptake and intracellular deiodination of T_4 by D2. Thus, D2 is believed to play a critical role in the maintenance of TH function in the CNS. D3 catalyzes the conversion of T_4 and T_3 into the inactive metabolites rT_3 and 3,3′-diiodothyronine (T_2), respectively, by inner ring deiodination. D3 is considered an inactivating enzyme, because rT_3 and T_2 do not activate the TH receptor. D3 localization is mainly neuronal. Both D2 and D3 activities have been previously demonstrated in the human brain (15). The topographical pattern of rT_3 distribution within the human CNS is coincidental with that of D3, suggesting that most of the rT_3 present in the CNS is locally generated from T_4 via the intraneuronal 5-deiodination pathway catalyzed by D3 (11–13, 15).

In this study we assessed TH levels in CSF and serum samples from patients with AD and healthy subjects. We focused on the rT_3 concentration as a potential indicator of changes in the cerebral metabolism of TH (16–18).

First Published Online October 13, 2004

Abbreviations: AbQ, Albumin quotient; AD, Alzheimer's disease; CNS, central nervous system; CSF, cerebrospinal fluid; D2, type 2 deiodinase; D3, type 3 deiodinase; T_2, 3,3′-diiodothyronine; TH, thyroid hormone; TT_3, total T_3; TT_4, total T_4; TTR, transthyretin.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Subjects and Methods

Subjects

Twenty-one subjects (14 men and seven women) with diagnosis of probable AD were included in this study. This cohort was a subset from 68 consecutive subjects admitted to the Department of Neurological Sciences, Second University of Naples, between January 1995 and December 2000. All included patients were within 24–36 months after the onset of dementia symptoms. Each subject underwent neurological examination, standard neuropsychological evaluation (Mini-Mental State Examination, Mental Deterioration Battery) and laboratory investigations (brain magnetic resonance imaging or computed tomography, electroencephalogram, and serum and CSF analyses). The 21 individuals included in this study matched the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association Work Group diagnostic criteria for probable AD (9). All subjects were revised 6–12 months after the first assessment to confirm the diagnosis of AD. At reassessment, none of the subjects showed signs of concomitant complicating neurological disease. Furthermore, family history data were negative for familiar AD or other degenerative CNS diseases in all subjects. None of the patients had thyroid autoimmunity or dysfunction.

At admission, each subject showed normal nutritional state (body mass index, 20–27) and normal liver and renal functions and was not taking any medication. The median Mini-Mental State Examination score in our patients was 8.0, indicating overt CNS involvement at the time of lumbar puncture.

Eighteen consecutive nondemented subjects (10 men and eight women) admitted to the Department of Neurological Sciences, Second University of Naples, during the same period served as controls (Table 1). They presented with symptoms requiring CSF analysis. This, however, as well as other laboratory investigations did not disclose any neurological or systemic disorders, so no diagnosis of neurological disease was made at the time of discharge. These control subjects matched the AD group for age, sex (Table 1), and level of education. Moreover, none of the control subjects was taking any medication at the time of lumbar puncture.

CSF and serum analysis

After obtaining informed consent, approximately 8 ml CSF were taken by lumbar puncture between 0800–1000 h together with 10 ml venous blood. An aliquot of each serum and CSF sample was used for routine analyses, and the remaining (3–6 ml) was frozen within 20 min from sampling and stored at −80 C until hormone determinations. Fresh serum routine analyses included glucose, albumin, and Igs (Nephelometry, Dade Behring, Deerfield, IL). Fresh CSF routine analyses included cell count, evaluation of glucose, total protein, albumin and Igs (Nephelometry; Dade Behring). The CSF/blood albumin quotient (AbQ) as well as the serum/CSF IgG index were calculated. All CSF hormone measurements were conducted at the same time within the same assay.

