AMPK/SIRT1-PPARγ-PGC1α-BACE1 信号通路及其相关因子在阿尔茨海默病病理改变中的作用

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摘要: 阿尔茨海默病(AD)是老年人常见的中枢神经系统退行性疾病, 主要病理表现为 β 淀粉样蛋白(Aβ)积聚形成神经炎性斑、过度磷酸化的微管 Tau 蛋白形成神经元纤维缠结、神经元缺失和胶质增生, 其中 Aβ 的生成和清除研究较多。大脑能量代谢异常可导致上述 AD 样病理变化, 而 AMP 活化的蛋白激酶(AMPK)活化后可改善大脑能量代谢, 通过抑制 β 位淀粉样前体蛋白裂解酶 1 表达及活性, 进而调节淀粉样前体蛋白的裂解, 以减少 Aβ 的生成, 过氧化物酶体增殖物激活受体 γ(PPARγ)及过氧化物酶体增殖物激活受体 γ 共激活因子 1α(PGC-1α)也具有类似的作用。此外, AMPK 与沉默信息调节因子 1 的激活及相互作用对 PPAR-γ、PGC-1α 的信号转导及生理功能起重要作用。

关键词: 阿尔茨海默病; β 淀粉样蛋白; AMP 活化的蛋白激酶; 沉默信息调节因子 1; 过氧化物酶体增殖物激活受体 γ; 过氧化物酶体增殖物激活受体 γ 共激活因子 1α; β 位淀粉样前体蛋白裂解酶 1; 淀粉样前体蛋白

Role of AMPK/SIRT1-PPARγ-PGC1α-BACE1 Signaling Pathway and Related Factors in Pathological Changes of Alzheimer's Disease

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Abstract: Alzheimer's disease(AD) is a common central nervous system degenerative disease in the elderly. Its main pathological manifestations are the accumulation of β-amyloid(Aβ) to form neuritic plaques, hyper phosphorylated microtubule Tau protein to form neurofibrillary tangles, neuronal loss and gliosis. Among them, the generation and elimination of Aβ is the mainstream research direction. Abnormal brain energy metabolism can lead to the above AD-like pathological changes, and activation of adenosine monophosphate-activated protein kinase(AMPK) improves brain energy metabolism, inhibits BACE1 expression and activity, and then regulates APP cleavage to reduce Aβ production. The peroxisome proliferator-activated receptor γ(PPARγ) and PPARγ coactivator-1α(PGC-1α) also have similar effects. Besides, the activation and interaction of AMPK and silent information regulator 1 play a crucial role in the signal transduction and physiological functions of PPAR-γ and PGC-1α.

Key words: Alzheimer's disease; Amyloid β-protein; Adenosine 5'-monophosphate (AMP)-activated protein kinase; Silent information regulator 1; Peroxisome proliferator-activated receptor γ; Peroxisome proliferator-activated receptor γ coactivator-1α; β-site amyloid precursor protein cleaving enzyme 1; Amyloid precursor protein

阿尔茨海默病(Alzheimer's disease, AD)是老年人常见的以进行性认知功能障碍为主要特征的中枢神经系统退行性病变, 主要病理改变为嗜银神经轴索突起包绕 β 淀粉样蛋白(β-amyloid, Aβ)形成神经炎性斑、过度磷酸化的微管 Tau 蛋白在神经元内高度螺旋化形成的神经元纤维缠结以及神经元缺失和胶质增生。据世界卫生组织统计, 25%~30% 的 85 岁以上老年人存在认知能力下降, 随着人口老龄化

