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抑郁症与应激、炎症和胰岛素抵抗之间关系的研究进展

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摘　要

抑郁症是一种危害全球人类生活质量的精神疾病，具有高患病率、高疾病负担、高致残率等特点。至今为止抑郁症的具体病理生理机制尚未明确，但抑郁症的炎症与生活事件导致的应激机制已被大众认可，近年来研究发现抑郁症与胰岛素抵抗存在高共患病率，胰岛素抵抗通过各种病理生理机制参与抑郁症的发生与发展，并有望成为新的抗抑郁治疗靶点。本文通过回顾近期国内外已发表的文献，总结了当前抑郁症与炎症、应激、胰岛素抵抗的相关性研究进展，并就胰岛素抵抗、炎症和应激三种因素相互之间可能存在的联系进行综述，为今后深入研究抑郁症机制和治疗方法提供思路和方向，为建设全民健康预防抑郁症提供新角度。

关键词

抑郁症，胰岛素抵抗，炎症，应激

Research Progress on the Relationship between Stress, Inflammation, Insulin Resistance and Depression

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Abstract

Depression is a mental illness that endangers the quality of human life around the world, with

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high prevalence, high disease burden, and high disability rate. So far, the specific pathophysiological mechanism of depression has not been fully understood, but the mechanism of inflammation and the stress caused by life events in depression has been widely recognized. In recent years, studies have found that there is a high comorbid rate between depression and insulin resistance, and insulin resistance is involved in the occurrence and development of depression through various pathophysiological mechanisms, and is expected to become a new target for antidepressant treatment. This article summarizes the current research progress on the correlation between inflammation, stress, insulin resistance and depression and the possible relationship between the three factors by reviewing the recent published literature at inland and abroad, so as to provide ideas and directions for in-depth research on the mechanism and treatment of depression in the future, and provide a new perspective for the construction of national health to prevent depression.

Keywords

Depression, Insulin Resistance, Inflammation, Stress

1. 引言

抑郁症(Major Depression Disorder, MDD)是一种复杂的异质性疾病，也是最常见的精神障碍，在世界范围内，抑郁症是精神健康相关疾病负担的主要原因，影响着大约 3 亿人[1]。2017 年全球疾病、伤害和风险因素研究中提示抑郁症是研究条件中疾病负担的第三大原因[2]。抑郁症不仅妨碍个人充分发挥潜力还会损害人力资源，并与过早死亡有关，是可持续发展的阻碍[1]。MDD 可以是慢性的，也可以是复发性的，通常与长时间的情绪低落和快感缺乏有关[3]。抑郁症还具有着令人不可忽略的社会经济后果，包括发病率增加、残疾、死亡率过高、经济成本高和自杀风险增加[4]。MDD 对患者的感受、思维和行为有负面影响，致使患病个体感到悲伤和(或)对以前愉快的活动失去兴趣。MDD 可导致各种与情绪和身体健康相关的问题，对患者在工作和家庭中的正常功能产生负面影响[5]。除了特征性的情绪症状外，还存在其他与认知(记忆力、反应力、注意力)和身体机能(慢性疲劳、性欲下降、食欲下降、失眠)相关的症状[6]。上述研究均表明抑郁症是一种多方面的心理健康障碍，影响着全球数亿人。虽然抑郁症的起源和机制仍有待阐明，但越来越多的证据表明，抑郁症不仅仅是神经递质功能紊乱的结果，而是多种因素复杂相互作用的结果。在这些因素中，应激、炎症和代谢过程的作用已经成为抑郁症发生和发展的重要因素。这些发现可能暗示着我们急需提高对抑郁症与胰岛素抵抗之间联系的认识并尽快搭建新的预防战略。

2. 抑郁症与应激

应激是一种由于心理、生理或环境刺激而引起的体内平衡失调状态。应激通过激活下丘脑－垂体－肾上腺(HPA)轴和交感神经系统(SNS)来改变身体的激素和神经递质环境，而作为应激反应机制产生的儿茶酚胺会影响血压和心率等重要参数[7]。这些反应是身体应对应激所必需的[8]。然而，对慢性应激的长期反应可能是有害的。慢性的持续应激不仅与动脉粥样硬化和高血压等心血管疾病(CVD)有关，还与如阿尔茨海默病(AD)、帕金森氏病(PD)和抑郁症等神经退行性疾病有关。此外，糖尿病和非酒精性脂肪性肝病(NAFLD)等代谢性疾病也可能是由长期应激引起的[9] [10]。抑郁症(MDD)，表现为快感缺乏、内疚、

