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针灸调节线粒体治疗缺血性脑卒中的实验研究进展

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摘　要

缺血性卒中因其高患病率、复杂发病机制及治疗困难性，一直是科学研究的重点领域。线粒体在细胞能量稳态中起重要作用，并参与缺血性卒中后的神经元死亡过程。因此，维持线粒体功能对缺血性卒中患者的神经元存活及神经功能改善至关重要，线粒体成为脑卒中研究中的关键治疗靶点。传统中医凭借高效性、低成本及高安全性优势，在缺血性卒中防治领域具有显著优势。大量研究从调控线粒体结构与功能的角度探讨了中医防治缺血性卒中的作用。本综述重点阐述线粒体参与缺血性卒中的分子机制，并总结当前通过调节线粒体实现中医防治缺血性卒中的研究进展，旨在为通过线粒体调控机制开展中医防治缺血性卒中提供新视角与启示。

关键词

中医，线粒体，分子机制，综述，缺血性卒中

Experimental Research Progress on Acupuncture Regulating Mitochondria in the Treatment of Ischemic Stroke

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Abstract

Ischemic stroke has long been a key area of scientific research due to its high prevalence, complex pathogenesis, and therapeutic challenges. Mitochondria play a vital role in cellular energy homeostasis and participate in the process of neuronal death following ischemic stroke. Therefore, maintaining mitochondrial function is crucial for neuronal survival and neurological function recovery in patients with ischemic stroke, making mitochondria a critical therapeutic target in stroke research. Traditional Chinese Medicine (TCM) has prominent advantages in the prevention and treatment of ischemic stroke owing to its high efficacy, low cost, and favorable safety profile. Numerous studies have investigated the effects of TCM on ischemic stroke by regulating mitochondrial structure and function. This review focuses on the molecular mechanisms by which mitochondria are involved in ischemic stroke and summarizes the current research progress of TCM in preventing and treating ischemic stroke through mitochondrial modulation. It aims to provide new perspectives and insights for TCM research targeting mitochondria in the management of ischemic stroke.

Keywords

Traditional Chinese Medicine, Mitochondria, Molecular Mechanism, Review, Ischemic Stroke

1. 概述

中风是全球范围内导致死亡的第二大病因，同时也是造成永久性残疾的主要原因[1]。每年新增中风患者约有 1220 万人，带来了巨大的家庭和社会负担，其中缺血性脑卒中每年新发病例超过 760 万，占所有卒中的 62%以上[2]。缺血性中风是由于大脑血液供应障碍，导致部分大脑组织缺血、缺氧性坏死，进而出现相应神经功能缺损症状[3]。

缺血性脑卒中发生时，脑部血流的急剧减少导致葡萄糖和氧气供应不足(OGD)，线粒体作为细胞的能量工厂，其功能障碍成为缺血后 OGD 的早期和初始事件。OGD 引起的 ATP 耗竭和 Na+/K+ATP 酶泵衰竭导致神经元膜去极化和谷氨酸过度释放，进而引发 Ca^{2+}内流和活性氧(ROS)产生，这些变化加剧了线粒体功能障碍，最终导致神经元细胞死亡[4]。及时恢复血流挽救缺氧组织是主要治疗目标。在许多研究中，使用重组组织纤溶酶原激活剂(Tissue Plasminogen Activator t-PA)进行静脉溶栓已被用作 AIS 的有效一线治疗方法[5]。然而，狭窄的时间窗、较低的再灌注率和出血转化风险限制了其临床应用。替奈普酶是一种新型溶栓剂，具有更高的再灌注速率和更好的功能结果，但目前替奈普酶尚未获得 FDA 批准用于 AIS 患者的静脉溶栓，且缺乏与阿替普酶相同水平的 AHA/ASA 推荐[6]。越来越多的研究证实了利用线粒体作为治疗缺血性脑卒中关键靶点的重要性[7]，探索保护线粒体功能、减轻其损伤的策略显得尤为重要。传统中医(TCM)以其独特的理论体系和治疗方法，为线粒体保护提供了新思路。

