电子、语音版

·综述·

维生素与阿尔茨海默病

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摘　要：阿尔茨海默病（AD）是多种病因导致的神经退行性疾病之一。维生素是人体不可或缺的微量元素。近年来，越来越多的证据表明，维生素与AD之间有一定的关联。维生素在AD的发生和发展过程中起着重要作用。该文对维生素B_{12}、维生素D、维生素E与AD的关系进行了综述。

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关键词：阿尔茨海默病；维生素B_{12}；维生素D；维生素E

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Vitamins and Alzheimer´s disease

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Abstract: Alzheimer's disease (AD) is one of the neurodegenerative diseases caused by various etiologies, and vitamins are essential trace elements for the human body. In recent years, an increasing number of evidence has shown that there is a significant association between vitamins and AD, and vitamins play an important role in the development and progression of AD. This article reviews the association of vitamin B_{12}, vitamin D, and vitamin E with AD.

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Keywords: Alzheimer's disease; vitamin B_{12}; vitamin D; vitamin E

维生素是维持人体健康不可或缺的营养素，在许多生物化学过程中扮演着关键角色。维生素可通过饮食摄入，对维持正常代谢、增强免疫力及促进细胞和组织的正常发育至关重要。维生素按其在体内的溶解性可以分为2类：水溶性维生素（如B族维生素）和脂溶性维生素（如维生素D和维生素E），每种维生素都有其独特的功能。

阿尔茨海默病（Alzheimer's disease，AD）作为最常见的中枢神经退行性疾病之一，已成为全球公共卫生的重大挑战[1]。AD不仅给患者及其家庭带来极大困扰，也对社会和医疗体系造成了沉重负担。AD主要表现为进行性认知功能障碍和行为损害，严重影响患者的日常生活和行动的独立性。研究显示，AD的发病与细胞内外沉积的β-淀粉样蛋白（amyloid beta-protein，Aβ）和神经元内神经原纤维缠结有关。这些物质主要影响记忆和认知功能相关的脑区，尤其是海马区和大脑皮质[2]。此外，神经炎症和氧化应激同样参与AD的发病机制。

近年来，科学研究开始探索维生素与神经退行性疾病，尤其对AD发展及AD导致的认知障碍的潜在影响。众多营养因素中，维生素对于AD的预防和管理被认为尤为重要，因其在神经保护、认知功能和大脑健康中的潜在

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作用而成为研究焦点。维生素的缺乏或不足可能增加AD的风险,但这种关联的确切性和具体机制仍需深入研究和证实。本综述回顾了相关研究,探讨了维生素与AD之间的关系,特别是维生素B_{12}、维生素D和维生素E,探讨了维生素缺乏与AD发展的潜在联系,旨在对未来AD研究和AD患者护理提供一定的参考。

1　AD与维生素B_{12}

维生素B_{12}又称钴胺素,是参与一碳代谢的水溶性维生素。在这一过程中,同型半胱氨酸(homocysteine, Hcy)是一种含硫氨基酸,在一碳代谢中作为辅酶的关键前体。近期研究表明,在AD的病理进程中,髓磷脂损伤可能起着关键作用,这种损伤甚至可能在Aβ沉积和tau蛋白形成之前就发生了[3]。维生素B_{12}通过产生髓磷脂的少突胶质细胞的DNA合成来参与髓磷脂的形成[4]。神经炎症的参与在AD的进展中发挥重要作用,维生素B_{12}可以通过调节白细胞介素-6等炎症因子的产生来防止炎症引起的氧化应激[5],而维生素B_{12}水平的降低与白细胞介素-6过量产生密切相关[6]。此外,白细胞介素-6通过影响细胞周期素依赖蛋白激酶5/p35通路,促进AD中tau蛋白的磷酸化[7]。Alam等[8]的研究表明,维生素B_{12}在体外可以抑制Aβ42的聚集,从而防止淀粉样蛋白诱导的细胞毒性。补充B族维生素可能降低血浆中Aβ40的水平,对预防AD有益[9]。

