Neurometabolite alterations in hippocampus in hypothyroid patients: An in-vivo 1H MRS Study

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Target audience: Researchers working in the field of endocrine disorders**.**

Purpose: It is known that the hippocampus is a thyroid hormone receptor-rich region of the brain[1]. The change in thyroid hormone levels may be responsible for alteration in hippocampal based functions such as learning, memory and attention. Neuroimaging studies have shown functional and structural changes in the hippocampus due to hypothyroidism in adult population [2, 3]. However, there are no studies regarding metabolic changes in the hippocampus due to alteration in thyroid hormone levels in adult population. Therefore, the present study was carried out to investigate metabolic alterations in brain of adult hypothyroid patients using in-vivo proton magnetic resonance spectroscopy (1H MRS).

Materials and Methods: In this study, we have taken 12 control subjects (mean age ± SD = 29.1±6.01) and 12 hypothyroid patients (mean age ± SD = 29.5±6.02). The informed consent was obtained from all the subjects prior to MRI study. All the patients recruited for the study were diagnosed with hypothyroidism for the first time and had not been treated earlier. Thyroid function tests, namely, free tri-iodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) were carried out in all hypothyroid patients and control subjects. The thyroid function tests were in the normal range for controls (FT3 = 2.8-7.1 pmol/l, FT4 =12.0-22.0 pmol/l and TSH = 0.27-4.2 µIU/ml). In hypothyroid group, patients with FT4 below normal and TSH of atleast 20 µIU/ml or above were recruited for the study. None of the subject had any history of neurological or psychiatric disorders. The study was approved by the Institutional ethics committee.
Imaging was performed on a 3-Tesla MRI scanner (Magnetom, Skyra, Siemens) with a 32 channel head coil and 25 mT/m actively shielded gradient system. The conventional MR imaging was done prior to MRS to rule out any structural abnormality using routine T2-weighted turbo spin-echo sequence. MRS was obtained using Point Resolved Spectroscopy sequence (PRESS) with acquisition parameters: TR/TE = 2000ms/33ms; 2048 spectral points; 1200 Hz spectral Bandwidth and 196 averages and a voxel size of 25 x 10 x 10 mm^3 for hippocampus region. Water suppression was achieved with a chemically selective suppression (CHESS) pulse sequence. Automated global shimming was used to minimize the Bo inhomogeneties and localized shimming was done to further minimize Bo field variations over the voxel of interest. Quantitative assessment of the neurometabolites was done using LC model. The LC-model fit for metabolites was fixed with Crame´r–Rao lower bound (CRLB) of 20 % or less. Total creatine (Cr+PCr) spectral intensity was used as the internal reference for relative quantitation.
Statistical analysis: Multivariate Analysis of Variance (MANOVA) using general linear model was performed to compare different metabolite ratios among the two groups. A p value ≤0.05 was considered to be statistically significant. All statistical analysis was conducted using SPSS (version 15.0, SPSS Inc, Chicago, IL, USA).

Results: On conventional MR imaging, none of the subject showed any abnormal signal intensity on T1-weighted and T2-weighted images. 1H MRS showed alteration at metabolite level in hippocampus due to hypothyroidism. The metabolites that were detectable and quantifiable in both control and patient group included glutamate (Glu), myo-inositol (mI), N-acetyl aspartate (NAA), combined peak of glycerophosphocholine and choline (tCh = total choline), combined peak of NAA and N-acetyl aspartyl glutamate (NAA+NAAG), combined peak of glutamate and glutamine (Glu+Gln; Glx) and creatine (tCr, creatine + phosphocreatine) (Table I). The representative figure and spectra acquired from right hippocampus region of control subject is shown in Fig 1 and Fig 2. Our results showed a significantly reduced Glu/tCr and mI/tCr ratios in hippocampus in hypothyroid patients as compared to controls.

Discussion: To the best of our knowledge, this is the first report of metabolic impairment in hippocampus region of brain in adult hypothyroid patients. Our findings showed significant decrease in Glu and mI levels in hypothyroid patients. It is known that Glu is an excitatory neurotransmitter and its metabolism depend on astrocytes whereas mI is considered as a glial marker and the most important osmolyte in astrocytes [4, 5]. Both are associated with astrocytic functions. It is also reported that astrocytes play an important role in thyroid hormone metabolism in the human brain [6]. Thyroid hormone regulates several aspects of astrocyte differentiation and maturation and thus controls neuronal growth [6]. If there is any alteration in astrocytes, then it may affect the Glu and mI levels. Therefore, the decreased Glu and mI levels in our study indicate the altered astrocytic functions in hypothyroid patients.

Conclusion: These metabolite alterations revealed by 1H MRS indicates that there might be alterations in astrocytic physiology and glutamate-glutamine cycle within hippocampus in hypothyroid patients. These findings provide preliminary evidence that hypothyroidism results in metabolic alterations which are associated with neurocognitive deficits in the adult human brain. However, the longitudinal study would be further continued on bigger sample size to see the metabolic changes in hippocampus, if any, after thyroxine treatment in these patients.

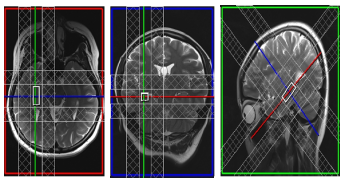

Fig.1: Location of 25×10×10 mm^3 voxel in right hippocampus of a normal subject.

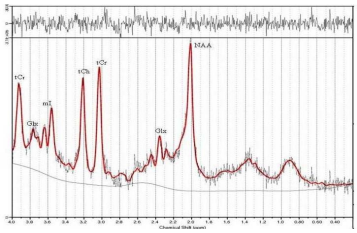

Fig.2: Typical spectrum from right hippocampus as analyzed by LCModel.

Table 1: List of metabolite ratios in control and hypothyroid patients obtained from right hippocampus. Asterisk indicate significant difference between groups (*p<0.05).

Metabolites	CRLB	Controls (N= 12)	Patients (N= 12)
Glu	< 12%	1.36 ± 0.13	1.21 ± 0.11*
mI	< 8%	1.00 ± 0.16	0.81 ± 0.21*
NAA	< 6%	1.01 ± 0.22	0.95 ± 0.07
GPC+ PCh	< 4%	0.30 ± 0.03	0.33 ± 0.05
NAA+ NAAG	< 6%	1.06 ± 0.21	1.03 ± 0.11
Glx	< 14%	2.01 ± 0.73	1.91 ± 0.38

References: 1. Martí-Carbonell MA et al. Acta Neurobiol Exp 2012; 72: 230-239.
2. Bauer M et al. J Clin Endocrinol Metab. 2009; 94: 2922-2929.
3. Cooke GE et al. Thyroid. 2014; 24(3):433-40.
4. Soares DP and Law M. Clin Radiol. 2009;64:12-2.
5. Van der Graaf M. Eur Biophys J. 2010; 39:527-540.
6. Anderson GW. Front. Neuroendocrinol. 2001; 22: 1-17.