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GABA能中间神经元在阿尔茨海默病病理进程中的重要作用*

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摘要 阿尔茨海默病（Alzheimer's disease，AD）是一种进行性神经退行性疾病，是老年痴呆症最常见的原因。其特征为认知功能下降、日常生活能力丧失以及行为和心理症状，严重影响患者生活质量，并给家庭和社会带来沉重负担。近年来的研究显示，GABA能中间神经元通过精确调控大脑节律振荡来维护神经网络的稳态，其功能受损不仅是β-淀粉样蛋白（Aβ）病理引发神经网络过度兴奋的重要因素，而且是AD认知衰退过程中的核心病理机制之一。本文系统综述AD进程中特定GABA能中间神经元亚型病理机制的差异性，GABA能中间神经元-兴奋性神经元环路失衡导致神经网络振荡异常的分子机制，以及基于GABA能系统调控的新型治疗策略，为深入理解GABA能中间神经元在AD病理中的损伤机制开辟了新的视角，并展望了通过精准神经调控实现转化医学前景的可能。

关键词 阿尔茨海默病，GABA能中间神经元，β-淀粉样蛋白，网络功能障碍
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阿尔茨海默病（Alzheimer's disease，AD）是一种以隐匿起病和进行性认知衰退为特征的神经退行性疾病，占老年期痴呆病例的60%~80%。其核心病理特征包括：a. 细胞外β-淀粉样蛋白（amyloid β-protein，Aβ）斑块沉积；b. 过度磷酸化tau蛋白介导的神经元原纤维缠结；c. 突触可塑性损伤伴随神经网络失同步化。Aβ作为淀粉样前体蛋白（amyloid precursor protein，APP）经β/γ分泌酶切割的产物，以单体、寡聚体及纤维化斑块形式存在，其异常聚集被广泛认为是AD病理级联反应的始动因素[1-2]。

早期研究显示，γ-氨基丁酸能中间神经元（γ-aminobutyric acidergic interneurons，GABA）对Aβ病理具有相对抗性，因此研究长期聚焦于兴奋性锥体神经元的AD病理机制。然而，近年来的研究表明，AD患者记忆与认知损伤的原因之一是GABA能中间神经元功能障碍导致的海马神经元过度兴奋[3-5]。在多种转基因AD模型小鼠（如hap-J20、5×FAD、3×Tg-AD和APP/PS1）中均观察到神经回路过度兴奋的现象[6-8]，提示由GABA能中间神经元异常所导致的兴奋与抑制失衡是AD认知障碍的核心机制之一。

1 阿尔茨海默病中GABA能中间神经元功能障碍的研究进展

大脑GABA能中间神经元可根据其分子标志物，分为神经肽类（如生长抑素（somatostatin，SST）、血管活性肠肽（vasoactive intestinal peptide，VIP））和血清合蛋白类（如小清蛋白（parvalbumin，PV））。具体而言，PV^+、SST^+和VIP^+神经元分别占约40%、30%和12%，它们在形态和环路功能存在显著差异[9-10]。PV^+神经元主要由篮状细胞和吊灯细胞组成，靶向锥体神经元胞体，主要主导高频γ振荡（30~80 Hz）的同步活动；SST^+神经元以马丁诺蒂细胞为主，靶向锥体神经元树突，调控低频θ振荡（4~12 Hz）及信号整合；VIP^+神经元则通过抑制SST^+神经元的活动，进而产生去抑制效应，参与到目标导向等行为的神

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经编码过程中（图1a）[11-12]。不同类型的GABA能中间神经元表现出功能性和病理易感性的差异，这决定了它们在病理条件下的响应差异[13-14]。表1展示了三类中间神经元的关键作用及近期的主要实验发现。

