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肠道微生物在阿尔茨海默病中的作用机制研究

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摘　要

阿尔茨海默病(Alzheimer's Disease, AD)是一种以进行性认知功能障碍为特征的神经系统退行性疾病，是老年人失智最常见的病因之一。近年来，肠道菌群与AD之间的关系成为研究AD疾病的一个重要方向。越来越多的证据表明肠道菌群在AD疾病的病理生理学中起到关键作用，为了探讨肠道微生物在AD中的发病机制，本文梳理了近年来国内外有关肠道菌群变化与AD相关进展关系的相关研究，以及调节肠道微生态在AD疾病治疗中的新进展。肠道微生物通过调节身体机能稳态维持健康，当肠道微生物异常将会导致神经炎症，神经炎症假说在AD的进展和预后中有决定性的作用。益生菌对于治疗各种胃肠道疾病有利的作用，适量摄入以益生菌类为特征的健康饮食其他营养成分相结合，可以延缓认知能力下降，降低患AD的风险。肠道微生物异常进而引发神经炎症等病变会增加患AD的风险，适量补充益生菌类食物可提高认知能力从而减少AD的发病。

关键词

肠道微生物，炎症，益生菌

Study on the Mechanism of Intestinal Microbiota in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive dysfunction, and is one of the most common causes of dementia in the elderly. In recent years, the relationship between gut microbiota and AD has become an important direction in the study of AD diseases. A growing body of evidence indicates that gut bacteria play a key role in the pathophysiology of AD disease, in order to explore the gut microbes in the pathogenesis of AD, this article combed the at home and abroad in recent years, the relationship between intestinal flora changes associated with AD progress of related research, as well as regulating the intestinal micro ecology in AD a new progress in the treatment of disease. Intestinal microorganisms maintain health by regulating body function homeostasis. Abnormal intestinal microorganisms will lead to neuroinflammation. Neuroinflammation hypothesis plays a decisive role in the progression and prognosis of AD. Probiotics have beneficial effects on the treatment of various gastrointestinal diseases. Moderate intake of other nutrients in a healthy diet characterized by probiotics, combined with other nutrients, can delay cognitive decline and reduce the risk of AD. Intestinal microbial abnormalities, which lead to neuroinflammation and other lesions, will increase the risk of AD. Appropriate supplementation of probiotic foods can improve cognitive ability and reduce the incidence of AD.

Keywords

Intestinal Microorganism, Inflammation, Probiotics

1. 引言

阿尔茨海默病(Alzheimer's Disease, AD)是老年人中最常见的慢性神经退行性疾病[1]，其特征是认知能力逐渐下降[2]。它是一种异质性和多因素疾病，AD 开始时最常见的症状与短期记忆障碍有关，短期记忆障碍会影响日常活动[3]。细胞外 β-淀粉样蛋白(Amyloid β-Protein, Aβ)沉积作为神经炎斑块的存在和作为神经原纤维缠结(Neurofibrillary Tangle, NFT)的超磷酸 tau 细胞内积聚仍然是 AD 诊断的主要神经病理学标准[2]。作为失智症最常见的形式，AD 已成为全球公共卫生重点，全世界超过 5000 万人受到影响[2]。持续增长的患病率和 AD 的沉重负担使得研究人员比以往任何时候都更迫切需要剖析 AD 发病机制并寻求疾病改善疗法。近年来，微生物群－肠道－脑轴已成为生物医学研究的焦点和治疗中枢神经系统(Central Nervous System, CNS)疾病的潜在治疗靶点[4]。特别是，微生物群－肠－脑轴功能障碍与 AD 的发病机制有关[4]。本文将总结肠道微生物群特征，分析肠道异常微生物调节引起的炎症反应在 AD 发病机制中的作用。

2. 肠道微生物与 AD 发病机制

人类微生物组计划扩展了我们对人类微生物组和疾病发展的理解[5]。在人类消化道[6]中约有 100 万亿个细菌，以 1000~1500 种为代表。肠道菌群是人体抵御胃肠道病原体和毒素的重要防线。大量证据表明，肠道菌群的动态平衡在人体生理和病理中发挥着重要作用，肠道菌群失调与许多疾病密切相关。人类肠道微生物通常保持稳态，但肠道菌群的组成会随着年龄的增长而变化。研究发现，与年龄相关的过

