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蛋白结合尿毒症毒素及其清除技术的研究进展 *

刘 旭 刘 静 丁嘉祥 张东亮 刘文虎△

(首都医科大学附属北京友谊医院肾内科 首都医科大学肾病学系 北京 100050)

摘要:尿毒症毒素是一大组体内代谢的产物,在肾功能衰竭患者体液中水平明显升高,并与尿毒症毒素代谢紊乱或临床表现密切相关。部分毒素可与蛋白结合,形成大分子复合物,称为蛋白结合毒素。它们具有多种生物学作用,产生一系列尿毒症并发症,如心血管疾病、免疫功能紊乱、脏器纤维化等。研究发现:血浆分离吸附、高通量血液透析、服用肠道吸附剂等方法可增加蛋白结合毒素的清除。评价尿毒症患者的透析充分性时,也应考虑到蛋白结合毒素。

关键词:终末期肾病;蛋白结合尿毒症毒素;清除技术

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Progress of the Protein-bound Uremic Toxins and Removal Techniques*

LIU Xu, LIU Jing, DING Jia-xiang, ZHANG Dong-liang, LIU Wen-hu△

(Department of Nephrology, Division of Nephrology, Beijing Friendship Hospital, Captial Medical University, Beijing, 100050, China)

ABSTRACT: Uremic toxins are a large group of metabolites, which have significantly higher levels in body fluids of renal failure patients, and are related with toxins metabolic disorders and clinical manifestations closely. Some of them can combine with protein, to form macromolecular complexes, which are called protein-bound uremic toxins. They have a variety of biological effects, to produce a series of uremic complications, such as cardiovascular disease, immune dysfunction, and organ fibrosis. Researchers found that plasma separation adsorption, high-flux hemodialysis, and taking intestinal adsorbents can increase the clearance of protein-bound uremic toxins. While evaluating dialysis adequacy in uremic patients, protein-bound uremic toxins should also be taken into account.

Key words: End stage renal disease; Protein-bound uremic toxins; Removal techniques

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前言

随着慢性肾脏病患者的肾功能不断恶化,进入终末期肾病后,一些物质在患者体内不断蓄积,可造成全身多系统多脏器的损害,这些物质称为尿毒症毒素(uremic toxins)。根据透析中的清除模式,可以将尿毒症毒素划分为三大类[1]:(1)水溶性小分子化合物,分子量一般不超过 500D,应用普通透析模式可充分清除;(2)中分子物质,分子量大于 500D,需要孔径足够大的透析膜,采用高通量透析或血液滤过的方式清除;以及(3)蛋白结合毒素,该物质本身分子量多小于 500D,但由于易与蛋白结合而难以清除。

在大量的蛋白结合尿毒物质中,关于硫酸吲哚酚与对甲酚的结合物,硫酸对甲酚(p-CS)和葡糖苷酸对甲酸(p-CG)的关注最为广泛,下文将主要对上述物质的研究进展做一介绍。

1 蛋白结合毒素的生物学作用

对甲酚是一种已知的白细胞功能抑制剂,而硫酸对甲酚可以诱导白细胞自由基产生,促进炎症的发生[2,3]。后来的研究表明硫酸对甲酚也可由血管内皮微粒释放,可提示一系列病理生理情况:如血管损伤[4],肾素 - 血管紧张素系统诱导的肾脏上皮细胞向间质细胞转化导致的纤维化[5],以及肾小管上皮细胞内 Klotho 基因甲基化而表达受限[6]。近期的一项研究发现了硫酸对甲酚引起白细胞的募集,用以评估内皮细胞和白细胞的串扰现象[7]。

虽然尿毒症患者体内的硫酸对甲酚的总浓度较葡糖苷酸对甲酸更高,但后者的蛋白结合率低,使得这两种化合物的活性浓度几乎相同[3]。尽管葡糖苷酸对甲酸本质上对于白细胞是无活性的,但它具有提高硫酸对甲酚诱导自由基产生的作用,提示尿毒症毒素之间可能具有协同作用[3]。这两种物质的共同作用也表现为引起内皮细胞的白蛋白漏出,而硫酸对甲酚单独作用并不引起这种现象发生[7]。

近期的研究显示硫酸对甲酚与患者的多种不良预后相关,包括肾功能进展[8],冠状动脉粥样硬化性心脏病[9]、血管钙化[10]的发生,心血管及全因死亡率[10,11]等。

许多硫酸吲哚酚的生物学效应都与心血管损伤相关,如血浆纤溶酶原活物 -1(PAI-1)激活及自由基产生[12],成骨细胞抵抗甲状旁腺激素潜在引起血管钙化[13],内皮细胞微粒释放[14],破坏内皮细胞的粘着连接[15],诱导细胞衰老并抑制再生[16],引起肾

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作者简介:刘旭(1983-),男,医学硕士,医师,研究方向:肾脏疾病的诊治与肾脏替代治疗,E-mail: liuxu_000@sina.com

