Pharmacological Reports 68 (2016) 782–786

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original research article

Allopurinol decreases serum uric acid level and intestinal glucose transporter-5 expression in rats with fructose-induced hyperuricemia

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ARTICLE INFO

Article history:
Received 22 March 2016
Received in revised form 20 April 2016
Accepted 23 April 2016
Available online 6 May 2016

Keywords:
Hyperuricemia
Glucose transporters
Fructose
Allopurinol
Benzbromarone

ABSTRACT

Background: High fructose consumption is considered to be related to the increasing prevalence of hyperuricemia (HUA). Glucose transporters (GLUT) 2 and 5 are crucial for fructose absorption and transporter. Effects of anti-HUA drugs, allopurinol (API) and benzbromarone (BBR), on expressions of GLUT5 and GLUT2 are not evaluated.
Method: Wistar rats were given 10% fructose in drinking water for 60 days to induce HUA, and 5 mg/kg API and 10 mg/kg BBR were intragastricly treated for 30 days. Serum level of uric acid and xanthine oxidase (XOD) activity in liver were determined. Expressions of GLUT2 and GLUT5 in intestine were analyzed by immunohistochemistry staining assay and Western blot assay.
Results: Treatment with API or BBR significantly decreased the serum level of uric acid in HUA rats induced by fructose. Meanwhile, API treatment significantly reduced the XOD activity in liver and GLUT5 expression in intestine. However, BBR treatment did not show inhibitory effects on hepatic XOD activity and intestinal GLUT5 expression. In addition, treatment with API or BBR did not show any effect on GLUT2 expression in intestine.
Conclusion: API decreases serum level of uric acid in fructose-induced HUA rats. The mechanisms are associated with suppressing XOD activity in liver to reduce uric acid production, and inhibiting GLUT5 expression in intestine to reduce fructose absorption.

Introduction

Uric acid, as the end-product of purine metabolism in human body, is dominantly produced in liver by xanthine oxidase (XOD) and excreted through kidney. Hyperuricemia (HUA) is charactered by an elevated level of uric acid in blood. HUA is the precursor of gout and is demonstrated to be associated with diabetes [1], kidney diseases [2] and coronary heart diseases [3]. HUA is a result of either overproduction of uric acid or underexcretion of uric acid in the urine. According to the pathogenesis, allopurinol (API), which reduces uric acid production, and benzbromarone (BBR), which enhances uric acid excretion, are frequently-used drugs for HUA treatment in current clinic [4].

During the past few decades, the prevalence and incidence of HUA have rapidly increased throughout the world [5]. Although the underlying causes behind this fact are complicated, it is indisputable that the considerable increase in sugar-sweetened soft drink and associated fructose consumption has coincided with the increasing trend of HUA [6]. The fructose consumption has increased substantially since the high fructose corn syrup (HFCS) came out in 1967. HFCS is a product manufactured from corn, and usually has a composition of 42%, 55% or 90% fructose [7]. Fructose has been demonstrated to increase uric acid production through inducing adenosine triphosphate (ATP) degradation to adenosine monophosphate (AMP), a uric acid precursor and ultimately, serum level of uric acid rises within minutes after fructose infusion [8].

Dietary fructose is absorbed in intestine and transported to blood by the way of two glucose transporters (GLUT), named GLUT5 and GLUT2. GLUT5 is dominantly expressed in enterocytes and it possesses a high specificity for fructose. The primary

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http://dx.doi.org/10.1016/j.pharep.2016.04.014
1734-1140/

function of GLUT5 is to facilitate the uptake of dietary fructose across the apical membrane of the small intestine [9]. GLUT2, a sodium-independent glucose and fructose transporter, is responsible for the transport of fructose and glucose out of the enterocytes across the basolateral membrane [10].

Researchers have revealed some modulating factors on GLUT5 or GLUT2 expression in intestine. GLUT5 expression appears to be tightly regulated by developmental patterns, glucocorticoids, thyroid hormones, nutrition, diurnal rhythm and its own substrate, fructose [11]. Glucose and fructose likely stimulate the transcription of intestinal GLUT2 just as fructose alone stimulates transcription of intestinal GLUT5 [12]. To this day, the effects of anti-HUA drugs on expressions of GLUT5 and GLUT2 are not totally elucidated. Therefore, we investigated the effects of API and BBR, two classic anti-HUA drugs, on expressions of GLUT5 and GLUT2 in intestine of fructose-induced HUA rats.

