REVIEW ARTICLE

CONTENTS

The gut-brain axis and its role in obesity-induced homeostatic dysregulation

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ABSTRACT

Aim: The gut–brain axis (GBA) plays a crucial role in maintaining systemic homeostasis through bidirectional communication between the central nervous system and the gastrointestinal tract. This review aims to summarize current evidence regarding the impact of obesity on GBA function and to discuss potential therapeutic strategies targeting this pathway.

Materials and Methods: A narrative literature review was conducted using scientific publications indexed in databases including PubMed, ScienceDirect, and the European Journal of Endocrinology. Studies addressing obesity-related alterations in neural signaling, gut microbiota composition, and peptide hormone regulation (e.g., cholecystokinin, peptide YY, ghrelin) were analyzed. Particular attention was given to mechanisms involving dopaminergic reward circuits and emerging therapeutic targets such as ghrelin antagonists, gamma-aminobutyric acid modulators, and melanocortin-4 receptor agonists.

Evidence indicates that obesity is associated with significant alterations in gut microbiota composition, vagal signaling, and neuroendocrine regulation of appetite and reward pathways. These changes contribute to dysregulation of nutrient absorption, inflammatory responses, and metabolic homeostasis. Both invasive and non-invasive interventions - including dietary modification, microbiome-targeted therapies, pharmacological agents, and neurostimulation techniques - show potential to modulate GBA signaling and restore physiological balance.

Conclusions: Understanding the complex relationship between obesity and the gut–brain axis may provide novel therapeutic targets for improving metabolic regulation and reducing obesity-related complications. Further clinical and translational studies are required to confirm the long-term effectiveness of GBA-oriented interventions.

KEY WORDS: obesity, vagus nerve, cholecystokinin, ghrelin

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INTRODUCTION

Over the last few years, numerous studies have been conducted on the gut-brain axis (GBA) due to its relevance in multifactorial diseases, including obesity [1]. The GBA is a bidirectional communication between the central and the enteric nervous system. The gut microbiota is a complex bidirectional communication system that can directly and/or indirectly interact with the following systems: the enteric nervous system, immune system, and enteroendocrine systems [1, 2]. Signal transmission via spinal nerves, the vagus nerve (VN), and the circulatory system to the central nervous system (CNS) is also facilitated by gut microbiota. In addition, neurotransmitters such as dopamine, serotonin, norepinephrine, gamma-aminobutyric acid (GABA), etc., are involved in bidirectional communication [1]. Modifications in the GBA have been shown to influence neurological disorders along with obesity.

With obesity turning into a global pandemic in this research review, we analyze and discuss the effect of obesity on the GBA, focusing our discussion on the pathophysiology of the neurological system and its influence on the gastrointestinal microbiota, along with future technologies and treatments that affect the GBA.

AIM

This article presents obesogenic diets and neuroplasticity in the mesolimbic pathway, vagal nerve stimulation, impact of diets on gut-brain communication, along with future technologies affecting obesity.

MATERIALS AND METHODS

The following article includes various original papers and research reviews from PubMed, Science Direct to the European Journal of Endocrinology using keyword combinations such as: "obesity", "gut-brain axis", "vagus nerve", "cholecystokinin" (CCK), "peptide YY" (PYY), "Glucagon-like peptide-1" (GLP-1). Ultimately, we included

40 resources selected on their high relevance describing the relationship between the gut-brain axis.

REVIEW AND DISCUSSION

VASAL PATHWAYS AND NEURAL FEEDBACK IN OBESITY

The VN is a key component of the nervous system responsible for relaying messages between the gut and the brain. It plays a central role in regulating metabolic homeostasis, appetite, and the stress response. Interestingly, the VN does not have direct receptors within the intestinal lumen [3]. Instead, it receives signals from enteroendocrine cells, which convey information about nutrient intake and gut distention to the afferent nerve. This signal is then transmitted to the brain, indicating satiety. Subsequently, the brain triggers changes in blood glucose levels, enzyme secretion, metabolic hormones, gallbladder contraction, gut motility, gastric acidification, and gastric emptying[4]. These responses collectively help regulate appetite, digestion, absorption, and overall energy homeostasis.

