甲基乙二醛参与阿尔茨海默病发病的研究进展

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阿尔茨海默病(Alzheimer's disease,AD)是一种神经退行性疾病,起病隐匿并逐渐损害行为和认知功能[1]。AD 是最常见的痴呆类型,占所有痴呆病例的 60%～70%[2]。该病的两大主要病理特征为细胞外 β 淀粉样蛋白(β-Amyloid,Aβ)形成的老年斑和细胞内磷酸化 Tau 聚集的神经原纤维缠结(Neurofibrillary tangles,NFTs)[3-4]。甲基乙二醛(Methylglyoxal,MG)是一种主要通过糖酵解途径形成的活性二羰基化合物[5]。血浆和大脑中的 MG 蓄积与 AD 患者认知功能损伤呈正相关[6-8],然而 MG 水平升高在 AD 发病机制中的作用尚不清楚。本研究将从 MG 衍生的糖基化终产物(Advanced glycation end products,AGEs)、氧化应激和线粒体功能等角度出发总结 MG 参与 AD 发病的研究进展。

1 MG 通过形成 AGEs,加重 AD 病变

糖基化是一种自发的、年龄依赖性的翻译后修饰,主要产生 AGEs 和 AGEs 前体[9-11]。MG 是 AGEs 主要的活性前体,大部分来源于糖酵解过程[12],且是一种有着神经毒性的羰基化合物[12-13]。此外,MG 还具有膜渗透性和极高反应性[14];过量的 MG 能够泄漏到周围的细胞和组织中[15]。在糖基化的非酶促反应中 MG 易与蛋白质的氨基酸残基(如精氨酸、赖氨酸和半胱氨酸)、核苷酸以及碱性磷脂发生反应,从而形成不可逆产物 AGEs,导致蛋白质等分子功能降低甚至丧失[14]。有研究认为 AGEs 介导神经退行性疾病的发生[5],可引起蛋白质的异常交联,导致蛋白质沉积和淀粉样变性[16]。在 AD 中 AGEs 促进包括 Aβ 和 Tau 在内的蛋白交联[17],使其耐受蛋白酶[18]。总之,过度糖基化加剧了 Aβ 和 Tau 的神经元毒性并导致神经变性[9-19]。

MG 衍生的 AGEs 广泛存在于血浆和全身组织中,在细胞内和细胞外均有分布,其在体内的水平比其他 AGEs 前体形成的 AGEs 高出数十倍[20-21]。生理情况下 MG 主要作为葡萄糖代谢的正常副产物产生(约占葡萄糖通量的 0.1%)[22],由磷酸二羟基丙酮和 3-磷酸甘油醛自发降解形成[23]。MG 的形成速率取决于细胞代谢和生理条件,如在高血糖、葡萄糖代谢受损、氧化应激或乙二醛酶 1(Glyoxalase 1,Glo1)活性受损时 MG 水平升高[23-24]。MG 和 AGEs 的蓄积在许多衰老相关疾病中起着重要作用,如糖尿病(Diabetes mellitus,DM)[7]、AD[17]、癌症[25]、动脉粥样硬化[26]和心血管疾病[27]。很多的研究都认为糖尿病是 AD 的危险因素之一,并且患有 DM 的 AD 患者皮质神经元变性加重[28]。有研究发现,与患有 AD 但没有 DM 的患者比较,同时患有 AD 与 DM 患者的 MG 和 AGEs 水平更高,与之伴随的是脑内更多的老年斑、NFTs 以及激活的小胶质细胞[6]。流行病学数据表明,AD 患者脑脊液中的 MG 比年龄匹配的健康对照者高 2 倍,脑脊液中的 MG 水平比血浆高 5～7 倍[29]。随着 AD 的进展,MG 可在神经元中蓄积,特别是在海马以及内嗅皮层的锥体神经元中[30]。临床研究结果表明,在老年人样本中血清中 MG 的水平与老年人认知功能的下降速度以及脑萎缩呈正相关[22-27]。与正常老年人比较,MG 和 AGEs 在 AD 患者脑中积累的更多[31]。MG 和 AGEs 的长期积累增加了 Tau 和 Aβ 等蛋白质的错误折叠,促进 NFTs 和老年斑的形成和沉积[32-33]。临床报告表明,AGEs 与 AD 中的老年斑和 NFTs 共定位[33,34],并且与年龄匹配的对照组比较,AD 患者老年斑中所含的 AGEs 高出 3 倍左右[34]。

