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· 综述 ·

三甲胺 N-氧化物与心血管疾病的研究进展

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[摘要] 肠道菌群是由人类的数万亿个微生物细胞在肠道中形成的一个复杂的微生物群落。目前已有研究表明, 肠道菌群与心血管疾病(cardiovascular disease, CVD)密切相关。此外, 肠道微生物的代谢产物三甲胺N-氧化物(trimethylamine N-oxide, TMAO)已被广泛证明可增加高血压、冠状动脉粥样硬化性心脏病(coronary atherosclerotic heart disease, CHD)、心力衰竭(heart failure, HF)和心房颤动(atrial fibrillation, AF)的风险。

[关键词] 三甲胺N-氧化物; 肠道菌群; 心血管疾病

Research progress of trimethylamine N-oxide and cardiovascular disease

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Abstract The intestinal flora is a complex microbial community formed by trillions of human microbial cells in the gastrointestinal tract. Nowadays, it has been reported that the intestinal flora is closely related to cardiovascular disease (CVD). Moreover, trimethylamine N-oxide (TMAO), a metabolite derived from intestinal microorganisms, has been widely shown to augment the risk of developing hypertension, coronary atherosclerotic heart disease (CHD), heart failure (HF), and atrial fibrillation (AF).

Keywords trimethylamine N-oxide; intestinal flora; cardiovascular disease

心血管疾病(cardiovascular disease, CVD)的流行率和病死率均不断上升, 给社会带来沉重的医疗和经济负担。CVD作为一种慢性进行性疾病, 其发展往往始于高脂血症、糖尿病、高血压、吸烟等危险因素, 而这些危险因素会不可逆地损害血管结构, 最终导致动脉血栓形成和缺血性脑卒中等有害的临床结果^[1]。虽然当今社会对CVD有

了相对完善的治疗体系, 但我们对CVD发病机制及其预防和治疗仍存在很大的进步空间。研究^[2-5]表明肠道菌群的主要代谢产物三甲胺N-氧化物(trimethylamine N-oxide, TMAO)与CVD的发生和不良心血管事件风险的增加密切相关。本研究回顾了TMAO的生物合成, 并重点介绍了TMAO与冠状动脉粥样硬化性心脏病(coronary atherosclerotic

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heart disease, CHD)、心力衰竭(heart failure, HF)、高血压、心房颤动(atrial fibrillation, AF)等CVD的关系, 以及通过改善饮食, 进行药物治疗等措施干预TMAO合成代谢继而为CVD的预防和治疗提供新的思路。

1 TMAO的合成与代谢

在人体中, TMAO是由肠道微生物代谢产生的一种无色的胺氧化物, 它不仅可以参与氧化反应、渗透反应和静水压的调节, 还能够调节各种酶和激素的活性^[6]。其具有促进内皮细胞功能障碍, 增强血小板活化, 促进血栓形成, 影响脂质代谢和炎症反应的生理作用^[7]。TMAO的产生过程分为2步, 首先人体在摄入富含磷脂酰胆碱、胆碱、肉碱和甜菜碱的物质后, 这些物质在肠道循环时可形成TMAO的前体物质三甲胺(trimethylamine, TMA)^[8]。TMA经过进一步的微生物代谢被宿主细胞吸收进入体循环, 其中大部分TMA通过肠上皮细胞膜被动扩散进入肝门静脉循环, 随后在肝中被黄素单加氧酶(flavin-containing monooxygenases, FMOs)氧化为TMAO, FMOs中主要是FMO1和FMO3发挥作用, 其中FMO3在肝中的活性是FMO1的10倍^[9]。在人体中, TMAO通过尿液、粪便和呼吸被排出体外^[10]。血浆中TMAO的水平与饮食、肠道菌群的组成、肝功能和代谢能力(肾功能、肺功能等)等密切相关^[10]。

2 TMAO与CVD

2.1 TMAO与CHD

CHD是最常见的CVD。CHD与血脂异常、巨噬细胞异常积聚和炎症细胞因子大量产生有关, 是终末期CVD(如心肌梗死或HF)发生的基础^[11-12]。脂代谢异常是CHD最重要的危险因素, 多与高胆固醇血症相关^[1]。近年来, 人们认为TMAO在CHD发展过程中起着重要的调节作用。Heianza等^[13]在一项超过19 000名参与者的研究中发现: TMAO浓度较高的参与者其CHD的患病率也显著增加, 这可能是因为TMAO通过调节体内胆固醇的含量, 影响血小板的活动, 导致动脉粥样硬化的发生。Senthong等^[14]在一项前瞻性研究中发现血浆中TMAO的水平与CHD患者病死率密切相关, 且血浆中TMAO水平升高对CHD具有很强的预后价值。他们认为TMAO与CHD之间的

