Uric Acid Oxidant/Antioxidant Paradox

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Extracellular uric acid (UA) exhibits antioxidant properties by effectively scavenging free radicals in human plasma, but this benefit might be disturbed by the hydrophobic lipid layer of the cell membrane. In contrast, intracellular free oxygen radicals are produced during UA degradation, and superoxide is further enhanced by interacting with NADPH oxidase. This intracellular oxidative stress, together with inflammatory cytokines induced by UA, stimulates osteoclast bone resorption and inhibits osteoblast bone formation. UA also inhibits vitamin D production and thereby results in hyperparathyroidism, which causes less UA excretion in the intestines and renal proximal tubules by inhibiting the urate transporter ATP-binding cassette subfamily G member 2 (ABCG2).

Keywords: uric acid ; osteoporosis ; oxidative stress ; inflammatory cytokines ; vitamin D deficiency ; secondary hyperparathyroidism

1. Introduction

Purines are found mostly in meat and internal organs such as the liver and kidneys, and its metabolism, mainly in liver, leads to the production of a waste product called uric acid (UA). Xanthine oxidase (XO) belongs to xanthine oxidoreductase, which catalyzes the oxidation of hypoxanthine into xanthine and, following, xanthine into UA. UA is the final oxidation product of purine catabolism in humans and higher primates, but it can be further oxidized into allantoin in most other mammal species. On average, the uric level in adult men is higher than that of women of similar age, which is due to different UA metabolisms in different sexes [1]. The mean value of UA in women is 2.5 to 7.5 mg/dL and in men 4.0 to 8.5 mg/dL [2].

Hyperuricemia is defined by increasing the serum UA level by 7.0 mg/dL in men and 5.7 mg/dL in women [3], which might result from the amplified production of UA or diminished UA excretion. Asymptomatic hyperuricemia is a term used to describe elevated UA levels that is accompanied with neither symptoms nor signs of monosodium urate (MSU) crystal deposition disease, such as gout arthritis or nephrolithiasis [4][5]. Urate-lowering therapy may be started until urate precipitates in urine sediment or there is urate articular damage examined by musculoskeletal ultrasound in asymptomatic hyperuricemia, because the benefit of urate-lowering therapy in asymptomatic hyperuricemia has not yet been proven regarding cardiovascular comorbidity or chronic kidney disease progression [6].

It is known that osteoporosis is a “metabolic” disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and increased risk of bone fracture. Osteoporosis is usually considered to be a bone disease. However, it has been recently shown that this pathology involves the entire musculoskeletal system, and it is strongly coupled with alterations of fat metabolism and, therefore, of fatty acids [7][8][9][10]. Bone remodeling is a necessary process to repair damaged bone and maintain mineral bone hemostasis. The bone remodeling unit is a group of cells that continuously adjusts the microarchitecture of bone by osteoclasts and osteoblasts. The coupling of osteoclasts and osteoblasts is tightly controlled by multiple coupling factors, such as receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG), wingless/integrated (Wnt) signaling, and semaphorin ligands. While coupling is deranged, the balance between bone resorption and bone formation is lost and results in bone loss [11][12].

2. The Clearance of Uric Acid (UA) in Humans

Kidneys are responsible for approximately two-thirds of UA elimination, while the intestine is responsible for one-third UA elimination [13]. Almost all UA is filtered from glomeruli; therefore, the extent of post-glomerular renal tubule UA reabsorption and secretion determine the final UA excreted in urine. The proximal renal tubule accounts for 90% of UA reabsorption, mainly the S1 segment. In the S2 segment of the proximal renal tubule, the amount of UA secretion is greater than its reabsorption. More distal sites of reabsorption in the proximal renal tubule are responsible for the remaining 10% of filtered UA [14]. There are three types of UA transporters in the regulation of uric acid levels in blood. Serum UA levels are mainly determined by urate transporters, which regulate the urate exchange in renal tubules, and

