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Gut Chemosensing: Interactions between Gut Endocrine Cells and Visceral Afferents

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Abstract

Chemosensing in the gastrointestinal tract is less well understood than many aspects of gut mechanosensitivity; however, it is important in the overall function of the GI tract and indeed the organism as a whole. Chemosensing in the gut represents a complex interplay between the function of enteroendocrine (EEC) cells and visceral (primarily vagal) afferent neurons. In this brief review, I will concentrate on new data on endocrine cells in chemosensing in the GI tract, in particular on new findings on glucose-sensing by gut EEC cells and the importance of incretin peptides and vagal afferents in glucose homeostasis, on the role of G protein coupled receptors in gut chemosensing, and on the possibility that gut endocrine cells may be involved in detection of a luminal constituent other than nutrients, the microbiota. The role of vagal afferent pathways as a downstream target of EEC cell products will be considered and, in particular, exciting new data on the plasticity of the vagal afferent pathway with respect to expression of receptors for GI hormones and how this may play a role in energy homeostasis.

Gut endocrine cells represent a very small proportion of the total epithelial cell population in the GI tract, yet their function is critical to normal digestive physiology and indeed to homeostasis of the whole organism. There are over twenty different kinds of EECs in the intestine; each synthesizes and secretes one or more regulatory peptides or bioactive molecules, and different EECs possess a variety of chemosensing mechanisms (see Dockray, 2006). The ability of gut endocrine cells to detect the presence of luminal chemicals was recognized early in the twentieth century with the observations of Bayliss and Starling that the presence of protons in the proximal small intestine elicited a strong stimulation of pancreatic fluid secretion, mediated not by nerves innervating the gut but by a blood born substance, a hormone they called secretin. Although GI hormones get scant attention in most textbooks of endocrinology, it is worthwhile to remember that the first hormonal pathway recognized was a gut hormone. Indeed, while insulin release from the pancreas is undoubtedly a master regulator of glucose homeostasis, increasing evidence suggests a very important role for gut incretin peptides and the vagus nerve in the regulation of blood glucose.

The well established role of gut EEC cells is in recognition of luminal nutrients (carbohydrates, triglycerides, or protein), resulting in release of their contents and initiation of wide spectrum of functional responses including inhibition of gastric emptying and

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gastric acid secretion (Raybould, 1999; Raybould et al, 2006), stimulation of gastric secretion, pancreatic exocrine (Owyang and Logsdon, 2004) and endocrine secretion (Drucker, 2007) and intestinal fluid secretion, and inhibition of food intake (Moran, 2009; Strader and Woods, 2005). While some functional changes are mediated via a true humoral pathway, many result from activation of intrinsic and extrinsic neuronal pathways; intrinsic and extrinsic sensory neurons (such as vagal afferents) express specific receptors for many gut hormones and neural pathways mediate many of the effects of gut hormones (Dockray, 2003).

In general, nutrient-sensing mechanisms in the intestine are not well understood but this is an area of increasing scientific interest and endeavor, given its importance in the regulation of normal and abnormal GI function, food intake and glucose homeostasis. EECs are difficult to study directly due to their sparse and irregular localization within the gut wall. Measurement of plasma levels of hormones is an indirect measure of EEC chemosensory function, since there is no indication of whether the stimulus driving secretion is acting directly on the EEEC or via an indirect mechanism. In addition, since many of the action of regulatory peptides released from EECs are mediated locally via paracrine actions (for example, activating nearby vagal afferent nerve terminals), plasma levels may not be helpful in assessing the role of a particular hormone or determining the mechanism of release. Thus, much of what we know about direct chemosensing by EECs comes from cell lines, such as STC-1, GLUTag and BON cells. These have been particularly useful in elucidating membrane and cytosolic signaling events, but it must be remembered that these are transformed cells and it is not clear how the complement of proteins expressed by cell lines or the response to stimuli represents normal EEC function in situ. Importantly, EECs are normally situated in an epithelium, surrounded by their neighbors, and connected by tight junctions to form distinct apical and basolateral poles; the expression of sensory elements on either or both of these membranes is not clear but is likely crucial for EEC cell function.

