Bahaa Aloqaily, PhD[1], Hyokjoon Kwon, Ph.D.[1], Sarmed Al-Samerria, PhD[2], Ariel L. Negron, PhD[3], Fredric Edward Wondisford, MD[4], Sally Radovick, MD[5].
[1]Robert Wood Johnson Medical School/ Rutgers University, New Brunswick, NJ, USA, [2]RUTGERS STATE UNIV OF NJ, New Bruniswick, NJ, USA, [3]Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, USA, [4]Rutgers University, New Brunswick, NJ, USA, [5]Robert Wood Johnson Medical School, New Brunswick, NJ, USA.

Kisspeptin, a neuroendocrine protein critical for the control of pubertal development and fertility has been shown to be modulated by nutritional signals. While the secretion of kisspeptin from specific hypothalamic nuclei is well-known to regulate GnRH-mediated pubertal maturation and reproduction, it remains unclear what role peripheral kisspeptin, specifically of hepatic origin, plays in regulating metabolism and glucose homeostasis. To define the role of kisspeptin in the liver, we developed a novel Kiss1$^{f/f}$ mouse line and targeted liver-specific Kiss1 ablation by injecting a AAV8-TBG-iCre virus via the tail vein (LKiss1KO). Control mice included Kiss1$^{f/f}$ male and female mice injected with AAV-GFP (LKiss1WT). We previously showed that deletion of hepatic kisspeptin did not affect body weight, but resulted in decreased insulin secretion and glucose intolerance in both sexes. To clarify the effects of liver-specific Kiss1 knockout on insulin action and glucose homeostasis *in vivo*, we conducted hyperinsulinemic-euglycemic clamp studies three weeks after tail injections. We noted a sexual dimorphism in the glucose infusion rate (GIR), female mice have a higher GIR to maintain euglycemia associated with an elevated glucose consumption rate, suggesting that female mice are more insulin sensitive than male mice. However, the deletion of liver kisspeptin had no effect on the glucose production rate in either sex. Indirect calorimetry assessment was conducted 4 weeks post-injection. Both male and female LKiss1KO mice showed significantly higher oxygen consumption, carbon dioxide production, and increased energy expenditure as compared to the LKiss1WT groups. However, there were no differences in either the respiratory exchange ratio or total ambulatory activity among treatments. These findings clearly define a pivotal role for hepatic Kiss1 in the modulation of insulin secretion to maintain glucose homeostasis without modulating glucose production as well as in maintaining energy homeostasis in both male or female mice.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

Loss of Intestine-Specific FFA3 Has Protective Effects Against Diet-Induced Obesity and Hyperglycemia in Mice on a Western Diet

Kristen Roan Lednovich, BS, Sophie Gough, BS, Medha Priyadarshini, PhD, Brian T. Layden, PhD, MD.
University of Illinois College of Medicine, Chicago, IL, USA.

Free fatty acid receptor 3 (FFA3) is a recently-deorphaned G protein-coupled receptor belonging to the free fatty acid receptor family. Its ligands are short-chain fatty acids (SCFAs), which are key nutrients that play a diverse role in physiological function, including the regulation of metabolic homeostasis and glycemic control. FFA3 is broadly expressed in a multitude of tissues including the intestine, pancreas, and central nervous system, and is thought to contribute to metabolic homeostasis via a summation of its tissue-specific effects. Consequently, FFA3 has been identified as a potential drug target for metabolic diseases including obesity and type-2 diabetes. FFA3 is highly expressed in enteroendocrine cells (EECs) within the intestinal epithelium - the major site of SCFA generation - and is hypothesized to play a role in the secretion of postprandial incretin hormones, which are a group of specialized gut peptides that regulate a variety of metabolic and digestive functions following a meal. However, due to a paucity of data, the role of FFA3 within the intestine and its effects on physiology and metabolism is largely unclear. Previous *in vivo* studies involving this receptor have largely relied on global knockout mouse models, making it difficult to isolate its effects in EECs. To overcome this challenge, we have generated a novel intestine-specific knockout mouse model for FFA3, utilizing Cre-mediated recombination under the expression of the *villin* promoter. Here, we report the first *in vivo* characterization of FFA3 in the intestine and reveal novel insights into receptor function. Following model validation, we conducted a general metabolic assessment of male Villin-Cre-FFA3 mice on normal chow and observed no major congenital or time-dependent defects. Because dietary changes are known to alter gut microbial composition, and thereby SCFA production, a pilot study was performed on male Villin-Cre-FFA3 mice and their littermate controls to probe for a phenotype on a high-fat, high-sugar "western diet." Mice were placed on either normal chow (NC) or western diet (WD) at 10 weeks of age and metabolically profiled for 25 weeks. Our data reveals that Villin-Cre-FFA3 mice on WD, but not NC, were protected from diet-induced metabolic dysfunction, and displayed significantly lower levels of fat mass as well as modestly improved glycemic control. Our findings suggest a novel role of FFA3 in mediating the metabolic consequences of a western diet - a state of high inflammation, dysbiosis and metabolic stress. Moreover, these data support an intestine-specific role of FFA3 in both glucose and lipid metabolism, and further suggest the receptor's role in whole-body metabolic homeostasis and in the development of adiposity and hyperglycemia.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

Osteocyte-Specific TGFβ Signaling Mitigates Obesity-Induced Deregulated Energy Metabolism and Compromised Bone Quality

Neha S. Dole, PhD, Cristal Yee, PhD, Tamara Alliston, PhD.
University of CA-San Francisco, San Francisco, CA, USA.

Bone fragility associated with obesity is well recognized and is attributed to a cumulative decline in bone quality despite high BMD. Moreover, novel insights into skeletal physiology have revealed that bone-derived factors are key regulators of systemic energy balance. Despite the revelation that bone is both a target and a driver of energy