

·综述·

阿尔茨海默病中肠道微生物群与血脑屏障关系研究进展[☆]何明月* 张巍**[△]✉

【摘要】阿尔茨海默病(Alzheimer disease, AD)是最常见的痴呆类型,给社会带来沉重负担。血脑屏障(blood-brain barrier, BBB)的改变可能是 AD 早期事件之一,肠道微生物群及其代谢产物可能通过影响 BBB 的结构和功能,参与 AD 的发生和进展。而靶向肠道微生物群和 BBB 的 AD 治疗新策略也日益受到重视,地中海饮食、益生菌可改善 BBB 结构和功能,益生元、粪便移植治疗则尚在动物研究阶段。探讨 AD 肠道微生物群的变化及其与 BBB 关系可为探索 AD 防治新靶点提供依据。

【关键词】阿尔茨海默病 肠道微生物群 代谢产物 脑-肠轴 血脑屏障 地中海饮食 益生菌 粪便移植

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【Abstract】Alzheimer disease (AD) is the most common type of dementia and imposes a heavy burden on society. The alteration of blood-brain barrier (BBB) may be one of the early events of AD. It has been found that the gut microbiota and their metabolites may be involved in the occurrence and progression of AD by affecting the structure and function of the BBB. New strategies targeting the gut microbiota and BBB for AD treatment are also receiving increasing attention. Mediterranean diet and probiotics can improve the structure and function of BBB, while probiotics and fecal transplantation therapy are still in the animal research. Exploring the alterations in gut microbiota of AD and their relationship with BBB can provide a basis for new targets for AD prevention and treatment.

【Key words】Alzheimer disease Gut microbiota Metabolites Brain-gut axis Blood-brain barrier Mediterranean diet Probiotics Fecal transplantation

阿尔茨海默病(Alzheimer disease, AD)是最常见的痴呆类型,其特征性病理改变为 β 淀粉样蛋白(β amyloid protein, $A\beta$) 在细胞外形成神经炎症斑,和过度磷酸化 tau 蛋白(phosphorylated tau, P-tau) 在细胞内形成神经原纤维缠

结^[1]。除神经免疫炎症、氧化应激、蛋白质自噬异常等机制外,近年来血脑屏障(blood-brain barrier, BBB)破坏被视为 AD 的又一重要机制^[2-3]。研究发现,肠道微生物群及其代谢产物可能通过 BBB 直接或间接地参与 AD 的发病和进展。

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因此,本文对AD肠道微生物群及其代谢产物与BBB的关系进行综述,旨在为AD的防治探索新靶点。

1 肠道微生物群与AD

人类肠道内大约聚集着100万亿个微生物,绝大多数是细菌,其中90%以上为厚壁菌门和拟杆菌门,此外还包括病毒、真菌及原核生物等。这些微生物群在维护肠道稳态、免疫调节、代谢合成与机体生长和发育等诸多方面发挥重要作用,被看作是人的“第二大脑”^[4]。

1.1 脑-肠轴与AD 肠道微生物群与AD等多种神经系统疾病关系密切,而脑-肠轴在其中发挥重要作用。脑-肠轴是指中枢神经系统与肠神经系统之间形成的双向通路,涉及神经、内分泌及免疫等多条途径^[5]。AD的肠道微生物群组成和丰度发生了明显改变,而肠道微生物群及其代谢产物反过来也可通过脑-肠轴影响AD病理和患者认知功能^[5]。

1.2 AD中肠道微生物群的变化 多项研究显示,AD患者肠道微生物群的组成发生了改变,但各研究结果不尽相同,这可能与研究对象的选择、饮食习惯和检测方法存在差异等因素有关^[6-12](表1)。

在AD动物模型中,与年龄匹配的野生型小鼠相比,8~12月龄的APP/PS1转基因小鼠肠道内疣微菌门和变形菌门丰度显著升高,而瘤胃球菌属和丁酸球菌属的丰度显著下降^[6]。另一项研究发现,与年龄匹配的野生型小鼠相比,3~8月龄APP/PS1转基因小鼠肠道中气味杆菌属和螺杆菌属的丰度显著升高,而普雷沃氏菌属丰度下降^[7]。