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的加剧，AD的患病风险随年龄增长大幅提高[1]。中国国家统计局《2017年国民经济和社会发展统计公报》数据显示，中国13.9亿人口中，60岁及以上老人2.409亿（17.3%）；65岁及以上人口数为1.583亿（11.4%），中国已成为世界上老龄化最严重的国家之一[2]。国际阿尔茨海默病协会报告显示，中国现约有950万痴呆患者，2030年可能超过1 600万[3]。最新数据显示，中国每例AD患者每年社会经济成本达到19 144.36美元，远远超过中国2017年9 481.88美元的人均国内生产总值[4]。以上数据提示，AD将是中国未来发展面临的重大公共卫生问题，AD发病机制迄今不明，临床上缺乏有效的早期诊断方法和治疗措施。因此，积极探索AD的发病机制和有效的药物防治措施具有重要的价值和意义。

研究发现，AMP活化的蛋白激酶（adenosine monophosphate-activated protein kinase，AMPK）活化后可改善大脑能量代谢，通过抑制β位淀粉样前体蛋白裂解酶1（β-site amyloid precursor protein cleaving enzyme protein 1，BACE1）表达进而调节淀粉样前体蛋白（amyloid precursor protein，APP）的裂解，以减少Aβ的生成与积聚；过氧化物酶体增殖物激活受体γ（peroxisome proliferator-activated receptor γ，PPARγ）和过氧化物酶体增殖物激活受体γ共激活因子1α（PPARγ coactivator-1α gene，PGC-1α）可通过降低BACE1表达及活性改善大脑能量代谢，减少Aβ生成。此外，AMPK与烟酰胺腺嘌呤二核苷酸沉默信息调节因子1（silent information regulator 1，SIRT1）的激活及相互作用对PPARγ、PGC-1α的信号转导及生理功能起重要作用。现对AMPK/SIRT1-PPARγ-PGC1α-BACE1信号通路在AD主要病理改变中的作用予以综述，以期为探索AD发病机制和有效药物防治措施提供理论依据。

1 AD病理改变及其与大脑能量代谢的关系

目前，关于AD发病机制的研究较多。研究发现，遗传因素、Aβ生成与清除失衡、中枢胆碱能、兴奋性氨基酸毒性、炎症与免疫机制、自由基与氧化应激、线粒体功能障碍、钙稳态失调、胰岛素相关糖代谢异常以及脂质代谢异常等均是AD发病的重要机制[5-6]。其中，Aβ学说作为最主流的研究方向已经超过20年，研究认为，Aβ产生和清除之间的不平衡导致寡聚或纤维状Aβ的积累和沉积是AD发生的主要原因[7]。研究表明，Aβ由APP代谢生成，主要有非淀粉样物质途径（APP的内切蛋白水解由α型、β型和γ型分泌酶催化，α型分泌酶途径释放非淀粉样蛋白产物sAPPα、p3和C83肽）和淀粉样物质生成途径（在β分泌酶途径中，除sAPPβ和C99片段外，还产生β淀粉样肽$A\beta_{40}$和$A\beta_{42}$，其中$A\beta_{42}$具有更强的神经毒性，较$A\beta_{40}$疏水性更强，具有更强的寡聚化和聚集倾向）两条APP代谢途径[8-9]。1999年，BACE1被确定为用于执行β分泌酶功能的功能性酶，也是最重要的β型分泌酶，在Aβ生成过程中起重要作用[10]。因此，有效抑制BACE1可以减少Aβ生成，减少Aβ聚集，被认为是AD有潜力的治疗靶点。随着抗Aβ疗法的失败和对AD发病机制的深入研究发现，Aβ异常聚集是炎症反应、Tau蛋白磷酸化、线粒体功能障碍和氧化损伤等多种神经生物学反应的结果和媒介[11-12]。仅聚焦于清除Aβ的AD模型过于简单线性化，应从各种通路发现其病理机制并找到其治疗药物的相关机制[13]。

