Advances in Clinical Medicine 临床医学进展, 2025, 15(2), 238-247
Published Online February 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.152339

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高尿酸血症影响肾功能作用机制的研究进展

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收稿日期：2025年1月11日；录用日期：2025年2月4日；发布日期：2025年2月11日

摘　要

人体血液中尿酸浓度过高会形成尿酸盐结晶(monosodium urate, MSU)，MSU在肾小管中沉积，导致肾间质和肾小管受损，引起痛风性肾病。此外，高尿酸可引起肾脏血流动力学改变、肾脏炎症反应和氧化应激等。多个信号通路参与了肾损伤过程，如：MAPK、Nrf2/ARE、NF-κB、PPAR等。高尿酸肾损伤可通过健康的生活方式预防，同时也需要规范化的药物治疗，但临床上降尿酸药物均存在一定的副作用，开发低毒高效的降尿酸药物具有重要的临床意义。本文综述了血尿酸水平升高引起肾损伤的机制，高尿酸血症的预防和治疗措施，为降尿酸保护肾脏的药物开发提供参考。

关键词

高尿酸血症，肾损伤，作用机制，信号通路，治疗策略

Research Progress on the Mechanism of Hyperuricemia Affecting Renal Function

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Received: Jan. 11th, 2025; accepted: Feb. 4th, 2025; published: Feb. 11th, 2025

Abstract

High uric acid concentration in human blood will form urate crystals (MSU), and MSU is deposited

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文章引用: 陈秀珍, 杨瑞, 余学志, 李田田, 李鸣, 张阳, 孙孔春. 高尿酸血症影响肾功能作用机制的研究进展[J]. 临床医学进展, 2025, 15(2): 238-247. DOI: 10.12677/acm.2025.152339

in renal tubules, leading to damage of renal interstitium and tubules and causing gouty nephropathy. In addition, high uric acid can cause alterations in renal hemodynamics as well as renal inflammatory response and oxidative stress. Signaling pathways associated with kidney injury include MAPK, Nrf2/ARE, NF-κB and PPAR. Hyperuric acid kidney injury can be prevented by a healthy lifestyle and also requires standardized drug therapy. However, all clinical uric acid-lowering drugs have certain side effects, and the development of safer and more effective uric acid-lowering drugs is urgent. This paper reviews the mechanism of kidney injury caused by elevated blood uric acid level, the prevention and treatment measures of hyperuricemia, and provides reference for the development of uric acid-lowering drugs to protect the kidneys.

Keywords

Hyperuricemia, Kidney Injury, Mechanism of Action, Signaling Pathway, Therapeutic Strategy

1. 引言

尿酸是嘌呤代谢的终产物，主要通过近端肾小管排泄。高尿酸血症主要是由于尿酸生成或排泄异常而导致的，男性血清尿酸(serum uric acid, SUA)水平 ≥ 70 mg/L (416.0 μmol/L)或女性 SUA 水平 ≥ 60 mg/L (357.0 μmol/L)被定义为高尿酸血症(hyperuricemia, HUA) [1]。HUA 是一种常见的代谢性疾病，其发病率在全球呈上升趋势，一般人们对高尿酸血症的认识往往仅局限于与痛风的关联，实际上，血液中尿酸含量长期过高会大大增加代谢综合征、糖尿病、高血压、心血管疾病和慢性肾脏疾病的患病风险[2]-[5]，给社会及家庭带来巨大负担。

血液中尿酸的水平高低取决于尿酸生成和排出之间的平衡。人体中尿酸的 60%至 70%经肾脏排泄[6] [7]，在高尿酸血症患者体内，长期高水平的尿酸会导致肾脏中尿酸结晶沉积、局部炎症反应、肾血管病变等病理反应，直接或间接损伤肾脏，肾损伤导致尿酸排出进一步受阻，最终加重肾脏损伤。这种恶性循环使得高尿酸血症与肾脏损伤之间的关系愈发紧密，因此如何通过药物干预等手段打破这一恶性循环从而保护肾脏，对于提高高尿酸血症患者的生存质量具有重要意义。

本文通过综合分析近年来相关文献，从高尿酸血症肾损伤的发生机制、临床表现、诊断和治疗方法等角度，对高尿酸血症影响肾功能的研究进行综述，旨在为更好地诊治高尿酸血症相关肾脏疾病提供参考。

