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转运体SLC26A6与草酸钙泌尿系结石的相互作用及影响因素的研究进展

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摘　要

泌尿系结石是我国最常见的泌尿外科疾病之一，在泌尿外科住院患者中占据首位，并且伴随着环境，饮食习惯等多种因素的影响，我国近年来的发病率正逐年上升。对于泌尿系结石，除了进一步开展更为有效的治疗方式，还应重视其预防手段的研究。转运体SLC26A6 (PAT1)与草酸钙类泌尿系结石存在重要联系。本篇综述通过分别阐述目前PAT1于肠道位点及肾脏近端小管位点对于草酸钙类结石的影响机制及其相关影响因素(包括肠道菌群及其代谢产物，雌激素等)的研究进展对预防草酸钙类泌尿系结石提出建议。

关键词

草酸钙结石，SLC26A6，泌尿系结石，肠道菌群

Research Progress on the Interaction between the Transporter SLC26A6 and Calcium Oxalate Urolithiasis and Its Influencing Factors

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Abstract

Urolithiasis is one of the most common urological diseases in China and ranks first among

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hospitalized patients in urology. Influenced by various factors such as environment and dietary habits, the incidence rate in China has been gradually increasing in recent years. For urolithiasis, in addition to developing more effective treatments, attention should also be given to research on preventive measures. Several studies have indicated that the transporter SLC26A6 (PAT1) is closely associated with calcium oxalate urolithiasis. This review discusses the research progress on the mechanisms by which PAT1 affects calcium oxalate stones at the intestinal and renal proximal tubule sites, as well as related influencing factors (including gut microbiota and its metabolites, estrogen, etc.), and provides recommendations for the prevention of calcium oxalate urolithiasis.

Keywords

Calcium Oxalate Stone, Transporter SLC26A6, Urinary System Stones, Gut Microbiota

1. 引言

SLC26 家族主要编码各种阴离子转运蛋白进行人体中的阴离子的转运，SLC26A6 作为 SLC26 家族的一员，为二级跨膜转运蛋白，c 端存在 STAS 结构域以及一个与囊性纤维化跨膜传导调节因子(CFTR)相同的 PDZ [1] [2]。在人体中，PAT1 主要存在于肾近端小管及肠道转运阴离子[3]，其转运功能广泛，不仅可以转运草酸盐[4]-[6]，还同时参与 Cl^-/甲酸盐、Cl^-/硝酸盐、和 Cl^-/OH^-等阴离子的转运[7]。

2. PAT1 在草酸盐转运中的作用

绝大多数草酸盐在人体中的排泄都是通过肾脏完成的[8]，但是草酸盐在通过消化道这一途径进行的排泄也不容忽视[9] [10]。以下将分别通过转运体 PAT1 在肾近端小管上皮位点以及肠道位点来阐述其在草酸转运中的作用。

2.1. 肠道位点

在消化道，转运体 PAT1 主要存在十二指肠以及近端结肠[11]。其主要通过主动运输将血液中的草酸转运至消化道中，从而减少血浆以及尿液中的草酸浓度[12]，泌尿系结石的产生基本都存在以下五个步骤，分别是：尿液过饱和、成核、结晶、生长和聚集[13]。当尿液中草酸浓度过饱和后，即开启了结石产生的第一个步骤[14] [15]，PAT1 在此处的作用是将血液中的草酸盐转运至消化道中进行排泄，从而降低尿液中草酸的浓度达到预防草酸类结石的产生的目的。已有研究表明，缺乏 PAT1 小鼠的尿草酸盐排泄量约为野生型小鼠排泄量的 4 倍[16]，在这种情况下，尿液中的草酸盐浓度大幅增加，将显著增加草酸盐类结石产生的可能性。

2.2. 肾近端小管位点

草酸盐作为代谢终产物，人体无法吸收[17]，绝大多数都是通过肾脏排泄，尽管其中主要是通过肾小球直接从血液中滤出[18]，但是肾近端小管位点处的 PAT1 也会直接参与草酸盐的分泌[19]。此处的 PAT1 主要采用 Cl^-/草酸盐交换的方式将细胞中的草酸盐分泌至尿液中并将 Cl^-回收入细胞[20] [21]。与此同时，PAT1 还以 SO_4^{2-}/草酸盐交换的方式将草酸盐从尿液重吸收进细胞中[17]，Greger R 有研究表明，在灌注实验中的肾脏近端小管的 S1 以及 S2 段处草酸盐浓度降低，然而在 S3 段时草酸盐浓度又出现了升高[19]。

