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Previews

A Gut Feeling for Obesity: 7TM Sensors on Enteroendocrine Cells

Maja S. Engelstoft,[1] Kristoffer L. Egerod,[1] Birgitte Holst,[1,2] and Thue W. Schwartz[1,3,*]
[1]Laboratory for Molecular Pharmacology, Department of Neuroscience and Pharmacology
[2]Rodent Metabolic Test Center
University of Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen, Denmark
[3]7TM Pharma, Fremtidsvej 3, DK-2970 Hørsholm, Denmark
*Correspondence: tws@sund.ku.dk
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Enteroendocrine cells, which secrete peptide hormones in response to sensation of food and gut microbiota products, can now be genetically tagged, isolated, cultured, and characterized for expression of the elusive chemosensors, as shown in publications in *PNAS* (Samuel et al., 2008) and in this issue (Reimann et al., 2008).

The enteroendocrine system constitutes the largest but also the least well understood endocrine organ of the body. Throughout the GI tract, enteroendocrine cells are found scattered in the epithelium among the enterocytes (Rindi et al., 2004). Typically these cells are conically shaped with a small apical pole decorated with microvilli facing the gut lumen and a broader base where peptide hormones are released from dense-core secretory granules (Figure 1). These cells often have basal, dendrite-like cytoplasmic processes for directed paracrine and apparently also for sensory functions (Larsson et al., 1979; Karaki et al., 2006). More than a dozen different types of enteroendocrine cells have been described based on morphological and immunohistochemical differences (Rindi et al., 2004)—and the corresponding list of gut hormones is even longer and probably far from complete yet (Figure 1). A major problem in this field of research has been that the enteroendocrine cells are difficult to study directly. This situation will change significantly as a result of two papers—one by Reimann and coworkers in this issue (Reimann et al., 2008) and another recently published by Samuel and coworkers (Samuel et al., 2008). In both studies specific enteroendocrine cell types are tagged genetically through the expression of a fluorescent protein under the control of the promoter for a peptide hormone precursor, i.e., proglucagon (GLP-1) and pro-CCK, respectively. This allows for subsequent isolation, purification by FACS, and even culturing of the specific subpopulation of cells. Consequently, individual enteroendocrine cell types can now—finally—be studied directly by biochemical and molecular biology techniques. For example, the primary cultures of purified GLP-1-producing L cells are subjected to detailed electrophysiology, fluorescence calcium imaging, and gene expression analysis—all illuminating novel aspects of enteroendocrine cell biology (Reimann et al., 2008).

Multiple, especially metabolic functions are regulated by gut hormones, which send information about the conditions in the various segments of the GI tract to a wide spectrum of organs and tissues in the body. These hormones function both through classical endocrine mechanisms and frequently also through activation of afferent, sensory nerves—i.e., in addition to their local, paracrine functions (Figure 1). Especially the effects of gut hormones on pancreatic endocrine function, on appetite, and on gastrointestinal motility have positioned several of these peptides in the front of the race for novel treatments for type 2 diabetes and obesity, i.e., GLP-1 mimetics (exenatide and liraglutide) and indirectly DDP-IV inhibitors. However, PYY and PP mimetics are also in clinical trials for obesity and diabetes, GLP-2 mimetics are being tested in chemotherapy-induced diarrhea and osteoporosis, and ghrelin mimetics for cancer cachexia and gut motility disorders.

For decades it has been known that the presence and nature of distinct food components in the lumen of the GI tract—proteins, lipids, and carbohydrates—are the main regulator of the secretion of individual gut hormones (Figure 1). However, it is only during the last couple of years that we have begun to understand the molecular basis for this important differentiated sensing of gut contents. A number of orphan receptors were recently shown to be activated, for example, by long-chain fatty acids (LCFA), by short-chain fatty acids (SCFA), by proteolytic degradation products, and by bile acids (Brown et al., 2005; Choi et al., 2007; Katsuma et al., 2005) (Figure 1). Several of these receptors have recently, in different ways, been specifically linked to enteroendocrine cells, and it was assumed that these would function as the elusive chemosensors of the enteroendocrine system in general (Karaki et al., 2006; Choi et al., 2007; Covington et al., 2006). Reimann and coworkers can now by QPCR analysis show that pure L cells express not only the acylethanolamine receptor GPR119 but also the LCFA receptors GPR40 and GPR120 and the bile acid receptor GPR131 (TGR5)—none of which are expressed in the non-enteroendocrine cell fraction.

