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Review

Industrialized diets modulate host eating behavior via the microbiome–gut–brain axis

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The gut microbiome is an important participant in the gut–brain axis and a key mediator of host–diet interactions that shape feeding behavior. These effects occur through microbial metabolism of dietary components – fiber, sugar, fat, and protein – into bioactive metabolites that influence microbiome–gut–brain signaling. Industrialized diets are enriched in highly processed, energy-dense foods characterized by elevated fat and sugar content and reduced fiber content. These diets have been implicated in altered eating behaviors involving the microbiome–gut–brain axis. We propose that different ratios of dietary substrates in industrialized diets perturb the microbiome–gut–brain axis, thereby driving changes in microbial metabolite production and downstream signaling with behavioral consequences. Integration of microbiome and neuroscience methodologies will help to delineate the causal mechanisms by which diet shapes interoceptive signaling and eating behavior.

Highlights

Gut microbes interact with dietary components – fiber, sugar, fat, and protein – and produce metabolites that influence host eating behavior.

The microbiome–gut–brain axis facilitates bidirectional communication between gut microbes and the brain to regulate host eating behavior through neural, hormonal, and immune pathways.

Industrialized diets shape the gut microbiome in ways that promote inflammation, impair satiety signals, and heighten reward responses, thus creating feedback loops that may drive overeating and potentially contribute to metabolic disorders.

Elucidating the contributions of the microbiome–gut–brain axis will enable us to better understand the ecological levers that shape ingestive behavior, and will reveal potential avenues for the treatment of metabolic disorders and psychopathologies of eating.

The industrialized diet remodels microbial metabolites and eating behavior

The **gut–brain axis** (see Glossary) differentially senses ingested nutrients – fiber, sugar, fat, and protein – and transmits information about nutritional, energetic, and satiety status to the brain to orchestrate feeding behavior [1]. Such behaviors include foraging when hungry and cessation of ingestion when satiated. This system maintains energy homeostasis by integrating chemical and mechanical cues from the gastrointestinal tract through specialized sensory pathways [2,3] (Boxes 1 and 2). In conjunction with this axis, the **gut microbiome** – a diet-sensitive and highly plastic community of microorganisms that reaches its highest density in the colon, along with their collective genes and products – plays a key role in host nutrition by metabolizing these dietary substrates into bioactive compounds [4–6]. Given its responsiveness to diet and metabolic capacities that far exceed our own, the gut microbiome is well positioned to influence gut–brain signaling and, in turn, feeding behavior. However, the dietary sensitivity of the gut microbiome may be a double-edged sword: following evolutionary conditions of relatively low energy availability, industrialization has produced an extraordinary abundance of energy-dense and readily digestible foods. The **industrialized diet** contains altered proportions of fiber, sugar, fat, and protein [7,8], and relies on extensive processing that increases nutrient digestibility in the small intestine [9]. These alterations raise the possibility that the industrialized diet may disrupt this microbially mediated nutrient-sensing network to drive altered eating behavior and energy imbalance. If so, these diet–microbiome interactions may contribute a hidden layer of signals to epidemics linked to industrialized lifestyles – including disordered eating and metabolic disease – that are largely unaccounted for in existing models.

The industrialized diet (which we refer to interchangeably as the ultra-processed diet and Western diet) comprises highly processed foods, refined carbohydrates, and increased abundances of animal products and saturated fats [8]. This diet has introduced a dramatic change in the substrates that the gut microbiome encounters, with implications for host eating behavior. Compared to both modern non-industrialized and ancestral (e.g., Paleolithic) diets – which are markedly

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Box 1. Chemosensory encoding of diet-derived macronutrients

Glucose sensing occurs within the portal-mesenteric system, where metabolic cues are encoded via vagal and spinal afferents. Vagal neurons that detect glucose metabolism in the hepatic portal vein relay signals via the nodose ganglion to the nucleus of the solitary tract and reinforce sugar preference by modulating dopamine release in the striatum [1]. A parallel portal vein–spinal axis ensures robust nutrient signal encoding [113]. This dual afferent network highlights the importance of sugar detection in feeding regulation.

Detection of a glucose deficit, however, engages a vagus-independent mechanism. The area postrema of the nucleus of the solitary tract circuit is a central hub for sensing **glucoprivation**, and there is evidence that vagotomy does not abolish glucoprivic feeding, whereas lesioning this circuit eliminates this response [114]. This suggests that glucose deficit detection likely relies on central glucoreceptors or spinal afferents. In addition, glucose suppresses Agouti-related peptide (AgRP) neurons through a vagus-independent pathway, supporting the involvement of other interoceptive mechanisms [115].

Lipid sensing, by contrast, shows a strict dependence on vagal afferents. Lipoprivic feeding responses are abolished by vagotomy, demonstrating that lipid metabolism deficits must be communicated via gut–brain signaling rather than by direct central detection [114]. Duodenal fat also requires vagal input to suppress AgRP neurons, and this reinforces the importance of vagal signaling [115]. One key mediator is oleoylethanolamide, a lipid-derived molecule synthesized in the proximal intestine that binds to peroxisome proliferator-activated receptor alpha (PPARα) receptors and modulates striatal dopamine signaling [116], possibly via vagal afferents projecting to the area postrema of the nucleus of the solitary tract. A chronic high-fat diet disrupts oleoylethanolamide signaling, thus weakening gut–brain communication and blunting fat-derived dopamine release, a maladaptive response that may drive compensatory overeating. Instead of acting as simple reinforcers, sugar and fat signals engage overlapping but distinct circuits; their co-occurrence amplifies dopamine release and promotes overconsumption beyond caloric requirements [1].

Protein-derived signals engage both vagal and non-vagal pathways, depending on protein form and physiological context. Hydrolyzed proteins such as peptones activate gut chemoreceptors and trigger cholecystokinin (CCK) release that stimulates vagal afferents [51] and activates gut–brain signaling involved in appetite regulation. This effect is abolished by vagotomy or CCK1 receptor blockade, confirming vagal dependence [117]. By contrast, intact proteins appear to regulate feeding via vagus-independent feedback, likely through plasma amino acid sensing or hepatic afferents [118]. Hepatoportal sensors detect circulating amino acids in a dose-dependent manner [119]. Under amino acid deficiency, vagal sensor sensitivity increases ~100-fold, thus amplifying compensatory drive [120]. This liver-centered mechanism enables dynamic regulation of protein intake based on nutrient availability.

variable both within and across populations [10] but typically less processed, higher in fiber, and lower in refined sugars and saturated fats – this shift represents a significant reconfiguration of macronutrient composition [11]. These changes offer a useful reference for assessing how dietary transitions influence microbial ecology and host physiology.

