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基于脑－肠轴理论探析阿尔茨海默病作用机制

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摘　要

阿尔茨海默病(Alzheimer's disease, AD)是一种神经退行性疾病，主要表现为认知障碍。近年来出现的脑－肠轴学说提供了AD新的研究方向。老年时期微生物群组成的显着变化可能在神经退行性疾病的发展中发挥重要作用，AD与衰老密切相关。本文通过微生物作用探讨脑肠轴与AD之间的联系，结合AD的发病机制与脑－肠轴学说的基本原理，对微生物的作用机制论述脑－肠轴学说的出现对AD的影响。AD病理包括淀粉样蛋白假说、tau蛋白过度磷酸化以及神经炎症等。微生物异常可介导神经炎症，进而影响AD病理进程。肠道微生物及其代谢产物影响血脑屏障(blood brain barrier, BBB)通透性，BBB调节功能受损，微生物及其有害代谢产物进入并影响大脑活动。因此，肠道微生物群的恶化可能导致脑功能障碍。而甘露特钠作为国际首个靶向脑肠轴的AD治疗新药，可预见的未来靶向肠道菌群治疗AD可能成重要的研究方向，为药物研发提供了全新的干预方法。

关键词

阿尔茨海默病，脑-肠轴学说，肠道微生物，甘露特钠

To Explore the Mechanism of Alzheimer's Disease Based on Brain-Gut Axis Theory

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Abstract

Alzheimer's disease (AD) is a kind of neurodegenerative disease, mainly manifested by cognitive impairment. In recent years, the brain-gut axis theory has provided a new research direction for AD.

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Significant changes in the composition of the microbiome in old age may play an important role in the development of neurodegenerative diseases, and AD is closely associated with aging. In this paper, the relationship between brain-gut axis and AD was investigated through microbial action. This paper combined the pathogenesis of AD with the basic principle of brain-gut axis theory, and discussed the effect of brain-gut axis theory on AD by the mechanism of microbial action. The pathology of AD includes amyloid hypothesis, tau hyperphosphorylation and neuroinflammation. Microbial abnormalities can mediate neuroinflammation, and then affect the pathological process of AD. Intestinal microorganisms and their metabolites affect the permeability of blood brain barrier (BBB), and the regulatory function of BBB is impaired. Microorganisms and their harmful metabolites enter and affect brain activities. Thus, deterioration of the gut microbiome may lead to brain dysfunction. As the first AD treatment drug targeting brain-gut axis in the world, Sodium Oligomannate become an important research direction for the treatment of AD targeting intestinal flora in the foreseeable future, providing a new intervention method for drug development.

Keywords

Alzheimer Disease, Brain-Gut Axis Theory, Enteric Microorganism, Sodium Oligomannate

1. 引言

阿尔茨海默病(alzheimer disease, AD)是一种进行性神经退行性疾病，到 2050 年，我国将有 800~1100 万 AD 患者[1]。AD 占全球失智症的 80%，尤其是 60 岁以上的老年人[2]。不溶性淀粉样蛋白(beta-amyloid, Aβ)胞外斑块和 P-tau 的神经纤维缠结(neurofibrillary tangles, NFT)是 AD 的特征[3]。AD 的病因是行为、遗传和环境危险因素的复杂组合，这些因素源自致病机制，最明显的是 Aβ 的异常积累、tau 蛋白过度磷酸化[4]。累积的 Tau 和 Aβ 病变，随后是大脑的细胞功能障碍，导致神经退行性变，在 AD 的临床表现之前不久发生，即认知障碍的发生[5]。轻度认知障碍(mild cognitive impairment, MCI)或轻度神经认知障碍是一种中间状态介于正常衰老和失智之间。这种状态可以进展为失智，主要以 AD 的形式出现[6]。研究表明，使用 Aβ 和 Tau 生物标记物可以在 AD 的早期阶段，即 MCI 患者中识别 AD，并对不典型表现的患者进行鉴别诊断[7]。此外，除了导致 AD 发病的遗传危险因素外，一些后天因素，如脑血管疾病、糖尿病、高血压、肥胖、血脂异常和微生物失调，也会增加患 AD 的风险[8]。肠道微生物群和大脑之间的双向交流被称为“肠－脑轴”，它与神经元发育、大脑功能、认知调节和衰老有关[9]。脑－肠道微生物群轴是连接肠道和大脑的通讯网络[10]。大脑通过固有层细胞释放信号分子或调节胃肠道的运动、分泌物和通透性，可以直接或间接地影响肠道微生物群的组成和功能[10]。肠道微生物群通过多种途径与 AD 的发病机制相互作用：神经炎症、Aβ 异常、Tau 磷酸化、神经递质失调和氧化应激(oxidative stress, OS)。这些途径在微生物群组成紊乱后失调，并与促进神经炎症、神经细胞丢失和最终 AD 的血脑屏障(blood-cerebral barrier, BBB)通透性增加有关[11]。本文通过对脑－肠轴与 AD 之间的作用机制展开综述。

