of GH action well past sexual maturation produces beneficial effects on insulin sensitivity and aging in mice.
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Diabetes Mellitus and Glucose Metabolism

IMPACTS OF ORGAN CROSSTALK AND SEX ON DIABETES PHENOTYPES

High-Fat Diet Accelerates Pathological Progression and Intestinal Inflammation in a Type 2 Diabetes Rodent Model

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Insulin signaling lowers postprandial glucose by stimulating cell surface translocation of the insulin sensitive glucose transporter 4 (GLUT4). In order to better understand how insulin resistance contributes to the pathophysiological progression of type 2 diabetes, we generated human *GLUT4* promoter-driven insulin receptor knockout (GIRKO) mice and characterized their metabolic features relative to control mice. Although the role of insulin resistance in diabetes is beyond dispute, our previous studies showed that GIRKO mice fed normal chow diet (NCD) had an unexpectedly low rate of frank diabetes despite severe insulin resistance in muscle, fat, and brain.
In the current study, we first sought to determine whether GIRKO mice would respond to high-fat diet (HFD) challenge with worsened glycemic outcome compared to control mice on HFD. Secondly, we sought to determine whether HFD-induced pathologies in GIRKO mice were caused by adaptations in the gastrointestinal (GI) tract and microbiome. We discovered that after beginning the HFD-feeding regimen, GIRKO mice rapidly developed hyperinsulinemia and hyperglycemia without excessive adiposity gain. Furthermore, GIRKO mice displayed dyslipidemia via increased hepatic lipid accumulation and serum lipid content. We used indirect calorimetry to characterize the metabolic features of single-housed mice. HFD-fed GIRKO mice had comparatively lower respiratory exchange ratio (RER), indicating relatively greater lipid metabolism compared to control mice on HFD. Despite having increased circulating incretins, GIRKO mice had impaired oral glucose tolerance and limited glucose-lowering benefit from Exendin-4 (Ex-4) injections. Since HFD promotes inflammation in the gastrointestinal (GI) tract, we performed gene expression analysis and pathway analysis of duodenal mRNAs to investigate whether inflammatory response, glucose transport, and lipid transport were altered in HFD-fed GIRKO mice. Among the top pathways discovered in pathway analysis were those involved with inflammatory signaling, carbohydrate transport, and xenobiotic metabolism, which supports that HFD-fed GIRKO mice have increased GI tract inflammation which may promote impaired glucose homeostasis.
In conclusion, our studies suggest that HFD increased intestinal inflammation and exacerbated insulin resistance, which catalyzed the pathological progression of diabetes. Future studies are necessary to identify the molecular and cellular signaling pathways which culminate in frank diabetes, which may lead to therapeutic targets for regulating glucose homeostasis in the context of insulin resistance.

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IMPACTS OF ORGAN CROSSTALK AND SEX ON DIABETES PHENOTYPES

Insulin Resistance and Gender Define a Cell Autonomous Supernetworkof Protein Phosphorylation

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Many hormones and growth factors, including insulin, act through networks of protein phosphorylation. Insulin resistance is an important factor in the pathophysiology of many metabolic disorders. The aim of this study was to uncover the cell autonomous determinants of insulin action and protein phosphorylation using induced pluripotent stem cell (iPSC)-derived myoblasts (iMyos) in vitro. Here, we show that iMyos from non-diabetic individuals in the highest quintile of insulin resistance show impaired insulin signaling, defective insulin-stimulated glucose uptake and decreased glycogen synthase activity compared to iMyos from the insulin sensitive individuals, indicating these cells mirror in vitro the alterations seen in vivo. Global phosphoproteomic analysis uncovered a large network of proteins whose phosphorylation was altered in association with insulin resistance, most outside the canonical insulin-signaling cascade. More surprisingly, we also observed striking differences in the phosphoproteomic signature of iMyos derived from male versus female subjects, involving multiple pathways regulating diverse cellular functions, including DNA and RNA processing, GTPase signaling, and SUMOylation/ubiquitination. These findings provide new insights into the cell autonomous mechanisms underlying insulin resistance in the non-diabetic population and provide evidence of a major, previously unrecognized, supernetwork of cell signaling differences in males and females that must be considered in understanding the molecular basis of sex-based differences in normal physiology and disease.

