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Regulation of uric acid metabolism and excretion

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ABSTRACT

Purines perform many important functions in the cell, being the formation of the monomeric precursors of nucleic acids DNA and RNA the most relevant one. Purines which also contribute to modulate energy metabolism and signal transduction, are structural components of some coenzymes and have been shown to play important roles in the physiology of platelets, muscles and neurotransmission. All cells require a balanced quantity of purines for growth, proliferation and survival. Under physiological conditions the enzymes involved in the purine metabolism maintain in the cell a balanced ratio between their synthesis and degradation. In humans the final compound of purines catabolism is uric acid. All other mammals possess the enzyme uricase that converts uric acid to allantoin that is easily eliminated through urine. Overproduction of uric acid, generated from the metabolism of purines, has been proven to play emerging roles in human disease. In fact the increase of serum uric acid is inversely associated with disease severity and especially with cardiovascular disease states. This review describes the enzymatic pathways involved in the degradation of purines, getting into their structure and biochemistry until the uric acid formation.

1. Introduction

Uric acid production and metabolism are complex processes involving various factors that regulate hepatic production, as well as renal and gut excretion of this compound. Uric acid is the end product of an exogenous pool of purines and endogenous purine metabolism. The exogenous pool varies significantly with diet, and animal proteins contribute significantly to this purine pool. The endogenous production of uric acid is mainly from the liver, intestines and other tissues like muscles, kidneys and the vascular endothelium [1].

Uric acid is a $C_5H_4N_4O_3$ (7,9-dihydro-1H-purine-2,6,8(3H)-trione) heterocyclic organic compound with a molecular weight of 168 Da. Many enzymes are involved in the conversion of the two purine nucleic acids, adenine and guanine, to uric acid. Initially, adenosine monophosphate (AMP) is converted to inosine via two different mechanisms; either first removing an amino group by deaminase to form inosine monophosphate (IMP) followed by dephosphorylation with nucleotidase to form inosine, or by first removing a phosphate group by nucleotidase to form adenosine followed by deamination to form inosine. Guanine monophosphate (GMP) is converted to guanosine by nucleotidase. The nucleosides, inosine and guanosine, are further converted to purine base hypoxanthine and guanine, respectively, by purine nucleoside phosphorylase (PNP). Hypoxanthine is then oxidized to form xanthine by xanthine-oxidase (XO), and guanine is deaminated to form xanthine by guanine deaminase. Xanthine is again oxidized by xanthine oxidase to form the final product, uric acid. Fig. 1 shows the enzymatic pathway for the purines degradation. At physiologic pH, uric acid is a weak acid with a pKα of 5.8. Uric acid exists majorly as urate, the salt of uric acid. As urate concentration increases in blood, uric acid crystal formation increases. The normal reference interval of uric acid in human blood is 1.5 to 6.0 mg/dL in women and 2.5 to 7.0 mg/dL in men. The solubility of uric acid in water is low, and in humans, the average concentration of uric acid in blood is close to the solubility limit (6.8 mg/dL). When the level of uric acid is higher than 6.8 mg/dL, crystals of uric acid form as monosodium urate (MSU). Humans cannot oxidize uric acid to the more soluble compound allantoin due to the lack of uricase enzyme. Normally, most daily uric acid disposal occurs via the kidneys [2].

Uric acid concentration might be measured in serum, plasma, urine and in exhaled breath condensate. Determination of uric acid concentration includes phosphotungistic acid methods (PTA), uricase methods, high-performance liquid chromatography methods, dry chemistry systems and biosensor methods. Prior to determination of urate in urine, alkalinization of urine might be necessary, because of urate crystallize at pH lower than 5.75 [3]. The production and catabolism of purines are relatively constant between 300 and 400 mg per day. The kidneys eliminate approximately two-thirds, while the gastrointestinal tract eliminates one-third of the uric acid load. Almost all uric acid is filtered from glomeruli, while post-glomerular reabsorption and secretion regulate the amount of uric acid excretion. The proximal tubule is the site of uric acid reabsorption and secretion, and approximately 90% is reabsorbed into blood. This is primarily accomplished at the proximal tubular level by transporters that exchange intracellular anions for

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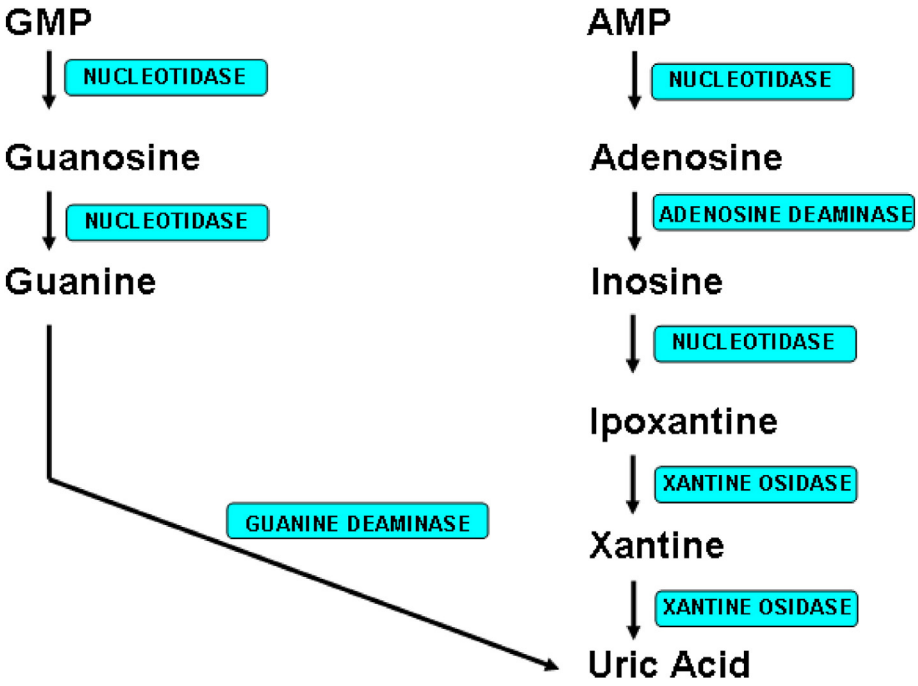

