Peripheral CB1 Blocker Improves Metabolism in DIO Mice
Independent of Hepatic FGF21

Obesity is associated with an overactive endocannabinoid system, and selective blockade of CB1R in peripheral tissues, including the liver, reverses HFD-induced metabolic abnormalities by restoring normal lipid and glucose homeostasis. Fibroblast growth factor-21 (FGF21) has emerged as a major endocrine regulator derived from the liver that reduces adiposity and hepatic steatosis and improves glucose tolerance and insulin sensitivity, with changes similar to those induced by CB1R blockade. Here we investigated whether FGF21 mediates the metabolic effects of CB1R blockade in DIO mice.

In C57BL/6J wild-type mice, HFD caused a robust increase in hepatic Fgf21 mRNA and serum FGF21 levels, which were reversed by chronic CB1R blockade to levels observed in STD or vehicle-treated hepatocyte-specific CB1R (LCB1-/-) mice, indicating activation of CB1R in the liver is largely involved in HFD-induced “FGF21-resistant” state. In contrast, the expression of the FGF21 receptor Fgfr1 and co-receptor β-klotho (Klb) were dramatically reduced by HFD in both epididymal fat and brain tissue in wild-type mice, and these effects were reversed by peripheral CB1R antagonist JD5037 treatment.

To address whether FGF21 mediated the metabolic effects of CB1R blockade, we repeated JD5037 treatment in liver-specific FGF21-/- (FGF21-LKO) mice. Surprisingly, JD5037 treatment was almost equally effective in both HFD-fed wild-type and in FGF21-LKO mice in reducing body weight and hepatic steatosis, attenuating hyperinsulinemia and hyperleptinemia. The current data suggest that peripheral CB1R blockade in obese mice improves insulin sensitivity and energy expenditure independently of hepatic FGF21.

Diabetes Mellitus and Glucose Metabolism

CLINICAL AND TRANSLATIONAL GLUCOSE METABOLISM AND DIABETES

Utility of Continuous Glucose Monitoring in Children with Type 1 Diabetes: Is Hba1c Enough?

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Utility of continuous glucose monitoring in children with Type 1 diabetes: Is Hba1c enough?

Introduction: Type 1 diabetes is an autoimmune condition resulting in insulin deficiency that requires daily insulin therapy and self-monitoring of blood glucose. Continuous glucose monitoring (CGM) systems allow for measurement of interstitial fluid glucose levels in a continuous fashion to identify variations and trends that are not feasible with conventional self-monitoring. Hemoglobin A1C (Hba1c) is the method used to assess adequate glycemic control and relates to future risk of developing complications. Current evidence has shown improvement in Hba1c with concomitant use of CGM in adults over 25 years of age with Type 1 diabetes, whereas studies in children and adolescents have failed to show this. However, it is important to note the limitations in Hba1c use as it is a marker of average blood glucose over 3 months but does not reflect glycemic variability. More recent data has suggested that factors such as time in range (TIR), which can be determined with CGM use, are also associated with decrease risk of diabetes complications.

Methods: The goal of our study was to analyze the change in Hba1c levels after using a CGM (DEXCOM G4, G5, G6) over a 6-month period in pediatric patients with Type 1 diabetes. Two Hba1c levels 3 months apart from 92 patients were collected before using a CGM and two while using a CGM. Results were compared by using a dependent samples t-test. IBM SPSS 25.0 was used for data analysis.

Results: Preliminary analysis indicates the average change in HBA1C among the patients (N=92) before (-0.08 ± 1.16) and while using the CGM (0.12 ± 1.00) was not significantly different (t (79) = -1.27, p = 0.21). The average change in HBA1C was also not significantly different (p>0.05) among the patients before and while using the CGM for gender (males and females), age groups (0-7 years, 8-14 years, and 15-24 years), and generations of DEXCOM used (G4, G5, and G6).

Conclusion: As has been shown in other studies, we did not find a significant change in Hba1c after CGM use for 6 months in our patients. While Hba1c is a reflection of blood sugars over a 3-month period, it does not provide information about glycemic excursions. Metrics derived from CGM use, such as TIR, can provide actionable information which we did not address in our study. There have been reports of the association between TIR and long-term complications of diabetes. Most data comes from studies in adults and pediatric data is lacking. We propose that future studies must look into CGM metrics such as TIR to better define glycemic control in pediatric patients with diabetes mellitus.

Diabetes Mellitus and Glucose Metabolism

METABOLIC INTERACTIONS IN DIABETES

Murine Cecal Ligation and Puncture (CLP) Perturbs Phosphorylation of Insulin Receptor Substrate 2 (IRS-2)

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Abstract: Hyperglycemia is a characteristic finding in sepsis, and its presence worsens outcome (1). Patients with sepsis need larger doses of insulin to reduce glucose levels. This abnormality has been termed “insulin resistance” but the molecular mechanism by which sepsis attenuates the insulin signaling pathway is unknown. Previous work has
shown impairment of phosphorylation in several intracellular signaling pathways following CLP, a well-validated murine model of sepsis (2). Phosphorylation of tyrosine in IRS-2 is essential for functional insulin signaling in hepatocytes (3). Therefore the aim of this study was to investigate the effects of CLP on IRS-2 phosphorylation.

