

硫酸吲哚酚、硫酸对甲酚在肾脏病领域的研究进展

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摘 要

慢性肾脏病是肾内科常见的疾病之一, 目前越来越多的研究证实尿毒症毒素与肾脏病患者的疾病进展、心血管事件的发生及远期不良预后密切相关。硫酸吲哚酚、硫酸对甲酚为肠源性尿毒症毒素中蛋白结合性毒素的代表, 对慢性肾脏病患者的疾病进展和预后具有重要影响。本综述针对硫酸吲哚酚、硫酸对甲酚, 围绕其产生代谢过程、肾脏及心血管毒性、清除策略等方面的研究进展进行详细阐述。

关键词

尿毒症毒素, 慢性肾脏病, 硫酸吲哚酚, 硫酸对甲酚

Research Progress on Indoxyl Sulfate and P-Cresyl Sulfate in the Field of Nephrology

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Abstract

Chronic kidney disease (CKD) is one of the common diseases in nephrology. Increasing evidence has demonstrated that uremic toxins are closely related to disease progression, cardiovascular events, and long-term poor prognosis in patients with kidney disease. Indoxyl sulfate and p-cresyl sulfate, as representatives of protein-bound toxins among gut-derived uremic toxins, have significant impacts on the disease progression and prognosis of patients with CKD. This review focuses on indoxyl sulfate and p-cresyl sulfate, detailing the research progress in their production and metabolism, renal and cardiovascular toxicity, and elimination strategies.

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Keywords

Uremic Toxins, Chronic Kidney Disease, Indoxyl Sulfate, P-Cresyl Sulfate

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1. 引言

慢性肾脏病(Chronic Kidney Disease, CKD)指的是肾脏结构或功能异常(如肾小球滤过率 ≤ 30 ml/min/1.73m² 或微量白蛋白尿 ≥ 300 mg/24h)超过 3 个月, CKD 是全球第 16 大致死原因, 患病率高达 8%~16%, 并且随着年龄的上升而不断升高[1]。尿毒症毒素(Uremic toxins)是指肾功能受损时不能经尿液有效清除、滞留在体内且有毒性作用的物质[2]。至 2012 年为止, 在 CKD 患者体内发现的尿毒症毒素多达 146 种[3]。欧洲尿毒症毒素工作组(EUTox)根据清除模式特征将其分成三类: 水溶性小分子物质, 相对分子质量(Molecular Weight, MW) < 500 Da, 如肌酐和尿素, 具有极低的蛋白结合率, 任何类型的透析模式均可有效清除; 中分子物质(MW ≥ 500 Da), 如甲状旁腺素、 β_2 微球蛋白, 常规血液透析效果不理想, 需采用大孔径透析膜的血液净化方式清除[4]; 蛋白结合性物质, 如硫酸吲哚酚(Indoxyl Sulfate, IS)和硫酸对甲酚(P-Cresyl Sulfate, PCS), 由于其与血浆蛋白高度结合, 通过常规透析难以清除[5]。

2. 硫酸吲哚酚、硫酸对甲酚的产生和代谢过程

2011 年 Meijers 等[6]提出了肠肾轴的概念——即在人体内肠道和肾脏构成一个整体: 肠道微生态, 肠道结构功能与肾脏功能相互影响, CKD 患者因肾小球滤过面积下降等原因, 尿毒症毒素不能及时代谢排出, 大量蓄积的毒素导致肠道菌群失调, 肠道屏障受损, 继而肠道内增多的条件致病菌导致肠源性尿毒症毒素进一步在血液中蓄积, 加速肾功能损伤。近年来, 多方研究人员已证实 IS、PCS 对慢性肾脏病的进展、心血管事件的发生具有重要的影响, 进一步导致 CKD 患者死亡率升高[7]。

在肾功能不全的病理状态下, 患者出现胃肠功能和肠道微生态的紊乱, 主要表现为益生菌的减少和致病菌的大量繁殖[8]。IS 来源于膳食蛋白质, 其分子量为 213 Da, 在肠道细菌(主要为大肠杆菌)作用下将膳食色氨酸转化成吲哚, 再经门静脉进入肝脏经羟化、硫酸化, 最终转化为硫酸吲哚酚[9]。而 PCS 则是在肠道厌氧菌(梭状芽孢杆菌等)发酵作用下将食物中的苯丙氨酸和酪氨酸转化为 4-羟基苯乙酸, 而后脱羧形成对甲酚, 经肠道黏膜吸收后在肠上皮细胞作用下转化为硫酸对甲酚, 其分子量为 188 Da [10]。IS 和 PCS 在血液中都是以蛋白结合物的形式存在。研究表明, 二者蛋白结合率高达 90% [11], 且在白蛋白上具有相同的高亲和力结合位点(site II), 同时抑制白蛋白与其他物质相结合[12]。

