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The role of gastrointestinal hormones in the pathogenesis and the treatment of obesity

Rola hormonów przewodu pokarmowego w patogenezie i leczeniu otyłości

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Summary

Obesity is an increasing problem in the world and affects a growing part of society on everyday basis. Its main causes are disorder of the hunger and satiety centers and metabolic disorders regarding to improper management of fatty acids, bile acids, carbohydrates and lipids. However, the exact mechanisms of the disease development are still poorly understood. In recent years more attention is focused on the role of gastrointestinal hormones in the pathogenesis of obesity, which also delivers new targets for pharmacotherapy.

This review aims to present the role of gastrointestinal hormones in the pathogenesis and the treatment of obesity. The abnormalities present in obese patients refer mainly to disturbances in concentration of adiponectin, leptin, peptide YY (PYY) and FGF-19.

Controlling and regulating the concentration of circulating gastrointestinal hormones is important in maintaining proper body mass and energy homeostasis. Currently, the most effective methods controlling the concentration of these hormones are pharmacology and bariatric surgery which improve also obesity-related comorbidities.

Streszczenie

Otyłość jest coraz większym problemem na świecie i dotyka codziennie coraz większej części społeczeństwa. Jej głównymi przyczynami są zaburzenia ośrodków głodu i sytości oraz zaburzenia metaboliczne związane z nieprawidłową gospodarką kwasów tłuszczowych, kwasów żółciowych, węglowodanów i lipidów. Niemniej jednak, dokładne mechanizmy rozwoju tej choroby są nadal słabo poznane. W ostatnich latach coraz więcej uwagi skupia się na roli, jaką pełnią hormony żołądkowo-jelitowe w patogenezie otyłości, która również zapewnia nowe punkty uchwytu w zakresie terapii farmakologicznej.

Celem niniejszej pracy jest przedstawienie roli hormonów żołądkowo-jelitowych w patogenezie i leczeniu otyłości. Zaburzenia, które wynikają z otyłości, zależą głównie od nieprawidłowej koncentracji hormonów żołądkowo-jelitowych, którymi są: adiponektyna, leptyna, peptyd YY (PYY) i FGF-19.

Kontrola i regulacja stężenia krążących hormonów żołądkowo-jelitowych jest ważna dla utrzymania prawidłowej masy ciała i homeostazy energetycznej. Obecnie najskuteczniejszymi metodami kontroli stężenia tych hormonów są terapia farmakologiczna i zabieg bariatryczny, które mają korzystny wpływ również na choroby współwystępujące związane z otyłością.

INTRODUCTION

Obesity is one of the most common metabolic disorders nowadays and it is a growing problem among world's population. According to World Health Organization (WHO), obesity has tripled worldwide since 1975 (1). It is believed that one out of five people will be obese until 2025 (2). As a matter of fact in 2016 upward of 1.9 billion adults over 18 years old were overweight, including 650 million classified as obese (1).

Obesity, defined as an excessive accumulation of body fat, exceeding its physiological needs and adaptive abilities, which can lead to adverse health effects (1, 3). It is

categorized on the basis of the body mass index (BMI). BMI above 25 kg/m^2 indicates overweight, while BMI exceeding 30 kg/m^2 distinguishes obesity (4).

Sedentary lifestyle and "western" diet are main factors contributing to the global obesity pandemic. This problem inevitably poses a challenge to global economy and public healthcare (2, 3).

It has been found that both obesity and overweight are associated with increased risk of comorbidities including type 2 diabetes mellitus, cardiovascular disease, metabolic syndrome and many others, which may lead to disability or shorten the life expectancy (3).

In reference to obesity the gastrointestinal system is a significant source of nourishment (3). Gastrointestinal hormones play an important role in regulation and control of food intake (5). Along with the growing problem of obesity in the world, gastrointestinal hormones have become one of the most popular topics of scientific research (3). These hormones exert exocrine actions, affect gut motility and also influence the secretion of insulin. They modulate releasing peptide neurotransmitters in the brainstem and abovementioned hypothalamic centres via gut-brain axis (5).

