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Targeted intestinal delivery of incretin secretagogues—towards new diabetes and obesity therapies

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ABSTRACT

A new strategy under development for the treatment of type 2 diabetes and obesity is to mimic some of the effects of bariatric surgery by delivering food-related stimuli to the distal gastrointestinal tract where they should enhance the release of gut hormones such as glucagon-like peptide-1 (GLP-1) and peptideYY (PYY). Methods include inhibition of food digestion and absorption in the upper GI tract, or oral delivery of stimuli in capsules or pelleted form to protect them against gastric degradation. A variety of agents have been tested in humans using capsules, microcapsules or pellets, delivering nutrients, bile acids, fatty acids and bitter compounds. This review examines the outcomes of these different approaches and supporting evidence from intestinal perfusion studies.

1. Introduction

Type 2 diabetes mellitus is an increasing cause of morbidity and mortality across the world and is strongly associated with obesity. Despite recent therapeutic advances, there remains an urgent need to identify new ways of treating diabetes and obesity. A major focus of new therapeutics is the enteroendocrine system, which produces a wide range of peptide hormones including glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), cholecystokinin (CCK) and peptideYY (PYY). These act as hormonal signals linking food absorption to physiological responses such as insulin secretion and satiety. GLP-1 mimetics and inhibitors of GLP-1 degradation (DPP4 inhibitors) are in widespread use for the treatment of type 2 diabetes, and GLP-1 mimetics are also licensed for the treatment of obesity [1]. Bariatric surgery is an even more effective therapy for diabetes, and is believed to act, at least in part, by mobilising endogenous stores of gut hormones such as GLP-1 and PYY by shifting food absorption from the upper to the lower small intestine, where these hormones are found in higher abundance [2]. Reproducing the hormonal changes observed after gastric bypass surgery using pharmacological or dietary manipulations is regarded as a potential new strategy for treating diabetes and obesity. One proposed method is to target the delivery of nutritional and other stimuli to enteroendocrine cells in the lower gut by approaches such as delayed digestion/absorption, stimulus encapsulation, or harnessing of microbial metabolism to produce locally active secretagogues. This review explores recent progress in, and the potential future of, this approach.

2. Enteroendocrine cell location and function

Enteroendocrine cells are located in the epithelium of the gastrointestinal tract from the stomach to the rectum. They mostly span the epithelial layer, having surfaces facing both the gut lumen and the basolateral space, and respond to a variety of nutritionally-related stimuli including fats, carbohydrates, proteins and bile acids [3]. The detection of ingested foods occurs downstream of food digestion, requiring the formation of small molecular species such as glucose, free fatty acids, monoacylglycerols, amino acids, di/tripeptides and bile acids. These are detected by a variety of G-protein coupled receptors and nutrient transporters, which are highly, and in many cases specifically, expressed on enteroendocrine cell populations [3].

In a number of cases it has been found that stimulus detection by enteroendocrine cells requires local ligand absorption. Detection of glucose, for example, is directly linked to its influx across the apical membrane of enteroendocrine cells by sodium coupled glucose transporters (SGLT1), which causes depolarisation of the cell membrane and voltage gated calcium entry [4]. Detection of long chain fatty acids and bile acids also seem to occur downstream of their local absorption, but

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in these cases the requirement is to bring ligands into contact with their target enteroendocrine cell receptors (FFA1 and GPBAR1) apparently located on the basolateral membrane [5,6]. Thus, in the upper small intestine, chylomicron formation is a key step linking ingested fat to the secretion of GLP-1, CCK and GIP [7,8]; and in the distal ileum, bile acid-triggered GLP-1 secretion occurs downstream of conjugated bile acid absorption by sodium coupled bile acid transporters [5]. The linkage of enteroendocrine cell activation to local nutrient absorption has the consequence that these ligands do not trigger gut hormone release if they only make transient contact with the apical surfaces of enteroendocrine cells as they pass by in the intestinal lumen, but only act if they are being actively absorbed in the local vicinity.

Many features of enteroendocrine cells, including their morphology and signalling pathways, are shared along the length of the gut, but there are marked regional differences in the hormones they produce. GIP and CCK, for example, are predominantly produced in the proximal small intestine, whereas GLP-1 and PYY are found at higher levels in the lower small intestine and colon [9]. Although proximal to distal signalling loops that recruit distal GLP-1 in response to proximal nutrient detection have been proposed [10,11], when nutrients are absorbed in the upper gut, they trigger a very different profile of gut hormones compared with when nutrient absorption is shifted to more distal regions of the gut. During normal physiology, the upper small intestine is the major site of nutrient digestion and absorption and the gut employs a battery of neurohormonal feedback pathways to limit the quantity of potentially absorbable food reaching the ileum and colon and the consequent risk of losing nutrients in the faeces. Pharmacological and surgical interventions, however, can overcome these systems and deliver large loads of nutrients into the distal gut, resulting in major shifts in post-prandial gut hormone profiles.

