of scoliosis, seizures, familial psychosocial health, sleep and behavioral changes with each medication. Annual assessments include: fasting lipids, thyroid panel, screening urinalysis. Patients should receive standard treatment for comorbid endocrine conditions, classically: hypercholesterolemia, hypothyroidism, growth hormone deficiency.
Clinical Case: 49-year-old Hispanic female with history of SMS who presented to endocrinology for type 2 diabetes mellitus (T2DM) management. Past medical history includes T2DM with peripheral neuropathy, hypertension, hypercholesterolemia, intellectual disability, anxiety, recurrent genitourinary infections, sleep apnea. Physical exam is remarkable for macroglossia, truncal obesity, scoliosis, extremity excoriations evident of skin picking and xerosis, syndactyly of 2nd-3rd toes. Patient exhibited maladaptive behaviors like page-flipping, self-hugging, tantrums. Over the past 3 years, BMI remained in the obese range (>30 kg/m^2) and A1c fluctuated from 7.0 to 10.6% averaging 8.8% (<5.7%). Patient is currently managed on insulin glargine, pioglitazone and liraglutide. She did not tolerate metformin due to dose-dependent diarrhea. Patient's mother chose against SGLT2 inhibitors due to diminished genitourinary hygiene. T2DM management was complicated by patient behaviors, including nocturnal consumption of fructose-containing food and beverages, exercise intolerance, and associated caregiver fatigue.
Conclusion: This case describes a patient managed for metabolic dysfunction in conjunction with a rare microdeletion disorder causing neurobehavioral disturbance with disrupted circadian sleep-wake patterns. The most difficult aspects of diabetes management included difficulty implementing lifestyle modifications to control the patient's hyperglycemia.

Steroid Hormones and Receptors

STEROID BIOLOGY AND ACTION

Improving the Diagnosis, Treatment, and Prevention of Endocrine Diseases Through Accurate and Reliable Laboratory Measurements with CDC's Clinical Standardization Programs

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SAT-733

Laboratory measurements are critical for the correct diagnosis and treatment of patients as well as in the investigation of chronic diseases such as hypogonadism, PCOS, and bone-and kidney-related diseases. Inaccurate measurements can lead to misclassification of patients and incorrect treatment. Furthermore, the effective use of research findings in patient care is prevented. The CDC Clinical Standardization Programs (CDC CSP) assess the analytical performance of assays against performance goals defined by clinical and medical organizations. The CDC CSP assist with assay calibration, the certification of analytical performance, and the monitoring of analytical performance during the measurement of patient and/or study samples. CDC CSP have programs in place for the calibration and certification of commercial assays and laboratory developed tests (LDTs) for total testosterone (TT), estradiol (E2), vitamin D (VD), free thyroxine (FT4), total cholesterol (TC), total glycerides (TG), HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C). The programs available for monitoring analytical performance during routine testing include TT, VD, TC, TG, HDL-C, apolipoprotein AI and B. CDC CSP also support accuracy-based external quality assurance surveys such as those offered by the College of American Pathologists. Enrollment of assays and LDTs in CDC's certification programs has resulted in improvements in calibration accuracy; i.e. the absolute mean bias of assays participating in the CDC Vitamin D Standardization Certification Program was well below the allowable bias of 5% each year. Assays standardized in CDC's certification programs also demonstrated higher accuracy in routine patient testing; i.e. CDC VD certified assays have a lower bias compared to non-certified assays. Similar observations were made with assays certified in the CDC's program for TT. Monitoring data over the past 10 years from the CDC Lipid Standardization Program indicated that the majority of TC measurements performed in routine testing were consistently within the recommended bias limits of ±3%. CDC CSP continue to improve the analytical performance of assays by addressing measurement bias caused by factors other than incorrect calibration such as interfering compounds. The programs are responding to new clinical and public health needs with the addition of new analytes such as PTH and glucose. The CDC CSP support projects aiming at establishing reference intervals and other research studies. The CDC CSP work with stakeholders, such as the Partnership for the Accurate Testing of Hormones and the Endocrine Society, to educate the clinical and laboratory communities about the importance of using standardized assays in patient care, research, and public health. References: Partnership for Accurate Hormone Testing (PATH). www.hormoneassays.org. College of American Pathologists (CAP). www.cap.org.

Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Dual Role of Carboxypeptidase E in Prohormone Processing and a Novel Neurotrophic Factor Mediating Neuroprotection and Cognitive Functions in Hippocampal CA3 Neurons in Mice

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SUN-260

Stress causes release of glucocorticoids from the adrenals which then circulate to the brain. High concentrations glucocorticoid from chronic severe stress results in pathophysiology in the brain, including neuronal degeneration, cell death and cognitive dysfunction, leading to diseases such as Alzheimer Disease and Major Depressive

