

综述

阿魏酸对阿尔茨海默病的神经保护作用

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摘要: 阿尔茨海默病(Alzheimer's disease, AD)是老年人最常见的疾病之一, 发病率高, 严重影响老年人生活质量, 属于年龄相关的记忆和思维能力障碍的疾病。AD发病机制复杂, 目前临床上尚无统一的结论和有效的治疗方法, 因此找到新的治疗药物是目前有待解决的问题。研究发现, 基于多酚饮食方式, 可有效预防或减缓AD进展。阿魏酸(ferulic acid, FA)是一种羟基肉桂酸衍生物, 属于多酚类化合物, 广泛分布于自然界中, 尤其是中草药、谷物麸皮和水果中。已知FA具有抗A β 聚集、抗氧化和抗炎等多种生物作用。FA及其衍生物对AD动物和细胞模型都具有显著的治疗作用, 可作为一种新的治疗AD的神经保护策略。本文主要对FA的各种生物作用进行综述, 为进一步探寻FA治疗AD的机制提供参考。

关键词: 阿尔茨海默病; 阿魏酸; β -淀粉样蛋白; 神经保护作用

The neuroprotective properties of ferulic acid in Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is one of the most common diseases among the elderly, with a high incidence rate and a significant impact on the quality of life of older individuals. It is characterized by age-related memory and cognitive impairments. The pathogenesis of AD is complex, and currently, there is no unified conclusion or effective treatment method in clinical practice. Therefore, finding new therapeutic drugs is an unresolved issue. Studies have found that a polyphenol-rich diet can effectively prevent or slow down the progression of AD. Ferulic acid is a hydroxycinnamic acid derivative, a polyphenolic compound widely distributed in nature, particularly in medicinal herbs, cereal bran and fruits. It is known to possess various biological activities, including anti-A β aggregation, antioxidant and anti-inflammatory effects. Ferulic acid and its derivatives have shown significant therapeutic effects in animal and cellular models of AD, making it a promising neuroprotective strategy for treating AD. This work provides a comprehensive review of the various biological effects of ferulic acid, serving as a reference for further exploration of the mechanisms underlying

收稿日期: 2024-03-24

基金项目: 国家自然科学基金面上项目(82171428); 湖南省自然科学基金青年项目(2020JJ5517); 湖南省教育厅科学研究项目(20C1671); 国家级大学生创新创业训练项目(S202010547043)

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ferulic acid therapeutic effects in AD.

Key Words: Alzheimer's disease; ferulic acid; amyloid β protein; neuroprotective effect

阿尔茨海默病(Alzheimer's disease, AD)是一种病因不明的慢性进行性神经系统疾病,主要表现为进行性的记忆力丧失、认知缺陷和行为障碍(如判断力和解决问题的能力差、找词困难、视觉空间能力下降、性格改变等)^[1]。2015年全球痴呆成本估计为9 575.6亿美元,2030年将达到25 400亿美元,2050年将达到91 200亿美元,远高于《2015年世界阿尔茨海默病报告》的预测^[2]。估计到2050年,全球将有超过1.52亿AD患者^[3],将产生巨大的社会、经济负担。脑内淀粉样 β 蛋白(amyloid β protein, A β)的异常沉积(老年斑)被认为是AD最为人知的病理方面病因^[4-7]。目前临床上使用的药物包括乙酰胆碱酯酶抑制剂(如卡巴拉汀、加兰他敏、多奈哌齐)和NMDA受体拮抗剂(如美金刚)^[8,9]和于2019年11月在中国首次获批用于治疗轻度至中度AD以改善认知功能靶向脑肠轴的低聚甘露酸钠(GV-971)^[10],另外还有单克隆抗体——抗A β 药物(Aducanumab、Lecanemab),但是这些药物都不能阻止神经退行性病变的进程^[11-13]。尽管抗A β 药物为AD患者提供了新的治疗选择和希望^[14]。但是一些专家对实验数据的真实性和药物治疗的有效性表示怀疑,同时安全性也值得衡量,它们可能会产生严重不良反应(如淀粉样蛋白相关成像异常)^[13]。抗A β 抗体的被动免疫疗法存在一些挑战和局限性,需要长期的纵向研究来评估其在更广泛的受试者中的疗效、不良反应和成本效益^[15]。目前,还没有治疗AD行之有效的方法,有必要开发新的治疗方法来治疗AD。天然产物和天然产物活性物质对药物发现和开发具有重要价值和意义,在1981–2019年间开发的1 881种药物中,直接由天然产物或天然产物衍生物开发的药物占比49.2%^[16]。天然化合物具有获取方便、来源广泛、不良反应小等特点,已成为研究热点。研究发现,通过改善饮食模式可减少氧化应激、神经炎症和A β 沉积、改善大脑可塑性和线粒体功能^[17]。其中,进食具有多种生物学活性的多酚引起广泛的关注^[18-20]。阿魏酸(ferulic acid, FA)属于酚酸,是多

