· 综述 ·

银杏萜类内酯治疗认知障碍机制研究进展

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【摘要】 认知障碍是一种获得性、进行性的智能障碍表现，其认知功能损伤包括学习、记忆、视空间等多方面能力异常，导致患者出现进行性记忆力下降、日常生活能力下降、精神行为异常等临床表现。认知障碍的病因复杂，包括阿尔茨海默病和血管性痴呆等。因此，针对多靶点的治疗是改善认知障碍药物疗效的关键，也是近年研究的热点和难点。银杏萜类内酯具有多靶点、多途径治疗特点，现以银杏萜类内酯主要成分，即银杏内酯A、B、C及白果内酯为切入点，从其抗氧化应激、抗炎性反应、抗凋亡等方面，对其治疗认知障碍作用机制进行探讨。

【关键词】 阿尔茨海默病；　痴呆，血管性；　银杏内酯类；　白果内酯；　综述

Effective mechanism of ginkgobiloba against dementia: a review of current literature　*Yan Yi, Ma Li*

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【**Abstract**】 Cognitive impairment is characterized as an acquired and progressive manifestation of intellectual impairment. Cognitive impairment includes learning, memory, visual space and other abnormal abilities, leading to progressive memory decline, daily living ability decline, mental and behavioral abnormalities and other clinical manifestations. The pathological mechanism of cognitive impairment is complex, including Alzheimer disease and vascular dementia. Currently, the treatment of multiple targets is the key to improve the efficacy of pharmacotherapy, and it is also possesses the most significant position in recent years. Ginkgobiloba has multi-target and multi-channel treatment characteristics. In this review, we will use the main components of ginkgo biloba lactone, namely ginkgolides A, B, C and bilobalide as the entry point, from its

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anti-oxidative stress, anti-inflammatory response, anti-apoptosis, etc., to explore its mechanism of treatment of cognitive impairment.

【Key words】 Alzheimer disease; Dementia, vascular; Bilobalides; Bilobalide; Review

随着人口老龄化,认知障碍发病率逐年上升,给社会和家庭带来沉重经济和精神负担。目前认知障碍的首要病因是阿尔茨海默病(Alzheimer disease, AD),其病理变化主要表现为细胞外β-淀粉样蛋白(Aβ)沉积,细胞内神经原纤维缠结及tau蛋白磷酸化。AD的发病机制复杂,具体发病的分子机制仍然不十分明确。主要有以下几种学说,经典Aβ瀑布学说占据主导地位,它认为Aβ由淀粉样前体蛋白(amyloid precursor protein, APP)经由β-分泌酶1(BACE1)异常水解产生过多Aβ,以Aβ为中心引起一系列病理变化。其次tau蛋白损伤学说、氧化应激学说、离子稳态失衡及基因突变在AD发病中也备受关注。痴呆的第二位病因是血管性痴呆,其病因主要为脑血管性病变。值得注意的是,在65岁以上老年人群中,AD合并血管性痴呆同样很常见。目前AD治疗以药物治疗为主,国内外大量针对Aβ斑块形成及神经原纤维缠结的治疗对认知障碍并未得到明显改善[1-2],于是胆碱酯酶抑制剂、N-甲基-D-天冬氨酸(N-methyl-D-aspartic acid, NMDA)受体拮抗剂在症状性痴呆中的疗效逐渐得到重视,并部分引入指南。银杏萜类内酯是中药提取物,具有多靶点、多途径的治疗特点,在心脑血管疾病治疗中已广泛应用并得到肯定。现主要针对银杏萜类内酯对预防及治疗认知障碍分子机制进行阐述,为进一步提高银杏萜类内酯药物活性、安全性及减少其不良反应提供一些参考。

银杏萜类内酯是20世纪60年代德、法两国科学家首次从银杏属植物中提取,主要用于预防及治疗心脑血管疾病。近来逐渐发现银杏萜类内酯对存在认知障碍患者的对症支持治疗中,也起到重要作用。银杏内酯根据其羟基键空间位置不同,主要分为银杏内酯A、B、C亚型。研究表明其可以干预AD和血管性痴呆的病理进程,具有修复损伤神经元线粒体[3]、改善受损海马神经元功能,提高神经元突触可塑性[4]、抑制Aβ沉积[5]、提高脑内血流微灌注状态[6]等作用。现对其具体机制进行如下综述。

