·综述·

童年创伤在抑郁症发病中的炎症机制

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DOI:10.3969/j.issn.1009-6574.2023.02.012

【摘要】 抑郁症以情绪低落、兴趣减退和快感缺失为主要临床特点。童年创伤作为重要的社会环境因素之一,增加了日后罹患抑郁症的风险。研究童年创伤与抑郁症发生的关系及机制对抑郁症的防治至关重要。炎性反应紊乱可能是童年创伤导致抑郁症的生物学机制之一,现就童年创伤经历与抑郁症发病之间的炎症机制进行综述。

【关键词】 抑郁症; 童年创伤; 炎症; 细胞因子; 综述
基金项目: 河北省卫生健康委科研基金(20201168);河北省邯郸市科技局基金项目(19422083009-5)

Inflammatory mechanisms of childhood trauma in the pathogenesis of the major depressive disorder

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【**Abstract**】 Depressive disorder is a chronic mental disorder characterized by low mood, decreased interest and anhedonia. As one of the important social environmental factors, childhood traumatic experience increases the risk of depression in the future. It is important to study the relationship and mechanism between childhood traumatic experience and depression for the prevention and treatment of depression. Inflammatory reaction disorder may be one of the biological mechanisms of childhood traumatic experience leading to depression. This article reviews the inflammatory mechanism between childhood trauma and depression.

【**Key words**】 Depressive disorder; Childhood trauma; Inflammation; Cytokines; Review
Fund programs: Hebei Provincial Health Commission Scientific Research Fund Project (20201168); Science and Technology Bureau Fund Project of Handan, Hebei Province (19422083009-5)

抑郁症以情绪低落、兴趣减退和快感缺失为主要临床特点[1]。根据2016年WHO统计数据显示,抑郁症占全球非致命疾病总负担的10%[2],预计到2030年将上升至世界疾病负担首位[3]。目前认为生物、心理、社会环境等因素共同导致抑郁症的发生,童年创伤作为重要的社会环境因素可以增加个体对抑郁症的易感性[4]。WHO的调查显示,全球超过1/3的人口曾经历过童年创伤,且伴有童年创伤的人群中约有28.9%的人未来可能会罹患精神障碍,对身心健康的影响贯穿整个生命过程[5]。因此,探讨童年创伤与抑郁症间的关系及机制对抑郁症的防治至关重要。既往研究表明,童年创伤与日后细胞因子水平增加呈正相关[6],而抑郁症发病的生物学机制又包括了慢性炎性反应[1],所以炎性反应紊乱可能是童年创伤导致抑郁症的生物学机制之一。此外,童年创伤对炎性反应造成的影响可能与神经内分泌系统表达紊乱有关[7]。童年创伤通过表观遗传调控机制导致糖皮质激素受体(glucocorticoid receptor, GR)甲基化增加、GR表达减少及功能障碍[8],继而加剧炎性反应[9]。本文就童年创伤与抑郁症发病之间的具体炎症机制进行综述。

一、童年创伤对抑郁症的影响

童年创伤是指童年期经历的躯体虐待、性虐待、情感虐待、情感忽视或躯体忽视等[10],是严重的环

境应激源之一，也是精神疾病发生的重要因素[11]。根据创伤的类型、严重程度和频率，在童年时期经历过虐待或忽视的人，其一生中罹患抑郁症或恶劣心境的可能性要比未经历童年创伤者高1.3～3.1倍[12]。一篇Meta分析对童年创伤进行亚种类分析，结果显示童年期经历情感虐待及情感忽视会增加罹患抑郁症的风险，而性虐待虽与抑郁症相关，但与情感虐待及情感忽视相比，罹患抑郁症的风险较低[13]。此外，Wiersma等[14]发现，躯体虐待和性虐待与抑郁症的复发风险相关。上述证据表明童年创伤可增加个体日后罹患抑郁症及复发的风险。

