生理学报 *Acta Physiologica Sinica*, April 25, 2025, 77(2): 318–326
DOI: 10.13294/j.aps.2025.0033 CSTR: 32202.14.j.aps.2025.0033 https://actaps.sinh.ac.cn

综 述

高压氧疗法对神经退行性疾病的作用机制及应用研究进展

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摘 要：神经退行性疾病(neurodegenerative diseases, NDD)导致死亡人数将于2040年超过癌症，成为继心脑血管疾病后的第二大致死因素。因此，寻求有效的干预措施已成为应对这一难题的首要任务。高压氧疗法(hyperbaric oxygen therapy, HBOT)在过去的50年里一直被用于治疗减压病、一氧化碳中毒和辐射损伤等疾病。近年来，研究证实HBOT在改善脑外伤和中风后的认知障碍、缓解NDD相关的神经变性和功能障碍等方面具有较好的效果。本文通过回顾NDD的发病机制和治疗现状，介绍HBOT在NDD动物模型和临床研究中的应用情况，从线粒体功能、神经炎症、神经发生和血管形成、氧化应激、细胞凋亡、微循环及表观遗传改变等方面阐述HBOT治疗NDD的应用潜力。

关键词：高压氧疗法；神经退行性疾病；氧化应激；神经炎症；临床应用

Progress on the mechanism and application of hyperbaric oxygen therapy for neurodegenerative diseases

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Abstract: In 2040, neurodegenerative diseases (NDD) will overtake cancer as the second leading cause of death after cardiovascular and cerebrovascular diseases. Therefore, the search for effective intervention measures has become the top priority to deal with this difficult burden. Hyperbaric oxygen therapy (HBOT) has been used for the past 50 years to treat conditions such as decompression sickness, carbon monoxide poisoning and radiation damage. In recent years, studies have confirmed that HBOT has good effects in improving cognitive impairment after brain injury and stroke, and alleviating neurodegeneration and dysfunction related to NDD. Here we reviewed the pathogenesis and treatment state of NDD, introduced the application of HBOT in animal models and clinical studies of NDD, and expounded the application potential of HBOT in the treatment of NDD from the perspective of mitochondrial function, neuroinflammation, neurogenesis and angiogenesis, oxidative stress, apoptosis, microcirculation and epigenetics.

Key words: hyperbaric oxygen therapy; neurodegenerative diseases; oxidative stress; neuroinflammation; clinical application

随着人口老龄化的快速发展，全世界有数百万人受到神经退行性疾病(neurodegenerative diseases, NDD)的影响，到2040年NDD将成为继心脑血管疾病后的第二大死亡因素[1]。尽管临床上一直在采用药物缓解和控制NDD症状[2]，却仍缺乏有效的治疗方法来减缓甚至治愈NDD。高压氧疗法(hyperbaric oxygen therapy, HBOT)即采用在大于一个大气压(atmosphere absolute, ATA)的环境压力下给予吸入100%氧气的治疗方法，临床上广泛用于减压病、空气栓塞、伤口(未愈合的糖尿病足溃疡)、烧伤组织修复、一氧化碳中毒、外周动脉闭塞性疾病、烟雾吸入、辐射损伤以及重症康复等治疗[3–6]。越来越多的研究证实，HBOT在治疗中风和阿尔茨海默病[7, 8]，甚至在治疗COVID-19方面都显示出较好的

This work was supported by the Application Promotion Project of China (No. 21AH0103) and Double First-class Construction Project (No. 23JX022).

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效果[9, 10]。

NDD包括阿尔茨海默病、帕金森病、肌萎缩侧索硬化症和亨廷顿病等，其主要特征是大脑或脊髓中特定易感神经元群的持续或进行性丧失[11]。NDD的主要影响因素包括氧化应激、程序性细胞死亡、神经炎症、线粒体功能障碍、表观遗传修饰、蛋白质毒性及其相关的泛素/蛋白酶体和自噬-溶酶体系统的损伤[12, 13]。最近的研究表明，NDD治疗将从单纯的症状控制到通过细胞保护机制预防进一步恶化的方式转变，氧化应激和炎症在神经变性中起着重要作用，因此这些病理生理学机制将成为神经保护的重要靶点[2]。HBOT可减轻严重脑功能障碍患者的神经炎症，并下调促炎细胞因子白介素-1β (interleukin-1β, IL-1β)、IL-12、肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)和干扰素-γ (interferon-γ, IFN-γ)表达，同时上调抗炎细胞因子IL-10表达，因而具有潜在的细胞保护作用[14]。本文通过阐述NDD的发病机制和治疗现状，介绍HBOT在NDD动物模型和临床研究中的应用情况，从线粒体功能、神经炎症、神经发生和血管形成、氧化应激、细胞凋亡、微循环及表观遗传改变等方面探讨HBOT治疗NDD的应用潜力。

