CLINICAL SCIENCE OF NUTRITION
Review Article
DOI: 10.62210/ClinSciNutr.2024.98

Gut-brain axis: The role of gut microbiota in energy balance and body weight regulation

Gülnur Pürdik Tatık[1], Özlem Baran[2], Ayhan Dağ[2]

[1]Department of Nutrition and Dietetic, Institute of Health Sciences, Lokman Hekim University, Ankara, Türkiye
[2]Department of Nutrition and Dietetic, Faculty of Health Sciences, Lokman Hekim University, Ankara, Türkiye

Cite this article as: Pürdik Tatık G, Baran Ö, Dağ A. Gut-brain axis: The role of gut microbiota in energy balance and body weight regulation. *Clin Sci Nutr*. 2024;Early View:1-8.

ABSTRACT

Obesity currently represents a major societal and health problem worldwide. Its prevalence has reached epidemic levels, and trends continue to increase; This, in turn, reflects the need for more effective preventive measures. Dietary composition is one of the main factors that modulate the structure and function of the gut microbiota. Therefore, abnormal dietary patterns or unhealthy diets can alter gut microbiota-diet interactions and alter nutrient availability and/or microbial ligands that transmit information from the gut to the brain in response to nutrient intake, thereby disrupting energy homeostasis. Accordingly, this review aims to examine how dietary composition modulates the gut microbiota and thus the potential effects of these biological products on energy homeostasis through gut-brain based mechanisms. It also assesses the knowledge gaps and advances needed to clinically implement microbiome-based strategies to improve gut-brain axis function and therefore combat obesity.

Keywords: Microbiota, gut-brain axis, energy balance, obesity

INTRODUCTION

According to the World Atlas of Obesity 2023 report, 38% of the world's population is overweight or obese. It is predicted that this rate will reach 51% by 2035.[1] Despite the urgent need for prevention and cure of obesity and obesity-related metabolic diseases, there are few successful treatment options available. Gut microbial modulation has emerged as a potential therapeutic approach in the treatment of obesity.[2] The gut microbiota is a complex community of microorganisms that live in the gastrointestinal tract and have established a close symbiotic relationship with the human host. It plays a very important role in maintaining health, allowing the metabolism of indigestible dietary components and the synthesis of certain vitamins, preventing pathogen colonization and contributing to the development of the immune system. The human gut microbiota is mostly made up of two dominant bacterial phyla, Firmicutes and Bacteroidetes, representing more than 90% of the total population, and other subdominant phyla including Proteobacteria, Actinobacteria, and Verrucomicrobia. It is reported that a higher rate of Firmicutes and a decreased population of Bacteroidetes are often observed in obese individuals, so an increased Firmicutes/Bacteroidetes ratio is reported as a marker of obesity.[3] This microbial imbalance can lead to changes in host metabolism, ultimately leading to body weight gain. In other words, the composition of the microbiota both can be a risk factor for obesity and lifestyle factors that cause the development of obesity can affect the composition of the microbiota.[2]

The gut-brain axis, on the other hand, is a two-way hormonal and neural signal pathway. There are several mechanisms that connect the gut to the brain in the regulation of metabolic homeostasis. Classically, signals from the gut in response to food intake during meals are transmitted to the brain, and the central nervous system (CNS) is informed about the size and composition of food.[4] The brain, specifically the hypothalamus, combines these gut-derived signals with others to coordinate the regulation of food intake, energy expenditure, and glucose

Corresponding author: Gülnur Pürdik Tatık
Email: diyetisyengulnurpurdik@gmail.com

Received: October 14, 2024 Accepted: November 24, 2024
Published: December 7, 2024

homeostasis. Accordingly, in this review, it is aimed to provide an overview of how the gut-brain axis contributes to energy balance and body weight regulation.

