

综述

慢性间歇性低氧与认知功能障碍研究进展

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摘要: 阻塞性睡眠呼吸暂停(obstructive sleep apnea, OSA)影响全球近10亿患者生命健康, 增加老年痴呆患病风险, 导致认知功能障碍。慢性间歇性低氧(chronic intermittent hypoxia, CIH)作为OSA核心病理机制, 可导致神经元突触可塑性损伤, 引起学习和记忆能力以及注意力下降等认知障碍表现。然而, 目前关于CIH导致突触可塑性损伤的确切分子机制并不完全明确, 尚无OSA并发认知障碍的针对性治疗措施。本文明确了OSA与认知功能障碍的相关性, 并从突触可塑性损伤、氧化应激、炎症、内质网应激、细胞凋亡、线粒体功能障碍和细胞自噬等方面具体阐明了OSA核心病理机制——CIH诱导认知功能障碍的相关机制。本文还概括了目前OSA并发认知障碍的治疗现状。

关键词: 阻塞性睡眠呼吸暂停; 慢性间歇性低氧; 认知功能障碍; 氧化应激; 炎症

Research progress on chronic intermittent hypoxia and cognitive impairment

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Abstract: Obstructive sleep apnea (OSA) affects quality of life and health in nearly 1 billion patients all over the world. With aging society, OSA increases the risk of Alzheimer's disease and leads to severe cognitive impairment. Chronic intermittent hypoxia (CIH), the core pathological mechanism of OSA, may induce synaptic plasticity damage and cognitive impairment, and decrease learning and memory and attention ability. However, the molecular mechanism underlying OSA is still not fully understood. And, there is no targeted treatment strategy for cognitive impairment in patients with OSA. Firstly, the correlation between OSA and cognitive dysfunction was summarized in this review. Secondly, the molecular mechanism of CIH-induced cognitive impairment was elucidated from the perspectives of synaptic plasticity damage, oxidative stress, inflammation, endoplasmic reticulum stress, apoptosis, mitochondrial dysfunction and autophagy. Finally, the current treatment strategy for cognitive impairment in patients with OSA was summarized.

Key words: obstructive sleep apnea; chronic intermittent hypoxia; cognitive impairment; oxidative stress; inflammation

阻塞性睡眠呼吸暂停 (obstructive sleep apnea, OSA) 是一种在人群中广泛发生的夜间呼吸障碍, 其特征是短暂频繁的呼吸中断, 具体表现为睡眠期间上气道部分或完全塌陷, 进而导致间歇性低氧、高碳酸血症和睡眠觉醒^[1]。既往研究表明, 脑组织因其高代谢和高能量消耗的特点, 对缺氧极敏感, 因而易受到缺氧损伤^[2]。以往研究表明, OSA 患者

伴发老年痴呆风险明显升高, 可导致包括注意力、记忆、推理、语言和视觉空间功能等神经认知功能障碍^[3-5]。慢性间歇性低氧 (chronic intermittent hypoxia, CIH) 作为 OSA 核心病理机制, 可诱发氧化应激、炎症、内质网应激 (endoplasmic reticulum stress, ERS)、细胞自噬、线粒体能量代谢障碍, 进而导致突触可塑性损伤, 影响认知功能。因此, 本

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文对 CIH 诱导认知功能障碍及其相关分子机制展开综述，归纳目前关于 OSA 并发认知功能障碍的治疗措施，旨在为临床提供针对性治疗策略。

