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Obesity and Gastrointestinal Regulation of Food Intake

Obezite ve Gıda Alımının Gastrointestinal Düzenlenmesi

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ABSTRACT

The aim in this review is to explain the role of the gastrointestinal system in obesity and related complications by focusing on the biological mechanisms between obesity and the gastrointestinal system, based on the latest evidence in the literature. A systematic search of the literatures in the PubMed and ScienceDirect databases was conducted. Factors such as inflammation, mechanical space-occupying effect, microbiota, and adipocyte peptides are involved the development of obesity-related gastrointestinal system comorbidities. However, obesity occurs when the connection between the gastrointestinal tract and the brain changes. Signaling dysfunction disrupts the brain-gut axis, leading to increased frequency of food intake and excessive fat accumulation. Obesity increases the risk of developing gastrointestinal system disorders. However, the gastrointestinal tract and its pathophysiology play a key role the regulation of food intake and subsequent progression to obesity.

Keywords: Brain-gut axis, Food intake, Gastrointestinal system, Obesity

ÖZET

Bu derlemedeki amaç, obezite ve gastrointestinal sistem arasındaki biyolojik mekanizmalara odaklanarak literatürdeki en son kanıtlara dayanarak gastrointestinal sistemin obezite ve ilişkili komplikasyonlardaki rolünü açıklamaktır. PubMed ve ScienceDirect veri tabanlarındaki literatürlerin sistematik bir taraması yapılmıştır. Obezite ile ilişkili gastrointestinal sistem komorbiditelerin gelişmesinde inflamasyon, mekanik olarak yer kaplayan etki, mikrobiyota, adiposit peptitler gibi faktörler yer almaktadır. Bununla birlikte gastrointestinal sistem ve beyin arasındaki bağlantı değiştiğinde obezite ortaya çıkmaktadır. Sinyal verme disfonksiyonu, beyin-bağırsak eksenini bozarak, artan gıda alım sıklığına ve aşırı yağ birikimine yol açmaktadır. Obezite, gastrointestinal sistem bozukluklarını geliştirme riskini artırmaktadır. Bununla birlikte gastrointestinal sistem ve patofizyolojisi, gıda alımının düzenlenmesinde ve ardından obeziteye doğru ilerlemede anahtar rol oynamaktadır.

Anahtar Kelimeler: Beyin-bağırsak ekseni, Gastrointestinal sistem, Gıda alımı, Obezite

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INTRODUCTION

Obesity is a global health problem that is associated with an increased risk of cardiovascular disease, diabetes, and other metabolic disorders. One of the key factors contributing to obesity is an imbalance between energy intake and expenditure.[1] The gastrointestinal (GI) tract plays a critical role in regulating food intake, and dysregulation of GI signaling pathways can lead to overeating and weight gain.[2] Food intake is regulated by a complex interplay between various physiological and psychological factors. Among these factors, gastrointestinal (GI) regulation plays a critical role in controlling food intake.[2] In this review, we will discuss the role of the GI tract in regulating food intake in obesity and the different mechanisms through which the GI tract regulates food intake. Several GI hormones are involved the regulation of food intake. One of the most well-known hormones is ghrelin, which is produced in the stomach and stimulates appetite. Ghrelin levels increase before meals and decrease after meals. Another important hormone is cholecystokinin (CCK), which is produced in the small intestine and signals satiety to the brain. CCK is released in response to the presence of food the small intestine, and stimulates the release of pancreatic enzymes and bile. Leptin is a hormone produced by adipose tissue that regulates energy balance by suppressing appetite and increasing energy expenditure. Leptin acts on the hypothalamus to reduce food intake and increase energy expenditure. Leptin levels increase with adiposity, and obese individuals are often resistant to the satiety signals of leptin. The gut-brain axis is a complex system that involves communication between the GI tract and the central nervous system (CNS). The vagus nerve plays a critical role in this communication, as it carries signals from the GI tract to the brain. The CNS responds to signals from the GI tract by modulating food intake and energy expenditure.[2,3,4] The gut microbiota is a diverse collection of microorganisms that reside in the GI tract. Emerging evidence suggests that gut microbiota may play a role in regulating food intake. The gut microbiota produces various metabolites that can affect appetite and energy expenditure. For example, short-chain fatty acids (SCFAs) produced by gut bacteria can stimulate the release of gut hormones and reduce appetite.[5] In conclusion, the GI tract plays a critical role in regulating food intake through various mechanisms, including the release of GI hormones, the action of leptin, the gut-brain axis, and the gut microbiota. A better understanding of these mechanisms may lead to the development of novel therapies for the treatment of obesity and other metabolic disorders.