酚类化合物,被认为是一种潜在的神经保护剂。

鉴于FA作为生物活性分子在AD中的重要作用,本文总结了有关FA的天然分布、化学特性,重点概述有关其神经保护特性和作用机制的新进展,并进一步探讨其未来在AD防治中的研究方向与策略。

1 FA概述

FA又名3-甲氧基-4-羟基肉桂酸(C₁₀H₁₀O₄),1986年首次从阿魏属植物香阿魏(一种伞形科药用植物)中分离得到^[21]。这种植物在印度、阿富汗和伊朗种植。随着研究的深入,人们发现,FA也存在于中国特有的植物当归中,也存在于中华水仙根^[22]、甘草^[23]以及川芎等药用植物中,此外FA还广泛存在于食用植物中,水果(如蓝莓、葡萄)、蔬菜(如红甜菜、萝卜、辣椒、黄瓜、菠菜、欧芹、西红柿、胡萝卜)^[24],特别是在谷物麸皮中(如玉米、高粱、黑麦和米糠),也是一种常见的酚酸。有研究发现,FA能缓解胃肠、呼吸和神经疾病^[25]。在中药中用作抗增殖和肾脏保护药物,并可用于治疗月经紊乱^[23],具有抗炎、抗氧化、神经保护以及降低胆固醇的特性^[26]。而且FA具有成本低、毒性低、不良反应小的特性^[27,28],已广泛用于制药、食品和化妆品行业^[29]。FA衍生物也具有抗氧化、清除自由基、抗炎、抗癌、抗胆碱酯酶、镇痛、神经保护和抗紫外线辐射活性^[30,31]。在体内,FA及其衍生物可减轻AD动物模型的学习记忆障碍。在体外,FA及其衍生物可抑制A β 聚集,提高AD细胞活性。天然草药单体FA及其衍生物独特的药理特性、易获得性、低毒性及不良反应小成为AD研发新药的最大优势。但FA及其衍生物的研究仍处于起步阶段。FA及其衍生物在AD治疗中的作用机制尚未完全阐明。

