Endocrine Mechanisms of an Orphan G Protein-Coupled Receptor Regulating Metabolic Homeostasis

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G protein-coupled receptors (GPCRs) are the largest protein family and amenable for pharmacological manipulation. GPCRs in the neuroendocrine and enteroendocrine systems respond to various biological cues and in turn exert crucial roles in maintaining whole body metabolic homeostasis. For example, GPCRs in the gastrointestinal tract are involved in maintaining glucose and energy homeostasis by regulating the release of gut hormones in response to luminal dietary nutrients as well as microbial metabolites. We recently identified that an orphan GPCR, Gpr17, was co-expressed in glucagon-like peptide-1 (GLP-1)-expressing EECs in human and rodent intestinal epithelium. We reported that acute genetic ablation of Gpr17 in intestinal epithelium (iKO) improved oral glucose tolerance and glucose-stimulated insulin secretion (GSIS) in female and male mice through increased secretion of incretin hormone in response to nutrient ingestion (Cell Reports, 2022). In the neuroendocrine system, we previously identified Gpr17 as the transcription target of Forkhead box protein O1 (FoxO1) in the hypothalamus and generated hypothalamic neuron specific Gpr17 knockout animals (Cell, 2012). Our results demonstrated that agouti-related peptide (AgRP) neuron Gpr17 knockout mice had increased satiety during fasting-refeeding challenge (Diabetes, 2015) and that proopiomelanocortin (POMC) neuron Gpr17 knockout mice had increased alpha-melanocyte stimulating hormone (aMSH) processing and increased firing of POMC neurons (Nutrition & Diabetes, 2019). However, how Gpr17 may regulate energy balance especially regarding leptin hormone signaling is unclear. To address this question, we used genetic knockout approach to generate Gpr17 conditional knockout in leptin receptor expressing neurons in the brain. We found Gpr17 deficiency in leptin receptor expressing neurons increased leptin sensitivity in animals and resulted in reduced food intake, which corresponded with reduced inflammatory response in the hypothalamus. Moreover, male Gpr17 whole body knockout mice have improved intraperitoneal glucose tolerance, and increased insulin sensitivity in hyperinsulinemic-euglycemic clamp studies. In conclusion, our collective body of work showed that ablation of Gpr17 signaling in the neuroendocrine and enteroendocrine systems led to improved neurohormonal regulation to maintain metabolic homeostasis, indicating functionally targeting this GPCR may lead to better therapeutic outcome of diabetes and obesity.

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