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Core Mechanisms and Research Advances in Gut Microbiota Regulation of Energy Metabolism Driving Obesity

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Abstract: The global obesity problem is still increasing, influenced not only by dietary patterns but also by the important part played by dysbiosis in the gut microflora. The gut bacteria control the body's energy metabolism through various pathways, interfering with the relationship between energy intake and expenditure to cause obesity. This study investigates the main mechanisms by which the gut microflora affect the energy metabolism to result in obesity, particularly involving the influence of short-chain fatty acids (such as acetic, propionic and butyric acids) on energy intake, lipid synthesis and insulin signalling; the promotion of fat absorption and disruption of energy expenditure through the FXR and TGR5 receptors by bile acids; the induction of chronic inflammation and insulin resistance by lipopolysaccharides; and the regulation of factors like leptin and adiponectin by the microflora to change the appetite and energy homeostasis. It also gathers the classic experimental data indicating the association between the microflora and obesity. Current research offers theoretical basis for the prevention and treatment of obesity by means of gut microflora intervention. However, it is necessary to carry out further investigations into the effectiveness of the microflora metabolites and personalized regulation of human microflora. Precise interventions focusing on the gut microflora will become an important direction in the management of obesity.

Keywords: Gut Microbiota; Obesity; Energy Metabolism; Short-chain Fatty Acids; Bile Acids; Lipopolysaccharides; FXR; TGR5.

1. Introduction

Obesity is now a major public health issue, and the effectiveness of conventional treatments is not satisfactory. Recently, the gut microbiota has been recognized as an important environmental factor affecting host metabolism, where its imbalanced structure is closely related to obesity. This systematic review investigates the main mechanisms by which the gut microbiota controls energy metabolism through the involvement of short-chain fatty acids, bile acids, lipopolysaccharides and bile factors, thus contributing to obesity. It also suggests new research directions in order to provide useful information for the prevention and treatment of obesity.

2. The Emergence of Gut Microbiota and Obesity Research

Research about the relationship between gut microbiota and obesity was started in 2004, when Backhed et al. proved that gut microbiota can affect the host's metabolism. In experimental studies on animals, they mainly compared germ-free (GF) mice with specific-pathogen-free (SPF) mice, providing the same polysaccharide diet to both groups and observing the metabolic changes. The results showed that the body fat content of GF mice was 42% lower than that of SPF mice, while their food intake was 29% higher. Then, scientists transferred the gut microbiota from SPF mice to 8-week-old germ-free mice and studied the changes for 14 days. They found that the body fat in the mice which were colonized increased about 57%, indicating that gut microbiota is one of the important factors causing obesity [1]. Later in 2006, Turnbaugh et al. chose genetically obese mice (ob/ob) and their normal littermates, and transplanted their gut microbiota into germ-free mice. They discovered that the obese mice had a higher Firmicutes/Bacteroidetes (F/B) ratio and approximately 47% more body fat, thus confirming that the gut microbiota can independently produce an obese phenotype [2]. At the same time, Ley et al. also verified this result through large-scale population investigations, showing that obese people usually have a high F/B ratio [3].

3. Gut Microbiota and Energy Metabolism

Having discovered the causal relationship between microbiota and obesity, researchers also investigated the fundamental mechanisms controlling energy metabolism at the molecular and pathway levels. Dysbiosis disrupts metabolic processes, thereby driving obesity. Key factors include the regulation of short-chain fatty acids (SCFAs), bile acid synthesis, and the involvement of lipopolysaccharides and leptin.