二、炎症、下丘脑－垂体－肾上腺(hypothalamus pituitary adrenal，HPA)轴在童年创伤与抑郁症发生中的关系

1.炎症在童年创伤与抑郁症之间的作用：炎症在精神疾病的病理生理学中发挥着重要作用[15]。近年来，有关炎性反应在精神疾病尤其是在抑郁症的发生与发展中发挥作用的研究逐年增多[16]。相关研究显示，抑郁症与炎性反应有关，而炎性反应又受细胞因子的驱动和调节[17]。细胞因子可能参与了抑郁症的发病过程[18]。Liu等[19]发现，抑郁症患者血清中的炎症标志物水平升高，其中包括CRP、IL-6和TNF-α，IL-6、TNF-α水平与抑郁症严重程度呈正相关[6, 20]。CRP是肝脏对细胞因子(尤其是IL-6和TNF)作出反应而产生的急性期反应物，并参与炎性反应[7]。既往有报道显示，CRP可能与抑郁症的快感缺失症状呈正相关[21]。相反，有研究提示，细胞因子会诱发抑郁样行为，例如Sukoff Rizzo等[22]将重组IL-6注入小鼠脑室内，小鼠产生了抑郁样行为。治疗丙型肝炎的研究发现，有1/4的患者在应用干扰素后发展为抑郁症[23]。在抗TNF治疗的研究中发现，抗TNF治疗后患者的抑郁症症状得到改善[24]。因此，炎症与抑郁症之间可能存在相互作用的关系。童年创伤可能会触发炎性反应。相关研究报道，个体过早地暴露于生活压力与炎症活动水平呈正相关[25]。一项动物实验证明，心理应激会使中枢神经系统中的细胞因子水平升高，尤其是海马区域[26]。Müller等[27]在研究中发现，童年创伤量表(Childhood Trauma Questionnaire，CTQ)亚量表分值与抗炎细胞因子IL-10之间不存在相关性，但与促炎细胞因子IL-6呈正相关。Baumeister等[7]针对童年创伤与成年炎症的一项Meta分析亦发现，童年创伤与TNF-α与的相关性最大，其次是IL-6和CRP。该Meta分析结论为童年创伤促进成年时期的炎性反应，表明童年创伤事件对炎性反应有显著的影响，且会延续到成年。此外，一项研究表明，在有童年创伤的受试者中，高水平的IL-6可能预测6个月后抑郁症发生的风险[28]。综上，童年创伤可能会触发炎性反应，这种影响可能会持续到成年，进而导致该个体对抑郁症的易感性增加。

2. HPA轴的调节因素GR在童年创伤与炎症之间的作用：相关研究表明，童年创伤对炎性反应造成的持续影响可能与神经内分泌系统表达紊乱有关[7]，具体原因可能是童年创伤亦会导致HPA轴的持续变化所致[29]。当个体受到创伤时，HPA轴会被激活，从而导致肾上腺释放糖皮质激素(glucocorticoid，GC)，GR与GC结合后参与HPA轴的负反馈调节过程[30]。因此，HPA轴功能活性受GR调节。此外，GR亦是机体中最容易受到压力影响的介质之一[31]。Marin等[32]在研究慢性应激对青少年女性HPA轴调节的影响时发现，在高度慢性应激环境下，青少年女性的GR表达减少，而在无慢性应激环境下其GR表达增加。由FKBP5基因编码的热休克蛋白-90-相关的共伴侣蛋白FK506结合蛋白51(FK506 binding protein 51，FKBP51)可以调节GR的活性，并且与童年创伤和抑郁症均有关联[33]。FKBP51参与调节细胞内GR活性的超短负反馈机制，通过减少与配体结合和阻碍受体复合物向核内转移改变GR的功能[30]。童年创伤使得FKBP5基因型特异性远端增强子去甲基化，导致FKBP51表达增多，负反馈机制增强，从而降低GR的活性[8]。总之，童年创伤通过影响GR及其伴侣蛋白FKBP5基因的甲基化过程调控HPA轴的功能，使得童年创伤对个体产生持久的影响[34]。GR本身不仅是HPA轴的调节因子，又是炎性反应的重要调节因子[7]。GR表达及功能障碍导致HPA轴负反馈调节障碍，继而使GC水平升高，高水平的GC会加剧炎症，对海马产生有害影响[9]。Kim等[35]发现，长期增加的GC介导了核因子－κB、丝裂原活化蛋白激酶和促炎细胞因子表达的增加，从而促进了持续的炎性反应。此外，另有研究得出不同的结论，显示炎性反应本身可以直接加剧受损的GR功能[36]，从而导致持续的GR抵抗进入成年期[7]。促炎细胞因子通过STAT5磷酸化抑制GR从细胞质向细胞核的易位以及通过激活GRβ(是GR的一种非活性形式)活性抑制GR功能[35]。GR功能障碍亦可导致抑郁症，

