·综　述·

氧化应激在肾结石防治中的研究进展

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摘要：泌尿系结石是一种泌尿系统的常见性、易复发性疾病，其病因及发病机制尚不明确。肾脏是对氧化还原失衡特别敏感的器官，过量生成的活性氧簇和氧化应激参与了肾小管上皮细胞损伤、炎症和肾结石的病理形成。肾脏Randall斑的存在证实了氧化应激可诱导肾脏损伤、结石生成。流行病学研究发现，肾结石与全身代谢性疾病密切相关，故可将肾结石视为一种慢性代谢性疾病，而氧化应激可能是它们共同的病理生理学基础。本文旨在阐释氧化应激在肾结石形成中的作用机制，总结归纳氧化应激作为肾结石治疗靶点的潜力，为泌尿系结石的防治提供新思路。

关键词：泌尿系结石；肾结石；氧化应激；活性氧；代谢性疾病；疾病防治

中图分类号：R692.4　　**文献标识码：**A　　**文章编号：**1674-7410(2021)03-0090-04

Research Progress on Oxidative Stress in the Prevention and Treatment of Kidney Stones

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Abstract: Urolithiasis is a common recurrent disease of the urinary system, and its etiology and pathogenesis remain unclear. The kidney is particularly sensitive to redox imbalance. Excessive reactive oxygen species and oxidative stress are involved in injury to renal tubular epithelial cells, inflammation and the pathological formation of renal calculi. The presence of renal Randall patches has confirmed that oxidative stress induces renal injury and stone formation. Epidemiological studies have shown that renal calculi are closely associated with systemic metabolic diseases and therefore can be regarded as a chronic metabolic disease. Furthermore, oxidative stress may be a pathophysiological basis shared by these diseases. This paper aims to explain the mechanisms of oxidative stress in the formation of renal calculi; summarize the potential of oxidative stress as a therapeutic target for renal calculi; and provide new ideas for the prevention and treatment of urinary calculi.

Keywords: Urinary calculi; Renal calculus; Oxidative stress; Reactive oxygen species; Metabolic diseases; Disease control

泌尿系结石指人体尿液中固体成分析出后在泌尿系统各部位形成的一种病理性生物矿化疾病，原发部位主要在肾脏。近年来我国泌尿系结石的发病率不断升高，最近的一项横断面流行病学调查显示，我国肾结石总患病率为6.5%，其中南方地区高达10%[1]。泌尿系结石复发率高，5年复发率为50%左右，10年复发率高达75%，给患者和社会带来了沉重的负担[2]。目前肾结石的病因和形成机制尚未明确，一般认为其形成过程主要包括尿液过饱和、异质成核、晶体生长与聚集、晶体黏附并沉积于肾。近年来大量的研究表明，草酸和晶体诱导的肾小管上皮细胞损伤、炎性反应与肾结石的病理形成密切相关，活性氧（reactive oxygen species，ROS）诱导的氧化应激（oxidative stress，OS）在其中发挥

基金项目：广东省自然科学基金博士启动纵向协同项目（No.2017A030310501）；广东省中医药局重点科研项目（No.20173009）；广州中医药大学“高水平大学建设”青年项目（No.A1-AFD01817Z11103）

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关键调控作用[3]。为此，本文将阐释OS在肾结石形成中的作用机制，总结归纳OS作为肾结石治疗靶点的潜力，为泌尿系结石的防治提供新思路。

1 肾脏的氧化/抗氧化病理、生理学基础

OS是指机体在内外环境中有害刺激的条件下，体内或细胞内氧自由基产生过多或清除不足，导致ROS在体内或细胞内蓄积，破坏机体氧化/抗氧化平衡系统所引起的氧化损伤病理过程[4]。OS的概念最早源自人类对衰老的认识，后来经过不断的探索、拓展而形成完整的理论体系。肾脏可能是由于富含长链多不饱和脂肪酸氧传感器，使其成为对氧化/抗氧化失衡特别敏感的器官[5-6]。生理条件下，ROS参与介导正常肾脏细胞的增殖、分化、凋亡和免疫防御；病理情况下，如暴露在高浓度草酸中，肾脏过量生成的ROS可诱导肾脏炎性反应，继而引起肾脏结构和功能的改变[5,7]。OS本质上是机体组织细胞氧化/抗氧化平衡失调的病理反应，表现为细胞膜脂质、蛋白质和DNA等的损伤与修饰，出现一系列OS标志物的活性异常，如细胞膜脂质过氧化标志物丙二醛和DNA损伤标志物8-羟基脱氧鸟苷等[3,8]。充分认识OS的分子生物学机制，探索OS在肾脏细胞中的病理及生理学变化，对于肾结石的病因学防治具有积极的指导意义。