There has been, however, considerable progress in understanding chemosensing in the gut. The use of transgenic mice with EEC cells tagged through expression of a fluorescent protein under the control of a promoter for the peptide precursor, has provided an excellent method for the study of native EEC cells (Parker et al, 2009). In addition, the de-orphanizing of several G protein coupled receptors has provided substantial evidence for a role of G protein coupled receptors in gut chemosensing (Engelstoft et al, 2008). The observation that EECs in the gut wall express G protein coupled receptors and associated G proteins that mediate taste modalities in the lingual epithelium suggesting a much broader sampling of luminal contents than hitherto appreciated (Dyer et al, 2007; Rozengurt, 2006; Sternini, 2007). Gut endocrine cells may be able to detect aspects of the intestinal microbiota, via expression of bacterial recognition receptors such as toll-like receptors, or receptors for bacterial products, such as short chain fatty acids (Brown et al, 2003; Samuel et al, 2008).

Gut endocrine cells, vagal afferents and glucose homeostasis

Gut endocrine cells as luminal sensors for glucose

Glucose in the intestinal lumen results in the release of a number of peptides and regulatory molecules, including the incretin hormones glucose-dependent insulinotropic peptide (GIP), glucagon-like peptides, GLP-1 and GLP-2 (Dube and Brubaker, 2007) and 5-hydroxytrypatmine (5-HT) (Raybould, 2007). There is evidence that several different mechanisms are involved in glucose-sensing in gut EECs. Considerable evidence suggests a role for metabolism of glucose leading to generation of ATP and closing of K_{ATP} channels in the cell membrane, a mechanism similar to that involved in insulin release from the pancreatic β cell (Reimann and Gribble, 2002; Schuit et al, 2001). This pathway was characterized in the murine EEC cell line GLUTag and from human NCI-H716 cells, both of

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which secrete GLP-1 (Gribble et al, 2003; Tolhurst et al, 2009) but has recently been corroborated with data from native EECs isolated and purified from mouse intestine (Parker et al, 2009; Reimann et al, 2008). These studies have confirmed a role for K_{ATP} channels in GLP-1 release from native L cells and in release of GIP from K cells. In support of this mechanism is the observation that L-cells from human intestine and isolated murine L cells express Kir6.2 that forms the pore of the K_{ATP} channel, together with the L-type calcium channel (Tolhurst et al, 2009; Theodorakis et al, 2006).

However, GLP-1 is also secreted in response to non-metabolizable sugars suggesting an additional mechanism of glucose-sensing. In GLUTag cells, evidence was obtained for a role of electrogenic transport of glucose and non-metabolizable glucose analogs via the sodium glucose cotransporter, SGLT-1 (Gribble et al, 2003). These cells express mRNA for SGLT-1 and release of GLP-1 was blocked by the specific antagonist of SGLT-1, phloridzin. We have studied activation of 5-HT-secreting enterochromaffin cells in the gut wall by glucose, using both a functional in vivo approach and also using a model for enterochromaffin cells, BON. Hexoses that are substrates for SGLT, but are non-metabolizable, induce changes in function via a phloridzin-sensitive pathway and also release 5-HT from BON cells (Kim et al, 2001). Recent evidence has raised the possibility that another member of the SLC-5 family of transport proteins maybe a glucose sensor, rather than a transporter (Diez-Sampedro et al, 2003). Human SGLT-3 (hSGLT-3) has 70% homology with hSGLT-1 and when transfected into oocytes, glucose was not transported across the membrane but depolarized the membrane with a Km of 20 mM; the depolarization was specific for D-glucose and was blocked by phloridzin. In the intestine, the protein was not expressed in enterocytes (unlike SGLT-1), but was expressed by enteric neurons, although whether SGLT-3 is expressed by EEC or 5-HT secreting enterochromaffin cells is not clear. We have preliminary evidence that SGLT-3 maybe involved in release of 5-HT; BON cells express SGLT-3 and galactose, which has a much lower affinity for SGLT-3 than glucose, does not activate BON cells (Raybould, unpublished observations), suggesting that SGLT-3 may be involved in glucose-sensing, at least in 5-HT-secreting cells.