虚弱、幻觉、食欲改变、精神激动、睡眠障碍和轻生观念[11]。这对患者及其家属的生活质量产生不利影响，甚至会导致许多自杀事件。根据世界卫生组织的数据，每年有超过 70 万人死于自杀，自杀是年轻一代死亡的第四大原因[12]。Peyrot 等人在荷兰抑郁和焦虑研究(NESDA)的成人样本中研究了儿童创伤史是否调节了多基因风险分数和严重抑郁症之间的联系，并发现了一种相互作用的证据，即多基因得分对严重抑郁风险的影响在报告有童年创伤史的个体中更强，进一步证明了压力应激与抑郁的相关性[13]。同年 Musliner 等人研究发现，遗传因素可能与生活压力事件(SLEs)相互作用，从而增加患抑郁症的风险，其数量比人们预期的每一个因素单独综合作用的风险要大，至少经历过一次生活压力事件的个体经历 4 种抑郁症状的几率是对照组的两倍多[14]。

3. 抑郁症与炎症

炎症会激活免疫系统，并指示它治愈受伤的组织和清除物质。当炎症呈持续性、低级别和全身性时，称为慢性低级别炎症[15]。在各种慢性疾病状态下均可观察到慢性低度炎症，例如：代谢障碍、肝脏问题、2 型糖尿病(T2DM)、心脏代谢障碍和精神疾病[16]。低级别慢性炎症是指机体免疫系统持续、低水平的激活，通常以细胞因子和 C 反应蛋白(CRP)等炎症因子水平升高为特征[17]。有研究表明，MDD 与低度慢性炎症之间存在关联[18] [19]。在过去的 20 年里，越来越多的证据表明，抑郁症与全身免疫激活有关，包括炎症标志物、免疫细胞数量和抗体滴度的异常等[20]。Eléonore Beurel 等人指出现在已经在多项荟萃分析中得到了很好的证实，与健康对照组相比，抑郁症患者的炎症因子和急性期蛋白增加，且抑郁症患者血液中 IL-6、TNF 和 c 反应蛋白(CRP)的增加是也是目前一致的共识[21]。研究表明，细胞因子介导的在免疫系统与大脑之间的信号通路参与了 MDD 的发病机制[22]。在外周和中枢神经系统中，IL-6 可以作为一种神经生长因子，导致神经突的发育和神经再生。在压力应激刺激反应中，IL-6 的合成增加，研究结果表明，在抑郁症中，较高的 IL-6 水平与更严重的疾病病程相关[23] [24] [25]。它似乎也与抑郁症的特定症状或亚型有关，如 IL-6 水平与食欲减退、睡眠障碍、情绪低落、无价值感等症状之间的关系已被证实[26]。另外有研究从反面印证炎症因子对抑郁症的作用，该研究表明外周细胞因子肯定有助于行为效应，阻断外周细胞因子可以收紧血脑屏障，并且阻止其被破坏，从而表现出抗抑郁作用。这意味着外周细胞因子对于抑郁症的发生和发展起着重要的作用。通过阻断外周细胞因子的作用，可以减少其对大脑功能的影响，从而改善抑郁症状。然而，具体的机制和方法仍需要进一步的研究和探索[27] [28]。并且并非所有 MDD 患者都表现出炎症增加，炎症标志物的增加可能与抑郁症的非典型症状有关[29]。

4. 抑郁症与胰岛素抵抗

胰岛素抵抗(insulin resistance, IR)是一种可改变的、新陈代谢的炎症状态，其特征是机体组织对胰岛素作用的反应减弱它的存在是一些躯体和大脑疾病的已知危险因素，包括心血管疾病，慢性肾脏疾病，阿尔茨海默病和抑郁症[30]。越来越多的生物学证据表明，IR 与抑郁症的发展有关[31] [32] [33]。在大脑中，IR 导致代谢低下、血管改变、神经可塑性失调和结构改变，这些都可以触发或放大抑郁症[31] [32] [34]。IR 动物模型显示抑郁症行为的风险增加，以及神经炎症、线粒体功能失调和神经新生减少，所有上述因素都被假设与人类抑郁有关[34] [35]。此外，研究表明对动物 IR 的治疗可以逆转类似抑郁的行为[36] [37] [38]。研究表明，抑郁症增加了随后发展为 2 型糖尿病和代谢综合征的风险，而众所周知的在这些内分泌疾病中，IR 也起着重要作用[35] [39] [40]。也有一些研究研究 IR 是否会增加 MDD 发生的风险。其中，一项对老年男性的研究发现，在 5 年随访期间，IR 与抑郁症发病的风险比为 2.3 [41]。荷兰的一项为期 9 年的前瞻性队列研究中，无抑郁或焦虑症病史的成年人中，胰岛素抵抗的三种替代测量正向预测抑郁症的发生率。此外，在入组和 2 年随访期间，前驱糖尿病的发生与抑郁症的发生呈正相关[42]。2023 年在

