Sasa borealis extract exerts an antidiabetic effect via activation of the AMP-activated protein kinase

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Abstract

Leaf of Sasa borealis, a species of bamboo, has been reported to exhibit anti-hyperglycemic effect. However, its antidiabetic mechanism is not fully understood. In this study, we examined whether an extract of S. borealis activates AMP-activated protein kinase (AMPK) and exerts anti-hyperglycemic effects. Treatment with the S. borealis extract increased insulin signaling and phosphorylation of AMPK and stimulated the expression of its downstream targets, including PPARα, ACO, and CPT-1 in C2C12 cells and PPARα in HepG2 cells. However, inhibition of AMPK activation attenuated insulin signaling and prevented the stimulation of AMPK target genes. The S. borealis extract increased glucose uptake in C2C12 cells and suppressed expression of the gluconeogenic gene, PEPCK in HepG2 cells. The extract significantly reduced blood glucose and triglyceride levels in STZ-induced diabetic mice. The extract enhanced AMPK phosphorylation and increased Glut-4 expression in the skeletal muscle of the mice. These findings demonstrated that the S. borealis extract exerts its anti-hyperglycemic effect through activation of AMPK and enhancement of insulin signaling.

Key Words: Antidiabetic effect, AMP-activated protein kinase, Sasa borealis, insulin signaling

Introduction

Type 2 diabetes is characterized by decreased secretion of insulin by the pancreas and resistance to the action of insulin in various tissues (e.g., muscle, liver, and adipose), leading to impaired glucose uptake [1]. The prevalence of type 2 diabetes has increased sharply in recent decades, and has tracked with similar increases in the prevalence of obesity, one of the primary risk factors for type 2 diabetes. Controlling hyperglycemia is the most important factor for reducing the risks associated with diabetes and diabetic complications. Management of type 2 diabetes usually begins with a change of diet and exercise [2], and most patients ultimately require pharmacotherapy such as an oral antidiabetic drug (OAD) [1]. OADs include sulfonylurea, non-sulfonylurea secretagogues, biguanides, thiazolidinediones, glucosidase inhibitors, and glucagon-like peptide-1 (GLP-1) inhibitors.

Plants are abundant sources of biologically active molecules that have played a critical role in pharmacology. On the basis of the knowledge of their traditional therapeutic applications, many of these natural products have been demonstrated to have beneficial medicinal attributes [3]. The use of herbal or natural medicines for the treatment of various disorders has a long and extensive history. Various medicinal herbal products, including herbs used in Chinese medicine, have beneficial effects on diabetes and are used as non-prescription treatments for diabetes [4]. Bamboo has been used for medicinal purposes and for making tea for centuries in Korea and other Asian countries. Various beneficial effects of bamboo leaves [5-9], shoot [10], shavings [11] and oils [12] on metabolic disorders and cardiovascular disease have been reported. Sasa borealis, a species of bamboo, has been reported to exhibit anti-hyperglycemic and antidiabetic activities by increasing insulin secretion [7], improving insulin resistance via modulation of inflammatory cytokine secretion, and decreasing oxidative stress [13], as well as demonstrating anti-obesity activity [6]. Furthermore, S. borealis leaf extracts had a beneficial effect on levels of adiponectin, resistin, and related molecules which are involved in cardiovascular disease such as C-reactive protein and homocysteine [6]. Although many medicinal effects of S. borealis have been proposed, the exact mechanisms involved in potentiating these effects still remains unclear.

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Adenosine monophosphate (AMP)-activated protein kinase (AMPK), a metabolic sensor that acts as a cellular fuel gauge in eukaryotes, is a well-characterized target of antidiabetic treatments. AMPK is activated under ATP-depleting conditions such as hypoxia, ischemia, reactive oxygen species (ROS), heat shock, and glucose deprivation and it subsequently induces ATP-generation pathways for maintaining cellular homeostasis [14]. In addition to controlling energy homeostasis, AMPK enhances insulin sensitivity through increased glucose uptake and lipid oxidation in skeletal muscle and inhibition of glucose and lipid synthesis in the liver [15]. Therefore, AMPK is a key molecule in controlling metabolic diseases such as type 2 diabetes, obesity, and cancer. Discovery and development of a molecule in controlling metabolic diseases such as type 2 diabetes, obesity, and cancer. Overcoming human diseases such as type 2 diabetes, obesity, and cancer. 

In this study, we examined the effect of an extract of *S. borealis* on AMPK activation, insulin signaling, and glucose uptake in C2C12 cells and on gluconeogenesis in HepG2 cells. Moreover, we also evaluated the hypoglycemic effect and AMPK activation in mice with streptozotocin (STZ)-induced diabetes.