We further explored this possibility from a functional perspective to provide data to support a role for SGLT-3 in the detection of monosaccharides in the intestinal mucosa (Freeman et al, 2006). In order to functionally discriminate between SGLT-1 and SGLT-3, we determined the effect of glucose versus galactose on inhibition of gastric motility, stimulation of vagal afferent activity, release of 5-HT and stimulation of intestinal fluid secretion. These results suggest that the mechanism involved in detection of glucose in the intestinal mucosa to initiate release of 5-HT and activation of the $5HT_3R$ dependent vagal afferent pathway (Raybould et al, 2003) involves SGLT-3 rather than SGLT-1. Interestingly, there is evidence that release of GLP-1 in response to glucose may also involve SGLT-3 (Gribble et al, 2003), as expression has been shown in GLUTag cells and in human duodenal EEC cells.

There is also evidence that G proteins may be involved in glucose-sensing in the gut. Recently, the subunits of the G protein coupled receptors, T1R, have been demonstrated to be expressed in the intestine, along with other elements of the sweet taste transduction pathway found in the lingual epithelium, including Gα-gustducin (Dyer et al, 2005, 2007). Furthermore, T1R2 and T1R3 and Gα-gustducin are co-expressed in mouse and human EEC cell lines (Dyer et al, 2005, 2007; Jang et al, 2007; Rozengurt et al, 2006; Sutherland et al, 2007). There is evidence for a role for T1Rs in the upregulation of the sodium-coupled transporter SGLT-1 and GLUT2 in the intestinal epithelium in response to glucose and also in the regulation of GLP-1 secretion (Jang et al, 2007; Margolskee et al, 2007). However, in isolated native L cells, although low levels of expression of T1R2 and T1R3 were detected

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along with Gα-gustducin, there was no effect of sucralose on GLP-1 release or changes in intracellular calcium (Reimann et al 2008). The T1R system has broad specificity for sweet-sensing and can be activated by natural sugars, sweet proteins and artificial sweeteners. Currently, the role of T1Rs in activation of visceral afferents innervating the gut by glucose or by other sweet tasting compounds is not established. For example, it is not clear if activation of vagal afferent nerves by luminal glucose is altered or abolished in T1R or gustducin null mice.

Activation of the extrinsic afferent pathway by glucose and glucose homeostasis

There is compelling evidence that activation of neuronal terminals in the gut wall respond to changes in luminal glucose occurs predominately via an indirect mechanism. Vagal afferent nerve terminals in the intestinal mucosa express receptors for a number of different regulatory peptides and neurotransmitters, including those released by glucose (GLP-1, GLP-2, 5-HT). Activation of extrinsic vagal afferent neurons, reflex inhibition of gastric motility and pancreatic secretion in response to intestinal glucose is mediated by 5-HT_3Rs located on vagal afferent nerve terminals. We and others have shown that intestinal glucose activates the vagal afferent pathway via release of 5HT and activation of 5-HT_3Rs on nerve terminals; this reflex pathway regulates gastric emptying, pancreatic exocrine and intestinal fluid secretion (Li et al, 2000, 2001; Raybould, 2007; Savastano et al, 2005).

The role of vagal afferent and activation of reflex pathways in the regulation of insulin secretion and glucose homeostasis is less clear. The maintenance of normal glucose blood levels requires a rapid insulin secretory response. Much attention has been given to the role of incretin factors in the regulation of insulin and blood glucose, and an agonist for the GLP-1 receptor is being used as a therapy for the treatment of type 2 diabetes (Baggio and Drucker, 2007). However, it is also established, although garnered less attention in the last few years, that the autonomic nervous system plays an important role in regulating the function of the endocrine pancreas. During the cephalic and oral phase of a meal, there is a small but significant increase in insulin secretion. The response is abolished by vagotomy and there is evidence that loss of this pre-absorptive insulin response impairs glucose tolerance. The presence of vagal afferents activated by luminal glucose via release of 5-HT or GLP-1 supports the hypothesis that this neural pathway may be involved in the regulation of pancreatic endocrine secretion in response to a meal. Although pancreatic β cells express receptors for GLP-1, the low postprandial rise in plasma levels of GLP-1 and the rapid degradation by the ubiquitous enzyme, dipeptidyl peptidase IV (DPPIV), suggested the involvement of a possible neural pathway in the incretin action of GLP-1 (Ahren, 2004). Recently it has been shown that systemic capsaicin treatment inhibits the secretion of insulin in response to GLP-1. The cell bodies of vagal afferents express GLP-1 receptors and these terminate in the hepatic portal vein and infusion of low doses of GLP-1 receptor antagonist into the portal vein induced glucose intolerance in rats (Vahl et al, 2007). Thus, there is evidence for a role for vagal afferents in glucose homeostasis and in regulation of insulin secretion.

