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Hans汉斯

肠道菌群代谢产物致阿尔茨海默病的促炎机制分析

李　雪*，方　芳#

重庆医科大学附属大学城医院神经内科，重庆

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摘　要

阿尔茨海默病(Alzheimer's disease, AD)是老年性痴呆中最常见的类型。AD具体发病机制不明确，研究数据表明中枢和外周免疫过程在其中都起着关键作用，已证实肠道微生物群及代谢产物具有外周、中枢促炎作用。本综述主要阐述肠道菌群代谢物促炎作用致AD样病理改变，期望通过靶向调节肠道菌群改善炎症反应，达到延缓AD发生发展的目的，提高患者生活质量，减少家庭和社会的经济负担。

关键词

炎症，阿尔茨海默病，肠道菌群

Analysis of the Pro-Inflammatory Mechanisms of Gut Microbiota Metabolites in Inducing Alzheimer's Disease

Xue Li*, Fang Fang#

Department of Neurology, University-Town Hospital of Chongqing Medical University, Chongqing

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Abstract

Alzheimer's disease (AD) is the most common type of senile dementia. The specific pathogenesis of AD is unclear, and the research data show that both central and peripheral immune processes play

*第一作者。
#通讯作者。

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a key role in it, and the intestinal microbiota and metabolites have been confirmed to have peripheral and central pro-inflammatory effects. This review mainly describes the pro-inflammatory effect of gut microbiota metabolites to cause AD-like pathological changes, hoping to improve the inflammatory response by targeting the intestinal microbiota, achieve the purpose of delaying the occurrence and development of AD, improve the quality of life of patients, and reduce the economic burden on families and society.

Keywords

Inflammation, Alzheimer's Disease, Gut Microbiota

1. 引言

阿尔茨海默病(AD)是一种慢性年龄相关的进行性神经退行性疾病，占所有痴呆病例的 60%~80%，影响全球约 4500 万人[1]，临床表现早期以记忆衰退为主，后期以全面性认知障碍为特点，严重时生活不能自理。AD 的病理特征包括脑组织中淀粉样 β (Aβ)沉积、过度磷酸化的 tau 蛋白和神经原纤维缠结(NFT) [2]。这些结构性和炎性病变导致大脑脆弱区域神经元的进行性丢失，从而导致 AD [3]。目前淀粉样蛋白级联假说已被广泛接受，但该假说不能解释 AD 的全部发病机制，研究者发现其他病理过程也参与其中。

在一项对 170 项炎性标志物行 meta 分析和系统综述的研究中显示，AD、轻度认知障碍(Mild cognitive impairment, MCI)的炎症标志物水平显著改变[4]。各种研究已表明神经炎症可以作为 AD 的独立因素[5]。近期在 AD 研究领域出现了两个新的科学证据：一方面是以小胶质细胞为重点的神经炎症[6] [7]和另一方面是肠道微生物组[8]在 AD 发展中的突出作用。

肠道微生物的代谢产物是肠道和大脑之间双向通讯的活性介质，常驻肠道微生物组可直接或通过代谢物的分泌与宿主相互作用。肠道微生物群和免疫系统之间的作用是复杂的，并且部分依赖于肠道微生物代谢物[9]。肠道菌群代谢物在调节免疫应答和慢性免疫相关炎性疾病中的作用已成为激烈研究的焦点。下面，就肠道菌群代谢产物在 AD 神经炎症反应的发病机制中所起的作用作一综述。

2. 神经炎症对 AD 的影响

神经中枢先天免疫系统应激源的激活会促进神经胶质的活化、炎症介质的释放和活性氧/氮物种(ROS/RNS)的产生[10]。小胶质细胞和星形胶质细胞作为先天免疫活性细胞，在神经炎症中起着关键作用，前者是主要参与者。小胶质细胞的生长发育依赖于肠道微生物群，如短链脂肪酸(SCFAs)是调节小胶质细胞成熟、形态和功能的关键分子[11]。

活化的小胶质细胞有助于减少 Aβ 沉积[12] [13]，但持续或慢性的激活可使促炎细胞因子释放，出现炎症级联反应，导致不可逆的中枢神经系统损伤，如影响神经元可塑性、改变部分神经递质受体的膜表达、损害记忆，而上述改变通常被认为是神经退行性疾病(如 AD)中组织损伤的典型驱动因素[14]。

