Microbiota-Gut-Brain Axis: Modulator of Host Metabolism and Appetite

Marcel van de Wouw, Harriet Schellekens, Timothy G Dinan, and John F Cryan

Abstract

The gut harbors an enormous diversity of microbes that are essential for the maintenance of homeostasis in health and disease. A growing body of evidence supports the role of this microbiota in influencing host appetite and food intake. Individual species within the gut microbiota are under selective pressure arising from nutrients available and other bacterial species present. Each bacterial species within the gut aims to increase its own fitness, habitat, and survival via specific fermentation of dietary nutrients and secretion of metabolites, many of which can influence host appetite and eating behavior by directly affecting nutrient sensing and appetite and satiety-regulating systems. These include microbiota-produced neuroactives and short-chain fatty acids. In addition, the gut microbiota is able to manipulate intestinal barrier function, interact with bile acid metabolism, modulate the immune system, and influence host antigen production, thus indirectly affecting eating behavior. A growing body of evidence indicates that there is a crucial role for the microbiota in regulating different aspects of eating-related behavior, as well as behavioral comorbidities of eating and metabolic disorders. The importance of intestinal microbiota composition has now been shown in obesity, anorexia nervosa, and forms of severe acute malnutrition. Understanding the mechanisms in which the gut microbiota can influence host appetite and metabolism will provide a better understanding of conditions wherein appetite is dysregulated, such as obesity and other metabolic or eating disorders, leading to novel biotherapeutic strategies.

Keywords: nutrition, microbiota, obesity, metabolism, behavior
forebrain regions (30). There are various peripheral anorexigenic hormones, such as glucagon-like peptide 1 (GLP-1)\(^6\), peptide YY (PYY), insulin, and leptin, that increase satiety, whereas ghrelin is able to induce hunger (31). Within the hypothalamus, pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript–containing neurons regulate satiety, whereas neurons that contain neuropeptide Y and those that contain agouti-related peptide are involved in hunger signaling (30). These hypothalamic neurons project to other brain circuits such as the mesolimbic rewards circuit, which is highly involved in food reward, addiction, and impulsive choice (32). As such, signaling of the previously mentioned peripheral hormones has also been implicated in both addiction (33) and impulsivity (34). This additionally highlights the involvement of physiologic and/or psychological components in eating disorders (35, 36). Importantly, the influence of the microbiota-gut-brain axis is becoming increasingly recognized in psychological and psychiatric disorders (37, 38), indicating that this axis could play a role in the physiologic and/or psychological components of metabolic and eating disorders.

This review focuses on the diverse mechanisms through which the gut microbiota influences host metabolism, feeding behavior, and appetite as a crucial piece of the puzzle in conditions wherein food intake and body weight are dysregulated. To focus on these, we first provide a brief overview of various food-related disorders in which the gut microbiota is involved. Then we further introduce the role of the gut microbiota in metabolic and eating disorders, with particular emphasis on obesity. After that, we discuss the involvement of gut microbial metabolites in the microbiota-gut-brain axis. Special emphasis is laid on SCFAs and the diverse mechanisms by which these are able to regulate host energy metabolism and appetite. In addition, we examine the interplay between the gut microbiota, intestinal barrier permeability, immune system functionality, and gut microbial mimicry. Further, we discuss mechanisms by which the gut microbiota could influence host nutrient and taste sensing throughout the gastrointestinal tract. Finally, we briefly emphasize the multifaceted nature of eating disorders in regard to their food-related behavioral components, other behavioral comorbidities such as anxiety and depression, and the role that the gut microbiota plays herein.

### Metabolic and Eating Disorders

The role of the gut microbiota in host metabolism and appetite has been primarily investigated in regard to obesity and metabolic syndrome. As such, less work has been done with other eating disorders associated with a positive energy balance, such as binge-eating disorder and drug-induced obesity, or with eating disorders associated with a negative energy balance, such as anorexia nervosa, cachexia, and infant malnutrition. It is crucial to note that, even though a dysfunctional energy balance is common between all mentioned disorders, each disorder has other specific malfunctioning physiologic and psychological factors. As such, each metabolic and eating disorder is discussed separately in the following section to emphasize their particularities and our current knowledge.

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**Obesity and metabolic syndrome.** Obesity and related metabolic syndrome have become one of the most prominent health concerns in developed countries worldwide (39), with the WHO estimating that nearly 600 million people worldwide are obese (40). Obesity is characterized by excessive adipose tissue, an imbalance between energy intake and expenditure favoring a positive energy balance, and it is associated with low-grade inflammation (41) and insulin resistance (42). As such, obesity is a risk factor for numerous medical conditions, such as cardiovascular disease, nonalcoholic fatty liver disease, endocrine and metabolic disorders, as well as certain cancers (43). Considerable focus is being put on the contribution of overeating and a positive energy balance to body weight gain. In addition, obesity is associated with an increased prevalence of compulsive food behavior (32), as well as food-related impulsivity (44). There is a growing realization that there is involvement of the gut microbiota in obesity, especially considering that gut microbiota features could be used to predict glucose responses, enabling personalized dietary interventions (45).

Notably, the gut microbiota is regarded as an important factor contributing to nonalcoholic fatty liver disease, which is often associated with obesity (46). For ≥25% of all nonalcoholic fatty liver disease patients, this condition progresses into a progressive form of liver disease called nonalcoholic steatohepatitis, potentially resulting in cirrhosis, hepatocellular carcinomas, and liver dysfunction (47). The importance of the gut microbiota in obesity is also emphasized by the fact that interventions targeting this disorder, including bariatric surgery, and Roux-en-Y gastric bypass surgery in particular, induce substantial weight loss and are associated with alterations in gut microbiota composition (21–23, 48). This is particularly important in regard to the mechanisms of actions, including changes in gut hormones, bile acid, and lipid metabolism, and neuronal signaling (49).

**Binge-eating disorder.** Binge-eating disorder is characterized by excessive, out-of-control, and rapid food intake (50, 51), and is recognized as a distinct eating disorder by the Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (52). It is the most common eating disorder, with an estimated lifetime prevalence of 1.9–2.8% in US adults, yet it often goes unrecognized (50, 53). Enhanced food-related impulsivity and compulsivity plays a critical role in the maintenance of this disorder (44). Binge-eating disorder is not only associated with obesity and metabolic syndrome, but also with gastrointestinal disorders, asthma, and, among women, menstrual dysfunction, pregnancy complications, intracranial hypertension, and polycystic ovary syndrome (54, 55). Even though the role of gut microbes in host eating behavior is being elucidated at a rapid rate (28), the link between binge-eating disorder and the gut microbiota currently remains unclear, and more research is warranted.

