Eggshell Membrane Ameliorates Hyperuricemia

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Hyperuricemia is the primary cause of gouty arthritis and other metabolic disorders. Eggshell membrane (EM) is an effective and safe supplement for curing pain and stiffness connected with osteoarthritis. However, the effect of EM on hyperuricemia is unclear. This study determines the effects of EM on potassium oxonate-injected hyperuricemia. Uric acid, creatinine, blood urea nitrogen concentrations in the serum, and xanthine oxidase activity in the liver are measured. Protein levels of renal urate transporter 1 (URAT1), organic anion transporters 1 (OAT1), glucose transporter 9 (GLUT9), and ATP-binding cassette transporter G2 (ABCG2) in the kidney are determined with renal histopathology. The results demonstrate that EM reduces serum uric acid levels and increases urine uric acid levels in hyperuricemic rats. Moreover, EM downregulates renal URAT1 protein expression, upregulates OAT1 and ABCG2, but does not change GLUT9 expression. Additionally, EM does not change xanthine oxidase activity in the liver or the serum. EM also decreases uric acid uptake into oocytes expressing hURAT1. Finally, EM markedly reduces renal inflammation and serum interleukin-1β levels. These findings suggest that EM exhibits antihyperuricemic effects by promoting renal urate excretion and regulating renal urate transporters. Therefore, EM may be useful in the prevention and treatment of gout and hyperuricemia.

Keywords: ATP-binding cassette transporter G2 ; gout ; urate transporter 1 ; uric acid ; potassium oxonate

1. Introduction

Eggshell membrane (EM) is the film attached to the inside of the eggshell and is one of the components of eggs, a major food for human health. It allows for the penetration of oxygen and blocks the invasion of microorganisms. EM is composed of organic material (70%), nonorganic material (10%), and water (20%), with 80% of the organic material made up of protein. In addition, it is composed of 2.3% fat and 3.4% carbohydrates [1][2]. Among the components of eggs, egg yolk and egg whites are used as raw materials for food, and eggshells are a raw material for calcium supplements to form and maintain teeth and bones [3]. However, EM is classified as a waste and is not frequently utilized.

The anti-arthritic effects of EM have been recently reported in a lipopolysaccharide-induced animal model and in human clinical studies [4][5]. EM has also improved inflammation in rats with collagen-induced rheumatoid arthritis [6]. In addition, EM has demonstrated anti-arthritic activity in monosodium iodoacetate-induced osteoarthritis rats [7]. Monosodium iodoacetate is an inducer of gout arthritis, and the accumulation of monosodium urate crystals in the joints can result in inflammation, leading to gouty arthritis. Hyperuricemia can cause crystals of uric acid (or urate) to form, and the deposition of these crystals in the joints causes gout, a form of arthritis that can be very painful. EM is a source of collagen, chondroitin sulfate, glucosamine, hyaluronic acid, and calcium, which have all been extensively investigated for the treatment of osteoarthritis [8]. The results of these studies show the potential usefulness of EM to prevent and treat gout and hyperuricemia.

Hyperuricemia is a major risk factor for the progress of insulin resistance, diabetes, obesity, hypertension, atherosclerosis, and cardiovascular disease, as well as gouty arthritis [9][10][11]. The appropriate control of hyperuricemia contributes to the prevention and treatment of these diseases. Hyperuricemia occurs with increased uric acid production or impaired uric acid excretion [12]. By reducing the production and enhancing the excretion of uric acid, urate-lowering treatment can play a crucial role in the control of hyperuricemia and hyperuricemia-associated disorders [13]. Commonly used urate-lowering medicines such as allopurinol and febuxostat, an inhibitor of uric acid synthesis, are widely used for the care of gout; however, these xanthine oxidase (XO) inhibitors can have severe adverse reactions, such as allopurinol hypersensitivity syndrome [14][15][16]. Benzbromarone is a uricosuric medication that has been used to control gout for the last 30 years, but due to severe hepatotoxicity side effects, it was withdrawn from the European market [17]. Thus, there is a need to develop drugs derived from natural products with no toxicity that are more effective for the prevention and long-term treatment of hyperuricemia-associated disorders. Therefore, this study investigates whether EM protects against hyperuricemia.

This study assesses the antihyperuricemic activity of EM in rats with hyperuricemia induced by potassium oxonate (PO). PO is a selectively competitive uricase inhibitor, which is widely used to inhibit the effect of liver uricase, which leads to hyperuricemia [18][19]. Thus, PO-treated rats are a practical animal model not only to investigate the pathology of hyperuricemia but also to evaluate potential medications [20]. To examine the activity and underlying mechanisms of EM on hyperuricemia, the dual mechanisms of EM via the inhibition of uric acid production and the enhancement of uric acid excretion are examined in hyperuricemic animals.

