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α7烟碱型乙酰胆碱受体在阿尔茨海默病中的作用*

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摘要 随着全球人口老龄化的加剧，阿尔茨海默病（Alzheimer's disease，AD）发病率持续上升，目前已成为最常见的神经退行性疾病之一。尽管研究人员对AD的病理特征有深入的了解，如淀粉样斑块、Tau蛋白异常磷酸化形成神经元纤维缠结等，但其确切的病因和发病机制仍不完全清楚。α7烟碱型乙酰胆碱受体（α7nAChR）是中枢神经系统中重要的乙酰胆碱受体亚型，广泛分布于大脑的多个区域，尤其是与学习和记忆相关的海马和皮质区域，在神经递质释放、神经可塑性、细胞信号转导以及炎症反应中发挥重要功能。近年来，α7nAChR在AD中的作用受到广泛关注。研究表明，α7nAChR参与β淀粉样蛋白（amyloid β-protein，Aβ）代谢、Tau蛋白磷酸化、神经炎症反应、氧化应激等AD发病进程中的多个重要环节，提示α7nAChR在AD的发病机制中扮演着重要角色，有望作为AD潜在治疗靶点。本综述旨在总结α7nAChR与AD发病的关联及其研究进展，为未来的疾病治疗提供可能的研究方向。

关键词 阿尔茨海默病，α7烟碱型乙酰胆碱受体，β淀粉样蛋白，Tau蛋白，神经炎症
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阿尔茨海默病（Alzheimer's disease，AD）是一种中枢神经系统的进行性神经退行性疾病，以记忆力减退、认知功能障碍和行为改变为主要临床特征[1]。流行病学研究显示，AD是老年人中最常见的痴呆形式，其发病率随年龄增长而上升[2]。随着病程的发展，患者的日常生活能力逐渐下降，最终可能完全丧失自理能力。据阿尔茨海默病协会和世界卫生组织估计，阿尔茨海默病占所有其他痴呆症病例的60%~70%，全球有超过5 500万人受其影响。到2050年，该病例数估计将增加一倍[3]。AD的病理特点包括神经元纤维缠结、β淀粉样蛋白（amyloid β-protein，Aβ）斑块的形成、神经元减少和突触损害等，尤其表现为在海马脑区、皮质脑区的神经元损伤和大脑萎缩[4]。

乙酰胆碱受体在大脑中广泛分布，与AD之间存在密切关联。乙酰胆碱受体包括两种，即烟碱型乙酰胆碱受体（nAChRs）和毒蕈碱乙酰胆碱受体（mAChRs）。这两类受体在维持认知行为中都起着重要作用。许多研究利用［3H］-烟碱和［3H］-乙酰胆碱作为AD患者大脑皮层的结合位点，用以评估AD患者中乙酰胆碱受体的数量和功能状态的变化。结果表明，随着nAChRs和mAChRs这两种受体数量的减少，其结合位点也随之减少[5-6]。根据动物和人类的研究发现，nAChRs的α4β2亚型和α7亚型占据了大脑中主要部分，并已被证明在改善认知功能中发挥作用[7]。在近期的AD研究中，揭示了α7nAChR在多个重要生物学过程中扮演关键角色。研究表明，α7nAChR通过调节Aβ代谢进而影响Aβ的形成、沉积和清除[8]。此外，α7nAChR还能影响Tau蛋白的磷酸化状态，进而影响神经元功能[6]。α7nAChR还可以调节神经炎症反应，减少氧化应激对神经元的损害[9]。同时，一些研究已经证明，α7nAChR通过激动剂、正向变构调节剂促进认知功能和神经保护[6]。因此，本综述将从α7nAChR影响Aβ代谢、Tau蛋白磷酸化、神经炎症反应和氧化应激等进程进行详细综述，以期为开发新的治疗策略提供潜在靶点。

