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衰老相关认知功能障碍发病机制及治疗策略的研究进展

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摘 要

衰老相关认知功能障碍发病率随着社会老龄化而逐年升高，严重影响老年人群的生活质量，已经成为全球关注的热点问题。本研究就衰老相关认知功能障碍的定义、诊断和评估、发病机制、预防和治疗手段进行归纳总结，以期为衰老相关认知功能障碍的早期发现、早期诊断、早期治疗提供理论基础。

关键词

衰老相关认知功能障碍，诊断评估，发病机制，预防，治疗

Advances in the Pathogenesis and Treatment Strategies of Aging-Related Cognitive Dysfunction

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Abstract

The incidence of aging-related cognitive dysfunction increases year by year with the aging of society, which seriously affects the quality of life of the elderly population and has become a hot issue of global

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concern. This study summarises the definition, diagnosis and assessment, pathogenesis, prevention and treatment of aging-related cognitive dysfunction, with a view to providing a theoretical basis for early detection, early diagnosis and early treatment of aging-related cognitive dysfunction.

Keywords

Aging-Related Cognitive Dysfunction, Diagnosis and Assessment, Pathogenesis, Prevention, Treatment

1. 引言

随着人类生命跨度的延长，社会老龄化问题越来越突出。目前，中国有超过 2 亿的 60 岁以上老年人口，全球老年人口中，我国占比已达到 25% [1] [2]。Jia 等人进行的 1 项全国性研究表明，中国有超过 1500 万的老年痴呆患者未得到规范诊疗，轻度认知功能障碍的发病率在中国老年人口中更是达到了 15.5% [3]。由此可见，认知功能下降是衰老过程中不可忽视的重要表现，而认知功能的下降会伴随年龄的增长缓慢发生，这种现象被称为脑老化[4] [5]。大多数人的大脑会经历非病理性老化，表现为正常的认知衰退，这种衰退通常不会显著影响日常生活和社会交往的质量[6]。然而，也有一部分人会发展为病理性认知功能障碍，如痴呆症和阿尔茨海默病等，这类情况严重影响个体的生活质量。因此，大脑健康已成为全球公共卫生领域最为关注的焦点之一，包括世界卫生组织在内的专业卫生机构呼吁关注痴呆症的发生，促进大脑健康，进而减轻卫生保健系统的压力和家庭的疾病负担[7]。然而当前研究对衰老引起认知功能障碍发病机制和康复的研究并不透彻，因此本研究就衰老相关认知功能障碍的定义、诊断和评估、发病机制、预防和治疗等方面进行阐述，期望能够为该疾病的早期发现、早期诊断、早期治疗提供理论依据，为这一疾病的预防和治疗带来新的希望，以解决未来的衰老相关认知功能障碍。

2. 衰老相关认知功能障碍概述

2.1. 衰老相关认知功能障碍相关概念

衰老是所有生物不可避免的、渐进且不可逆的生理过程[8]。其特点是各种神经生理功能的持续衰退，最终导致包括认知功能障碍在内的各种生理功能障碍[9] [10]。即使是健康成年人，随着年龄的增长，认知功能也会逐渐下降[11]。认知功能涵盖一系列心智能力，涉及对外界和内心世界的感知，以及快速准确地获取知识、技能和理解。主要认知领域包括感觉－知觉处理、心智和运动速度、注意力、学习、记忆、语言、推理、问题解决和执行功能[11] [12]。因此，衰老相关认知功能障碍是指随着年龄的增长，上述认知领域中的一项或多项功能受损，其中最常见的是记忆能力下降[13]。尽管认知功能下降通常被视为衰老的正常现象，但持续的衰退无疑会干扰日常生活，并最终可能演变为痴呆症[14]。

2.2. 衰老相关认知功能障碍的诊断与评定

美国国立精神卫生研究院(National Institute of Mental Health, NIMH)在 1994 年对衰老相关认知功能障碍的诊断标准做出了如下定义：① 至少有 1 份个人或可靠的知情人士的报告确认认知功能已经下降；② 认知功能的衰退必须是渐进式的，且已持续 6 个月以上；③ 认知功能的障碍至少涉及以下一个领域：记忆和学习能力、注意力、思维(如解决问题、抽象思维)、语言(如理解、找词)、视觉空间功能。④ 在相对

健康的人群中，有年龄和教育条件限制的定量认知评估(如神经心理测试、心理状态评估)表现异常[15]。

在认知功能筛查工具方面，由 Folstein 等人于 1975 年编制的简易智能精神状态量表(Mini-Mental State Examination, MMSE)和由加拿大蒙特利尔神经学研究所的 Ziad Nasreddine 教授等人根据临床经验并参考简易智能精神状态量表的项目和评分而制定的蒙特利尔认知评估量表(Montreal Cognitive Assessment, MoCA)是临床和研究领域应用最广泛的 2 种工具，两者均能有效筛查早期认知功能障碍患者[16]-[19]。