1 NDD的发病机制及治疗现状

NDD主要表现为神经元的退化或丧失，从而导致多种神经、精神问题。根据神经变性的生理学位置(如锥体外系反应、额颞叶变性或脊髓小脑变性)、原发性分子异常(如β-淀粉样蛋白、朊蛋白、微管相关蛋白、α-突触核蛋白)或主要临床特征(如帕金森病、运动神经元障碍或痴呆)等，NDD包括阿尔茨海默病、帕金森病、肌萎缩侧索硬化症以及亨廷顿病等[11, 12]。

阿尔茨海默病是导致老年人记忆力、认知能力和行为模式下降甚至痴呆的主要因素[15, 16]，其特征是大脑中异常蛋白聚集，包括β-淀粉样蛋白的累积[17]。目前，尚无有效的阿尔茨海默病治疗方法，胆碱酯酶抑制剂和美金刚等药物可缓解症状并减缓认知能力下降[18]。帕金森病是大脑黑质中产生多巴胺的神经元逐渐恶化而引起的运动功能进行性下降[19]。多巴胺是一种神经递质，参与调节和协调肌肉的精确运动，左旋多巴作为多巴胺的替代药物，通常用于缓解运动症状[20]。此外，治疗药物还包括多巴胺补充药物，如多巴胺激动剂和单胺氧化酶-B抑制剂[21]。肌萎缩侧索硬化症主要特征是大脑和脊髓中的神经细胞逐渐恶化，进而导致运动神经元退化[22]，使大脑启动和调节肌肉动作的能力减弱。利鲁唑是一种FDA批准的通过减轻对运动神经元的伤害来减缓肌萎缩侧索硬化症的药物[23]。亨廷顿病是由于亨廷顿基因(HTT)突变引起的一种遗传性和进展性的神经系统疾病[24]。这种基因突变使得大脑特定区域恶化，导致患者身体、认知和精神出现问题。

目前临床上采用的NDD治疗药物多为缓解患者症状，但是由于存在血脑屏障和药物不良反应，药物生物利用度低，使患者生存率降低[11, 25]。除了传统的药物疗法，近来也有一些采用生物材料等新技术在分子检测、靶向药物递送和疾病诊断方面具有潜力的研究报道。如基因治疗使用质粒DNA或病毒载体等载体将新基因直接引入NDD患者[25]；免疫疗法使用抗体和特异性抗原来引发针对NDD患者的适应性免疫反应[26]。以上新兴疗法在给NDD患者带来希望的同时也使他们面临着高昂的医疗费用，因此，亟需找寻新的安全、无创、经济、可耐受的治疗方案。

2 HBOT的临床应用

常压氧(20.8%氧气)是维持人体有效代谢所必需的条件，任何轻微的偏离该浓度都会导致重大的生理改变[27]。HBOT通常将压力增加到2.0~2.5 ATA，暴露于100%氧气中，持续90~120 min，并根据治疗情况需要进行多次治疗[28]。HBOT的作用机制包括依赖于压力的气泡减少作用(Boyle-Marriott定律)和组织的高氧作用[29]。气泡减少作用与减压病和空气/气体栓塞有关[30]，高氧状态有利于坏死性组织、辐射损伤、烧伤、隔室综合征和气性坏疽的治疗[30, 31]。压力增加导致细胞氧气输送能力改善[27]，氧气增加刺激干细胞增殖、迁移和分化[27]。HBOT仍然是目前治疗减压病的唯一方法，减压病是由于潜水员过快上升到水面使氮气压力部分增加，组织和血液中的氮气形成气泡所致的全身性疾病[32]。HBOT还可用于治疗一氧化碳中毒，当空气中存在一氧化碳时，血液携带氧气能力下降。HBOT通过增加氧气在血浆中溶解，并通过释放血红蛋白中的一氧化碳来为组织提供氧气[32]。此外，HBOT在多种炎症或感染性疾病模型(如结肠炎、败血症)中被用作辅助治疗手段而发挥作用[29]。基于HBOT的抗