Materials and Methods

*S. borealis* and preparation of leaf extract

*S. borealis*, which was purchased from the Kyungdong Oriental Herbal market, Korea, was identified by Prof. Su In Cho, one of the authors. A voucher specimen was deposited at the School of Korean Medicine, Pusan National University. Fresh leaves of *S. borealis* were washed thoroughly with tap water and dried at 30°C for 30 h, and pulverized using a mill. Five volume of 70% methanol was added to the pulverized samples and the mixture was stirred for 24 h. Finally, extracts were filtered through a cheese cloth, concentrated by using a vacuum batch evaporator (Best Korea Co.), and freeze-dried with a lyophilizer (SFDTS 10K, Samwon Freezing Engineering Co., Korea). The yield was 9.5 % w/w dry matter.

Cell culture and treatment

The HepG2 hepatocytes and C2C12 skeletal myoblasts were obtained from the American Type Culture Collection (ATCC, USA). The HepG2 cells were cultured in Dulbecco’s modified Eagle’s medium (DMEM) containing glucose (Invitrogen, USA), supplemented with 10% (v/v) fetal bovine serum (Gibco BRL, USA). The C2C12 cells were grown in DMEM supplemented with 2% horse serum to induce differentiation into myotubes. To investigate the effect of the *S. borealis* extract on AMPK activation or expression of AMPK target genes, HepG2 and C2C12 cells were treated with 40 μg/mL of the extract for 24 h. To see the effects of *S. borealis* extract on insulin signaling, HepG2 or C2C12 cells were treated with 40 μg/ml of the extract for 24 h, and then incubated with 100 nM insulin for 1 h. Compound C-treated cells were preincubated with 10 μM of compound C or vehicle (DMSO) with the extract. Compound C was purchased from Calbiochem (La Jolla, CA, USA).

Western blot analysis

Total protein was extracted from cells with the PRO-PREP reagent (iNtRON Biotechnology, Korea), resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and immunoblotted with antibodies against AMPK and the phosphorylated form of AMPK (pAMPK), insulin receptor substrate-1 (pIRS-1), and Akt (pAkt) (Santa Cruz Biotechnology, USA). The immune complexes were visualized with an enhanced chemiluminescence detection system (Amersham Biosciences, Sweden) according to the manufacturer’s instructions, in conjunction with ImageQuant LAS 4000 luminescence image analyzer (GE Healthcare, USA).

Reverse transcription-polymerase chain reaction (RT-PCR)

Total RNA was extracted from cells using the TRIzol lysis reagent (Invitrogen). The mRNA in the samples was reverse-transcribed using the Superscript™ First Strand Kit (Invitrogen). The resulting cDNA was amplified by PCR using primer pairs specific for peroxisome proliferator-associated receptor α (PPAR α), F (5'-CGTCCTGGCCCTTCAACGTAG-3') and R (5'-CCT GTAAGCTCTC TCGCA TGGCAGG-3'), acetyl-CoA oxidase (ACO), F (5'-TCAAGCCAGGTGAAC CGAA-3') and R (5'-TGCTTA TGCTTTCCAGTTTG-3'), and carnitine palmitoyltransferase-1 (CPT-1), F (5'-AAATCGCAATCTCGTACCA-3') and R (5'-GGAAAAACTTCTGTCACGA ACA-3'). The housekeeping gene, Actin, was amplified using the sense primer 5'-GCCCTGAGG CACTCTTCCA-3' and the antisense primer 5'-GAAGG TAGT TTGCTGG ATGCC A-3'.

Measurement of glucose uptake

Glucose uptake assays were performed using the glucose analog 2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino]-2-deoxy-d-glucose (2-NBDG; Invitrogen), a fluorescent indicator for direct glucose uptake. Differentiated C2C12 cells were treated with vehicle or extract (40 μg/ml) and 1 μM insulin in the presence or absence of 10 μM 2-NBDG for 1 h. The fluorescence intensity of 2-NBDG was recorded using a FACS flow cytometer (FACSCanto™ II Flow Cytometry System : BD Biosciences, USA). To rule out false-positives, the fluorescence intensity of cells treated with extract in the absence of 2-NBDG was measured and this value was considered as the background level. The relative fluorescence intensities, minus the background level, were used for data analysis.
Measurement of gluconeogenic gene expression

HepG2 cells were treated with 40 μg/ml of the *S. borealis* extract for 24 h, washed 3 times with pre-warmed DMEM, and then stimulated by cAMP (100 μM)/dexamethasone (500 nM) in the presence of 40 μg/ml of the extract for 24 h. Total RNA was prepared from the cells and RT-PCR was performed using phosphoenolpyruvate carboxykinase (PEPCK)-specific primers.