Disorders. Neurotrophic/growth factors such as BDNF, NGF and NT3 have been linked to these pathological conditions. Carboxypeptidase E (CPE), a proneuropeptide/prohormone processing enzyme, also named neurotrophic factor-α1(NFα1) is highly expressed in the stress-vulnerable hippocampal CA3 neurons, and was shown to have neuroprotective activity from *in vitro* studies. Here we investigated if CPE-NFα1 functions *in vivo,* independent of its enzymatic activity, and the mechanism underlying its action. We generated knock-in mice expressing a non-enzymatic form of CPE, CPE-E342Q, but not wild-type CPE. The CPE-E342Q mice showed significantly decreased neuropeptide content and exhibited obesity, diabetes and infertility due to lack of prohormone processing activity, similar to CPE-KO mice. However, they showed no hippocampal CA3 degeneration, exhibited neurogenesis in the dentate gyrus, and displayed normal spatial learning and memory, similar to CPE wild-type mice, after weaning stress; unlike CPE-KO mice which showed hippocampal CA3 neuronal degeneration and cognitive deficits. Binding studies showed that radiolabeled CPE bound hippocampal cell membrane specifically, in a saturable manner. Binding of CPE and CPE-E342Q to hippocampal neurons activated Erk signaling and pre-treatment with either of these proteins protected neurons against H_2O_2- or glutamate-induced neurotoxcity by increasing BCL2 expression. *In vitro* and *in vivo* inhibitor studies demonstrated that this neuroprotective effect was independent of tyrosine kinase receptor signaling. Taken together, the data provide evidence that CPE-NFα1 is a unique neurotrophic factor which acts through a non-tyrosine kinase receptor to activate Erk-BCL2 signaling to protect hippocampal CA3 neurons against stress-induced neurodegeneration and maintaining normal cognitive functions in mice.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

TSH Synthesis and Secretion Are Unperturbed in Male IRS4 Knockout Mice

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SAT-286

It was recently reported that mutations in the insulin receptor substrate 4 (*IRS4*) gene cause a novel form of X-linked congenital central hypothyroidism (OMIM 300904). To date, four different mutations, three frameshift and one nonsense, have been reported, with two affected male patients showing decreased basal, pulsatile, and total thyroid-stimulation hormone (TSH) secretion (PMID 30061370).

Members of the IRS family canonically act as scaffold proteins between tyrosine kinase receptors and their downstream effectors. *IRS4*/*Irs4* expression is enriched in the pituitary; however, its role in the hypothalamic-pituitary-thyroid (HPT) axis has not been studied in detail.

We generated novel whole-body *Irs4*-knockout mouse lines using CRISPR-Cas9. A specific guide RNA was used to target the Cas9 enzyme to the 5' end of the single exon *Irs4* gene. A two-nucleotide deletion was introduced into *Irs4*, resulting in a frameshift and premature stop codon. We hypothesized that like *IRS4* deficient patients, these mice would exhibit central hypothyroidism. Given that *Irs4* is X-linked, we focused our initial characterization on males.

Under normal laboratory conditions, *Irs4* knockout mice do not exhibit differences in pituitary expression of *Tshb*, which encodes one of the subunits of the TSH heterodimer. Expression of the gene encoding the thyrotropin-releasing hormone (TRH) receptor, *Trhr1*, is also unperturbed in these knockout mice. Additionally, there are no differences in their serum thyroid hormones, T3 (triiodothyronine) and T4 (thyroxine). When *Irs4* knockout males were placed on a low-iodine diet supplemented with propylthiouracil (PTU) for 3 weeks and rendered hypothyroid, their serum TSH increased similarly to wild-type males. Overall, *Irs4* knockout males do not exhibit central hypothyroidism or phenocopy *IRS4* deficient patients. Compensation by another IRS protein may explain euthyroidism in these mice.

Healthcare Delivery and Education

EXPANDING CLINICAL CONSIDERATIONS FOR PATIENT TESTING AND CARE

Improving the Accuracy and Reliability of Free Thyroxine (FT4) Measurements Through the CDC Clinical Standardization Programs (CSP)

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MON-130

Reliable free thyroxine (FT4) measurements are essential for assessing thyroid function and for correctly diagnosing and treating thyroid disorders. Thyroid hormones play an important role in normal brain development of the fetus, and abnormal FT4 during pregnancy is associated with adverse pregnancy outcomes. Standardization of FT4 measurements, is critical to improving the accuracy and reliability of current methods and thus to improve diagnosis, treatment and prevention of thyroidal illnesses. Currently, there are no serum-based reference materials available for FT4 to assess the accuracy and reliability of FT4 assays. CDC CSP is collaborating with the International Federation of Clinical Chemistry and Laboratory Medicine, and the Partnership for the Accurate Testing for Hormones to address these issues through development of an accurate and sensitive higher-order Reference Measurement Procedure (RMP) for FT4 that will be used to assign target value to serum-based materials. The CDC CSP FT4 reference method is using equilibrium dialysis in combination with liquid chromatography tandem mass spectrometry (LC-MS/MS). FT4 in serum is isolated from the binding proteins in 1 mL equilibrium dialysis cells for 4 hours at 37°C. FT4 is further isolated by extractions prior to LC-MS/MS analysis. To determine the concentration of FT4 in serum, certified primary reference materials are used to prepare calibration materials. Chromatographic separation is achieved using a C18 reverse phase column with a gradient of methanol and water with 0.1% formic acid. Quantification by selective reaction monitoring is performed in the positive mode using electrospray ionization. Two transitions are monitored