The composition of dietary components is a primary driver of gut microbiome structure and function [9]. Across both human cohorts and experimental animal models, distinct macronutrient profiles consistently elicit specific microbial and metabolic responses [12,13]. For instance, a controlled human feeding study showed that two isocaloric diets with matched macronutrient ratios, but differing in fiber content and processing, produced markedly different microbial profiles, fermentation activity, and host energy availability [14]. The reorganization of dietary substrates in the industrialized diet reduces the availability of fermentable compounds that are essential for maintaining a diverse and resilient microbial community [15]. Moreover, because the gut microbiome is known to influence various host processes such as immunity [16], metabolism [4], neurotransmission [17], and endocrine status [18,19], major dietary changes could alter the metabolic output of the gut microbiome [20,21], with cascading effects on host physiology and behavior.

Our primary aim in this Review is to integrate the gut microbiome into current models of gut–brain communication shaping feeding behavior. To this end, we examine how the microbial metabolism of fiber, sugar, fat, and protein generates bioactive **metabolites** that influence satiety, reward, and nutrient-seeking behaviors, and consider how industrialized diets may alter these patterns. The general hypothesis we develop is that dietary metabolites generated by the gut microbiome may potentiate the health consequences of an industrialized diet (Figure 1). We

Glossary

Colonization factor: a gene or molecular component that enables a microbe to establish and maintain residence within a host environment by supporting functions such as nutrient acquisition, adhesion, and resistance to host defenses or microbial competition.
Dysbiosis: an imbalance or shift in the composition of the gut microbial community that is typically associated with lower biodiversity, less resilience, and impaired microbiome function.
Eating disorders: complex psychiatric conditions marked by abnormal eating behaviors that disrupt physical and emotional well-being.
Ecological plasticity: the capacity of a microbial community to adapt to environmental changes – such as shifts in diet, host physiology, or antibiotic exposure – by altering its composition, functional potential, or metabolic output while maintaining ecological persistence.
Fermentability: the capacity of dietary fiber to be metabolized by gut microbes into bioactive compounds through fermentation. Fermentability depends on molecular structure, and specific features selectively enrich for microbial strains equipped to degrade them in the competitive colonic environment.
Glucoprivation: a physiological state characterized by insufficient glucose availability for cellular metabolism, particularly in the brain, that triggers compensatory responses such as increased food intake or activation of counter-regulatory hormonal pathways to restore energy balance.
Gut–brain axis: the bidirectional communication network that links the gastrointestinal tract and the central nervous system through neural, hormonal, and immune pathways, and integrates gut-derived signals with brain-regulated processes such as appetite and energy balance.
Gut microbiome: the collection of microorganisms (including bacteria, viruses, fungi, and other eukaryotes) that inhabit the gastrointestinal tract, together with their genes and gene products.
Industrialized diet: a dietary pattern dominated by ultra-processed foods, refined sugars, and saturated fats that replace typically fiber-rich, whole-food ingredients. Such diets fundamentally alter nutrient availability to the gut microbiome and disrupt host metabolic and behavioral regulation. The term is

Box 2. Mechanosensory encoding of gastric distension

Mechanosensation provides an additional layer of gut–brain signaling that can convey gastric distension and meal size independently of nutrient composition. Vagal sensory neurons expressing oxytocin receptors function as mechanosensors that respond to gastric and duodenal stretch and relay mechanical signals to the nucleus of the solitary tract [121]. These mechanosensitive afferents influence circuits governing satiety and energy balance, and their activation suppresses food intake and induces a torpor-like state characterized by reduced energy expenditure and heightened hypothalamic–pituitary–adrenal (HPA) axis activity. Beyond vagal pathways, spinal afferents also transmit mechanosensory signals, with dorsal root ganglion-mediated pathways conveying GLP-1-mediated gastric relaxation to the lateral hypothalamus [55].

However, mechanosensory pathways do not operate in isolation; instead, they interact with chemosensory inputs from enteroendocrine cells [122,123]. For example, serotonin-producing enterochromaffin cells, which are known to respond to luminal irritants, also contribute to gut motility and accelerate intestinal transit to aid in toxin clearance [122]. Furthermore, glucagon-like peptide-1 (GLP-1)- and CCK-releasing cells, which slow gastric emptying [122], may work in concert with vagal mechanosensors to prolong satiety. This crosstalk between nutrient-derived and mechanical signals fine-tunes feeding behavior, encouraging adaptive responses to varying meal compositions.

By integrating chemosensory inputs from nutrient composition with mechanosensory signals encoding gastric distension, the afferent arm of the gut–brain axis ensures that feeding behavior is dynamically regulated based on both the metabolic and mechanical properties of ingested food [121–123]. The convergence of vagal and spinal afferent pathways in the brainstem allows finely tuned modulation of appetite and energy balance. Alongside these neural pathways, enteroendocrine cells serve as an integrative hub that translates luminal nutrient signals into hormonal and neural outputs that shape gut motility and feeding behavior, thereby further refining the interoceptive control of energy homeostasis.

then consider how the microbial metabolism of industrialized diets intersects with chronic low-grade inflammation and **eating disorders**, both of which are enriched in industrialized societies.

Microbe-derived metabolite profiles from industrialized diets govern host eating behavior

Diet outweighs genetic influences in shaping gut microbiome composition and function [22,23], which typically exhibit high **ecological plasticity** [9,24]. The influence of diet on the composition and function of the gut microbiome is readily observable in studies comparing plant-based versus animal-based diets [25], Mediterranean versus Western diets [26,27], rural African high-fiber versus urban European diets [28,29], and cooked versus raw diets [30]. The sensitivity of the gut microbiome to diet make it both an important marker and target when considering how industrialized lifestyles affect

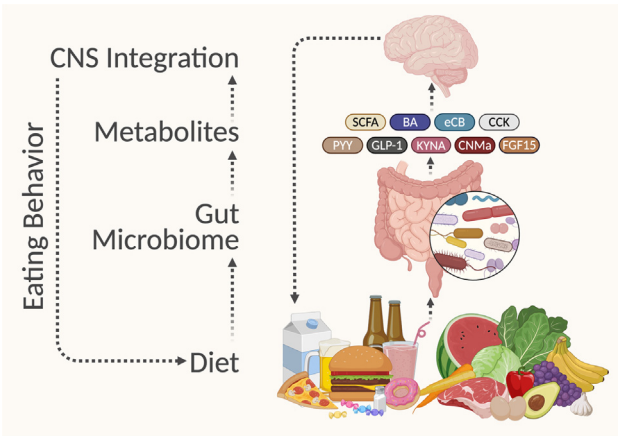

Figure 1. Diet-driven modulation of the microbiome–gut–brain axis may reinforce dysfunctional eating behavior. Diet shapes the gut microbiome, which in turn influences the production of bioactive microbial metabolites such as short-chain fatty acids (SCFAs), bile acids (BAs), endocannabinoids (eCBs), and gut peptides [e.g., CCK, peptide YY (PYY), GLP-1]. These molecules act on gut–brain pathways to modulate nutrient sensing and feeding behavior. Industrialized diets rich in fat, sugar, and processed ingredients and low in fiber shift gut microbial metabolism away from homeostatic signals and toward reward-enhancing and proinflammatory outputs. These metabolic shifts engage the neural circuits that govern appetite and reward and may therefore promote overeating and reinforce dietary patterns that perpetuate microbiome dysbiosis. This feedback loop provides a mechanistic framework linking industrialized diets to altered food preferences and disordered eating. Abbreviations: CNMa, CNMamide; FGF15, fibroblast growth factor 15; KYNA, kynurenic acid. Figure created with BioRender.

used interchangeably with Western and ultra-processed diets in this Review.

