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糖尿病与卒中后抑郁的研究进展

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摘　要

卒中后抑郁是一种常见的卒中并发症，对患者的康复和生活质量有着显著影响。约三分一卒中患者伴有糖尿病，而糖尿病可加剧卒中后抑郁的风险，两者之间在病理生理学上存在相互促进的关系。本文将探讨糖尿病与卒中后抑郁之间的病理生理学联系，并从药物治疗的角度进行分析，旨在为合并糖尿病的卒中后抑郁患者提供预防和诊治参考。

关键词

糖尿病，卒中后抑郁

Research Progress of Diabetes and Post-Stroke Depression

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Abstract

Post-stroke depression is a common complication of stroke, significantly affecting patients' recovery and quality of life. Approximately one-third of stroke patients are diagnosed with diabetes, and diabetes can exacerbate the risk of post-stroke depression. There is a mutually reinforcing relationship between the two in terms of pathophysiology. This article will explore the pathophysiological connection between diabetes and post-stroke depression and analyze it from the perspective of drug therapy, aiming to provide prevention and treatment references for patients with post-stroke depression who also have diabetes.

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Keywords

Diabetes, Post-Stroke Depression

1. 前言

卒中后抑郁(post-stroke depression, PSD)是一种普遍且严重的神经精神疾病并发症。卒中后 5 年内，抑郁的累积发病率介于 39%至 52%之间[1]，对患者的认知功能、日常活动和卒中康复过程产生严重不利影响，须受到充分关注。糖尿病和高糖化血红蛋白是 PSD 的独立预测因素，与 PSD 的发生有着密切的关联。而且，卒中急性期血糖水平的短暂升高也可能增加患者患 PSD 风险[2] [3]。合并糖尿病的 PSD 患病率高、严重影响患者预后，但目前对其筛查、诊断及治疗仍存在重视度不够、缺乏有效治疗药物等问题。本文旨在探讨糖尿病与 PSD 之间的相关性，并综述防治合并糖尿病的 PSD 药物的临床特点。

2. 血糖升高增加卒中后抑郁发生率

尽管目前尚缺乏关于 PSD 合并糖尿病患病率的临床统计数据，但一项队列研究显示，在排除使用抗抑郁药物的患者后，血糖水平与卒中后 18 个月内的抑郁状况存在关联。特别是当患者入院时的葡萄糖水平超过 7 mmol/l 时，他们更有可能发生 PSD [2]。此外，在轻度糖代谢异常的个体中，PSD 的风险也会增加。对于糖化血红蛋白(HbA1c)水平在 5.7%至 6.4%的糖尿病高危人群，PSD 的发生风险是正常水平的两倍，并且与卒中后 1 个月内的抑郁状况相关[4]。在糖尿病与卒中后迟发性抑郁的相关性研究中，排除早期抑郁的患者，糖尿病是轻度卒中 3 个月后抑郁的危险因素；并且空腹血清葡萄糖大于 7.49 mmol/l 和糖化血红蛋白大于 6.8%可以作为预测卒中后迟发性抑郁的指标，特异性为 84.4% [5]。

3. 糖尿病与卒中后抑郁的病理生理学

3.1. 下丘脑－垂体－肾上腺(Hypothalamic-Pituitary-Adrenal, HPA)轴与交感神经失调

糖尿病可激活 HPA 轴，导致皮质醇分泌过多和昼夜节律异常，诱发 5-羟色胺功能受损，而 5-羟色胺功能异常参与抑郁症进展。慢性压力应激刺激肾上腺轴与交感神经，导致皮质醇激素分泌过多，这种激素作用于大脑的海马区域，影响神经细胞生长，而抑郁与糖尿病的发病均与该区域相关[6] [7]。卒中急性事件发生后 HPA 过度激活，导致交感神经张力增加，促进细胞因子、炎症介质(IL-6, IL-8, TNF-β)释放、消耗副边缘区域的血清素，并诱发抑郁症的发生[8]。高皮质醇与炎症反应相互促进，促炎因子参与皮质醇的过量释放，同时高皮质醇诱发炎症反应，HPA 轴进一步失调，卒中后抑郁临床症状也随之加重[9] [10]。