在临床研究中,与认知功能正常者相比,AD患者肠道

内厚壁菌门和放线菌门的丰度明显下降,拟杆菌门的丰度明显升高,且丰度升高的菌门与脑脊液 $A\beta_{1-42}/A\beta_{1-40}$ 呈负相关,与P-tau和P-tau/ $A\beta_{1-42}$ 呈正相关^[8]。此外,轻度认知功能障碍(mild cognitive impairment, MCI)患者的肠道微生物群也发生了与痴呆患者类似的改变,这提示AD的肠道菌群变化在疾病早期即已发生^[9]。

2 AD中肠道微生物群与BBB的关系

BBB是神经-血管单元的核心组分,主要是由脑毛细血管内皮细胞及包绕在其外的周细胞、星形胶质细胞足突和基底膜构成,是中枢神经系统和外周血液循环之间重要的生理屏障^[13]。BBB破坏可能是AD的早期事件之一,甚至早于神经病理蛋白沉积和脑萎缩^[2-3]。

2.1 肠道微生物群对BBB的影响 多项研究发现,肠道微生物群参与AD中BBB的改变^[13-14]。与常规饲养的小鼠相比,无菌小鼠的闭合蛋白(occludin)和紧密连接蛋白(claudin)-5等紧密连接(tight junctions, TJs)相关蛋白的表达下降,导致BBB通透性增加^[15]。采用含有双歧杆菌和乳杆菌的益生菌处理SAMP8小鼠,其claudin-1、occludin和胞质紧密粘连蛋白(zonula occludens, ZO)-1的表达水平明显升高^[16]。另有研究表明长期西式饮食会造成AD患者肠道微生物群功能失调,厌氧微生物、拟杆菌属和嗜胆菌属等促炎菌属增加,嗜粘蛋白-阿克曼氏菌等抗炎菌属减少,这会进一步诱导周细胞功能障碍,造成BBB破坏;而地中海饮食可使双歧杆菌及普拉梭菌丰度增加,瘤胃球菌丰度减少,提高短链脂肪酸(short chain fatty acids, SCFAs)的水平,上调TJs

表1 AD患者肠道微生物群的研究

研究	研究对象	地域	检测方法	菌群变化
KONG等 ^[10]	AD果蝇模型	中国广东	粪便 16S rRNA	醋杆菌属和乳酸菌属的丰度下降
ZHANG等 ^[6]	APP/PS1转基因小鼠和野生型小鼠	中国北京	粪便 16S rRNA	疣微菌属、变形菌属的丰度升高,瘤胃球菌属和丁酸球菌属的丰度下降
SHEN等 ^[7]	APP/PS1转基因小鼠和野生型小鼠	中国山东	粪便 16S rRNA	臭气杆菌属和螺杆菌属的丰度显著升高,普雷沃氏菌属的丰度下降
ZHUANG等 ^[11]	AD患者和认知功能正常者	中国重庆	粪便 16S rRNA	拟杆菌门、放线菌门、瘤胃球菌科和毛螺菌科等的丰度升高
LI等 ^[9]	AD源性MCI患者、AD痴呆患者和认知功能正常者	中国上海	粪便 16S rRNA	多尔氏菌属、乳酸菌属、链球菌属、双歧杆菌属、布劳氏菌属和大肠杆菌属的丰度升高,另枝菌属、拟杆菌属、副拟杆菌属、萨特氏菌属和异普雷沃氏菌的丰度下降
CATTANEO等 ^[12]	AD患者和认知功能正常者	意大利	粪便 16S rRNA	<i>E.rectale</i> 的丰度下降,埃希氏菌属、志贺菌属的丰度升高
VOGT等 ^[8]	AD患者和认知功能正常者	美国	粪便 16S rRNA	厚壁菌门和放线菌门的丰度下降,拟杆菌门的丰度升高

注:MCI,轻度认知功能障碍;16S rRNA,16S核糖体RNA。

相关蛋白的表达,进而改善BBB的通透性^[17-19]。

2.2 肠道微生物群代谢产物对BBB的影响 一些肠道微生物群的代谢产物,包括脂多糖(lipopolysaccharide, LPS)、SCFAs、胆汁酸(bile acids, BAs)和三甲胺N-氧化物(trimethylamine N-oxide, TMAO),也可能影响BBB的结构和功能^[15, 20-24]。

