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衰老过程中行为和认知功能退化的调控机制研究

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摘要: 随着人类预期寿命延长, 人口老龄化问题越来越严重。过去几十年关于衰老的研究使人们对长寿的生物学机理有了一定的认识, 然而延长寿命应以保持老年个体健康的行为和认知功能为前提, 近期研究显示延长寿命不一定延缓衰老过程中的行为和认知功能退化。衰老相关行为退化的调控机制目前知道的还很少, 如何实现老年人口健康的衰老是现代社会极具挑战也是迫切需要解决的问题。衰老过程伴随着明显的认知等行为的退化, 过去的研究对这些功能的退化进行了比较详细的描述, 包括情节记忆、工作记忆、信息处理速度等认知功能的衰退, 运动能力降低, 节律紊乱等。随着神经科学与技术的发展, 越来越多的研究集中到大脑的结构和功能随衰老的改变。本文在简单描述衰老过程中行为功能退化现象的基础上, 主要对大脑结构和网络连接、神经元形态和功能、大脑基因表达以及一些保守的生物学信号通路等方面在衰老过程中的改变的研究进展展开综述性介绍, 重点关注这些变化与行为和认知功能退化之间的联系。目前大部分的研究结果还只建立了这些变化与行为和认知功能退化的相关关系, 因果关系的确立还有待进一步的研究。相信更多对衰老过程中行为和认知功能退化的调控机制的研究将对改善老年人的生活质量有极大帮助, 同时对寻找预防神经退行性疾病发生的方法也有指示作用。

关键词: 衰老; 认知功能; 行为退化; 突触; 神经递质; 线粒体; 氧化压力; 表观遗传

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The regulatory mechanisms of behavioral and cognitive aging

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Abstract: With the increase of life expectancy, the world's population is aging rapidly. Previous work in the field of aging greatly increases our understanding of biological mechanisms underlying longevity. Researchers have unraveled a number of longevity pathways conserved from yeast to mammals. However, recent evidence shows that mechanisms regulating the life span and those regulating age-related behavioral decline could be dissociated. The regulatory mechanisms underlying behavioral and cognitive aging is largely unknown. Previous work has described a significant age-related decline in cognitive behaviors including episodic memory, working memory, processing speed, as well as motor function deterioration and circadian dysfunction. With the advance of neuroscience and technology, more and more studies have focused on the age-related changes in structure and function of the brain. In this review, we briefly describe the deterioration of cognitive function and other behaviors in the aging process, and survey the role of age-related changes in brain structure and network, neuron morphology and function, transcriptome in brain and some conserved biological pathways on age-related cognitive and behavioral decline. Further studies on the mechanisms underpinning age-related cognitive and behavioral decline may provide clues not only for improving the quality of life for the ageing population, but also for developing intervention approaches for neurodegenerative diseases.

Keywords: aging; cognitive function; behavioral deterioration; synapse; neurotransmitter; mitochondrion; oxidative stress; epigenetic

随着年龄增加, 人们的各项生理功能逐渐退化, 其中认知等各种行为功能的降低是衰老最为明显的特征之一^[1,2]。现代社会, 人们的平均寿命大幅度提高, 人口老龄化也日益严重。根据国家统计局数据, 到 2019 年末, 我国 60 岁及以上老年人口已有 2.54 亿, 占总人口的 18.1%; 预计到 2050 年, 我国社会将进入深度老龄化阶段, 60 岁及以上人口占总人口比例将超过 30%。除此之外, 我国失能老人的总数和比例也在不断增加。失能老人是指失智或行动不便, 丧失生活自理能力的老人。据国家统计局数据, 到 2020 年我国大约有 4190 万失能老人, 到 2050 年这个数字将增加一倍到 9700 万。这将严重影响着老年人的生活质量, 给家庭和社会带来巨大压力。衰老是阿尔兹海默病(Alzheimer's disease, AD)等神经退行性疾病的最主要风险因素。因此, 如何实现老龄人口健康地老去, 减少失能老人的数量, 预防老年性疾病的发生是现代社会极具挑战, 也是迫切需要解决的问题。

科学意义上的衰老研究历史始于 1935 年, 科学家发现节食可以延长大鼠(*Rattus*)寿命^[3], 这说明衰老是一个可调节的过程。随着实验方法的发展, 人们对于衰老的理解逐渐丰富, 科学家相继提出了很多理论试图解释衰老。20 世纪 50 年代提出的衰老进化理论认为进化会选择对生命早期发育和生长繁殖有利的基因突变, 然而这些突变在生命晚期则会加速衰老^[4]。1961 年, 美国科学家 Hayflick 博士发现细胞老化现象即细胞的分裂能力是有限的, 经过有限次数的分裂之后细胞就进入老化时期, 这种现象也称为“海弗利克极限”^[5]。人们进一步发现正常细胞每经过一次有丝分裂, 位于染色体末端的端粒会随之逐渐缩短, 当端粒长度缩短到临界水平的时候细胞便停止分裂进入老化阶段^[6]。20 世纪 50 年代之后, 现代生物学理论对衰老的解释主要归为两类: 程序性和损伤/错误累积理论。程序性理论认为衰老就像发育过程一样遵从从一个程序性的生物学时间表, 这个过程依赖于时序性的开启或者关闭特定

基因的表达来控制衰老。损伤/错误累积理论则认为衰老是随机的,不可控的过程,环境因素对细胞和分子逐渐侵蚀破坏,导致损伤累积,进而引起衰老。尽管科学家们提出了上百个理论来解释衰老,还没有一个单独的理论可以全面的解释衰老过程^[7]。随着分子生物学的发展,从20世纪90年代开始衰老研究进入基因时代,1983年美国科学家 Klass 首先在模式动物秀丽隐杆线虫(*Caenorhabditis elegans*, 简称线虫)中发现有些基因突变的线虫相对野生型线虫存活时间更长^[8]。后来美国科学家 Kenyon 教授发现单个基因 *daf-2* 突变可以使线虫寿命延长一倍^[9]。接下来的30年,科学家发现了上百个长寿基因,大部分这些基因从酵母到哺乳动物中都是保守的,它们参与到不同的信号通路^[10]。人们对于寿命的调控机制有了一定的认识。

值得注意的是,衰老不仅仅包括寿命,还伴随着行为和认知功能的退化。最近的一些研究表明并不是所有长寿途径都能改善衰老的行为退化^[11,12],这暗示机体对行为退化和寿命的调节可能存在不一样的调控机制。然而,对于认知和行为退化的分子机制目前人们知道的还很少,是衰老研究领域的重点和难点。本文将综合介绍行为和认知功能的不同方面在衰老过程中发生了怎样的变化;这些变化与大脑中的结构和神经元的功能之间有着怎样的联系;哪些分子细胞调控机制可以解释这些变化;目前的研究发现了哪些可以延缓行为和认知功能退化的方法等研究进展。

1 衰老过程中行为和认知功能的退化

正常衰老过程中人类(*Homo sapiens*)的行为衰退包括认知能力退化,运动能力降低,睡眠和节律紊乱等等(图1)。认知是通过感觉、经验以及思考获得知识并指导日常活动的过程,包涵很多方面,比如学习、记忆、决策、注意和执行能力等^[2]。当人们老的时候可能会变得更有智慧,但也会经历记忆力变差,反应变慢的情况。这也反映了衰老过程中认知功能的不同方面随衰老的变化并不是统一的,认知能力在衰老过程中的变化主要分为两种类型:一类如情节记忆、短期工作记忆、信息处理速度以

