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Modulating gut microbiota as an anti-diabetic mechanism of berberine

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Summary

Berberine, one of the main constituents of a Chinese traditional herb used to treat bacterial diarrhea, has an effect of lowering glucose, which has been recently confirmed by many studies. However, the mechanism of berberine's antidiabetic effect has not yet been well explained. Recent evidence suggests that the gut microbiota composition is associated with obesity and type 2 diabetes, which are closely associated with a low-grade inflammatory state. The protective effect against diabetes of gut microbiota modulation with probiotics or antibiotics has been confirmed in recent observations. Berberine has significant antimicrobial activity against several microbes through inhibiting the assembly function of FtsZ and halting the bacteria cell division. Because berberine acts topically in the gastrointestinal tract and it is poorly absorbed, berberine might modulate gut microbiota without systemic anti-infective activity. Our hypothesis is that gut microbiota modulation may be one mechanism of the antidiabetic effect of berberine. Our hypothesis may provide a novel explanation for berberine's therapeutic effect in patients with diabetes mellitus.

key words: **berberine • diabetes mellitus • gut microbiota**

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Background

Berberine, one of the main constituents of *Rhizoma coptidis*, is usually used to treat bacterial diarrhea in China, and it has also been used to treat diabetes for thousands of years in traditional Chinese medicine. In 1988, the glucose-lowering effect of berberine was reported when 60 diabetic patients were treated with berberine for diarrhea in China [1]. Since then, there have been many studies that confirmed berberine's antidiabetic effect. In a pilot study, Yin J et al. [2] found that berberine significantly decreased HbA1c levels in diabetic patients who took 500 mg berberine 3 times daily for 13 weeks (from 9.5% to 7.5%) and the effect of decreasing HbA1c was comparable with that of metformin. In addition, a randomized, double-blind, placebo-controlled and multiple-center trial [3] showed that treatment with berberine (0.5 g, twice daily) for 3 months in 57 type 2 diabetic patients significantly reduced levels of fasting and postprandial plasma glucose and HbA1c by 1.4, 3.1 mmol/liter, and 0.9%, respectively, which was accompanied with decreasing triglyceride and total cholesterol concentrations by 35.9% and 18%, respectively.

The mechanisms through which berberine reduces blood glucose are not entirely clear at present. A previous study showed that berberine reduced body weight and improved insulin resistance in db/db mice and high fat-fed Wistar rats. Berberine upregulated AMP-activated protein kinase (AMPK) activity in adipocytes and myotubes, and facilitated GLUT4 translocation in myotubes [4]. Kong WJ et al. reported that berberine reduced levels of fasting blood glucose and fasting serum insulin, increased insulin sensitivity, and elevated insulin receptor (InsR) mRNA in the liver of type 2 diabetes mellitus rats. Berberine also improved glucolipid metabolism through modulating metabolic-related PPARalpha/delta/gamma protein expression [5]. In addition, berberine decreased gluconeogenesis through upregulation of the glucokinase and glucose-6-phosphate dehydrogenase activities and downregulation of glucose-6-phosphatase activity [6]. Yin J et al. [7] reported that berberine enhanced glucose metabolism by stimulation of glycolysis. Berberine significantly inhibited the activities of intestinal disaccharidases and beta-glucuronidase in diabetic rats [8], so it could significantly lower postprandial blood glucose levels induced by sucrose or maltose loading in normal rats [9]. Recent studies indicated that berberine enhanced glucagon-like peptide-1 (GLP-1) secretion in streptozotocin-induced diabetic rats and normal rats [10,11]. GLP-1 is secreted by the intestinal L cell and induces glucose-dependent stimulation of insulin secretion. Berberine could also regulate glucose homeostasis through decreased oxidative stress [6], and many studies have shown that diabetes mellitus is associated with increased oxidative stress [12].

Why does a traditional antibacterial herb have an anti-diabetic effect? Is there any relation between berberine's antibacterial activity and glucose-lowering effect?

Gut Microbiota Associated with Obesity and Diabetes Mellitus

The adult human intestine is colonized by approximately 100 trillion bacteria, which is about 10 times the number of total cells of the human body [13]. Recent evidence suggests that the gut microbiota composition is associated with obesity and type 2 diabetes. Ley RE et al. [14] analyzed 5088 bacterial 16S rRNA gene sequences from the gut microbiota of genetically obese ob/ob mice and their lean counterparts. They found that ob/ob mice had a 50% reduction in the abundance of Bacteroidetes and a proportional increase in Firmicutes. They also observed similar differences in the gut microbiota of obese *vs.* lean humans [15]. Furthermore, they found that the gut microbiota in the ob/ob mice had a more effective capacity to harvest energy from the diet than the lean littermates, and that this capacity could be transmitted to germ-free mice who were transplanted with caecal microbiota from ob/ob mice [16].

Type 2 diabetes in humans is also associated with compositional changes in gut microbiota. Researchers found that the proportions of Firmicutes and Clostridia were significantly reduced, while the relative abundance of Bacteroidetes and Betaproteobacteria was increased in the diabetic group compared to the control group [17]. Recently, obesity, insulin resistance and type 2 diabetes have been closely associated with a low-grade inflammatory state characterized by abnormal cytokine production, increased acute-phase reactants and activation of a network of inflammatory signal pathways [18]. The low-grade inflammation was induced by the change of gut microbiota, which promoted metabolic endotoxemia and triggered the development of inflammation via the LPS and CD14/TLR4-dependent mechanism [19].

