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肠道内产丁酸细菌与神经变性疾病的相关性研究进展

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摘　要

产丁酸细菌(Butyric acid producing bacteria, BAPB)是利用碳水化合物发酵产生丁酸的一类细菌，其主要代谢物丁酸能促进肠道黏膜及血脑屏障完整性防止有害物质进入大脑引起神经元损伤。丁酸是BAPB的主要产物，发挥抗炎、抑制细胞增殖、诱导免疫耐受及促进黏膜屏障完整性等作用。大量的研究表明，BAPB的丰度和丁酸的水平在不同的神经变性疾病中均显著下降。因此提高BAPB丰度及促进丁酸产生可能成为神经变性病干预中的新靶标。本文一方面介绍了神经变性疾病的发病机制以及丁酸的生理功能，另一方面综述了与神经变性病相关的BAPB的种类及特点，目的是提供更全面的与变性疾病相关的BAPB类型，为进一步研究提供可选择的靶细菌。

关键词

产丁酸细菌，丁酸，神经变性疾病

Research Progress on the Correlation between Butyric Acid Producing Bacteria in Intestine and Neurodegenerative Diseases

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Abstract

Butyric acid producing bacteria (BAPB), a class of bacteria using carbohydrate fermentation to produce butyrate, can promote the integrity of intestinal mucosa and blood-brain barrier and prevent harmful substances from entering the brain through microbial gut-brain axis causing neuronal damage. Butyrate is the main product of BAPB, which plays the role of anti-inflammation, inhibiting cell proliferation, inducing immune tolerance and promoting the integrity of mucosal barrier. A large number of studies have shown that BAPB abundance and butyric acid levels are significantly decreased in different neurodegenerative diseases. Therefore, remodelling the intestinal flora, especially increasing BAPB abundance, may be a new target for intervention in neurodegenerative diseases. On the one hand, the physiological function of butyric acid and the role of the gut-brain axis in BAPB and diseases are introduced. On the other hand, the types and characteristics of BAPB associated with neurodegenerative diseases are reviewed; the aim is to provide a more comprehensive version of BAPB associated with degenerative diseases and to provide an alternative strain of intervention for further research.

Keywords

Butyric Acid Producing Bacteria (BAPB), Butyrate, Neurodegenerative Diseases

1. 介绍

人类肠道中大约含有 10^{14} 个细菌，1000 多个物种[1]。肠道内细菌主要存在于结肠，据估计，结肠有 300~400 种[2]细菌，其中门水平以厚壁菌门(Firmicutes)和拟杆菌门(Bacteroidetes)为主。产丁酸细菌(Butyric acid producing bacteria, BAPB)主要隶属于厚壁菌门，可通过消化膳食纤维产生丁酸。丁酸参与人体多种代谢活动，介导着丰富的生化反应，维持机体内环境稳态。大量研究表明，微生物菌群失调会破坏肠粘膜屏障及血脑屏障并激活炎症信号通路，通过释放大量炎症因子介导神经、内分泌及免疫途径干预神经细胞的免疫功能及能量代谢水平，最终发展为神经变性病。

阿尔兹海默病(Alzheimer's disease, AD)是老年期最常见的痴呆类型，到 2050 年，全世界将有 1 亿多 AD 患者[3] [4]，给世界经济造成巨大压力，然而目前仍缺乏延缓疾病进展的有效治疗。AD 以细胞外 β-淀粉样蛋白(Amyloid-beta protein, Aβ)沉积形成老年斑、细胞内 Tau 蛋白过度磷酸化导致的神经元纤维缠结以及小胶质细胞增生为主要病理机制。临床上患者主要表现为进行性认知功能障碍、日常生活能力减退及丰富的精神行为症状，后期会因生活能力完全丧失出现并发症而最终死亡。帕金森病(Parkinson' disease, PD)是仅次于阿尔茨海默病的第二大中枢神经系统退行性疾病，流行病学调查显示，目前全球约 600 多万人患有 PD，据估计，到 2030 年我国将有 500 多万 PD 患者[5]。PD 是一种以黑质致密部多巴胺神经元选择性凋亡及残余神经元中路易小体沉积为主要病理特征的神经变性疾病。PD 患者主要临床表现为运动迟缓、肌强直、静止性震颤、姿势不稳。既往研究表明，遗传因素、环境因素、衰弱、氧化应激均可能参与多巴胺能神经元的变性[6]。然而目前尚不清楚导致 PD 这一病理改变的确切原因。来自粪便样本的 16S rRNA 测序数据表明，AD 和 PD 患者肠道微生物菌群多样性及丰度与健康对照组相比有显著性变化，其中以 BAPB 丰度下降和肠杆菌丰度增高为主要特征[7]。本文就肠道菌群与 AD、PD 发生机制