程可以影响肠道菌群的多样性，并导致代谢改变，具有潜在的有害影响[7]。

肠道菌群在以下几个方面对人类健康有益：

1) 肠道菌群在代谢合成氨基酸和维生素、代谢类固醇分子和生物活性化合物、增强免疫系统等方面发挥着至关重要的作用[8]。

2) 肠道菌群产生代谢产物，如 16 结肠是生产短链脂肪酸的主要部位，通过发酵膳食纤维分解释放短链脂肪酸[9]。短链脂肪酸(SCFAs)是碳原子数为 2~6 的饱和脂肪酸的总称，包括乙酸、丙酸、丁酸、戊酸和己酸[9]。其可调节肠上皮屏障(Intestinal Epithelial Barrier, IEB)通透性，维持宿主免疫系统稳态和葡萄糖稳态[10]；另一方面，调节小胶质细胞的成熟和功能。此外，在衰老小鼠中短链脂肪酸(Short Chain Fat Acid, SCFA)通过抑制小胶质细胞和星形胶质细胞的促炎作用发挥抗炎作用[11]。

3) 受微生物群调节的神经内分泌系统可调节神经递质产生，如 5-羟色胺和酪胺。神经内分泌系统共同维持免疫系统、IEB 和血脑屏障(Blood Brain Barrier, BBB)的完整性。

2.1. 淀粉样蛋白

Aβ 是一种多肽，是一种蛋白质前体氨基酸链，它可以在脑细胞上积累，导致在 AD 患者中大量发现的斑块，这些 Aβ 斑块被认为是 AD 导致失智的主要因素之一。淀粉样前体蛋白(Amyloid Precursor Protein, APP)一种具有单个跨膜结构域的跨膜蛋白，其中 42~43 个氨基酸的 Ab 结构域被预测部分嵌入质膜[12]是 AD 发生发展的一个关键分子，Aβ 最常见的亚型是 Aβ40 和 Aβ42，其中 Aβ42 具有神经毒性。脑脊液Aβ42 水平降低是诊断 AD 的重要支持证据，Aβ42 水平降低伴随着大脑淀粉样斑块的发展，以及认知正常老年人发作性记忆变差和大脑海马体积减小具有相关性，对于认知功能正常者和轻度认知障碍(Mild Cognitive Impairment, MCI)患者的疾病进展具有预测作用。Aβ42 纤维形态的形成被认为是导致 AD 发病的初始毒性事件。Aβ 肽是由 β 和 γ 分泌酶裂解 APP 产生的；而 Aβ 的产生又被 α-分泌酶(α-secretase)活性所阻止，α-secretase 活性可在 Aβ 结构域内切割 APP [13]。Aβ 正电子发射断层扫描(Positron Emission Tomography, PET)异常或脑脊液(Cerebrospinal Fluid, CSF)中 Aβ 降低 Aβ42/Aβ40 比值被认为是 Aβ 沉积的证据[14]。

2.2. tau 蛋白

tau 蛋白介导的神经变性：tau 蛋白是一种微管相关蛋白(Microtubule Associated Protein, MAP)，主要分布在神经元的轴突上，可促进微管蛋白聚集成微管，稳定神经元细胞骨架，是 AD 发生的关键病理事件。在成人大脑的大多数区域中，3R 和 4R tau 蛋白亚型的比例为 1:1，偏离这一比例是神经变性 tau 蛋白病[15]的特征。在生理学上，tau 蛋白可结合并因此稳定微管(Microtubule, MT)，tau 蛋白与 MT 的结合受其磷酸化水平的调节，由激酶(Cdk5、GSK3β、MARK 和 ERK2)介导的 tau 蛋白磷酸化可能导致 tau 蛋白与 MT 的分离，从而引起 MT 解聚[16]。在病理状态下，激酶和磷酸酶之间的这种作用平衡被打破，激酶活性的增加和磷酸酶活性的降低会导致 tau 蛋白过度磷酸化。过度磷酸化的 tau 蛋白发生错误折叠，降低了 tau 蛋白与 MT 的亲和力，同时增加了 tau 蛋白的聚集和纤维化，聚集成成对螺旋细丝(Paired Helical Filaments, PHFs)。这些结构转变将导致更有组织的聚集，并最终在神经元内形成神经原纤维缠结(Neurofibrillary Tangle, NFT)，组成 AD 神经纤维缠结的主要成分。因此，tau 蛋白的过度磷酸化有助于微管的分解，导致神经元和突触结构受损，形成神经纤维缠结[2]。