Wang等[37]向小鼠的海马内注射GR抑制剂，使其海马神经元内的GR表达降低从而建立了产后抑郁模型，说明GR表达降低，HPA轴功能过度活跃可能会导致抑郁症。同时有研究认为，芍药苷可通过恢复GR相关功能障碍和下调HPA轴功能活性改善抑郁样行为[38]。Adzic等[39]在研究童年创伤与健康人群的消极情绪时发现，外周血单核细胞中的GRα翻译亚型介导了童年创伤对应激相关的精神障碍风险的影响。其中40-kDa GRα亚型介导了童年创伤对消极情绪的影响，其可以通过涉及全长GRα和FKBP5的直接和间接途径影响个体的消极情绪。总之，炎性反应通过影响GR功能导致HPA轴负反馈调节障碍，HPA轴则处于过度活跃状态。此外，炎性反应系统亦会直接激活HPA轴，导致促肾上腺皮质激素释放激素和促肾上腺皮质激素的产生，并增加5-HT和儿茶酚胺的转换[15]，促进抑郁症的发生。

童年创伤是先通过影响GR功能从而导致炎性反应？还是通过炎性反应继而影响GR功能形成反馈环路？这一先后顺序还有待进一步研究。但是，可以说明炎症和激活的细胞因子信号通路与GR信号通路相互作用的串扰机制共同参与了童年创伤与抑郁症的发病过程。一项Meta分析认为，对于童年创伤影响GR功能从而导致炎性反应这一关系可能接受度更高[7]，即童年创伤及随后促炎细胞因子的释放会导致GR功能异常及慢性炎症。此外，GR负反馈调节应激会引起包括炎性反应及HPA轴在内的许多生理过程。总之，GR作为童年创伤与抑郁症之间的中介之一，与促炎细胞因子形成一个恶性循环，共同影响HPA轴功能与炎性反应过程，这使得个体持续处于慢性炎性反应之中。

三、总结和展望

目前，童年创伤作为抑郁症的发病因素一直备受关注，其过程可能与GC、GR及促炎细胞因子密切相关，特别是炎症和神经内分泌变化是否实际上在同一个体中同时发生以及童年创伤对GR及炎性反应的影响先后顺序需要在未来研究中进一步探讨。将这些数据置于更广泛的生物系统中可能对于确定为什么有些人经历童年创伤后会持续发展为精神疾病，而其他人仍然保持心理健康至关重要。此外，未来的研究应将上述因素与中枢神经解剖改变和遗传易感性联系起来，进一步探讨抑郁症的发病机制，或可为抑郁症的治疗策略提供新的思路，如可以从改善个体GR信号转导减轻炎症和抑郁症状的角度出发寻找替代或辅助治疗抑郁症的方案。

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 论文撰写为封俊杰、王小曼，构思与设计为丁莉莉、李天舒，论文修订为尤红、段蕾梅、金圭星

参 考 文 献

[1] Visentin A, Colombo R, Scotton E, et al. Targeting inflammatory-mitochondrial response in major depression: current evidence and further challenges[J]. Oxid Med Cell Longev, 2020, 2020: 2972968. DOI: 10.1155/2020/2972968.

[2] Morampudi S, Das N, Gowda A, et al. Estimation of lung cancer burden in Australia, the Philippines, and Singapore: an evaluation of disability adjusted life years[J]. Cancer Biol Med, 2017, 14(1): 74-82. DOI: 10.20892/j.issn.2095-3941.2016.0030.

[3] 李睿楠，王刚，周晶晶.抑郁症运动干预治疗的研究进展[J].中华精神科杂志，2019，52(2)：159-162. DOI：10.3760/cma.j.issn.1006-7884.2019.02.011.

[4] De Bellis MD, Zisk A. The biological effects of childhood trauma[J]. Child Adolesc Psychiatr Clin N Am, 2014, 23(2): 185-222, vii. DOI: 10.1016/j.chc.2014.01.002.

[5] 王蕾蕾，宋崇升，石超，等.童年期创伤与抑郁症的关系[J].中华行为医学与脑科学杂志，2019，(5)：476-480. DOI：10.3760/cma.j.issn.1674-6554.
Wang LL, Song CS, Shi C, et al. The relationship between childhood trauma and depression[J]. Chin J Behavioral Med & Brain Sci, 2019, (5): 476-480.

[6] D'Acunto G, Nageye F, Zhang J, et al. Inflammatory cytokines in children and adolescents with depressive disorders: a systematic review and Meta-analysis[J]. J Child Adolesc Psychopharmacol, 2019, 29(5): 362-369. DOI: 10.1089/cap.2019.0015.

