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已应用于中药研究的阿尔茨海默病动物模型综述

裴金英[1],刘佳林[1],刘 斌[1*],董晓红[1],丛树园[2],任秀敏[3],周勇杰[4]

(1.黑龙江中医药大学,哈尔滨 150040;2.云南中医药大学,昆明 650500;
3.佳木斯大学,黑龙江 佳木斯 154007;4.黄渡社区卫生服务中心,上海 201804)

【摘要】 阿尔茨海默病(Alzheimer's disease, AD)是一种与年龄相关的神经退行性疾病,临床主要表现为进行性认知障碍以及记忆、语言功能的减退等。随着我国人口老龄化进程的加快,我国患 AD 的人数也在不断增加,而 AD 的确切发病机制尚不明确,目前治疗策略也仅是对症治疗为主。动物模型是临床前研究的重要工具,用于探索疾病的分子机制、行为功能和治疗策略。未来对 AD 的机制研究和药物开发需要建立与临床病理特征相符合的动物模型。本文主要对近年来研究报道中常用的 AD 动物模型进行总结,并详细阐述相关 AD 动物模型的品系、年龄、造模方式、造模剂量、中药组分研究及药效机制,以期为未来建立新的动物模型或深入探讨中药中各组分的具体药理活性、靶点、代谢途径、临床应用等提供一些参考。

【关键词】 阿尔茨海默病;动物模型;啮齿动物;中药组分;药效机制
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Review of animal models of Alzheimer's disease applied in traditional Chinese medicine research

PEI Jinying[1], LIU Jialin[1], LIU Bin[1*], DONG Xiaohong[1], CONG Shuyuan[2], REN Xiumin[3], ZHOU Yongjie[4]

(1. Heilongjiang University of Chinese Medicine, Harbin 150040, China.
2. Yunnan University of Chinese Medicine, Kunming 650500. 3. Jiamusi University, Jiamusi 154007.
4. Huangdu Community Service Center, Shanghai 201804)

【Abstract】 Alzheimer's disease (AD) is an age-related neurodegenerative disease that mainly manifests clinically as progressive functional impairments in cognition, memory, and language. With the accelerated transition toward an older population in China, the number of people suffering from AD in China is increasing. The exact pathogenesis of AD remains unclear, with current therapeutic strategies mainly limited to symptomatic treatments. Animal models are important tools for preclinical research, enabling explorations of molecular mechanisms, behavioral functions, and treatment strategies of diseases. Future mechanistic research and drug development of AD should involve the establishment of animal models that are consistent with clinical pathological characteristics. This review summarizes the AD animal models commonly used in research, providing details on the strains, age, modeling method and doses. It also discusses research on traditional Chinese medicine (TCM) components and their pharmacodynamic

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[**作者简介**]裴金英(1991—),女,在读硕士研究生,主治医师,研究方向:中药防治老年性疾病。E-mail:peijinying2023@126.com
[**通信作者**]刘斌(1970—),男,博士,教授,研究方向:中药防治老年性疾病。E-mail:liubin169@163.com

mechanisms in related AD animal models, aiming to provide references for the development of new animal models and in-depth exploration of the specific pharmacological activities, targets, metabolic pathways, and clinical applications of each TCM component.

【Keywords】 Alzheimer's disease; animal model; rodents; Chinese medicine components; mechanism of action

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阿尔茨海默病(Alzheimer's disease, AD)是发生于老年和老年前期,以进行性认知功能障碍和行为损害为特征的中枢神经系统退行性病变,是老年期痴呆最常见的类型,占所有病例的 60%~70%[1]。现有的研究主要集中在 AD 的两个主要病理特征上:细胞外 β-淀粉样蛋白(Amyloid β-protein,Aβ)异常沉积形成的老年斑(senile plaque,SP)和细胞内异常过度磷酸化 tau 蛋白聚集形成的神经原纤维缠结(neurofibrillary tangles, NFTs)。AD 发病机制存在多种假说,如 Aβ 假说、tau 蛋白过度磷酸化、氧化应激、神经炎症、线粒体功能障碍、胆碱能假说等[2]。根据民政部发布的《2023 年度国家老龄事业发展公报》数据显示,截至 2023 年末,全国 60 岁及以上老年人口为 29 697 万人,约占总人口的 21.1%,中国的老龄化呈现出规模大、速度快、程度深、高龄占比高的特点[3]。随着人口老龄化的程度进一步加深,AD 患病率也逐年上升,2021 年我国现存的 AD 及其他痴呆患病人数达 16 990 827 例,给社会和家庭都带来了沉重的负担[4]。目前,AD 的治疗药物主要分为两大类:胆碱酯酶抑制剂与 NMDA 受体拮抗剂。虽然可在一定程度上缓解 AD 症状,但治疗作用却因人而异,且无法治愈或阻止疾病的进展。