2. AD 的发病机制

2.1. Aβ 沉积

Aβ 是淀粉样前体蛋白(amyloid precursor protein, APP)的切割产物，APP 是一种 695~770 个氨基酸的

单膜跨越蛋白，在神经系统中强烈表达。Aβ 主要在内体中产生，其释放到细胞外空间受突触活性的影响[12]。Aβ 是具有自聚集特性的独特蛋白质，其积累可导致细胞功能障碍[13]。Aβ 的形成是引发所有其他与 AD 相关的病理现象的起点，并最终在大脑中沉积 Aβ 斑块[14]。在 AD 中，细胞外 Aβ 斑块形成于基底部、颞部和眶前额皮质。在严重的 AD 病例中，斑块扩散到海马体[15]。一项研究表明脑脊液 Aβ 水平随年龄的增长而降低，这表明随着时间的推移，Aβ 在大脑中的沉积增加[16]。Aβ 的积累与突触和神经元损伤密切相关，进而导致神经元逐渐死亡和皮质及皮质下结构的恶化，即脑萎缩[17]。高水平的 Aβ 的产生与其他关键事件直接相关，如缠结的形成、神经元的丢失、突触的丢失和神经传递的功能障碍[18]。Aβ 和早期细胞内 Aβ 的过度表达形成导致不同的线粒体功能障碍(线粒体的内部运输、轴突运输和突触耗竭)[19]。Aβ 可能通过与线粒体裂变蛋白、动力蛋白相关蛋白 1 相互作用改变线粒体动力学[20]。此外，由于线粒体 DNA 缺失而缺乏功能性呼吸链，$A\beta_{25-35}$ 未能诱导活性氧(reactive oxygen species, ROS)生成、caspase 激活或细胞色素 c 释放[21]。Aβ 还通过影响促生存蛋白 Bcl-2 而导致线粒体功能紊乱，Bcl-2 家族蛋白触发线粒体介导的 caspase 通路，释放细胞色素 c，最终导致细胞凋亡[22]。Aβ 的沉积也可发生在毛细血管壁、动脉和小动脉中，引起淀粉样脑血管病，导致血管壁成分退化和血流恶化，此外还容易引起脑实质内出血[23]。

2.2. Tau 蛋白过度磷酸化

Tau 是一种微管相关蛋白，调节微管蛋白组合的稳定性，主要集中在轴突中，但也存在于树突中[24]。病理学上，AD 与 Aβ 斑块和高磷酸化和错误折叠的 Tau 蛋白的毒性积聚有关，Tau 蛋白在海马体启动并最终扩散到皮质[25]。过度磷酸化的 Tau 蛋白是 AD 患者大脑中 NFT 的主要成分，其进化可以反映 NFT 的形态阶段，其中包括：1) 预缠结期，一种 NFT，磷酸化的 Tau 蛋白积聚在生长树突状区室中而不形成螺旋丝，2) 成熟的 NFT，其特征是 Tau 蛋白的丝状聚集，细胞核向体细胞的外围部分位移，3) 细胞外缠结或幽灵 NFT 阶段，这是由于大量丝状 Tau 蛋白引起的神经元丢失，对蛋白水解有部分抵抗力[26]。另外，Aβ 激活 GSK-3β 和 CDK-5 磷酸化 Tau 蛋白，激活 caspase-3 和 calpain 1 水解 tau 蛋白，形成 tau 寡聚物[27]。Tau 寡聚物是 Tau 的一种中间形式，在 NFT 形成之前就出现了，是有毒的[28]。Tau 蛋白一旦过度磷酸化，就会失去其在微管合成和稳定中的功能，导致神经元损伤和促进细胞毒性[29]。

