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促炎细胞因子与卒中后抑郁：讨论与思考

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摘　要

脑卒中后抑郁症是脑卒中后最常见的精神疾病之一，属于创伤后应激障碍，是一种以持续情绪低落、兴趣下降为特征的心境障碍。它可能对患者生活的不同领域产生或大或小的负面影响。炎症作为机体生长发育和疾病进展中不可缺少的一部分，在脑卒中后抑郁中也起着重要作用，全身性炎症导致脑卒中风险增加和脑卒中后预后不良，这已被许多学者证实。当然，在炎症反应过程中有促炎细胞因子和炎性细胞因子的参与，促炎细胞因子可以帮助激活多种类型的免疫细胞，促进炎症的发生和发展，它们与抑郁症的病因密切相关，如果与其他诱发因素结合，反应会导致炎症过程延长，长期各轴不平衡，导致压力、疼痛、情绪变化，进而加重焦虑和抑郁。抑郁症的病理生理机制复杂多样，脑卒中后抑郁的机制尚未阐明，本文探讨促炎细胞因子与脑卒中后抑郁的关系，希望进一步解释脑卒中后抑郁的机制。

关键词

炎症，促炎细胞因子，脑源性神经营养因子，中风后抑郁症，创伤后应激障碍

Pro-Inflammatory Cytokines and Post-Stroke Depression: Discussion and Thought

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Abstract

Post-stroke depression is one of the most common mental illnesses after stroke, which belongs to

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post-traumatic stress disorder, and is a mood disorder characterized by persistent low mood and decreased interest. It can have a negative impact, large or small, on different areas of the patient's life. As an indispensable part of the body's growth and development and the progression of the disease, inflammation also plays an important role in post-stroke depression, and systemic inflammation leads to an increased risk of stroke and poor prognosis after stroke, which has been confirmed by many scholars. Of course, in the inflammatory response process has the participation of pro-inflammatory cytokines and inflammatory cytokines, pro-inflammatory cytokines can help activate a variety of types of immune cells to promote the occurrence and development of inflammation, they are very closely related to the cause of depression, if combined with other predisposing factors, the response will lead to prolonged inflammatory processes, long-term imbalance of various axes, resulting in stress, pain, mood changes, and then aggravate anxiety and depression. The pathophysiological mechanism of depression is complex and diverse, and the mechanism of post-stroke depression has not yet been elucidated, this article discusses the relationship between pro-inflammatory cytokines and post-stroke depression, hoping to further explain the mechanism of post-stroke depression.

Keywords

Inflammation, Pro-Inflammatory Cytokines, Brain-Derived Neurotrophic Factor, Post-Stroke Depression, Post-Traumatic Stress Disorder

1. 介绍

抑郁症是一种常见的精神疾病，严重限制了人类心理社会功能的进展，降低了生活质量。在 2008 年，世界卫生组织将抑郁症列为全球疾病负担的第三大原因，预计到 2031 年，抑郁症将排在第一位[1]。抑郁症常表现为显着且持续的情绪低落、思维迟钝、意志力下降，严重影响人们的日常生活。虽然抑郁症的病理生理学研究取得了长足的进步，但目前还没有完整、系统的模型可以描述抑郁症。不同的应激源，如疾病、创伤，生活和学习压力，可能会导致不同的抑郁症病理生理机制。脑卒中是由脑梗塞、脑出血和蛛网膜下腔出血等血管原因引起的中枢神经系统急性局灶性损伤引起的神经功能缺损，是全球致残和死亡的主要原因[2]。在中国，脑卒中是居民的第一死因，死亡率远高于癌症和心血管疾病。脑卒中可分为缺血性脑卒中和出血性脑卒中，其中，缺血性脑卒中在我国最为常见，约占 75%~90% [3]。通常，脑卒中后患者可能因脑损伤而出现许多后遗症，其中脑卒中后精神障碍是最常见的后遗症之一，主要为抑郁症，我们称之为脑卒中后抑郁症(Post-stroke depression, PSD)。虽然目前先进的医疗手段已经大大提高了脑卒中患者的生存率和生活质量，但脑卒中后抑郁症仍然会长期陪伴患者，给他们带来很大的困扰[4] [5]。炎症在机体发育和疾病进展过程中起着重要作用。如我们所熟知的肥胖，大多由于不健康的饮食导致，在进食这类食物过程中，机体会产生或多或少的炎症反应[6]。另外，肥胖是一种多因素的疾病，与高脂肪饮食以及肠道菌群的改变之间存在密切联系[7]。有证据表明，肠道菌群的破坏会激活肠道的适应性和先天免疫力，并通过置换免疫原性细菌产物来增加炎症水平。虽然炎症是机体对外来病原体入侵的正常和自动防御反应，但过度的炎症反应会导致一系列疾病，如肥胖的产生[7]。然后，“肥胖微生物群”间接影响下丘脑基因表达，并通过增加全身炎症和小胶质细胞活化来促进暴饮暴食，从而影响迷走神经活动[8]。脂肪组织的炎症会促进血管生成。血管生成是组织重塑和肥胖发展的关键事件。通过提高循环