一、银杏内酯A

银杏内酯A是银杏属植物提取物主要成分之一,其羟基键在空间构型上位于第1号位点。银杏内酯于1932年Furukawa等首次从植物中提取出,1967年首次明确其化学结构。一项针对银杏内酯A分子水平研究发现,银杏内酯A可以改善Aβ诱导的神经元异常去极化,并通过AD动物模型小鼠体内实验进一步证实其改善记忆力的作用[7]。银杏内酯A改善神经元去极化状态可能存在两种分子机制:(1)银杏内酯A直接结合Aβ分子,抑制其活性。然而在Kuo和Rajesh[8]的体外试验研究中发现银杏内酯A并不能直接结合Aβ;(2)银杏内酯A作为NMDA受体和α-氨基-3-羟基-5-甲基-4-异恶唑丙酸(α-amino-3-hydroxy-5-methyl-4-isoxa-zolep-propionate, AMPA)受体竞争性拮抗剂,阻断NMDA/AMPA诱导的去极化,阻断NMDA受体信号通路细胞毒性兴奋性作用。这与经典NMDA受体拮抗剂美金刚有着相同的作用基础。另外研究也发现,银杏内酯A可逆转JNK信号通路磷酸化,缓解Aβ诱导的神经元病理生理进程,而美金刚可以逆向干预JNK信号通路磷酸化。目前银杏内酯A竞争性拮抗NMDA受体的具体机制仍需进一步研究。随着AD发病机制研究地不断深入,磷酸化tau蛋白在AD发病中的病理作用逐渐引起学者注意。磷酸化tau蛋白作为Aβ通路的下游,对神经元损伤性退行性变发挥重要致病作用。银杏内酯A可以减低tau蛋白磷酸化水平和GSK-3β细胞裂解水平,增强细胞活动,上述作用在Kang等[6]的研究中得到证实。以上结论都表明了银杏内酯A在神经系统变性病中的多重有益作用。尽管如此,目前特异性针对银杏内酯A在AD发病分子水平和动物模型中的研究仍然十分有限。银杏内酯是否能够阻止认知障碍进行性下降仍不明确。

炎性损伤、急性脑缺血等都会导致脑内血小板活化因子(platelet activating factor, PAF)异常增多,PAF通过与其受体结合,以自分泌、旁分泌、内分泌的形式产生多种炎性蛋白,激活一系列信号通路。大量研究证实PAF促进炎性反应发生和促进血栓形成等作用[7]。一项体外实验发现,提前注射30 mg/kg银杏内酯A,可减少炎性介质(诱导型一氧化氮合酶等)产生。研究者把这种现象归因于银杏内酯A阻断了PAF诱导的PI3K途径[8]。另一项体外实验证实银杏内酯A可以减少由PAF引起的神经元细胞死亡。银杏内酯A通过调节STAT3介导的炎性损伤,

减少由高血糖导致的血管内皮损伤，对血管性痴呆起到保护作用[9]。此外银杏内酯A可以减少STAT磷酸化，减少神经元死亡并提高预后[10-11]。

二、银杏内酯B

大脑对缺氧异常敏感，过度的氧耗启动活性氧/氮自由基(reactive oxygen/nitrogen species，ROS/RNS)氧化应激反应，诱导神经元死亡。脑内Aβ异常沉积是启动神经元氧化应激的主要因素，也是AD重要的病理标志。目前关于治疗AD研究中，抗氧化应激机制细胞及分子水平研究成为热点。研究发现细胞内Aβ沉积干扰过氧化物歧化酶(superoxide dismutase，SOD)1活性[12]。进一步研究发现SOD 1辅酶缺失又会通过异常激活APP途径导致Aβ过沉积[13]。综上，SOD活性减低加快了AD的病理进程。谷胱甘肽(glutathione，GSH)具有重要抗氧化应激作用，在神经退行性病变中发挥非常重要的作用。神经元GSH缺失启动ROS/RNS氧化应激反应并导致神经元细胞凋亡[14]。一项针对银杏内酯预处理的体内体外试验证实，银杏内酯B可明显改善$Aβ_{1-42}$诱导的ROS/RNS反应，并帮助贮存GSH活性[15]。此外，银杏内酯B的神经元保护作用在AD小鼠模型体内实验和海马神经元体外实验NO诱导的神经元毒性中，也得到了证实[16]。由于上述阐述Aβ诱导的神经元损伤与细胞SOD功能缺失相关，研究也证实银杏内酯B能帮助贮存SOD活性，从另一个方面解释了银杏内酯B在抗氧化应激中的神经元保护作用[17]。

