



DOI:10.11817/j.issn.1672-7347.2019.01.016
<http://xbyxb.csu.edu.cn/xbwk/fileup/PDF/201901100.pdf>

脂联素与认知障碍的研究进展

吴莉峰^{1,2}, 唐娅辉^{1,2}, 石镇港^{1,2}, 曾贵荣², 王宇红¹, 姜德建^{1,2}

- (1. 湖南省中药粉体与创新药物省部共建国家重点实验室培育基地, 长沙 410208;
2. 湖南省药物安全评价研究中心, 新药药效与安全评价湖南省重点实验室, 长沙 410331)

[摘要] 脂肪细胞因子是一类由脂肪细胞分泌、具有广泛的生物活性的多肽或蛋白质。脂联素是一种具有胰岛素增敏作用的脂肪细胞因子, 具有抗糖尿病、抗动脉粥样硬化和抗炎等作用。脂联素可参与并调控着认知障碍的发生、发展, 被认为是一个新的认知障碍的调节因子。

[关键词] 脂联素; 脂联素受体; 认知障碍; 发病机制

Research progress in adiponectin and cognitive impairment

WU Lifeng^{1,2}, TANG Yahui^{1,2}, SHI Zhengang^{1,2}, ZENG Guirong², WANG Yuhong¹, JIANG Dejian^{1,2}

(1. Hunan Province Traditional Chinese Medicine Power and the Ministry of Innovative Drugs to Build the National Key Laboratory Cultivation Base, Changsha 410208; 2. Hunan Center of Drug Safety Evaluation and Research of Drugs; Hunan Key Laboratory of Pharmacodynamics and Safety Evaluation of New Drugs, Changsha 410331, China)

ABSTRACT

Adipocytokines are polypeptides or proteins that are secreted by fat cells with a wide range of biological activities. Adiponectin is a fatty cytokine with insulin sensitization. It possesses the function of anti-diabetes, atherosclerosis and anti-inflammation. Adiponectin may participate in regulating the development of cognitive impairment, which is considered as a new regulatory factor for cognitive impairment.

KEY WORDS

adiponectin; adiponectin receptor; cognitive impairment; pathogenesis

认知障碍是指记忆障碍、注意力、语言、执行力和视空间功能等认知功能不同程度的受损的病态

行为学疾病。目前我国轻度认知障碍患病人群约有2 500万, 大于65岁的发病率约为20.8%, 推测到2050

收稿日期(Date of reception): 2018-04-27

第一作者(First author): 吴莉峰, Email: 825131345@qq.com, ORCID: 0000-0002-9903-4133

通信作者(Corresponding author): 姜德建, Email: jiangdejian@hnse.org, ORCID: 0000-0001-7685-3753

基金项目(Foundation item): 湖南省重点研发项目(2017NK2282)。This work was supported by Key R&D Program of Hunan Province, China (2017NK2282).

年认知功能障碍的患病率将是现今的3倍以上^[1]。认知障碍发病机制目前尚不明确。

脂肪细胞因子是一类由脂肪细胞分泌的具有广泛的生物活性的多肽或蛋白质。脂联素(adiponectin, APN)是一种具有胰岛素增敏作用的脂肪细胞因子，具有抗糖尿病、抗动脉粥样硬化和抗炎等作用^[2]。APN与认知障碍有着密切的关系，可能参与并调控着认知障碍的发生和发展，被认为是一个新的认知障碍的调节因子。本文综述近年来认知障碍临床患者与APN水平以及APN调节的认知机制。

1 APN/APN受体的中枢神经作用

APN由244个氨基酸构成，分子量为28~30 kD (1 D=1 u)。人类APN是位于3q27的apM1基因编码，约16 kb，包括3个外显子和2个内含子^[3]。APN在血液中根据不同数量单体组装构成的同源多聚体大小可分为4类，即单体、低分子量的3聚体、中分子量的6聚体和高分子量的多聚体。循环中的血浆APN浓度约为5~30 μg/mL，脑脊液中APN水平约为血浆浓度的1/1000。