Metabolic burden: the physiological strain that arises when nutrient intake or metabolism exceeds the capacity of the body to efficiently process and eliminate byproducts, potentially leading to toxicity, disrupted homeostasis, or reduced fitness.

Metabolites: small molecules that function as intermediates or end-products of metabolism, some of which act as signaling molecules to regulate enzyme activity, gene expression, and cellular processes such as nutrient sensing, immune activation, and differentiation.

Microbiome–gut–brain axis: an extension of the gut–brain axis that incorporates the gut microbiome as an active participant in bidirectional communication between the gastrointestinal tract and the brain, thereby influencing host behavior, appetite, and physiology.

Protein leverage theory: a framework proposing that humans and other animals regulate total food intake to achieve a target level of protein consumption. When dietary protein is diluted by excess fats or carbohydrates, individuals overconsume energy to meet protein needs, potentially contributing to obesity in modern diets.

individual health. In particular, the shift to an industrialized diet may exert significant compositional and functional changes on the gut microbiome of relevance to eating behavior.

Compared to many non-industrialized diets, the industrialized diet is characterized by sharply reduced quantities of fiber, coupled with elevated quantities of sugar, fat, and protein [10]. The gut microbiome primarily metabolizes the fraction of these host-consumed nutrients that resist digestion in the small intestine, producing a wide array of bioactive small-molecule metabolites that distinguish the industrialized diet from other diets [31]. Across both animal model studies and human studies, diet emerges as the central determinant of gut microbial ecology, reshaping not only community composition but also the genomic, transcriptomic, and metabolomic programs that mediate microbe–host interactions [24,32]. Metabolites generated by the gut microbiome upon exposure to dietary substrates include short-chain fatty acids (SCFAs), amino acid metabolites, modified bile acids, and neurotransmitters [33], with their production dependent on macronutrient availability in the lumen [31]. These metabolites alter the local gut environment, fecal and plasma metabolome profiles, and systemic energy regulation, among other effects on host physiology [34]. Crucially, these metabolites interact with peripheral and central neurons to affect host eating behavior. Table 1 and Figure 1 provide overviews of how gut microbial metabolism of dietary substrates generates bioactive metabolites that influence neural circuits involved in appetite regulation and feeding behavior. In the following sections, we describe microbial interactions with each of the main dietary components.

Dietary fiber

Industrialized diets are distinguished by their relatively low fiber content and relatively high levels of refined carbohydrates. This profile of dietary substrates fosters a microbial environment that promotes proinflammatory and reward-sensitive metabolic pathways at the expense of those that promote satiety and metabolic balance [35–37]. The extent to which dietary fiber shapes the gut microbiome depends on its **fermentability**: fermentable fibers (e.g., inulin) more strongly modulate microbial composition and activity, whereas non-fermentable fibers (e.g., cellulose) are minimally metabolized and contribute little to the energy pool of the host [38].

Cellulose, although it is capable of inducing intestinal distension, is relatively metabolically inert and elicits minimal SCFA production or growth of beneficial taxa *in vitro* [39]. Although it can activate vagal signaling, its effects are weaker compared to those of metabolically active nutrients such as fats and sugars [1]. Interestingly, microbial fermentation capacity may influence host food preferences: a recent study found that mice prefer dietary fibers that their resident microbes cannot ferment relative to fibers they can ferment [40]. Thus, fermentability may govern not only microbial and metabolic outcomes but also behavioral responses to dietary fiber.

Fiber-rich meals induce acute changes in gut motility, gastric emptying, and enteroendocrine signaling [41]. These effects unfold across distinct temporal scales. In the short term, fiber consumption increases satiety through gastric distention and delayed nutrient absorption, thus reducing meal size [42]. Over days to weeks, sustained fiber intake reconfigures microbiome composition and metabolic signaling pathways [34], enhancing enteroendocrine hormone secretion [43] and leading to persistent alterations in appetite regulation and energy homeostasis [44]. Chronically, high-fiber diets are associated with lower energy intake and body weight regulation [45].

The fermentation of dietary fiber is also the principal source of SCFAs (chiefly butyrate, acetate, and propionate) [38]. SCFAs have emerged as important modulators of gut–brain communication and have significant relevance for eating behavior [46]. Butyrate suppresses food intake by engaging vagal afferent neurons, reducing activity in the nucleus of the solitary tract and dorsal

vagal complex, and inhibiting neuropeptide Y (NPY)-expressing orexigenic neurons in the hypothalamus. The appetite-suppressive effects of butyrate require vagal nerve integrity because vagotomy abolishes this response [47]. Acetate and propionate also exert significant anorexigenic effects when administered intraperitoneally [48,49]. In fasted mice, systemic SCFA injections lead to a dose-dependent reduction in food intake, with butyrate displaying the most potent effect, followed by propionate and acetate [48]. Mechanistically, this SCFA-induced appetite suppression is mediated by vagal afferent neurons because both capsaicin-mediated vagal denervation and vagotomy abolish these effects [48]. Furthermore, vagal afferent neurons express genes encoding free fatty acid receptors (*ffar2*, *ffar3*) through which SCFAs exert their effects, providing an avenue for microbial metabolites to regulate host feeding behavior independently of classical enteroendocrine signaling pathways [50].

