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Nutrition and L and K-enteroendocrine cells

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Abstract

Purpose of review—The review highlights the influence of nutrients over the secretion of several hormones produced by enteroendocrine cells in the gastrointestinal tract that secrete incretin hormones. These hormones influence glucose homeostasis; food intake; gastric, pancreatic and hepatic secretions; and gastric and intestinal motility, and these aspects are summarized in this review.

Recent findings—This study provides an overview of recent advances in our understanding of the physiology of the incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), as well as of oxyntomodulin. A better understanding of the secretion and action of these hormones at their receptors was made possible by new techniques that allow investigation of individual enteroendocrine cells.

Summary—The better understanding of the function of the gastrointestinal incretin hormones and their implications for improving glucose homeostasis and perhaps influencing food intake and appetite as well, new research in this area will help combat metabolic diseases such as type 2 diabetes and obesity.

Keywords

glucagon; glucagon-like peptide-1; glucose-dependent insulinotropic polypeptide; incretin; oxyntomodulin

Introduction

Nutrition refers to the net gain of energy, vitamins and minerals (i.e. nutrients) derived from ingested food. Research concerning the efficiency of deriving nutrients from food has considerable interest due to the impact on health-threatening disorders such as starvation, overweight and obesity. When food is eaten, it enters the gastrointestinal tract. A major function of the gastrointestinal tract is to digest food so that usable molecules can be absorbed from its lumen into the blood and the lymph. The gastrointestinal tract is composed of numerous cell types, many of which secrete enzymes into the lumen in which they help break down the ingested food (called chyme) and then absorb the released nutrients. The topic of this review is the secretions of certain enteroendocrine cells (EECs) located in the intestinal wall. These cells are polarized, with finger-like projections extending into the lumen (Fig. 1). These projections express chemoreceptors that are sensitive to various classes of nutrients and other compounds in food. The other end of the EEC is located near

capillaries and nerve endings, and it contains secretory vesicles that contain peptides that are secreted by the cell in response to information from the luminal chemoreceptors.

To date, more than 30 peptides have been identified that are released by different types of EECs in response to consumed nutrients (Table 1). Individual gastrointestinal hormones produced and secreted by the EEC influence appetite and food intake, gastric, pancreatic and hepatic secretions, gastric and intestinal motility, and glucose homeostasis and metabolism. In carrying out these functions, the gut peptides act both as classic hormones, traveling through the blood to act on receptors on distant organs, and as neuromodulators, acting on receptors expressed on autonomic nerves whose endings are in close proximity to the site of secretion (see Fig. 1).

Other enteroendocrine peptides and their function with regard to nutrition are reviewed elsewhere [2–4]. This article focuses on secretions from intestinal K and L cells, that is, glucose-dependent insulinotropic polypeptide (GIP) from K cells and glucagon-like peptide-1 (GLP-1) and oxyntomodulin (OXM) from L cells, and highlights advances published over the past year.

Enteroendocrine K and L cells

All EECs sense nutrients present in the lumen. Whereas the molecular mechanisms by which specific nutrients are detected, and their impact on the secretion of different peptides, is still poorly understood, it is now recognized that the receptors involved are often the same molecules that are expressed by taste cells in the tongue, that is, EECs express receptors for sweet, bitter and other tastants, and this is especially true for K and L cells [5]. K cells are predominantly found in the duodenum [6], whereas L cells are located in the ileum and colon [7]. However, a recently described population of K/L cells secretes both GIP and GLP-1 [8,9].

Novel molecular genetic techniques have begun to reveal important nuances of EEC. As one example, transgenic mice expressing the yellow fluorescent protein, Venus, attached to the proglucagon or to the GIP promoter, have helped identify individual L and K cells *in vivo*, respectively. Use of this tool has identified the sodium glucose co-transporter 1 (SGLT1) and ATP-sensitive K⁺ channels (K_{ATP}) as being important in GLP-1 and GIP release [10*, 11]. Other studies found that the intestinal epithelial ablation of *Foxa1* and *Foxa2* reduces the number of L cells, resulting in less GLP-1, GLP-2 and peptide YY [12]. Mice with an intestinal-specific ablation of neurogenin 3, a gene implicated in pancreatic and intestinal cell differentiation, frequently die during the first week of life, and those that survive have impaired lipid absorption, reduced weight gain, and improved glucose homeostasis [13**]. These findings underline the crucial function of EEC and their implication in metabolism.