APN主要通过APN受体发挥生物学效应，后者目前有3类，即脂联素受体1(AdipoR1)、脂联素受体2(AdipoR2)和T-钙黏蛋白(T-cadherin)。APN能通过同时激活AdipoR1和AdipoR2而激活细胞内信号转导通路，而APN与T-cadherin结合能减弱AdipoR1/AdipoR2介导的信号通路，提示APN通过APN的3个受体亚型发挥了不同的作用且存在拮抗关系^[4]。APN受体在动物大脑的每个区域内均有表达，特别在弧形核、旁氏下丘核的神经元和星形胶质细胞中表达较为丰富。下丘脑与基底核存在AdipoR1提示APN可能参与维持大脑功能的完整性，特别是在记忆和认知过程中起重要作用。AdipoR1和AdipoR2可激活大脑内80%的神经元，通过调节K⁺通道的转导率来改变神经递质和受体的传递，从而调控神经元兴奋性^[5]。在局部缺血的情况下，大脑皮质中的AdipoR1表达水平上升，从而使神经元凋亡增加^[6]。T-cadherin最初表达于胚胎的神经系统，对神经系统细胞的生长呈负性调节作用，能抑制星形胶质细胞和胶质母细胞瘤的细胞系的生长^[7]。

2 APN与认知障碍的关系

2.1 血清APN水平与患者认知障碍的关系

临床研究^[8,9]发现：老年糖尿病轻度认知障碍患者体内的血清APN较正常人低，而阿尔茨海默病患者和血管性认知障碍患者的血清APN含量却呈现上升趋势。APN基因缺乏会导致β淀粉样蛋白(amyloid-β，

Aβ)的沉积，在老年患者早期血浆中的含量明显升高，随着病情的进展，Aβ含量逐渐降低^[10]。早期认知功能障碍患者的血清APN含量呈下降趋势，后期血清APN的含量上升，据此推测可能与APN受体的不敏感性引起的负反馈调节导致的APN代偿性增生有关，但APN水平并不与认知功能障碍呈线性关系。

2.2 APN的抗认知障碍作用

APN缺乏可能会导致大脑神经元和突触的丧失，大脑Aβ42水平增加，Aβ淀粉样蛋白的沉积，微神经胶质和星形胶质增多等，具体表现为空间记忆和学习障碍，恐惧的记忆缺失和焦虑^[11]。APN可以调节记忆与认知障碍，并有助于解除对阿尔茨海默症中观察到的葡萄糖代谢和线粒体功能失调的影响，同时通过调节脂肪酸分解代谢和抗炎系统的敏感性来达到抗认知损伤的目的^[12-13]。

3 APN抗认知障碍的相关机制

3.1 抗炎作用

神经炎性参与认知障碍的发展，研究^[14]表明脑内Aβ沉积和tau蛋白磷酸化可刺激星形胶质细胞和小胶质细胞激活，释放大量炎症因子。APN可减轻女性2型糖尿病患者的炎症反应，血液中APN的含量与血糖含量和血脂变化具有一定的相关性^[15]。炎症引起的脑血管疾病是血管性认知障碍(vascular cognitive impairment, VCI)的主要病理机制，血清中C-反应蛋白(C-reactive protein, CRP)、白介素6(interleukin 6, IL-6)含量的升高可致血管狭窄，APN与其水平呈负相关，并可诱导抗炎介质IL-10和IL-1受体拮抗剂(interleukin-1 receptor antagonist, IL-1RA)含量的增加和树突细胞的数目增加^[16]。IL-1和IL-2等促炎因子可被IL-10抑制。APN能促进抗炎细胞因子含量增加、减少前炎性细胞因子的数量而起到抗炎的作用。在细胞体外的实验研究^[17]中，APN对粒-单系祖细胞的生成和成熟巨噬细胞的吞噬活性有着明显的抑制作用，可减少肿瘤细胞坏死因子-α(tumor necrosis factor-α, TNF-α)的产生，对巨噬细胞的吞噬作用是通过调节一种补体C1受体所介导的。APN受体的向上调节可导致抗原特异性T细胞的凋亡及增值抑制。APN终止炎症反应的主要表现为在急性期炎症中通过抑制成熟巨噬细胞的功能，在晚期慢性炎症中通过抑制粒-单系祖细胞系的生长而避免过度的免疫反应^[18]。

