The brain-gut-microbiome axis modulation of food intake in health and in obesity: Links beyond the 16S rRNA

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ABSTRACT

Obesity is a global health threat affecting a large number of individuals living in the Latin America region. Gut-microbiota (GM) is a major regulator of the energy homeostasis in health and in obesity. This review attempts to summarize some of the most relevant information about mechanisms mediating interactions between the GM and the host’s brain-gut axis in the regulation of appetite and ingestive behaviors. This paper goes beyond the data on obesity-related changes in GM composition to describe some of the microbial-derived products that are directly or indirectly involved in modulating the signaling from and to the enteroendocrine cells, the enteric nervous system and vagus nerve to the brain centers in charge of regulating hunger, satiety and ingestive behaviors. Momentous progress has been achieved in this field in the past few years, and these advances carry the promise of innovative ways to prevent and to treat obesity. (NeuroGastroLatam Rev. 2019;3(3):137-150)

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INTRODUCTION

The worldwide prevalence of obesity almost tripled between 1975 and 2016, with more than 1.9 billion adults being overweight and 650 million adults being obese\(^1\). Accordingly to a recent report by the Pan American Health Organization, overweight affects 58% and obesity 23% of the people inhabiting the Latin American and Caribbean regions\(^2\). While genetics plays an important role in obesity development; a shift toward more sedentary lifestyle combined with an easy access to cheap, highly palatable and fattening foods are the pivotal factors determining the current worldwide obesity epidemics\(^3\)\(^-\)\(^5\).

STUDYING THE HUMAN GUT-MICROBIOTA (GM)

After the initial sequencing of the human microbiome in 2001, enormous progress has been achieved in our understanding of the human microbiome thanks to newer and more accessible techniques to study the DNA/RNA. The new technology allowed not only for the characterization of the human microbiome taxonomy but also to infer their functional capabilities (metagenomics)\(^6\)\(^-\)\(^8\). Despite the advances in high-throughput approaches, collectively referred to as next-generation sequencing (NGS). The great majority of the published data so far, have used targeted 16S rRNA NGS to describe GM composition and diversity. However, this
technique suffers from poor resolution below the bacterial genus level, therefore, it is not possible to differentiate between closely related species. Furthermore, the lack of standardization of the methodologies used for DNA extraction, including the type of primers used, contributes to a concerning high variability and discrepancy in the findings between studies. Third-generation sequencing and shotgun metagenomic sequencing (SMS) may resolve some of the problems inherent to the use of NGS for metagenomics analysis. These newer techniques carry the promise of obtaining a higher/deeper resolution in the taxonomic analysis of the GM and in the case of SMS, and the ability of identifying non-bacterial members of the ecosystem, including fungus and viruses. However, they are more expensive than NGS and they require higher complexity levels of bioinformatic analysis limiting their use by a greater number of researchers.

Studying the human GM has shown to be especially challenging. Indeed, several studies have revealed an immense inter-individual variability in GM composition, even within pairs of adult mono- and dizygotic twins\(^9,10\). For example, in a study of concordant lean and obese female twins, Turnbaugh et al. found that no single, identifiable abundant (defined as representing > 0.5% of the microbiota) bacterial species were shared by all individuals participating in the study\(^9\). The use of metagenomics to study not only the taxonomy but also the function of the GM carries the promise to find possible mechanisms of interaction between the GM and the host, but it also shares some of the limitations mentioned above, and it requires to have libraries of reference genomes to compare the obtained data to. Metabolomics or metabolic profiling is a more promising tool that has been used recently for investigating the crosstalk between the GM and the host through bioactive metabolites. Studies in germ-free animal models have revealed an extensive metabolic interplay between the GM and the host. This interplay includes a large number of metabolites found only in the blood of conventionalized mice suggesting that they arise only from the GM\(^11,12\). In addition, the presence of the GM significantly altered in the host serum levels of a number other important metabolites including neuroactive products such as serotonin and tryptophan\(^12\).

This review will give an overview of the role of the interactions between GM and the host in the regulation of appetite and possible pathways of microbial regulation of ingestive behaviors in health and in obesity. Several other mechanisms linking diet, GM, and obesity have been the object of extensive research (among them, white fat regulation, lipid, and carbohydrate absorption, liver metabolism, and circadian rhythm) and are beyond the scope of this review.

