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线粒体功能异常在抑郁症发病机制中的重要作用及中药调控干预的研究进展

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【摘要】 抑郁症是一种常见的精神疾病,对人类的健康和生活造成了严重威胁。尽管其具体发病机制尚未完全阐明,近年来的多项研究显示,抑郁症与线粒体功能异常之间存在密切联系。本文从 4 个方面探讨了线粒体功能失常在抑郁症发病机制中的重要作用,包括能量代谢障碍、氧化应激和炎症反应、线粒体 DNA 损伤和突变以及质量控制系统失衡,并总结了近年来中药通过调控线粒体功能来改善抑郁症的研究进展,显示了中药在提高线粒体能量代谢、减少氧化应激和炎症反应、改善线粒体 DNA 和调控包括线粒体生物发生、动力学功能、自噬在内的线粒体质量控制系统方面的潜力,为深入研究抑郁症的发病机制及其中药治疗提供了新思路。

【关键词】 抑郁症;线粒体;中药;发病机制;治疗
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Research progress on the critical role of mitochondrial dysfunction in the pathogenesis of depression and the regulatory interventions of traditional Chinese medicine

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【Abstract】 Depression is a common mental disorder with adverse effects on human health and quality of life. Although its pathogenesis remains unclear, numerous recent studies have indicated a close association between depression and mitochondrial dysfunction. This review explores the critical role of mitochondrial dysfunction in the pathogenesis of depression from the aspects of energy metabolism disorders, oxidative stress and inflammatory responses, mitochondrial DNA damage and mutations, and the imbalance of the mitochondrial quality control systems.

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We also summarize recent advances in the use of traditional Chinese medicine (TCM) to treat depression by regulating mitochondrial function. The findings show the potential of TCM in enhancing mitochondrial energy metabolism, reducing oxidative stress and inflammatory responses, improving mitochondrial DNA, and modulating the mitochondrial quality control systems, including for the in-depth study of the pathogenesis of depression and its treatment with TCM.

【Keywords】 depression; mitochondria; traditional Chinese medicine; pathogenesis; treatment

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抑郁症(depression)是一种常见精神疾病,其主要特征是抑郁情绪或愉悦感丧失,并伴有其他影响个体功能能力的认知、行为或植物神经症状。全球大约有 2.8 亿人患有抑郁症,且预计到 2030 年,抑郁症将位居全球疾病负担首位[1]。抑郁症的发病机制复杂,目前公认的发病机制假说主要包括单胺类神经递质假说、神经可塑性假说和下丘脑-垂体-肾上腺(hypothalamus-pituitary-adrenal, HPA)轴假说等[2]。基于上述理论,临床上有多种抗抑郁药物用于治疗抑郁症,如单胺氧化酶抑制剂、三环类抗抑郁药和选择性 5-羟色胺再摄取抑制剂等[3]。这些药物虽然能在一定程度上改善抑郁症状,但仍存在起效慢、耐受性差、副作用大和复发率高等问题[4]。因此,进一步探索抑郁症的病理生理机制并制定更为有效的治疗策略已成为抑郁症研究的重要方向。近年来,越来越多的研究表明,抑郁症的发生与线粒体功能异常有着密切的关联[5]。随着对中药的深入研究,中药在调控线粒体功能方面展现出了独特的潜力,可以为抑郁症的治疗提供新的视角[6]。本文就线粒体功能失常在抑郁症发病机制中的重要作用以及中药调控干预作用的研究展开综述。