中药和针灸是 TCM 的重要组成部分。在以往的研究与实验中，TCM 在预防和治疗缺血性脑卒中中取得疗效[8]。近几年，对于中药治疗缺血性脑卒中进行了众多研究报道，通过中药调节线粒体自噬与凋亡[9]、控制线粒体质量[10]，维持线粒体功能以促进神经元存活和改善神经功能。但针灸作为 TCM 的一部分，在恢复线粒体功能治疗缺血性脑卒中进行全面综述的研究较少。本文通过探讨针灸调控线粒体在

治疗缺血性脑卒中的潜在价值并总结最新研究进展，为针灸治疗缺血性脑卒中提供新视角。

2. 线粒体在缺血性脑卒中中的作用

线粒体在缺血性脑卒中的病理中扮演着重要角色，通过其异常产生的 ROS、钙积累、线粒体生物合成缺陷、通过诱导 MPTP 和激活凋亡触发细胞死亡、破坏 ATP/ADP 比率以及降低 NAD+水平。

2.1. 线粒体结构和功能障碍

缺血性脑卒中发生时，脑组织血流量显著下降，缺氧和能量不足导致细胞内紊乱，造成脑损伤。线粒体通过线粒体呼吸链和氧化磷酸化产生大部分 ATP，以满足大脑需求，缺血时，ATP 减少，导致细胞膜上的 Na+/K+-ATP 酶失活[11]以及 GS 无法正常工作，谷氨酸无法有效转换为谷氨酰胺，加剧了神经元周围谷氨酸浓度[12]，谷氨酸受体(如 NMDA 受体、AMPA 受体等)被过度激活，导致细胞膜上的离子通道开放，造成钙离子内流，诱导 MPTP 开放，导致线粒体肿胀、膜电位下降[13]和促凋亡因子释放。而在缺血/再灌注损伤后，OPA1 的表达下降，导致线粒体破裂、嵴结构紊乱增加了细胞色素 c 释放，并启动凋亡[14]。细胞色素 C 通常局限于线粒体嵴，缺血后 OPA1 的表达下降，其蛋白水解加工后重新分布到膜间隙，并通过线粒体外膜透化释放[15]。并且 mtDNA 也会随着外膜透化释放到细胞质中，从而激活下游的 cGAS-STING 通路和 NLRP3 炎症体通路[16]，促进炎症因子(如 IL-1、IL-1β)的产生[17]使组织损伤加重。

此外，线粒体是 ROS 的主要来源。缺血后，ETC 复合物去磷酸化以促进最大活性，$\Delta\Psi m$ 的过度极化导致大量的 ROS 产生，而再灌注产生的 ROS 则加剧损伤[18]，造成线粒体功能障碍的恶性循环。并且随着持续的氧化应激，线粒体通过电子传递链从线粒体 NO 合酶和超氧化物产生 NO，与超氧阴离子反应生成过氧亚硝酸盐(Peroxynitrite, PN) [19]。PN 是一种强氧化剂和硝化剂，与缺血性脑损伤的发病机制有关，能够显著抑制线粒体的呼吸功能，对线粒体内的多种敏感靶点进行不可逆的修饰，包括蛋白质、脂质和 DNA[20]，导致线粒体功能障碍。PN 也影响线粒体膜的通透性转换孔(MPTP)的开放，释放细胞色素 C 等促凋亡分子到细胞质中，细胞色素 C 与 Apaf-1 和 Procaspase-9 结合，形成凋亡体，激活 Caspase-9，进而激活 Caspase-3 [21]，最终诱导细胞凋亡。具体机制见图 1。

