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.

Diabetes Mellitus and Glucose Metabolism

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