·专家论坛·

具有抗炎作用的药物在抑郁症治疗中的研究进展

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【摘要】 抑郁症是常见的精神疾病之一，其发病机制尚未完全明确，机体炎症水平升高是目前公认的抑郁症发病机制之一。大量研究表明，非甾体类抗炎药、ω-3脂肪酸、他汀类药物、吡格列酮、米诺环素、N-乙酰半胱氨酸、皮质类固醇等药物可能通过抗炎作用发挥抗抑郁疗效。本文就上述药物在抗抑郁治疗中的应用进行综述，探讨具有抗炎作用的药物对抑郁症治疗的效果及其可能的作用机制，为未来抗炎干预在抑郁症治疗中的应用提供参考。

【关键词】 抑郁症；抗炎作用；疗效；炎症机制

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Research progress of anti-inflammatory agents in the treatment of major depressive disorder

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【**Abstract**】 Major depressive disorder is one of the common mental disorders, and its pathogenesis is not yet fully understood. Elevated levels of inflammation are recognized as one of the mechanisms contributing to the onset of major depressive disorder. Numerous studies have indicated that non-steroidal anti-inflammatory drugs, omega-3 fatty acids, statins, pioglitazone, minocycline, N-acetylcysteine, corticosteroids and other medications may exert anti-depressant effects through their anti-inflammatory actions. This article provides a comprehensive review of the application of these drugs in the treatment of major depressive disorder, exploring the therapeutic effects and potential mechanisms of action of different anti-inflammatory agents, thereby offering a reference for the future application of anti-inflammatory interventions in the treatment of depression. [Funded by The Ministry of Science and Technology of the People's Republic of China (Number, 2022ZD0211700)]

【**Keywords**】 Major depressive disorder; Anti-inflammatory effects; Efficacy; Inflammatory mechanism

抑郁症是常见的精神疾病之一，目前我国至少有5 000万抑郁症患者[1]。抑郁症发病率逐年增长，预计到2030年，抑郁症将成为我国疾病负担的主要原因之一[1]。抑郁症因其高发病率、高致残率和高自杀率，对个人、家庭和社会都造成了严重负担[2]。然而即使经足量足疗程抗抑郁药物治疗后，仍有约三分之一及以上的患者治疗无效，并且药物治疗起效时间长[3-4]，患者常常出现胃肠道不适、性欲减退等副作用，治疗依从性欠佳[5]。

大量研究显示，抑郁症患者体内炎症细胞因子水平升高，包括白细胞介素-6（interleukin-6，IL-6）、肿瘤坏死因子-α（tumor necrosis factor-alpha，TNF-α）和C-反应蛋白（C-reactive protein，CRP）等[6-8]。既往研究显示，IL-6参与多种生理病理过程，包括HPA轴的激活、促肾上腺皮质激素释放激素活性、凋亡途径和氧化应激的诱导，这些都与抑郁症可能的病理机制相关[9-11]。既往一项综述报道，TNF-α对血清素代谢和HPA轴的影响可能通过增强大脑中多巴胺转运体的活性及影响脑细胞中糖皮质激素受体的功能，进而影响脑细胞代谢，这可能导致抑郁症的发生[12]。同时，促炎细胞因子可激活大脑中小胶质细胞，促炎细胞因子水平升高，可激活吲哚胺2，3-双加氧酶（Indoleamine 2，3-dioxygenase，IDO），促进色氨酸代谢为犬尿氨酸，并减少5-羟色胺（5-Hydroxytryptamine，5-HT）的产生。在炎症状态下，活化的小胶质细胞促进犬尿氨酸转化为喹啉酸，导致谷氨酸过度积累，抑制脑源性神经营养因

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子(Brain-derived neurotrophic factor,BDNF)的合成,从而影响神经元的可塑性和完整性,导致抑郁情绪[13]。这些研究提示,调节个体炎症因子表达水平,可能有助于改善其抑郁症状。

