Diabetes Mellitus and Glucose Metabolism

METABOLIC INTERACTIONS IN DIABETES

Appetite Suppressing Effects of Glucoregulatory Chimeric Peptides Devoid of Nausea

Christian Ludwig Roth, MD, Brandon T. Milliken, BS, Clinton Elfers, BS, Ian Sweet, PhD, Robert Doyle, PhD

1Seattle Children’s Research Institute, Seattle, WA, USA, 2Syracuse University, Syracuse, NY, USA, 3University of Washington, Seattle, WA, USA, 4Syracuse University, Syracuse, NY, USA.

SUN-660

Current treatments for type 2 diabetes (T2D) and obesity do not reliably achieve long-term weight-loss and up to 50% of patients experience nausea and vomiting. Thus, there is a critical need for obesity medications that provide glycemic control with enhanced hypophagic response without nausea. Based on rational design and in silico modelling of the glucagon-like peptide 1-receptor agonist (GLP1RA) exendin-4 (Ex4) and the neuropeptide Y2 receptor (Y2R) agonist peptide YY (PYY) 3–36, our group has developed and tested several new monomeric chimeric peptides that display dual agonism of the anorectic Y2R and the glucoregulatory GLP1R. In addition, we explored a third agonistic behavior at the neuropeptide Y1 receptor (Y1R), which potentially relates to pancreatic beta-cell protection. Our current lead, GEP44, binds and robustly activates the Y2R, Y1R, and GLP1R. In our experiments, half maximal effective concentration (EC50) values for GEP44 were 10 nM at Y2R, 24 nM at Y1R, and 330 pM at GLP1R for dose responses of cell-based fluorescence resonance energy transfer assays. For the control substrates PYY3–36, PYY1–36 and Ex4, EC50 values were 16 nM, 12 nM, and 16 pM at the Y2R, Y1R, and GLP1R, respectively. We tested effects of daily injections of these chimeric peptides in adult Sprague-Dawley rats on food intake (FI), body weight (BW) changes, blood glucose levels and an indicator of nausea (kaolin intake). GEP44 produced profound reduction in FI (2-d average GEP44 at 20 nmol/kg FI -71%; Ex-4 20 nmol/kg FI -40%). Anorectic doses of GEP44 did not trigger a pica response assessed by kaolin consumption in treated rats, while in Ex4 treated rats, kaolin consumption accounted for 28% of total daily solid intake, indicating a clear nausea response. During 11 d of treatment with GEP44, FI was consistently reduced resulting in a significantly stronger reduction of BW compared to Ex4 at the end of treatment (GEP44 -7.6%, Ex4 -3.7%, p<0.05). Furthermore, 5-day injections of GEP44 showed greater reduction of glucose levels than for Ex4 in diet induced obese rats receiving intraperitoneal glucose. These results were supported by results generated using a customized perfusion system that demonstrated acute stimulation of insulin secretion by exposure of isolated rodent and human islets to GEP44 and Ex4 (both p<0.01 vs. vehicle). In conclusion, simultaneously targeting serial anorectic pathways with single molecule chimeric peptides developed by our group can address multiple coexisting conditions, namely obesity and T2D, to more efficaciously reduce FI, BW and blood glucose levels thereby reducing off target effects.
2006-2018 that were found to have EPP. Pituitary hormone function was evaluated in the majority of the patient population.

**Results:** Of the 26 patients with EPP, [16 males (M) and 10 females (F)], mean chronicologic age was 5.98±5.18 yrs, only 20 patients had an endocrine evaluation at SCHC. Of the 20 children, 14 had CPHD and 4 had IGHD. Patients were classified into 3 groups (upper, middle & lower) according to EPP location along the pituitary stalk. Of the 21 patients with upper EPP, 17 had pituitary dysfunction (14 with CPHD, 3 with IGHD). Of the 4 children with middle EPP, only 1 had pituitary dysfunction which was IGHD. One patient had lower EPP with hyperprolactinemia. Diabetes insipidus was not identified in any of the children.

**Conclusion:** Our study supports previous reports that CPHD and IGHD are frequent in patients with EPP. Similarly, our data further demonstrate that no cases of diabetes insipidus have been reported in children with EPP. In our study, EPP is most commonly located along the upper third of pituitary stalk at the median eminence level, with a higher prevalence of CPHD and IGHD, a finding similar to prior studies. No CPHD was reported in middle/lower but IGHD was found in the middle EPP group.

