

The Mechanisms of Microbiota Induced Obesity and Possible Treatment

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ABSTRACT: *Obesity is a complex metabolic disease involving excess body fat. The basic cause of obesity is the imbalance in energy consumption and energy expenditure. While there are multiple of factors that can cause obesity, a number of studies have found strong interrelations between obesity and gut microbiota which is responsible for the improvement of energy and nutrition absorption, changes in metabolic pathways, and changes in brain activities and behaviors. Based on the understanding of the relationships between gut microbiota and obesity, effective treatments have also been designed. The paper will review current understandings on how changes in gut microbiota cause obesity and current effective treatments on obesity.*

KEYWORDS: *Obesity, gut microbiota, energy absorption, metabolic pathway, brain activity, treatment for obesity.*

Introduction

Since the 1970s, obesity has become one of the most prevalent diseases around the world. Worldwide obesity has nearly tripled since 1975, reaching 2 billion in 2019.[1]. In the meantime, obesity is also related to other diseases and health problems, such as cardiovascular diseases, diabetes, fatty liver diseases, and certain cancer.[2]

Gut microbiota plays a huge role in food digestion. Although human cells are able to produce enzymes that digest large food molecules into small, absorbable molecules, the human genomes encode only for a small number of digestive enzymes. A large portion of enzymes is actually encoded by the gut microbiota.[3] Therefore, gut microbiota also plays a huge role in obesity, and studies have shown that gut microbiota is able to affect various things that are related to obesity.

Besides gut microbiota, the cause of obesity can be various, including age, environment, lack of exercise, and diet. Due to the complexion of obesity, current treatments, such as anti-obesity drugs and for obesity are sometimes ineffective and dangerous.[5] However, based on the strong relation between obesity and microbiota, manipulation of gut microbiota can be a safe and efficient treatment for obesity. This

paper is focused on the mechanisms and possible treatments of microbiota-induced obesity.

Improvement on energy and nutrition absorption

Obesity implies an imbalance between the energy intake and expenditure, which means that the energy one gets from food is excessive compared to the energy one consumes, leading to body adiposity. With more food digested, meaning degrading large food molecules to small, absorbable food molecules, more energy will be absorbed by the host, and further leading to the growth of adipose tissue in order to store the extra energy. Therefore, it has been proposed that obese individuals have a higher energy harvesting efficiency than lean individuals. When researchers transplanted microbiota from obese mice to germ-free mice, the germ-free mice, given the same amount of food, underwent a significant increase in body fat.[4] The study shows that the gut microbiota is vital to the efficiency of food digestion and energy absorption, which varies from person to person due to different composition of gut microbiota.

Microbiota is composed by several microorganisms, but mainly composed by two phyla: Firmicutes and Bacteroidetes, representing 90% of gut microbiota.[4] A number of studies and experiments conducted on both rodents and human have suggested that there is a reduction in Bacteroidetes and increase in Firmicutes in obese subjects compared to lean subjects. Microbial fermentation, conducted by these two phyla, is thought to be the main cause of weight gain due to two end products— Monosaccharides and short chain fatty acid (SCFA).[4] Bacteroidetes are gram negative bacteria, colonizing the human gut at densities up to $5-8 \times 10^{10}$ CFU per gram of feces. The dominant genre of Bacteroidetes are Bacteroides and Prevotella.[6] Studies have shown that the microbiome of Bacteroidetes encode carbohydrates-active enzyme(CAZymes), which helps to digest polysaccharides into monosaccharides, increasing the efficiency of energy absorption.[3] Some groups of Bacteroidetes also produce SCFA through microbial fermentation, specifically propionate and acetate, which can be easily absorbed by intestines. Moreover, propionate can be the metabolic disruptor that increases the risk of obesity and diabetes, and is produced through succinate pathway by Bacteroidetes from hexose sugar.[7] Firmicutes, in the other way, is the major producer of butyrates.[4] Accompanied with the production of SCFAs, other chemicals, including H₂, CO₂, CH₄, phenols, and amines, are also produced, which in turn influence the rate of cholesterol synthesis.[4] SCFAs can be easily absorbed by human, leaving only 5-10% in feces; most of SCFA are metabolized in three ways: in the colonic epithelium as the energy substrate, in the hepatocytes for gluconeogenesis and lipogenesis, and in muscle cells.[4] Butyrates, in this case, is metabolized in the colonic epithelium and hepatocytes, which explains why a high Firmicutes and Bacteroidetes ratio is present in obese individuals' gut microbiota. Therefore, with an abnormal composition of microbiota, SCFAs would be excessively produced, and further increasing the energy absorption and causing obesity.

Besides the direct effects of SCFA on energy absorptions, there are also evidence that SCFA activates the GPR 41/43. The answer for whether GPR is beneficial or harmful to the organisms is inconsistent. The studies suggest that GPR may exert both anti or pro inflammatory effects on tissues.[8] Considering that inflammation and immune activation are strongly associated with body adiposity and obesity,[4] SCFA has the potential to cause obesity by activating GPR 41/43, causing inflammatory actions, and eventually bringing body adiposity, which is a completely different way. Knowing that GPR41/43 is related to chronic inflammation which affects gut microbiome, we can take GPR as therapeutic targets to treat obesity.[8]

Changes in metabolic pathways

Gut microbiota is strongly related to various metabolic pathways. Firstly, gut microbiota can affect the lipid metabolism and host's lipid level. A small portion of gut microbiota have the ability to secrete bile acids apart from the bile acids produced by hosts. These bacteria produced bile acid would enter blood stream and modulate systemic lipid and carbohydrate metabolism through G-protein coupled receptor(GPCR).[9] Moreover, bile acids can activate nuclear receptor FXR, which stimulates the transcription of gene that regulates several metabolic pathways, including cholesterol synthesis pathways and glucose metabolism[4]. Another way that gut microbiota affects lipid metabolism is through the production of SCFA. The production of propionate, acetate, and butyrate would be efficiently absorbed by intestines, as mentioned before, which also affects the lipid level.[4,9] There are also speculations that gut bacteria would generate intermediate precursor that further metabolized by host and directly affect the lipid level after metabolism.[9]