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1　α7nAChR的基础生物学特性

α7nAChR是由5个相同的α7亚基组成，形成同源五聚体。每个亚基由502个氨基酸和4个跨膜结构域（M1、M2、M3和M4）组成[10]（图1）。M2结构域是离子通道的主要组成部分，N端的肽可以与M2结构域中的氨基酸残基相互作用，从而改变通道的构象和电荷分布。这种相互作用可以促进正离子流入通道，增加通道的通透性[11]。α7nAChR由位于15号染色体q14的CHRNA7基因编码，该基因全长75 000 bp，包含1个1 509 bp的cDNA、10个外显子和9个内含子。研究表明，由第4、第6和第7外显子编码的蛋白质结构构成了α7nAChR激动剂的结合位点。当激动剂与α7nAChR结合时，能引起中心离子通道的开放，导致Ca^{2+}迅速流入细胞。α7nAChR通过调节Ca^{2+}的流入，增强神经递质（如乙酰胆碱、多巴胺、谷氨酸等）的释放，进而调节神经元之间的通讯[12]。α7nAChR正向变构调节剂的结合位点位于胞外区域，在五聚体的两个相邻亚基的交界处。正向变构调节剂的结合会增强α7nAChR的活性，导致更多的Ca^{2+}流入细胞，从而增加神经细胞的兴奋性[13]。

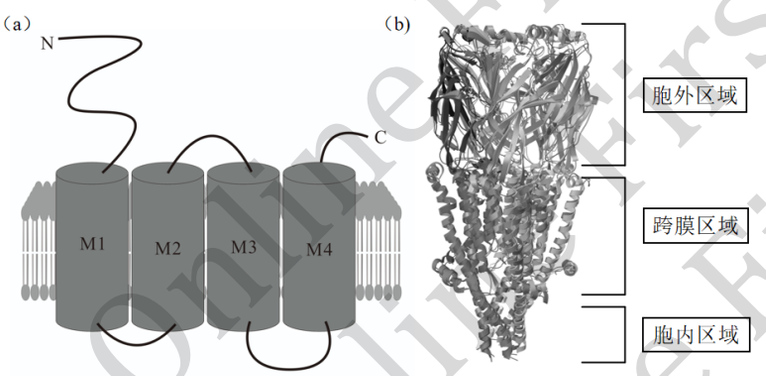

Fig.1　Diagram of α7nAChR structure

图1　α7nAChR结构示意图

（a）M1、M2、M3和M4是α7nAChR的跨膜结构域，（b）未结合天然配体形式的人源α7nAChR示意图（PDB ID-7EKI）

α7nAChR在大脑多个区域广泛分布，尤其集中于海马、皮层、杏仁核和基底前脑等区域[14]。在海马和皮层，α7nAChR受体的分布与学习、记忆形成及认知功能密切相关，参与调节突触可塑性和神经网络的稳定性[15]。杏仁核是处理情绪反应，尤其是恐惧和焦虑的脑区。通过调节杏仁体中的信号传递，α7nAChR可能影响情绪反应的强度和持续时间[16]。在基底前脑，α7nAChR的作用与注意力和觉醒状态的调控相关。这些区域在维持警觉状态、注意力集中以及执行功能等方面起着关键作用[17]。因此，α7nAChR在维持大脑功能和神经系统的正常运作中起着关键作用。

2　α7nAChR在AD发病进程的影响

2.1　α7nAChR影响Aβ的形成、沉积和清除

研究表明，α7nAChR通过多种机制影响Aβ的形成、沉积和清除。

首先，α7nAChR通过调节神经递质的释放，间接影响Aβ的形成。α7nAChR激活可以促进乙酰胆碱、谷氨酸等神经递质的释放，这些神经递质通过激活5-羟色胺受体、N-甲基-D-天冬氨酸受体（N-methyl-D-aspartic acid receptor，NMDAR）等参与调控Aβ前体蛋白（amyloid percusor protein，APP）的加工过程。乙酰胆碱可以增加α分泌酶的活性，进而促进APP沿非淀粉样蛋白生成途径加工，减少Aβ的形成[18-19]。然而，也有一些研究报告截然相反的结果。星形胶质细胞是中枢神经系统中最丰富的细胞类型，它们AD中扮演着关键角色。研究发现，α7nAChR的过度激活可能会导致星形胶质细胞功能紊乱，从而加重Aβ的积累[20]。

其次，α7nAChR直接参与Aβ的沉积过程。Cao等[21]使用APPswe/PSEN1dE9双转基因小鼠模型，以PNU-282987为特异性激动剂研究AD小鼠病理的变化，结果表明，激活a7nAChR可减少海马中Aβ诱导的突触损失和Aβ的沉积，维持海马突触的整体结构，从而改善APPswe/PSEN1dE9双转