炎和抗氧化作用，它有可能成为一种治疗NDD的新方法。

3 HBOT对NDD的作用机制

目前，已经确定的12种生物衰老标志包括基因组不稳定性、端粒损耗、表观遗传学改变、蛋白质稳态丧失、营养感应失调、线粒体功能障碍、干细胞耗竭、细胞间通讯改变、细胞衰老、大自噬失能、慢性炎症和肠道微生物群失调[33, 34]，NDD的发展与这些生物衰老标志的累积效应相关[35]。HBOT影响着对细胞和神经元恢复至关重要的多种细胞和分子途径，包括线粒体功能、神经炎症、神经发生和血管形成、氧化应激、细胞凋亡、微循环和表观遗传改变等方面(图1)[36, 37]。

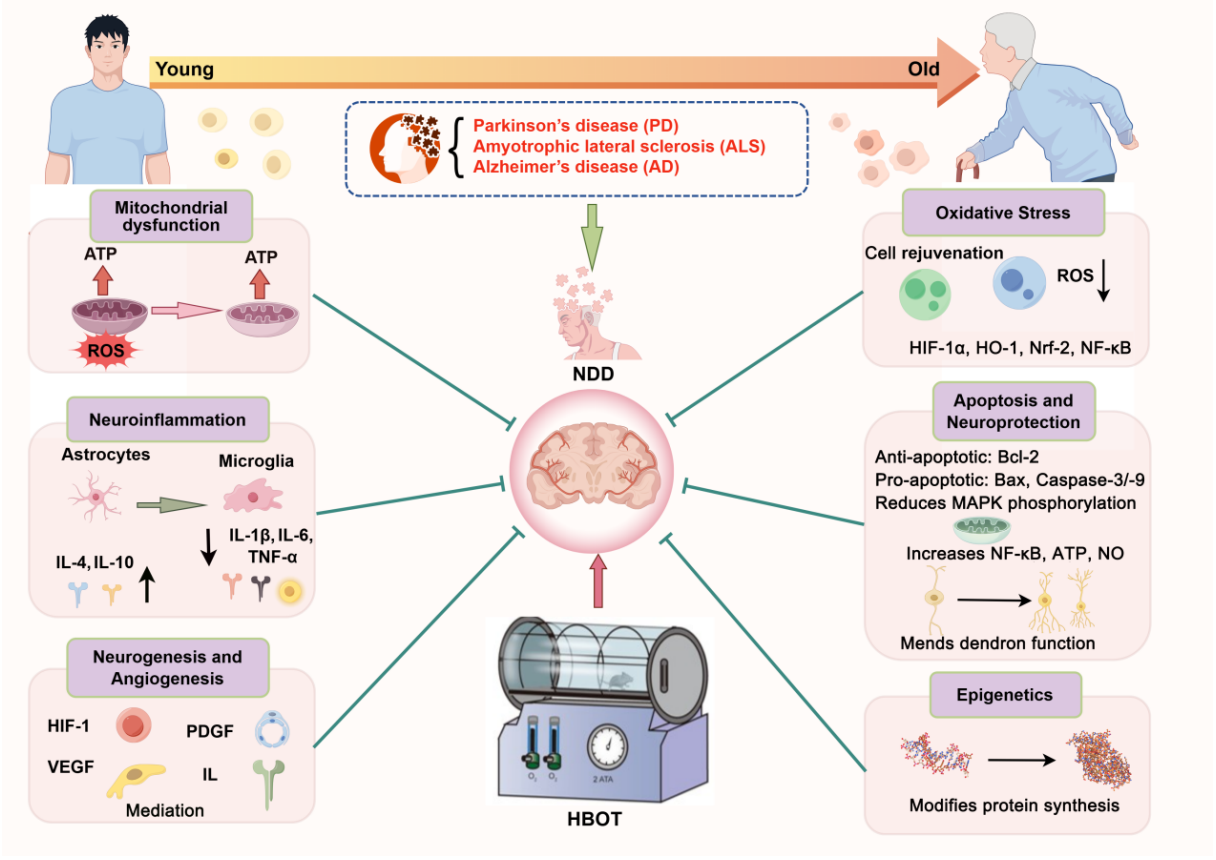

图 1. 高压氧疗法对神经退行性疾病(NDD)的作用机制

Fig. 1. The mechanism of hyperbaric oxygen therapy (HBOT) for neurodegenerative diseases (NDD). (1) Mitochondrial function: HBOT induces the production of reactive oxygen species (ROS) to protect mitochondrial integrity by maintaining mitochondrial membrane potential and reducing mitochondrial apoptosis. (2) Neuroinflammation: HBOT down-regulates pro-inflammatory cytokines, interleukin-1β (IL-1β), IL-12, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), and up-regulates anti-inflammatory cytokines (IL-4, IL-10). (3) Neurogenesis and angiogenesis: HBOT affects growth factors related to neurogenesis and angiogenesis, including hypoxia inducible factor-1 (HIF-1), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and interleukin (IL). (4) Oxidative stress: ROS produced by HBOT activates nuclear factor erythroid 2-related factor 2 (Nrf2), hypoxia inducible factor-1α (HIF-1α) and heme oxygenase 1 (HO-1), which play a crucial role in the regulation of cell proliferation, oxidation/antioxidant system and apoptosis. HBOT also activates nuclear factor κB (NF-κB), which is involved in oxidative stress and inflammation. (5) Apoptosis and neuroprotection: HBOT can