Signals that stimulate the VN and induce hunger include ghrelin and galanin. Conversely, leptin, CCK, GLP-1, insulin, short-chain fatty acids, the melanocortin-4 receptor (MC4R) gene, and PYY suppress vagal activity. Under stressful conditions, the VN is also suppressed, as it is a key regulator of parasympathetic nervous system activity. Stress compromises the optimal environment for *Lactobacillus* populations—beneficial bacteria in the human gut microbiota—leading to increased gut permeability, sympathetic overactivity, and lymphoid tissue abnormalities [5, 6]. Stress disrupts immune function, metabolic patterns, and gut microbiome composition. Under chronic stress, however, the VN may become overstimulated, resulting in aging-like changes in intestinal stem cells, including growth arrest and mitochondrial fragmentation [7].

Aside from normal physiological responses, damage to vagal afferent and efferent nerves may influence the development of obesity. Individuals with low vagal tone typically exhibit delayed gastric emptying, causing food to remain in the stomach for a longer period, particularly within the proximal–distal region of the small intestine[8]. However, hypersensitivity of vagal afferent nerves may also contribute to functional dyspepsia [9]. High-fat diet consumption has been shown to reduce vagal afferent sensitivity to stretch and mucosal stroking, resulting in hyperphagic behavior [9, 10]. Specifically, chronic high-fat intake dampens vagal afferent responses to GLP-1 signaling, leading to a delayed sensation of satiety [11].

The circadian system has also been shown to modulate vagal afferent sensitivity, leading to alterations in meal size and feeding behavior [12]. Obesity impairs leptin-mediated vagal afferent signaling through the actions of protein tyrosine phosphatase 1B and suppressor of cytokine signaling 3, resulting in hyperleptinemia and an impaired satiety response [13]. Although impaired vagal afferent signaling contributes to physiological imbalance, Lyu et al. demonstrated that inactivation of the dorsal motor nucleus of the VN reduces the length of intestinal microvilli, suggesting a potential mechanism for decreasing fat absorption [14].

FOOD REWARD, CRAVING, AND BRAIN CIRCUIT MODULATION

Food-seeking behavior arises from both a survival instinct and the brain's reward system, which reinforces this behavior. However, the reward system can also promote increased appetite and food cravings, regardless of the calories required to fuel the body. Ghrelin and liver-expressed antimicrobial peptide 2 stimulate the growth hormone secretagogue receptor (GHSR), regulating the mesocorticolimbic pathway and modulating complex reward-related behaviors toward various stimuli [15]. Animal studies have shown that GHSR stimulation causes rodents to gravitate toward palatable stimuli due to ghrelin signaling, independently of caloric needs.

Cholecystokinin (CCK), released by enteroendocrine cells (ECs) in the intestine, stimulates the VN to promote sugar preference, though it does not specifically influence fat preference [16]. The sodium glucose-linked transporter 1 (SGLT1) receptor, located on intestinal ECs, has been identified as the primary sugar-preference receptor. Concurrent signaling from fat-only and combined sugar, fat, and amino acid vagal pathways in the intestinal tract is required to establish fat-preference behavior. Both circuits utilize G protein-coupled receptors, GPR40 and GPR120, which serve as gut–brain receptors for fat preference. Notably, fat, sugar, and amino acid signals converge at a unique class of vagal neurons (VIP-UTS2b) before behavioral preference is triggered. McDougle et al. confirmed that the gut vagal system contains two distinct sensory populations that regulate physiological responses to fat or sugar ingestion [17]. When these populations are activated simultaneously by combined fat and sugar consumption, nigrostriatal dopamine release increases exponentially compared to their separate activation, resulting in motivated feeding behavior and overeating. Specifically, ventral tegmental area (VTA) dopamine neurons increase activity following sugar ingestion [18]. However, impairment

of the hepatic branch of the VN disrupts post-ingestive activation of VTA dopamine neurons.

These findings support the development of an obesogenic diet characterized by excess calories, high saturated fat, and high sugar intake, including ultra-processed foods, fast food, and sugary beverages, coupled with low consumption of fruits, vegetables, and whole grains [19]. Natural sugars can activate the preference circuit, whereas artificial sweeteners fail to fully replicate this effect [20]. High-fat consumption reduces the responsiveness of nodose ganglion neurons to CCK and serotonin in obese mice, delaying satiety and promoting hyperphagia [10]. Moreover, insulin receptor signaling is dampened, dopamine transmission is impaired, and striatal dopaminergic network responsiveness is blunted [21]. Although this remains to be fully confirmed, these changes may create a cycle of increased intake of obesogenic foods, further exacerbating hyperphagic behavior.

