Differential regulation of monocarboxylate transporter 8 expression in thyroid cancer and hyperthyroidism

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Abstract

Objective: Thyroid hormone (TH) transporters are expressed in thyrocytes and most play a role in TH release. We asked whether expression of the monocarboxylate transporter 8 (MCT8) and the L-type amino acid transporters LAT2 and LAT4 is changed with thyrocyte dedifferentiation and in hyperfunctioning thyroid tissues.

Design and methods: Protein expression and localization of transporters was determined by immunohistochemistry in human thyroid specimen including normal thyroid tissue (NT, n = 19), follicular adenoma (FA, n = 44), follicular thyroid carcinoma (FTC, n = 45), papillary thyroid carcinoma (PTC, n = 40), anaplastic thyroid carcinoma (ATC, n = 40) and Graves’ disease (GD, n = 50) by calculating the ‘hybrid’ (H) score. Regulation of transporter expression was investigated in the rat follicular thyroid cell line PCCL3 under basal and thyroid stimulating hormone (TSH) conditions.

Results: MCT8 and LAT4 were localized at the plasma membrane, while LAT2 transporter showed cytoplasmic localization. MCT8 expression was downregulated in benign and malignant thyroid tumours as compared to NT. In contrast, significant upregulation of MCT8, LAT2 and LAT4 was found in GD. Furthermore, a stronger expression of MCT8 was demonstrated in PCCL3 cells after TSH stimulation.

Conclusions: Downregulation of MCT8 in thyroid cancers qualifies MCT8 as a marker of thyroid differentiation. The more variable expression of LATs in distinct thyroid malignancies may be linked with other transporter properties relevant to altered metabolism in cancer cells, i.e. amino acid transport. Consistent upregulation of MCT8 in GD is in line with increased TH release in hyperthyroidism, an assumption supported by our in vitro results showing TSH-dependent upregulation of MCT8.

Introduction

Thyroid hormones (TH) are essential for cell differentiation, growth and metabolism (1). TH influx and efflux in tissues is regulated by TH transporters. So far, the most specific TH transporter is the monocarboxylate transporter 8 (MCT8) (2, 3) which is expressed in brain, heart, kidney, liver, skeletal muscle, placenta, testis and the basolateral plasma membrane of thyroid epithelial cells consistent with its role in thyroxine (T4) export from thyroid follicles (4, 5, 6). The preferred substrate of MCT8 is 3,3′,5-triiodothyronine (T3), but pharmacological studies showed that other THs such as T4, reverse T3 (rT3) and 3,5-diiodo-L-thyronine (T2) are transported as well (7). Secondary TH transporters, i.e. the large neutral amino acid transporters LAT2 and LAT4 facilitate in and...
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Subjects and methods

Thyroid samples

Thyroid tissue samples from 238 patients were investigated. Histological classification of tissue specimen according to WHO criteria was obtained by certified pathologists. TH transporter expression was investigated on paraffin-embedded tissues of 19 NTs, 44 follicular adenomas (FA), 45 follicular thyroid carcinomas (FTC), 40 papillary thyroid carcinomas (PTC), 40 anaplastic thyroid carcinomas (ATC) and 50 Graves’ disease (GD) thyroid specimens.

Immunohistochemistry

For immunohistochemical analysis the following antibodies were used: anti-MCT8/SLC16A2 (1:150, #HPA003353, Atlas Antibodies, Bromma, Sweden), anti-LAT2 (1:200, #0142-10, immunoGlobe, Himmelstadt, Germany) and anti-LAT4 (1:10, #HPA021564, Atlas Antibodies). All tissue sections were deparaffinized and rehydrated through graded series of alcohols (70%-96%-100% v/v ethanol, Sigma-Aldrich). Pretreatment was performed for 20 min in citrate buffer (pH 6.0) at 95°C. Tissue sections were blocked in an aqueous hydrogen peroxide solution (3% v/v H2O2, Carl Roth, Karlsruhe, Germany). Primary antibodies were incubated for 30 min at RT. Immunoreactivity was demonstrated using a classical polymer system (Zytomed, Berlin, Germany). Cell nuclei were stained with haematoxylin (1:8; Dako) for 5 min and sections were mounted in Entellan (Merck). All steps were performed in a semi-automated fashion using the Dako Autostainer (Dako). Paraffin-embedded human kidney tissue sections were used as positive control. Negative controls (no primary antibody) were included in the experimental set-up. The Olympus BX51 upright microscope (Olympus) was used for light microscopy. Tumour staining intensities were evaluated by calculating the ‘hybrid’ (H) scores as previously described (13).

