HHS Public Access

Author manuscript

J Endocrinol. Author manuscript; available in PMC 2023 September 27.

Published in final edited form as:

J Endocrinol. 2023 August 01; 258(2): . doi:10.1530/JOE-23-0019.

Endocrine regulation of metabolic homeostasis via the intestine and gut microbiome

Rachel K. Meyer[1], **Frank A. Duca**[2,3]

[1]School of Nutritional Sciences and Wellness, University of Arizona, Tucson, USA

[2]School of Animal and Comparative Biomedical Sciences, College of Agricultural and Life Sciences, University of Arizona, Tucson, USA

[3]BIO5 Institute, University of Arizona, Tucson, USA

Abstract

The gastrointestinal system is now considered the largest endocrine organ, highlighting the importance of gut-derived peptides and metabolites in metabolic homeostasis. Gut peptides are secreted from intestinal enteroendocrine cells in response to nutrients, microbial metabolites, and neural and hormonal factors, and regulate systemic metabolism via multiple mechanisms. While extensive research is focused on the neuroendocrine effects of gut peptides, evidence suggests that several of these hormones act as endocrine signaling molecules with direct effects at the target organ, especially in a therapeutic setting. Additionally, the gut microbiota metabolizes ingested nutrients and fiber to produce compounds that impact host metabolism indirectly, through gut peptide secretion, and directly, acting as endocrine factors. This review will provide an overview of the role of endogenous gut peptides in metabolic homeostasis and disease, as well as the potential endocrine impact of microbial metabolites on host metabolic tissue function.

Introduction

Energy and glucose homeostasis are tightly controlled by coordinated neural and endocrine signals that facilitate tissue crosstalk and central nervous system (CNS) integration to regulate food intake, energy expenditure, and glycemia. The liver, pancreas, and adipose tissue are traditionally considered organs of the endocrine system involved in regulating metabolic homeostasis. The endocrine pancreas secretes insulin in response to the postprandial rise in blood glucose, repressing hepatic glucose production and facilitating glucose uptake in adipose tissue and skeletal muscle while glucagon secretion generally opposes these actions (Campbell and Newgard, 2021). Further, adipocytes secrete adipokines, including leptin and adiponectin, to regulate food intake and maintain fat stores (Scheja and Heeren, 2019). The textbook functions of the gastrointestinal (GI) system are digestion and nutrient absorption; however, the gut is now considered the largest endocrine

Corresponding Author: Frank A Duca, faduca@arizona.edu, Phone: 520-621-9544; Address: ACBS Building, 1117 E Lowell Street, Tucson AZ 85711.

Declaration of Interest

The authors declare no conflicts of interest.

organ, maintaining energy and glucose homeostasis both directly and indirectly via gut peptides produced by enteroendocrine cells (EECs) and endocrine metabolites produced or altered by the gut microbiota (Ahlman and Nilsson, 2001).

EECs are dispersed throughout the GI tract, comprising only 1% of the total intestinal epithelial cell population (Worthington et al., 2018). Despite the low abundance of EECs, they have a major role in the maintenance of energy and glucose homeostasis, evidenced by glucose intolerance in mice lacking normal EEC development (Terry et al., 2014). Gut peptides are secreted in response to the sensing of luminal contents and function to coordinate digestion, nutrient absorption, appetite, energy expenditure, and insulin secretion (Table 1) (Gribble and Reimann, 2019). Recent advances have demonstrated the complexity and redundancy of these signaling molecules, as peptides impacting metabolic homeostasis are still being identified while the mechanisms of action and metabolic effects of previous peptides are continually redefined or discovered. While a large proportion of gut peptides act in a paracrine fashion on nearby intestinal epithelial cells or peripheral nerves, like vagal afferent neurons or spinal afferents that can signal to the brain (Wachsmuth et al., 2022), studies suggest many intestinally-derived peptides can enter the bloodstream and act in an endocrine fashion. This review focuses on the endocrine signaling capabilities of gut peptides, as other recent reviews have highlighted the role of neural signaling in regulating the metabolic effects (see Wachsmuth et al. (2022), Duca et al. (2021) for more).

While the role of the intestine in regulating food intake and glucose homeostasis is well documented, the gut microbiota is also now considered a critical component of the intestinal endocrine system (Clarke et al., 2014). The gut microbiota, composed of all bacteria, archaea, and fungi residing in the GI tract, is both directly and indirectly implicated in host metabolic homeostasis (Howard et al., 2022). Many of the effects of the gut microbiota on energy and glucose homeostasis are linked to compounds produced or altered by gut bacteria that act directly on EECs, or alternatively enter circulation and target metabolic tissue function (Agus et al., 2021). For example, short chain fatty acids (SCFAs) produced by gut bacterial fermentation of ingested fiber induce secretion of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) from EECs, thereby indirectly impacting the gut endocrine system, but also enter circulation to impact hepatic glucose metabolism (Shimizu et al., 2019), lipid metabolism (Yu et al., 2019), and regulate brown adipose thermogenesis (Christiansen et al., 2018, Cani et al., 2006). In addition, molecular components of microbes, like LPS, can activate EECs via innate immune recognition (Nguyen et al., 2014, Anhê et al., 2021). As the gut microbiota-metabolome axis impacts host metabolism, this review will discuss several metabolites and bacterial components with endocrine action that participate in host maintenance of energy and glucose homeostasis. Given the complex interaction of diet, gut microbiota, and the GI tract, it is crucial to better understand how these pathways work in unison to impact host metabolic health.

Gut Peptides/Hormones

EECs are specialized secretory cells located throughout the GI tract. While EEC subtypes are classically characterized based on the gut peptide they produce (e.g. K-cells secrete glucose-dependent insulinotropic peptide (GIP), L-cells secrete PYY and GLP-1, and I-cells

secrete cholecystokinin (CCK); see Fig. 1), it is now accepted that EEC location may more accurately dictate peptide expression based on migration from crypt to villus (Beumer et al., 2018) and anatomical location (e.g. small intestine vs. colon) (Habib et al., 2012). Here we review the endocrine effect of gut peptides, while there is substantial evidence that many gut peptides act in a paracrine fashion on vagal and spinal afferent neurons innervating the gut to regulate energy and glucose homeostasis (see (Wachsmuth et al., 2022, Duca et al., 2021) for more). For example, CCK is a gut hormone secreted by I-cells of the upper small intestine in response to luminal fat and protein, and the CCK receptor is expressed in the GI tract and vagal afferent neurons (Fakhry et al., 2017, Wang et al., 2019). A gut-brain vagal signaling axis is implicated in the effects of CCK on gallbladder contraction (Sonobe et al., 1995), gastric emptying (Schwartz et al., 1993), pancreatic exocrine secretion (Li and Owyang, 1993), brown adipose tissue thermogenesis (Blouet and Schwartz, 2012), hepatic glucose production (Cheung et al., 2009) and control of feeding behavior (Lorenz and Goldman, 1982). However, non-neural signaling pathways for gut peptides are also critical for metabolic homeostasis, especially in the effect of incretin hormones.

Incretin hormones

There are over 20 known gut peptides secreted by EECs that have both independent and overlapping effects on metabolism. A subset of gut peptides, termed incretins, are released in response to ingested nutrients and perpetuate glucose-stimulated insulin secretion from pancreatic β-cells, accounting for 50–70% of total insulin secretion following meal consumption (Nauck et al., 1986). The incretin hormones, GIP and GLP-1 are secreted in response to meal consumption, with the magnitude of secretion proportional to both rate of nutrient appearance (or rate of gastric emptying) and energy content (Vilsbøll et al., 2003, Ahrén, 2022). Traditionally, K-cells located in the duodenum and upper jejunum were thought to exclusively secrete GIP, and L-cells located in the ileum and colon were thought to exclusively secrete GLP-1. However, GIP and GLP-1 have been shown to colocalize in a subset of human, rat, and porcine small intestinal EECs, indicating simultaneous postprandial secretion of these peptides (Mortensen et al., 2003, Habib et al., 2012). GIP, the first identified incretin hormone, is secreted in response to luminal glucose and lipids (Wu et al., 2017, Wu et al., 2012). Interestingly, in humans, GIP secretion is greater in response to fat than carbohydrates, despite the glucose-dependent insulinotropic effect of this peptide (Wu et al., 2017). GLP-1 is secreted in response to ingested macronutrients and fiber, as well as neural and hormonal factors (Wang et al., 2015). Further, GLP-1 secretion in response to nutrients and other secretagogues appears to be specific to L-cell localization in the intestine. For example, L-cells of the small intestine are indispensable for the secretion of ingested nutrient-induced GLP-1 (Sun et al., 2017), whereas colonic L cells mediate GLP-1 secretion in response to activation of the G-protein coupled receptors, GPR119 and melanocortin 4 receptor (MC4R), metformin, bile acids, as well as maximal LPS-induced GLP-1 secretion (Panaro et al., 2020, Christiansen et al., 2019). In addition, microbial metabolites, such as SCFAs, can induce incretin hormone secretion (see section below). Both GIP and GLP-1 are degraded by dipeptidyl-peptidase 4 (DPP-4) within minutes of secretion (Kieffer et al., 1995), such that only a small percentage of these hormones reach systemic circulation, calling into question the endocrine ability of these peptides.

