human development. iHeps are robustly responsive to TH with over 1000 regulated genes. Importantly, they allow us to use CRISPR/Cas9 to determine molecular physiology and mechanism of disease. To demonstrate the role of TRs in TH signaling in human liver cells we have focused on TRβ1 the main TR isoform expressed in liver. we knocked out TRβ1 (THRBKO) using guide RNAs (gRNAs) we engineered to specific genomic loci to truncate the expression of this isoform at the DNA binding domain. Also, to define mechanisms of TR action in the context of RTH, we used this same approach to introduce the Δ337T mutation found in human TRβ1 that causes RTH. Both THRBKO and Δ337T lines are karyotypically normal and flow cytometry analysis in both lines demonstrated that these lines differentiated normally into hepatocytes after gene editing with CRISPR/Cas9. Once clones were identified the edited iHeps were treated with PBS (vehicle) or T3 (10nM) for 24 hours. Real-time quantitative PCR (RT qPCR) was done to assess mRNA expression of T3 target genes. RT qPCR analysis confirmed the success of TRβ1 deletion as the response to T3 was lost on both positive and negative THRB targets. In the Δ337T iHeps, the response to TH was diminshed indicating the successful generation of this line. These preliminary results confirm our ability to edit IPSCs and then to differentiate into hepatocytes, allowing us to further study the action of TH and the mutations involved in RTH.

Thyroid

THYROID HORMONE METABOLISM AND ACTION

Nuclear Receptor Corepressors NCoR1 and SMRT Plays Unique Roles in Central Nervous System

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The nuclear corepressor 1 (NCoR1) and the silencing mediator of retinoid and thyroid hormone receptors (SMRT) are critical coregulators of the thyroid hormone receptor (TR), mediating transcriptional repression via histone deacetylation. Thyroid hormone (TH) plays an essential role in many physiological processes via the TR. How the corepressors regulate TR signaling is not fully understood, especially in central nervous system (CNS). To determine the role of NCoR1 and SMRT in the CNS, we used mice with conditional NCoR1 ($NCoR1^{lox/lox}$) and SMRT ($SMRT^{lox/lox}$) alleles in combination with mice that express *Cre* recombinase in a neuronal specific fashion (Snap25-Cre). Global deletion of NCoR1 or SMRT during embryogenesis results in lethality. We also showed that NCoR1/SMRT double knock-out mice die within two weeks after induction of Cre activity in adult mice. Now, we found that neuronal specific NCoR1 or SMRT KO mice survive without obvious impairment of neuronal development. However, NCoR1/SMRT double knock-out mice die within postnatal 1-2 weeks and have impaired body growth. Thus, both NCoR1 and SMRT have important roles in maintaining normal neuronal function. Recently, cased of mutations in NCoR1 and SMRT in humans have been reported. These cases report phenotypes including Autism Spectrum Disorder (ASD) and intellectual disability. The cerebellum has been thought to contribute to motor control and learning. Surprisingly, it has also been shown to be a key brain structure involved in social cognition and its dysfunction may play a role in ASD. The Purkinje cell is the main neuron in the cerebellum. Thus, we generated cerebellar Purkinje cell specific NCoR1/SMRT knock-out mice using L7/Pcp2-Cre mice. In contrast to neuronal specific KO mice, both NCoR1 or SMRT single or double knock-out mice survive until adulthood. SMRT Purkinje cell knock-out mice showed abnormalities in 3ch social interaction test indicating impaired social functioning, similar to some ASD symptoms. Electrophysiological testing showed current injection evoked more action potentials in SMRT KO mice. These results suggest Purkinje cell dysfunction caused by SMRT deletion may result in social disability. Our data demonstrate for the first time that NCoR1 and SMRT have separate functions in different areas of the brain but also have some redundant function when knocked out together in all neurons.

Thyroid

THYROID HORMONE METABOLISM AND ACTION

Physiologic Effects of Levothyroxine and Liothyronine in the in Older Individuals With Persistent Subclinical Hypothyroidism: A Randomized, Double-Blind, Cross-Over Study

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Background: Subclinical hypothyroidism is common in older individuals, but the physiologic responses to treatment with levothyroxine (LT4) and liothyronine (LT3) are not well defined in this age group. **Methods:** We conducted a randomized, double-blind, cross-over study of LT4 and LT3 treatment in men and women aged 70 years and over without anti-thyroid peroxidase antibodies with persistent subclinical hypothyroidism, defined as having a TSH level between 4.5 and 19.9 μIU/mL with a normal free thyroxine (FT4) level at two consecutive time points. Physiologic outcome measures assessed after achieving a TSH level of 0.5-1.5 μIU/mL with each therapy included vital signs, weight and body composition, bone mineral content and bone density, lipids, resting energy expenditure (REE), cognitive function, quality of life, and thyroid symptoms. **Results:** Thirteen participants [mean (SD) age 77 (5) years], 4 women and 9 men, completed the study. Baseline mean TSH was 4.84 (1.29) μIU/mL. The mean LT4 dose was 105 (36) μg/day [1.4 (0.5) μg/kg/day] and LT4 dose was 34 (9) μg/day [0.4 (0.1) μg/kg/day]. Mean time on LT4 was 200 days and on LT3 was 231 days, with a 28 day washout period. Compared with baseline, participants had an average weight loss of 1.1 kg on LT4 ($p<0.02$) and 2.5 kg on LT3 ($p<0.001$), which was significantly different between