PV^+神经元广泛分布于皮层与海马，具有独特的高频放电特性，并通过其抑制性反馈机制及前馈机制投射至锥体神经元，调节至关重要的θ和γ节律振荡[15]。在AD中，PV^+神经元的功能障碍具体表现为θ和γ节律的紊乱、神经网络的同步性失调以及认知功能的下降[16-17]。近年来的研究表明，PV^+神经元的活性在AD进程中呈现出显著的双相变化特征。具体而言，在疾病早期阶段（如3月龄APP/PS1转基因小鼠模型中），海马区域的PV^+神经元表现出短暂的过度兴奋状态，同时伴随胞外基质成分的增加以及抑制性突触传递的显著增强；而在疾病晚期（如7月龄模型小鼠中），PV^+神经元活性显著下降，而锥体神经元则出现过度兴奋现象（图1b）[5, 16, 18]。与此相对应，通常被认为由PV^+神经元主导的γ振荡也显示出与PV^+神经元活性一致的双相变化趋势[19-20]。重要的是，在AD早期抑制PV^+神经元活动或晚期增强PV^+神经元活动，均能恢复APP/PS1小鼠的认知功能[21]。这些结果表明，PV^+神经元活性的时间依赖性双相变化可能在AD记忆障碍中起因果性作用，针对时间依赖性的调控具有治疗潜力。除了功能异常，PV^+神经元在AD中还存在数量下降的现象，但目前的研究结果仍存在一定争议。部分研究表明，在多种AD小鼠模型中，PV^+神经元的数量显著减少[22-23]；然而，另有研究并未观察到明显的神经元丢失现象[21, 24]。在上述研究中，无论模型小鼠的神经元数量是否减少，其行为学指标均出现了不同程度的恶化。进一步研究表明，通过化学遗传学或光遗传学技术激活残留的PV^+神经元（以补偿其活性不足），或者通过移植外源性GABA能中间神经元（以补充细胞数量损失），均可有效恢复神经网络的节律振荡功能[23]。综合现有证据，PV^+神经元在AD进展过程中可能经历动态演变：早期主要表现为PV表达下调及突触传递效率下降（可逆性功能障碍），而晚期则可能发展为不可逆的神经元丢失。这种阶段特异性机制或许能够解释不同研究结果之间的矛盾。

SST^+神经元相较于PV^+神经元能够维持长时间的反复放电活动，并通过靶向锥体神经元树突及与其他抑制性中间神经元，抑制自发背景活动并进行精细的信息整合[25-26]。与PV^+神经元相比，SST^+神经元在Aβ诱导的钙离子异常中展现出更高的敏感性。在AD中，Aβ通过钙离子过载导致SST^+神经元过度活跃，并引发细胞兴奋性毒性死亡[27]。早年的临床与动物研究均提示，SST浓度在AD患者及模型小鼠的脑组织和脑脊液中均显著下降，且与Aβ水平呈负相关，二者空间分布高度重叠[28-29]。过去的研究表明，SST的缺乏可能会导致脑啡肽酶（neprilysin，NEP）活性下降，从而影响Aβ的正常降解过程，最终导致其在脑内的异常沉积[30-31]。然而，这一假说近期受到挑战。Williams等[32]发现，与普通AD模型小鼠相比，*SST*基因敲除的AD小鼠虽然表现出脑内淀粉样斑块数量增加，但其全脑提取物中脑啡肽酶的表达水平和活性并未发生显著改变。这一发现提示，SST可能通过直接调控Aβ的聚集过程来抑制淀粉样斑块的形成。值得注意的是，SST与Aβ的共定位现象与SST所具有的神经保护作用之间，似乎存在一种矛盾的关联。进一步研究表明，尽管单体状态下的SST可通过抑制Aβ纤维化发挥神经保护功能，但某些特定的SST聚集形态（例如SST-14异构体）可能具有潜在的有害效应[33-35]。Almeida[36]在总结过往研究的基础上对该问题提出新的病理模型。AD的发病机制关键在于SST^+神经元的功能紊乱，具体机制为SST^+神经元部分丢失，进而失去对大脑内侧区域过度活动的有效控制。剩余的SST^+神经元出现代偿性超兴奋，这种过度的GABA能抑制，促进了轴突Aβ的产生。同时，过量的SST-14释放与Aβ结合形成有毒混合寡聚体，进一步加剧了淀粉样斑块形成和SST^+神经元的丢失（图1c）。这一系列级联反应最终推动AD的神经退行性进展。