3.2. 肠道菌群失调

诸多研究显示肠道菌群紊乱参与了糖尿病与 PSD 的发生。肠道微生物分解代谢物短链脂肪酸、内源性分子代谢物等信号分子可在局部发挥作用，通过肠屏障与血脑屏障炎症氧化应激等机制在大脑等肠外器官发挥生理病理作用[11] [12]。临床研究显示评估肠道微生物的失调与 PSD 之间的联系。与非卒中后抑郁合并认知障碍组对比，PSD 合并认知障碍组观察到某些产生短链脂肪酸(Short-Chain Fatty Acids, SCFA)的细菌显著减少，例如 *Fusicatenibacter* 和 *Lachnospiraceae* [13] [14]。这些细菌是肠道微生物群中

的重要成员，其变化可能与肠道菌群的整体功能失调有关。在 SCFA 类别中，乙酸盐水平与抑郁水平呈正相关，丁酸盐和丙酸盐水平与抑郁样症状呈负相关[15]。这一现象提示，不同 SCFA 在肠－脑轴的信号传导中可能发挥不同的作用。丁酸盐已被证明具有抗炎、抗氧化、抑制脑源性神经营养因子(Brain-Derived Neurotrophic Factor, BDNF)的降低以及调节肠道健康的功效，且在改善抑郁样行为方面表现出显著的潜力[16]-[18]。此外，荟萃分析显示与健康受试者相比，PSD 患者肠道中拟杆菌门、变形菌门和梭菌门的丰度明显较高，厚壁菌门的丰度较低[19]。与健康人相比，糖尿病患者肠道内产生丁酸盐的细菌减少，影响着大脑功能行为[20]。糖尿病伴抑郁患者，降低血糖水平，提高益生菌数量，可缓解情绪低落等抑郁症状[21] [22]。

3.3. 神经营养因子失调

BDNF 是神经可塑性的标志物，参与神经细胞的生长分化，调节学习记忆情绪活动[23] [24]。临床研究显示与非抑郁对照受试者相比，PSD 患者的血清 BDNF 水平较低，不能满足海马和背外侧前额叶皮层的神经营养活动，促进 PSD 的发生[25] [26]。除此之外，BDNF 激动相应受体起着维持能量和血糖平衡的作用，改善胰岛素抵抗和糖脂紊乱，BDNF 通路的紊乱与代谢性疾病发生有关[27]。动物实验证实，海马内 BDNF/CREB 信号通路的失活与糖尿病小鼠抑郁的发生和发展有关；皮下注射 BDNF 不仅能增强胰岛素敏感性，还能改善情绪和认知功能[28]。BDNF 功能受损参与糖代谢紊乱与卒中后神经精神疾病的病理改变。

3.4. 胰岛素抵抗

胰岛素抵抗加速了糖尿病与 PSD 的进程。胰岛素抵抗阻碍了胰岛素保护神经元的正常生理作用，胰岛素抵抗是缺血性卒中的独立危险因素，胰岛素信号转导中断，血管扩张因子 NO 减少，血管收缩因子增加，破坏内皮正常功能，导致血栓形成，加速了动脉粥样硬化的形成[29]。糖尿病患者中较高的胰岛素水平与自杀、消极意念之间存在显著关联[30]。胰岛素抵抗意味着脑细胞摄取葡萄糖的能力相对不足，血糖利用失调，导致情感情绪、活动行为改变[31]。此外，胰岛素抵抗可导致神经元结构功能改变，促进神经元凋亡。杏仁核与海马体都是富含胰岛素受体的区域，胰岛素受体激活与多种信号分子级联反应相关，参与学习记忆过程和调节神经元的发生[32]。由此胰岛素抵抗与认知学习和情绪缺损，以及焦虑抑郁等精神障碍相关，同时也更容易导致神经退行性变[33]，是促进糖尿病患者 PSD 的机制之一。