reduce the phosphorylation of p38 mitogen-activated protein kinase (MAPK), thereby improving cognitive function and alleviating hippocampal damage. HBOT can also decrease the expression of Bax and the activity of Caspase-9/-3, thereby reducing the apoptosis. (6) Epigenetics: Dysregulation of epigenetic mechanisms such as DNA methylation and histone post-translational modification is associated with NDD, and HBOT plays a role by down-regulating the expression of DNA methyltransferase 3a (DNMT3a) mRNA and protein. By Figdraw (www.figdraw.com).

3.1 HBOT对线粒体功能的影响

线粒体是产生能量、调节代谢功能和钙水平、控制细胞凋亡和活性氧(reactive oxygen species, ROS)产生的复杂细胞器[38]，消耗人体吸入的大约85%到90%的氧气。HBOT诱导ROS的产生，通过维持线粒体膜电位和减少线粒体凋亡来保护线粒体完整性[39]。线粒体自噬激活与神经性疼痛显著减少有关[40]，增加氧气溶解量可显著减轻神经性疼痛。研究显示，HBOT对血管性痴呆症有治疗作用，HBOT治疗后，血管性痴呆症患者血清中人线粒体来源的神经保护肽Humanin水平升高[41]，提示HBOT对增强线粒体活性发挥重要作用，从而改善血管性痴呆患者的认知功能。Lippert等发现HBOT可以促进线粒体从星形胶质细胞向神经元细胞转移，使其增强抵抗神经炎症能力[42]。在液压冲击损伤模型中，HBOT可改善Sprague Dawley (SD)大鼠严重创伤性脑损伤后的恢复，大鼠认知恢复和神经细胞ATP水平提高，提示HBOT可增强线粒体功能[43]。此外，在大鼠阿尔茨海默病模型中，HBOT通过上调抗凋亡的Bcl-2 (B-cell lymphoma 2)表达和下调促凋亡的Bax (Bcl-2-associated X protein)表达来阻断线粒体介导的凋亡信号转导，降低细胞毒性和氧化应激水平[44]。以上研究表明，HBOT可通过减轻线粒体功能障碍而缓解NDD发生。

3.2 HBOT对神经炎症的影响

HBOT可减轻严重脑功能障碍患者的神经炎症。Kudchodkar等研究显示，HBOT在动脉粥样硬化啮齿动物模型上具有下调促炎细胞因子(IL-1β、IL-12、TNF-α和IFN-γ)和上调抗炎细胞因子(IL-10)的作用[14]。创伤性脑损伤通常伴有炎症增加、细胞凋亡和神经胶质瘤、神经元细胞死亡以及认知和运动功能障碍。在创伤性脑损伤大鼠模型中，HBOT被证明可以减轻神经炎症并提高抗炎细胞因子IL-10的水平，从而改善认知缺陷[45]。在阿尔茨海默病小鼠模型中，HBOT可逆转缺氧状态，改善脑组织病理损伤和小鼠行为表现[15, 46]，这种变化与促炎细胞因子(如IL-1β、IL-6和TNF-α)水平降低以及抗炎细胞因子(如IL-4和IL-10)水平提高有关，从而减轻神经炎症。