上述两种毒素通过普通血液透析的方式不能有效地清除, 且对机体有很大的损害, 除了肾脏毒性外, 还与心脑血管疾病、肾性骨营养不良、肾性贫血、神经系统病变等诸多疾病密切相关, 严重影响患者生存率及其生活质量。

3. IS、PCS 的肾脏毒性

IS、PCS 的肾脏毒性主要表现为: IS 通过诱导活性氧簇(Reactive Oxygen Species, ROS)产生[13], 破坏肾脏抗氧化系统[14]以及诱导纤维化和炎症产生肾毒性, 造成肾功能恶化[15]。通过诱导肾小管近端细胞产生 ROS, 激活核因子 κ B (Nuclear Factor-kappa B, NF- κ B), 上调纤溶酶元活化抑制因子 1 (Plasminogen

activator inhibitor-1, PAI-1)及转化生长因子 $\beta 1$ (Transforming Growth Factor- $\beta 1$, TGF- $\beta 1$)的表达,降低小管细胞的增殖能力,诱导小管上皮间质转化(Epithelial-Mesenchymal Transition, EMT),促使小管间质纤维化[16]。同时 NF- κ B 的激活还降低了具有肾脏保护作用的衰老抑制基因 klotho 蛋白的表达[17]。此外,实验研究发现 IS 小鼠的 TNF- α 、IL-6 和 IL-1 β 显著增加,这表明 IS 显著促进了这些细胞因子的升高,并导致全身炎症[18]。

PCS 与 IS 毒性作用相类似,主要表现为诱导氧化应激、肾脏纤维化及炎症,其机制主要包括:1) 通过增加肾素、血管紧张素原和血管紧张素 1 (Angiotensin 1, AT1)受体表达,降低体外和体内 AT2 受体表达,激活肾内肾素-血管紧张素-醛固酮系统(Renin-Angiotensin-Aldosterone System, RAAS),从而促进肾间质成纤维细胞增殖加重肾组织纤维化[19]。2) Sun 等人发现接受 PCS 注射的小鼠肾小管中 Klotho 表达明显减少,PCS 通过促进 DNA 甲基转移酶表达,促使 Klotho 蛋白超甲基化,降低小鼠肾小管 klotho 基因表达,加重肾脏损伤[20]。3) PCS 的促炎作用,体外实验证明 PCS 通过增加近端肾小管细胞中 TGF- $\beta 1$ 的表达[21],后者作为一种纤维化和炎症细胞因子,在肾损伤中起着关键作用。

4. IS、PCS 的心血管相关毒性

硫酸吡啶酚和对甲酚可加速慢性肾脏病的进展,并且可以加速慢性肾脏病心血管疾病的发生。大量研究证实[7], IS、PCS 水平与心血管疾病的发生及全因死亡率密切相关。IS 主要通过氧化应激引起内皮损伤,其作为芳基烃受体(Aryl hydrocarbon Receptor, AhR)的内源性激动剂,参与氧化应激、炎症、血管重塑和动脉粥样硬化形成。IS 通过 OAT-1 和 OAT-3 被心肌细胞吸收,激活诱导心肌肥厚和纤维化相关因子表达相关通路,如 p38 和 p42/44 丝裂原活化蛋白激酶(Mitogen-Activated Protein Kinase, MAPK)和 NF κ B,从而加速心肌纤维化和心肌肥厚的进展[22]。Koppe 等人研究发现,IS 可上调高血压大鼠主动脉弓血管平滑肌细胞(Vascular Smooth Muscle Cells, VSMCs)衰老相关标志物 p53 及核纤层蛋白前体(prelamin A)表达,促进 β -半乳糖苷酶活性,加重 VSMCs 成骨样转化及动脉钙化[23]。