4. 降糖药抗抑郁的研究进展

研究显示，二甲双胍通过改变肠道菌群的代谢物和衍生物的结构及丰度，改善肠道菌群的紊乱状态，从而缓解小鼠的焦虑和抑郁样行为，并且作用于海马体、基底神经节区的 AMPK 通路，增加神经可塑性，改善学习和认知[34] [35]。二甲双胍还可通过调节 CREB/BDNF 和 Akt/GSK3 通路，抑制氧化应激和炎症反应，改善海马神经元凋亡，抑制神经退行性变；通过抑制 CREB 蛋白、GSK3 和 AKT 蛋白表达，上调 BDNF 蛋白水平增强神经可塑性，建立神经保护屏障[36]。有趣的是二甲双胍可增强 GLP-1 活性，促进其穿过血脑屏障，增加在脑垂体、额叶皮层和海马浓度，发挥神经保护作用。此外，二甲双胍通过 AMPK 通路降低 ACTH、糖皮质激素水平，这与抑郁症发生的机制相契合[36]。临床研究表明二甲双胍可显著改善双向情感障碍病人抑郁症状，并且逆转胰岛素抵抗，在 26 周焦虑抑郁的改善效果最佳[37]。

磺脲类药物中的 K^+-ATP 通道抑制剂具备独特的药理学特性，能够穿越血脑屏障抵达大脑内部，在多个关键脑区，诸如海马、垂体以及前额叶皮层等部位的 K-ATP 通道上锚定并发挥作用，进而呈现出显著的神经保护效能[38] [39]。在缺血性卒中患者中，减少梗死体积，改善神经损伤，增加侧支循环，促进神经细胞再生，改善血管内皮功能，抑制梗死后的氧化应激水平，明显降低卒中后的脑水肿和出血转换、

认知障碍发生率[40]-[42]。一项动物实验显示格列本脲可作用于 HPA 轴，降低皮质酮水平，纠正 HPA 失调，改善焦虑抑郁行为[43]。值得一提的是，针对慢性压力应激所诱发的 HPA 轴紊乱，及其连锁引发的胰岛素抵抗与抑郁样症状，格列本脲能够靶向抑制上游分子 TXNIP，有效削减 NLRP3 炎症小体及各类炎症介质的异常积聚，逆转胰岛素抵抗和焦虑抑郁状态[42]。

胰高血糖素样肽-1 受体激动剂(GLP-1RA)可预防高风险糖尿病患者心脑血管事件，其改善认知障碍及情绪障碍的作用也逐渐被发掘[44]。利拉鲁肽可上调 VEGF，抑制氧化应激，减少神经组织的梗死面积，同时促进神经突触再生和增强神经突触传递[44] [45]。基础研究中，皮质酮诱导的抑郁模型中，利拉鲁肽可增强海马区 CA1 突触的可塑性、抑制 GSK3β 的过度活化、促进海马齿状回神经的再生、使得 ACTH 水平正常，从而逆转焦虑抑郁症状[46] [47]。GLP-1R 激动剂 Exendin-4 上调 BDNF 水平，在强制游泳行为中显著减少了焦虑抑郁行为[48] [49]。长期服用抗精神药物奥氮平，可导致抑郁样行为和代谢异常，利拉鲁肽治疗五周后可显著改善代谢紊乱，并在小鼠强制游泳实验中改善奥氮平导致的不活动时间增加，改善抑郁状态[50]。新诊断糖尿病的前瞻性研究显示，接受 GLP-1RA 治疗患者，一年后抑郁症状明显改善，抑郁评分、炎症指标 C 反应蛋白均有改善[51]。然而，有病例报告记录了数名无抑郁症的患者使用 GLP-1RA 数月后出现焦虑抑郁情绪[52]。同时队列研究显示使用 GLP-1RA 的患者患重度抑郁症的风险是未使用这类药物患者的 2 倍[53]。目前关于 GLP-1 与 PSD 之间的关系，尚存争议，未来需要开展更多的前瞻性研究来深入探讨 GLP-1RA 与抑郁之间的联系。

