Abstract In recent decades, the incidence and prevalence of type 2 diabetes (T2DM) have increased such that it is becoming a major worldwide public health problem. Berberine is a natural product from a Chinese herb, which has been used as anti-diabetic and anti-inflammation medication for centuries. More recently, berberine has also proven its long-term effect on improving patient and animal models with T2DM via several intracellular signal pathways. Here, we summarize its acute and chronic anti-diabetic effect both in vitro and in vivo. It is projected that the efficacy and safety of berberine will be proven in clinical trials and animal experiments in future, and this herb extract might be known as a new class of anti-diabetic drug.

Keywords Diabetes Mellitus, Traditional Chinese Medicine, Berberine, Insulin Resistance

1. Introduction

Berberine (BBR), which is known as a form of broad-spectrum antimicrobial agent widely used in bacteria-associated diarrhoea and other gastrointestinal infections in china, is extracted from rhizoma coptidis. Further studies have found that it also has significant anti-cancer and anti-heart failure properties as well as a significant effect on arrhythmia, atherosclerosis and fatty liver disease. In recent years, some clinical studies have found that BBR has a long-term effect on lowering glucolipid (lipids with a carbohydrate attached) metabolism and that it can delay the long-term complications of diabetes.[1-3] In order to further study the potential applications of BBR on diabetes, many studies have been carried out and a systemic review is given in what follows.

2. The long-term effects of BBR on the hypoglycaemic mechanism

For thousands of years, BBR has been held to have a documented effect on the treatment of diabetes. However, it is not until recent decades that studies have reported BBR’s glucose-lowering effect in the treatment of human diabetic patients, animal diabetic models and cell models. This has led to multiple studies designed to help in
understanding BBR’s mechanism of action regarding its hypoglycaemic effect.

2.1 The study on patients with T2DM

In 1988, the first clinical study reported that 60 patients with T2DM treated with BBR, such that 90% of patients saw an increase of their plasma insulin level after one to three months of administration. A study designed for newly diagnosed T2DM patients were randomly assigned for treatment with BBR or metformin for 13 weeks found that BBR could significant decrease haemoglobin A1c (HBA1c) by 2%, fasting blood glucose (FBG) by 3.8mmol/L and postprandial glucose (PGB) by 8.8mmol/L, while the triglycerides and total cholesterol also decreased by 0.24mmol/L and 0.57mmol/L at the end of the study, comparable with that of metformin. Another group of T2DM patients with poor glucose-control were treated with a combination of metformin and BBR or BBR mono-therapy for three months and showed that glucose could increasingly decline in the first two weeks and remain at a nadir level thereafter, saving insulin and HOMA-IR[1]. The studies demonstrated that the mechanism for BBR in lowering lipid and plasma glucose could stimulate the AMPK in the liver, muscle and adipose tissue [3,4].

2.2 The study in animals

In vivo studies revealed that BBR plays a role in feeding, lowering plasma glucose, reducing plasma lipids and decreasing insulin resistance. After two weeks gavage feeding of BBR, the db/db mice lost weight and saw a significant improvement in glucose tolerance.[5] Furthermore, BBR could reduce high-fat-fed, body weight and plasma triglycerides in Wistar rats as well as improving insulin action.[5] In diet-induced obese rats, BBR improved insulin resistance, similar to that with metformin.[6] In another study, the impaired-glucose tolerance rats induced by STZ were subjected to an oral glucose tolerance test. After four weeks administration with BBR, the plasma level of FFA, TC, TG, APOB were significantly reduced compared with that in the metformin group.[7] These studies in vivo have shown that BBR may broadly act on lipid and insulin in addition to glucose per se.

