· 综述 ·

阿尔茨海默病药物联合治疗研究进展

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【摘要】 阿尔茨海默病(AD)是一种神经退行性疾病，为痴呆最常见的类型。当前AD发病机制不明，新药研发困难。多年来，临床上一直采用“一分子一靶点”的策略治疗AD，然而效果并不理想，在其他疾病如癌症、艾滋病和结核病中，多靶点药物联合治疗显示出较好的临床获益，而针对AD的药物联合治疗尚处在初步阶段，现从作用机制出发，就这一方面研究进展展开综述。

【关键词】 阿尔茨海默病； 药物联合治疗； 综述

Research advances of drug combination treatment in Alzheimer disease *Zhu Dandi, Pan Weigang, Liu Chaomeng, Ma Xin, Mao Peixian*

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【Abstract】 Alzheimer disease (AD) is a neurodegenerative disease, which is the most common type of dementia. At present, the pathogenesis of AD is still unclear, and it is difficult to develop new drugs. For many years, the strategy of "one molecule, one targe" has been used to treat AD, but the effect is not ideal. In other diseases such as cancer, AIDS and tuberculosis, multi-target drug combination therapy has shown good clinical benefits, while the drug combination therapy for AD is still in its initial stage. Thus, in this paper, the research progress is summarized from the mechanism of action.

【Key words】 Alzheimer disease； Drug combination therapy； Review

阿尔茨海默病(Alzheimer disease, AD)是一种起病隐匿、慢性、进展性神经退行性疾病，占全部痴呆的65%～70%[1]。目前全球有3 000多万例AD患者，预计到2050年将达到1亿例左右[2]。AD是一种复杂的多因素疾病，其病理特征主要为β淀粉样蛋白(β-amyloid, Aβ)沉积和微管相关蛋白tau(microtubule-associated proteins tau)过度磷酸化导致的神经原纤维缠结[3]。迄今为止，AD的发病机制不明，主流假说有胆碱能假说、Aβ神经毒性假说、磷酸化tau蛋白假说、氧化应激假说以及神经炎性假说等[4]。

目前针对AD的治疗方案有2种，一种是“症状性治疗”，可延缓患者认知功能的下降或改善其激越、焦虑等症状，但无法阻止AD的疾病进程；另一种为“疾病修饰治疗”(disease-modifying therapy, DMT)，即通过干预疾病进程中导致细胞凋亡的潜在病理生理改变，从而发挥持久的治疗作用[5]。多年来，临床上一直采用“一分子一靶点”的策略治疗AD，由于其发病机制尚未明确，所以治疗效果并不理想。当前多靶点药物联合(combination-drugs-multi-targets, CDMT)的治疗方式得到了越来越多的肯定，CDMT在其他疾病如癌症、艾滋病和结核病中取得了良好的治疗效果，这可能是AD未来的治疗方向[6]。针对AD的CDMT可以是2种及以上对症治疗药物的组合，或2种及以上DMT药物的组合，也可以是对症治疗与DMT药物的联用。现从AD的发病机制出发，总结了CDMT治疗方案的研究进展。

一、基于不同发病机制的CDMT治疗现状

1.胆碱能假说：在AD的病因学中胆碱能假说最早被提出[7]。有研究发现，AD患者脑内乙酰胆碱(acetyl choline, Ach)含量可降低至年轻时的20%，这可能与乙酰胆碱转移酶(choline acetyltransferase, ChAT)和乙酰胆碱酯酶(acetylcholine esterase, AchE)活性降低、脑组织中胆碱能神经元数量减少有关[8]。谷氨酸能假说认为[9]，谷氨酸负责中枢神经系统中

大部分兴奋性神经递质的传递，与记忆功能有关。当N-甲基-D-天冬氨酸(N methyl D aspartic acid，NMDA)受体被谷氨酸激活时，钙离子内流进入神经元，导致“慢性中毒性”退行性病变的发生，进而促进了AD的发展[10]。