2 FA抗AD的作用机制

FA具有多种生物学活性,在治疗AD中具有潜在作用。本文将从FA抑制A β 聚集、抗氧化、抗炎、

抗胆碱酯酶活性、抗凋亡及FA衍生物、FA联合用药等方面总结其抗AD的作用及机制, 为研究天然抗AD药物提供参考。

2.1 抑制A β 聚集

A β 是由淀粉样前体蛋白(amyloid precursor protein, APP)经 β -和 γ -分泌酶的蛋白水解作用而产生的含有39~43个氨基酸的多肽^[32]。无毒的A β 单体可以聚集成低聚物、原纤维和淀粉样原纤维的具有神经毒性的组装体。A β 具有从单体到低聚体形式到原纤维的分子生命周期, A β 的原纤维或无定形多聚体的细胞外沉积物形成典型的病理斑块和弥漫性沉积物^[33-35]。A β 生成与清除失衡导致沉积是AD发病的重要因素^[36]。毛细血管的收缩、直径和密度的减小是导致脑内A β 生成和清除失衡的重要原因, 毛细管收缩由内皮素1(endothelin 1, ET1)介导的ET1受体A(ET1 receptor A, ETRA)完成, FA抗ETRA治疗ET1介导的毛细血管收缩, 从而防止海马毛细血管密度和直径的降低, 抑制A β 沉积^[37]。FA也可降低 β -淀粉样前体蛋白/早老素1(amyloid precursor protein/presenilin 1, APP/PS1)小鼠的 β APP裂解酶1(β APP cleaving enzyme 1, BACE1)表达和 β -分泌酶活性来抑制APP代谢, 减少A β 生成, 减轻脑淀粉样变性, 改善行为障碍^[38]。FA还能通过诱导BACE1和基质金属蛋白酶2(matrix metalloproteinase 2, MMP2)通路降低BACE1表达, 提高MMP2和MMP9水平, 抑制A β 聚集^[39]。FA处理转基因秀丽隐杆线虫发现, FA可增加自噬报告基因*LGG-1*的表达, 激活HLH-30转录因子, 可以通过自噬降解错误折叠的A β 蛋白^[7]。FA还能通过减轻AD中PP2B/DARPP32/PP1轴介导的富含纹状体的蛋白酪氨酸磷酸酶(striatal-enriched protein tyrosine phosphatase, STEP)增加和A β 负担, 改善突触可塑性和认知障碍^[40]。在体外, FA以剂量依赖性的方式抑制A β 25-35、A β 1-40和A β 1-42的聚集; 在细胞中, FA预处理初级大脑皮层神经元对A β 25-35诱导的细胞毒性有显著保护作用^[41]。而且, FA是A β 聚集的抑制剂, 可以稳定A β , 增加分子内氢键的数量, 增加螺旋和降低非螺旋倾向来影响A β 的折叠^[35]。由此可知, FA可以影响A β 生成与清除过程中的多个环节, 进而阻止A β 聚集, 从

而达到治疗或减缓AD进程的治疗效果。

2.2 抗氧化

氧化应激在多种疾病的发生发展中起着关键作用^[42]。氧化应激被认为是AD的临床标志之一, 活性氧(reactive oxygen species, ROS)和A β 是氧化应激的主要介质^[43]。氧化应激时体内产生过多的ROS, 不能被机体抗氧化酶系统和非抗氧化酶系统抵消, 超过机体抗氧化的能力, 引起炎症, 导致组织变性、过早衰老和细胞凋亡。同时, 若大脑中含量低时, 抗氧化酶容易被ROS破坏^[44]。A β 的积累和炎症反应与体内氧化应激有关, 引起脑内环境/细胞功能紊乱, 导致AD的发生^[45]。在转基因Tg2576小鼠中, 氧化应激可能是通过启动内皮APP处理的淀粉样变性途径在脑血管系统中引起A β 沉积的主要危险因素^[46]。有研究表明, FA的抗氧化作用是通过清除自由基, 抑制ROS的产生, 并调节参与氧化应激控制的几种信号通路发挥作用的^[26,27]。超氧化物歧化酶、氧化型谷胱甘肽、谷胱甘肽的上调和丙二醛水平的下调是发挥抗氧化活性的重要途径^[47]。当给予APP/PS1转基因小鼠FA灌胃处理后, 给药组小鼠较AD组小鼠脑内超氧化物歧化酶活性显著升高, 丙二醛含量略降低。核因子红系2相关因子2(the nuclear factor erythroid-2 related factor 2, Nrf2)是氧化应激反应的主要协调因子, Nrf2/血红素加氧酶-1(heme oxygenase-1, HO-1)信号通路是细胞内防御氧化应激的主要调控途径^[48]。研究发现, FA的抗氧化活性与转录因子Nrf2核易位表达的增加有关。特别是Nrf2结合*HO-1*基因启动子区域的抗氧化反应元件(antioxidant response elements, ARE), 并增加其转录, 从而增强内源性抗氧化防御。ARE调控的抗氧化酶基因包括*HO-1*和谷胱甘肽-S-转移酶, 它们的表达升高有助于清除ROS和增加抗氧化剂谷胱甘肽合成^[44,49,50]。此外, FA还可诱导的Nrf2活化通过磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)和细胞外调节激酶(extracellular-regulated kinase, ERK)信号通路在FA抗氧化应激的细胞保护作用中起关键作用^[49]。FA的抗氧化作用通过多种信号通路发挥作用。具有神经元特性的PC12细胞被广泛用于模拟AD的病理过程^[51]。在体外研究中, FA可以增加缺氧应激的PC12细胞的活力, 这一效果可