**Hypothesis:** CLP attenuates phosphorylation of IRS-2.

**Methods:** All studies were approved by the Feinstein IACUC and conformed to ARRIVE guidelines. CLP was performed on C57Bl6 mice. Before CLP, animals were identified for sacrifice at specific post-procedure time points. To stimulate phosphorylation of IRS-2, insulin was injected in control and CLP mice at 24 and 48 hours post CLP. Following sacrifice, protein was isolated from liver tissue. Protein abundance was determined using immunoblotting. The detection of the phosphorylated form of these proteins was determined by enzyme-linked immunosorbent assay (ELISA) with a phospho-insulin receptor antibody. Statistical significance was determined using ANOVA for repeated measures with a Sidak post-hoc correction.

**Results:** Relative to the control, tyrosine phosphorylation of IRS-2 was significantly (p<0.05) reduced at 24 and 48 hours following CLP.

**Conclusions:** Tyrosine phosphorylation of hepatic IRS2 is attenuated at early time points following CLP. These results are consistent with other studies examining the effects of CLP on intra-cellular signal transduction pathways (1). Further, these results provide evidence that changes in the insulin signaling transduction underlie CLP-induced “insulin resistance”.

**References:**
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**Steroid Hormones and Receptors**

**STEREOID BIOLOGY AND ACTION**

**HNRNPA2B1 Mediates Endocrine-Sensitivity and Alters PSAT1 in Breast Cancer Cells**

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Higher expression of the RNA binding protein HNRNPA2B1 (Heterogeneous Nuclear Ribonucleoprotein A2/B1), a reader of the N(6)-methyladenosine (m6A) mark in transcribed RNA, is found in endocrine-resistant, estrogen receptor (ERα)+ LCC9 and LY2 breast cancer cells derived from MCF-7 endocrine-sensitive luminal A cells (1). HNRNPA2B1 interacts with DGCR8 in the DROSHA complex to promote processing of pri-miRNAs to pre-miRNAs. We identified HNRNPA2B1-regulated miRNAs by RNA seq and target pathways, including serine family amino acid metabolic processes, TGFβ signaling, response to estrogen, and cell junction by MetaCore enrichment pathway analysis (1). Stable 4.5-fold overexpression of HNRNPA2B1 in MCF-7 cells (MCF-7-A2B1 cells) results in ablation of growth inhibition by 4-hydroxytamoxifen (4-OHT) and fulvestrant. This was not due to loss or decrease of ERα; in fact, ERα was increased ~ 1.6-fold. Conversely, transient knockdown of HNRNPA2B1 expression in LCC9 and LY2 cells sensitized the cells to growth inhibition by 4-OHT and fulvestrant, without changing ESR1 expression. MCF-7-A2B1 cells showed increased migration, reduced E-cadherin and increased vimentin, suggestive of EMT; however, they exhibited reduced clonogenic survival. Follow-up on the identification of HNRNPA2B1-miRNA regulation of the serine pathway revealed higher expression of phosphoglycerate dehydrogenase (PHGDH) and phosphoserine aminotransferase (PSAT1) transcripts and proteins in LCC9, LY2, and MCF-7-A2B1 compared to MCF-7 cells. We identified two miRNAs, miR-424-5p and miR-145-5p downregulated in MCF-7-A2B1 cells that directly targeted the PSAT1 3’UTR in dual luciferase assays. Lower miR-424-5p and miR-145-5p in endocrine-resistant LCC9 and LY2 correlate with increased PSAT1 and higher PSAT1 is associated with reduced overall and metastasis-free survival in breast cancer patients. Overall, our data suggest a role for increased HNRNPA2B1 in tamoxifen-resistance. **Reference:**(1) Klinge CM, Piell KM, Teoley CS, Rouchka EC. HNRNPA2/B1 is upregulated in endocrine-resistant LCC9 breast cancer cells and alters the miRNA transcriptome when overexpressed in MCF-7 cells. Sci. Rep. 2019; 9:9430.

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**Thyroid**

**THYROID DISORDERS CASE REPORTS I**

**Thyrotoxic Periodic Paralysis in Adolescence Patient a Case Report and Literature Review**

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**Background:** Thyrotoxic periodic paralysis (TPP) is an uncommon disorder characterized by acute flaccid paralysis due to hypokalemia. It is diagnosed primarily in Asian adult males and is rare in children and adolescents. Here we report an adolescent male patient of Vietnamese descent who presented to the emergency department with an episode of syncope, muscle weakness, and shortness of breath one day after the initiation of methimazole treatment for Graves' disease. The laboratory revealed significant hypokalemia. In this report we also included and summarized the reported cases of TPP in adolescent patients since 1997.

**Clinical Case:** A 17-year-old Vietnamese American male who was recently diagnosed with Graves' disease presented to the emergency department after an episode of syncope, muscle weakness, and difficulty breathing. Two months previously, he began having episodes of tachycardia. He was diagnosed with hyperthyroidism with a TSH of 0.007 mIU/mL and free T 4 > 7 ng/dL (0.8-1.9). He was subsequently evaluated by Cardiology and started on atenolol. He was then seen by Endocrinology 5 days after and started on methimazole 15 mg twice daily. On the next morning after starting methimazole, he reported feeling weak and passed out. His father had found him on the floor, weak and unable to move, approximately 30 minutes after his father "heard a thud upstairs". The patient recalled that his legs gave out and he “hitting his face on a table”. In the emergency...