TABLE 1. Age; sex; serum TSH, free T_4, free T_3, and rT_3 concentrations; as well as neuropsychological scores [Mini Mental Score Examination (MMSE)] in the 21 AD patients and 18 healthy subjects in the study

	Healthy subjects	Patients with AD	*P* values
Cases	18	21	
Sex (F/M)	8/10	7/14	0.50
Age (yr)	58.7 ± 3.5	59.6 ± 2.4	0.32
Serum thyroid function			
TSH levels (μU/liter)	1.89 ± 0.17	1.78 ± 0.19	0.37
Free T_4 levels (pg/ml)	12.0 ± 0.61	12.4 ± 0.50	0.83
Free T_3 levels (pg/ml)	3.1 ± 0.10	3.2 ± 0.08	0.20
rT_3 levels (ng/dl)	19.7 ± 0.30	22.0 ± 0.43	0.20
Neuropsychological score			
MMSE	27 ± 2.3	8 ± 1.5	<0.001

Data are the mean ± SEM. Unit conversion factors: TSH, μU/ml = mU/liter; free T_3, pg/ml = pmol/liter = 1.536; free T_4, pg/ml = pmol/liter = 1.887; rT_3, ng/dl = nmol/0.01536.

F, female; M, male.

For assessment of thyroid function, TSH, free T_4, free T_3, rT_3, and transthyretin (TTR) levels were evaluated in serum samples by standard procedures. Total T_4 (TT_4) and T_3 (TT_3), rT_3, and TTR levels were determined in CSF samples by highly sensitive RIAs, following the procedure described by Campos-Barros *et al.* (15). The rT_3 assay was validated by recovery tests using two different rT_3 amounts (5 and 10 ng) added to CSF aliquots. The recovered amounts were 101 ± 3.1% and 98.3 ± 0.8%, respectively. The sensitivity limits of the assays were 3.0 ng/dl (0.03 nmol/liter), 2.0 (0.03 nmol/liter), and 1.5 ng/dl (0.05 nmol/liter) for TT_4, TT_3, and rT_3, respectively.

Because TT_3 concentrations in individual CSF samples were close to [AD patients, 0.5–1.5 ng/dl (0.0076–0.023 nmol/liter); controls, 1.8–4.6 ng/dl (0.027–0.070 nmol/liter)] or even below the limit of determination (2.0 ng/dl) of the assay, TT_3 determinations were carried out in concentrated pools of CSF samples (16).

Each pool consisted of four or five CSF samples (AD patients) or three CSF samples (controls). The pooling of samples was performed blindly without knowledge of the results of previous hormone assays. According to the procedure described by Nishikawa et al. (16), 1.6-ml CSF aliquots were lyophilized and reconstituted with 125 μl charcoal-treated, iodothyronine-free CSF (concentration factor, 1 × 12.8). One hundred microliters of the concentrated samples were used for the TT_3 RIA. Each assay was carried out in duplicate. The intraassay variations were 5.4%, 5.6%, and 6.7% for TT_4, TT_3, and rT_3, respectively. CSF TTR levels were evaluated by nephelometry using commercially available kits (Dade Behring).

Statistical analysis

Data are expressed as the mean ± SEM. Statistical comparisons were performed using the *t* test for unpaired data. Frequencies were compared using the χ^2 test, with Fisher's correction, when appropriate. The relationship between variables was analyzed using Pearson's correlation coefficient. Statistical significance was assumed at $P \leq 0.05$.

Results

In AD patients, serum concentrations of TSH, free T_4, free T_3, and rT_3 were not significantly different from those in the control group (Table 1). Moreover, no significant differences were found in the CSF levels of TT_4 [107.9 ± 7.3 ng/dl (1.4 ± 0.09 nmol/liter) *vs.*98.9 ± 5.2 ng/dl (1.3 ± 0.07 nmol/liter); $t = -0.98$; $P = 0.34$], TTR [151.0 ± 1.4 mg/liter (27.5 ± 0.25 mmol/liter) *vs.* 145.0 ± 0.81 mg/liter (26.4 ± 0.15 mg/liter); $t = 1.33$; $P = 0.43$], AbQ (0.49 ± 0.02 *vs.* 0.47 ± 0.01; $t = 0.61$; $P = 0.81$), and the IgG index (0.45 ± 0.02 *vs.* 0.44 ± 0.02; $t = 0.43$; $P = 0.67$) between AD patients and healthy subjects.