2.3. 氧化应激

OS 是 ROS 产生超过细胞抗氧化防御系统的一种状态[30]。中枢神经系统特别容易受到 OS 的影响，原因包括其高耗氧量、在信号传递过程中使用不同的活性物质以及缺乏抗氧化代谢[31]。促氧化剂损伤水平的增加和抗氧化防御机制的减弱在老年人中最常见，这表明老年人口受相关破坏性退行性疾病的影响最大[32]。OS 可加速 Aβ 沉积，并引发氧化反应[33]。体外和体内研究表明，OS 引起的蛋白磷酸酶 1/蛋白磷酸酶 2A (PP1/PP2A)失活与 Tau 蛋白的过度磷酸化和细胞外受体激酶(ERK) 1/2 的延长磷酸化有关[34]。线粒体功能障碍可能与 AD 发病和进展过程中氧化应激的启动和/或扩增有关[35]。从将线粒体功能障碍和 ROS 产生增加与 AD 发展联系起来的观察中，出现了对疾病机制的另一种解释[36]。有证据表明，OS 与 AD 的几个主要病理过程密不可分，包括 Aβ 诱导的神经毒性、Tau 病理学、线粒体功能障碍[37]。线粒体功能障碍和随之而来的更大的 OS 及其相互作用有可能形成一个恶性循环，成为 AD 患者普遍存在的细胞功能不全、代偿不足和变性的特征[35]。

2.4. 脑－肠轴学说

人体微生物群具有免疫系统稳态、调节宿主代谢、防止病原体入侵和改善上皮屏障功能等重要的生物学功能[38]。微生物群－肠－脑轴已成为生物医学研究治疗中枢神经系统疾病潜在治疗靶点的焦点，通

过神经、内分泌、免疫和代谢途径将肠道微生物群与中枢神经系统(central nervous system, CNS)连接起来，这对于维持大脑稳态至关重要[39]。肠道－脑轴微生物群的功能障碍与 AD 的发病机制有关[40]。哺乳动物肠道微生物群包括细菌、病毒、真菌、酵母菌和噬菌体，这个群体在出生时就开始发育，在人类体内持续 2~3 年，直到达到稳定的组成[41]。肠道微生物群落的组成在整个生命周期中不断变化，肠道微生物通过促进宿主消化能力，促进信号转导途径和调节免疫功能的物质的产生[42]。肠道微生物群也能以神经递质的形式接收来自大脑的信号，包括乙酰胆碱、修饰的氨基酸谷氨酸和 γ-氨基丁酸，以及生物胺多巴胺、血清素和组胺，与大脑相互作用[43]。此外，肠道微生物多样性和密度的变化会导致全身性和神经性炎症以及小脑和海马体的功能障碍[44]。肠道微生物多样性不足会导致免疫效能下降、外周炎症增加和屏障通透性增加，所有这些都可能扰乱大脑的稳态，最终导致 AD 的发病[45]。

3. 肠道菌群对 AD 的潜在作用

3.1. 肠道菌群在 AD 中的变化

目前，广泛使用的 AD 模型是三重转基因 3xTg-AD 小鼠，它携带三个突变的转基因(人类 $PS1_{M146V}$，APP_{Swe} 和 Tau_{P301L})，并出现进行性、年龄依赖性 Aβ 斑块和 NFT，以及记忆缺陷。转基因小鼠模型是破译 AD 病理机制和疾病机制某些方面的宝贵工具[46]。大多数转基因啮齿动物模型是在小鼠中开发的，并且具有针对 APP 和 PS1 基因的突变[47]，和外源性人类 tau 突变(h-Tau)，分别改变 APP 和 tau 加工，加速 AD 病理[48]。研究使用新开发的转基因 AD 小鼠模型，发现小鼠在疾病早期发作前与野生型(wild type, WT)小鼠之间的肠道菌群组成没有显着差异，但这种差异在小鼠六个月时开始患病时出现，这表明 AD 的病理状况可能导致肠道菌群发生变化。这表明大脑状态的变化也会影响肠道菌群的组成[49]。APP/PS1AD 小鼠模型的组织学和认知特征与肠道菌群变化相关。具体地说，相对于对照组，科水平的螺杆菌科和脱硫弧菌科以及属级的臭细菌和螺杆菌数量增加[50]。另有研究证实，与 WT 对照小鼠相比，AD 小鼠肠道微生物群落多样性发生改变，短链脂肪酸水平降低，且肠道菌群的改变会影响 AD 小鼠模型中的几种代谢途径，从而导致认知缺陷、Aβ 沉积和肠道异常[51]。另外，AD 小鼠肠道菌群的清除与中枢 Aβ 水平有关，AD 小鼠的微生物群移植后，在大脑中发现 Aβ 积累增加[52]。