3.2 抗氧化应激

有学者^[19]认为：氧化应激作为阿尔茨海默病患

者脑内最早出现的特征,是引起疾病的主要起源,若能保护神经元的氧化应激所带来的损伤,则能成功地预防该种疾病。淀粉样积累诱发导致的氧化应激和线粒体功能紊乱导致的功能障碍是阿尔茨海默病的发病机制。在细胞体外实验中,APN能保护过氧化氢(H_2O_2)诱导的氧化应激反应产生的细胞毒性,这与APN结合AdipoR1/AdipoR2后激活腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)进一步启动体内调节配适器APPL1后抑制核因子(nuclear factor-kappa B, NF- κ B)的表达有关^[20]。APN可通过与细胞表面的AdipoR1与AdipoR2结合激活APPL1, APPL1结合N-末端胞内域的受体后可激活AMPK,并抑制AMPK介导的NF- κ B和血管内皮生长因子(vascular endothelial growth factor, VEGF)转导通路而达到保护神经的作用^[21]。NF- κ B转录因子为氧化还原敏感因子,可增加NO的产生,使活性氧簇(reactive oxygen species, ROS)生成增加,而ROS又参与氧化型低密度脂蛋白的形成,后者可激活NF- κ B,引起额外的ROS生成,从而介导氧化应激^[22]。抗氧化剂可逆转3T3-L1型脂肪细胞APN的表达,短期暴露在高浓度的 H_2O_2 和持续暴露在低浓度的 H_2O_2 均能明显地引起APN基因表达的变化^[23]。这意味着氧化应激和APN的调节是双向性的。

3.3 抗糖脂代谢失常

胰岛素抵抗可导致异常的糖原合成酶3(glycogen synthase kinase 3, GSK3)的活化,引起细胞内和细胞外A β 淀粉样蛋白沉积,从而导致阿尔茨海默病。在阿尔茨海默病患者脑脊液中,胰岛素和胰岛素生长因子-1(insulin-like growth factor-1, IGF-1)水平明显低于正常大脑,胰岛素和IGF-1的表达功能随着阿尔茨海默病的进展而恶化^[24-25]。临床研究^[26]发现:糖尿病患者体内的APN水平要低于正常人,APN具有抗胰岛素抵抗作用。其机制可能与APN可增加血液中胰岛素的含量而保证大脑糖利用,减少神经纤维缠结,同时通过抑制胰岛素降解酶而减少 β 样淀粉样蛋白的聚集有关^[27-28]。在C57BL/6小鼠的体内实验中发现:5氨基-4咪唑甲酰胺核苷酸(5-amino-4-imidazolecarboxamide riboside, AICAR)作为AMPK的激活剂可被APN激活,从而提高胰岛素的利用率和脂肪酸的氧化反应^[29]。APN在瘦素的信号通路下,不仅激活磷酸肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)而调节ATP依赖的钾离子通道,同时通过激活蛋白激酶 β 来增强Tau蛋白的磷酸化表达,促进代谢淀粉样前体蛋白和 β 淀粉样蛋白的清除^[30]。此外,APN基因启动子上有过氧化物酶增殖激活受体(peroxisome proliferators-activated receptor, PPAR)的结合位点,可参与PPAR的转录与目标基因的表达^[31]。PPAR属于细胞核激素受体