Materials and methods

Chemicals and reagents

All chemicals and reagents were purchased from Sigma-Aldrich (USA) unless otherwise specified. BBR tablets were purchased from Excella GmbH (Germany). API tablets were purchased from Chongqing Qingyang Pharmaceutical Co., Ltd (China). Antibodies against GLUT2, GLUT5 and β-actin were purchased from Santa Cruz (USA). Polyvinylidene fluoride (PVDF) membrane and enhanced chemiluminescence (ECL) reagents were purchased from Milipore (USA). Ethylene diamine tetraacetic acid (EDTA)-free protease inhibitor cocktail was purchased from Roche (Switzerland). Enhanced bicinchoninic acid (BCA) protein assay kit was purchased from Beyotime Biotech (China). Uric acid detection kit was purchased from Nanjing Jiancheng Biotech (China). Two-step polymer (non-biotin) detection kit was purchased from GBI (USA).

Experimental animals

Male Wistar rats (180 ± 20 g) were purchased from Chongqing Medical University (China). The rats were housed in a temperature-controlled room (23 ± 2 °C) under a 12-h light/dark cycle with available food and water ad libitum. The rats were allowed one week to adapt to their environment before initiation of the experiments. All animal procedures were approved by the institutional animal care and use committee of Chongqing Technology and Business University (Ethics No. CTBU2015-019).

Induction of HUA and drugs treatment

In this study, rats were given 10% fructose in drinking water to induce HUA as previously described [13]. Rats were divided into 4 groups, which were (1) Control group, (2) HUA group, (3) 5 mg/kg API group, (4) 10 mg/kg BBR group. Each group had 10 rats. The doses of API and BBR used in this study were determined according to published literatures [13,14]. Rats of (2), (3) and (4) groups were given 10% fructose in drinking water, and rats of (1) group were given normal drinking water, for 60 consecutive days. From the 31st day to 60th day during 10% fructose treatment, rats of (3) and (4) groups were intragastricly treated with API or GTP, and rats of (1) and (2) groups were intragastricly treated with saline. On the day 60 all the rats were sacrificed under anesthesia 1 h after the last drugs treatment.

Blood, liver and intestine samples collection

Blood samples were collected from hearts under anesthesia. Blood coagulated at 4 °C overnight and serum was separated by centrifuge at 3000 g for 20 min. Serum samples were stored at −20 °C and used for the test of uric acid level.

Liver tissues of rats were rapidly separated on ice plate, snap-frozen in liquid nitrogen, and stored at −70 °C. For XOD activity assay, liver tissues were sufficiently homogenized in 9 volumes of 80 mmol/L sodium phosphate buffer (pH 7.4) in ice bath. Subsequently, the homogenate was centrifuged at 4,000 g for 20 min at 4 °C. After lipid layer was carefully removed, supernatant was further centrifuged at 10,000 g for 10 min at 4 °C and the final supernatant was used for XOD activity assay. Protein concentration of the final supernatants was determined by the BCA method and performed according to manufacturer's instructions.

The small intestine was quickly removed and rinsed in saline. Five small intestine samples from five rats were fixed in 4% paraformaldehyde for 24 h. Then the tissues were embedded in paraffin and serial paraffin sections (5 μm) were prepared for the subsequent histological analysis. Five small intestine samples from remaining five rats were opened and scraped with a glass slide. The mucosal scrapings were snap-frozen in liquid nitrogen and stored at −70 °C for the subsequent total protein extract. Briefly, the mucosal scrapings were sufficiently homogenized in lysis buffer (50 mM Tris-HCl, 150 mM NaCl, 1% NP-40, 0.5% sodium deoxycholate, 0.1% SDS, pH 7.6) and EDTA-free protease inhibitor cocktail in ice bath. Subsequently, the homogenate was centrifuged at 10,000 g for 10 min at 4 °C and the final supernatant was used for Western blot assay. Protein concentration of the supernatant was determined by the BCA method and performed according to manufacturer's instructions.

Uric acid assay

Serum level of uric acid was analyzed by the uric acid detection kit. The experimental process was performed according to manufacturer's instructions.

XOD activity assay

XOD activity in liver extracts was analyzed by the XOD activity detection kit. The experimental process was performed according to manufacturer's instructions.