Table 1. Microbial metabolism of dietary substrates and effects on host eating behavior

Substrate	Microbe-mediated product/target	Mechanism	Putative effect on host eating behavior	Refs
Fiber	SCFAs	Activates vagal afferent neurons	Suppresses appetite	[47,48]
		Engages hepatic branch of vagus nerve	Exerts anorectic effects	[48]
		Fructan-utilizing microbes produce acetate, which activates arcuate hypothalamic neurons and conditions host dietary preference	Favors consumption of non-fermentable carbohydrates over fermentable ones	[40]
	CCK	Activates CCKAR-expressing vagal neurons that respond to multiple nutrients	Drives preference for sugar, fat, and amino acids	[2,106]
	GLP-1	Activates GLP-1R-expressing vagal neurons	Exerts anorectic effects	[55,56]
	PYY	Activates FFAR2 (free fatty acid receptor 2) on colonic enteroendocrine L cells to increase PYY secretion	Exerts anorectic effects	[61]
Sugar	*roc* gene	Suppresses fiber-degrading *B. thetaiotaomicron* and alters colonization dynamics	Potentially reduces SCFA production and promotes appetites	[68]
	Immune cell population	Promotes loss of Th17-inducing commensals, leading to Th17 cell depletion and increased lipid absorption	Suppresses immune-derived satiety signaling, potentially increasing food intake	[69]
	Vagus nerve	Induces endotoxemia and promotes vagal afferent withdrawal	Potentially impairs satiety signaling	[70]
Protein	Amino acids	*Acetobacter pomorum* and lactobacilli mimic amino acid sufficiency	Suppresses protein appetite in the context of essential amino acid deprivation	[77]
	CNMamide	Microbes producing essential amino acids suppress CNMamide expression	Blunts compensatory appetite for essential amino acids	[78]
	Kynurenic acid	Loss of *F. prausnitzii* reduces and restoration rescues luminal KYNA levels	Reduces preference for highly palatable foods and decreases binge-like intake	[80]
	Tryptophan	Herbivory-conditioned microbiome shifts tryptophan metabolism toward biosynthesis	Reduces voluntary carbohydrate intake	[79]
	Tyrosine/Tyramine	*Providencia* converts tyrosine into tyramine, which is transformed by the host into the neurotransmitter octopamine	Decreases olfactory aversion and increases preference for food sources containing *Providencia*	[82]
Fat	Bile acids	Reduces microbial transcription of genes important for secondary bile acid biosynthesis (e.g., K00076, K07007)	Facilitates dysregulated eating behavior	[99]
		Activates lipid sensor GPR119 in enteroendocrine cells	Promotes satiety and decreases dietary fat consumption	[100]
		Microbial 7α-dehydroxylation converts cholic acid (CA) to deoxycholic acid (DCA), which activates TGR5 on vagal afferent neurons	Promotes satiety signaling and reduces food intake	[92]
		Dietary cholesterol promotes bile acid release, activating intestinal FXR to induce FGF15/19 expression	Suppresses exploratory locomotor activity in response to hunger or environmental cues	[124]
	Endocannabinoids	Unsaturated fat increases jejunal anandamide and 2-arachidonoylglycerol, enhancing local endocannabinoid signaling	Promotes preference for unsaturated fats over saturated fats	[107]

SCFAs not only act directly on vagal afferents but also stimulate enteroendocrine cells to release hormones that modulate feeding behavior and energy homeostasis through activation of the G protein-coupled receptor FFAR2 (GPR43) on enteroendocrine L cells. Among these, CCK, GLP-1, and PYY are key regulators of gut–brain signaling and satiety (Figure 2).

CCK influences feeding behavior through its action on vagal neurons [51,52]. CCK induces anorectic effects via vagal afferent fibers, and vagotomy abolishes these effects, highlighting its causal role in acute satiety [53]. Microbe-derived propionate stimulates CCK expression in the ileum and cecum by directly upregulating *Cck* mRNA and peptide levels in enteroendocrine cells, both *in vitro* and *in vivo* [54]. CCK shapes nutrient-specific preferences, including the