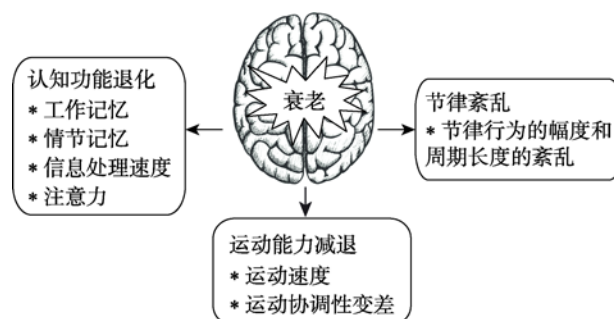


图1 衰老过程中认知和运动等行为的退化

Fig. 1 Age-related decline in cognitive, motor and circadian behaviors

正常衰老过程中人类的行为衰退包括认知能力退化,运动能力降低和节律紊乱等。认知功能的衰退主要包括工作记忆、情节记忆、信息处理速度以及注意力等在衰老过程中显著退化。运动能力减退主要是运动速度减缓和运动协调性变差。节律紊乱主要表现为节律行为的幅度和周期长度的扰乱。大脑是行为和认知功能的控制中心,大脑衰老导致了这些行为功能的退化。

及注意力等在衰老过程中显著降低,另一类以知识和经验为代表的语义记忆和内隐记忆在衰老中相对保持不变^[2,13,14]。情节记忆可以使个体记录、存储并检索关于自身经历的情景。不同的研究均表明情节记忆在衰老过程中是下降的^[15],而且被认为是正常衰老过程中下降最为明显的一类长期记忆^[16]。在猕猴(*Macaca mulatta*)、大鼠和小鼠(*Mus musculus*)中也一致发现情节记忆的下降^[17]。工作记忆是暂时性存储和处理信息用于后续复杂决策等的认知行为过程,是一类易受衰老影响的认知行为^[2,14]。在猕猴中的工作也表明工作记忆在衰老过程中会显著降低,而且主要是由于前额叶皮层的一类延迟神经元发放减弱导致^[18]。工作记忆主要依赖于前额叶皮层,这个脑区相对于其他脑区对衰老更为敏感,人们认为这个脑区在老年个体的缺陷导致了工作记忆能力在衰老时下降。此外,很多研究认为工作记忆的缺陷对衰老相关长期记忆、解决问题能力以及决策能力的退化有重要影响^[19]。执行能力是一系列认知过程的组合,支持个体为新的情境或目标组织资源,调整策略,作出适应性的行为调整。复杂的认知功能依赖于一系列的执行能力,大量研究表明执行能力在衰老过程中的退化是很多认知功能退化的重要原因^[20]。额叶纹状体回路在衰老时候的变化,可能是执行能力退化的主要原因^[21]。信息处理速度反映的是刺激引起运动反应的过程,大量研究表明信息处理速度

在 30 岁左右开始下降,并在后续的生命过程中持续降低^[13]。纵向分析个体从 20 岁到 60 岁之间认知能力变化,发现信息处理速度是受衰老影响最大的一个模块^[22]。信息处理速度的降低或许可以解释为什么老年人需要花更多的时间来学习新的知识。注意力的退化表现为老年人对于一项任务中令其分心的信息更加难以忽略。老年人同时处理两项或多项信息,或者同时完成多项任务的能力随年龄增加而明显降低,尤其是当任务复杂度增加的时候这种能力下降显得更加明显,这也反应大脑处理资源的能力在正常衰老过程中是下降的^[23]。

有一些认知能力在衰老过程中并不表现出随衰老而退化的现象,而是能够得到很好的维持,甚至随年龄增长还有所增加。语义记忆主要是关于一般事实和知识的记忆,研究发现语义记忆在衰老过程中不会下降,甚至在 55 岁以后会有略微增加^[24]。内隐性记忆包括程序记忆,它的形成和使用是无意识的,内隐记忆受衰老的影响也很小^[13]。此外,情感调节的能力在衰老过程中反而会得到加强,老年人情感稳定性明显提高,这可能与内侧前额叶系统的可塑性有关^[25-27]。

运动功能在衰老过程中也易受影响。运动功能的下降在各个物种中都是保守的^[17]。相对于年轻个体,老年个体的运动速度和协调控制能力会降低。研究表明衰老时运动速度会有大约 15%~30% 的下降,这可能与大脑信息处理速度在衰老时的衰退有关^[28,29]。老年个体运动的协调性变差,如平衡能力和步态出现问题,这是老年人跌倒并导致疾病和损伤的主要风险因素之一^[30]。并且老年人很难同时处理多个动作,这种现象与小脑缺陷的病人相似,说明衰老过程中小脑的退化可能对运动失调有贡献^[29]。当然衰老过程中运动能力的退化除了与大脑内中枢神经系统的失调相关以外,周围神经系统和肌肉系统的退化也有贡献。

衰老过程中节律紊乱主要表现为节律行为的幅度和周期长度的扰乱。动物的节律行为主要受大脑的视交叉上核(Suprachiasmatic nucleus, SCN)脑区控制。有报道显示在大鼠中,随年龄增加 SCN 脑区的神经元会减少^[31];而猕猴中的研究则发现该脑区的神经元数目并没有减少^[32]。在哺乳动物中节律行为

受一系列节律基因的控制,如正向转录调节基因 *Clock*、*Bmal1*, 负向转录调节基因 *Cry* 和 *Per*^[33]。近期的研究发现在小鼠的 SCN 脑区中, SIRT1 参与调控了中枢节律控制行为,大脑中 *Sirt1* 和节律基因的表达随衰老显著降低^[34]。在大脑中特异性敲除 *Sirt1* 使小鼠表现出衰老相似的节律紊乱行为,而在小鼠大脑中过表达 *Sirt1* 则可以保护衰老相关的节律失调;其作用机制是 SIRT1 可以直接结合并调控节律基因的表达^[34]。

2 行为和认知功能退化的调控机制

2.1 大脑结构和网络在衰老过程中的变化

早在 20 世纪 30 年代开始就有研究描述衰老过程中的认知功能退化,而直到近 50 年随着技术和神经学科的发展,人们对行为和认知退化的研究集中到了神经科学的机制方面^[35]。大脑是行为和认知功能的控制中心,大脑衰老导致了这些行为功能的退化,衰老过程中大脑的结构,神经元之间的连接和功能也发生了明显的变化。

脑成像技术如正电子发射计算机断层显像(positron emission tomography, PET)和功能核磁共振成像技术(functional magnetic resonance imaging, fMRI)的发展,一方面促进了对大脑结构的理解,另一方面对正在执行认知测试任务的个体进行大脑成像可以帮助人们了解哪些脑区参与了这种行为,在衰老过程中参与这一行为的脑区和神经元的活动有哪些变化。从整体上看,大脑不同脑区的活动以及互相之间的功能连接在衰老过程中出现扰乱,主要表现为在某些任务中,老年人的大脑活动在局部脑区相对于年轻人有减弱;另一方面,面对同一任务,老年人所调用的脑区和年轻人相比有很大区别,这些可能与行为退化有关。比如完成执行能力相关的任务过程中,年轻个体的前额叶皮层左侧区域会出现很强的活动,而在老年个体中该区域的活动很低^[36,37]。另外在完成策略编码的任务过程中,表现较好的老年人的双侧前额叶皮层都会激活,而年轻人以及任务中表现较差的老年人,则只有左侧的前额叶皮层会激活^[38]。这暗示老年大脑运用一种补偿