肠道微生物及代谢产物可直接或间接促进神经元炎性反应。在动物模型中发现肠道细菌及代谢物可激活肠道中的 NLRP3 炎症小体，进而激活炎性细胞因子，并通过血循环增加中枢神经系统炎症反应[15]。Hoogland 等通过建立大肠杆菌腹部感染模型发现，脂多糖(革兰氏阴性菌的高免疫原性细胞壁成分，LPS)可通过激活小胶质细胞中的 toll 样受体(TLRs)来引发神经炎症[16]。TLRs 在共生定植、体内平衡维持和

肠屏障完整性等方面具有重要作用[8]。

3. 肠道微生物代谢产物对 AD 的影响

根据来源和合成，肠道微生物代谢产物可大致分为三类：a) 由肠道细菌从饮食成分中产生的代谢物(如短链脂肪酸、色氨酸代谢物、氧化三甲胺)；b) 由宿主产生并由肠道细菌修饰的代谢物(如次级胆汁酸)；c) 由肠道细菌从头合成的代谢物(如支链氨基酸、多胺) [17]。

3.1. 短链脂肪酸

短链脂肪酸(SCFAs)是肠道微生物代谢膳食纤维的产物，其浓度取决于微生物群组成、肠道转运时间、宿主－微生物群代谢通量和宿主饮食的纤维含量[17]，SCFAs 主要包括乙酸盐、丙酸盐和丁酸盐，其中丁酸盐在肠道中尤为重要[18] [19]。丁酸盐是一种抗炎物质，产生丁酸盐的细菌广泛分布在革兰氏阳性厚壁菌门中[20]。丁酸盐可改善突触可塑性、增加突触相关蛋白的表达，同时抑制小胶质细胞的活化，减少 Aβ 的积累[21]。研究表明血浆中的丁酸盐水平与认知障碍患者的 Aβ 沉积呈负相关[22]。

SCFAs 对宿主生理学和免疫具有重要作用。SCFAs 维持肠上皮完整性和加强肠道屏障，有助于免疫稳态[23]-[25]，可通过上调紧密连接蛋白表达和为脑能量代谢提供替代底物来增强血脑屏障的完整性，达到抗炎作用[26] [27]。SCFAs 除了能促进合成神经活性化合物，如组胺、血清素等[28]，同时也是信号分子中的一员，如 SCFAs 作为 GPCR41 (即 FFAR3)和 GPCR4 (即 FFAR2)的配体，在肠道中与以上受体结合发挥抗炎作用[29]。故通过调节有利于产生 SCFAs 的肠道微生物群来改善 AD 神经元稳态是可行、可持续的方法。

3.2. 色氨酸及代谢产物

色氨酸(TRP)是从饮食中获得的必需氨基酸之一。TRP 的代谢物包括吲哚、吲哚乙醇(IE)、吲哚丙酸(IPA)等等，其代谢物的类型和水平主要受肠道微生物群的影响，同时膳食色氨酸是芳香烃受体(AHR)激动剂的重要来源，该激动剂可通过降低星形胶质细胞和小胶质细胞的致病活性限制中枢神经系统炎症[30] [31]。

TRP 参与犬尿氨酸途径(KP)，该途径被认为是其降解的主要途径，代谢物主要包括犬尿氨酸(KYNA)、喹啉酸(QUIN)、3-羟基犬尿氨酸(3-HK)和吡啶甲酸(PIC) [32] [33]。KYNA 是具有神经活性的抗内源性 NMDA 拮抗剂，具有神经保护作用[34]，QUIN 则能介导过度刺激 NMDA、引起脂质过氧化和活性氧的产生、诱导星形胶质细胞产生多种趋化因子(如 TNF-α、IFN-γ 和 IL-1β)、抑制谷氨酰胺合酶等机制引起神经变性坏死[35] [36]。

部分研究表明 KP 途径失调是发生 AD 的原因之一[37]。β 淀粉样蛋白(Aβ1-42)与 QUIN 二者均可诱导细胞因子产生和抑制星形胶质细胞摄取谷氨酸[38]。色氨酸及其衍生物对中枢神经系统的作用似乎为开发大脑保护剂提供了新的希望前景。

