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Effects of functional oligosaccharide on regulating gut microbiota in obese mice: a short review

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Abstract

Obesity is considered a complex and multifactorial disease that is rapidly spreading around the world, and it has become a global epidemic. As an "invisible organ" carrying the "second gene" of the human body, the intestinal flora participates in the metabolism of nutrients and energy in the human body. Current research suggested that gut microbiota might play a role in the development of obesity and associated comorbidities, affecting energy intake, lipid metabolism, immune responses, and endocrine functions. Functional oligosaccharides can be utilized by intestinal microorganisms to produce short-chain fatty acids, which affect the body's energy metabolism, absorption, and intestinal permeability, thereby mediating the occurrence and development of obesity. This study took obese mice as the main object and reviewed the effect of obesity on the gut microbiota, the effect of functional oligosaccharides on gut microbiota structure, and the mechanisms of gut microbiota in improving obesity, which aimed to provide therapeutic ideas for the prevention and treatment of obesity.

Keywords: functional oligosaccharides; obesity; gut microbiota; obese mice.

Practical Application: The effect of obesity on the gut microbiota, the effect of functional oligosaccharides on gut microbiota structure, and the mechanisms of gut microbiota in improving obesity were reviewed.

1 Introduction

Obesity is one of the most prevalent chronic metabolic diseases in the world, mainly caused by an energy imbalance, resulting in abnormal or excessive accumulation of body fat (Wang et al., 2022; Yildiz et al., 2021). With the advent of fast-paced life and changes in diet, the global obesity problem is rapidly spreading among adults, adolescents, and even children. Obesity can lead to various diseases and conditions, especially cardiovascular disease, type-2 diabetes, obstructive sleep apnea, cancer, osteoarthritis, and depression (Kleinert et al., 2018).

As an environmental factor, the gut microbiota can modulate the intake, absorption, and storage of energy in the host, thereby causing obesity. Prebiotic is an important example, it was defined as a substrate that is selectively utilized by host microorganisms conferring a health benefit (Gibson et al, 2017; Zhang et al., 2022). The findings suggest that gut microbiota dysbiosis can cause metabolic syndrome such as obesity. Compared with normal microbiota, the gut microbiota of obese hosts has lower gene richness and higher dietary energy acquisition capacity (Cotillard et al., 2013). A high-fat diet can alter the gut microbiota, leading to an increase in gut permeability and bacterial metabolites (e.g. endotoxin LPS). Excessive fat intake can lead to the increase of chylomicrons in the intestine. Endotoxin can combine with these chylomicrons, penetrates into the blood, and participates in systemic circulation, causing inflammation and metabolic diseases such as obesity (Boulangé et al., 2016; Cani et al., 2009). Prebiotics such as oligosaccharides and dietary fiber can alter gut microbiota structure, improve the integrity of gut connections, reduce endotoxemia, and prevent obesity. Of which, *Lactobacillus* and *Bifidobacterium* can regulate the intestinal microbial colony of mice with metabolic syndrome induced by a high-fat diet, as well as ease metabolic syndrome such as obesity (Wang et al., 2015). However, because of potential safety concerns, direct administration of probiotics to patients is not recommended. Studies have shown that oligofructose can reduce fat accumulation in high-fat mice, increase cecal weight, modulate gut microbiota, and increase fecal short-chain fatty acids (SCFAs) content (Respondek et al., 2013; Wang et al., 2017; Kao et al., 2018). Intake of xylooligosaccharides in mice can reduce serum cholesterol levels and increase the number of *Bifidobacteria* and *Lactobacilli* (Li et al., 2015). Moreover, Neyrinck et al. found that arabinoxylan oligosaccharides could control body weight and fat mass in mice with a high-fat diet by modulating the microbiota structure (Neyrinck et al., 2012). Therefore, the intake of functional oligosaccharides could be considered an effective method for reducing obesity-induced inflammation and intestinal dysbiosis.

2 The effect of obesity on gut microbiota

Under normal circumstances, the gut microbiota and the host are in an intricate dynamic balance, interacting with each other. For example, the host usually provides nutrients, and the gut microbes absorb them. At the same time, the host needs to use microbes to degrade substances that the host can not decompose and absorb. At present, studies have found that obvious changes

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in the gut microbiota could characterize obesity. Le et al. used metagenomics to analyze the gut microbial composition of 123 non-obese and 169 obese individuals in Denmark (Le Chatelier et al., 2013). The results showed that the number of gut microbial genes and the abundance of gut bacteria differed between the two groups. Individuals with low bacterial abundance have more pronounced overall obesity, insulin resistance, dyslipidemia, and inflammation than individuals with high bacterial abundance. Zmora et al. (2019) showed that a high-fat diet could easily induce obesity, and the increase of gram-negative bacteria for producing LPS in the intestine led to the imbalance of intestinal flora. In addition, LPS could stimulate CD14 and Toll-like receptor 4, resulting in increased white fat volume. Meijnikman et al. (2018) suggested that obesity decreased butyrate-producing bacteria. By comparing, it was found that obesity was associated with changes in the relative abundance of bacteria and proteus. Metagenomic and biochemical analysis indicated these changes affected the metabolic potential of the mouse gut microbiota. The results showed that the obesogenic microbiota could improve the ability to obtain energy from the diet (Turnbaugh et al., 2006). Finally, several prospective studies have shown that individuals with higher levels of *Staphylococcus aureus* and lower levels of *Bifidobacterium* in the gut during childhood were more likely to be overweight in adulthood (Guzzardi et al., 2022).