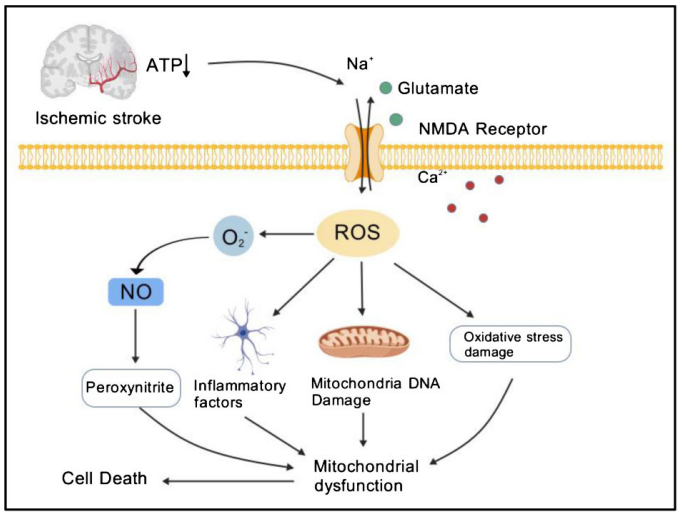

Figure 1. Mechanism diagram of reactive oxygen species-mediated mitochondrial dysfunction and cell death after ischemic stroke
图 1. 缺血性脑卒中后线粒体功能障碍及细胞死亡机制示意图

2.2. 线粒体动力学

线粒体动力学包括裂变和融合。通过维持两者之间的动态平衡保证线粒体功能以及细胞能量需求。线粒体分裂可以选择性去除功能失调的线粒体，确保健康线粒体种群[22]，其中心介质是动力蛋白相关蛋白 1 (Drp1)。线粒体融合涉及多个步骤，包括动力蛋白相关 gtpase 的激活、线粒体外膜和内膜的融合以及线粒体内成分的混合，主要由有丝分裂蛋白 Mfn1 和 Mfn2 以及 Optic Atrophy 1 (Opa1)介导[23]。脑 IR 诱导线粒体分裂，过度分裂的线粒体无法产生足够的呼吸复合物，导致 OXPHOD 减少、ROS 生成增加以及细胞色素 C 等促凋亡因子的释放[24]；此外，线粒体过度裂变可诱导细胞内 Ca^{2+}过载和兴奋性毒性死亡，加剧了神经元的死亡[25]。但线粒体的裂变并不总是有害的，研究表明，线粒体在缺血性脑卒中发生时开始分裂，从而减轻线粒体功能障碍[26]。Drp1 被认为在局灶性脑缺血中起关键作用，研究人员发现下调 Drp1 蛋白水平可减少梗死面积、线粒体 ROS 产生和氧化应激[19]。相比之下，活性氧(ROS)的生成以及线粒体通透性转换孔(mPTP)的开放共同作用，抑制了缺血性卒中时线粒体的融合。线粒体融合可以增强线粒体功能完整性，并通过线粒体嵴重塑上调 ATP 合酶的活性来产生额外的能量[27]。实验结果显示，脑缺血再灌注后，Fis1 和 Drp1 升高，Mfn2 和 Opa1 均下调，表明脑缺血再灌注诱导线粒体过度分裂，阻止线粒体融合。然而，当 Mfn2 和 Opa1 的水平上升时，线粒体分裂和融合的不平衡得到纠正，减少了神经元死亡[28]。

另外，嵴重塑也是线粒体动力学的一方面，CJ 的完整性对于保留线粒体凋亡分子细胞色素 C 在嵴腔内也很重要[29]。Mfn2 是线粒体网络损伤后重塑所必需的[30]。相关研究表明，Mfn2 过表达可以减轻线粒体功能障碍并逆转缺氧诱导的线粒体形态变化[31]。