机制以更好地完成认知活动。正常衰老过程中, 前额叶皮层结构和网络上的改变看起来对衰老相关的多种记忆功能的降低有重要贡献。这种大脑高级系统活动的变化可能与很多因素有关, 如突触密度、神经元活动、兴奋性和抑制性连接强度、神经递质的结合强弱随衰老的改变, 以及包裹在神经元轴突周围的髓鞘在衰老过程中出现损伤^[13,39]。对大脑结构的研究表明衰老过程中大脑体积的减少并不是均匀地发生在全脑, 人们发现最先在衰老过程中看到变化的脑区是前额叶皮层, 其次是内侧颞叶, 顶叶皮层和小脑^[20]。枕叶皮层的体积在衰老过程中没有明显变化。额叶皮层体积的减少与执行功能的减弱、情节记忆和工作记忆的退化等密切联系^[19,40]。

2.2 神经元形态和功能在衰老过程中的变化

近期的研究发现, 大脑体积在衰老时减少的主要原因并不是神经元死亡, 而可能是树突分枝和突触形态以及密度的改变^[41]。海马以及旁边的内侧颞叶在情节记忆等长期记忆中作用非常重要, 研究显示正常衰老过程中在人^[42,43]、非人灵长类^[44,45]、以及大鼠^[46,47]的海马和新皮层并没有明显的细胞死亡, 而海马区的神经元丢失是阿尔兹海默病的一个显著特征。衰老过程中前额叶皮层的神经元似乎更容易受衰老的影响。有报道显示在年老的非人灵长类中, 虽然背外侧前额叶皮层没有明显的神经元丢失^[48], 前额叶皮层的8A区则有明显的神经元减少(~30%), 这种减少还与工作记忆的缺陷有非常显著的相关性, 而前额叶皮层的46区神经元数目则保持不变^[49]。在人^[50~52]、非人灵长类^[53]和大鼠^[54]的前额叶皮层检测到锥体神经元的树突分枝减少, 而海马一些亚区的神经元树突分枝在衰老过程中并没有出现明显的变化^[41]。在人^[55,56]、非人灵长类^[57]和啮齿类^[58~60]中的研究一致的发现小脑浦肯野细胞在衰老过程中会减少, 浦肯野细胞的树突分枝会出现回缩^[61,62], 这些可能与年老个体运动功能变差等有关。

大量研究发现, 人和其他哺乳动物大脑中神经元的突触密度随衰老减少, 然而并非所有脑区突触对衰老的敏感程度都是一样的, 前额叶皮层以及海马区的突触变化相对其他脑区要更加明显, 这也能解释为什么这两个脑区所调控的行为在正常衰老过

程中退化更为明显^[41]。前额叶皮层突触密度的改变主要表现为大量的轴棘突触减少, 尤其是瘦小型的树突棘组成的突触, 灵长类第三层神经元轴棘突触丢失的程度与认知缺陷的程度显著相关^[63,64]。由于瘦小型树突棘是易于动态变化的, 衰老过程中这种类型突触的减少可能对工作记忆和执行能力等这些灵活度要求高的认知行为影响较大。比如在猕猴中在体记录前额叶皮层的神经元活动, 发现有一类在工作记忆中延迟发放的神经元的发放频率从中年时期开始减弱, 到老年时期减弱更为严重, 这种延迟神经元的发放减弱可以通过抑制 cAMP 信号, 或者抑制某些亚型的钾离子通道而得到部分恢复^[18]。电镜结果显示参与抑制这一信号通路的基本蛋白复合物组分都出现在瘦小型树突棘^[65], 暗示衰老相关瘦小型树突棘的丢失在工作记忆的退化中起重要作用。研究显示衰老过程中海马的很多亚区突触形态和密度有明显改变, 如猕猴海马下托区的突触密度减少明显^[66]; 大鼠 CA3 区分子层的突触密度明显减少^[67], CA1 区的突触数目虽没有随年龄增加而减少^[68], 但该区域突触后致密区的大小的减少与空间学习记忆的缺陷有很好的相关性^[69]。与正常衰老不同, CA1 区突触数目的减少是早期 AD 的一个显著特征^[41,70]。海马区主要与形成长期记忆有关, 因此突触也从简单的轴棘突触转变为复杂的穿孔突触和多突触轴突棒头。与前额叶皮层不同, 在海马中是复杂型的突触更容易受衰老影响。大鼠齿状回的穿孔突触减少以及猕猴齿状回的多突触轴突棒头减少与海马相关的认知行为退化有关^[66,71,72]。观察小鼠小脑浦肯野细胞的突触结构在衰老过程中的变化也发现树突棘和突触密度都有减少^[73]。在人、猫和大鼠中一致发现, 纹状体的突触数目随年龄增加而减少, 其形状相对于年轻个体也会有所改变^[74~76]。对大鼠杏仁核的研究显示, 这个脑区的突触密度并不会随年龄增加出现变化^[77,78], 这可能与老年个体情感功能的维持有密切关系。

衰老过程中除了突触形态和密度会发生改变, 突触功能也有明显的变化, 包括突触连接强度、可塑性和神经递质信号的减少等。与海马区形态学观察到的结果一致, 老年大鼠齿状回记录到的兴奋性突触后膜电位减少^[79,80]。研究恒河猴的前额叶皮层

第二、三层椎体神经元的突触电生理特性发现,兴奋性突触后电流的频率在老年猴中显著降低,而抑制性突触后电流频率显著增加^[81],说明突触功能的衰退导致了大脑兴奋性和抑制性环路的失衡。线虫中的研究显示,突触传递过程在衰老时出现明显衰退,通过化合物刺激来提高突触传递的功能可以提高老年线虫的运动能力^[82]。这些结果都表明突触功能在衰老过程中出现缺陷。神经元形态、生理特性以及突触间连接强度的改变对衰老神经元可塑性的影响可以通过记录长时程增强(long-term potentiation, LTP)和长时程抑制(long-term depression, LTD)来反映,这方面的研究在大鼠的海马区开展得比较多。突触可塑性的变化主要表现为 LTP 的诱导和维持出现问题,老年大鼠的 LTP 的诱导阈值变高,而且 LTP 在维持阶段更快地衰减^[80,83],LTP 的衰减速度与空间记忆行为的表现相关。长时程抑制的结果与长时程增强是相反的,老年大鼠神经元对 LTD 更为敏感,表现为 LTD 的诱导阈值降低^[84]。这些结果提示老年个体更难形成新的记忆,也更容易忘记新形成的记忆^[85]。LTP 的形成和维持过程都依赖于钙信号,衰老大脑中钙稳态的失衡对神经元可塑性的缺陷有重要贡献^[86]。如在中老年小鼠中,可以通过抑制 L 型钙通道或者钙依赖的钙释放来恢复由于 LTP 功能缺陷而引起的记忆行为衰退^[87]。

神经递质是介导神经元之间信号传递的化学物质,神经递质系统在衰老过程会发生变化,这种变化与衰老过程中的行为和认知功能退化密切相关。比如衰老过程中多巴胺的水平在人和其他动物大脑中都是下降的^[13,88],使用多巴胺的前体物 L-DOPA 提高老年人多巴胺的水平,可以提高奖赏相关的学习行为的效率,并改变纹状体区域的脑活动状态^[89],说明多巴胺水平的下降是行为衰退的重要原因,提高多巴胺水平可能可以改善老年人认知行为表现。老年人大脑多巴胺的受体和转运体在前皮层和纹状体中表达都下降^[90],衰老时人纹状体中 D2 受体的降低比较明显,用正电子断层成像的方法发现 D2 受体的可用量与注意力等行为表现有关^[91]。给老年猕猴服用 D2 受体激动剂,可以缓解延迟记忆行为能力降低^[92]。5-羟色胺功能的下降和年老的时候认知、情感和睡眠等行为失常(如睡眠质量下降^[93]、性行为