中的炎性细胞因子，全身地促进能量消耗。炎症反应还会引起胰岛素抵抗和高血糖。因此，及时调节炎症对于机体健康发育至关重要[9]。且在这一生长过程中，机体会遇到多种外来的侵袭，身体可以记住过去与过敏原、病原体、伤口和刺激物的接触，并对下一次经历做出更快的反应有助于我们应对新的威胁[10]。炎症或炎症过程是免疫系统激活的结果，常表现为局部发热、发红、肿胀、疼痛，或全身表现为发热和身体机能和稳态的破坏，其中促炎细胞因子、抗炎细胞因子和某些细胞在此过程中起着极其重要的作用，如：IL-6、肿瘤坏死因子、IL-1b 和干扰素、IL-10 和巨噬细胞和小胶质细胞等[11]。卒中后抑郁症是中风后最常见的精神疾病之一。它属于创伤后应激障碍，是一种以持续抑郁和兴趣低落为特征的情绪障碍。这种疾病的发病机制尚未完全阐明，但越来越多的学者证明炎症或炎症反应起着重要作用。由于炎症反应可能调节脑卒中期间的神经可塑性，而神经可塑性的变化可能与脑卒中后抑郁症的发病机制有关，因此脑卒中诱导的脑中免疫反应也可能影响脑卒中后抑郁症的病程。另外，我们发现，在卒中后抑郁期间，几种炎症标志物、促炎细胞因子和促炎/抗炎比值增加，补体表达降低[12]。在本文中，我们描述了两种不同类型的卒中(缺血性和出血性)，并总结了促炎细胞因子在整个卒中中的作用。然后，我们阐述了卒中后抑郁症，并总结了促炎细胞因子对卒中后抑郁症的影响。

2. 缺血性卒中

缺血性脑卒中又称脑梗塞，占脑卒中发病率的绝大部分，其中，颈内动脉系统脑梗死占 80%，颈内动脉是闭塞的常见血管。由于脑组织供血不足，将发生组织功能的可逆性丧失，如果超过大脑可以承受的缺血时间，毛细血管释放的氧气扩散到脑细胞线粒体所需的有效氧分压梯度消失，脑细胞缺氧会导致细胞膜离子泵失效导致细胞内和细胞外离子平衡的破坏，并发生脑细胞水肿、坏死等一系列不可逆的损伤[13]。例如，缺氧通过 miR-212-3p/MCM2 轴抑制脑微血管内皮细胞的细胞周期进程和细胞增殖[14]。另外，缺氧可以通过缺氧诱导因子 1-α/Epas1 信号介导的少突胶质细胞前体细胞中血管内皮生长因子的表达，从而影响血脑屏障的通透性，进一步影响脑细胞的生存环境，引发脑细胞的坏死、水肿[15]。在脑组织在发生缺血缺氧的时候，会诱导铁死亡的发生，如会导致丙二醛的升高，谷胱甘肽和超氧化物歧化酶活性的降低以及大量活性氧的产生，从而使得脑细胞坏死和水肿的产生及进一步加重[16]。根据目前已知的局部脑组织缺血性坏死机制，脑梗死可分为脑血栓形成、脑栓塞和血流动力学机制引起的脑梗死三种病理生理类型。脑血栓形成和脑栓塞是由脑供血动脉急性闭塞或严重狭窄引起的，约占所有急性脑梗死的 80%~90%。在血流动力学机制引起的脑梗死中，供动脉无急性闭塞或严重狭窄，这是由于近端大血管严重狭窄合并血压下降，导致局部脑组织灌注不足，导致缺血性坏死，约占所有急性脑梗死的 10%~20%。在缺血性卒中中，与炎症最相关的成分是小胶质细胞和星形胶质细胞、趋化因子和细胞因子以及浸润外周血细胞[17]。在脑梗死中，梗死区的病理变化之一是反应性星形胶质细胞增生和胶质瘢痕形成，以及驻留小胶质细胞和浸润性单核细胞/巨噬细胞的激活[18]。局部炎症涉及星形胶质细胞、活化的常驻小胶质细胞、中性粒细胞和浸润性单核细胞或单核细胞来源的巨噬细胞(MDM)，并上调促炎因子 IL-6、一氧化氮合酶-2、IL-1β、肿瘤坏死因子-α (TNF-α)和抗炎因子(CCL22、YM1、CXCL13、转化生长因子 β、CD163)的表达[19] [20]。根据神经炎症的严重程度以及促炎和抗炎信号的调节，神经炎症可能在中风损伤和康复中发挥积极和消极的作用。