关系与胆固醇的代谢相关, 其研究^[14]表明TMAO是一种促进动脉粥样硬化的代谢物, 它可能会增加斑块的形成, 并减少胆固醇的逆向运输, 从而导致患者CHD的死亡风险增加。Cheng等^[15]通过分析冠状动脉内皮细胞, 确定TMAO与组织因子(tissue factor, TF)水平升高相关, 在ST段抬高型心肌梗死(ST-segment elevation myocardial infarction, STEMI)的患者中已经证明TF可以启动凝血途径, 从而导致动脉粥样硬化斑块的形成, 并最终导致斑块破裂, 因此TMAO与血栓形成密切相关。研究^[16]发现在STEMI急性期和慢性期血浆中TMAO含量显著增加, 慢性期的TMAO含量高于急性期, 该研究结果表明: 慢性期患者血浆中TMAO水平升高与冠状动脉斑块的进展有关, 并且在STEMI慢性期TMAO水平能够作为独立因素预测心血管事件。Swanepoel等^[17]证实了TMAO与CHD之间的关系, 他们认为TMAO参与了CHD的发生、发展, 增加了CHD的患病风险。研究^[18]发现TMAO可能是动脉粥样硬化的一种致病因子。上述的大量研究证明TMAO与CHD密切相关, 因此降低TMAO被认为是一种治疗CHD有前景的策略, 但TMAO与CHD之间的相互作用尚未完全清楚, 因此需要进一步研究, 为CVD的预防和治疗提供新的方向。

2.2 TMAO与HF

HF被认为是一种不可逆的终末期疾病, 是导致人类死亡的主要原因之一。据报道^[19], 预测到2030年, HF的患病率将增加约50%。在HF患者中, 因心输出量的减少和血液再分配, 导致肠道灌注减少和肠道屏障被破坏, 同时越来越多的研究证实了“心脏衰竭的肠道假说”。虽然肠道菌群与HF密切相关, 但其因果关系尚未得到明确证实^[20]。有研究^[21]表明: 在HF患者的血浆中TMAO水平升高, TMAO水平与心脏舒张功能障碍相关, 并且认为TMAO是收缩期HF患者病死率的独立预测指标。在Organ等^[22]的一项实验研究中, 他们在实验组小鼠的饲料中添加TMAO(0.12%)或胆碱(1.2%)后, 与对照组相比, 喂食TMAO或胆碱补充饲料的小鼠发生肺水肿、心脏体积增大和左心室射血分数降低的风险增加, 导致HF的严重程度显著增强。Wang等^[23]同样证明了通过降低TMAO水平, HF小鼠的心脏功能得到改善。Jin等^[24]在对HF机制的研究中表明TMAO与HF的发生密切相关, 他们认为TMAO通过促进微管蛋白的致密化和聚合, 亲联蛋白再分配, 从而导致心肌细胞Ca²⁺处理

功能障碍,对心肌细胞产生有害影响。综上所述,这些结果表明了TMAO在HF中具有关键作用,TMAO可能成为HF的一个潜在的治疗靶点^[25]。

2.3 TMAO与高血压

高血压是CVD发生、发展的关键环节,对血管和心脏造成严重损害。近年来,肠道菌群在高血压的治疗中的价值已被广泛研究^[26]。在Li等^[27]的研究中,将高血压小鼠的粪便移植到无菌小鼠的肠道内,随着微生物群的转移,这些小鼠的血压也升高,表明肠道菌群在高血压中发挥了作用。Tang等^[28]在大鼠模型中灌注血管紧张素II(angiotensin II, AngII)和TMAO(单独或联合),结果显示:单独灌注AngII组的实验动物只有在灌注时血压升高,然而联合灌注AngII/TMAO组的实验动物在停止灌注后血压仍明显升高。这表明TMAO可能导致的小鼠体内代谢改变,进而提高了小鼠高血压的易感性。Ge等^[29]研究了TMAO浓度与高血压患病率之间关系,他们发现与体内较低浓度的TMAO的患者相比,高浓度TMAO患者高血压患病风险增加了12%。此外,Ge等^[29]的研究报道也表明TMAO的浓度升高会导致患者高血压的持续时间延长。以上研究表明TMAO与高血压的发生密切相关,但未来还需要进一步的研究来阐明TMAO在高血压中的作用。