基因小鼠的学习和记忆能力。

α7nAChR还可以与Aβ直接结合，这种结合可能导致受体的功能改变，影响钙离子通道的活性，进而影响神经细胞的生存[22]。在Aβ形成前期，神经元细胞最初可能过表达α7nAChR试图恢复神经元细胞中的钙信号转导，以保持正常的神经元功能。Ren等[23]使用人体神经母细胞瘤SH-SY5Y细胞稳定过表达α7nAChR，在添加1 μmol/L $Aβ_{1-42}$寡聚物（AβO）的情况下，研究α7nAChR表达水平的变化是否会改变Aβ的神经毒性，结果发现，α7nAChR过量表达可以提高SYP、SNAP-25和PSD-95等神经突触相关蛋白质的表达水平，减弱Aβ对这些突触蛋白表达的抑制作用及神经毒性。然而，神经元细胞上的α7nAChR长期暴露于高水平的可溶性Aβ可能导致这些受体脱敏，并容易与Aβ一起发生内吞作用。当Aβ在细胞内达到毒性水平时，Aβ斑块可随之形成。同时，过度的Aβ与α7nAChR的结合，可能会导致Ca^{2+}内流过量，进而引发神经元的毒性反应，如氧化应激、线粒体功能障碍和细胞凋亡等，最终导致神经元损伤和死亡。使用星形胶质细胞和神经元共培养系统的体外研究表明[24]，纳摩尔水平的可溶性Aβ在与星形胶质细胞α7nAChR结合后，会导致谷氨酸释放异常和突触外NMDAR的过度激活，从而导致谷氨酸兴奋性毒性的建立，最终导致神经元死亡。

再次，α7nAChR还参与调控Aβ清除。激活α7nAChR可以促进小胶质细胞活化，增强其对Aβ的吞噬能力[25]。多项实验表明，通过使用α7nAChR激动剂调节星形胶质细胞，可能在疾病早期阶段阻止Aβ的扩散[26-27]。然而，也有一些研究并没有观察到α7nAChR激动剂能够有效阻止Aβ的扩散[28]。这可能是因为α7nAChR的激活对Aβ的清除作用并不强。因此，关于α7nAChR激动剂是否能够阻止Aβ的扩散，目前的研究结果并不一致，需要进一步的研究来阐明。α7nAChR还可能影响血脑屏障的完整性，间接影响Aβ清除。α7nAChR功能受损可能导致血脑屏障的通透性增加，使得外周循环中的Aβ更易进入大脑，同时降低大脑清除Aβ的效率，最终导致Aβ在大脑中的积累[29]。因此，α7nAChR在Aβ的形成、沉积和清除过程中发挥着复杂的作用，这对于理解其在AD发病机制中的作用至关重要。

2.2　α7nAChR影响Tau蛋白磷酸化

Tau蛋白是微管稳定相关蛋白，其异常磷酸化会导致微管结构破坏，进而形成神经纤维缠结，是AD的主要病理特征之一[30]。研究发现，α7nAChR能够通过多种信号转导途径影响Tau蛋白的磷酸化状态。激活α7nAChR能够增加细胞内的Ca^{2+}浓度，进而激活一系列下游信号分子，如蛋白激酶C（protein kinase C，PKC）以及糖原合成激酶3β（glycogen synthase kinase-3β，GSK-3β）等，这些激酶都能够直接或间接地调节Tau蛋白的磷酸化水平，从而影响Tau蛋白的磷酸化和神经元纤维缠结的形成[31-34]。ABT107是一种高亲和力、高选择性的α7nAChR部分激动剂，Bitner等[35]通过对小鼠、大鼠和猴子急性给药，发现ABT-107可增加信号转导分子细胞外信号调节激酶（extracellular signal-regulated kinase，ERK）和环磷腺苷效应元件结合蛋白（cAMP-response element binding protein，CREB）的磷酸化水平，改善实验动物的学习和记忆功能。同时，在AD转基因小鼠皮下注射ABT-107 10 d后，发现GSK-3β在Ser-9位点的磷酸化导致其活性降低，进而降低了Tau过磷酸化水平。α7nAChR与Tau蛋白磷酸化之间的关系还会受到α7nAChR的表达水平、激活状态以及与其他信号分子的相互作用等多种因素影响[36]。总之，α7nAChR与Tau蛋白磷酸化之间的相互作用在不同的生理和病理条件下有所不同，这些相互作用对于维持神经细胞的正常功能至关重要，可能有助于缓解AD病程的发展。

