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Current Opinion in Pharmacology

Targeting gastrointestinal nutrient sensing mechanisms to treat obesity

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Gut hormones have important roles in the regulation of appetite and glucose homeostasis. Understanding how macronutrient sensing in the gastrointestinal tract modulates gut hormone release may reveal novel pharmacological or dietary approaches to metabolic disease. In this short review we discuss the mechanisms by which the gut senses macronutrients and the products of macronutrient digestion, and their putative utility in treating obesity and related conditions.

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Current Opinion in Pharmacology 2017, **37**:16–23

This review comes from a themed issue on **Endocrine and metabolic diseases**

Edited by **Gavin Bewick**

http://dx.doi.org/10.1016/j.coph.2017.07.005

Introduction

Obesity is associated to comorbidities including cancer and diabetes [1]. The most effective therapy is gastric bypass but it is expensive and invasive. Some of the benefits of gastric bypass are attributed to changes in patients' gut hormone profiles [2]. Gut hormones, secreted by enteroendocine cells (EECs), are crucial in appetite regulation. They respond to a variety of stimuli, such as nutrients in the lumen, which are detected by a wide range of sensors [3•]. These sensors may be useful anti-obesity targets capable of modulating endogenous gut hormone secretion to promote weight loss. This review will focus on extracellular nutrient sensors expressed in the gut, their role in gut hormone secretion and their potential use as anti-obesity targets (Figure 1).

Macronutrients are classified as carbohydrates, fats or proteins. Upon ingestion, these macronutrients are converted by endogenous and bacterial enzymes to metabolites that are detected by sensors in the gut.