Obesity

Obesity, according to the definition of the World Health Organization (WHO), is the excessive or abnormal storage of fat in adipose tissue in a way that impairs health. Body Mass Index (BMI) and waist circumference measurement formulated by WHO are generally used the diagnosis and classification of obesity. BMI is calculated by dividing the person's weight in kilograms by the square of their height in meters (BMI=kg/m^2) (Table 1). BMI does not provide information about body fat distribution, which is associated with complications of obesity. Therefore, in addition to BMI, waist circumference measurement >88 cm in women and >102 cm in men is used in the diagnosis of obesity.[6]

Table 1. Classification of obesity according to BMI

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal	18.5-24.9
Overweight	25-29.9
Obese Class I	30-34.9
Obese Class II	35-39.9
Obese Class III	>40

Obesity, which is basically the result of an imbalance between energy intake and expenditure, is a global health problem caused by many factors such as genetic, metabolic, hormonal, hypothalamic, psychological, physical inactivity, and socio-economic level. The prevalence of obesity is increasing all over the world and in Turkey.[1,6] According to the 2015 report of the Global Burden of Disease (GBD) Obesity Collaboration Group, the obese population in the world has reached 711.4 million (107.7 million children and 603.7 million adults). According to WHO estimates, 3% of adults worldwide were overweight and 13% were obese in 2016. In the field study "Turkey Nutrition and Health Survey (TBSA)" completed in 2010, the prevalence of obesity in adults over the age of 18 was 30.3% (female 41%, male 20.5%), the frequency of morbid obesity was 2.9% (female 5.3%, male 0.7%).[7]

Obesity causes a serious increase in morbidity and mortality by negatively affecting the quality of life, and duration of people leading to health problems such as cardiovascular diseases, especially type 2 diabetes and

prediabetes, hypertension, hyperlipidemia, cerebrovascular disease, various cancers, Obstructive Sleep Apnea (OSA), Non-Alcoholic Fatty Liver Disease (NAFLD), Gastroesophageal Reflux Disease (GERD), Polycystic Ovary Syndrome (PCOS), infertility, osteoarthrosis, and depression.[1,7]

The gastrointestinal tract (GIS) plays an important role in obesity. Impairment of GI function and mechanisms regulating appetite and satiety cause obesity. Obesity also brings many health risks, disrupts the energy balance, and affects the GIS. Therefore, GIS is seen as the main target in obesity intervention. It is not clear whether the role of GIS in obesity is the cause or effect of this disease. Discussions can be made for both sides. Therefore, obesity can be considered as a disease of the GIS and/or concomitant obesity as a disease that affects GIS morbidity.[4,5]

Gastrointestinal Regulation of Food Intake

Energy intake is mainly regulated by the brain-gut axis. Incorporation of food -calories- into the GIS; It triggers a brain-gut axis response to regulate calorie consumption, stop signals, and appetite return. The GIS and its pathophysiology are key points the regulation of food intake and subsequent progression toward obesity.[8]

There are three main mechanisms that control food intake:

1) Hypothalamus: It acts as a center for the integration of nutrition and related neuroendocrine and GI activities.

2) GIS: Provides a rich source of hunger and satiety factors (hormones, nutrients, vagal stimulation, etc.) that regulate meal intake and termination.

