the two treatments (p=0.01). Fat mass decreased by an average of 0.7 kg on LT4 (p=0.03 vs. baseline) and 1.5 kg on LT3 (p<0.01 vs. baseline) and differed between treatments (p=0.01). There was a significant difference in total cholesterol of 13.3 mg/dL (p<0.001) and in low-density lipoprotein cholesterol (LDL) of 10.8 mg/dL (p<0.001) between LT4 and LT3 treatment arms; for both, the levels were lower on LT3 than LT4. No differences were seen in the other assessed outcomes. **Conclusions:** In a cross-over study of treatment of LT4 or LT3 in persistent subclinical hypothyroidism, participants lost fat mass and weight after each treatment, with a greater decrease after treatment with LT3. These findings support different physiologic responses to LT4 compared with LT3.

Thyroid

THYROID HORMONE METABOLISM AND ACTION

Postnatal Hypothyroidism Permanently Disrupts Neural Stem Cell Fate in the Murine Subventricular Zone

Pieter Vancamp, PhD, Barbara Demeneix, Professor, Sylvie Remaud, PhD.
Centre National de la Recherche Scientifique, Paris, France.

The subventricular zone (SVZ) of the adult mammalian brain harbors neural stem cells (NSCs) that generate neurons and oligodendrocytes throughout life. Single-cell RNA-Seq analysis on mouse SVZ-NSCs isolated at different developmental stages established they gradually acquire their adult neurogliogenic identity between postnatal day (P) 7 and 20. However, the factors governing this transition remain elusive. As a key factor driving transcriptional responses during brain development, as well as NSC lineage commitment in the adult SVZ, we hypothesized that thyroid hormone (TH) could fulfil this role. TH serum levels rise postnatally and peak around P15. Re-analysis of single-cell data from the P2 and P20 SVZ revealed a dynamically increased expression of the TH transporters *Mct8* and *Oatp1c1*, as well as the TH-(in)activating deiodinases *Dio2* and *Dio3* in NSCs, signs that local TH action is promoted. Immunostainings showed a concomitant burst in SVZ-neurogenesis between P4 and P21. Then, to study what occurs if TH synthesis is blocked, we fed dams a 0.15% propylthiouracil-enriched diet from embryonic day 15 to P21. Postnatal hypothyroidism decreased PH3-positive mitotic cell numbers at P4 and P21, whereas increased *Sox2* expression coincided with a larger proportion SOX2-positive SVZ-NSCs and progenitors. In the dorsal SVZ, the main site of neurogliogenesis, less neuroblasts were detected at P21, while numbers of OLIG2-positive oligodendroglia precursors did not change significantly. Next, we prepared *in vitro* neurospheres from dissected SVZs of control and PTU-treated mice, and allowed them differentiate with or without exogenous T_3. The neuro/glia balance in neurosphere cultures prepared from P4 animals of either condition did not change when T_3 was added, suggesting perinatal NSCs are irresponsive to TH. The balance did change in T_3-treated neurospheres prepared from control P21 animals, however, not in those from P21 PTU-exposed mice, suggesting hypothyroid NSCs are irresponsive to T_3. Lastly, we examined 3-month-old mice that regained a normal diet following developmental PTU exposure. Fewer oligodendroglia precursors in the SVZ resulted in a lasting altered neuro/glia output. A reduced ability to remember earlier-presented odors indicates impaired olfaction, a behavior strongly depending on SVZ-neurogenesis. Taken together the data indicate that developmental hypothyroidism affects postnatal SVZ organization and permanently alters NSC lineage commitment. Our study allows to determine relevant new read-outs to identify adverse outcome events on brain development and will permit comparison with events following exposure to endocrine disruptors.

Thyroid

THYROID HORMONE METABOLISM AND ACTION

Reverse T3 Level and T3 to Reverse T3 Ratio in Dried Blood Spot Samples at Birth May Facilitate Early Diagnosis of MCT8 Deficiency

Hideyuki Iwayama, MD, PhD[1], Hiroki Kakita, MD, PhD[1], Masumi Iwasa, BE[1], Shinsuke Adachi, MD, PhD[2], Kyoko Takano, MD, PhD[3], Masahiro Kikuchi, MD, PhD[4], Yasuko Fujisawa, MD,PhD[5], Hitoshi Osaka, MD, PhD[6], Yasumasa Yamada, MD, PhD[1], Akihisa Okumura, MD, PhD[1], Samuel Refetoff, MD[7].
[1]Aichi Medical University, Nagakute, Japan, [2]Fukuchiyama City Hospital, Fukuchiyama, Japan, [3]Shinshu University Hospital, Matsumoto, Japan, [4]Hitachi General Hospital, Hitachi, Japan, [5]Hamamatsu University School of Medicine, Hamamatsu Shizouka, Japan, [6]Jichi Medical School, Shimotsuke, Japan, [7]University of Chicago, Chicago, IL, USA.

Background: Monocarboxylate transporter 8 (MCT8) deficiency is an X- chromosome-linked neurodevelopmental disorder resulting from impaired thyroid hormone transporter across cell membrane. The diagnosis of MCT8 deficiency is typically delayed owing to the late appearance of signs and symptoms as well as inability of standard biomarkers of neonatal screening to make an early diagnosis. Here, we report for the first time the ability to identify MCT8 deficiency at birth using dried blood spot (DBS) samples.
Methods: We measured T3, T4, and reverse T3 (rT3) levels in DBS samples obtained at birth in healthy neonates (n = 42) and neonates with genetically confirmed diagnosis of MCT8 deficiency (n = 6). T3, rT3 and T4 levels were measured in 8 mm diameter DBS samples using liquid chromatography-tandem mass spectrometry.
Results: Mean ± SD level of T3 tended to be higher in the MCT8 group than that in healthy neonates (0.941 ± 0.183 ng/mL vs. 0.742 ± 0.195 ng/mL, p = 0.0525). More importantly rT3 level in the MCT8 group was significantly lower than that in healthy neonates (0.317 ± 0.065 ng/mL vs. 0.768 ± 0.196 ng/mL, p < 0.0001) and the T3/rT3 ratio in the MCT8 group was significantly higher (3.04 ± 0.67 vs. 1.01 ± 0.34, p < 0.0001) with no overlap of values. T4 was lower in the MCT8 group than in healthy babies (93.4 ± 22.4 ng/mL vs. 156.7 ± 35.9 ng/mL, p < 0.0005) and the T3/T4 ratio of the MCT8 deficient group was higher (0.0105 ± 0.0029 vs. 0.0051 ± 0.0010, p< 0.0001).
Conclusion: rT3 and T3/rT3 ratio measured in the DBS obtained from neonates can serve as biomarkers for diagnosis of MCT8 deficiency at birth.