3.2. 肠道炎症对 AD 的影响

最新的理论认为 AD 不仅是局限性脑炎症的结果，而且也是外周炎症反应的结果[53]。肠道微生物群与 AD 之间的联系被假设为炎症在该病理学中的作用[54]。炎症(如 NLPR3 炎症小体)、细菌或病毒的慢性感染、衰老和炎症分子(OS、ROS 和 TMAO)生成增加等因素都会导致微生物群组成的变化、微生物失调和 ENIS 改变，这些都会导致脑内 AD 病理学改变[55]。肠道生态失调和/或小肠细菌过度生长和肠道通透性增加而导致对先天免疫系统的过度刺激可能产生全身性和/或中枢神经系统(central nervous system, CNS)炎症[56]。肠道失调引起的全身炎症反应对脑损伤后脆弱的小胶质细胞产生影响，进一步加剧神经炎症，进而诱发或加速 AD 的发生和发展[57]。细菌产生的脂多糖等内毒素可激活外周免疫系统(如免疫细胞激活、细胞因子释放等)，促进外周免疫细胞向脑内浸润，从而引发中枢神经系统炎症[58]。在炎症过程中，肠道微生物群释放出其他可能对大脑有害的蛋白质，如促炎细胞因子和宿主体内的其他先天免疫激活剂[59]。因此，肠道微生物异常引起炎症反应进而影响 AD 病理进程。

3.3. 血脑屏障失调对 AD 的影响

BBB 是一种将 CNS 与外周血循环分开的多细胞血管结构[60]。BBB 破裂导致微生物病原体进入，神经毒性物质积累，血脑屏障运输缺陷，红细胞外渗和神经毒性游离铁(Fe^{2+})释放，产生 ROS 和 OS [61]。

微生物有害的代谢物会削弱肠道屏障和 BBB，引起全身炎症反应、神经元细胞死亡和组织损伤(如脱髓鞘)，导致炎症条件加重中枢神经系统疾病[62]。BBB 的通透性会使大脑接触到可能导致神经炎症的细胞因子，广泛接触促炎性细胞因子可损害小胶质细胞，降低小胶质细胞清除毒性 Aβ 的能力，降低小胶质细胞的突触重塑能力，导致不可逆的神经元损伤[63]。一些微生物群的病原体相关分子模式可以通过激活辅助性 T 细胞产生 1 型细胞因子来促进 BBB 的通透性[64]。啮齿动物模型表明，正常肠道菌群的丧失会导致 BBB 的通透性增加，而无病原体的肠道菌群则会恢复 BBB 的功能[65]。微生物群落的减少导致小鼠 BBB 中紧密连接蛋白 occludin 和 claudin-5 损失 75%，增加了 CNS 对外源性刺激的敏感性[65]。

4. 结论与展望

近年来，脑肠轴理论及其研究作为在 AD 研究方向上的热门之一。肠道微生物群的生态失调是通过微生物群－肠道－脑轴影响大脑功能和行为的关键因素，导致 AD 的发展。2019 年 11 月甘露特钠作为国际首个靶向脑肠轴的 AD 治疗新药，于获得国家药监局批准上市。肠道生态失调在调节微生物群－肠－脑轴方面起着至关重要的作用，并加快 AD 的发病进程。肠道菌群通过各种途径与 AD 发病机制相互作用；Aβ 异常、Tau 磷酸化、神经炎症和 OS，微生物群－肠道－脑轴对 AD 的作用及其重要的影响，不仅关系到大脑的功能，还会影响机体新陈代谢。因此，关于在脑肠轴理论研究方向上对于 AD 的作用研究将有着深远的未来。虽然目前仍难以确切指出肠道微生物群对于 AD 患者所发生的作用机制，但大多数的微生物研究所表明的都是肠道微生物与 AD 之间的关联，对于肠道微生物群与 AD 存在着的因果关系尚未明确。对于脑肠轴理论研究的 AD 方向上，研究明确指出肠道微生物群同 AD 的因果关系是首要任务。未来，可能有望通过脑肠轴的理论研究促成在 AD 方向上的研究新突破。

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参考文献

[1] Jia, L., Du, Y., Chu, L., *et al*. (2020) Prevalence, Risk Factors, and Management of Dementia and Mild Cognitive Impairment in Adults Aged 60 Years or Older in China: A Cross-Sectional Study. *The Lancet Public Health*, **5**, e661-e671. https://doi.org/10.1016/S2468-2667(20)30185-7

[2] Deture, M.A. and Dickson, D.W. (2019) The Neuropathological Diagnosis of Alzheimer's Disease. *Molecular Neurodegeneration*, **14**, 32. https://doi.org/10.1186/s13024-019-0333-5