Role Of G Protein Coupled Receptors In Chemosensing In The GI Tract

Recent work has provided convincing evidence that EECs in the gut express several G protein coupled receptors involved in chemosensing (Engelstoft et al, 2008; Hirasawa et al, 2008). These include receptors that are activated by bitter substances, umami, glucose (see above), calcium, protein hydrolysates, and both long and short chain fatty acids.

The best evidence for a role for G protein coupled receptors in the sensing of intestinal lipid is for GPR120. GPR120 is activated by free fatty acids of chain length C14 to C18 for saturated fatty acids and C16 to C22 for unsaturated fatty acids (Hirasawa et al 2008). It is

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highly expressed in the human and mouse intestine, and in STC-1 cells; in mouse intestine GPR120 colocalizes with GLP-1 (Hirasawa et al, 2005). In STC-1 cells, fatty acids induce release of CCK and GLP-1; secretion of CCK in response to fatty acids was inhibited by transfection with short hairpin mRNA, demonstrating a role for the receptor in release of CCK (Tanaka et al, 2008). Moreover, in vivo, fatty acid induced secretion of GLP-1 was markedly reduced in GPR120 null mice (Hirasawa et al, 2005). This exciting data provides strong evidence for a role for GPR120, but further evaluation awaits the role of this receptor in overall lipid-sensing and in regulation of GI function and food intake. Whether there are changes in expression of this receptor in the gut with long term ingestion high fat diets is an intriguing possibility that awaits further investigation.

Products of hydrolysis of protein are major stimulants for secretion from gut EECs and also for inducing changes in function, including inhibition of gastric emptying, acid secretion, stimulation of pancreatic exocrine secretion and regulation of food intake (Dockray 2003). However, the exact mechanism by which protein and protein hydrolysates are detected by the gut epithelium is not clear but, like glucose and lipid-sensing, likely involves several different mechanisms. The group of Aponte et al provided the first evidence for a role for a G protein coupled receptor in protein sensing in the gut (Choi et al, 2007). Using STC-1 cells, this group showed that increasing the expression of GPR93 increases CCK mRNA expression and increases release of CCK. To date, there is no information on the localization of this receptor to native EECs but this remains an intriguing possibility.

Bitter taste receptors in the gut

In the taste buds of the lingual epithelium, members of the G protein coupled family of receptors, T1Rs and T2Rs have been shown to function as taste receptors (Adler et al, 2000; Chandrashekar et al, 2000). There are three distinct subunits of T1Rs that form heterodimers that mediate either sweet taste (T1R2 and T1R3) or sense amino acids or umami (T1R1 and T1R3). The T2R receptor family contains over thirty genes encoding for different receptor transcripts that mediate bitter taste. These receptors are expressed in the oral cavity and all couple to Gα proteins, in particular Gα-gustducin and transducin (Caicedo et al, 2003).

