· 抑郁症专题 ·

脂联素水平与抑郁症相关性研究进展

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DOI：10.3969/j.issn.1009-6574.2020.11.008

【摘要】 抑郁症是发病率最高的精神疾病，破坏力强、致残率高，是全球医疗负担的主要疾病之一。研究发现脂联素不仅是代谢性疾病的发病机制，而且与抑郁症的发生发展密切相关。现对抑郁症与脂联素的关系，就国内外研究的进展作一综述。

【关键词】 抑郁症； 脂联素； 认知功能； 发病机制； 综述

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【**Abstract**】 Depression has the highest incidence among mental diseases. It has strong destructive power and high disability rate. It is one of the main diseases of global medical burden. It is found that adiponectin is not only the pathogenesis of metabolic diseases, but also closely related to the occurrence and development of depression. This article reviews the relationship between depression and adiponectin, and the related research progress at home and abroad.

【**Key words**】 Depressive disorder； Adiponectin； Cognitive function； Pathogenesis； Review

抑郁症的核心症状为心境低落、兴趣减退、快感缺失，常常伴有神经认知功能障碍以及代谢性疾病，影响疾病的病程和预后。至2020年已经成为仅次于心血管疾病的第二大疾病负担源，是最具破坏性的精神疾病，给患者和医疗保健系统带来了巨大的经济负担[1-2]。抑郁症可严重影响患者的生活质量，导致了自伤、自杀等严重后果，医疗保健资源的消耗增多，增加离职及失业的风险，给个人和社会带来严重后果。

现有的研究结果显示，抑郁症患者脂联素水平低下。脂联素参与并调节5-HT能神经元的功能，这可能是脂联素参与情绪调节的机制。脂联素可以穿过血脑屏障并靶向循环至脂联素受体的多个脑区域[3]。其受体激动剂可以促进成人脑神经的发生，重塑包括海马区域、下丘脑、背沟核中的突触可塑性，并在成年小鼠中观察到脂联素的抗抑郁作用[4]。这种对抑郁障碍的新认识，指导了一类针对脑结构和脑神经可塑性的新型抗抑郁治疗方案。目前，脂联素系统是有效和快速作用的抗抑郁反应的潜在治疗方式[5-6]，并且其影响抑郁症的发生机制，以及对抑郁症预防复发的作用已经越来越被重视。

一、脂联素对抑郁样行为的影响

1.脂联素及其受体的作用：脂联素是由脂肪细胞释放的循环激素，它以多种形式存在于人体内，是通过全长脂联素的蛋白水解产生的一种激素。脂联素通过与其受体激动剂结合而起作用，它们在中枢神经系统的不同区域(例如海马区域、下丘脑等)中表达。抑郁症被认为是一种神经认知障碍，伴有成人神经发生以及神经回路的相关损伤[7-8]。有证据表明，脂联素直接作用于大脑可增强N-甲基-D-天冬氨酸(NMDA)受体功能[9]，该受体对神经元回路的形成起着关键作用[10]，是学习和记忆过程中一类至关重要的受体。其在重度抑郁症的治疗中诱导快速并持久的抗抑郁作用[11]。外周脂联素水平的表达对抑郁的影响与其有着相似的作用。它的作用是增加谷氨酸能传递、突触再生、突触可塑性和神经营养因子表达[12]，参与情绪调节的关键大脑区域，如前额叶皮质和海马，它可以作用相应的受体，包括海马和内侧前额叶皮质[13]。此外，脂联素受体激动剂的全身给药可以在抑郁小鼠中引发抗抑郁反应[14]，表明它对大脑的直接影响。因此，脂联素信号传导途径，通过对中枢神经系统的不同区域的调节，以及对突触可塑性及神经营养因子有益作用来影响个体的抑郁样行为，也揭示了一种新的抗抑郁治疗策略。