Despite the short half-life, GIP and GLP-1 function to amplify glucose-stimulated insulin secretion via direct activation of the GIP receptor (GIPR) and GLP-1 receptor (GLP-1R) expressed on pancreatic β-cells. Both are members of the B family of G-protein coupled receptors and have overlapping signaling mechanisms to potentiate glucose-stimulated insulin secretion (Mayo et al., 2003). Binding of GIP or GLP-1 to their associated receptors induces recruitment and activation of the G_{as} protein, adenylate cyclase activation and elevated intracellular cyclic AMP (cAMP), resulting in protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC)-mediated potentiation of insulin granular exocytosis (Kashima et al., 2001, Kaihara et al., 2013, Dyachok et al., 2006). Further, GLP-1 and GIP activate divergent, PKA-independent signaling mechanisms to promote β-cell survival and proliferation (Li et al., 2005, Kim et al., 2005). In addition to the insulin stimulating effects of incretins, GLP-1, but not GIP, inhibits glucagon secretion from α-cells, with equal contributions from glucagon inhibition and insulin secretion on glucose homeostasis (Hare et al., 2010). Although there is evidence for a neural GLP-1-mediated regulation of glucose homeostasis, potentially mediated by hepatic portal vein or gut-innervating GLP-1R expressing neurons (Balkan and Li, 2000, Vahl et al., 2007, Burcelin et al., 2001, Borgmann et al., 2021), recent work involving transgenic mice highlights the importance of pancreatic GLP-1R in glucose homeostasis (Lamont et al., 2012). Indeed, knockdown of the GLP-1R in β-cells abolishes the effects of GLP-1 on insulin secretion (Smith et al., 2014). Further, whole-body GLP-1R-deficient mice have impaired glucose-stimulated insulin secretion and glucose tolerance, whereas reintroduction of the GLP-1R only in pancreatic islets normalized glucose homeostasis and glucose-stimulated insulin secretion (Lamont et al., 2012) while deletion of GLP-1R in neurons does not impair oral glucose-stimulated insulin secretion (Varin et al., 2019, Sisley et al., 2014), all indicating that GLP-1 likely augments glucose-stimulated insulin secretion in an endocrine fashion via pancreatic rather than neural GLP-1Rs.

In addition to direct receptor binding on pancreatic islet cells, GLP-1 is proposed to act on the peripheral and CNS to induce satiation and decrease food intake postprandially. The GLP-1R is expressed on neurons in the hindbrain and hypothalamus (Turton et al., 1996, Adams et al., 2018), key regions regulating feeding behavior, as well as a subset of vagal afferent neurons in the nodose ganglion (Nakagawa et al., 2004). Both central and peripheral GLP-1 administration decreases food intake and GLP-1 secretion activates vagal afferent neurons (Davis et al., 1998, Turton et al., 1996, Nakabayashi et al., 1996, Buckley et al., 2020), sparking debate regarding the neural circuit involved in the effect of GLP-1 on food intake. However, studies utilizing vagal lesioning and deafferentation prompted in part by the rate of GLP-1 degradation by DDP-4 suggest that endogenous GLP-1 acts as a paracrine peptide through a gut-brain vagal circuit to regulate feeding behavior (Diepenbroek et al., 2017, Abbott et al., 2005a, Plamboeck et al., 2013, Brierley and de Lartigue, 2022, Borgmann et al., 2021). Conversely, more recently, the impact of vagal GLP-1R on energy homeostasis has been debated, as viral and transgenic knockout studies have shown a limited role in vagal afferent GLP-1 signaling on energy homeostasis (Varin et al., 2019, Sisley et al., 2014, Brierley et al., 2021). Interestingly, in an elegant study, it was demonstrated that the effects of GLP-1 on food intake and gastric emptying are mediated by GLP-1R expressing ileal enteric neurons (Zhang et al., 2022). Thus, while the endocrine action of

GLP-1 is likely limited to the pancreas, the overall impact of neural endogenous GLP-1 signaling is contentious (see McLean et al. (2021) for more detailed endocrine and paracrine signaling of GLP-1).

Oxyntomodulin, like GLP-1, is derived from posttranslational modifications of proglucagon, is secreted postprandially by colonic EECs, and binds both the GLP-1 and glucagon (GCG) receptor (Baggio et al., 2004, Baldissera et al., 1988). Similar to GLP-1, oxyntomodulin acutely decreases food intake in rodents when administered directly to the brain (Dakin et al., 2001) and peripherally (Dakin et al., 2004), likely dependent on hypothalamic GLP-1R activation (Baggio et al., 2004). Further, oxyntomodulin production is blunted individuals with type 2 diabetes (T2D) (Wewer Albrechtsen et al., 2016), and treatment with oxyntomodulin is beneficial for glucose homeostasis via amplification of glucose-stimulated insulin secretion and body weight in individuals with T2D and obesity (Shankar et al., 2018, Wynne et al., 2005, Maida et al., 2008). However, more research is needed into determining the mechanism of action of oxyntomodulin, given it has a longer half-life than GLP-1 (~12 min) (Schjoldager et al., 1988).

GLP-2

Glucagon-like peptide 2 (GLP-2), co-secreted with GLP-1 from intestinal L cells in response to nutrients (Hartmann et al., 2000), has intestinotrophic as well as metabolic effects. At the intestine, GLP-2 plays a protective role in gut barrier function (Benjamin et al., 2000, Chen et al., 2012, Chang et al., 2021) and enhances nutrient absorption (Meier et al., 2006). Additionally, GLP-2 induces glucagon secretion, but has no effect on glycemia, in healthy individuals, suggesting minimal contribution of this peptide in normal glucose homeostasis (Meier et al., 2006, Sørensen et al., 2003). On the contrary, GLP-2 signaling is an attractive target for obesity-associated hyperglycemia, given that, in rodents with obesity, blocking endogenous GLP-2 action worsens glucose tolerance (Baldassano et al., 2015), and peripheral GLP-2 analog treatment improves glucose tolerance independent of body weight (Ejarque et al., 2021). Further, GLP-2 signaling is necessary and sufficient for the metabolic improvements associated with prebiotic supplementation in high fat feeding (Cani et al., 2009). The effect of GLP-2 on glucose regulation is hypothesized to occur due to decreased adipose tissue inflammation (Ejarque et al., 2021), improved gut barrier that attenuates metabolic endotoxemia (Cani et al., 2009), and/or neuroendocrine action via activation of Pro-opiomelanocortin (POMC)-expressing neurons of the hypothalamus (Shi et al., 2013); however, the exact mechanism remains to be fully elucidated.

PYY

PYY is a gut peptide expressed in L-cells of the distal intestine, where it is co-secreted with GLP-1 (Habib et al., 2013). PYY exists in two isoforms: PYY1–36 and PYY3–36, formed by DPP-4 mediated N-terminal cleavage following secretion (Mentlein et al., 1993). PYY3–36, the dominant form in circulation postprandially (Grandt et al., 1994), principally binds the Y2 receptor found in the CNS, including the hypothalamus and brain stem, as well as peripheral tissues, including the colon and kidney (Yi et al., 2018). PYY is secreted in response to luminal lipids and protein (Mangan et al., 2019, Batterham et al., 2006), as well as neural and gut microbial factors, including SCFAs (Zhang et al., 1993, Larraufie et al.,

2018) (see below). PYY functions to inhibit gastric acid secretion, gastric emptying, and pancreatic exocrine secretion (Adrian et al., 1985, Grandt et al., 1995, Moran et al., 2005). Exogenous PYY administration also decreases food intake in rodents and humans (Challis et al., 2003, Degen et al., 2005), suggesting a role for this peptide in suppression of food intake following meal consumption. Indeed, mice lacking PYY develop obesity, and replacing PYY via once daily injection or continuous delivery via osmotic minipump induces weight loss these mice (Batterham et al., 2006), indicating that PYY is an endogenous regulator of food intake. Mechanistically, PYY is proposed to activate Y2 receptors in the nucleus tractus solitarius and/or the arcuate nucleus of the hypothalamus, activating anorexigenic neurons and inhibiting orexigenic neurons (Batterham et al., 2002, Blevins et al., 2008, Gustafson et al., 1997, Abbott et al., 2005b), indicating a clear endocrine action. However, the hypophagic effect of PYY is likely at least in part mediated by a gut-brain vagal circuit, as vagotomy and midbrain transection abolish the effect of PYY on food intake in rats (Koda et al., 2005).

In addition to energy homeostasis, PYY is also implicated in control of glucose homeostasis. In the pancreas, PYY is co-expressed with glucagon in α-cells and somatostatin in δ-cells (Böttcher et al., 1989, Khan et al., 2016), suggesting an endocrine effect of PYY on insulin secretion. In accordance with the inhibitory actions of this peptide, PYY inhibits glucose-stimulated insulin secretion *in vivo* (Böttcher et al., 1989). However, as PYY3–36 has no effect on insulin secretion in isolated islets and the Y2 receptor is not expressed in pancreatic islets (Chandarana et al., 2013), locally secreted PYY1–36 can act directly at the islet, whereas gut-derived PYY3–36 has no direct effect on β-cell insulin secretion. In contrast, peripheral PYY3–36 administration improves glucose tolerance likely via EEC Y2 receptor activation and increased GLP-1 secretion that subsequently increases insulin release (Chandarana et al., 2013). Thus, PYY1–36 secreted within pancreatic islets may represent a negative feedback mechanism for glucose-stimulated insulin secretion.

5-hydroxytryptamine (Serotonin)

While 5-hydroxytryptamine (5-HT, also known as serotonin) is canonically considered a neurotransmitter, serotonin is also synthesized by enterochromaffin (EC) cells of the intestine from tryptophan, a process critically regulated by tryptophan availability, tryptophan hydroxylase (the rate-limiting enzyme in serotonin synthesis), and gut microbial metabolism of tryptophan (Yano et al., 2015, Yabut et al., 2019). Serotonin is secreted from EC cells in response to changes in luminal nutrients, microbial metabolites, or stretch following meal consumption (Wang et al., 2017, Martin et al., 2017, Reigstad et al., 2015). Following secretion, the majority of serotonin is taken up and stored or degraded in platelets (Mercado and Kilic, 2010), with a small proportion remaining in plasma to act as a signaling factor in peripheral tissues. Because serotonin typically cannot cross the blood-brain barrier, the actions of peripheral serotonin are distinct from central serotonin; as such, gut-derived serotonin is an independent regulator of metabolic tissue function.