VIP^+神经元的分类十分复杂。与多数GABA能中间神经元通过靶向锥体神经元的不同亚细胞域提供抑制以调控神经活动的机制不同，VIP^+神经元主要抑制其他GABA能中间神经元，进而通过去抑制作用激活锥体神经元[37]。这种独特的神经调控模式在目标导向学习、空间导航及情景记忆编码等高级认知功能中发挥着关键作用[38-40]。近期的研究发现，尽管成年3×Tg-AD小鼠的海马体中VIP^+神经元的密度和形态未见显著改变，其放电特性却发生了明显变化，表现为更宽的脉冲和更低的放电频率，导致海马的CA1网络功能出现早期紊乱，并可能影响AD病理进展[41]。VIP^+神经元的异常除了直接影响电生理的过程，还通过影响其分泌功能造

成影响[42]。VIP具有显著的神经保护作用，麻省理工学院的蔡立慧团队[43]近期揭示了VIP⁺神经元与VIP在AD治疗中的潜在价值。研究发现，40 Hz声光刺激能够促进表达VIP⁺神经元释放更多的VIP，进而促使类淋巴管道扩张、邻近血管搏动增强，最终增加颈部淋巴结的淀粉样蛋白排泄，而阻断VIP释放则会使声光刺激无法增强淀粉样蛋白的清除（图1d）。这些研究结果不仅证实了VIP⁺神经元在AD病理过程中的重要性，也为其作为AD治疗的潜在靶点提供了有力证据。

Table 1　Overview of research on GABAergic interneuron dysfunction in Alzheimer's disease

表1　阿尔茨海默病中GABA能中间神经元功能障碍研究概览

中间神经元类型	近期主要发现	参考文献
PV⁺神经元	PV⁺神经元活性在AD病程中呈现双相变化	Hijazi等，2020[21]
	AD小鼠未存在明显的PV⁺神经元丢失，但出现学习记忆障碍	Sanchez-Mejias等，2020[24]
SST⁺神经元	SST可能直接调控Aβ的聚集过程来抑制淀粉样斑块的形成	Williams等，2023[32]
	提出SST⁺神经元通过GABA能抑制作用促进Aβ生成，并形成毒性聚集体的AD病理机制模型	Almeida，2024[36]
VIP⁺神经	VIP⁺神经元放电特性异常导致CA1网络早期功能紊乱	Michaud等，2024[41]
	40Hz刺激促进VIP释放，增强类淋巴清除淀粉样蛋白	Murdock等，2024[43]