Western blot assay

Equal amounts of protein samples were separated by SDS-PAGE electrophoresis and transferred onto PVDF membranes. After blocked with 5% nonfat milk in Tris-buffered saline (TBS) and Tween 20 buffer (10 mM Tris-HCl, 150 mM NaCl, 0.1% Tween 20, pH 7.6) for 1 h at room temperature, PVDF membranes were incubated with anti-GLUT2, anti-GLUT5 or anti-β-actin antibody at 4 °C overnight. Then the membranes were incubated for 1 h at room temperature with appropriate horseradish peroxidase-conjugated (HRP)-conjugated secondary antibody. The protein bands were detected with ECL reagents. Chemiluminescent signals were detected and analyzed using the ChemiDoc XRS imaging system (Bio-Rad, USA).

Immunohistochemistry (IHC) staining

Prepared serial paraffin sections were stained using a two-step polymer (non-biotin) detection kit according to manufacturer's instructions. Briefly, the sections were deparaffinized and blocked for 20 min with 3% hydrogen peroxide at room temperature. Heat-induced epitope retrieval was performed in Tris/EDTA buffer (10 mM Tris-HCl, 1 mM EDTA, 0.05% Tween 20, pH 9.0) by a pressure cooker. Subsequently, the sections were incubated with anti-GLUT2 antibody or anti-GLUT5 antibody overnight at 4 °C.

Negative controls were performed with the omission of the primary antibody. Subsequently, the sections were incubated with HRP-conjugated secondary antibody for 1 h at room temperature. The complex was visualized using 3,3′-diaminobenzidine for 10 min. Bright field images were acquired digitally on a Nikon 80i microscope (Nikon, Japan). The expressions of GLUT2 and GLUT5 in small intestine were subjected to microscopic analysis. Briefly, after IHC staining, positive-stained cells in small intestine were selected for analysis. The intensity of the staining signal was measured and documented using the NIS-elements 3.0 image analysis software (Nikon, Japan). The mean densitometry of the digital image (×200) is designated as representative staining intensity. The signal density of tissue areas from five randomly selected visions were counted blindly and subjected for statistical analysis.

Statistical analysis

All data were presented as mean ± standard deviation (SD). Statistical comparisons were evaluated by one-way analysis of variance (ANOVA) test using SPSS 19 software. Results were considered significant at $p < 0.05$.

Results

Effect of API or BBR on serum level of uric acid

Drinking 10% fructose for 60 days significantly induced the elevation of serum level of uric acid about 45% in HUA group rats compared with Control group rats ($p < 0.01$, Fig. 1). Treatment with 5 mg/kg API or 10 mg/kg BBR significantly decreased the serum level of uric acid about 31% or 30%, respectively, compared with HUA group rats (both $p < 0.01$, Fig. 1).

Effect of API or BBR on XOD activity in liver

XOD activity in liver of HUA group rats significantly enhanced about 66% compared with Control group rats ($p < 0.01$, Fig. 2). Treatment with 5 mg/kg API significantly decreased the XOD activity in liver about 42% compared with HUA group rats ($p < 0.01$, Fig. 2). However, treatment with 10 mg/kg BBR did not significantly affect the XOD activity in liver compared with HUA group rats (Fig. 2).

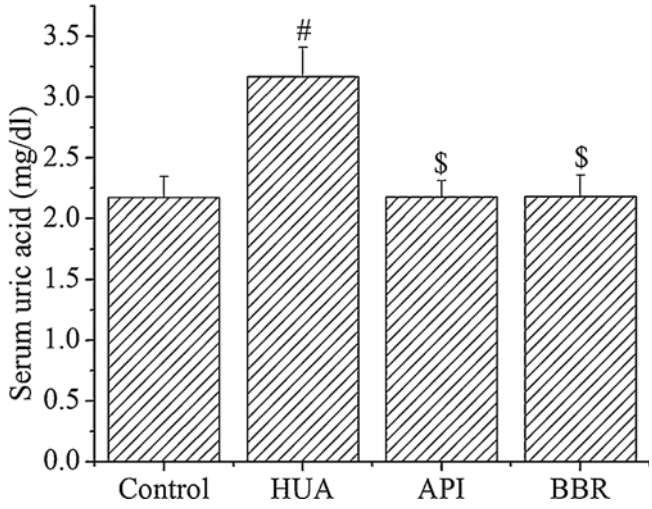

Fig. 1. Effect of API or BBR on serum level of uric acid in fructose-induced HUA rats. Data expressed as mean ± SD; $^{\#}p < 0.01$ compared with Control group, $^{\$}p < 0.01$ compared with HUA group.