Samuel and coworkers specifically focus on the SCFA receptor GPR41 and mainly use the isolated enteroendocrine cells to demonstrate that these cells, in contrast to the surrounding cells, express GPR41 (Samuel et al., 2008). SCFAs such as proprionate, acetate, and butyrate are generated in the gut lumen through microbial degradation of complex polysaccharides. Both rodent and human studies have suggested that gut microbiota and the generated SCFAs could contribute significantly to host energy balance and to adiposity (Turnbaugh et al., 2006, 2008). By use of GPR41-deficient mice, Samuel and coworkers now show that the SCFAs apparently function not only

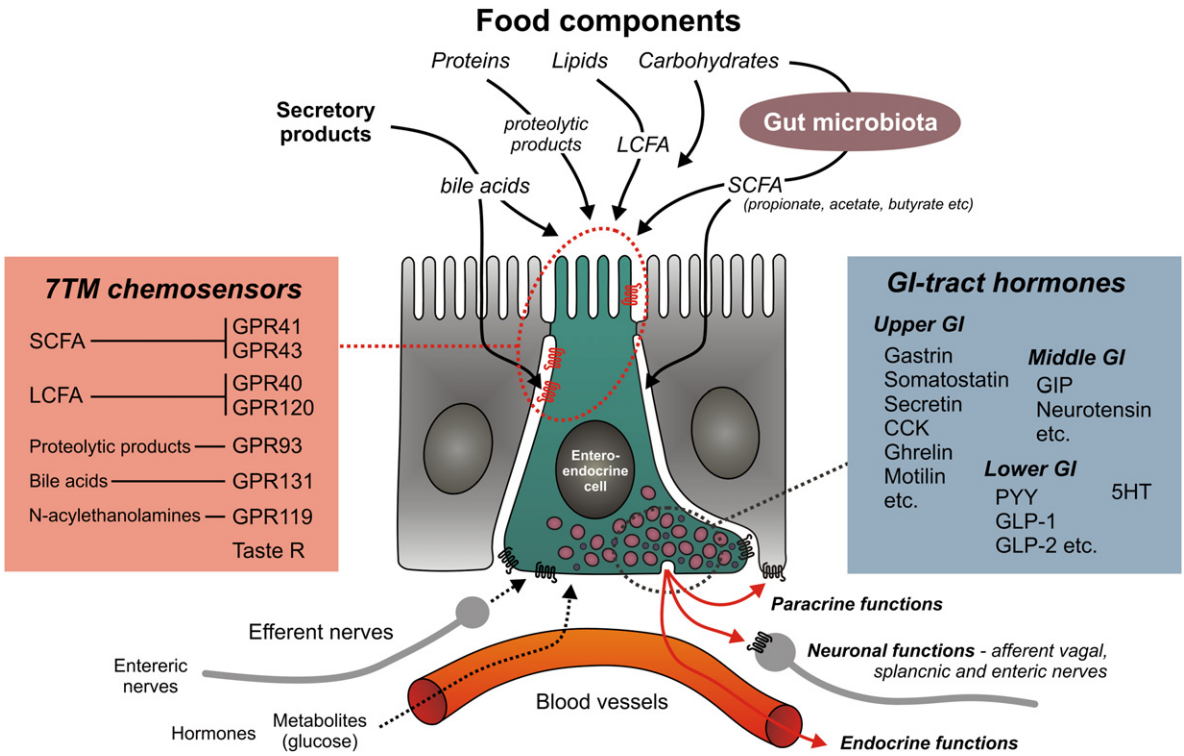

Figure 1. A Schematic Overview of Sensory and Secretory Functions of Enteroendocrine Cells of the Gut