**Drug-induced obesity.** A change in body weight is often a side-effect of various medications. Atypical antipsychotics represent the mainstay of treatment for schizophrenia and bipolar disorder, and they are known for their various side-effects, such as weight gain and metabolic dysfunction (56–58). In particular, the drug olanzapine is known for its weight-gaining effects (59, 60). Rodents receiving olanzapine also have an altered gut microbiota composition (61, 62). In addition, rats that also received an antibiotic cocktail had reduced olanzapine-induced body weight gain and various markers of metabolic dysfunction, further highlighting the involvement of the gut microbiota (61). Another medication is the second-generation antipsychotic risperidone, often used to treat bipolar disorder and schizophrenia in children and adolescents (63). Chronic

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\(^6\) Abbreviations used: ClpB, caseinolytic protease B; CNS, central nervous system; FFA2, FFA receptor 2; FFA3, FFA receptor 3; FXR, farnesoid X receptor; GABA, \(\gamma\)-aminobutyric acid; GF, germ-free; GIP, gastric inhibitory polypeptide; GLP-1 glucagon-like peptide 1; GPCR, G protein–coupled receptor; MSH, melanocyte-stimulating hormone; POMC, pro-opiomelanocortin; PYY, peptide YY.
risperidone treatment results in altered gut microbial composition, with enriched pathways that have been implicated in weight gain (64). Furthermore, mice receiving risperidone treatment displayed altered gut microbiota composition and body weight gain, which was primarily attributed to decreased energy expenditure (65). In addition, this trait was transmissible via fecal matter transplantation and via treatment with phage isolated from risperidone-treated microbiota (65).

Anorexia nervosa. Anorexia nervosa is characterized by a distorted body image leading to restricted food intake and subsequently severe weight loss, which in addition is associated with hyperactivity and hypothermia (66). Anorexia nervosa has the highest mortality rate among psychiatric illnesses and significantly affects quality of life (67, 68). There is currently no clear understanding of its etiology, nor is there any medication present. The role and involvement of the gut microbiota is largely unclear in this disorder, even though current evidence indicates that it could represent a potent intervention target (25).

Cachexia. Cachexia is a metabolic condition caused by severe illness that is characterized by the loss of skeletal muscle mass, both dependent of and independent of fat mass loss (69). Fifty to eighty percent of all cancer patients are affected by this condition, and it ultimately reduces quality of life and survival (70). Central elements in the pathophysiology of cancer cachexia are a reduced food intake and an abnormal metabolism leading to a negative protein and energy balance (71). These are primarily driven by the central nervous system (CNS) and inflammatory pathways (69). Even though the role of the gut microbiota in cancer cachexia is unclear, the former does play a role in both CNS and immune system regulation (72, 73), indicating that it may be a potential therapeutic target (26). In particular, appetite-related signaling might be of interest here, with the novel ghrelin-receptor agonist anamorelin recently having demonstrated that it increases lean body mass, as well as quality of life, in patients with cachexia (74, 75).

Infant malnutrition. A mature gut microbiota configuration resembling that of an adult is reached after the first 2–3 y of age (76). Disturbances within this critical time period can result in an immature gut microbiota (77). Of note, the consequences of having an immature gut microbiome in later life in will be discussed in the section Key Determinants of the Adult Gut Microbiota Composition in Metabolic and Eating Disorders. In early life, gut microbiota maturity is a crucial contributory factor to the prevalence and severity of kwashiorkor, an enigmatic form of severe acute malnutrition that affects millions of children (20). Notably, this condition is transferrable by gut microbiota transplantation, highlighting its importance (78, 79). In addition, a recent study by Wagner et al. (80) demonstrated that gut microbiota transplantation from undernourished 24-mo-old Bangladeshi children into mice resulted in drastic weight loss, which was transmissible from the dams to their offspring. The importance of the gut microbiota is emphasized by the fact that antibiotics such as amoxicillin and cefdinir reduce mortality in children with kwashiorkor (81, 82).

The Gut Microbiota as a Key Player in Obesity and Metabolic and Eating-Related Disorders

One of the early and pivotal experiments demonstrating the key role of the gut microbiota in host energy metabolism showed that mice with an absent microbiota [i.e., germ-free (GF) mice], had dramatically decreased body fat despite having higher food intake, both of which were normalized after colonization with a conventional gut microbiota (83). Shortly after this, it was discovered that there was a different gut microbial ecology associated with obesity (84, 85), and that the gut microbiota connected with obesity was associated with an increased capacity for dietary energy harvest (86). Indeed, colonization of GF mice with a gut microbiota originating from an obese human resulted in a substantial increase in total body fat compared with a lean gut microbiota (86). Nonetheless, even though a tremendous body of evidence indicates that the gut microbiota plays a key role in metabolic disorders, it was shown recently that a high-fat diet was able to drive obesity in mice, regardless of the gut microbial composition (87). In addition, a recent meta-analysis demonstrated that the association between the gut microbiota composition found in human feces and obesity is relatively weak (88).

The majority of the composition of the gut microbiota is composed of the phyla Firmicutes (including Lactobacillus, Clostridium, and Enterococcus) and Bacteroidetes (including Bacteroides), with less from the phyla Actinobacteria (Bifidobacteria), Proteobacteria (Escherichia coli), Fusobacteria, Verrucomicrobia, and Cyanobacteria (6, 89). Recently, 2 population-based gut microbiome analysis studies demonstrated that the core microbiota within human populations is considerably robust (90, 91). Nonetheless, distinct compositional differences have been demonstrated in individuals with obesity (14, 16), anorexia nervosa (17–19, 92, 93), and kwashiorkor (20). In regard to obesity, phylum-level changes, such as increased Actinobacteria (14) and Firmicutes and decreased Bacteroidetes, have been reported (84), as well as genus-level changes (16). Notably, the changes in Firmicutes and Bacteroidetes have not consistently been reported (94, 95). Interestingly, anorexia is also associated with decreased Bacteroidetes and increased Actinobacteria and Verrucomicrobia levels (19).