3) Adipose-derived leptin: plays a role in long-term regulation of energy intake and expenditure.[2,8]

Diet lipid intake causes slowing of gastric emptying and transit time, release of GI peptides, and satiety. However, chronic diet lipid intake causes a significant impact on the complexity of factors that interact at various levels of the brain-gut axis and ultimately influence the regulation of body weight. It causes increased energy intake and consequently body weight gain through changes in sensitivity to satiety signals such as Glucagon-Like Peptide 1 (GLP-1), Peptide YY (PYY), CCK. Moreover, chronic exposure of the gut microbiota to diet lipid causes a significant impact on the host's metabolic functions.[9]

Apolipoprotein A-IV (apoA-IV) is secreted into lymph on chylomicrons in response to diet lipid intake. It is an acute satiety factor and plays a role in lipid metabolism and energy homeostasis. Many rodent and human studies show that diet lipid intake initially increases apoA-IV synthesis and secretion, but with chronic intake significantly reduces its response to diet lipids. This makes it more likely to contribute to obesity.[10]

Brain-Gut Axis

Many peptides such as ghrelin, insulin, GLP-1, PYY, oxyntomodulin (OXM), CCK, Pancreatic Polypeptide (PP) affect appetite. Peptides except ghrelin, cause a feeling of fullness and also some of them affects intestinal motility. They interact with the brain via the gut-brain axis, where they modulate peptide neurotransmitter release via the hypothalamic and brainstem centers.[4]

The hypothalamus is considered the center of hunger and satiety. The arcuate nucleus (ARC) located in the hypothalamus has two types of neurons expressing different peptides:

Group 1 neuron (orexigenic peptides): Neuropeptide Y (NPY) and agouti-related peptide (AgRP) are co-expressed. They stimulate food intake by initiating the feeling of hunger.

Group 2 neuron (anorexigenic peptides): Proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) are expressed. They stop food intake by creating a feeling of satiety.

Both of these subpopulations of neurons have projections to the lateral hypothalamic area and to the paraventricular nucleus. Their interactions are fundamental to energy homeostasis.[11]

Since the blood-brain barrier is semipermeable in the ARC nucleus, neurons are exposed to many hormones (mostly of intestinal origin). The signal from gut hormones provides the ARC with an energy state that either induces or suppresses food intake.

The GI tract provides the hypothalamus with necessary information regarding the chemosensory and mechanosensory mechanisms, and the amount of food digested and suitable for metabolism. This feedback is important for short- and long-term appetite control.[12] For example, vagal stimulation by mechanical stretching of the stomach wall; It causes short-term satiety, suppression of food intake, and release of gut hormones.[11] In contrast, leptin is the long-term regulator of the body's energy state.

Leptin is a hormone released by adipose tissue. Both serum and plasma leptin levels are positively correlated with BMI and total body fat. Leptin inhibits AgRP/NPY neuron activity and stimulates POMC neurons, providing

a long-term fat and energy store signal to the Central Nervous System (CNS). This results in decreased food intake and increased energy expenditure. Changes in leptin pathway signaling (leptin resistance, leptin receptor defect, etc.) can cause weight gain and obesity.[2]
Insulin is secreted in the pancreas by the islets of Langerhans. It supports the storage of energy, and its circulation increases in response to food intake and cases of obesity. Insulin receptors are expressed in the CNS, and injection of insulin into the brain in insulin-deficient animals significantly reduces eating behavior.[4]
Enterostatin, derived from the precursor protein procalipase produced by the exocrine pancreas and expressed in the gastric mucosa, reduces insulin secretion and stimulates adrenal corticosteroid secretion. It causes a feeling of fullness and especially reduces fat consumption.[13]
Ghrelin is a hormone synthesized from epithelial cells of the gastric fundus. Ghrelin stimulates the appetite and creates a positive energy balance. It also increases gastric motility.[8] Ghrelin modulates the synthesis and secretion of several neuropeptides the hypothalamus that stimulate feeding and regulate related hypothalamic functions. Unique among gut hormones, plasma ghrelin levels gradually increase with fasting and decrease soon after a meal. Plasma ghrelin levels also increase with diet-induced weight loss, suggesting that ghrelin may counteract diet-induced weight loss by stimulating hunger and increasing energy intake.[14]
The release of PP is proportional to the digestion of lipids and the caloric content of the food. PP induces satiety in animals and humans, suggesting potential anti-obesity effects. This results in reduced food intake and slowed weight gain.[15]
The effects of OXM are to reduce gastric secretion and food intake when administered centrally to rodents or peripherally to rodents/humans. No separate receptor has been identified for OXM. However, OXM binds to the GLP-1 receptor, and causes similar central neuronal activation patterns after peripheral administration.[16]
Gastrointestinal Inhibitory Peptide (GIP) is secreted from K cells in the duodenum and proximal jejunum a few minutes after food ingestion the presence of glucose and fat. Although GIP promotes energy storage through a direct effect on adipose tissue, it is not known to have an effect on food intake.[11]

