Triiodothyroacetic acid treatment in MCT8 deficiency: a word of nuance

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The Allan-Herndon-Dudley syndrome (AHDS) is caused by a defect in the thyroid hormone (TH) transporter MCT8 (1,2). The clinical phenotype comprises a "central" component due to impaired psychomotor development with severe intellectual disability, axial hypotonia and dystonia, and a ''peripheral'' component dominated by signs of thyrotoxicosis, caused by elevated serum T3 levels. The combination of high serum T3, low or low-normal serum (F)T4 and normal to modestly elevated serum TSH levels are very typical for AHDS (3).

During the last decade, important clues about the pathophysiology of ADHS have evolved largely through studies of mouse models. *Mct8* KO mice faithfully mimic the peripheral phenotype of AHDS patients, and studies in these mice have yielded important insights into the mechanisms by which these changes in serum TH levels occur (4-6). Unfortunately, *Mct8* KO mice do not show any neuromotor abnormalities. This is probably explained by the compensatory role of the specific T4 transporter Oatp1c1 in mice, which ensures sufficient TH levels in brain for normal development (7). Indeed, *Mct8*/*Oatp1c1* double KO mice exhibit neuromotor abnormalities, caused by the hypothyroid state in the brain (8).

The therapeutic options for AHDS patients are currently limited. Many reports mention the empirical use of levothyroxine supplementation, prompted by the low serum FT4 and slightly elevated TSH, without any positive clinical effects (3). The combination of propylthiouracil plus levothyroxine normalizes the peripheral thyrotoxic state, although beneficial effects on neurocognitive function are not observed as expected (9,10).

Recently, the use of T3 analogs, which do not require MCT8 for cellular uptake, has been explored as a potential therapy for AHDS patients. DITPA (3,5-diiodothyropropionic acid) was shown to improve markers of the peripheral thyrotoxic state in *Mct8* KO mice (11). Subsequently, some patients were treated with DITPA, with improvement of serum T3 concentrations and markers of peripheral T3 action (12).

The TH metabolite Triac (3,5,3,'-triiodothyroacetic acid) has also been proposed as candidate for T3 analog treatment of AHDS patients. *In vitro* studies have clearly shown that Triac acts similarly in MCT8-deficient and control cells, indicating that MCT8 is not involved in cellular entry of Triac. Studies in

Mct8/*Oatp1c1* double KO mice indicated that daily administration of a low Triac dose (50 ng/g body weight) improved cerebellar development and cortical myelination, although only a high Triac dose (400 ng/g body weight) was able to completely prevent these abnormalities (13).

In the present issue, Bárez-López et al. describe the results of Triac administration (30 ng/g body weight daily) to *Mct8* KO mice (14). The authors show that plasma T3 and T4 concentrations are lowered after 10 days of Triac treatment, suggesting that Triac reduces peripheral thyrotoxicosis by suppression of TSH secretion. The main goal was to study the effects of Triac on two different brain areas (cortex and striatum). After treatment, T3 levels were lowered in brains of *Mct8* KO mice, although only significantly in the cortex. Expression of most T3-responsive genes was grossly unaltered, although *Aldh1a1* expression was slightly decreased in the striatum and *Flywch2* expression was decreased in both brain areas. The authors suggest that in their studies Triac did not reach the brain and that the low plasma T4 levels could be harmful to the brain. In the title, the authors add a warning flag that Triac treatment in MCT8 deficiency should be considered with caution.

The study by Bárez-López et al. is important as it shows that Triac can attenuate the thyrotoxicosis of *Mct8* KO mice. However, the results based on studies performed on *Mct8* KO mouse brains should be interpreted in the context of the model used and the safety profile obtained in humans.

First, as *Mct8* KO mice lack any overt neurological deficit, they do not provide an optimal model for the neurocognitive phenotype of AHDS. Recent, histological studies on brains of AHDS patients carried out by the same group are highly compatible with severe cerebral hypothyroidism (15). In contrast with brains of *Mct8*/*Oatp1c1* double KO mice, which are deeply hypothyroid, brains of *Mct8* KO mice are only mildly hypothyroid and apparently undergo normal development (8). Therefore, given that Triac decreases plasma T3 and T4 concentrations in *Mct8* KO mice, it is not surprising that brain TH content is decreased as well, very similar to the findings in the wild type littermates (14). As a consequence, expression of T3-dependent genes is reduced if brain T4 and T3 concentrations are not counterbalanced by increased brain Triac levels. In view of the strong reduction in plasma TH content, it is rather surprising that

only a few genes show decreased expression. This could be explained by sufficient amounts of Triac reaching the brain.

Second, the dose and route of Triac should be taken into account. In the study by Bárez-López et al., a dose of 30 ng/g was chosen as this reflects doses used previously in humans (5-50 ug/kg) (14). As Triac was administered to the drinking water, and assuming that mice mainly drink water at night, this situation is very different from treatment of humans, where Triac is administered 1-3 times daily. With a half-life of approximately 6 hours, the latter regimen results in high peaks in serum and probably also tissue Triac levels, which is different from the more stable but lower levels during continuous Triac ingestion during half a day (night). The tissue Triac peaks may result in more pronounced T3-like effects. This is supported by studies in *Mct8*/*Oatp1c1* double KO mice in which Triac was injected only once daily, thus improving the hypothyroid state in the brain (13).

Third, it should be realized that there is over 20 years of clinical experience with Triac for various diseases. Triac therapy has been safely applied to patients with different thyroid disorders, including long-term treatment in patients with resistance to TH due to mutations in THRB (16). Although Triac has a limited application, no adverse effects have been reported so far (information brochure Triac 2014, available upon request).