In addition to compositional differences, studies have reported a decrease in gut microbial diversity in obesity (14), and anorexia nervosa (17–19). Interestingly, a recent study reported that weight gain in anorexia nervosa did not result in the recovery of intestinal microbiota composition perturbations, but did lead to increased microbial richness (19). This decreased gut microbial diversity could play a key role in the associated dysregulation of appetite, metabolism, and food-related behaviors. Alcock et al. (27) hypothesized that decreased microbial diversity, which tends to be associated with larger populations of the same species, results in individual species having more energy and resources and a higher capacity for host manipulation, because fewer resources are spent on competition. This, combined with the fact that many microbes are specialized in the use of specific nutrients, may result in the possibility that microbes influence the host to consume their preferred nutrients, or to influence host eating behavior in general (96). This concept is in agreement with the work of Fetissov (28), who showed that bacterial components and metabolites are able to influence intestinal satiety pathways, thus controlling host appetite and satiety.

Key Determinants of the Adult Gut Microbiota Composition in Metabolic and Eating Disorders

Gut microbial composition, especially in early life, is determined by various factors (97, 98). Perturbation of the gut microbiota in the form of severe acute malnutrition during this period is
associated with persistent relative microbiota immaturity (77), and this could also result in alterations in the development of organs, tissues, and/or body systems (99), which may subsequently increase the predisposition to various diseases at an older age (100). Indeed, it is postulated that microbiota immaturity could be causally related to the neurologic abnormalities associated with child malnutrition (100). It is likely that this could also affect the neuroendocrine systems associated with appetite, food intake, and body weight both during this developmental phase and later in life. Notably, perturbation of the gut microbiota by antibiotic exposure during this period increases the risk of being overweight or obese later in childhood (101–104), whereas probiotics have been postulated to have beneficial effects on both offspring at risk of chronic disease and offspring who are healthy (105).

Furthermore, various other factors, such as host genetics and day-to-day diet, play a crucial role (106). In regard to diet, it is important to note that specific nutrients are correlated with an increase in microbes that have the ability to utilize them (107–109). For example, the genus *Bacteroides* is associated with increased consumption of a high-carbohydrate, high-glycemic index diet, as well as with an increased long-term consumption of dietary protein and animal fat (110, 111). Conversely, the genus *Prevotella* is associated with an increased long-term carbohydrate intake (110). *Bifidobacteria* have the capacity to use host-indigestible complex carbohydrates, which subsequently can stimulate their proliferation and metabolic activity (111–113). A recent study also demonstrated that host-microbiome interactions were particularly influenced by nitrogen intake, of which dietary reduction was associated with health (114). It is also interesting to note that consumption of the noncaloric artificial sweetener saccharin alters both gut microbiota composition and functionality, ultimately resulting in glucose intolerance (115). Nutrient-microbe interactions also include more specific food products and bacterial strains. For instance, children in a rural African village in Burkina Faso who are often raised on a polysaccharide-rich diet were found to harbor unique microbes associated with an increased capacity to digest cellulose (116). In addition, the gut microbiota of Hadza hunter-gatherers is more enriched in bacteria associated with the breakdown of dietary fibers, resulting in an enhanced ability to digest and extract nutrients from fibrous plant foods (117, 118). Furthermore, marine bacterial-derived enzymes have been discovered in the gut microbiota of healthy Japanese individuals, which was linked to increased local seaweed consumption (119, 120). It is important to note that specialized taxa can be driven into low abundance from decreased consumption of the nutrients they thrive on, potentially resulting in the extinction of such taxa (121).

The interplay between appetite, metabolism, and gut microbiota is not only restricted to what is being eaten, but is also influenced by when food is consumed, and thus host circadian rhythm. It is long known that the circadian clock facilitates the anticipation of regularly timed periodic events such as food consumption, resulting in optimized energy supply and demand, and thus maximized metabolic fitness (122). The disruption of behavioral and molecular circadian rhythms in diet-induced obese mice suggests that the circadian clock is an important part of understanding the mechanisms behind obesity and other metabolic disorders (123). This disruption is not limited to the host’s endogenous circadian rhythm, but also disrupts the daily oscillations in gut microbiota composition and function (124–126). Interestingly, restricting feeding to a specific period of time (i.e., time-restricted feeding) results in a period of fasting and potentially ketosis and alleviates these cyclical fluctuations in the gut microbiota (125). In addition, time-restricted feeding and fasting reverses numerous features of the metabolic syndrome (125, 127–129).

Overall, there is a growing body of evidence linking the gut microbiota with nutrition, host metabolism, appetite, and circadian rhythm. As such, influencing one of these factors will most likely result in alterations in the others, making the gut microbiota easily accessible and manipulatable for targeting host metabolism and appetite control.

### Gut Microbiota and Its Metabolites as a Therapeutic Target in Host Metabolism and Appetite Control

There are ≥4 primary means by which the gut microbiota can be modulated: 1) the administration of live beneficial bacterial strains (probiotics), 2) the administration of host-indigestible dietary fibers, which undergo bacterial fermentation and subsequently stimulate the growth of certain types of bacteria (prebiotics), 3) the administration of targeted antibiotics, and, finally, 4) fecal microbiota transplantation (Table 1). Both probiotics and prebiotics have already been demonstrated to represent a potent strategy to significantly improve metabolism in overweight and obese individuals (12, 130). Conversely, the effects of pre- and probiotics on undernourished individuals have been relatively poorly studied, even though current evidence indicates that these could improve therapeutic outcomes (26, 140). Rodent studies have demonstrated that probiotic supplementation enhances recovery from starvation (141–143). Nonetheless, much is still unknown about the underlying mechanisms under which pre- and probiotics influence host physiology and behavior. The study of gut microbiota-host interactions is therefore crucial for the development of effective therapeutics targeting the gut microbiota. Since the development of next-generation sequencing-based metagenomics, our understanding of the composition, diversity, and role of the gut microbiota in human health and disease has greatly expanded. However, gut microbial composition provides little insight into the interactions between the microbiota and its host. Research is therefore moving away from just compositional analysis toward a more functional metabolic parsing of microbiota-host interactions (144). In regard to diet and microbiota-gut-brain axis interactions, human brain imaging in particular is a crucial tool to elucidate microbiota-host interactions (100, 145). This approach will help us understand how the microbiota influences brain function, and will likely identify underlying microbiota-gut-brain axis mechanisms (145).