Choline has also been found to have a relation with microbiota. The microbial activities on dietary choline have been found to affect the diversity of microbiota, which in turn cause obesity.[4] In addition, the metabolism of choline into TMAO is also correlated to cardiovascular diseases.[4] Other metabolic pathways, such as the essential amino acids pathways, also have the potential to cause obesity, but the underlying mechanism are not clear.[4]

Changes in brain activities and behaviors

A number of studies have concluded that microbial activities can affect brain activities and behaviors. Evidence have suggested that alterations of microbiota may related to brain diseases and emotional behaviors such as anxiety, autism spectrum disorder, and chronic pain.[10] Based on the studies on germ-free animals, scientists speculate that gut microbiota is related to the hippocampal expression of BDNF, a key protein that involved neuronal plasticity and cognition, and gene expression changes in cerebellum and hippocampus.[10] Moreover, a research conducted in 2018 found that there is a strong correlation between the microbial disorder and major disorder depression disorder(MDD).[11] For patients who have MDD, the diversity of Firmicutes in their gut microbiota significantly decreased, suggesting a causal relation between the decrease of Firmicutes and MDD.[11]

Regarding obesity, accumulating evidence on the relationship between depression and obesity tells us how gut microbiota is able to cause obesity in the nervous level. Based on experiments, the body mass index(BMI) was found to have a positive effect on depression and percentage of depression individuals.[12] The speculation of such results is that depressed individuals may overeat.[12] Currently, there are no consistent agreement on the relation between depression and overeat, but the statistical data shows that obese individuals have a higher risk of depression, and depressed individuals have a higher obese rate than normal people,[13] imply a mutual relationship between depression and obesity.

Other studies have also suggested that gut microbiota has the potential to manipulate behaviors by changing food preferences.[4] Researchers found that for germ-free mice, the taste receptors for fat and sweets are changed, and germ-free mice consumed more sweet solution than normal mice.[4] In addition, long-term high-fat diet results hyperphagia in animal model. A possible explanation is presence of lipopolysaccharides(LPS) in diet, which activates the toll-like receptors 4(TLR4) on vagal afferent neurons.[4] The activation will eventually lead to TLR4's insensitivity to the effect of leptin, a protein involved in the regulation of food intake and weight control, and CKK, a chemical that involves in appetite suppression, leading to hyperphagia and obesity.[4]

Possible treatments

Currently, there are no effective treatments for obesity except bariatric surgery. Although bariatric surgery is effective, it cannot guarantee long-term effects on weight loss, meaning there will be possibilities that the weight regains. A short-term efficacy may lead to further bariatric surgeries, which is dangerous and invasive to the body. Knowing that the composition of microbiota is able to strongly affect obesity, the use of probiotics, prebiotics, and antibiotics are promising effective treatments for obesity.

The theory that probiotics work is applying a adequate amount of healthy microbes to gut and create benefits such as modification of the gut microbiota, increased adhesion to intestinal mucosal surface, production of anti-microorganism substances and modulation of immune systems.[13] Experimental tests on probiotics such as Lactobacillus and Bifidobacterium have been done, and the results are positive: the subjects show significant reduce in BMI, weight, and body fat after probiotic treatments.[13]

Prebiotics are a selected molecule or chemical that results in specific changes in the composition of microbiota. Prebiotics are usually oligosaccharides that promote the growth of Lactobacillus and Bifidobacterium.[13] In the meantime, they can also reduce the population of Bacteroidetes and firmicutes. Moreover, the combination of use of probiotics and prebiotics, called synbiotics, is also effective on the treatment of obesity

Engineered microbes are also a promising treatment of obesity. Engineered microbes can directly deliver substances that contribute to weight loss, such as N-

acyl-phosphatidylethanolamines (NAPEs). A group of scientists has tried to use synthesized recombinant probiotics *E. Coli* that secrete NAPEs, which resulted in weight loss and reduction of body fat.[13]

Fecal microbiota transplant(FMT) is a potential treatment of obesity and diabetes. The mechanism of FMT is to transplant feces with healthy microbiota to obese individuals and improve the diversity of microbiota which contributes to weight loss. However, the treatment doesn't work for all. Studies have shown that FMT treated individuals are divided into two groups: responders and non-responders, with responders having a significant increase in microbiota diversity.[14] In addition, the effects of FMT is transient, which means further improvement on FMT have to be done.

Besides the use of microbial treatments, a number of studies have also found the effects of phenol on the composition of microbiota. An increase in phenol may contribute to the diversity of microbiota, which would facilitate weight loss.[4] In addition, rodents experiment suggests that the phenol in grapes can help to control weight and facilitate weight loss by increasing brain's sensitivity to leptin, which triggers a series of compensatory mechanisms and reduce the intake of fat.[15] Based on this results, the use of phenols is a promising way to reduce the appetite which contributes to weight loss, but more experiments and human tests are needed.

Conclusion

Lots of evidence has shown that the changes in the composition of microbiota is strongly related to obesity as it is able affect energy absorption, metabolism, and brain activities. Moreover, there are strong interrelations between diet, microbiota, and brain. With more studies and experiments figuring out the complex interrelationships between gut microbiota and hosts, we have promised to fully understand the mechanism of microbiota induced obesity, and more effective treatments will be designed.

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