Between two enterocytes, a prototypical, conical enteroendocrine cell is shown in green with its microvillus decorated apical pole reaching the gut lumen and with peptide hormone-filled secretory granules at the base. In the blue box to the right are listed a selection of classical gut hormones and with red arrows at the bottom are indicated the three main modes of action of such hormones: paracrine (and autocrine), neuronal, and endocrine functions. At the top are indicated the three main food components that are known to regulate gut hormone expression and secretion (proteins, lipids, and carbohydrates) and some of the main metabolites that are believed to be sensed by the enteroendocrine cells (LCFA, long-chain fatty acids; SCFA, short-chain fatty acids). The gut microbiota is responsible for degrading complex polysaccharides to the main SCFAs: propionate, acetate, and butyrate. Secretory products such as bile acids—but conceivably also other components—from more proximal parts of the GI tract also affect enteroendocrine function. In the red box to the left are listed a number of 7TM G protein-coupled receptors that today are assumed to function as chemosensors in the enteroendocrine cells (GPR131 is still often called TGR5). By small, red serpentine symbols are indicated the presumed location of these chemosensors on the basolateral membrane of the cell (Karaki et al., 2006), and potentially also at the apical pole. Long black arrows—for simplicity only shown for SCFA and bile acids—indicate that a major site for chemosensing very likely could be the lateral space between the enteroendocrine cell and the enterocytes. Small, black serpentine symbols indicate 7TM receptors for hormones and neurotransmitters (neuropeptides and monoamines) and for the gut hormones themselves.

as fuel but that they may act also as signaling molecules because the GPR41 receptor is required for the full metabolic effect of these metabolites (Samuel et al., 2008). The increase in body and fat pad weight, which is normally observed in germ-free mice upon colonization with specific saccharolytic bacterial strains—conceivably due to production of SCFA in the colon—is not observed in GPR41$^{-/-}$ mice. Similarly, the increase in levels of the gut hormone PYY normally observed upon bacterial colonization is also blunted by deletion of GPR41. This is, by Samuel and coworkers, being linked to the decreased intestinal transit time observed in the GPR41$^{-/-}$ mice—which should lead to decreased utilization of energy from the diet (Samuel et al., 2008).

Although, the study by Samuel and coworkers clearly demonstrates that GPR41 is involved in the changes in host energy balance related to gut microbiota and its effect on adiposity, there are still many open ends. Notably GPR41 is not only expressed on enteroendocrine cells but is in fact most highly expressed in adipose tissue and the pancreas (Brown et al., 2005). So, global deletion of this receptor may also directly affect the function of these tissues. Moreover, all PYY cells of the distal gut also express the other receptor for SCFA, GPR43, as convincingly demonstrated by immunohistochemistry (Karaki et al., 2006). Consequently, it will be interesting to identify the relative role of GPR41 versus GPR43 as sensors for SCFA in the enteroendocrine system (Figure 1). Also, at least GLP-1 should be considered as a player in the game as it is often co-stored and -released with PYY in the distal gut.

Nevertheless, the whole field of 7TM chemosensors as regulators of gut hormone expression and secretion is currently opening up for real. It is likely that there are in fact several more receptors involved in the sensing of gut contents than those listed in the figure. Importantly, these receptors are highly interesting drug targets. It is currently believed that truly efficacious regimens for obesity and type 2 diabetes will involve various forms of combination treatments. In principle it should be possible instead to exploit a "natural combination treatment" through modulation of 7TM chemosensors on the

enteroendocrine cells as these cells co-store and co-release physiological mixtures of gut hormones, for example GLP-1 together with PYY and GLP-2 in the lower gut and ghrelin together with motilin in the upper gut. Moreover, pharmacokinetically you may only have to obtain efficient receptor exposure in the gut epithelium—with all the benefits this would have in respect to limited side effects, etc. On the other hand, you may have to ensure that the drug is released and is active only in a particular segment of the gut as the same chemosensor may be used on different enteroendocrine cells and may serve different purposes in different parts of the GI tract. All of this will become much clearer when we get a better picture of this interesting control system through technologies as described by Reimann and coworkers (Reimann et al., 2008) and Samuel and coworkers (Samuel et al., 2008). Nevertheless, the first compounds that function, at least partly, through the release of gut hormones are already in clinical trials, i.e., GPR119 agonists. Although the focus for these compounds initially was on their effects on pancreatic insulin secretion, attention has recently included their effects on GLP-1 release from the gut (Chu et al., 2008). It is, however, highly likely that GPR119 agonists will also release at least PYY and GLP-2, because these peptides—as mentioned above—are co-stored and co-released, but possibly also other gut hormones.