[7] Baumeister D, Akhtar R, Ciufolini S, et al. Childhood trauma and adulthood inflammation: a Meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α[J]. Mol Psychiatry, 2016, 21(5): 642-649. DOI: 10.1038/mp.2015.67.

[8] Klengel T, Mehta D, Anacker C, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions[J]. Nat Neurosci, 2013, 16(1): 33-41. DOI: 10.1038/nn.3275.

[9] Sorrells SF, Munhoz CD, Manley NC, et al. Glucocorticoids increase excitotoxic injury and inflammation in the hippocampus of adult male rats[J]. Neuroendocrinology, 2014, 100(2/3): 129-140. DOI: 10.1159/000367849.

[10] Dannlowski U, Stuhrmann A, Beutelmann V, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging[J]. Biol Psychiatry, 2012, 71(4): 286-293. DOI: 10.1016/j.biopsych.2011.10.021.

[11] Ratanatharathorn A, Koenen KC, Chibnik LB, et al. Polygenic risk for autism, attention-deficit hyperactivity disorder, schizophrenia, major depressive disorder, and neuroticism is associated with the experience of childhood abuse[J]. Mol Psychiatry, 2021, 26(5): 1696-1705. DOI: 10.1038/s41380-020-00996-w.

[12] Poole JC, Kim HS, Dobson KS, et al. Adverse childhood experiences and disordered gambling: assessing the mediating role of emotion dysregulation[J]. J Gambl Stud, 2017, 33(4): 1187-1200. DOI: 10.1007/s10899-017-9680-8.

[13] Mandelli L, Petrelli C, Serretti A. The role of specific early trauma in adult depression: a meta-analysis of published

literature. Childhood trauma and adult depression[J]. Eur Psychiatry, 2015, 30(6): 665-680. DOI: 10.1016/j.eurpsy.2015.04.007.

[14] Wiersma JE, Hovens JG, van Oppen P, et al. The importance of childhood trauma and childhood life events for chronicity of depression in adults[J]. J Clin Psychiatry, 2009, 70(7): 983-989. DOI: 10.4088/jcp.08m04521.

[15] Ng A, Tam WW, Zhang MW, et al. IL-1β, IL-6, TNF-α and CRP in elderly patients with depression or alzheimer's disease: systematic review and Meta-analysis[J]. Sci Rep, 2018, 8(1): 12050. DOI: 10.1038/s41598-018-30487-6.

[16] Miller AH, Haroon E, Felger JC. Therapeutic implications of brain-immune interactions: treatment in translation[J]. Neuropsychopharmacology, 2017, 42(1): 334-359. DOI: 10.1038/npp.2016.167.

[17] Vogelzangs N, de Jonge P, Smit JH, et al. Cytokine production capacity in depression and anxiety[J]. Transl Psychiatry, 2016, 6(5): e825. DOI: 10.1038/tp.2016.92.

[18] Ting EY, Yang AC, Tsai SJ. Role of interleukin-6 in depressive disorder[J]. Int J Mol Sci, 2020, 21(6): 2194. DOI: 10.3390/ijms21062194.

[19] Liu JJ, Wei YB, Strawbridge R, et al. Peripheral cytokine levels and response to antidepressant treatment in depression: a systematic review and meta-analysis[J]. Mol Psychiatry, 2020, 25(2): 339-350. DOI: 10.1038/s41380-019-0474-5.

[20] Köhler CA, Freitas TH, Maes M, et al. Peripheral cytokine and chemokine alterations in depression: a Meta-analysis of 82 studies[J]. Acta Psychiatr Scand, 2017, 135(5): 373-387. DOI: 10.1111/acps.12698.

[21] Felger JC, Haroon E, Patel TA, et al. What does plasma CRP tell us about peripheral and central inflammation in depression?[J]. Mol Psychiatry, 2020, 25(6): 1301-1311. DOI: 10.1038/s41380-018-0096-3.

[22] Sukoff Rizzo SJ, Neal SJ, Hughes ZA, et al. Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes[J]. Transl Psychiatry, 2012, 2(12): e199. DOI: 10.1038/tp.2012.120.

[23] Udina M, Castellví P, Moreno-España J, et al. Interferon-induced depression in chronic hepatitis C: a systematic review and Meta-analysis[J]. J Clin Psychiatry, 2012, 73(8): 1128-1138. DOI: 10.4088/JCP.12r07694.