Cell culture

For cell culture experiments the rat follicular thyroid cell line PCCL3 (14) was used (kindly provided by Pilar Santisteban, Instituto de Investigaciones Biomédicas ‘Alberto Sols’ CSIC-UAM, Madrid, Spain). Cells were cultured in Ham’s F12 (Invitrogen) medium with 5% w/v fetal bovine serum (FBS, Invitrogen), 5 µg/mL transferrin, 10 µg/mL insulin, 10 ng/mL somatostatin, 1 µM thyroid stimulating hormone (TSH) and 10 nM hydrocortisone (all from Sigma-Aldrich). PCCL3 cells were used between passages 5 and 15. Cells were grown at 37°C and 5% CO2. PCCL3 cell line was re-authenticated by mRNA expression profile of TH markers (Tg, Tpo, Nis and Thox1).

Three-dimensional culturing of PCCL3 cells

For cultivation of PCCL3 cells in a hanging drop culture, Methocel medium containing Ham’s F12 and methylcellulose powder (Sigma-Aldrich) was prepared. The powder (0.012 g/mL) was dissolved in warm medium (50°C) and swirled for three days at RT. Subsequently 2 mL of the Methocel medium were mixed with 8 mL of normal PCCL3 medium and 400 000 PCCL3 cells. Then droplets with a total volume of 25 µL were placed on a cell culture dish and incubated upside down for 48–72 h at 37°C and 5%
CO₂. The formed spheroids in the droplets were harvested and centrifuged for 7 min at 200 g. After supernatant was removed, spheroids were suspended in 200 µL of warm Histogel (Thermo Scientific) and placed in a Cryomold on ice. After curing, cells were fixed with Histofix (Carl Roth) for 24 h. Subsequently cells were paraffin-embedded and analysed by immunohistochemistry.

**Stimulation of PCCL3 cells**

For stimulation experiments, PCCL3 cells (50 000 cells/mL) were seeded in 6-well plates and cultured for three days until 70–80% of confluence. Prior to stimulation cells were starved for 72 h with medium containing Ham’s F12 without serum and hormones (starvation medium). Then cells were incubated in presence of 10 U/mL TSH (Sigma-Aldrich) for 8 h.

**Immunoblot**

The following antibodies were used: anti-MCT8 (1:1000, #HPA003353, Atlas Antibodies), anti-LAT2 (1:200, #0142-10, immunoGlobe), anti-LAT4 (1:10, #HPA021564, Atlas Antibodies), anti-GAPDH (1:6000, #ACT001P, Acris Antibodies, Herford, Germany), anti-rabbit IgG HRP-linked antibody (1:2000, #7074, Cell Signaling) and anti-rabbit IgG DyLight 488 (1:5000, #35553, Thermo Fisher). Whole protein lysates were extracted by radio-immunoprecipitation assay lysis (RIPA)-buffer (150 mM sodium chloride, 50 mM Tris hydrochloride, 1% v/v Tergitol (NP-40), 0.5% w/v sodium deoxycholate, 0.1% w/v sodium dodecyl sulphate, 2 mM ethylenediaminetetraacetic acid and 50 mM sodium fluoride, all from Sigma-Aldrich). In addition, a phosphatase and protease inhibitor cocktail (both from Roche) were added to the buffer. Lysed cells were incubated on ice for 20 min and then centrifuged for 20 min at 4°C and 13 300 rpm. Extracted proteins were quantified by BCA protein assay (Pierce/Thermo Scientific). Aliquots of proteins (20 µg) were separated on an 8% SDS-gel, blotted onto a polyvinylidene difluoride (PVDF, BioRad) membrane using the wet-blot technique at 4°C overnight (BioRad). Unspecific binding sites were blocked with 5% w/v non-fat milk (Carl Roth) or 5% w/v bovine serum albumin (BSA, Sigma-Aldrich) for 1 h at RT. Primary antibodies were incubated overnight at 4°C in 5% w/v BSA/T-BST. Incubation of the secondary antibody was performed for 2 h at RT in 2.5% w/v non-fat milk/T-BST. The visualization of the proteins was done by luminescence using the Immun-Star WesternC Kit (BioRad) or by fluorescence dependent on the secondary antibody. Differences in protein expression levels were quantified by densitometry using the ImageLab Software (BioRad). Relative values of the loading control GAPDH as well as MCT8, LAT2 or LAT4 were calculated. The target protein values were divided by the calculated relative values of the respective control. The adjusted values were used to calculate the geometric mean of the controls and target protein followed by calculation of the percent of protein level alteration.