简易智能精神状态量表设计简便，文化程度要求低，检查全面，能全面评估定向力、记忆力、注意力、计算力、语言能力和视觉空间能力等多个方面。总分 30 分，评价认知功能时，需考虑患者的文化水平，初中或以上文化程度大于 24 分为正常，小学文化程度大于 20 分为正常，文盲大于 17 分为正常。

蒙特利尔认知评估量表是一个 10 分钟的纸笔测验，涵盖记忆、语言、执行功能、视觉空间技能、计算、抽象、注意力、集中力和定向力等 8 个认知领域。得分低于 26 分可认为存在认知功能障碍(若受教育年限小于 12 年，总分加 1 分)。

研究表明，蒙特利尔认知评估量表在检测轻度认知功能障碍方面优于简易智能精神状态量表，因为后者在多项研究中显示出较低的灵敏度[20]-[22]。与简易智能精神状态量表相比，蒙特利尔认知评估量表的记忆测试涉及更多的单词、更长的回忆延迟，这可能是其高灵敏度的原因。此外，蒙特利尔认知评估量表在检测阿尔茨海默病患者的轻度认知障碍方面，尤其是在检测阿尔茨海默病患者和其他疾病相关的认知障碍方面更为敏感。此外，蒙特利尔认知评估量表在区分阿尔茨海默病轻度认知障碍患者与健康对照组方面，也具有极高的灵敏度和特异性[23]。

因此，对于存在认知功能障碍但日常生活活动(Activities of Daily Living, ADL)未受影响的受试者，首选蒙特利尔认知评估量表进行评估；而对于认知功能和日常生活活动均受影响的受试者，应首先使用简易智能精神状态量表进行评估，如结果正常，再使用蒙特利尔认知评估量表进一步评估。

3. 衰老相关认知功能障碍发病机制

3.1. 氧化应激

1956 年，Denham Harman 教授提出了关于衰老的自由基理论，认为衰老过程中的退行性变化是由细胞正常新陈代谢过程中产生的自由基所介导的[24]，在众多衰老学说中，这是迄今为止最具影响力的学说。在机体的代谢活动中会产生活性氧(Reactive Oxygen Species, ROS)并生成自由基。自由基的生成是一个正常且有益的代谢活动，有助于维持细胞在生理范围内的功能、自我保护和生存[25] [26]。然而，活性氧的生成和中和失衡可能导致活性氧中间产物的积累，这些产物被认为是有害的，可能会打破正常状态下，活性氧和自由基之间氧化和抗氧化的平衡状态，进而引发氧化应激(Oxidative Stress, OS) [27]。氧化剂——抗氧化剂系统之间的不平衡决定了细胞损伤的程度。氧化应激被认为是衰老相关神经退行性疾病的重要机制[28]，并在神经元损伤的过程中发挥关键作用[29]，活性氧通过破坏氧化还原反应导致神经元损伤，具体表现为抗氧化酶(如超氧化物歧化酶和过氧化氢酶)活性的降低，以及抗氧化剂(如抗坏血酸和生育酚)水平的下降，这都会导致活性氧过剩[30]。此外，氧化应激还会诱发线粒体信号异常(如活性氧信号的调节异常) [31]，进而导致线粒体的动态平衡被打破，并造成年龄依赖性细胞损伤[32] [33]。活性氧的不断产生会降低清除酶的活性，使细胞处于过氧化状态，从而导致细胞衰老[34] [35]。据报道，线粒体超氧化物歧化酶和过氧化氢酶的耗竭会导致小鼠氧化应激，从而导致过早衰老[36]。

3.2. 炎症反应

衰老过程中在没有感染的情况下发生慢性的、低级别的、全身性的炎症被称为炎症性衰老，这是衰老的一个基本属性[37]。炎症性衰老这一概念由 Claudio Franceschi 教授在 2000 年提出，他试图利用网络