维生素B_{12}缺乏会破坏细胞内氧化还原平衡,引发氧化应激,并与AD的发展密切相关。缺乏维生素B_{12}会减少Hcy转化为蛋氨酸,导致细胞内Hcy升高,加速氧化应激和自由基的产生,进一步加剧AD的进程[4]。研究表明,Hcy升高与AD患者认知功能下降相关的脑区萎缩成正比[10]。另外,萎缩性胃炎可导致内因子和胃酸分泌减少,影响维生素B_{12}的吸收。早期研究显示,萎缩性胃炎患者中有2.5%呈现维生素B_{12}水平低下,同时胃炎可能增加痴呆症的风险[11]。Choi等[12]的研究发现,胃切除后患者患AD的风险高于一般人群,但持续补充维生素B_{12}可降低这一风险。有研究认为,尽管维生素B_{12}补充能降低Hcy水平,但对改善认知障碍无显著效果[13-14]。相关的Meta分析和4项随机对照试验都得出了类似的结论[15-16]。虽然维生素B_{12}对于改善AD认知障碍的效果尚未确定,但积极补充维生素B_{12}可能有助于延缓AD的进展。

2　AD与维生素D

维生素D是一种类固醇激素,也被称为脂溶性维生素,主要功能是调节钙和磷的代谢。维生素D被血液吸收后,转化为25-羟基维生素D_3形式[17],并与其受体(vitamin D receptor, VDR)特异性结合后,发挥作用。在海马体和大脑皮质中存在维生素D代谢必需的酶和VDR[18-19],VDR缺乏或抑制可能增加AD的风险[19]。VDR与维生素D作用和代谢相关基因的变化可导致维生素D利用率下降,增加神经元受损及患神经退行性病变的风险[20]。与Aβ生成增加相比,Aβ清除率下降则是迟发性AD进展的主要原因[21]。Aβ清除的主要途径之一是血管介导的Aβ通过外排泵或受体穿过血脑屏障从大脑中清除。Aβ是P-gp和LRP-1转运蛋白的底物。而维生素D通过VDR的调节能够增强这些转运蛋白对Aβ蛋白的清除作用,并促进小胶质细胞吞噬Aβ蛋白[19, 22],从而减少Aβ沉积。维生素D与AD之间存在一定关系[23],血清维生素D缺乏(25~50 nmol/L)与AD风险略有关联[18],而维生素D严重缺乏(<10 ng/mL)与痴呆和AD风险为显著关联[24]。

对AD患者死后大脑的分析显示,海马区的VDR mRNA水平降低[25]。小鼠模型研究显示,维生素D能逆转海马体中与年龄相关的炎症变化[26]。这种神经保护作用可能源于大脑中促炎细胞因子的抑制。补充维生素D能增强大脑能量平衡和蛋白磷酸酶2A活性,并调节氧化还原状态,减少年龄相关的tau蛋白过度磷酸化和认知障碍。有研究表明,维生素D结合蛋白与Aβ有相互作用[27]。体外研究证明,DBP能抑制Aβ的寡聚化,并防止Aβ引发的海马突触丧失及相关记忆障碍[20]。Kalra等[28]的Meta分析发现,血清维生素D缺乏者的痴呆和AD风险显著高于正常水平者。此外,研究表明,体内维生素D水平低与AD认知能力下降的风险密切相关[29]。Wang等[21]的研究发现,充足的维生素D补充可增加Aβ清除,并预防Aβ相关的认知功能减退。Mehri等[30]的动物实验证明,维生素D的应用可有效减轻Aβ引起的记忆损害,为治疗AD等神经退行性疾病提供了有力的证据。适量补充维生素D能在一定范围内改善认知障碍,同时VDR有潜力成为治疗AD认知障碍的新靶点。