3. 出血性卒中

狭义上的脑出血是指非创伤性脑出血，约占我国所有脑卒中的 10%~25%，即使发生率远低于脑梗死，其病死率也远高于脑梗死。常见病因有颅内动脉瘤破裂和高血压合并小动脉硬化，颅内小动脉长期在高血压作用下慢性病灶破裂，最常见的受累动脉是豆动脉，常发生在壳核和基底核的内囊区，在此期间由

于血液的快速积聚会出现颅内压增高，意识障碍和一些身体症状，严重者可能危及生命[21]。脑出血的发病机制复杂，主要包括血肿占位效应引起的神经和神经胶质细胞机械性骨折、兴奋性氨基酸毒性、ROS等小分子水平升高引起的自由基对颅内细胞的破坏、血管内炎症细胞(中性粒细胞、巨噬细胞等)和脑组织中活化的小胶质细胞引起的炎症，以及多种机制引起的细胞凋亡[22] [23]。小胶质细胞是脑出血后引起继发性损伤的主要细胞类型，因为它们释放细胞因子、趋化因子、前列腺素、蛋白酶、亚铁和其他免疫活性物质，延迟脑出血的恢复[24] [25]。在脑出血后脑组织的炎症反应中，最基本的标志物是小胶质细胞的激活和炎症细胞的浸润[26]。血肿释放的白细胞和巨噬细胞浸润并阻断微血管，从而降低脑灌注，破坏血脑屏障，TNF-α 和 IL-1β 等细胞毒性分子对神经元造成损害[27]。血肿附近脑组织中的小胶质细胞和星形胶质细胞可能调节脑出血后脑细胞的可塑性[28]，星形胶质细胞 HO-1 的过表达显示出明显的神经保护作用[29]。

4. 抑郁症和卒中后抑郁

脑卒中后抑郁症是脑卒中后最常见的精神疾病之一，约占脑卒中幸存者的 1/3，是脑卒中的一种创伤后应激障碍，是一种以持续性情绪低落、兴趣下降为特征的心境障碍。可对患者生活的不同领域产生或大或小的负面影响，严重影响患者的死亡率、功能结局、康复效果和生活质量，脑卒中后抑郁症患者的死亡风险比非抑郁症患者高 1.22~1.41 倍[30] [31]。许多学者对脑卒中后抑郁症的病变进行了研究，但结果并不一致。张等人的一项前瞻性研究表明，后肢、膝关节内囊和颞叶皮质－皮质下区域的病变可能与 PSD 的发生有关[32]。在 Robinson 等人关于 PSD 病变的两项早期研究中，左额叶或左基底神经节病变的脑卒中患者发生重度或轻度抑郁的频率明显高于其他病变患者，缺血性损伤前缘与左额叶极的距离与皮质和皮质下区域抑郁的严重程度显着相关。PSD 与左额叶和左基底神经节病变的相关性仅限于脑卒中后的前 2 个月，抑郁严重程度仅在脑卒中后的前 6 个月与左大脑半球病变前缘到额极的距离显着相关[33] [34]。对于 PSD 的治疗，目前上市的抗抑郁药可以改善 PSD 的抑郁症状，但目前还没有明确的方案，其中 5-羟色胺药物更受欢迎。PSD 的病理生理机制尚未完全阐明，在许多学者的研究中，已经表明 PSD 的发生和发展与炎症密不可分。炎性细胞因子可引起炎症、脑卒中康复和多种生长因子失调导致 PSD，神经炎症通过刺激 IL-33/NF-κB 轴抑制脑源性神经营养因子的表达，从而激活引起抑郁症的途径，Yirmiya 等人也认为神经炎症是抑郁症的根本原因之一[35] [36]。