Consequently, this review focuses on the role of gastrointestinal hormones in the pathogenesis and the treatment of obesity. We took an in-depth look at the following hormones: adiponectin, leptin, peptide YY (PYY) and FGF-19.

REVIEW

Adiponectin

Adiponectin, known as adipocyte complement-related protein, is composed of 244 amino acids with a weight of approximately 30 kDa (6). Adiponectin is a cytokine produced by mature fat cells (6, 7). The hormone principally modulates fatty acid catabolism and glucose homeostasis (7). This adipokine is involved in inhibiting energy expenditure and increasing lipid accumulation in fat cells, which contributes to the increase in adipocyte differentiation and inhibition of lipolysis (8).

The level of adiponectin in serum of obese people is decreased. Adiponectin levels correlate inversely with adipose tissue and WHR, which shows a significant enhancement after weight loss (7). It is also known that plasma adiponectin concentration is negatively correlated with plasma insulin concentrations. What is more, the latest research proves that the level of adiponectin increases following bariatric surgery. Weight reduction in obese patients undergoing bariatric surgery is associated with increased insulin sensitivity and reduced insulin secretion (9). Due to the fact that the secretion of adiponectin is impaired as a result of obesity, the bariatric surgery is a practical therapeutic approach to restore the tissue's ability to produce adiponectin.

Leptin

Leptin is a protein composed of 146 amino acids with a molecular weight of 16 kDa (10). It is secreted mostly by adipocytes (7). Leptin transport is regulated by two receptors: ObRa, which is involved in the transport of leptin across the blood-brain barrier, and ObRe, which acts inversely to ObRa (11). These receptors are found throughout the body particularly in the central nervous system (12).

Leptin is a hormone that participates in regulating the energy management of the body via controlling glucose metabolism and appetite (7). It passes across the blood-brain barrier to act trough its receptor, inhibiting oxygenicity and stimulating anorexigenic neuropeptides located in the arcuate nucleus of the hypothalamus, which leads to reduction in food intake (13).

The conducted tests on serum leptin concentration revealed a significant positive correlation between leptin level and weight, BMI, WHR and body fat percentage (7). Leptin levels are markedly reduced by bariatric surgery, which correlates to the loss of body weight and limiting the consumption of calories (14). Leptin has been found to be a key indicator of energy storage in the body. It provides obesity signals to the hypothalamus, which as a result of these signals regulates energy homeostasis by maintaining a balance between energy intake and expenditure (11).

Numerous studies have proven that obese adults exhibit high levels of leptin with a significantly greater level of peripheral leptin than the content of leptin in the cerebrospinal fluid, which indicates the impairment of leptin transport across the blood-brain barrier. Forasmuch leptin is a large molecule its transport through the barrier requires the participation of the transport system. Therefore, elevated leptin levels in the circulation of obese people may cause saturation of leptin transporters in the transport system thus impairing the uptake of leptin. In the state of obesity, the ability of leptin to regulate appetite and energy expenditure is extremely reduced, which affects the weight gain (11).

Many studies have been conducted showing that the lack of leptin receptors or the genetic deficiency of leptin cause severe obesity (11). As a result, leptin replacement therapy markedly alleviates metabolic disorders related to obesity (15). Although leptin monotherapy cannot be used to effective obesity treatment, however, combination therapy of leptin with other substances that sensitize the body to leptin can achieve the appropriate therapeutic target (11). Moreover, it is known that bariatric surgery not only brings astonishing effects in improving body weight but also provide a significant impact on leptin concentration. Studies have shown a decrease in leptin concentration associated with a significant improvement in the metabolic and biochemical parameters of the blood after 6 months of surgical intervention (16). Therefore, leptin may be an important mediator of metabolic benefits induced by bariatric surgery.