GUT-BRAIN AXIS IN ENERGY BALANCE

Increased intake of high-energy-density, palatable foods disrupts brain circuits that control energy homeostasis; inadequate response of these circuits to food signals alters feeding behavior, which in turn contributes to an individual's body weight gain. Accordingly, the restoration of nutrient signaling via the gut-brain axis represents a promising strategy to improve the central control of energy homeostasis in response to meals, thereby helping to combat obesity.[5,6] The gut microbiota is a biological factor that can directly or indirectly influence nutrient perception, and theoretically, modulation of it could help restore gut-brain communication and maintain energy homeostasis.[2,4]

Major mediators of the gut-brain axis

The intestinal wall is the largest surface barrier between the human body and the outside world. The components of this barrier include microbiota, mucus, epithelial monolayers, and immune cells. Intestinal epithelial cells consist of apical and basolateral area. Immune cells are located in the lamina propia.[7] Bidirectional communication between the brain and gut microbiota is mediated by various pathways, including the immune system, neuroendocrine system, enteric nervous system (ENS), circulatory system, and vagus nerve.[8] Signals from the brain are transmitted to the gut mainly through the autonomic nervous system and the hypothalamic-pituitary axis to regulate many physiological processes.[9] The vagus nerve is called the "wandering nerve" because of its long extensions that originate from the brain stem and stimulate many internal organs. Inside the intestine, the vagal afferent ends are scattered in different layers. The physiological function of a large number of vagal afferent neurons, *which are important for the regulation of energy and glucose homeostasis*, is that they contain receptors for intestinal peptides released by enteroendocrine cells (EECs).[10] Intestinal epithelial cells, EECs, neuropod cells, and enterochromaffin cells (ECs) secrete intestinal peptides, including *glucagon-like peptide-1 (GLP-1), Cholecystokinin* (CCK), *glucose-dependent insulinotropic polypeptide (GIP),* and *Peptide YY* (PYY) on the basolateral side.[6,8] These intestinal peptides are released in the immediate vicinity of vagal afferent neurons that connect the intestinal mucosa to the nervous system and activate these neurons. Vagal afferent neurons send signals to the nucleus tract solitarius (NTS), which can send signals to high-grade brain regions such as the curved nucleus (ARC).[4] ARC includes two subpopulations of neurons;αα those expressing anorexigenic propiomelanocortin (POMC), α precursor to melanocyte-stimulating hormone (α-MSH), and cocaine and amphetamine-regulated transcript (CART); and neurons expressing the agouti gene-related peptide (AgRP) and neuropeptide Y (NPY). Vagal afferent neurons are also activated through the ENS, known as the "second brain," which can regulate GI function independently of CNS action; this system can be activated by the release of gut-derived neurotransmitters such as 5-HT from ECs and intraganglionic laminar endings that sense gut tension.[5,7]

Main Points

- The gut microbiota produces metabolites and microbial products such as short-chain fatty acids and secondary bile acids that regulate the host's energy balance and body weight regulation.
- The gut microbiota metabolites act as signaling molecules that regulate energy intake and storage and energy expenditure by affecting the gut-brain axis and interact with the host in multiple ways.
- Enteroendocrine cells in the intestinal epithelium perceive nutritional and microbial signals and can regulate enteric and vagal neuronal pathways in response to microbial signals, thereby contributing to energy balance and body weight regulation.

How Does Food Sensing Occur by Enteroendocrine Cells?

Different macronutrients act through alternative pathways to drive the release of the gut peptide.[10] Fatty acids can signal through multiple receptors on both the apical and basolateral membranes. Signaling in the basolateral membrane requires the uptake and packaging of fats into chylomicrons in enterocytes, followed by the release and breakdown of these chylomicrons on the basolateral surface.[11,12] Fatty acids bind to their receptors on enteroendocrine cells, and these activate a downstream signaling cascade that leads to the fusion of vesicles containing the gut peptide and the release of their contents across the basolateral membrane.[13]

Glucose sensing occurs in the apical membrane of an EEC and requires its uptake into the cell along with Na^+ via the Sodium/glucose cotransporter 1 (SGLT-1). Na^+ entry into EEC causes depolarization followed by activation of Ca^{+2} channels, resulting in vesicle fusion and intestinal peptide release.[14]