2.3. 神经炎症

神经炎症可能在 AD 的进展和预后中发挥最决定性的作用。神经炎症假说是在 AD 患者的大脑中，

错误折叠和聚集的蛋白与小胶质细胞和星形胶质细胞上聚集和活化，识别受体结合引发的固有免疫反应，这决定了各种炎症通路的激活和炎症因子的释放。小胶质细胞在神经炎症中起重要作用，小胶质细胞是存在于哺乳动物大脑和 CNS [17]中的巨噬细胞样细胞。作为一种特殊类型的免疫胶质细胞，小胶质细胞被认为是 CNS 的"保护者"在 AD 患者的大脑中，小胶质细胞可以通过与 PRRs 结合的可溶性 Aβ 寡聚体和原纤维或细菌脂多糖(Lipopolysaccharide, LPS)被激活[18]。小胶质细胞吞噬增多的细胞外 Aβ 可引起溶酶体破坏和组织蛋白酶 B 释放到细胞质，触发炎症小体活化[17]。NLRP3 基因抑制已被证明可以保护 Aβ 沉积和记忆损害。因此，抑制小胶质细胞特异性 NLRP3 可降低 Aβ 胞外堆积，并改善突触功能，改善认知功能[19]。

3. 肠道微生物代谢调节对 AD 的影响

肠道微生物群将饮食成分(包括宏、微量营养素、纤维蛋白和多酚)转化为一系列代谢产物，包括短链脂肪酸、三甲胺、氨基酸衍生物和维生素。这些微生物衍生的代谢物和膳食成分具有重要的代谢和信号功能，可以调节宿主体内平衡，包括 BBB 的完整性和大脑功能[20]。除微生物或其结构成分外，肠道微生物代谢产物也进入宿主体内，如小鼠血液中大约 10%的代谢物来自微生物群[21]。尽管微生物产生的某些神经递质是否真的改变了内源性代谢尚待证实，但有些已被证明能激活肠－脑轴，并与内源性代谢的调节有关。例如，人们早就知道 γ 氨基丁酸是由肠道微生物群产生的，包括双歧杆菌和乳酸菌属[22]。越来越多的研究表明，在 AD 患者，肠道菌群与宿主的共代谢关系逐渐发生改变，会导致肠道菌群失调，微生物分泌及代谢产物失衡。肠道微生物群会分泌 LPS，LPS 则是由革兰阴性菌产生的强效促炎介质。Aβ 肽与 LPS 共孵育可增强淀粉样纤维的形成[23]。在野生型和转基因 AD 小鼠中，系统性注射 LPS 可导致更严重的 Aβ 沉积和 tau 蛋白病理[24]。随着年龄的增长，肠上皮通透性增加，促进革兰阴性菌和 LPS 进入血[25]。在革兰氏阴性细菌侵入肠道固有层和肠系膜淋巴结，导致肠道炎症反应，增加肠道和血脑屏障的通透性，LPS 进入大脑，因此许多 AD 患者海马和颞叶上新皮质内存在 LPS，与非 AD 对照组相比，AD 患者大脑中的 LPS 水平更高[26]，LPS 结合蛋白增加将会触发神经炎症。