说明在肾脏的草酸盐代谢过程中存在分泌以及重吸收两个过程，这是一种保护尿草酸盐浓度处于正常范围的机制。同时，研究显示，若增强小鼠肾脏中 PAT1 表达会导致尿液草酸浓度和结石形成速率显著增加[22]。以此 PAT1 在两个位点中的作用均总体表现为分泌排泄草酸盐，但排泄后的全局表现却并不相同。总而言之，两处位点的功能整体表现为，吸收尿液中的草酸盐并增加消化道的排泄，减少尿液草酸浓度的作用[23]，使尿液中草酸盐浓度得以下降预防草酸盐过饱和以及发展为草酸类泌尿系结石产生等情况的发生。

3. 影响 PAT1 表达的相关影响因素

PAT1 在调节草酸盐的代谢中的作用对于预防草酸钙类泌尿系结石相当重要[22]。因此，探寻影响 PAT1 的表达水平的相关因素也许会对草酸钙类泌尿系结石的预防提供方向，以下将从对肠道草酸盐的影响(肠道菌群及肠道代谢产物)以及对尿道草酸盐的影响(雌激素)两个方面的进一步阐述。

3.1. 肠道草酸盐的影响因素

3.1.1. 肠道菌群

肠道菌群与泌尿系结石的联系已得到不少的文献支持[24]-[26]，但肠道菌群具体通过何种机制影响泌尿系结石还未得到明确的阐述。对于 PAT1 而言，肠道菌群，尤其是草酸杆菌对其最可能具有影响。Arvans 等人通过对人肠道 Caco2-BBE 细胞(C2)进行草酸杆菌培养基(CM)处理，然后分离总 RNA 进行 qPCR 分析。与 UT 未处理细胞(UT)相比，CM 对 PAT1 mRNA 表达的影响不显著，表明草酸杆菌并非通过影响 PAT1 的表达量来影响 PAT1 对于草酸盐的吸收的，但是，使用 siRNA 技术敲低 C2 细胞中的 PAT1 表达又使其对草酸盐的摄取率降低了 49%，这表明了草酸杆菌对于草酸盐在肠道分泌的影响很大程度上是因为 PAT1，然而其并未影响 PAT1 的表达量，因此，草酸杆菌很可能分泌一种生物活性因子影响 PAT1 进而影响肠道中的草酸盐分泌[27]。

在 Arvans 的最新研究中，他们通过质谱法明确了 Sel1 样蛋白是介导 CM 对肠道细胞草酸盐转运的刺激作用的主要草酸杆菌衍生的分泌因子，其中，OxBSel1-14 衍生的小肽 P8 和 P9 被鉴定为主要因子，其中 P8；P9 通过草酸盐转运蛋白 SLC26A2 和 SLC26A6 和 PKA 激活密切体现了 CM 的作用[28]。Sel1 样蛋白属于 Sel1 样重复(SLR)蛋白家族并参与蛋白质－蛋白质相互作用和信号转导途径(比如 PKA 激活)[29]。

尽管预计 PAT1 不会拥有 PKA 激活位点，但其可通过于囊性纤维性蛋白(CFTR)相互刺激(CFTR 结构域的 PKA 依赖性磷酸化促进其与 SLC26 交换子结构域的结合，导致 CFTR 和 SLC26 交换体显著相互激活[30])参与进入 CM 诱导的草酸盐摄取率的改变中[27]，与此同时，研究表明，CFTR 可能作为 PAT1 的上游蛋白而存在[22]，其本身也可进一步促进 PAT1 的蛋白表达[30] [31]。Felix Knauf 等人发现，CFTR 基因缺陷的小鼠肠道 PAT1 的表达量及肠道草酸盐分泌量明显降低[32]，基于 Shigeru B H Ko 的研究提示，CFTR 的共表达可以刺激 Cl^--碱基交换的 PAT1 转运活性[31]，Felix Knauf 等人进行了进一步的调查，单独表达 CFTR 的卵母细胞并未出现草酸盐的外排现象，而单独表达 PAT1 的卵母细胞在含 Cl^-培养基中初始出现草酸盐外排而后在不含 Cl^-的培养基中可逆的消除外排现象，这说明 CFTR 的共表达显著刺激了 PAT1 的 Cl^--草酸盐的转运[32]。