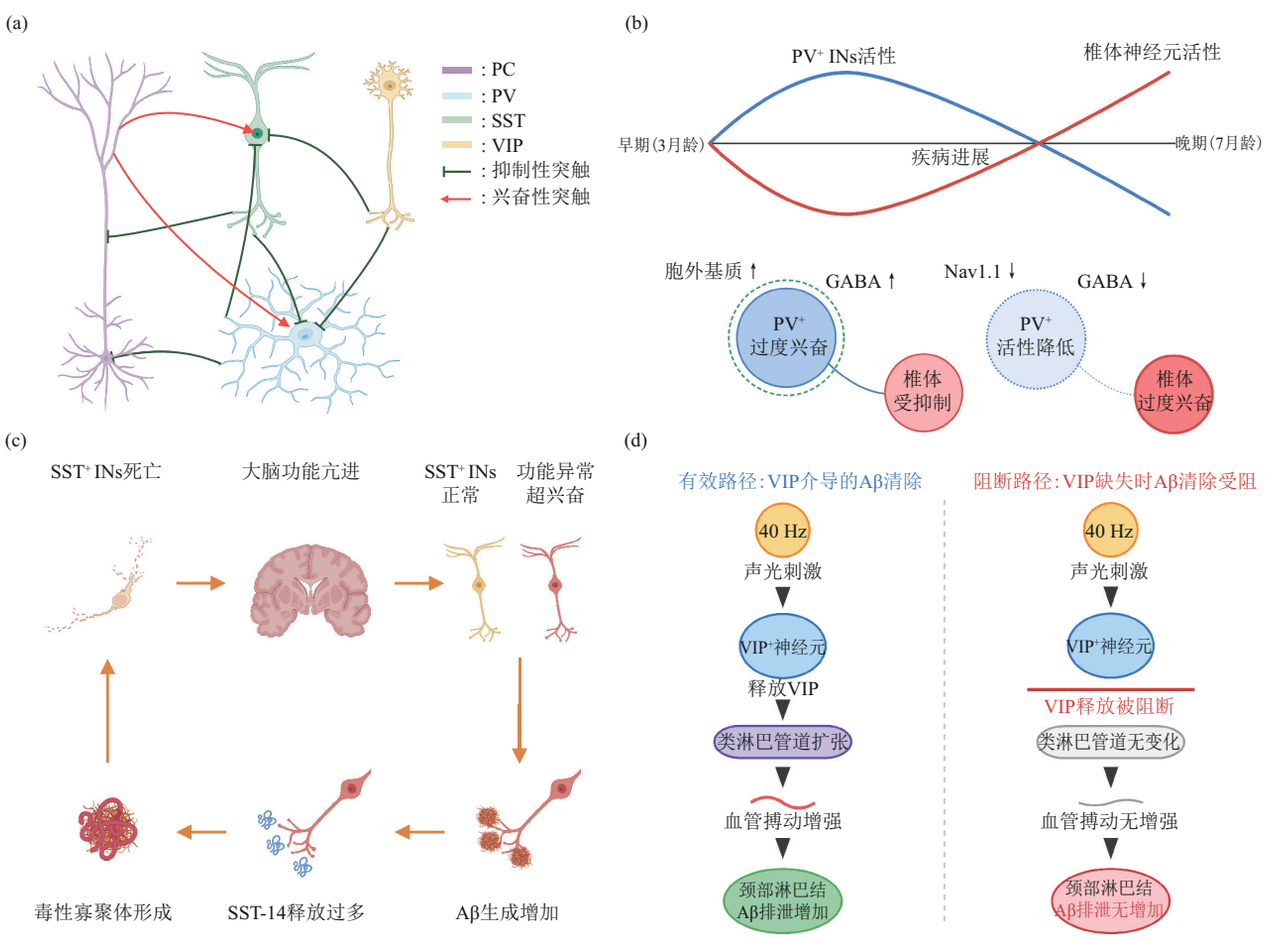

Fig. 1　Neural circuit interactions and disease mechanisms in cortical networks

图1　皮层神经网络中的神经环路相互作用和疾病机制

（a）不同神经元类型（PC，PV，SST，VIP）之间连接的示意图，包括抑制性（绿色）和兴奋性（红色）突触连接。（b）AD小鼠发育早期（3个月）和晚期（7个月）疾病阶段PV⁺中间神经元活性（蓝色）和锥体神经元活性（红色）的变化，以及对应的病理改变。（c）SST⁺中间神经元功能障碍导致神经退行性变化的AD病理模型。（d）40 Hz声波刺激后，完整（左）和中断（右）的VIP介导的Aβ清除通路比较。本图使用BioRender制作。