衰退以及老年抑郁行为^[94])有密切关联。有关在正常衰老过程中 5-羟色胺水平的变化情况目前存在一些争议:在人的多个脑区没有检测到 5-羟色胺水平的明显变化^[95],在小鼠中则有所增加^[96];而在大鼠中,5-羟色胺水平在很多脑区如前皮层、纹状体和下丘脑等都是下降的,且老年大鼠前皮层和枕叶皮层 5-羟色胺水平的降低与记忆行为的缺陷密切相关^[97-102]。这种差异可能与不同研究中研究对象的年龄、性别、所检测的脑区及所用的检测方法不同有关^[103]。运用 PET 方法发现,人脑中的 5-羟色胺转运体在衰老过程中是下降的^[104,105];5-羟色胺的受体亚型较多,通过 PET 方法在体研究,发现人 5-羟色胺受体 1A 和 2A 在人的前皮层和海马是减少的^[94],5-羟色胺 2A 受体在尾状核和壳核也是减少的^[106]。我们实验室在线虫中的研究发现,衰老过程中线虫的多巴胺和 5-羟色胺水平都有明显下降,这两种递质的降低导致了咽喉肌肉跳动行为、雄虫交配行为以及线虫对食物响应行为的衰退,外加多巴胺和 5-羟色胺可以提高老年线虫的这些行为表现^[11],表明这两种神经递质在衰老时候的下降是相关行为退化的原因。

在哺乳动物的中枢神经系统中,谷氨酸是介导大部分兴奋性突触的神经递质^[107,108]。大量研究显示,谷氨酸参与的很多行为如学习记忆、动机和运动功能在衰老过程中有明显退化。老年人运动皮层的谷氨酸水平较年轻人的低^[109]。人纹状体区域的谷氨酸含量随衰老也有明显减少,且与一些复杂的认知和运动行为功能退化相关^[110]。研究大鼠大脑中谷氨酸含量在衰老过程中的变化,发现谷氨酸水平在前皮层和海马中有显著的降低,而在颞叶和枕叶皮层中没有明显变化,在纹状体的一些亚区中则是增加的^[111]。此外,大鼠中谷氨酸能神经末梢处的高亲和性谷氨酸转运体的表达水平随衰老而减少^[112,113]。在啮齿类中的研究发现,谷氨酸受体 N-甲基-D-天冬氨酸(N-methyl-D-aspartate, NMDA)受体在多个脑区如海马、前皮层和纹状体中随衰老明显降低^[114,115], α -氨基-3-羟基-5-甲基-4-异恶唑(α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA)受体在海马的一些亚区域也出现减少^[116]。NMDA 受体的激活对 LTP 的诱导具有重要作用,而 AMPA 受体则参与 LTP

的维持, 这两个受体在衰老过程中的改变对老年大脑的突触可塑性有重要影响。海马区细胞表面 AMPA 受体 GluR1 的下降程度与小鼠空间记忆行为表现变差的程度呈相关关系^[117], 另外 NMDA 和 AMPA 受体在海马区的减少与小鼠衰老时空间记忆功能缺陷呈正相关^[118]。这些研究表明谷氨酸介导的突触传递在大脑衰老过程中降低, 且与认知功能的退化密切相关。γ-氨基丁酸(γ-aminobutyric acid, GABA)是大脑中主要的抑制性神经递质, 与观察、注意等行为有密切关系^[119]。利用磁共振波谱分析发现人前皮层的 GABA 水平在老年时期持续降低, 且与运动和认知功能的缺陷密切相关^[120,121]。其他研究结果也发现正常衰老个体中前皮层的 GABA 水平较年轻时期有减少^[122]。GABA 递质系统的变化可能改变了大脑中抑制性和兴奋性神经递质之间的平衡, 脑成像研究中观察到的老年人前额叶皮层的脑活动增加也可能是由于抑制性神经递质减少导致的, 从而导致老年个体倾向于神经兴奋毒性^[1]。

近几十年来成像技术的发展促进了对大脑结构

和网络连接的理解。衰老过程中大脑体积减少主要发生在前额叶和海马区域^[123], 大脑中神经元的形态和功能在衰老过程中发生了一系列的变化, 包括突触密度减少和突触可塑性降低^[124], 还有神经递质系统的减少(图 2)。这些方面的变化在前额叶皮层和海马脑区更为明显, 对应这两个脑区调控的认知功能也是衰老过程中退化最为明显的。这些变化是由什么机制调控的, 又是如何导致行为功能衰退的, 还需要进一步的研究来阐明。

2.3 衰老过程中大脑基因表达的变化

通过全基因组基因芯片分析人大脑前额叶皮层的基因表达水平在衰老过程中的变化, 发现突触功能相关基因的表达变化最为明显^[125], 其中参与学习和记忆和突触可塑性的相关基因, 如 AMPA 受体的亚基 GluR1 (glutamate receptor 1, GluR1)及 NMDA 受体, 还有 GABAA 受体亚型都在中年以后表达显著降低。另外, 突触钙信号系统和囊泡运输相关基因的表达水平也有明显降低。其他一些重要生物学过

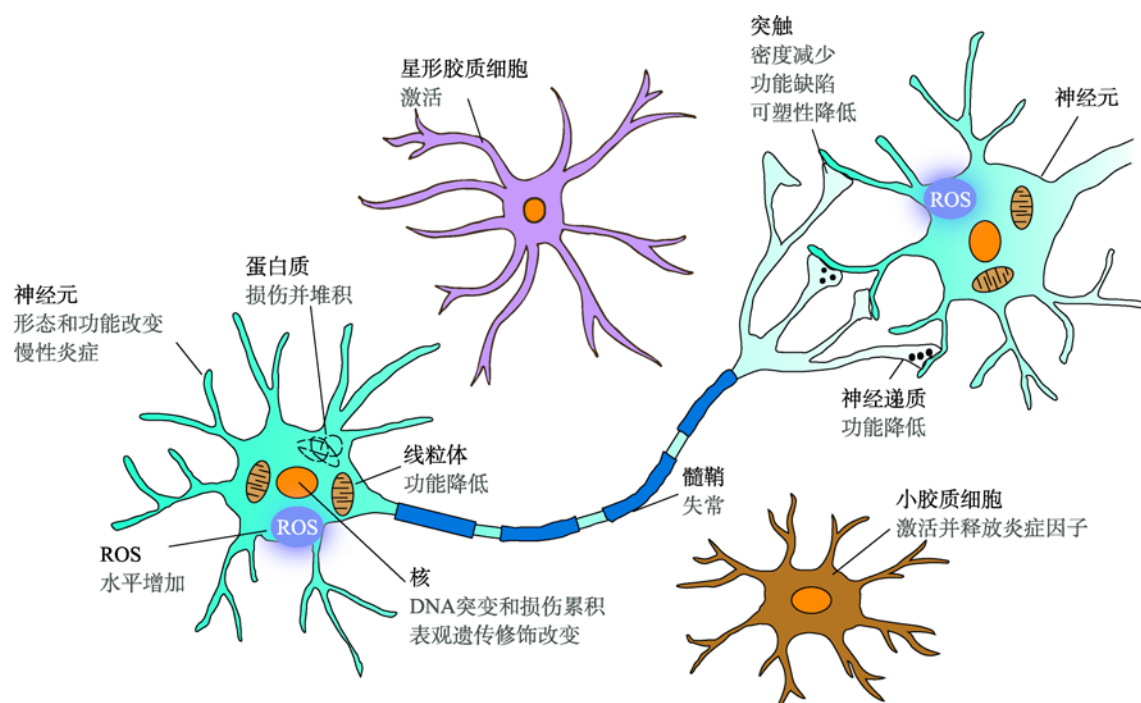


图 2 衰老过程中行为和认知功能退化的可能机制

Fig. 2 Possible mechanisms underpinning age-related cognitive and behavioral decline