Microbial metabolites can affect host metabolism through a variety of pathways, including direct interactions with the gastrointestinal tract and peripheral tissues (Figure 1). These interactions include influencing host gene expression through epigenetic mechanisms (146), affecting the enteric nervous system and directly inducing vagus nerve signaling (147, 148), altering bile acid signaling (149), and affecting central appetite pathways integrating host energy status (150). It is also worth noting that individual gut microbes can influence the overall gut microbiota composition and its metabolites. Interestingly, this particularly plays an important role in SCFA production through a process called bacterial crossfeeding, wherein one species of bacteria provides nutrients for another species (151). The mechanisms described above are mostly mediated through gut microbial metabolites, which include, but are not limited to, SCFAs (152), bile acids (153), and various neuroactive substances.
One of these gut microbial neuroactives is γ-aminobutyric acid (GABA), which is produced by several *Lactobacillus* and *Bifidobacterium* strains (154). *L. reuteri* is able to produce histamine (155, 156), and acetylcholine is produced by both bacteria and fungi (157, 158). In addition, tryptophan decarboxylase enzymes have been detected in the human gut microbiota, suggesting that the gut microbiota could produce the neurotransmitter tryptamine (159). Furthermore, gut microbial β-glucuronidase activity can increase concentrations of catecholamines as noradrenaline and dopamine (160). Interestingly, close to one-half of the dopamine formed in the human body is produced in the gastrointestinal tract (161). Finally, indigenous spore-forming gut bacteria are able to modulate local and peripheral host serotonin production (162). Much research is still needed to identify how local elevations in the gut of these transmitters can affect host metabolism and even brain function, if, indeed, they can. Interestingly, with regard to serotonin-modulating bacteria, they have been demonstrated to affect host physiology, modulating gastrointestinal motility and platelet function (162).

As for bile acids, the gut microbiota has a dynamic interplay with bile acid metabolism, conversion, and subsequent signaling (149, 163). When food is consumed, primary bile acids stored in the gall bladder are secreted in the duodenum, after which these can be deconjugated by gut microbes (i.e., removal of the glycine or taurine conjugate), preventing reuptake in the small intestine. These deconjugated bile acids subsequently enter the colon and are metabolized into secondary bile acids. At this level, the gut microbiota is able to influence primary bile acid synthesis in the liver, both the deconjugation of these bile acids and conversion into secondary bile acids in the colon (164), and finally the reabsorption of primary bile acids in the ileum (165, 166). The production of bile acids is highly regulated through the nuclear farnesoid X receptor (FXR) by negative feedback inhibition (167), through which bile acids are able to signal as both agonists and antagonists (149). GF and antibiotic studies highlight the importance of the gut microbiota in bile acid metabolism and FXR signaling (168–171), both of which are crucial for host metabolism and appetite (169, 172). In addition, Takeda G protein–coupled receptor 5 is highly expressed in enteroendocrine L cells, which, upon activation, results in the peripheral release of the anorexigenic hormones GLP-1 and PYY (173, 174). As such, enhancing the production of secondary bile acids through the increase of bacterial bile salt hydrolase enzymes results in reduced weight gain, serum cholesterol, and liver TGs (175). It is also interesting to note that bile acids influence gut microbial composition, indicating a bidirectional interaction (149). This is highlighted in FXR-deficient mice, which have an altered microbiota and bile acid composition (169).

The impact of the gut microbiota is not only restricted to the periphery, but can also influence central metabolites. For instance, GF mice have decreased hypothalamic histamine perturbations, and are associated with decreased energy intake, body weight, insulin secretion, and circulating lipids and inflammatory markers.

Prebiotic administration
- Host-indigestible dietary fibers pass through the stomach and small intestine and are subsequently fermented, stimulating the growth of certain types of bacteria.
  - These increase satiety and affect postprandial glucose and insulin concentrations. They also have been inconsistently reported to be associated with decreased energy intake, body weight, insulin secretion, and circulating lipids and inflammatory markers.

Antibiotic administration
- Antibiotics have been the cornerstone for treating infectious disease. They deplete specific gut microbial taxa, depending on the particular antibiotic given, resulting in long-term alterations in gut microbial composition.
  - Prenatal exposure to antibiotics affects birth weight, obesity, and related metabolic sequelae later in life and increases the risk of childhood overweight and obesity when administered at an early age. Antibiotics interfere with the gut microbiota–immune interaction, resulting in immune system perturbations, and are associated with *Clostridium difficile* infection when consumed later in life.

Fecal microbiota transplantation
- This procedure normally is used after antibiotic treatment results in microbiota depletion, or in studies of germ-free animal models, since fecal microbiota transplantation provides an elegant way to demonstrate gut microbial–dependent effects.
  - Transplantation of an “obese” gut microbiota in mice results in a transfer of obesity-associated symptoms; similar results are obtained in studies of kwashiorkor.
reward, addiction, and impulsive choice (32). In addition, the gut microbiota plays a role in the regulation of brain-derived neurotropic factor (180–182), a key player in the support of the survival of existing neurons, the growth and differentiation of new neurons, and the formation of new synapses (183). Regulation of central receptor expression has also been reported. For instance, *Lactobacillus rhamnosus* is able to regulate central GABA receptor expression in a vagus nerve-dependent manner (184), and it was recently shown to increase central GABA concentrations (185). Notably, the role of GABAergic neurotransmission is becoming increasingly recognized in host energy metabolism (186). Thus, bacterial strains producing or altering these neurochemicals could provide a potent therapeutic for neurological diseases, and could most likely play a pivotal role in influencing appetite and energy metabolism via modulation of the CNS (187, 188).

