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Mini-review

Uric acid as a modulator of glucose and lipid metabolism

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ABSTRACT

In humans, uric acid is the final oxidation product of purine catabolism. The serum uric acid level is based on the balance between the absorption, production and excretion of purine. Uric acid is similarly produced in the liver, adipose tissue and muscle and is primarily excreted through the urinary tract. Several factors, including a high-fructose diet and the use of xenobiotics and alcohol, contribute to hyperuricaemia. Hyperuricaemia belongs to a cluster of metabolic and haemodynamic abnormalities, called metabolic syndrome, characterised by abdominal obesity, glucose intolerance, insulin resistance, dyslipidaemia and hypertension. Hyperuricaemia reduction in the Pound mouse or fructose-fed rats, as well as hyperuricaemia induction by uricase inhibition in rodents and studies using cell culture have suggested that uric acid plays an important role in the development of metabolic syndrome. These studies have shown that high uric acid levels regulate the oxidative stress, inflammation and enzymes associated with glucose and lipid metabolism, suggesting a mechanism for the impairment of metabolic homeostasis. Humans lacking uricase, the enzyme responsible for uric acid degradation, are susceptible to these effects. In this review, we summarise the current knowledge of the effects of uric acid on the regulation of metabolism, primarily focusing on liver, adipose tissue and skeletal muscle.

1. Introduction

Uric acid is a metabolite derived from the oxidation of purine compounds [1]. Since 1981, uric acid has been considered as a powerful chemical antioxidant, present in human plasma in concentrations much higher than ascorbate [2]. It was hypothesized that uric acid can provide an antioxidant defense in humans against oxidant- and free radicals-caused ageing and cancer, because uric acid protects erythrocyte membrane against lipid peroxidation and lysis induced by *t*-butylhydroperoxide in concentrations below those normally found in plasma [2]. Uric acid scavenges free radicals under hydrophilic conditions, thereby inhibiting lipid peroxidation on the lipid-aqueous boundary, but this antioxidation is only slight under lipophilic conditions [3]. In the presence of pre-formed lipid hydro-peroxides, uric acid might accelerate the copper-induced peroxidation of human LDL, even in the presence of endogenous antioxidants [4]. Thus, in hydrophobic environments, uric acid loses antioxidant ability and becomes a strong pro-oxidant.

More recently, uric acid effect on the development of insulin resistance, dyslipidaemia and hypertension, important signals of

Abbreviations: ABCG2, ATP-binding cassette transporter 2; ACC, acetyl-CoA carboxylase; ADH, alcohol dehydrogenase; Akt, protein kinase B; AMP, adenosine 5'-monophosphate; AMPK, AMP activated kinase; ATP, adenosine triphosphate; ChoRE, carbohydrate response elements; ChREBP, carbohydrate responsive element binding protein; ERK, extracellular signal-regulated kinase; FAS, fatty acid synthase; G6P, glucose-6-phosphate; G6Pc, glucose-6-phosphatase; GLUT, glucose transporter; GMP, guanosine 5'-monophosphate; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IMP, inosine 5'-monophosphate; IRS, insulin receptor substrate; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MRP4, multi drug resistance protein4; NAD, nicotinamide adenine dinucleotide; NEAC, nonenzymatic antioxidant capacity; NO, nitric oxide; NPT, Na^{+}-phosphate cotransporter; OAT, organic anion transporter; PEPCK, phosphoenolpyruvate carboxykinase; PI 3-kinase, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SREBP, sterol responsive element binding protein; SMCT, sodium-dependent monocarboxylic acid transporters; TAG, triacylglycerol; TORC2, transducer of regulated CREB activity 2; URAT1, urate-anion exchanger.

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Table 1
Biochemistry and haemodinamics changes induced by fructose or uric acid.

Fructose	***Model***
Hyperuricaemia, hypertriglyceridaemia, hypertension	Rats [20,26]
Steatosis	Rats [21]
Increase of lipogenesis[a]	Hep G2 [29]
Inhibition of AMPK phosphorylation[a]	Hep G2 [40]
Uric acid	***Model***
Hypertriglyceridaemia, hypertriglycaemia, hypertension	Humans [6,7], Rats [28]
Increase of lipid content[b]	Hep G2 [29]
Inhibition of aconitase	Hep G2 [29]
Inhibition of Akt and IRS-1 phosphorylation	Liver, adipose tissue and muscle of mice, HepG2 [49]
Stimulation of gluconeogenesis	Hep G2 [9]
Inhibition of AMPK phosphorylation	Hep G2 [9]
Stimulation of NADPH oxidase	Hep G2 [29], 3T3-L1 adipocytes [34]
Inhibition of nitric oxide production	3T3-L1 adipocytes [34]
Stimulation of renin-angiotensin system	3T3-L1 adipocytes [58]
Decrease of adiponectin RNAm	3T3-L1 adipocytes, human subcutaneous adipocytes [27]

[a] Uric acid dependent.
[b] Fructokinase independent. [Reference].

metabolic syndrome, has been suggested by clinical and epidemiological studies [5–8] (Table 1).

