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Commentary

Time to reconsider urate: Neuroprotective potential may prevail on cardiovascular risk in animal models and clinical trials

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In this issue of *EBioMedicine*, Chen and colleagues investigated the association between urate, the anionic form of uric acid, and blood pressure (BP), by studying three groups of genetically engineered mice with different levels of urate, and by reanalysing data from a clinical trial using inosine to increase urate levels in Parkinson's disease (PD) [1,2].

Urate is the enzymatic end-product of purine metabolism in apes and humans, and is traditionally thought to be a cardiovascular risk factor, contributing to chronic inflammation within the endothelium and, ultimately, to its dysfunction with subsequently higher BP [3,4]. However, higher urate is not necessarily a cause of hypertension, nor its consequence, and could be merely an association. Based on this, authors acquired BP measurements from three complementary lines of genetically engineered mice: urate oxidase (UOx) conditional knockout (cKO), global KO (gKO), and transgenic (Tg) mice with mildly elevated, markedly elevated, and substantially reduced serum urate, respectively. These knockout models were specifically selected to mimic the evolutional mutations in UOx gene, making them as much “humanized” as an animal model could possibly be. Also, authors re-analysed data from the SURE-PD, a phase 2 clinical trial aiming at evaluating safety of inosine in increasing urate levels in early PD. [1] Results consistently did not support any positive association between long-term urate elevation and BP variations in neither animal models nor generally-healthy early PD. [2] Biological and clinical relevance of these findings go far beyond this study, and will impact on basic and clinical research on neurodegenerative diseases, where urate-elevating strategies have been tested.

Urate accounts for 60% plasma antioxidant capacity and acts as a scavenger of free radicals, exerting neuroprotective effects on animal models of brain/spinal cord injury, multiple sclerosis (MS), and stroke [4,5]. Further neuroprotectant evidence comes from epidemiological studies showing lower levels of urate being associated with a higher risk of developing amyotrophic lateral sclerosis (ALS) [5], multiple sclerosis (MS) [6], multiple system atrophy (MSA) [7], and PD. [4] Not least, clinical observational studies found lower levels of urate being associated with worse outcomes in MS [8], MSA [7], PD [4,9], and stroke [10]. Based on this, urate-elevating strategies have been tested for safety and efficacy in phase 2 and, more recently, phase 3 clinical trials (Table 1). Most of these studies have used an urate precursor, inosine, that is taken orally and rapidly metabolized to urate [5]. Overall, phase 2 clinical trials proved inosine safe in elevating plasma and CSF urate in the long term, and did not support any association between elevated urate and any cardiovascular comorbidity (e.g., hypertensive, hyperglycaemic, dyslipidaemic and obesity components of metabolic syndrome) [1,6]. Encouraging clinical results were shown in a phase 2/3 clinical trial (URICO-ICTUS) where the combination of intravenous urate with thrombolysis in acute ischemic stroke resulted in improved clinical outcomes, especially in woman and in patients more vulnerable to oxidative stress and reperfusion injury (e.g., hyperglycaemia at stroke onset) [10]. Further clinical results are expected from the ongoing phase 3 clinical trial in PD (SURE-PD3), potentially leading to the first disease-modifying therapy for PD.

In the future, basic scientists might consider using animal models as described by Chen and colleagues to study consequences of urate elevation on motor/behavioural tasks, though an effect is not necessarily implied considering that the urate pathway is rather specific of hominoids, and, possibly, relates to more developed cerebral function [4]. Also, it is worth noting that PD patients included in the SURE-PD were at early stage with neither severe neurological symptoms nor cardiovascular comorbidities [1]. Thus, generalizability of these findings should be examined on more heterogenous cohorts where a number of variables should be considered (e.g., physical exercise, medication, concomitant cardiovascular diseases and diet).

In conclusion, we feel we need to thank Chen and colleagues for their elegant study, providing basic and clinical scientists with evidence suggesting there is little risk of increasing blood pressure while applying urate-elevating strategies, that, thus, could be further moved towards treatment of neurodegenerative diseases.

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Table 1
Urate in clinical trials.
Table shows ongoing and completed clinical trials using treatment with uric acid or with urate-elevating strategies. For each trial, phase, intervention(s), primary and secondary outcomes, sample size, year of start and current status, and ClinicalTrials.gov reference are reported.

Conditions	Phase	Interventions	Primary outcome	Secondary outcomes	Sample size	Year at start	Reference
Acute Ischemic Stroke	2/3	Uric acid or Placebo	Degree of disability after stroke	Other clinical outcomes Radiological outcomes	421	2011-completed	ClinicalTrials.gov/show/NCT00860366
ALS	1	Inosine	Safety Tolerability	Blood outcomes Radiological outcomes	32	2015-completed	ClinicalTrials.gov/show/NCT02288091
	2	Inosine or Placebo	Safety Tolerability		30	2017-ongoing	ClinicalTrials.gov/show/NCT03168711
Healthy	1	Inosine	Pharmacokinetics	Safety /Tolerability	18	2015-completed	ClinicalTrials.gov/show/NCT02614469
	1	Uric acid or Rasburicase	Change in inflammatory markers		97	2009-completed	ClinicalTrials.gov/show/NCT01323335
	1	Montmorency cherry concentrate	Change in uric acid	Change in inflammatory markers	12	2012-completed	ClinicalTrials.gov/show/NCT01825070
MSA	2	Inosine or Placebo	Change in uric acid Safety/Tolerability	Rate of clinical decline	80	2018-ongoing	ClinicalTrials.gov/show/NCT03403309
PD	2	Inosine or Placebo	Safety /Tolerability	Change in uric acid	75	2009-completed	ClinicalTrials.gov/show/NCT00833690
	3	Inosine or Placebo	Rate of clinical decline	Safety /Tolerability Other clinical outcomes Patient reported outcomes	270	2016-ongoing	ClinicalTrials.gov/show/NCT02642393
RRMS	2	Inosine	n.r.	n.r.	30	2001-completed	ClinicalTrials.gov/show/NCT00067327

ALS: Amyotrophic Lateral Sclerosis; MSA: Multiple System Atrophy; PD: Parkinson Disease; RRMS: Relapsing-Remitting Multiple Sclerosis; n.r.: not reported.

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The authors declare no conflict of interest.

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