能量代谢在不同AD相关机制中起关联性作用。大脑是能量消耗巨大的器官，其能量主要来源于脑内葡萄糖的有氧氧化[14-16]。大脑有氧呼吸提供的能量是维持神经元递质传递和结构功能完整的基础。研究表明，脑葡萄糖代谢紊乱与AD的发生密切相关，在认知功能下降前，脑能量代谢异常就已经存在[17]。临床发现异常的能量代谢最终会导致神经病理级联反应，可使大脑的摄取速率和代谢率降低，最终导致AD患者认知功能下降[18]。目前，大脑能量代谢异常后主要通过以下途径导致AD的病理改变：①促进神经元凋亡；②导致小胶质细胞异常应答；③活性氧自由基大量生成；④M受体数量下降；⑤自噬系统异常等，并且这些改变之间还有复杂的相互作用[6,14]。因此，通过改善大脑异常的能量代谢，不仅可维持大脑神经元的正常生理功能，还对延缓AD病理改变有重要意义。

2 AMPK在AD病理改变中的作用

AMPK是调节细胞能量状态的重要丝氨酸/苏氨酸蛋白激酶，在真核细胞中广泛存在，作为能量传感器和调节器，在调节细胞能量稳态中起关键作用，并且与神经元形态和功能密切相关[14,19]。AMPK

结构和功能受腺苷二磷酸水平的调节，当细胞内腺苷二磷酸水平增加或 ATP 水平降低时，AMPK 被激活，以应对细胞能量状态改变并调节能量代谢过程，从而维持能量供求平衡[20-27]。代谢功能障碍可加剧 AD 的发病率和病程进展，而 AMPK 介导的信号通路与 AD 发病中能量代谢过程密切相关，其活性强弱是 Aβ 沉积和 Tau 蛋白过度磷酸化的主要影响因素之一，在 Aβ 生成的病理过程中发挥重要作用，AMPK 激活可通过调节 APP 代谢而减少 Aβ 生成[28-34]。研究显示，AMPK 敲除大鼠皮质神经元中 Aβ 生成增加，当 AMPK 被激活剂 5-氨基咪唑-4-甲酰胺核苷酸转甲酰酶激活后，大鼠皮质神经元中 Aβ 的产生也随之降低[6,35]。5-氨基咪唑-4-甲酰胺核苷酸转甲酰酶也可通过激活 AMPK，降低大鼠原代神经元培养物中磷酸化 Tau 蛋白水平，提高链脲佐菌素诱导大鼠 AD 模型的 ATP 水平、线粒体膜电位和复合物Ⅰ活性，改善线粒体功能，从而改善大鼠的认知功能[20,36]。此外，激活 AMPK 能显著降低高胆固醇喂养快速老化大鼠的胆固醇水平，下调 BACE1 表达水平，进而降低脑组织中 Aβ 的产生和沉积，并且腹腔注射 AMPK 抑制剂来拮抗其保护作用[16,37]。采用小檗碱激活稳定表达人瑞典突变体 APP695 的 N2a 小鼠神经母细胞瘤细胞、N2a 细胞和原代皮质神经元中的 AMPK，也可减少 Aβ 的生成，并降低 BACE1 的表达[38]。综上所述，AMPK 活化后可直接或间接参与调节 AD 的病理改变，在大脑能量代谢得到改善的同时，通过抑制 BACE1 表达进而调节 APP 的裂解，以减少 Aβ 的生成，防止 AD 病理改变的发生。