归因于其抗氧化能力^[52]。在体内研究中, FA (30 mg/kg, 3个月)可逆转基因APP/PS1小鼠的空间学习和记忆缺陷, 并减少A β 沉积、星形细胞增生、小胶质细胞增生、突触毒性、淀粉样APP加工、神经炎症和氧化应激^[53]。另外, FA的自身结构也使其成为良好的抗氧化剂。FA具备酚核和延伸的侧链共轭, 它很容易形成共振稳定的苯氧自由基, 从而发挥中和自由基的作用^[54]。Kanski等^[55]亦指出, FA三级结构具有的相邻不饱和C-C双键与羧基团可以通过共振或者提供额外的位点来防止自由基膜攻击来稳定自由基。故FA可以通过清除氧自由基、调节多种氧化应激相关信号通路及利用自身独特的结构特点发挥抗氧化作用。

2.3 抗炎

炎症与年龄相关的一些慢性疾病有关, 如AD和糖尿病。炎症是大脑产生的一种自我保护的免疫反应。如果免疫反应持续或免疫系统能力丧失, 就会发生慢性炎症, 导致神经元损伤^[56]。过度的炎症反应和持续的慢性炎症可能是AD发生的重要原因, 加速了A β 的沉积^[57]。炎症反应产生的炎症因子引起神经胶质细胞的过度激活, 导致营养缺乏, 影响突触的形成^[58]。而突触丧失与AD的认知能力下降密切相关^[59]。小胶质细胞和补体在AD中的受累归因于神经炎症^[60]。小胶质细胞是大脑的主要免疫细胞。A β 多聚体的持续形成和沉积导致免疫系统的慢性激活和小胶质细胞清除功能的紊乱^[61]。在AD的动物模型中, 小胶质细胞和星形胶质细胞吞噬更多的突触^[59]。亦有研究表明, 当暴露于可溶性A β 低聚物时, 成人大脑中的小胶质细胞会在CR3(经典补体级联反应的起始蛋白)依赖性过程中吞噬突触物质^[60]。A β 的沉积、神经毒素和生长因子蛋白特性的改变引发一系列炎症反应, 影响A β 的清除, 加剧AD进展^[62]。有研究表明, FA可以在多种疾病中发挥抗炎作用, 如AD、糖尿病、肝肾功能障碍^[26,63]。神经系统的星形胶质细胞和小胶质细胞主要参与吞噬和分泌细胞因子。因此, 抑制胶质细胞的聚集和激活可能是缓解炎症反应的重要途径^[64]。A β 1-42提高了海马星形胶质细胞标记物胶质纤维酸性蛋白和白细胞介素-1 β (interleukin-1beta, IL-1 β)的免疫反应性, 而FA预处理抑制这种反应^[65]。FA预处理4周同样可抑制脑