**Gut Microbial SCFAs and Their Impact on Host Appetite and Metabolism**

SCFAs are perhaps the most extensively studied molecules with respect to how the gut microbiota influences host energy metabolism and appetite (Figure 2). Numerous studies have reported that overweight and obese individuals have increased SCFA concentrations (86, 95, 189, 190), even though this is not always consistently reported (191). It is also interesting to note that the previously mentioned second-generation antipsychotic risperidone, known to induce weight-gain in children and adolescents, also increases gut microbial–derived SCFA concentrations (64). Conversely, individuals with anorexia nervosa have been demonstrated to have decreased concentrations of both acetate and propionate (18), which were not altered after weight gain (19). SCFAs are generated by the
fermentation of nonhost-digestible dietary fibers by the gut microbiota and can provide ≤10% of total daily caloric intake (86, 192). As such, the “obese” gut microbiota has an increased capacity for energy harvest through SCFA production (86). Nonetheless, SCFA supplementation tends to result in a reduction in body weight in both humans (193) and rodents (194–196), and ameliorates gut microbial alterations found in mice with diet-induced obesity to a more lean phenotype (196). In addition, GF mice are resistant to diet-induced obesity, and even though they have drastically lower SCFA concentrations (197–199), this has not been attributed directly to SCFA concentrations (197).

Over 95% of gut microbial–derived SCFAs are made up of acetate, propionate, and butyrate (200). With respect to their use as an energy source, butyrate is highly used by colonocytes (201–203), and propionate is primarily used by hepatocytes in the liver (204). As such, only acetate is thought to reach the peripheral circulation at relatively high amounts (205), resulting in a SCFA concentration gradient. In line with this theory are studies investigating SCFA concentrations in human subjects during surgery and sudden-death victims, in whom butyrate and propionate are reported to be in the circulation at 5- to 20-μmol/L concentrations, whereas acetate tends to be within a range of 100–200 μmol/L (205–207). In addition, a recent study demonstrated that systemic availability of colonic-administered acetate, propionate, and butyrate was 36%, 9%, and 2% respectively (208).

**SCFA-induced signaling.** SCFAs have many effects at the cellular level, one of which is the regulation of histone acetylation and methylation, resulting in altered gene expression (209). This is likely mediated through the facilitation of histone acetyltransferase availability and inhibition of histone deacetylase (210–212). In particular, acetate increases histone acetyltransferase availability (213), whereas butyrate is the most potent inhibitor of histone deacetylase classes I and IIa (211, 214). In addition, acetate is converted to acetyl-CoA, after which it is integrated into the citric acid cycle (Krebs cycle), and finally used as a mitochondrial energy source (215). Notably, this increase in cellular energy also boosts the mechanistic target of rapamycin, which is known to be an ATP sensor and thus a homeostatic cellular energy sensor (216).

![Figure 2](https://i.imgur.com/9Q5Q5.png)

**FIGURE 2** Gut microbial–derived SCFAs and their impact on host appetite and metabolism. SCFAs are the product of microbial fermentation in the colon, in which they are able to induce histone deacetylase inhibition, increase histone acetyltransferase availability, increase serotonin synthesis, and activate various GPCRs. Activation of these receptors results in the release of anorexigenic hormones, such as GLP-1 and PYY, into the peripheral circulation. In addition, SCFAs increase concentrations of leptin and insulin. SCFAs are also able to pass through the intestinal epithelium to the portal vein, in which portal nerves express FFA3, where they are able to induce vagus nerve signaling. In regard to their concentrations in the circulation and brain, only acetate reaches high concentrations because of both colonic and hepatic clearance. Nonetheless, propionate is able to induce a decreased anticipatory reward response through currently unknown mechanisms. All these factors cumulatively affect both short- and long-term host energy homeostasis and appetite. FFA2, FFA receptor 2; FFA3, FFA receptor 3; GLP-1, glucagon-like peptide 1; GPCR, G protein–coupled receptor; GPR109A, niacin receptor 1; HAT, histone acetyltransferase; HDACi, histone deacetylase inhibition; Olfr78, olfactory receptor 78; PYY, peptide YY; 5-HT, serotonin.
Locally in the gut, SCFAs are able to enhance colonic serotonin production and secretion (217–219), as well as facilitating the secretion of the anorexigenic hormones GLP-1 and PYY from L cells in the gastrointestinal tract into the circulation (220). These effects are largely mediated through the G protein–coupled receptors (GPCRs) FFA receptor 2 (FFA2/GPR43) and FFA receptor 3 (FFA3/GPR41) (194, 221, 222). The SCFAs receptors FFA2 and FFA3 are also expressed in adipocytes, where they increase the expression and secretion of the anorexigenic hormone leptin in vitro (223–226). Notably, FFA3 expression has not been consistently reported in adipocytes (223, 224, 227). The importance of these receptors was particularly emphasized by a recent study in which it was demonstrated that supplementation with all individual SCFAs, in addition to with a mix of all 3 principal SCFAs, in mice with diet-induced obesity resulted in an attenuation of the obesity-associated decrease in FFA2 and FFA3, which subsequently correlated with various biomarkers of obesity (196). In addition, mice overexpressing FFA2 specifically in adipose tissue remained lean even on high-fat diets, whereas FFA2-deficient mice were obese while on a normal diet (228).

In regard to the nervous system, FFA3 in particular is expressed in the enteric nervous system (229) and vagal afferents (230) and throughout the peripheral nervous system (227, 231). In addition, butyrate is able increase the proportion of cholinergeic enteric neurons through epigenetic mechanisms, indicating that the effects of SCFAs on the nervous system are not limited to neuronal activation (232). Importantly, de Vadder et al. (230) demonstrated that signaling through FFA3 expressed on portal nerves by propionate resulted in increased activity in the dorsal vagal complex, which receives inputs from the vagus nerve and the hypothalamus, a key brain region in the control of appetite and metabolism.

SCFAs have also been reported to exhibit potent immunomodulatory properties (233, 234). These include the regulation of the chemotaxis and inflammation of neutrophils (235–237) and the suppression of inflammatory cytokine production of monocytes and macrophages (238, 239), as well as T regulatory, T helper 1, and T helper 17 cell differentiation and subsequent cytokine production (240–243). Moreover, SCFAs alleviate blood-brain barrier permeability and microglia immaturity in the CNS in GF mice (244, 245). It is important to note that several of these anti-inflammatory effects have also been demonstrated in mice with diet-induced obesity, indicating the multifaceted role of SCFAs in conditions with disordered metabolism and appetite (195, 196).