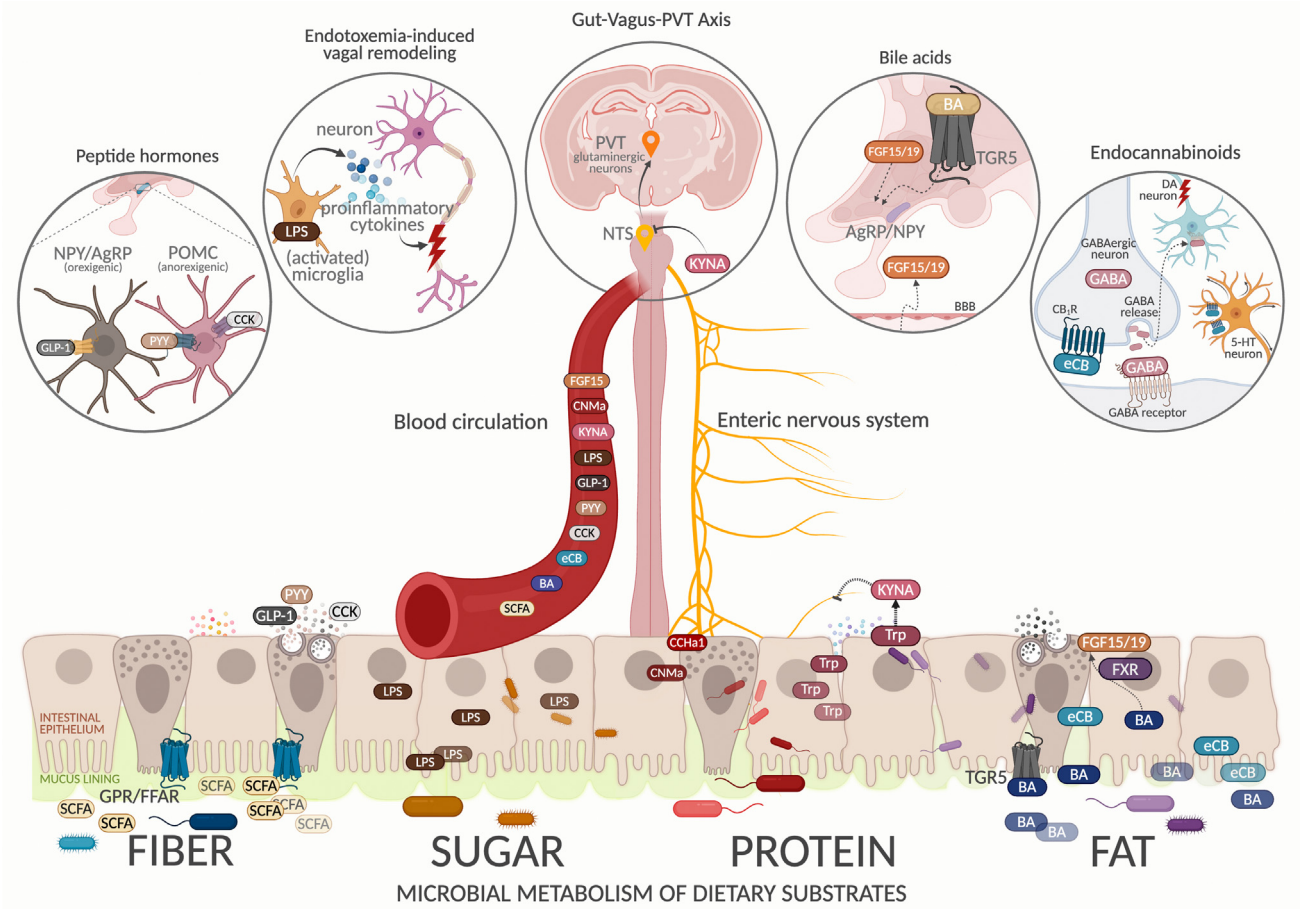

Figure 2. Microbial metabolism of dietary substrates governs host eating behavior. We illustrate the differential microbial metabolism of dietary fiber, sugar, protein, and fat, and the subsequent effects on neural circuits that regulate appetite and feeding behavior. Fiber-derived metabolites, including SCFAs, as well as SCFA-induced gut peptides like GLP-1 and PYY, enter the systemic circulation and interact with afferent pathways along the gut–brain axis, thereby affecting host appetite. Sugar metabolism produces lipopolysaccharides, which can lead to endotoxemia, vagal remodeling, and altered eating behavior. Protein-derived metabolites such as tryptophan, tyramine, and kynurenic acid, as well as other gut-derived neuropeptides, modulate neural pathways involved in satiety and reward-based eating. Fat metabolism generates bioactive bile acids and endocannabinoid-like molecules which play roles in the regulation of feeding behavior through interactions with the endocannabinoid system and higher-order brain structures. Abbreviations: AgRP, Agouti-related peptide; BA, bile acid; BBB, blood–brain barrier; CB_1R, cannabinoid receptor 1; CNMa, CNMamide; DA, dopamine; eCB, endocannabinoid; FFAR, free fatty acid receptor; FGF15/19, fibroblast growth factor 15/19; FXR, farnesoid X receptor; GPR, G protein-coupled receptors; 5-HT, 5-hydroxytryptamine (serotonin); KYNA, kynurenic acid; LPS, lipopolysaccharide; NTS, nucleus of the solitary tract; PVT, paraventricular nucleus of the thalamus; TGR5, Takeda G-protein-coupled receptor 5; Trp, tryptophan; POMC, pro-opiomelanocortin-expressing neurons; LPS, lipopolysaccharide; CCHa1, CCHamide1. Figure created with BioRender.

development of fat preference [2]. Intragastric fat infusion activates distinct vagal neuron populations, and CCK serves as a crucial transmitter in this circuit [2]. Blockade of CCK signaling abolishes vagal responses to sugar, fat, and amino acids and prevents the development of post-ingestive preference for these nutrients, demonstrating that CCK is essential for nutrient-driven appetitive behavior [2]. However, fat preference can still emerge via a parallel CCK-independent gut–brain circuit, highlighting the existence of both general nutrient-sensing and fat-specific pathways in preference formation [2]. Dietary fiber intake enhances microbial fermentation and promotes CCK release, linking dietary fiber to gut–brain signaling via microbial activity.

GLP-1 is another key regulator of appetite and glycemic control that acts through GLP-1 receptor-expressing (GLP1R) vagal afferents [55–57]. These neurons densely innervate the stomach and small intestine – specifically the duodenum and jejunum – and project to the nucleus of the solitary tract where they integrate satiety-related signals [56]. GLP1R-expressing vagal afferents mediate the anorexigenic and metabolic effects of GLP-1, reducing food intake and enhancing glycemic control by promoting glucose uptake in peripheral tissues [58]. The necessity of this pathway is demonstrated by lentivirus-mediated knockdown of GLP1R in vagal afferents, which abolishes GLP-1-induced meal size reduction and postprandial glycemic improvements [59]. Endogenous GLP-1 also exerts its effects via an alternative enteric–sympathetic circuit by acting locally on ileal neurons, which project to abdominal sympathetic ganglia to regulate gastric motility and appetite suppression [55]. Both GLP-1 and PYY, a gut-derived hormone that contributes to satiety and energy balance, are modulated by microbe-derived SCFAs, which acutely stimulate their secretion via FFAR2 on colonic L cells [60]. Upon chronic exposure, SCFAs also enhance PYY output by expanding the L cell population through FFAR2/PAX4-dependent differentiation [61]. Similarly, PYY3–36 exerts its anorectic effects by binding to Y2 receptors on vagal afferents, which relay inhibitory signals to the arcuate nucleus (ARC), reducing neuropeptide Y (NPY) expression and promoting the activation of pro-opiomelanocortin (POMC) neurons [62]. Consumption of dietary fiber drives SCFA production by colonic microbes, positioning it as a key regulator of GLP-1- and PYY-mediated gut–brain signaling.

Although interactions between microbe-produced SCFAs and enteroendocrine hormones shape satiety and energy homeostasis, microbial metabolism of dietary fiber may also shape host food preferences through alternative pathways. Initial evidence for a microbial role in dietary selection derives from fiber-supplementation studies showing that inulin shifts food preference toward fat over sugar, and this change correlated with distinct microbial profiles, including increased abundance of *Oscillospiraceae* spp., *Bacteroides acidifaciens*, and *Clostridiales* spp. [63]. This shift, however, lacks mechanistic resolution, leaving open the question of whether these effects are attributable to diet-induced changes in microbiome composition, SCFA production, or other aspects of microbial metabolism. Nevertheless, studies in a controlled gnotobiotic model reinforce the idea that bacterial metabolic activity causally conditions host dietary choices [40]. Colonization of mice with *Bacteroides thetaiotaomicron* or *Bacteroides ovatus*, which selectively ferment distinct fructans into SCFAs, shifts host preference away from fermentable fructans and toward non-fermentable fructans – and this effect was abolished when microbial fructan metabolism was disrupted by targeted deletion of the *susC/D* genes involved in polysaccharide uptake [40]. This study demonstrates that gut microbial metabolism of dietary fiber influences host food choice, but whether these altered dietary preferences confer benefits for the host remains unclear.

Complementing these murine findings, human studies provide preliminary evidence that gut microbial fermentation of fiber influences neural processing of food-related cues [64,65].

Supplementation with inulin-type prebiotic fiber in overweight adults has been shown to alter brain activation patterns in response to high-calorie food stimuli [65]. Specifically, fMRI analysis showed that prebiotic supplementation reduces activation in brain regions associated with reward valuation, such as the ventral tegmental area and orbitofrontal cortex [65]. Although these neural shifts did not directly translate into changes in food intake or preference, the authors propose that microbial metabolites, such as SCFAs, may influence brain evaluation of nutrient-rich foods and potentially prime individuals for long-term dietary adaptations [66]. However, these effects remain correlational because prebiotic-induced changes in the gut microbiome and SCFA metabolism have yet to be directly linked to altered eating behavior in humans.

Taken together, the evidence presented in the preceding section suggests that industrialized diets that are low in fiber content reduce microbial production of SCFAs, thereby disrupting gut–brain communi-cation by weakening satiety signaling through vagal afferents and diminishing the secretion of satiety hormones such as CCK, GLP-1, and PYY. As a result, loss of dietary fiber may contribute to decreased satiety, promoting overconsumption and impairing energy balance.