3.1.2. 肠道菌群的代谢产物

肠道菌群的代谢产物一般包括短链脂肪酸(SCFA)，氨基酸及胆汁酸等。研究显示，肾结石患者肠道微生物群中产生 SCFA 的肠道细菌以及与短链脂肪酸的产生相关的代谢途径要低得多，而在补充 SCFA 之后可见小鼠肾脏结晶明显减少[33]，针对短链脂肪酸影响肾结晶产生的作用机制，Liu 的研究发现短链

脂肪酸(乙酸盐，丙酸盐，丁酸盐)主要是通过调节 SLC26A6/SLC26A3 的分子表达，降低大鼠肾 CaOx 结石和尿草酸盐水平，减少草酸在体内的蓄积，从而降低尿液中草酸盐的浓度，减少结石形成的风险[34]，最新研究显示：SCFA 通过 GPR43 依赖的免疫调节增加 $CX3CR1^{+}CD24$ 巨噬细胞的频率，减少肾脏中依赖 CaOx 晶体的 $GR1^{+}$中性粒细胞浸润，从而减少肾脏 CaOx 晶体的形成[35]。即使在肠道菌群耗尽后口服短链脂肪酸仍能减少肾结石的产生风险，这表明短链脂肪酸也可作为预防肾结石产生的益生元。

3.2. 尿路草酸盐的影响因素

雌激素

统计学结果表明，女性泌尿系结石患者的数量显著低于男性泌尿系结石患者，有部分研究表明，泌尿系结石的产生与雌激素或者雌激素受体(ER)存在一定联系[36] [37]。

人体尿草酸盐大部分来源于肝脏的内源性产生[17]。肝脏中存在乙醛酸氨基转移酶(AGT1)，该转移酶可将草酸的直接前体(乙醛酸盐)转化为甘氨酸(人体可以自由利用及排泄) [38]-[40]。雌激素及其受体对于草酸盐的影响存在两种途径，其一是影响 AGT1 [41]。研究表明，ERβ 通过直接结合 AGT1 基因的 5′启动子来增强肝脏 AGT1 的表达，进而减少人体尿草酸盐的产生[42]。其二在于雌激素直接抑制肾脏中的 PAT1 的表达，导致草酸转运活性降低[43]。Lee 的进一步研究表示，雌激素治疗会降低表达高度显性 PAT1 的肾单位的活性[37]，进而减少尿草酸盐的分泌，预防草酸钙类结石的产生。

4. 展望

面对泌尿系结石的高发率，当今的医疗水平更为集中于泌尿系结石的治疗而非该疾病的预防，因此，往后的医疗发展我们应将目光更多地投向该疾病的预防中。草酸钙类结石作为人类泌尿系结石的主要类型，更加值得我们对其预防的重视，可以通过上述对于 PAT1 的影响因素的研究发展针对提升 PAT1 对于草酸的转运的方法进而实现对草酸钙类结石的预防。已有研究显示，PAT1 的抑制剂吡唑并－吡啶－嘧啶酮 PAT1inh-B01 可以完全抑制 PAT1 介导的阴离子交换，可以通过此类 PAT1 抑制剂药物阻断远端小肠的液体吸收从而预防或者治疗胎粪性肠梗阻以及囊性纤维化的梗[44]。Tifany Chu 等同样提出，PAT1 抑制剂是治疗囊性纤维化相关小肠疾病的新型候补药物[45]，对于 PAT1 在草酸钙结石的预防中作用而言，我们也许可以将注意投向 PAT1 抑制剂的选择性上，如前所述，PAT1 对于草酸盐的代谢在肠道中增加草酸盐排泄，在肾脏中则吸收尿液中的草酸盐，因此，我们应发展针对不同位点的 PAT1 的增强剂，在肠道位点应增强其排泄能力，在肾脏位点则增强其吸收能力，与此同时，还应注重 PAT1 各种离子交换的选择性，不影响到肠道其他离子的正常转运。Felix Knauf 的最新研究表明，草酸盐在肠道中的浓度取决于草酸盐通过细胞旁途径的吸收与依赖 SLC26A6 活性的跨细胞草酸盐分泌之间的相对平衡，即减少草酸盐在细胞旁途径的吸收或者增强 PAT1 在消化道的分泌将降低患高草酸血症以及草酸结石的风险[46]。总而言之，PAT1 与预防草酸钙结石产生的相关机制还需我们继续深入的研究。

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