5. 抗抑郁药物对血糖及其卒中后抑郁预后的影响

越来越多研究发现抗抑郁药具有神经细胞保护作用，并且此作用不依赖其抗焦虑抑郁的作用。选择性 5-羟色胺再摄取抑制剂(Selective Serotonin Reuptake Inhibitor, SSRI)西酞普兰是临床治疗焦虑和抑郁的首选药之一[54]。基础研究中，西酞普兰抑制脑梗死后神经兴奋性氨基酸的释放，保护海马 CA1 神经元[55]。西酞普兰还可抑制炎症因子丙二醛、基质金属蛋白酶和凋亡标志物的产生、抑制氧化应激水平，减少神经细胞凋亡，保证血脑屏障的完整性，减少脑梗死体积，改善了神经功能预后[56]。小鼠卒中模型中，西酞普兰治疗脑梗死 7 天后，BDNF 在梗死周围表达上调，增加缺血半暗带血管密度，促进新生血管的形成[57]。在 3 个月的前瞻性研究中，西酞普兰可显著改善非抑郁患者的神经功能预后，提高患者生活质量[58]。西酞普兰不仅保护神经细胞，增加神经发生、侧支循环，还可能改善胰岛素抵抗[59] [60]。一项回顾性研究表明，艾司西酞普兰在抑郁症患者中使用能有效地降低糖化血红蛋白水平，并且显示出很高的安全性[61]。

基础研究发现抗抑郁药 SSRI 氟西汀可抑制炎症因子产生，发挥神经保护作用[62]。氟西汀提高 Camp 水平，增加 BDNF 的表达，一方面激活各种抗氧化酶，抑制氧化炎症反应，另一方面增加神经突触再生、树突再生，提高神经元可塑性[63] [64]。在缺血再灌注模型中氟西汀抑制 BV2 细胞 INF-α 等炎症因子的表达，下调 NF-κB 通路，抑制各种炎症应激因子的释放，保护脑卒中后缺血再灌注损害[65]。一项荟萃分析显示氟西汀可降低卒中后抑郁的发生率，促进卒中后的运动恢复[66]。一项为期 8 周临床研究显示，氟西汀能降低重度抑郁患者空腹血糖，改善糖代谢异常[67]。

基础研究显示另一种 SSRI 抗抑郁药舍曲林也能够保护神经元，减轻脑缺血再灌注损伤。在小鼠光栓模型中，舍曲林改善脑血流量自动调节，直接舒张脑血管，增加脑血流量，抑制缺血半暗带的扩大。除此之外，舍曲林促进血红素加氧酶 1 (HO-1)和缺氧诱导因子 1α (HIF-1α)表达，减少神经元缺血缺氧损伤[68]。脑缺血再灌注小鼠模型中，舍曲林减少自由基和脂质过氧化物的产生，恢复谷胱甘肽系统，起着抗氧化的作用。此外，其通过一氧化氮-cGMP 信号传导，改善线粒体功能障碍[69] [70]。前瞻性临床试验中高 PSD 风险患者，在卒中发生后 4 天内接受舍曲林 50 mg 每天治疗，3 个月的良好功能预后是非舍曲林

组的 3 倍，早期摄入舍曲林可能对卒中的预后有改善作用[71]。一项前瞻性研究发现，每天服用舍曲林 50 mg，可降低体重、缩小腰围、空腹血糖、餐后血糖，调节胰岛素敏感性，减少食物摄入量，对碳水化合物代谢产生有利影响，在抗抑郁的同时，血糖与体重都得到了控制[72] [73]。相较于其他抗抑郁药物，三环类抗抑郁药和单胺氧化酶抑制剂对神经系统的保护作用较为有限，并且它们可能会引起体重增加、血糖控制困难以及加剧胰岛素抵抗等不良反应[74]。

6. 总结和展望

糖尿病与 PSD 在发病机制中相互促进，对患者的预后和生活质量造成重大影响。PSD 发病率高，临床实践中应高度重视对卒中患者的定期抑郁筛查，尤其是对于合并糖尿病的患者，以便实现早期发现和及时干预。现有证据表明，二甲双胍作为一线降糖药物可能具有抗抑郁作用，更适合用于合并糖尿病的 PSD 患者。在抗抑郁药物领域，SSRI 类药物对血糖影响较小且安全性较高，同时具有潜在的神经血管保护作用，更利于糖尿病合并 PSD 患者的血糖管理。然而，目前仍缺乏强有力的证据来确定各类药物在预防或治疗糖尿病合并 PSD 中的最佳剂量、治疗时机以及潜在的不良反应。基于 PSD 和糖尿病之间的共同发病机制，挖掘有效防治药物是后续研究的方向。

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