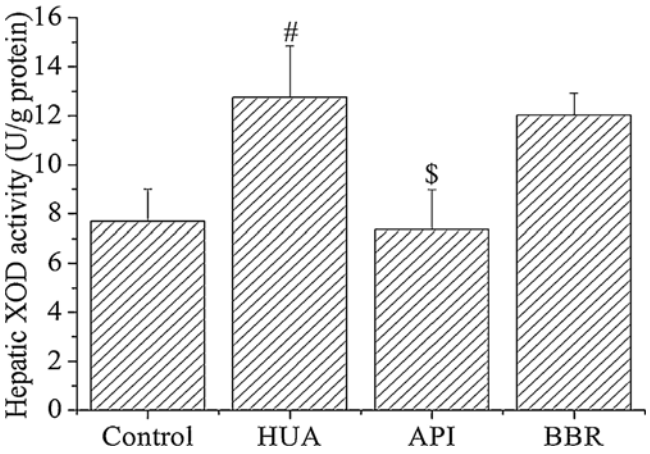

Fig. 2. Effect of API or BBR on hepatic XOD activity in fructose-induced HUA rats. Data expressed as mean ± SD; $^{\#}p < 0.01$ compared with Control group, $^{\$}p < 0.01$ compared with HUA group.

Effect of API or BBR on GLUT5 expression in small intestine

First, we analyzed the GLUT5 protein expression in small intestine by Western blot assay. In HUA group rats, GLUT5 protein expression in small intestine significantly increased by drinking 10% fructose compared with Control group rats ($p < 0.001$, Fig. 3). Treatment with 5 mg/kg API significantly decreased the GLUT5 protein expression in small intestine compared with HUA group rats ($p < 0.01$, Fig. 3). However, treatment with 10 mg/kg BBR did not significantly affect the GLUT5 protein expression compared with HUA group rats (Fig. 3).

Subsequently, we observed the GLUT5 protein expression and location in small intestine by IHC staining assay. Positive staining, which suggested the GLUT5 expression, primarily occurred in enterocytes of small intestine. In accord with the results by Western blot assay, drinking 10% fructose significantly increased the GLUT5 protein expression, and 5 mg/kg API, not 10 mg/kg BBR, markedly reduced the GLUT5 protein expression.

Effect of API or BBR on GLUT2 expression in small intestine

Using Western blot assay, we found that GLUT2 protein expression significantly elevated by 10% fructose consumption in rat small intestine ($p < 0.001$, Fig. 4). Neither treatment with 5 mg/kg API nor 10 mg/kg BBR significantly affected the fructose-induced GLUT2 protein expression in rat small intestine (Fig. 4).

Whereafter, we found the similar results about API or BBR on GLUT2 protein expression by IHC assay. Positive staining, which suggested the GLUT2 expression, dominantly occurred in the enterocytes and basolateral membrane of rat small intestine. Drinking 10% fructose induced a significant elevation of GLUT2 protein expression in rat small intestine ($p < 0.001$, Fig. 4). However, treatment with 5 mg/kg API, or 10 mg/kg BBR, did not affect GLUT2 protein expression in rat small intestine (Fig. 4).

Discussion

In the present study, we found that API and BBR both decreased the serum level of uric acid in fructose-induced HUA rats. Meanwhile, we demonstrated that API reduced the hepatic XOD activity and lowered intestinal GLUT5 expression, and however, BBR did not show the inhibitory effects on both hepatic XOD activity and intestinal GLUT5 expression. In addition, both API and BBR did not affect the intestinal GLUT2 expression.

In recent years, researchers have paid much attention to HUA for its increasing prevalence [15]. Several life-style factors are