3.3 HBOT对神经发生和血管形成的影响

研究表明，HBOT影响血管形成和新生[47]。缺氧诱导因子1 (hypoxia inducible factor-1, HIF-1)、血管内皮生长因子(vascular endothelial growth factor, VEGF)、表皮生长因子(epidermal growth factor, EGF)、血小板源性生长因子(platelet-derived growth factor, PDGF)、白细胞介素(interleukin, IL)等细胞因子参与调节血管形成和新生[48]。HBOT可通过增加VEGF的生成促进新血管的形成[49]。在骨髓中，HBOT影响髓质一氧化氮合酶(nitric oxide synthase, NOS)的活性，NOS参与合成一氧化氮(nitric oxide, NO)，并在干细胞的转移、促进血管新生和愈合中发挥作用[50]。HBOT可通过影响干细胞增殖改善认知能力。Yang等发现HBOT可提高脑室下区和齿状回中5-溴-2-脱氧尿苷水平，从而促进缺氧缺血性新生大鼠内源性神经干细胞的神经发生[51]。此外，HBOT可显著提高海马CA3区N-乙酰天冬氨酸/肌酸和N-乙酰天冬氨酸/胆碱的比值，促进神经细胞修复，从而改善创伤性脑损伤大鼠的空间学习和记忆能力[52]。在短暂性大脑中动脉闭塞(middle cerebral artery occlusion, MCAO)模型中，HBOT还可促进骨髓干细胞向缺血区域的移动，提高神经营养因子[脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)，神经生长因子(nerve growth factor, NGF)和神经胶质源性神经营养因子(glial-derived neurotrophic factor, GDNF)]水平，从而加速脑和神经元的恢复，促进神经发生[53]。在急性一氧化碳中毒导致的迟发性脑病患者中，HBOT可上调外周血中$CD34^+/CD90^+$和$CD34^+/CD133^+$双阳性细胞等循环干细胞数量，并通过上调BDNF、神经标记物nestin和突触小泡SYP蛋白表达改善患者认知功能[54]。

3.4 HBOT对氧化应激的影响

HBOT可显著提高人体中抗氧化酶(如超氧化物歧化酶、过氧化氢酶和谷胱甘肽过氧化物酶)水平[29]。此外，除了压力依赖的气泡减少作用和组织的高氧饱和作用外，HBOT的作用机制还包括所产生的ROS的生理作用[55]。HBOT产生的ROS包括超氧自由基和过氧化氢[56]，通过一系列步骤激活核因子红系2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2)和缺氧诱导因子-1α (hypoxia inducible factor-1α, HIF-1α)及其主要靶蛋白血红素加氧酶-1 (heme oxygenase 1, HO-1)，从而在细胞增殖、分化、氧化/抗氧化系统和细胞凋亡的调控中发挥重要作用[57]。

HBOT治疗期间，人体组织中氧气含量经历了从21%增加到100%又降低到21%两个阶段，这种

氧浓度的波动表现为人体组织中氧含量升高时激活Nrf-2，而氧含量降低时则释放缺氧信号并激活HIF-1α [27, 58]。Nrf2参与多种细胞防御机制，介导受损蛋白的修复和降解[59, 60]。HIF-1α参与血管生成、红细胞生成、糖酵解、铁转运和生存[59, 61]。在高氧条件下，参与氧化应激和炎症的核因子-κB (nuclear factor κB, NF-κB)也被激活[58]，从而介导炎症和免疫反应。HIF-1α是细胞和组织适应低氧环境的基础转录因子，与阿尔茨海默病、帕金森病、亨廷顿病和肌萎缩侧索硬化症等多种NDD有关，并已成为潜在的药物靶点[8, 62]。