REFERENCES

Brown, A.J., Jupe, S., and Briscoe, C.P. (2005). DNA Cell Biol. *24*, 54–61.

Choi, S., Lee, M., Shiu, A.L., Yo, S.J., Hallden, G., and Aponte, G.W. (2007). Am. J. Physiol. Gastrointest. Liver Physiol. *292*, G1366–G1375.

Chu, Z.L., Carroll, C., Alfonso, J., Gutierrez, V., He, H., Lucman, A., Pedraza, M., Mondala, H., Gao, H., Bagnol, D., et al. (2008). Endocrinology *149*, 2038–2047.

Covington, D.K., Briscoe, C.A., Brown, A.J., and Jayawickreme, C.K. (2006). Biochem. Soc. Trans. *34*, 770–773.

Karaki, S., Mitsui, R., Hayashi, H., Kato, I., Sugiya, H., Iwanaga, T., Furness, J.B., and Kuwahara, A. (2006). Cell Tissue Res. *324*, 353–360.

Katsuma, S., Hirasawa, A., and Tsujimoto, G. (2005). Biochem. Biophys. Res. Commun. *329*, 386–390.

Larsson, L.I., Goltermann, N., de Magistris, L., Rehfeld, J.F., and Schwartz, T.W. (1979). Science *205*, 1393–1395.

Reimann, F., Habib, A.M., Tolhurst, G., Parker, H.E., Rogers, G.J., and Gribble, F.M. (2008). Cell Metab. *8*, this issue, 532–539.

Rindi, G., Leiter, A.B., Kopin, A.S., Bordi, C., and Solcia, E. (2004). Ann. NY Acad. Sci. *1014*, 1–12.

Samuel, B.S., Shaito, A., Motoike, T., Rey, F.E., Backhed, F., Manchester, J.K., Hammer, R.E., Williams, S.C., Crowley, J., Yanagisawa, M., and Gordon, J.I. (2008). Proc. Natl. Acad. Sci. USA *105*, 16767–16772.

Turnbaugh, P.J., Ley, R.E., Mahowald, M.A., Magrini, V., Mardis, E.R., and Gordon, J.I. (2006). Nature *444*, 1027–1031.

Turnbaugh, P.J., Backhed, F., Fulton, L., and Gordon, J.I. (2008). Cell Host Microbe *3*, 213–223.

A Two-Step Pathway to Resist Fasting

Klaus H. Kaestner[1,*]
[1]Institute for Diabetes, Obesity and Metabolism and Department of Genetics, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA
*Correspondence: kaestner@mail.med.upenn.edu
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All vertebrate animals have developed a sophisticated regulatory system to cope with frequent and unpredictable episodes of fasting. A recent letter to *Nature* suggests that a switch from early gluconeogenic gene activation via CRTC2 (also known as TORC2) to late action of FOXO1 is critical to this process.

Maintenance of glucose homeostasis is critical to survival and well-being, as evidenced by the severe clinical consequences resulting from diabetes. The liver contributes to the control of glucose metabolism by uptake and storage of glucose after a carbohydrate-rich meal or by the activation of glucose production under conditions of hypoglycemia. These processes are orchestrated by insulin, glucagon, and glucocorticoids. Changes in these hormone levels have a pronounced effect on the hepatic transcriptional program. For example, the activation of genes encoding gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and Glucose-6-Phosphatase (G6Pase) is controlled by complex sets of *cis*-regulatory elements and their cognate DNA-binding proteins (reviewed in Lucas and Granner, 1992). A new study published in *Nature* adds an interesting twist to the story and proposes a two-step model to elicit and maintain activation of the gluconeogenic transcriptional program (Liu et al., 2008).

More than 15 years ago it was discovered that two classes of transcriptional regulators cooperate to ensure that the gluconeogenic program is activated only in the appropriate cell types, that is mainly in the hepatocytes of the liver (Schmid et al., 1993). The promoters and enhancers controlling the expression of the gluconeogenic genes contain binding sites for both liver-enriched transcription factors such as HNF4α and Foxa2 and also ubiquitously expressed transcription factors that mediate the activation of these genes in response to the changes in the hormonal milieu, such as the glucocorticoid receptor and the CREB family of