It is widely accepted that changes in dietary intake can affect the composition of the gut microbiota. Conversely, alterations in microbiota composition may also influence host food preferences. Various animal models have demonstrated that shifts in microbiota can significantly impact host food preference behaviors [22, 23]. Peterson et al. observed that bacterial families such as *Ruminococcaceae* and *Lachnospiraceae* influence behavioral measures of impulsivity, attention, reward learning, and locomotor responses to novelty in both male and female rats [23]. Additionally, the genus *Barnesiella* specifically affects impulsivity in female rats.

In a randomized controlled human trial, fecal microbiota transfer was associated with increased brain dopamine transporter (DAT) levels, with *Bacteroides* correlating with increased DAT and *Prevotella* spp. correlating with decreased DAT [24]. Lower food-addictive behavior was observed in participants whose microbiota contained the genus *Blautia* and members of the phylum Actinobacteria, and intake of non-digestible carbohydrates such as lactulose and rhamnose is known to promote *Blautia* growth [25].

Overall, bacterial taxa including *Prevotella*, *Bacteroides*, *Lactobacillus*, *Bifidobacterium*, *Clostridium*, *Enterococcus*, and *Ruminococcus* have been shown to affect dopamine signaling, thereby influencing food preference behaviors in animals and contributing to pathological conditions related to dopaminergic dysfunction [26].

THERAPEUTIC INTERVENTIONS TARGETING THE GUT–BRAIN AXIS IN OBESITY

MICROBIOME-MODULATING THERAPIES

Microbiome-modulating therapies are treatments for obesity primarily targeted on the gut's microbial ecosystem. Research shows that the human gut contains around 100 trillions microbes with more than 5,000 species. Since the gut microbiome plays a crucial role in nutrient absorption, metabolism, energy regulation and appetite regulation, making it a potential target for obesity treatment. Common approaches include dietary modification, taking prebiotics and probiotics (combining both called synbiotics) and using fecal microbiota transplantation (FMT).

Obesity and gut microbial ecology are closely linked, with normal-weight individuals having higher Bacteroidetes and lower Firmicutes than obese individuals. The gut microbiota comprises Firmicutes and Bacteroidetes, comprising 70-90% of the population. Recent research has shown a positive association between obesity and the Firmicutes: Bacteroidetes (F/B) ratio in humans. However, this relationship may not be universally applicable across different populations. Obese individuals often have a higher F/B ratio compared to lean individuals, with studies showing an increase in body mass index (BMI) and a positive correlation with metabolic markers. Dysbiosis, an imbalance in gut microbiota, is linked to obesity [27].

Probiotics are live microorganisms and prebiotics are indigestible fibers that feed those good bacterias, combining them together is called synbiotics. In a randomized, double-blind, placebo-controlled trial, eighty individuals with obesity were given daily synbiotics supplement for a 12-weeks period to observe its effect. The participants were assigned either to placebo group or synbiotic group, with body composition, blood lipids, gut hormones, bile acids, and gut microbiota measured before and after the intervention. The synbiotic group result showed significantly reduced body fat percentage, waist circumference, and LDL-C, alongside increases in satiety-related hormones. Additionally, synbiotic supplementation improved gut microbial balance and enhanced beneficial bile acids, including chenodeoxycholic acid. These changes were more significant in people who had high cholesterol, suggesting that synbiotics may help with weight loss by improving gut health, bile acid levels, and appetite-related hormones [28].

FMT is a medical procedure that involves transferring processed fecal matter from a healthy donor into the gastrointestinal tract of the recipient. It works by restoring gut microbial diversity and improving immune regulation, which can help with metabolic health and weight control. The effectiveness of FMT, however, depends on several factors including donor microbiota, recipient characteristics, and diet or medication. Major challenges include the absence of standardized methods, donor screening, and limited knowledge of

gut microbiota dynamics. Further research should focus on identifying the key microbes and advanced personalised FMT strategies for better results [29].

PHARMACOLOGICAL INTERVENTIONS

Pharmacological interventions for weight loss and obesity have become more widely adopted in recent years due to their efficacy in clinical studies and positive outcomes, complementing lifestyle modification strategies. GLP-1 receptor agonists (GLP-1RA)—such as semaglutide, liraglutide, and tirzepatide—are among the widely used agents in class. They enhanced satiety which then reduced calories intake. In addition, emerging pharmacotherapies including dual and triple incretin analogs, ghrelin antagonists, GABA modulators, and MC4R agonists, offer novel mechanisms to modulate homeostasis and promote weight loss.

