short, this newly developed organoid culture of murine and human wild type TFCs as well as tumour tissue opens up an extensive area of research that will help understand the drivers for growth and development of thyroid (cancer) cells and enable studies upon drug responsiveness.

Thyroid

THYROID BIOLOGY, HYPOTHALAMIC-PITUITARY-THYROID AXIS

Leptin Regulates Hypothalamus-Pituitary-Thyroid Axis via TRH in Energy Expenditure During Fasting: The Study on TRH Deficient Mouse

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Objectives: The hypothalamic-pituitary-thyroid (HPT) axis plays a significant role in the regulation of energy expenditure. Previous reports demonstrated that thyroid hormones are critically involved in metabolic process, and hypothyroidism was induced by fasting. The mechanism by which TRH neurons sense alterations in peripheral energy stores is supposed to be regulated by leptin, an adipose tissue-derived hormone. Leptin was initially considered as a hormone to prevent obesity, it was later showed that the major role of leptin is to signal the switch from the fed to the starved state at the hypothalamic level. Recently, we generated TRH-deficient mice ($TRH^{-/-}$). The mice exhibit tertiary/central hypothyroidism with characteristic elevation of serum TSH level and diminished TSH biological activity. In this study, we used $TRH^{-/-}$ to investigate the physiological role of TRH in fasting energy expenditure, including the mechanism regulated by leptin. **Methods:** Twelve-week-old male F2 hybrid ICR mice were used in this study. (1) Wild-type mice (WT) and $TRH^{-/-}$ were fasted up to 50 hrs. Blood samples were collected from tail veins at various points. Anterior pituitary samples were obtained from euthanized mice before and after 16 hrs fasting. (2) Serum free T4 (FT4) and TSH levels assessed. (3) The expression level of TSHβ mRNA in anterior pituitary were detected using qPCR assays. (4) We repeated these experiments using mice with leptin administration; leptin (0.5μg/g・BW) was administrated every 6 hours starting at after 2 hours fasting. **Results:** In WT, the level of FT4 was decreased chronologically during fasting to approximately 50% at 50 hrs after fasting. Serum TSH decreased to 70% and the expression level of TSHβ mRNA in anterior pituitary also decreased to 30% compared to before fasting. Administration of leptin recovered the level of FT4 to basal level. However, the level of serum TSH and TSHβ mRNA in pituitary were not recovered to basal levels. By contrast, in $TRH^{-/-}$, the level of FT4 were also decreased after fasting indicating that the decrease of FT4 by fasting was independent of TRH. However, the level of FT4 was not recovered by leptin suggesting that the recovery of FT4 by leptin was TRH dependent. Serum TSH level decreased to 75% after fasting, and no recovery to basal level with leptin administration was observed in $TRH^{-/-}$ same as WT. In TRH-/-, the pituitary TSHβ mRNA expression level was about 50% of WT before fasting. It did not correlate with the serum TSH level. In addition, no increase in TSHβ mRNA expression level by leptin administration was observed in TRH-/-. These findings suggested that the TSHβ mRNA expression level in the pituitary is completely TRH-dependent in $TRH^{-/-}$. **Conclusion:** Fasting-induced hypothyroxinemia was independent of TRH. Leptin regulates H-P-T axis via TRH during fasting-induced energy expenditure. Leptin may modulate the biological activity of TSHβ.

Thyroid

THYROID BIOLOGY, HYPOTHALAMIC-PITUITARY-THYROID AXIS

Maternal Hypothyroidism Delayed Retinal Opsin-Development in the Neonatal Period: Analysis of TRH-Deficient Mice

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Introduction: Retinal cone photoreceptor cells contain short (S) and medium (M) wavelength opsins, which are light-sensitive substances involved in color vision and visual acuity by sensing lights of different wavelengths. Thyroid hormones promote M-opsin expression and suppress S-opsin expression during the differentiation of cone photoreceptors. It was previously reported that M-opsin expression was delayed and S-opsin expression increased in TSH receptor-deficient mice and methimazole-induced hypothyroid mice. In addition, no M-opsin expression and increased S-opsin expression were observed in thyroid hormone receptor (TR) β2-deficient mice (Ng L et al, Nature Genetics. 2001; 27(1): 94-98.). This suggested that impaired thyroid function affects opsin development. We therefore examined retinal development in TRH-deficient mice, which are a model of central hypothyroidism established in our laboratory. **Methods:** We performed HE staining of the retina at postnatal 30 days and electroretinography at postnatal 10 weeks using TRH-/- and wild-type (WT) mice. We also examined expression levels of S/M opsin mRNA in WT, TRH-/- and TRH-/- pups born from TRH-/- dams at postnatal 12,17 and 30 days, and TRβΔ337T knock-in mice (TRβmut/mut) at postnatal 30 days. Furthermore, we performed immunohistochemistry to examine S/M opsin protein expression in these mice. **Results:** The retinal structures by HE staining and retinal functions by electroretinography in TRH-/- mice were unchanged compared with those in WT

mice. Although M-opsin expression was not detected and S-opsin expression was higher in TRβmut/mut mice than in WT mice, the mRNA and protein expression levels of S/M-opsin did not significantly differ between TRH-/- pups born from TRH+/- dams and WT pups at all postnatal days. TRH-/- pups born from TRH-/- dams exposed to maternal hypothyroidism had similar serum total T4 levels to TRH-/- pups born from TRH+/- with normal maternal thyroid function. In contrast, the mRNA expression level of M-opsin was significantly lower (1.00±0.06 vs 0.64±0.05: mean ± SE, p<0.01) and the protein expression level was lower in TRH-/- pups born from TRH-/- dams than in WT pups at postnatal 12 days. However, these differences disappeared after postnatal 17 days, and there was no difference in M-opsin expression in TRH-/- pups born from TRH-/- dams compared with WT pups. **Conclusions:** Although no delay in opsin development was observed in TRH-/- pups born from TRH+/- dams, TRH-/- pups born from central hypothyroid dams exhibited delayed opsin development, suggesting that maternal hypothyroidism affects the development of retinal opsin in the neonatal period.