[24] Davies KA, Cooper E, Voon V, et al. Interferon and anti-TNF therapies differentially modulate amygdala reactivity which predicts associated bidirectional changes in depressive symptoms[J]. Mol Psychiatry, 2021, 26(9): 5150-5160. DOI: 10.1038/s41380-020-0790-9.

[25] Baldwin JR, Arseneault L, Caspi A, et al. Childhood victimization and inflammation in young adulthood: a genetically sensitive cohort study[J]. Brain Behav Immun, 2018, 67: 211-217. DOI: 10.1016/j.bbi.2017.08.025.

[26] Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression[J]. Psychol Bull, 2014, 140(3): 774-815. DOI: 10.1037/a0035302.

[27] Müller N, Krause D, Barth R, et al. Childhood adversity and current stress are related to pro- and anti-inflammatory cytokines in major depression[J]. J Affect Disord, 2019, 253: 270-276. DOI: 10.1016/j.jad.2019.04.088.

[28] Miller GE, Cole SW. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity[J]. Biol Psychiatry, 2012, 72(1): 34-40. DOI: 10.1016/j.biopsych.2012.02.034.

[29] Ridout KK, Carpenter LL, Tyrka AR. The cellular sequelae of early stress: focus on aging and mitochondria[J]. Neuropsychopharmacology, 2016, 41(1): 388-389. DOI: 10.1038/npp.2015.301.

[30] Cattaneo A, Riva MA. Stress-induced mechanisms in mental illness: a role for glucocorticoid signalling[J]. J Steroid Biochem Mol Biol, 2016, 160: 169-174. DOI: 10.1016/j.jsbmb.2015.07.021.

[31] Seewoobudul V, 陆邵佳, 王汨. 儿童期创伤对抑郁症患者糖皮质激素受体 1F 启动子区域 DNA 甲基化的影响[A]//中华医学会第十一次全国精神医学学术会议、第三届亚洲神经精神药理学术会议[C].2013.

[32] Marin TJ, Martin TM, Blackwell E, et al. Differentiating the impact of episodic and chronic stressors on hypothalamic-pituitary-adrenocortical axis regulation in young women[J]. Health Psychol, 2007, 26(4): 447-455. DOI: 10.1037/0278-6133.26.4.447.

[33] Matosin N, Halldorsdottir T, Binder EB. Understanding the molecular Mechanisms Underpinning Gene by environment interactions in psychiatric disorders: the FKBP5 model[J]. Biol Psychiatry, 2018, 83(10): 821-830. DOI: 10.1016/j.biopsych.2018.01.021.

[34] Tyrka AR, Ridout KK, Parade SH. Childhood adversity and epigenetic regulation of glucocorticoid signaling genes: Associations in children and adults[J]. Dev Psychopathol, 2016, 28(4pt2): 1319-1331. DOI: 10.1017/S0954579416000870.

[35] Kim YK, Na KS, Myint AM, et al. The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression[J]. Prog Neuropsychopharmacol Biol Psychiatry, 2016, 64: 277-284. DOI: 10.1016/j.pnpbp.2015.06.008.

[36] Zunszain PA, Anacker C, Cattaneo A, et al. Glucocorticoids, cytokines and brain abnormalities in depression[J]. Prog Neuropsychopharmacol Biol Psychiatry, 2011, 35(3): 722-729. DOI: 10.1016/j.pnpbp.2010.04.011.

[37] Wang J, Yun Q, Ma SF, et al. Inhibition of expression of glucocorticoids receptors may contribute to postpartum depression[J]. Biochem Biophys Res Commun, 2020, 523(1): 159-164. DOI: 10.1016/j.bbrc.2019.12.040.

[38] Li YC, Zheng XX, Xia SZ, et al. Paeoniflorin ameliorates depressive-like behavior in prenatally stressed offspring by restoring the HPA axis- and glucocorticoid receptor- associated dysfunction[J]. J Affect Disord, 2020, 274: 471-481. DOI: 10.1016/j.jad.2020.05.078.

[39] Adzic M, Glavonic E, Nesic MJ, et al. Glucocorticoid receptor alpha translational isoforms as mediators of early adversities and negative emotional states[J]. Prog Neuropsychopharmacol Biol Psychiatry, 2019, 90: 288-299. DOI: 10.1016/j.pnpbp.2018.12.011.

(收稿日期: 2022-06-21)
(本文编辑: 赵金鑫)