良好的 AD 动物模型是研究 AD 病因和机制,寻找特效治疗药物的关键环节。如何基于 AD 临床病症的特点,复制出与临床状态相一致的动物模型,进行新型疗法的临床前测试,是目前研究的重点内容之一。近几十年来,已经报道了各种与 AD 相关的动物模型,但 AD 临床试验的成功记录并不乐观,在某种程度上,这种高失败率可能与动物模型仅反映了 AD 病理学结果有关[5]。选择合适的实验动物模型是解决这一难题的前提条件。深入地了解每种模型的优缺点,并使用多模型来评估潜在疗法,将有助于提高从临床前研究到患者治疗的转化成功率。本文分析探讨了不同 AD 动物模型的特征和局限性,以及在不同 AD 动物模型中,相关中药组分研究的现状,以期为未来构建或选择 AD 相关模型以及 AD 相关中药组分的研究提供参考。

1 文献检索策略

文献检索策略:计算机检索 PubMed 和中国知网数据库,检索时间设定为 2020 年 1 月~2025 年 1 月。中文检索词包括"阿尔茨海默病""动物模型""啮齿动物""中药组分""药效机制",英文检索词包括"Alzheimer's disease""animal model""rodents""Chinese medicine components""mechanism of action"。共检索到 3562 篇文献,最后纳入综述 96 篇文章,该领域的年度发文量呈上升趋势。纳入标准:文献涉及啮齿动物、动物模型、中药组分、药效机制等与阿尔茨海默病相关的内容。排除标准:与本文主题无关联,未公开的、无法获取原文的文献。

2 常见 AD 动物模型

实验动物是模拟疾病的载体,可靠的动物模型对 AD 的基础研究和药物开发至关重要。目前,基于病理生理学建立的 AD 模型主要有 3 种类型:自然衰老动物模型、转基因动物模型、药物介入性动物模型[6]。啮齿动物因为其体型小、寿命短、繁殖能力强、维护成本低以及可基因修饰的胚胎干细胞,长期以来一直作为开发 AD 模型的主要资源。由于 AD 发病机制尚不明确,如何模拟构建出完全符合疾病发病机制特点的模型依旧是未来需要攻克的难题。2022 年 12 月,美国颁布了 FDA 现代化法案 2.0,取消了新药开发中对动物试验的强制性要求[7],这种变化从另一方面也反映了人工智能和器官芯片技术的进步,为评估吸收、分布、代谢、排泄和毒性提供了阶段

性变化[8]。尽管有这些发展,目前 AD 的动物实验模型对于提高转化成功率仍然至关重要。

2.1 自然衰老动物模型

某些哺乳类动物,如非人灵长类动物(nonhuman primate,NHP)模型、伴侣动物模型(驯养的猫和狗)、树鼩等,可随着年龄的增长而自然发展为认知障碍出现主要的 AD 样病症。恒河猴的大脑结构和功能比啮齿动物更像人类,且 NHP 的行为与人类相似,具有易于圈养和快速发育等优点,是 NHP 模型中使用最广泛的物种。有团队研究了从年轻到极老(至 38 岁)的恒河猴,以捕捉 tau 磷酸化的早期阶段及其在脑内进展到纤维化的过程,其中最老的动物可达到 Braak III/IV 期[9]。但这种模型也存在发育缓慢、体型庞大、对社会关系的依赖性等问题。众所周知,伴侣动物和人类共享相似的环境,它们表现出相对较长的寿命,并拥有与衰老中相似的神经病理学,包括磷酸化 tau(phosphorylated tau,p-tau)、NFT、斑块、血管性脑淀粉样血管病、髓鞘破坏、脂褐素、神经元液泡、轴突变性和胆碱能神经元异常,就像在 AD 中观察到的那样[10]。此外,在成年(约 1 岁)和老年(6 岁或以上)树鼩的认知测评中发现,后者表现出明显的认知能力受损,还发现与 AD 相似的病理特征,包括 Aβ 积累和 p-tau 水平增加、突触和神经元丢失以及皮层和海马组织中的反应性神经胶质增生[11]。

以上这些动物比啮齿动物的遗传亲和力要密切得多,所以这些动物模型可用于 AD 发病机制和治疗剂效果的研究。然而,这些哺乳动物和人类之间的 AD 病理学存在一些差异,以及其他因素,如高维护成本、低生殖输出、操作挑战和人畜共患的传播风险[12]。2023 年 12 月,首届非传统动物模型 AD 和衰老国际会议在智利举行,会议讨论和强调了新的研究方向、替代动物模型和创新方法,以促进 AD 和衰老研究领域的发展[13]。