Furthermore, obesity could also be characterized by increased tone of the endocannabinoid (eCB) system and mild inflammation. It has been reported that the gut microbiota could modulate the hue of the gut eCB system, which in turn modulated gut permeability and plasma lipopolysaccharide (LPS) levels (Muccioli et al., 2010; Liu et al., 2003). The eCB system was found to control gut permeability and lipogenesis. LPS acted as a master switch by blocking cannabinoid-driven adipogenesis to control adipose tissue metabolism *in vivo* and *in vitro*. The results suggested that the gut microbiota determined adipose tissue physiology through the LPS-eCB system regulatory circuit and might play a key role in adipose tissue plasticity during obesity (Muccioli et al., 2010; Liu et al., 2003). Caesar et al. (2015) established an obese mouse model with a feed rich in lard. The study showed that *Bacteroides*, *Tulsibacterium*, and *Bisporium acidophilus* proliferated in the mouse gut, and the proliferation of these bacteria led to intestinal inflammation and insulin resistance.

Interestingly, obesity can also lead to altered gut microbiota in offspring. Animal experiments have shown that the gut microbiota of the offspring of obese mothers differs from controls (Ley et al., 2005). At the phylum level, the *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* of obese mothers increased, whereas Firmicutes of the offspring decreased. This resulted in an increased *Bacteroidetes*/*Firmicute* ratio in the gut microbiota of the offspring. At the genus level, *Bacteroides*, *Pasteurella*, *Desulfovibrio*, and *Myxospira* were more abundant in the offspring of obese mothers, while *Altobacterium*, *Clostridium cluster XIVa*, *Lachnospira Genus*, and *Oscillatory sp*. were less abundant.

3 The effect of functional oligosaccharides on gut microbiota structure

3.1 Metabolism of functional oligosaccharides

After the functional oligosaccharide enters the human body, it will not be digested and absorbed in the gastric and small intestine environments. Therefore, the function of functional oligosaccharides is mainly realized through the bacterial fermentation process in the large intestine (Meyer & Stasse-Wolthuis, 2009). On the one hand, gut bacteria could utilize oligosaccharides, leading to changes in the microbiota composition. On the other hand, after reaching the intestinal tract and fermenting, bacteria could ferment oligosaccharides to produce short-chain fatty acids, which were used as energy sources for intestinal cells and probiotics, thereby promoting probiotic proliferation, inhibiting the growth of harmful bacteria, enhancing intestinal immunity. It is worth mentioning that the utilization of oligosaccharides by microorganisms requires the participation of glycosidases and transporters, which mainly include two ways: 1) hydrolyzed first and then transported, 2) transported first and then hydrolyzed.

3.2 Effects of functional oligosaccharides on the microbiota structure of obese mice

Functional oligosaccharides can alter the gut microbiota structure, improve the integrity of gut connections, and reduce blood endotoxemia in obese mice. Wang et al. studied the effects of konjac mannose oligosaccharides on the gut microbiota of obese mice, and the results showed that the intake of konjac mannose oligosaccharides increased the beneficial effects of *Akkermansia muciniphila*, *Bacteroides acidifaciens*, *Lactobacillus gasseri*, and *Bifidobacterium pseudolongum* in the intestinal tract of obese mice, as well as decreased the ratio of *Firmicutes*/*Bacteroidetes* (Wang et al., 2018). Respondek et al. (2013) showed that short-chain fructooligosaccharides could reduce fat deposition, increase cecal weight, and regulate some specific bacteria in obese mice. Cheng et al. (2018) studied the changes in gut microbiota after galacto-oligosaccharide intake in obese mice, and the results showed that the abundance of *Ruminococcaceae* and *Oscillibacter* decreased, while the abundance of *Alloprevotella*, *Bacteroides*, and *Parasutterella* increased. Zheng et al. (2018) used chitin oligosaccharide to improve obesity in mice and found that the abundance of *Bifidobacterium*, *Lactobacillus*, *Akkermansia,* and *Bacteroides* in the intestine of obese mice was lower than that of mice fed with chitin oligosaccharide. Hoving et al. (2018) studied the effect of konjac mannose oligosaccharide intake on the gut microbiota of obese mice and found that the abundance of *Bacteroidetes* was increased while the abundance of *Firmicutes* was decreased. Therefore, it was suggested that *Bifidobacterium*, *Lactobacillus*, *Akkermansia,* and *Bacteroides* abundances are negatively correlated with the obesity degree and can improve obesity symptoms (Dao et al., 2016; Moya-Pérez et al., 2015; Herrmann et al., 2017), while *Oscillospira*, *Coprococcus,* and *Ruminococcus* are positively associated with obesity (Tims et al., 2013). As mentioned by Cornejo-Pareja et al., ingested functional oligosaccharides were fermented by intestinal microorganisms to produce a large amount of short-chain fatty acids, which were utilized by microorganisms to increase the richness of the flora (Cornejo-Pareja et al., 2018).