Dietary sugar

Dietary sugar constitutes a substantial portion of industrialized diets; for instance, annual per capita availability of caloric sweeteners in the USA peaked at 153.6 pounds (69.7 kg) in 1999 and remained significant at 123.5 pounds (56.0 kg) in 2023[i]. Although the gut microbiome plays a well-established role in fermenting dietary fiber into SCFAs, its interactions with dietary sugar are limited because sugar is readily digested in the small intestine. This dramatically reduces the quantity of sugar that reaches the largest gut microbial populations in the colon. However, under conditions of excess sugar intake – as expected in some industrialized diets – unabsorbed sugars can spill over and reach the colon [67], initiating a cascade of microbiome, immune, and neurophysiological changes that may indirectly influence host feeding behavior. These mechanisms include altered SCFA production [68], immune–microbiome interactions [69], and vagal remodeling [70] – all of which intersect with metabolic and behavioral regulation.

Glucose is typically absorbed almost completely in the small intestine, whereas fructose metabolism is more variable [71]. When fructose does reach the largest communities of gut microbes in the colon, it alters colonization dynamics by suppressing key fiber-degrading bacteria, such as *Bacteroides thetaiotaomicron*, through repression of the *roc* gene that encodes a crucial **colonization factor** [68]. This shift disrupts microbial community stability, potentially leading to reduced SCFA production [72]. Given that SCFAs act as metabolic signaling molecules that engage the gut–brain axis via vagal pathways and neurotransmitter modulation (as discussed above), reducing their availability should perturb feeding behavior and metabolic homeostasis.

Unlike dietary fiber, which directly fuels microbial metabolism to generate bioactive metabolites, dietary sugar exerts a more indirect influence on microbiome–immune interactions. One such mechanism is through depletion of T helper 17 (Th17) cells, an immune cell population that is crucial for gut homeostasis [69]. High-sugar diets favor the expansion of sugar-adapted microbes at the expense of Th17-inducing commensals, leading to loss of Th17 cells in the gut mucosa [69]. Disruption of Th17 cells reduces the production of IL-17, a cytokine that acts directly on hypothalamic neurons to suppress food intake by increasing POMC expression and activating anorexigenic signaling pathways, and thus contributes to altered feeding behavior by suppressing this immune-derived satiety signal [73]. In parallel, Th17 cells regulate intestinal lipid absorption via IL-17 and downregulate CD36, a key lipid transporter [69]. The loss of this immune regulatory function increases lipid absorption, suggesting that microbiome-mediated metabolic

consequences of sugar consumption are intertwined with immune suppression and microbial disruptions rather than with microbial metabolite production *per se*.

These findings collectively highlight a distinct but underappreciated pathway through which dietary sugar may shape feeding behavior – not by serving as a microbial substrate but instead by reprogramming host–microbe interactions in ways that drive metabolic and neurophysiological effects (Figure 2). Although dietary sugar has been linked to structural shifts in the microbiome, immune modulation, and vagal remodeling, direct experimental evidence demonstrating how these changes translate into altered feeding behavior remains limited. However, this pathway has important implications for industrialized diets because chronic sugar intake may reinforce dysregulated feeding behavior through persistent microbiome–gut–brain alterations.

Dietary protein

Protein leverage theory postulates that organisms prioritize protein intake over total energy intake, leading to compensatory overconsumption of fats and carbohydrates when dietary protein is diluted in available foods [74,75]. This phenomenon has been observed across species, including humans [76], and highlights protein appetite as an important driver of feeding behavior. Although studies to date [74–76] have focused on host mechanisms – such as sensory detection of amino acids, hormonal feedback loops, and central neural pathways governing protein appetite – the role of the gut microbiome in shaping protein-driven feeding behaviors remains largely unexplored.

Gut microbes can play a role by modulating amino acid availability, buffering the host against dietary protein scarcity. For instance, flies colonized with the essential amino acid-producing bacterium Acetobacter pomorum exhibit reduced protein-seeking behavior, indicating that microbial amino acid synthesis can suppress host compensatory feeding [78]. By contrast, colonization with Lactobacilli, which lack biosynthetic pathways for essential branched-chain amino acids (leucine, isoleucine, valine), does not suppress protein appetite under essential amino acid deprivation – consistent with the hypothesis that microbial biosynthesis of essential amino acids is required for this appetite-modulating effect [77]. This suggests that microbial suppression of compensatory feeding responses depends on specific biosynthetic capabilities [77,78].

Microbiome-driven interactions with essential amino acids may also influence broader macronutrient preferences. Mice colonized with gut microbes from herbivorous donors exhibited elevated plasma tryptophan and greater preference for protein, whereas those colonized with gut microbes from omnivorous or carnivorous donors consumed more carbohydrates [79]. Although this study did not establish causality or identify the neural mechanisms underlying this relationship, other studies have implicated the kynurenine pathway in the effects of microbiome-driven tryptophan metabolism on feeding behavior.

Microbial metabolism of tryptophan to kynurenic acid modulates feeding behavior through a gut–brain circuit involving vagal afferents and central appetite pathways [80]. Chronic stress and dieting history can shift gut microbial composition and reduce luminal kynurenic acid levels. This depletion disinhibits vagus nerve terminals, leading to increased food intake via hyperactivation within the nucleus of the solitary tract and paraventricular nucleus of the thalamus [80]. Building on this model, intestinal kynurenic acid signals through the GPR35 receptor on vagal afferent terminals to activate AgRP neurons, offering direct mechanistic evidence of microbiome-mediated control over feeding behavior [81]. Restoring kynurenic acid levels through probiotic

supplementation with *Faecalibacterium prausnitzii* or direct kynurenic acid administration normalizes feeding behavior, confirming that the kynurenine pathway is a microbial metabolic regulator of compulsive overeating (Figure 2).

Additional mechanistic examples from invertebrate models further highlight how microbial metabolites of protein can shape host behavior. In *Caenorhabditis elegans*, tyramine produced from tyrosine by gut-colonizing *Providencia* spp. is converted by host enzymes into octopamine, which acts on OCTR-1 receptors in ASH sensory neurons to reduce aversion to bacterial odors [82]. Remarkably, this modulation of olfactory behavior biases worms toward food sources containing their native symbiotic bacteria, thus promoting mutualistic host–microbe interactions [82].

The drive for protein intake, however, is not unidirectional. Organisms also suppress excessive protein consumption to mitigate **metabolic burden**. In *D. melanogaster*, excessive protein intake is suppressed by CCHamide1, a gut-derived peptide that signals through enteric neurons [83]. Disruption of CCHamide1 signaling in enteric neurons led to increased protein intake, hyperammonemia, and reduced lifespan, demonstrat-ing that organisms not only respond to protein scarcity but also possess mechanisms to regulate protein overconsumption. Whether the gut microbiome contributes to this regulation of protein overconsumption remains unknown and warrants further investigation.