在机制方面 Tau 的糖基化促进 Tau 聚集的成对双螺旋丝的形成,且降低 Tau 结合微管的能力[31]。Aβ 的糖基化导致 Aβ 在老年斑中的交联聚集,且引起周围细胞的氧化应激[35]。斑块中聚集的 Aβ 大部分以糖修饰的交联形式存在[35]。MG 形成的 AGEs 促进 Aβ 的 β 折叠、寡聚体和原纤维的形成,且增加聚集体的大小[31]。目前普遍认为,Aβ 毒性最强的形式是 Aβ 的寡聚体[35]。已经证明糖基化可以延长 Aβ 在寡聚体构象中的停留时间[35]。此外,有研究表明 MG 修饰后的 Aβ 比未被修饰的 Aβ 更具有毒性[21]。MG 修饰后的 Aβ 能够与其糖基化终产物受体(Receptors for advanced glycation end products,RAGE)结合,从而促进糖原合酶激酶 3β(Glycogen synthase kinase-3β,GSK-3β)的激活,导致细胞活力降低、细胞凋亡增加和海马神经元的突触损伤[7,21,33]。GSK-3β 是介导 Tau 磷酸化的激酶之一[36]。GSK-3β 的过度激活可导致 AD 中 Tau 的过度磷酸化和神经原纤维病变[36]。因此,阻断 RAGE/GSK-3β 通路可能改善 AD 样病理变化和记忆减退[21]。在大鼠中阻断 RAGE 减弱了 AGEs 诱导的 GSK-3β 异常活化和 Tau 过度磷酸化,进而

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改善突触功能、逆转记忆障碍[21]。除了激活 GSK-3β，MG 还可通过激活 p38（MAPK 家族成员）来诱导 Tau 磷酸化[24]。氨基胍是一种 MG 清除剂，能够有效抑制 GSK-3β 或 p38，阻止了 MG 诱导的 Tau 过度磷酸化[29]。在 AD 的小鼠模型中氨基胍能够挽救小鼠的早期认知功能缺陷[19]。此外，利拉鲁肽是一种胰高血糖素样肽-1（Glucagon-like peptide-1，GLP-1）类似物[37]，可通过抑制 GSK-3β 来减弱 MG 诱导的 Tau 的过度磷酸化[24]。

2　MG 诱导氧化应激和线粒体功能障碍

氧化应激是由氧化剂如活性氧（Reactive oxygen species，ROS）和抗氧化剂之间的产生失衡引起的，是导致衰老和衰老相关疾病（如动脉粥样硬化、AD 和癌症）的重要因素之一[38-40]。ROS 包括超氧阴离子、羟基自由基和非自由基分子（如过氧化氢），是由活体细胞中的线粒体电子传递链和诸多氧化反应产生，且生理量的 ROS 是维持细胞稳态的基础[41-43]。大脑耗氧量高，且含有丰富的易氧化脂质细胞，比其他器官更容易受到氧化应激的损伤[44]。