3.1. Short-Chain Fatty Acids (SCFAs)

Short-chain fatty acids (SCFAs) constitute a class of saturated fatty acids with carbon chains comprising 1–6 carbon atoms, primarily including acetate (C_2), propionate (C_3), and butyrate (C_4). These arise when certain dietary carbohydrates (such as dietary fibre) cannot be directly digested and absorbed by the small intestine, subsequently entering the large intestine where they serve as fermentation substrates for the gut microbiota . Symbiotic bacteria within the large intestine (predominantly from the phyla Firmicutes and Bacteroidetes) ferment and break down these dietary fibres anaerobically using their own enzymatic systems. This process releases energy whilst producing metabolic

byproducts—short-chain fatty acids [4-5]. SCFAs are typically present in the gut and can be absorbed into the bloodstream. Some SCFAs are excreted via respiration, urine, and faeces.

Imbalance in SCFA ratios constitutes a core mechanism underlying obesity.

3.1.1. Acetic Acid

Acetic acid is the main SCFA generated by gut microbiota fermentation, constituting more than 60% of the total SCFA produced.

In the obese people, the phylum Firmicutes has higher levels while the phylum Bacteroidetes has lower levels, which increases the capacity for polysaccharide degradation. This results in an increase of acetate production. Acetate affects the metabolism through two ways: firstly, its low molecular weight and high lipophilicity allow it to easily pass through the blood-brain barrier and stimulate the vagus nerve (DMV) (which is the tenth cranial nerve and the longest, most widespread parasympathetic nerve in the human body, controlling 'visceral autonomic regulation'). Stimulation of the vagus nerve causes the pancreas to secrete a large amount of insulin independent of glucose, leading to hyperinsulinaemia. This will promote fat synthesis and storage, thus resulting in obesity [6].

At the same time, some acetate is transported to the liver through the portal vein, where it is converted into acetyl-CoA by acetyl-CoA synthase 2 (ACSS2). This leads to the synthesis of fatty acids and triglycerides, which results in lipid accumulation and is helpful for the development of obesity. Moreover, this process also promotes the growth of tumour cells [7]. At the same time, some acetate directly induces fat formation, suppresses lipolysis and intensifies lipid deposition.

3.1.2. Propionic Acid

High fat diets cause a change in the internal microflora and result in the increase of propionic acid. Excessive acetic acid can activate the sympathetic nervous system (one of the branches of the autonomic nervous system which is concerned with stress reactions, energy supply, accelerated metabolism and raised blood sugar and pressure, in contrast with the parasympathetic [vagus] function). Excitement of the sympathetic nervous system leads to the release of noradrenaline (NE) which significantly increases the level of glucagon. This will promote the gluconeogenesis process in the liver (the process by which non carbohydrate substances such as amino acids, glycerol, propionic acid, lactate etc. are mainly converted into glucose in the liver), resulting in the breakdown of glycogen and an increase of blood glucose. At the same time, in the adipose tissue, the adipokine FABP4 (which is responsible for the transport, storage and release of fatty acids) is produced by the adipocytes. The elevation of FABP4 has the ability to directly inhibit the insulin signal and also promotes the breakdown of triglycerides in the adipocytes to form free fatty acids (FFAs). The elevated levels of FFAs in muscles, liver and adipose tissue inhibit the IRS-1/PI3K/Akt insulin signal pathway, thus further inducing insulin resistance. This resistance prevents the decrease of blood glucose and causes hyperinsulinaemia which is beneficial to the development of obesity. In 2019, Linares et al. proved through animal experiments that propionic acid can cause metabolic disorders and confirmed this effect in humans [8]. The main difference between acetate and propionate in inducing obesity is their action mechanisms: acetate can stimulate insulin secretion by activating the vagus nerve, while propionate causes obesity by exciting the sympathetic nervous system to compensate for hyperinsulinaemia.