include the following: two reabsorptive transporters—urate/organic anion exchanger (URAT1) and GLUT9—and two secretory transporters—members of the organic acid transporter (OAT) family and ATP-binding cassette subfamily G member 2 (ABCG2) (also called the breast cancer resistance protein or BCRP) [13][15]—where ABCG2 is also expressed in the intestinal epithelium. Among these exporter dysfunctions, ABCG2 is the most relevant genetic factor in the pathogenesis of hyperuricemia and gout patients based on genome-wide association study (GWAS). In hyperuricemic Japanese male, ABCG2 dysfunction decreased intestine urate excretion and, thus, increase the risk of renal overload [16]. In another association analysis in a hyperuricemic Japanese male, ABCG2 dysfunction caused significant underexcretion of renal urate [17][18]. Therefore, ABCG2 dysfunction contributes to the pathogenesis in both renal overload hyperuricemia and renal underexcretion hyperuricemia. Furthermore, loss-of-function mutation in *ABCG2 rs2231142* (*Q141K*) is associated with an increased risk of hyperuricemia and gout by decreased renal proximal tubule transport [15]. In addition, *ABCG2 rs2231142* is also significantly related to the poor response to allopurinol [19]. In the Taiwanese population, the *ABCG2 rs2231142-A* allele had a higher frequency of hyperuricemia in males or obese individuals [20].

3. Osteoporosis

3.1. Normal Bone Remodeling

Bone remodeling is a lifelong process wherein old bone is removed from the skeleton by bone resorption and replaced with new bone by bone formation. The bone remodeling unit comprises the osteoclast (OC), osteoblast (OB), and osteocytes. The bone remodeling process can be divided into six phases: quiescent, activation, resorption, reversal, formation, and mineralization [21]. In normal conditions, the length of the bone remodeling process is about 200 days, and the remodeling cycle is longer in cancellous bone than in cortical bone. The duration of bone remodeling is shortened in hyperthyroidism and hyperparathyroidism, and it is longer in low bone turnover diseases like adynamic bone disease or osteomalacia [22].

Osteoblastic cells regulate osteoclast differentiation and activation through receptor activator of nuclear factor kappa-B ligand (RANKL)-mediated signaling pathways. RANKL expressed in osteoblasts can be induced by 1,25 vitamin D, parathyroid hormone (PTH), and IL-6. The RANKL receptor is called RANK and is expressed in osteoclast progenitors to promote osteoclast differentiation and maturation. Macrophage colony-stimulating factor (M-CSF) is another important element to promote osteoclast proliferation and differentiation, and it is constitutively expressed in osteoblasts. Osteoprotegerin (OPG) is an inhibitory factor that inhibits osteoclast differentiation and activation by interfering with the binding of RANKL to RANK [23].

3.2. Coupling of Bone Stimulators and Turnover Inhibitors

There is increasing evidence to support the important role of ephrin and ephrin receptor (Eph) bi-directional signaling in normal bone coupling of bone resorption to bone formation [24]. Cells in the osteoclast lineage produce various coupling stimulators and inhibitors during the bone resorption process, which act on osteoblasts or their progenitors. The bone matrix also secretes transforming growth factor β (TGF-β) and insulin-like growth factor-I (IGF-I) during osteoclastic bone resorption and, subsequently, activates osteoblast bone formation. Several other coupling factors, such as semaphorin 4D, cardiotrophin-1, sphingosine-1-phosphate, bone morphogenetic protein 6, and Wnt 10b, have also been identified in bone unit communication [25].

3.3. The Pathogenesis of Osteoporosis

Several possible mechanisms of osteoporosis have been proposed, including:

(a) Increased inflammatory cytokine-associated osteolysis. It leads to excessive activity of osteoclasts and leads to more bone resorption than bone formation. This phenomenon can be seen in gouty arthritis, inflammation, and vitamin D deficiency [26].

(b) Incoordination of the RANK/RANKL system. Increased RANK/RANKL signal in OC strengthens the performance of osteoclasts and brings about more bone resorption. There are many clinical scenarios such as in hyperparathyroidism and some autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and estrogen deprivation (postmenopausal women) [26][27].