的联系、丁酸的生理功能及神经变性病相关的 BAPB 的种类及特点进行总结，旨在于为 AD、PD 的治疗提供相关依据。

2. 肠道菌群与肠脑轴的联系

微生物肠脑轴(Microbiota-gut-brain-axis, MGB)是由肠道微生物群、肠道及神经系统共同构成，是人体的“第二大脑”。MGB 在肠脑交互作用中发挥重要作用[8]，大量研究均提示 MGB 可以通过迷走神经、神经内分泌、细胞免疫等途径将肠道细菌的代谢产物运输至延髓、脑干及大脑，调节神经炎症、黏膜屏障功能和神经递质活性从而参与神经变性疾病的发生。Braak 和他的同事[9]发现异常折叠的 α-突出核蛋白始于肠道，经延髓、迷走神经背核、嗅球到中脑黑质致密部，最后累及前脑。消化性溃疡患者接受迷走神经切断术后发生 PD 的风险显著下降。临床上 PD 患者首先出现便秘、嗅觉障碍等非运动症状，大约 10 年后才出现运动症状。有意思的是，人体 90%的血清素和 50%的多巴胺都在肠道中产生，肠道微生物通过调节神经递质影响神经系统。近期研究发现补充益生菌和粪便移植[10]可能改善紊乱的肠道菌群来延缓疾病。综上所述，肠道菌群诱导神经变性疾病发生可能与 MGB 有关。

3. 丁酸盐的功能

短链脂肪酸(Short chain fatty acids, SCFAs)是肠道膳食纤维经细菌发酵后形成的产物，主要包括丙酸、丁酸和戊酸。BAPB 是以产生丁酸为主要特征的一类细菌，在健康人群及长寿老人肠道菌群中丰度较高。作为肠脑交互作用的中间代谢物，丁酸能促进肠道黏膜的完整性和增强机体免疫功能[11]。越来越多的研究表明，丁酸盐(Sodium Butyrate, NaB)功能丰富，例如与细胞表面 GPR43 或 GPR109A 受体偶联缓解肠道炎症、通过调节线粒体功能来减轻氧化应激[12]，通过转运体和溶质载体家族 5 成员 8 (SLC5A8)调节肠道紧密连接蛋白[13]、增加小鼠杯状细胞数量及 Muc2 表达来促进肠道上皮完整性及降低 DNA 氧化损伤作用[14]。研究表明 NaB 通过抑制 HDAC 影响蛋白表达来改善 6-OHDA 诱导的大鼠认知及运动症状[15]。有趣的是，NaB 还能改善 AD 小鼠认知障碍并且降低脑内 Aβ 沉积[16]，NaB 能直接结合和激活游离脂肪酸受体(FFAR)2 和 FFAR 3 发挥抗 PD 作用。总之，丁酸盐为结肠细胞提供能量，同时通过免疫炎症通路等途径参与神经变性病的发生过程中。

4. AD 发生机制及与肠道菌群的关系

由于衰老及病理因素存在，正常可溶的 Aβ1-40 因淀粉样前体蛋白(APP)基因、早老素 1(PS1)、PS2 或载脂蛋白 E (Apolipoprotein E, APOE4)基因突变形成更易聚集的 Aβ1-42，同时因 AD 患者单核巨噬细胞功能下降引起 Aβ 生成和清除平衡被打破最终导致 AD 产生。研究表明 Aβ 主要沉积在海马区，一方面通过破坏细胞内钙离子稳态激活细胞周期素依赖性激酶-5 (CDK5)导致 tau 的磷酸化，另一方面促进自由基形成引起氧化应激以激活 Toll 受体(Toll-like receptor, TLR)及激活小胶质细胞释放 TNF-α 和 IL-1β、IL-18 和炎症小体 NLR (Nod 样受体)等炎症因子参与中枢神经系统炎症反应，加速 AD 进展[17]。目前具体机制尚不清楚，大量研究已证实肥胖、胰岛素抵抗、环境、高脂饮食、衰老、APOE 基因突变及肠道菌群失调是认知障碍的危险因素[18]。研究发现与健康组相比，AD 患者的 BAPB 丰度及丁酸水平下降，同时也发现丁酸能阻断 Aβ 沉积[8]。一项动物实验也证明丁酸通过促进前额叶皮质区(pre-frontal cortex, PFC)髓鞘的生成改善抗生素处理的幼年小鼠成年后的认知水平[19]。综上所述，恢复肠道菌群多样性可能通过增加丁酸水平来缓解 AD 进展[20]。