2. 高尿酸血症影响肾功能的作用机制

2.1. 肾脏尿酸盐结晶的形成和沉积

正常生理状态下，大部分尿酸经肾小球滤出，再由近端肾小管重吸收，最后被远曲小管分泌最终排出[8]。但当血液中尿酸浓度持续过高，微溶的尿酸在过饱和状态下持续析出，形成的 MSU 堵塞肾脏排泄通路并持续刺激肾脏产生急性炎症，造成肾损伤，最终造成慢性肾病和肾衰竭[9]-[11]。

2.2. 肾脏血流动力学的影响

高水平尿酸能够引起血管收缩和血管平滑肌细胞的增殖，诱发血管内皮细胞功能障碍，激活局部的

环氧合酶 2 (cyclooxygenase-2, COX2)和肾素–血管紧张素(renin-angiotensinsystem, RAS)系统，进而引发与尿酸盐结晶无关的氧化应激[12] [13]。这一系列反应会引起肾小球的动脉病变，最终导致肾缺血。

2.3. 肾脏炎症反应和氧化应激相关通路

如 2.1 中所述，肾脏中尿酸盐结晶沉积会引发肾脏炎症和氧化应激，造成肾损伤[14]，研究发现：尿酸盐氧化酶基因敲除的大鼠肾脏受损严重，表现为肾脏间质纤维化增加，巨噬细胞浸润，NLRP3 炎症小体和白细胞介素-1β (IL-1β)的表达增加，其他细胞内能量代谢(如细胞自噬等)等多种信号通路被激活[15]，此外，高浓度尿酸可以诱导炎症反应和活性氧损伤肾脏[16] [17]。关于高尿酸血症中炎症及氧化应激的相关通路的研究主要有：

1) MAPK 信号通路：丝裂原激活蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路在肾脏炎症中具有重要作用，p38 MAPK 信号通路是 MAPK 通路的重要分支，参与了细胞凋亡、炎性反应及纤维化的发生和发展过程。研究表明：过高的尿酸水平会促使活性氧(reactive oxygen species, ROS)的产生增加[18]。ROS 能够激活 MAPK 信号通路中的凋亡信号调节激酶 1 (apoptosis signal regulating kinase-1, ASK1)，激活的 ASK1 可以进一步激活 p38 MAPK 通路进而引起一系列炎症因子的表达的上调，如 IL-1β、白细胞介素-6 (IL-6)、肿瘤坏死因子-α (TNF-α) [19]。这些炎症因子会引起血管内皮细胞的功能障碍，包括内皮细胞的通透性增加、一氧化氮(NO)生物利用度降低等。细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)通路是 MAPK 通路的另一个重要分支，高浓度尿酸引起 p38 MAPK 的磷酸化水平增高，激活 ERK 通路，导致肾小管上皮细胞的增殖[20]。这可能是因为激活的 ERK 通路磷酸化了一些与细胞周期相关的蛋白，促使细胞从 G1 期进入 S 期，从而促进细胞增殖。这种异常的细胞增殖可能与高尿酸血症引起的肾脏病变有关，如肾小管间质纤维化。另外，p38 MAPK 的激活会诱导下游 NLRP3 炎症小体的产生[21]-[23]，从而介导细胞的凋亡[24]、焦亡[22]和氧化应激[17] [25] [26]。研究发现通过抑制 p38 MAPK 的活性，可以减轻炎症反应、减少细胞凋亡、延缓肾脏损伤等[27]-[29]。因此，研究 p38 MAPK 炎症信号通路在高尿酸血症中的作用机制，对于寻找治疗高尿酸血症及肾病的新靶点具有重要意义，有望为临床治疗提供新的思路和方法。