2.2 转基因动物模型

基因工程的进步使得更多转基因 AD 模型的产生成为可能。转基因 AD 动物模型可以在分子水平上模拟 AD,呈现典型的症状和体征,而且在稳定性和可靠性方面优于其他 AD 相关模型,但开发成本相对较高[14]。大鼠在生理、形态和遗传特征上与人类更相似,有更丰富的行为表型,在实验中也更容易操作。但由于相对较低的繁殖能力、对住房空间的需求较大以及调节技术有限,转基因大鼠模型的发展一直很缓慢[15]。相较而言,小鼠繁殖周期短、维护成本相对较低和已建立相对完善的研究体系,因此,AD 研究中使用的绝大多数动物模型是转基因小鼠。迄今为止,已经生成了 170 多个包含 AD 相关突变的转基因小鼠模型来研究这种神经退行性疾病,这些发现促进了我们对 AD 的理解[16]。

有研究发现,在品系为 Tg12099 的人类 tau 表达突变(P301S)的转基因大鼠中发现,tau 蛋白的区域传播和神经变性更接近于人类原发性的 tau 蛋白[17]。在 McGill-R-Thy1-APP 转基因大鼠的研究中发现,在 Aβ 斑块之前,神经元内 Aβ 积累诱导了海马神经元中突触可塑性基因的早期氧化应激、DNA 损伤和适应不良表达[18]。野生型小鼠 APP(695 亚型)与人 APP 具有 97%的序列同源性,而小鼠和人之间的序列差异包括 Aβ 序列中的 3 个氨基酸(R5G、Y10F 和 H13R),虽然这种模型展现出增加了 Aβ 产生,但未能一致地显示出广泛的 AD 相关神经病理学[19]。研究发现,Thy1-ApoE4/C/EBPβ 转基因小鼠在没有任何人类淀粉样前体蛋白(amyloid precursor protein,APP)或早老素-1/早老素-2(Presenilin 1/Presenilin 2,PS1/PS2)突变的情况下,以年龄依赖性方式展示了关键的 AD 病理,可充当散发性 AD 模型[20]。此外,在 PS1/PS2 条件性双敲除(DKO)和双转基因(DTG)小鼠的实验中,通过研究其海马组织中纤维蛋白 1(Fibulin 1,FBLN1)基因甲基化改变,可增强对 AD 表观遗传机制的理解[21]。3xTg-AD 小鼠是将突变基因 APPSwe 和 tauP301L 注入单转纯合子小鼠 PS1M146V 的胚胎干细胞进行培育。其脑内可逐渐出现细胞内沉积、细胞外沉积形成的 Aβ 斑块和高度磷酸化的微管相关蛋白及随后由它形成的 NFT,更符合临床 AD 患者的病理表现[22]。此外,5xFAD 小鼠从 2~6 个月的进展,有效地模拟了人类从临床前 AD 到轻度认知障碍(mild cognitive impairment,MCI)的转变。进一步分析发现,其大脑中 Aβ 积累、髓鞘变性和神经胶质增生呈现年龄依赖性增加,并涉及到皮质乙酸酯代谢和海马葡萄糖代

谢[23]。这些转基因小鼠模型的一个主要限制是缺乏 AD 中发生的广泛的神经变性和局部脑萎缩。大多数情况下这些模型阐述了可能的潜在机制,然而,有些在家族性 AD 模型中被证明成功的疗法却在晚发性 AD 的人体临床试验中进行评估时失败了[24]。现对已应用于中药研究的转基因啮齿类 AD 动物模型进行介绍(见表 1)。

2.3 药物介入性动物模型

药物介入性 AD 动物模型是通过向模型鼠脑部、皮下或腹腔注射特定物质来建立模型。常见的用于建立 AD 动物模型的药物有 Aβ、鹅蒿蕈氨酸(ibotenic acid, IBO)、链脲佐菌素(streptozotocin,STZ)、D-半乳糖(D-galactose,D-gal)、铝、冈田酸(okadaic acid,OA)、东莨菪碱(scopolamine,SCOP)。经由药物介入的造模方式具有快速诱导记忆障碍、易操作和花费少的基本特点,更重要的是它在模拟人类 AD 的典型临床的同时也具备一些组织病理学和关键免疫学特征。然而这些单一的模型复制方法,只能从某一角度反映 AD 的病理机制,未能全面呈现出 AD 中多病理改变的特征[31]。存在实验动物发病晚、个体差异大、实验持续时间长、死亡率高等局限。