5. 颅内免疫

人类在生长发育过程中一直受到免疫系统的保护，免受各种感染的侵袭，炎症和炎症反应是免疫系统激活的结果。免疫系统有三个屏障，皮肤和粘膜形成第一道屏障，当然血脑屏障也是其中的一部分，可以抵抗一些抗原；第二道屏障由体内的各种炎症细胞组成，第三道防线是细胞免疫和体液免疫，可以产生各种抗体和细胞因子。颅内免疫集中在第二和第三屏障。进入体内的抗原可被巨噬细胞、B 淋巴细胞等抗原呈递细胞识别，进而通过 T 细胞介导的细胞免疫、TNF-α、IL-2、IFN 等和 B 细胞介导的体液免疫参与多种炎症因子的分泌，产生抗体，共同参与消除抗原的过程[37]。参与大脑内免疫反应的主要细胞是小胶质细胞和巨噬细胞，小胶质细胞被认为是对不同脑损伤的神经炎症反应前沿的前哨细胞。由于血脑屏障的存在，外周循环白细胞难以进入颅骨，但脑缺血炎症的特征是血脑屏障(BBB)的破坏，外周血白细胞的渗透，胶质细胞的活化，以及损伤细胞释放损伤相关分子模式(DAMP)以激活免疫细胞，而活化的免疫细胞又释放炎性细胞因子和细胞毒性介质，导致缺血性损伤加重[38]。

5.1. 小胶质细胞

小胶质细胞来源于间充质来源，起源于卵黄囊来源的红髓祖细胞，小胶质细胞在围产期和产后阶段

迅速扩增，到第二周结束时完全定植于大脑，通过自我更新维持，且在稳态下未发现循环单核细胞的募集[39] [40] [41]。小胶质细胞通过调节突触可塑性或冗余突触的吞噬作用来动态塑造神经回路。脑出血或缺血后，小胶质细胞会被激活，成为影响神经元和其他脑细胞的神经元。急性小胶质细胞活化是炎症、保护、恢复和毒性过程的主要协调者和执行者，通常通过清除入侵的病原体和细胞碎片来促进组织修复；而持续的小胶质细胞活化会导致慢性神经元炎症，从而加重病情[42]。给予已知会激活小胶质细胞的免疫刺激，例如内毒素(脂多糖)，会导致抑郁症状，其严重程度与血液中炎性细胞因子水平升高高度相关[43] [44]。在应激作用下，血脑屏障的通透性会增加，使外周细胞因子通过血脑屏障增加，异常触发小胶质细胞的促炎反应。其中，TNF-α、IL-1β、IL-6 和 IL-8 已被确定为介导外周免疫细胞－脑通讯的主要细胞因子，并与抑郁症和中风后抑郁症有关[45] [46] [47] [48]。在 Wang 等人的研究中，在长期慢性应激中观察到 NLRP3 炎症小体的激活和炎症介质的上调，这可能是由于不同类型的小胶质细胞的激活，这些小胶质细胞产生促炎细胞因子或抗炎细胞因子，从而介导慢性轻度应激诱导的抑郁和焦虑样行为以及海马神经炎症[49]。在 PSD 小鼠模型中，小胶质细胞可以促进海马中促炎细胞因子(IL-1、TNF-α、iNOS 和 IL-1β)的表达[50]。