2.3　α7nAChR影响炎症反应

在AD的病理过程中，神经炎症是一个重要的环节。长期的炎症环境不仅会加速Aβ的沉积，还会导致神经细胞的损伤和死亡，加剧疾病的发展[37]。胆碱能抗炎通路是机体自身的一种重要抗炎机制，该通路通过迷走神经的作用，释放乙酰胆碱，乙酰胆碱通过作用于α7nAChR来发挥抗炎作用[38-39]。当α7nAChR被激活时，可以抑制炎症关键转录核因子κB（nuclear factor-κB，NF-κB）的激活，减少肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）、白介素-1β（interleukin-1β，IL-1β）等炎症因子产生，从而发挥抗炎作用[40]。Wang等[41]在星形胶质细胞原代培养实验中发现，烟碱通过激活α7nAChR发挥作用，阻止Aβ诱导的IL-1β、IL-6、TNF-α等炎症因子的释放。此外，α7nAChR还可以通过JAK2-STAT3信号通路调节炎症反应和细胞的抗炎状态[42]。同时，激活胆碱能抗炎通路还可能改善神经元的通信功能，通过保护

突触健康，维持神经传递物质的平衡，从而对抗AD引起的认知功能下降[43-44]。总之，α7nAChR可通过激活胆碱能抗炎通路发挥抗炎作用，减轻神经炎症，保护神经细胞，在调节AD相关炎症过程中起着重要作用。

2.4 α7nAChR影响氧化应激反应

氧化应激是AD发展进程的关键因素之一，氧化应激会导致活性氧（reactive oxygen， ROS）的产生，ROS过量积累会破坏细胞膜的完整性，损伤细胞内蛋白质、脂质和核酸，最终导致细胞功能障碍或死亡[9, 45]。α7nAChR通过多种机制介入氧化应激过程，从而影响AD发展进程。首先，Aβ与α7nAChR结合可以直接引发氧化应激反应。Aβ与α7nAChR结合可导致Ca^{2+}内流增加，进而刺激ROS的产生[34]。其次，α7nAChR还可以通过影响细胞内信号通路调节氧化应激反应。研究发现，α7nAChR可以激活下游的磷脂酰肌醇3-激酶/蛋白激酶B（PI3K/Akt）信号通路，激活Akt可以抑制细胞凋亡，增强细胞对氧化应激的抵抗力[46]。Guo等[47]使用大鼠原代海马神经元细胞进行实验研究，发现染料木素能够通过α7nAChR激活PI3K/Akt信号通路，促进核转录因子红系2相关因子2（nuclear factor-erythroid 2-related factor 2， Nrf2）的活化，进而增加抗氧化酶的表达量，如超氧化物歧化酶（superoxide dismutase， SOD）和谷胱甘肽过氧化物酶（glutathione peroxidase， GSH-Px），降低Aβ引起的氧化应激损伤，保护神经元。Dong等[5]使用低浓度烟碱刺激小鼠海马细胞系HT-22细胞，发现激活α7nAChRs/Erk1/2信号通路可以降低H_2O_2诱导的氧化应激并发挥神经保护作用。NF-κB信号通路在不同的细胞和生理环境中可能会有不同的效应。在某些情况下，它可能需要被抑制以防止过度的炎症反应。而在其他情况下，它可能会被激活以提供抗氧化保护。因此，α7nAChR还可以通过激活NF-κB信号通路，调节抗氧化酶的表达，如SOD和GSH-Px，进一步增强细胞对ROS的清除能力[48-49]。最后，α7nAChR还可通过减少炎症因子的释放，从而间接降低ROS的产生，减轻氧化应激[50]。Yamini等[18]使用C57BL/6小鼠构建AD模型后，使用α7nAChR选择性激动剂GTS-21给药21 d，并用Morris水迷宫（morris water maze， MWM）和新物体识别（novel object recognition， NOR）进行神经行为评估，发现α7nAChR激活能够改善小鼠记忆和识别能力。同时，GTS-21治疗还能显著降低大脑皮层和海马区的氧化应激、炎症标志物和胆碱能功能障碍[51]。综上所述，α7nAChR的激活对氧化应激反应具有保护作用，可以通过多种途径减轻氧化应激引起的损伤和炎症反应，对AD的发展进程产生影响。