2 基于GABA能中间神经元的阿尔茨海默病靶向治疗

GABA能中间神经元在神经系统中的关键作用使其成为AD治疗研究的重要靶点。在AD的病程发展中，GABA能中间神经元不仅数量显著减少，其神经活性也呈现下降趋势。提升GABA能中间神经元的数量，或可成为AD治疗的一种潜在有效策略。在药物治疗方面，选择性5-羟色胺再摄取抑制剂西酞普兰展现出多重治疗潜力。体外试验证实其可减少Aβ的形成，并降低APP/PS1小鼠的Aβ负荷[44]。皮质PV^+神经元通过维持皮质回路可塑性，对短期记忆和社会互动的保持具有重要作用。在6月龄APP/PS1小鼠中观察到的皮质PV^+神经元减少现象，可通过西酞普兰治疗进行改善，从而挽救行为学表现[45]。此外，干细胞疗法也是一种增加GABA能中间神经元数量的途径。研究显示，将人胚胎干细胞移植至AD小鼠海马后可分化为功能正常的GABA能中间神经元，这种移植显著改善了神经元回路功能的障碍，提高了AD小鼠的认知能力[46]。

除了增加数量，改善GABA能中间神经元活性也是治疗AD的潜在方式。药物方面，低剂量左乙拉西坦能通过恢复PV^+神经元活动，增强AD小鼠模型中受损的γ振荡节律性[47]。还有研究表明，通过靶向调控PV^+神经元的特定分子（如激活代谢型谷氨酸受体mGluR5或递送神经肽NPTX2、Nrg1等），增强PV^+神经元的兴奋性和突触可塑性，能够恢复AD小鼠神经网络的γ振荡及其记忆功能[48]。非侵入性神经调控技术也显示出良好的应用前景。研究发现，重复经颅磁刺激（repetitive transcranial magnetic stimulation，rTMS）、伽马感觉刺激（gamma entrainment using sensory stimulation，GENUS）可以通过外部40 Hz节律刺激诱导神经网络同步振荡，改善PV^+神经元介导的抑制性调控，促进记忆巩固并减少Aβ沉积，这与近期40 Hz治疗机制研究上的进展相符合[43，48]。此外，微创性技术如电针刺激（electroacupuncture，EA）被发现能够减少5×FAD小鼠的海马体SST^+神经元丢失，改善小鼠的认知损伤和记忆缺陷[49]。

和改善GABA能中间神经元数量及活性目标相似的，针对GABA系统直接进行干预也被证明为潜在的治疗途径。临床研究发现，AD患者颞叶及顶叶皮层GABA和谷氨酸水平显著降低，提示突触功能和神经元传递存在缺陷[50]。此外，AD患者皮层SST表达也减少50%[51]。动物实验表明，APP/PS1小鼠海马和脑脊液中GABA水平显著降低，对该模型小鼠早期给予GABA可改善其认知功能，而在6月龄或8月龄给药则无此效果，提示早期GABA干预可能具有治疗AD的潜力[52]。这些研究成果不仅为基于GABA能中间神经元的AD治疗奠定了坚实的理论基础，还提供了丰富的实验证据，为探索和开发新型AD治疗策略指明了方向。

3 总结与展望

在AD的发展中，PV^+、SST^+和VIP^+中间神经元表现出不同的病理反应特征，这些研究深化了对AD病理机制的理解。以GABA能信号通路为靶点，结合精准生物标记物的检测手段，可能实现更早期、更有效的干预。然而，未来研究需解决以下关键问题：a. 解析GABA能中间神经元亚型间的相互作用及其对神经网络的影响；b. 探索不同亚型受损机制的分子通路及潜在治疗策略；c. 制定基于疾病阶段和个体病理特征的个性化神经调控方案。总之，维持和恢复GABA能中间神经元的功能对延缓AD进程至关重要。从单一神经元活性调节扩展到网络功能重塑的研究方法，将为AD的预防、诊断和治疗提供新方向，并为其他神经退行性疾病研究带来启示。

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The Critical Roles of GABAergic Interneurons in The Pathological Progression of Alzheimer's Disease*