Thyroid

THYROID BIOLOGY, HYPOTHALAMIC-PITUITARY-THYROID AXIS

Monitoring Thyroid Function Tests in Patients With Type 1 Diabetes Mellitus: Adherence to Recommended Guidelines and Comparison of Practice Patterns in a Health Care System

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Approximately 1.7 million people in the U.S. have type 1 diabetes mellitus. Autoimmune thyroid disease occurs in 17 to 30% of patients with type 1 diabetes. The American Diabetes Association recommends that thyroid function be assessed at diagnosis of type 1 diabetes and repeated every 1 to 2 years thereafter or sooner if clinically indicated. With Centricity, our former electronic medical records (EMR) system, an EMR aid automatically imported key diabetes metrics including the TSH test. Our new EMR system, MedConnect, does not have an EMR aid that imports these metrics. We hypothesized that the screening rate for thyroid dysfunction in type 1 diabetic patients would be higher with the previous EMR system than with the new EMR system. We also hypothesized that the screening rate in patients followed by an endocrinologist would be higher than in those followed by a primary care physician.
Methods: We compared practice patterns with Centricity (from June 1, 2013, to May 30, 2016) versus MedConnect (from January 1, 2017, to December 31, 2019) in both primary care and endocrinology clinics. A total of 502 patients (271 Centricity, 231 MedConnect) were identified by chart review with age ≥18 years and ICD 9/10 codes for type 1 diabetes mellitus in outpatient clinics in our multicenter system.
Results: Baseline TSH was done in 253 of 271 (93.4%) Centricity patients and in 181 of 231 (78.4%) MedConnect patients. The odds of baseline TSH with Centricity was 3.88 times higher compared to MedConnect (OR = 3.88, 95% CI=2.19,6.88). Of the 214 patients with normal baseline TSH, 135 (63.1%) had repeat TSH done in 1-2 years; and of the 136 MedConnect patients with normal baseline TSH, 86 (63.2%) had repeat TSH done in 1-2 years. Of 434 patients with baseline TSH, 81 (18.6%) had abnormal TSH. Of these patients, 67 (82.7%) had hypothyroidism, 1 (1.2%) had hyperthyroidism, 8 (9.8%) had subclinical hypothyroidism, and 5 (6.1%) had subclinical hyperthyroidism. Of the total 502 patients, 380 (75.7%) were followed by an endocrinologist and 122 (24.3%) were followed by a primary care provider. Among patients followed by an endocrinologist, 348 (91.6%) had a baseline TSH result. Only 86 of 122 (70.5 %) patients followed by a primary care physician had a baseline TSH. Endocrinologists had 4.6 times higher odds of TSH screening at baseline compared with primary care physicians (p <0.0001).
Conclusion: Thyroid function was not assessed at baseline in all patients with type 1 diabetes mellitus and was not followed at the recommended intervals per the guidelines. Higher screening rates were seen with an EMR aid. Endocrinologists screened significantly more patients than primary care physicians. Education of providers regarding the guidelines is needed, and addition of an EMR aid may help to improve detecting thyroid dysfunction in patients with type 1 diabetes mellitus.

Thyroid

THYROID BIOLOGY, HYPOTHALAMIC-PITUITARY-THYROID AXIS

The Growth Stimulatory Effects of Thyrotropin and Thyroid Hormones on Thyroid Cancer Depend on Expression of Thyrotropin Receptor and Integrins

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Background: The long-term management of metastatic thyroid cancer (TC) consists of thyrotropin (TSH) suppression with supraphysiologic doses of thyroid hormones (TH) via a negative feedback loop. The goal of TSH suppression is to prevent TSH stimulation of the TSH receptor (TSHR), as it has been shown to promote proliferation of cancer cells. However, TH (T3 and T4) have also been shown to stimulate cancer cell proliferation via αvβ3 integrin signaling. Since both TSH and TH have mitogenic potential, we aimed to investigate which one is a more potent growth stimulus-TSH or TH by analyzing its growth stimulatory effects in TC models. **Methods:** We analyzed the mRNA expression of TSHR and ITGAV (αv), ITGB3 (β3) integrins in 496 human TC tissue samples, including 65 paired samples of normal tissue (NT) and the corresponding tumor included in The Cancer Genome Atlas (TCGA). We used 13 TC cell lines and analyzed the mRNA expression of 24 genes (4 thyroid-specific genes, 2 TH receptor genes, and 18 integrin genes) with an emphasis on the expression of cell surface receptors αv, β3 integrins, and TSHR. The protein expression of αv, β3, and TSHR was analyzed by immunoblotting. To test the effects of TH and TSH on cell proliferation and