2) NF-κB 信号通路：高尿酸可刺激炎症细胞释放 TNF-α、IL-1β 等炎症因子[30] [31]。NF-κB 作为这些炎症因子的核因子，进入细胞核后，可调控多种基因的表达，包括诱导型一氧化氮合酶(iNOS)、环氧化酶-2 (COX-2)等[32] [33]。这些基因的表达会进一步促进 ROS 和活性氮(RNS)的产生，加重氧化应激[34] [35]。同时，NF-κB 还可以抑制抗氧化酶的表达，削弱细胞的抗氧化能力[36]。此外，激活的 NF-κB 可以上调一些细胞因子和趋化因子的表达，而这些细胞因子和趋化因子又可以反过来激活 MAPK 信号通路中的某些激酶[37]。有研究发现通过抑制 MAPK/NF-κB 信号通路的激活，可以改善小鼠肾间质纤维化，抑制炎症反应[26] [36] [38]。因此，进一步研究 NF-κB 信号通路的调控机制，可有助于理解高尿酸水平引起的炎症反应和氧化应激，有望为开发新的治疗策略提供依据。

3) Nrf2/ARE 信号通路：正常生理情况下，核因子–红细胞 2 相关因子 2 (nuclear factor erythroid 2-related factor 2, Nrf2)与 Kelch 样环氧氯丙烷相关蛋白-1 (kelch-like ECH-associated protein 1, Keap1)结合，处于相对稳定的失活状态[39] [40]。当受到氧化应激刺激(如 p38 MAPK 信号通路诱导的炎症因子氧化应激刺激)时，Nrf2 与 Keap1 解离并进入细胞核，与抗氧化反应元件(antioxidant response element, ARE)结合[41]，启动下游抗氧化基因的表达及转录，如超氧化物歧化酶(SOD)、谷胱甘肽过氧化物酶(GPx)和血红素氧合酶-1 (HO-1)等[42]-[44]。研究发现，在 Nrf2 基因敲除小鼠实验中，Nrf2 可以缓解肾脏细胞氧化应激状态，缓解高尿酸血症肾损伤[44]-[46]。另外，高尿酸能刺激炎症细胞释放炎症因子，如 IL-1β、TNF-α 等，这些炎症因子可通过各种反应抑制 Nrf2/ARE 信号通路[47]，如 IL-1β 可以激活一些蛋白激酶，磷酸

化的 Nrf2 与 Keap1 蛋白的结合更加稳定，阻碍 Nrf2 进入细胞核发挥转录激活作用；或者影响 Nrf2 与 ARE 的结合能力，降低下游抗氧化基因的表达，削弱细胞的抗氧化防御能力。这一系列机制揭示了 Nrf2/ARE 在高尿酸导致的氧化应激及高尿酸血症相关肾损伤过程中的关键调控作用，该通路可能成为治疗高尿酸血症肾损伤潜在的靶点[48]。

4) PPAR 信号通路：过氧化物酶体增殖物激活受体(peroxisome proliferators-activated receptors, PPAR)是一类核受体，参与调节脂质代谢、炎症反应及氧化应激等多种生物学过程[49]-[52]。高浓度的尿酸会引起细胞内一系列应激反应，激活炎症信号通路，产生炎症因子(TNF-α、IL-6)等。高尿酸可能通过影响 PPAR 通路来调节下游基因的表达，从而改变氧化应激状态。例如，PPARγ 被激活后，能够对 NF-κB 通路的激活起到抑制作用，降低炎症因子的生成以及氧化应激水平[53] [54]。此外，PPAR 还可调节脂肪酸代谢，降低脂质过氧化产物的生成，从而缓解氧化应激对细胞的损伤[55]。有研究表明激活 PPAR 从而通过影响脂质代谢和减轻炎症反应等途径在大鼠体内发挥降尿酸作用[56]-[58]。因此，激活 PPAR 通路不仅有助于改善代谢紊乱，还可能为高尿酸血症的治疗提供新思路，对于开发有效的治疗药物具有重要意义。

2.4. 肠道菌群对高尿酸血症肾病的影响

高水平尿酸会破坏肠道菌群的平衡状态，使肠道微生态环境发生改变。研究发现，高尿酸血症患者或动物模型中，肠道菌群的组成和多样性出现显著变化，其中产脂多糖(Lipopolysaccharides, LPS)的革兰氏阴性菌数量明显增多[59] [60]。这可能是由于高尿酸影响了肠道内的理化环境，如 pH 值、氧化还原电位等，为某些细菌的生长提供了更有利的条件，同时抑制了其他有益菌的生长。增多的革兰氏阴性菌产生大量 LPS，LPS 作为一种内毒素，可与肾脏细胞表面的 Toll 样受体 4 (Toll-like receptor 4, TLR4)结合，激活下游信号通路，促进 TNF-α 等炎症因子的释放[61]，最终导致肾损伤。