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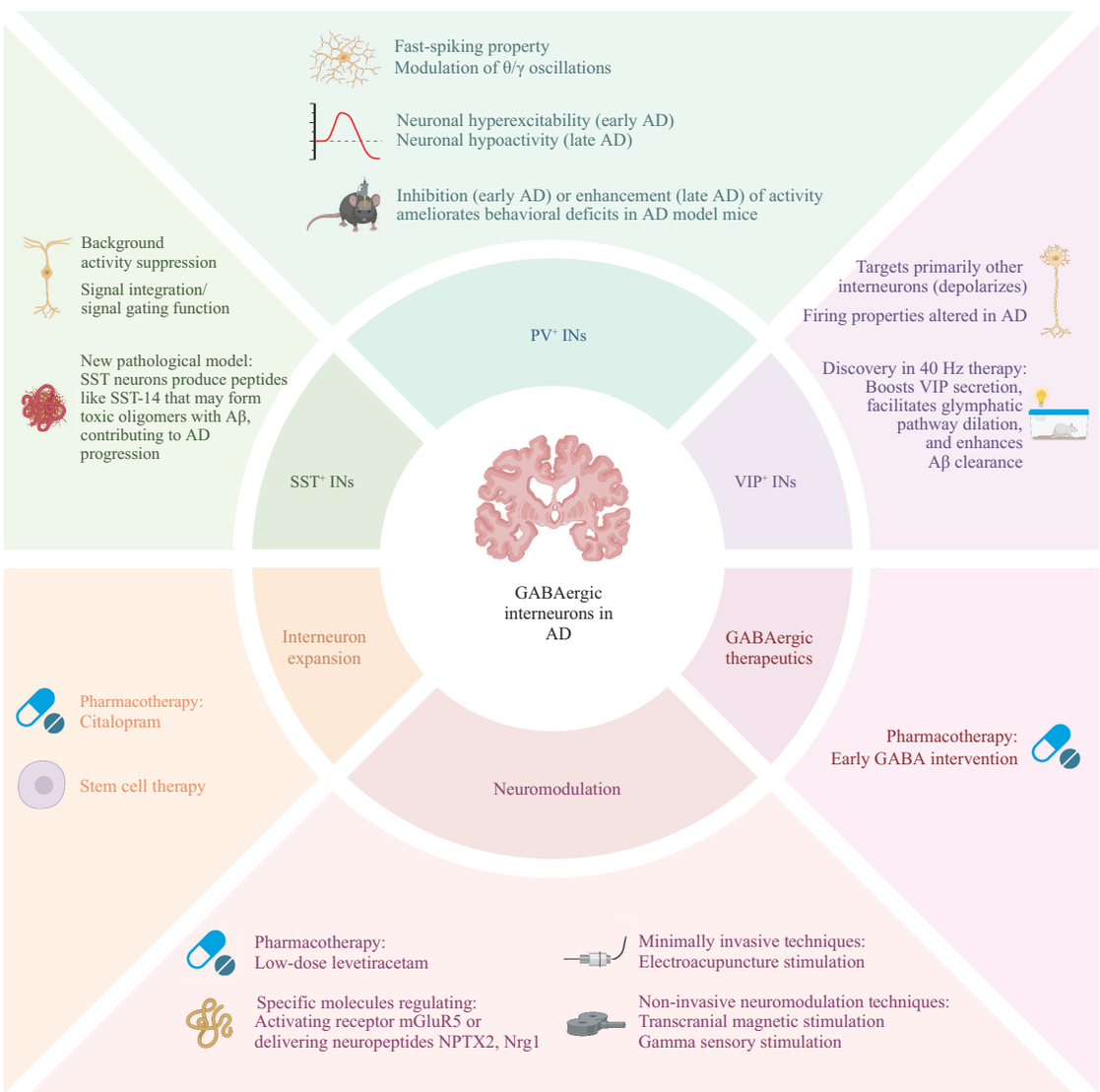
Graphical abstract