Amino acid signaling in the enteroendocrine cell involves the uptake of peptides and Na^+ via peptide transporter 1 (PepT1) in the apical membrane. This Na^+ can depolarize cells, but research is still needed to determine the exact mechanism of action. Amino acids are transported outside the cell via the basolateral membrane, where they can activate the calcium-sensing receptor (CaSR), leading to

Ca^{+2} release and vesicle fusion. CaSR may also be present in the apical membrane, but research is still needed to elucidate the exact mechanism of protein-derived intestinal peptide release.[15,16]

Effect of Intestinal Peptides on Energy Balance and Regulation of Body Weight

Activation of the nutrient sensors of EECs initiates the secretion of gut peptides, and these peptides trigger downstream processes that are essential for maintaining post-meal energy homeostasis.[17] The gut peptides that have been studied most extensively are cholecystokinin which is secreted mainly in the upper part of the intestine, GIP, and glucagon-like peptide-1, which is secreted mainly in the distal part, and the peptide tyrosine tyrosine.[18]

*Incretins;*The 2 hormones responsible for increasing insulin secretion after oral food intake are intestinal peptides, *GLP-1* and *GIP*.[19] *GLP-1* can also modulate satiety: Chronic treatment with Glucagon-like peptide-1 receptor (GLP1R) agonists (compounds that bind to cell receptors to create a response in the cell) in the long-term control of food intake serves to suppress food intake and promote weight loss.[6] Suppression of food intake with the GLP-1R agonist requires GLP-1R expression on glutamatergic neurons of the CNS.[20] However, prolonging the half-life of endogenous GLP-1 by inhibiting dipeptidylpetidase-4 (DPP4) is also reported to be ineffective in modifying food intake, although it potentiates the incretin effect of endogenous GLP-1.[21]

Intestinal GIP is secreted from K cells in the duodenum and proximal jejunum in response to food intake and by acting as an incretin, increases glucose-dependent insulin release from pancreatic β cells and contributes to the normalization of postprandial plasma glucose and thus energy balance.[19]

Peptide YY (PYY) is a 36-amino acid gastrointestinal hormone secreted predominantly by intestinal L cells.[22] PYY, or more specifically its active form PYY3-36, is known for its role in the "ileal break," which slows the passage of chyme to ensure adequate digestion in the proximal intestine.[23] In addition to its satiety-enhancing effect through ileal break, PYY3-36 may also reduce food intake through independent mechanisms without reducing intestinal motility. PYY exerts an anorexigenic effect through vagal afferents and crossing the blood-brain barrier.[24] PPYY3-36 also directly and indirectly stimulates POMC activity through inhibition of NPY neurons and nerve terminals that activate adjacent POMC neurons and induces prolonged upregulation of POMC mRNA expression.[25] In this respect, PYY analogues, together with GLP-1 receptor agonists, are reported as a promising therapeutic approach for obesity with their beneficial effects on energy balance and food intake preference.[26]

Microbial Metabolites Mediating Energy Balance and Body Weight Regulation

Gut microbiota is reported as an environmental factor that regulates the host's energy balance.[2] It increases the host's ability to obtain energy from food and produces metabolites and microbial products such as short-chain fatty acids, secondary bile acids, and lipopolysaccharides. These metabolites and microbial products act as signaling molecules that regulate appetite, intestinal motility, energy intake and storage, and energy expenditure.[8,10]

Short Chain Fatty Acids

Adding fermentable carbohydrates, including dietary fibers and resistant starch, to the diet reduces food intake and body weight gain and improves glucose metabolism in rodents and humans.[25] It has been stated that these effects are partly mediated by short-chain fatty acids (SCFAs). SCFAs are produced in a fermentation process from carbohydrates (resistant starch, dietary fiber, and other low-digestible polysaccharides) that cannot be digested by the microbiota in the colon and distal small intestine. Acetate, propionate, and butyrate are the predominant SCFAs in the intestinal lumen in humans and rodents.[27]