室内注射的A β 1-42诱导海马中活化的星形胶质细胞中内皮型一氧化氮合酶(endothelial nitric oxide synthase, eNOS)和3-硝基酪氨酸(3-nitrotyrosine, 3-NT)免疫反应性增加和海马中的IL-1 α 免疫反应性的增加^[66]。孟锐等^[67]的研究也发现, FA可以使大脑中星形胶质细胞的形态改变以及减弱脑内炎症。Kim等^[68]发现, 使用FA(饮用水中0.006% w/v)对小鼠进行4周预处理, 可抑制侧脑室注射A β 1-42 8h后海马中小胶质细胞的激活。FA对脂多糖(lipopolysaccharide, LPS)诱导的BV-2小胶质细胞神经炎症也有抑制作用。Huang等^[69]发现, FA以剂量依赖性方式显著抑制LPS刺激的BV-2小胶质细胞中一氧化氮(nitric oxide, NO)、前列腺素E2 (prostaglandin E2, PGE2)、IL-1 β 的产生, 并降低诱导的诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)和环氧化酶-2(Cyclooxygenase-2, COX-2)蛋白表述。Huang等^[70]也得出了类似的观点, FA剂量依赖性预处理能够抑制LPS诱导的PC12细胞中的肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)和IL-1 β 的产生以及磷酸二酯酶4B (phosphodiesterase 4B, PDE4B) mRNA的上调, 逆转环磷腺苷效应元件结合蛋白(cAMP-response element binding protein, CREB)和pCREB下调。口服FA(5.3 mg/kg·d⁻¹) 6个月后, 转基因APP/PS1小鼠模型中神经炎症的减少, 与额叶皮层中A β 沉积和IL-1 β 水平的减少有关^[71]。FA能下调Toll样受体4 (Toll-like receptor 4, TLR4)蛋白的表达抑制炎症因子生成, 如IL-1 β 、NO、COX-2等的生成, 发挥抗炎作用^[72]。核因子- κ B(nuclear factor kappa-B, NF- κ B)是促炎细胞因子信号通路的关键因子, 能促进IL-1 β 、IL-6和TNF- α 的合成, 导致神经炎症。FA可以抑制NF- κ B来减少额叶皮层神经炎症, 还抑制核苷酸结合寡聚化结构域样受体蛋白3 (nucleotide binding oligomerization domain-like receptor protein 3, NLRP3)炎性小体的产生^[73]。在NF- κ B抑制后, FA可下调促炎因子, 如iNOS、COX-2、TNF- α 、IL-1 β 、血管细胞黏附分子-1和细胞间黏附分子-1^[74,75]。而血管细胞黏附分子-1和细胞间黏附分子-1能促进炎症细胞迁移和浸润, 加剧炎症反应^[26]。在动物实验中, 静脉注射FA (100 mg/kg)降低了细胞间黏附分子-1 mRNA的水

平和小胶质细胞/巨噬细胞的数量, 随后下调了炎症诱导的氧化应激和氧化应激相关细胞凋亡^[76]。Nrf2/HO-1轴除了调节氧化还原系统外, Nrf2/HO-1轴已被证明还能通过抑制核苷酸结合NLRP3炎症小体来抑制炎症反应^[77]。Lampiasi和Montana的报告表示, FA可以通过上调Nrf2的表达和下调NF- κ B来平衡氧化和炎症臂^[78]。FA不仅可以影响神经胶质细胞和炎症因子在AD病程发挥作用。还能调节氧化还原反应抑制炎症反应从而发挥作用。

2.4 抗胆碱酯酶活性

有研究表明, AD与胆碱能神经元的大量损失以及乙酰胆碱的活性和数量下降有关^[79]。胆碱能神经元广泛分布在大脑区域, 在认知功能中具有重要意义。乙酰胆碱是胆碱能神经元分泌的一种兴奋性神经递质, 参与学习、记忆和其他高级行为。因此, 抑制胆碱酯酶活性, 促进乙酰胆碱的产生是改善AD症状的重要环节^[80]。Salau等^[81]的研究指出, FA能够抑制乙酰胆碱酯酶和丁酰胆碱酯酶的活性, 并增加ATP酶的活性。实验表明, FA可通过激活抗氧化剂和胆碱能受体拮抗美加明、东莨菪碱、中枢乙酰胆碱能神经毒素乙基胆碱芥子氮吡啶离子(central acetylcholinergic neurotoxin ethylcholine mustard aziridinium ion, AF64A)和A β 1-40诱导的认知缺陷^[82], 使AD模型的症状得到改善。FA还能显著提高乙酰胆碱转移酶和超氧化物歧化酶的活性, 降低乙酰胆碱酯酶活性和丙二醇水平, 逆转A β 1-40引起的认知功能障碍, 明显提高AD小鼠的认知能力^[83]。乙酰胆碱在学习、记忆等高级行为中发挥了重要作用。FA通过抑制乙酰胆碱酯酶活性、激活胆碱能受体及提高乙酰胆碱转移酶活性等多种途径, 提升乙酰胆碱水平, 改善AD模型认知功能。