2.3.1 Aβ

AD 病理的标志之一,是 Aβ 聚集到患者大脑中的淀粉样蛋白斑块中,将 Aβ 片段注射到侧脑室或海马 CA1 区中,可模拟 AD 患者中 Aβ 对中枢神经的毒性[32]。Aβ 肽长度可以在 37 到 49 个氨基酸之间变化,一般有 3 种,即 Aβ1-42、Aβ1-40 和 Aβ25-35,其中 Aβ1-42 是当中最危险的形式[33]。研究发现每一种寡聚体都具有独特的特

表 1 转基因啮齿类 AD 动物模型

Table 1 Transgenic rodent AD models

造模动物品系 Model animal strains	年龄 Age	造模方式 Modeling method	已应用评价的中药组分 Traditional Chinese medicine components that have been evaluated	中药组分的药效机制 Pharmacodynamic mechanisms of Chinese herbal medicine components
雄性 APP/PS1 小鼠[25] Male APP/PS1 mice	6 月龄 Six-month old	基因编辑 Gene editing	人参皂甙 Rg1 Ginsenoside Rg1	抗炎,改善突触功能障碍,抑制自噬 Anti-inflammatory, improves synaptic dysfunction, inhibits autophagy
雄性 APP/PS1 小鼠[26] Male APP/PS1 mice	8 月龄 Eight-month-old	基因编辑 Gene editing	毛蕊花糖苷 Verbascoside/acteoside	抗炎,抑制小胶质细胞和星形胶质细胞激活 Anti-inflammatory, inhibits microglia and astrocyte activation
雄性 3xTg 小鼠[27] Male 3xTg mice	3 月龄 3-month old	基因编辑 Gene editing	补骨脂乙素 Isobavachalcone	缓解突触功能障碍,抑制 Aβ 的寡聚化和原纤化,抑制 tau 形成和聚集,影响胆汁酸代谢、酪氨酸代谢、嘌呤代谢 It alleviates synaptic dysfunction, inhibits the oligomerization and fibrillation of Aβ, inhibits tau formation and aggregation, and affects bile acid metabolism, tyrosine metabolism, and purine metabolism
雄性 3xTg 小鼠[28] Male 3xTg mice	11~13 月龄 11 ~ 13-month-old	基因编辑 Gene editing	高丽参的多糖 Korean red ginseng polysaccharide	减轻神经元损失,改善 Aβ 沉积、神经变性和神经炎症 Reduces neuronal loss, improves Aβ deposition, neurodegeneration, and neuroinflammation
5xFAD 小鼠[29] 5xFAD mice	6 月龄 Six-month-old	基因编辑 Gene editing	枸杞提取物 Lycium barbarum extract	抗炎,减少小胶质细胞活化,促进了小胶质细胞吞噬作用,调节突触可塑性 Anti-inflammatory, reduces microglial activation, promotes microglial phagocytosis, regulates synaptic plasticity
5xFAD 小鼠[30] 5xFAD mice	5 月龄 Five-month-old	基因编辑 Gene editing	艾蒿提取物 *Artemisiae iwayomogii* herba extract	调节小胶质细胞活化和自噬-溶酶体途径,改善神经炎症和 Aβ 积累 Regulates microglia activation and autophagy-lysosomal pathways, improves neuroinflammation and Aβ accumulation

征,Aβ 原纤维构象差异会对 Aβ 抗体检测产生根本性影响[34]。Aβ 诱导的 AD 模型大脑内可出现,Aβ 沉积明显、反应性胶质增生、氧化应激、神经炎症以及突触和记忆缺陷等 AD 病理表现[35]。这种造模方式对脑组织造成的穿透性损伤具有不确定性,其急性发病与 AD 慢性起病的特点也存在差异。现对已应用于中药研究的 Aβ 诱导啮齿类 AD 动物模型进行介绍(见表 2)。

2.3.2 IBO

IBO 是一种有效的谷氨酸受体激动剂,可导致胆碱能神经系统损伤,继而影响动物认知功能。IBO 可优先与神经元胞体或树突上的 NMDA 受体结合,导致延长激活和类似于谷氨酸的兴奋性毒性。研究发现,IBO 诱导的模型会损害前额叶皮层,令杏仁核的树突棘减少,表现出工作记忆和社交行为的缺陷[42]。此外,将 IBO 注入大鼠梅纳特基底核后,可选择性地破坏该区域的神经元胞体,造成被动逃避反应潜伏期缩短。其组织学检查可见,腹侧丘脑和小丘脑外侧区损毁,苍白球腹内侧核胆碱能神经元大部分消失,胶质细胞增生等病理症状[43]。虽然这种动物模型可表现有胆碱能系统功能丧失和学习记忆损害,但无全身衰老的表现,且难以诱导产生 AD 的病理学特征,还可能损害临近部位的非胆碱能神经元。现对已应用于中药研究的 IBO 诱导啮齿类 AD 动物模型进行介绍(见表 3)。