当前临床上用于治疗AD的药物主要有2类，一类是非竞争性的NMDA受体拮抗剂盐酸美金刚，另一类为胆碱酯酶抑制剂(cholinesterase inhibitors，ChEI)，如多奈哌齐、卡巴拉汀、加兰他敏和盐酸他克林等[11]。一项回顾性研究比较了不同ChEI类药物联合美金刚治疗AD的疗效[12]，在114例轻中度AD患者中随机给予多奈哌齐或加兰他敏治疗，6个月后再分别与美金刚联用，结果显示，与单独治疗相比，联用美金刚治疗6个月后两组患者简明精神状态检查量表(Mini-Mental State Examination，MMSE)和长谷川痴呆量表(Hasegawa Dementia Rating，HDS-R)得分均显著提高，此外，加兰他敏联用美金刚组患者额叶功能评价量表(Frontal Assessment Battery，FAB)得分在联用治疗3个月、6个月时有显著提高，提示NMDA受体拮抗剂联用ChEI类药物可能优于单药治疗，加兰他敏与美金刚联用可能有助于改善AD患者的执行功能。一项前瞻性研究比较了多奈哌齐联用美金刚或安慰剂治疗中重度AD的疗效，结果表明，与安慰剂组相比，24周治疗结束时试验组患者认知功能和日常生活能力均显著改善，两组间不良事件发生率无明显差异[13]。此外，一项纳入54项研究的Meta分析显示，美金刚与多奈哌齐联用在改善AD患者认知、日常生活能力和精神症状方面均优于单药治疗[14]，这可能与美金刚可以延缓AD的进程有关。

2. Aβ淀粉样蛋白沉积假说：AD典型的病理特征之一为Aβ蛋白沉积[3]。Aβ低聚物可与中枢神经系统中多种受体结合，导致神经元细胞内钙超载、小胶质细胞膜电位下降，进而引起严重的神经元损伤[15]。此外，Aβ蛋白的沉积还可减少树突棘的形成，增加神经炎症和tau蛋白病发生的风险[16]。2021年6月初，美国食品药品监督管理局(Food and Drug Administration，FDA)批准了单克隆抗体Aduhelm(又名Aducanumab)用于治疗早期AD[17]，这是一种重组人源化免疫球蛋白G抗体，可以选择性地与Aβ蛋白的寡聚体结合[18]。一项Ⅰ期临床试验表明，经Aduhelm注射治疗后，与安慰剂组相比，AD患者认知功能的下降有所减缓，脑内Aβ蛋白含量也随之降低[19]，不过之后的Ⅲ期临床试验并没有观察到这种变化[20]。可能的原因是，Aduhelm更多的是阻止Aβ蛋白斑块的聚集，而不是帮助吸收现有沉积的Aβ蛋白[21]。Donanemab被认为是最有潜力的Aβ蛋白降解剂之一，一项Ⅱ期临床研究发现，其有效降低了AD患者脑内Aβ蛋白和tau蛋白水平，整合AD量表得分(Integrated Alzheimer's Disease Rating Scale，iADRS)表现也优于安慰剂组，不过两组AD评估量表-认知子量表(The Cognitive Subscale of AD Assessment Scale，ADAS-Cog)得分差异无统计学意义[22]。鉴于AD的复杂病理以及Aβ蛋白和tau蛋白之间的潜在协同作用，Aduhelm和Donanemab的联用在改善AD患者认知功能方面可能比单一疗法更有效[23]。

Aβ肽是由β和γ两种分泌酶介导淀粉样前体蛋白水解产生的，β-分泌酶1(β-site APP cleaving enzyme 1，BACE1)在β位点上对前体蛋白的切割是产生Aβ肽的限速步骤[24]。因此，抑制BACE1是治疗AD最有吸引力的方案之一[25]。一项临床Ⅰ期的研究表明，AD患者服用BACE1抑制剂JNJ-54861911 2周后，脑脊液中$Aβ_{40}$水平下降了80%以上，但个别患者出现了肝损害[26]。Gantenerumab是一种新型抗Aβ抗体，动物研究发现，与单用gantenerumab或BACE1抑制剂RO5508887相比，两者联用可以更有效地降低AD模型小鼠脑内Aβ淀粉样蛋白含量[27]。目前有关BACE1抑制剂治疗AD的研究尚处在临床前阶段，其有效性与安全性有待进一步研究。

3. 氧化应激假说：当机体氧化还原系统障碍、自由基产生过多时，氧化应激就会发生，由于大脑耗氧量大、含脂量丰富，对氧化应激比较敏感，因此极易受到自由基损伤[28]。活性氧具有维持止血的功能，在细胞内级联反应中起到第二信使的作用，当氧化还原系统失衡、活性氧产生过多时，神经细胞就会出现功能障碍[29]。褪黑素是一种由色氨酸衍生来的激素，具有强大的抗氧化作用，在清除体内自由基、调节机体昼夜节律方面发挥着重要作用[30]。动物研究发现，与单用美金刚或褪黑素相比，两者联用可有效降低AD模型小鼠Aβ淀粉样蛋白含量，其情景记忆表现也随之好转[31]。西洛他唑是一种选择性磷酸二酯酶Ⅲ抑制剂，具有抑制局部血管氧化应激的作用[32]。一项回顾性研究发现，与单用多奈哌齐相比，联用西洛他唑可显著改善轻度AD患者的认知功能，但在重度AD组中未发现这种差异[33]。可能的原因是，AD早期神经退行性病变较轻，血管