**THE BRAIN-GUT-MICROBIOME AXIS (BGM)**

The BGM consists of the central nervous system (CNS), the hypothalamic-pituitary-adrenal axis, the autonomic nervous system, the enteric nervous and neuroendocrine systems, the vagus nerve, and the GM. The delicate and precise regulation of many homeostatic processes is determined by a constant bidirectional interplay between the different systems comprising the BGM, and as in the case of the regulation of the appetite, and body weight, the BGM also receives key input from other organs including the adipocytes and
the skeletal muscle. Enteroendocrine cells (EEC) play an important role in gut chemosensing the lumen content to coordinate appropriate responses to a variety of stimuli ranging from nutrients, food degradation products, toxic chemicals, microorganisms, and microbial products. A great deal of homeostatic information of the BGM travels through vagal innervation, which provides afferent and efferent information to regulate the gastrointestinal (GI) secretions and motor function, appetite and ingestive behaviors, visceral sensations, and immune responses.

Studying the modulatory effects of the GM over local and distal organs function is challenging but intriguing. The Human Microbiome Project has provided important information about the structure and function of the human GM and, as a result, has expanded our appreciation for the microbial ecosystem that resides within the human intestinal tract. This system is comprised microorganisms such as bacteria, archaea, fungus, and viruses that are distributed throughout the entire GI tract, achieving greater diversity and concentrations in the colon. Despite the progress obtained in the past few decades in technology aimed to integrate high-output omics, so far we have only a glimpse into the complex interactions between GM and host in health and in disease.

**REGULATION OF BODY WEIGHT, INGESTIVE BEHAVIORS, AND APPETITE**

The regulation of homeostatic food intake by the CNS depends on a delicate balance between contemporaneous afferent homeostatic signals from the GI tract, from signals from adipose tissue, and from skeletal muscle. For example, leptin, an adipocyte-derived hormone, results in long-term decreases in food intake through the activation of G protein-coupled receptors (GPCRs) receptor (Ob-R) present on afferent visceral nerves, in the nucleus of the tractus solitarius (NTS) and the hypothalamic arcuate nucleus (ARC). At the ARC one group of neurons releases orexigenic peptides, neuropeptide Y (NPY), and agouti-related protein (AgRP), while other group releases anorexigenic peptides, pro-opiomelanocortin (POMC), and cocaine- and amphetamine-regulated transcript (CART). Both NPY/AgRPergic and POMC/CARTergic neurons express high levels of the main form of the leptin receptor, the ObRb consequently, high levels of leptin result in decreased levels of NPY and AgRP. To regulate short-term, meal-to-meal food intake, vagal afferents work in conjunction with the EECs to convey information on visceral mechanic and chemical stimuli to the brain. For example, several peptides, such as cholecystokinin (CCK), peptide YY (PYY), and glucagon-like-peptide-1 (GLP-1), are released by ECCs in response to presence of nutrients in the GI tract lumen and work at the hypothalamus at the ARC to induce satiation and stop food intake by inhibiting the release NPY and AgRP. Ghrelin, a gut peptide released, in response to food deprivation, is the main hormone involved in the generation of hunger, and inducing food intake by stimulating the release of NPY and AgRP, and by enhancing the rewarding aspects of food consumption. Gut peptides are released by EEC and signal the CNS centers through vagal afferents, or directly through release into the blood stream. For more information on appetite-related gut hormones, their actions and interactions with GM are shown in table 1.
An additional layer to the regulation of eating behaviors is the reward aspect of food intake that include the processing of the sensory properties of food including appearance, taste, palatability, and reward value with interoceptive memories of previous food ingestion generating a multidimensional food-related experience which ultimately determines the ingestive behavior. The rewarding aspects of food result from dopamine release at the nucleus accumbens (NAcc) and ventral tegmental area (VTA). Certain foods, particularly those rich in sugars and fat, are more rewarding than others. The combination of the rewarding value of the food and a weak impulse control by the prefrontal cortex can result in over-eating (eating that is beyond the energetic needs), trigger learned associations between the stimulus and the reward, and result in altered eating behaviors.