Serotonin primarily acts on peripheral tissues via activation of one of fourteen 5-HT receptors (HTRs), all except one of which are classified as G-protein coupled receptors (Sahu et al., 2018). Peripheral serotonin participates in intestinal homeostasis, including

regulation of gut motility via enteric neuron signaling and intestinal inflammation (Heredia et al., 2013, Margolis et al., 2014). In addition, serotonin is implicated in adipose tissue lipid metabolism, as it promotes adipocyte glucose uptake and decreases lipolysis via HTR_{2A} receptor activation (Hansson et al., 2016), and may also play a role in inhibition of brown adipose tissue thermogenesis, especially during diet-induced obesity (Crane et al., 2015). However, adipocytes synthesize and reuptake serotonin directly, so many of the actions of serotonin on adipose tissue are attributed to local, adipocyte-derived serotonin (Kinoshita et al., 2010, Oh et al., 2015). Interestingly, serotonin is increased during fasting, and promotes hepatic gluconeogenesis and inhibits hepatic glucose uptake, and promotes adipose tissue lipolysis via HTR_{2B} activation in the fasted state (Sumara et al., 2012). On the contrary, during states of nutrient availability, serotonin may increase hepatic triglyceride accumulation (Osawa et al., 2011), providing evidence for the potential of HTR_3 antagonists for treatment of non-alcoholic fatty liver disease (Haub et al., 2011).

INSL5

As previously mentioned, there are over 20 identified gut peptides, and recent research has identified novel gut peptides as well as functions of known peptides in metabolism. Among these, insulin-like peptide 5 (INSL5), produced by colonic L-cells (Billing et al., 2018), is secreted during fasting and has orexigenic properties (Lewis et al., 2020, Grosse et al., 2014); however, this effect is inconsistent (Zaykov et al., 2019). Interestingly, INSL5 receptor (relaxin/insulin-like family peptide receptor 4) expressing neurons in the hypothalamus were recently found to play a role in the regulation of feeding behavior associated with INSL5 (Lewis et al., 2022). However, as evidence for INSL5 production or presence in the brain is lacking, the physiological role of these neurons in INSL5-mediated feeding behavior is unclear, and it is unknown if these neurons are targeted by gut-derived INSL5. While the biological role of INSL5 is not fully elucidated, INSL5 signaling may participate in islet development and insulin secretion, as mice lacking INSL5 have decreased basal and glucose-stimulated insulin secretion and smaller pancreatic islets compared to wild-type controls, likely due to decreased INSL5-mediated activation of the relaxin family peptide receptor 4 (Burnicka-Turek et al., 2012). Further, INSL5 expression is regulated by the gut microbiota and may act to increase hepatic glucose production, in accordance with its secretion profile during low nutrient availability (Lee et al., 2016).

Neurotensin

Neurotensin, secreted by enteroendocrine N-cells and hypothalamic neurons (Polak et al., 1977), has major implications in the physiology of the CNS, but also plays a role in intestinal and metabolic homeostasis. Neurotensin is secreted primarily in response to luminal lipids (Draviam et al., 1990), acting locally to increase lipid absorption via increasing bile acid reabsorption and gallbladder motility (Gui and Carraway, 2001, Yamasato and Nakayama, 1988, Li et al., 2021b). Further, neurotensin may regulate glucose homeostasis, as systemic neurotensin administration results in hepatic glucose production from glycogenolysis and hyperglycemia (Carraway et al., 1976); this effect is likely due to the regulatory effect of neurotensin on insulin, glucagon, and somatostatin secretion from pancreatic islets (Dolais-Kitabgi et al., 1979, Béraud-Dufour et al., 2010). While peripheral neurotensin certainly plays a role in metabolic homeostasis, much of the research is focused

on the effects of intracerebroventricular neurotensin on metabolic and energy homeostasis. Further, as the half-life of this peptide is ~30 seconds in rodents (Aronin et al., 1982), the endocrine effects of peripheral neurotensin have yet to be fully elucidated but are likely extremely limited.

Gut Microbiota

The complex gut microbiota-host relationship integrates intestinal and systemic metabolism, impacting gut peptide secretion and overall metabolic tissue function (Agus et al., 2021). As mentioned earlier, the gut microbiota encompasses all microbes residing in the GI tract. However, the majority of research thus far has focused on the impact of the gut bacteria, while only recently have other microbes, like fungi or bacteriophages, been implicated in regulating host metabolic health (Sun et al., 2021a, Heisel et al., 2017, de Jonge et al., 2022).

Interaction of the gut microbiota and gut peptide signaling

The gut microbiota is a key factor for coordinated gut peptide secretion, as germ-free and antibiotic-treated mice have alterations in nutrient-sensing and chemosensory machinery, EEC number, and gut peptide release (Table 2) (Duca et al., 2012, Lee et al., 2016, Modasia et al., 2020). For example, germ-free mice exhibit dysregulated diurnal GLP-1 secretion and consistently increased circulating basal and fed GLP-1 (Martchenko et al., 2020, Bäckhed et al., 2004, Heiss et al., 2021, Zarrinpar et al., 2018), despite discrepancies in intestinal expression in the literature (Duca et al., 2012, Wichmann et al., 2013). This increase in GLP-1 secretion likely mediates the increase in gut transit time observed in germ-free mice compared to conventional mice (Wichmann et al., 2013); however, this has also been attributed to modulation of bile acids by intestinal bacteria (Li et al., 2021c). Similarly, INSL5 expression is increased in antibiotic-treated and germ-free mice (Lee et al., 2016), whereas circulating PYY is decreased in germ-free mice during fasting and in response to ingested lipids (Samuel et al., 2008, Duca et al., 2012), suggesting that the gut microbiota regulate L-cell secretion profiles. Germ-free mice also have decreased colonic tryptophan hydroxylase expression and circulating serotonin (Sjögren et al., 2012, Wikoff et al., 2009, Yano et al., 2015), likely due to the key role of the gut microbiota in tryptophan metabolism and serotonin biosynthesis.

Further, germ-free mice have lower fasting insulin and body weight, and it is therefore proposed that the gut microbiota coordinates nutrient harvest and lipid metabolism and storage as a beneficial survival mechanism (Bäckhed et al., 2004). In addition, modulation, rather than ablation, of the gut microbiome with fermentable fiber supplementation induces GLP-1 secretion and glucose tolerance in healthy animals (Massimino et al., 1998a), providing a more physiologically relevant model implicating the importance of the gut microbiota in metabolic homeostasis. Thus, modifying the gut microbiota is a promising therapy for obesity and glucose intolerance. Indeed, fermentable fiber supplementation reduces body weight gain in models of diet-induced obesity (Meyer et al., 2022b) and improves glucose tolerance and insulin sensitivity in diabetic rodents dependent on GLP-1R signaling (Cani et al., 2005, Cani et al., 2006). However, this effect remains controversial in human studies, as fermentable fiber supplementation in individuals with T2D has shown

both no effect on postprandial GLP-1 secretion (Birkeland et al., 2021) and increased postprandial GLP-1 and improved glucose tolerance (Zhao et al., 2018). The impact of fiber on GLP-1 signaling could be due to increased number of L-cells or expression of the preproglucagon gene (Massimino et al., 1998b, Kaji et al., 2011, Everard et al., 2011), although alterations in the gut microbiota via fermentable fibers induce myriad of other effects that could impact host metabolism, such as production and alterations in gut-derived metabolites (Meyer et al., 2022a). For example, both SCFAs and bile acids have been linked with the effect of dietary fiber on gut peptide secretion and subsequent effects on host metabolic homeostasis (Makki et al., 2022, Cani et al., 2006). The specific signaling pathways for which SCFAs, bile acids, and other gut derived metabolites is discussed in detail in the following section. Altogether, the gut microbiota has a significant impact on secretion of gut peptides that can impact metabolic homeostasis.

Gut-derived Metabolites

Perhaps the most investigated mechanism by which the gut microbiota impacts the energy and glucose homeostasis is via the host metabolome, as gut microbes metabolize dietary components and endogenous substances to produce novel bioactive chemicals (Agus et al., 2021). A notable class of compounds produced by intestinal bacteria is SCFAs generated by gut bacterial fiber fermentation. Specifically, fermentable soluble fibers, including resistant starch, β-glucan, inulin/inulin-type fructans, pectin, and soluble corn fiber, are well-established substrates for SCFA production by intestinal bacteria (Martinez et al., 2021). SCFAs can induce gut peptide secretion locally or can enter systemic circulation to act on peripheral metabolic tissues like the liver and adipose tissue (Li et al., 2018b, den Besten et al., 2015). Further, amino acids from the diet are modified by gut microbial metabolism, resulting in altered circulating metabolites that act as endocrine factors to regulate energy and glucose homeostasis (Jo et al., 2021, Hubbard et al., 2015). For example, branched chain amino acids (BCAAs) are produced by bacterial metabolism of the amino acids, glycine, serine, or threonine (Amorim Franco and Blanchard, 2017, Gojda and Cahova, 2021). Similarly, bacterial metabolism of histidine produces imidazole propionate, which regulates hepatic metabolism (Koh et al., 2018), and bacterial metabolism of tryptophan produces tryptamine, indoleacetic acid, indole aldehyde, and others, that regulate inflammation and metabolism via cellular signaling mechanisms (Roager and Licht, 2018). Endogenous compounds can also be modified by intestinal bacteria. Bile acids, produced in the liver, are modified by gut bacteria via deconjugation by bile salt hydrolase and production of exogenous bile acid species (termed secondary and tertiary bile acids) by coordinated bacterial dihydroxylation, oxidation, and epimerization enzymes and resulting in a diverse bile acid pool (Guzior and Quinn, 2021); these modifications impact host receptor signaling to alter gut peptide secretion and tissue metabolism (Ridlon et al., 2014). As these compounds both impact intestinal endocrine function and act as endocrine factors themselves, this review will discuss in detail the effects of metabolites produced or altered by the gut microbiota on host energy and glucose homeostasis.