1 OSA与认知功能障碍

OSA 是一种在成年人中普遍存在的疾病，影响全球近 10 亿成年人的生命健康^[6]。据报道，OSA 在全球成年人中的患病率为 9%~38%，其中中度至重度 OSA 患者约占成年男性的 20% 和绝经后女性的 10%^[7, 8]。有学者用蒙特利尔认知评估量表 (Montreal Cognitive Assessment, MoCA) 进行认知功能评估，发现有 40.53% 的 OSA 患者存在认知功能障碍^[9]。而最近的回顾性研究也发现，OSA 与阿尔茨海默病 (Alzheimer's disease, AD) 的发病率具有独立且显著的相关性。与非 OSA 个体相比，OSA 患者发生 AD 的风险高出 58%，并且从诊断为 OSA 开始进展到 AD 的平均检测期为 5.44 年^[10-12]。一方面，OSA 患者表现出的日间过度嗜睡会影响其注意力和短期记忆力^[13]。另外，临床研究发现中重度 OSA 存在脑白质病变和海马体积减少，影响记忆和其他认知功能^[14, 15]。OSA 因其普遍性使其易被患者忽略，但对认知功能影响的隐匿性以及治疗手段的局限性，使得 OSA 合并认知障碍患者生活质量受到较大影响。然而，目前关于 OSA 并发认知障碍的具体机制尚不完全明确。

2 CIH作为OSA的核心病理机制，其诱导神经元损伤与认知障碍密切相关

OSA 的特征是睡眠期间反复发作的上呼吸道壅

陷，导致夜间 CIH 和睡眠片段化。目前研究认为，CIH 的低氧-复氧模式可能是 OSA 并发多种病理生理损伤的关键机制。研究人员通过建立 CIH 暴露动物模型发现，CIH 暴露后小鼠认知功能明显受损，突触后致密物减少，神经元受损甚至凋亡 (表 1)。其中，海马 CA1 区神经元细胞体萎缩，排列紊乱，甚至出现明显丢失和凋亡可能与 CIH 诱导认知障碍密切相关^[16-18]。并且，在对 AD P301S 转基因小鼠进行 CIH 暴露后，发现 CIH 促进了小鼠突触可塑性损伤及微管相关蛋白 tau 蛋白 (microtubule-associated protein-tau) 的播种及磷酸化，进一步加剧了小鼠的认知障碍表现^[19]。值得注意的是，研究发现 CIH 暴露 4 周的 CD-1 小鼠出现认知功能下降，暴露 2 周却对小鼠认知功能无明显影响^[20]。该结果提示 CIH 暴露时间可能是认知功能障碍的密切相关因素。随着 CIH 暴露时间的延长，受损线粒体积累伴随线粒体活性氧 (mitochondrial reactive oxygen species, mtROS) 的释放^[16, 21]，进一步诱导炎症反应、ERS 等，进而导致突触可塑性损伤和认知功能障碍^[22-24]。

总之，目前研究可认为 OSA 相关的认知障碍可能与 CIH 诱导不可逆的脑损伤^[21]密切相关，主要表现为 CIH 可通过诱导氧化应激、炎症、自噬及线粒体功能障碍，甚至细胞凋亡导致神经元形态及功能受损 (表 2)。有一项研究结果显示，CIH 暴露可导致神经元细胞密度降低，细胞形态出现不同程度的皱缩、变圆、碎片增多，伴随线粒体结构受损和线粒体膜电位降低^[25]。另有研究发现，将小胶质细胞和神经元细胞在 CIH 条件下进行共培养可出现

表1. 动物模型中慢性间歇性低氧暴露诱导神经元损伤与认知障碍密切相关

Table 1. Chronic intermittent hypoxia (CIH)-induced neuronal damage is closely related to cognitive impairment in animal models			
动物	模型	结果	文献
C57BL/6小鼠	O ₂ : 21%–9%, 90 s/cycle, 7 h/d, 4 weeks	CIH组小鼠记忆错误增加，海马CA1区神经元凋亡	[17]
CD-1小鼠	O ₂ : 21%–6%, 1.5 min/cycle, 8 h/d	CIH暴露4周小鼠认知功能下降，但CIH暴露2周无明显影响	[20]
P301S小鼠	O ₂ : 21%–8%, 6 min/cycle, 8 h/d, 8 weeks	CIH显著加剧了P301S小鼠记忆和突触可塑性损伤	[19]
SD大鼠	O ₂ : 21%–8.0%, 3 min/cycle, 8 h/d	CIH暴露28天，海马神经元明显受损	[23]
SD大鼠	O ₂ : 21%–10%, 90 s/cycle, 12 h/d	CIH暴露神经明显损伤，且损伤随着时间增长而加剧；CIH暴露可诱导星形胶质细胞由A2向A1转化	[49]
C57BL/6小鼠	O ₂ : 21%–10%, 90 s/cycle, 8 h/d, 4 weeks	CIH组小鼠行为学成绩明显下降、小鼠焦虑增加	[22]
C57BL/6小鼠	O ₂ : 21%–9%, 3 min/cycle, 8 h/d, 5 weeks	CIH暴露后小鼠水迷宫和Y迷宫成绩明显下降，海马神经元染色变浅、突触后致密物减少	[24]
C57BL/6小鼠	O ₂ : 21%–9%, 3 min/cycle, 8 h/d, 3 weeks	CIH暴露21天，行为学成绩明显下降；海马CA1区神经元明显丢失和凋亡	[18]