Diabetes Mellitus and Glucose Metabolism

IMPACTS OF ORGAN CROSSTALK AND SEX ON DIABETES PHENOTYPES

Liver-Specific Expression of Constitutively Active $G_s\alpha$ Leads to Hyperglycemia With Impaired Insulin Secretion

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Liver-specific Expression of Constitutively Active $G_s\alpha$ Leads to Hyperglycemia With Impaired Insulin Secretion
The ubiquitously-expressed G protein $G_s\alpha$ couples hormone receptors to the stimulation of intracellular cAMP generation. We previously showed that mice with liver-specific $G_s\alpha$ deficiency (LGsKO) have improved glucose tolerance and enlarged pancreatic islets[1]. In the present study, we have generated mice with liver-specific expression of a constitutively activated $G_s\alpha$ (LGsR201C) by breeding mice containing a Lox-STOP-Lox-$G_s\alpha$R201C transgene within the Hipp11 locus with albumin-Cre mice. Male LGsR201C mice had normal survival but reduced body weight and increased liver weight. Compared to control littermates, LGsR201C mice had significantly increased hepatic cAMP levels and enhanced hyperglycemic response to glucagon, confirming the activation of liver $G_s\alpha$/cAMP signaling in LGsR201C mice. As a consequence, LGsR201C mice showed elevated blood glucose levels during both fed and fasting states, as well as enhanced hepatic gluconeogenesis evidenced by pyruvate tolerance test. Serum levels of insulin, glucagon, free fatty acids and triglycerides were comparable between control and LGsR201C mice in the fed state. Results of glucose and insulin tolerance tests showed that LGsR201C mice had severe glucose intolerance with normal insulin sensitivity. Unlike control mice, when given a high dose of glucose (3mg/g ip.), LGsR201C mice had completely blunted first- and second-phase insulin secretory responses to glucose. Since LGsR201C mice exhibited normal pancreatic islet size and insulin content examined with immunohistochemistry, the impaired glucose tolerance in LGsR201C mice probably resulted from an impaired insulin secretion. Results of RNA-seq analysis revealed that an array of genes was oppositely regulated in the liver of LGsKO mice vs. LGsR201C mice. Thus, our data indicate possible organ-to-organ communication between liver and pancreatic β-cells that is regulated by liver $G_s\alpha$ signaling. 1.Chen M., et al., JCI 115:3217, 2005

Diabetes Mellitus and Glucose Metabolism

IMPROVING DIABETES CARE: HOSPITAL DISCHARGE, COMPLICATIONS, AND NOVEL INSULIN THERAPY

Employing User-Centered Design and Learning Science Theory to Enhance Remote Delivery of Diabetes Education and Survival Skills at Hospital Discharge

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Learning diabetes mellitus (DM) survival skills is critically important, especially for those newly diagnosed upon discharge. COVID-19 has created new educational challenges, as DM self-management education and support is difficult to deliver remotely and can be time intensive. Content and format have not been re-designed for remote delivery; however, learning sciences research can help us create effective remote education strategies. We conducted interviews with users to identify critical needs in assuming immediate DM self-care at discharge from the hospital. We then mapped these user needs to relevant learning science theories to inform potential re-designs for remote delivery of DM education and survival skills at discharge.
We conducted 12 semi-structured interviews with "users," which included 18 participants (8 minority; 6>65 years): patients newly diagnosed with DM at discharge (N=6 [33%]), their caregivers (N=4 [22%]), and laypersons new to DM (N=8 [45%]). Users were asked about their discharge needs, laypersons about perceived needs. Three investigators performed iterative rounds of inductive coding of the transcripts (using MAXQDA software), utilizing a constant comparative method to identify codes describing dominant user needs. Learning science theory was applied to identify potential re-designs for remote delivery.
Dominant user needs during hospitalization included being overwhelmed with DM self-care information (6/12 sessions) and difficulty organizing self-care equipment (5/12 sessions). Dominant user needs at home included remembering DM self-care steps (6/12 sessions), understanding correct insulin dosing (9/12 sessions), feeling fearful injecting insulin (9/12 sessions), with some noting difficulty in tracking glucose (4/12 sessions) and confusing insulin types (4/12 sessions). When learning science theory was applied, analysis mapped to three discrete educational strategies, most dominant of which is the *spiral design* approach—cycles of teaching the same topic but with increasing complexity. This design follows the *pre-teaching principle*—curriculum-based conceptual overview of self-care. Self-care at home mapped to the need for *segmented learning* and *goal directed practice and feedback*, with the potential need for *behavioral therapies to reduce fear*.
Learning sciences has demonstrated that learning complex procedures and concepts, such as DM self-care, requires time, repetition, and continued support. With short hospital stays and the complexity of learning DM self-care, patients cannot gain needed *knowledge structures* to organize the information received during hospitalization. This study suggests specific learning science strategies for the design of an effective remote delivery of DM education and skills.

Diabetes Mellitus and Glucose Metabolism

IMPROVING DIABETES CARE: HOSPITAL DISCHARGE, COMPLICATIONS, AND NOVEL INSULIN THERAPY

Hypoglycemia Impairs Baroreflex Sensitivity: Implications for Autonomic Control of Cardiovascular Function in Diabetes