5. PD 发生机制及与肠道菌群的关系

PD 患者的尸检发现，黑质致密部存在 α-突触核蛋白聚集形成的路易小体。有意思的是，PD 动物模

型研究发现，肠神经系统内的 α-突触核蛋白能通过迷走神经转运到脑干黑质纹状体系统形成路易小体[21] [22]。正常情况下 α-突触核蛋白高度可溶，相反在病理状态下，α-突触核蛋白极易聚集成不溶的纤维蛋白沉淀，一方面可能是因 DJ-1、LRRK2 [23]及葡糖脑苷脂酶(GBA)基因突变[24]等引起 α-突触核蛋白降解异常导致 α-突触核蛋白病发生，另一方面模式识别受体 TLR4 特异性结合细菌代谢物脂多糖并激活 TLR4-MyD88-NF-κB 信号通路产生炎症因子，同时削弱小胶质细胞对 α-突触核蛋白的吞噬作用，超载的 α-突触核蛋白聚集形成路易小体沉积在黑质纹状体系统[25]。肠道菌群和炎症细胞因子相关性分析表明 PD 患者血浆中 TNF-α 和 IFN-γ 显著高于健康对照组并且与菌群多样性相关[26]。一项回顾性队列研究表明，与健康对照组相比，PD 患者外周血中性粒细胞比淋巴细胞比值升高[27] [28]。在 PD 患者及动物模型中也发现渐进性 DA 神经元死亡的 IFN-γ 信号，而且 IFN-γ 信号基因和编码 α-突触核蛋白的基因 SNCA 基因共表达[29]。临床上观察到 IBD 患者更容易发生 PD，其黏膜屏障紧密连接蛋白的缺乏会增加肠道黏膜及血脑屏障通透性进一步损伤神经元。综上所述，肠道菌群失调通过炎症反应、氧化应激等引起 PD 发生。

6. 产丁酸细菌代表菌特征及与 AD、PD 联系

6.1. 普氏栖粪杆菌 *Faecalibacterium prausnitzii*

F. prausnitzii 属于厚壁菌门、梭菌科，柔嫩梭菌属，是不产芽孢严格厌氧的革兰阴性菌，处于“专性厌氧菌”中氧气耐受的极末端，是健康人群粪便中检测到最丰富的细菌之一，约占粪便细菌总数的 5% [30]。*F. prausnitzii* 的抗炎作用在临床资料中得到证实[31]，其上清液和代谢物丁酸均能抑制炎症细胞因子 IL-8 发挥抗炎作用。近期，以 *F. prausnitzii* 作为干预菌种的一项动物研究表明，与 AD 组和轻度认知障碍组(MCI)相比，健康组的 *F. prausnitzii* 丰度高，给予 AD 小鼠口服 *F. prausnitzii* 后认知障碍改善[32]。PD 患者肠道菌群中 *F. prausnitzii*、Enterococcaceae 丰度较年龄匹配的健康组低，同时其代谢物乙酸、丙酸。丁酸水平均减低[33]。

6.2. 罗氏菌属 *Roseburia*

Roseburia 属于厚壁菌门、梭菌纲、梭菌目和毛螺菌科，是轻微弯曲，含鞭毛，杆状专性厌氧的革兰氏阳性细菌，自人类粪便样本分离出[34]。近期一项基于机器学习预测 AD 模型的研究表明，*Roseburia hominis* 丰度下降与磷酸化 Tau 蛋白较高有关[35]。XIE A 等发现 *Roseburia*，*Romboutsia*，and *Prevotella* 丰度与 PD 患者抑郁症状呈负相关[7]。

6.3. 真杆菌 *Eubacterium*

直肠真杆菌 *Eubacterium rectale* 是厚壁菌门、梭菌目、毛螺菌科厌氧革兰阳性菌，多呈直杆状或稍微弯曲。近期 Lu H.等[36]发现与移植健康人群粪便的小鼠相比，通过补充 *E. rectale* 能抑制 TLR4/MyD88/NF-κB 通路减轻接受淋巴瘤患者粪便移植的小鼠体内 TNF 水平并改善肠道微环境。霍氏真杆菌 *Eubacterium* hallii 是兼性厌氧革兰阴性菌。孟德尔随机化分析表明，*Eubacterium*、*Blautia* 与 AD、重度抑郁及精神障碍有关[37]。对 31 名 PD 患者和 28 名健康对照粪便宏基因鸟枪测序分析提示 PD 患者 *Eubacterium biforme* 丰度下降[38]，Prevotellaceae、*Akkermansia muciniphila* 丰度增高。