表 2 Aβ 诱导啮齿类 AD 动物模型

Table 2 Aβ-induced rodent AD models

造模动物品系 Model animal strains	造模方式 Modeling method	药物剂量 Drug dosage	年龄 Age	已应用评价的中药组分 Traditional Chinese medicine components that have been evaluated	中药组分的药效机制 Pharmacodynamic mechanisms of Chinese herbal medicine components
雄性 C57BL/6J 小鼠[36] Male C57BL/6J mice	Aβ25-35, i. c. v.	200 μmol/L	6~7 周龄 6 ~ 7-week-old	新补骨脂异黄酮 Neobavaisoflavone	改善海马神经元损伤及神经炎症,减少细胞凋亡、氧化应激和线粒体膜电位,并调节免疫细胞 Improve hippocampal neuronal damage and neuroinflammation, reduce apoptosis, oxidative stress and mitochondrial membrane potential, and regulate immune cells
雄性 SD 大鼠[37] Male SD rats	A0β25-35, i. c. v.	5 μL	成年 Adult	戈米辛 N Gomisin N	减轻 Aβ 积累和神经元死亡,改善氧化应激 Reduces Aβ accumulation and neuronal death, and improves oxidative stress
雄性 ICR 小鼠[38] Male ICR mice	Aβ25-35, i. c. v.	2 μL	未提及 Not mentioned	藏红花素 Crocin	减轻海马神经元损伤,抑制神经炎症 Reduces hippocampal neuronal damage and inhibits nerve inflammation
雄性 C57BL/6J 小鼠[39] Male C57BL/6J mice	Aβ25-35, i. c. v.	200 μmol/L	6 周龄 6-week-old	山茱萸提取物 Cornus officinalis extract	缓解海马体的突触损伤及免疫失衡,调节线粒体动力学紊乱,减轻胶质细胞异常激活引发的免疫炎症 It alleviates synaptic damage and immune imbalance in the hippocampus, regulates mitochondrial kinetic disorders, and alleviates immune inflammation caused by abnormal activation of glial cells
雄性 Wistar 大鼠[40] Male Wistar rats	Aβ1-42, i. c. v.	2 μL	4 月龄 4-month-old	锁阳总黄酮 Cynomorium songaricum flavonoid extract	抑制神经元凋亡,恢复神经递质的产生,并增加突触可塑性 Inhibits neuronal apoptosis, restores neurotransmitter production, and increases synaptic plasticity
雄性 ICR 小鼠[41] Male ICR mice	Aβ1-42, i. c. v.	3 μL	6~8 周龄 6~8-week-old	淫羊藿苷 Icariin	修复海马神经元损伤,改善突触可塑性 Repair hippocampal neuronal damage and improve synaptic plasticity

表 3 IBO 诱导啮齿类 AD 动物模型
Table 3 IBO-induced rodent AD models

造模动物品系 Model animal strains	造模方式 Modeling method	药物剂量/(μg/μL) Drug dosage	年龄 Age	已应用评价的中药组分 Traditional Chinese medicine components that have been evaluated	中药组分的药效机制 Pharmacodynamic mechanisms of Chinese herbal medicine components
雄性 SD 大鼠[44] Male SD rats	IBO, i. c. v.	4	3 月龄 3-month-old	淫羊藿苷 Icariin	抑制促凋亡因子表达,上调钙结合蛋白表达来调节 Ca^{2+} 稳态,以促进海马神经元的存活 Inhibition of pro-apoptotic factor expression and up-regulation of calcium-binding protein expression to regulate Ca^{2+} homeostasis to promote the survival of hippocampal neurons
SD 大鼠,雌雄各半[45] SD rats, half male and half female	IBO, i. c. v.	5	3 月龄 3-month-old	胡椒碱 Piperine	抗炎,调节胆碱能系统,抑制神经元凋亡和氧化应激 Anti-inflammatory, regulates the cholinergic system, inhibits neuronal apoptosis and oxidative stress
雄性 SD 大鼠[46] Male SD rats	IBO, i. c. v.	2	成年 Adult	淫羊藿次苷 Icariside II	抑制神经元凋亡反应,减轻兴奋性氨基酸毒性的损害 Inhibits neuronal apoptotic responses and attenuates damage from excitatory amino acid toxicity
雄性 Wistar 大鼠[47] Male Wistar rats	IBO, i. c. v.	5	未提及 Not mentioned	白藜芦醇 Resveratrol	改变谷氨酸能和胆碱能途径、减少氧化应激 Alter glutamatergic and cholinergic pathways and reduce oxidative stress
Wistar 大鼠[48] Wistar rats	IBO, i. c. v.	5	成年 Adult	富含百里醌的黑孜然油 Thymoquinone-rich black cumin oil	调节胆碱能、谷氨酸能和氨基酸能神经传递,抗神经炎症 Regulates cholinergic, glutamatergic and amino acid neurotransmission, anti-neuroinflammation
雄性 SD 大鼠[49] Male SD rats	IBO, i. c. v.	5	3 月龄 3-month-old	木通皂苷 D Akebia saponin D	影响胆碱能途径,抑制凋亡 Affects cholinergic pathways, inhibits apoptosis