Even though many of the previously mentioned effects can be induced by all SCFAs, there are distinct differences between the principal gut microbial–derived SCFAs in the manner in which they affect their host that are important to keep in mind: 1) not all SCFAs are increased or decreased to the same extent in different pathophysiological conditions; 2) only acetate reaches the circulation at high concentrations, also resulting in the suggestion that only gut microbial–derived acetate will induce the GPCR signaling of FFA2 and FFA3, whenever SCFAs are required to travel through the peripheral circulation before GPCR activation; 3) only acetate directly increases histone acetyltransferase availability, and butyrate is the most potent histone deacetylase inhibitor, indicating that the effects of the individual SCFAs via epigenetic means might differ; and 4) even though all SCFAs activate FFA2 and FFA3, various GPCRs are specific to 1 or 2 of the principal SCFAs as olfactory receptor 78, which is only activated by acetate and propionate (246), and niacin receptor 1, which is activated by butyrate (247).

**Acetate.** The word acetate comes from the Latin word for vinegar, “acetum,” in which it is very abundant. Other dietary means of increasing endogenous acetate are alcohol consumption (248), and gut microbial production of acetate. The latter is mediated by the acetyl-CoA or the Wood-Ljungdahl pathway (249), after which a part is converted into butyrate by bacterial crossfeeding (250, 251). In regard to the effects of acetate on host metabolism, dietary acetate supplementation in obese mice does not significantly affect cumulative food intake, but does ameliorate body weight gain, TG concentrations, fasting insulin, and leptin (194, 196). This is without affecting fasting glycemia and oral glucose tolerance, all of which were completely restored when either propionate or butyrate were administered (194). In addition, acute oral administration of acetate does not alter GLP-1, PYY, insulin, gastric inhibitory polypeptide (GIP), or amylin concentrations (194). Acute acetate injection does, however, decrease circulating concentrations of FFAs (252), result in appetite suppression, and suppress hypothalamic neuronal activation patterning, as well as inducing a change in the expression profile of regulatory neuropeptides, favoring appetite suppression (253). In addition, acetate infusions into the distal colon of overweight or obese men increase postprandial glucose and insulin concentrations and fat oxidation (254). Interestingly, a recent study showed that rats with diet-induced obesity had an increased whole-body acetate turnover, as well as increased plasma and fecal acetate concentrations (255). It was subsequently demonstrated that acetate increased glucose-stimulated insulin secretion, ghrelin secretion, hyperphagia, and obesity through the parasympathetic nervous system (255). These data indicate that acetate may have a causal role in obesity (256). This is contrary to data demonstrating that acetate could improve metabolic variables associated with obesity (194, 196, 253, 254). As such, Bindels and Leclercq (257) recently discussed the current acetate controversy and stressed the importance of location within the gastrointestinal tract as a contributing factor for the differential effects of acetate on host metabolism (i.e., proximal or distal colon).

**Propionate.** Propionate is widely used in Europe (European food additive codes: E280–E282) as a food additive because of its antifungal properties (258, 259). Its formation by gut microbes is mediated via the succinate, acrylate, and propandiol pathways (260, 261). With respect to its effects on host metabolism, dietary propionate supplementation ameliorates body weight gain, oral glucose tolerance, TG concentrations, and fasting insulin and leptin in mice (194, 196). In addition, acute oral administration increases GIP, insulin, and amylin without significantly altering PYY and GLP-1 (194). This could be due to the fact that oral propionate would most likely not reach the colon, where PYY- and GLP-1–containing L cells are located. This is in line with the fact that intracolonic administration of propionate does result in increased concentrations of PYY and GLP-1 in the circulation (222). Furthermore, acute administration of inulin-propionate ester, which delivers propionate directly to the colon, leads to an increase in plasma propionate, PYY, and GLP-1, and a decrease in energy intake and appetite compared with inulin alone in healthy adults (193, 262). This intervention also decreases caudate and nucleus accumbens activity, indicating that colonic propionate could attenuate reward-based eating behavior via striatal pathways. However, this study did not detect any alterations in GLP-1, PYY, or serum propionate, which were found in the former study (263). This does indicate that the observed effects on caudate and nucleus accumbens activity were independent of GLP-1 and
PYY and are more likely mediated through currently unknown mechanisms. Long-term supplementation for 24 wk with this inulin-propionate ester in overweight adults did not significantly affect overall body weight, but did result in decreased body weight gain, without altering basal PYY and GLP-1 concentrations (193). As such, these conflicting results call into question the therapeutic potential of propionate in the regulation of metabolism and host appetite, and further research is warranted.

**Butyrate.** Butyrate, which is infamous for its strong smell of rancid butter and milk (264), has its etymologic roots in the Greek word for butter. Butyrate is also widely known for its potent histone deacetylase inhibitory effects, which, combined with its ability to cross the blood-brain barrier, has resulted in butyrate being studied extensively as a neuropharmacologic agent (at somewhat supraphysiologic doses) to investigate epigenetic mechanisms in brain and behavior research (265). Nonetheless, research performed on butyrate from this perspective has limited relevance to the effect of gut microbial–derived butyrate, with many of the studies being focused on the administration of acute, systemic, and high doses. The production of butyrate by gut microbes is mediated through the enzyme butyryl-CoA:acetate CoA transferase (266). Interestingly, both this enzyme and butyrate have a diurnal variation, which is ablated in mice with diet-induced obesity (126). This also appeared to be the case for the less-pronounced diurnal variation of propionate, whereas no variation at all was demonstrated for acetate (126). In regard to butyrate’s effect on host metabolism, dietary butyrate supplementation ameliorates body weight gain, TG concentrations, oral glucose tolerance, and fasting insulin, as well as leptin in mice (194, 196). In addition, acute oral administration increases GIP, insulin, amylin, PYY, and GLP-1 (194). Oral administration of tributyirin, a TG that contains 3 butyryl moieties, reduces body weight gain in mice with diet-induced obesity, likely because of increased energy expenditure, which is accompanied by an attenuation in glucose and insulin tolerance (195).

The fact that obesity and metabolic syndrome seem to be associated with increased SCFA concentrations (86, 95, 189, 190), whereas supplementation with SCFAs tends to decrease acute food intake and markers associated with these disorders (193–196), highlights the fact that much is still unknown about the role and impact of SCFAs on long-term energy homeostasis and metabolism. In addition, much is still unclear about the mechanisms in which gut microbial–derived SCFAs can influence host appetite and metabolism. In particular, the impact of SCFAs in peripheral nervous system signaling remains largely understudied. Nonetheless, current evidence indicates that SCFAs represent a potential therapeutic strategy for diseases with alterations in metabolism and appetite.