2.2.1 LPS LPS是革兰氏阴性菌细胞壁外壁的组成成分,由脂质和多糖组成^[25]。研究发现,AD患者血中LPS水平明显升高^[20]。LPS可通过以下机制损害BBB^[26-27]:①直接机制,LPS可直接损伤内皮细胞^[26-27],破坏晚期糖基化终产物受体结构,进而影响BBB以及A β 经BBB的转运^[20];②间接机制,循环中LPS与Toll样受体4结合,通过驱动核因子 κ B(nuclear factor- κ B, NF- κ B)的表达启动系统性炎症,产生白介素6、肿瘤坏死因子- α 及前列腺素E2等炎症因子^[28],进而增加TJs的通透性,诱导周细胞变性和内皮细胞凋亡。持续的炎症也过度激活小胶质细胞和星形胶质细胞,激活相关细胞毒性通路的转录,吞噬星形胶质细胞足突,从而破坏BBB^[29]。

2.2.2 SCFAs SCFAs是肠道微生物群发酵非消化底物(如膳食纤维和内源性肠道黏液等)产生的主要代谢产物,包括乙酸盐、丙酸盐和丁酸盐等。部分SCFAs可到达全身循环,跨过BBB进入脑内^[30]。无菌小鼠在接受产生SCFAs的丁酸梭菌或拟杆菌定植后,TJs相关蛋白表达上调,BBB功能得以改善^[15];SCFAs还通过上调G蛋白偶联受体41和下调NF- κ B信号通路,减轻炎症反应,进而改善BBB功能^[31]。

2.2.3 BAs BAs是以胆固醇为原料在肝脏中经过一系列酶促反应而合成的胆烷酸的总称,是胆汁的主要成分。BAs产生和重吸收过程需要多种酶的催化,而这些酶的产生和表达受到肠道微生物群调节^[22]。与认知功能正常者相比,AD患者血清中初级BAs水平明显下降,而次级BAs水平增加^[21]。BAs可通过重新分配occludin、ZO-1和ZO-2的定位,诱导occludin磷酸化^[32]。部分BAs(甘氨酸鹅脱氧胆酸、牛磺石胆酸等)会促进活性氧生成,诱发脑内炎症反应^[22],从而损伤BBB。

2.2.4 TMAO 肠道微生物通过摄取海鱼、鸡蛋、肝脏及豆类等食物中的膳食营养素(如胆碱、卵磷脂和左旋肉碱),在胆碱三甲胺裂解酶的催化作用下产生三甲胺,后者经过门脉循环进入肝脏,并被黄素单加氧酶氧化生成TMAO^[24]。

TMAO与心血管疾病、2型糖尿病和肿瘤的关系已被广泛报道^[33-35],但其与AD之间关系的研究尚处于起步阶段。2017年,研究人员首次在AD患者脑脊液中检测到TMAO,

提示TMAO可能通过BBB进入AD患者脑内^[23]。与认知功能正常者相比,AD患者脑内TMAO水平有所升高,后者会促进神经病理蛋白的产生和神经变性^[24, 36]。但TMAO对BBB的作用尚存在争议:高水平TMAO可诱导氧化应激,过度激活胶质细胞,造成神经免疫炎症反应,从而损伤BBB^[37]。但最新研究发现,生理剂量的TMAO可通过诱导酶联蛋白-A1对BBB完整性发挥积极的调节作用^[38],提示TMAO和BBB的关系可能存在剂量依赖性。

3 靶向肠道微生物群和BBB的AD治疗研究

调整饮食模式、补充益生菌、粪移植等手段可能会影响肠道微生物群组成及其代谢产物的产生,通过介导BBB的结构和功能改变,进而影响AD神经病理和认知功能^[19, 39-43]。

3.1 饮食模式 地中海饮食是以大量的橄榄油、豆科植物、天然谷物和蔬菜,适量的鱼、乳制品及少量肉制品为特色的饮食模式^[39]。流行病学研究发现,长期地中海饮食可延缓AD进展1.5~3.5年,增加大脑皮层厚度,改善认知功能^[40-41]。地中海饮食影响BBB的潜在机制包括:①地中海饮食富含抗炎和抗氧化物质(如多酚),同时可增加具有抗炎作用的肠道细菌数量(如双歧杆菌和普拉梭菌),减少具有促炎作用的肠道细菌数量(如瘤胃球菌),通过抑制炎症反应对BBB发挥保护作用^[19];②长期地中海饮食可提高粪便和循环中SCFAs的水平,降低TMAO水平,增加TJs相关蛋白的表达,从而改善BBB的结构和功能^[44]。