The study of Bárez-López et al. touches on an important issue in the treatment of AHDS patients with Triac, and this concerns the selection of the optimal Triac dose. This is determined by the delicate balance between its central and peripheral effects (Figure 1). As in other clinical settings (TH resistance, thyroid cancer), the beneficial peripheral effects of Triac are mediated by potent suppression of TSH secretion with consequent decreases in serum TH levels. The beneficial nature of this treatment indicates that the effects of decreased serum TH levels are not outweighed by the thyromimetic effects of Triac. Potentially beneficial central effects of Triac in AHDS patients depend on the possibly negative impact of decreased supply of serum TH, which could offset the positive effects of Triac on the brain. Since MCT8 is the major transporter for T4 and T3 in the human blood-brain barrier, the impact of the decreased serum TH levels in response to Triac administration to AHDS patients may well be

negligible. However, the question remains to be answered exactly how much Triac should be given to AHDS patients to improve the thyroid state of both the brain and peripheral tissues. This can only be studied in well-designed clinical trials. For an optimal beneficial effect, any therapy should be initiated as soon after (or before) birth as possible.

Given the severity of the disease and the limited treatment options, it is paramount to carefully evaluate each potential therapy, including but not limited to T3 analog treatment. In particular, if transition from animal models to patients is considered, Triac treatment as well as other therapies should be applied carefully to AHDS patients in well-controlled trials such as the Triac Trial (NCT02060474 on https://clinicaltrials.gov/). Therefore, as for other rare diseases, it is important to join forces in the treatment of AHDS by sharing and centralizing clinical experience and expertise. It is reassuring to see how researchers and clinicians in this field collectively strive to explore therapies for this devastating disease, exemplified by the study of Bárez-López et al. (14).

Disclosure Statement

Dr. W. Edward Visser is the principal investigator of the above-mentioned Triac Trial in AHDS patients. Otherwise, the authors have nothing to disclose.

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Figure 1. Schematic showing that MCT8 mutations result in decreased TH levels in the CNS and elevated T3 levels in peripheral tissues. Administration of Triac to AHDS patients is expected to decrease peripheral T3 levels and increase TH action in the brain.

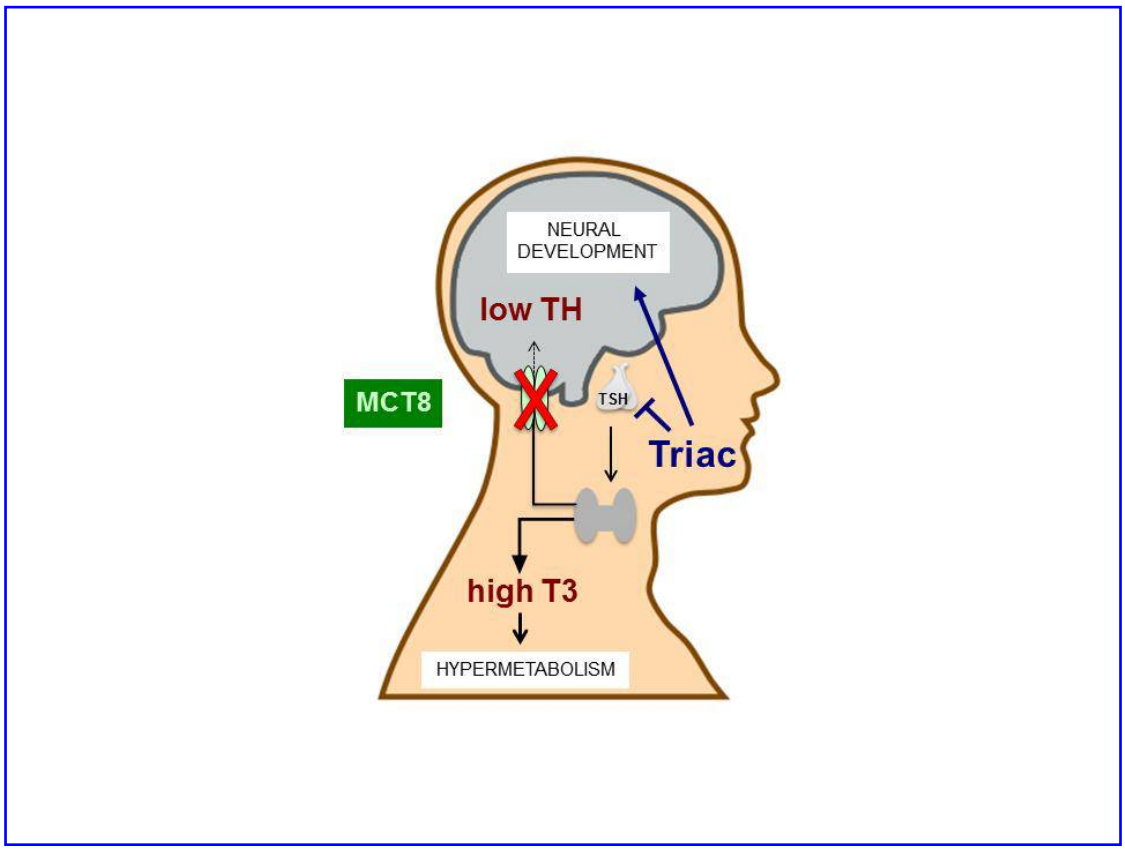

Figure 1