[3] Kang, S., Lee, Y.H. and Lee, J.E. (2017) Metabolism-Centric Overview of the Pathogenesis of Alzheimer's Disease. *Yonsei Medical Journal*, **58**, 479-488. https://doi.org/10.3349/ymj.2017.58.3.479

[4] Plascencia-Villa, G. and Perry, G. (2021) Preventive and Therapeutic Strategies in Alzheimer's Disease: Focus on Oxidative Stress, Redox Metals, and Ferroptosis. *Antioxidants & Redox Signaling*, **34**, 591-610. https://doi.org/10.1089/ars.2020.8134

[5] Long, J.M. and Holtzman, D.M. (2019) Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. *Cell*, **179**, 312-339. https://doi.org/10.1016/j.cell.2019.09.001

[6] Jongsiriyanyong, S. and Limpawattana, P. (2018) Mild Cognitive Impairment in Clinical Practice: A Review Article. *American Journal of Alzheimer's Disease & Other Dementias*, **33**, 500-507. https://doi.org/10.1177/1533317518791401

[7] Villemagne, V.L., Dore, V., Burnham, S.C., *et al*. (2018) Imaging Tau and Amyloid-Beta Proteinopathies in Alzheimer Disease and Other Conditions. *Nature Reviews Neurology*, **14**, 225-236. https://doi.org/10.1038/nrneurol.2018.9

[8] Silva, M., Loures, C., Alves, L., *et al*. (2019) Alzheimer's Disease: Risk Factors and Potentially Protective Measures. *Journal of Biomedical Science*, **26**, 33. https://doi.org/10.1186/s12929-019-0524-y

[9] Cryan, J.F., O'riordan, K.J., Sandhu, K., *et al*. (2020) The Gut Microbiome in Neurological Disorders. *The Lancet*

Neurology, **19**, 179-194. https://doi.org/10.1016/S1474-4422(19)30356-4

[10] Cryan, J.F., O'riordan, K.J., Cowan, C., *et al*. (2019) The Microbiota-Gut-Brain Axis. *Physiological Reviews*, **99**, 1877-2013. https://doi.org/10.1152/physrev.00018.2018

[11] Rutsch, A., Kantsjo, J.B. and Ronchi, F. (2020) The Gut-Brain Axis: How Microbiota and Host Inflammasome Influence Brain Physiology and Pathology. *Frontiers in Immunology*, **11**, Article ID: 604179. https://doi.org/10.3389/fimmu.2020.604179

[12] Walker, L.C. (2020) A*β* Plaques. *Free Neuropathology*, **1**, 31.

[13] Sampson, T.R., Challis, C., Jain, N., *et al*. (2020) A Gut Bacterial Amyloid Promotes Alpha-Synuclein Aggregation and Motor Impairment in Mice. *Elife*, **9**, e53111. https://doi.org/10.7554/eLife.53111

[14] Mcgeer, P.L. and Mcgeer, E.G. (2013) The Amyloid Cascade-Inflammatory Hypothesis of Alzheimer Disease: Implications for Therapy. *Acta Neuropathologica*, **126**, 479-497. https://doi.org/10.1007/s00401-013-1177-7

[15] Tiwari, S., Atluri, V., Kaushik, A., *et al*. (2019) Alzheimer's Disease: Pathogenesis, Diagnostics, and Therapeutics. *International Journal of Nanomedicine*, **14**, 5541-5554. https://doi.org/10.2147/IJN.S200490

[16] Craig-Schapiro, R., Perrin, R.J., Roe, C.M., *et al*. (2010) YKL-40: A Novel Prognostic Fluid Biomarker for Preclinical Alzheimer's Disease. *Biological Psychiatry*, **68**, 903-912. https://doi.org/10.1016/j.biopsych.2010.08.025

[17] Magalingam, K.B., Radhakrishnan, A., Ping, N.S., *et al*. (2018) Current Concepts of Neurodegenerative Mechanisms in Alzheimer's Disease. *BioMed Research International*, **2018**, Article ID: 3740461. https://doi.org/10.1155/2018/3740461

[18] Wang, Z., Yang, L. and Zheng, H. (2012) Role of APP and Abeta in Synaptic Physiology. *Current Alzheimer Research*, **9**, 217-226. https://doi.org/10.2174/156720512799361691

[19] Zhao, X.L., Wang, W.A., Tan, J.X., *et al*. (2010) Expression of Beta-Amyloid Induced Age-Dependent Presynaptic and Axonal Changes in Drosophila. *Journal of Neuroscience*, **30**, 1512-1522. https://doi.org/10.1523/JNEUROSCI.3699-09.2010