Fig. 1. Enzymatic degradation of purines in humans.

uric acid. Almost all reabsorption of uric acid occurs at the S1 segment of the proximal tubule. In the S2 segment of the proximal tubule, uric acid is secreted to a greater extent than that which undergoes reabsorption. Post-secretory reabsorption occurs at a more distal site of the proximal tubule, and approximately 10% of the filtered uric acid appears in the urine [1]. Hyperuricemia is a key risk factor for the development of gout, renal dysfunction, hypertension, hyperlipidemia, diabetes and obesity. Hyperuricemia occurs as a result of the increased uric acid production, the impaired renal uric acid excretion, or a combination of the two [4]. It is characterized by high uric acid level in the blood, causing deposition of urate crystals in the joints and kidneys [5]. Generally, hyperuricemia in adults is defined as a blood uric acid concentration greater than 7.0 mg/dL in men and 6.0 mg/dL in women. In normal humans, uric acid is excreted in urine. However, uric acid excretion may be impaired by kidney disease, leading to hyperuricemia [2].

Three urate transporters, URAT1/SLC22A12, GLUT9/SLC2A9, and ABCG2/BCRP, have been reported to play important roles in the regulation of serum uric acid (SUA), and their dysfunctions cause urate transport disorders. Among them, common dysfunction of ABCG2 exporter has proved to be a major cause of hyperuricemia and gout. Furthermore, renal hypouricemia is caused by increased renal urate excretion [6]. The molecular identification of URAT1 as the dominant apical urate exchanger of the human proximal tubule was a landmark event in the physiology of urate homeostasis. The URAT1 protein is encoded by the SLC22A12 gene, part of the large SLC22 family of organic ion transporters. URAT1 is a member of the organic anion transporter (OAT) branch of this gene family. Heterologous expression in Xenopus oocytes indicates that human URAT1 is capable of urate transport (^{14}C-labeled urate uptake), with a Km of 371 ± 28 μM. The basolateral entry of urate into renal proximal tubule cells is driven at least partially by the outwardly directed gradient for dicarboxylates such as α-ketoglutarate (α-KG), which in turn is generated by Na^+-dependent uptake via SLC13A1. Thus, in renal basolateral membrane vesicles, urate exchange is significantly trans-stimulated by α-KG. OAT1 and OAT3 appear to exchange urate with divalent anions such as α-KG, suggesting that they are suited to basolateral entry of urate, driven by intracellular α-KG, during urate secretion. Genetic variation in human ABCG2, an ATP-driven efflux pump, has emerged as a major factor in human hyperuricemia. A loss of or reduction in ABCG2-mediated renal urate secretion would lead to increased renal urate reabsorption, given that reduced renal excretion of urate is considered to be the underlying hyperuricemic mechanism in the vast majority of gout patients [7].

GLUT9 (SLC2A9) membrane transporter is distinct among other members of the glucose transporters (GLUT or SLC2) family due to its substrate specificity and sequence identity. While the majority of 14 members of the GLUT superfamily transport glucose or other monosaccharides, GLUT9 was shown to transport essentially urate. Single nucleotide polymorphisms in the SLC2A9 genes have also been associated with gout, coronary artery disease, and myocardial infarction. All 14 GLUT members share common structural features such as 12 transmembrane helices, cytoplasmic amino and carboxytermini, and an N-linked glycosylation site, although the glycosylation site varies across the family. Regarding GLUT9, two isoforms, SLC2A9a and SLC2A9b, have been described encoding the two proteins hGLUT9a and b that differ only by the first 29 residues of the N-terminal domains. GLUT9a is expressed ubiquitously, while GLUT9b is restricted to the main organs involved in urate transport, such as liver and kidney. GLUT9-mediated urate transport has been characterized. It is independent of sodium, chloride and anions, but is voltage dependent and currents have been recorded at physiological pH. Altogether, the data provided so far are compatible with a transport model in which GLUT9 is a uniport, without having formally excluded all other possibilities [8].

In addition to problems with uric acid excretion due to kidney dysfunction, hyperuricemia can also result from the increased generation of uric acid. Diets heavy in purine or fructose, or exposure to lead can also contribute to high uric acid levels. Fructose is a unique sugar molecule in that it rapidly depletes ATP and increases the amounts of uric acid. In certain humans, a deficiency of enzymes resulting from genetic mutations may also cause increased blood uric acid levels. For example, hypoxanthine-guanine phosphoribosyl transferase (HGPRT) catalyzes the formation of IMP and GMP for recycling purine bases with 5-phoshorbosyl-alpha-pyrophosphate (PRPP) as a co-substrate. Lesch–Nyhan syndrome, a rare inherited X-linked disorder caused by the deficiency of HGRPP, leads to the accumulation of purine and PRPP, which are used in the salvage pathway of hypoxanthine and guanine. The HGPRT defect results in the accumulation of hypoxanthine and guanine, which further leads to high uric acid levels. The excess PRPP also increases the rate of de novo synthesis of purine, and consequently

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