In addition to the mechanisms prescribed previously, the stimulation of incretin could be another mechanism on the action of BBR on T2DM. Glucagon-like peptide (GLP)-1 is an incretin hormone released in response to nutrient ingestion, mainly produced in the enteroendocrine L cells. Previous studies have indicated that GLP-1 can promote insulin gene transcription and the synthesis and secretion of insulin on the islet beta cells in stimulating the islet beta cells proliferation and differentiation and inhibiting apoptosis in the pancreatic islet beta cells. Moreover, GLP-1 can inhibit glucagon release from pancreatic islet alpha cells, which is another contributor to hyperglycaemia in T2DM. In an in vivo study, a five week treatment using BBR in STZ-injection diabetic rats enhanced the GLP-1 secretion revealed by the glucose load, promoted proglucagon mRNA expression and increased plasma insulin levels as well as the number of beta cells in the pancreas [8].

2.3 The study in the cells

In hepatocytes, adipose tissue and muscle, BBR can increase glucose consumption and/or glucose uptake in a manner similar to that of metformin,[9] In HepG2 human hepatoma cells, BBR could inhibit cholesterol and TG synthesis by the activation of AMP-activated protein kinase (AMPK).[10] AMPK is the receptor in cell energy metabolism and plays an important role in fatty acid oxidation and adipose synthesis according to the AMP/ATP ratio. The effects of berberine on AMPK activity in both adipocytes and myoblasts were pronounced and followed by the increase of AMPK phosphorylation and ACC phosphorylation, while in L6 myotube cells BBR stimulated AMPK activity by accreted GLUT4 translocation.[5] GLUT1 exists in all human tissues with high glucose affinity and can transport extracellular glucose at a relatively lower concentration of glucose. In 3T3-L1 adipocytes and preadipocytes, BBR did not increase GLUT1 gene expression but increased glucose transport by enhancing the activity of GLUT1.[11] In Min6 cells, BBR also increased insulin secretion and enhanced the survival of Min6 cells by the induction of IRS2 leading to potentiating insulin/IGF-1 signalling cascade.[12] In NCI-H716 cells - which is the model of the intestinal L-cell - BBR was found to stimulate GLP-1 secretion and biosynthesis in a dose-dependent manner.[13]

3. Acute hypoglycaemic effects of BBR in cells and animals

Previous studies showed that 6 hour or 24 hour exposure to BBR in 3T3-L1 cells increased GLUT1 synthesis with no change in GLUT4.[11, 14] Recently, a study measured GLUT1 in L929 fibroblast cells and confirmed that BBR could activate acute glucose uptake glucose within 5 minutes and that it plateaus at about 30 minutes. [15] This evidence shows the acute effect of BBR on lowering plasma glucose. Moreover, our recent study focusing on the acute hypoglycaemic effect of BBR in vivo and indicated that BBR could play an acute role in lowering glucose in wild rats.

In summary, the mechanism of BBR on the glucose metabolism is unclear. Previous studies have confirmed that BBR’s enhancing of glucose metabolism may be due
to: (1) the stimulation of glycolysis, which is related to the inhibition of oxidation in mitochondria;[6] (2) the increased glucose consumption and/or glucose uptake through the activation of GLUT4 or GLUT1 translocation;[12] (3) the increased phosphorylation of AMPK, ACC and p38 MAPK; (4) the regulation of gene expression in lipid synthesis and oxidation; (5) possibly its role as an alpha-glucosidase inhibitor in blocking glucose transportation across the intestinal epithelium;[16] (6) its insulin sensitizing effect in reducing insulin resistance both in vivo and in vitro similar to metformin; (7) its role in the activation of the insulin-signalling pathway as well as the exercise-mediated or AMP kinase-mediated pathway in both 3T3-L1 adipocytes and L6 myotube cells; (8) its improvement of GLP-1 secretion and GLP-1 biosynthesis. BBR, which has a long history of use in the treatment of T2DM has shown its hypoglycaemic mechanism on insulin, lipid, glucose and intracellular AMPK pathways in animal and cell lines. The exploration of its mechanism on hyperglycaemia, hyperlipidaemia and hyperinsulinaemia both in vivo and in vitro could lead to new drug therapies for metabolic syndrome, pre-diabetes and advanced 2TDM [17].

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5. References