### ROLE OF THE BGM IN THE REGULATION OF INGESTIVE BEHAVIORS AND APPETITE

Although a lot of interest has been placed in studying the interactions between host and GM in the regulation of body weight and appetite, there is still much to learn. A well-known pathway of regulation of appetite by the gut hormones involves the production of short-chain fatty acids (SCFA) by the GM, table 1. In preclinical studies, the diet administration of fermentable complex carbohydrates contained in fiber resulted in an increased number of L cells in the intestine, elevated GLP-1 and PYY secretion and an enhanced response to leptin; suggesting mechanisms by which GM could modulate appetite through modulating the release of these gut peptides. In both preclinical and clinical studies, administration of fiber prebiotics was linked to decreased adiposity, decreased energy intake, and with changes in neuronal signaling at the hypothalamus and NTS consistent with satiety as well as with decreased intestinal permeability and inflammatory markers. SCFA stimulate GLP-1 release from enteric L-cells through stimulation of the G protein-coupled free fatty acid receptor (FFAR). In a clinical study, the delivery of high doses of propionate, a SCFA, to distal GI tract resulted in decreased food intake and weight gain over a 24-week period. Furthermore, SCFAs have shown to affect the brain reward processes related to food cues: a recent study in healthy men showed that an acute increase in

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**Table 1.** Gut hormones in appetite regulation and their interactions with the GM

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Released by</th>
<th>Stimulated by</th>
<th>Main effects</th>
<th>Interactions with GM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCK</td>
<td>Intestinal L-cells</td>
<td>Fat and proteins</td>
<td>↑ satiety</td>
<td>↓ by SCFA and tryptophan or ↑ by indole</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Intestinal L-cells</td>
<td>Macronutrients</td>
<td>↑ satiety, ↓ gastric emptying, incretin effect, ↓ food reward</td>
<td>↑ by SCFA and tryptophan or ↓ by SCFA</td>
</tr>
<tr>
<td>PYY</td>
<td>Intestinal L-cells</td>
<td>Macronutrients</td>
<td>↑ satiety</td>
<td>↑ by SCFA and bile acids</td>
</tr>
<tr>
<td>GIP</td>
<td>Intestinal K-cells</td>
<td>Macronutrients</td>
<td>Incretin effect</td>
<td>↑ by SCFA</td>
</tr>
<tr>
<td>Amylin</td>
<td>Pancreatic beta cells</td>
<td>Macronutrients</td>
<td>↑ satiety, ↓ gastric emptying, incretin effect, ↓ food reward</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Gastric X/A-like cells</td>
<td>Fasting</td>
<td>↑ hunger, food intake, ↑ food reward</td>
<td>↓ by SCFA or ↓ by antibiotics</td>
</tr>
</tbody>
</table>

GM: gut microbiota; CCK: cholecystokinin; SCFA: short-chain fatty acids; GLP-1: glucagon-like-peptide-1; BCAA: branched-chain amino acids; LPS: lipopolysaccharides; GIP: glucose-dependent insulinotropic peptide; PYY: peptide YY.
production of propionate by GM lead to a decreased brain response to highly palatable food pictures at regions involved in reward-processing, and this reduction in reward activation was associated with reduced food intake23.

Preclinical studies showed that SCFAs (butyrate and propionate) were associated with beneficial effects on weight control and glucose tolerance through regulation of genes involved in intestinal gluconeogenesis either by direct induction of these genes, in the case of butyrate; while propionate acted through FFAR3 signaling from the periportal nervous system that fed into a gut-brain-gut neural circuit to regulate enterocyte gluconeogenesis24.

Other less well-studied bacterial products that have shown to modify appetite regulation include byproducts of amino acid fermentation, biliary acids, and components of the bacterial membrane. Indole is a microbial intercellular signaling molecule that plays an important role in the regulation of bacterial physiology and inter-kingdom communication. In short term, indole induces local release of GLP-1 by the host’s enteric L-cell, resulting in vagal stimulation and meal stop, while in long exposures indole tends to decrease GLP-1 secretion25,26. Secondary biliary acids also play a role in appetite regulation, directly, by activating brain centers in charge of regulating appetite or indirectly by stimulating GPCRs such as FFAR2 and FFAR3 on vagal and spinal afferents27,28. Both Bacteroides intestinalis and Bacteroides fragilis and Escherichia coli are involved in the generation of secondary bile acids in the colon. The presence in portal circulation of lactate, a microbial metabolite produced by Lactobacilli, Enterobacteriaceae, and Bifidobacteria from fermentable carbohydrates, was associated with reduced meal size29.