5.2. 炎性细胞因子

细胞因子是由各种免疫细胞(如巨噬细胞、神经胶质细胞、肥大细胞等)分泌的低分子量蛋白，作为与免疫系统反应相关的通讯网络的重要介质参与免疫，负责动态调节免疫细胞的成熟、生长和反应[51]。此外，细胞因子在发育、代谢、衰老和癌症的调节中发挥着多种作用。它们包括干扰素、趋化因子、淋巴因子、白细胞介素、转化生长因子-β、集落刺激因子和肿瘤坏死因子，其特点是功能冗余和多效性。血清、血液、粪便、唾液、汗液等多种生物体液中细胞因子水平的变化，为多种疾病的诊断、分期和预后提供有价值的信息。对于免疫反应，细胞因子可分为促炎细胞因子和抗炎细胞因子，其中促炎细胞因子包括 IL-1β、IL-6、IL-8 和 TNF-α 等，促进炎症反应。反应并激活免疫细胞，IL-1 受体拮抗剂(IL-1ra)、IL-4、IL-10、IL-13、白血病抑制因子(LIF)、INF-α 和 TGF-β 是抗炎细胞因子。当然，并不意味着某种细胞因子只是促炎或抗炎细胞因子。例如，IL-6 既是促炎细胞因子又是抗炎细胞因子。病理状况，例如本文提到的中风，可能导致促炎细胞因子的过量产生，这可能对中枢神经系统产生不利影响。特别是，它们可能损害神经元结构和功能，导致神经可塑性缺陷以及神经系统感知、响应和适应外部或内部刺激的能力降低。神经可塑性或神经元可塑性是指神经系统对环境挑战的反应和适应性，包括一系列可能导致神经元重塑、新突触形成和新神经元诞生的功能和结构机制[52]。

促炎细胞因子的血药浓度，包括白细胞介素 1β (IL-1β)、白细胞介素 6 (IL-6)、肿瘤坏死因子-α (TNF-α)和其他急性期蛋白、C 反应蛋白、触珠蛋白和新蝶呤[53]。在几项荟萃分析中发现，抑郁症患者 C 反应蛋白、IL-3、IL-6、IL-12、IL-18、sIL-2R 和肿瘤坏死因子-α 的平均水平升高，尤其是 TNF-α 和 IL-6 以及 IL-1β，表明促炎细胞因子与抑郁症之间存在很强的关系[54] [55]。

5.2.1. IL-6

白细胞介素 6 (IL-6)在感染和组织损伤后快速、短暂地产生，它通过刺激急性期反应、造血和免疫反应来促进宿主防御，是一种非常重要的促炎细胞因子。尽管 IL-6 的表达受到转录和转录后机制的严格控制，但也有特殊情况，例如 IL-6 的连续合成失调，对慢性炎症和自身免疫有负面影响[56]。人 IL-6 由 184 个氨基酸组成，具有两个潜在的 N-糖基化位点和四个半胱氨酸残基，大小为 21~26 kDa，核心蛋白约为 20 kDa [56]。Hirano T 等人率先发现一些星形细胞瘤和胶质瘤细胞系在 IL-1β 刺激下表达 IL-6，这促使人们猜测 IL-6 可能在中枢神经系统中发挥作用，其中 IL-6 可以诱导大鼠嗜铬细胞瘤 PC12 细胞系的神经元分化，有点类似于神经营养因子[57]。IL-6 的作用被其可溶性受体亚基 sgp130 和 sIL-6R 修饰，并且 IL-6 炎症反应的诱

导可能通过 sgp130 (一种潜在的 IL-6 拮抗剂)的瞬时下调而增强[58]。ICH 患者 24 小时内 IL-6 水平与血肿扩大风险较高相关，可作为 90 天后功能预后不良的标志物[59]。在 Kang 等人的一项前瞻性研究中，发现较高的 IL-6 和 IL-18 水平与中风后早期(2 周内)和慢性期(1 年内)抑郁症有关[60]。有趣的是，一系列研究发现，星形胶质细胞-IL-6/IL-17 还可以促进脑卒中后的血管生成和神经功能恢复[61] [62] [63]。