因此，维持线粒体动力学平衡对于健康的线粒体网络至关重要。抑制线粒体过度裂变，促进线粒体融合，有利于缺血性卒中的恢复。

2.3. 线粒体生物合成

线粒体生物发生对于细胞增加的能量需求以及增殖过程中填充线粒体内容物至关重要。过氧化物酶体增殖体激活受体 γ 共激活因子-1α (PGC-1α)、amp 激活蛋白激酶(AMPK)、线粒体转录因子 A (TFAM)和 sirtuin 1 (SIRT1)是线粒体生物发生的关键调控因子[32]。IS 后，PGC-1α 通过磷酸化和乙酰化被上游 AMPK 和 SIRT1 激活，小胶质细胞内 PGC-1α 表达在短时间内上调，显著减少缺血性损伤后的神经功能缺损，神经炎症减少，线粒体自噬增强[33]。氧化应激下，NRF1 与线粒体转录因子 A (TFAM)基因启动子的结合增强。激活的 TFAM 促进 mtDNA 复制、转录和相关蛋白质合成，最终诱导线粒体生物发生[34]。同时，PGC1-α 是激活超氧化物歧化酶 2 (SOD2)和解偶联蛋白 2(UCP2)的主调控因子；两者都是线粒体蛋白，有助于神经元存活和 ROS 清除[35]。线粒体生物合成的激活维持了线粒体的稳态，并作为一种内源性保护机制在缺血性卒中中发挥着重要作用，被认为是减轻线粒体损伤和缺血性脑损伤的治疗新策略。

2.4. 线粒体自噬(Mitophagy)

线粒体自噬是线粒体质量控制的一种机制，可以选择性识别和去除功能失调的线粒[36]。在病理状态时，通过自噬机制保护神经元免受缺血性损伤[37]。目前的研究表明，线粒体自噬涉及四种起始途径：pten 诱导的激酶 1 (PINK1)/Parkin 途径、bcl2-腺病毒 E1B 19 kDa 蛋白相互作用蛋白 3 (BNIP3)/nip3 样蛋白 X (NIX)途径、FUN14 结构域含蛋白 1 (FUNDC1)途径和心磷脂途径[38]。缺血性脑卒中发生时，FUNDC1 通过与 LC3 相互作用调节线粒体的程序性消除，减轻氧化应激损伤[39]。而 Nix 介导的线粒体自噬在缺氧条件下更容易被激活，并通过 LC3 将线粒体与自噬囊泡结合，促进线粒体自噬[40]。然而，线粒体自噬具有双重特征，过度的自噬会诱发程序性细胞凋亡[41]。葛根素是一种传统的中草药，已被证实可以抑

制自噬蛋白表达，从而缓解缺血/再灌注后的脑功能障碍[42]。同样，在已发表的其他文章中也证实了抑制过度自噬可以减轻缺血后再灌注损伤[43] [44]。

线粒体自噬在脑 I/R 损伤的发病机制中具有重要作用，尽管有关其在缺血性卒中中的一些作用问题尚不清楚，但在缺血性卒中中通过调节线粒体自噬发挥神经保护作用具有重要意义。

2.5. 线粒体转移

在缺血性卒中发生后，神经系统中存在线粒体转移现象。神经细胞间线粒体转移通过隧道纳米管(Tunneling Nanotubes, TNT) [45]、细胞外囊泡(Extracellular Vesicles, EV) [46]等质量控制结构实现[47]。有学者通过实验证实了小胶质细胞通过 TNTs 提供线粒体支持受损神经元的代谢需求，并且可以是双向的[48]。此外，功能性线粒体通过 TNT 细胞从健康周细胞转移到缺氧和无糖(缺血)星形细胞，可使其免于凋亡[49]。在另一项研究中发现，装载 NGF mRNA 的 ev 被输送到脑缺血小鼠模型的缺血皮层，与炎症有关的经典活化小胶质细胞显著减少，为输送 NGF 治疗急性脑缺血提供了理想的平台[50]，从而促进其功能恢复。

缺血后，TNT 及 EV 作为桥梁或船舶，将附近健康细胞中的健康线粒体转移至含有受损线粒体的细胞中用于恢复 ATP 水平，并迅速减少缺血性中风引起的能量不足。通过线粒体转移恢复不平衡的线粒体动力学可能是减轻中风引起的神经元死亡的一种潜在方法。