Over the last few years, it has been clearly demonstrated that these bitter taste receptors and their G proteins are expressed in the gut epithelium and pancreas of rodents and humans, and also in EEEC cell lines. Colocalization of Gα-gustducin with peptide YY (PYY) and glucagon-like peptide-1 in enteroendocrine L cells of human colonic mucosa has been reported (Rozengurt et al, 2006). In addition, Gα-gustducin is colocalized with glucagon-like peptide-1 and 5-hydroxytryptamine in the mouse small intestine (Sutherland et al, 2007). T2R mRNA has been identified in the mucosa of stomach and duodenum (Wu et al, 2002) and in the human colon (Rozengurt et al, 2006). The presence of transcripts corresponding to the putative denatonium benzoate (DB) and phenylthiocarbamide (PTC) receptors, mT2R108 in mouse (rT2R16 in rat) and mT2R138 (rT2R38), respectively, have been demonstrated in mouse and rat upper GI tract, and in a mouse GI enteroendocrine cell line, STC-1 (Wu et al, 2007). Application of ligands for the T2Rs, including DB and PTC to STC-1 cells, induces rapid Ca2+ signaling (Chen et al, 2006), indicating that T2Rs in these cells are functional. Release of cholecystokinin (CCK) is induced by application of DB to STC-1 cells. Thus there is evidence to demonstrate the existence of T2Rs in the GI tract and enteroendocrine cell lines, but little is known of their function.

What is the functional significance of expression of the receptors and G proteins in the GI tract that are associated with bitter taste in the oral cavity? We have shown that intragastric administration of either denatonium or PTC can activate neurons in the NTS, the region where vagal afferents terminate, and that this response is blocked by subdiaphragmatic vagotomy (Hao et al, 2008, 2009). Activation of the vagal pathway by denatonium is

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dependent on CCK1Rs and Y2Rs. Thus activation of specific T2Rs might be able to initiate protective responses such as decreased gastric emptying, decreased food intake and increase intestinal fluid secretion to limit toxin spread and effect. However, we await further elucidation on the role of T2Rs in the GI tract.

Entero-Endocrine Cells and Vagal Afferents As Bacterial Sensors: a Bug-Gut-Brain Axis?

The gut represents a large barrier between the outside world and the inside of the body and employs many different strategies to maintain this barrier. Toll-like receptors are transmembrane molecules that recognize bacterial breakdown products, such as lipopolysaccharide (LPS), bacterial lipoproteins, double stranded DNA (such as CpG containing oligodeoxynucleotides) and flagellin (Abreu et al, 2005). Recently, it has been shown that gut EECs express these bacterial recognition receptors. Human ileal and colonic epithelium express TLR1,2 and 4 and are colocalized with 5-HT (Bogunovic et al 2007). Both mRNA and protein for TLR4, 5 and 9 was shown to be present in STC-1 cells; activation of these receptors by their cognate ligands (LPS, flagellin and CpG-ODN) induced secretion of CCK via a PKC-dependent pathway, a known signaling pathway downstream of TLRs (Bogunovic et al 2007; Palazzo et al, 2007). siRNA for MyD88 (the adapter molecule associated with TLRs) significantly attenuated the release of CCK in response to TLR ligands, but had no effect on the response of STC-1 cells to free fatty acids, suggesting specific pathways for sensory recognition of TLR ligands or free fatty acids. Furthermore, this study demonstrated that activation of TLRs by bacterial ligands, but not free fatty acids, resulted in release of chemokines and also defensin, again, suggesting differential signaling induced by different ligands (Bogunovic et al 2007). These last two observations are important as free fatty acids are weak ligands of TLRs but the ability to differentiate responses to LPS and free fatty acids provides evidence for response specificity.

Taken together, these data suggest that EECs may be involved in detection of the bacterial content of the lumen. That this can activate pro-inflammatory pathways within EECs raises the possibility that these cells participate in mucosal defense. However, it also raises the intriguing possibility that bacterial products can regulate other GI function such as gastric emptying and food intake, glucose homeostasis, function we know to be regulated by release of regulatory molecules from EEC cells and activation of visceral afferent pathways, suggesting the possible existence of a “bug-gut-brain axis”.

Indeed, the existence of a bug-gut-brain pathway has already been established; vagal afferent neurons themselves express TLR4 suggesting the possible direct sensing of bacterial products by visceral afferents. Vagal activation by TLR4 ligand LPS is involved in the regulation of fever and other effects (Goehler et al, 2000). However, the recent findings of expression of bacterial recognition molecules in EEC cells imply a more complex interaction between the intestinal microbiota and visceral afferents.