衰老大脑内细胞、分子和功能发生明显改变, 是行为和认知功能退化的可能机制。神经元之间的连接改变, 主要是突触的密度减少、功能减弱、突触可塑性降低, 神经递质系统的功能降低; 神经元内线粒体功能降低, 氧化应激增加, 蛋白稳态失衡导致聚集的蛋白斑块堆积, DNA 甲基化和组蛋白表观遗传修饰等随衰老发生改变; 胶质细胞激活导致大脑神经元的持续慢性炎症。

程相关的基因也随衰老发生明显改变,如线粒体功能相关的基因表达下调,免疫调节和压力应答相关的基因表达上调,而且这些信号通路的基因在衰老过程中的表达变化在不同物种中都是相似的^[1,126]。表达下调的基因启动子区域的 DNA 损伤可能是导致这些基因在衰老中表达下降的原因^[125]。另外有研究荟萃分析多个人前额叶皮层基因表达数据库,也一致地发现突触传递相关基因的表达下调是该脑区衰老时最显著的特征,神经再生相关基因的表达降低,炎症和免疫相关过程的基因表达上调也是普遍现象^[127]。不同数据库对人海马等脑区的研究结果也显示,突触传递和可塑性相关的基因在衰老过程中表达下调,炎症和免疫应答相关的基因表达上调^[128]。此外,在非人灵长类^[129]、大鼠^[130]和小鼠^[131,132]的衰老大脑中这几个生物学信号通路相关基因的变化与人大脑基因表达变化趋势基本上是一致的(表 1)。蛋白组学分析的结果与转录组学的结果相似,衰老过程中猕猴海马脑区蛋白水平明显降低的主要有电子呼吸传递链的蛋白和胞质核糖体蛋白,而抗氧化蛋白的表达则增加^[133];小鼠海马和皮层中蛋白表达量受衰老影响最为明显的是线粒体功能、氧化压力、突触、核糖体功能等相关通路上的蛋白^[134,135]。

总体看来,不同物种大脑中的基因表达水平和蛋白水平受衰老的影响类似:响应氧应激的基因以及免疫炎症相关基因的表达显著增加,线粒体功能和突触传递相关基因的表达则显著降低。这暗示不同物种的大脑衰老可能具有非常保守的分子调控机制。其中突触功能相关的蛋白减少很可能导致了衰老动物中神经元之间的连接减弱,高级认知功能的缺陷。免疫应答和炎症相关的基因上调则暗示大脑可能处于长期的慢性炎症状态,尽管适度的免疫激活有神经保护的作用,但持续的慢性免疫炎症将

增加大脑的认知退化和神经退行性疾病发生的风险^[136]。线粒体是细胞的能量工厂,对神经元发挥正常功能至关重要,线粒体能量代谢相关基因的表达降低在认知功能障碍和 AD 病人中表现得更为明显^[137,138]。

2.4 保守的生物学信号通路在调节衰老相关行为和认知功能退化中的作用

2.4.1 线粒体功能和氧化应激

大脑是非常耗能的器官,成年人的大脑大约只占身体总重量的 2%,却消耗了大约 20%的总耗氧量。线粒体产生的 ATP 对神经元的存活、兴奋性形成和突触信号传递等功能至关重要。神经元中的线粒体还可以调节钙信号稳态、突触可塑性、细胞存活和死亡^[139]。线粒体功能降低是衰老的一个显著特征^[140],线粒体在衰老过程中的变化包括形态和功能的改变。近期的研究发现老年猕猴前额叶皮层神经元突触前末梢的线粒体形态由长管状转变为环状或者圈状,且环状线粒体的数目与工作记忆的表现有负相关关系^[141]。研究显示衰老过程中大鼠大脑中线粒体的总量没有明显变化,而线粒体的电子传递的效率有降低。线粒体电子呼吸传递链上不同的复合物对衰老的敏感程度是不一样的,复合物 I 和复合物 IV 的活性随衰老而降低^[142,143],而复合物 II 的活性在衰老过程中维持较好^[144]。电子呼吸传递链上的复合物 I 和复合物 IV 的活性降低与认知功能的衰退呈线性相关^[142]。线粒体氧化磷酸化的过程是产生氧自由基(reactive oxygen species, ROS)的主要来源,大量研究表明衰老过程中线粒体电子呼吸传递链的效率降低,线粒体功能减弱,导致副产物 ROS 的量增加^[145];另外,衰老大脑中抗氧化蛋白过氧化物歧化

表 1 衰老大脑中基因表达变化的主要特征

Table 1 Main features of gene expression changes in aging brain

基因类别	人	非人灵长类	啮齿类	果蝇或线虫
突触功能	下调	下调	下调	不变
线粒体功能	下调	下调	下调	下调
压力应答	上调	上调	上调(小鼠某些脑区中下调)	上调
免疫和炎症	上调	不变	上调	果蝇中上调

其中人、非人灵长类和啮齿类为大脑的基因表达变化,果蝇和线虫为整个生物体的基因表达变化。

酶(superoxide dismutase, SOD)、过氧化氢酶和谷胱甘肽的活性降低,导致清理 ROS 的能力在衰老中逐渐降低^[142,146],累积的 ROS 会进一步导致线粒体呼吸链上的蛋白复合物和线粒体 DNA 氧化损伤,进而导致线粒体功能继续失调^[142,147,148]。这样一个有害的反馈环路使得大脑中神经元这样耗能高的细胞对衰老特别敏感。提高线粒体功能可以改善年老动物的行为表现并能延长寿命,如在线虫中提高氧化磷酸化的辅酶 NAD⁺水平可以阻止衰老相关的线粒体功能衰退,并提高线虫的运动能力,延长线虫的寿命^[149]。最新的研究发现,通过给老年小鼠注射从年轻小鼠分离的线粒体增加了大脑和骨骼肌组织的 ATP 水平、降低了 ROS 水平,并且老年小鼠的认知和运动行为得到明显改善^[150]。

大量研究认为衰老过程中线粒体功能降低主要由于线粒体 DNA 突变累积所致^[151-153],在人类大脑衰老过程中线粒体 DNA 的突变确实是增加的^[154-156]。为了研究线粒体 DNA 突变是不是衰老的一个重要原因,科学家构建了表达突变形式的线粒体 DNA 聚合酶(该酶只保留了 DNA 聚合的功能,失去了校对修复功能)的转基因小鼠模型,该转基因小鼠表现出明显的早衰表型,如毛发减少、驼背、生育力下降并且寿命显著缩短,其线粒体 DNA 突变累积明显增加,但有意思的是 ROS 水平和氧化损伤水平并没有增加^[152,157]。值得注意的是这种转基因小鼠线粒体 DNA 突变累积的频率要比正常衰老过程中线粒体 DNA 突变累积的频率高得多^[148],另外衰老大脑是伴随有 ROS 水平增加、氧化损伤累积的,因此正常衰老过程中线粒体 DNA 突变所起的作用还有待进一步研究。我们实验室的工作发现表观遗传因子 BAZ2B 和 EHMT1 可通过抑制线粒体功能相关基因的表达,从而抑制线粒体功能^[158]。在衰老的大脑中这两个因子表达量增加,暗示衰老大脑中表观遗传的变化对线粒体功能缺陷有重要贡献。

衰老过程氧化应激和抗氧化之间的平衡对神经元维持正常结构以及发挥正常功能是必需的。衰老过程中氧化应激增加使神经元累积损伤和聚集的蛋白、损伤的线粒体、超氧化的磷脂、损伤的核和线粒体 DNA 等,导致细胞膜特性改变、酶和受体蛋白的功能受损、钙信号失衡和突触功能降低^[159,160]。研