负担较重，而西洛他唑可通过非内皮依赖性的血管扩张来改善血管活性[34]，这为轻中度AD的联合治疗提供了新思路。维生素E是体内重要的抗氧化剂，一项纳入561例轻中度AD患者的随机对照研究发现，与安慰剂相比，接受维生素E(α-生育酚)治疗的患者认知功能下降减缓，不过单用美金刚组与美金刚联用维生素E组患者ADAS-Cog量表得分差异无显著[35]，一种可能的推测是美金刚干扰了维生素E的抗氧化作用，不过这需要进一步验证。

4.神经炎症假说：研究发现，AD早期便可出现小胶质细胞的活化，产生炎性介质如细胞因子、趋化因子等，炎性损伤的发生可导致神经元变性[36]。此外，小胶质细胞分泌的炎性因子如白细胞介素-1β、肿瘤坏死因子-α、白细胞介素-6等可激活星形胶质细胞，进而介导神经元的凋亡[37]。吡格列酮是一种过氧化物酶体增殖物激活受体γ激动剂，可抑制神经炎症发生，减少Aβ淀粉样蛋白沉积，改善大脑能量利用与脂质代谢[38]。一项回顾性研究发现，吡格列酮可降低2型糖尿病患者罹患AD的风险[39]。瘦素是一种参与细胞存活的炎性细胞因子，研究发现，瘦素具有神经保护作用，可减少Aβ淀粉样蛋白的产生、抑制tau蛋白的过度磷酸化[40]。动物研究表明，吡格列酮与瘦素联用可显著降低AD模型小鼠脑内Aβ蛋白水平，改善其记忆表现，且效果优于两者的单独治疗，神经保护与抗炎药物的联用为AD的联合治疗提供了新途径[41]。

二、其他CMDT治疗组合

现代医学肯定了中医治疗痴呆的效果。研究发现，益肝散、黄连解毒汤、柴胡疏肝散和六味地黄汤等方剂均可在一定程度上改善AD患者的认知功能[42]。此外，针灸治疗AD也引起了人们的关注[43]。一项纳入15项随机对照研究的Meta分析从整体上评价了传统医学治疗AD的效果[44]，试验组给予针灸(指压、针刺、穴位、艾灸和耳穴疗法)联合中药(祛痰降浊汤、聪脑汤、补肾活血方、醒脑益智汤、补肾益气活血方和开窍醒脑通络汤等)治疗，对照组给予西药(胞磷胆碱钠、石杉碱甲、吡拉西坦、脑复新、二氢麦角碱和多奈哌齐)治疗，结果发现试验组治疗有效率和MMSE评分均优于对照组，且安全性良好。一些研究也从多个角度探索了传统医学治疗AD的可能机制，涉及调节炎性过程、减轻氧化应激、抑制tau蛋白的过度磷酸化以及改善胆碱能系统功能等[45-48]。

近年来，越来越多的研究表明肠道菌群失调在AD进展中扮演重要角色[49]。研究发现，AD模型小鼠肠道微生物组成的改变致使外周苯丙氨酸和异亮氨酸积累过量，进而刺激辅助性T细胞1的增殖、分化，导致M1型小胶质细胞激活[50]，而这与AD的炎症机制假说有关。甘露特纳可通过抑制苯丙氨酸、异黄酮的积累，调节肠道菌群分布，进而达到控制神经炎性反应，改善认知的目的[50]。2019年12月，用于治疗AD的新药甘露特钠胶囊(GV-971)正式在国内上市，研究表明，GV-971在改善轻中度AD患者认知功能方面疗效显著且安全性良好[51]，其潜在的作用机制可能与改善肠道微生物环境、重塑机体菌群生态有关[52]。这也为AD的联合治疗提供了新的思路。

三、展望

当前FDA批准用于治疗AD的药物包括ChEI、NMDA受体拮抗剂以及单克隆抗体Aduhelm。其中前两者只能缓解症状，不能阻止神经变性的进行性加重，而Aduhelm治疗AD的效果尚存在争议[20, 53]。自2003年以来，已有超过200种化合物进入Ⅱ期临床试验，但均以失败告终[54]，这也提示，AD的生物学机制可能是多样的、复杂的。采用传统的“一分子—靶点”方法治疗AD是不够的，针对不同靶点的药物联合治疗或许是今后的发展方向之一。多靶点药物联合治疗不仅可以提高疗效，降低单一治疗可能出现的不良反应，更重要的是有效的干预手段的联用对临床实际应用也有着很好的指导意义。目前尚无明确的联合治疗指南，文中提到的不同药物间的联合治疗，更多是一种探索性的尝试，尚未达成共识。不过随着研究的深入，相信CDMT治疗将会为AD患者带来新的曙光。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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