2.3.3 STZ

STZ 是一种氨基葡萄糖-亚硝基脲类化合物,会损害胰腺的 β 细胞并导致胰岛素抵抗。此前多项研究表明,AD 患者的脑葡萄糖代谢显著失调,胰岛素信号传导在一定程度上参与调节认知能力、Aβ 代谢、tau 表达和磷酸化[50]。据此,向动物脑内注射胰岛素细胞毒素 STZ 后,会产生脑内胰岛素抵抗状态,破坏脑胰岛素信号传导,导致全身能量代谢失衡。在细胞水平上表现为神经重塑性降低、受体调节神经元释放神经递质功能下降和神经元摄取葡萄糖减弱,最终引起 Aβ 和 NFT 的积累与进行性认知障碍的发生[51]。有研究发现,STZ(5 mg/kg)给药后 7 d 诱导了斑马鱼模型的认知缺陷,同时观察到 AD 的淀粉样变和 tau 病理特征[52]。表明了 STZ 诱导的模型作为研究散发性 AD 病理生理学和快速筛选治疗散发性 AD 分子的潜力。现对已应用于中药研究的 STZ 诱导啮齿类 AD 动物模型进行介绍(表 4)。

2.3.4 D-gal

D-gal 是一种天然的还原性单糖。高水平的 D-gal 通过醛糖还原酶的催化转化为半乳糖醇,在细胞中不断积累导致细胞肿胀、功能障碍,并最终导致细胞老化。或者通过另一种代谢途径产生活性氧(reactive oxygen species,ROS)和晚期糖基化终产物(advanced glycation end products, AGEs),从而加速衰老过程[58]。该造模过程表现出接近 AD 自然老化的生理特点,多用于制备脑老化模型。此前有研究发现,皮下注射 D-gal

(1000 mg/kg)1 周,可产生与轻度认知功能障碍特征和病理过程一致的变化[59]。近期研究发现,在切除雌性大鼠卵巢和注射 D-gal 建立的 AD 模型中,出现了学习和记忆的减退。其作用机制可能与 D-gal 诱导的神经炎症改变、肠道微生物群失调有关,引发海马组织中的细胞死亡和淀粉样斑块沉积[60]。总的来说 D-gal 诱导的 AD 动物模型可造成 Aβ、tau 蛋白的异常表达,破坏神经元结构,诱导机体氧化应激、中枢炎症反应[61]。这种造模方式的诱导机制复杂多样,各机制间的关系尚不明确,导致目前该模型的实际运用存在局限性[62]。现对已应用于中药研究的 D-gal 诱导啮齿类 AD 动物模型进行介绍(见表 5)。

2.3.5 铝中毒

铝是地壳中天然存在的微量元素,对人类具有潜在毒性。通过对小鼠侧脑室或腹腔注射氯化铝($AlCl_3$)造成空间学习障碍和记忆损伤建立衰老模型。由于铝在大脑中被清除需要 100 多天,这个漫长的清除过程导致铝在大脑中积累,进而引起神经毒性作用[69]。铝纳米颗粒的毒性与 AD 的神经原纤维缠结和神经炎斑块的发展相关,其过程可能涉及神经变性和由于氧化应激、炎症、DNA 损伤、Aβ 聚集等引起的行为改变[70]。长期接触铝可诱导大鼠海马神经元凋亡,破坏突触可塑性,损害大鼠的学习和记忆功能[71]。研究发现,对大鼠进行口服 $AlCl_3$(20 mg/kg)24 周,可显著增加大脑中 Aβ1-42、p231-tau 以及促炎细胞因子 TNF-α 和 IL-6 水平,减少 GSH 等抗氧化标志物水平[72]。总的来说,铝的神经性机制复杂,这种造模方式的病理特征和特异性仍待进一步研究。现对已应用于中药研究的 $AlCl_3$ 诱导啮齿类 AD 动物模型进行介绍(见表 6)。