THE ROLE OF THE BGM AXIS IN OBESITY

The importance that the GM plays in the development of obesity was highlighted as a result of pivotal studies by Turnbaugh et al. and by Ridaura et al., showing that the obesity phenotype could be transmitted via GM transplantation and did so independently from genetic factors30,31. Multiple studies have shown that obesity and metabolic syndrome are associated with changes in the GM composition and function or the so-called dysbiosis. It is clear that GM diversity is reduced in obesity, and this change precedes, even by decades, the obesity onset, and furthermore, the presence of dysbiosis could predict the development of insulin resistance and weight gain9,31,32. Strikingly, the introduction of single strains into germ-free mice, including Lachnospiraceae strain AJ110941, Enterobacter cloacae B9, and Clostridium ramosum resulted in an increased propensity to develop obesity33-35. Many members of the GM have been associated with the obesity phenotype; however, there is a noticeable lack of consistency between different studies. In contrast, a couple of GM members have been consistently identified as having protective properties against obesity and metabolic syndrome, including the Faecalibacterium prausnitzii, the Akkermansia muciniphila, and the family Christensenellaceae32,36,37.

Interactions between diet and GM function in obesity

Diet is a major factor that can shape gut the microbiota structure and function and determine host’s health38,39. In humans, consumption of a fiber-rich diet was associated with
increased GM diversity and abundance, while diets high in simple carbohydrates and fat were associated with reduced GM diversity; remarkably, this diet-generated dysbiosis was transmitted over generations\textsuperscript{40,41}. In USA based diet, the GM displays enrichment of enzymes involved in the degradation of amino acids; as well in the degradation of simple sugars while in Malawian/American diet, glutamate synthase, and alpha-amylase were overrepresented when compared to the USA based diet\textsuperscript{39}. Diets rich in fat and sucrose like the western diet have a rapid and profound effect on GM composition resulting in decreased diversity even before obesity and metabolic syndrome are developed\textsuperscript{42-44}. Diet-induced changes in amino acid pathways and their microbial metabolite profiles precede and predict the development of obesity and metabolic syndrome\textsuperscript{44,45}. Microbial derived products and cometabolites such as Trimethylamine N-oxide, and phenylacetylglutamine and hippurate were able to predict the development of obesity and insulin resistance in rodent model of diet-induced obesity (DIO)\textsuperscript{45}. Likewise, caloric-restriction partially and temporarily improves GM diversity, reduces obesity measures and lowers pro-inflammatory markers\textsuperscript{46}. This close interplay between diet and GM makes very difficult to tease out how much of the changes in body weight and metabolic pathways are determined mainly by diet or by GM alone.

Currently, there is only fragmented but compelling evidence of the role of the BGM in the development and maintenance of obesity and metabolic syndrome. As mentioned above, attempts to identify specific GM members associated with human obesity have been disappointing. However, there is strong evidence that some bacterial-derived products interact with the host’s metabolic pathways and may result in obesity and metabolic syndrome in the host. For example, studies in large human cohorts have shown association between higher blood levels of aromatic amino acids (AAA) and branched-chain amino acids (BCAA) with insulin resistance and metabolic syndrome\textsuperscript{47-50}. Moreover, elevated plasma concentrations of BCAA, phenylalanine, and tyrosine were early predictors of diabetes onset in humans\textsuperscript{51,52}. Insulin resistance has been associated with GM displaying an increased potential for lipopolysaccharide (LPS) and BCAA biosynthesis and reduced potential for BCAA transport into bacterial cells and methanogenesis\textsuperscript{53}. BCAA not only regulate the protein metabolism by the skeletal muscle and peripheral insulin resistance but they also regulate the release of gut hormones (leptin, GLP-1, and ghrelin) that can affect food intake and body weight\textsuperscript{54}. Elevated glutamate levels are associated with obesity and the administration of \textit{Bacteroides thetaiotaomicron}, a glutamate fermenting bacteria, prevented weight gain in a DIO mouse model, underscoring a link between diet, GM, amino acids profiles, and weight regulation\textsuperscript{55}. In addition, glutamate has shown to decrease production of GLP-1 by enteric L cells\textsuperscript{56}.

**BGM regulation of appetite and ingestive behaviors in obesity**

Although obesity is a multifactorial disease, several disruptions in the control of eating behaviors play a major role in obesity development. For example, obese subjects display a greater drive to consume highly palatable foods compared with normal-weight subjects\textsuperscript{57,58}. 
Large population cohorts have shown that weight gain is associated with high scores for uncontrolled eating and consumption of larger amounts of highly palatable, rich in fat processed foods. Furthermore, impulsivity has a larger effect on obesity development than genetic factors such as the fat mass and obesity-associated gene. Alterations in dopamine (D2 and D4) receptors at the level of the striatum and prefrontal cortex have been associated with greater impulsivity and hedonic eating in children and adults. In obesity, abnormal dopamine pathways activation within brain reward areas by highly hedonic foods overrides satiety signals and results in hedonic hunger and food overconsumption independently from caloric needs or hunger levels.