Incretins: glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1

An incretin is a hormone produced by the gut in response to nutrient ingestion that augments insulin secretion from pancreatic B cells. The incretin effect is best demonstrated when glucose is orally ingested, compared to when the same amount of glucose is administered intravenously [14,15]. GLP-1 and GIP are the best known incretins, with GLP-1 being more potent [16].

Glucose-dependent insulinotropic polypeptide

Glucose-dependent insulinotropic polypeptide is synthesized in K cells by being cleaved from the prohormone, pro-GIP, by proprotein convertase subtilisin/kexin type 1 (PC1/3) to

yield GIP₁₋₄₂, the active form. A second bioactive form of GIP, amidated GIP₁₋₃₀, is processed by PC2 in K cells and in glucagon-secreting pancreatic A cells [17,18], but has yet to be well characterized.

GIP₁₋₄₂ is secreted after meals and undergoes rapid degradation by the enzyme, dipeptidyl peptidase IV (DPP-IV) [19]. GIP binds to G-protein-coupled GIP receptors 1 and 2 (GIPr 1–2) that are present in pancreatic A and B cells as well as in the gastrointestinal tract, adipose tissue, bone, pituitary and brain [20].

Glucose-dependent insulinotropic polypeptide and GLP-1 are secreted in response to luminal carbohydrate, with GIP being more sensitive than GLP-1 [21]. Both GIP and GLP-1 are also secreted in response to dietary lipid. GLP-1 appears to be more sensitive in this regard, and it reduces intestinal motility provoking a better proximal fat absorption [22]. GIP facilitates glucose-stimulated insulin secretion, thus improving glucose tolerance and accounting for its incretin effect [23]. In addition to regulating glucose homeostasis, GIP may have a role in obesity. Mice lacking K cells [24] or GIPr [25] are protected against high-fat diet-induced obesity. GIP also is important for fatty acid uptake and lipogenesis by adipocytes [26,27].

During digestion, lipids are reduced to free fatty acids and monoacylglycerides that are absorbed by cells lining the intestinal lumen and are re-esterified into triacylglycerides by the enzymes monoacylglycerol acyltransferase-2 and diacylglycerol acyltransferase-1. The triacylglycerides are then packaged into chylomicrons and released into lymph vessels supplying the intestine. Disruption or malfunction of this pathway prevents GIP secretion from K cells [28], but has no effect on the secretion of GLP-1 or PYY from L cells, implying that chylomicron formation is essential for GIP secretion [29*].

Animals maintained on a high-fat diet have increased GIP secretion, due in part to a proliferation of stem endocrine cells that differentiate into K cells [30]. In humans, in addition to improving glucose homeostasis, GIP increases hydrolysis of circulating triacylglycerides and the subsequent re-esterification of the free fatty acids into triacylglycerides within adipocytes, thus increasing fat storage. These effects of GIP do not occur under fasting conditions [31]. In summary, GIP is an incretin hormone that is directly stimulated by fat and its secretion is dependent on chylomicron formation.

Glucagon-like peptide-1

Several aspects of GLP-1 secretion and action are discussed below.

Proglucagon gene and the glucagon-like peptide-1 receptor—The proglucagon gene, which is expressed in pancreatic A and intestinal L cells and some neurons in the nucleus of the solitary tract (NTS) in the hindbrain, codes for proglucagon. Proglucagon is cleaved by prohormone convertase enzymes. In A cells, PC2 generates glucagon, whereas in L cells, PC1/3 produces GLP-1, GLP-2 and OXM, and this is also thought to occur in the hindbrain [32]. Active GLP-1 can have one of two forms, GLP-1_{7-36amide} or GLP-1₇₋₃₇, and both have insulinotropic activity [33]. GLP-1, like GIP, has a short half-life and is inactivated by DPP-IV. Synthetic GLP-1 agonists (e.g. exendin-4) have a longer half-life due to an inability of DPP-IV to degrade them. DPP-IV inhibitors and exendin-4 are adjunct therapies for type 2 diabetes to improve glucose homeostasis. Exendin-9 (exendin₉₋₃₉) is a GLP-1 antagonist that binds competitively to the GLP-1 receptor (GLP-1r). GLP-1r is expressed in pancreatic islets, the gastrointestinal tract, lungs, kidneys and many regions in the brain, including the hippocampus, hypothalamus and hindbrain.