3.5 HBOT对细胞凋亡及神经保护的影响

HBOT已被发现可降低海马p38丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)的磷酸化水平，从而改善认知功能，减轻海马损伤[63]。HBOT单独或联合银杏叶提取物可下调Bax的表达和Caspase-9/-3的活性，从而降低$A\beta_{25\text{-}35}$诱导的大鼠的氧化应激水平和海马神经元凋亡率[44]。HBOT预处理可通过上调沉默调节蛋白1 (sirtuin 1, SIRT1)诱导脑缺血耐受，SIRT1是一种III类组蛋白去乙酰化酶，参与神经保护[64]，SIRT1上调导致Bcl-2表达上调和Caspase-3裂解减少[64]，这进一步证实了HBOT的神经保护和抗凋亡作用。HBOT对脑血管系统有多种保护作用，包括改善血脑屏障通透性[65]、促进血管生成[36]和减少水肿[37]。HBOT除了提供大量的氧气进入组织外，还通过激活VEGF等转录因子以及神经干细胞的增殖、分化起到神经保护和修复脑损伤作用[51]。综上所述，HBOT对脑组织具有多方面的神经保护作用，包括神经系统和血管系统，从而增强和恢复脑损伤患者的认知能力。

3.6 HBOT对表观遗传学改变的影响

表观遗传修饰如DNA甲基化、组蛋白尾部修饰和microRNA在调节染色质结构和基因转录中起着至关重要的作用[66]。赖氨酸特异性去甲基化酶1 (lysine specific demthylase 1, LSD1)是第一个被发现的组蛋白去甲基化酶，LSD1失调与NDD密切相关，是一个具有潜力的新治疗靶点[67]。在大脑中，与年龄相关的表观遗传修饰调节突触变化、学习记忆和神经发生相关基因的表达[68, 69]。Hachmo等人研究显示，HBOT暴露显著增加老龄化人群中端粒长度和衰老细胞的清除[70]，提示HBOT可能通过表观遗传修饰从而在遗传水平上对人体产生影响。Hwang等发现表观遗传机制的失调如DNA甲基化和组蛋白翻译后修饰与NDD有关[71]。HBOT在神经病理性疼痛中的镇痛作用被认为部分是通过下调DNA甲基转移酶3a (DNA methyltransferase 3a, DNMT3a) mRNA和蛋白表达介导的，DNMT3a是一种在表观遗传修饰中影响线粒体自噬而在突触可塑性、记忆形成和行为可塑性中起重要作用的酶[72]，这进一步表明HBOT可通过表观遗传修饰对NDD发挥作用。

4 HBOT对NDD动物模型的作用研究

Shapira等研究显示，在阿尔茨海默病小鼠模型中，HBOT可减少小胶质细胞和星形胶质细胞增生，降低促炎细胞因子的分泌来减少神经炎症发生，进而改善认知功能[15]。HBOT和银杏叶提取物联合使用也可以通过阻断线粒体介导的凋亡信号转导[44]、激活NF-κB [75]和增强海马组织超氧化物歧化酶的活性来抑制氧化应激，从而改善阿尔茨海默病模型大鼠的认知和记忆障碍[73]。HBOT预处理也被证明可以降低海马p38 MAPK磷酸化，从而减轻海马损伤[63]。

在帕金森病动物模型中，HBOT单用或和美多巴联用均可减轻阿帕吗啡诱导的大鼠帕金森病症状，并对黑质多巴胺能神经元具有神经保护作用[74]。在另一种帕金森病诱导模型即1-甲基-4-苯基-1, 2, 3, 6-四氢吡啶(1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine, MPTP)小鼠中，Hsu等研究显示，HBOT对神经元和运动功能具有保护作用，HBOT预处理增加了SIRT-1、PGC-1α、TFAM和VDAC的表达水平，表明HBOT通过SIRT-1/PGC-1α/TFAM通路刺激MPTP处理的小鼠脑中的线粒体生物发生[75]。

在运动神经元疾病模型中，HBOT也被证明可以改善Wobbler小鼠运动皮层和脊髓中的线粒体功能障碍，显著延迟了运动神经元疾病的发作[76]。在大鼠衰老模型(D-半乳糖诱导)以及衰老和肥胖模型中，HBOT通过平衡自噬来改善D-半乳糖和高脂饮食诱导的外周胰岛素抵抗、海马自噬受损和海马胰岛素受体功能下降，从而增强大鼠认知能力[77]。在小鼠衰老(D-半乳糖诱导)模型中，HBOT通过增强胆碱能通路、抗凋亡作用减轻衰老小鼠认知障碍[78]。此外，Wang等研究发现HBOT使老龄(22月龄) C57BL/6小鼠突触后组织、突触组织和轴突发生基因表达显著上调，表明HBOT可改善老龄小鼠