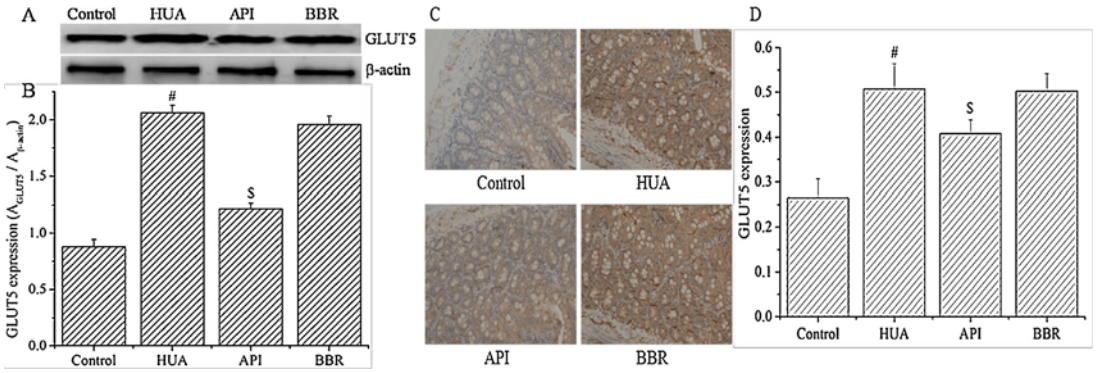

Fig. 3. Effect of API or BBR on intestinal GLUT5 expression in fructose-induced HUA rats. (A) GLUT5 protein was analyzed by Western blot assay. (B) Bar chart showed quantitative evaluation of GLUT5 bands by densitometry. Three independent experiments performed in duplicate. (C) GLUT5 expression in the small intestine was analyzed by IHC assay. Representative results in all groups were presented (200×). (D) Bar charts show semi-quantitative evaluation of positive-stained cells. All the data expressed as mean ± SD; $^{\#}p < 0.001$ compared with Control group, $^{\$}p < 0.01$ compared with HUA group.

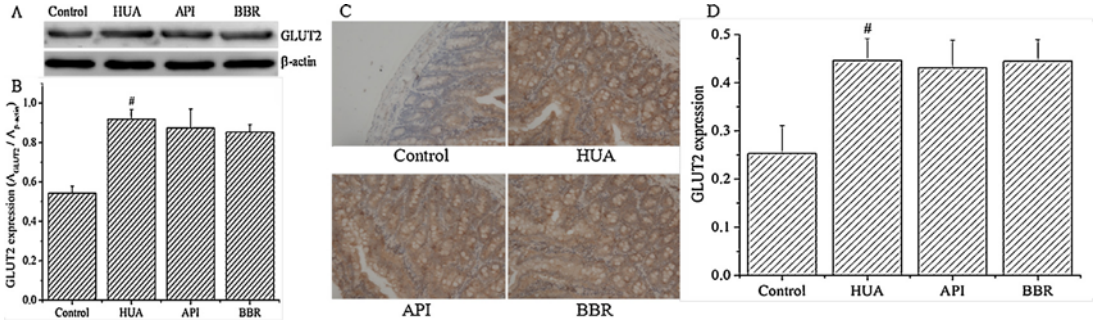

Fig. 4. Effect of API or BBR on intestinal GLUT2 expression in fructose-induced HUA rats. (A) GLUT2 protein was analyzed by Western blot assay. (B) Bar chart showed quantitative evaluation of GLUT2 bands by densitometry. Three independent experiments performed in duplicate. (C) GLUT2 expression in the small intestine was analyzed by IHC assay. Representative results in all groups were presented (200×). (D) Bar charts show semi-quantitative evaluation of positive-stained cells. All the data expressed as mean ± SD; $^{\#}p < 0.001$ compared with Control group.

considered to be closely related to HUA [16], and among them, high fructose consumption is supported by massive documents to play a positive role, although the contradictory opinion exists [17]. In the liver, fructose is phosphorylated by fructokinase, which uses ATP as phosphate donor. Accumulation of fructose-1-phosphate leads to accelerating ATP degradation to AMP. Finally, nucleotides are degradated to uric acid and serum level of uric acid rises quickly [18]. Therefore, 10% fructose drinking [19] or 60% fructose diet [20] is commonly used to induce HUA in rodents. In this study, administration of 10% fructose drinking for 60 days significantly increased the serum level of uric acid in rats. Simultaneously, activity of XOD, a key enzyme mediated the uric acid production from purine [21], elevated markedly in fructose-induced HUA rats. These results suggest once more that high fructose consumption is associated with high serum level of uric acid. API and BBR both are frequently-used drugs for HUA treatment in clinic [22]. In this study, 5 mg/kg API or 10 mg/kg BBR significantly decreased serum level of uric acid in fructose-induced HUA rats. Meanwhile, API markedly inhibited hepatic XOD activity, and however, BBR did not show the inhibitory effect on hepatic XOD activity in fructose-induced HUA rats. These data result from the different mechanisms of the two hypouricemic drugs, that is, API is a XOD inhibitor to decrease uric acid production, and BBR is a uricosuric agent to accelerate uric acid excretion.