3.3. 氧化三甲胺(TMAO)

三甲胺 N-氧化物(TMAO)是三甲胺(TMA)通过肝脏黄素单加氧酶(FMO3)氧化而成。通过动物模型发现 TMAO 使促炎细胞因子，如肿瘤坏死因子-α (TNF-α)、白细胞介素-1β (IL-1β)表达较高，抗炎细胞因子(IL-10)表达降低[39]。徐和王[40]基于网络的综合计算方法证明 TMAO 是一种与 AD 的各个方面显著相关的代谢物，同时 TMAO 与 AD 生物标志物存在 9 条共同遗传途径，为饮食和微生物代谢物在 AD 病因学中的作用提供了支持证据[40]。TMAO 可促进 tau 蛋白和微管蛋白之间的结合，这可能是致 AD 的机制之一[41]。也有研究认为 TMAO 可减少紧密连接蛋白的表达从而破坏血脑屏障进入大脑[42]，但尚未在

人体内得到证明。这种饮食代谢物在中枢神经系统病理生理学中的实际影响仍需要进一步研究。

3.4. 胆汁酸、支链氨基酸、多胺

胆汁酸经过一系列复杂的酶促反应及转化后成为次级胆汁酸，即脱氧胆酸(DCA)、石胆酸(LCA)和熊去氧胆酸(UDCA)，这个过程很大程度上受肠道微生物群的调节[43]。研究表明胆汁酸可通过增加细胞膜通透性和造成细胞损伤来直接抑制细菌的生长，同时作为配体可通过激活相应的受体参与代谢和免疫过程的调节[44]。饮食是支链氨基酸(BCAAs)的主要来源，也可由肠道微生物群合成。BCAAs 除了增强蛋白质合成和通过分解代谢提供能量以外，还通过激活 mTOR 途径调节细胞功能[17]。肠道中高水平的多胺来源于饮食以及宿主和微生物细胞的从头产生。多胺代谢在调节免疫中具有核心作用，在神经退行性疾病中多胺水平往往会发生变化，但上述肠道代谢物在 AD 中研究相对较少，其作用、机制仍需探索。

4. 肠道微生物及代谢产物对 AD 影响的发病机制

外周炎症诱导的中枢神经炎症的作用机制包括血脑屏障的破坏、与全身免疫激活相关的神经胶质细胞的激活以及微生物－肠－脑轴(MGBA)失调[45]。肠道微生物组及代谢产物有机会通过上述通路增加神经炎症可能。

4.1. 血脑屏障的破坏

血脑屏障(BBB)由微血管内皮细胞与紧密连接蛋白偶联组成，限制了有害物质从循环系统向中枢神经系统的细胞旁扩散，同时允许营养必需纤维执行大脑的基本生理功能[46]。血脑屏障内皮细胞通过产生血管活性物质和改变紧密连接结构来增加屏障通透性，从而对炎症刺激做出反应[47]，其完整性遭到破坏可使有害毒素从外周进入，进而导致神经紊乱，如 AD 的发生。

研究者在新皮层和海马体中检测到 LPS 在 AD 大脑中的丰度增加了约 7 至 21 倍[48]。LPS 通过激活免疫细胞、释放促炎因子引起神经和肠道炎症，进一步增加肠道和血脑屏障的通透性，使进入大脑成为可能[49]。促炎因子 TNF-α、IL-6 和 IL-1b 等可通过改变脑血管紧密连接的阻力损害血脑屏障的完整性，进一步促进神经炎症发生[50]。研究者发现肠道菌群相关产物可通过破坏内皮细胞功能影响脑淀粉样蛋白的沉积[51]。

4.2. 小胶质细胞的活化

如前所述，小胶质细胞对疾病的病理生理学具有双重作用。Serrano-Pozo A 等通过分析 40 名 AD 患者颞叶皮层斑块周围分布的小胶质细胞和星形胶质细胞，普遍观察到脑部炎症，主要由星形胶质细胞增生和小胶质细胞活化组成[52]。

小胶质细胞配备了 TLRs 来检测病原体相关分子模式(PAMPs)或损伤相关分子模式(DAMPs)。当下游 TLRs 通路被激活时(如遇肠道致病菌及代谢物)，TLRs 以炎症依赖的方式上调，小胶质细胞可释放促炎因子应对组织损伤，大量炎症因子的聚集反过来促进小胶质细胞的活化，诱导神经细胞的炎症性凋亡，最终破坏患者的记忆和认知能力[53]。