The BGM plays a pivotal in the regulation of the appetite and ingestive behaviors involved in homeostatic control of energy intake and on reward oriented ingestive behaviors, figure 1. Studying the role of GM in modulating their host’s complex behaviors such as in the case of eating behavior and food preferences is very challenging. Transplantation of altered GM...
was sufficient to result in hyperphagia (and metabolic syndrome) in the germ-free recipients; while in another study, the administration of a commercially available probiotic reduced weight gain and food intake in a DIO model\textsuperscript{72,73}. The GM could affect appetite and ingestive behaviors in obesity through several mechanisms, including, among others, microbial products that can modulate the release of satiety signals by EECs and afferent vagal signaling; neuroinflammation causing hypothalamic resistance to satiety signals, and modulation of food-reward responses. Although there is limited information in this field, this review will attempt to summarize some of the more compelling data.

**GM and disruption of EEC and vagal signaling in obesity**

In rats, chronic consumption of high-fat-diet (HFD) results in higher energy intake and elevated blood levels of bacterial products, including LPS than low-fat-fed controls\textsuperscript{74}. This chronic increase in LPS is associated with increases in cytokines and other inflammatory markers in the adipose tissue, liver, and muscle and it is known as “metabolic endotoxemia.” The effects on body weight and insulin resistance of the “metabolic endotoxemia are mediated by toll-like receptor 4 (TLR-4; the pattern recognition receptor for LPS). The hyperphagia seen in HF diet is mediated by desensitization of vagal afferent neurons to the effects of nutrients, leptin, and gut satiety hormones such as CCK as a response to metabolic endotoxemia\textsuperscript{75,76}. Similarly, other, bacterial products, such as lipopeptide (bacterial lipopeptide) and flagellin, interact with TLRs located at the EECs, modulating the secretion of satiety-related gut hormones\textsuperscript{77}. Acetate, another SCFA, increased ghrelin secretion and subsequent food intake through activation of parasympathetic pathways\textsuperscript{78,79}.

Microbial products could also directly affect the energy balance. Using metagenomics, it has been shown that the “obese GM” had an increased capacity for energy extraction from the diet, specifically from indigestible dietary polysaccharides, and that the transplantation of this microbiota resulted in increased adiposity in germ-free recipients\textsuperscript{31}. The metagenomics analysis of this obese microbiome showed that the major end products of fermentation were SCFA (butyrate and acetate). Energy-starved germ-free mice are characterized by hyperphagia, elevated number of L-cells, and GLP-1 levels, all of which were reduced after being colonized with fiber-fermenting bacteria\textsuperscript{80}.

**GM and hypothalamic neuroinflammation in obesity**

Obesity is associated with resistance to satiety signals following food intake resulting in hyperphagia\textsuperscript{17,81-85}. HFD and obesity are linked to neuroinflammation at the level of the hypothalamus. Leptin and insulin work together at the hypothalamus to regulate adiposity and work synergistically at the NPY/AgRPergic and POMC/CARTergic neurons at the ARC to decrease food intake. In HFD, the increased circulating LPS activates proinflammatory pathways through TLR4/MyD88, resulting in activation of the microglia cells at the hypothalamus and leading to insulin and leptin resistance. Several
pathways have been implicated in this hypothalamic dysfunction. Both tumor necrosis factor-α and the consumption of fat-rich diets can induce the activation of the serine-kinase JNK in hypothalamic cells. Activated JNK targets insulin receptors reducing their ability to respond to insulin, resulting in increased food intake\textsuperscript{84,85}.

More support of the central role of GM in the development of neuroinflammation came from a study that showed that the transplantation of HFD microbiota resulted not only in disruption of the intestinal barrier and increased circulating LPS but also in brain neuroinflammation in the non-obese mouse recipient, underscoring that the brain neuroinflammation was related to GM alterations and not to the obese phenotype\textsuperscript{86}. Recently, it was shown that interactions between macrophages and brain microglia were critical for the development of HFD-induced hypothalamic inflammation and the resulting hyperphagia\textsuperscript{87}. There is also evidence of ongoing communication between microglia and the host’s GM, for example, the use of pre- and probiotics downregulated HFD induced microglia activation and neuroinflammation and improved brain function\textsuperscript{88}.