认知能力；HBOT显著降低微管相关蛋白过度磷酸化，表明HBOT增强突触可塑性和神经营养支持；机制研究结果显示，HBOT通过激活AMPK-mTOR信号通路增加自噬，上调Beclin-1和LC3蛋白水平并下调p62蛋白水平[79]，该研究为HBOT改善年龄相关认知障碍的机制研究提供了新的方向。

5 HBOT对NDD的临床应用研究

HBOT可以使NDD患者认知功能改善，脑代谢增加，空间工作记忆能力提高。Harch等报告了一个临床病例，一名58岁女性阿尔茨海默病患者接受HBOT治疗8周，总治疗时间为50 min，每天1次，每周5天，压力为1.15 ATA[80]；至治疗21天时，患者精力更加充沛，完成画钟、日常生活等任务的能力有所提高；PET成像显示相应的脑代谢区域整体增加[80]。Xu等研究显示，帕金森病患者接受HBOT治疗30天后，重度抑郁和焦虑的非运动症状得到改善[81]。Boussi-Gross等研究显示，HBOT治疗(每天60 min，压力为1.5 ATA)可减轻脑卒中后患者的记忆障碍[82]。Chen等研究显示，HBOT (40 min，每天1次，持续20天)可显著改善遗忘性轻度认知障碍(amnestic mild cognitive impairment, aMCI)患者迷你精神状态检查(mini-mental state examination, MMSE)、蒙特利尔认知评估(montreal cognitive assessment, MoCA)和日常生活活动(activities of daily living ADL)量表评估的认知功能指标[83]。Slade等报告了一个病例，一名55岁男性丘脑疼痛综合征患者经过多种药物治疗无法缓解并发生中风，采用HBOT干预后患者的症状和生活质量显著改善[84]。

研究表明，HBOT还可改善健康老年人的年龄相关认知缺陷[85]。Jacobs等研究显示，30次间歇暴露于2.5 ATA的100%氧气治疗显著提升智力退化患者认知功能[86]。一项随机对照临床试验结果显示，64岁以上的健康成年人暴露于HBOT 3个月后，灌注磁共振成像测量脑血流量(cerebral blood flow, CBF)的区域变化验证了HBOT可促进健康老年人的认知改善[87]。此外，HBOT还可以改善记忆丧失的老年患者的认知功能并增加CBF [88]。以上研究结果充分证明了HBOT在NDD临床治疗上的应用前景。

6 总结与展望

由于NDD的发病机制和影响因素尚未完全阐明，因此如何开发安全有效的治疗方案仍然面临挑战。此外，NDD治疗的难点在于血脑屏障使药品向大脑的输送受到限制，从而降低生物利用度。作为NDD免疫反应的主要部位，大脑是一个高度代谢的器官，具有高浓度的过渡金属，能够与过氧化氢发生反应，产生高反应性的自由基，同时它的抗氧化能力相对较低，这些因素增加了其对氧化应激和神经元损伤的易感性[89]。

众所周知，缺氧会导致微管相关蛋白过度磷酸化、血脑屏障功能障碍、β-淀粉样蛋白积累和神经元变性[90]。在中风和脑缺血等缺氧条件下，阿尔茨海默病等NDD的发病率会大大增加。在阿尔茨海默病中，低氧脑损伤会增强α-突触核蛋白的表达和聚集，导致氧化应激和线粒体功能障碍[91]。另一个影响NDD进展及导致认知能力下降的因素是脑微血管，脑微循环受损与血管认知能力障碍有关[37]。上述NDD都与脑组织缺氧相关，解决这一问题的关键是增加脑循环中的氧气，因此HBOT可能是一种可行的干预措施。

HBOT的适用性、可靠性和安全性经历了时间的考验。尽管临床上已经有HBOT用于NDD辅助治疗的研究报道，但仍然需要对其治疗方案和作用机制进行深入探索。总之，HBOT对与细胞和神经元恢复相关的多种细胞和分子通路产生影响，包括氧化应激、线粒体功能、炎症、凋亡、微循环和表观遗传改变等方面。未来的研究方向可以基于不同症状、性别、年龄等特征来制定针对性治疗方案，以最大程度发挥HBOT治疗NDD的应用潜力。

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