Gut Microbiota Modulation as an Antidiabetic Mechanism

The protective effect of gut microbiota modulation against diabetes had been confirmed in recent observations. Probiotics are nonpathogenic live microorganisms that, when ingested, confer health benefits to the host. Calcinaro et al. investigated the effects of oral administration of the probiotics compound on the occurrence of diabetes in 4-week-old non-obese diabetic (NOD) mice. At 32 weeks of age, 21% (4/19) of mice in the probiotics-treated NOD group were diabetic, in comparison with 81% (17/21) of the phosphate buffered saline (PBS)-treated group ($p<0.001$). Protected mice showed reduced insulitis and a decreased rate of beta cell destruction [20]. In another animal study, researchers observed that a fermented milk product, dahi, which contains probiotic bacteria, significantly delayed the onset of glucose intolerance, hyperglycemia, hyperinsulinemia, dyslipidemia, and oxidative stress in high fructose induced diabetic rats [21].

The ob/ob mouse is a mutant mouse that eats excessively and becomes profoundly obese with hyperinsulinemia and dyslipidemia. Given norfloxacin and ampicillin in drinking water (1g/L each) for 2 weeks, with free access to sterile food and water, the numbers of cecal aerobic and anaerobic bacteria in ob/ob mice were maximally suppressed. The treated animals showed a significant improvement in fasting glycemia and oral glucose tolerance. The enhanced insulin sensitivity was independent of food intake, weigh loss or adiposity, which was not due to a defect in glucose absorption, as the expression of sodium glucose cotransporter 1 (SGLT-1) and glucose transporter 2 (GLUT2) in jejunum was not affected by gut microbiota modulation. Endotoxins such as LPS from gram-negative bacteria in the gut have

been shown to play an important role in the development of insulin resistance. In this study, both plasma LPS levels and the expression of jejunal TNF-α level were significantly lower in the antibiotic-treated than the control and pair-fed mice, suggesting that modulating gut microbiota by norfloxacin and ampicillin ameliorated the inflammatory status in the intestine of ob/ob mice [22]. When the diet-induced obese and insulin resistance (DIO) mice were treated with non-absorbable antibiotics polymyxin B and neomycin, the mice demonstrated a gradual reduction in glycemia during a washout period, associated with modified cecal microbiota profile [23]. In brief, modulation of gut microbiota ameliorated glucose intolerance in mice and altered the inflammatory and metabolic status of the host.

Berberine Modulates Gut Microbiota as an Antimicrobial Agent

Berberine has been shown to have significant antimicrobial activity against bacteria, fungi, parasites, worms, and viruses. In term of bacteria, berberine has demonstrated highly significant activity against *Staphylococcus*, *Streptococcus*, *Salmonella*, *Klebsiella*, *Clostridium*, *Pseudomonas*, *Proteus*, *Shigella*, *Vibrio*, and *Cryptococcus* species [24]. Berberine also exhibited effectiveness in combating enterotoxigenic *Escherichia coli* diarrhea [25]. Moreover, berberine inhibited the overgrowth organisms such as staphylococci and coliforms, while having no effect on indigenous lactobacilli and bifidobacteria [26].

Berberine is thought to act topically in the gastrointestinal tract, and it is poorly absorbed [27], so berberine might modulate gut microbiota without systemic anti-infective activity. Berberine blocks adhesion of bacteria to epithelial cells [28], inhibits the intestinal secretory response of cholera and *E. coli* toxins, and normalizes mucosal histology following cholera toxin damage [29]. Berberine also inhibits growth of *Salmonella Typhi* through decrease arylamine N-acetyltransferases activity and gene expression [30]. Domadia et al. [26] reported that berberine inhibited the assembly function of FtsZ and halted Escherichia coli cell division. FtsZ is an essential cell division protein in bacteria, which is well conserved across bacterial species. This result provides a novel explanation for inhibition of bacteria by berberine.

Hypothesis

Modulating gut microbiota may be one mechanism of the antidiabetic effect of berberine.

Testing the Hypothesis

To date there has been no experimental or clinical investigation that can reveal the modulating gut microbiota property of berberine in antidiabetic treatment. It is thereby necessary to introduce animal experiments to investigate the antidiabetic mechanism of berberine. Male *db/db* diabetic mice, ages 5–8 months, can be treated with different doses of berberine or placebo in their drinking water for a certain period. At the end of the treatment, an OGTT can be performed, and plasma triglyceride, insulin, cholesterol, and adiponectin levels can be measured. Plasma LPS and TNF-α concentrations can be determined to examine the inflammatory status of *db/db* mice. Cecal content should be collected for bacterial 16S rRNA gene sequence analysis after the mice are killed. The link between alteration of microbial-community composition in the distal intestine and metabolic amelioration should be evaluated. Furthermore, to avoid the interaction between modulating gut microbiota and other mechanisms of berberine such as activation of AMPK, some methods that do not change the gut microbiota should be carried out. The diabetic mice can be treated with berberine through intravenous injection, which does not change the gastrointestinal flora markedly. Using germ-free *db/db* diabetic mice in the research can exclude the gut microbiota modulation effect of berberine. These results may reversely support our hypothesis.

Conclusions

We have sufficient reason to believe that modulating gut microbiota is an antidiabetic mechanism of berberine. Our hypothesis might provide a novel elucidation for berberine's therapeutic effect in patients with diabetes mellitus. With the aid of well-designed prospective studies, this hypothesis could be partially or fully confirmed.

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