3.1.3. Butyrate

Butyrate acts as an energy supply for colonic cells which thus increases the absorption of dietary energy in the gut. For the same diet, a person who absorbs more calories will have more fat reserves and may become obese easily. According to the three-level verification model proposed by Canfora EE in 2015, the study on human colonic/intestinal epithelial cells (Caco-2), mice and humans indicates that butyrate enhances the absorption of sugars and fats by intestinal cells directly. This absorption effect is more obvious in high-fat diets and is connected to the occurrence of obesity [9]. Furthermore, butyrate can control the differentiation of adipocytes and lipid metabolism. It activates the PPARγ signal pathway, resulting in the differentiation of preadipocytes into mature adipocytes and increasing fatty acid synthesis while decreasing the rate of lipolysis. The research done by Peng et al. in 2009 shows that the intervention of butyrate can increase the weight of white adipose tissue in animals, leading to fat accumulation [10]. In conclusion, butyrate affects the maintenance of a positive energy balance and the occurrence of obesity by improving the intestinal absorption of nutrients, promoting fat synthesis and storage, and reducing lipolysis. It performs an important function as a molecular mediator linking the gut microbiota with the development of obesity.

At the same time, besides SCFAs, bile acids play an important role as key mediators in the energy metabolism regulated by the microbiota.

3.2. Bile Acids

Bile acids are an organic acid group produced by the liver, which is an important part of bile. They are related to energy metabolism. The primary bile acids are mainly synthesized in the liver from cholesterol. This reaction is mainly carried out by cholesterol 7α-hydroxylase (CYP7A1), which transforms cholesterol into 7α-hydroxycholesterol and finally produces cholic acid (CA) and chenodeoxycholic acid (CDCA). In the intestine together with bile, cholic acid (CA) is converted to chenodeoxycholic acid (CDCA) by bacterial 7α-dehydroxylase, while chenodeoxycholic acid (CDCA) is changed into lithocholic acid (LCA)[11].

3.2.1. Regulation Mediated by the Farnesoid X Receptor (FXR)

FXR is an important nuclear receptor for bile acids, mainly located in the liver and intestine. When intestinal FXR is activated by a great deal of bile acids (e.g., TDCA), it represses the expression of CYP7A1, a key gene in bile acid synthesis. Therefore, the total amount of bile acids decreases, affecting the efficiency of fat emulsification and energy utilization. At the same time, FXR increases the amount of intestinal fatty acid transporter CD36/FATP4, thus improving fat absorption and reducing the level of GLP-1 which causes insulin resistance and encourages energy conservation. As a result, the energy balance is disrupted because of 'less expenditure and more absorption', connected with obesity.

3.2.2. G protein-coupled Receptor 5 (TGR5)-mediated Regulation

TGR5 is a G protein-coupled receptor that is specifically stimulated by bile acids.

Sahuri (2021) pointed out that bile acids can enhance fat absorption by activating TGR5 receptors on intestinal cells,

which might cause obesity. When binding to TGR5, bile acids generate intracellular signals to stabilize and increase the number of fat-absorbing carriers on the intestinal surface, thus improving the gut's fat absorption ability [12]. At the same time, the TGR5 signal extends the emulsification and digestion of fats in the gut, enabling the body to obtain more energy from the food. Under a long-term high-fat diet, this process becomes stronger, leading to an increase in calorie absorption. The excess energy is converted into fat and stored in the body, resulting in weight gain and obesity. Therefore, the enhancement of intestinal fat absorption by TGR5 is one of the ways in which bile acids participate in the occurrence of obesity [13]. Furthermore, FXR and TGR5 work together to control fat absorption and energy expenditure, which is involved in the development of obesity.

Lipopolysaccharide (LPS) also plays a crucial role in the development of obesity.

3.3. LPS Promotes Inflammation, Thereby Inducing Obesity

LPS plays an important role in the outer layer of the cell wall in Gram-negative bacteria (like Escherichia coli and Salmonella, etc.). The dysbalance of gut microbiota leads to an increase in harmful bacteria and a decrease in beneficial bacteria, which may result in the weakening of the intestinal barrier. When the intestinal barrier is injured, LPS binds to the TLR4-MD2-CD14 complex on the cell surface (where TLR4 is a pattern recognition receptor, MD2 aids in the recognition, and CD14 increases the binding) [14].