1 线粒体功能失常在抑郁症发病机制中的重要作用

1.1 能量代谢障碍

线粒体是细胞动力工厂,通过氧化磷酸化(oxidative phosphorylation, OXPHOS)过程合成三磷酸腺苷(adenosine triphosphate, ATP),为细胞的各种活动提供能量。脑组织高度依赖葡萄糖,把葡萄糖作为主要的能量来源,其代谢生成的 ATP 约占脑内 ATP 的 90%~95%[7]。临床研究发现,重度抑郁障碍(major depressive disorder, MDD)患者脑内 ATP 酶的表达明显降低,且 ATP 水平普遍较低[8]。MDD 患者脑部存在双侧岛叶、边缘系统对氟代脱氧葡萄糖(18F-fluorodeoxyglucose, 18F-FDG)代谢活性降低[9]。皮质酮诱导的抑郁症模型小鼠脑内 ATP 生成减少[10]。慢性社会挫败应激(chronic social defeat stress, CSDS)小鼠抑郁模型前额叶皮质(pre-frontal cortex, PFC)的 ATP 表达严重不足,PFC 局部注射 ATP 或刺激星形胶质细胞(astrocyte, As)ATP 释放,能够快速缓解小鼠的抑郁样行为[11]。同时,阻断小鼠大脑海马区 As ATP 的释放可导致抑郁样行为,注射 ATP 或刺激 As 释放 ATP 后可在一周内明显改善抑郁样行为[12]。研究结果显示,中枢神经系统中线粒体能量代谢障碍导致的 ATP 减少,可能是抑郁症发病的机制之一。

不仅如此,在 MDD 患者的肌肉中也发现线粒体 ATP 生成减少[13],母婴分离(maternal separation, MS)早期应激小鼠抑郁模型中存在肌肉中线粒体含量标志物下降和 ATP 生成减少[14]。这表明与抑郁症相关的线粒体能量代谢障碍不仅限于大脑,也存在肌肉中。

1.2 氧化应激和炎症反应

氧化应激(oxidative stress, OS)是指体内的活性氧(reactive oxygen species, ROS)和活性氮(reactive nitrogen species, RNS)等自由基的产生与抗氧化系统对多余自由基的清除失衡,使蛋白质、脂质、DNA 等发生过氧化,导致细胞损伤的一种生理病理过程[15]。线粒体是 ROS 主要细胞内来源,约 90% 的 ROS 在线粒体 OXPHOS 过程中产生[16]。临床研究发现 MDD 患者体内 OS 标志物水平显著升高,抗氧化酶水平降低[17],改善 OS 或抗氧化功能可达到抗抑郁的目的[18-19]。动物研究也发现慢性应激诱导的动物抑郁模型中脑内 OS 标志物水平升高和抗氧化酶水平降低[20]。

以上研究说明线粒体功能障碍介导的 OS 与抑郁症的发病密切相关。

免疫炎症反应也与抑郁症的发病密切相关,MDD 患者的先天性免疫系统和适应性免疫系统都存在失调[21]。线粒体是损伤相关分子模式(damage associated molecular patterns, DAMPs)的来源,DAMPs 是在免疫细胞中起关键调节作用的分子,可以启动多种炎症信号通路[22]。MDD 患者脑脊液(cerebrospinal fluid, CSF)和脑实质中促炎细胞因子白介素-6(interleukin-6, IL-6)和肿瘤坏死因子-α(tumor necrosis factor, TNF-α)水平升高[23]。慢性应激诱导的小鼠抑郁模型中海马和血清白介素-1β(interleukin-1β, IL-1β)水平升高,而用炎症小体 NOD 样受体热蛋白结构域相关蛋白(NOD-like receptor thermal protein domain associated protein 3, NLPR3)抑制剂 VX-765 预处理可降低 IL-1β 水平,缓解抑郁样行为[24]。此外,在 MDD 患者血清中观察到抗炎细胞因子白介素-4(interleukin-4, IL-4)和白介素-10(interleukin-10, IL-10)减少[25]。说明免疫炎症反应包括促炎细胞因子水平的升高和抗炎细胞因子水平的降低可能是抑郁症发病的重要途径之一。因此,线粒体功能障碍引起的炎症反应可能与抑郁症的发病有关。

综上所述,线粒体功能障碍引起的 OS 和炎症反应与抑郁症的发病密切相关。线粒体来源的 ROS 还会引发多种促炎介质释放,并激活多种促炎信号通路[26]。而这些反应会进一步损害线粒体功能,导致 OS 和炎症反应更加严重,形成恶性循环,促进抑郁症的发生发展。