3　AD与维生素E

维生素E又称生育酚,作为脂溶性抗氧化剂,在动植物中发挥重要生理功能。维生素E具有神经保护、抗氧化、降低胆固醇和抗炎等特性,对生命体至关重要。脑脊液尸检分析显示,α-生育酚水平与患者的知觉速度和AD病理呈正相关[31]。此外,大鼠神经元培养实验中,应用维生素E能够预防Aβ相关的氧化应激反应,并降低氧化应激标志物的水平[32]。大脑中α生育酚水平低会导致影响髓鞘形成、突触发生、神经元囊泡运输和神经胶质功能的基因表达下降。一项结合体外和体内实验的研究,通过模拟维生素E缺乏的动物模型,证实了维生素E通过抑制tau蛋白过度磷酸化抑制氧化应激反应的机制[33]。维生素E能激活磷脂酶A2的活性,可能会改变细胞神经酰胺和鞘磷脂比例,增加Aβ多肽的产生。维生素E刺激磷脂酶A2活性,增加花生四烯酸释放,改变细胞脂质平衡。鞘磷脂能抑制Aβ产生,而花生四烯酸可激活鞘磷脂酶。过高水平的维生素E可能间接增加细胞神经酰胺与鞘磷脂比例,导致Aβ产生增加,进而诱发AD[34],过多的Aβ沉

积诱导AD发病。研究显示,AD患者血浆中的维生素E水平显著降低[35-36]。血浆中较高的维生素E浓度和增加维生素E或α-生育酚摄入量,可降低AD风险[37]。维生素E可防止原代大鼠胚胎海马神经元培养物因Aβ诱导而发生的蛋白质氧化、活性氧生成和神经毒性。维生素E不仅减少Aβ引起的氧化应激,也有助于改善记忆和认知障碍[38]。Nolan等[39]对77名AD患者的前瞻性研究发现,补充维生素E组在记忆力和情绪测评中表现优于安慰剂组。维生素E的减少与AD发生有关,并可能有助于改善认知功能。

4　结语

近年来国内外对维生素与AD关系的研究报道越来越多。维生素是否能够防治AD,并改善AD导致的认知功能障碍已成为一大讨论点。补充维生素B_{12}、维生素D、维生素E均能通过不同途径减少Aβ的沉积,延缓AD的发生进展。但其是否能改善认知障碍尚存在争议,有待进一步考证。

参　考　文　献

[1] JIA JP, WANG F, WEI CB, et al. The prevalence of dementia in urban and rural areas of China[J]. Alzheimers Dement, 2014, 10(1): 1-9.

[2] JAHANSHAHI M, NIKMAHZAR E, SAYYAHI A. Vitamin E therapy prevents the accumulation of congophilic amyloid plaques and neurofibrillary tangles in the hippocampus in a rat model of Alzheimer's disease[J]. Iran J Basic Med Sci, 2020, 23(1): 86-92.

[3] PAPUĆ E, REJDAK K. The role of myelin damage in Alzheimer's disease pathology[J]. Arch Med Sci, 2020, 16(2): 345-351.

[4] LAUER AA, GRIMM HS, APEL B, et al. Mechanistic link between vitamin B_{12} and Alzheimer's disease[J]. Biomolecules, 2022, 12(1): 129.

[5] KINNEY JW, BEMILLER SM, MURTISHAW AS, et al. Inflammation as a central mechanism in Alzheimer's disease[J]. Alzheimers Dement (N Y), 2018, 4: 575-590.

[6] POLITIS A, OLGIATI P, MALITAS P, et al. Vitamin B_{12} levels in Alzheimer's disease: association with clinical features and cytokine production[J]. J Alzheimers Dis, 2010, 19(2): 481-488.

[7] QUINTANILLA RA, ORELLANA DI, GONZÁLEZ-BILLAULT C, et al. Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway[J]. Exp Cell Res, 2004, 295(1): 245-257.