究表明 L 型钙通道,以及 NMDA 受体氧化还原状态的改变可以影响细胞内钙稳态,从而影响海马区神经元的兴奋性^[161,162],并影响突触的可塑性^[163]。另有一些研究表明,抗氧化能力减弱,清理氧化损伤能力降低将导致行为等功能的加速退化。如在果蝇和小鼠中降低过氧化物歧化酶 SOD2 的水平会加速运动行为退化、损伤神经元 DNA 并诱导神经退行性疾病的发生^[164,165]。小鼠过表达细胞外 SOD1 可以增加海马神经元的可塑性,提高运动行为和空间学习行为的能力^[166]。另外大鼠海马中过表达 SOD1 也可以延缓认知功能的降低,然而氧化损伤的降低与认知行为的表现并没有很好的相关性^[167],暗示氧化损伤本身可能并不是导致行为和认知功能退化的主要原因,而与氧化还原信号相关的信号通路可能更为重要。近期有很多其他研究也对氧自由基的衰老理论提出了挑战。在线虫中的研究显示低水平的氧化胁迫反而可以延长寿命,如受抗霉素 A 或低浓度百草枯处理的线虫以及一些线粒体功能降低的突变线虫中,虽然 ROS 水平增加了,但其寿命却延长了^[168-170]。因此,虽然氧化水平增加,氧化损伤累积是大脑衰老的一个重要特征,但是氧化胁迫是如何影响行为和认知功能退化的,是衰老过程 ROS 水平增加导致了大脑功能受损,还是 ROS 作为细胞内信号分子参与的信号通路出现问题从而导致了大脑功能衰退,还有待更多的研究。

2.4.2 蛋白稳态

正常衰老过程中,蛋白质量控制系统如自噬和蛋白酶体系统功能降低^[171,172],大脑中聚集的蛋白斑块累积增加。在模式动物果蝇(*Drosophila*)和小鼠中,抑制自噬会引起神经退行性病变并缩短寿命,这种神经退行性病变同时伴随着泛素化的蛋白聚集^[173-175]。果蝇中提高基础的自噬功能可延长寿命^[176],而且研究发现一些长寿突变体通常都激活了自噬功能,自噬对这些长寿突变体的寿命延长是必需的^[177,178]。另外有研究表明影响线粒体自噬通路的基因 PINK1 和 PARKIN 的突变将引起神经退行性病变,如家族性帕金森病以及晚发性阿尔兹海默病^[179]。在小鼠模型中降低大脑蛋白酶体的功能,会增加一些蛋白的堆积,其中有些是之前报道在 AD 疾病中表达发生变

化的蛋白,并且小鼠的空间记忆功能受损^[180]。这些结果说明衰老过程中蛋白稳态失衡对认知和行为功能退化有重要贡献,而且可能是阿尔兹海默病、帕金森病等其他蛋白毒性的神经退行性疾病中蛋白出现折叠异常和聚集的重要机制^[181,182]。

2.4.3 慢性炎症

炎症相关的基因表达增加是不同物种大脑衰老过程中基因表达变化的一个共有特征,胶质细胞介导了大脑中的神经炎症反应^[183],衰老过程中星形胶质细胞和小胶质细胞激活的标志基因表达都明显增加^[184,185],如小鼠星形胶质细胞的标志性蛋白 GFAP^[186,187]。降低小鼠星形胶质细胞的 GFAP 的水平可以提高 LTP 和神经元存活^[188,189]。小胶质细胞是大脑中的免疫细胞,老年大脑中激活的小胶质细胞数目增加,具有更高的炎症标志水平,处于持续的慢性炎症状态^[190]。大脑中炎症因子变化的特点主要有白细胞介素(IL)1 β 、IL-6 以及肿瘤坏死因子等炎症因子增加,而 IL-10 和 IL-4 抗炎因子减少^[190]。长期的过多的神经性炎症可以导致神经元突触损伤^[191]、功能缺陷^[192,193]以及一些神经推行性疾病的发生^[194,195]。

2.5 行为和认知退化的遗传和表观遗传因素

虽然在动物模型中发现了上百个长寿基因,但科学家对人类的长寿机理了解并不多,目前主要发现了 *APOE* 和 *FOXO3A* 的遗传变异可能与人类长寿相关^[196,197]。关于认知和行为功能退化的遗传因素,近年有些研究将一些基因,如脑源性神经营养因子(brain-derived neurotrophic factor, *BDNF*)、载脂蛋白 E(apolipoprotein E, *APOE*)和儿茶酚-O-甲基转移酶(catechol-O-methyltransferase, *COMT*)与老年人的认知功能退化联系起来^[198,199]。*BDNF* 参与海马依赖的学习和记忆行为,它的表达水平在正常衰老过程中逐渐降低^[200],可导致衰老大鼠认知功能下降^[201]。*APOE* 基因位点的变异不仅与晚发型阿尔兹海默病有关,还与正常衰老的认知退化有关^[202]。*COMT* 是降解多巴胺、肾上腺素和去甲肾上腺素的关键酶,*COMT* 上的一个遗传变异会影响该酶的活性并与前额叶依赖的执行能力的退化有关^[198]。这些单个基因

对于衰老相关认知和行为功能的影响很小,由于认知和行为功能的退化是一个非常复杂的表型,可能有大量基因参与调控同一行为表型,而且很多认知行为是互相关联的,可能需要一个精细的基因网络的调控。现代测序技术的发展对寻找新的影响认知等行为功能退化的基因将会有很大帮助。

基于双胞胎的研究表明遗传物质的不同可能只能解释个体之间寿命差异的 20%~30%,至少有 70% 的寿命差异是受环境因素影响的^[203~205]。越来越多的研究表明个人所处的环境和生活状态,饮食习惯等对维持老年时候良好的行为功能,以及预防退行性疾病的发生有很重要的影响^[206,207]。环境因素明显影响着正常和疾病状态下的大脑衰老,表观遗传调控因子是联系环境因素和细胞信号的重要分子。虽然大部分衰老相关的表观遗传的研究结果主要是在外周组织获得的,大脑中表观遗传的特征也发生与衰老相关的变化。由于大脑中绝大部分的神经元在产前发育时期就已经脱离细胞周期,成为不再分裂的细胞,因此 DNA 甲基化、组蛋白修饰以及表观遗传组的其他分子对于维持整个生命过程中神经元的健康和功能非常重要^[208]。

衰老大脑中 DNA 甲基化和组蛋白修饰都发生了明显改变。DNA 甲基化主要发生在 CpG 双核苷酸位点。近年来随着 DNA 甲基化芯片和二代测序技术的发展,人们对不同组织和细胞 DNA 甲基化水平在生命过程中的变化有了比较全面的了解,发现特定位点的 DNA 甲基化水平与衰老有很大相关性,可以比较准确的预测个体的出生年代,还可以指示个体的生物学年龄以及衰老相关的风险因素^[209,210]。研究人大脑皮层 DNA 甲基化在衰老过程中的变化,发现 DNA 胞嘧啶甲基化水平在一些特定基因的启动子区域是增加的,这种增加会抑制突触信号相关基因的表达以及其他一些大脑功能^[211,212]。组蛋白乙酰化修饰是基因活化的标志,乙酰化修饰的降低会抑制被修饰基因的表达。老年人前额叶皮层中一些与 GABA 能神经信号传递、5-羟色胺信号以及线粒体功能相关基因的启动子远端区域,组蛋白乙酰化水平降低^[213]。啮齿类动物的研究也有类似的发现,海马区域与记忆形成和稳定相关的基因的 H4K12 乙酰化水平在老年小鼠中明显降低^[214]。这些基因上的