Stimulation of glucagon-like peptide-1 secretion—Like GIP, GLP-1 improves glucose homeostasis by increasing insulin secretion during meals [23]. GLP-1 also suppresses glucagon secretion and gastrointestinal motility, reduces food intake and inhibits the secretion of digestive enzymes into the lumen (reviewed in [34]). GLP-1 secretion from the gastrointestinal tract occurs in association with meal-taking, especially meals rich in carbohydrates and fat [35]. Plasma GLP-1 increases sooner during carbohydrate than during fat ingestion [36], perhaps due to stimulation of sweet taste receptors on the tongue initiating a neural reflex to the L cells. Glucose in the distal intestinal lumen in which L cells are located also elicits GLP-1 secretion.

Several mechanisms are hypothesized to mediate glucose-stimulated release of GLP-1 from L cells, including glucose metabolism and consequent closure of ATP-sensitive potassium (K_{ATP}) channels, increased sodium-glucose co-transporter 1 (SGLT-1) activity, and/or activation of sweet taste receptors on L cells themselves, as reviewed in [37–39]. Stimulation of the intestinal glucose-sensor SGLT1 induces GLP-1 secretion and reduces hyperglycemia in response to a nonmetabolizable glucose analog (α -methyl-glucopyranoside), which is a SGLT1 substrate [40*].

The mechanism by which lipids influence GLP-1 secretion is less clear. Fat hydrolysis in the proximal intestine produces long-chain fatty acids that stimulate cholecystokinin (CCK) release from I cells, and GLP-1 secretion in turn is increased by CCK binding to the CCK-1 receptor on L cells [41**]. Other proposed mechanisms include lipid-responsive G-protein-coupled receptors such as GPR119 [37]. Oleoylethanolamide (OEA), a fatty acid signal synthesized in intestinal cells, is an endogenous ligand for GPR119. Exogenous OEA dose-dependently reduces food intake without causing malaise [42,43] and OEA stimulates GLP1 secretion via GPR119 on L cells [44**,45**]. Mice genetically lacking GPR119 have increased body weight and plasma insulin and leptin, but normal plasma glucose and lipid levels, suggesting that GPR119 does not directly influence glucose homeostasis. Moreover, OEA inhibits food intake in both GPR119-knockout mice and their wild-type controls, indicating that GPR119 is not essential for appetite suppression [45**]. Thus, GPR119 signaling and the consequent secretion of GLP-1 appear to be involved in body weight regulation; however, their impact on food intake remains unclear.

The bile receptor TGR5 is expressed by L cells and induces GLP-1 secretion. Activity at the TGR5 receptor increases energy expenditure and attenuates diet-induced obesity by its action on mitochondrial oxidative phosphorylation in brown adipose tissue and muscle. The TGR5 receptor also triggers mitochondrial phosphorylation in L cells resulting in an increased ATP/ADP ratio, followed by calcium mobilization provoking the release of GLP1, thereby improving glucose homeostasis in obese mice [46**].

Glucose homeostasis—Glucagon-like peptide-1 is both an incretin, stimulating insulin secretion, and a satiating factor that reduces meal size. The relative functions of central and peripheral GLP-1 signaling have generally been considered to be separate, with central GLP-1 influencing food intake and peripheral GLP-1 regulating glucose homeostasis. However, this dualistic paradigm has been challenged by recent evidence that activation of GLP-1r in the hypothalamic arcuate nucleus improves glucose homeostasis by increasing glucose-stimulated insulin secretion and reducing hepatic glucose production [47]. Other studies indicate that peripheral GLP-1 enhances the ability of insulin to stimulate glucose disposal and inhibit glucose and VLDL-TG metabolism, whereas central GLP-1 inhibits endogenous glucose production [48*].

