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 [4,5]. Asymptomatic hyperuricemia was notwithstanding also a strong risk factor for resistant HT in the elderly [6]. These results contrast with a Mendelian randomization study, where no evidence for causal associations between UA and ischemic heart disease or stroke, kidney diseases and endothelial dysfunction [7,8].

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 [9]. Importantly, a very low UA level is linked to endothelial dysfunction [10] and there is a J-shaped relation between cardiovascular events and UA level in essential hypertension [11]. Secondly, UA increases salt sensitivity and may have maintained BP in the poor salt environment of these early 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.

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, arterial vascular damages occur such as afferent arteriopathy 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 [13,14]. Another model is the induction of hyperuricemia by liver-specific deletion of Glut9, a UA transporter that provides UA to the hepatocyte enzyme uricase [15]. 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 (II-6 and II-8), tumor necrosis factor alpha (TNF-α), intercellular adhesion molecule one (ICAM-1), vascular cell adhesion molecule one (VCAM-1) and monocyte chemotaxic protein one (MCP-1). These mechanisms are attributed to the ROS production from NADPH oxidase stimulation and Nuclear Factor Kb (NF-kβ) expression via mitogen activated protein (MAPK) kinases (p38 and p44/p42 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/p42 MAPK with production of CRP. In rats VSMCs, UA activates the RAS through the activation of specific MAPK, with de novo induction of cyclooxygenase-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-kβ and activator protein one, AP-1). UA stimulates the synthesis of II-6, II-1b and TNF-α from human mononuclear cells [16,17,18,19].

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 [20]. In another randomized trial, 60 obese children received allopurinol, probenecid or placebo for 7 weeks. UA-lowering therapies (ULT) decreased BP by 10 mmHg [21]. 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 [22]. 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 renal function [17]. 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 damages. These data suggest that the impact of UA on BP is secondary to the occurrence of renal damages, to which UA may contribute.

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REFERENCES