SCFAs are known to regulate food intake by modulating hypothalamic function, reaching the systemic circulation to the brain, or directly through food signaling mediated by GLP-1 and PYY produced/released in EECs, or through vagal afferents (such as activating adipose tissue to release leptin hormone).[28] Its microbial-derived SCFAs are absorbed into the bloodstream and affect whole-body physiology through mechanisms that may include G protein-coupled receptors (GPCRs), also called free fatty acid receptors (FFARs).[29] Among SCFAs, acetate appears to reach the brain through systemic pathways, while propionate and butyrate mainly activate nutrient sensing pathways in the gut. Of these SCFAs, propionate, in particular, is reported to centrally control intestinal gluconeogenesis, a process that confers metabolic benefits, including reduced endogenous glucose production, independent of insulin.[30] Furthermore, like acetate, elevated plasma propionate levels promote hypothalamic anorexigenic neuronal activation by inducing leptin release from adipocytes through FFARs-dependent mechanism. Butyrate, on the other hand, is reported to be the most potent stimulant of anorexigenic peptides and the most potent suppressor of food intake.[27] Intestinal butyrate can transmit satietogenic signals by stimulating GLP-1 and GIP secretion in L cells and K cells, respectively, and these effects are potentiated by ghrelin inhibition.[31] These fatty acids also increase insulin sensitivity and mitochondrial function in muscle cells, support pancreatic function, including insulin secretion and beta cell activity, and reduce lipid accumulation and glucose production in the liver.[28] Gut

bacterial SCFA-activated free fatty acid receptors 2 and 3 (FFAR2/3) modulate adipose tissue physiology of the host by activating AMP-activated protein kinase (AMPK) in white adipose tissue (BAD), inhibiting cyclic adenosine monophosphate (cAMP) activation, adipogenesis, activation of UCP-1, and browning by increasing fatty acid oxidation, thereby reducing body weight and whole-body metabolic It regulates homeostasis.[29]

The mechanism involving the production of leptin, the satiety hormone derived from adipose tissue, under the influence of SCFAs, is the most studied mechanism.[32] It has been reported that leptin binds to receptors in the brain and inactivates NPY and AgRP in normal physiological conditions, suppressing appetite, as well as inducing POMC mRNA expression.[33] The released leptin is transported across the blood-brain barrier (BBB) to perform its function, and Leptin Receptor-a (LepRa) is needed in this process.[34]

Pathologically, in obese individuals, an excessively high level of leptin in plasma causes saturation of LepRa and thus leads to leptin resistance reducing the rate of leptin transport across the blood-brain barrier (BBB). A number of factors and specific mechanisms underlying the development of this condition are linked to cellular signaling of leptin.[35] Two points are emphasized regarding the disruption of leptin cellular signaling. First, neurons expressing LepR are not sensitive enough to measure circulating leptin levels, which reduces the effectiveness of leptin's binding to LepR. Second, the signaling ability of LepR-expressing cells is impaired. For example, it has been reported that proinflammatory factors such as IL-6 may increase with intestinal dysbiosis and indirectly affect leptin secretion and functionality, and their importance in energy metabolism and body weight regulation has been reported.[33] In addition, circulating leptin-binding proteins such as plasma-soluble LepR and C-reactive protein bind competitively to leptin and promote the development of leptin resistance. Binding of leptin to circulating leptin-binding proteins inhibits leptin transport to the CNS, suppresses the interaction between leptin and LepR neurons, and induces phenotypes associated with leptin resistance. Leptin resistance develops not only in the brain but also in peripheral tissues such as skeletal muscle, adipose tissue, and liver, which may provide new perspectives on obesity treatment.[36]