2. Development and Findings

In humans, the kidneys play an important role in uric acid homeostasis, as more than 70% of urate excretion is renal, while the remaining 30% is excreted in the feces from the intestine [21][22]. However, urate excretion may be impaired by renal disorders, leading to hyperuricemia. The excretion of uric acid relies on transporter proteins in the proximal tubules of the kidney to control the secretion of uric acid in the blood and filtrate [23]. Renal urate transporters URAT1, located at the luminal membrane, and GLUT9, at the apical membrane of the kidney proximal tubules, comprise the primary pathway of urate reabsorption in the kidney [24][25]. OAT1, located in the basolateral membrane of the proximal tubule, and ABCG2, located at the apical membrane, are mainly responsible for urate secretion from the blood to epithelial cells [26]. The regulation of these urate transporters is considered a major therapeutic target for hyperuricemia.

In this study, the EM effectively decreased renal URAT1 levels in PO-injected hyperuricemic rats, although GLUT9 protein expressions did not change. Moreover, OAT1 and ABCG2 protein expressions were upregulated in the kidney after the EM treatment, thereby exhibiting a uricosuric effect. This study confirmed the inhibitory activity of the EM on urate uptake by URAT1 in URAT1-overexpressing oocytes and that this effect was effective for reversing URAT1-promoted urate uptake. In total, 90% of urate reabsorption is obtained through renal URAT1 [27]. The control of these kidney urate transporters by the EM treatment may contribute to the promotion of renal uric acid excretion in hyperuricemia rats.

Creatinine and urea nitrogen are biomarkers of abnormal kidney function, indicating the ability of the kidney to excrete protein metabolites [23]. The results demonstrated that PO increases serum uric acid and BUN concentrations with renal dysfunction. However, the 200 mg/kg EM reversed this increase with improved renal function.

The enzyme XO catalyzes the oxidation of hypoxanthine or xanthine to uric acid [27]. The XO inhibitors, such as allopurinol, reduce serum uric acid concentrations and the overproduction of reactive oxygen species primarily associated with XO overactivity, which often generates inflammatory cell damage to the vascular endothelium, contributing to the development of metabolic syndrome and cardiovascular disorders [28]. Therefore, the inhibition of XO overactivation may be a therapeutic target to control the harmful effects of excess uric acid. However, our study showed that EM did not reverse serum and liver XO activity in rats with PO-induced hyperuricemia.

Hyperuricemia may be a risk element for kidney dysfunction [22]. In the present study, kidney dysfunction was characterized by increased serum BUN and inflammatory cytokine IL-1β levels and renal inflammation in hyperuricemic rats. These renal dysfunctions were attenuated by the EM treatment, suggesting an improvement in renal inflammation. However, the drug benzbromarone elevated serum IL-1β levels in hyperuricemic rats, and renal damage was reported as a primary adverse effect of uricosuric drugs, including benzbromarone and probenecid [29].

EM contains naturally occurring glucosamine, chondroitin sulfate, hyaluronic acid, collagen, peptides, and other sulfur-containing amino acids [8]. Previous studies reported that glucosamine and chondroitin have demonstrated anti-inflammatory and anti-osteoarthritic effects [30][31]. Hyaluronic acid exhibited anti-inflammatory and antihyperuricemic effects in monosodium urate crystal-induced animal models for acute gouty arthritis and hyperuricemia [32]. The results of these studies show the potential usefulness of these components to prevent and treat hyperuricemia. However, our study did not show which components of the EM enhanced the excretion of uric acid. The effects of bioactive components derived from EM must be further investigated.

In this study, we demonstrated that the PO-induced hyperuricemia and kidney inflammation was inhibited by EM treatment. Therefore, EM could be a promising antihyperuricemic agent. Suppose an effective dose of EM in rats is 100 mg/kg (maximum dose; 200 mg/kg). Based on body surface area, the human equivalent dose of EM is 16.2 mg/kg (972 mg/day in adult). From these in vivo studies, the recommended daily dosage of EM in mild conditions is 486 mg or 972 mg daily, and a maximum dose is 1944 mg daily for severe conditions. However, the dosage can differ depending on the treatment duration and age. Based on these results, a human clinical study of EM will proceed in the near future.

3. Conclusions

These findings demonstrate for the first time that EM improves hyperuricemia by promoting renal uric acid excretion. These effects are achieved by regulating urate transporters and promoting urate excretion.

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