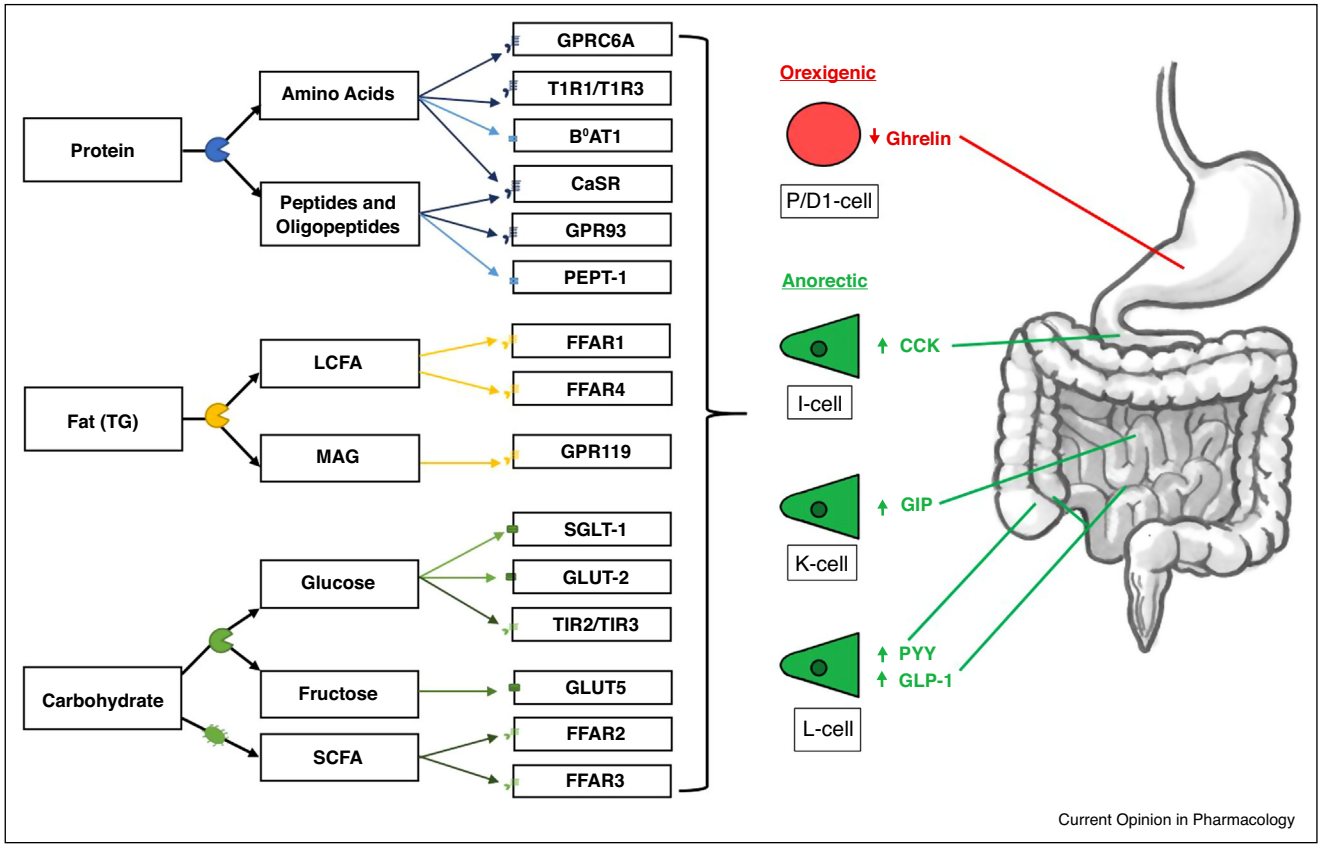
Carbohydrate

Glucose, a common carbohydrate and break-down product of larger carbohydrates, potently stimulates the release of the incretin and appetite-regulating hormones gastric-inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP-1) when administered orally but not intravenously [4•,5,6]. In the small intestine, this effect is primarily mediated by the sodium-dependent glucose co-transporter SGLT-1, which is expressed in both K-cells and L-cells; GIP and GLP-1 expressing EECs, respectively [5]. The entry of sodium, coupled to glucose, depolarizes the cell membrane, opening voltage gated calcium channels and stimulating hormone exocytosis [4•,7•]. Knockout of SGLT-1 in mice abolishes peak glucose-induced GIP and GLP-1 secretion [8,9], but at later time points, circulating levels of GLP-1 and the anorectic gut hormone peptide YY (PYY) are increased in both SGLT-$1^{-/-}$ and antagonist treated mice [9], suggesting alternative glucose sensing mechanisms in the distal gut. Specifically inhibiting intestinal SGLT-1 in mice also resulted in a trend for increased GLP-1 following a glucose challenge, but importantly highlighted potential gastrointestinal side effects consistent with the malabsorption observed in knockout mice and humans with SGLT-1 inactivating mutations [8,10].

In humans, SGLT-1 inhibition resulted in decreased postprandial GIP and increased postprandial GLP-1 levels [11]. Longer term human studies have used antagonists such as LX4211 that also target SGLT-2. Inhibiting SGLT-1/2 in diabetic patients improved glycemic control and resulted in a trend for decreased weight and increased GLP-1 and PYY levels [12]. Decreased weight gain, regardless of increased food intake was observed in animal models [13]. As an adjunct therapy to insulin in diabetic patients, LX4211 improved glycemic control, increased post-prandial PYY levels and promoted weight loss [14]. Some FDA approved SGLT-2 inhibitors also lead to weight loss [15]. Whether the gut hormone effects resulting from SGLT-1 antagonism contribute to this needs further investigation. Overall, SGLT-1 partial antagonism, to minimise malabsorption side effects, may be a better anti-obesity strategy than SGLT-1 agonism.

Glucose transporter 2 (GLUT-2) may also mediate glucose-induced gut hormone secretion. GLUT-2 inhibition and knockout in mice reduced glucose-stimulated GLP-1 secretion by ~11% and 55% respectively [4•,16]. Intestinal specific GLUT-2 knockout did not alter basal GLP-1

Figure 1



Simplified overview of gastrointestinal nutrient sensors of the gut. Macronutrients are broken-down by endogenous and bacterial enzymes in the gut, producing metabolites which can be detected by G-protein coupled receptors and transporters. This leads to the modulation of the secretion of appetite-regulating hormones by enteroendocrine cells. This schematic does not include intracellular nutrient sensors. Abbreviations: long chain fatty acids (LCFA), 2-monoacylglycerols (MAG), short chain fatty acids (SCFA), G protein-coupled receptor family C group 6 member A (GPRC6A), amino acid sensing heterodimer taste receptor type 1 member 1/taste receptor type 1 member 3 (T1R1/T1R3), neutral amino acid transporter (B^0AT1), calcium sensing receptor (CaSR), G protein-coupled receptor 93 (GPR93), peptide transporter 1 (PEPT-1), free fatty acid receptor 1 (FFAR1), free fatty acid receptor (FFAR 4), G protein-coupled receptor 119 (GPR119), sodium-dependent glucose co-transporter 1 (SGLT-1), glucose transporter 2 (GLUT-2), sweet taste receptor taste receptor type 1 member 3/taste receptor type 1 member 3 (T1R2/T1R3), glucose transporter 5 (GLUT-5), free fatty acid receptor 2 (FFAR 2), free fatty acid receptor 3 (FFAR 3), cholecystokinin (CCK), gastric inhibitory polypeptide (GIP), glucagon-like peptide 1 (GLP-1), peptide YY (PYY).

levels but resulted in lower L-cell density, compensated for with an 80% increase in GLP-1 content per cell [17•], suggesting the long-term effects of targeting GLUT-2 may differ from the acute effects. Additionally, human mutations in GLUT-2 result in Fanconi-Bickel syndrome, suggesting it may not be a useful target in the treatment of obesity [18].

The essential role of SGLT-1 and the contributory role of GLUT-2 in GLP-1 secretion is in agreement with mathematical spatial models and transporter knockout models, but the effect of GLUT-2 knockout on glucose-induced GIP secretion is less clear [8,16,19]. Overall, SGLT-1 appears more important than GLUT-2 in peak glucose-induced gut hormone secretion.

The clinical utility of targeting the heterodimer sweet taste receptor T1R2/T1R3 may also be limited. Expression of its subunits is low in K-cells and L-cells, and studies in perfused rat intestine required toxic levels of sweeteners to stimulate GLP-1 release [20]. In humans, sweeteners which activate the receptor failed to increase gut hormone release [21]. Additionally, lactisole, a T1R2/T1R3 antagonist, failed to suppress the secretion of incretins in response to glucose in one study [22] but not in another [23].

ATP-sensitive potassium channels (K_{ATP}) on EECs have also been suggested as potential sensors due to their role in β-cell glucose sensing. In rat perfused intestine, K_{ATP} inhibition increases GLP-1 release [4•]. However,