[8] ALAM P, SIDDIQI MK, CHATURVEDI SK, et al. Vitamin B_{12} offers neuronal cell protection by inhibiting Aβ-42 amyloid fibrillation[J]. Int J Biol Macromol, 2017, 99: 477-482.

[9] FLICKER L, MARTINS RN, THOMAS J, et al. B-vitamins reduce plasma levels of beta amyloid[J]. Neurobiol Aging, 2008, 29(2): 303-305.

[10] SHEN L, JI HF. Associations between homocysteine, folic acid, vitamin B_{12} and Alzheimer's disease: insights from meta-analyses[J]. J Alzheimers Dis, 2015, 46(3): 777-790.

[11] MOMTAZ YA, HAMID TA, IBRAHIM R. Gastritis may boost odds of dementia[J]. Am J Alzheimers Dis Other Demen, 2014, 29(5): 452-456.

[12] CHOI YJ, SHIN DW, JANG W, et al. Risk of dementia in gastric cancer survivors who underwent gastrectomy: a nationwide study in Korea[J]. Ann Surg Oncol, 2019, 26(13): 4229-4237.

[13] SUN Y, LU CJ, CHIEN KL, et al. Efficacy of multivitamin supplementation containing vitamins B_6 and B_{12} and folic acid as adjunctive treatment with a cholinesterase inhibitor in Alzheimer's disease: a 26-week, randomized, double-blind, placebo-controlled study in Taiwanese patients[J]. Clin Ther, 2007, 29(10): 2204-2214.

[14] AISEN PS, SCHNEIDER LS, SANO M, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial[J]. JAMA, 2008, 300(15): 1774-1783.

[15] ZHANG DM, YE JX, MU JS, et al. Efficacy of vitamin B supplementation on cognition in elderly patients with cognitive-related diseases[J]. J Geriatr Psychiatry Neurol, 2017, 30(1): 50-59.

[16] CHEN H, LIU S, GE B, et al. Effects of folic acid and vitamin B_{12} supplementation on cognitive impairment and inflammation in patients with Alzheimer's disease: a randomized, single-blinded, placebo-controlled trial[J]. J Prev Alzheimers Dis, 2021, 8(3): 249-256.

[17] CUI XY, GOOCH H, GROVES NJ, et al. Vitamin D and the brain: key questions for future research[J]. J Steroid Biochem Mol Biol, 2015, 148: 305-309.

[18] YANG K, CHEN J, LI XG, et al. Vitamin D concentration and risk of Alzheimer disease: a meta-analysis of prospective cohort studies[J]. Medicine (Baltimore), 2019, 98(35): e16804.

[19] PATEL P, SHAH J. Role of vitamin D in amyloid clearance via LRP-1 upregulation in Alzheimer's disease: a potential therapeutic target[J]. J Chem Neuroanat, 2017, 85: 36-42.

[20] BANERJEE A, KHEMKA VK, GANGULY A, et al. Vitamin D and Alzheimer's disease: neurocognition to therapeutics[J]. Int J Alzheimers Dis, 2015, 2015: 192747.

[21] WANG LY, HARA K, VAN BAAREN JM, et al. Vitamin D receptor and Alzheimer's disease: a genetic and functional study[J]. Neurobiol Aging, 2012, 33(8): 1844.e1-1844.e9.

[22] ITO S, OHTSUKI S, NEZU Y, et al. 1α,25-dihydroxyvitamin D_3 enhances cerebral clearance of human amyloid-β peptide(1-40) from mouse brain across the blood-brain barrier[J]. Fluids Barriers CNS, 2011, 8: 20.

[23] POGGE E. Vitamin D and Alzheimer's disease: is there a link?[J]. Consult Pharm, 2010, 25(7): 440-450.

[24] CHAI BY, GAO FL, WU RP, et al. Vitamin D deficiency as a

risk factor for dementia and Alzheimer's disease: an updated meta-analysis[J]. BMC Neurol, 2019, 19(1): 284.