In contrast, TT_3 levels in the concentrated CSF pools were significantly and markedly lower in AD patients (n = 5) than in controls [n = 6; 57.7 ± 3.2 ng/dl (0.89 ± 0.05 nmol/liter) *vs.* 148.9 ± 13.9 ng/dl (2.3 ± 0.21 nmol/liter); $t = 5.87$; $P < 0.001$], whereas CSF rT_3 levels were significantly enhanced (Fig. 1A) in AD patients compared with controls [12.6 ± 0.9 ng/dl (0.19 ± 0.02 nmol/liter) *vs.* 6.1 ± 0.29 ng/dl (0.10 ± 0.004 nmol/liter); $t = -4.5$; $P < 0.001$]. Moreover, as shown in Fig. 1, B and C, TT_3/TT_4 molar ratios (0.009 ± 0.001 *vs.* 0.026 ± 0.003; $t = 5.6$; $P < 0.001$) were significantly lower in AD patients than in healthy subjects, whereas a significant increase in the rT_3/TT_4 molar ratio (0.14 ± 0.008 *vs.* 0.09 ± 0.008; $t = -4.0$; $P < 0.001$) was observed in AD patients compared with controls.

CSF rT_3 concentrations were significantly correlated with CSF TT_4 levels ($r = 0.68$; $P < 0.001$) in normal controls as well as in AD patients ($r = 0.62$; $P < 0.003$), thus indicating that in both cases the amount of rT_3 in CSF was linked to T_4 metabolism.

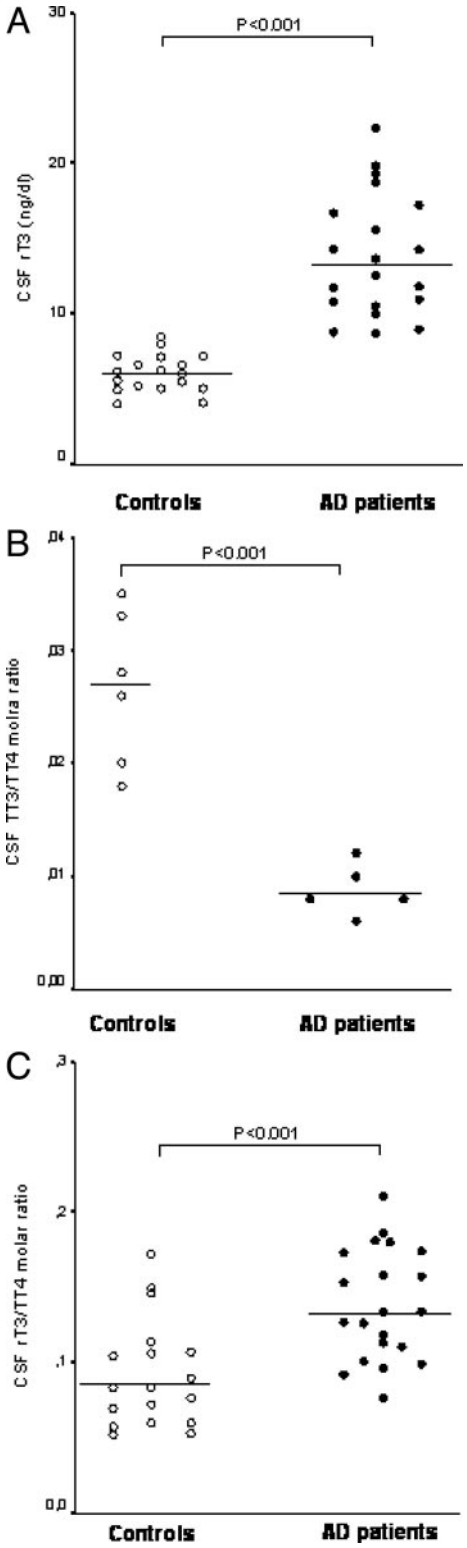

FIG. 1. rT_3 concentrations (A), TT_3/TT_4 molar ratios (B), and rT_3/TT_4 molar ratios (C) in the CSF of 21 AD patients and 18 healthy subjects (controls) participating in the study. TT_3/TT_4 molar ratios were calculated from determinations carried out in 12.8-fold concentrated CSF sample pools from AD patients (n = 5 pools) or controls (n = 6 pools). AD patient pools consisted of four or five CSF samples; control pools consisted of three CSF samples. *Solid lines* indicate the mean values for each group. Unit conversion factors for rT_3: ng/dl = nmol/0.01536.

Discussion

In this study, patients with overt AD were found to have normal thyroid function, as assessed by standard evaluation of serum TH levels. CSF rT_3 concentrations were, however, significantly enhanced compared with those in healthy subjects, suggesting an impairment of intracerebral TH metabolism during development of the disease.