2.脂联素抗抑郁研究：一项由横断面(n=575)和纵向(n=262)组成的研究表明，抑郁症患者的症状严重程度与脂联素水平有关[15]。最近的一项荟萃分析显示，与健康人群相比，抑郁患者的脂联素水平降低[16]。脂联素也称为抗感染细胞因子，参与调节炎性反应[17]。代谢紊乱和心血管疾病均可观察到脂联素水平改变，抑郁症通常与这些疾病状态共存[18]。一项大型横断面研究(n=1 227)报道了脂联素水平降低与抑郁严重程度的变化趋势[19](P=0.09)。在动物模型中已经显示了脂联素的抗抑郁作用，对抑郁样行为和恐惧记忆消退有特异性作用[20]。脂联素信号激活后功能性神经可塑性的变化[21]，也可能是抗抑郁作用的基础。因此，显而易见脂联素系统不仅可以诱导快速和持续的抗抑郁作用，还可以调节与抑郁症有关的代谢功能障碍。尽管脂联素在神经可塑性中起作用的机制仍有一些拮抗作用有待解释，但脂联素系统是一种有前途的抗抑郁途径。

二、脂联素与神经认知功能相关性研究

脂联素对各种脑部疾病(包括阿尔茨海默病)有潜在神经保护作用[22]。脂联素受体不仅在外周组织表达，在情感相关性脑区也有表达，如皮层、下丘脑、垂体和海马，而海马是学习和记忆过程的重要区域[8]。脂联素血浆水平的改变与神经系统疾病有关，包括阿尔茨海默病和重度抑郁症[23]。为了更好地了解脂联素在海马突触功能中的作用，首先确定了脂联素受体1(AdipoR1)、脂联素受体2(AdipoR2)的突触定位[24]。通过使用行为和电生理技术将脂联素基因敲除(APN-KO)小鼠与健康小鼠组对照进行比较[18]，研究脂联素对认知和突触功能的影响。脂联素受体能改善APN-KO小鼠突触可塑性中的缺陷。其中AdipoR2显示在突触前和突触后定位增加，而AdipoR1大量存在于突触前和突触后部分[25]。APN-KO小鼠在新型物体识别(NOR)和迷宫测试中显示出认知缺陷[26]。这可以通过APN-KO小鼠海马侧支通路的长时程增强(long-term potentiation，LTP)缺陷来反映，LTP被称为学习和记忆的细胞关联[27]。LTP的缺陷可以通过与脂联素受体一起孵育海马片而挽救，表明脂联素受体会影响突触功能[28]。由此可以看出脂联素受体在海马区域的高表达是改善认知的重要作用。在痴呆的大鼠模型中已显示出脂联素对记忆、认知缺陷的有益作用。综上所述，这些结果表明脂联素是海马区域中认知和突触功能的重要调节剂。

三、脂联素对抑郁症的影响机制

1.下丘脑－垂体－肾上腺(HPA)轴：研究表明，HPA轴的功能亢进会导致抑郁的发生。人脂联素可通过调控HPA轴[29]的功能，改善抑郁症状[29]。HPA轴的亢进与低脂联素水平有关[30]。脂联素调节几种关键促感染和抗感染细胞因子的表达[31]，包括降低肿瘤坏死因子－α(TNF-α)的分泌并诱导产生抗感染细胞因子[32]。在以往的研究中，常见精神障碍中都描述了免疫过度活化和细胞因子相应关系的失调，脂联素水平的降低由于其抗感染特性而表现出慢性炎症状态，在啮齿类动物模型中阐述了这一观点[33]。脂联素不足增加了对压力诱发抑郁行为的敏感性，并损害了HPA轴的功能，功能异常的脂联素信号传导在大脑中通过其受体激动剂发生作用[34]，并直接影响重要的大脑功能[35]，影响海马神经发生和突触可塑性。研究发现，脂联素受体激动剂(AdipoRon)[36]的日常治疗主要是通过口服新型小分子脂联素受体激动剂，不仅可以预防皮质酮引起的肥胖症以及代谢综合征的相关问题，而且还可能逆转小鼠模型中皮质酮诱导的抑郁样状态[37]。