On a certain path, TLR4 combines with MyD88 (a signal transmitting protein) and subsequently activates TRAF6 (Tumour Necrosis Factor Receptor-Associated Factor). Then, TRAF6 phosphorylates TAK1 (Transforming Growth Factor-β Activated Kinase 1). TAK1 activates the IKK (IκB Kinase) complex, leading to the degradation of IκB and the release of NF-κB (p65/p50 homodimer). When NF-κB enters the nucleus, it controls the expression of pro-inflammatory cytokines like TNF-α and IL-6, thus promoting and intensifying the inflammatory response. This persistent mild inflammation may cause insulin resistance, fat accumulation and the occurrence of obesity. Additionally, TLR4 can interact with TRIF to activate TRAF3 or RIP1.TRAF3 activates TBK1/IKKε, which phosphorylates IRF3. Nuclear translocation of IRF3 leads to the transcription of type I interferons (e.g., IFN-β). The alternative pathway, RIP, activates caspase 11 to activate the non-canonical inflammasome. Working together with the NLRP3 inflammasome, it cleaves pro-IL-1β and pro-IL-18 into mature cytokines, causing strong inflammation and affecting the regulation of glucose. These type I interferons and inflammatory substances like IL-1β and IL-18 also directly interfere with the insulin signal transduction pathway, decreasing the glucose uptake and utilization in the liver and muscles. At the same time, they inhibit the thermogenesis of brown adipose tissue, reducing energy consumption. Ultimately, this further drives obesity through insulin resistance and reduced energy consumption [14-15].

Beyond this, adipokines also influence energy metabolism, thereby contributing to obesity.

3.4. Gut Microbiota and Adipocytes

The gut microbiota influences energy metabolism and insulin sensitivity by regulating the secretion of cytokines such as leptin and adiponectin from adipocytes, thereby participating in obesity regulation.

3.4.1. Leptin

Although gut microbiota does not directly synthesise leptin, they can modulate host adipose tissue leptin expression, secretion, and central leptin sensitivity via metabolites and inflammatory signals. This contributes to the imbalance in energy intake and expenditure homeostasis, thereby driving obesity.

Leptin is primarily secreted by white adipose tissue. Circulating leptin acts on hypothalamic leptin receptors. Increased adipose mass elevates plasma leptin levels, thereby suppressing appetite-promoting neurons (NPY/AgRP) and activating appetite-suppressing prohormone POMC neurons, reducing food intake and maintaining weight equilibrium. Concurrently, it stimulates brown adipose tissue (BAT) thermogenesis via the sympathetic nervous system, increasing energy expenditure. However, in obesity, leptin signalling may be disrupted, leading to leptin resistance (a condition where the body exhibits reduced sensitivity to leptin or leptin fails to exert its physiological effects normally, characterised by elevated leptin levels [hyperleptinaemia] , it fails to effectively suppress appetite or increase energy expenditure, leading to persistent weight gain or difficulty in weight reduction). Chronic low-grade inflammation mediated by gut microbiota dysbiosis is the core cause of leptin resistance. Inflammatory factors suppress hypothalamic leptin receptor expression and disrupt intracellular leptin signalling, ultimately reducing the body's sensitivity to leptin. This results in uncontrolled appetite regulation, where energy intake exceeds expenditure, thereby promoting obesity [16].