Short chain fatty acids

As previously mentioned, fiber consumption induces gut peptide secretion at least in part by increasing SCFA production by gut bacteria. It is thought that SCFAs impact

gut peptide secretion via the G-protein coupled receptors GPR41 (FFAR3) and GPR43 (FFAR2) expressed on EECs (Fig. 2, Table 3) (Brooks et al., 2017, Christiansen et al., 2018). Knockout of either FFAR2 or FFAR3 reduces GLP-1 secretion in response to either propionate or acetate (Tolhurst et al., 2012), and activation of a mutant FFAR2-DREADD unresponsive to SCFAs induces GLP-1 secretion similar to propionate administration in wild-type mice (Bolognini et al., 2019). Because the concentration of certain SCFAs, like acetate, in the intestinal lumen is consistently maintained to achieve FFAR2 activation (Cummings et al., 1987), it is proposed that SCFAs may impact gut peptide secretion via basolateral receptor activation. In line with this, FFAR2 has been shown to be expressed on the basolateral EEC membrane, and dietary and vascular SCFAs have differential effects on GLP-1 and PYY secretion (Christiansen et al., 2018, Karaki et al., 2006), indicating that absorption may be necessary for SCFA sensing. However, FFAR3 has a higher affinity for butyrate than acetate and propionate (Brown et al., 2003, Le Poul et al., 2003); therefore, luminal butyrate may be sensed by FFAR3 to induce gut peptide secretion. Nonetheless, it is possible that despite the open-faced nature of EECs to the luminal environment, SCFAs may induce gut peptide secretion via an endocrine mechanism that targets the basolateral side of the EECs; the reasoning and exact pathway for this unique mechanism warrants further investigation.

In addition to their role in the stimulation of gut peptide secretion, SCFAs are also absorbed into general circulation and can act as endocrine factors in metabolically active tissues (Fig. 3). The majority of SCFAs are removed via first pass by the liver, where they impact hepatic metabolism. For example, butyrate decreases lipogenesis and increases hepatic oxidative respiration and beta-oxidation via activation of AMP-activated protein kinase (AMPK) (Mollica et al., 2017), dependent on peroxisome proliferator- activated receptor gamma (PPAR-γ) (den Besten et al., 2015). Acetate and propionate can also be used by hepatocytes for ATP production and gluconeogenesis, respectively(Fujino et al., 2001, Anderson and Bridges, 1984). A small amount of SCFAs escape hepatocyte uptake and enter general circulation to regulate adipocyte thermogenesis and browning. Specifically, butyrate, and, to a lesser extent, acetate, are consistently shown to induce adipocyte browning and increase thermogenesis in mice (Gao et al., 2009, Wang et al., 2020, Li et al., 2019a, Sahuri-Arisoylu et al., 2016). However, there are differential effects of circulating acetate compared to acetate derived from adipocytes acting as a paracrine signal (Sun et al., 2021b), indicating the effect acetate on adipocyte browning may be dependent on source and concentration. Circulating SCFAs alter tissue metabolism via two primary mechanisms: activation of GPCR signaling and epigenetic regulation. As GPR41 and GPR43 are widely expressed (Brown et al., 2003), these receptors may mediate the endocrine actions of SCFAs in the liver (Aoki et al., 2021) and adipose tissue (Kimura et al., 2013). SCFAs also directly impact gene expression via epigenetic modulation to regulate metabolic function. Indeed, SCFA administration in diet-induced obese mice induces expression of adiponectin and resistin via decreasing CpG methylation at adiponectin and resistin promotor regions (Lu et al., 2018). In addition, butyrate acts as a histone deacetylase (HDAC) inhibitor to alter gene expression (Vidali et al., 1978), including hepatic fibroblast growth factor 21 (FGF21) through HDAC3 inhibition (Li et al., 2012) and skeletal muscle insulin receptor substrate 1 (IRS1), peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC1a), and

sirtuins to regulate insulin receptor signaling (Chriett et al., 2019). The effects of butyrate on HDAC inhibition have also been extensively investigated in the context of inflammatory bowel disease (Li et al., 2021a) , gut immunity (Yang et al., 2020) and asthma (Islam et al., 2022), implicating butyrate as a key epigenetic regulator of both metabolic and immune cell function. However, the impact of endogenous SCFA on host metabolism is less resolved, as a majority of the studies outlined above utilize orally or intraperitoneally administrated SCFAs, which is not physiologically relevant. Additionally, several studies suggest SCFAs act in a neural fashion to regulate host metabolism (Goswami et al., 2018, Muller et al., 2020, Li et al., 2018a), and at least one study demonstrated that intravenous administration had no impact on improving energy homeostasis (Li et al., 2018a). Future studies examining the metabolic impact of SCFAs should aim to deliver SCFAs directly to the large intestine to more closely mimic endogenous production, or at the very least, should try to replicate post prandial levels in portal and general circulation (Meyer et al., 2022b). At least one study though has elegantly demonstrated that endogenous SCFAs derived from dietary fiber fermentation can enter circulation and reach the CNS to impact energy homeostasis (Frost et al., 2014), thus underscoring the need for further investigation.

Bile acids

Bile acid concentrations increase in the intestinal lumen postprandially, playing a critical role in lipid absorption in the proximal small intestine as emulsifying agents. However, it is now known that bile acid signaling is a critical regulator of metabolic homeostasis, via paracrine and endocrine actions that are mediated in part by interactions with the gut bacteria. For example, bile acids regulate food intake through distinct signaling pathways via induction of gut peptide secretion by acting as ligands for both the G-protein coupled bile acid receptor-1 (Gpbar1, also known as TGR5) and Farnesoid X Receptor (FXR) (Fig. 2, Table 3) (Chiang, 2013). Indeed, the effects of intraluminal bile acids on gut peptide secretion is well-documented in rodents (Kuhre et al., 2018, Christiansen et al., 2019) as well as humans (Adrian et al., 1993, Adrian et al., 2012, Hansen et al., 2016), and is induced via TGR5 (Christiansen et al., 2019). TGR5 is highly expressed in the colon, where secondary bile acids are produced; as such, the endogenous ligands of TGR5 are conjugated secondary bile acids produced by gut bacteria from host-derived primary bile acids, with taurine-conjugated lithocholic acid being the most potent agonist (Duboc et al., 2014). While luminal bile acids were thought to induce GLP-1 and PYY secretion dependent on apical TGR5, more recent research suggests that bile acid absorption and basolateral TGR5 are required for the effect of bile acids on gut peptide secretion (Kuhre et al., 2018, Brighton et al., 2015), as intraluminal TGR5 agonism has no effect on gut peptide secretion, but intravascular administration of a TGR5 agonist induces robust GLP-1 responses (Christiansen et al., 2019). Additionally, based on the gut peptide-stimulating effect of TGR5 agonism, this signaling pathway has recently been implicated in treatments for obesity and T2D (Zheng et al., 2021), including fiber supplementation and gastric bypass surgeries (Ding et al., 2016, McGavigan et al., 2017), both of which are associated with increased plasma GLP-1 and attenuated food intake.

FXR is expressed in the ileum where primary bile acid concentrations are the greatest, thus FXR activity is largely regulated by primary bile acid species, with chenodeoxycholic

acid (CDCA) being the most potent agonist, and rodent taurine-conjugated beta-muricholic acid a potent FXR antagonist (Sayin et al., 2013, Makishima et al., 1999). Whereas TGR5 induces gut peptide secretion, FXR inhibits proglucagon expression and GLP-1 secretion via interaction with cAMP response element binding protein (CREB) in EECs (Li et al., 2019b, Li et al., 2019c, Trabelsi et al., 2015). Further, FXR activation impairs SCFA-induced gut peptide secretion via inhibition of FFAR2 signaling (Ducastel et al., 2020), demonstrating complex interactions and converging signaling pathways between different classes of microbial metabolites. Interestingly, despite the antagonistic role of FXR signaling in bile acid- and SCFA-mediated GLP-1 secretion in metabolically healthy individuals, FXR activation promotes weight loss and improvements in glucose regulation following gastric bypass surgery (Ryan et al., 2014) and increases intestinal EEC number *ex vivo* (Kim et al., 2022), suggesting dynamic FXR signaling dependent on physiological state. Additionally, FXR is localized in peripheral metabolic tissues (Zhang et al., 2014, Cariou et al., 2006), and it is plausible that the differing metabolic outcomes observed during studies involving FXR are due to action in the intestine versus other tissues like the liver.