理论来理解压力因素如何影响其自身的反馈机制，以及它们对衰老的共同影响[38]。自此，“炎症性衰老”这一概念成为老年科学最重要的理论之一，也被认为是老年相关疾病(Age-Related Diseases, ARD)的主要原因之一[39] [40]。在衰老过程中，炎症机制被证明在神经退行性疾病、认知功能障碍和记忆力减退的发展过程中起着核心作用[41]-[43]。炎症因子穿过血脑屏障，导致海马体萎缩、小胶质细胞活化、氧化应激增加和突触功能减退，从而造成认知障碍[44] [45]。研究证实，在低剂量的内毒素作用下，促炎因子的升高会导致人类[46]和小鼠[47] [48]的认知功能障碍，这也证实了全身性炎症在认知功能下降中的致病作用。此外，Moon 等人的研究发现，通过给予痴呆症模型小鼠 6-姜烯酚减少海马内小胶质细胞和星形胶质细胞增生，能够提高海马的神经生长因子水平和突触前后标记物，改善记忆损伤。这表明，减轻神经炎症可缓解认知功能的下降[49]。

3.3. 突触可塑性减退

几十年前，人们普遍认为衰老相关认知功能障碍与参与记忆和学习过程的大脑区域，如内侧颞叶的神经元细胞的死亡有关。然而，神经细胞突触可塑性机制改变的假说如今已被更为广泛地接受。突触可塑性是指神经元连接强度发生变化的能力，这一机制长期以来被认为是学习和记忆的核心组成部分，主要表现为长时程增强作用(Long-Term Potentiation, LTP)和长时程抑制(Long-Term Depression, LTD) [50]。在与学习和记忆有关的大脑区域，如海马和前额叶皮层，已经有研究者观察到突触的数量和功能发生的变化[51] [52]。此外，研究发现与年轻大鼠相比，老年大鼠的长时程增强作用的诱发阈值更高[53] [54]。Dieguez 等人进一步证实，与年轻大鼠相比，在衰老大鼠的脑组织中维持齿状回(Dentate Gyrus, DG)和海马 CA3 区细胞中的长时程增强作用变得更加困难，这表明随着年龄的增长，长期记忆形成的基础——晚期长时程增强作用会下降[55]。此外，随着钙离子浓度的升高，老年大鼠在海马 CA3 区和 CA1 区之间的突触更容易诱发长时程抑制作用[56]。O’Riordan 等人的研究也已经证实 β-淀粉样蛋白(Amyloid β-Protein, Aβ)会促进大鼠左侧海马长时程抑制作用[57]。因此，在衰老过程中观察到的突触可塑性的衰退可能会影响到大脑的认知功能，这种变化可能与 α-氨基-3 羟基-5 甲基-4 异恶唑受体(AMPAR)的转运失调有关[58]。这些研究表明，突触可塑性相关蛋白的表达变化可能成为衰老的生物标志物。因此，通过调节突触可塑性，有望对认知功能产生积极影响。

3.4. 表观遗传修饰

表观遗传修饰是指对基因表达的调控，通过化学修饰改变染色体上的 DNA 和蛋白质，从而影响基因的表达，对生物体的发育、生长、分化和繁殖等过程起到重要作用。表观遗传修饰通过 DNA 甲基化、组蛋白修饰和非编码 RNA (Non-Coding RNA)在衰老和衰老相关疾病中发挥关键作用[59]。

DNA 甲基化是在 DNA 甲基转移酶(DNMTs)，包括 DNMT1、DNMT3A 和 DNMT3B 的催化作用，形成 5-甲基胞嘧啶(5-mC)，从而导致基因沉默[60]。在衰老过程中，基因组的甲基化程度普遍较低[61]。随着年龄的增长，DNMT1 的表达减少，这会导致 DNA 甲基化水平下降[62]。相反，DNMT3A 和 DNMT3B 的表达会随着年龄的增长而增加，这有助于哺乳动物细胞中 CpG 岛的从头甲基化[63]。因此，DNA 甲基化在衰老过程中发挥着重要作用。

组蛋白修饰可激活或抑制基因表达，并调节衰老过程。组蛋白修饰的类型包括甲基化、乙酰化、磷酸化、泛素化等[64]。其中赖氨酸残基的甲基化和乙酰化是目前研究最为广泛，也是已知明确会影响衰老过程的修饰。有研究表明，H3K9me3、H4K20me3、H3K27me3 和 H3K9ac 的水平在衰老过程中均会发生变化[65]。

越来越多的研究表明，非编码 RNA 在衰老中也发挥着关键作用。近年来，有关非编码 RNA 在衰老

中的作用的研究主要集中在微小 RNA (miRNA) [66]。微小 RNA 长度约为 22 个核苷酸，是非编码单链短 RNA，与目标 mRNA 的 3′-UTR 结合，以降解这些 mRNA 或抑制其翻译。研究人员利用包含 863 个微小 RNA 的微阵列发现，与年轻人相比，长寿人群中有 64 个微小 RNA，如 miR-30d 和 miR-339-5p，上调，16 个微小 RNA，如 miR-107，下调[66]。此外，在衰老过程中，微小 RNA-p53 通路可以维持长寿人群基因组的完整性[66]。评估微小 RNA 在衰老过程中的作用，应用最广泛的模式生物是秀丽隐杆线虫(*C. elegans*)。研究表明，靶向调控转录因子 lin-14 的微小 RNA lin-4 不仅在秀丽隐杆线虫的发育过程中是必需的，而且在衰老过程中也是必需的[67]。