**Immunofluorescence**

PCCL3 cells (50 000 cells/mL) were seeded on cover slides and incubated at 5% CO₂ and 37°C for 48 h. Cells were washed twice with phosphate buffer saline (PBS, Invitrogen) for 5 min and then fixed with 4% paraformaldehyde (PFA, Sigma-Aldrich) for 15 min at RT. PFA was aspirated, cells were washed three times with PBS and were permeabilized with 0.1% v/v Triton X-100 (Sigma-Aldrich) in PBS for 10 min at RT. Blocking was performed by using 3% w/v BSA (Sigma-Aldrich) in PBS for 1 h at RT. Cells were washed three times with 0.1% w/v BSA/PBS and a specific primary antibody against MCT8 (1:1000, #HPA003353, Atlas Antibodies) was diluted in 0.1% w/v BSA/PBS. After incubation with the primary antibody (4°C, overnight) cells were washed six times with 0.1% w/v BSA/PBS. Then, cells were incubated with the secondary antibody AlexaFluor 488 goat anti-rabbit (1:250, Invitrogen) for 1 h at RT in 0.1% w/v BSA/PBS. Cells were washed six times with 0.1% w/v BSA/PBS for 5 min and detection of the cytoskeleton was performed by incubation with Phalloidin 555 (1:60, Invitrogen) in 0.1% w/v BSA/PBS for 20 min at RT. Visualizing of the nucleus was performed with Draq5 (1:500, BioStatus, Loughborough, UK) for 1 h at RT. Cover slides were embedded in ImmuMount (Thermo Scientific) and viewed with an LSM 510 Meta confocal microscope (Carl Zeiss Jena GmbH).

**Statistical analysis**

Results of the H-Score analysis are shown as mean ± standard error of the mean (s.e.M.). Analysis was performed by one-way analysis of variance (ANOVA) with Bonferroni’s multiple comparison post-hoc test using GraphPad Prism 5 software (GraphPad). Expression in thyroid carcinoma samples was compared to follicular adenoma and NTs. Expression in GD tissues was compared to NTs. For
immunoblot analysis Student’s t-test was performed. Differences were considered statistically significant if *\(P<0.05\), **\(P<0.01\) and ***\(P<0.001\).

**Results**

**TH transporter expression differs significantly between benign and malignant thyroid tumours**

TH transporter expression was investigated in FA, FTC, PTC, ATC and NTs respectively. Plasma membrane staining was found for MCT8 and LAT4 while LAT2 showed mainly cytoplasmic localization (Fig. 1).

The mean H-Score of MCT8, LAT2 and LAT4 differed between thyroid tumour entities. MCT8 was significantly downregulated in malignant thyroid tumours as compared to NT. LAT2 was significantly upregulated in PTC as compared to NT. LAT4 was significantly downregulated in ATC as compared to NT, whereas LAT4 staining in other thyroid tumours revealed a more heterogeneous expression pattern (Fig. 1 and Table 1).

**TH transporter expression is increased in hyperfunctional Graves’ disease tissues**

To address whether expression of TH transporters is altered in hyperfunctional thyroid tissues, immunohistochemical analysis of MCT8, LAT2 and LAT4 was performed in GD tissue and was compared to NTs. Significantly enhanced staining was observed for MCT8, LAT2 and LAT4 in Graves’ tissues (Table 2). Membrane localization was confirmed for MCT8 and LAT4 while LAT2 was localized in the cytoplasm (Fig. 2).

**MCT8 expression in rat thyroid cells is upregulated by TSH stimulation**

To investigate which pathway may contribute to TH transporter expression, we performed in vitro experiments in rat thyroid PCCL3 cells and focused on MCT8, LAT2 and LAT4 because these TH transporters showed distinct expression patterns for hyperfunctional thyroid tissues and/or malignant thyroid tumours. MCT8 expression and localization was determined in PCCL3 cells using...
By immunofluorescence, MCT8 was mainly located at the plasma membrane (Fig. 3A, arrows). Immunohistochemistry of a hanging drop culture of PCCL3 cells revealed exclusive membrane staining of MCT8 in PCCL3 cells (Fig. 3B).

Since hyperthyroidism, i.e. due to GD involves augmentation of cyclic adenosine monophosphate (cAMP) signalling, we asked whether TSH stimulation impacts TH transporter expression in PCCL3 cells. MCT8 protein expression was significantly upregulated after 8h of TSH stimulation (Fig. 4A).

Notably investigation of LAT2 and LAT4 expression in PCCL3 cells under TSH stimulation demonstrated that

Table 1  Immunohistochemical analysis of MCT8, LAT2 and LAT4 in human tissue of NT, FA, FTC, PTC and ATC.