**Reproductive Endocrinology**

**CLINICAL STUDIES IN FEMALE REPRODUCTION II**

**Light and Exercise Therapy Improves Depression in Women with Premenstrual Syndrome**

Tino Michelle Tskirai, BS¹, Francisco Ramirez, MD², Neil Nedley, MD¹.

¹Weimar Institute, Weimar, CA, USA. ²Nedley Clinic, Colfax, CA, USA.

**SUN-006**

**Objective** This study documents the effects that light and exercise therapy have in women experiencing premenstrual syndrome (PMS). **Design Methods** Study participants were fertile-aged females that were involved in a non-profit community depression and anxiety education program. Participants met in once a week and were taught about the effects of healthful cooking, regular exercise (at least 40 minutes of exercise five times a week), bright light exposure (20 - 40 minutes of exposure) from the sun or from a light box, and other healthy behaviors on their mental health. All participants took a 75-item questionnaire at the beginning and the end of the program to establish a baseline and measure changes in depression levels. The questionnaire measured depression level based on DSM-5 [The Diagnostic and Statistical Manual of Mental Disorders Volume 5] criteria. Participants were asked to provide their demographical information and patient history, including information about premenstrual syndrome. Depression was classified into 4 categories as none (0-6), mild (7-10), moderate (11-19) or severe (20 or more). **Results** From 1968 females 803 reported suffering from PMS mean age 38.8, SD 8.9. Baseline mean depression was 15.3, SD 15.3, median 16 and mode of 18. At the end from the 803, 280 established exercise and light therapy, that group had a depression average of 6.2 (SD 5.5), median 5, mode 0 and 83 (29.6%) of them reported no longer PMS symptoms. At the end those 125 did not established the exercise and light therapy had a depression average of 7.7 (SD 5.5), median 7 and mode 8 and 34 (27.2%) no longer reported PMS symptoms. **Conclusions** Women experiencing PMS exhibit improved mental health as a result of light and exercise therapy. Lifestyle intervention for maladies related to this syndrome may be an effective alternative to pharmaceutical medications.

**Thyroid**

**THYROID DISORDERS CASE REPORTS II**

**An Unusual Presentation of Hypothyroidism**

Anju Sukumaran, MD.

University Of Mississippi Medical Center, Jackson, MS, USA.

**SAT-494**

**Introduction:** Pediatric Endocrinologists see many children with congenital hypothyroidism. Complications from long standing untreated hypothyroidism reports are rare in children. This is a case report on an unusual presentation of hypothyroidism caused by noncompliance.**Clinical Case:** A 11-year-old boy with history for congenital hypothyroidism, lost for follow up for 10 months, presented to an outside hospital with pain on face, joints and all over his body. Initial labs showed elevated creatinine, liver enzymes and TSH >300 mcIU/mL with free T4 <0.1 ng/dL. He was transferred to University for further care. In our Emergency Room, patient had normal vitals. On exam he had puffy appearance, sluggish reflexes otherwise unremarkable exam. Chest X-ray was done due to cough and congestion symptoms and showed cardiomegaly. EKG showed low voltage complexes otherwise normal. ECHO obtained showed normal left ventricular function and small pericardial effusion. Cardiology recommended no intervention at this time. Endocrinology was consulted due to abnormal thyroid labs. Patient had normal mental status, no hypothermia or bradycardia or hypotension or hypoventilation. He had normal sodium. He had macrocytic anemia. Recommended to get creatinine kinase (CK) levels as he had elevated serum creatinine. CK levels came back at 3600 U/L. He was started on intravenous hydration and Synthroid. Doses were increased daily. Once serum creatinine trended down and glomerular filtration rate (GFR) normalized he was discharged home. CK was still elevated but trended down. He had Tanner 3 testes size on exam. His LH and testosterone levels were pubertal consistent with central puberty activation and not just macroorchidism. He was seen as outpatient a month after discharge. His thyroid levels were normal. Serum creatinine and CK had normalized and he continues to progress in puberty. **Conclusion:** Long standing untreated hypothyroidism can cause multiple organ dysfunctions. Our patient presented with cardiomegaly, acute kidney injury from rhabdomyolysis. It is important to look out for other system involvement as this happen rarely in children and myxedema coma can be life threatening.