△通讯作者:刘文虎,男,医学博士,主任医师,教授,博士生导师,研究方向:肾脏疾病的诊治与肾脏替代治疗,E-mail:liuwh2002@yahoo.cn

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脏[16]和心脏的纤维化[17]。

学者 Ito 等通过体外实验研究白细胞和内皮细胞的相互作用，显示内皮细胞核转录因子 κB(NF-κB)激活与白细胞粘附有关[18]。Adijiang 等通过实验动物体内研究，显示了硫酸吲哚酚对于血管结构的损伤：他们使用盐敏感高血压 Dahl 大鼠，给予尿毒症水平的硫酸吲哚酚后，可诱导血管壁的钙化，而在对照组的非给药 Dahl 大鼠和野生型大鼠中，未观察到血管的类似病变[19]。在一项最近的研究中，学者发现硫酸吲哚酚引起白细胞发生募集作用的程度与脂多糖相当[7]。

其他一些临床研究结果也显示，硫酸吲哚酚相关与下列临床情况相关，包括体内白介素 -6(IL-6)浓度[20]，冠状动脉粥样硬化性心脏病[21]，血管损伤[22]，肾功能进展[8]以及全因死亡[22]。

2 蛋白结合毒素的清除策略

通过调整透析策略或增加透析膜的孔径都很难增加蛋白结合毒素的清除[23]。有学者提出增加血液滤过置换量可增加部分蛋白结合毒素的清除率[24]，降低透前水平[25]，然而这种幅度的降低是否带来临床获益尚不清楚。

血浆分离和吸附技术是用于治疗重症肝衰竭的血液净化方法，有学者测量该方法清除的蛋白结合毒素的量可达高通量透析的二倍，然而该方案存在凝血难以控制及成本过高等原因难以推广到临床[26]。尽管如此，该研究还是给我们提供了启示：血液吸附技术可能是清除蛋白结合毒素的有效方法。

Evenepoel 等证实：高通量血液透析和腹膜透析相比，具有更好的蛋白结合毒素清除率，这也可以解释腹膜透析更好的残余肾功能保护作用[27]。然而，腹透患者体内此类毒素水平却更低，这其中的原因目前尚无定论，有学者猜测这可能与腹膜透析患者肠道内蛋白结合毒素的产生与代谢的差异有关，这还需要未来的研究所证实[28]。

蛋白结合毒素及其前体的产生主要来自于肠道微生物对于氨基酸的分解代谢[29]，通过对结肠切除术后患者体内蛋白结合毒素的浓度代谢分析，进一步证实了肠道产生此类毒素的观点[30]。因此，通过医学方法影响改变尿毒症患者的肠道代谢状况，可能是一种降低蛋白结合毒素水平的潜在方法[29]。然而，过度严格地限制蛋白摄入可能会增加发生营养不良的风险。更可行的方法则是合理应用抗性淀粉或低聚果糖丰富的菊粉 [31]等益生元，双歧杆菌等益生菌，以及肠道吸附剂克里美净(AST-120，Kremezin)等[32]。Kikuchi 等应用液相色谱 / 电串联质谱法(LC/ESI-MS/MS)检测给予 AST-120 后的尿毒症大鼠的血清，显示与未经处理的对照组相比，包括硫酸吲哚酚、马尿酸、硫酸苯酯和对硫酸甲酯等 11 种物质的浓度有所降低[33]。

一些研究显示了 AST-120 具有延缓肾功能进展的作用，可以推迟进入透析的时间[34]，放慢肾小球滤过率的下降速度[35]。另一项随机对照研究发现中度蛋白尿的糖尿病肾病患者中，应用 AST-120 治疗组的血清肌酐水平上涨较慢[36]。最后，在透析前期应用 AST-120，即使患者之后开始血液透析，仍可改善他们的生存率[37]。

3 评价透析充分性应考虑蛋白结合毒素

顾名思义，包括蛋白结合毒素在内的全部尿毒症毒素都是经由肾脏排泄，然而我们目前用来评价肾脏滤过功能的常用指标，如肾小球滤过率(GFR)对于蛋白结合毒素排泄能力情况的评估存在局限性[38]。无论是估算的肾小球滤过率(eGFR)或是实际测量的数值，都无法准确评价肾脏对于中分子毒素和蛋白结合毒素的滤过清除能力，它们的浓度与机体的合成、新陈代谢、以及肾小管功能都有关[39]。单纯通过计算肾小球滤过率来判断患者进入透析的时点，而忽略综合评价患者的尿毒症症状，是不恰当的。

尽管目前评价透析充分性的计算方法还主要依赖测量血浆尿素氮的下降水平，但多种尿毒症症状却不只与此类小分子毒素有关。因此，当我们希望优化透析效果，提高尿毒症患者的生存质量是，不应仅仅关注于此。

4 小结

目前已有充分的证据表明，蛋白结合毒素的生物学影响与尿毒症患者的预后密切相关。通过透析技术只能清除非蛋白结合状态的此类毒素。需要更多关注此类物质的体内动力学，以开放更加有效的血液净化方法以实现更好的清除效率。利用体外或肠内的毒素吸附治疗方法可能会是一个研究方向，目前体外吸附法多受困于凝血问题；有研究显示肠内吸附可能为延缓肾衰竭进展带来帮助。然而，上述观点都需要更大规模的临床试验以证实。

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