5.2.2. IL-1β

IL-1 有两个因子，IL-1α 和 IL-1β，它们首先经过大小为 31 kDa 的前体多肽，然后在半胱天冬酶 1 加工后转化为分子量为 17 kDa 的物质[64] [65]。它们通过 IL-1R-1 信号通路产生类似的促炎反应，主要由单核细胞和巨噬细胞产生，其他细胞类型(包括中性粒细胞、内皮细胞、淋巴细胞、平滑肌细胞和成纤维细胞)数量较少[66]。IL-1β 的主要作用是刺激免疫细胞产生促炎细胞因子，激活小胶质细胞，调节生长因子的活性[67]。IL-1 可诱导外周炎症介质，如白细胞介素-6、IL-1 受体拮抗剂(IL-1Ra)的增加，可显着降低血浆 IL-6 和血浆 C 反应蛋白水平，抑制脑卒中急性缺血性外周炎症反应[68]。在 Li 等人的研究中，敲除 IL-1β 缓解了脂多糖诱导的小鼠记忆缺陷和焦虑抑郁样行为，并消除了神经肽(Neuropeptides, VGF)和脑源性神经营养因子(Brain-derived Neurotrophic Factor, BDNF)毕竟脂多糖诱导的外周炎症反应在啮齿动物的神经精神功能障碍中起着重要作用[69]。Goshen 等人证明，大脑 IL-1 通过激活肾上腺皮质和抑制暴露于刺激后的海马神经发生来介导小鼠慢性应激诱导的抑郁[70]。核因子-κB (NF-κB)的激活直接影响海马体中的细胞和神经发生，或通过其受体(IL-1R1)的直接相互作用。Natsuki 的研究小组发现，IL-6 依赖性激活蓝斑神经元诱导抑郁样行为，IL-1β 诱导的瘦素水平增加增强 α1 肾上腺素受体介导的抑郁样行为[71]。银杏内酯 B (GB)通过抑制 STAT3 通路减轻抑郁样行为并降低 IL-1β 的表达。反映 STAT 通路和 IL-1β 在抑郁症中起着不可或缺的作用[72]。许多杆菌还可以通过调节肠道微生物群和核因子-κB (NF-κB)激活来抑制 IL-1、TNF-α 和 BDNF 表达，从而缓解焦虑/抑郁和认知障碍[73] [74] [75]。

5.2.3. TNF-α

肿瘤坏死因子-α (TNF-α)是巨噬细胞/单核细胞在急性炎症过程中产生的一种炎性细胞因子，大小为 17kDa，负责细胞中的各种信号转导事件，导致坏死或凋亡。已知肿瘤坏死因子-α 通过肿瘤坏死因子-R1 和肿瘤坏死因子-R2 介导其作用。TNF-R1 在所有细胞类型上表达，而 TNF-R2 主要在造血细胞和内皮细胞上表达[76] [77]。许多炎症细胞除了具有有害作用外，还可以参与脑损伤后的组织重塑，TNF-α 被认为是这种双重作用细胞因子之一，然而，它在中风后早期上调是有害的，加剧了组织损伤并恶化了中风患者的预后[78]。TNF-α 通过 NF-κB 信号通路调节系统性红斑狼疮伴抑郁症中的小胶质细胞活化，小胶质细胞衍生的 TNF-α 介导内皮坏死，加重缺血性脑卒中细胞凋亡后血脑屏障破坏[79]。低剂量 TNF-α 引起神经元快速而严重的线粒体功能障碍，这种神经毒性作用由 TNF-R1 介导，导致半胱氨酸酶的激活和线粒体膜电位的崩溃，线粒体释放细胞色素 c，激活线粒体诱导的细胞凋亡。已知 TNF-α 会加重梗死面积，这可能是由于 TNF-α 在不断发展的缺血核心中释放导致 ATP 产生显着和快速减少[80]。

6. 脑源性神经营养因子

脑源性神经营养因子是中枢神经系统中最丰富、分布最广的神经营养因子，由神经(如肌肉)和星形胶质细胞支配的组织产生，在神经系统的生长和分化过程以及认知中起着非常重要的作用[81]。BDNF 的功能由复杂的下游信号级联系统介导，通过两个受体系统，酪氨酸激酶 B (TrkB)和 p75NTR (一种神经营养因子受体)。BDNF 与 TrkB 结合激活细胞内区域，引起 TrkB 自磷酸化增强，进而激活 Ras-MAPK 通路，最后在 CAMP 反应组件结合蛋白(CREB)丝氨酸位点激活 CREB。CREB 通过增加 BDNF 基因和抗凋亡蛋白基因 BCL-2 的表达来促进神经细胞的存活，增加突触可塑性和神经发生[82] [83]。抑郁症样行为被认为