3. 针灸调控线粒体防治缺血性脑卒中研究进展

基于以上总结，从线粒体角度确定了治疗缺血性脑卒中的几个靶点。在临床与试验研究中，TCM 在预防和治疗缺血性脑卒中方面已显示出显著的疗效。近几年，有关 TCM 作用机制的多项研究成果陆续发表。因此，本文对针灸在治疗缺血性脑卒中方面的文献进行综述，希望从调节线粒体的角度进一步阐述针灸改善缺血性脑卒中的分子机制。

3.1. 针灸预处理对线粒体的保护作用

MCAO/R 组表现出明显的线粒体异常，包括肿胀、空泡化、内膜和嵴破裂/不规则/消失、自噬体和溶酶体的形成，以及脂滴被溶酶体吞噬[51]。EA 预处理减轻了线粒体损伤，线粒体数量明显增加，肿胀减轻[52]、膜和嵴相对完整[53]，以及减少了自溶酶体的数量、膜电位损失[51] [54]。实验结果表明，EA 预处理可以抑制氧化应激[55]和自由基生成[56]，促进线粒体能量代谢和呼吸链功能恢复。电针预处理通过调节线粒体自噬相关蛋白表达，降低 FUNDC1、LC3-II/I 比值和 p62，提高 p-mTORC1/mTORC1 比值，减轻脑缺血/再灌注损伤[54]。Chen 等人通过电针预处理 GV20 可以激活 Wnt/GSK3β 信号通路，进而抑制 mTOR 依赖的自噬，减轻缺血性脑损伤[57]。此外，电针预处理 GV20 可以增强神经元 TREM2 依赖的自噬通量来诱导缺血耐受[58]，增加 NRF-1、TFAM 和 mtDNA 的表达水平，并通过激活 cb1r 依赖性 PGC-1α 进一步促进线粒体生物发生[56]。研究发现，对“百会穴(GV20)”和“大椎穴(GV14)”进行强度为 1 mA、频率为 2 Hz、连续 20 分钟的电针预处理，可以调节 cofilin 蛋白的表达来减轻缺血性脑损伤，改善神经功能[59]。并且 EA 组在再灌注后 6、24 和 48 小时的 Cyto-Cyt-c 表达显著降低 IR 组[60]。在 Hu [61]等人的实验中也证实了 EA 预处理后线粒体中 Cyto-Cyt-c 的释放减少。在 Long 等人的实验中通过 EA 预处理百会穴、双侧肾俞穴、三阴交穴上调丙二醛(MDA)和细胞色素 C 以及下调超氧化物歧化酶(SOD)和谷胱甘肽(GSH)呈现了抗氧化潜力[62]。

综上所述，EA 预处理减轻了线粒体损伤，在再灌注 24 小时后 EA 预处理减少了 FUNDC1 表达，降低了 p62 蛋白表达水平，增加了线粒体膜电位，增强了能量代谢。此外，EA 预处理促进线粒体生物发生、

