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·综述·

鸢尾素的抗炎机制在卒中后抑郁治疗中的研究进展

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摘　要：卒中后抑郁指脑卒中后发生的抑郁状态，是脑卒中的一种常见后遗症，为患者家庭及社会带来了严重的经济负担。近年来，鸢尾素作为一种新型抗抑郁药物备受关注。然而，鸢尾素在缓解卒中后抑郁中的作用机制尚无相关文献进行总结。该文综述了相关研究，从抗炎机制探讨了鸢尾素在治疗卒中后抑郁中的相关作用，如改善能量代谢、神经保护、调节神经递质水平等，讨论其作为卒中后抑郁治疗药物的可能性，以期为临床缓解卒中后抑郁提供更多的药物选择，为进一步的研究提供参考。

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关键词：卒中后抑郁；鸢尾素；治疗；机制

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Research advances in the anti-inflammatory mechanism of irisin in treatment of post-stroke depression

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Abstract: Post-stroke depression refers to the depressive state that occurs after stroke and is a common sequela of stroke, bringing serious economic burden to the families of patients and the society. In recent years, irisin has attracted much attention as a new type of antidepressive agent; however, no articles have summarized the mechanism of action of irisin in alleviating post-stroke depression. This article reviews related studies and discusses the anti-inflammatory mechanism of irisin in the treatment of post-stroke depression, such as improving energy metabolism, protecting the nerves, and regulating the levels of neurotransmitters, as well as the possibility of irisin as a treatment drug for post-stroke depression, in order to provide more drug options for clinical relief of post-stroke depression and a reference for further research.

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Keywords: post-stroke depression; irisin; treatment; mechanism

脑卒中后约三分之一的患者出现卒中后抑郁（post-stroke depression, PSD），其发生的高危风险因素包括既往抑郁史、脑卒中严重程度、病变部位等，其诊断主要基于各种抑郁量表[1]。目前PSD的发生机制可能包括下丘脑-垂体-肾上腺（hypothalamic-pituitary-adrenal, HPA）轴的调节异常[2]、炎症因子增加、单胺水平降低、谷氨酸介导的兴奋性毒性和异常的神经营养反应等[3]。传统药物（如三环类抗抑郁药和选择性血清素受体抑制剂）对于PSD的早期干预可能有效[3]，但由于药物不良反应及个体差异，导致治疗效果不理想，故选择新型药物具有十分重要的意义。2012年，鸢尾素的发现使得PSD的治疗有了新的可能。鸢尾素不仅对于PSD的发生具有预测作用，并且能够在一定程度上缓解患者的抑郁症状，因此具有十分重要的研究意义。本文主要讨论鸢尾素在PSD治疗

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中的研究进展。

1　鸢尾素概况

鸢尾素是近年来发现的一种肌细胞因子,是由含Ⅲ型纤连蛋白域蛋白5(recombinant fibronectin type Ⅲ domain containing protein 5, FNDC5)基因编码的一种Ⅰ型膜蛋白,FNDC5经蛋白水解切割后释放鸢尾素[4]。鸢尾素含有112个氨基酸,包括N-末端、纤连蛋白Ⅲ结构域和C-末端尾部,是经水解处理后分泌到血液中的多肽激素[5]。其主要在运动过程中由骨骼肌分泌,分布于骨骼肌、脂肪组织、肝脏和大脑中,在肌肉的发育和再生,以及其他代谢过程中具有重要作用[6]。目前关于鸢尾素的研究涉及人体多个系统的疾病,包括神经系统疾病[7]、内分泌系统疾病[8]、循环系统疾病[9]、运动系统疾病[10]等。

在中枢神经系统中,鸢尾素分布在大脑皮质、海马、壳核和下丘脑,穿过血脑屏障,在小脑浦肯野细胞中高度表达,参与神经发生、神经元增殖和神经元分化。对于神经系统具有保护作用,其机制:①通过过氧化物酶体增殖受体γ辅激活因子α(peroxisome proliferators-activated receptor γ coactivator l alpha, PGC-1α)/FNDC5/脑源性神经营养因子(brain derived neurotrophic factor, BDNF)信号通路改善脑缺血。②激活瞬时细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)磷酸化,增加细胞外BDNF的水平,保护神经功能。③通过ERK/核因子κB(nuclear factor-κB, NF-κB)信号通路改善血脑屏障功能障碍,但相关机制及其来源尚不明确[11]。

