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URIC ACID AND HYPERTENSION: AN UPDATE

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Introduction

The first link between hypertension (HT) and uric acid (UA) was hypothesized in the 1870s in gout patients [1]. In 1966, it appeared that 47% of an hypertensive population was hyperuricemic [2]. Since then, many epidemiological studies showed a strong association between UA and HT and particularly the risk of developing HT. A recent systematic review and meta-analysis of 18 prospective cohort studies revealed that a 1 mg/dl increase in UA level was associated with an increased risk of incident HT by 13% (pooled RR = 1.13). These effects were significantly larger in women and in younger population studies [3]. Therefore, UA is often considered as an independent factor for HT, especially earlier in the life course than at a later stage [1,4,5]. Asymptomatic hyperuricemia was notwithstanding also a strong risk factor for resistant HT in the elderly [1]. These results contrast with a Mendelian randomization study, where no evidence for causal associations between UA and ischemic heart disease or blood pressure (BP) was found [4]. In this analysis, body mass index appeared to be the major confounder.

An association exists also between UA and cardiovascular diseases and mortality, metabolic syndrome, subclinical atherosclerosis, stroke, kidney diseases and endothelial dysfunction [1,4,6,7].

All these data suggest that high UA levels may contribute to the pathogenesis of cardiovascular, renal and metabolic diseases. Yet, in adults, there is still no convincing evidence that lowering UA levels improves BP control or prevents HT. Thus, the potential beneficial role of UA-lowering strategies on HT remains to be demonstrated.

Metabolism

During the Miocene, around 15 million years ago, great apes and humans lost the urate oxidase activity (uricase enzyme which catalyzes UA into allantoin) as a result of 3 different mutations. Hence, humans disclose higher UA levels than other mammals. This loss of function provided supposedly some evolutionary advantages. Firstly, UA acts as an antioxidant and represents more than 60% of the antioxidant capacity of the plasma. It can scavenge single oxygen, peroxyl and hydroxyl radicals, reacts with peroxynitrite and stabilizes eNOS activity. Its antioxidant effects need the presence of ascorbate [8]. Importantly, a very low UA level is linked to endothelial dysfunction [9] and there is a J-shaped relation between cardiovascular events and UA level in essential hypertension [6]. Secondly, UA increases salt sensitivity and may have maintained BP in the poor salt environment of these early times. Thirdly, UA increases fat storage and lipogenesis. Fruits contain more fructose at the end of the summer, resulting in an enhanced lipid deposition to better cope with the nearby winter.

UA is the last product of purine metabolism. The last two steps of the pathway are catalyzed by the xanthine oxidoreductase (XOR) which exists under two interconvertible isoforms: the xanthine dehydrogenase (XDH), which uses NAD+ as an electron acceptor, and xanthine oxidase (XO), which uses oxygen as an electron acceptor. Only the XO is able to create reactive oxygen species (ROS) during the generation of UA. This latter form is more activated during ischemia, extensive surgery and stress, and is mainly present in the liver, the intestine and the vascular wall. UA is mainly excreted by the kidney (85%) as poorly soluble substance [4].

Causes of hyperuricemia

Normal serum UA levels are comprised between 3 to 7 mg/dl (180 to 415 µmol/l). Reduced UA excretion is a common cause of hyperuricemia and found in renal failure and in the presence of insulin resistance, in part due to an increased renal reabsorption under the effect of high insulin levels. High cell turnover and western diet are also a large source of UA production: fatty and red meats, seafood, alcohol and sugar-sweetened (especially with fructose) beverages are well known to increase UA levels. Loop and thiazide diuretics reduce renal UA excretion. Genetic polymorphism in urate transporter one (URAT-1) and Glut 9 transporter can also result in hyperuricemia [1].

The consumption of fructose has highly increased these last decades, and is linked by some authors with the epidemic of obesity in the United States through the consumption of High Fructose Corn Syrup (HFCS) in beverages. Fructose is the only sugar which can raise UA level. It is almost completely extracted from the portal vein to be metabolized in the liver by the phosphofructokinase in fructose-1-phosphate (F1P). This non-limiting step consumes a large amount of adenosine triphosphate (ATP), resulting in substrates for the purine metabolism. F1P will be converted into glucose, glycogen, lactate and lipids. Some animal and human studies showed that a large quantity of fructose leads to hyperuricemia and elevated BP [1].

Animal models

Although the translation of results from animal models to humans is sometimes challenging, these studies provided important information about the pathogenic role of UA in HT. Knockout rodents for the uricase gene die in a few weeks after tubular crystal deposition and renal failure. The most studied animal model uses oxonic acid, an uricase inhibitor, which moderately raises UA. This mild-to-moderate experimental hyperuricemia is associated with a rise in BP after several weeks. This oxonic acid-induced elevated BP occurs in the absence of crystal deposition in kidney. These studies revealed that HT develops in two steps. Firstly, UA was shown to activate the renal renin-angiotensin system (RAS) (juxtaglomerular renin increases), to reduce nitric oxide (NO) bioavailability (NO synthase expression decreased) and to increase oxidative stress in the macula densa, leading to an endothelial dysfunction and renal vasoconstriction. This first step is UA-dependent, and occurs without any renal structure abnormality. Secondly, after several weeks, architectural vascular damages occur such as afferent arteriolopathy and mild interstitial inflammation (with low-grade tubulointerstitial injury) resulting into a salt-sensitive and UA-independent HT. These latter changes are similar to those observed in most subjects with essential HT. The above mentioned first step could be reversible before renal damages occur. These deleterious oxonic acid effects can be blocked by XO inhibitors (XOI) (allopurinol and febuxostat), uricosurics (benzbromarone and

probenecid), L-arginine supplementation (substrate for NO synthase) or RAS blockers [10,11]. Another model is the induction of hyperuricemia by liver-specific deletion of Glut9, a UA transporter that provides UA to the hepatocyte enzyme uricase [12]. In this model, hyperuricemia can be increased gradually by the addition of inosine to the diet. In this model, a 3-4 fold increase in uricemia was not associated with change in 24h BP at least until the developed renal lesions. These data suggest that the impact of UA on BP is secondary to the occurrence of renal damages, to which UA may contribute.