Aside from their role in the induction of gut peptides, bile acids can also impact host metabolism in peripheral tissues and within the CNS (Fig. 3). As bile acids undergo enterohepatic circulation, they can both directly and indirectly alter systemic physiology through hepatic and intestinal FXR, respectively; however, the role of FXR remains contentious in individuals with normal metabolic function and metabolic syndrome. For example, while global FXR deficient mice on a normal chow diet display peripheral insulin resistance and elevated serum free fatty acids (Cariou et al., 2006), mice with global, but not liver-specific, FXR deficiency are protected from diet-induced obesity and insulin resistance (Prawitt et al., 2011). On the contrary, intestinal FXR agonism prevents diet-induced obesity and insulin resistance (Fang et al., 2015), further complicating the role of FXR in obesity and metabolic disease. Intestinal FXR may exert beneficial effects via secretion of FGF19 (rodent FGF15) that acts on the fibroblast growth factor receptor 4 (FGFR4) to control bile acid, glucose, and lipid metabolism (Stroeve et al., 2010), as FGF15/19 represses gluconeogenic enzyme expression and postprandial lipogenesis and induces glycogen synthesis (Kim et al., 2020, Potthoff et al., 2011, Kir et al., 2011). However, bile acids also exert an FGF19-independent effect on hepatic lipid metabolism through FXR, as hepatic FXR-deficiency induces hepatic triglyceride accumulation and elevated serum cholesterol, whereas intestinal FXR-deficiency has no effect on hepatic or circulating lipids (Schmitt et al., 2015). FGF15/19 is also involved in the adipose tissue thermogenic response to cold (Fang et al., 2015, Morón-Ros et al., 2021). Finally, levels of the FXR agonist taurochenodeoxycholic acid (TCDCA) increase with high fat-feeding due to small intestinal gut microbiota modulation and impair insulin action in the dorsal vagal cortex dependent on FXR (Zhang et al., 2021, Meyer et al., 2022a), implicating central FXR in control of glucose homeostasis.

TGR5, on the other hand, is consistently reported to be metabolically beneficial. Following a meal, bile acids increase temporally in the hypothalamus, where TGR5 activation participates in satiety and decreases food intake (Perino et al., 2021). Therefore, TGR5 is a prime target for obesity, as central TGR5 agonism in obesity reduces body weight and food intake and increases energy expenditure via the sympathetic nervous system

(Castellanos-Jankiewicz et al., 2021). Peripheral TGR5 also increases energy expenditure in humans (Broeders et al., 2015) and mice via TGR5-mediated intracellular thyroid hormone activation and adipose tissue beiging (Velazquez-Villegas et al., 2018, Watanabe et al., 2006).

Amino acids and derivatives

Large scale metabolomic studies have identified gut microbiota-related amino acid metabolites that regulate metabolic homeostasis via endocrine action. Among these, BCAAs are essential amino acids derived from the diet or gut bacterial biosynthesis. Following absorption, BCAA catabolism occurs primarily in skeletal muscle, where activity of the first enzyme in the BCAA catabolic pathway, branched-chain-amino-acid aminotransferase, is high. In healthy individuals, BCAAs, especially leucine, promote protein synthesis and inhibit proteolysis through mammalian target of rapamycin (mTOR) signaling (Suryawan et al., 2008). In the brain, BCAAs compete for transport with other aromatic amino acids (tryptophan, tyrosine, and phenylalanine) and can thus decrease production of certain neurotransmitters, including serotonin (Gijsman et al., 2002, Choi et al., 2013). In addition, BCAA catabolism results in production of alanine, a key gluconeogenic amino acid, and can therefore promote hepatic glucose production during starvation when BCAA levels increase (Fig. 3) (Holecek et al., 2016). These metabolic effects provide the basis for BCAA supplementation for athletes; however, human studies suggest that the benefits of BCAAs are limited (Plotkin et al., 2021).

Interestingly, plasma BCAAs are elevated in obesity and correlate with insulin resistance and are a predictor of T2D (Newgard et al., 2009, Vanweert et al., 2021, Felig et al., 1969, Wang et al., 2011b). Evidence suggests that both peripheral and hepatic insulin resistance occurs with elevated BCAAS in obesity and T2D, independent of body weight. BCAA supplementation in diet-induced obesity induces skeletal muscle insulin resistance via phosphorylation of mTOR and IRS1, in accordance with the known functions of BCAAs in skeletal muscle (Newgard et al., 2009). Mechanistically, elevated BCAAs in T2D occurs at least in part due to altered expression of enzymes involved in BCAA metabolism in liver, skeletal muscle, and adipose tissue (She et al., 2007, Lian et al., 2015), as well as due to increased abundance of BCAA-producing bacteria and decreased abundance of bacteria that uptake BCAAs in the gut (Pedersen et al., 2016). In the liver, enzymes that regulate BCAA catabolism also control hepatic lipogenesis; therefore, dysregulated expression of these enzymes could contribute to hepatic insulin resistance (White et al., 2018). On the other hand, strategies that reduce circulating BCAAs, like gastric bypass surgery, improve peripheral insulin sensitivity independent of body weight (Lips et al., 2014, Magkos et al., 2013) at least in part by decreasing muscle fatty acyl CoA and glycine accumulation (White et al., 2016).

In addition to BCAAs, imidazole propionate (IMP), a metabolite produced by gut bacterial histidine metabolism, has recently gained attention in the context of T2D. Individuals with T2D have increased portal vein and circulating IMP levels (Koh et al., 2018), increased pro-inflammatory gut bacteria (Molinaro et al., 2020), and low gut microbial diversity (Menni et al., 2020). Despite no differences in dietary histidine intake, IMP is

positively correlated with saturated fat and negatively correlated with fiber and unsaturated fat consumption in individuals with T2D, indicating that diet-mediated gut microbiota modulation is critical for IMP production (Molinaro et al., 2020). Following absorption, IMP impairs glucose tolerance and insulin signaling in mice through a p38γ mitogen activated protein kinase (MAPK)-p62-mTOR complex 1 (mTORC1) signaling axis (Fig. 3) (Koh et al., 2018). Interestingly, individuals with T2D and high blood glucose taking metformin have increased IMP levels, and the blood glucose lowering effect of metformin is blunted with IMP pretreatment in mice, dependent on p38γ MAPK-Akt mediated inhibitory AMPK phosphorylation (Koh et al., 2020). Taken together, these data provide promising framework for therapeutics targeting IMP-producing bacteria for treatment of T2D.

The amino acid tryptophan is also metabolized by gut bacteria, producing metabolites that impact host receptor activity. While over 95% of dietary tryptophan is metabolized directly by the host via indoleamine 2,3-dioxygenase 1 (IDO1), gut bacteria can metabolize tryptophan into tryptamine and indole metabolites. Production of the metabolite tryptamine in the gut is impacted by bacterial metabolism of tryptophan, as germ-free mice have lower fecal tryptamine than humanized mice (Marcobal et al., 2013), and it is estimated that >10% of individuals harbor gut microbes that express at least one of the enzymes for decarboxylation of tryptophan to produce tryptamine (Williams et al., 2014). Further, metabolic syndrome is associated with blunted production of tryptamine and indole metabolites from dietary tryptophan due to gut microbiome dysbiosis (Natividad et al., 2018). Although a relatively low-abundance metabolite, tryptamine induces serotonin secretion from gut EC cells (Takaki et al., 1985), potentially indirectly impacting peripheral tissue metabolism. Tryptamine is also a proposed therapeutic for gut inflammatory disorders, as it induces mucus secretion from goblet cells via the G-protein coupled serotonin receptor 5-HTR_4 (Bhattarai et al., 2020). The effects of tryptophan metabolites on metabolic homeostasis are at least partially dependent on the aryl hydrocarbon receptor (AHR). Indeed, high fat-fed mice treated with either an AHR agonist or *Lactobacillus reuteri*, a bacteria with high AHR ligand production, have improved gut barrier function and metabolic homeostasis possibly mediated by AHR-induced GLP-1 secretion from EECs (Natividad et al., 2018). However, a previous study found that indole induces acute GLP-1 secretion from EECs via voltage-gated K^+ channel inhibition (Chimerel et al., 2014); therefore, multiple potential intersecting pathways may be responsible for indole-mediated GLP-1 secretion (Fig. 2, Table 3). On the other hand, exposure to the AHR agonist 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, also known as dioxin) is correlated with hyperglycemia and insulin resistance in humans (Henriksen et al., 1997, Cranmer et al., 2000), and mice expressing a low-binding affinity AHR variant and global AHR deficient mice are resistant to diet induced obesity and associated metabolic perturbances (Xu et al., 2015, Kerley-Hamilton et al., 2012, Wang et al., 2011a). Taken together, while these data indicate a potential impact of indole metabolites impacting metabolic homeostasis via AHR, there is much to be determined in regards to the site of action and mechanism. Indeed, AHR is expressed in a variety of cell types, and is a critical regulator of NF-KB inflammatory signaling (Ishihara et al., 2021). Thus, it is possible that there exists a balance of pro- and anti-inflammatory signaling required to maintain homeostasis, that is further dependent on the specific tissue affected. For example, intestinal AHR activation improves intestinal

inflammation associated with obesity (Postal et al., 2020), and promotes secretion of anti-inflammatory cytokines in the intestine to improve gut barrier and metabolic homeostasis in mice challenged with high fat feeding (Lin et al., 2019). Nonetheless, bacterially-derived tryptophan metabolites represent an exciting new area of research in metabolic disease, and warrant further research.