GLP-1RA are primarily used as a type 2 diabetes treatment to lower blood glucose levels and contribute to weight loss. Its mechanism is to mimic the hormone GLP-1, which leads to glucagon-dependent insulin secretion, inhibition of glucagon release, delayed gastric emptying and increased satiety. Available agents include both short-acting and long-acting GLP-1RA such as exenatide and semaglutide, respectively, as well as dual and triple receptor agonists such as tirzepatide, and retatrutide. These agents show significant efficacy in sustainable weight loss for obesity and type 2 diabetes as a monotherapy or in combination with lifestyle modification. Furthermore, they improve glycemic control, regulate appetite, and enhance cardiovascular health. The most common side effects are gastrointestinal symptoms, which are typically transient and manageable. Potential risks such as pancreatitis, thyroid disorder and depression, remain under investigation and require careful monitoring of use. Overall, GLP-1RAs represent promising therapeutic benefits, though ongoing research is needed to elucidate their long-term safety and optimize clinical use [30].

Novel therapeutic targets for obesity include ghrelin antagonists - blocking action of ghrelin at its receptor primarily in the hypothalamus, thereby, reduce appetite, GABA modulators - altering neural circuits to reduce food intake and increase satiety, and MC4R agonists - decreases food consumption and promotes energy utilization.

Ghrelin is a peptide hormone secreted mainly in the stomach and often called hunger hormone. It stimulates appetite and growth hormone secretion through activation of GHS-R1 receptors. Ghrelin levels are typically suppressed in obese individuals, resulting in decreased growth hormone release. Blocking ghrelin signaling reduces appetite, thereby representing a potential therapeutic approach for obesity management.

GABA is the primary inhibition neurotransmitter in the human brain and is commonly used for stress reduction and improved sleep. Although it has limited ability to cross the brain-blood barrier, GABA may regulate appetite and body weight through vagal nerve signaling when administered with food.

In conclusion, there are several pharmaceutical interventions in obesity management that targets the GBA. Each with its own unique advantages and clinical benefits, treatments should be individualized to optimize the best outcomes for each patient.

NEUROSTIMULATION AND BIOELECTRONIC MEDICINE

Neurostimulation and Bioelectronic Medicine are the use of electrical stimulators to modulate and restore neuronal activity. Various neurostimulation approaches have been one of the key alternative interventions for obesity management, including vagal nerve stimulation (invasive and non-invasive), transcranial magnetic stimulation (TMS) and deep brain stimulation.

The parasympathetic VN, a key component of the autonomic nervous system, regulates satiety, gastric motility and gastric emptying. Dysfunction of theVN is commonly observed in obese patients, hence reducing its efficacy. Vagus nerve stimulation(VNS) can be either non-invasive(n-VNS)—using external stimulators or invasive(iVNS)—surgical implantation of the device. nVNS devices are either placed on the outer ear to activate the auricular branch of VN or on the neck to activate the cervical branch of VN. Studies have shown that transcutaneous auricular VNS (taVNS) promotes the efficacy of gastric emptying since it activates the VN to regulate motility and secretion [31]. The invasive VNS device is placed subcutaneously in the chest wall, an electrode cuff positioned around the left cervical VN, and connected through the flexible wire. Research supporting the therapeutic potential of using VN stimulators has continued to grow for various treatments such as epilepsy, headache, pain-related disorders, cardiovascular disease and obesity [32].

TMS targets the dorsolateral prefrontal cortex of the brain. This area is crucial for cognitive control over food consumption and cravings. TMS is a non-invasive technique using an electromagnetic coil placed on a patient's scalp to deliver magnetic resonance to the targeted nerve cells.Studies demonstrated encouraging results, though further research is necessary to validate this outcome.

Electrical stimulators are directly targeted by GBA, modulating gut signals via the nervous system through

both invasive and non-invasive approaches. These interventions represent promising therapeutic alternatives for obesity management.