血清低鸢尾素水平与缺血性脑卒中的发生呈正相关[12],原因在于低鸢尾素水平涉及动脉粥样硬化[13]、糖尿病[14]、心房颤动[15]等与缺血性脑卒中发生相关的多个危险因素。同时,低鸢尾素水平也与缺血性脑卒中患者的不良预后,如生活能力下降、认知障碍[16-17]、抑郁状态[18-19]相关,是缺血性脑卒中患者早期功能预后不良的预测因子[20]。2018年,Tu等[21]在一项前瞻性队列研究中纳入1 205名首次急性缺血性脑卒中患者,测定入院时血清中鸢尾素水平,并在6个月的随访研究中调查其与PSD的相关性,发现入院时低水平鸢尾素是卒中6个月时PSD发生的危险因素。2023年,一项基础实验通过对行大脑中动脉闭塞手术的小鼠给予纳豆激酶治疗,记录其游泳模式,发现纳豆激酶可以通过上调大脑中动脉闭塞小鼠血浆鸢尾素水平促进海马神经发生和认知功能改善[22]。此外,一项前瞻性队列研究纳入20名参与者进行为期8周每周3 d的运动计划,在运动组中观察到循环系统中鸢尾素水平增加,与肌肉力量和心肺耐力呈正相关,得出运动可以提高鸢尾素水平,可能对于中风相关的肌肉功能下降有一定预防作用的结论[23]。

2　鸢尾素的抗炎机制对PSD的治疗作用

神经炎症在PSD的发展中具有核心作用。过度的炎症反应可以激活N-甲基-D-天冬氨酸受体来促进谷氨酸兴奋性毒性,拮抗5-HT,降低突触可塑性和神经元存活,从而导致PSD的发生[24]。鸢尾素通过抗氧化应激及抗炎作用不仅能够产生抗动脉粥样硬化作用[25],有效预防及治疗缺血性脑卒中[26],也能够改善PSD相关症状[18]。

2.1　鸢尾素的抗炎机制

鸢尾素的抗炎机制有多条途径:①鸢尾素通过过氧化物酶体增殖物激活受体γ启动M2型巨噬细胞极化,降低炎症因子[如肿瘤坏死因子α(tumor necrosis factor-α, TNF-α)、白细胞介素(interleukin, IL)-1β等]的表达,从而发挥抗炎作用,同时通过抑制缺血区域的细胞凋亡,减轻脑损伤[27]。②鸢尾素通过下调NF-κB通路发挥抗炎作用[28-29],降低多种促炎细胞因子,从而减轻神经炎症[30]。③鸢尾素通过增加抗氧化酶(包括超氧化物歧化酶、谷胱甘肽过氧化物酶和过氧化氢酶9)的表达,增强巨噬细胞的活性和增殖,提高其吞噬能力,并减少活性氧的产生,发挥抗氧化作用。

高浓度的鸢尾素减弱了Toll样受体4的表达,并减少了脂多糖对巨噬细胞中MyD 88衔接蛋白的刺激,抑制促分裂原活化的蛋白激酶级联信号通路,降低NF-κB核转录因子、c-Jun N-末端激酶和ERK磷酸化水平,从而减少关键促炎细胞因子(如IL-1β、IL-6、TNF-α、角质形成细胞趋化因子、巨噬细胞趋化蛋白1和高迁移率族蛋白1)蛋白的释放,降低慢性炎症对神经的损害[31]。此外,在脑缺血的情况下,鸢尾素可抑制脑组织中基质金属蛋白酶9的表达和活性,保护血脑屏障[32],减少氧化应激、胰岛素抵抗、神经营养因子失衡,从而减少脑梗死体积、脑水肿,改善神经功能缺损[33]。2016年,Li等[34]进行的一项研究,通过监测鸢尾素水平的变化,证明了鸢尾素通过激活脑组织中细胞内信号通路(Akt和ERK 1/2),抑制促炎细胞因子(如TNF-α和IL-6)的分泌,从而减少氧化应激,改善神经功能缺损,减少了脑梗死体积、神经功能缺损和脑水肿。有实验证明,当脑卒中患者入院时血清中的鸢尾素浓度较高时,其神经功能缺损的恢复相对较好[35]。

