

Letter to The Editor: Nanocrystalline Uric Acid as an Evolutionary Mechanism for Ammonia Detoxification

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Letter to the Editor

Uric Acid (UA), a biphasic byproduct of purine metabolism resulting from the evolutionary loss of uricase, is primarily excreted through the kidneys (70%) and intestines (30%). Disruptions in urate transporters, particularly URAT1 and GLUT9, disturb systemic balance and contribute to chronic hyperuricemia, which is implicated not only in gout and nephrolithiasis but also in metabolic-inflammatory disorders. Through the activation of xanthine oxidase and NADPH oxidase, excess UA promotes Reactive Oxygen Species (ROS) production, mitochondrial dysfunction, endothelial injury, and inflammatory signaling cascades such as the NLRP3 inflammasome and toll-like receptor pathways, highlighting its dual antioxidant and pro-oxidant roles [1].

Thornton et al. [2] provide compelling evidence that reptilian urates consist of Uric Acid Monohydrate (UAM) nanocrystals arranged in multilayered, ionizable structures with high surface area, challenging the long-standing assumption that UA is merely a metabolic waste. Their multispecies comparative analysis identifies two urate patterns: primitive reptiles (e.g., pythons, boas) directly excrete microspherical UAM, whereas advanced snakes produce granular Ammonium Urate Hydrates (AUH), with UAM acting as a precursor. Using powder X-ray diffraction, scanning electron microscopy, and infrared spectroscopy, the authors demonstrate that UAM is metastable, nanocrystalline, and capable of binding key ions, including potassium, sodium, calcium, and magnesium, thus facilitating osmoregulation and safe nitrogen excretion [2]. The ability of UAM to interact with ammonia to form ammonium urate represents a potentially evolved mechanism for ammonia detoxification and water conservation.

This reinterpretation positions UA as a dynamic,

multifunctional molecule rather than a metabolic endpoint. The reptilian model suggests that the physicochemical behaviour of UA is highly context-dependent, shaped by evolutionary pressures, and potentially modifiable - a perspective that may hold relevance for human hyperuricemia, where UA contributes to ROS generation and inflammation [3]. These findings raise important questions about whether humans possess underexplored mechanisms influencing UA crystallinity or ion interactions.

Future research should include nanoscale imaging of human urate crystals to determine parallels with reptilian UAM [4], as well as biochemical studies examining how pH, temperature, and ionic composition influence UAM metastability. Moreover, the evolutionary interpretations presented by Thornton et al. would be strengthened by genomic and functional analyses of uricase repression and urate transporter evolution across species [5]. Integrating reptilian UA biology with patient-based studies on URAT1 and GLUT9 variants may further clarify mechanisms of urate handling and crystal formation [1].

Overall, these findings challenge the long-standing view of UA as merely a waste product and instead highlight its structural versatility and regulatory potential. The demonstration that nanocrystalline UAM can modulate electrolyte balance and ammonia detoxification broadens the framework through which human UA metabolism and disease are understood [2]. Continued investigation into UA structure-to-function dynamics, comparative transporter genomics, and ion-interaction behaviour may support the development of more targeted therapies for hyperuricemia and gout [4].

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