组蛋白修饰的变化将影响基因的表达水平, 进而影响神经元的功能以及信号传递。提高年老小鼠 H4K12 乙酰化水平可以恢复年老小鼠衰老相关基因的表达水平和学习能力^[215]。另有研究表明, 使用组蛋白去乙酰化酶(histone deacetylase, HDAC)抑制剂处理小鼠可以改善小鼠的长期记忆行为并增加海马的神经再生能力^[216,217]。目前已发现 HDAC 抑制剂对 AD 等多种神经退行性疾病的动物模型有神经保护和促进神经再生的作用^[218-222]。在早衰模型小鼠的大脑中, H4K20me1 和 H3K36me3 的水平在衰老的时候显著降低, 并伴随有抑制性的表观遗传标志 H3K27me3 增加^[223]。在果蝇的整体组织中 H3K9me3 和 HP1 蛋白是降低的, 但在头部组织中 H3K9me3 是增加的, 说明衰老过程中不同组织中的组蛋白修饰的变化是不一样的^[224]。

我们实验室的研究发现人大脑前额叶皮层 H3K9 甲基转移酶 EHMT1 和表观遗传识别因子 BAZ2B 的表达水平随衰老逐渐增加, 在 AD 病人的大脑中有进一步增加, 并且与疾病进程正相关。它们的线虫同源蛋白, 分别是 SET-6 和 BAZ-2, 可以结合到线粒体功能相关基因的启动子区域, 调控这些基因的 H3K9me3 甲基化修饰, 抑制线粒体功能相关基因的表达。敲除 *set-6* 和 *baz-2* 可以延缓线虫行为功能退化, 这是通过提高线粒体功能实现的。这种调控机制在小鼠中也是保守的, 敲除小鼠中的同源基因 *Baz2b* 可以阻止小鼠认知行为随衰老的退化^[158]。此外, 有其他研究支持这一发现, 在 AD 病人和 AD 模型小鼠的大脑中, EHMT1 的表达水平增加, 利用小分子药物抑制 EHMT1 蛋白功能可以改善 AD 模型小鼠的突触功能和学习记忆行为^[225,226]。

总的来看在衰老大脑中在神经元存活、突触传递以及学习记忆相关基因的启动子区域, 主要是促进基因表达的表观遗传修饰如组蛋白乙酰化、H3K36me3、H4K20me1 水平降低, 而抑制基因表达的表观遗传修饰如 DNA 甲基化、H3K9me2/3 和 H3K27me3 水平增加, 从而导致这些目标基因表达随衰老下降。目前关于大脑衰老的表观遗传组学图谱还不完整, 衰老中表观遗传的变化是如何调控行为衰退的仍很不清楚, 需要更多进一步的研究。由于表观遗传修饰的可逆性, 是否可以通过药物干预表

观遗传状态来改善老年人的认知行为是值得关注的。

3 延缓衰老相关行为和认知功能退化的方法

3.1 节食

自 1935 年首次报道节食可以延长寿命以来, 已有大量文献报道节食对衰老的调控作用, 在不同物种中节食都有延长寿命的作用^[227]。此外, 研究发现节食可以改善多种衰老相关认知功能的退化, 比如学习记忆行为。在人的研究中发现, 持续两年的轻度节食可以略微提高健康老年人的工作记忆^[228]; 另外, 三个月的节食提高了老年人的语言记忆, 但并没有明显改善其他方面与衰老相关的记忆退化^[229]。在灵长类中, 节食减轻了衰老过程中的大脑萎缩, 降低发病率^[230], 长期慢性节食提高了老年猴的工作记忆^[231]。在啮齿类中的研究发现大鼠经长期节食饲养可以改善年老时期的迷宫行为表现^[232], 此外给小鼠间歇性的节食饲养也可以增强中年小鼠的学习记忆, 促进突触可塑性, 增加某些脑区 NMDA 受体的表达^[233]。节食还可以抑制 AD 模型小鼠大脑中 A β 的聚集^[234], 改善糖尿病病人衰老相关的认知退化^[235]。尽管大部分的研究都显示节食可改善老年个体的认知和行为功能, 但有些研究发现长期的节食对大鼠记忆并无改善作用^[236], 这暗示节食的起始时间、持续时间、程度、方式等对衰老相关行为功能退化的作用还是值得细究的^[237]。节食改善衰老时的行为能力的机制还不是很清楚。目前认为节食改善大脑功能的可能机制涉及保护线粒体功能^[238,239]、减少氧自由基释放、增加抗氧化能力、减少神经元氧化压力^[240,241]、促进突触可塑性^[242,243]、诱导压力应答基因以及神经营养因子的表达^[244]和增加神经再生等^[245,246]。

3.2 Sirtuins 和 NAD⁺

Sirtuins 属于一个进化上保守的蛋白家族, 是一类以烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD⁺)作为辅助底物的去乙酰化酶。研究发现过表达 Sirtuin 的成员在多个物种中都有延长

寿命的作用^[247], 且有研究发现 Sirt1 介导了节食引起的长寿信号通路^[248]。近期的研究还发现 SIRT1 在小鼠海马神经元中表达, 参与了学习记忆以及突触可塑性调控^[249,250], 过表达 SIRT1 可以促进健康衰老^[251], 并有预防神经退行性疾病的作用^[252]。NAD⁺是能量代谢中的辅酶, 也是 Sirtuin 去乙酰化酶的限速底物, 研究表明 NAD⁺水平和 Sirtuin 的活性在衰老过程中降低^[253,254]。通过药物或遗传方法提高 NAD⁺水平可以延长线虫寿命, 并提高年老线虫的运动行为^[149]。通过在小鼠海马 CA1 区域特异性敲低 NAD⁺合成酶降低大脑 NAD⁺水平致使小鼠表现出衰老类似的认知缺陷的表型^[255]。给小鼠长期服用 NAD⁺前体物质烟酰胺单核苷酸, 可减轻小鼠与衰老相关的各种生理功能的衰退, 包括运动和视力退化^[256]。此外, NAD⁺处理 AD 模型的小鼠可以部分阻止记忆丢失^[257]。进一步研究 Sirtuin 激动剂和增加 NAD⁺水平对人类衰老相关行为和认知功能是否有改善, 对多种疾病是否有缓解作用值得期待。

3.3 运动和脑力训练

虽然很多研究都关注开发药物来实现健康衰老, 事实上很多的研究显示运动以及智力训练可以保护大脑功能, 甚至可以改善神经退行性疾病引起的行为缺陷。大量研究表明, 持续适度的锻炼对认知、运动等各项生理功能具有积极的作用^[258,259], 另外还可以减少痴呆和 AD 等疾病的发病率^[260]。其可能的机制包括, 增强线粒体功能、增加大脑自噬水平^[261]、降低炎症水平^[262]、增加神经营养因子水平、增强突触可塑性及刺激神经再生^[263]。运动能增加人血清中的 BDNF 水平^[264], 小鼠中的研究表明运动引起的 BDNF 增加可以促进神经元的可塑性和大脑健康^[265,266], 抑制 BDNF 信号通路会消除运动对认知的改善^[267]。另外近期研究显示跑步可增加小鼠, 猴子和人血浆中肌肉细胞分泌的因子组织蛋白酶 B。在人的血浆中组织蛋白酶 B 的水平与记忆力是正相关的, 小鼠中组织蛋白酶 B 介导了运动促进老年动物神经再生和改善记忆行为的作用^[268]。除了运动, 脑力训练也是有助于延缓衰老相关认知退化的一种方式。有研究表明教育可以降低认知行为的下降速率^[269-271]。老年人如果更多地参与到社会活动及要