抑制 cofilin 线粒体易位以及氧化应激等机制，减少细胞凋亡和神经元丢失。

3.2. 针灸治疗对线粒体的修复作用

MOCA 组线粒体缺乏典型的管状或椭圆形形状，双膜结构消失，空泡增加，嵴肿胀，EA 治疗明显抑制了上述变化，通过 GV20 和 GV14 的 EA 治疗下调了 Drp1 的表达，上调线粒体融合相关蛋白(Mfn2、Mfn2 和 Opa1)的表达，保持线粒体的动态平衡，从线粒体动力学角度减轻脑 I/R 损伤[63]。针刺 GV20 和 BL23 可以增强了抗凋亡蛋白 Bcl-2 的活性，同时降低了 Bax 和 caspase-3 的表达，改善了线粒体嵴紊乱、融合消失的情况[64]。在后续的实验中，Meng 等人得出了电针通过调节 Bcl-2 和 caspase-3 基因启动子区域的 H3K9/H3K27 乙酰化水平来发挥对神经的保护作用，从新的分子机制解释了电针对缺血性脑卒中的治疗作用[65]。Lin [66]等人以 1-3mA 的刺激参数处理 DU20 和 DU24 调节了细胞凋亡机制，并且电针增加了 SOD 和 GPx 活性以及降低了 MDA 水平，减轻氧化应激损伤。最近的研究结果显示，针刺 DU20 和 DU24 可有效刺激 PGC-1α、NRF-1 和 TFAM 的蛋白水平表达，增加电子传递链复合物I、IV和V的水平，维持线粒体膜电位，促进线粒体生物发生[67]。Liu 以疏密波 EA 治疗内关(PC6)、水沟(GV26)、三阴交(SP6)减轻线粒体损伤，并有效改善了神经功能缺损症状[68]。Lang 等人通过针刺风池、风府、大椎降低 MCAO 大鼠神经功能缺损评分以及 OS 损伤[69]。既往研究表明，连续 8 天电针处理 GV20 和 GV24 后，EA 组的 PI3K、mTOR 和 Beclin-1 的 mRNA 和蛋白表达显著增加，而 p53 的表达降低[70]。在 Wang 等人的研究中，进一步发现 EA 治疗显著增加了 P62 和 LAMP-1 的表达以及降低了 LC3II/I 比值，通过抑制过度自噬，减轻了缺血性中风后的脑损伤[71]。再灌注后 24 h 内的 EA 可以增加 Pink1/parkinson 介导的线粒体自噬清除来减少受损线粒体的积累 55，从而保护细胞免受脑 I/R 神经元损伤。在[72]试验数据表明，EA 刺激 DU20 和 DU24 穴位可以抑制 cofilin 的线粒体易位和 caspase-3 的破裂，显著减轻缺血性脑卒中后神经元的凋亡和损伤。

综上所述，针灸治疗可以改善线粒体的结构和功能，恢复自噬平衡，抑制凋亡相关蛋白的表达，并减轻氧化应激损伤。

4. 结论与展望

本综述总结了线粒体在缺血性脑卒中中的机制以及通过针灸调节线粒体功能在缺血性脑卒中的预防和治疗中展现出巨大潜力。然而，目前的研究仍存在一些局限性，需要在未来进一步探索和完善：第一，目前针灸调控线粒体的研究报道较少，处于初步探索阶段，机制研究不够深入，确切的分子机制尚不完全清楚，并且试验研究多集中在某一信号通路或调节因子，缺乏全面评估。未来可进行多学科交叉研究，加强针灸学与分子生物学、细胞生物学等多学科研究，例如利用基因编辑技术探索针灸对线粒体相关蛋白表达的影响。第二，实验设计标准化不足，中医诊疗标准(如取穴、针刺深度等)不够统一，EA 刺激参数缺乏标准化，研究结果之间难以进行比较与整合，影响了针灸在国际医学领域的认可度。建立统一的诊疗标准，开展更多规范、系统的实验是必然趋势。第三，MCAO 缺血模型与临床存在差异，上述研究的缺血范围大部分占同侧的 21%~45%，而临床大多数患者缺血范围小且伴有代谢性疾病。许多模型仅是单中心或特定人群，并且动物模型无法完全复制人类疾病的复杂性，特别是在认知功能和行为方面的评估存在挑战。因此，多模型结合，建立个体化治疗也是必要的。第四，扩大研究范围，例如从血管内皮细胞、神经胶质细胞等方向着手开发防治缺血性脑卒中的新策略。

未来研究可探索针灸与其他治疗手段的联合应用以提高治疗效果；并结合影像学与分子生物学技术，更直观地观察针灸对线粒体功能的影响，为针灸治疗缺血性脑卒中提供更有力证据。同时，鉴于针灸低成本、高安全性和高效性等特点，其临床应用前景广阔。随着研究的不断深入和技术的不断进步，针灸

有望成为缺血性脑卒中治疗的重要手段之一。

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