Bacterial Components

Chronic low-grade inflammation often occurs in obesity and obesity-associated metabolic disorders, at least in part due to LPS exposure. Western-style high fat diet-feeding and loss of gut barrier integrity in obesity promote LPS absorption, resulting in host low-grade inflammation and impaired glucose homeostasis, termed metabolic endotoxemia (Fig. 3) (Pendyala et al., 2012, Cani et al., 2007a). High fat diet-fed mice have increased circulating LPS, and chronic LPS exposure increases body weight, worsens glucose tolerance and insulin sensitivity, and increases inflammatory cytokine expression dependent on the cell surface receptor cluster of differentiation 14 (CD14) (Cani et al., 2007a). Both rodent and human obesity is associated with increased adipose tissue expression of proinflammatory cytokines, including tumor necrosis factor (TNF)-α that is correlated with hyperinsulinemia and inhibits insulin receptor tyrosine kinase activity through IRS-1 (Hotamisligil et al., 1993, Hotamisligil et al., 1995, Hotamisligil et al., 1996). Further, OFS supplementation in high fat-feeding improves glucose homeostasis, reduces adipose and circulating inflammatory cytokines, and increases gut *Bifidobacterium* sp. that are negatively associated with endotoxemia, further implicating the gut microbiota composition and in the detrimental inflammatory and metabolic effects of high fat-feeding (Cani et al., 2007b). Circulating LPS forms a complex with LPS-binding protein, which can interact with cell surface receptors CD14, toll-like receptor 4 (TLR4), and toll-like receptor 2 (TLR2), inducing proinflammatory cytokine release (Mohammad and Thiemermann, 2020). As such, some reports suggest that CD14 and TLR4 deficient mice are protected from diet-induced obesity and insulin resistance (Kim et al., 2007, Poggi et al., 2007, Jia et al., 2014, Roncon-Albuquerque et al., 2008), whereas others suggest that neither TLR4 or CD14 mediate diet-induced obesity (Dalby et al., 2018, Young et al., 2012). These discrepancies in the literature may be due to differences in knockout tissue specificity, genetic background, or diet, and indicate a need to further elucidate the significance of TLR4 in the pathophysiology of metabolic disorders. Interestingly, hexa-acylated LPS derived from *Escherichia coli* induces GLP-1 secretion from enteroendocrine L-cells in response to intestinal injury to reduce inflammation via TLR4 activation (Fig. 2, Table 3) (Lebrun et al., 2017), whereas penta-acylated LPS from *R. sphaeroides* has no effect on GLP-1 secretion (Table 3) (Anhê et al., 2021), indicating that the effects of LPS on metabolism are dependent on diet, physiological state, and species-specific LPS type. In addition to TLR4, bacterial LPS agonizes TLR2, altering cellular metabolism and immune cell activation (Kirschning et al., 1998). Further, mice lacking TLR2 are resistant to diet-induced obesity and glucose intolerance (Guo et al., 2021, Ehses et al., 2010), and inhibition of TLR2 signaling improves insulin sensitivity (Caricilli et al., 2008). On the contrary, flaggelin, the primarily protein found in bacterial flagella, may reduce metabolic endotoxemia via TLR5-mediated gut microbiota remodeling. Upon activation by flaggelin, TLR5, expressed in the intestinal epithelium, modulates the presence of pathogenic gut bacteria (Carvalho et al., 2012).

Interestingly, mice lacking whole body and intestinal TLR5 develop metabolic endotoxemia, with increased body weight and adiposity and abnormal glucose regulation, as well as susceptibility to colonization with pathogenic bacteria (Chassaing et al., 2014, Vijay-Kumar et al., 2010), implicating an intestinal feedback loop in which pathogenic bacteria stimulate TLR5 that, in turn, impairs pathogenic bacterial growth to regulate intestinal inflammation and prevent metabolic endotoxemia. Together, these studies suggest a role for multiple TLRs in inflammation-associated metabolic perturbances.

The nucleotide-binding oligomerization domain-containing proteins, NOD1 and NOD2, are ubiquitously expressed pattern recognition receptors that recognize bacterial cell wall components, including peptidoglycans from gram-negative and some gram-positive bacteria (Rivers et al., 2019). In particular, NOD1 and NOD2 have been studied in bacterial induction of inflammatory signaling that results in insulin resistance. Expression of NOD1 and NOD2 is elevated in individuals with metabolic syndrome (Lappas, 2014, Zhou et al., 2015, Shiny et al., 2013) and diet-induced obese rodents (Sharma et al., 2022), and mice lacking NOD1, but not NOD2, are resistant to diet-induced body weight gain and glucose intolerance (Amar et al., 2011). Further, activation of NOD1 is consistently linked to adipose tissue inflammation and peripheral insulin resistance (Zhao et al., 2011, Schertzer et al., 2011, Zhou et al., 2012). Taken together, inflammatory signaling induced by bacterial activation of TLRs and/or NOD-like receptors may be a promising target for treatment of metabolic disease.

The bacterial protein, caseinolytic peptidase B protein homolog (ClpB), expressed by *E. coli* has been identified as an antigen mimetic protein of α-melanocyte stimulating hormone (α-MSH) (Tennoune et al., 2014), a key neuropeptide involved in regulation of food intake. While little is known about the physiological effects of ClpB, this protein has been implicated in the development of eating disorders, and, more recently, obesity, as gut bacterial ClpB-like gene function is negatively correlated with obesity in humans (Arnoriaga-Rodríguez et al., 2020). Further, chronic intragastric *E. coli* treatment decreases food intake, while treatment with Clpb-deficient *E. coli* has no effect on food intake (Tennoune et al., 2014); this effect is proposed to be mediated by increased PYY secretion with ClpB exposure (Dominique et al., 2019). Additionally, treatment with a strain *Hafnia alvei* expressing ClpB with an α-MSH-like motif reduces food intake and body weight in diet-induced obese mice, reduces food intake in genetically obese *ob/ob* mice (Legrand et al., 2020) and improves body weight loss in humans (Déchelotte et al., 2021), providing the foundation for research into novel probiotic ClpB-expressing bacterial strains for obesity.

Conclusions and Future perspectives

Given the expanding viewpoint for the GI tract as an important endocrine organ in the regulation of metabolic homeostasis, it is no surprise that several of the most successful treatment options for obesity and diabetes are gut-derived in nature. For example, two classes of drugs, GLP-1R agonists (GLP-1RA), like liraglutide, and DPP-4 inhibitors, like sitagliptin, improve T2D via activating GLP-1R signaling mechanisms. Interestingly, GLP-1RAs possess a long half-life, while DPP-4 inhibitors increase the half-life of endogenous GLP-1 (Nauck et al., 2021, Omar and Ahrén, 2014); therefore, these drugs

can target endocrine actions of GLP-1R signaling. For example, it is likely that GLP-1RAs improve glucose homeostasis via amplification of glucose-stimulated insulin secretion at the β-cell and induce significant weight loss via CNS action (Varin et al., 2019, Lamont et al., 2012). More recently, clinical trials investigating both dual GLP-1R/GIPR agonists and GLP-1/glucagon receptor (GCGR) agonists as well as GLP-1R/GIPR/GCGR triagonists indicate positive effects on weight loss and glycemia, with GCGR and GLP-1R agonism promoting weight loss and GIPR agonism negating the effects of glucagon signaling on hepatic glucose production (Capozzi et al., 2018, Frias et al., 2018, Coskun et al., 2018, Ji et al., 2021). For example, the "twincretin" tirzepatide is generally more effective at reducing glycemia and body weight compared to the GLP-1 analog semaglutide with the same safety profile (Vadher et al., 2022), whereas GLP-1R/GIPR/GCGR triagonists show early synergistic effects on metabolism, improving glycemic control and body weight to a greater extent than dual incretin receptor agonists in rodents (Finan et al., 2015). However, with all these current treatments, there are moderate side effects, including nausea, diarrhea, and, to a lesser extent, vomiting, constipation, abdominal pain, and dyspepsia (Filippatos et al., 2014). Therefore, future studies must continue to understand the endocrine action of gut peptide signals, as a better understanding of potential sites of action could lead to more personalized and targeted therapies that limit side effects.

In contrast to the establishment and success of GLP-1-mediated therapies, therapies targeting the vast potential of the gut microbiota are still in infancy. As such, while many studies have highlighted the potential of various probiotics in metabolic homeostasis (Bauer et al., 2018, Stenman et al., 2014), only a few have been successful in clinical trials (Bernini et al., 2016, Minami et al., 2015, Kadooka et al., 2010, Depommier et al., 2019). However, as sequencing efforts become more advanced, there is a greater likelihood that gut bacteria will be discovered that have novel roles in mediating energy and glucose homeostasis. For example, one group has discovered a gut bacteria that is capable of producing ClpB, which could have major implications in metabolism (Tennoune et al., 2014). Additionally, there is the emerging field of bioengineered bacteria, with several groups generating bacteria capable of producing specific metabolites, like leptin and GLP-1, that target metabolic organs to prevent or treat metabolic disease (Bermúdez-Humarán et al., 2007, Arora et al., 2016). Nonetheless, despite these efforts, it is possible that probiotic treatment may be highly personalized, as some individuals are permissive to colonization of probiotics while others are resistant, depending on their pre-existing gut microbiota (Zmora et al., 2018). Indeed, the gut microbiome is highly complex and individualized, thus baseline gut microbiome and metabolome conditions could influence whether treatments targeting the gut microbiome are successful. For example, an individual's baseline gut microbiome and metabolome can dictate the successful glucoregulatory effect of exercise, while machine-learning algorithm can this information to predict if an individual will "respond" to exercise based on microbial characteristics (Liu et al., 2020). A similar program uses a machine learning algorithm to personalize dietary interventions for glucose tolerance using baseline gut microbial signatures in combination with diet and health information (Berry et al., 2020). Altogether, this highlights the importance of comprehensive clinical studies that incorporate not only phenotypic characteristics, but also baseline gut metagenomic and metabolomic analyses to determine if drug-gut interactions dictate the successful or failure of treatments toward

obesity and diabetes. While the exact mechanisms are not completely elucidated, it is evident that both gut peptides and gut microbiota-derived compounds act as endocrine factors to impact host signaling and metabolic homeostasis, representing a relatively novel and exciting collection of compounds and receptors that can be targeted for treatment of metabolic disease.

Funding

This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH (R01DK121804).