Animal studies

ICR mice aged 8 weeks were purchased from the Oriental Bio (Daejeon, Korea) and housed individually in polycarbonate cages under a 12-h light-dark cycle at 21-23°C and 40-60% humidity. The hyperglycemia was induced by intraperitoneal injection of streptozotocin (STZ) (100 mg/kg body weight) in citrate buffer (pH 4.5) after 12 h fasting for 7 d, and the body weight and fasting blood glucose level of STZ-treated mice were measured. The mice with the fasting glucose levels above 200 mg/dl were considered hyperglycemia and included in this study. On the basis of the fasting glucose levels, the mice were divided into 3 groups (n = 7, each); (1) diabetic control (treated with STZ alone), (2) low-dose treatment (treated with STZ + 300 mg/kg body weight *S. borealis* extract), (3) high-dose treatment (treated with STZ + 500 mg/kg body weight *S. borealis* extract). All groups were fed a standard AIN-76 semi-synthetic diet (American Institute of Nutrition, USA), and experimental groups were administered 300 mg/kg or 500 mg/kg of the extract orally for 2 weeks. After starvation for 12 h, the mice were anesthetized with ether and blood samples were collected from the inferior vena cava for measuring blood biomarkers. All animal procedures were in accordance with the Pusan National University guidelines for the care and use of laboratory animals.

Fasting blood glucose and biomarker analyses

The fasting blood glucose concentration was measured by using a Glucometer (GlucoDr, Allmedicus, Korea) with venous blood drawn from the mouse tail vein after a 12 h fast. Blood samples were centrifuged at 1,000 × g for 15 min at 4°C for biochemical analysis. The insulin level was measured with an enzyme-linked immunosorbent assay (ELISA) kit (ALPCO Diagnostics, USA). The lipids such as total cholesterol and triglycerides were determined with commercial kits (Sigma-Aldrich, USA), while the plasma free fatty acid (FFA) concentration was determined with an acyl-CoA synthetase (ACS)-ascorbate oxidase (ACOD) method (Wako Pure Chemical Industries, Japan).

Statistical analysis

All data are presented as the means ± SE. The data were evaluated by one-way ANOVA and the differences between means were determined using Duncan’s multiple-range test. Values were considered statistically significant at *P* < 0.05.

Results

*S. borealis* extract augments insulin signaling in C2C12 and HepG2 cells

We first examined the cytotoxicity of *S. borealis* extracts with three different concentrations (10, 20, 40 μg/ml) on C2C12 and HepG2 cells. As shown in Fig. 1, the extracts had little influence on the viability of both cells. Next, we investigated the effect of the 40 μg/ml of *S. borealis* extract on insulin action in insulin-sensitive cells. After C2C12 and HepG2 cells were treated with the extract for 24 h and incubated with insulin for 1 h, the insulin-stimulated phosphorylation of IRS-1 and Akt was evaluated. Insulin stimulated tyrosine phosphorylation of IRS-1, and cotreatment with the extract significantly increased the level of phosphorylated IRS-1 (Fig. 2) in both cells. Similarly, serine phosphorylation of Akt also increased significantly with the extract (data not shown), suggesting that the extract augmented insulin signaling.

![Fig. 1. Cytotoxicity of Sasa borealis extracts. C2C12 or HepG2 cells were treated with three different concentrations of the extract (Ext) (10, 20, 40 μg/ml) for 24 h. Cell cytotoxicity was measured by MTT assay.](image)

![Fig. 2. Sasa borealis extract augments insulin signaling in C2C12 and HepG2 cells. C2C12 or HepG2 cells were treated with the extract (Ext) (40 μg/ml) for 24 h and then incubated with insulin (100 nM) for 1 h. Levels of phosphorylated IRS-1 (pIRS-1) was evaluated by western blotting. All experiments were performed three times, and representative figures are shown. The bars represent the relative densitometric values compared to untreated samples. The values are expressed as the mean ± SE (*P* < 0.05).](image)
Antidiabetic effect of *Sasa borealis* via AMPK

It has been reported that AMPK is an attractive therapeutic target for the treatment of type 2 diabetes and obesity [15]. Therefore, we next investigated the effect of the extract on AMPK activation. To this end, C2C12 and HepG2 cells were incubated with the extract for 24 h and the pAMPK levels and expression of its target genes were determined by western blotting and RT-PCR, respectively. Treatment with the extract increased pAMPK levels in C2C12 cells, whereas treatment with compound C, an inhibitor of AMPK, blocked the increase in pAMPK levels (Fig. 3A). Consistent with the increase in pAMPK levels, treatment with the extract stimulated the expression of AMPK target genes, including PPARα, ACO and CPT-1 in C2C12 cells (Fig. 3A). Treatment with the extract increased the pAMPK and PPARα expression in HepG2 cells as well (Fig. 3B). These results demonstrated that the extract activates AMPK in skeletal muscle and liver cells.