<table>
<thead>
<tr>
<th>TH transporter</th>
<th>Thyroid entity</th>
<th>Number</th>
<th>Mean H-score ± s.e.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCT8</td>
<td>NT</td>
<td>19</td>
<td>53.9 ± 7.8</td>
</tr>
<tr>
<td></td>
<td>FA</td>
<td>44</td>
<td>49.6 ± 8.5</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>45</td>
<td>18.6 ± 5.8</td>
</tr>
<tr>
<td></td>
<td>PTC</td>
<td>40</td>
<td>22.6 ± 7.5</td>
</tr>
<tr>
<td></td>
<td>ATC</td>
<td>40</td>
<td>3.3 ± 2.0</td>
</tr>
<tr>
<td>LAT2</td>
<td>NT</td>
<td>19</td>
<td>55.8 ± 9.7</td>
</tr>
<tr>
<td></td>
<td>FA</td>
<td>19</td>
<td>68.7 ± 7.8</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>45</td>
<td>73.3 ± 4.3</td>
</tr>
<tr>
<td></td>
<td>PTC</td>
<td>40</td>
<td>98.6 ± 6.7</td>
</tr>
<tr>
<td></td>
<td>ATC</td>
<td>40</td>
<td>39.1 ± 5.4</td>
</tr>
<tr>
<td>LAT4</td>
<td>NT</td>
<td>5</td>
<td>106.3 ± 41.6</td>
</tr>
<tr>
<td></td>
<td>FA</td>
<td>5</td>
<td>52.0 ± 38.1</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>5</td>
<td>22.0 ± 19.5</td>
</tr>
<tr>
<td></td>
<td>PTC</td>
<td>5</td>
<td>11.0 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>ATC</td>
<td>5</td>
<td>0 ± 0</td>
</tr>
</tbody>
</table>

ATC, anaplastic thyroid carcinoma; FA, follicular thyroid adenoma; FTC, follicular thyroid carcinoma; LAT2, L-type amino acid transporter type 2; LAT4, L-type amino acid transporter type 4; MCT8, monocarboxylate transporter 8; NT, normal thyroid tissue; PTC, papillary thyroid carcinoma.

Table 2  Immunohistochemical analysis of MCT8, LAT2 and LAT4 in human tissue of NT and GD.

<table>
<thead>
<tr>
<th>TH transporter</th>
<th>Thyroid entity</th>
<th>Number</th>
<th>Mean H-score ± s.e.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCT8</td>
<td>NT</td>
<td>19</td>
<td>53.9 ± 7.8</td>
</tr>
<tr>
<td></td>
<td>GD</td>
<td>50</td>
<td>126.6 ± 6.5</td>
</tr>
<tr>
<td>LAT2</td>
<td>NT</td>
<td>19</td>
<td>55.8 ± 9.7</td>
</tr>
<tr>
<td></td>
<td>GD</td>
<td>50</td>
<td>143.5 ± 7.7</td>
</tr>
<tr>
<td>LAT4</td>
<td>NT</td>
<td>5</td>
<td>106.3 ± 41.6</td>
</tr>
<tr>
<td></td>
<td>GD</td>
<td>5</td>
<td>210.0 ± 10.0</td>
</tr>
</tbody>
</table>

GD, Graves’ disease tissue; LAT2, L-type amino acid transporter type 2; LAT4, L-type amino acid transporter type 4; MCT8, monocarboxylate transporter 8; NT, normal thyroid tissue.
neither LAT2 nor LAT4 expression levels were altered by TSH stimulation of PCCL3 cells (Fig. 4B and C). These in vitro data suggest TSH-dependent regulation of MCT8 but no other investigated transporters in thyroid tissues.

**Discussion**

In this study, we asked whether TH transporter expression in human thyroid tissues is linked to morphology and functional tissue status, which to our knowledge has not been investigated in detail so far. For immunohistochemistry we employed a large series of 238 thyroid tissues, comprising NTs, FA, FTC, PTC, ATC and GD tissues and used a semi-quantitative scoring system to convert expert, but still subjective perception of protein expression into quantitative data which can be used for statistical analysis. The H-Score scoring system is a reproducible scoring system which is applied by pathologists for routine immuno-analysis of human tissue specimen (13).