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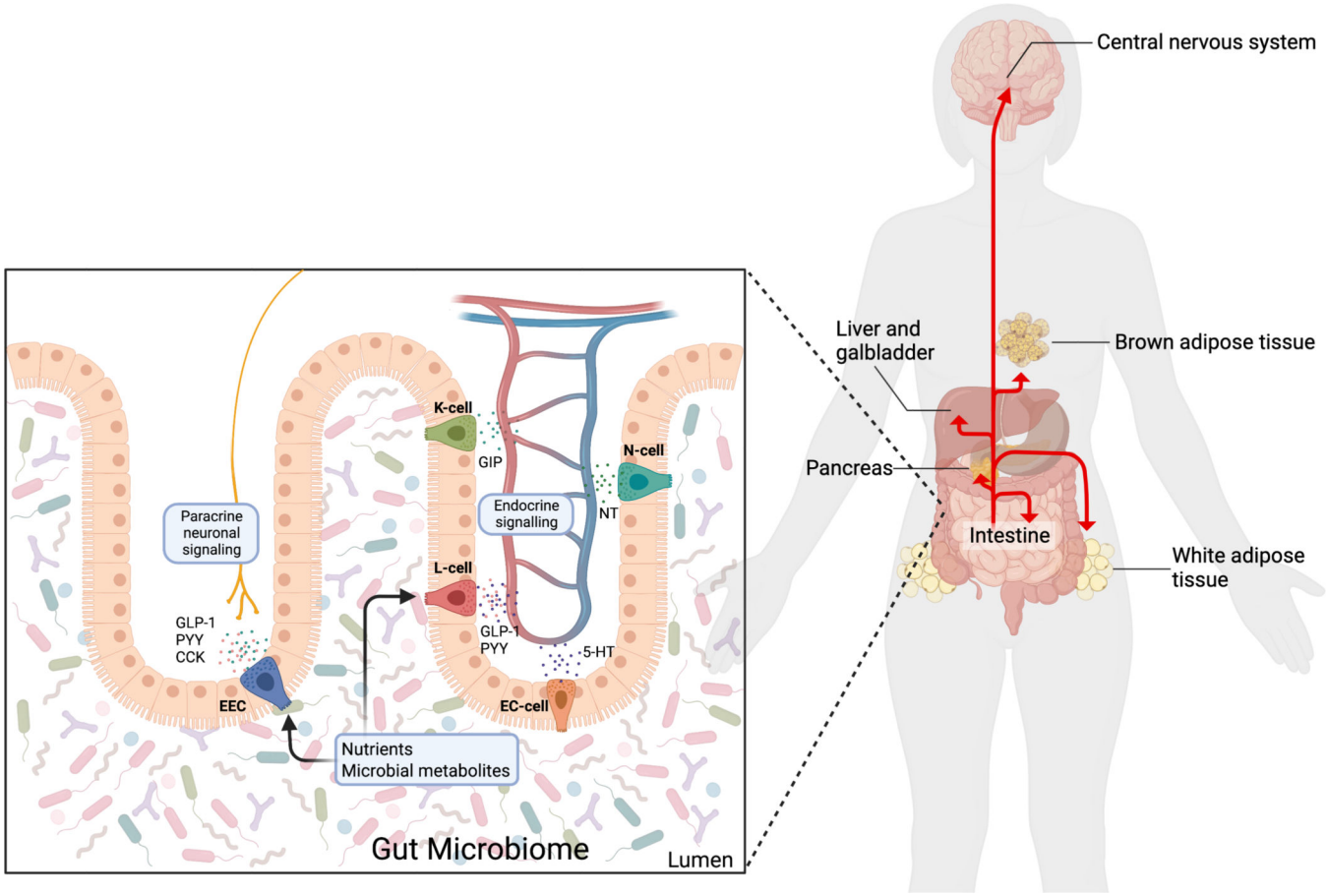

Figure 1. Gut peptide secretion and endocrine effects.

Enteroendocrine cells (EECs), dispersed throughout the intestine, sense luminal nutrients and microbial metabolites and secrete gut peptides that impact metabolism. K-cells secrete glucose-dependent insulinotropic peptide (GIP); L-cells secrete glucagon-like peptide 1 (GLP-1) and peptide YY (PYY); enterochromaffin cells (EC cells) secrete 5-hydroxytryptamine (5-HT, also known as serotonin); and N-cells secrete neurotensin (NT). Some of these gut peptides, especially GLP-1, PYY, and CCK, impact metabolism via paracrine neuronal signaling. Further, gut peptides enter circulation and act as endocrine factors at the intestine, pancreas, liver, gallbladder, central nervous system, and brown and white adipose tissue. Figure created with BioRender.com.

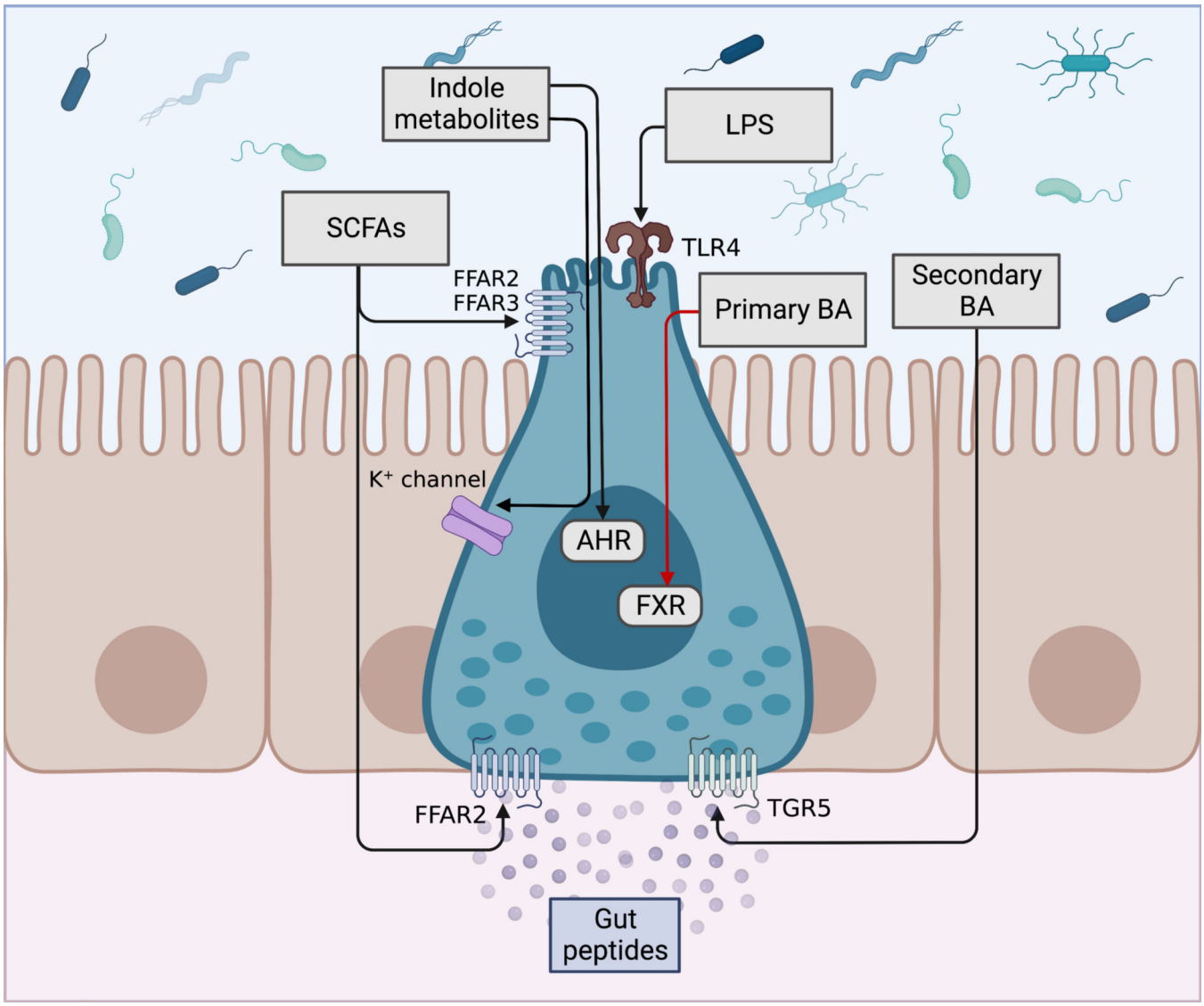

Figure 2. Signaling mechanisms of gut peptide secretion by microbially produced metabolites.

Metabolites produced or altered by the gut microbiota that impact gut peptide secretion include short chain fatty acids (SCFAs), indole metabolites produced from bacterial metabolism of tryptophan, primary bile acids (BAs) that can be deconjugated by bacterial bile salt hydrolase, and secondary BAs produced by bacterial metabolism of primary Bas, among others. SCFAs are proposed to induce secretion of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) via FFAR2 and/or FFAR3; however, some studies suggest that SCFA absorption and basolateral FFAR2 is responsible for SCFA-induced gut peptide secretion. Indole metabolites inhibit voltage-gated K^+ channels to increase EEC action potential and intracellular Ca^{2+}, and induce GLP-1 secretion; alternatively, indole metabolites may activate the aryl hydrocarbon receptor (AHR) to induce GLP-1 secretion. Bacterial lipopolysaccharide (LPS) induces GLP-1 secretion via toll-like receptor 4 (TLR4). Primary BAs primarily activate the Farnesoid X receptor (FXR) to inhibit GLP-1 secretion, whereas secondary BAs primarily activate the basolateral G-protein bile acid receptor 1

(Gpbar1, also known as TGR5) to induce gut peptide secretion. Black arrows indicate signaling pathways resulting in induction of gut peptide secretion; red arrow indicates signaling pathways resulting in inhibition of gut peptide secretion. Figure created with BioRender.com.