4. 肠道异常微生物引起的炎症反应对 AD 的影响

4.1. 肠道异常微生物调节炎症反应机制

肠道微生物群产生的致病微生物代谢物、促炎细胞因子和其他分子，包括脂多糖，与神经元死亡和神经炎症有关[27]。研究证明 5xFAD 小鼠的 M1 极化神经炎症是肠道微生物群异常产生氨基酸(包括苯丙氨酸和异亮氨酸)的结果。与浸润 CNS 的 Th1 细胞串扰导致 M1 激活增加，导致病理性神经炎症和认知功能下降[28]。肠道菌群的异常导致重视 CNS 和单纯疱疹病毒性脑炎病理中聚集的单纯疱疹 1 型负担，这与过活化的小胶质细胞介导的神经炎症有关[29]。胃肠道炎症是先天性免疫防御的重要组成部分，通过修复内膜损伤和平衡肠道微生物群，维持肠道生理功能至关重要[30]。微生物群的异常，或广谱抗生素诱导的失调，触发了非肥胖糖尿病(Non-Obese Diabetes, NOD)样受体家族 pyrin 结构域(PYD)-含 6 (NLRP6)/Caspase 11 (Casp11)炎症体介导的通路，并随后导致 iEANs 的丢失和肠神经病变[31]。重要的是，这与胃肠道介导的并发症尤其相关，这些并发症通常与神经退行性疾病相关，胃肠道运动障碍、慢性低级别炎症和肠神经损伤被广泛观察到[32] [33]。如胃肠道炎症增加了肠道的通透性，从循环中吸收免疫细胞，但也允许炎症细菌成分穿过屏障进入外周循环系统，引发全身炎症[25]。当迷走神经感知到胃肠道炎症和促炎细胞因子产生的变化时，传入纤维将这一信息传递到大脑并影响神经炎症[34]。因此，肠道微生物群和相关代谢物的异常改变可能会导致炎症的系统性变化，这可能会导致 AD 的神经炎症[35]。

4.2. 肠道异常微生物对 AD 的影响

人类肠道由一组非常复杂的肠道微生物群组成，它们影响神经精神疾病的风险[36] [37]。每一种神经退行性疾病都有其独特的病理学和临床特征。然而，神经炎症和较高的肠道通透性是它们的共同特征[38]。研究发现细菌、病毒、原生动物和真菌是与AD相关的全身感染的潜在因素[39]。有证据表明，大脑中的真菌感染可伴有细菌感染，这表明AD患者大脑中的多微生物感染可能与发病机制和神经炎症有关[40]。AD患者与年龄相关的神经炎症的主要驱动因素是反应性胶质增生，或激活CNS的胶质细胞以预防和修复组织损伤[41]。高丰度的促炎肠道菌群伴随着增强的全身炎症和神经炎症过程。肠道生态失调导致小胶质细胞的成熟、分化和功能缺陷，其激活有助于AD的进展。几种肠道特异性微生物产生一氧化氮和无规聚丙烯(Atactic Polypropylene, APP)，激活小胶质细胞，从而加重AD的发展[42]。最近的研究表明肠道微生物群影响星形胶质细胞的功能，这种微生物产物LPS能促进星形胶质细胞产生炎症介质，导致神经退行性变[43]。三项研究表明，当AD患者与非失智、年龄匹配的对照组相比时，肠道菌群组成中SCFA产生菌的数量减少，促炎细菌数量增加[44] [45] [46]。人类肠道微生物群通过产生促炎细胞因子和细菌代谢物来影响AD患者的神经炎症，这些细胞因子和代谢物可以进入循环并到达大脑，对神经元免疫细胞群起作用[47]。此外，促炎性细胞因子一旦进入大脑就会增强Aβ沉积、tau磷酸化、小胶质增生和星形胶质增生，加重AD病理的严重程度[48]。