Plasticity of Receptor Expression by Vagal Afferent Neurons

The afferent vagus nerve is an important target of GI hormones released from EECs and has been shown to be important in regulation of GI and pancreatic secretion, GI motility and in the regulation of food intake and body weight regulation. Vagal afferent neurons express receptor for many of the gut hormones, including CCK, PYY, ghrelin, leptin, GLP1/2, and orexin (Strader and Woods, 2005). The vagus nerve expressed receptors for many of the regulatory molecules shown to influence food intake; these can be divided into orexigenic factors (orexin, cannbinoids, ghrelin) and anorexigenic factors (CCK, PYY, GLP-1).

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Recent evidence has demonstrated that expression of receptors by vagal afferent neurons can be altered by the nutritional status of the animal (Dockray, 2009). Thus, expression of cannabinoid 1 receptor (CB1R) and melanin concentrating hormone 1 receptor (MCH1R) and MCH peptide are increased by fasting; these are orexigenic signals. Expression of peptide YY type 2 recepotor (Y2R) and CART (cocaine and amphetamine regulated transcript) are decreased by fasting. The CCK1R seems to be important in regulating expression of these receptors; refeeding of fasted rats increases expression of CART and Y2Rs and decreases expression of MCH, MCH1R and CB1R via a CCK1R-dependent pathway. Thus it appears as if CCK can "switch" the phenotype of vagal afferent neurons depending on the nutritional status of the animal. Thus, when the animal is fasted, the increased expression of MCH1R, MCH and CB1R possibly plays a role in increasing the urge to eat and will increase food intake (Burdyga et al, 2004, 2006). Conversely, after food ingestion these receptors are no longer required and are thus downregulated, together with an upregulation of receptor for anorexigenic factors such as PYY (Y2Rs) which serve to terminate food intake and induce short term satiety (Burdyga et al, 2008). Is there a functional correlate to these findings in nodose neurons? We have shown that the activation of the gut-brain axis as measured by fos in the NTS in response to PYY and the inhibition of gastric emptying are dependent on the CCK1R as they are markedly reduced in CCK1R null mice (Burdyga et al, 2008).

It is well established that there is a decrease in activation of the gut-brain axis in response to both CCK and lipid in response to high fat diets, and this may play a role in the hyperphagia and increase in body weight observed on these diets (Savanstano and Covasa, 2005). Sprague Dawley rats differ their response to high fat diets; some rats are prone to the obesigenic effects of the high fat diets while others remain relatively resistant to diet-induced obesity. This is thought to involve differences in the development of leptin resistance although the mechanism is not understood (Levin et al, 2005). WE were interested in whether long term ingestion of high fat diets alters the expression of receptors in vagal afferent neurons and demonstrated that in diet-induced obese prone rats, there was a 7 fold increase in the expression of the ghrelin receptor in nodose neurons compared to either chow fed controls or diet-induced obese resistant rats (Paulino et al, 2009). The significance of this is not clear at this time, but one can speculate that an increase in the ghrelin receptor may increase the urge to eat and increase food intake, thus contributing to diet induced obesity during intake of high fat foods. In addition, Dockray et al have shown that ghrelin can inhibit the phenotypic changes in nodose receptor expression, thus causing a mismatch between the nutritional status and information being sent to the brain via the vagal afferent pathway (Burdyga et al, 2006; De Lartigue et al, 2007).

Conclusions

This review has concentrated on some of the new observations on chemosensing in the gut wall. At this point, we are beginning to understand more about the mechanisms of gut chemosensing in terms of EEC cells function. It is clear that there are many different receptors and pathways involved in detection of nutrients, potential harmful toxins and bacterial products. Many of these stimuli result in the release of the same hormones, such as CCK, PYY and GLP-1, all of which can activate vagal afferent fiber activity. Thus it is unclear how the brain may "decode" this information. The challenge that lies ahead is to dissect out the vagal afferent pathway more clearly in terms of differences in the properties of vagal afferents between regions of the gut and in projection to the central nervous system.

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