在AD等神经退行性疾病中，凋亡是神经元死亡的主要发生机制[18]。凋亡主要由内源性和外源性两种方式来完成[19]。内源性凋亡途径主要通过线粒体依赖的通路实现，包括结合凋亡相关蛋白、释放细胞色素C、激活细胞色素凋亡蛋白酶-3、形成凋亡小体等，而外源性凋亡途径包括上调细胞表面受体、激活细胞色素凋亡蛋白-8等来实现[20]。越来越多证据表明炎性反应与凋亡存在密切相关性，NF-κB在炎性凋亡中作用引起重视[21]，NF-κB可下调抗凋亡蛋白表达，上调细胞色素凋亡蛋白-3、NO合酶等凋亡蛋白酶表达。研究发现银杏内酯B可通过抑制NK-κB激活、抑制小神经胶质细胞启动和减少炎性细胞因子生成[22]。氧化核酸堆积降低了核酸的修复能力。内源性及外源性因素通过启动例如ROS/RNS反应，诱导DNA基因链断裂。正常生理情况下，断裂的DNA链产物由线粒体自噬、碱基切除修复(base-excision repair，BER)等方式等清除。APE1酶是完成碱基切除修复过程的重要酶物质，它具有多种生理功能，参与DNA损伤修复及调节氧化还原反应[23]。损伤DNA修复功能异常会导致氧化磷酸化发生诱导神经元细胞死亡，产生神经功能缺损等临床症状[24]。研究发现，银杏内酯B可以加强APE1的神经元保护作用[25]。但是其具体机制仍不十分明确。

银杏内酯B也是重要的PAF拮抗剂，这已经在20世纪90年代一项针对革兰阴性菌感染患者的双盲随机Ⅲ期临床试验中得到证实[26]。急性脑缺血及缺血再灌注损伤可通过PAF诱导的中性粒细胞及细胞因子大量释放引起。在急性脑缺血动物模型中，银杏内酯B能够减少缺血再灌注损伤，考虑银杏内酯B通过减少组织蛋白酶B和L表达及溶酶体表达减少缺血后脑细胞死亡[27]。

三、银杏内酯C

银杏内酯C是银杏内酯重要亚型之一。但由于其PAF拮抗剂活性不及银杏内酯B[28]，其作用逐渐被取代。研究分析其低活性的原因与甲基化进程快相关。值得关注的是，银杏内酯C具有重要的抗血小板聚集作用。一项体外实验研究结论推测银杏内酯C可能通过激活基质金属蛋白酶活性发挥抑制血小板聚集的作用[29]。综上，如何克服银杏内酯C药物代谢率快，发挥其抗血小板聚集作用，是未来研究工作重点。

四、白果内酯

白果内酯是银杏内酯中倍半萜类内酯，研究发现其与银杏内酯A有着相同的PAF受体拮抗剂作用，表现为在基因层面呈剂量依赖性的下调PAF受体水平[30]。同时，下调PAF炎性信号通路蛋白表达，从而减轻由急性缺血带来的脑组织炎性损伤[31]。除此之外，白果内酯还从其他多种途径发挥其抗炎性反应的作用。Lang等[32]在小鼠模型体内实验证实白果内酯在挽救脑组织缺血半暗带时，通过减少谷氨酸盐释放作用，发挥神经元保护作用。白果内酯治疗组与对照组相比，谷氨酸盐释放减少10倍以上，减少细胞外毒性，并成功挽救缺血半暗带，缩小梗死面积，保护神经元损伤。白果内酯通过减少谷氨酸释放发挥保护神经元的作用，在年龄相关性疾病和神经系统退行性疾病中，也同样发挥重要作用[33]。

Wnt/β-catenin是经典信号通路。正常情况下，wnt-β-catenin通路处于休眠状态，当wnt与其受体结合后，β-catenin易位至细胞核结合TCF/LEF，促进下游基因转录及翻译，促进细胞增殖。研究发现，白果内酯通过GSK-3β磷酸化启动wnt信号通路，

促进细胞增殖，在神经退行性疾病治疗中具有潜在治疗价值[34]。一项白果内酯预处理AD动物模型研究中观察到白果内酯抑制GSK-3β活性，GSK-3β是主要的促进tau蛋白磷酸化蛋白酶，抑制其活性可能会减少tau蛋白磷酸化，延缓AD病理进程[35]。综上，白果内酯在AD及血管性痴呆的治疗机制，仍需要更多的基础研究。

另外，最新的针对AD转基因模型体内及体外实验首次发现，白果内酯可能通过激活神经元自噬，起到到保护神经元的作用。但具体机制自噬作用机制仍需进一步阐明[36]。

银杏萜类内酯作为经典的具有多重生物活性的天然植物提取物，本文结合大量体内体外实验研究，对其通过拮抗PAF抗感染、抑制Aβ诱导的神经元去极化等发挥抗感染、抗细胞凋亡的作用从而改善认知障碍进行综述。但是目前针对银杏萜类内酯在临床应用中有效性及安全剂量临床研究证据仍不十分充分。因此未来的工作重点主要是：(1)银杏萜类内酯治疗症状性痴呆的分子机制有待进一步研究。(2)需要充分的随机双盲对照临床研究确认其对AD和血管性痴呆是否有疗效。

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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