近年来,多篇荟萃分析探讨了具有抗炎作用的药物在改善抑郁症状方面的应用价值。研究显示,非甾体类抗炎药(non steroidal anti-inflammatory drugs,NSAIDs)、ω-3脂肪酸、他汀类药物、米诺环素、吡格列酮、N-乙酰半胱氨酸(N-acetylcysteine,NAC)、皮质类固醇等药物可能通过抗炎作用改善抑郁症状[14-20]。Bai等[21]还比较了具有抗炎作用的药物单独或辅助治疗抑郁症的效果和安全性,包括NSAIDs、ω-3脂肪酸、他汀类药物、吡格列酮、皮质类固醇、米诺环素、NAC和细胞因子抑制剂。结果表明,与安慰剂相比,单独使用上述具有抗炎作用的药物或联合抗抑郁药物使用均可减轻抑郁症状,NSAIDs、ω-3脂肪酸、他汀类药物和米诺环素有助于改善个体的抑郁情绪,且仅胃肠道事件发生率稍高于安慰剂组,提示以上药物具有较高的安全性。Köhler-Forsberg等[22]同样指出,与安慰剂相比,NSAIDs、他汀类药物、米诺环素、细胞因子抑制剂、吡格列酮、糖皮质激素有助于改善重度抑郁症患者的抑郁症状。Hang等[23]使用网状荟萃分析比较了NSAIDs、皮质类固醇、细胞因子抑制剂、他汀类药物、吡格列酮、米诺环素、NAC、ω-3脂肪酸及安慰剂在抑郁症治疗中的作用,结果表明,在上述药物中,抑郁症患者对NSAIDs的接受度最高,NAC表现出最佳的抗抑郁疗效。本文总结了具有抗炎作用的药物在抗抑郁治疗中的研究进展,以期为未来抗炎干预在抗抑郁治疗中的应用提供参考。

1 NSAIDs

NSAIDs是一种解热镇痛药。有研究表明,与安慰剂相比,NSAIDs中的阿司匹林、酮洛芬、塞来昔布均有助于缓解患者的抑郁症状[24-26]。塞来昔布是近年来被研究最多的NSAIDs[27-29]。塞来昔布是一种环氧化酶-2(cylooxygenase-2,Cox-2)抑制剂,可抑制前列腺素E2(prostaglandin E2,PGE2)合成,从而抑制IDO激活介导的炎症反应,减少色氨酸向犬尿氨酸转化[30],这可能是NSAIDs改善抑郁症状的作用机制。同时,综合疗效及药物副作用,相比于其他抗炎药物,抑郁症患者对NSAIDs的接受度较高[29,31]。但近年来也有随机对照研究表明,塞来昔布和安慰剂缓解抑郁症状的效果差异无统计学意义[32-33]。未来需要更多高质量的临床试验来阐明NSAIDs在抑郁症治疗中的作用。

2 ω-3脂肪酸

ω-3脂肪酸是一种多不饱和脂肪酸,既往大量研究表明,ω-3脂肪酸可能通过抗炎作用发挥抗抑郁效果[34-36]。2019年国际营养精神病学研究协会(International Society for Nutritional Psychiatry Research,ISNPR)发布的第一份临床指南提出,ω-3脂肪酸在抑郁症治疗中具有临床应用价值[37]。其中,超重的抑郁症患者补充ω-3脂肪酸的抗抑郁治疗效果更好[38]。ω-3脂肪酸可能通过以下潜在机制治疗抑郁症:ω-3脂肪酸可以抑制促炎因子释放、抑制血小板聚集,改善脑血流;ω-3脂肪酸可以维持细胞膜的完整性和流动性,增加脑细胞受体对各种神经递质如BDNF的亲和力;ω-3脂肪酸可阻止细胞因子诱导的神经发生减少和细胞凋亡,减少中枢神经的炎症反应和恢复细胞平衡[15]。ω-3脂肪酸被认为是一种具有应用前景的改善抑郁症状的药物。

3 他汀类药物

他汀类药物是一种通过抑制胆固醇合成酶活性、减少胆固醇合成、从而降低血液中总胆固醇和低密度脂蛋白胆固醇水平的药物,广泛用于治疗高胆固醇血症和预防心血管疾病[39]。同时,他汀类药物可以降低促炎因子及C-反应蛋白水平来减少机体炎症反应[17]。近年来,不少研究结果显示,他汀类药物可能通过抗炎作用发挥抗抑郁效果[17,40-41]。瑞典的一项大型队列研究表明,在40岁以上的人群中,与未使用他汀类药物的患者相比,使用他汀类药物者罹患抑郁症的风险低8%左右,表明他汀类药物可能具有降低抑郁症发病风险的潜力[42]。他汀类药物可以抑制核因子kB(nuclear factor-kappa B,NF-kB)信号通路,降低TNF-α、IL-1β和IL-6等促炎因子的表达水平,诱导小胶质细胞和星形胶质细胞活化,并调节BDNF表达[43-44]。提示他汀类药物的抗抑郁作用可能与其减少促炎细胞因子释放有关。一项随机对照试验结果显示,短期使用低剂量瑞舒伐他汀辅助选择性5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitors,SSRIs)治疗重度抑郁症,可通过调节关键情绪相关区域(前束/亚束前扣带加眶额皮质以及后扣带回)的脑血流,进而改善患者的抑郁症状及神经认知功能[45]。特别是对于伴急性心梗、中风史等基础疾病的抑郁症患者,他汀类药物能有效改善其抑郁症状[46]。

