THYROID HORMONE TRANSPORTERS ARE EXPRESSED IN THE HUMAN HYPOTHALAMUS

Alkemade A, Friesema EC, Kalsbeek A, Swaab DF, Visser TJ, Fliers E. **Expression of thyroid hormone transporters in the human hypothalamus.** J Clin Endocrinol Metab 2011;96: E967-71. Epub April 20, 2011.

SUMMARY

BACKGROUND

Three revolutions have markedly advanced our knowledge of thyroid hormone action: the discovery of deiodinases (DIO) and of nuclear thyroid hormone receptors in the 1970s to 1980s and the detection of plasma membrane transporters in the past 10 years. MCT-8 (monocarboxylate transporter) was the first transporter to be identified. Inactivating mutations of MCT8 result in the severely debilitating Allan–Herndon–Dudley syndrome. This transporter is mainly responsible for neuronal influx of triiodothyronine (T_3) with dramatic consequences when it fails in the function of the human brain. Meanwhile two other transporters, the MCT10 and the OATP1C1 (organic anion transporting polypeptide 1C1) have been identified in humans, the former being relevant for neuronal efflux of thyroid hormones, the latter being mainly a thyroxine (T_4) transporter. Since their function in the central nervous system (CNS) is essential, it is important to localize them in the human hypothalamus. MCT8 has been identified earlier in the neurons and glial cells of the human hypothalamus. The present work extends these findings by convincingly demonstrating that not only MCT8 but also MCT10 and OATP1C1 are expressed in the hypothalamus.

METHODS AND RESULTS

Postmortem hypothalamus specimens from 10 euthyroid subjects and 1 hyperthyroid subject were investigated by immunocytochemical staining. For the OATP1C1 transporter, the adequacy of the antisera was carefully tested in transfected COS cells functionally expressing the transporter.

OATP1C1 was present in the paraventricular nucleus (PVN), supraoptic nucleus, and infundibular nucleus and in tanocytes along the third ventricle. The signal for MCT8 was restricted to nuclei, but the OATP1C1 signal was also found scattered throughout the hypothalamus in glial cells, particularly along the wall of the third ventricle. MCT10 was equally present in these nuclei and also in other hypothalamic nuclei (for details see Figure 2 of the article). Interestingly, there was no correlation with the corresponding thyroid hormone concentrations either in the euthyroid subjects or in the hyperthyroid subject. It is conceivable that the conditions of tissue collection may limit the value of the conclusions.

CONCLUSIONS

The studies show that the T_4 transporter OATP1C1 is ubiquitously present in the glial cells of the hypothalamus, thus supporting the assumption that this transporter allows entry of T_4 into deiodinase type 2 (DIO2)–rich cells. The resulting T_3 is then further transported by MCT8 into neurons. The neurons of the PVN also stain for OATP1C1 and can therefore import T_4. Since these cells in humans do not contain DIO2, the function of this transporter in these cells is not clear. MCT10, which enhances the export of thyroid hormones, may be implicated—together with the T_3- and T_4-deiodinating DIO3—in the reduction of thyroid hormone action.

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COMMENTARY

Receptors, deiodinases, and membrane transporters are critically linked to each other (1). The study of their colocalization in hypothalamic structures helps us to understand central thyroid hormone action. As an example, colocalization of DIO2 and OATP1C1 in glial cells preserves T_3 production in the PVN in MCT8 mutant mice, which may explain the absence of a neurologic phenotype in mice.

Meanwhile, TSH, free T_4 and free T_3 levels are still the only clinical tools for evaluating peripheral thyroid hormone action. By reading about the remarkable progress of thyroid hormone transport, clinicians will realize that our clinical judgment is only a crude appreciation of thyroid hormone function at the level of the target cell. Indeed, it may be quite different in the CNS and pituitary in comparison with the periphery. Perhaps, because of the new insights into the function of thyroid hormone transporters and action we will be able to give more refined answers to many clinically relevant questions.

— Albert G. Burger, MD

REFERENCE

1. Visser WE, Friesema EC, Jansen J, Visser TJ. Thyroid hormone transport in and out of cells. Trends Endocrinol Metab 2008;19:50-6.