超家族,主要功能是参与肝脂肪代谢和脂肪细胞的分化。

3.4 抗神经损伤

神经突触的丢失,神经数量的减少,神经功能的下降等均是认知障碍的发病诱因。在以脑缺血为模型的APN基因敲除小鼠(adiponectin-knockout, APN-KO)和野生型(wild type, WT)小鼠中^[32],APN-KO组表现出脑梗死面积的扩大和神经系统的缺陷,而体内注射APN可使脑梗死面积减小而保护神经系统。在体外培养的成年Fisher大鼠研究^[33]中发现,APN可以促进P38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38MAPK)磷酸化来促进大鼠海马神经干细胞/祖细胞(neural stem/progenitor cells, hNSCs)的增殖。P38MAPK作为AMPK下游靶点可有效地抑制PPAR- α 的转录基因和目标基因的表达,可抑制脂肪酸氧化。APN可对抗神经母细胞瘤细胞SH-SY5Y中产生的A β 神经毒性作用^[34],减少海人酸产生的兴奋毒性及特异性半胱氨酸蛋白酶-3(caspase-3)的激活,从而减少神经细胞凋亡来保护神经系统^[35]。此外,APN可通过诱导AMPK上调抗氧化酶,调节Bcl-2和Bax来改善线粒体功能,减少细胞毒性,以及刺激海马神经再生^[36]。

4 结语

目前在认知功能的治疗中,主要药物有胆碱功能抑制药(如多奈哌齐、他克林)、抗炎药(如布洛芬、双氯芬酸)、抗氧化剂(如维生素E、银杏提取物)等。认知功能障碍常常在很多疾病的后期变化中作为伴随症状出现,如脑卒中、糖尿病等。综上所述,APN兼具抗认知障碍及胰岛素增敏特性的特性,可用于新型抗认知障碍的研究与开发,特别是对早期认知功能障碍和前驱糖尿病的患者具有重要作用。APN作为一种新型的抗认知障碍分子,其机制尚不完善,对于其在认知功能障碍发展过程中的变化,以及其抗认知障碍作用和相关受体仍需进一步研究。

利益冲突声明: 作者声称无任何利益冲突。

参考文献

- [1] 刘晋,赵敬堃,段淑荣,等.轻度认知障碍的研究进展[J].现代生物医学进展,2017,17(11):2170-2173.
- LIU Jin, ZHAO Jingkun, DUAN Shurong, et al. Advances in mild