3.2 益生菌和益生元

3.2.1 益生菌 益生菌是定植在人体内、对宿主有益的活性微生物,具有调节免疫、减轻氧化应激和改善肠上皮屏障等功能^[45]。动物研究发现,喂养双歧杆菌可改善AD小鼠的肠道菌群失调,降低其粪便和血液中LPS和炎症因子的水平,增加TJs相关蛋白的表达,从而减轻脑内A β 负荷,改善认知功能^[46]。在一项随机、双盲、对照的临床试验中,连续给予AD患者益生菌乳(含乳杆菌和双歧杆菌)共12周后,患者体内炎症因子水平明显下降,BBB功能得以改善^[47]。

3.2.2 益生元 益生元是一种膳食补充剂,在上消化道中难以被消化,进入大肠后被肠道菌群发酵,刺激有益菌生长,改善宿主的健康^[45]。常见的益生元包括低聚果糖、抗性淀粉、低聚半乳糖及菊粉等。研究给予5 $\times$ FAD小鼠甘露寡糖连续喂养8周后,小鼠粪便中产丁酸盐的菌属及乳杆菌属丰度明显增加,炎症反应受到抑制,BBB的通透性得到调节,小鼠的空间记忆、焦虑和强迫行为改善^[48]。低聚果糖可减

轻AD大鼠脑内氧化应激和神经炎症水平^[49],对BBB产生积极的保护作用。连续16周给予菊粉可促进5×FAD小鼠体内TJs相关蛋白的表达,进而改善BBB通透性^[50]。

3.3 粪便移植 动物模型研究发现,将野生型小鼠的粪便连续4周移植至AD小鼠体内,可减少AD小鼠脑内的A β 沉积,减轻胶质细胞过度激活和继发的神经炎症水平,减轻BBB的通透性,从而改善小鼠的认知功能^[51-52]。目前,粪便菌群移植在临床实施中较为复杂和困难,研究证据尚少,有待进一步的临床探索。

4 总结与展望

不断加速的人口老龄化进程导致AD的患病率逐年攀升。BBB的改变可能是AD的早期事件之一,肠道微生物群及其代谢产物可通过影响BBB的结构和功能,参与AD的发生和进展。因此,肠道微生物群与BBB的关系是早期防治AD的新靶点。但目前关于AD肠道微生物群与BBB的研究尚少,今后还需更多、更可靠的动物和临床研究来探讨不同种族、地区的AD患者肠道微生物群的变化异同,探讨肠道微生物群作用于BBB的潜在机制,为早期AD防治提供新策略。

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·综述·

抗癫痫药物性脑病研究进展☆

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【摘要】抗癫痫药物性脑病指在癫痫治疗过程中由抗癫痫药物诱发的与药物相关的脑病,为中枢神经系统毒性反应,严重者可致死亡。该病发生率低,临床表现呈非典型性,容易被忽略甚至误诊,及时明确诊断是争取合理治疗的关键。传统与新型抗癫痫药物所致脑病不尽相同,本文围绕不同抗癫痫药物性脑病的临床表现、脑电图改变、发病机制及治疗原则进行综述,发现其临床表现主要为神经系统受累的症状,其中丙戊酸钠脑病、托吡酯脑病、唑尼沙胺脑病、吡仑帕奈脑病以高血氨脑病最为常见,卡马西平脑病可表现为后部可逆性脑病综合征,苯妥英钠脑病可表现为小脑综合征。脑电图改变以背景活动减慢、放电波形增加为主,缺乏特异性。发病机制与药物本身的作用机制相关,其中奥卡西平与拉莫三嗪可通过阻滞钠通道发挥作用,唑尼沙胺、托吡酯、丙戊酸钠、吡仑帕奈之间相互作用引起血氨显著升高。治疗原则以抑制吸收、促进排泄和对症治疗为主,预后较好。

【关键词】抗癫痫药物 脑病 高血氨脑病 脑电图 后部可逆性脑病综合征 左旋肉毒碱 γ -氨基丁酸

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