2.2　抗炎机制与前额叶皮质区能量代谢的改善

PSD的发生与受损部位及能量代谢相关。额叶是情绪障碍发生的重要部位,其受损可显著增加情绪障碍(如PSD)发生的可能[3]。线粒体能量代谢在PSD发病机制中具有极其重要的作用[36]。线粒体代谢稳态的失衡可能是多种有害级联反应的初始过程,包括炎症浸润、神经元凋亡、氧化应激等[37],导致单胺氧化酶水平增加和多巴胺减少,从而出现抑郁症状[38]。

鸢尾素在降低氧化应激,改善线粒体稳态失衡方面具有独特的优势[39],通过增加线粒体腺苷三磷酸(adenosine triphosphate, ATP)的产生、抑制线粒体氧化应激及细胞凋亡来减轻线粒体功能障碍,在调节代谢紊乱

的同时稳定线粒体功能[40],改善内皮功能障碍和微血管损伤,预防缺血-再灌注损伤[41]。2019年,一项有关5′-腺苷单磷酸活化蛋白激酶(5′-adenosine monophosphate-activated protein kinase, AMPK)通路与线粒体保护作用的研究结果提示,鸢尾素通过激活AMPK通路维持细胞活力、改善内皮功能障碍、减弱细胞的氧化应激、改善细胞ATP生物遗传学及维持线粒体电位,最终促进细胞存活,该研究强调了鸢尾素对细胞损伤的治疗作用[42]。2016年,一项关于鸢尾素在大鼠慢性抑郁样行为调节中的作用的研究发现,重组鸢尾素注射可逆转大鼠的行为缺陷,逆转程度与剂量呈正相关。其原因可能是鸢尾素增加了前额叶皮质线粒体复合物Ⅰ、Ⅱ和Ⅳ及肌酸激酶的活性,通过升高体内和体外Ⅰ型和Ⅱ型己糖激酶、葡萄糖转运体及ATP水平,显著提高葡萄糖转运和磷酸化水平,对暴露于慢性应激条件下大鼠的抑郁样行为具有改善作用[43]。

2.3　抗炎机制与神经保护作用

BDNF是一种具有促进神经生长活性的蛋白质[44],与原肌球蛋白激酶B受体结合,在中脑边缘多巴胺回路中表达[45],对神经元的发育、存活、生长、分化和可塑性等方面具有重要作用。在脑损伤的急性期,静止储存的内源性神经干细胞(neural stem cells, NSCs)被激活,抑制神经元凋亡[35],参与神经修复过程。

炎症反应对BDNF表达的影响可能涉及多种机制。炎症反应可以抑制*BDNF*基因的转录和转录后修饰,影响BDNF受体的表达和信号转导通路,干扰BDNF的分泌和转运过程,从而减少BDNF的合成及释放,导致焦虑和抑郁症状[46]。

BDNF的表达减少是PSD的重要发病机制之一。PSD的发生伴随着BDNF的减少,入院时较低的BDNF血清水平是3个月随访时PSD发生的独立预测因子[47]。在大鼠实验中发现,PSD大鼠海马神经元退行性变、坏死,BDNF表达减少,抑郁样行为加重。增加海马体中BDNF的表达可以明显改善大鼠的抑郁样行为[48],在PSD的治疗中表现出积极作用[49]。2023年,Smaniotto等[50]研究了抗氧化剂IL-4对小鼠慢性不可预测的轻度应激诱导的抑郁样行为的影响,发现鼻内给予IL-4可以恢复小鼠BDNF的表达,调节小鼠的神经炎症反应,进而改善小鼠的抑郁样行为。

鸢尾素可诱导海马中BDNF的表达,调节能量代谢,改善卒中后患者的抑郁症状[18]。相关机制可能是鸢尾素通过cAMP→PKA→BDNF分子通路,作用于星形胶质细胞,减少基质金属蛋白酶9分泌,降低炎症因子的产生[51],从而导致神经可塑性级联激活,促使BDNF的成熟[52],调节能量代谢[53],改善情绪、学习和记忆,减少缺血、急性应激和神经变性疾病的发生[5],BDNF作为下游因子,对鸢尾素的神经保护具有增强作用[40]。