4 吡格列酮

吡格列酮是一种过氧化物酶体增殖物激活受体γ(peroxisome proliferator-activated receptor, PPAR-γ)激动剂,也是一种重要的神经保护、抗炎和抗氧化药物。它与炎症相关的代谢产物以及BDNF发生相互作用[47]。在压力诱导的抑郁症动物模型中,吡格列酮可以减少诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)的活性,抑制NF-κB和TNF-α表达[48]。一项随机双盲试验结果表明,与安慰剂相比,吡格列酮辅助西酞普兰可早期改善(2周内)不伴代谢综合征和糖尿病的重度抑郁症患者的抑郁症状[49]。对于伴有代谢综合征的抑郁症患者,吡格列酮不仅可以改善患者的抑郁症状,还有助于改善患者的心脏代谢风险指标,如胰岛素抵抗和高密度脂蛋白水平等[50]。因此,伴有代谢综合症的抑郁症患者能从吡格列酮治疗中获益较多。

5 米诺环素

米诺环素又称二甲胺四环素或美满环素,是一种广谱抗菌的四环素类抗生素,能与tRNA结合,达到抑菌的效果。米诺环素可以通过抑制小胶质细胞的激活,进而抑制机体的炎症状态[51]。研究显示,米诺环素辅助抗抑郁药有助于减轻难治性抑郁症患者的抑郁症状严重程度[52]。但Hellmann-Regen等[53]研究表明,与接受安慰剂治疗的患者相比,接受米诺环素辅助治疗的难治性抑郁症患者抑郁症状改善情况差异无统计学意义。因此,米诺环素对抑郁症状的改善作用可能需要更多高质量的研究进一步探讨。

6 NAC

NAC是一种氧化还原活性谷胱甘肽前体。NAC通过补充谷胱甘肽来帮助大脑进行抗氧化防御,并减少大脑皮层、海马和血浆中的促炎细胞因子,调节谷氨酸,促进神经发生,减少细胞凋亡,具有一定的抗抑郁作用[54-56]。一项随机对照试验结果显示,接受NAC辅助抗抑郁药物治疗16周后,患者的抑郁症状显著改善,但NAC治疗抑郁症的起效时间较长。该研究中,在治疗第12周,患者仍无明显改善,且与安慰剂组相比,接受NAC治疗的患者胃肠道和肌肉骨骼不良事件的发生率更高[57]。基于以上原因,NAC在临床抗抑郁治疗中的应用受限。

7 皮质类固醇

皮质类固醇可以调节下丘脑-垂体-肾上腺轴中的负反馈环路,并参与个体免疫调节以达到抗抑郁效果[58]。研究显示,氟化可的松可通过刺激盐皮质激素受体(mineralocorticoid receptor, MR),加速缓解患者的抑郁症状,其平均起效时间为16天[20]。但并非皮质类固醇治疗对所有患者均有效,在该研究中,氟化可的松有助于降低抑郁症患者的皮质醇水平;接受氟化可的松治疗后抑郁症状无明显改善的患者外周血皮质醇水平高于抑郁症状明显改善的患者,皮质类固醇治疗可能对存在皮质醇水平明显升高的抑郁症患者的疗效较差,且该研究仅纳入64例严重抑郁症患者,未纳入轻中度的患者群体,样本量较小且样本代表性受限[59]。

8 小结与展望

以上药物可能通过抗炎作用发挥抗抑郁作用,通过降低抑郁症患者中枢炎症因子水平,改善脑血流及神经可塑性和完整性来减轻患者的抑郁症状。具有抗炎作用的药物对伴有炎症水平升高、超重、心血管病史等基础疾病的抑郁症患者效果更好。但关于这些药物治疗抑郁症的研究均存在一定局限,比如样本量较小,纳入患者存在抑郁严重程度、年龄、基础疾病史等方面的差异,可能会对研究结果产生一定的影响。因此,将来需更多高同质性的大样本研究,探索具有抗炎作用的药物在抗抑郁治疗中的效果、安全性及作用机制,为抗炎干预在抑郁症治疗中的应用提供参考,推动抑郁症的个体化精准医疗。

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