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Background: Intermittent energy restriction (IER) is gaining popularity as a weight-loss strategy. However, the effect of short-term energy restriction on thyroid hormone dynamics is not well characterized. **Methods:** Nineteen healthy women age 23.36± 2.08 yr (mean ± SD) with normal baseline thyroid function and negative anti-thyroid antibodies underwent two 5-day interventions of a prescribed diet and identical standardized exercise in the early follicular phase of two menstrual cycles - neutral energy availability (NEA) 45 kCal/kg*LBM/d followed by deficient energy availability (DEA) 20 kCal/kg*LBM/d. Energy requirements were estimated as previously described (doi.org/10.1210/jendso/bvaa046.1468) and were used to generate a diet and exercise regimen for each participant. On day 5 of both interventions, body composition was assessed by BodPod®. Standardized NEA or DEA breakfast and lunch were provided as appropriate as well as a standardized NEA snack on both sampling visits. Blood sampling was performed for 8 hours starting at ~0800 h with measurement of TSH and growth hormone (GH) every 10 min, cortisol every 30 min, total T3 (TT3), reverse T3 (rT3) and total T4 (TT4) every 60 min, free T3 (FT3), free T4 (FT4) and TBG at the beginning and end of sampling. Liquid chromatography-tandem mass spectrometry (LC-MS) was used for measurements of all thyroid hormones, with the exception of TSH and TBG which were measured by ELISA as were GH and cortisol. Data were analyzed using ANOVA-RM and linear mixed models. Results are presented as mean or least squared mean ± sem. **Results:** Body mass index, bodyweight and % fat mass were not different between interventions. GH and cortisol were unaffected by DEA (p=0.46, p=0.63). TBG was not affected by time of day or dietary intervention (p=0.95, p=0.41). However, compared with NEA, TT3 (89.15 ± 2.89 vs 95.55 ± 2.89 ng/dL for DEA and NEA, respectively; p<0.0001) and TSH (0.92 ± 0.08 vs 1.03 ± 0.09 µIU/mL; p=0.0011) were lower after DEA, while TT4 (6.26 ± 0.25 vs 6.06 ± 0.25 µg/dL; p=0.04), FT4 (3.37 ± 0.26 vs 2.94 ± 0.25 ng/d;, p=0.0052) and rT3 (11.77 ± 0.58 vs 8.85 ± 0.51 ng/dL; p<0.0001) were higher. Regardless of dietary intervention, FT3 (p=0.0005), TT3 (p<0.0001), TT4 (p<0.0001) and TSH (p<0.0001) decreased across the day. **Conclusion:** Using LC-MS for as a more robust measure of thyroid hormones, we have now shown that changes in thyroid hormone dynamics occur after only 5 days of 55% energy restriction in the absence of alterations in body composition, cortisol, GH, TBG or the circadian pattern of thyroid hormone secretion. The decrease in TSH combined with the decrease in TT3 and increase in rT3 support the contribution of both central and peripheral mechanisms to these changes. Taken together these results provide support for a multi-level adaptation in thyroid hormone dynamics to conserve energy expenditure in response to short-term energy restriction.

Thyroid

THYROID HORMONE METABOLISM AND ACTION

The Role of Nuclear Receptor Corepressors NCoR1 and SMRT on Physiologic Function in the Adult Mouse

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Thyroid hormone (TH) plays an essential role in maintaining homeostasis and regulating metabolism in all organ systems beginning with embryogenesis and continuing throughout life. TH action is mediated by the thyroid hormone receptor (TR), which is a nuclear receptor, and it's coregulators. The nuclear receptor corepressor 1 (NCoR1) and the silencing mediator of retinoid and thyroid hormone receptors (SMRT) are two critical corepressors of the TR that inhibit gene transcription in the absence of TH. Repression is mediated by complexing with histone deacetylase 3 (HDAC3), which is stabilized by NCoR1 and SMRT. NCoR1 and SMRT are critical for maintaining metabolic homeostasis and act to mediate energy expenditure, insulin sensitivity, and body weight. We sought to elucidate the roles of NCoR1 and SMRT in maintaining global physiologic function in the adult mouse. In order to study the post-natal role of these corepressors, we used a tamoxifen-inducible Cre recombinase (UBC-Cre-ERT2) to knock-out (KO) NCoR1, SMRT, or NCoR1 and SMRT together in adult mice because global deletion of either corepressor during embryogenesis is lethal. Mice were injected with tamoxifen at 8 weeks of age to KO either NCoR1 (NCoR1-KO; NKO), SMRT (SMRT-KO; SKO), or both NCoR1 and SMRT (double KO; DKO) and metabolic parameters were analyzed. While postnatal deletion of either NCoR1 or SMRT did not impact mortality, KO of both NCoR1 and SMRT resulted in a rapidly lethal phenotype heralded by weight loss, hypoglycemia and hypothermia. Metabolic phenotyping confirmed a loss of body mass and in particular fat mass in addition to a reduction in energy expenditure and increase in fecal caloric density. Further analysis showed the rapid development of hepatosteatosis and disturbances in lipid metabolism with a profound increase in beta-oxidation. We also found a reduction in HDAC3 protein levels in the DKO mice but no rapidly lethal phenotype in HDAC3 KO mice. Overall, we show that NCoR1 and SMRT together are critical for life as their deletion results in a rapidly lethal phenotype. While NCoR1 and SMRT are required to stabilize the corepressor complex, including HDAC3, HDAC3 KO resulted in a distinct and separate phenotype.