Microbial Metabolites of Bile Acids

Bile acids (BA) are steroid acids synthesized from cholesterol in the liver, conjugated to taurine or glycine, and released in the duodenum after food intake to facilitate the absorption of dietary lipids and fat-soluble vitamins.[37,38] The majority of primary BA secreted in the gut is actively reabsorbed in the ileum and transported back to the liver via the portal circulation.[39] The remaining small portion of the primary BA is deconjugated and dehydroxylated by gut bacteria in the ileum and colon and converted into secondary BAs.[37,40] Bacterial bile salt hydrolases (BSH) are enzymes required for the deconjugation of primary BAs to secondary BAs. BAs have also been shown to play a role in the regulation of glucose and lipid metabolism and energy expenditure through activation of BA receptors in the liver, intestine, and peripheral tissues. The effect of secondary BAs resulting from gut microbiota activity on the brain is still poorly studied, but current studies report that secondary BAs can potentially modulate food intake and energy homeostasis through afferent pathways through TGR5-GLP-1 and/or 5-HT gut sensing pathways.[41,42] Specifically, secondary bile acids stimulate GLP-1 secretion by activating G protein-coupled receptors (TGR5) on L cells, and thus its role in stimulating saturation in vagal afferent neurons has been demonstrated.[43] TGR5 receptors are also found in skeletal muscle and brown adipose tissue, where they increase energy expenditure promoting the conversion of inactive thyroxine (T4) to active thyroid hormones (T3).[44] Bile acids have been shown to act on farnesoid X receptors (FXR). Insulin release increases during BA binding of FXR to pancreatic β cells. Bile acid activation of intestinal FXR-containing cells stimulates the secretion of fibroblast growth factor-19 (FGF-19), a protein that contributes to the improvement of peripheral glucose excretion and lipid homeostasis, increasing metabolic rate, and reducing weight. FGF-19 may improve glucose tolerance by regulating insulin-independent glucose flow and hepatic glucose production.[45] Thus, secondary bile acids exert potential effects on the host's energy balance, glucose homeostasis, and body weight regulation.

Amino Acid-Derived Metabolites

Also known as serotonin, 5-HT is synthesized from tryptophan, an important amino acid derived from dietary proteins in the gut as well as in the brain. 5-HT is released from enterochromaffin cells upon intraluminal pressure and leads to activation of receptors and peristaltic action.[46] Derived from the intestines, 5-HT has also been shown to be important for starvation-induced adaptation by promoting lipolysis in adipose tissue and gluconeogenesis in the liver, thereby increasing energy availability for other organs in the body.[47] 5-HT receptors are expressed in many cell types in the gut, including enterochromaffin cells, goblet cells, enterocytes, vagal and spinal afferent nerves, and enteric nerves. The gut microbiota, through its metabolites, is reported to induce the release of 5-HT in the colon and indirectly in the small intestine by stimulating GLP-1 secretion.[42]

Tryptophan can be fermented into indole, a ligand of the arylhydrocarbon receptor (AHR), a transcription

factor that regulates gene expression. In vitro assay with GLUTag cell lines shows that activation of AHR with an agonist increases GLP-1 secretion as well as proglucagon expression.[48] Obesity in mice has been associated with an increase in gut IDO1, an enzyme that catalyzes the breakdown of tryptophan via the kynura pathway, thereby limits bacterial indole production from tryptophan and increases its derivatives such as kynurinin and kyuronic acid.[49] Intraperitoneal administration of kynuronic acid in mice has been shown to induce energy expenditure without affecting food intake.[50]

To date, studies on the effect of γ-Aminobutyric acid (GABA), which is produced by the gut microbiota from the dietary amino acid glutamate, on gut-brain communication and thus the control of energy homeostasis are insufficient. GABA is the main inhibitory neurotransmitter in the central nervous system. Peripheral GABA cannot cross the blood-brain barrier, but it has been reported to activate nutrient sensing signaling pathways in the gut.[51] However, more studies are needed to understand its contribution to energy homeostasis and the regulation of body weight.