4. 衰老相关认知功能障碍的预防和治疗

4.1. 衰老相关认知功能障碍的预防

不存在脑老化或认知功能障碍相关的病理变化和分子标记的大脑被称为“健康”的大脑。控制可改变的风险因素对延缓或预防衰老相关认知功能障碍起着至关重要的作用。

2020 年柳叶刀(The Lancet)委员会共确认了 12 个可改变的痴呆症风险因素：受教育程度低、高血压病、听力受损、吸烟、肥胖、抑郁、缺乏运动、糖尿病、社会交际少、酗酒、脑外伤和空气污染。理论上，控制这些风险因素可以大大降低认知功能障碍的风险[68]。研究表明，这些可改变的风险因素确实可能会导致大脑老化和认知功能的下降[69] [70]。因此，将加强健康教育放在首要位置对于衰老相关认知功能障碍的预防至关重要。

4.2. 药物治疗

对于轻中度患者，临床上主要使用多奈哌齐等胆碱酯酶抑制剂，通过抑制突触间隙中的乙酰胆碱酯酶，减少从突触前神经元释放到突触间隙的乙酰胆碱的水解来缓解症状[71] [72]。然而，随着年龄的增长，活跃神经元的数量会减少，这使得胆碱酯酶抑制剂的效果大大降低。此时往往使用 N-甲基-D-天冬氨酸(NMDA)受体拮抗剂，具有代表性的药物是美金刚，它可以拮抗 NMDA 受体并调节谷氨酸的活性，用于治疗晚期疾病患者[72] [73]。虽然这些药物可以缓解认知功能障碍并改善生活质量，但过去多年的证据表明，这些药物对疾病的发生或发展并没有显著影响[74]。

4.3. 非药物治疗

越来越多的证据表明，坚持参与认知要求较高的活动可以预防认知功能下降。该现象通常用“认知储备”这一概念进行解释，它通常被描述为一种缓冲或抵消的力量，可以减轻导致机体功能障碍或退化的不良因素的影响[75]。这一观点认为，认知功能在面临挑战时会使知识和概念的神经表征更强大、分布更广泛，从而减少与疾病相关的组织退化所造成的功能性后果。这种“挑战”可以通过各种与生活方式相关的活动或技能来实现，比如抗阻运动、以瑜伽和舞蹈为代表的协调运动、音乐和语言学习，这些干预措施可预防或逆转认知能力下降[76] [77]。

5. 结语

随着年龄的增长，身体机能逐渐下降，尤其是脑部的老化尤为明显。衰老相关认知功能障碍是氧化应激、炎症性衰老、突触可塑性和表观遗传修饰等多个机制共同作用的结果。目前，临床上常用蒙特利尔认知评估量表和简易智能精神状态量表进行筛查和病情评估，同时，胆碱酯酶抑制剂、N-甲基-D-天冬氨酸受体拮抗剂等药物与运动、音乐等非药物治疗手段也被广泛应用。然而，最为关键的仍然是早期的预防。尽管如此，衰老相关认知功能障碍的发病机制仍需要进一步探索，特别是在早期筛查、干预措施

和新药物研发方面仍有许多待解决的问题。本综述虽对衰老相关认知功能障碍的定义、诊断和评估、发病机制、预防和治疗手段进行了探讨，但仍存在一定局限性。由于篇幅和主题的限制，本文主要聚焦于发病机制与治疗策略，未能充分涉及一些重要领域。例如，神经影像学在认知功能障碍早期诊断中的潜力尚未被完全挖掘，特别是脑结构和功能变化的早期检测仍有待进一步研究。同时，随着人工智能技术的发展，基于大数据的认知干预手段将成为未来研究的重要方向。尽管面临诸多挑战，公众对认知功能衰退的认识和关注需要进一步加强，以更好地应对衰老带来的社会挑战。通过不断深入探索衰老相关认知功能障碍的发病机制，结合现代医学的各项研究成果，并融入社会健康干预措施，未来有望为广大老年群体提供更为有效的干预手段和治疗选择，从而减缓衰老进程、提高生活质量，并为应对日益严峻的老龄化社会提供可持续的解决方案。

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