3　PPARγ 在 AD 病理改变中的作用

PPARγ 是调节目标基因表达的核内受体，与脂肪细胞分化、机体免疫调节及胰岛素抵抗关系密切。流行病学调查发现，迟发性 AD 是最常见临床 AD 类型，PPARγ 基因与迟发性 AD 的发病关系密切[39]。PPARγ 激动剂三氯化萘可增强细胞核内 PPARγ 与 BACE1 启动子的结合，抑制 BACE1 的转录和翻译，进而抑制 BACE1 的活性，最终减少 Aβ 的产生[40]。此外，有研究发现，人参皂苷 Re 可降低 AD 动物模型中 Aβ 的水平，且在 N2a/APP695 细胞中可使 $A\beta_{1\sim40}$ 和 $A\beta_{1\sim42}$ 水平降低，可能由于人参皂苷 Re 的干预可显著增加 PPARγ 蛋白和 mRNA 表达水平，抑制 N2a/APP695 细胞中的 BACE1 活性，最终减少 $A\beta_{1\sim40}$ 和 $A\beta_{1\sim42}$ 的产生，而 PPARγ 拮抗剂 GW9662 可有效抑制人参皂苷 Re 对 BACE1 的作用，表明 PPARγ 激活后可抑制 BACE1 的表达及活性，减少 $A\beta_{1\sim40}$ 和 $A\beta_{1\sim42}$ 的产生，进而缓解 AD 病理改变的发生[41]。球形脂联素可诱导促进小胶质细胞向 M2 抗炎表型转化，并通过对 PPARγ 信号的调节，降低 Aβ 所致的毒性炎症反应，并且可在罗格列酮干预后的链脲佐菌素诱导大鼠模型中激活 PPARγ，从而抑制 BACE1 发挥神经保护作用[42]。综上所述，PPARγ 激活后可抑制 BACE1 的表达及活性，在 AD 病理改变中发挥重要作用，并与调节 Aβ 分泌和毒性中的重要作用有关。

4　PGC-1α 在 AD 病理改变中的作用

PGC-1α 为 PGC-1 家族的一员，为核转录辅助激活因子，可与 PPARγ 共同作用，增强基因转录活性。PGC-1α 也是骨骼肌[43]及棕色脂肪[44-45]中线粒体生物发生和氧化代谢的关键调节剂，在能量需要量较大的组织（如脂肪组织、肝脏、骨骼肌、心脏、肾脏和脑部）大量表达，PGC-1α 对调节大脑能量代谢起重要作用，并与各种神经退行性疾病有关[46-49]。研究发现，AD 患者脑中 PGC-1α 的表达水平下调，并且 PGC-1α 在 N2a 神经母细胞瘤细胞中的过表达可使 Aβ 分泌水平降低，其原因可能与 PGC-1α 过表达使 BACE1 启动子活性降低以及 BACE1 表达和转录减少有关；PGC-1α 干扰小 RNA 转染下调 PGC-1α 表达水平后 BACE1 表达增加表明，PGC-1α 表达水平上调可减少 Aβ 的产生，进而缓解 AD 的病理改变，同时其表达上调亦可改善由 AD 引起的认知功能障碍[46,50]。此外，AD 患者死后的脑组织和 AD 转基因小鼠模型中 PGC-1α 及其下游靶标均降低，可能与 PPARγ 有关[51]。PGC-1α 缺陷 Tg2576 小鼠和干扰小 RNA 转染沉默 PGC-1α 的原代神经元中 Aβ 水平均显著增加，而烟酰胺核糖核苷是烟酰胺腺嘌呤二核苷酸的前体，可促进大脑中 PGC-1α 的表达，以降低 Aβ 的产生，改善 Tg2576 小鼠的认知水平，可能与烟酰胺核糖核苷促进 PGC-1α 介导的 BACE1 泛素化和降解有关，从而阻止脑中 Aβ 的产生[52]。在 APP/PS1 双转基因 AD 小鼠模型中，使用神经营养因子激活神经营养通路可以激活 PGC-1α，降低 BACE1 表达及活性，减少 Aβ 生成[53]。因此，AD 中

PGC-1α被认为与Aβ生成有相关性，并且可能与其调节BACE1表达及活性有关[49,54]。最新研究表明，厚朴酚可以通过增加AMPK、环腺苷酸反应元件结合蛋白和PGC-1α的表达抑制BACE1的表达及活性，从而降低Aβ水平[55]。由此可见，PGC-1α表达上调可能通过降低BACE1的表达及活性，改善大脑中能量代谢，并减少Aβ生成，表明PGC-1α在AD病理改变中的重要作用与其调控BACE1降低的Aβ生成有关。