表2. 慢性间歇性低氧诱导神经元损伤的机制

Table 2. Mechanism of chronic intermittent hypoxia (CIH)-induced neuronal damage

细胞	模型	结果	文献
BV2细胞	O ₂ : 22%–0%, 30 min/cycle, 24 h	IH暴露使细胞活力显著下降, 且诱导炎症因子产生	[26]
HT22细胞	O ₂ : 21%–1% IH1: 10 min/cycle IH2: 30 min/cycle IH3: 100 min/cycle	不同IH暴露, 细胞受损程度不同, IH1组细胞密度减少最明显。相同暴露时间, IH频率越高, 细胞损伤越严重	[28]
BV2细胞	O ₂ : 21%–5%, 30 min/cycle, 分别暴露3、6、12、24 h	IH暴露激活NLRP3炎症小体, IH可以触发小胶质细胞中线粒体破碎化, 随后诱导线粒体自噬	[16]
原代海马神经元	O ₂ : 21%–1.5% IH1: 7 min/cycle IH2: 15 min/cycle IH3: 30 min/cycle	IH3组海马神经元损伤最严重	[29]
BV2细胞、HT22细胞	O ₂ : 21%–1.5%, 2 min/cycle, 24 h	相同条件下, 与BV2细胞共培养时HT22细胞凋亡更明显	[27]
PC12细胞	O ₂ : 21%–0.1%, 60 min/cycle, 8 h	IH组线粒体结构受损、线粒体膜电位降低	[25]

IH: 间歇性低氧。

更明显的细胞凋亡^[26, 27]。这可能与CIH诱导NLRP3炎症小体激活, 进而导致神经炎症有关。近期的研究结果还发现不同的间歇性低氧刺激频率或时间可对特定类型的细胞引起截然相反的结果^[28, 29]。综上研究结果提示, CIH暴露可导致神经元损伤与认知障碍, 但是受暴露时间、频率等因素的影响, 其具体的分子机制有待于进一步研究。

3 CIH诱导认知障碍的相关机制

3.1 突触可塑性损伤

突触是神经元之间信息传递以及神经回路形成和重塑的重要结构, 神经元信息能否顺利传递、处理和存储取决于突触结构和功能的完整性。突触可塑性是改变突触结构和功能以适应环境变化和 Information 存储的能力, 其在长期记忆的形成过程中起着关键作用, 是学习和记忆的神经基础, 突触可塑性的变化与认知功能直接相关^[30]。研究发现, CIH暴露可导致突触发生受损和神经元髓鞘化程度降低, 表明CIH引起的功能性突触损伤与认知功能障碍密切相关^[31]。突触后致密物-95 (postsynaptic density-95, PSD-95) 是一种在海马和皮质中发现的特殊蛋白, 其结合NMDA受体, 介导突触可塑性并参与神经元信号转导。有研究发现, CIH暴露后小鼠出现认知功能障碍, 伴随海马树突棘密度和突触后致密物厚度下降^[32]。CIH暴露后突触后可塑性的变化最直接的证据在于长时程增强 (long-term potentiation, LTP) 的损伤。CIH暴露P301S小鼠出现双脉冲易

化 (paired-pulse facilitation, PPF) 受损和LTP损伤, 表明CIH还影响了突触前神经递质释放, 导致长时间记忆缺陷^[19]。CIH可引起LTP早期和持续的下降, 干扰正常活动依赖的突触可塑性, 与记忆缺陷密切相关。以上研究结果提示, CIH可通过影响突触的正常结构与功能来引起突触可塑性损伤, 进而引起认知功能障碍。