表 4 STZ 诱导啮齿类 AD 动物模型

Table 4 STZ-induced rodent AD models

造模动物品系 Model animal strains	造模方式 Modeling method	药物剂量/(mg/kg) Drug dosage	年龄 Age	已应用评价的中药组分 Traditional Chinese medicine components that have been evaluated	中药组分的药效机制 Pharmacodynamic mechanisms of Chinese herbal medicine components
雄性 C57BL/6 小鼠[53] Male C57BL/6 mice	STZ, i.c.v.	3	3 月龄 3-month-old	枸杞多糖 Lycium barbarum polysaccharides	保护突触结构,调控胰岛素信号通路,抑制 tau 蛋白过度磷酸化和提高突触蛋白表达 It protects synaptic structure, regulates insulin signaling pathway, inhibits tau hyperphosphorylation and improves synaptic protein expression
雄性 SD 大鼠[54] Male SD rats	STZ, i.p.	45	9~10 周龄 9~10-week-old	姜黄素 Curcumin	增加抗氧化活性和减少糖尿病引起的氧化应激 Increases antioxidant activity and reduces oxidative stress caused by diabetes
雄性 C57BL/6N 小鼠[55] Male C57BL/6N mice	STZ, i.c.v.	3	6~8 周龄 6~8 week-old	熟地黄粉 Radix rehmanniae praeparata extracted	改善脑胰岛素信号传导,调节肠道菌群丰度和多样性 Improve cerebral insulin signaling and regulate the abundance and diversity of intestinal microbiota
雄性 SD 大鼠[56] Male SD rats	STZ, i.c.v.	3	成年 Adult	萝卜硫素 Sulforaphane	抑制小胶质细胞和星形胶质细胞激活,减少促炎细胞因子的释放,促进抗炎介质的产生 Inhibits microglia and astrocyte activation, reduces the release of pro-inflammatory cytokines, and promotes the production of anti-inflammatory mediators
雄性 Wistar 大鼠[57] Male Wistar rats	STZ, i.c.v.	3	60~90 天 60~90-day-old	穿心莲内酯 Andrographolide	影响星形胶质细胞和小胶质细胞激活。 Affects astrocyte and microglia activation

表 5 D-gal 诱导啮齿类 AD 动物模型
Table 5 D-gal-induced rodent AD models

造模动物品系 Model animal strains	造模方式 Modeling method	药物剂量/(mg/kg) Drug dosage	年龄 Age	已应用评价的中药组分 Traditional Chinese medicine components that have been evaluated	中药组分的药效机制 Pharmacodynamic mechanisms of Chinese herbal medicine components
雌性 ICR 小鼠[63] Female ICR mice	D-gal, i. p.	100	4 周龄 4-week-old	矮牵牛素-3-O-芸香糖苷(反-对香豆酰)-5-O-葡萄糖苷 Petunidin-3-O-(trans-p-coumaroylrutinoside)-5-O-glucoside	抗衰老,减轻神经炎症、氧化应激和肝肾损伤 Anti-aging, alleviates neuroinflammation, oxidative stress and liver and kidney damage
雄性昆明小鼠[64] Males Kunming mice	D-gal, i. p.	150	6 周龄 6-week-old	白术多糖 Atractylodes macrocephala polysaccharides	调节肠道菌群,改善大脑皮层病理形态和超微结构,清除自由基和减少线粒体氧化损伤 Regulates intestinal flora, improves the pathological morphology and ultrastructure of the cerebral cortex, scavenges free radicals and reduces mitochondrial oxidative damage
雄性 C57BL/6J 小鼠[65] Male C57BL/6J mice	D-gal, i. p.	150	7~8 周龄 7 ~ 8-week-old	石榴苷 Punicalin	改善了记忆和学习缺陷,抗炎、抗氧化、减少小胶质细胞活化,减少星形细胞增多 Improves memory and learning deficits, anti-inflammatory, antioxidant, reduces microglial activation, and reduces astrocytosis
雄性 ICR 小鼠[66] Male ICR mice	D-gal, i. p.	150	6 周龄 6-week-old	牛蒡多糖 *Arctium lappa L.* polysaccharide	抗炎、抗氧化应激,调节肠道菌群,恢复肠道屏障功能,缓解肝肾功能障碍 Anti-inflammatory, anti-oxidative stress, regulates intestinal flora, restores intestinal barrier function, and alleviates liver and kidney dysfunction
雄性 C57BL/6 小鼠[67] Male C57BL/6 mice	D-gal, i. p.	150	6 周龄 6-week-old	牡荆素 Vitexin	抗氧化,抑制大脑衰老并改善与衰老相关的认知障碍,减少炎症,抑制应激诱导的衰老 Antioxidant, inhibits brain aging and improves aging-related cognitive impairment, reduces inflammation, inhibits stress-induced aging
雄性 SD 大鼠[68] Male SD rats	D-gal, s. c.	150	12 周龄 12-week-old	黄精多糖 Polygonatum polysaccharide	减弱脂质过氧化,抑制铁死亡 Attenuates lipid peroxidation and inhibits ferroptosis