Food intake—A large literature documents the ability of exogenous GLP-1 and of synthetic GLP-1 agonists to reduce food intake in animals and in humans [49,50]. When

animals and people are anticipating eating a scheduled meal, they make a series of cephalic responses before the food ingestion actually begins. This includes anticipatory increases of insulin, ghrelin [51,52] and many other meal-related hormones. GLP-1 was found to also have an anticipatory phase, with a secretory peak occurring around 1 h prior to feeding time [53**]. The administration of a GLP-1r antagonist prior to the anticipatory increase of GLP-1 secretion reduced meal size, implying that the ability to eat a large anticipated meal is facilitated by a premeal secretion of GLP-1, perhaps to prime the B cells to produce more insulin.

Co-infusion of GLP-1's antagonist exendin₉₋₃₉ along with GLP-1 attenuates its satiating effect. On the basis of this, and if endogenous GLP-1 functions as a satiating factor, administration of the antagonist alone would be expected to increase food consumption. However, findings addressing this are controversial, with some studies failing to observe a change of food intake following exogenous GLP-1 [54] and others observing increased intake [55,56]. Another controversy concerns the site of action of peripherally administered GLP-1 to reduce food intake, with different studies ruling in or out receptor populations in the hepatic portal vein, the liver, and/or the brain [53**,57,58]. Since the GLP-1 signal must access the brain in order to influence behavior, there is compelling evidence that an intact vagus nerve is necessary for this mechanism [59], although a case can also be made for a direct action of peripherally administered GLP-1 on the brain [60*]. An intriguing question concerns whether GLP-1 and the GLP-1 agonist, exendin-4, act on the same receptors and/or in the same way to reduce food intake in the brain. In one experiment, equimolar doses of exendin-4 had a longer duration of action than GLP-1, and the central anorectic effect of exendin-4 was insensitive to GLP-1r antagonists although its effect was blunted in GLP-1r knockout mice [61]. Administering GLP-1 directly into the brain also reduces food intake [62] and decreases lipid storage in white adipose tissue, independent of nutrient intake or body weight, an effect mediated by the sympathetic nervous system. However, this regulation is lost in diet-induced obese mice [63**].

Glucagon-like peptide-1 and the vagus nerves—The coordination among the brain, the autonomic nervous system and the enteric nervous system is known as the gut–brain axis [36]. During a meal, GLP-1 stimulates sensory axons of the vagus nerve, acting on receptors in the hepatic portal vein [64,65] or perhaps on nerve endings within the intestine itself. The signal passes to the brain and activates efferent signals from the brain to other tissues that regulate glucose metabolism. While influencing glucose homeostasis, hepatic vein GLP-1 receptors do not have an impact on food intake regulation [60*]. In contrast, activation of the enteric and dorsal-trunk vagal neurons did reduce food intake in response to a GLP-1r agonist [66*]. It has been proposed that the increased vagal afferent excitation by GLP-1 is due to the inhibition of repolarizing Kv current [67*]. The inhibition of gastric emptying by peripheral GLP-1 depends upon vagal afferents interacting with other signals in the NTS [68], and this signal has been found to interact with other signals related to gastric distension but not by duodenal nutrient infusion [69].

Oxyntomodulin

Oxyntomodulin, another cleavage product of proglucagon, is produced along with GLP-1 in L cells and in the brain. OXM is co-secreted with GLP-1 and PYY in response to food ingestion and in proportion to ingested calories. Central or peripheral administration of OXM reduces food intake [70,71]. To date, no OXM receptor has been cloned, and it has been proposed that OXM action is mediated by the GLP-1r, although OXM has a lower affinity for GLP-1r than GLP-1 [70].

Oxyntomodulin administration increases c-fos expression in the arcuate nucleus, suggesting a hypothalamic site of action [71]. Importantly, peripheral administration of GLP-1 or OXM results in differential hypothalamic neuronal activation, implying that OXM and GLP-1 act via different hypothalamic pathways [72]. Central OXM administration suppresses circulating ghrelin, and this was suggested to be mediated by GLP-1r [73^{**}]. The anorectic effect of OXM might therefore be partially mediated by reduced ghrelin as well as by an increased release of the anorectic peptides [71]. Administration of the GLP-1 agonist, exendin-4, also suppressed ghrelin levels, but this was not blocked by peripheral administration of the antagonist, exendin-9 [74]. The difference between the two findings lies in whether the antagonist is administered centrally or peripherally, and suggests that the effects of OXM and exendin-4 are made via different receptor populations. Electrophysiological studies found that OXM and GLP-1 reverse ghrelin inhibition of arcuate neurons and that this is mediated by GLP-1r stimulation [75].