与明显的可塑性损伤和神经损伤有关，例如内侧前额叶皮层(mPFC)和海马的神经元萎缩和突触丢失[84]。

“抑郁症神经营养假说”认为，低水平的脑源性神经营养因子与重度抑郁症(MDD)有关，并已被世界各地的学者验证。在卒中后抑郁症患者中，血清 BDNF 水平较低，脑源性神经营养因子水平在卒中后抑郁症患者的死后脑组织中显着降低，表明 BDNF 可能是 PSD 的独立预测因子[85] [86] [87] [88]。荟萃分析研究表明，卒中早期血清 BDNF 浓度显着降低可能使患者易患 PSD [53] [89]。

鉴于脑源性神经营养因子作为神经可塑性的重要介质的作用，许多人认为促炎细胞因子和 BDNF 之间存在一些特定的联系，基于它们对神经发生的积极影响与有害影响相比，并进行研究以证实。研究表明，炎症显着影响脑源性神经营养因子在大脑中的表达。海马体中 IL-1β 敲低显着减弱了 LPS 诱导的小鼠记忆缺陷以及焦虑和抑郁样行为。此外，IL-1β 敲低改善了 LPS 诱导的氧化和神经炎症反应，并消除了 VGF 和 BDNF 的下调[69]。腹腔注射 IL-1β 或 LPS 后，大鼠海马及部分皮质区脑源性神经营养因子表达水平显着降低[90] [91]。在外周免疫过程中，BDNF 增加活化的外周血单个核细胞中细胞 IL-2、IL-17 和 IFN-γ 表达以及 IL-2 和 IFN-γ 分泌[91]。缺氧和 TNF-α 可降低海马神经元中 BDNF 的表达[92]。同时，研究发现 BDNF 可以抑制脂多糖(LPS)刺激的巨噬细胞中白细胞介素-1β、肿瘤坏死因子 α 和白细胞介素 6 的分泌[93]。这让人不禁怀疑 BDNF 和促炎细胞因子之间是否存在“负反馈”信号。

7. 卒中后抑郁的治疗

PSD 的治疗尚无完整的指南或完善的治疗方案，采用药物治疗和心理治疗来治疗 PSD，此外，三环类抗抑郁药(TCAs)、选择性 5-羟色胺再摄取抑制剂(SSRIs)、5-羟色胺和去甲肾上腺素再摄取抑制剂(SNRIs)和单胺氧化酶抑制剂是目前主流的抗抑郁药，似乎对 PSD 的防治有很好的效果。认知行为疗法(CBT)也被认为对抑郁症有效。简短的社会心理行为干预可以显着改善抑郁症长达 2 年，并且比单独的常规护理更有效[94] [95]。中药对 PSD 的治疗也有一定的效果，如：柴虎舒干粉(CHSG)、舒肝解肝胶囊、柴虎家龙骨牡蛎汤，以及最常见的中医治疗方法——针灸，对 PSD 的治疗都有着有一定的效果[96] [97] [98]。

8. 总结

总之，我们试图找到促炎细胞因子与卒中后抑郁症之间的关系，越来越多的证据表明促炎细胞因子和脑源性神经营养因子是 PSD 的标志物和潜在的治疗靶点。尽管已经有很多研究证实了它们在 PSD 中的作用，但仍有许多未知的工作需要完成，例如 1) 促炎细胞因子以及 BDNF 如何影响 PSD 的症状。2) 目前缺乏多种细胞因子、免疫细胞亚群和微生物群落物种的功能来预测 PSD 的可能性。3) 脑卒中部位是否对促炎细胞因子和 BDNF 的表达和分泌有影响。因此，我们需要进一步的研究、更多的队列研究以及更详细和一致的 PSD 诊断标准，来进行疾病的诊断和治疗。

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