3. 高尿酸血症肾病的临床表现

3.1. 慢性尿酸性肾病

慢性尿酸性肾病多见于中老年男性，患者早期尿浓缩功能减弱，后出现肾小球滤过率降低、血肌酐升高，逐渐发展为慢性肾功能不全。该病还可能因肾内或尿道尿酸盐结晶导致尿流阻塞并引发感染，患者有轻微蛋白尿症状。该病常合并轻中度高血压、高脂血症及代谢综合征，易引发心血管疾病和肾动脉硬化。

3.2. 急性尿酸性肾病

该病形成原因是短期内大量细胞被破坏产生了大量尿酸，尿酸盐结晶堵塞肾小管，导致患者出现血肌酐、血氮质水平迅速上升，进而出现少尿或无尿的症状。在骨髓增生性疾病、化疗、癫痫持续状态、中暑、Lesch-Nyhan 综合征以及多个实体肿瘤自发性坏死时较为多见[10] [62]。结晶阻塞集合管是导致急性肾衰竭的原因之一，结晶压迫远端肾血管，使得出球动脉和肾小管旁毛细血管压力升高是另一重要原因。

4. 高尿酸血症肾病的预防和治疗策略

4.1. 预防策略

2024 年国家卫生健康委发布了《成人高尿酸血症与痛风食养指南》，建议高尿酸患者在日常饮食中，应确保食物的种类丰富多样，以满足身体对各种营养成分的需求。增加蔬菜和低脂奶制品的摄入，不仅能补充维生素和矿物质，还能有效帮助控制尿酸水平。然而，要特别注意减少高嘌呤食物的摄入，如红肉、内脏和某些种类的海鲜以及含有高果糖的食品和饮料，以避免尿酸升高，保护肾脏健康。在保证每

天足量饮水的同时尽量限制饮酒，有助于尿酸的排泄。因时因地因人选择适合自己的膳食方案，在健康饮食的基础上适度锻炼，实现饮食与运动的良好平衡[63]。合理的饮食和运动对于预防高尿酸血症至关重要，而定期进行全面的日常体检，能够及时发现身体潜在的健康问题，尤其是对于高尿酸血症的早期筛查具有重大意义。对血尿酸水平及肾功能进行监测，一旦发现异常及时进行干预和治疗，以防止病情进一步恶化。

4.2. 治疗策略：

当男性血尿酸水平 > 420 μmol/L，女性 > 360 μmol/L 时建议采用如 4.1 中所述的生活干预，我国建议血尿酸 ≥ 540 μmol/L 或≥480 μmol/L 且有合并症的患者启动药物治疗。

1) 慢性尿酸性肾病治疗

单纯慢性高尿酸血症伴肾病患者，以降低尿酸水平，防止关节炎，保护肾脏为准。目前降尿酸药物主要有三类[64]，第一类是以别嘌醇和非布司他为代表的尿酸生成抑制剂，通过抑制黄嘌呤氧化酶(XOD)抑制尿酸合成。第二类是以苯溴马隆为代表的促尿酸排泄类药物，通过抑制肾小管重吸收尿酸盐来降低血清尿酸水平。氯沙坦作为血管紧张素II受体拮抗剂(ARB)，其降尿酸机制也是抑制肾小管对尿酸盐的重吸收，但因其可以阻滞局部的环氧合酶 2 (COX2)和肾素－血管紧张素(RAS)系统从而有良好的降压和肾脏保护作用[12] [65] [66]，且能有效降低蛋白尿。第三类是以拉布立酶为代表的促尿酸溶解类药，属于重组尿酸氧化酶，但其价格昂贵。通常根据患者的具体病情来选择不同的降尿酸药物[67]，对于肾功能不全患者，应根据肾功能损害的程度选择合适的药物。在此情况下，尿酸生成抑制剂如别嘌醇和非布司他通常更合适，将氯沙坦与尿酸生成抑制剂联用达到降尿酸并保护肾脏的效果。