3 α7nAChR作为AD治疗靶点的研究进展

α7 nAChR存在于神经元和星形胶质细胞上。在AD细胞模型中，α7nAChR与神经元膜上的可溶性Aβ形成复合物，从而诱导受体脱敏和复合物的内化[24, 52]。随后，神经元释放Aβ-α7nAChR复合物，该复合物被星形胶质细胞吞噬，随后星形胶质细胞裂解释放Aβ斑块。可溶性Aβ还与星形胶质细胞膜上的α7nAChR相互作用，并诱导这些受体的过度表达[53]。从长远来看，Aβ导致Ca^{2+}通过α7nAChR流入星形胶质细胞，进而触发星形胶质细胞过量释放谷氨酸。谷氨酸过度激活突触外NMDA受体，从而导致谷氨酸兴奋性毒性的建立，最终导致神经元死亡。总体而言， α7nAChR、星形胶质细胞和可溶性Aβ之间存在异常相互作用。因此，开发针对该受体的激动剂作为治疗手段已成为研究焦点。α7nAChR激动剂通过激活α7nAChR，有望改善神经元功能，减轻Aβ的毒性影响，从而改善AD患者的认知能力和日常生活能力。近年来，已有多项临床试验评估α7nAChR激动剂在AD治疗中的安全性和有效性。一项针对α7nAChR激动剂ABT-126的临床试验研究[54]表明，与安慰剂组相比，ABT-126能够在一定程度上改善患者的认知功能，尤其是在注意力和执行功能方面，但一些患者也会出现轻微到中度的不良反应，如恶心和头痛。另一项针对α7nAChR的新型部分激动剂Encenicline（EVP-6124）的临床结果表明[55]，EVP-6124在提高AD患者的认知功能方面显示出一定的潜力，且具有良好的耐受性和安全性。此外，α7nAChR部分激动剂GTS-21（DMXB-A）的临床试验中表明[56]，该药剂能够改善轻度至中度AD患者的认知功能。

目前，以α7nAChR为治疗靶点的药物临床研究结果表明，该类化合物对AD患者具有改善和治疗作用，但尚未达到广泛应用于临床的程度，其药物研发仍面临多项挑战[57]。首先，药物的特异性是一个关键问题，因为α7nAChR广泛分布于中枢神经系统和外周组织中，特异性低的激动剂可能会影响多个生理过程，导致非预期的副作用。因此，

开发高特异性、能够精确靶向大脑中α7nAChR的药物是一大挑战。其次，即使是特异性较高的药物，也可能伴随着副作用，如心脏问题、消化系统反应等，这些副作用可能限制了药物的临床应用和患者的耐受性。最后，药物递送方法也是一个挑战。中枢神经系统具有血脑屏障（blood-brain barrier，BBB），这对药物分子而言是一个重要的自然屏障，限制了很多潜在治疗药物的大脑内递送。开发能有效穿越血脑屏障，且能在大脑中适当释放的药物递送系统，是实现α7nAChR靶向治疗的关键。总之，虽然针对α7nAChR的AD治疗策略具有潜力，但要克服上述问题和挑战，还需进一步的研究和创新。

4　总结及展望

α7nAChR在神经系统中的广泛分布，其在AD中的作用已被广泛研究。α7nAChR在减少Aβ生成、沉积、降低Tau蛋白磷酸化水平、减轻神经炎症反应、氧化应激反应以及保护神经元等方面十分重要，尤其在AD发病早期具有调节作用，这些研究结果强调了α7nAChR作为AD治疗潜在靶点的重要性。尽管α7nAChR药物开发面临着特异性、副作用和精准递送等挑战，α7nAChR依旧是AD研究中一个有希望的治疗靶点。深入研究α7nAChR在AD治疗中的作用至关重要，这将有助于促进基于α7nAChR的新型AD治疗策略的发展，为AD患者提供更有效的治疗选择方案和药物。

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The Role of α7nAChR in Alzheimer's Disease*