Thyroid

THYROID HORMONE METABOLISM AND ACTION

Thyroid Function in 3000 Cases of Patients With Atrial Fibrillation Treated With Catheter Ablation

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Objective: Thyroid hormones have various effects on cardiac and circulatory systems, leading to arrhythmias and heart failure. In Europe and the United States, it has been reported that elevated thyroid hormones within the normal range have been reported to be associated with a risk of atrial fibrillation, however, there was no report on Japanese cases, a country that differs in iodine intake and ethnicity from the West. Therefore, we evaluated the abnormality of thyroid function in a large number of cases of atrial fibrillation (AF) who received catheter ablation (RFCA) in Japan. **Methods:** We evaluated 2,937 cases of atrial fibrillation (2,084 males, mean age 64.1±10.7 years and 853 females, 69.0±8.5 years) who underwent RFCA at the Gunma Prefectural Cardiovascular Center between 2012 and 2018. As a control we used a total of 15,660 participants for health check-up (9,176 males, mean age 49.7±9.8 years and 6,484 females, 48.9±10.3 years) from 2006 to 2013, and we evaluated thyroid function after adjusting for gender-specific age. **Results:** The prevalence of overt hyperthyroidism was significantly higher in the RFCA-treated male group (0.43%) than in the control group (0.07%), even after adjusting for age ($p<0.01$). Similarly, the prevalence of subclinical hyperthyroidism was also significantly higher in the RFCA-treated male group (3.12%) than in the control group (0.94%) after adjusting for age ($p<0.01$). On the other hand, subclinical hypothyroidism was significantly lower in the RFCA-treated group after adjusting for age (2.97% in the RFCA-treated group and 3.93% in the control group, $p<0.01$). Females showed the same results as males. **Conclusions:** In an iodine rich country Japan, not only overt hyperthyroidism but also subclinical hyperthyroidism is an obvious risk factor for severe atrial fibrillation in Japan. Intriguingly, subclinical hypothyroidism might contribute to the prevention of atrial fibrillation, suggesting that slightly higher serum TSH levels might be better for elderlies.

Thyroid

THYROID HORMONE METABOLISM AND ACTION

Thyroid Hormone Action in Liver: A Coregulator Shift Rather Than the Canonical Switch

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Thyroid hormone receptors (TR) are transcription factors that mediate the effects of thyroid hormones (TH) in development, physiology, and metabolism. TR canonically activates gene expression via a "switch" whereby TH converts chromatin-bound TR from a transcriptional repressor to an activator. In this model, the unliganded repressed state is mediated by binding of the nuclear receptor corepressor (NCoR), while the TH-activated state is caused by dismissal of NCoR and stabilization of binding of coactivators including CREB-binding protein (CBP). TH also negatively regulates gene expression, although the mechanism is controversial. Elucidation of the TR transcriptional mechanism *in vivo* has been hampered by the low concentration of endogenous TRs and the unavailability of high quality antibodies. To address this, we generated a mouse line in which endogenous TRβ1 was epitope-tagged to allow precise analysis at physiological levels, and explored TR function in liver where the actions of TR regulate body weight, cholesterol, and liver fat. ChIP-seq analysis revealed TRβ binding at genomic sites with epigenomic characteristics of enhancers, at sequences enriched for the canonical DR4 motif bound by TR with its RXR partner, at both positively- as well as negatively-regulated genes. The NCoR/HDAC3 corepressor complex was reduced but not completely dismissed by TH at positive enhancers and, surprisingly, at enhancers associated with negatively. CBP binding was also not "all or none" but, rather, shifted toward increased binding at enhancers in their active state, i.e., in the presence of TH for activated genes, but in the absence of TH for repressed genes. Thus, TH action is due to a shift, not an on/off switch, in coregulator association with TRβ-regulated enhancers determines their activity and transcriptional outcomes.

Thyroid

THYROID HORMONE METABOLISM AND ACTION

Transcriptional and Genomic Regulation of Pituitary Function by Thyroid Hormone Receptor Beta

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Background: The pituitary is a key target for thyroid hormone but underlying transcriptional mechanisms are poorly understood. Thyroid hormone modifies expression of hormones, including growth hormone (GH) and thyroid-stimulating hormone (TSH, thyrotropin). Wider transcriptome responses are undefined. Thyroid hormone receptor beta (TRb) encoded by *THRB* are expressed in the anterior pituitary and *THRB* mutations cause human resistance to thyroid hormone. **Method:** To investigate genomic genomic regulation by TRb, we derived *Thrb*-HAB knockin mice that express TRb protein with a tag that is biotinylated *in vivo* in presence of an *R26*-BirA allele. Specific, sensitive streptavidin pull-down facilitated Chromatin-Affinity-Purification-sequencing (ChAPseq) to identify genomic TRβ binding sites in pituitary of male mice. Hypo- and hyperthyroidism were produced using methimazole (MMI) in drinking water for 4 weeks with/without added thyroid hormone (T3) for the 4th week. Pituitaries from wild type and *Thrb*-KO mice were also isolated for RNA-sequencing (RNA-seq). Selected expression changes were confirmed by quantitative PCR. Epigenetic changes were determined by ChIPseq for histone acetylation and methylation and open chromatin analysis (ATAC-seq). **Results:** Transcriptome analysis revealed genes with