2.5 抗凋亡

王玥等^[84]的研究发现, 在AD模型的小鼠脑内存在大量的细胞凋亡。氧化应激、炎症和A β 沉积可导致神经元功能受损, 进而导致神经元凋亡并加速AD的进展^[85]。在异常条件下抗凋亡蛋白Bcl-2对线粒体膜电位的维持和离子通道形成发挥重要作用^[86]。B淋巴细胞瘤-2基因(B-cell lymphoma 2, Bcl-2)通过与Bcl-2相关X蛋白(Bcl-2-associated X protein, Bax)结合, 阻断Bax形成的孔隙, 阻碍一

些小分子跨膜, 起到细胞保护作用^[87]。Bcl-2表达异常可损伤线粒体功能, 进而导致细胞凋亡^[88]。给予APP/PS1转基因小鼠低(20 mg/kg)、中(40 mg/kg)、高(100 mg/kg)浓度的FA灌胃处理后发现, 凋亡相关蛋白(Bax、p-JNK、p-C-Jun、caspase-3)的表达水平较APP/PS1小鼠降低, Bcl-2表达有所升高, 其中40 mg/kg处理组的效果最明显^[84]。在使用50 μ mol/L红藻氨酸诱导PC12细胞凋亡建立的AD神经细胞模型中, 予以FA(25、50和100 μ mol/L)处理后, PC12细胞存活率上升, 凋亡率减少。其神经保护机制可能是通过抑制Bax和细胞色素C(CytC)的表达, 增加Bcl-2表达和Bcl-2/Bax比值, 阻断内源性细胞凋亡通路, 从而提高神经细胞的存活率^[89]。类似地, FA预处理(100和200 mg/kg灌胃3周)可抑制细胞凋亡级联反应, 特别是侧脑室给药A β 1-40诱导的caspase-9、caspase-3和caspase-7激活^[90]。另外, 利用重组A β 42寡聚体处理海胆胚胎引起叉形头转录因子的高表达, 叉形头转录因子O亚型(FOXO3A)激活后, 可调节多种依赖凋亡的基因, FA可扭转这一现象, 使得FOXO3A和凋亡蛋白p53的表达下降^[30]。可见, FA能够通过调节凋亡基因及抗凋亡基因的表达, 从而发挥治疗AD的作用。

3 FA衍生物

与FA相比, FA的衍生物经分子修饰后具有较强的抗氧化活性和较强的抗胆碱能作用。阿魏酸丁酯是FA的衍生物之一, 拥有比FA更强的清除细胞外 β 聚集物诱导的自由基的能力。用阿魏酸丁酯预处理细胞可显著减弱A β 1-42诱发的细胞内ROS形成。此外, 阿魏酸丁酯可以通过调节Keap1-Nrf2-ARE信号通路来上调抗氧化防御系统^[50]。FA在神经保护作用上具有明显的优势, 但FA的水溶性低、血脑屏障渗透率低、生物利用度低和口服给药后从胃肠道快速消除, 使得其应用受限^[41,91-93]。而FA衍生物在具备同样优势的基础上, 在一定程度上弥补了FA本身的不足。水溶性是影响药物生物利用度的最重要因素之一。要使药物被吸收, 它首先必须是水溶性的, 然后具有穿过生物膜的能力^[94]。Kikugawa等^[41,95]开发出的两种水溶性FA衍生物——1-阿魏酰甘油和1-阿魏酰二甘