3.2 氧化应激

研究认为, 氧化应激导致神经元损伤和认知功能障碍与OSA密切相关。细胞内累积的氧自由基可能是导致神经退行性疾病如AD的关键机制之一。CIH暴露类似于缺血再灌注过程, 反复的低氧和复氧导致超氧化物歧化酶 (superoxide dismutase, SOD) 和丙二醛 (malondialdehyde, MDA) 异常表达和生成, 破坏氧化和抗氧化系统平衡, 增加活性氧 (reactive oxygen species, ROS) 的产生, 导致氧化应激的发生^[33–35]。由于中枢神经系统富含脂质成分, 相对缺乏抗氧化酶但耗氧量高, 容易出现海马神经元氧化应激损伤^[36]。CIH模型大鼠海马中氧化应激水平随暴露时间的延长而逐渐加重^[6]。此外, 氧化应激也可损害下丘脑-垂体-肾上腺 (hypothalamic-pituitary-adrenal axis, HPA) 轴, 进一步启动神经退行性进程^[37]。虽然ROS是生理功能所必需的代谢副产物, 但大量ROS的积累会产生毒性作用, 细胞内累积的ROS通过破坏DNA并引起神经细胞损伤来诱导错义突变^[38], 也可激活JNK/SREBP/ACC通路导致脂质过氧化, 加剧神经元损伤^[39]。总之, 越来越多

的证据表明,氧化应激可能是 CIH 诱导认知功能障碍的启动分子机制,其可直接导致线粒体功能障碍,也可与炎症反应相互促进,直接或间接地引起神经元凋亡,导致认知功能障碍。

3.3 炎症

炎症是机体对损伤做出的防御反应,但是过度炎症反应也是认知障碍发生的重要因素^[26]。促炎细胞因子和抗炎细胞因子之间的持续失衡会导致脑内皮细胞功能障碍,从而减少脑血流量,以及干扰谷氨酸神经递质和脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 合成,损害神经元功能,导致海马依赖性学习和记忆障碍^[16, 40-43]。小胶质细胞作为中枢神经系统的常驻免疫细胞,在调节大脑炎症方面起着重要作用^[10]。许多研究已经证明,小胶质细胞的过度激活会加重神经元轴突和突触损伤,增加脱髓鞘,并损害多个脑区白质的完整性^[44, 45]。神经炎症引起的神经元凋亡可能是 CIH 诱导认知障碍的重要机制之一^[46]。研究发现,小胶质细胞在 CIH 刺激下被迅速激活,进而分泌大量的促炎细胞因子,如肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α) 和白细胞介素 (interleukin, IL)-1 β , 导致神经元凋亡^[47]。除此之外,CIH 暴露还可导致反应性星形胶质细胞增加,促进 IL-1 β 、IL-6、IFN- γ 和 TNF- α 等炎症因子分泌,从而诱发认知功能障碍^[48, 49]。CIH 还可促进 NLRP3 炎症小体释放,进一步促进 IL-1 β 的释放^[16, 50, 51]。总之,CIH 诱导的炎症反应在神经细胞损伤和认知障碍中起到关键作用。

3.4 ERS

ERS 是细胞的一种适应性机制,适宜的 ERS 可起到缓解刺激、保护细胞的作用。而过度或持续的 ERS 可通过激活 PERK/eIF2 α /ATF4/CHOP 凋亡途径,也可引起自噬向凋亡转变,导致神经元凋亡^[50, 52]。ERS 可通过直接调节炎症途径、诱导小胶质细胞激活以及介导细胞自噬等途径,促进神经元细胞发生凋亡,进而导致认知功能障碍。研究发现,CIH 暴露可导致神经元细胞 ROS 的累积,而 ROS 又在诱发 ERS 中起关键作用^[53]。研究发现,CIH 暴露后,小鼠海马细胞产生大量 ROS,而抑制 ROS 产生后,ERS 标志分子 CHOP 等表达和细胞凋亡均减少^[54]。另外,CIH 暴露后机体产生大量 IL-1 β 也可通过 ERS 介导的 PERK/eIF2 α /ATF4/CHOP 凋亡途径促进海马神经元凋亡,从而导致学习和记忆受损^[50]。总之,ERS 在 CIH 中发挥着重要作用,可与氧化