- cognitive impairment[J]. *Progress in Modern Biomedicine*, 2017, 17(11): 2170-2173.
- [2] 党洁梅, 刘婵桢, 张洁清. 脂联素、胰岛素抵抗与子宫内膜癌的发生发展[J]. *国际妇产科学杂志*, 2017, 44(2): 159-162.
- DANG Jiemei, LIU Chanzhen, ZHANG Jieqing. Research progress in adiponectin, insulin resistance and endometrial carcinoma[J]. *International Journal of Gynecology and Obstetrics*, 2017, 44(2): 159-162.
- [3] Ambroziak M, Kolanowska M, Bartoszewicz Z, et al. Adiponectin gene variants and decreased adiponectin plasma levels are associated with the risk of myocardial infarction in young age[J]. *Gene*, 2018, 64(2): 498-504.
- [4] Thundyil J, Pavlovski D, Sobey CG, et al. Adiponectin receptor signalling in the brain[J]. *Brit J Pharmacol*, 2012, 165(2): 313-327.
- [5] Miranda-Martínez A, Mercado-Gómez OF, Arriaga-Ávila V. Distribution of adiponectin receptors 1 and 2 in the rat olfactory bulb and the effect of adiponectin injection on insulin receptor expression[J]. *Int J Endocrinol*, 2017, 12(31): 89-98.
- [6] Thundyil J, Tang SC, Okun E, et al. Evidence that adiponectin receptor 1 activation exacerbates ischemic neuronal death[J]. *Exp Transl Stroke Med*, 2010, 2(1): 15-23.
- [7] Obata Y, Kita S, Koyama Y, et al. Adiponectin/T-cadherin system enhances exosome biogenesis and decreases cellular ceramides by exosomal release[J]. *JCI Insight*, 2018, 3(8): 19-21.
- [8] Fagerberg B, Kellis D, Bergström G, et al. Adiponectin in relation to insulin sensitivity and insulin secretion in the development of Type 2 diabetes: a prospective study in 64-year-old women[J]. *J Intern Med*, 2011, 269(6): 636-643.
- [9] Teixeira AL, Diniz BS, Campos AC, et al. Decreased levels of circulating adiponectin in mild cognitive impairment and Alzheimer's disease[J]. *Neuromol Med*, 2013, 15(1): 115-121.
- [10] Shang J, Yamashita T, Fukui Y, et al. Different associations of plasma biomarkers in Alzheimer's disease, mild cognitive impairment, vascular dementia, and ischemic stroke[J]. *J Clin Neurology (Seoul, Korea)*, 2018, 14(1): 29-35.
- [11] Ng CL, Cheng OY, Jian M, et al. Chronic adiponectin deficiency leads to Alzheimer's disease-like cognitive impairments and pathologies through AMPK inactivation and cerebral insulin resistance in aged mice[J]. *Mol Neurodegener*, 2016, 11(1): 71-87.
- [12] Song J, Lee JE. Adiponectin as a new paradigm for approaching Alzheimer's disease[J]. *Anat Cell Biol*, 2013, 46(4): 229-234.
- [13] Waragai M, Ho G, Takamatsu Y, et al. Importance of adiponectin activity in the pathogenesis of Alzheimer's disease[J]. *Ann Clin Transl Neurol*, 2017, 4(8): 591-600.
- [14] Bednarska-Makaruk M, Graban A, Wiśniewska A, et al. Association of adiponectin, leptin and resistin with inflammatory markers and obesity in dementia[J]. *Biogerontology*, 2017, 18(4): 561-580.
- [15] Højlund K. Metabolism and insulin signaling in common metabolic disorders and inherited insulin resistance[J]. *Dan Med J*, 2014, 61(7): 48-60.
- [16] Kyriazi E, Tsiora PC, Boutati E, et al. Effects of adiponectin in TNF- α , IL-6, and IL-10 cytokine production from coronary artery disease macrophages[J]. *Horm Metabolic Res*, 2011, 43(8): 537-544.
- [17] Yamaguchi N, Kukita T, Li YJ, et al. Adiponectin inhibits induction of TNF- α /RANKL-stimulated NFATc1 via the AMPK signaling[J]. *Febs Lett*, 2008, 582(3): 451-456.
- [18] van Stijn CM, Kim J, Lusis AJ, et al. Macrophage polarization phenotype regulates adiponectin receptor expression and adiponectin anti-inflammatory response[J]. *FASEB J*, 2015, 29(2): 636-649.
- [19] Frühbeck G, Catalán V, Rodríguez A, et al. Involvement of the leptin-adiponectin axis in inflammation and oxidative stress in the metabolic syndrome[J]. *Sci Rep*, 2017, 7(1): 66-97.
- [20] Cheng KK, Lam KS, Wang Y, et al. Adiponectin-induced endothelial nitric oxide synthase activation and nitric oxide production are mediated by APPL1 in endothelial cells[J]. *Diabetes*, 2007, 56(5): 1387-1394.
- [21] Song J, Choi SM, Whitcomb DJ, et al. Adiponectin controls the apoptosis and the expression of tight junction proteins in brain endothelial cells through adipoR1 under beta amyloid toxicity[J]. *Cell Death Dis*, 2017, 8(10): 491-504.
- [22] Chan KH, Lam KS, Cheng OY, et al. Adiponectin is protective against oxidative stress induced cytotoxicity in amyloid-beta neurotoxicity[J]. *PLoS One*, 2012, 7(12): 52-64.
- [23] 张秀娟, 王丽静, 刘小莺, 等. 氧化应激对3T3-L1脂肪细胞MCP-1、PAI-1、脂联素表达的影响[J]. *福建医科大学学报*, 2012, 46(1): 1-6.
- ZHANG Xiujuan, WANG Lijing, LIU Xiaoying, et al. Effect of oxidative stress on the expression of MCP-1, PAI-1, adiponectin in 3T3-L1 adipocytes[J]. *Journal of Fujian Medical University*, 2012, 46(1): 1-6.
- [24] Orrù S, Nigro E, Mandola A, et al. A Functional interplay between IGF-1 and adiponectin[J]. *Int J Mol Sci*, 2017, 18(10): 21-45.
- [25] Wang W, Yu JT, Tan L, et al. Insulin-like growth factor 1 (IGF1) polymorphism is associated with Alzheimer's disease in Han Chinese[J]. *Neurosci Lett*, 2012, 531(1): 20-23.
- [26] Kim Y, Lim JH, Kim MY, et al. The adiponectin receptor agonist adiporone ameliorates diabetic nephropathy in a model of Type 2 diabetes[J]. *J Am Soc Nephrol*, 2018, 29(4): 1108-1127.
- [27] Waragai M, Ho G, Takamatsu Y, et al. Importance of adiponectin activity in the pathogenesis of Alzheimer's disease[J]. *Ann Clin Transl Neurol*, 2017, 4(8): 591-600.
- [28] 徐璐, 张青, 秦毅, 等. 胰岛素抵抗小鼠脂联素及其受体1与MMP-9表达的相关性研究[J]. *宁夏医科大学学报*, 2017,