油, 其在体外和体内都表现出与FA相同的神经保护作用。阻止A β 聚集、破坏聚集的A β 原纤维的稳定性和抑制星形胶质细胞中NF- κ B通路的炎性细胞因子的过表达是1-阿魏酰甘油和1-阿魏酰二甘油发挥神经保护作用的机制。Lan等^[96]设计合成的FA衍生物4a在表现出良好的抗胆碱酯酶、抗A β 聚集、抗氧化作用的同时, 展现出良好的穿过血脑屏障的能力(使用PAMPA-BBB测定法)。在Phadke等^[97]纳入的FA衍生物2、5、6、7、15中, 除了具备其抗胆碱酯酶或抑制iNOS的作用外, 还表现出穿越血脑屏障的作用。Bautista-Aguilera等^[94]合成的FA衍生物化合物4, 除了是人类乙酰胆碱酯酶抑制剂和抗氧化剂, 还具有合格的血脑屏障通透性, 满足Lipinski的五法则的口服生物利用度, 满足Jorgensen三法则(number of violations of Jorgensen's rule of three, ROT)的生物利用度和良好的水溶性。FA衍生物相较于FA有更加突出的特性, 这将为我们研究如何提升FA生物作用提供思路。

4 FA联合用药

药物中的一种或多种与一种或多种药物相结合可能成为未来的AD治疗选择之一。Mori等^[53]研究发现, 来自具有治疗效果的天然膳食化合物没食子酸辛酯(octyl gallate, OG)和FA联合应用在脑淀粉样变性的APP/PS1转基因小鼠模型中, 可显著减轻神经炎症、氧化应激和突触毒性。Mori等^[98]继续将FA和植物来源的 α -分泌酶激活剂(-)-表没食子儿茶素-3-没食子酸酯(epigallocatechin gallate, EGCG), 联合应用于APP/PS1转基因小鼠模拟的脑淀粉样变性, 结果显示, 在Y迷宫中APP/PS1转基因小鼠的空间工作记忆明显恢复, 表明FA-EGCG联合治疗可逆转大部分学习和记忆中的认知障碍。此外, 与单独使用EGCG或FA相比, FA-EGCG联合处理的小鼠脑实质和脑血管A β 沉积物得到明显改善, A β 丰度降低, 可能是通过阻止APP的分解, 减少 β -淀粉样蛋白在脑内的沉积。姜黄素(curcumin, Cur)是一种脂溶性多酚, 富含姜黄。一些体内和体外研究发现, Cur同样具有抗氧化和抗炎作用, 可以抑制A β 聚集(包括体外和体内的寡聚化)^[99,100]。有研究发现, Cur和FA联合治疗比单独使用Cur和FA更能抑制A β 诱导的神经毒性^[101]。

有实验发现, 芍药苷、FA和白术内酯Ⅲ单独或联合使用可显著减少IL-6、IL-1 β 、TNF- α 等炎症因子的产生, 且芍药苷、FA和白术内酯Ⅲ在减少BV2小胶质细胞LPS诱导的炎症因子释放方面具有协同作用^[102]。以上研究表明, FA与其他药物联用减少 β -淀粉样蛋白沉积效果更好。这将为FA治疗AD提供新的思路。

5 结论

随着人口老龄化的加剧, 神经退行性疾病已成为严重威胁老年人生活质量的一类疾病。FA在神经退行性疾病中发挥积极的治疗作用, 特别是AD。无论是在AD模型中的体内研究还是体外研究, FA都表现出良好的抗A β 聚集、抗炎、抗氧化、抗胆碱酯酶和抗凋亡的特性, 并改善神经元功能。FA衍生物生理活性提高, 更容易通过血脑屏障及拥有更高的水溶性, 使其在AD的治疗中发挥更大的作用。这些研究结果都提示, FA可能是治疗AD的潜在药物。但FA对AD作用的分子机制目前尚不十分清楚, 需要更多的基础研究来揭开迷雾。另外, 由于FA的穿越血脑屏障的渗透率低、水溶性低, 需要设计和合成具备FA本身生理特性的同时能够改善其本身不足的衍生物。同时, 也需要寻找新的传递形式(如纳米颗粒、多糖等)或给药方式, 以提高FA的生物利用度和吸收水平, 从而提升实际使用的可能性; 也需要寻找合适的生物技术方法提升天然产物中FA的含量; 也迫切需要更多的临床研究来证实FA及其衍生物对AD患者的疗效。

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