Protein homeostasis relies on gut-derived neuropeptides that engage enteric and central circuits to adjust feeding behavior in response to amino acid availability [80], and the gut microbiome further shapes this process by contributing to nutrient balance. This is exemplified by microbial synthesis of essential amino acids – such as tryptophan and branched-chain amino acids – in cases where their biosynthesis suppresses host compensatory feeding in response to protein scarcity [77,78]. Together, these mechanisms provide proof-of-concept evidence for microbial involvement in protein leveraging, and demonstrate that both host-driven gut–brain signaling and microbial metabolism regulate protein intake.

The well-documented effects of dietary fiber and protein on gut microbiome composition and microbe-derived metabolites [84,85] highlight the need to consider their combined effect on host eating behavior. Although nondigestible carbohydrates are the primary substrates for microbe-mediated SCFA production, undigested dietary proteins and amino acids in the colon can also serve as precursors for SCFA synthesis [86]. Importantly, microbes in the colon can access nitrogen even in the absence of dietary protein by metabolizing host-derived materials such as mucus and sloughed epithelial cells. Because these endogenous substrates remain available irrespective of dietary intake, certain aspects of microbial protein metabolism may operate similarly across both industrialized and non-industrialized diets [31].

The interplay between fiber- and protein-derived metabolites may counteract some of the adverse metabolic effects associated with Western diets, which are typically low in fiber and high in fat and protein [87]. Metabolic and microbial outcomes of diet are shaped not only by the presence of individual macronutrients but also by their relative proportions and interactions [88,89]. Coadministration of fermentable fibers (e.g., inulin) with high-quality protein sources (e.g., egg or whey) can reduce direct energy absorption and modulate gut microbiome composition through increased microbial exposure to fermentable substrates [88]. In parallel, lowering the protein-to-fiber ratio within high-fat diets improves glycemic control and lipid profiles while favoring the expansion of SCFA-producing bacterial taxa [89]. Determining whether optimizing protein-to-fiber ratios can shift microbial metabolism toward increased SCFA production and

reduced proteolytic byproducts may reveal a strategy to counteract the feeding dysregulation and metabolic dysfunction associated with fiber-deficient Western diets.

Dietary fat

Dietary fat influences host feeding behavior through mechanisms beyond caloric load or sensory reward, and emerging evidence implicates gut-derived metabolic signals in the regulation of fat preference and satiety [90,91]. The high fat and low fiber contents of industrialized diets rapidly shift gut microbial communities toward bile-tolerant organisms while reducing fiber-fermenting species, leading to functional changes including altered bile acid metabolism [25].

Bile acids serve as key microbiome-derived metabolites that integrate dietary cues with host metabolism and neural control of feeding [92,93]. Traditionally recognized for their role in lipid emulsification and absorption, bile acids are now understood to be bioactive signaling molecules that engage gut hormone pathways, vagal afferent neurons, and central appetite circuits [92,94,95]. The reciprocal relationships between diet, gut microbiome composition, bile acid composition, and feeding behavior suggest a dynamic regulatory system wherein dietary fat alters microbial bile acid metabolism and bile acid composition, in turn, modulates fat sensing, satiety, and food intake.

A high-fat Western diet disrupts this regulatory balance by reshaping the gut microbiome and bile acid pool, with downstream consequences for gut–brain signaling [96]. These shifts are driven in part by microbial deconjugation and dehydroxylation of primary bile acids into secondary forms that alter receptor signaling in the gut and liver [37]. For instance, mice exposed to a Western diet exhibit shifts in bile acid composition that reduce the activation of key receptors involved in metabolic regulation, including farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5), leading to impaired gut hormone secretion and metabolic dysfunction [96–98]. In humans, uncontrolled eating behavior has been associated with enrichment of *Ruminococcus torques* and *Bifidobacterium* spp. and a concomitant reduction in expression of microbial gene involved in bile acid metabolism and neurotransmitter production [99].

The impact of bile acid composition on feeding behavior is dynamic because bile acids also shape how dietary fat is sensed and metabolized [100]. Loss of 12α-hydroxylated bile acids in mice, caused by disruption of a key bile acid-producing enzyme (CYP8B1), alters intestinal lipid sensing. This change enhances GPR119-mediated gut hormone secretion, leading to increased satiety and reduced high-fat diet consumption [100]. In these mice, dietary fat bypasses small intestinal digestion as a result of impaired triglyceride hydrolysis, allowing lipids to reach the colon where they amplify gut hormone release [100]. This supports the hypothesis that bile acids not only regulate lipid digestion efficiency but also function as metabolic signals that influence fat intake and preference [100].

Although bile acids modulate fat digestion and satiety primarily through gut hormone signaling and vagal activation, endocannabinoids extend this regulatory function by directly engaging reward pathways to reinforce fat preference (Figure 2). The endocannabinoid system works by fine-tuning dopamine and serotonin signaling through CB1 receptor-mediated suppression of inhibitory and excitatory inputs, leading to disinhibition of dopamine release in reward-related regions while modulating serotonin transmission in a region-specific manner – mechanisms that collectively shape motivated behaviors [19], including feeding and reinforcement learning [101]. Diet-induced shifts in gut microbiome composition influence these processes by modulating the synthesis and degradation of bioactive endocannabinoids such as anandamide and 2-

arachidonoylglycerol, leading to parallel changes in ileal and plasma endocannabinoid levels [102–104]. Accordingly, restricting and intermittently exposing animals to a high-fat diet alters brain endocannabinoid signaling and induces binging-like behavior [102,105].

The selective engagement of endocannabinoid signaling in response to dietary fat ingestion provides a mechanistic point of entry to understanding how the gut endocannabinoid system drives fat intake behavior via CB1 receptor activation. In a controlled feeding model, intestinal levels of anandamide and 2-arachidonoylglycerol rapidly increase in response to fat but not to carbohydrates or proteins [105]. Direct administration of these endocannabinoids is sufficient to induce fat preference, and vagotomy abolishes both their fat-induced accumulation in the jejunum and the behavioral response, reinforcing the gut–brain axis as a conduit for fat-driven reward signaling. Consistent with this, selective ablation of gut-innervating vagal sensory neurons impairs lipid-specific satiation and promotes overeating in response to high-fat diets, highlighting the essential role of vagal input in modulating fat-driven feeding behavior [106]. Further refining the specificity of this response, some unsaturated fatty acids – particularly oleic acid and linoleic acid – selectively drive gut endocannabinoid accumulation in the gut [107]. The preference for these fats is abolished when CB1 receptor activity is blocked, thereby functionally linking gut-derived endocannabinoid signaling to dietary fat selection [107].

A key question that emerges is whether the gut microbiome itself synthesizes bioactive lipid mediators that influence host food intake. Gut bacteria can convert dietary ω-3 polyunsaturated fatty acids into endocannabinoid-like molecules, indicating that microbial metabolism might at least extend the spectrum of host lipid signaling [103]. Importantly, microbiome-dependent modulation of plasma bioactive lipids – both bile acids and endocannabinoids – occurs in both mice and humans, highlighting the translational promise of further work to delineate these processes [91,103].