韩国的一项具有全国代表性的横断面研究提示 IR 与非肥胖个体的认知/情感和躯体抑郁症状呈正相关[43]。国内的一项胰岛素抵抗新指标(TyG 指数)与中老年社区人群抑郁症状的相关性研究结果提示控制干扰因素后中老年人的 TyG 指数越高，抑郁评分越高，说明胰岛素抵抗与中老年人抑郁症状严重程度密切相关。基线期 TyG 指数与随访 3 年后的抑郁评分有关，进一步说明了胰岛素抵抗不仅与抑郁症的发生有关，还与其症状的持续存在密切相关[44]。

5. 胰岛素抵抗、炎症、应激如何相互联系并作用于抑郁症？

根据上文我们知道了应激、炎症、胰岛素抵抗都与抑郁症密切相关，且似乎这三个因素往往共同存在。研究表明，应激、慢性炎症和抑郁这三者是相互关联的，是由代谢紊乱引起的。理解这一界面的一个关键概念是心理社会和生理压力在触发和加剧这些疾病中的作用。有应激经历会导致严重的精神疾病，如精神分裂症、躁郁症、焦虑症和严重抑郁症[45]。研究发现生活压力与肥胖、2 型糖尿病(T2D)和肝脏疾病的风险增加有关，与抑郁症和心血管疾病的风险存在着更高的相关性。更甚者，应激会作为催化剂促进代谢疾病转变至合并症和死亡[46]。生命早期和整个生命过程中的应激经历，以及损害健康的行为会增加患 2 型糖尿病和抑郁症的风险。反过来，抑郁和糖尿病又增加了患痴呆症的可能性，例证了应激的终生影响以及外周和中心机制之间持续的相互作用，它们相互干扰，在一个人身上产生多种慢性疾病[47]。值得注意的是，越来越多的研究支持胰岛素抵抗是这些慢性疾病的共同元凶[30]。应激、炎症和胰岛素抵抗或许是通过异位稳态系统联系起来的。“异位稳态”是指被新颖的、潜在威胁的经验激活的多种适应和神经处理生存促进系统。这些机制中就包括通过下丘脑－垂体肾上腺(HPA)轴产生皮质醇，通过肾上腺和交感神经系统产生肾上腺素。同时它们还涉及副交感神经系统的激活及促炎、抗炎细胞因子和代谢激素的释放[48]。在皮质醇浓度高的情况下胰岛素分泌会减少，同时，胰岛素会提高促肾上腺皮质激素和皮质醇激素水平，促进 HPA 轴的激活[49] [50]。胰岛素具有抗炎作用，对其抗炎作用的抵抗可能导致促炎细胞因子循环水平的增强，从而导致持续的低级别炎症。行为和心理因素也可能与代谢综合征和抑郁症有关。代谢综合征与久坐的生活方式和由于肥胖的污名而产生的负面自我认知有关，而肥胖是代谢综合征的一个组成部分，会导致患抑郁症的风险增加[51]。不少研究中也指出腹型肥胖、BMI、非酒精性脂肪肝等都与抑郁症相关[52]，荷兰的队列研究也指出腰围增加也是抑郁症的危险因素[42]，而以上种种“肥胖”指标同时又与炎症和应激密不可分。

6. 小结

在发展中国家和发达国家，精神障碍在患有慢性身体疾病的个人中普遍存在的[53]。随着抑郁症在全球流行，到 2030 年，它可能超过心血管疾病，成为第二大死亡原因[54]。如今我们已经初步了解了抑郁症与应激、炎症、胰岛素之间的相关性，接下来我们需要进一步明确抑郁症与这些因素之间的关系及其相互作用的具体机制，并通过对这种关系的理解可以进一步发展靶向胰岛素抵抗、炎症的药物和针对减少生活事件导致应激的行为干预，并改善或尽可能预防其对抑郁症的长期影响。在全民健康的角度为更广泛人群提供通过抗炎、抗高血糖、抗胰岛素抵抗等改善生活方式及饮食习惯来预防或改善抑郁的新思路。

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