对于高尿酸血症肾病伴痛风患者，痛风发作时推荐单独或联合运用非甾体抗炎药(NSAIDs)、秋水仙碱以及皮质类固醇进行治疗[67]。低剂量秋水仙碱是首选，但应根据肾功能和药物相互作用调整剂量。非甾体抗炎药通常效果良好，但在某些患者中可能有禁忌。皮质类固醇适用于有多种合并症的患者，关节内注射可用于少数关节受累的情况。白细胞介素 1 抑制剂(如 Canakinumab)有效[68]，但成本较高，目前仅限于其他选择无效或禁忌的患者。同时，痛风发作时应向患者教育长期降尿酸治疗的重要性，以预防未来的发作和关节损伤。

2) 急性尿酸肾病

急性尿酸性肾病通常是可逆的，关键在于预防。要密切监测患者的生化指标及临床症状，对于具有高危因素的患者，比如肿瘤患者接受化疗后、严重创伤后以及大量进食高嘌呤食物等情况，应积极进行补液治疗，必要时使用袢利尿剂以保持尿量大于 0.1 L/h。

一旦确诊为急性尿酸性肾病，需积极干预进行治疗，具体干预措施如下：首先要严格执行低嘌呤饮食，其次要进行水化治疗，在没有禁忌的情况下，液体摄入量应达到 3 L/d。再者要碱化尿液，将尿液 pH 值控制在 6.2~6.9 之间。在降尿酸药物的选择上，首选减少尿酸生成的药物如别嘌醇，非布司他，对于肿瘤溶解综合征患者则首选尿酸酶，并且要禁用别嘌醇，以防黄嘌呤性肾病或黄嘌呤性结石形成。必要时还需采用肾脏替代治疗，例如血液透析治疗[69]。

3) 高尿酸血症肾病候选药物

目前已上市的治疗药物均存在一定程度的副作用，如别嘌醇的不良反应中有死亡率高达 25%的中毒性表皮坏死综合征[70] [71]。尽管非布司他相对别嘌醇安全性更高，但根据美国食药监局的临床调查，非布司他引发的心血管疾病比安慰剂高[72] [73]。苯溴马隆因其具有严重的肝毒性[74]，在美国未获得 FDA 的批准使用。

考虑到现有药物的不良反应问题，一些中医方剂及中药单体药物已显示对高尿酸血症肾病有治疗效

果[66] [75] [76]。有研究表明沙利霉素可能通过抑制 XOD 和 URAT1 维持 HN 小鼠尿酸稳态，通过上调 NRF2/HO-1 改善 HN 小鼠的纤维化、炎症和氧化应激，或可成为改善高尿酸血症肾病的新药[77]。《中国高尿酸血症相关疾病诊疗多学科专家共识(2023 年版)》[69]指出高尿酸血症与肾脏、内分泌代谢、心脑血管等系统的疾病存在密切而复杂的联系，应遵循多学科联合治疗的原则，降尿酸同时兼顾对靶器官保护，做到早防治，早治疗。

5. 总结与展望

高尿酸通过肾脏尿酸盐结晶的形成和沉积、肾脏血流动力学的影响、肾脏炎症反应和氧化应激等影响肾功能，导致急、慢性肾损伤。除了健康的生活方式、定期体检等预防策略，药物治疗是治疗高尿酸肾损伤的重要手段，可选择尿酸生成抑制剂、促尿酸排泄类药物和促尿酸溶解类药进行降尿酸治疗。高尿酸血症应遵循多学科联合治疗的原则，降尿酸的同时也要兼顾对靶器官的保护。

高尿酸对肾功能的影响机制复杂，各个通路之间的复杂网络关系亟待阐明，但是较为明确的是这些损伤机制均与肾脏细胞损伤密切相关，因此开发针对保护高尿酸血症肾细胞受损的药物与降尿酸药物联合使用是更为理想的治疗方法。此外也应关注高尿酸血症与其他代谢性疾病的相互关系，综合考虑多种因素，探索新型的降尿酸药物或治疗策略，力求在有效降低尿酸水平的同时，最大程度减低药物的毒副作用，为高尿酸血症的精准治疗提供可能。

基金项目

大学生创新训练项目(S202410678071)，2024 年云南省天然药物药理重点实验室开放研究基金项目(YKLPNP-G2408)，昆明医科大学研究生创新基金项目(2024S1930)。

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