**The reward value of food and the GM**

It is difficult to study the BGM in humans, especially when focusing on linking GM to complex behaviors such as food preferences and the reward value of food cues. Obese subjects characteristically display an enhanced preference for highly palatable-high-energy foods, higher scores in food craving scales, and lower inhibitory control over impulsive eating behaviors than lean subjects\textsuperscript{89,90}. Obesity is also associated with abnormal functional responses in core brain areas that process the reward and sensory aspects of food, including the NAcc, the amygdala (AMY), the insula, and the VTA. Notably, a preliminary clinical study showed an association between GM composition, measures of obesity, and obesity-related alterations in brain microstructure at regions of the extended reward networks, including the hypothalamus, caudate nucleus, and AMY\textsuperscript{91}. The hedonic aspects of food are mediated by the release of dopamine at the mesolimbic and mesocortical dopamine pathways. Serotonin, endogenous opiates, as well as GABA modulate dopamine levels in the brain reward pathway. Amazingly, bacteria have the capacity to synthesize many neuroactive products, and the host relies on GM for many of the neurotransmitters and precursors of these neurotransmitters. For example, preclinical studies showed that the host’s serotonin levels more than double, and neuroactive AAA concentrations increased significantly after germ-free mice were colonized by GM\textsuperscript{11,12}. Indeed, several neurotransmitters or their precursors such as serotonin, GABA, dopamine, and tryptophan are produced and/or released by members of the GM. These bacteria include, among others, *Bifidobacterium infantis* 35624, *Streptococcus thermophilus*, *Bacillus cereus*, *Lactobacillus plantarum*, *E. coli*, *Lactobacillus rhamnosus*, *Serratia marcescens*, *Proteus vulgaris*, and *Staphylococcus aureus*\textsuperscript{92}. Our own exploratory data in obese women undergoing bariatric surgery showed significant associations between post-operative weight loss, improved appetite, and reduced preferences for highly palatable foods with changes in
GM and in microbial-derived metabolites, including indole, phenolic products, and glutamate\textsuperscript{93,94}. Likewise, our group showed in an exploratory study in healthy volunteers with normal to high body mass index (BMIs) that fecal microbial metabolites were associated with brain connectivity at the NAcc, specifically indole, which was also associated with BMI and indirectly with food addiction scores\textsuperscript{95}.

Another interesting aspect is the regulation of GI taste receptors by the GM. For example, germ-free mice displayed an increased concentration of intestinal sweet taste receptors, such as type 1 taste receptor 3, $\alpha$-gustducin, and sodium-glucose luminal transporter 1 and an exaggerated preference for high-sucrose solutions\textsuperscript{96}. GM composition differed in rodents with high versus low preference for saccharin consumption phenotypes independently of the saccharin intake thus suggesting a diet-independent interaction between saccharin preference and the GM\textsuperscript{97}. Germ-free mice also display an exaggerated preference for fats that were associated with increased concentrations of taste receptors in the tongue and altered EEC in ileum and colon when compared to normal mice\textsuperscript{98}. Additional evidence for a role of GM in modulating complex feeding behaviors such as food preferences was found in a study that showed that the GM determined host’s feeding preferences to achieve a balance between beneficial microbial acquisition and nutritional needs in a Drosophila melanogaster model\textsuperscript{99}.

In a clinical study, subjects with a preference for chocolate displayed different metabolic profile than subjects that were “indifferent” to chocolate; remarkably differential metabolism of AAA was involved and specifically a microbial cometabolite, phenylacetylglutamine from the tyrosine pathway, was a major marker for “chocolate desire”\textsuperscript{100}.

**CONCLUSIONS**

The crosstalk between GM and the host’s brain gut axis is currently one of the most exciting areas of scientific research. The GM is able to secrete a wide range of substrates and metabolites that directly or indirectly modulate brain regulation of appetite and eating behaviors. Despite the considerable progress that has been made in recent years in the understanding of several metabolic pathways used by GM to communicate with the EECs, the enteric nervous system and the brain in health and in obesity; still our current knowledge is fragmented, it lacks consistency in the findings and there are significant gaps in methodological approaches to assess interactions within the BGM. We should aim for studies in larger populations and also control for important dietary, environmental and host’s factors that deeply modulate the GM function to get a clearer picture of the role that the BGM plays in body weight and appetite regulation and in the onset of obesity.

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