应激、炎症等多种应激反应相耦联,进而导致神经系统损伤。

3.5 线粒体功能障碍

线粒体在神经发生、突触可塑性和神经传递中发挥重要作用,特别是神经元容易受到线粒体功能障碍的影响。线粒体功能障碍主要表现在线粒体形态结构改变、ATP 合成减少、ROS 过度产生、动力学失衡和线粒体 DNA 损伤。线粒体被认为是 ROS 合成的主要来源^[55, 56],线粒体缺陷和功能障碍是诱发突触变性和功能衰竭的关键因素^[57]。CIH 暴露可导致受损线粒体的积累,增加了 mtROS 的释放,促进了线粒体自噬和 NLRP3 炎症小体活化^[16, 58]。有研究认为,线粒体功能障碍可能是小胶质细胞初始和持续激活的关键作用^[59, 60]。线粒体功能障碍还可导致钙信号传导过程受损,导致能量产生不足和细胞凋亡增多,这些都可导致神经元变性^[61]。线粒体功能障碍可与氧化应激相互作用并可激活细胞自噬、炎症和细胞凋亡的发生,可为 CIH 条件下神经元损伤的针对性治疗提供新靶点。

3.6 细胞自噬和凋亡

细胞自噬是一种特异性自我消化的过程,能够限制炎症的发展,进而抑制神经炎症的产生^[62]。自噬已被证明是调节氧化应激和改善脑损伤的关键生理过程^[63]。在 AD 的早期阶段,自噬通过去除异常的细胞内蛋白来维持细胞内环境的平衡,从而对神经元具有保护功能。而在 AD 后期,过度激活的自噬又可引起神经元的损伤^[64]。失调的自噬途径导致神经元丢失和突触可塑性损伤^[65],研究发现自噬指标 LC3-II 在镉诱导的小鼠脑损伤中下调,伴随认知功能下降^[63]。有学者通过设置不同低氧/复氧模型发现,低频率且长时间的间歇性低氧刺激可通过调控细胞自噬导致神经元明显损伤^[29]。并且,CIH 暴露可诱发小胶质细胞线粒体的破碎化,随后诱导线粒体自噬^[16]。研究提示,CIH 对自噬的不同作用取决于其严重程度、持续频率以及时间。上述研究提示,CIH 可引起机体产生大量 ROS 及炎症因子等诱导细胞自噬失调,进而导致神经元凋亡。因此,通过调控自噬改善神经元凋亡可能会为 CIH 诱导的认知功能障碍提供创新性治疗靶点。

综上所述,CIH 暴露可通过诱导氧化应激、炎症反应、ERS,线粒体功能障碍以及细胞自噬失调等途径,导致神经元凋亡和突触可塑性损伤,进而引起认知功能障碍(图 1)。