PCS 与血管炎症、血管钙化和动脉粥样硬化发生有关。调查发现,伴有颈动脉粥样硬化斑块的血液透析患者中血清 PCS 水平较高,其浓度与斑块总面积的增加呈正相关,血清 PCS 水平与颈动脉粥样硬化斑块的发生率和进展独立相关[24]。研究发现,PCS 通过 PKC 或 PI3K 途径增加 NADPH 氧化酶的表达,诱导血管内皮细胞和平滑肌细胞产生 ROS,而 ROS 产生诱导促炎因子表达增加,PCS 还增加平滑肌细胞中成骨细胞特异性蛋白 mRNA 水平,促使血管钙化[25]。体外研究发现,PCS 通过刺激白细胞和血管之间的串扰来发挥促炎作用,导致血管损伤[26]。

5. IS、PCS 的其他毒性

PCS、IS 在一定程度上显示出骨毒性。Niikono 等人报道 IS 可经 OAT-3 进入小鼠成骨细胞,诱导氧化应激从而损害成骨细胞功能,并下调甲状旁腺素(Parathyroid Hormone, PTH)受体表达,诱导骨骼对 PTH 抵抗,阻止骨骼钙化,导致肾性骨病[27]。

此外,有体外实验发现,IS 能促使红细胞膜发生皱缩,并呈量效关系导致红细胞衰亡[28]。临床研究显示,CKD 患者血清总 IS 水平与血红蛋白呈显著负相关,并认为 IS 可能抑制肝脏和肾脏中促红细胞生长素的合成,加重肾性贫血[29]。

Koppe 等人实验证明 PCS 诱导肌肉胰岛素抵抗,同时伴有 IRS、PI3K、Akt 通路的缺陷,表明 PCS 与胰岛素抵抗之间存在因果联系,同时实验过程中发现在 PCS 小鼠中,与载体小鼠相比,血浆胆固醇水平增加 50% [30]。

慢性肾衰竭患者出现肾性脑病,以认知障碍为突出表现。有学者研究发现 IS 通过激活 NF- κ B 和 AhR,导致中枢神经系统细胞的炎症和氧化应激,并以剂量依赖性方式诱导神经元细胞死亡[31]。

6. 蛋白结合性尿毒症毒素的清除策略

(一) 膳食调节

由于 IS、PCS 均来自于氨基酸在肠道的分解代谢, 其含量随膳食蛋白质的摄入增加而增加, 故而减少尿毒症毒素生成的一个重要措施为严格限制蛋白质摄入[32]。Rossi 等人研究表明膳食纤维与游离和总血清 PCS 呈负相关, 而蛋白质纤维指数与血清总 IS、PCS 水平呈正相关[33]。膳食纤维摄入增加显著降低 IS、PCS 水平, 一项动物研究数据显示, 高纤维饮食喂养的大鼠血清和尿 IS 分别降低了 36%和 66%, 尿 PCS 则降低了 47% [34]。

然而, 低蛋白饮食在降低肠源性尿毒症毒素产生的同时, 存在加重 CKD 患者尤其是血液透析患者营养不良的风险。因此严格限制蛋白质摄入不能作为降低 CKD 患者尿毒症毒素水平的根本解决方案, 低蛋白饮食总体效益仍需进一步研究。

(二) 调节肠道菌群

益生菌是一种能够平衡宿主肠道内菌群, 主要包括乳酸菌、链球菌、芽孢杆菌等。益生元则是指能促进益生菌增殖的食物纤维成分, 包括菊粉、低聚果糖、低聚半乳糖等[35]。多项研究表明, 益生菌、益生元、合生元(益生菌和益生元组合制剂)可降低血清肠源性尿毒症毒素水平[36]。Meijers 等人[37]给予维持性血液透析(Haemodialysis, HD)患者益生元-菊粉(inulin), 结果显示其显著降低了 HD 患者硫酸对甲酚生成速率及血清浓度。Furuse 等人[38]对肾功能不全的模型鼠进行低聚半乳糖(Galacto-Oligosaccharides, GOS)灌胃, 结果显示模型鼠盲肠吲哚和血清 IS 显著降低, 肾脏损伤也随着浸润巨噬细胞的减少而得到改善。