2.脂联素通过5-HT系统对抑郁症的病理机制产生影响：(1)研究发现AdipoR1在背沟核中表达，并与5-HT神经元标记色氨酸羟化酶2(TPH2)共定位[26]，5-HT神经元中AdipoR1的选择性缺失可引起小鼠的快感不足，嗅闻时间、对蔗糖的偏好性降低表现为类抑郁样行为[38]。在5-HT神经元缺乏AdipoR1的小鼠中，TPR2的表达水平下调，同时背沟核及其两个主要投射区域海马和内侧前额叶皮层(mPFC)中的5-HT免疫反应性降低，5-HT转运蛋白(SERT)的表达在背沟核区域上调。SERT[39]是单胺类转运体家族中的一员，负责从突触间隙重新摄取5-HT，是细胞外环境5-HT的最有力的调控者，与5-HT高亲和力的特性使其发挥严格控制5-HT的强度和持续时间的作用，因此SERT的微量变化可引起多种生理功能紊乱。结果发现，脂联素通过AdipoR1受体作用于5-HT神经元增加突触间隙中5-HT的水平[40-41]，起到抗抑郁的治疗作用。(2)大多数抗抑郁药，特别是选择性5-HT再摄取抑制剂(selective serotonin reuptake inhibitors，SSRIs)，都会增加突触的5-HT活性[42]。有研究查找了脂联素信号传导对5-HT系统影响的生物学基础[43]。研究表明抑郁患者中存在5-HT缺乏症，色氨酸(5-HT的必需氨基酸前体)的快速消耗可降低5-HT的合成，缓解患者的抑郁复发。在AdipoR1条件性基因敲除小鼠，确定了在5-HT神经元中AdipoR1缺失对抑郁和焦虑相关行为，发现选择性敲除5-HT神经元中的AdipoR1降低了背沟核中的TPH2[44]水平，同时降低了小鼠的细胞体区域和两个末端区域(即mPFC和海马)的5-HT免疫反应性。减少5-HT合成将减缓

5-HT释放和传播。在5-HT神经元中缺乏AdipoR1的小鼠对SSRIs类药物氟西汀的抗抑郁效果差，表明AdipoR1是调节正常的5-HT神经传递所必需的[45]，即只有功能正常的脂联素受体才会使氟西汀产生抗抑郁作用，而功能异常的受体，信号传导会导致与抑郁相关的行为。脂联素受体作用下降会导致SERT的表达增高，降低突触间隙5-HT的浓度。动物实验研究表明，中缝背核(DRN)中的5-HT神经元编码奖励信号[46]，激活5-HT神经元，刺激5-HT神经元诱导发生[47]。实验结果表明脂联素及受体信号在5-HT神经元中与抑郁相关的行为和抗抑郁反应中的重要作用，参与了5-HT神经传递关键成分的调节。综合上述的研究结果可以发现，脂联素能抑制HPA轴的相关作用，可以有效地改善抑郁症状，在啮齿动物中也进一步证实类似的结果。与抑郁症状发生最相关的5-HT神经元的反应性也受脂联素水平的影响，其在背沟核DRN区域，以及在抗感染、氧化应激等多途径改善抑郁样症状。

四、局限性与展望

抑郁障碍与循环脂联素水平的差异有关，其特定的结构与功能决定了其广泛地参与着机体的各种生理病理过程。脂联素水平和抑郁症状的关联是显而易见的。尽管这些文献研究没有解释因果关系，但不同人群之间的关联性表明，循环脂联素可能是诊断和监测常见精神健康疾病的有前途的生物标志物。需要进一步来探讨改变脂联素水平是否是确切的抗抑郁治疗的途径，脂联素及其信号通路可能代表了创新的治疗策略，特别是在存在抑郁障碍–代谢性疾病合并症的地方。为此，应展开进一步研究以阐明脂联素在抑郁障碍中的病理生理学作用以及在药物治疗中的作用，为攻克抑郁障碍在诊疗的难题上增添新的证据。

利益冲突 文章所有作者共同认可文章无相关利益冲突

作者贡献声明 资料收集整理及论文撰写为张金慧，选题设计及论文修改为邬素萍

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(收稿日期: 2020-09-10)
(本文编辑: 戚红丹)