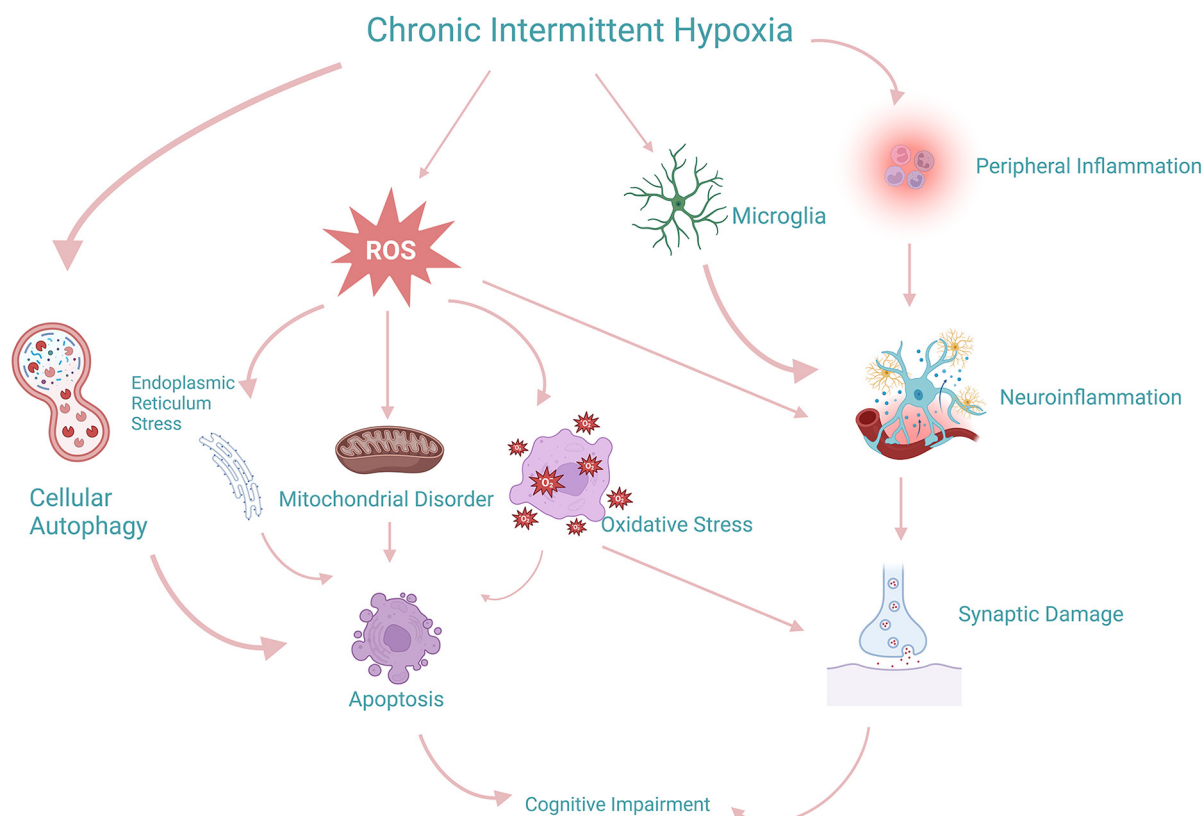


图 1. 慢性间歇性低氧可通过炎症反应、氧化应激、细胞自噬、内质网应激以及线粒体功能障碍等途径导致神经元凋亡及突触损伤, 进而导致认知功能障碍

Fig. 1. Chronic intermittent hypoxia induces cognitive impairment. The mechanism may be related to neuronal apoptosis and synaptic damage through inflammatory response, oxidative stress, cell autophagy, endoplasmic reticulum stress, and mitochondrial dysfunction. ROS: reactive oxygen species.

4 OSA并发认知障碍的治疗现状

4.1 现代医学治疗

4.1.1 持续气道正压通气(continuous positive airway pressure, CPAP)治疗

CPAP 目前被认为是 OSA 的一线治疗^[7]。CPAP 治疗可以显著提高重度 OSA 患者的注意力和信息处理速度^[66]。有学者招募了 54 名轻度认知障碍 (mild cognitive impairment, MCI) 患者, 通过其对 CPAP 依从性进行分组, 最终发现 CPAP 依从性高的患者较 CPAP 依从性差的患者白天嗜睡和认知功能有明显改善^[67]。Canessa 等人已证实 CPAP 治疗后出现认知缺陷的可逆性变化, 提示坚持 CPAP 可导致大脑结构和认知功能恢复^[68]。CPAP 治疗目前仍是 OSA 的重要治疗手段, 及时且依从性高的 CPAP 治疗似乎可减缓认知能力的下降, 降低 OSA 并发认知障碍的风险。但由于其效果与依从性密切相关, 且许多患者无法坚持长期使用, 使得 CPAP 治疗并