Peptide YY (PYY)

PYY is an anorexigenic neuropeptide formed of 36 amino acids synthesized mainly in endocrine L cells of the colon and ileum, secreted at the beginning of

the digestion of the meal. The YY peptide occurs in two main forms, PYY 1-36 and PYY 3-36, the latter being the most common form of biologically active PYY and a specific agonist for the Y2 receptor (17).

One of the main functions of PYY is to reduce the appetite and decrease the amount of food intake by reducing gastric motility and enhancing satiety (17). Additionally, the other functions of PYY include: slowing gastric emptying and peristalsis of the digestive system, inhibiting the secretion of gastric acid and pancreatic enzymes, which affects the regulation of food intake (18).

Lower fasting level of PYY and reduced postprandial secretion are observed more frequent in obese people compared to non-obese individuals. This remark suggests that lowering the PYY feedback may be an important mechanism for obesity (19).

Studies have confirmed that intraperitoneal administration of PYY in mice results in decreased appetite over a period of approximately 24 hours. Moreover, the effect of satiety caused by the administration of PYY was noticed in obese people, which clearly indicates the lack of resistance to biological actions of this hormone in obesity. Despite the high therapeutic potential of PYY in obesity, therapies based on the use of PYY are not common. It is believed that one of the reasons for the lack of clinical use of PYY is a too short half-life of approximately 4 hours. In addition, many side effects have been reported after administration of the YY peptide (20).

Currently bariatric surgery is becoming increasingly popular as a method that not only gives great results in the reduction of unnecessary body weight but also as a method significantly affecting metabolic processes. In many scientific studies on the topic of bariatric surgery, it was observed that the postprandial PYY concentration correlates positively with response of weight loss after the surgery (19).

FGF-19

FGF-19 is a hormone-like member of the fibroblast growth factors (FGFs) family and is produced in the distal small intestine, ileum, brain and gall bladder. The FGF-19 transcription is controlled by bile acids through communication with nuclear receptor called the farnesoid X receptor (FRX) Therefore, along with the postprandial accretion of bile acids, the expression of FGF-19 increases (21).

The primary function of FGF-19 in adults is a regulation of bile acids homeostasis, which are amphipathic molecules released from the gall bladder into the small intestine and playing a key role in lipid solubilization (22). In addition, FGF-19 has insulin-independent stimulating effects on protein synthesis in the liver and induces glycogen production. Moreover, it improves glucose metabolism, and increases energy expenditure, which contributes to reduction of fat mass (23). FGF-19 produced in response to the absorption of bile acids, acts on the liver in order to inhibit cholesterol 7α hydroxylase (CYP7A1), which is a rate-limiting enzyme in the classical pathway of bile acid synthesis (24).

There are reports on the protective effect of FGF-19 against obesity caused by abnormal nutritional habits, and treatment with FGF-19 causes weight loss (25). Pharmacological activation of FRX receptors is considered to provide protection against insulin resistance and obesity. Therefore, the use of FRX receptor agonists, and induction of FGF-19 production, as a form of obesity therapy may prove to be an effective and non-invasive method of treating this metabolic disorder (26). The conducted research revealed that after the bariatric treatment there is an increase in circulating FGF-19, which is the result of direct stimulation of FRX by bile acids. These observations indicate the mechanism whereby bariatric surgery initiates metabolic regulation (21). The bile acids – FGF-19 axis may play a key role in the successful surgical induction of weight loss and improvement of metabolism (27).

CONCLUSIONS

To conclude, gastrointestinal hormones pose a significant role in maintaining energy balance and food consumption by affecting areas of the brain particularly associated with the regulation of appetite and nutritional behavior. The control of the concentration of these hormones and their signaling pathways may turn out to be a perspective target for obesity treatment. Bariatric surgery is the most effective therapy to achieve sustained and significant weight loss in obese patients. These innovative methods of obesity treatment improve also obesity-related comorbidities like blood pressure, diabetes, dyslipidemia or cardiovascular disease. Better knowledge about the mechanisms of action of individual hormones and their role in the pathogenesis of obesity may help finding more effective treatment strategies for the treatment of obesity.

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