In vitro studies

In Human Umbilical Vein Endothelial Cells (HUVECs), UA blocks NO release by reduction of phosphorylation of eNOS, increases angiotensin II and I receptors expression, induces oxidative stress and stimulates production of C-reactive protein (CRP), angiotensin II, interleukin 6 and 8 (Il-6 and Il-8), tumor necrosis factor alpha (TNF-α), intercellular adhesion molecule one (ICAM-1), vascular cell adhesion molecule one (VCAM-1) and monocyte chemoattractant protein one (MCP-1). These mechanisms are attributed to the ROS production from NADPH oxidase stimulation and Nuclear Factor kB (NF-κB) expression via mitogen activated protein (MAP) kinases (p38 and p44/42 MAPk) pathway and lead to apoptosis and inhibition of cell proliferation.

In human Vascular Smooth Muscle Cells (VSMCs), UA enters via URAT-1 and activates their proliferation and migration via p38 and p44/42 MAPk with production of CRP.

In rats VSMCs, UA activates the RAS through the activation of specific MAPk, with de novo induction of cyclo-oxygenase-2 (COX-2), local thromboxane (TXA) and upregulation of platelet-derived growth factor A (PDGF-A). UA stimulates also MCP-1 synthesis by p38 MAPk and nuclear transcription factors (NF-κB and activator protein one, AP-1). UA simulates the synthesis of Il-6, Il-1b and TNF-α from human mononuclear cells [1,4,13,14].

Human clinical trials

In children and adolescents, hyperuricemia (over 5.5 mg/dl, 330 µmol/l) is observed in 89% of newly primary hypertensive. In a small double-blind, placebo-controlled crossover study in 30 adolescents, allopurinol normalized BP in 2/3 after 4 weeks [1]. In another randomized trial, 60 obese children received allopurinol, probenecid or placebo for 7 weeks. UA-lowering therapies (ULT) decreased BP by 10 mmHg [1]. Allopurinol also enhanced anti-hypertensive effects of enalapril in hyperuricemic essential hypertensive children [15].

In adults, results are less convincing due to the limited number of well-conducted randomized prospective studies. In a non-randomized study, allopurinol reduced BP and CRP in asymptomatic hyperuricemic adults [16]. A phase 2, randomized placebo-controlled study, has recently showed that febuxostat decreased systolic BP in a preplanned subgroup analysis of hyperuricemic hypertensive patients with normal renal function [17]. Others studies on older patients did not show any effects on BP, in line with the lack of correlation between serum UA and HT in the elderly population [18]. A randomized, noninferiority trial compared the cardiovascular safety of febuxostat and allopurinol in high cardiovascular risk patients with gout [19]. Cardiovascular death and death from any cause were significantly higher in the febuxostat group. A larger proportion of patients had UA levels under 5 mg/dl (300 µmol/l) in the febuxostat group. There was no effect on BP in both groups, but the patients had a median age of 64 years, were at high cardiovascular risk, and the study was no placebo-controlled and had a high discontinuation rate.

Importantly, nowadays, according to a recent meta-analysis, there is still a lack of evidence to recommend the use of allopurinol or other ULT as a treatment of HT [20]. In heart failure patients, allopurinol improved endothelial function in contrast to probenecid, but more data are needed [21].

Is UA per se or the ROS produced by XO responsible for the above mentioned deleterious effects? An argument against a causal relationship between UA per se and HT is that UA infusion does not alter endothelial function in healthy participants. In contrast, it improves endothelial function in type 1 diabetics and regular smokers [22]. A protective effect of UA on coronary arteries has been shown in isolated perfused hearts in the 1980s [23].

Conversely, early UA infusion after an acute ischemic stroke did not improve functional outcomes at 90 days [24]. A growing hypothesis is that UA acts as an antioxidant factor in the extracellular space, but as a pro-oxidant factor inside the cell [4,5]. As such, UA infusion would improve antioxidant extracellular properties, while XOI reduce UA level and oxidative stress within the cells instead, an effect not seen with probenecid [5].

Conclusion

A strong association exists between hyperuricemia, HT and cardiovascular diseases. Evidence from animal models, in vitro studies and human trials, warrant further studies to assess the precise pathogenic role of UA and whether ULT are beneficial for early diagnosed primary HT, and especially so in children, adolescents and young adults. Large interventional studies are needed to determine if reductions in UA levels can prevent HT and major cardiovascular events, especially in young population with pre-HT. Although allopurinol generated a large interest, this medication has several pitfalls. With newer and more specific XOI [25], there is a renewed opportunity to further test the HT - UA hypothesis, and to improve our understanding of the possible cardiovascular consequences of elevated UA levels.

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