3.4.2. Adiponectin

Adiponectin, secreted by white adipose tissue, antagonises leptin action and serves as a key regulator of metabolic homeostasis. Its plasma levels correlate inversely with body fat content, with reduced adiponectin expression being prevalent in obese individuals. Gut microbiota dysbiosis constitutes the primary causative factor. Microbiota regulate the level of adiponectin mainly by two ways: firstly, the disturbance of short-chain fatty acids and abnormal bile acid metabolism affect the production and secretion of adiponectin by adipocytes; secondly, the persistent low-level inflammation caused by microbiota inhibit the expression of adiponectin gene through inflammatory mediators, which leads to its binding to the target cell receptors and thus reducing its biological activity. Adiponectin can activate some signal transduction pathways such as AMPK, increase insulin resistance, promote lipolysis and oxidation while inhibit fat synthesis. It can also enhance glucose uptake and utilization in liver and muscle tissues, decrease lipid accumulation and increase energy consumption. When the concentration of adiponectin decreases and its function is impaired because of the imbalance of microorganisms, its regulation on metabolism will be weakened. Consequently, there will be less lipolysis, more fat synthesis and storage, and less energy consumption, finally disrupting the balance of energy and causing insulin resistance and promoting the occurrence of obesity. Restoring the composition of gut microbiota and promoting the growth of beneficial bacteria can change the metabolic environment, reduce chronic inflammation and re-establish the normal secretion and function of adiponectin. This provides a theoretical basis for regulating microorganisms to modify adiponectin for the prevention and treatment of obesity [17].

4. Results

In brief, gut microbiota dysbiosis plays an important role in the development of metabolic disorders and obesity by mainly influencing host metabolism via four main pathways. The imbalances of short-chain fatty acids (SCFAs) like acetate, propionate and butyrate produced during microbial fermentation can lead to lipogenesis and induce insulin resistance by affecting the vagus and sympathetic nerves or by increasing intestinal nutrient absorption. Bile acids, regulated by FXR and TGR5 receptors, not only enhance intestinal fat absorption but also decrease energy expenditure. Moreover, the lipopolysaccharides (LPS) released by Gram-negative bacteria cause the deterioration of intestinal barrier function, resulting in chronic low-grade inflammation which further interferes with the insulin signaling pathways and reduces energy expenditure. Concurrently, the microbiota modulates adipocyte secretion of adipokines such as leptin and adiponectin, inducing leptin resistance and diminishing adiponectin's metabolic regulatory effects. These systems affect the equilibrium of energy intake and utilization, resulting in the appearance and progression of obesity. Some typical experiments, such as the colonization of germ-free mice and microbiota transfer, have also indicated, at both animal and human levels, the effect of microbial features, like a high Firmicutes/Bacteroidetes ratio, on different kinds of obesity. This provides a solid theoretical foundation for the prevention and treatment of obesity by modifying the gut microbiota.

5. Conclusion

Although the essential mechanisms and main molecular targets in the regulation of energy metabolism through gut microbiota-induced obesity have been clarified, there are still some important issues that need to be studied: Firstly, the effects of metabolites like short-chain fatty acids (e.g., acetate, propionate) and bile acids show both concentration and target specificity, and the possible synergistic or antagonistic actions on energy metabolism in various combinations have not been fully explained yet; Secondly, the interaction mechanisms between the signaling pathways mediated by microbiota and the regulatory pathways of adipokines require more systematic experimental verification. Furthermore, the interventions directed towards the gut microbiota, such as probiotics and prebiotics, mainly still belong to the stage of basic research. The effects of these interventions on modifying the microbial composition, their long-term effectiveness in practical applications, and the individual differences in response should be investigated in depth. In the future, research in this field will concentrate on two main aspects: improving the understanding of the mechanisms and developing precise interventions. Firstly, the specific mechanisms of the interactions between microbial metabolites and the cross-talk between different pathways will be explored, and the core functional bacteria and key target points in the regulation of obesity will be identified; At the same time, by using multi-omics technologies and taking into account the personalized characteristics of human gut microbiota, precise intervention strategies will be established to regulate the ratio of Firmicutes/Bacteroidetes, reduce the release of LPS, and restore the normal secretion of leptin and adiponectin. Moreover, we will integrate the regulation of gut microbiota with dietary interventions to investigate the dietary patterns which can stabilize the beneficial gut bacteria and maintain the balance of metabolites, thus forming a comprehensive prevention and treatment scheme including "microbiota regulation combined with traditional treatments". We think that as the research advances, precise interventions aimed at the gut microbiota will have an important role in the prevention and clinical treatment of obesity, providing more targeted new methods to solve the global obesity problem.

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