Drug development related to incretin hormones

Several drugs mimicking the actions of incretin hormones have been developed for treatment of type 2 diabetes and obesity [20,76]. Most research in this area has utilized the GLP-1 ligands exendin-4 (agonist) and/or exendin-9 (antagonist). However, there is evidence that exendin-4 may exert its incretin and anorectic actions through some unknown mechanism in addition to acting at the GLP-1r, and hence may act differentially than endogenous GLP-1 [61]. Perhaps related to this, the acute administration of high doses of exendin-4, peripherally or centrally, increases blood glucose in rats via mediation of the sympathetic nervous system [77^{*}]. These studies underscore the need for better understanding the actions of the GLP-1r ligands and potential repercussions with regard to therapies for type 2 diabetes and obesity.

Another pharmacological approach is using long-acting DPPIV inhibitors to improve glucose tolerance by elevating endogenous GLP-1 and GIP [78]. Administration of glucagon-GLP-1 chimeric compounds that stimulate both the glucagon and the GLP-1 receptor results in reduced body fat resulting from decreased food intake and increased energy expenditure. These co-agonist compounds also normalized glucose and lipid metabolism and reduced liver steatosis [79^{**}]. Similar results were observed by an OXM analog, the DualAG peptide, which is also an agonist to GLP-1r and the glucagon receptor [80^{**}].

Conclusion

Diverse nutrients can have multiple effects in the stimulation and secretion of gastrointestinal hormones that have a pivotal role in the control of metabolism. During the past year, many new tools have been developed to understand the physiology of the ECC, and in particular the L and K cells, that have enhanced our knowledge of the differentiation, production and secretion of the incretins GIP and GLP-1, as well as other peptides. The next few years are expected to reveal specific mechanisms of secretion of these hormones in response to specific nutrients, as well as new protein targets for the development of therapeutic and research pharmaceuticals. Research over the previous year has highlighted the principle that the use of analogs of hormones and their receptors does not necessarily reflect the endogenous mechanism(s) of action and may lead to unanticipated outcomes. By furthering our knowledge of the gastrointestinal incretin peptides and their implications for improving glucose homeostasis and perhaps influencing food intake and appetite as well, new research in this area will help combat metabolic diseases such as type 2 diabetes and obesity.

Acknowledgments

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References and recommended reading

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Key points

- Generation of novel molecular genetic techniques allows the identification of individual L and K cells.
- GIP is stimulated by fat and its secretion is dependent on chylomicron formation.
- GLP-1 is stimulated by long chain fatty acids via CCK receptors.
- Analogs of hormones and their receptors do not necessarily reflect the endogenous mechanism(s) of action.

Figure 1. Enteroendocrine cells of the gut

The enteroendocrine cells (EECs) are located in the intestinal wall and express finger-like projections reaching into the gut lumen. Chemoreceptors on these luminal projections enable detection of specific classes of nutrients and cause the secretion of peptides contained in the secretory granules on the other (basal) side of the EECs. These peptides then activate receptors on proximal cells (paracrine function), or enter into the blood via local capillaries (endocrine function), or stimulate receptors on local autonomic or enteric neurons. Modified with permission from. [1].

Table 1

Gastrointestinal hormones

Peptide	Enteroendocrine cell type
GIP	K (proximal gut)
GLP-1	L (distal gut)
OXM	L (distal gut)
PYY	L (distal gut)
CCK	I (proximal gut)
Amylin	Pancreatic B cells
Apo-AIV	Villus epithelia
Bombesin	Stomach
Ghrelin	X/A-like (gastric mucosa)
PP	Pancreatic F cells, colon and rectum
Gastrin	Gastric antrum
Motilin	Proximal gut
Secretin	Proximal gut
Neuromedin B	Proximal gut

Apo-AIV, apolipoprotein AIV; CCK, cholecystokinin; GIP, glucose-dependent insulintropic hormone; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, peptide tyrosine-tyrosine.