1.3 线粒体 DNA 损伤和突变

线粒体是唯一具有自身 DNA 的细胞器。线粒体 DNA(mitochondrial DNA, mtDNA)由 37 个基因组成,包括 13 种蛋白质编码基因,主要与呼吸链复合物中的蛋白质亚基有关,还包括 22 种转运 RNA(transfer RNA, tRNA)和 2 种核糖体 RNA(ribosomal RNA, rRNA)[27]。临床研究发现,MDD 患者血液中的 mtDNA 拷贝数显著增加[28]。与非精神病对照受试者相比,MDD 患者背外侧 PFC 中线粒体有 16 个基因表达有差异,这些基因不仅与线粒体转运蛋白家族有关,还与氧化应激和细胞凋亡有关[29]。可见,mtDNA 异常与抑郁症的发病密切相关。同时,mtDNA 及其代谢损伤也在抑郁症的发病中有重要作用[30]。MDD 患者的 DNA 损伤增加可能是由氧化应激和 DNA 损伤修复率降低导致[31],而线粒体缺乏完整的核 DNA 修复机制[32],因此 mtDNA 更容易受到上述因素的影响而受损。临床研究进一步说明 mtDNA 的修复受损与抑郁症的生理病理变化有关[33]。此外,mtDNA 的突变也与抑郁症的发病密切相关,但其具体作用机制尚未明确[34]。在一项临床研究中发现,两名不相关 MDD 患者都存在线粒体 ND1 基因中 T3394C 的突变,这表明 T3394C 突变可能与抑郁症的发病有关[35]。综上所述,mtDNA 的损伤和突变都在抑郁症的发病中起着重要作用。

1.4 线粒体质量控制系统失衡

1.4.1 线粒体蛋白稳态失衡

线粒体蛋白稳态(mitochondrial protein homeostasis)是指线粒体通过调节蛋白质的合成、导入、折叠、修饰和降解的动态过程来维持的线粒体内蛋白质数量和功能的平衡状态,其中线粒体未折叠蛋白反应(mitochondrial unfolded protein response, UPRmt)是关键的细胞反应之一,它是由线粒体内蛋白质错误折叠或积聚引起的应激反应[36]。线粒体蛋白稳态失衡会导致线粒体功能障碍[37]。动物研究发现,慢性束缚应激(chronic restraint stress, CRS)小鼠模型表现出明显的抑郁样行为,且 UPRmt 相关分子水平显著升高,如 Hspa9、Hspd1、Ubl5、Abcb10 和 ClpP 等[38]。这表明 UPRmt 与抑郁症的发病有关,因而有可能作为抗抑郁药物的新靶点。

1.4.2 线粒体生物发生障碍

线粒体生物发生(mitochondrial biogenesis)是指细胞对可能引起能量需求增加的外部压力的生理反应,是一种维持线粒体数量的再生程序[39]。诱导线粒体生物发生的调节因子包括过氧化物酶体增殖物激活受体 γ 共激活因子 1α(peroxisome proliferator-activated receptor-γ coactivator-1α, PGC-1α)、5'-AMP 活化蛋白激酶(AMP-activated protein kinase, AMPK)、核呼吸因子 1(nuclear respiratory factor 1, Nrf1)、核呼吸因子 2(nuclear respiratory factor 2, Nrf2)、乙酰化酶 1(sirtuin 1, SIRT1)、线粒体转录因子 A

(mitochondrial transcription factor A, TFAM)等[40]。其中 PGC-1α 是线粒体生物发生的主要调节因子[41]。临床研究表明,与健康对照组相比,MDD 患者的全血 PGC-1α 水平显著降低[42]。动物研究也发现,海马中 PGC-1α 表达下调的小鼠表现出抑郁样和被动的压力应对行为,而海马中 PGC-1α 表达上调的小鼠则表现出压力应对行为的增加[43]。以上研究说明,PGC-1α 水平的降低与抑郁症的发病密切相关。同时,在临床研究中发现,MDD 患者外周血液中的 SIRT1 mRNA 减少[44]。另一动物研究中也发现,小鼠内侧 PFC 中的 SIRT1 敲除诱导了抑郁样行为,而向小鼠的内侧 PFC 或侧脑室注射 SIRT1 激活剂(SRT2104)后,小鼠的抑郁样行为明显减少[45]。产前束缚应激(prenatal restraint stress, PRS)诱导的子代动物抑郁模型中,海马体内 AMPK、Nrf2 水平降低[46]。综上所述,线粒体生物发生相关调节因子水平的降低可能与抑郁症发病有关。