(c) Excessive Wnt signaling inhibitors in osteoblasts. Dickkopf-1, sclerostin, and secreted frizzled related proteins lead to diminished functioning of osteoblasts via a decrease in Wnt signaling activity, then reduced bone formation. This has been proven in chronic kidney disease, glucocorticoid-induced osteoporosis, and vascular calcification-related bone loss [28].

4. The Uric Acid Oxidant and Antioxidant Paradox

4.1. Antioxidant Properties of Uric Acid in Human Plasma

In human plasma, circulating UA acts as an antioxidant in several mechanisms (**Figure 1**). UA reacts with different oxidants including superoxide anions, hydrogen radicals, and, at the highest affinity, peroxynitrite. Peroxynitrite is a potent oxidant, generated by the rapid combination of free radical nitric oxide (NO) and superoxide, which can induce the inflammation response, lipid peroxidation, and tyrosine nitration [29][30]. Peroxynitrite also acts as an oxidant of tetrahydrobiopterin and leads to the uncoupling of nitric oxide synthase (NOS) [31]. Hence, peroxynitrite can increase superoxide and decrease NO production by eNOS uncoupling, and UA has protective effects against it. Besides, UA is an effective scavenger for peroxyl radicals (ROO^-). Compared to ascorbic acid, UA is the major important water-soluble antioxidant in human plasma. Plasma UA levels are higher than plasma ascorbic acid levels, and UA has a higher reduction potential that leads to less iron and copper production, which is important for the Fenton reaction and hydroxyl radical generation [32][33]. Additionally, UA is an iron chelator to reduce iron-catalyzed oxidative stress reaction [34][35][36]. UA at physiologic concentrations has the ability to scavenge reactive oxygen species (ROS) and protect the erythrocyte membrane from lipid oxidation and further hemolysis [37]. Acute elevation of UA has a protective effect on cultured hippocampal neurons after ischemic insult and suppress the accumulation of reactive oxygen species after excitotoxic and metabolic insults [38]. Moreover, administration of UA can significantly attenuate the formation of nitrotyrosine in liver injury by hemorrhagic shock [39]. At the same time, UA can reduce neutrophil infiltration, which suggests that UA can prevent proinflammatory cell activation by oxidant stress [39]. Treatment with UA at a physiologic dose led to greater functional performance of the heart damaged by radicals and oxidants [40].