4 The mechanisms of gut microbiota in improving obesity

4.1 Probiotic

In general, functional non-digestible oligosaccharides, such as isomalt oligosaccharides, fructooligosaccharides, and

raffinose mixed lactose, can selectively promote the proliferation of *Bifidobacteria*, inhibiting the corrupt microorganisms multiply. Studies have found that many gut bacteria can use functional oligosaccharides. It was found that galacto-oligosaccharides, raffinose, or arabino-oligosaccharides could be used by *Rectobacter*, *Roche*, *Erwinia*, *Bacteroides,* and *Clostridium*. Short-chain fatty acids produced by gut microbial fermentation of oligosaccharides could induce thermogenesis in adipose tissue, by activating the intestinal receptor GPR43 or brown fat and downregulating peroxisome proliferator-activated receptor γ, thereby reducing body weight in high-fat diet-induced obese individuals (Rooks & Garrett, 2016). In conclusion, the possible mechanisms of oligosaccharides in the treatment of obesity include: 1) regulating gut microbes, 2) strengthening intestinal barrier, 3) inhibiting pathogens, and 4) regulating immunity. Among them, reducing the risk of obesity by regulating gut microbiota is the most popular in current research, attracting extensive attention from researchers.

4.2 Brain-gut axis

The brain-gut interaction is critical for energy homeostasis, which will be disrupted in obesity, leading to positive energy balance and weight gain. Perry et al. found that changes in rodent gut microbiota could increase acetate production (Perry et al., 2016), activating parasympathetic nerves, promoting insulin secretion, muscle augmentation, and ghrelin secretion, ultimately leading to violent pathological feedback pathways of binge eating. As an autoactive substance, 90% of 5-hydroxytryptamine (5-HT) is distributed in enterochromaffin cells and is often stored in cell granules together with ATP and other substances and will be secreted and released after being stimulated. It was found that the 5-HT is more present in the cerebral cortex and nerve synapses, which can control human appetite, reduce energy intake, increase energy consumption, and achieve the purpose of weight loss (Wu & Liu, 2017). Furthermore, Zmora et al. indicated that the body could ingest functional oligosaccharides to produce a large amount of short-chain fatty acids (Zmora et al., 2019), which could improve obesity symptoms, by stimulating the short-chain fatty acid receptor GPR41, exciting the central nervous system to promote intestinal glycogenesis, and inhibiting the production of LPS.

4.3 Chronic inflammation

The gut microbiota is currently considered having a potential effect on the development of obesity and its associated comorbidities. It is well known that excessive fat intake can cause an imbalance of intestinal flora in animals. The gut microbiota imbalance can lead to increased intestinal permeability and endotoxemia, further leading to low-grade chronic inflammation in animals. Therefore, chronic inflammation plays an important role in the induction and promotion of obesity (Al-Assal et al., 2018). Functional oligosaccharides can promote the proliferation of beneficial bacteria in the body, inhibit the release of endotoxin, reduce intestinal permeability, and indirectly prevent endotoxin from entering the blood through the intestine and binding to endotoxin-binding proteins, thereby reducing the activation of gene encoding inflammatory effectors to improve obesity. Boulangé et al. (2016) suggested that chronic inflammation was closely related to LPS-induced macrophage infiltration, obesity, and related metabolic diseases, and it could impact the gut microbiota.

5 Conclusion and prospects

As prebiotic, functional oligosaccharides can improve obesity by regulating the gut microbiota, and the mechanism is related to the proliferation of beneficial bacteria, the regulation of metabolism based on the brain-gut axis, and the inhibition of chronic inflammation. The various effects of gut microbiota and its metabolites on the host need more basic and clinical trials to study to provide a more theoretical basis for the prevention and treatment of obesity. With the development of metagenomics and metabolomics, intestinal intervention can be carried out for sensitive bacteria, such as the development of prebiotic-specific strains, intestinal transplantation of sensitive strains, and development of agonists or blockers related to the action of metabolites, which can provide guidelines for the prevention and treatment of chronic diseases. In addition, more and more multifunctional oligosaccharides have been discovered, such as human milk oligosaccharides, bird's nest polysaccharides, and wolfberry polysaccharides, and their functional properties are being studied to provide a scientific basis for the development of functional food ingredients.

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