1.4.3 线粒体动力学功能障碍

线粒体动力学(mitochondrial dynamics)是指线粒体沿细胞骨架运输,并与其他亚细胞结构相互作用,以及通过融合和裂变塑造其线粒体内膜(inner mitochondrial membrane, IMM)和线粒体外膜(outer mitochondrial membrane, OMM)的能力[47]。线粒体融合涉及的主要融合蛋白是视神经萎缩蛋白 1(optic atrophy 1, Opa1)、线粒体融合蛋白 1(mitofusin 1, Mfn1)和线粒体融合蛋白 2(mitofusin 2, Mfn2),它们与 IMM 和 OMM 结合;而裂变主要由线粒体动力相关蛋白 1(dynamin-related protein 1, Drp1)介导,Drp1 与 OMM 结合并在细胞器周围形成环状结构,使其分裂成两个独立的细胞器[48]。临床研究发现,MDD 患者神经元源性细胞外囊泡(neuron-derived extracellular vesicles, NDEVs)中 Mfn2 水平降低,在用选择性 5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitor, SSRI)治疗 8 周后,Mfn2 恢复正常水平[49]。动物研究发现,高度焦虑的动物表现出的抑郁样行为增加,以及线粒体 GTP 酶 Mfn2 在伏隔核(nucleus accumbens, NAc)中的表达降低[50]。PRS 诱导的子代大鼠抑郁模型中,Mfn1、Mfn2 和 Drp1 表达增强[51]。综上所述,线粒体动力学功能障碍包括线粒体融合、裂变蛋白异常可能与抑郁症的发病有关。

1.4.4 线粒体自噬失调

线粒体自噬(mitophagy)是指细胞通过自噬机制去除多余或功能失调的线粒体并维持线粒体微调数从而平衡线粒体和细胞内稳态的一种细胞保护机制[52]。线粒体自噬机制通常分为泛素(ubiquitin, Ub)依赖性途径和 Ub 非依赖性途径两类[53]。在 Ub 依赖性途径中,最常见的是 PTEN 诱导的假定激酶 1(PTEN-induced kinase 1, PINK1)/帕金森蛋白(Parkin)通路。在线粒体应激或损伤时,PINK1 募集并活化 Parkin,Parkin 泛素化线粒体外膜蛋白,进一步引发线粒体自噬[54]。动物研究发现,敲除 PINK1 降低了 CRS 诱导小鼠抑郁样行为的阈值[55]。产前暴露于糖皮质激素地塞米松(dexamethasone, DEX)诱导的子代大鼠抑郁模型中,PINK1 的表达水平降低,这可能与 PINK1/Parkin 通路相关[56]。此外,一系列可以直接与微管相关蛋白 1-轻链 3(microtubule-associated protein 1-light chain 3, LC3)结合而不会引起广泛泛素化的线粒体自噬受体参与 Ub 非依赖性途径,其中包括多种线粒体外膜蛋白,如 Bcl-2/腺病毒 E1B 19 kDa 相互作用蛋白 3(Bcl-2/adenovirus E1B 19 kDa-interacting protein 3, BNIP3)、Nip3 样蛋白 X(Nip3-like protein X, NIX)以及 FUN14 结构域包含蛋白 1(FUN14 domain containing 1, FUNDC1)等[57]。研究发现,在 TNF-α 诱导的小鼠抑郁模型中,小鼠内侧 PFC 脑区过表达 NIX 基因可以逆转小鼠的抑郁样行为[58]。在 CSDS 小鼠抑郁模型中,小鼠腹侧海马脑区过表达 FUNDC1 也可以逆转小鼠抑郁样行为[59]。在习得性无助(learned helplessness, LH)小鼠抑郁模型中,用三环类抗抑郁药丙咪嗪治疗后,BNIP3 mRNA 的表达增强[60]。综上所述,线粒体自噬过程中 Ub 依赖性途径和 Ub 非依赖性途径障碍都与抑郁症的发病密切相关。