Since plentiful documents suggest the positive relation between high fructose consumption and HUA, researchers focus on exploring the drug targets to regulate uric acid production from absorptive fructose [23]. Actually, regulating fructose absorption in the intestine should also be a promising method to improve fructose-induced HUA. Fructose is transported across the small intestine by two members of the facilitative glucose transporter family, namely GLUT5 at the brush-border and GLUT2 at the basolateral membrane in the body [11,24]. GLUT5 is specific for fructose absorption, and however, GLUT2 transports both glucose and fructose [25]. In this study, drinking water with 10% fructose caused a significant elevation of expressions of GLUT5 and GLUT2 in small intestine of rats compared with that of rats with drinking normal water, which suggested that high fructose consumption induced both enhancement of absorption and transport of fructose. Our results agreed with other studies which showed that fructose might increase both GLUT5 and GLUT2 expressions [26,27].

Several factors may regulate GLUT2 or GLUT5 expression. GLUT5 mRNA levels increase with age, and are highest in small intestine of the adults [11]. An interesting study verified that GLUT5 mRNA and protein in rats followed a circadian rhythm, with a marked increase in mRNA and protein at the end of the light cycle as compared with early in the light cycle [28]. Mahraoui et al. found that treatment of Caco-2 cells with forskolin significantly increased GLUT5 protein and mRNA levels [29]. Inflammatory mediators may also regulate fructose transport. For example, tumor necrosis factor-α significantly decreases fructose transport and GLUT5 protein expression in jejunum of rabbits [30]. At the same time, glucose, fructose and galactose may increase intestinal GLUT2 expression in rats fed sugar-enriched diets [31]. Low insulin and high glucose levels increase GLUT2 expression in the intestine and liver of rats with streptozotocin-induced diabetes, suggesting that glycemia and insulinemia regulate GLUT2 expression [26,31]. API and BBR are urate-lowering drugs applied in clinic, and the effects of API and BBR on fructose absorption and transport in the intestine are not fully elucidated. In this study, using high fructose-induced HUA rats, we found high fructose drinking markedly increased both GLUT2 and GLUT5 expressions in the

intestine. Simultaneously, API significantly decreased GLUT5 expression, but did not affect GLUT2 expression in the intestine. However, BBR was of no effect on both GLUT2 and GLUT5 expressions in the intestine.

In recent years, non-hypouricemic activity of API has been revealed. Zhou et al. found that pretreatment with API had a protective effect on kidney ischemia/reperfusion injury, which might be related to the inhibition of high mobility group box 1 expression [32]. Agarwal et al. found that API was associated with a small but significant reduction in blood pressure, and this effect could be potentially exploited to aid in controlling blood pressure in hypertensive patients with HUA [33]. Interestedly, it has been demonstrated that API may be effective to prevent the skeletal muscle damage induced by highly intensive physical exercise in top level soccer players [34–36]. These documents, combining with results in our study, suggest that API has multi-pharmacological activities.

In conclusion, high-fructose consumption has been documented to be related to HUA, fatty liver, hypertension, metabolic syndrome and obesity. Regulating fructose absorption or transport may be a promising method to improve fructose-related pathological conditions. In this study, we demonstrated that API and BBR both significantly reduced the serum level of uric acid in fructose-induced HUA rats. At the same time, we also verified that API reduced the hepatic XOD activity and lowered intestinal GLUT5 protein expression. Nevertheless, BBR did not show the inhibitory effects on both hepatic XOD activity and intestinal GLUT5 expression. In addition, both API and BBR did not affect the intestinal GLUT2 expression. These results suggest that the hypouricemic activity of API may be associated with regulating GLUT5-mediated fructose absorption. Our findings reveal a new pharmacological mechanism of hypouricemic activity of API, and provide clues about improving fructose-related pathological conditions. In the further study, we would elaborate details of API on fructose uptake in vitro using the intestinal sheet method, and explore the molecular mechanisms of API on GLUT5 expression and the potential signal transduction pathway.

Conflict of interests

None of the authors has any conflict of interests regarding this study.

Funding

This work was supported by grants from Scientific Research Project of Chongqing Technology and Business University (No. 1352010).

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