[20] Manczak, M., Calkins, M.J. and Reddy, P.H. (2011) Impaired Mitochondrial Dynamics and Abnormal Interaction of Amyloid Beta with Mitochondrial Protein Drp1 in Neurons from Patients with Alzheimer's Disease: Implications for Neuronal Damage. *Human Molecular Genetics*, **20**, 2495-2509. https://doi.org/10.1093/hmg/ddr139

[21] Morais, C.S., Swerdlow, R.H. and Oliveira, C.R. (2002) Induction of Cytochrome c-Mediated Apoptosis by Amyloid Beta 25-35 Requires Functional Mitochondria. *Brain Research*, **931**, 117-125. https://doi.org/10.1016/S0006-8993(02)02256-4

[22] Kamat, P.K., Kalani, A., Rai, S., *et al*. (2016) Mechanism of Oxidative Stress and Synapse Dysfunction in the Pathogenesis of Alzheimer's Disease: Understanding the Therapeutics Strategies. *Molecular Neurobiology*, **53**, 648-661. https://doi.org/10.1007/s12035-014-9053-6

[23] Cortes-Canteli, M., Paul, J., Norris, E.H., *et al*. (2010) Fibrinogen and Beta-Amyloid Association Alters Thrombosis and Fibrinolysis: A Possible Contributing Factor to Alzheimer's Disease. *Neuron*, **66**, 695-709. https://doi.org/10.1016/j.neuron.2010.05.014

[24] Carlyle, B.C., Nairn, A.C., Wang, M., *et al*. (2014) cAMP-PKA Phosphorylation of Tau Confers Risk for Degeneration in Aging Association Cortex. *Proceedings of the National Academy of Sciences of the United States of America*, **111**, 5036-5041. https://doi.org/10.1073/pnas.1322360111

[25] Serrano-Pozo, A., Frosch, M.P., Masliah, E., *et al*. (2011) Neuropathological Alterations in Alzheimer Disease. *Cold Spring Harbor Perspectives in Medicine*, **1**, a6189. https://doi.org/10.1101/cshperspect.a006189

[26] Breijyeh, Z. and Karaman, R. (2020) Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules*, **25**, 5789. https://doi.org/10.3390/molecules25245789

[27] Zhang, H., Wei, W., Zhao, M., *et al*. (2021) Interaction between Abeta and Tau in the Pathogenesis of Alzheimer's Disease. *International Journal of Biological Sciences*, **17**, 2181-2192. https://doi.org/10.7150/ijbs.57078

[28] Shafiei, S.S., Guerrero-Munoz, M.J. and Castillo-Carranza, D.L. (2017) Tau Oligomers: Cytotoxicity, Propagation, and Mitochondrial Damage. *Frontiers in Aging Neuroscience*, **9**, 83. https://doi.org/10.3389/fnagi.2017.00083

[29] Khan, S.S. and Bloom, G.S. (2016) Tau: The Center of a Signaling Nexus in Alzheimer's Disease. *Frontiers in Neuroscience*, **10**, 31. https://doi.org/10.3389/fnins.2016.00031

[30] Mecocci, P., Boccardi, V., Cecchetti, R., *et al*. (2018) A Long Journey into Aging, Brain Aging, and Alzheimer's Disease Following the Oxidative Stress Tracks. *Journal of Alzheimer's Disease*, **62**, 1319-1335. https://doi.org/10.3233/JAD-170732

[31] Cobley, J.N., Fiorello, M.L. and Bailey, D.M. (2018) 13 Reasons Why the Brain Is Susceptible to Oxidative Stress. *Redox Biology*, **15**, 490-503. https://doi.org/10.1016/j.redox.2018.01.008

[32] Thapa, A. and Carroll, N.J. (2017) Dietary Modulation of Oxidative Stress in Alzheimer's Disease. *International Journal of Molecular Sciences*, **18**, 1583. https://doi.org/10.3390/ijms18071583

[33] Nam, E., Derrick, J.S., Lee, S., *et al*. (2018) Regulatory Activities of Dopamine and Its Derivatives toward Metal-Free and Metal-Induced Amyloid-beta Aggregation, Oxidative Stress, and Inflammation in Alzheimer's Disease. *ACS Chemical Neuroscience*, **9**, 2655-2666. https://doi.org/10.1021/acschemneuro.8b00122