2 中药对抑郁症线粒体功能异常的调控干预作用

中医在治疗抑郁症方面具有悠久的历史,并积累了丰富的临床经验[61]。与传统抗抑郁药物相比,中药因具有多成分、多靶点和多途径的整

体调节特点,在提高疗效、减少副作用及改善机体功能方面展现出独特的抗抑郁优势[62]。因此,深入探讨中药对抑郁症线粒体功能异常的调控干预作用,对深入理解抑郁症的病理生理机制及优化临床治疗方案具有重要意义。

2.1 调控能量代谢

近年来随着研究的不断深入,中药通过调控线粒体能量代谢障碍来改善抑郁症的研究已经取得了一定进展。四逆散是疏肝解郁,调和肝脾的祖方。研究表明,四逆散可以通过改善突触和线粒体的损伤,提高海马 ATP 的水平,并逆转 Mfn2 和 Drp1 的表达水平,来缓解 MS 大鼠的抑郁样和焦虑样行为[63]。还有研究表明,四逆散可以通过下调血清中 IL-1β 含量改善慢性不可预知应激(chronic unpredictable mild stress, CUMS)大鼠抑郁样行为[64]。四君子汤是治疗脾胃气虚证的基础方,可以通过提高脾虚大鼠 ATP 酶活性和减轻线粒体氧化损伤缓解抑郁症状[65]。逍遥散为肝郁血虚,脾失健运之证而设,能够显著改善 CUMS 大鼠肝线粒体形态和功能,提高肝线粒体 ATP 水平,发挥抗抑郁作用[66]。养心解郁方由人参、麦冬、五味子、淫羊藿、玫瑰花、合欢花、薤白、郁金、石菖蒲和青皮组成。研究表明,在 CUMS 诱导的青幼期大鼠抑郁模型中,养心解郁方能够通过调控三羧酸循环和丙酸代谢通路,有效维持线粒体的能量代谢功能,从而发挥抗抑郁作用[67]。黄连素可以拮抗慢性皮质酮(chronic corticosterone, CORT)对线粒体氧化磷酸化过程的影响,并改善小鼠的抑郁样行为[68]。槲皮素可以通过降低 ROS 和线粒体膜电位水平,并增加耗氧率和 ATP 产生来缓解甲基苯丙胺(methamphetamine, MA)诱导的小鼠焦虑、抑郁症状[69]。

2.2 调控氧化应激和炎症反应

随着研究的进展,目前已经有很多研究表明中药可以通过降低促炎细胞因子水平,提高抗炎细胞因子水平,防止氧化应激和炎症信号通路的激活来缓解抑郁症。开心散由远志、人参、茯苓和菖蒲组成。研究发现,开心散可以显著减少小鼠海马体中 IL-1β、IL-2 和 TNF-α 的表达来发挥抗抑郁作用[70]。柴胡疏肝散可以用于疏肝行气、活血止痛,其通过降低 IL-1、IL-6 水平抑制大鼠海马炎症,有效改善抑郁情况[71]。通督安神方可以改善情绪、缓解疼痛及提升睡眠质量等,其可以降低血清 TNF-α 含量水平,并显著改善 CUMS 大鼠抑郁样行为[72]。藏红花可以通过降低 TNF-α、IL-1 和 IL-6 水平来抗炎、抗氧化应激对抑郁症进行干预[73]。白芍总苷通过下调血清 IL-1β 水平,恢复线粒体功能,激活自噬和减少炎症介导的焦亡,发挥抗抑郁的作用[74]。黄精多糖可以通过降低 TNF-α 和 IL-10 活性起到改善抑郁的作用[75]。隐丹参酮通过抑制 IL-1β、IL-6 和 TNF-α 的表达,对抑郁症状有改善作用[76]。