**The Interplay between Gut Microbiota and the Immune System on Host Appetite and Metabolism**

Gastrointestinal barrier functionality and permeability are highly affected by the gut microbiota (267). This barrier not only regulates the absorption of nutrients, electrolytes, and water, but also prevents toxic substances and pathogens from entering the circulation from the lumen, which makes intestinal barrier functionality a crucial player in the influence of the gut microbiota on its host (268). Barrier function and permeability are affected by several stimuli, including pathogens, commensal bacteria, and bacterial products (267, 269). Low-level translocation of substances or microbes across the tight junctions of these luminal antigens is normal and shape a proper adaptive immune system (270). Nonetheless, excessive intestinal permeability, often colloquially referred to as “leaky gut,” is associated with the development of low-grade chronic inflammation and sepsis, in which inflammatory mediators are thought to exacerbate intestinal permeability (271). Interestingly, decreased intestinal permeability has been reported in individuals suffering from anorexia nervosa (272), whereas increased intestinal permeability has been observed in obesity (273, 274) and protein-energy wasting (for in-depth discussion see (275)). Of note, SCFA supplementation has been demonstrated to improve deficits in intestinal permeability (276–278). Obesity-associated increases in intestinal permeability can lead to an increased translocation of Gram-negative bacterial-derived LPS into the circulation, resulting in chronic low-grade systemic inflammation (273, 279, 280), in a condition called metabolic endotoxemia (281–283). Interestingly, administration of the antibiotics ampicillin and neomycin decreases cecal LPS content and metabolic endotoxemia in both mice with diet-induced obesity and ob/ob mice, further emphasizing the role of the gut microbiota in metabolic endotoxemia (284).

Increased intestinal permeability can facilitate the translocation of gut microbial metabolites into the peripheral circulation. Some of these gut microbial metabolites have a structure similar to the host’s own molecules that is divergent enough to be recognized as foreign by the host’s immune system, in a phenomenon known as molecular mimicry (285).

Various gut microbes have the capacity to produce protein sequences of ≥5 amino acids that share a sequence that is identical to various appetite-regulating peptides, and can thus trigger the production of Ig (286, 287). Ig has the ability to reduce the rate of degradation of gut-derived hormones and neuroendocrine factors, which was demonstrated to be the case for the orexigenic hormone ghrelin (288), or can initiate an autoimmune response. Co-administration of the hunger hormone ghrelin, together with IgG from obese individuals or ob/ob mice, increased food intake in rodents, whereas IgG from anorectic patients or control animals did not (288). In addition, GF rats have increased concentrations of IgG directed at the orexigenic hormone ghrelin, and decreased concentrations of IgA directed at the anorexigenic neurotransmitter agonist-related peptide and the anorexigenic melanocyte-stimulating hormone (MSH) (286).

Moreover, a rat model of intestinal inflammation and anorexia induced by the chemotherapeutic agent methotrexate has been reported to have decreased concentrations of α-MSH IgG, which likely plays a role in observed changes in food intake and body weight (289). Acute administration of α-MSH IgG results in increased food intake (290), even though long-term effects may actually potentiate α-MSH-mediated signaling (291). Importantly, E. coli, a prominent inhabitant of the gut microbiota, is able to produce a small protein sequence and antigen-mimetic of α-MSH called caseinolytic protease B (ClpB) (290, 292, 293). ClpB is elevated in a variety of eating disorders associated with inadequate food intake (i.e., anorexia nervosa, bulimia nervosa, and binge-eating disorder), and its concentrations have been correlated with various psychopathologic traits (294). Interestingly, E. coli produces relatively more ClpB in the stationary phase of proliferation than in its exponential growth phase, indicating that E. coli induces a more potent anorexigenic effect whenever nutrients for E. coli stabilize. In addition, systemic administration of E. coli in the stationary phase also...
increases c-Fos expression in POMC neurons of the arcuate and ventromedial nucleus of the hypothalamus generally associated with decreased food intake (293). Notably, this study harvested E. coli proteins by means of centrifugation, meaning that the observed effects were not necessarily ClpB-mediated (293). Nonetheless, the administration of ClpB-producing E. coli results in a short-term reduction in body weight and food intake compared with the administration of ClpB-deficient E. coli (290). In addition, ClpB induces neuronal firing in POMC neurons in the arcuate nucleus of the hypothalamus, which is associated with a decrease in food intake (293). It is also worth noting that female rats exhibit increased concentrations of and affinity for α-MSH IgG in response to acute oral E. coli administration, whereas males had increased α-MSH IgM concentrations indicating sex-specific differences (292).

The Gut Microbiota in Host Nutrient and Taste Sensing

The ability to sense and taste nutrients throughout the gastrointestinal tract plays a crucial role in the maintenance of nutrient balance, the rewarding aspects of consuming food, and the identification of spoiled food. Interestingly, animal models have demonstrated that specific signaling mechanisms affect the responsiveness of different tastes (i.e., sweet, bitter, salty, sour, and umami). As such, modulation of these signaling mechanisms by gut microbes could influence the host to eat specific nutrients, therefore increasing their food substrates and survival. One can therefore expect that individuals with eating disorders have an altered taste responsiveness corresponding with their phenotype. Indeed, obesity is associated with a lowered responsiveness to sweet and fatty tastes, resulting in a shift toward liking foods with higher concentrations of these tastes (295). In addition, individuals with anorexia nervosa have impaired taste perception (296, 297), which has been shown to improve with weight gain (298, 299).

Signals conveying taste are detected by taste receptor cells on the tongue that are subsequently transmitted through the solitary tract into the thalamus, signaling to other brain regions (300, 301). These taste receptor cells also express the anorexigenic hormones GLP-1, PYY, and cholecystokinin, indicating a peripheral signaling pathway via gastrointestinal hormone secretion, resulting in decreased appetite (302–305). Interestingly, PYY knockout mice have a decreased behavioral response to both fat- and bitter-tasting compounds (306). Subsequent reconstitution of salivary PYY concentrations in these mice improves their response to fat, but not bitter taste (306). In addition, higher concentrations of circulating TNF-α, insulin-like growth factor 1, and leptin have been detected in individuals with increased taste-responsiveness, indicating that these particular circulating hormones could play a role in taste perception (307).