2 Randall斑：OS诱导肾损伤的临床证据

20世纪30年代，Randall对1 154例尸肾进行研究首先发现，19.6%尸肾的肾乳头上皮组织下存在着一种乳白色钙化斑病灶（Randall斑），这种钙化斑的主要成分是磷酸钙和碳酸钙，草酸钙结石依附在其表面生长以致形成结石[9]。Randall认为，肾乳头上皮下间质磷酸钙和碳酸钙沉积是形成肾结石的原始病灶，尿液过饱和与肾小管损伤参与诱发结石形成[9]。随着泌尿外科腔内镜、微型CT影像学和光学显微病理技术的进步[10]，EVAN等[11-12]进一步在特发性草酸钙结石患者中证实，钙盐结晶的起始部位是髓襻细支的上皮基底膜表面，成分是磷灰石，逐渐延伸至直小管和终末集合小管周围的间质组织，经过非晶磷灰石以及草酸钙晶体层，最后结晶沉积在肾乳头。草酸钙结晶对细胞具有毒性，不仅能引起OS，还能引起炎性反应。损伤和死亡的细胞释放到尿路中，促进结晶的异质成核；损伤的细胞膜也为结晶附着提供了部位，最终使结晶滞留在肾脏中。肾上皮细胞的损伤可能有利于结晶从肾小管移动到肾间质，也可能有利于Randall斑的形成，而炎性反应可能是导致Randall斑溃烂到肾乳头表面的原因[13-14]。总之，肾脏Randall斑从特发性结石（无全身性疾病）的角度，证实了OS能诱导肾损伤，但其深入的机制有待进一步阐明。

3 OS是全身代谢性疾病与肾结石的共同通路

随着肾结石病因学研究的不断深入，研究者发现肾结石与全身代谢性疾病关系密切，而非单纯局限于泌尿系统的疾病。流行病学研究显示，肾结石与肥胖、高血压、糖尿病、血脂异常、代谢综合征、冠心病以及慢性肾脏病等疾病有关[15-21]。大量的研究证明，OS在全身代谢性疾病相关的肾损伤病理机制中至关重要[22]。考虑到OS在肾损伤和肾结石形成中的关键作用，KHAN[23]推断OS可能是肾结石和全身代谢性疾病的共同病理生理学基础（共同通路）。为了探索代谢异常条件下肾结石的形成机制，研究人员在体外构建了肾小管细胞脂肪细胞和/或巨噬细胞共培养体系，采用草酸钙晶体干预引起肾小管细胞单核细胞趋化蛋白1、骨桥蛋白、肿瘤坏死因子等炎性分子表达上调，这种旁分泌机制证实了OS与炎性反应同时参与了代谢综合征与肾结石形成的调控[24-25]。在高草酸尿症大鼠模型中证实，代谢综合征可加重肾损伤、上调骨桥蛋白的表达，促进肾结石形成[26]。肥胖转基因小鼠尿草酸水平增高，其机制是SLC26A6草酸转运体的下调，引起了肠道局部及全身炎性反应，而减肥可以减少代谢综合征大鼠的结石形成[27-28]。

4 还原型辅酶Ⅱ（nicotinamide adenine dinucleotide phosphate，NADPH）氧化酶：一个新兴的肾结石治疗靶点

体外细胞研究、体内动物研究和临床病例研究均表明，暴露于草酸和/或草酸钙晶体或磷酸钙晶体的肾小管上皮细胞会过量生成ROS，引起OS和炎性反应。肾小管上皮细胞损伤是结石形成的初始因素，它进一步促进了晶体聚集、生长、黏附于上皮而滞留于肾脏[3]。然而，抑制ROS引起的OS并不容易，应该阻断ROS的病理生成。一般而言，线粒体损伤是草酸和/或草酸钙结晶刺激肾脏上皮细胞生成ROS的经典来源[29]。有研究发现，草酸和/或草酸钙晶体上调肾小管上皮细胞中NADPH氧化酶的活性，使用NADPH氧化酶特异性抑制剂可以显著减少草酸、草酸钙结晶导致的肾脏上皮细胞ROS的生

成，下调相关炎性蛋白的表达，提示NADPH氧化酶参与了草酸和/或草酸钙晶体刺激的ROS的生成[30]。在体动物实验证实，NADPH氧化酶的异常活化参与了肾结石形成的进程[31]。坎地沙坦、氯沙坦、阿托伐他汀等降压、调脂药物，可以通过抑制NADPH氧化酶介导的ROS的生成，从而抑制肾草酸钙结石的形成[32-34]。这些研究进一步证实了全身代谢性疾病和肾结石的相关性，NADPH氧化酶可以作为肾结石的新兴治疗靶点[35]。

5 小结

泌尿系结石是一种多因素、多步骤的代谢相关性疾病，OX介导的肾小管上皮细胞损伤在结石形成中发挥关键作用，NADPH氧化酶介导生成ROS，是肾结石一个的新兴治疗靶点，靶向OX是泌尿系结石病因学预防的重要策略[36]。

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