2.3 调控线粒体 DNA

虽然很多研究已经证明 mtDNA 在抑郁症的发病过程中起着重要作用,但其相关的中药研究较少。醒脾解郁方由西洋参、石菖蒲、郁金、贯叶连翘组成,可以通过提高肝 ATP 含量、改善肝细胞 mtDNA,从而提高能量代谢,调节线粒体功能,显著改善 CUMS 大鼠的抑郁状态[77]。小建中汤为桂枝汤倍芍药加胶饴组成,有温中补虚、和里缓急的功效。小建中汤通过上调海马区 PINK-1/Parkin 途径介导的线粒体自噬水平,并增加 mtDNA 拷贝数,改善线粒体功能,有效改善 CUMS 大鼠的抑郁情况[78]。

2.4 调控线粒体质量控制系统

基于线粒体质量控制系统失衡,中药的调控干预作用的研究也取得了一定的进展。在线粒体生物发生方面,加味大柴胡汤由柴胡、黄芩、姜半夏、白芍、生姜、枳实、大黄、郁金、金钱草、大枣组成,研究发现其提取物可以通过上调 SIRT1/PGC-1α 信号的传导来缓解 CUMS 小鼠抑郁样行为[79]。姜黄素可以通过增强 PGC-1α 的表达,发挥其抗抑郁的作用[80]。人参皂苷 Rg1 的抗抑郁作用,可能是通过增强 Nrf2 的表达,改善线粒体功能障碍实现的[81]。黄芩苷通过直接结合 AMPK 激活 AMPK/PGC-1α 通路,并增强 NIX 介导的线粒体自噬,改善 CUMS 小鼠的抑郁症状[82]。白藜芦醇可能通过激活 SIRT1 改善 SIRT1/PGC-1α/SIRT3 的表达,调节线粒体功能和线粒体自噬来缓解抑郁样行为[83]。在线粒体动力学方面,天文草提取物通过降低 CRS 大鼠线粒体裂变蛋白的表达,维持线粒体功能,缓解其抑郁症状[84]。松果菊苷可以通过增强磷酸化

Drp1 的表达,减轻 CUMS 大鼠线粒体损伤,发挥其抗抑郁作用[85]。在线粒体自噬方面,左归降糖解郁方由熟地黄、山萸肉、枸杞子、菟丝子、牛膝、杜仲、黄芪、丹参、牡丹皮、姜黄和贯叶连翘组成,有滋阴益气和化瘀解郁功效。研究发现,其抗抑郁的机制可能是抑制体外海马神经元线粒体自噬流、线粒体 ROS 释放和海马神经元凋亡,减少线粒体自噬介导的海马神经元凋亡[86]。乌灵散可以通过改善 18 kDa 转运蛋白(translocator protein, TSPO)介导的线粒体自噬信号通路来发挥抗抑郁作用[87]。巴戟天寡糖可以通过上调 Mfn2 介导的线粒体自噬,改善大鼠抑郁样行为[88]。芍药苷改善 CUMS 小鼠的抑郁样行为可能是通过促进线粒体自噬,并抑制 NLRP3 炎性小体的激活实现的[89]。冬凌草甲素也能通过激活线粒体自噬抑制 NLRP3 炎性小体来缓解抑郁症状[90]。

3 小结

综上所述,线粒体功能失常在抑郁症的发病机制中扮演着重要角色,包括线粒体能量代谢障碍、氧化应激和炎症反应、线粒体 DNA 损伤和突变以及质量控制系统失衡都对抑郁症的发病有重要作用。而中药通过提高线粒体能量代谢、减少氧化应激和炎症反应、改善线粒体 DNA 和调控包括线粒体生物发生、动力学功能、自噬在内的线粒体质量控制系统,为抑郁症的治疗提供了新的思路。很多动物和临床研究已表明,中药能通过多种途径调控线粒体功能来改善抑郁症,因此,未来的研究应系统分析不同中药成分对线粒体功能的多途径调控作用,以明确其在抑郁症治疗中的具体机制,并可以通过基因编辑、转录组学等技术,深入研究中药对线粒体相关基因表达的影响,明确其潜在的治疗靶点。此外,应开展多中心、随机对照临床试验,进一步评估中药通过调控线粒体功能治疗抑郁症的有效性与安全性,从而加速基础研究向临床应用的转化。最后,应基于对线粒体功能的调控,结合现代药理学与中药传统治疗优势,开发新的中药复方或单体药物,推动中药治疗抑郁症的创新性发展。

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