PHARMACY REVIEW

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Gut Microbiota and Obesity: Potential Therapeutic Targets and Probiotic Treatment

Abstract: *The gut bacteria model attributes obesity to the variable makeup of gut microbiota and its ability to modulate host energy homeostasis, adiposity and inflammation. To counteract these deleterious effects, strains of probiotics have been developed to manipulate gut microbiomes and improve health. The current article explores the mechanisms by which gut microbiota modulate host metabolism and highlights recent human study data assessing the effects of probiotic supplementation on the prevention and treatment of obesity.*

Keywords: obesity; gut; bacteria; probiotics

Obesity is a complex concept with various models attempting to define and describe the nature of the condition. The gut bacteria model is one such example.[1] This model attributes obesity to the variable makeup of gut microbiota and its ability to modulate host energy homeostasis, adiposity, and inflammation.

Evolving evidence implicates specific gut bacteria profiles in the pathophysiology of obesity.[2] The human intestine harbors a complex bacterial "ecosystem" called the gut microbiota. Normobiosis characterizes a composition of the gut ecosystem in which microorganisms with potential health benefits predominate. In contrast, dysbiosis refers to a gut composition in which potentially harmful microorganisms dominate. Gut microbiomes are the result of both host genetics and environment. Diet, specifically high consumption of saturated/trans fat and simple sugars has been associated with deleterious changes in gut microbiomes resulting in pro-inflammatory environments and disrupted intestinal barrier function.[3]

To counteract the negative effects of altered gut microbiota on energy homeostasis, adiposity and inflammation, strains of probiotics have been developed to manipulate gut microbiomes and improve health.

The purpose of this article is to describe the gut bacteria model by exploring the mechanisms by which gut microbiota modulate host metabolism and highlight recent human study data assessing the effects of microbiota manipulation (specifically through probiotic supplementation) on the prevention and treatment of obesity.

The Interaction Between Gut Bacteria and Obesity

Most of the data describing the pathophysiological mechanisms through which gut bacteria promote obesity are derived from animal studies. Early studies found that germ-free mice (mice devoid of bacteria and bred in sterile isolators) have less total body fat stores than conventionally raised mice (mice possessing their own microbiota), require 30% more calories to maintain their body weight than conventionally raised mice and seem to be protected from diet-induced obesity.[4,5] However, colonization of germ-free mice with conventional microbiota results in increased adiposity,

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hepatic triglyceride formation, fasting glucose levels, and insulin resistance.[6] The mechanisms behind these findings are still being explored but may be related to the body's ability to harvest energy from diet, regulate appetite, and alter eating behavior.

The obese microbiome is thought to increase the body's capacity to harvest energy from the diet as well as decrease the body's ability to produce gut factors that inhibit fat deposition.[2,7] Gut bacteria are able to process complex dietary plant polysaccharides, otherwise inaccessible to humans, to short-chain fatty acids (SCFAs) and monosaccharides through bacterial fermentation. SCFAs are an important source of fuel for the body but also act as signaling molecules, affecting metabolism and energy intake through modulation of the intestinal transit rate. Obese microbiomes have been associated with slower intestinal transit rates, greater caloric extraction from the diet, higher total body fat stores and increased insulin resistance.[2] The increased capacity of obese microbiomes to degrade otherwise indigestible polysaccharides promotes absorption of monosaccharides from the gut lumen, which in turn promotes de novo lipogenesis and triglyceride storage in the liver and adipose tissue.[6,8]

Short-chain fatty acids may also play a role in appetite regulation and eating behaviors, as increased SCFA production increases satiety and reduces food intake.[9] These effects are further mediated by SCFA-signaled secretion of glucagon-like peptide 1, which decreases appetite and caloric consumption, and by a SCFA-signaled decrease in the release of ghrelin, which increases caloric consumption.[10]

Another mechanism by which gut microbiota may play a role in the pathogenesis of obesity is through its effect on intestinal permeability and inflammation. Obesity is often associated with low-grade inflammation and chronic activation of the immune system. The origin of this inflammation is unclear but may be provoked by lipopolysaccharide, a component of Gram-negative bacterial membranes. Lipopolysaccharide is transported from the intestine to systemic circulation in response to obesogenic diet and triggers the secretion of pro-inflammatory cytokines. Gut microbiota dysbiosis modulates gut barrier function through an increase in intestinal permeability, leading to increased low-grade inflammation and metabolic endotoxemia. Recent studies suggest disruption of gut barrier function and gut microbiota-derived endotoxemia may contribute to the pathogenesis of obesity and other metabolic disorders.[11]

Probiotics as Therapeutic Agents for Obesity

Probiotics have been shown to improve lactose tolerance, prevent diarrhea, stimulate immune response, reduce inflammation, and restore obesity-associated gut dysbiosis.[12] Probiotics are food supplements that contain living bacteria that when administered in adequate amounts, confer health benefits to the host. Prebiotics are nondigestable, fermentable food ingredients that stimulate growth of gut microbes. Prebiotics are often used in combination with probiotics to enhance their functionality.

Probiotics exhibit their potential therapeutic effect on the body through direct alteration of gut microbiota and modulation of intestinal inflammation and permeability.

Recent human studies of probiotic effects on metabolic disorders found that 8 to 12 weeks of probiotic supplementation may confer benefits such as decreased body weight, body mass index (BMI), total and low-density lipoprotein cholesterol, systolic and diastolic blood pressure, A1c, and high-sensitivity C-reactive protein levels as well as decreased body weight gain, fat accumulation, and prevention of insulin resistance.[3] Various strains of probiotics were used during these evaluations, which took place in a wide range of human subjects.

A recent meta-analysis assessing the effects of probiotic supplementation on body weight and BMI found probiotic therapy to be in-effective in decreasing weight and BMI.[13] The authors noted that the total number of randomized controlled trials included in the meta-analysis along with the small sample size and heterogeneity of research limited the analysis's ability to draw definitive conclusions. More research is necessary to determine which strains may be most efficacious and the ideal candidates for probiotic therapy.

Conclusions

Growing evidence supports the role of gut microbiota in the pathogenesis of obesity. Mechanisms by which intestinal microbiota are associated with obesity include altered energy harvest from the diet, fat storage and expenditure, incretin secretion, and decreased intestinal permeability and systemic inflammation.[14] Early research suggests probiotics may be beneficial in the prevention and treatment of obesity, though more research is necessary to uncover which probiotic strains prove most efficacious as well as the ideal candidates for probiotic therapy. AJLM

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