[25] Sutherland MK, Somerville MJ, Yoong LK, et al. Reduction of vitamin D hormone receptor mRNA levels in Alzheimer as compared to Huntington hippocampus: correlation with calbindin-28k mRNA levels[J]. Brain Res Mol Brain Res, 1992, 13(3): 239-250.

[26] Moore TB, Koeffler HP, Yamashiro JM, et al. Vitamin D_3 analogs inhibit growth and induce differentiation in LA-N-5 human neuroblastoma cells[J]. Clin Exp Metastasis, 1996, 14(3): 239-245.

[27] Briones TL, Darwish H. Decrease in age-related tau hyperphosphorylation and cognitive improvement following vitamin D supplementation are associated with modulation of brain energy metabolism and redox state[J]. Neuroscience, 2014, 14(262): 143-155.

[28] KALRA A, TEIXEIRA AL, DINIZ BS. Association of vitamin D levels with incident all-cause dementia in longitudinal observational studies: a systematic review and meta-analysis[J]. J Prev Alzheimers Dis, 2020, 7(1): 14-20.

[29] SHEN L, JI HF. Vitamin D deficiency is associated with increased risk of Alzheimer's disease and dementia: evidence from meta-analysis[J]. Nutr J, 2015, 14: 76.

[30] Mehri N, Haddadi R, Ganji M, et al. Effects of vitamin D in an animal model of Alzheimer's disease: behavioral assessment with biochemical investigation of Hippocampus and serum[J]. Metab Brain Dis, 2020, 35(2): 263-274.

[31] Hensley K, Barnes LL, Christov A, et al. Analysis of postmortem ventricular cerebrospinal fluid from patients with and without dementia indicates association of vitamin E with neuritic plaques and specific measures of cognitive performance[J]. J Alzheimers Dis, 2011, 24(4): 767-774.

[32] Yatin SM, Varadarajan S, Butterfield DA. Vitamin E prevents Alzheimer's amyloid-beta-peptide (1-42)-induced neuronal protein oxidation and reactive oxygen species production[J]. J Alzheimers Dis, 2000, 2(2): 123-131.

[33] BOCCARDI V, BARONI M, MANGIALASCHE F, et al. Vitamin E family: role in the pathogenesis and treatment of Alzheimer's disease[J]. Alzheimers Dement (N Y), 2016, 2(3): 182-191.

[34] GRIMM MOW, METT J, HARTMANN T. The impact of vitamin E and other fat-soluble vitamins on Alzheimer's disease[J]. Int J Mol Sci, 2016, 17(11): 1785.

[35] LOPES DA SILVA S, VELLAS B, ELEMANS S, et al. Plasma nutrient status of patients with Alzheimer's disease: systematic review and meta-analysis[J]. Alzheimers Dement, 2014, 10(4): 485-502.

[36] MANGIALASCHE F, XU WL, KIVIPELTO M, et al. Tocopherols and tocotrienols plasma levels are associated with cognitive impairment[J]. Neurobiol Aging, 2012, 33(10): 2282-2290.

[37] MANGIALASCHE F, KIVIPELTO M, MECOCCI P, et al. High plasma levels of vitamin E forms and reduced Alzheimer's disease risk in advanced age[J]. J Alzheimers Dis, 2010, 20(4): 1029-1037.

[38] GUGLIANDOLO A, BRAMANTI P, MAZZON E. Role of vitamin E in the treatment of Alzheimer's disease: evidence from animal models[J]. Int J Mol Sci, 2017, 18(12): 2504.

[39] NOLAN JM, POWER R, HOWARD AN, et al. Supplementation with carotenoids, omega-3 fatty acids, and vitamin E has a positive effect on the symptoms and progression of Alzheimer's disease[J]. J Alzheimers Dis, 2022, 90(1): 233-249.

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