Gastric Function

The stomach plays an important role in suppressing food intake. In addition to its storage and digestive properties, it is an organ with well-defined nervous and hormonal control mechanisms. Due to its continuity with the proximal location in the esophagus and GI tract, and rich vagal afferent innervation, it works as an early calorie and volume sensor during meals. The vagus nerve is stimulated by mechanical stretching of the stomach wall. This interaction includes enteroendocrine cells (EECs) and vagal afferent fibers. Volumetric tension also stimulates gastric enterochromaffin cells that secrete serotonin. These responses trigger the signal that reduces food intake.[17]
CCK is synthesized by the L cells of the small intestine and secreted in the proximal duodenum. CCK activates vagal afferents, and thereby relaxes the proximal stomach, reduces antral contractility, and activates pyloric tone, slowing gastric emptying. CCK has a half-life of only 1 to 2 minutes, suggesting that it is a short-term appetite regulator.[4,18]
Gastric emptying is a process that occurs by simultaneous inhibition and stimulation of the motor activity of the pylorus and duodenum. It is also affected by the nutritional content of the food. For example, a meal high in carbohydrates and protein, and low in fat has a low gastric emptying rate. Accelerated gastric emptying has been associated with obesity.[3]

Enteroendocrine Cells

EECs are distributed along the GI epithelia from the stomach to the rectum. EECs act as nutrient sensors of ingested food, sending further signals to the CNS and peripheral tissues mainly via humoral pathways. They are adjacent to the luminal contents throughout the intestine and colon, and contain numerous food-specific G protein-coupled receptors for sensing nutrients, bile acids, or fatty acids. Stimulation of these receptors induces the secretion of specific peptides that interact with other organs to regulate energy intake. EECs also regulate glucose homeostasis, bile acid enterohepatic circulation, nutrient absorption, and GI motility. [19]
GLP-1 and PYY are secreted by EECs. These peptides show their effects by affecting the postrema area or hypothalamic areas by afferent vagal and spinal nerve fibers or by crossing the blood-brain barrier as hormones.[3,20] GLP-1 receptor agonists facilitate glucose control by several different mechanisms, providing a subtle but long-lasting satiety effect. GLP-1 plays an important role in improving glucose homeostasis by stimulating insulin secretion and suppressing glucagon

secretion. GLP-1 has been shown to delay gastric emptying and intestinal transit time. PYY is another intestinal hormone that has a significant effect on ileal break and regulation of food intake. PYY3-36, the main form of PYY, reduces acute food intake in normal-weight individuals by regulating appetite circuits in the hypothalamus. Physiological effects of PYY3-36 include delayed gastric emptying and reduced gastric secretion.[20] Obesity occurs when the connection between the GI and the brain changes. Signaling dysfunction disrupts the brain-gut axis, promoting increased frequency of food intake and excessive fat accumulation. There will be no compensation in appetite for these increased energy stores.[3]

CONCLUSION AND RECOMMENDATIONS

In conclusion, GIS plays a key role in obesity. Obesity is a complex disease that results in increased health risks and diseases with a positive energy balance. The mechanism of appetite and satiety is mostly regulated by the neuroendocrine, gut-brain-adipose tissue axis. The GIS and its pathophysiology play an important role the regulation of food intake and subsequent progression to obesity. Although it is not clear whether the role of GIS in obesity is the cause or the result of this disease, consistent data in the literature seem to support the relationship between obesity and the increased risk of developing GI disorders.

Authorship contribution statement

Consept and desing: ÖD, AS.
Acquisition of data: ÖD.
Analysis and interpretation of data: ÖD.
Drafting of the manuscript: ÖD, AS.
Critical revision of the manuscript for important intellectual content: ÖD, AS.
Supervision: ÖD, AS.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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