3. Gut hormone changes after bariatric surgery

Surgeons have developed a variety of bariatric procedures, including gastric banding, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy, that are each effective therapies for obesity but have different effectiveness on type 2 diabetes [2]. Many studies have demonstrated that RYGB and sleeve gastrectomy, but not gastric banding, have beneficial effects on glucose metabolism and diabetes beyond those predicted by weight loss alone, but the underlying explanations remain disputed and are likely multifactorial. RYGB and sleeve gastrectomy have a number of physiological consequences that might contribute to weight loss and enhanced insulin secretion, including changes in the enteroendocrine axis [12,13], increased plasma bile acids [14] and calorie restriction [15]. Both procedures result in an increased rate of nutrient delivery to the distal gut, because the stomach is either bypassed or cut down to form a tube with limited storage capacity. RYGB and sleeve gastrectomy have been associated with dramatically elevated post-prandial plasma concentrations of GLP-1 and PYY [2], and are likely accompanied by a range of other gut hormone changes consequent upon the predominant direct stimulation of distal as opposed to proximal enteroendocrine cells.

The following sections outline different approaches that have been taken to mimic the effects of gastric bypass surgery by delivering stimuli to endocrine cells in the distal gut. In this review, we take the position that measurable elevations in plasma hormone concentrations will be a good marker of an effective approach to increase secretion from distal enteroendocrine cells, although subtle, locally-restricted increases in distal gut hormone levels might have their own beneficial effects, given that GLP-1 receptors are found in the direct vicinity of the secreting cells [16].

4. Experimental intestinal infusions for targeted stimulus delivery

To investigate how gut hormone release is influenced by the position at which nutrients are delivered, a number of investigators have used controlled nutrient infusions into the stomach, duodenum and jejunum of humans. Gastric infusions enable the bypassing of the oropharynx, and therefore the taste and olfactory cues associated with eating. Although there is little evidence to suggest that gut hormone responses are triggered by the cephalic phase of eating, these studies do enable a defined rate of nutrient delivery that is difficult to achieve by oral ingestion. Gastric infusions cannot, however, provide a guaranteed rate of nutrient delivery into the small intestine because the pylorus acts downstream of the infusion, and closely regulates gastric emptying.

Duodenal infusions have been studied to investigate the dependence of gut hormone secretion on the nutrient stimulus and its rate of delivery. These studies have established that low dose infusions of carbohydrates, fats and proteins are each able to stimulate secretion of hormones produced by the duodenum (GIP, CCK), but that higher infusion rates are required to trigger a robust elevation of plasma GLP-1 or PYY [17–19]. The proposed explanation is that higher infusion rates exceed the maximal absorption capacity of the upper gut and therefore result in nutrient delivery more distally where there is a higher density of cells producing GLP-1 and PYY.

A few studies have placed cannulae more distally in the gut and demonstrated robust elevation of GLP-1 and PYY secretion in response to glucose [20,21]. In interpreting results from infusion studies performed lower down the intestine, it is important to remember that only the digestion products of macromolecules are effective gut hormone secretagogues, and that some molecules are dependent on sodium for their absorption. Delivery of macromolecular polymers that require pancreatic enzymes for their digestion is therefore unlikely to trigger a large secretory response, and infusion of glucose will have limited effect unless there is an adequate supply of sodium ions from the infusion itself, bile or local secretion.

In situ intestinal perfusion studies have also been carried out using animal models, such as the pig, rat or mouse. In these studies, the intestinal arterial supply is isolated for vascular perfusion and the portal vein cannulated for venous collection. Additional cannulae in the gut lumen enable luminal perfusion of candidate stimuli. These studies enable stimulus delivery to a defined segment of the gut, and can target intestinal regions not readily accessible in man, such as the distal ileum and colon. They permit the co-application of candidate pharmacological inhibitors and agonists and therefore enable a closer interrogation of the pathways underlying nutrient detection. Comparisons between the effectiveness of different stimuli delivered either through the lumen or vasculature have confirmed, for example, that luminal glucose only triggers gut hormone secretion in the presence of luminal sodium ions [22], that bile acids are more effective when delivered via the vasculature than from the lumen [5], and that the long chain free fatty acid receptor FFA1 is more accessible from the vascular than the luminal direction [6].

5. Pharmacological agents causing increased delivery of stimulant to the distal gut

There are a number of existing therapies that increase GLP-1 secretion in humans likely because they increase nutrient delivery to the distal gut. A variety of mechanisms have been implicated, including reduced nutrient absorption in the proximal intestine and inhibition of nutrient digestion.

5.1. Alpha glucosidase inhibitors

Acarbose, miglitol and voglibose are alpha glucosidase inhibitors that slow starch and sucrose digestion in the proximal gut, leading to increased delivery of undigested carbohydrate to the distal intestine. Plasma GLP-1 levels were higher in healthy volunteers [23] and patients with T2DM treated with acarbose following sucrose ingestion [24] but not after a mixed meal [25], whereas concentrations of GIP were lowered by acarbose in patients with T2DM [24,25]. In a group of