To our knowledge, few studies have investigated the role of the gut microbiota in host nutrient and taste sensing. A recent study by Lyte et al. (308) demonstrated with the use of the selectively bred occidental low- and high-saccharin-consuming rat model that rats innately more prone to saccharin consumption have a gut microbiota composition that is different from those less prone to saccharin consumption. In addition, studies in GF mice suggest that the gut microbiota is able to influence taste receptors and, subsequently, taste. For instance, an increase in intestinal sweet taste receptors, such as type 1 taste receptor 3, α-gustducin, and sodium-glucose luminal transporter 1, as well as increased sucrose preference, has been reported in GF mice (309). Furthermore, GF mice have an increased oral preference for and expression of lingual FA translocase (CD36), but decreased intestinal expression of the FA receptors GPR40, FFA3, FFA2, and GPR120, indicating decreased fat signaling (310).

Current knowledge about the impact of the gut microbiota on nutrient and taste sensing and, thus, gustatory function suggests that these effects could be modulated through the immune system by affecting the continual supply of differentiated taste-receptor cells. These cells are essential in the detection of taste compounds and transmit subsequent signals either directly or indirectly via taste bud cells, resulting in oral taste perception (301, 311). Continual supply of differentiated taste receptor cells is crucial for normal taste function, and disruption of this supply can be detrimental to taste signaling (312). Activation of the immune system results in decreased cell renewal and lifespan in both taste receptor and taste bud cells on the tongue (313–315), which is potentially mediated through mammalian toll-like receptors and type-I and -II IFN receptors, as these are localized in taste cells (314–316). Several studies furthermore have pointed to the involvement of immune system functionality in taste. For instance, IL-10–knockout mice have a reduced number of taste buds and taste receptor cells and have an increased inflammatory response to LPS-induced inflammation (317). In addition, TNF-knockout mice have a decreased response to various bitter compounds, but not to other tastes (318).

Interestingly, systemic administration of the bacterial-derived toxin LPS results in an inflammatory response in the tongue, combined with decreased taste cell lifespan and decreased taste preference (313, 314, 319–323). Furthermore, prolonged oral LPS administration in mice results in decreased sweet taste receptor expression and a decreased response to sucrose (324). Notably, LPS administration also results in sickness behavior, which includes both anhedonic and anxiogenic components, and it could therefore be a confounding factor when investigating behavior in vivo (325, 326). However, LPS administration decreases c-Fos expression in the lingual taste epithelium, indicating that there is local inhibited cellular activity (314). In addition, subcutaneous injection of LPS to the ventral surface of the tongue results in leukocyte recruitment and inhibits sodium-induced taste signaling via the chorda tympani, a primary sensory afferent nerve (327). Cumulatively, these results indicate that the gut microbiota could influence host nutrient and taste signaling, and thus gustatory function, through immune system regulation, of which LPS is a potential mediator.

The Microbiota-Gut Brain Axis in Eating-Related Behavior

It is highly likely that other eating-related behaviors besides gustatory function are influenced by the gut microbiota and its metabolites. Although direct links with the gut microbiota have not been investigated extensively yet, it is likely that olfactory function, food-related cognitive processing, food-related impulsivity and compulsivity, and the social aspects of food intake are susceptible to microbiome regulation. Interestingly, the gut microbiota has recently been hypothesized to play a key role in addiction (328), which could have particular relevance to the controversial concept of food addiction. In addition, the gut microbiota has already been linked to cocaine use in mice (329).
and alcohol-dependence in humans (330). It is also interesting to note that the administration of the principal psychoactive constituent of cannabis, Δ⁹-tetrahydrocannabinol, alleviates the high-fat diet-induced increases in fat mass and body weight that are associated with an altered gut microbiota, although it is unclear whether the altered gut microbiota composition in conjunction with Δ⁹-tetrahydrocannabinol treatment played a causative role in this reduction in fat mass and body weight (331). Overall, much is still unknown about the role of the gut microbiota in food addiction, and other eating-related behaviors in particular, and additional research is warranted for a more comprehensive picture of the role of the gut microbiota in eating-related behavior.

The Microbiota-Gut-Brain Axis in Metabolic and Eating Disorder Comorbidities

Eating and metabolic disorders are often associated with other behavioral comorbidities, such as anxiety and depression (35, 36), and it is thus conceivable that there is a strong bidirectional interplay between these behaviors. It is therefore also likely that microbes or microbial-derived metabolites that affect these food-related behaviors will invariably alter the host's appetite and metabolism (Figure 1). Importantly, the influence of the microbiota-gut-brain axis is also becoming increasingly recognized in behaviors such as anxiety and depression (37, 38, 144, 332–334). As such, findings in regard to anxiety, stress, depression, sociability, and other behaviors are pivotal for a comprehensive understanding of eating and metabolic disorders. Importantly, a recent study indeed demonstrated that the gut microbiota composition and diversity in individuals with anorexia nervosa at inpatient admission is correlated with levels of depression, anxiety, and eating disorder psychopathology (17). In addition, many food-related behavioral findings in regard to the microbiota-gut-brain axis are often mediated through pathways similar to the ones involved in gut microbiota interactions with host metabolism and appetite, including modulation of the immune system (37), vagus nerve signaling (184, 335), and the production of neurochemicals (336).

Conclusion

It is clear that the gut microbiota is a key regulator of host appetite and metabolism. However, the majority of research has been focused on obesity and its comorbidities. As such, less is known about other disorders wherein appetite and metabolism are dysregulated, such as binge-eating disorder, drug-induced obesity, cachexia, anorexia nervosa, and infant malnutrition. Nonetheless, mechanisms in which the gut microbiota influences the host’s appetite and metabolism are being elucidated at a rapid rate, providing a better understanding of its role in disorders with both a positive and negative energy balance. Such information will be crucial for elucidating in which instances alterations in gut microbiota composition and function are causative, or merely correlative, because many studies up until now have only identified associations. In this article, we have portrayed many of these direct and indirect mechanisms. Gut microbes are able to secrete various substrates and metabolites, affecting appetite- and metabolism-regulating systems and the host’s ability to sense and taste nutrients, as well as eating-related behaviors and other behavioral comorbidities. This information, cumulatively contributing to a greater understanding of the gut microbiota and its metabolites in appetite and energy metabolism, will therefore ultimately result in better therapeutic strategies for obesity and eating disorders.

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