4.3. 微生物－肠－脑轴的失调

微生物－肠－脑轴(MGBA)包括内分泌、免疫、代谢和神经通路，肠道和大脑通过 MGBA 紧密相连。肠道环境的细菌代谢物或毒素可通过 MGBA 对中枢神经系统产生毁灭性影响。肠道微生物群一方面可以调节肠道免疫，另一方面与适应性免疫的调节有关，其失调则会导致肠道免疫紊乱，出现炎症反应。研究发现炎症性肠病(IBD)患者罹患 AD 的风险较非 IBD 患者增加，进一步说明不可忽视促炎性肠道环境在

AD 发生机制中的作用[54] [55]。

5. 调节肠道微生物群对治疗 AD 的可能

目前尚没有有效的治疗方法治愈 AD，临床上对 AD 的药物治疗主要包括胆碱酯酶抑制剂、N-甲基-D-天冬氨酸受体拮抗剂。通过靶向肠道微生物调节炎症治疗让人们看到了新的希望，治疗策略包括饮食、益生元及益生菌、粪便微生物群移植(FMT)等。

5.1. 饮食

肠道微生物及代谢物与饮食明显相关。目前地中海饮食被认为是有益于 AD 的饮食方式，其中包括蔬菜、豆类、水果、谷物以及大量摄入的不饱和脂肪酸和多酚。研究表明多酚可能减少线粒体中 β-淀粉样蛋白聚集和活性氧[56]。

5.2. 益生菌及益生元

益生菌被认为是对宿主健康有益的细菌。最广泛使用的益生菌是双歧杆菌和乳杆菌属。益生菌可以分泌和产生细菌毒素(如细菌素)，可抑制细菌入侵并阻断病原体与上皮细胞的黏附，与致病菌竞争营养和结合位点。益生元被定义为被宿主微生物选择性利用赋予健康益处的底物。最常见的益生元是乳果糖、低聚果糖、低聚半乳糖和菊粉。益生元通常与益生菌联合使用，命名为合生元。益生元不仅促进益生菌的生长和代谢活性，还可影响肠道微生物代谢物 SCFAs 和胆汁酸的产生[57]，并以此缓解肠道炎症。

通过人群及动物研究表明以大量摄入益生元和益生菌以及其他营养素为特征的健康饮食模式可以延缓认知能力下降，降低阿尔茨海默病的风险[58]。合生元对于 AD 的长期治疗可能是安全的，并且口服药物摄入的可接受性和较少的副作用显然是优选的方法，但这种治疗的功效仍有待证明，需要更多的研究来确定明确的益处和潜在机制。

5.3. 粪便微生物群移植

粪便移植(FMT)是将供体的粪便移植到受体的肠道。该方法可用作将粪便物质从健康供体转移到受体的肠道中以直接改变其微生物组成以提供健康益处的创新方法，这种方法提供了健康个体的完整微生物群谱，甚至可能治疗尚未表征的疾病的生态失调状况。但 FMT 目前尚未用于临床治疗，其安全性及长期影响方面仍需进一步研究。

6. 未来展望

AD 目前尚不可治愈，确定有效的治疗干预是我们这个时代的主要挑战。炎症和肠道微生物组及相关衍生物在 AD 中的作用已成为研究焦点。生活方式、地理位置、药物假设和饮食习惯能够不断改变肠道微生物群的组成。研究表明富含饱和脂肪和简单碳水化合物的饮食会增加痴呆症的风险，而地中海饮食这样的高质量饮食可降低患 MCI 和 AD 的风险[59]。使用益生菌、益生元和其他饮食干预来调节肠道微生物群组成的可能性代表了一种有前途和可持续的方法。目前大多数肠道微生物群衍生的代谢物尚未被鉴定，并且已知代谢物的功能仍未被完全了解，因此需要更多的努力来确定在人类疾病中重要的微生物代谢物途径，尤其是神经退行性疾病。代谢组学和信息学的快速进步将有助于管理来自当前进行的和未来开展的微生物群研究的庞大数据库。

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