Animal studies have shown that in the euthyroid brain, approximately 70–80% of the nuclear-bound T_3 originates from intracerebral T_4 to T_3 conversion, whereas only a modest 20–30% is obtained from the plasma pool (11, 13, 19). The amount of nuclear-bound T_3 in the brain is regulated by the fine-tuned and well coordinated activities of D2 and D3 deiodinases (11, 13, 15). A critical role is played by the D3 enzyme, which transforms T_4 and T_3 into the inactive metabolites rT_3 and T_2, respectively, protecting neuronal cells from excessive T_3 exposure. In fact, D3 activity increases in hyperthyroidism, whereas it decreases in the hypothyroid status (10). The increased CSF rT_3 concentration as well as the reduced CSF T_3 levels found in AD patients may reflect an enhancement of D3 activity in this disease. This hypothesis is supported by the 2-fold increase in the rT_3/T_4 molar ratio we found in the CSF of AD patients, which suggests that a considerable amount of T_4 is transformed into rT_3 in the CNS of AD patients. This might implicate the incidence of local hypothyroidism at the level of brain tissue, given the known inverse relationship between rT_3 and T_3 production (13).

An increase in the CSF rT_3 concentration has been found in other degenerative, vascular, and inflammatory diseases of the CNS (16–18, 20). This finding could be linked to a relatively unspecific passage of rT_3 from the serum into the CSF across an eventually damaged blood-CSF barrier, or it could reflect an enhancement of D3 activity in the CNS. In previous studies, markers of blood-CSF barrier integrity (*i.e.* AbQ) and indexes of intracerebral inflammation (*i.e.* IgG index) were not reported (16–18, 20). Moreover, the small size and clinical heterogeneity of the patient groups investigated in those studies (16–18, 20) did not allow us to draw any conclusion about the specificity of TH changes observed in the examined disorders. Therefore, in our study we investigated the status of brain TH metabolism in a cohort of AD patients that was homogenous with respect to clinical diagnostic criteria, disease duration, and various physiological parameters (*i.e.* TTR, IgG index, AbQ, and total T_3) that may affect intracerebral TH metabolism.

The CSF rT_3 concentrations determined in our study were lower than those found in previous reports (16–18), but compare well with values reported more recently by Labudova *et al.* (20). Indeed, different RIA protocols for iodothyronine determinations may not always generate comparable results, especially if they are conducted with different antisera, which may display variable antigen selectivities.

We cannot conclude whether the increased production of rT_3 in the CNS of AD patients is an adaptive phenomena to the disease or is a relevant physiopathological event (21). Cytokines are involved in the pathological process underlying AD (22), and they may enhance the activity of D3 with a consequential increase in rT_3 production, as observed in the systemic euthyroid sick syndrome (13, 23). A decrease in the

T_4 to T_3 conversion rate may favor the development of senile plaques due to the lack of T_3 inhibitory effects on β-amyloid gene expression (4) or may promote the formation of the amyloid precursor protein isoforms preferentially expressed in the brain of patients with AD (5). Moreover, rT_3 itself is known to be a very effective competitive inhibitor of D2-mediated deiodination of T_4 to T_3 and has also been reported to be a physiological regulator of D2 activity during development (24, 25). This suggests that an increase in local rT_3 production could hypothetically contribute to induce a local hypothyroid status. In addition to this, D2 activity is known to be predominantly expressed in astrocytes (26), which appear to be the primary affected targets of early pathophysiological events in AD (27). Thus, an impairment of astrocytic D2 activity might be the primary event affecting TH metabolism in AD brain. This could, in turn, explain the lower T_4 to T_3 conversion rate, as indicated by the lower T_3/T_4 ratio, and the increase in CSF rT_3 levels, as observed in our AD patients.

In the CSF, TTR is the main iodothyronine-binding protein transferring T_4 from the blood into the brain across the blood-choroid plexus barrier (28, 29). Although, an adequate concentration of TTR in the CSF does not seem to be required for preservation of the euthyroid status of the brain (30), it might be important for maintaining the intracerebral proteins as amyloid fibrils in soluble form (31). Indeed, previous studies reported decreased CSF TTR concentrations in late-onset AD patients, possibly due to epithelial atrophy of the choroid plexus (31, 32). However, we did not observe any significant difference in CSF TTR levels between AD patients and healthy subjects. Such a discordant result is probably due to the different age and post-disease onset stage of our patients compared with those previously studied by others (31).