5. 肠道微生物对人体内的分布及作用

5.1. 实验动物模型研究和临床研究

人类肠道包含数万亿种不同的微生物。微生物群落多样性的丧失导致肠道生态失调，从而导致几种复杂的疾病[49]。近年来的许多研究强调了肠道微生物群在AD病理生理学中的作用[50] [51]。肠道微生物群能够参与AD病理生理学的证明主要来自实验室动物的研究。在这方面，用无啮齿动物病原体，即所谓的无菌病原体进行的研究是重要的。在这些动物中，观察到Aβ病理学显著减少，当小鼠暴露于对照小鼠的肠道微生物群时，这种情况再次出现[52]。最近，与未经治疗的AD小鼠相比，用益生菌治疗的转基因AD小鼠表现出更好的认知能力，并减少了海马中淀粉样斑块的数量[53]。在另一项研究中，记录了益生元给药后对转基因AD小鼠认知功能的类似影响[54]。在人类中，许多研究最近也表明，病毒或细菌感染可能是AD的触发原因之一。已经表明，慢性螺杆菌、幽门与未受感染的患者相比，AD患者的感染会触发炎症介质的释放，并与简易智力状态检查量表(Mini-Mental State Examination, MMSE)评分降低相关[55]。一项比较25名AD患者和25名对照者的微生物群的研究显示，AD患者的微生物多样性降低。此外，观察到厚壁菌门数量的减少和拟杆菌门百分比的增加[56]。另一项比较非失智患者和失智患者的微生物组的研究发现，与非失智患者相比，失智患者中的类杆菌减少[57]。此外，已经从日本AD患者的微生物群中分离出了参与认知功能的可培养的产丁酸盐细菌[58]。接下来的研究提供了证据，在对中国AD和轻度认知障碍患者以及健康人的研究中，与轻度认知障碍患者和健康受试者相比，AD患者粪便的微生物多样性降低。此外，厚壁菌门的数量减少，变形菌门的数量增加[59]。

5.2. 益生菌补充剂对 AD 效益

益生菌是对接受者的健康有有益作用的细菌，而益生元主要是作为这些细菌的食物的纤维物质[60]。评估益生菌用于治疗各种胃肠道疾病的临床试验正在进行中，其中许多已经显示出非常有利的结果[61]。其他研究发现：肠道微生物群落可以帮助预防AD的发展，部分是通过支持SCFA的产生，从而干扰有毒的可溶性淀粉样聚集体的形成[62]。口服短双歧杆菌A1改善了在AD小鼠中观察到的认知衰退。基因图谱

分析显示，食用短双歧杆菌A1抑制了由Aβ诱导的海马和免疫反应基因中的炎症[63]。同一组进行的一项研究表明，补充短双歧杆菌A1可以对有记忆问题的老年人的认知功能产生有益影响[64]。另一项研究表明，摄入乳制品中的生物活性肽可以改善认知功能[59]。此外，涉及1056人的流行病学研究显示，饮食中摄入奶酪与认知障碍患病率较低有关。此外，一项对1006名年龄在60~80岁的无失智症的日本人进行的为期15年的观察研究表明，大量食用牛奶和乳制品可降低失智症的风险[59]。数据清楚地表明，以大量摄入益生元和益生菌为特征的健康饮食模式与其他营养成分相结合，可以延缓认知能力下降，降低患AD的风险[65]。此外，已经表明食用含有益生菌发酵乳制品不仅影响正常的大脑活动，还能显著改善AD患者的认知能力[66]。这些效应可由肠道微生物群落的恢复引起[66]。在这一点上，我们可以认真考虑用前、前或抗生素改变肠道微生物区系，以获得预防和治疗AD的有益效果[55]。

6. 结论与展望

综上所述，虽然有许多因素会导致AD的发生，如遗传、生活方式等，但有证据表明肠道微生物代谢调节对认知功能的发展、大脑健康和神经退行性变存在潜在的影响。由于肠道异常微生物引起的炎症反应会加剧AD的发生及病情恶化。而AD的高发期是65岁以上老年群体，肠道微生物群在老年人体内会影响星形胶质细胞的功能，加重AD病理严重程度。随着年龄的增加，肠道功能在逐渐的减弱，更容易发生AD，对此老年群体的肠道方面也应得到重视。适量摄入益生元和益生菌为特征的健康饮食可延缓认知下降，从而降低或预防患AD的风险。同时，补充短双歧杆菌A1也可提高老年人认知功能。肠道菌群失调对AD疾病的发生、发展有着重要影响，通过调节肠道菌群来改善AD疾病的预后，将是未来的重要发展方向。

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