[34] Schulz, E., Wenzel, P., Munzel, T., *et al*. (2014) Mitochondrial Redox Signaling: Interaction of Mitochondrial Reactive Oxygen Species with Other Sources of Oxidative Stress. *Antioxidants & Redox Signaling*, **20**, 308-324. https://doi.org/10.1089/ars.2012.4609

[35] Wang, X., Wang, W., Li, L., *et al*. (2014) Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease. Biochim Biophys Acta, **1842**, 1240-1247. https://doi.org/10.1016/j.bbadis.2013.10.015

[36] Tönnies, E. and Trushina, E. (2017) Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. *Journal of Alzheimer's Disease*, **57**, 1105-1121. https://doi.org/10.3233/JAD-161088

[37] Zhao, Y. and Zhao, B. (2013) Oxidative Stress and the Pathogenesis of Alzheimer's Disease. *Oxidative Medicine and Cellular Longevity*, **2013**, Article ID: 316523. https://doi.org/10.1155/2013/316523

[38] Malard, F., Dore, J., Gaugler, B., *et al*. (2021) Introduction to Host Microbiome Symbiosis in Health and Disease. *Mucosal Immunology*, **14**, 547-554. https://doi.org/10.1038/s41385-020-00365-4

[39] Cheng, X., Wang, H., Zheng, Z., *et al*. (2021) Alzheimer Disease Effects of Different Stages on Intestinal Flora: A Protocol for Systematic Review and Meta-Analysis. *Medicine* (*Baltimore*), **100**, e28462. https://doi.org/10.1097/MD.0000000000028462

[40] Kim, M.S., Kim, Y., Choi, H., *et al*. (2020) Transfer of a Healthy Microbiota Reduces Amyloid and Tau Pathology in an Alzheimer's Disease Animal Model. *Gut*, **69**, 283-294. https://doi.org/10.1136/gutjnl-2018-317431

[41] Mueller, N.T., Bakacs, E., Combellick, J., *et al*. (2015) The Infant Microbiome Development: Mom Matters. *Trends in Molecular Medicine*, **21**, 109-117. https://doi.org/10.1016/j.molmed.2014.12.002

[42] Wang, G., Huang, S., Wang, Y., *et al*. (2019) Bridging Intestinal Immunity and Gut Microbiota by Metabolites. *Cellular and Molecular Life Sciences*, **76**, 3917-3937. https://doi.org/10.1007/s00018-019-03190-6

[43] Briguglio, M., Dell'Osso, B., Panzica, G., *et al*. (2018) Dietary Neurotransmitters: A Narrative Review on Current Knowledge. *Nutrients*, **10**, 591. https://doi.org/10.3390/nu10050591

[44] Pistollato, F., Sumalla, C.S., Elio, I., *et al*. (2016) Role of Gut Microbiota and Nutrients in Amyloid Formation and Pathogenesis of Alzheimer Disease. *Nutrition Reviews*, **74**, 624-634. https://doi.org/10.1093/nutrit/nuw023

[45] Fox, M., Knorr, D.A. and Haptonstall, K.M. (2019) Alzheimer's Disease and Symbiotic Microbiota: An Evolutionary Medicine Perspective. *Annals of the New York Academy of Sciences*, **1449**, 3-24. https://doi.org/10.1111/nyas.14129

[46] Chen, Y., Liang, Z., Blanchard, J., *et al*. (2013) A Non-Transgenic Mouse Model (icv-STZ Mouse) of Alzheimer's Disease: Similarities to and Differences from the Transgenic Model (3xTg-AD Mouse). *Molecular Neurobiology*, **47**, 711-725. https://doi.org/10.1007/s12035-012-8375-5

[47] Gotz, J., Bodea, L.G. and Goedert, M. (2018) Rodent Models for Alzheimer Disease. *Nature Reviews Neuroscience*, **19**, 583-598. https://doi.org/10.1038/s41583-018-0054-8

[48] Sasaguri, H., Nilsson, P., Hashimoto, S., *et al*. (2017) APP Mouse Models for Alzheimer's Disease Preclinical Studies. *EMBO Journal*, **36**, 2473-2487. https://doi.org/10.15252/embj.201797397

[49] Hang, Z., Lei, T., Zeng, Z., *et al*. (2022) Composition of Intestinal Flora Affects the Risk Relationship between Alzheimer's Disease/Parkinson's Disease and Cancer. *Biomedicine & Pharmacotherapy*, **145**, Article ID: 112343. https://doi.org/10.1016/j.biopha.2021.112343

[50] Shen, T., Yue, Y., He, T., *et al*. (2021) The Association between the Gut Microbiota and Parkinson's Disease, a Meta-Analysis. *Frontiers in Aging Neuroscience*, **13**, Article ID: 636545. https://doi.org/10.3389/fnagi.2021.636545