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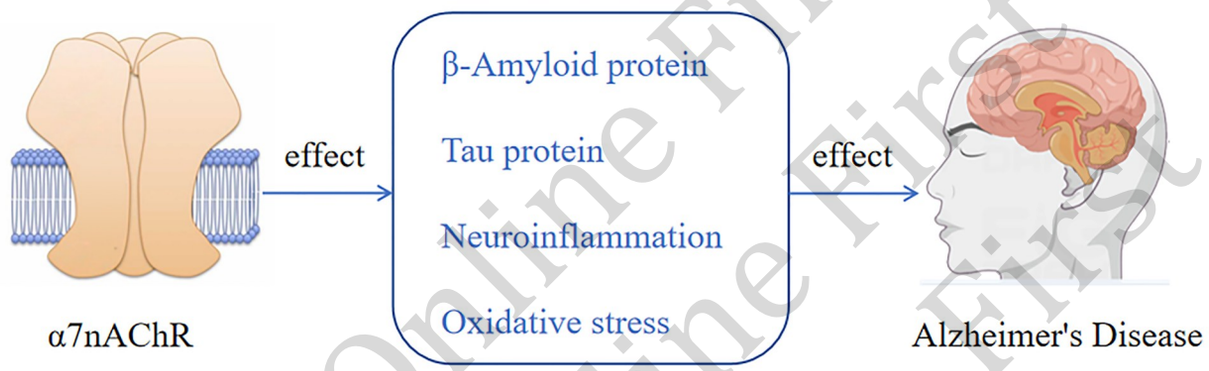
Graphical abstract



Abstract As the global population continues to age, the incidence of Alzheimer's disease (AD), one of the most common neurodegenerative diseases, continues to rise significantly. As the disease progresses, the patient's daily living abilities gradually decline, potentially leading to a complete loss of self-care abilities. According to estimates by the Alzheimer's Association and the World Health Organization, AD accounts for 60%—70% of all other dementia cases, affecting over 55 million people worldwide. The case number is estimated to double by 2050. Despite extensive research, the precise etiology and pathogenesis of AD remain elusive. Researchers have a profound understanding of the disease's pathological hallmarks, which include amyloid plaques and neurofibrillary tangles resulting from the abnormal phosphorylation of Tau protein. However, the exact causes and mechanisms of the disease are still not fully understood, leaving a vital gap in our knowledge and understanding of this debilitating disease. A crucial player that has recently emerged in the field of AD research is the α7 nicotinic acetylcholine receptor (α7nAChR). α7nAChR is composed of five identical α7 subunits that form a homopentamer. This receptor is a significant subtype of acetylcholine receptor in the central nervous system and is widely distributed in various regions of the brain. It is particularly prevalent in the hippocampus and cortical areas, which are regions associated with learning and memory. The α7nAChR plays a pivotal role in several neurological processes, including neurotransmitter release, neuronal plasticity, cell signal transduction, and inflammatory response, suggesting its potential involvement in numerous neurodegenerative diseases, including AD. In recent years, the role of α7nAChR in AD has been the focus of extensive research. Emerging evidence suggests that α7nAChR is involved in several critical steps in the disease progression of AD. These include involvement in the metabolism of amyloid-beta (Aβ) proteins, the phosphorylation of Tau protein, neuroinflammatory response, and oxidative stress. Each of these processes contributes to the development and progression of AD, and the involvement of α7nAChR in these processes suggests that it may play a crucial role in the disease's pathogenesis. The potential significance of α7nAChR in AD is further reinforced by the observation

that alterations in its function or expression can have significant effects on cognitive abilities. These findings suggest that α7nAChR could be a promising target for therapeutic intervention in AD. At present, the results of drug clinical studies targeting α7nAChR show that these compounds have improvement and therapeutic effects in AD patients, but they have not reached the degree of being widely used in clinical practice, and their drug development still faces many challenges. Therefore, more research is needed to fully understand its role and to develop effective treatments based on this understanding. This review aims to summarize the current understanding of the association between α7nAChR and AD pathogenesis. We provide an overview of the latest research developments and insights, and highlight potential avenues for future research. As we deepen our understanding of the role of α7nAChR in AD, it is hoped that this will pave the way for the development of novel therapeutic strategies for this devastating disease. By targeting α7nAChR, we may be able to develop more effective treatments for AD, ultimately improving the quality of life for patients and their families.

Key words　Alzheimer's disease, α7nAChR, β-Amyloid protein, Tau protein,neuroinflammation
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