6.4. 臭杆菌属 *Odoribacter*

Odoribacter 属拟杆菌门，是普遍存在于人类肠道的一类产丁酸的厌氧菌。*Odoribacter* 丰度下降与多种有关，如非酒精性脂肪肝、囊胞性纤维症和炎症性肠病[39]。结肠辅助性 T 细胞 17 (T helper cell 17, Th17)具有免疫抑制功能，有研究证明了内脏臭杆菌 *Odoribacter splanchnicus* 是一种诱导 Th17 分化来保护小鼠免受结肠炎和结直肠癌的细菌[40]。针对 AD 和野生型小鼠粪便 16SrRNA 分析表明，AD 小鼠 *Odoribacter*

在属水平上的丰度显著高于野生型小鼠，而在野生型小鼠中 *Prevotella* 的丰度显著高于 AD 小鼠[32]。6-OHDA 和抗生素诱导的双打击 PD 小鼠模型实验表明，与假手术组和 6-OHDA 组相比，目标模型组 *Odoribacter*、*Bacteroides*、*Prevotella*、Lachnospiraceae、Papillibacter 丰度下降，然而唯一增加的是 *Ruminococcus*，给予丁酸钠干预后与假手术组相比，*Odoribacter*、*Prevotella*、*Dorea* 丰度增加，*Butyricicoccus*、*Ruminococcus*、*Oscillospira* 丰度下降[41]。

6.5. 布劳氏菌 *Blautia*

Blautia 属于厚壁菌门毛螺菌科产丁酸和乙酸的厌氧菌[42]，由 Liu 等人于 2008 年首次提出。*Blautia intestinalis* sp. nov.是从中国一名自闭症儿童的粪便标本中分离到一株严格厌氧细菌，相比于健康儿童，自闭症患儿 *Blautia* 属丰度下降[43]。有意思的是，*Blautia* 与 AD 发生风险关联方向的研究有差异，但一致的是 *Blautia* 依赖的精氨酸代谢的下游产物 GABA 与 AD 风险的降低有关[37]。近期 Guo X. [44]等发现 *Blautia* 是一个在 PD 的粪便、血液及大脑样本中持续消耗的独特菌属，而且该菌属的丰度与能量代谢有关，对神经系统退行性疾病和代谢疾病有同样作用[44]。

6.6. 丁酸梭菌 *Clostridium butyricum*

C. butyricum 属于厚壁菌门芽孢杆菌科梭状芽孢杆菌属，是产芽孢严格厌氧的革兰氏阳性菌。*C. butyricum* 通过增长肠道微绒毛、增加粘膜层厚度和上调紧密连接蛋白的表达以及增加脑源性神经营养因子和胰高血糖素样肽(GLP-1)来激活脑内 Akt 通路增加肠道黏膜屏障紧密连接作用[45]。研究发现，Akt 信号通路的失调与神经退行性疾病和代谢性疾病以及癌症有关[46] [47] [48]。Sun 等证明口服 *C. butyricum* 可防止 APP/PS1 转基因小鼠认知障碍、脑内 Aβ 沉积以及提高丁酸水平[49]。同时丁酸梭菌还能通过 GLP-1 途径改善 PD 小鼠的运动障碍[50]。

6.7. 普雷沃菌属 *Prevotella*

Prevotella 属于拟杆菌门普氏菌科，是非运动性、杆状厌氧革兰氏阴性菌，主要存在于黏膜表面，已从口腔、胃肠道及泌尿生殖道分离出。*Prevotella* 含有黏液蛋白降解相关酶，可能导致肠道通透性增加。研究发现，*Prevotella* 丰度在自闭症、过敏及多发性硬化患者中显著下降，而在局部和全身炎症明显的患者中丰度较高，如细菌性阴道病、肥胖、炎症性肠病、牙周炎、类风湿性关节炎等[51]。载脂蛋白 E 靶向替代(APOE-targeted replacement, APEO-TR)转基因小鼠肠道菌群中 Prevotellaceae、Ruminococcaceae 及几种产丁酸细菌丰度较正常小鼠下降[52]。