- 39(5): 497-500.
- LU Xu, ZHANG Qing, QIN Yi, et al. The relationship of expressions of adiponectin, adiponectin receptor 1 and matrix metalloproteinase-9 in insulin resistance mice[J]. Journal of Ningxia Medical University, 2017, 39(5): 497-500.
- [29] Oki K, Arias EB, Kanzaki M, et al. Prior treatment with the AMPK activator AICAR induces subsequently enhanced glucose uptake in isolated skeletal muscles from 24 month-old rats[J]. Appl Physiol Nutr Metab, 2018, 43(8): 795-805.
- [30] Huang XF, Chen JZ. Obesity, the PI3K/Akt signal pathway and colon cancer[J]. Obes Rev, 2009, 10(6): 610-616.
- [31] Guo M, Li C, Lei Y, et al. Role of the adipose PPAR γ -adiponectin axis in susceptibility to stress and depression/anxiety-related behaviors[J]. Mol Psychiatr, 2016, 22(7): 1056-1068.
- [32] Ng RC, Cheng OY, Jian M, et al. Chronic adiponectin deficiency leads to Alzheimer's disease-like cognitive impairments and pathologies through AMPK inactivation and cerebral insulin resistance in aged mice[J]. Mol Neurodegener, 2016, 11(1): 71-87.
- [33] Zhang D, Guo M, Zhang W, et al. Adiponectin stimulates proliferation of adult hippocampal neural stem/progenitor cells through activation of p38 mitogen-activated protein kinase (p38MAPK)/glycogen synthase kinase 3 β (GSK-3 β)/ β -catenin signaling cascade[J]. J Biol Chem, 2011, 286(52): 44913-44920.
- [34] Ko JH, Nam D, Um JY, et al. Bergamottin inhibits adipogenesis in 3T3-L1 cells and weight regulation in diet-induced obese mice[J]. Am J Chin Med, 2018, 46(3): 601-615.
- [35] Qiu G, Wan R, Hu J, et al. Adiponectin protects rat hippocampal neurons against excitotoxicity[J]. AGE, 2011, 33(2): 155-165.
- [36] Weisz F, Piccinin S, Mango D, et al. The role of adiponectin receptors in the regulation of synaptic transmission in the hippocampus[J]. Synapse, 2017, 71(5): 21-38.

(本文编辑 傅希文)

本文引用: 吴莉峰, 唐娅辉, 石镇港, 曾贵荣, 王宇红, 姜德建. 脂联素与认知障碍的研究进展[J]. 中南大学学报(医学版), 2019, 44(1): 100-104. DOI:10.11817/j.issn.1672-7347.2019.01.016

Cite this article as: WU Lifeng, TANG Yahui, SHI Zhengang, ZENG Guiyong, WANG Yuhong, JIANG Dejian. Research progress in adiponectin and cognitive impairment[J]. Journal of Central South University. Medical Science, 2019, 44(1): 100-104. DOI:10.11817/j.issn.1672-7347.2019.01.016