未达到理想状态, 后续需在改进 CPAP 治疗模式、提高 CPAP 长期使用率方面寻找新的治疗思路。

4.1.2 药物治疗

目前研究发现, 许多抗炎药物可有效抑制炎症过程, 改善认知功能障碍。在 AD 小鼠模型中, TLR-4 受体拮抗剂显著改善了神经炎症和认知功能损伤^[69]。右美托咪可通过降低海马体中炎症细胞因子水平和神经胶质细胞活性, 进而逆转神经退行性变和神经元凋亡^[70, 71]。有研究发现, 用于治疗睡眠障碍的莫达非尼具有神经保护作用, 可抑制小胶质细胞活化和白细胞浸润中枢神经系统, 进而缓解神经和全身炎症^[72]。自由基清除剂依达拉奉也可增加 CIH 暴露大鼠的线粒体数量以及 BDNF 的表达水平, 进而减轻 CIH 诱导的认知功能障碍^[73]。而褪黑素也可以通过增强自噬活性抑制 NLRP3 炎症小体介导的炎症反应, 从而减轻 CIH 引起的认知障碍^[74]。总之, 目前关于 OSA 并发认知障碍的药物治疗研究多集中于通过抑制炎症反应缓解症状。但是, 由

于OSA患者主要表现为气道频繁塌陷、通气受阻,目前尚无针对性治疗药物,这依赖于OSA并发认知障碍分子机制的进一步深入研究。

4.2 中医药治疗

OSA在中医学中归属“鼾症”,属本虚标实,认为本病发生是因气虚痰凝血瘀,痰瘀蒙蔽于上,清窍为之壅塞,脑失所养而出现认知功能障碍^[75]。在此基础上,Chen等以益气活血、化痰通窍法立方,以加味涤痰汤干预CIH模型大鼠,发现其可显著改善认知功能障碍,可能与其抑制氧化应激反应相关^[76]。也有研究发现,苍术可抑制CIH诱导的M1型小胶质细胞活化来改善OSA相关认知功能障碍^[77]。总之,目前中医药治疗并无明确的对症方药,且大多限制在动物实验阶段,并未涉及大规模临床观测数据,因此基于临床中医辨证分型确定针对性中医治法是中医药治疗的关键。OSA并发认知障碍作为慢性神经退行性疾病,与病程及年龄密切相关。中医认为,肾主骨生髓,且久病及肾,髓减脑消,进而导致认知功能障碍。我们前期的研究基于“补肾填精益髓”角度,确立“益气滋阴补肾”中医治则,发现CIH暴露小鼠表现出气阴两虚症状,应用益气滋阴方药可有效改善气阴两虚症状,通过调控谷氨酸能信号通路改善认知障碍^[32, 78],为OSA并发认知障碍的针对性中医药治疗策略提供了可行性理论和实验基础。

4.3 其他治疗

针对OSA并发认知障碍的治疗目前主要为基于原发病的治疗,确保上气道通畅是其关键所在,例如舌下神经刺激、口腔矫正器(oral appliances, OA)治疗、倒刺复位咽成形术(barbed reposition pharyngoplasty, BRP)治疗、口面部肌功能治疗(orofacial myofunctional therapy, OMT)、手术治疗、减重治疗以及辅助治疗(如体位治疗)。而肥胖是OSA的高危因素之一,注意生活方式、控制体重可以有效改善呼吸暂停症状,降低睡眠呼吸暂停低通气指数(apnea-hypopnea index, AHI)。除此之外,氢作为一种新的抗氧化剂,可以显著抑制氧化应激,为OSA合并认知功能障碍提供了潜在的治疗方法^[36]。

综合目前OSA并发认知障碍的治疗现状来看,CPAP作为目前的一线治疗,可以有效地改善OSA并发的认知障碍,但由于其依从性较差,使得治疗并未达到理想状态。而药物治疗多为抗炎及清除体内自由基,其改善认知功能障碍的疗效有限。手术

及矫正治疗在中老年居多的OSA患者中适用度低,而中医药治疗大多为辅助治疗手段,且对OSA并发认知障碍尚未有统一针对性治疗方案。

综上所述,CIH通过诱导氧化应激和炎症反应等导致神经元凋亡和突触可塑性损伤可能是OSA并发认知障碍的关键病理机制。目前对于OSA并发认知障碍尚缺乏针对性治疗方案,因此,进一步阐明CIH诱导神经元损伤的核心作用靶点,研发针对性临床治疗方案对于OSA并发认知障碍的治疗非常关键。

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