求脑力的活动中, 则可以推测他们的认知能力在后续衰老过程中退化更缓慢, 发生痴呆和阿尔兹海默病的可能性更低^[272,273]。而且更重要的是老年时期而不是年轻时期的脑力活动, 更影响衰老相关认知功能的退化^[274], 法国生物学家拉马克提出的“用进废退”可以很好地概括这种脑力训练对认知衰老的保护作用。这种改善大脑认知衰退的机制目前还不清楚, 可能与大脑本身的可塑性有关^[275,276], 还可能与神经再生有关, 如在丰富环境中饲养的小鼠突触密度更高, 海马的神经再生能力更强^[277]。

3.4 改善认知和行为功能的化合物

模式动物中的研究表明, 一些延长寿命的信号通路也可延缓行为和认知退化。雷帕霉素通过抑制 mTOR 信号通路, 可以延长多种模式动物包括酵母、果蝇和小鼠的寿命^[278-280]。在早衰模型的大鼠中, 雷帕霉素减少了焦虑行为, 并提高了运动和探索行为, 同时抑制了大脑萎缩^[281]。大量研究显示雷帕霉素对衰老大脑的各项功能有保护作用。长期低剂量的雷帕霉素处理提高了老年小鼠的认知功能, 其作用机制是通过降低大脑的炎症水平, 并增加海马的 NMDA 信号^[282]。其他研究也发现长期给小鼠服用雷帕霉素, 小鼠的多巴胺和 5-羟色胺等单胺类神经递质水平都有显著提高, 并阻止了衰老相关的认知退化, 还可以改善衰老相关的焦虑和抑郁行为^[283]。给大鼠服用雷帕霉素也得到了类似的发现^[284]。雷帕霉素还可以减少 AD 模型小鼠 A β 的堆积, 并提高认知功能^[285,286]。mTOR 对调节蛋白稳态是非常关键的信号通路, 同时控制着蛋白合成和降解。服用雷帕霉素的量、起始时间、持续时间对衰老相关行为退化的改善作用很关键, 这是为什么有些研究发现给老年小鼠服用雷帕霉素并没有改善认知功能的原因^[287]。

近几年来异种共生的方法(即将年轻和年老小鼠通过手术联合在一起, 使小鼠共享血液循环系统)在衰老研究中的应用, 发现血液中有影响衰老的因子。年轻小鼠的血液使年老小鼠的多个组织, 包括肌肉、大脑、骨骼的功能都显得年轻化^[288,289]。科学家进一步发现给老年小鼠注射年轻小鼠的血浆就足以改善海马相关的学习记忆行为, 增加神经再生的能力; 反过来老年小鼠血浆注射到年轻小鼠使

得年轻小鼠的神经再生能力降低, 学习记忆能力也变差^[290,291]。进一步研究血浆中到底哪种蛋白或生化因子可以调控大脑衰老, 科学家发现了 CCL11、GDF11、TIMP2 等因子可以调控衰老相关行为退化。在衰老过程中趋化因子 CCL11 在血液中是增加的, 而且其水平与学习记忆表现负相关, 增加年轻小鼠血液中 CCL11 水平会降低小鼠的神经再生和学习记忆功能^[290]。GDF11 可以增加大脑神经再生和血管完整性^[291]。此外, 近期研究发现人脐带血中含有的蛋白 TIMP2 可以增加老年小鼠海马神经再生功能和神经元的可塑性, 并且提高老年小鼠的空间记忆以及认知行为^[292]。这些结果说明血液中具有调节行为退化的因子, 有些检测年轻血液对神经退行性疾病的作用的临床试验正在进行中。

4 结语与展望

过去几十年对不同动物中衰老相关认知和行为退化以及大脑衰老的研究已经积累了大量进展, 在人类和其他模式动物中一致地发现一些认知行为如情节记忆、空间记忆、工作记忆、信息处理速度等, 运动能力和节律行为在衰老过程中有明显退化。大脑结构, 网络连接, 以及神经元形态和功能, 神经递质水平等在不同的脑区会呈现不同程度的变化, 其中前额叶皮层和海马是受衰老影响比较大的两个脑区。这些变化与衰老过程中认知和行为退化之间有着密切的联系。随着高通量测序、蛋白组学等分析方法的发展, 行为退化的分子细胞机制也逐渐展现。目前的研究已发现有一些策略是可以延缓衰老相关行为衰退的, 比如节食、运动和脑力训练还有应用一些化学因子等, 表明衰老相关行为退化是一个可塑的过程, 找到合适的方法可以延缓行为和认知功能衰退, 提高老年人的生活质量。

除了目前已取得的研究进展, 关于衰老过程中认知和行为退化的分子的分子机制还有很多问题有待解答, 如为什么老年人行为退化的程度存在很大的个体之间差异? 尽管大多数的老年人都出现明显的行为和认知功能的退化, 有一些老年人却能维持很好的行为功能。研究这些老年人之间的个体差异有助于我们理解衰老如何影响认知能力, 哪些因素

可以阻止行为退化。部分研究表明遗传变异对这种个体差异可能有一定贡献^[293], 通过构建动物模型(如不同地区野生型的线虫、杂交品系的小鼠或者大鼠)模拟人类的遗传变异来研究老年动物行为的个体差异可能是很好的突破点。另外, 衰老过程中大脑结构、神经元形态以及互相之间连接的变化是如何产生的, 又是如何导致行为衰退的? 目前还是相关性的研究为主, 很难得到因果关系的证据。新发展起来的 CRISPR/Cas9 基因编辑技术在哺乳动物上的应用, 以及克隆猴的成功为研究这些问题提供了新的策略。大脑衰老过程中基因表达变化在不同的物种都有比较保守的特征, 那么这些保守的生物学信号通路的变化是如何协同调控的? 很可能表观遗传调控在其中起了重要的作用。越来越多的研究关注到除了延长寿命, 延缓行为和认知功能的退化也是延缓衰老的重要目标。相信未来对衰老相关行为退化调控机制的进一步研究, 可以找到更多更有效的延缓认知和行为退化的方法, 为实现健康衰老, 预防退行性疾病的发生奠定基础。

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中国科学院脑科学与智能技术卓越创新中心离子通道调控研究组简介

中国科学院脑科学与智能技术卓越创新中心(原神经科学研究所)离子通道调控研究组于 2009 年组建,组长为蔡时青研究员,他于 2019 年获国家杰出青年科学基金资助。课题组研究方向主要包括两个方面,一方面是健康衰老的分子生物学机制研究,前期通过分析寿命与衰老相关行为退化的关系,发现有些长寿途径虽然延长了寿命但不能延缓老年动物神经递质减少以及相关的行为功能退化,提高神经递质可改善老年动物行为能力;之后以神经递质系统在衰老中的变化为衰老的标记,通过解析个体之间衰老速度差异的遗传基础,发现了一条新的胶质细胞-神经元信号通路调控衰老速度;同时进行全基因组筛选寻找调控行为退化的基因,找到一系列候选基因,阐明了两个全新的抗衰老靶标基因调节认知衰老的机制。另一方面是离子通道功能调控机制研究,利用线虫模式动物和哺乳动物细胞系,结合遗传学、生物化学、电生理等手段系统性地研究钾离子通道的表达和运输机制;构建了线虫离子通道疾病动物模型,通过小分子化合物筛选发现了可以纠正致病突变体功能的化合物,并探究其机制。实验室相关研究成果已发表在 *Nature*、*Mol Cell*、*Journal of Neuroscience* 和 *Nat Commun* 等国际著名期刊。