To investigate the ability of the *S. borealis* extract to activate insulin signaling through AMPK activation, we assessed the phosphorylated forms of IRS-1 in C2C12 cells and HepG2 cells pretreated with compound C. Co-incubation of cells with the extract and insulin stimulated phosphorylation of IRS-1. However, pretreatment with compound C blocked the increase in pIRS-1 (Fig. 4), suggesting that the *S. borealis* extract activates insulin signaling through AMPK activation.

*S. borealis* extract enhances glucose uptake in C2C12 cells and suppresses PEPCK gene expression in HepG2 cells

AMPK activation increases insulin-mediated glucose uptake in skeletal muscle cells. Furthermore, AMPK is known to suppress the gene expression of gluconeogenic genes, including glucose-6-phosphatase (G-6-Pase) and phosphoenolpyruvate (PEPCK), and inhibit hepatic glucose production [15]. Therefore, we measured insulin-stimulated glucose uptake in C2C12 cell treated with the extract. A fluorescent indicator of direct glucose uptake, 2-NBDG, was used in the glucose uptake assay. Insulin or the extract stimulated 2-NBDG uptake in C2C12 cells (Fig. 5A). Co-treatment of the cells with the extract increased the insulin-stimulated 2-NBDG uptake in C2C12 cells. Then, we...
examined the effect of the *S. borealis* extract on gluconeogenic gene expression in HepG2 cells. Dexamethasone and cAMP increased the expression of PEPCK, but the extract efficiently prevented the increase in PEPCK gene expression (Fig. 5B).

**S. borealis** extract decreases blood glucose and triglyceride levels in mice with STZ-induced diabetes

To examine the *in vivo* antidiabetic effects of the *S. borealis* extract on diabetes, STZ-induced diabetes were treated orally with 2 different concentrations of the extract (300 and 500 mg/kg body weight) every day for 2 weeks (from 10 to 12 weeks of age). Compared to untreated normal mice, STZ-treated mice showed a marked increase in blood glucose levels and a significant decrease in blood insulin levels. Administration of the extract did not have any significant effect on their body weight or food intake (data not shown). However, treatment with 500 mg/kg of the extract led to a significant reduction in the fasting blood glucose level (Fig. 6A), whereas the extract did not affect the blood insulin level (Fig. 6B). Next, the effects of the extract on plasma levels of triglycerides, free fatty acid, and total cholesterol were investigated. In particular, treatment with 500 mg/kg of the extract led to a significant decrease in plasma triglyceride levels (Fig. 6C), but not free fatty acid levels (Fig. 6D). Total cholesterol was decreased slightly at 500 mg/kg of the extract, but not statistically (data not shown).

We also determined the effect of the *S. borealis* extract on AMPK activation *in vivo*. To this end, we measured the pAMPK levels in soleus skeletal muscle of the STZ-mice treated with the extract. Treatment with 500 mg/kg of extract increased pAMPK levels in the skeletal muscle of STZ-mice treated with the extract, compared with non-treated STZ-mice (Fig. 7A). Consistent with the increase in pAMPK levels, 500 mg/kg of extract also increased the expression of the Glut4 gene in skeletal muscle (Fig. 7B).

**Discussion**

Several *in vitro* and animal studies have reported that bamboo extract has beneficial effects in controlling serum glucose levels [6,7]. Among all bamboos, one species of bamboo, *S. borealis*, has been reported to exert anti-hyperglycemic anti-diabetic, and antiobesity activity. Furthermore, *S. borealis* leaf extracts have a beneficial effect on many proteins involved in cardiovascular disease [7]. *S. borealis* prevented chronic hyperglycemia-induced oxidative stress and apoptosis in human umbilical endothelial cells [16]. In this study, we characterized a new molecular target of the antidiabetic activity of *S. borealis*. We observed that the *S. borealis* extract activates AMPK in both skeletal muscle and liver cells and increases insulin sensitivity, leading to enhancement of glucose uptake in skeletal muscle and suppression of gluconeogenesis in the liver.