In this regard, the maintenance of normal CSF TTR values in the subjects included in the present study support the hypothesis that the increase in CSF rT_3 levels was not secondary to an advanced stage of AD disease, because at the time of lumbar puncture, the choroid plexus epithelium still produced normal amounts of TTR. Note that our AD group included subjects who were within the range of 24–36 months post-disease onset, because our aim was to investigate whether alterations in brain TH metabolism could play a role in the development of overt AD symptoms.

rT_3 has been previously reported to cross the choroid plexus-CSF barrier (33). Because our AD patients had serum rT_3 levels comparable to those in control subjects, and the choroid plexus-CSF barrier was likely to be intact, we infer that the increase in CSF rT_3 levels was caused by abnormal intracerebral TH metabolism. This interpretation is supported by the findings of, respectively, decreased and increased TT_3/TT_4 and rT_3/TT_4 ratios in AD patients compared with control subjects.

In conclusion, our study reveals an increased CSF concentration of rT_3 and a higher rT_3 to TT_4 molar ratio in the face of decreased CSF TT_3 levels and a lower TT_3/TT_4 ratio in patients with overt AD. These findings suggest that even with an apparent systemic euthyroid status, local or tissue hypothyroidism may occur during the progress of the disease. Follow-up studies should clarify whether this condition is also present during early AD and how it develops during the advanced stages of the disease.

Acknowledgments

Received June 8, 2004. Accepted September 28, 2004.

Address all correspondence and requests for reprints to: Dr. Simone Sampaolo, Dipartimento di Scienze Neurologiche, Seconda Università degli Studi di Napoli, Piazza Miraglia 2, 80138 Naples, Italy. E-mail: simone.sampaolo@unina2.it.

References

1. **Calza L, Giardino L, Aloe L** 1997 Thyroid hormone regulates NGF content and $p75^{LNGFR}$ expression in the basal forebrain of adult rats. Exp Neurol 143:196–206
2. **Patel AJ, Hayashi M, Hunt A** 1987 Selective persistent reduction in choline acetyltransferase activity in basal forebrain of the rat after thyroid deficiency during early life. Brain Res 422:182–185
3. **Sutherland MK, Wong L, Somerville MJ, Handley P, Yoong L, Bergeron C, McLachlan DR** 1992 Reduction of thyroid hormone receptor c-erbAα mRNA levels in the hippocampus of Alzheimer as compared to Huntington brain. Neurobiol Aging 13:301–312
4. **Belandia B, Latasa MJ, Villa A, Pascual A** 1998 Thyroid hormone negatively regulates the transcriptional activity of the β-amyloid precursor protein gene. J Biol Chem 46:30366–30371
5. **Latasa MJ, Belandia B, Pascual A** 1998 Thyroid hormones regulate β-amyloid gene splicing and protein secretion in neuroblastoma cells. Endocrinology 139:2692–2698
6. **Yoshimasu F, Kokmen E, Hay ID, Beard CM, Offord KP, Kurland LT** 1991 The association between Alzheimer's disease and thyroid disease in Rochester, Minnesota. Neurology 41:1745–1747
7. **Ganguli M, Burmeister LA, Seaberg EC, Belle S, DeKosky ST** 1996 Association between dementia and elevated TSH: a community-based study. Biol Psychiatry 40:714–725
8. **Kalmijn S, Mehta KM, Pols HA, Hofman A, Drexhage HA, Breteler MM** 2000 Subclinical hyperthyroidism and the risk of dementia. The Rotterdam study. Clin Endocrinol (Oxf) 53:733–737
9. **McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM** 1984 Clinical diagnosis of Alzheimer's disease: report of the NINCDS ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34:939–944
10. **Dratman MB, Crutchfield FL, Gordon JT, Jennings AS** 1983 Iodothyronine homeostasis in rat brain during hypo and hyperthyroidism. Am J Physiol 245:E185–E193
11. **Leonard JL** 1992 Regulation of T_3 production in the brain. Acta Med Austriaca 19(Suppl 1):5–8
12. **Silva JE, Leonard JL, Crantz FR, Larsen PR** 1982 Evidence for two tissue-specific pathways for in vivo thyroxine 5′-deiodination in the rat. J Clin Invest 69:1176–1184
13. **Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR** 2002 Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 23:38–89
14. **Galasko D** 1999 Cerebrospinal fluid opens a window on Alzheimer disease. Arch Neurol 56:655–656
15. **Campos-Barros A, Hoell T, Musa A, Sampaolo S, Stoltenburg G, Pinna G, Eravci M, Meinhold H, Baumgartner A** 1996 Phenolic and thyrosyl ring iodothyronine deiodination and thyroid hormone concentrations in the human central nervous system. J Clin Endocrinol Metab 81:2179–2185
16. **Nishikawa M, Inada M, Naito K, Ishii H, Tanaka K, Mashio Y, Nakao K, Nakai Y, Udaka F, Imura H** 1981 3,3′,5′-Triiodothyronine (reverse T_3) in human cerebrospinal fluid. J Clin Endocrinol Metab 53:1030–1035
17. **Thompson Jr P, Burman KD, Wright FD, Potter MW, Wartofsky L** 1982 Iodothyronine levels in human cerebrospinal fluid. J Clin Endocrinol Metab 54:653–655
18. **Kirkegaard C, Faber J** 1991 Free thyroxine and 3,3′,5′-triiodothyronine levels in cerebrospinal fluid in patients with endogenous depression. Acta Endocrinol (Copenh) 124:166–172
19. **Malin JP, Kodding R, Fuhrmann H, von zur Muhlen A** 1989 T_4, T_3 and rT_3 levels in serum and cerebrospinal fluid of patients with amyotrophic lateral sclerosis. J Neurol 236:57–59
20. **Labudova O, Cairns N, Koeck T, Kitzmueller E, Rink H, Lubec G** 1999 Thyroid stimulating hormone-receptor overexpression in brain of patients with Down syndrome and Alzheimer's disease. Life Sci 64:1037–1044
21. **van Doorn J, van der Heide D, Roelfsema F** 1983 Sources and quantity of 3,5,3′-triiodothyronine in several tissues of the rat. J Clin Invest 72:1778–1792
22. **Eikelenboom P, Van Gool WA** 2004 Neuroinflammatory perspectives on the two faces of Alzheimer's disease. J Neural Transm 111:281–294