(三) 肠道吸附

目前针对肠道吸附, 减少胃肠道吸收研究较多的为 AST-120 活性炭。Kobayashi 等[39]一项动物研究中证明, AST-120 治疗降低了早期肾功能衰竭大鼠的尿白蛋白排泄和血清 IS 水平, 并预防了肾小球硬化。研究证实, AST-120 可吸附至少 6 种负电荷及 17 种带正电荷的尿毒症毒素, 包括 IS 和 PCS 前体, 从而降低血清 IS 和 PCS 水平[40]。

(四) 血液透析和肾移植

肠源性尿毒症毒素 IS、PCS 由于与白蛋白紧密结合, 常规通量血液透析模式只能清除游离溶质, 总体清除效率较低。国外研究显示, HD 对于 IS、PCS 这类蛋白结合型毒素(90%~95%)清除率在 35%以下[41]。部分研究显示, 相较于 HD, 血液透析滤过(Hemodiafiltration, HDF)对于 PCS 的清除效果更好[42], 既往研究表明延长 HD 与 HDF 时间、提高透析液流量和透析膜面积可提高蛋白结合类毒素的清除效率[43]。在体外实验中, 研究者使用活性炭吸附剂, 通过体外直接血液灌流吸附 IS、PCS 也取得了一定的效果[44], 临床使用吸附剂的有效性安全性仍需进一步研究。

而在肾移植患者中, 研究人员发现与对照组相比, 在移植后的每个时间点移植受者的血清 PCS、IS 均水平显著降低[45], 而这些变化可能是由于免疫抑制剂、抗生素、其他药物、移植本身, 仍需进一步研究阐明其机制。

(五) 中医治疗

现代医学对肠源性尿毒症毒素的干预治疗目前仍处于研究阶段, 在中国, 许多 CKD 患者得益于中医药治疗。祖国医学认为, 本病属“水肿、尿血、腰痛、虚劳、癃闭、关格”等范畴, 以脾肾为中心, 累及多个脏腑的虚实夹杂病症, 然 CKD 患者病程冗长, 脾虚多湿, 邪郁化热, 最终演变为浊毒之邪, 因此通腑泄浊法减轻浊毒内蕴是延缓疾病进展的关键。邹川等[46]纳入 96 例慢性肾衰竭患者, 根据患者意愿分为灌肠治疗组合对照组, 两组均按非透析期临床治疗方案给予基础治疗, 治疗组加用中药结肠洗液灌肠

治疗,总疗程为2周,结果显示治疗组治疗后 Scr、BUN、IS 水平均较治疗前明显降低。戴铭卉等人[47]将 91 例 CKD 患者分为中药结肠透析治疗组、HDF 组及 HD 组,中药结肠透析组共 31 例,常规治疗的基础上给予中药结肠透析,结果显示中药结肠透析可明显降低 CKD 患者尿素、硫酸吡啶酚、肌酐等水平($P < 0.05$)。尽管邹川、戴铭卉等人研究显示中药灌肠可降低 IS 水平,但现有证据存在显著局限性:1) 两项研究样本量均不足 100 例且缺乏随机对照设计;2) 未明确活性成分与毒素清除的具体机制(如肠道吸附、菌群调节等);3) 未报道治疗对硬终点(如 eGFR 下降速率、心血管事件)的影响。值得注意的是,刘广[48]等人研究发现大黄素可能通过抗氧化应激以及抑制凋亡等途径对 IS 诱导的细胞损伤起到一定的保护作用,这为中药机制研究提供了新思路。未来需要开展多中心 RCT 研究,建立中医药干预与毒素代谢组学的关联模型。

7. 小结

IS 和 PCS 作为肠源性尿毒症毒素中蛋白结合性毒素的代表,对 CKD 患者的疾病进展和预后具有重要影响。针对肠源性尿毒症毒素的临床干预具有重要的意义,如调整饮食、口服微生物调节剂、毒素吸附剂、血液净化、通腑泄浊中药口服及灌肠治疗等。然而,目前尚缺乏大规模临床研究,益生菌和吸附剂的长期疗效仍需进一步验证,中医药应用具体机制仍需深入研究。未来研究方向可聚焦于新型清除技术的临床转化,如竞争性白蛋白结合剂、仿生吸附材料的开发等,结合菌群移植、膳食干预和药物治疗,优化毒素清除方案,均需要进行大规模的随机对照试验,进一步确定其是否能延缓 CKD 的进展和减少 CKD 相关心血管事件的发生。

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