THE EFFECT OF DIETS' MACRONUTRIENT RATIO CHANGES ON ENERGY BALANCE AND BODY WEIGHT REGULATION THROUGH MICROBIOTA-GUT-BRAIN COMMUNICATION

Dietary interventions, such as high-protein or high-fat diets, which are characterized by large differences in macronutrient ratios, affect the composition and function of the gut microbiota.[52] The composition in the macronutrients of these diets exerts a significant influence on the availability of gut microbiota-derived ligands, luminal content, which can control food intake and energy metabolism. The availability of these ligands depends on many biological processes, including microbiota-mediated catabolism of digested nutrients and their absorption by enterocytes.[10,17]

It has been reported that in normal-weight or obese individuals, high-protein meals provide the most satiety compared to isocaloric diets containing high carbohydrates or fats, and this effect is due to PYY, the secretion of which is preferentially increased by proteins.[7,8] In addition to gut peptides, high-protein diets modulate the gut-brain axis to control food intake and energy metabolism by stimulating gut gluconeogenesis from the postprandial to postabsorption periods.[53] Peptides digested in the small intestine antagonize μ-opioid receptors in the spinal and vagal afferents of the portal vein, whic is a signal that centrally activates intestinal gluconeogenesis. In addition, enriched protein meals are a source of gluconeogenesis substrates such as glutamine and glutamate for the intestines. Compared to carbohydrates and fats, proteins also have the highest effect on triggering thermogenesis. Although the underlying mechanisms need to be elucidated specifically for proteins, thermogenesis-dependent gut-brain axis mechanisms mediated by gut hormones have been identified.[54] For example, GLP-1 centrally enhances thermogenesis through sympathetic efferents, and the duodenal hormone secretin activates thermogenesis postprandial to induce satiety.[55] High-protein diets also increase the amount of amino acids that can be fermented by the gut microbiota in the colon to obtain energy and produce nutrient-sensing ligands. These include amino acid-derived SCFAs, branched-chain fatty acids, and other molecules derived from tryptophan or glutamate. Compared to carbohydrates, fermentation of proteins produces less SCFA, but still contributes significantly to the production of microbial organic acids. However, there are few studies that address the relational or causal links between gut microbiota and high-protein diets on the control of food intake and energy homeostasis via the gut-brain axis. Furthermore, additional studies are needed to evaluate the risks and benefits of high-protein dietary interventions in improving metabolic health. There are studies reporting that such dietary interventions reduce butyrate production and increase the levels of mucosal and renal toxic compounds.[56,57]

Low-carbohydrate diets, on the other hand, have been reported to have a lower capacity to stimulate brain regions associated with food intake, compared to diets high in carbohydrates.[58,59] However, the exact mechanisms underlying the satiety effects caused by these diets, particularly those dependent on the gut microbiota, still remain unclear. Some studies suggest that diet-induced ketogenesis mediates decreased circulating ghrelin levels associated with decreased appetite in overweight/obese individuals following a low-energy diet, although ketone bodies inhibit GLP-1 release by EECs and directly activate orexigenic hypothalamic pathways in the brain.[60,61] Similar to SCFAs, ketone bodies have also been reported to initiate GPR41 and GPR43 signaling to control energy metabolism.[62] To date, it has not been investigated how these ketone bodies affect the hypothalamus via GPR41/43, and more research is needed.

CONCLUSION

The gut microbiota plays a crucial role in maintaining energy balance and glucose homeostasis. EECs in the GI tract can sense nutrients and release a variety of gut peptides to affect both energy balance and glucose homeostasis. However, more studies are needed to fully understand the mechanisms by which various nutrients activate EECs and release gut peptides. The hypothalamic

circuits, which control energy balance in response to food intake, need to be studied further in terms of body weight management.

Author contributions: Concept – G.P.T.; Design – G.P.T., Ö.B.; Supervision – Ö.B.; Resources – G.P.T.; Materials – A.D.; Literature Search – G.P.T.; Writing Manuscript – G.P.T.; Critical Review – Ö.B., A.D.

Funding: The authors declare the study received no funding.

Conflict of interest: The authors declare that there is no conflict of interest.

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