2.4 TMAO与AF

AF是临床上常见的心律失常之一,随着年龄增加,AF的发生率也在增加。AF患者大大增加了脑卒中和血栓栓塞的风险,给人类健康带来严重威胁。多项证据^[1,30]表明肠道菌群的变化可能是AF发生的重要诱因。Svingen等^[31]对数千例无AF病史的患者进行了研究,发现新发AF患者的血浆中TMAO水平比未发生AF的患者高20%。一项体外研究^[32]中也表明血浆中TMAO水平升高与房颤的患病率增加有关,其可能的原因是TMAO水平升高使炎症细胞因子增加,造成心房电位不稳定,从而促进自主神经功能改变,导致房颤的发生。AF的发病机制极其复杂,虽上述相关研究表明TMAO与房颤发生、发展相关,但TMAO与AF的关联性还需要进一步评估。

3 TMAO的干预

3.1 调整饮食

研究^[17,20,33-34]表明饮食调节能够改变血浆中

TMAO的水平。Annunziata等^[35-38]研究表明:白藜芦醇、大蒜素、辣椒素和苹果、乌龙茶、天然麦麸和低脂饮食中的膳食成分可以降低TMAO水平。然而高脂肪饮食和高蛋白饮食等会增加TMAO水平^[39]。肠道菌群通过代谢胆碱、磷脂酰胆碱、肉碱和甜菜碱而生成TMA, TMA进而被FMOs氧化为TMAO^[8],然而胆碱和肉碱等成分主要存在于红肉、鸡蛋、鱼、牛奶等物质中,因此这些物质可以通过多种途径影响TMAO的水平,包括TMA的代谢和肠道菌群进而改变血浆中TMAO的水平。然而,值得注意的是, TMAO水平可以受肾功能、TMA前体摄入量、肝氧化TMA和尿中TMAO排泄等因素影响,在血浆中蓄积,导致三甲胺尿症,并引发一些新的疾病^[10]。因此我们还需要进一步的临床研究,以评估这些膳食成分对TMAO水平及其前体的影响。

3.2 益生菌的管理

益生菌是一种具有活性的微生物,研究^[40]表明一定量的益生菌会给宿主带来益处,其可以通过调整宿主细胞中低密度脂蛋白/高密度脂蛋白比值来调节代谢,同时还具有胆盐水解酶的活性从而分解初级胆汁酸,增加其排泄。研究^[41]表明产气肠杆菌、植物乳杆菌和副干酪乳杆菌等一些益生菌可以通过肠道菌群重塑来降低血浆中TMAO和TMA水平。Wang等^[42]在研究中同样发现植物乳杆菌可以抑制TMAO合成和TMA的产生。然而,Chen等^[43]通过在年轻男性中补充益生菌(嗜酸乳杆菌、动物双歧杆菌和长双歧杆菌)4周后,并未发现血浆中TMAO和TMA水平有所降低。由此可见,不同菌株对胆碱代谢和TMAO水平的影响不同,一些有益菌株如产气肠杆菌、植物乳杆菌等可以降低体内TMAO的水平,然而嗜酸乳杆菌、动物双歧杆菌等对TMAO的水平并没有影响。

3.3 潜在的药物治疗

Roberts等^[44]在一项研究中发现3, 3-二甲基-1-丁醇(3,3-dimethyl-1-butanol, DMB)对体内微生物胆碱TMA裂解酶的活性具有抑制作用,导致TMA合成受阻,继而降低体内TMAO的水平。因TMAO具有增强血小板活性和体内血栓形成的潜力,故这有可能成为一种新的抗血栓治疗方案。DMB通过抑制TMA合成的关键酶来降低血浆TMAO水平,从而降低CVD的风险。DMB可减轻心肌纤维化,改善心肌功能^[45]。此外,DMB可以通过抑制氧化应激反应,降低老年大鼠血浆中TMAO水平,对血

管内皮起到保护作用。Konop等^[46]发现依那利普实验大鼠血浆中TMAO水平明显下降, 24 h后尿液中的TMA和TMAO排泄量呈上升趋势, 表明依那普利治疗HF的机制可能也与促进TMAO排泄有关。

4 结语

综上所述, TMAO与CVD之间的发生、发展存在着密切关系, 这意味着TMAO在未来极有可能作为CVD早期诊断的生物标志物。因此, 我们应该开发降低TMAO水平的药物, 从而降低由这种具有威胁性的肠道代谢物导致的CVD的风险。虽然许多研究已经证明CVD风险的增加与TMAO水平升高之间具有很强的相关性, 然而, 仍然存在许多问题需要我们进一步研究。例如, 我们尚未明确TMAO对CVD的具体作用机制, 还需要进一步的探索TMAO和心血管风险增加之间的因果关系, 以及是否有可能将这种相互作用关系用于预防和治疗CVD。

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