First, we addressed MCT8 since it is the most specific and best investigated TH transporter. By immunohistochemistry, we found moderate plasma membrane staining for MCT8 in human thyroid tissue samples. Furthermore we observed downregulation of MCT8 in thyroid cancers (FTC, PTC and ATC) compared to NT. Since MCT8 has been shown to play a role in TH export from thyroid follicles, this is in line with a decrease in efficient TH synthesis as known for thyroid cancers (15). Hence MCT8 could represent a suitable marker of thyroid differentiation. A potential role for MCT8 and alterations of TH intra-thyroidal tissue states has been discussed on the basis of a case report of PTC diagnosed in a patient with MCT8 deficiency and the finding of papillary thyroid structures in the Mct8 knock-out mouse model at 600 day of age (16). Studies using mice with a global deficiency in MCT8, and those doubly deficient in MCT8 and the related MCT10, revealed a molecular mechanistic explanation for such auto-thyrotoxic states (6). Upon altered TH transport capabilities of thyrocytes due to lacking MCT8 and/or MCT10, thyroglobulin storage is affected and enhanced utilization of thyroglobulin for TH liberation is observed (6), thereby explaining the increased intra-thyroidal TH levels (17). The pivotal role of MCT8 in TH synthesis and release is also illustrated in our analysis of GD specimen showing markedly increased MCT8 transporter expression, consistent with a functional role of MCT8 in augmented TH release in hyperthyroidism. One shortcoming of this study is that clinical data of our patients are lacking. On the other hand, we clearly show a regulation of MCT8 expression in thyroid tumours and hyperfunctioning tissues of GD. Furthermore, MCT8 expression is upregulated by TSH stimulation shown in our in vitro experiments in PCCL3 cells suggesting a cAMP dependent upregulation of MCT8 consistent with other proteins relevant for efficient TH synthesis including the sodium iodide symporter (NIS) (18). We also addressed the localization pattern of MCT8 in the rat thyroid cell line PCCL3. Results are in agreement with immunohistochemical studies of human tissue samples in that MCT8 is mainly located at the cell surface between neighbouring cells, i.e. at the basolateral plasma membrane domain of thyrocytes.

Interestingly, a similar regulation pattern as for MCT8 was found for the TH transporter LAT4 both in human ATC and hyperfunctional thyroid tissues in vitro and in vivo. Although previous studies suggest that LAT4 does
LAT4 expression patterns in GD tissues strongly suggest that this TH transporter contributes to adaptation of thyroidal TH homeostasis in hyperthyroidism if not exerting a functional role in TH release. In contrast to TSH-dependent upregulation of MCT8 in PCCL3 cells, LAT4 protein level was not altered by TSH. Therefore, LAT4 downregulation in ATC as well as LAT4 upregulation in GD tissues might hint to other functional roles of this transporter like amino acid rather than TH transport.

For LAT2 immunostaining of human thyroid specimen revealed a heterogeneous expression pattern. Thus, for LAT2 we found moderate staining mainly in the cytoplasm. Normally, plasma membrane localization would be expected for TH transporters exporting TH from thyrocytes (19, 20). However, in our series LAT2 was mainly located in cytoplasmic structures, presumably in vesicles of the endocytic pathway, which might be linked to the hypothesis of an endo-lysosomal functioning protein of LAT2 in the thyroid. Quantification of immunohistochemical analysis showed a significant upregulation of LAT2 in PTC compared to NT. Likewise, in GD, we found significant upregulation for LAT2. Thus, expression pattern of LAT2 observed in the different tissues are more likely reflecting other transporter properties of LAT2, i.e., to maintain influx of essential amino acids. In accordance, TSH stimulation of PCCL3 cells did not affect LAT2 expression.

In summary, we observed a gradual downregulation of MCT8 in FA and thyroid carcinomas (FTC, PTC and ATC) which would be in agreement with the activation of TK signalling pathways over cAMP dependent maintenance of thyroid cell differentiation during thyroid carcinogenesis. Additionally, upregulation of the TH transporter MCT8 in hyperfunctioning GD tissues is TSH-dependent and consistent with the proposed role in TH release.

In conclusion, MCT8 represents as a novel thyroid differentiation marker and could be involved in excessive TH supply in states of hyperthyroidism, thereby contributing to disease manifestation.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Figure 4
MCT8 expression is regulated by TSH stimulation in PCCL3 cells. Immunoblot analysis of PCCL3 cells after stimulation with thyroid stimulating hormone (TSH, 1 U/mL) for 8 h at 37°C. (A) Significant upregulation of monocarboxylate transporter 8 (MCT8) after TSH stimulation. (B) No differences in L-type amino acid transporter type 2 (LAT2) expression by TSH stimulation of PCCL3 cells. (C) No differences in LAT4 expression by TSH stimulation of PCCL3 cells. Representative examples are shown. Data are represented as mean ± s.e.m. of three independent experiments, Student's t-test, ***P < 0.001.
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