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Control of metabolism by proglucagon-derived hormones from the gut.

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Enteroendocrine cells are scattered throughout the epithelial lining of the gut wall and synthesise and secrete over 15 different hormones. Many of these, including the proglucagon-derived hormone GLP-1, PYY, and serotonin, have important metabolic roles. We have shown that enteroendocrine cells sense and respond to changes in their environment including nutrients [1], immune regulators [2] and drugs such as metformin [3], that their density and function change in humans with obesity [4] and gastroparesis [5], and that bi-directional signalling occurs between the gut microbiome and these cells [6] to modulate host glucose metabolism [7]. Co-application of GLP-1 and PYY has synergistic effects on reducing food intake and we therefore study how L cells can be activated, using human gut tissue, as a logical approach to treating metabolic disease. We utilised a combination of *ex vivo* secretion assays in human and mouse gut tissue, immunohistochemistry, single cell gene expression and transgenic mouse models to define the pathway through which nutrients such as carbohydrates trigger GLP-1 release in human gut [1], and find that this has similarities and differences to that in rodents. We additionally demonstrate *ex vivo* in humans that the melanocortin 4 receptor (MC4R) and its endogenous ligand α-MSH, normally associated with central control of body weight and metabolism, exist within the human gut as an intrinsic signalling system which activates GLP-1 and PYY release and modulates L cell nutrient sensing [8]. Importantly, this is supported by *in vivo* clinical experiments in individuals carrying a heterozygous loss-of-function mutation in MC4R. Recent reports indicate this differs to rodents. In addition to this, we provide evidence that glucagon is a gut-derived peptide that plays an intrinsic role in regulating gut motility and cholesterol absorption. Such complex interactions between enteroendocrine cells and their local environment are of potential relevance to metabolic disorders such as type 2 diabetes and obesity and their treatment, and species differences are observed that provide some caution when interpreting outcomes from rodents.

1.Sun*, et al*. Diabetes, 2017. 66:2144-2149. **2.**Findeisen*, et al*. Nature, 2019. 574:63-68. **3.**Bahne*, et al*. JCI Insight, 2018. 3 **4.**Young*, et al*. Int J Obes, 2018. 42:1880-89. **5.**Wei*, et al*. Gastroenterology, 2021. 160:2451-2466. **6.**Ye*, et al*. Cell Host Microbe, 2021. 29:179-196. **7.**Martin*, et al*. PNAS, 2019. 116:19802-19804. **8.**Sun*, et al*. Gastroenterology, 2021. 161:536-547.