6.8. 嗜黏蛋白阿克曼氏菌 *Akkermansia muciniphila*

Akkermansia muciniphila 是人类肠道中疣微菌门(Verrucomicrobia)的唯一代表，是可以分解黏蛋白的一种革兰阴性菌。研究表明，粪便样本测序表明该菌的丰度在代谢性疾病、AD、PD [53]和结直肠癌患者中显著增加。另有研究发现人类粪便中 *Akkermansia* 的丰度与内侧颞叶萎缩正相关[53]。*Akkermansia muciniphila* 灌胃后显著增加了 AD 小鼠肠道微生物群落的多样性[54]，并降低了厚壁菌门与拟杆菌门的比值，而这一比例曾被证明与炎症增加有关[55]。一项通过肠道菌群预测 PD 早期进展的随机森林模型表明，*Akkermansia* 丰度增加以及 *Faecalibacterium* 和 *Blautia* 丰度下降预示着 PD 快速进展。

6.9. 瘤胃球菌 Ruminococcaceae

Ruminococcaceae 是厚壁菌门毛螺菌科的一种革兰氏阳性厌氧细菌，可为肠道上皮细胞提供 70%的能量。一项横断面研究证实了肠道菌群中的瘤胃球菌与多个代谢综合征相关[56]。研究发现地中海生酮饮食

[57]能增加产丁酸菌 Ruminococcaceae 的丰度，延缓 AD 发展。

6.10. 丁酸单胞菌 *Butyricimonas*

Butyricimonas 属拟杆菌门厌氧菌，是产丁酸细菌之一。在未经治疗的多发性硬化患者中，该菌数量减少。一项针对 AD 患者粪便 16S rRNA 基因结果表明与健康组相比，AD 组中产丁酸细菌 *Prevotella*、*Butyricimonas* 丰度下降，*Akkermansia*、*Dorea*、*Blautia* 丰度增加[53]。研究发现，PD 患者肠道中该菌丰度显著高于健康对照组[26]。

6.11. 丁酸弧菌 *Butyrivibrio*

Butyrivibrio 是厚壁菌门梭状芽孢杆菌目毛螺菌科的一种产丁酸的厌氧菌。与野生型 AD 小鼠相比，AD 小鼠 *Butyrivibrio* 丰度较低[58]。粪便菌群宏基因组测序结果表明，与健康组相比，PD 患者肠道菌群中毛螺菌科显著丰度显著下降，主要包括 *Butyrivibrio*、假丁酸弧菌(*Pseudobutyrivibrio*)、粪球菌(*Coprococcus*)以及 *Blautia*[59]。

6.12. 丁酸球菌 *Butyricicoccus*

Butyricicoccus 是厚壁菌门梭状芽胞杆菌目的厌氧菌。一项针对 AD 患者粪便 16S rRNA 基因结果表明，与健康组相比，*Butyricicoccus*、*Faecalibacterium* 丰度与简易智力状况表(MMSE)正相关[53]。MMSE 是认知障碍评分量表，MMSE 评分越低认知障越严重。

6.13. 粪肠球菌 *Enterococcus faecalis*

Enterococcus faecalis 属于厚壁菌门肠球菌科，是过氧化氢阴性的革兰阳性球菌，其产物天然抑菌物质可以改善肠道微环境。*Enterococcus faecalis* 可能促进 AD 病理进展[60]。

6.14. 颤螺菌属 *Oscillospira* 和 *Dorea*

Oscillospira 属于厚壁菌门瘤胃球菌科，是厌氧的革兰阳性细菌属，与肥胖、消瘦、胆结石及慢性便秘有关。研究表明，*Blautia* 和 *Dorea* 丰度与 MMSE 负相关[53]。

6.15. 粪球菌属 *Coprococcus*

Coprococcus 属厚壁菌门毛螺菌科，是不运动、严格厌氧的革兰阳性菌，在抑郁、PD、AD、多发性硬化患者粪便中丰度较低[61]。

7. 小结

肠道微生物失调在神经系统疾病发生发展中有重要作用，而产丁酸菌可以通过重塑肠道菌群改善黏膜通透性延缓疾病进展。随着脑肠轴的提出，研究人员相继发现肠心轴、肠肺轴、肠淋巴轴、肠肝轴等，提示我们肠道微生物群通过特定轴影响人体不同方面，饮食、环境、情绪及睡眠等诱因能引起肠道微生物失平衡出现一系列相关症状。AD 和 PD 患者肠道菌群多样性不同，多数 BAPB 在 AD 和 PD 中均下降，某些 BAPB 只与 PD 或者 AD 有关，有趣的是一些 BAPB 在 AD 患者中减少而在 PD 患者中可能升高。目前对 AD 和 PD 的菌群干预治疗仍仅限于成熟细菌，对其它有积极作用的 BAPB 需进一步在动物体内验证并明确具体机制，为神经变性疾病提供新的靶标及依据。

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