Purine compounds can be derived from exogenous sources, such as high protein diets, or endogenous sources, such as the catabolism of genetic material. The degradation of purine derivatives, such as adenosine 5'-monophosphate (AMP) and guanosine 5'-monophosphate (GMP), generates precursors for the synthesis of endogenous uric acid [1]. Uric acid synthesis is initiated with the cleavage of phosphate groups from AMP and GMP through 5'-nucleotidases, releasing adenosine and guanosine molecules, respectively. Adenosine deaminase converts adenosine into inosine, while guanosine is converted into free guanine. Inosine is subsequently hydrolysed to hypoxanthine by purine nucleoside phosphorylase. Xanthine oxidase catalyses the last two steps of uric acid synthesis: the conversion of hypoxanthine into xanthine and uric acid. Guanine is directly converted into xanthine, which is subsequently converted into uric acid by xanthine oxidase [1]. AMP deaminase also converts AMP into inosine 5'-monophosphate (IMP), which is then converted into inosine by nucleotidases [9,10]. Xanthine oxidase is competitively inhibited through drugs, such as allopurinol and febuxostat, which are used in the treatment of pathologies characterised by hyperuricaemia [11].

In most mammals, uric acid is subsequently converted into allantoin by uricase; thus, serum uric acid levels are typically low [12]. However, between 8 and 12 million years in the Miocene period, as a result of different point mutations, human ancestors and other modern primates lost the ability to express the uricase, and consequently serum uric acid levels have increased [12,13]. It has been suggested [14] that the loss of uricase in these evolutionary ancestors might have amplified the effects of fructose to enhance fat stores. These increased lipid reserves could be mobilised in times of energy demand, e.g., during the migration through large territorial extensions. However, the loss of uricase also increases blood pressure in response to salt [15]. Previous studies have shown that humans have maintained the set of genes encoding this enzyme in the liver, however two premature stop codons do not allow its expression [14,15].

In the absence of uricase, uric acid is the excretion product of purine metabolism [1]. Uric acid is a weak acid with a high dissociation constant (pK_a 5.8). Sodium urate is predominantly (98%) deprotonated at physiological pH in the bloodstream. Renal (70%) and biliary (30%) systems are responsible for the removal of urate from the bloodstream [1,16,17]. Renal excretion depends on the dynamic equilibrium between filtration, reabsorption and tubular secretion. Approximately 90% of the filtrated urate is reabsorbed through a transport system mediated by urate-anion exchanger (URAT) 1. This transmembrane protein reabsorbs urate and secretes anionic organic compounds, such as lactate, ketone bodies and xenobiotics, through countertransport (Fig. 1). These anionic organic compounds are released into renal tubular cells through sodium-dependent monocarboxylic acid transporters (SMCT), such as SMCT1/2. During secretion, urate enters the cell at the basolateral membrane via exchange with alpha-ketoglutarate, mediated by OAT1 and OAT3, or through exchange with unknown anions via OAT2. At the apical membrane, urate is secreted via multi-drug resistance protein4 (MRP4), adenosine triphosphate (ATP)-binding cassette transporter 2 (ABCG2), Na^+-phosphate cotransporter (NPT) 1, and/or NPT4 [1,17].

Serum uric acid levels are controlled through the balance between urate synthesis and excretion. Several exogenous and endogenous factors can impair this balance, inducing hyperuricaemia [18]. The excessive consumption of fructose, primarily used in sweetened beverages, has been considered an important inducer of hyperuricaemia (Fig. 1) [19,20]. Excess fructose increases fructokinase activity through a positive feedback mechanism via the activation of carbohydrate responsive element binding protein (ChREBP) [21]. Fructokinase is responsible for the metabolism of fructose into fructose-1-phosphate, resulting in adenosine triphosphate (ATP) depletion in the liver, and this reaction occurs rapidly and without any negative feedback [22]. The decrease in intracellular phosphate stimulates AMP deaminase, which catalyses the degradation of AMP to inosine monophosphate, resulting in a significant increase in serum uric acid levels (Fig. 1) [9,10]. Fructose and uric acid have been associated with cardiometabolic diseases [21,23], thus the growing consumption of sweetened beverages in developed and developing countries must be controlled. Phytocompounds have also been associated with hyperuricaemia. Methylxanthines, derived from coffee, might be demethylated and subsequently converted into uric acid through xanthine oxidase (Fig. 1). Flavonoids stimulate DNA degradation and inhibit uric acid excretion, thereby elevating serum uric acid levels (Fig. 1) [24]. In addition, some drugs also inhibit uric acid excretion. Pyrazinamide, used in the treatment of tuberculosis, and niacin, used in the treatment of dyslipidaemia, activate URAT1 transporter, thereby stimulating the reabsorption of filtrated urate (Fig. 1) [1,17]. Alcohol also stimulates this carrier by increasing the amount of lactate (Fig. 1). In this case, the hepatic metabolism of the