AMPK is a cellular energy sensor that inhibits ATP-consumption and stimulates ATP production under energy-depleted conditions. The kinase activity of AMPK is induced by a high AMP/ATP ratio. AMP binds to the γ-subunit of AMPK and induces a conformational change that allows Thr172 of the α-subunit to be phosphorylated by AMPK kinases [14]. AMPK is activated by upstream kinases, including liver kinase B1 (LKB1) [17] and calmodulin-dependent protein kinase kinase (CaMKK) [18]. Activation of AMPK has been shown to suppress gluconeogenic gene expression and inhibit hepatic glucose production [15]. Furthermore, AMPK activation stimulates glucose uptake by increasing Glut4 translocation to the cell surface and increasing Glut4 gene expression in skeletal muscle [15]. We showed here that *S. borealis* extract increases the phosphorylation of AMPK and stimulates the expression of AMPK target genes in both skeletal muscle and liver cells, indicating that *S. borealis* activates AMPK. Several reports suggest that activation of AMPK enhances insulin sensitivity and increases glucose...
uptake in vitro and in vivo [15]. Therefore, we investigated whether AMPK activation is involved in S. borealis extract-stimulated insulin signaling. Treatment with S. borealis further increased insulin-stimulated pIRS-1 and pAkt levels. However, blocking AMPK activation by treatment with compound C prevented the increase in pIRS-1 and pAkt, suggesting that activation of AMPK by S. borealis enhances insulin sensitivity in both skeletal muscle and liver cells. We also monitored the glucose uptake in C2C12 cells. Treatment with the extract enhanced the insulin-stimulated glucose uptake in C2C12 cells. AMPK activation also suppresses gluconeogenesis in the liver through inhibition of gluconeogenic genes such as PEPCK and G-6-Pase. In the current study, treatment with the extract suppressed dexamethasone/cAMP-induced PEPCK gene expression in HepG2 cells. Then, we confirmed the hypoglycemic effect of S. borealis and AMPK activation in STZ-induced diabetic mice. Treatment with the extract efficiently reduced blood glucose levels and increased pAMPK levels in skeletal muscle tissue. Taken together, these results demonstrated that S. borealis activates AMPK and increases insulin sensitivity, which lead to increased glucose uptake. Furthermore, AMPK activation by S. borealis decreased PEPCK gene expression, which may be involved in the reduction of blood glucose levels. Cellular glucose uptake is regulated by both insulin-dependent PI3K/Akt signaling and insulin-independent AMPK signaling [19]. The current study demonstrated that the S. borealis extract enhances insulin signaling, and that AMPK activation is necessary for the extract-enhanced insulin signaling. Therefore, the increase in glucose uptake by treatment with the S. borealis extract may be due to AMPK activation itself, as well as AMPK-enhanced insulin signaling.

A previous study reported various pharmacological components of bamboo leaf extracts, including flavones, glycosides, phenolic acids, coumarone lactones, anthraquinones, and amino acids, which have been utilized as therapeutic agents [20]. S. borealis leaf extracts have high levels of polyphenols and flavonoids, and the major phenolic compounds identified in the extracts included protocatechuic acid, p-hydroxybenzoic acid, caffeic acid, syringic acid, p-coumaric acid, leuteolin-6-glucoside, and tricine-7-glucoside. Triterpenoids present in S. borealis, friedelin and glutiol, were reported to have a potential to inhibit fat deposition [7]. Many kinds of triterpenoids extracted from several important Chinese herbal drugs such as Panax ginseng and bamboo shavings are being studied increasingly and their physiological activities and medicinal values have been the focus of recent investigations [11]. Triterpenoids extracted from the roots of Rosa rugosa have anti-inflammatory potential [21]. Furthermore, isoorientin, a flavonoidal glycoside, and its derivative were found in S. borealis [22]. These components have free radical scavenging activity and strong cytoprotective effects against tert-butyl hydroperoxide-induced oxidative stress in HepG2 cells [10]. In addition, a flavonoidal glycoside-containing S. borealis leaf extract has been reported to have a potential insulin-sensitizing activity [23]. However, the exact component involved in the antidiabetic effect of S. borealis has not been characterized yet. Therefore, further studies are required to identify and characterize the phytochemical component which contributes to AMPK activation and to delineate the molecular mechanism of S. borealis-mediated AMPK activation.

In summary, S. borealis exerts an anti-hyperglycemic activity through AMPK activation and increases insulin sensitivity, which, in turn, enhances glucose uptake and suppresses gluconeogenesis, resulting in the reduction of blood glucose levels.

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