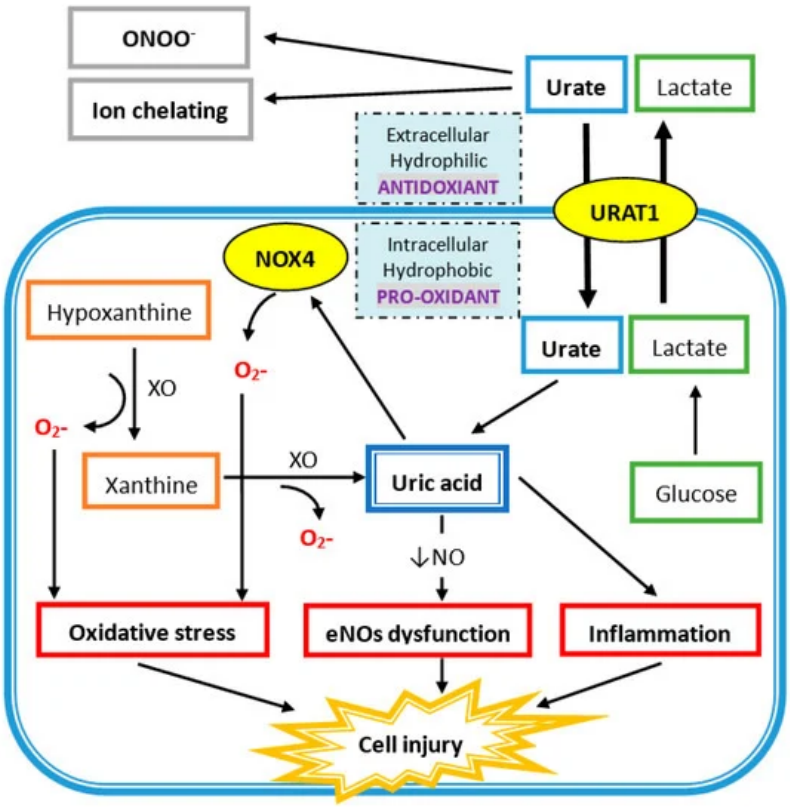

Figure 1. Uric acid (UA) acts as a hydrophobic pro-oxidant within the cell and a hydrophilic antioxidant outside the cell. Urate enters the cell via UA transporter 1 (URAT1) on the cell membrane. UA is produced from xanthine via xanthine oxidase (XO) in the cell and also generates superoxide ions (O_2-), which also promotes oxidative stress by superoxide free radicals produced via NADPH oxidase (NOX4). UA intracellularly induces endothelial nitric oxide synthase (eNOs) with a decrease in nitric oxide (NO) generation. It also directly increases inflammation, which leads to cell injury.

4.2. Intracellular Uric Acid Acts as a Pro-Oxidant to Damage Tissue

As shown in **Figure 1**, xanthine oxidase (XO) is the enzyme that catalyzes the oxidation of hypoxanthine to xanthine and of xanthine to UA, and there are two superoxide radicals produced during this process. Nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase 4; NOX4) belongs to the NOX catalytic enzyme family that generates ROS. NADPH oxidase is located on the cell membrane and functions in intracellular electron transfer across the cell membrane, which converts extracellular molecular oxygen into superoxide radicals. Extracellular superoxide can dismutate to hydrogen peroxide. Both extracellular superoxide radicals and hydrogen peroxide can penetrate the cell membrane through chloride channel-3 (ClC3) and aquaporin channels, respectively, and subsequently initiate intracellular signaling and oxidative stress [41][42].

In addition, free radicals are produced during the process of UA degradation inside the cell. For example, an unpaired electron of the urate anion free radical is located on the five-membered ring of purine [43], and a carbon-centered free radical forms during the reaction of peroxynitrite to purine [31]. The reaction between UA and peroxynitrite is on a second-order rate and needs to consume oxygen. The final products of urate and peroxynitrite are allantoin, alloxan, and aminocarbonyl radicals. Allantoin and alloxan are produced during urate oxidation by other oxidants, whereas the aminocarbonyl radical is produced by peroxynitrite oxidation [44]. At physiological concentrations of UA, around 0.5 nM in human plasma, UA can increase the oxidation of liposomes and LDL promoted by the peroxynitrite-attacked end product, especially the aminocarbonyl radical [44]. It is worth to note that UA can react with peroxynitrite to produce radicals, and these radicals can further react with peroxynitrite to produce radicals in chain reaction. Furthermore, the antioxidant property of extracellular uric acid would be hindered by the hydrophobic conditions created by the lipid layer of the cell membrane, and oxidized lipids can convert uric acid into an oxidant with the help of copper [45][46]. The shift of UA between oxidant and antioxidant is related to the availability of lipid hydroperoxides formed during the early phase of LDL oxidation [46]. In differentiated mouse adipocytes and human subcutaneous primary adipocytes, UA significantly increases ROS production [47]. UA can also increase NAPHD oxidase activity directly and enhance intracellular superoxide generation. Production of peroxynitrite contributes to an inflammatory response that damages tissues by inducing lipid peroxidation. Both superoxide and peroxynitrite induce osteoclast detachment and exert osteoclast inhibition [48]. After interferon-gamma induction, nitrotyrosine production of human trabecular bone osteoblast increases, which means peroxynitrite is generated after inflammatory cytokines are stimulated in human osteoblast cells. The addition of peroxynitrite decreases the differentiation and proliferation of human trabecular bone osteoblasts [49]. All these findings suggest that high intracellular UA levels represent high inflammatory and oxidative stress, which contributes to the development of bone loss by disturbing osteoclast and osteoblast activities.

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