DIET AND BEHAVIORAL INTERVENTIONS

Overconsumption is what causes obesity. Dietary and behavioral modification are the most effective, accessible and sustainable methods for weight loss. Dietary choices such as mediterranean diets and ketogenic diets have gained more attention in the past years since it influences gut microbiota composition and improves communication between GBA, thereby supporting weight management. In addition, mind-gut therapies, including mindfulness and cognitive-behavioral therapy, help regulate eating behaviors, stress-related metabolic effects and appetite.

Ketogenic diets , focus on consumption of high-fat food, adequate amount of protein and minimal carbohydrate intake. Patients with ketogenic diets show an improvement of weight management as well as glycemic control, lower HbA1C level and increased high-density lipoprotein level [33]. Mediterranean diets promote beneficial gut microbiota, and ketogenic diets shift metabolism toward ketone bodies; therefore both diets influence GBA and support appetite regulation.

Mind-gut therapies are a key factor for sustained weight loss by improving self-awareness and eating behaviors. Mindfulness promotes awareness of food choices and portion control, while cognitive-behavioral therapy helps patients develop healthier coping strategies. Together, these approaches support long-term health management, self-esteem, overall body functioning and patients quality of life.

Despite pharmaceutical and dietary advancements obesity remains a global pandemic. With emerging technologies such as metabolomics and neuroimaging we have a greater understanding of the relationship between the GBA.

Advancements in technology have opened new avenues for studying the GBA in obesity. Multimodal approaches have enabled researchers to examine this topic from various perspectives. Metagenomic studies focus on the entire microbial community within the human gut using sequencing technologies. This approach provides insight into the composition, function, and diversity of the gut microbiota.

In metagenomics, genetic material is obtained and sequenced, with short DNA fragments assembled to analyze the types of species present. Previously, many of these microorganisms were difficult or nearly impossible to culture in the laboratory and were therefore largely unstudied. In addition to identifying microbial species, metagenomic studies allow researchers to assess the functions these organisms perform.

With respect to the GBA and obesity, metagenomic analyses have been instrumental in revealing that microbial imbalances can alter the production of metabolites such as short-chain fatty acids and lipopolysaccharide. These changes can disrupt gut barrier function, indirectly contributing to obesity development. Applying this knowledge may inform therapeutic strategies, such as probiotics or prebiotics, offering potential preventative measures against obesity [34].

Metabolomics is the study of metabolic processes in the body through the analysis of metabolites. Therapeutic diets, including prebiotics, probiotics, and fiber-rich nutrition, have been shown to influence metabolism. By detecting molecules involved in biochemical activities, researchers can gain insight into metabolic pathways and alterations. In the context of obesity, investigations have revealed varying levels of free fatty acids, which can alter lipid metabolism [35]. Other studies have examined changes in metabolism following dietary or exercise interventions, focusing on amino acid levels. These studies demonstrate that amino acid profiles can shift in response to different dietary patterns [36]. Notably, linear increases in cysteine levels have been associated with the progression of metabolic dysfunction [37].

Neuroimaging involves the use of computational and imaging techniques to study the structure and function of the CNS in disease. In obesity research, neuroimaging has been instrumental in understanding structural and functional changes in the human brain. Structural abnormalities have been observed through imaging, and importantly, longitudinal studies allow researchers to track changes over time. Magnetic resonance imaging techniques, for example, have been used to monitor alterations in the frontal cortex related to insulin sensitivity [38]. Other studies have examined sex-specific differences in obesity treatment, comparing outcomes and treatment responses between male and female participants, as well different types of brain imaging performed [39]. Applying similar neuroimaging technology can allow for the study of brain connectivity in relation to GBA. Thus, neuroimaging has proven important in showing how imbalances in microbiota can affect structures and connectivity within the brain, showing links between differences in GBA and obesity [40].

CONCLUSIONS

This study aimed to analyze the correlation between the gut–microbiota–brain axis and obesity. In recent years, the prevalence of obesity has increased dra-

matically. Obesity itself has been linked to numerous conditions and diseases, including, but not limited to, type 2 diabetes, cardiovascular disease, and sleep apnea. Recent studies have explored the role of the GBA - a communication network between the CNS and the microbiota of the enteric nervous system - in obesity. Examining the influence of the intestinal microbiome on obesity and its associated pathways may inform the development of individualized treatments targeting the microbiome. While neuroimaging studies and research involving diverse populations can help guide therapy design, further investigation is required to confirm the effectiveness and efficiency of GBA-targeted interventions in obesity.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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