23. **Wartofsky L, Burman KD** 1982 Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome." Endocr Rev 3:164–217
24. **Kaplan MM** 1986 Regulatory influences on iodothyronine deiodination in animal tissues. In: Henneman G, ed. Thyroid hormone metabolism. New York: Marcel Dekker; 231–253
25. **St Germain DL, Galton VA** 1997 The deiodinase family of selenoproteins. Thyroid 7:655–668
26. **Guadano-Ferraz A, Obregon MJ, St Germain DL, Bernal J** 1997 The type 2 iodothyronine deiodinase is expressed primarily in glial cells in the neonatal rat brain. Proc Natl Acad Sci USA 94:10391–10396
27. **Abramov AY, Canevari L, Duchen MR** 2003 Changes in intracellular calcium and glutathione in astrocytes as the primary mechanism of amyloid neurotoxicity. J Neurosci 23:5088–5095
28. **Chanoine JP, Alex S, Fang SL, Stone S, Leonard JL, Korhle J, Braverman LE** 1992 Role of transthyretin in the transport of thyroxine from the blood to the choroid plexus, the cerebrospinal fluid, and the brain. Endocrinology 130:933–938
29. **Dratman MB, Crutchfield FL, Schoenhoff MB** 1991 Transport of iodothyronines from the bloodstream to brain: contributions by blood:brain and choroid:cerebrospinal fluid barriers. Brain Res 554:229–236
30. **Palha JA, Fernandes R, de Escobar GM, Episkopou V, Gottesman M, Saraiva MJ** 2000 Transthyretin regulates thyroid hormone levels in the choroid plexus, but not in the brain parenchyma: study in a transthyretin-null mouse model. Endocrinology 141:3267–3272
31. **Serot JM, Christmann D, Dubost T, Couturier M** 1997 Cerebrospinal fluid transthyretin: aging and late onset Alzheimer's disease. J Neurol Neurosurg Psychiatry 63:506–508
32. **Riisoen H** 1988 Reduced prealbumin (transthyretin) in CSF of severely demented patients with Alzheimer's disease. Acta Neurol Scand 78:455–459
33. **Hennemann G, Docter R, Friesema ECH, De Jong M, Krenning EP, Visser TJ** 2001 Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. Endocr Rev 22: 451–476

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.