5 AMPK/SIRT1-PPARγ-PGC1α信号通路在AD病理改变中的作用

SIRT1是Sirtuins家族成员之一，功能多样，可与多种信号通路相关蛋白相互作用，使组蛋白、赖氨酸残基及转录因子去乙酰化，发挥基因调节作用。SIRT1具有对抗衰老、延长寿命和调节新陈代谢的作用，是线粒体生物发生的重要调节因子[56-57]。SIRT1与AMPK在控制细胞稳态的调节中关系密切，共同发挥作用，且在氧化代谢和炎症调节中也有交叉作用。SIRT1可促进肝激酶B1的脱乙酰化，从而触发AMPK激活；反过来，AMPK可增加细胞烟酰胺腺嘌呤二核苷酸水平，诱导SIRT1激活[58-59]。此外，AMPK激活可以诱导SIRT1活性增加，但SIRT1的表达水平没有明显变化；当SIRT1基因敲除后，细胞内AMPK活性出现代偿性增加，两者相互作用可诱导线粒体生物发生和调节PGC-1α活性，而PGC-1α与PPARγ相结合对与线粒体生物合成调节相关的蛋白起调控作用，可促进与线粒体氧化磷酸化有关的基因和线粒体DNA复制，从而正性调节线粒体功能和代谢[60-62]。

AMPK/SIRT1-PPARγ-PGC1α途径也在运动和温度诱导的线粒体生物合成中发挥重要作用，抑制其传导可引起线粒体生物发生受损[63-64]。SIRT1激活后可通过抑制PGC-1α乙酰化和促进PGC-1α活性，进而促进线粒体生物发生，并可减少AD小鼠模型海马中的神经变性，降低PGC-1α和p53的乙酰化，改善小鼠学习记忆障碍，在AD小鼠模型中发挥明显的神经保护作用[65-68]。$A\beta_{25\sim35}$可下调SIRT1和PGC-1α的表达，抑制AMPK/SIRT1-PPARγ-PGC1α途径信号转导，导致线粒体生物发生减少和线粒体功能损害，使大脑能量代谢异常，进而导致AD发生；当AMPK依赖性途径激活后，Aβ诱导的神经干细胞中线粒体功能障碍得到改善[69-70]。将Aβ注射入小鼠海马内，损害小鼠空间学习和记忆能力后，海马中AMPK活性和PGC-1α蛋白水平下降，在中等跑步运动治疗后AMPK活性和PGC-1α水平也随之恢复，进而改善Aβ诱导的空间学习和记忆障碍[54]。综上所述，AMPK与SIRT1的激活及相互作用对PPARγ、PGC-1α的信号转导及生理功能起重要作用，并且在改善线粒体功能、大脑能量代谢及Aβ诱导的神经毒性中发挥重要作用。AMPK、PPARγ、PGC-1α三者均可参与调节BACE1的表达及活性，进而调节Aβ的合成分泌，对AD的发生、发展起重要调节作用。

6 小 结

AD是一种与年龄相关的神经退行性疾病，主要表现为记忆缺陷和认知功能下降。过量的Aβ聚集并形成可溶性寡聚体和不溶性脑淀粉样斑块被广泛认为是AD的潜在致病机制，目前尚未开发出有效治疗药物。研究表明，AMPK/SIRT1-PPARγ-PGC1α信号通路涉及能量代谢、线粒体功能和细胞凋亡等，可通过参与线粒体功能的调节，维持大脑能量代谢平衡，在保护脑神经元功能中发挥作用[71-72]。AMPK/SIRT1-PPARγ-PGC1α信号通路在AD病理改变中可起到调节大脑能量代谢，改善大脑的摄取速率和代谢率，防止神经元退变和死亡的作用；还可调节BACE1的转录、合成和活性，减少APP的淀粉样代谢，使Aβ生成和积累减少，进而减少淀粉样斑块的形成，防止AD的发生、发展。因此，进一步验证AMPK/SIRT1-PPARγ-PGC1α-BACE1信号通路在AD病理改变中的作用，明确该信号通路相关因子的相互作用关系，并通过药物对其中1个或多个靶点进行干预，将有望成为治疗及预防AD的新途径，对延缓AD病理改变及预防具有极其重要的意义。

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