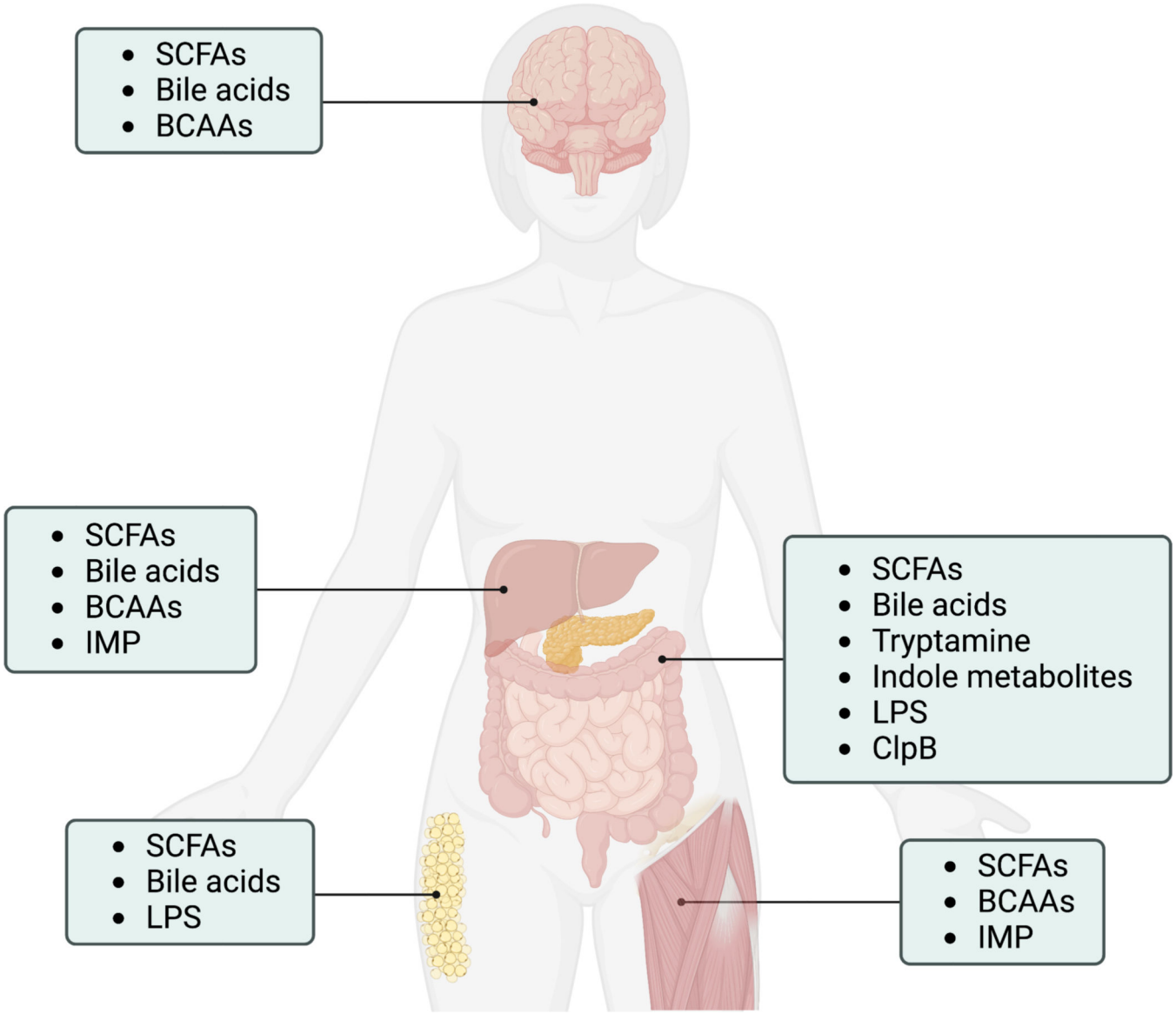

Figure 3. Microbial metabolites enter circulation and impact metabolic organ function.
Microbial metabolites discussed in the text are listed with their metabolic organ targets. Short chain fatty acids (SCFAs); branched chain amino acids (BCAAs), imidazole propionate (IMP), lipopolysaccharide (LPS); caseinolytic peptidase B protein homolog (ClpB). Figure created with BioRender.com.

Table 1.

Summary of intestinal gut peptides.

Peptide	EEC Type	Tissue Location of Secretion	Function	References
Serotonin	Enterochromaffin Cell	Throughout the GI tract	Regulation of intestinal motility and inflammation, gluconeogenesis and glucose uptake, adipose tissue lipolysis, brown adipose tissue thermogenesis	(Sumara et al., 2012, Heredia et al., 2013, Margolis et al., 2014, Crane et al., 2015)
CCK	I cell	Small intestine	Regulation of gallbladder contraction, gastric emptying, pancreatic exocrine secretion, brown adipose tissue thermogenesis and hepatic glucose production, decreases food intake	(Blouet and Schwartz, 2012, Cheung et al., 2009, Li and Owyang, 1993, Lorenz and Goldman, 1982, Schwartz et al., 1993, Sonobe et al., 1995)
GIP	K cell (also found in some GLP-1 secreting cells)	Small intestine	Amplifies glucose-stimulated insulin secretion, promotes β-cell survival and proliferation	(Gasbjerg et al., 2019, Kim et al., 2005)
Neurotensin	N cell	Small intestine	Increases bile acid reabsorption and gallbladder motility, regulates insulin, somatostatin and glucagon secretion	(Dolais-Kitabgi et al., 1979, Yamasato and Nakayama, 1988, Béraud-Dufour et al., 2010, Li et al., 2021b)
GLP-1	L cell	Small intestine through rectum	Amplifies glucose-stimulated insulin secretion, promotes β-cell survival and proliferation, decreases food intake, delays gastric emptying	(Li et al., 2005, Hare et al., 2010, Lamont et al., 2012, Turton et al., 1996, Davis et al., 1998, Zhang et al., 2022)
GLP-2	L cell	Small intestine through rectum	Increases epithelial cell proliferation, intestinal barrier function and intestinal hexose transport, inhibits gastric acid secretion	(Drucker et al., 1996, Benjamin et al., 2000, Wøjdemann et al., 1999, Cheeseman and Tsang, 1996)
PYY	L cell	Small intestine through rectum	Inhibits gastric acid secretion, gastric emptying and pancreatic exocrine secretion, decreases food intake	(Adrian et al., 1985, Grandt et al., 1995, Moran et al., 2005, Challis et al., 2003, Degen et al., 2005)
Oxyntomodulin	L cell	Colon	Decreases food intake, amplifies glucose-stimulated insulin secretion	(Dakin et al., 2004, Maida et al., 2008)
INSL5 *	L cell	Colon	Increases food intake and hepatic glucose production, regulates islet development and insulin secretion	(Grosse et al., 2014, Lee et al., 2016, Zaykov et al., 2019, Burnicka-Turek et al., 2012)

(GI, gastrointestinal; CCK, cholecystokinin; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2; PYY, peptide YY; INSL5, insulin-like peptide 5).

*Several actions of INSL5 are debated; see text for more details.

Table 2.

Summary of gut peptide and expression in germ-free mice compared to conventional mice.

Peptide	GF vs. conventional mice	References
Serotonin	Decreased in circulation	(Sjögren et al., 2012, Yano et al., 2015, Wikoff et al., 2009)
CCK	Increased in circulation	(Martinez-Guryn et al., 2018)
	Decreased expression in the proximal intestine	(Duca et al., 2012)
GIP	Increased GIP+ cells in jejunum and colon	(Modasia et al., 2020)
Neurotensin	No data	
GLP-1	Increased in circulation	(Heiss et al., 2021, Wichmann et al., 2013, Zarrinpar et al., 2018)
	Increased cecal and colon Gcg expression	(Wichmann et al., 2013)
	Decreased expression in the proximal intestine	(Duca et al., 2012)
GLP-2	No data	
PYY	Decreased in circulation and decreased expression in the proximal intestine	(Duca et al., 2012)
	Decreased in circulation compared to mice colonized with *B. thetaiotaomicron* and *M. smithii*	(Samuel et al., 2008)
Oxyntomodulin	No data	
INSL5	Increased expression in colon	(Lee et al., 2016)

(GF, germ-free; GI, gastrointestinal; CCK, cholecystokinin; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2; PYY, peptide YY; INSL5, insulin-like peptide 5).

Table 3.

Effects of microbial metabolites or components on gut peptide secretion.

Compound	Effect on gut peptide secretion	Proposed Mechanism	References
SCFA	Increased GLP-1 and PYY	Activation of FFAR2/FFAR3	(Brooks et al., 2017, Christiansen et al., 2018, Tolhurst et al., 2012)
Primary and some secondary bile acids	Decreased GLP-1	Activation of FXR	(Li et al., 2019b, Li et al., 2019c, Trabelsi et al., 2015)
Secondary bile acids	Increased GLP-1 and PYY	Activation of TGR5 (Gpbar1)	(Brighton et al., 2015, Christiansen et al., 2019, Kuhre et al., 2018)
Tryptophan metabolites	Increased GLP-1	Activation of AHR	(Natividad et al., 2018)
	Increased GLP-1 (acute)	Inhibition of voltage-gated K^+ channels (acute)	(Chimerel et al., 2014)
	Decreased GLP-1 (prolonged)	Decreased ATP production via inhibition of NADH dehydrogenase	
LPS (*E. coli*)	Increased GLP-1	Activation of TLR4	(Lebrun et al., 2017, Anhê et al., 2021)
LPS (*R. sphaeroides*)	No effect on GLP-1 secretion	No (or possibly antagonistic) effect on TLR4 activation	(Anhê et al., 2021)

(SCFA, short chain fatty acids; FFAR2, free fatty acid receptor 2; FFAR3, free fatty acid receptor 3; GLP-1, glucagon-like peptide 1; PYY, peptide YY; FXR, Farnesoid X Receptor; TGR5, G-protein-coupled bile acid receptor (Gpbar1); AHR, arylhydrocarbon receptor; LPS, lipopolysaccharide; TLR4, toll-like receptor 4).