尽管人类还未完全了解 AD 的病因和发病机制，但有研究表明大脑中过度的氧化应激和葡萄糖代谢紊乱是 AD 的关键致病因素之一[29,45]。过度的氧化应激在 AD 的早期就出现，早于大多数斑块和缠结的发展，并在整个疾病进展过程中持续存在[46-47]。有趣的是，在 AD 患者的大脑和血浆中观察到 MG 和 AGEs 水平升高[5,34,48]，与 AD 中氧化应激的增加密切相关[17]。AD 中 MG 的积累增加氧化应激的机制包括促进自由基产生、增加促氧化酶活性、降低抗氧化酶活性和引起线粒体功能障碍[30]。线粒体是产生活性氧（Reactive oxygen species，ROS）的主要来源[49]。正常量的 ROS 可促进线粒体的生物合成，而过量的 ROS 降低线粒体酶的活性，并导致线粒体功能障碍，诱导细胞凋亡[49]。神经元的传递、完整性和存活都依赖于有效的线粒体，线粒体负责 ATP 的产生（神经递质的运输和释放所必需），并有助于钙稳态和细胞凋亡控制[50]。结构和功能受损的线粒体导致生成 ROS 增多和产 ATP 的效率明显降低，也是 AD 患者的特征之一[51]。

神经元培养研究显示，高水平的 MG 导致产生 ROS 增多，并且出现了线粒体功能障碍和 Tau 过度磷酸化[30]；高水平的 MG 会导致大鼠的脑线粒体损伤[48,52]；基于人类和小鼠大脑的研究，发现 MG 的蓄积引起 ROS（如过氧化氢）水平明显升高，线粒体膜破裂、线粒体呼吸链复合体 I 和 IV 的活性降低以及能量衰竭[38,49]。MG 通过诱导 ROS 和 AGEs 形成损害线粒体功能，造成进一步的 ROS 产生和损伤[48]。ROS 的过多产生还能够加速 MG 修饰蛋白（包括糖基化 Tau 和 Aβ）的形成，并加剧 AGEs 诱导的氧化应激和毒性[49]。此外，MG 可损害酶促和非酶促抗氧化防御系统[53]。MG 通过与谷胱甘肽还原酶和谷胱甘肽过氧化物酶等抗氧化酶反应，导致其失活以增加氧化应激[53]。在培养的大鼠海马神经元中 MG 诱导氧化应激依赖的细胞损伤[54]，降低抗氧化酶的酶活性和表达水平[54]。

脑室内注射链脲佐菌素（Streptozotocin，STZ）已被广泛用于制作 AD 样痴呆动物模型[55]。有研究表明，MG/RAGE/NADPH 氧化酶-2（NADPH oxidase-2，NOX-2）通路在 STZ 处理的大鼠海马中持续激活，引起大鼠海马损伤和记忆障碍[55]。包括 NOX-2 在内的 NADPH 氧化酶（NADPH oxidase，NOX）是一种多亚基酶，在细胞和组织中充当 ROS 的主要生产者[56]。RAGE 和 NOX-2 的激活增强了中枢神经系统的氧化应激[55]。

MG 还能诱导神经元凋亡[57]。B 细胞淋巴瘤 2（B-cell lymphoma 2，Bcl-2）和 Bcl-2 相关 X 蛋白（Bcl-2-associated X protein，Bax）作为 Bcl 家族中两种典型的抑制和促进细胞凋亡的蛋白，在调节线粒体膜通透性、线粒体功能和细胞色素 c 释放等方面发挥着关键作用[58]。在 AD 中 MG 通过激活神经元中促凋亡的 Bax 和胱天蛋白酶-3（Caspase-3，Casp-3）、减少抗凋亡的 Bcl2 以及降低线粒体跨膜电位，触发神经元凋亡[57]。