Industrialized diets remodel the microbiome–gut–brain axis to reinforce maladaptive eating

Through its direct and indirect influences on host feeding, the gut microbiome expands the classic gut–brain axis framework to a **microbiome–gut–brain axis**. Microbial metabolism differentially transforms dietary substrates into bioactive metabolites, which in turn engage gut–brain pathways to influence feeding behavior. Emerging work reinforces this perspective by demonstrating that microbiome-derived metabolites (i.e., SCFAs, bile acids, and amino acid catabolites) can modulate neural circuits governing food intake (Figure 2).

Industrialized societies have experienced a rising prevalence of disordered eating [108], reflecting an uncoupling of eating behavior from internal signals that regulate satiety. Ultra-processed foods – a hallmark of industrialized diets – may play a role by enhancing reward sensitivity and encouraging intake beyond physiological satiety signals [87]. These observations thus highlight the need to consider microbial metabolism as a potential factor linking industrialized diets to maladaptive eating behavior. By providing an altered ratio of dietary substrates that are also highly processed, the industrialized diet may shape the gut microbiome and its metabolic output both by changing resources in the intestinal lumen and through its broader effects on host health. Downstream changes in gut microbial metabolites then serve as both a potential driver and reinforcer of altered eating behavior, specifically through the effects on reward pathways and inflammatory processes (Figure 2). Industrialized microbiomes, shaped by both diet and lifestyle, exhibit reduced microbial diversity and an enrichment of oxidative stress-related pathways, reflecting an ecologically vulnerable and proinflammatory state [15]. Through these cascading effects, the interaction between the industrialized diet and the microbiome–gut–brain axis has the potential to create a biochemical feedback loop that may foster food addiction and other pathological eating behaviors.

Although human diets vary widely in both industrialized and non-industrialized contexts [10], industrialized diets often contain lower amounts of fiber and higher amounts of sugar, protein, and fat, as well as higher overall caloric content [87]. These changes in macronutrient balance are expected to alter the microbiome-derived metabolites that interact with host signaling pathways. For instance, reduced dietary fiber diminishes the microbial production of SCFAs, which are crucial signals for satiety and metabolic regulation. Consequently, impaired SCFA signaling may weaken the gut–brain pathways that govern satiety, and thus promote overeating and caloric excess [109]. Concomitant increases in dietary sugar drive increases in the abundance of sugar-adapted microbes at the expense of fiber-fermenting microbes, and compromise appetite regulation indirectly via the loss of SCFAs and directly via Th17-mediated reductions in anorexigenic signaling and increases in lipid absorption [69,70]. Elevated dietary protein drives microbial metabolism toward generating neuroactive amino acid metabolites such as kynurenic acid [80,81] and tyramine [82] that are capable of disrupting host nutrient-sensing and reinforcing protein-seeking or generalized dysregulated feeding behaviors. Likewise, high dietary fat intake increases the abundance of bile-tolerant organisms that participate in bile acid metabolism [37] and enhance endocannabinoid production [91], changes that have the potential to activate reward pathways and foster compulsive eating behaviors specifically targeting fatty foods.

Synthesizing current evidence, we propose that these microbiome-mediated metabolic shifts may contribute to a self-sustaining feedback loop – an altered metabolite profile that reinforces maladaptive host eating behaviors and perpetuates dietary choices that maintain or further exacerbate gut microbial **dysbiosis** (Figure 1). This gut microbiome-mediated feedback framework offers a coherent explanation for how prevalent conditions linked to industrialized diets, including chronic low-grade inflammation [111] and disordered eating patterns [112], may be interconnected outcomes of diet-driven disruptions in the microbiome–gut–brain axis. Importantly, a recent study found that adoption of a 'non-industrialized' dietary pattern – in this case, plant-based, minimally processed, high in fiber, and low in energy density and glycemic index – helped to restore health-associated microbiome features and improve cardiometabolic outcomes [110]. Such data raise the possibility that shifts to more healthful eating may attenuate or reverse the vicious cycle promoted by the industrialized dietary pattern, encouraging better regulation of eating behavior via the microbiome-gut-brain axis.

Concluding remarks and future perspectives

By explicitly recognizing the gut microbiome as a mediator in dietary conditioning and eating behaviors, this framework identifies potential new therapeutic targets. Interventions designed to reshape microbiome composition and metabolic function could disrupt maladaptive feedback cycles, thereby restoring healthier appetite regulation and potentially mitigating some of the burden of eating disorders and metabolic diseases that characterizes industrialized societies.

Although we offer a lens through which to reinterpret the impact of industrialized diets, many of the causal mechanisms by which microbial metabolism influences host feeding behavior remain unresolved (see Outstanding questions). Addressing this knowledge gap requires integration of microbiome and neuroscience approaches to establish mechanistic links. Gnotobiotic models provide a controlled system to isolate the effects of microbial communities and enable mechanistic dissection of the influences of microbial composition and metabolic capacity in host physiology. Multi-omic approaches, particularly metabolomics, will be indispensable for mapping the repertoire of microbiome-derived metabolites and identifying candidate signaling molecules that may act on host neurocircuits. Neural tools such as circuit

Outstanding questions

What is the causal influence of specific bacterial taxa on pathological eating behaviors?

What mechanisms and conditions determine whether microbial nutrient metabolism benefits microbial fitness at the expense of host nutritional status?

How does chronic low-grade inflammation induced by microbiome dysbiosis alter neural circuits involved in reward and satiety to promote maladaptive eating behaviors?

Can microbial metabolites with pleiotropic actions, including SCFAs and bile acids, be functionally classified according to their influence on homeostatic versus hedonic neural circuits? What determines their net effect under industrialized dietary conditions?

Under what conditions do short-term dietary shifts provoke durable or reversible microbiome-driven alterations in host eating preferences, and how can these dynamics be leveraged therapeutically?

How does microbial amino acid metabolism modulate host protein-seeking behavior, and can microbiome composition predict susceptibility to compensatory overconsumption when dietary protein is diluted by fats or carbohydrates?

Can personalized microbiome-targeted dietary interventions sustainably enhance satiety or reduce pathological cravings for highly palatable foods, and what microbial biomarkers reliably predict intervention success?

mapping and genetic manipulation will be instru-mental in verifying the downstream behavioral effects of these microbial metabolites acting on feeding-related neural pathways. By leveraging these complementary approaches, future research can move beyond correlational associations to identify precise causal pathways through which microbial metabolism shapes host eating behavior, and ultimately refine our understanding of diet–microbiome–brain interactions.

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Declaration of interests

The authors declare no competing interests.

Resources

[i]https://www.ers.usda.gov/data-products/charts-of-note/chart-detail?chartId=110515&utm

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