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Abstract Alzheimer's disease (AD), a progressive neurodegenerative disorder and the leading cause of dementia in the elderly, is characterized by severe cognitive decline, loss of daily living abilities, and neuropsychiatric symptoms. This condition imposes a substantial burden on patients, families, and society. Despite extensive research efforts, the complex pathogenesis of AD, particularly the early mechanisms underlying cognitive dysfunction, remains incompletely understood, posing significant challenges for timely diagnosis and effective therapeutic intervention. Among the various cellular components implicated in AD, GABAergic interneurons have emerged as critical players in the pathological cascade, playing a pivotal role in maintaining neural network integrity and function in key brain regions affected by the disease. GABAergic interneurons represent a heterogeneous population of inhibitory neurons essential for sustaining neural network homeostasis. They achieve this by precisely modulating rhythmic oscillatory activity (*e.g.*, theta and gamma oscillations), which are crucial for cognitive processes such as learning and memory. These interneurons synthesize and release the inhibitory neurotransmitter GABA, exerting potent control over excitatory pyramidal neurons through intricate local circuits. Their primary mechanism involves synaptic inhibition, thereby modulating the excitability and synchrony of neural populations. Emerging evidence highlights the significant involvement of GABAergic interneuron dysfunction in AD pathogenesis. Contrary to earlier assumptions of their resistance to the disease, specific subtypes exhibit vulnerability or altered function early in the disease process. Critically, this impairment is not merely a consequence but appears to be a key driver of network hyperexcitability, a hallmark feature of AD models and potentially a core mechanism underlying cognitive deficits. For instance, parvalbumin-positive (PV^+) interneurons display biphasic alterations in activity. Both suppressing early hyperactivity or enhancing late activity can rescue cognitive deficits, underscoring their causal role. Somatostatin-positive (SST^+) neurons are highly sensitive to amyloid β-protein (Aβ) dysfunction. Their functional impairment drives AD progression *via* a dual pathway: compensatory hyperexcitability promotes Aβ generation, while released SST-14 forms toxic oligomers with Aβ, collectively accelerating neuronal loss and amyloid deposition, forming a vicious cycle. Vasoactive intestinal peptide-positive (VIP^+) neurons, although potentially spared in number early in the disease, exhibit altered firing properties (*e.g.*, broader spikes, lower frequency), contributing to network dysfunction (*e.g.*, in CA1). Furthermore, VIP release induced by 40 Hz sensory stimulation (GENUS) enhances glymphatic clearance of Aβ, demonstrating a direct link between VIP neuron function and modulation of amyloid pathology. Given their central role in network stability and their demonstrable dysfunction in AD, GABAergic interneurons represent promising therapeutic targets. Current research primarily explores three approaches: increasing interneuron numbers (*e.g.*, improving cortical PV^+ interneuron counts and behavior in APP/PS1 mice with the antidepressant citalopram; transplanting stem cells differentiated into functional GABAergic neurons to enhance cognition), enhancing neuronal activity (*e.g.*, using low-dose levetiracetam or targeted activation of specific molecules to boost PV^+ interneuron excitability, restoring neural network γ-oscillations and memory; non-invasive neuromodulation techniques like 40 Hz repetitive transcranial magnetic stimulation (rTMS), GENUS, and minimally invasive electroacupuncture to improve inhibitory regulation, promote memory, and reduce Aβ), and direct GABA system intervention (clinical and animal studies reveal reduced GABA levels in AD-affected brain regions; early GABA supplementation improves cognition in APP/PS1 mice, suggesting a therapeutic time window). Collectively, these findings establish GABAergic interneuron intervention as a foundational rationale and distinct pathway for AD therapy. In conclusion, GABAergic interneurons, particularly the PV^+, SST^+, and VIP^+ subtypes, play critical and subtype-specific roles in the initiation and progression of AD pathology. Their dysfunction significantly contributes to network hyperexcitability, oscillatory deficits, and cognitive decline. Understanding the heterogeneity in their vulnerability and response mechanisms provides crucial insights into AD pathogenesis. Targeting these interneurons through pharmacological, neuromodulatory, or cellular approaches offers promising avenues for developing novel, potentially disease-modifying therapies.

Key words Alzheimer's disease, GABAergic interneurons, amyloid β-protein, network dysfunction
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