[51] Zhang, L., Wang, Y., Xiayu, X., *et al*. (2017) Altered Gut Microbiota in a Mouse Model of Alzheimer's Disease. *Journal of Alzheimer's Disease*, **60**, 1241-1257. https://doi.org/10.3233/JAD-170020

[52] Harach, T., Marungruang, N., Duthilleul, N., *et al*. (2017) Reduction of Abeta Amyloid Pathology in APPPS1 Transgenic Mice in the Absence of Gut Microbiota. *Scientific Reports*, **7**, Article No. 41802. https://doi.org/10.1038/srep41802

[53] Le Page, A., Dupuis, G., Frost, E.H., *et al*. (2018) Role of the Peripheral Innate Immune System in the Development of Alzheimer's Disease. *Experimental Gerontology*, **107**, 59-66. https://doi.org/10.1016/j.exger.2017.12.019

[54] Calsolaro, V. and Edison, P. (2016) Neuroinflammation in Alzheimer's Disease: Current Evidence and Future Directions. *Alzheimer's & Dementia*, **12**, 719-732. https://doi.org/10.1016/j.jalz.2016.02.010

[55] Angelucci, F., Cechova, K., Amlerova, J., *et al*. (2019) Antibiotics, Gut Microbiota, and Alzheimer's Disease. *Journal*

of Neuroinflammation, **16**, 108. https://doi.org/10.1186/s12974-019-1494-4

[56] Mulak, A. and Bonaz, B. (2015) Brain-Gut-Microbiota Axis in Parkinson's Disease. *World Journal of Gastroenterology*, **21**, 10609-10620. https://doi.org/10.3748/wjg.v21.i37.10609

[57] Sundman, M.H., Chen, N.K., Subbian, V., *et al*. (2017) The Bidirectional Gut-Brain-Microbiota Axis as a Potential Nexus between Traumatic Brain Injury, Inflammation, and Disease. *Brain*, *Behavior*, *and Immunity*, **66**, 31-44. https://doi.org/10.1016/j.bbi.2017.05.009

[58] Caspani, G. and Swann, J. (2019) Small Talk: Microbial Metabolites Involved in the Signaling from Microbiota to Brain. *Current Opinion in Pharmacology*, **48**, 99-106. https://doi.org/10.1016/j.coph.2019.08.001

[59] Alam, R., Abdolmaleky, H.M. and Zhou, J.R. (2017) Microbiome, Inflammation, Epigenetic Alterations, and Mental Diseases. *Neuropsychiatric Genetics*, *Part B of the American Journal of Medical Genetics*, **174**, 651-660. https://doi.org/10.1002/ajmg.b.32567

[60] Obermeier, B., Daneman, R. and Ransohoff, R.M. (2013) Development, Maintenance and Disruption of the Blood-Brain Barrier. *Nature Medicine*, **19**, 1584-1596. https://doi.org/10.1038/nm.3407

[61] Sweeney, M.D., Sagare, A.P. and Zlokovic, B.V. (2018) Blood-Brain Barrier Breakdown in Alzheimer Disease and Other Neurodegenerative Disorders. *Nature Reviews Neurology*, **14**, 133-150. https://doi.org/10.1038/nrneurol.2017.188

[62] Park, J. and Kim, C.H. (2021) Regulation of Common Neurological Disorders by Gut Microbial Metabolites. *Experimental & Molecular Medicine*, **53**, 1821-1833. https://doi.org/10.1038/s12276-021-00703-x

[63] Navarro, V., Sanchez-Mejias, E., Jimenez, S., *et al*. (2018) Microglia in Alzheimer's Disease: Activated, Dysfunctional or Degenerative. *Frontiers in Aging Neuroscience*, **10**, 140. https://doi.org/10.3389/fnagi.2018.00140

[64] Daniels, B.P., Holman, D.W., Cruz-Orengo, L., *et al*. (2014) Viral Pathogen-Associated Molecular Patterns Regulate Blood-Brain Barrier Integrity via Competing Innate Cytokine Signals. *mBio*, **5**, e1414-e1476. https://doi.org/10.1128/mBio.01476-14

[65] Braniste, V., Al-Asmakh, M., Kowal, C., *et al*. (2014) The Gut Microbiota Influences Blood-Brain Barrier Permeability in Mice. *Science Translational Medicine*, **6**, 158r-263r. https://doi.org/10.1126/scitranslmed.3009759