氧化应激是 ROS 产生过多、线粒体功能障碍和抗氧化系统受损或这些因素组合的结果[42]。如果抗氧化防御系统有足够的能力清除产生的活性物质，那么增加的 ROS 一般不足以导致病理状态[42,46]。有研究表明，在 AD 进展患者大脑中还出现了内源性抗氧化系统的破坏，如乙二醛酶系统[15]。乙二醛酶系统是一种普遍存在的抗氧化防御系统[38]，是真核细胞中 MG 和其他活性二羰基化合物的主要解毒系统，包括 Glo1 和乙二醛酶 2（Glyoxalase 2，Glo2）[59]。乙二醛酶系统在细胞防御糖基化和氧化应激中起着关键作用[60]，对神经保护至关重要[38]。在生理条件下乙二醛酶系统将 MG 代谢解毒，使超过 99% 的 MG 转化为无害的代谢物（如 D-乳酸），并提供针对 MG 介导的糖基化的酶促防御[61]。具体而言，在谷胱甘肽依赖性的乙二醛酶系统中 MG 和还原型谷胱甘肽可逆性的结合形成半硫缩醛；半硫缩醛在限速酶 Glo1 的作用下被催化为 S-D-乳酰谷胱甘肽；最后，Glo2 将 S-D-乳酰谷胱甘肽转化为 D-乳酸，同时产生一分子的谷胱甘肽[48]。此外，与年龄匹配的对照组比较，AD 患者大脑的谷胱甘肽水平显著降低[46]。过度的氧化应激会降低甚至耗竭细胞中的谷胱甘肽，破坏乙二醛酶系统，增加细胞内 MG 和 AGEs 形成[62,63]。

目前的研究主要聚焦 Glo1 和 Glo2 的活性和表达调控及其在生理过程和疾病发展中的作用[64]。Glo1 在 MG 解毒途径扮演重要角色，其作用产物 S-D-乳酰谷胱甘肽是一种无毒化合物；相较于 Glo2，Glo1 的激活更能够加速 MG 的降解，并抑制 MG 诱导的毒性[38,48]。在 AD 患者大脑中 Glo1 的表达和酶活性在疾病早期上调，但在疾病中晚期逐渐下调且低于正常水平[65]。Glo1 在 AD 早期的上调，可能是因为 AD 早期大脑中的某些神经元糖酵解增强，使 MG 产生增加，从而刺激了 Glo1 的表达[66]。与健康对照组比较，早期 AD 患者大脑中 Glo1 阳性神经元的数量有所增加[6]，这种增加可能代表着一种针对 MG 等二羰基化合物和 AGEs 水平升高的补偿机制[30]。然而，由于 AD 中晚期大脑中转录受损或转录因子的失活，Glo1 在疾病中晚期逐渐下调[24]。总之，随着 AD 病情的加重，内源性抗氧化系统的 Glo1 表达减少可导致 MG 异常积累所诱导的氧化应激、神经元损伤、

细胞凋亡，Glo1 的表达减少可能是老年斑和 NFTs 中 AGEs 形成的原因之一[65]。

3 结束语

AD 是一种神经退行性疾病，该疾病的神经病理学特征包括大脑中细胞外老年斑和神经元内 NFTs 的形成[47]。MG 是一种二羰基化合物，主要由乙二醛酶系统代谢[67]。MG 可有效促进神经退行性疾病的病理性级联反应[68]。这是由于蓄积的 MG 会与蛋白质和核酸等分子发生反应，导致过量的 AGEs 形成[67]。MG 通过促进 AGEs 形成诱导 Tau 过度磷酸化[29]。过度磷酸化的 Tau 是 NFTs 的主要蛋白质成分，NFTs 是 AD 的标志之一[29]。MG 还参与 Aβ 聚集[69]，且在老年斑中也检测到 AGEs 相关的交联反应[70]。糖基化后的 Aβ 毒性更大[19]。因此，越来越多的证据将 MG 与 AD 的发病机制联系起来[49,71]。

代谢失衡造成 MG 的过度积累，而产生的 MG 导致 AGEs 形成增加、氧化应激增强、线粒体功能损害以及细胞死亡，加重 AD 病变[23]。降低 MG 水平或者提高 Glo1 活性可以抑制氧化应激和 AGEs 产生，从而在一定程度上缓解 AD 的症状[24]。清除 MG 并减轻其毒性的治疗策略包括使用维生素 B1 补充剂和羰基清除剂如氨基胍、肌肽和替尼西坦等[72-75]。此外，抗氧化酶的激活或线粒体靶向抗氧化剂的应用也可能是一种新的治疗选择，用于清除老化相关的有毒代谢物（如 MG 和 AGEs）的积累，阻止 AD 的进展[76]。

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