鸢尾素也能够通过增加能量交换和ATP产生来调节神经能量和代谢。其可以通过诱导结构蛋白、调节蛋白和酶来促进神经功能,还通过上调二硫键异构酶和超氧化物歧化酶蛋白质而具有神经营养作用,在周围神经病变和其他神经损伤的治疗中具有显著效果[54]。

2.4　抗炎机制与神经递质水平的调节

5-HT是一种重要的神经递质,在情绪的调节中起着关键作用[55]。在急性缺血性脑卒中的神经炎症反应中,促炎细胞因子刺激HPA轴释放糖皮质激素[36],使血糖升高、神经递质异常[56]、5-HT含量下降[57],从而导致患者抑郁的发生。

鸢尾素可以通过多个方面调节神经递质的产生。2021年,一项有氧运动是否具有改善甲状腺功能减退后抑郁的能力并探究其相关机制的研究中,分析了鸢尾素与5-HT的相关性,结果提示,与甲状腺功能正常对照大鼠相比,甲状腺功能减退大鼠脑丙二醛水平和脑促凋亡标志物(brain pro-apoptotic marker, BAX)/脑抗凋亡标志物(brain anti-apoptotic m arker, Bcl2)比值显著增加,表明神经元凋亡和神经炎症在抑郁状态中起着促进作用。运动治疗后的甲状腺功能减退大鼠血清鸢尾素水平显著增加,BDNF表达水平及5-HT水平增加,与BAX/Bcl2比率呈显著负相关[58]。一方面,BDNF可增强脑中含5-HT神经元的功能,并刺激其生长[59],促进5-HT的合成,缓解抑郁症状[60]。另一方面,鸢尾素通过抗炎作用间接维持HPA轴的稳态,减少糖皮质激素对神经系统的慢性损伤。此外,鸢尾素可能通过调节肌动蛋白重排和生长锥的形成,改善神经的动态潜能、发育过程和再生能力,从而改善神经结构和轴突运输,并且通过增加一氧化氮合酶辅酶和去除酶抑制剂诱导一氧化氮的产生来增加突触可塑性,增加神经递质的产生[54]。目前关于鸢尾素调节神经递质的相关研究相对较少,近年鲜有相关文献报道。

3　小结与展望

鸢尾素已经被证明在缓解PSD方面具有一定的作用。通过对其抗炎作用机制的研究,我们可以更好地理解鸢尾素对于大脑神经系统的影响,并为未来的药物研发提供一定的参考。虽然目前已经有一些研究证实了鸢尾素的抗抑郁作用,但还需要进一步探索其生物学作用机制、安全性和有效性,以及如何最大程度地发挥其作用。此外,我们还需要进行更多的临床研究,以评估鸢尾素的抗抑郁作用对人类的效果,并确定其最佳用量和治疗时间。

鸢尾素对于神经系统作用的近年研究进展汇总见表1。

表1　鸢尾素对于神经系统作用的近年研究进展汇总

时间/年	作者	研究类型	结论
2017	Li等[34]	基础研究	鸢尾素通过激活蛋白激酶B(protein kinase B, PKB,亦称Akt)和ERK 1/2信号通路减轻缺血诱导的神经元损伤,参与运动对脑缺血的神经保护作用
2018	Tu等[21]	临床研究	低鸢尾素浓度与卒中患者预后不良相关
2019	Wu等[20]	临床研究	低血清鸢尾素水平是缺血性脑卒中患者早期预后不良的预测因子
2021	Cheng等[61]	基础研究	外源性鸢尾素可以抗氧化应激,具有潜在的抗癫痫的神经保护作用
2022	Bilek[62]	临床研究	有氧运动可提高鸢尾素水平,对多发性硬化患者抑郁、疲劳症状有明显改善作用
2022	Tang等[28]	基础研究	有氧运动通过上调鸢尾素表达逆转NF-κB/NLRP3炎症小体/5-羟色胺(5-hydroxytryptamin, 5-HT)通路,从而减轻PSD
2023	Lima-Filho等[63]	基础研究	鸢尾素的减少可能是重度抑郁症及阿尔茨海默病之间的共同病理机制
2023	Avgerinos等[7]	综述	外源性鸢尾素给药可减少多巴胺能神经元的损失,同时改善运动功能,可能成为改善帕金森患者运动症状的一种替代方案

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