2.3.6 OA

OA 是一种有效的蛋白磷酸酶 1(protein phosphatase 1, PP1)和蛋白磷酸酶 2A(protein phosphatase 2A, PP2A)抑制剂,可引起与神经原纤维变性相关的神经毒性。在向大鼠脑室内注射 OA 并暴露于低氧条件下 3 d,会呈现出 tau 过度磷酸化以及 Aβ 上调,同时伴有神经递质系统功能障碍、认知缺陷、氧化应激增强[79]。这些都被认为是 AD 发病机制的主要参与者。因此,OA 可用作 AD 实验模型的神经毒素,通过产生过量的 ROS 及 p-tau,诱导神经细胞凋亡和炎症改变[80]。此外,其细胞实验还表现出脂质过氧化水平升高,tau 相关激酶(GSK3β、ERK1/2 和 AMPK)的过度激活,以及 tau 蛋白磷酸化水平的显著增加[81]。另外,OA 可减弱大鼠海马齿状回神经元的突触可塑性。该模型可以模拟在 AD 中观察到的大多数神经病理学、神经行为学和神经化学变化,但缺乏在 AD 中观察到的淀粉样蛋白病理学。现对已应用于中药研究的 OA 诱导啮齿类 AD 动物模型进行介绍(见表 7)。

2.3.7 SCOP

SCOP 是一种胆碱能受体阻滞剂,可穿过血脑屏障。通过腹腔注射 SCOP 能够降低脑内乙酰胆碱水平,诱发中枢神经系统中的胆碱能神经通路及记忆环路的功能紊乱,造成动物短期学习和记忆障碍,可模拟 AD 患者多动、焦虑样行为的异常表现[88]。有研究发现,SCOP 对脑血容量信号的影响很小,但会导致各个大脑区域之间的功能连接总体降低[89]。另外,SCOP 可引发记忆功能障碍,表现出海马体中的突触蛋白表达异常,如突触素、突触素 1(synaptojanin 1,SYNJ1)、突触后密度蛋白 95(postsynaptic density protein 95,PSD-95),可能由 BDNF-ERK-CREB 信号通路影响突触可塑性[90]。该模型操作简单、快速有效、广泛用于 AD 药物筛选。其局限性表现为动物模型缺乏 AD 中神经元变性、Aβ 沉积、tau 蛋白异常等典型病理改变,需结合其他模型进行综合研究,而且 SCOP 引起的胆碱能功能损害具有一过性特征,不适合长期研究。现对已应用于中药研究的 SCOP 诱导啮齿类 AD 动物模型进行介绍(见表 8)。

表 6 $AlCl_3$ 诱导啮齿类 AD 动物模型

Table 6 $AlCl_3$-induced rodent AD models

造模动物品系 Model animal strains	造模方式 Modeling method	药物剂量/(mg/kg) Drug dosage	年龄 Age	已应用评价的中药组分 Traditional Chinese medicine components that have been evaluated	中药组分的药效机制 Pharmacodynamic mechanisms of Chinese herbal medicine components
雄性 C57 小鼠[73] Male C57 mice	AlCl3, i. g.	200	未提及 Not mentioned	益母草碱 Leonurine	提高机体的抗氧化水平,促进神经递质的表达与传递,降低氧化应激和神经炎症水平 Improves the body's antioxidant level, promotes the expression and transmission of neurotransmitters, and reduces oxidative stress and neuroinflammation levels
雄性 SD 大鼠[74] Male SD rats	AlCl3, i. p.	70	未提及 Not mentioned	酢浆草甲醇提取物 Methanolic extract of *Oxalis corniculata Linn.*	通过抗氧化、抗炎和抗凋亡,发挥神经保护作用 Exerts neuroprotective effects through antioxidant, anti-inflammatory, and anti-apoptosis
SD 大鼠[75] SD rats	AlCl3, p. o.	100	9 周 9-week-old	小檗碱 Berberine	抑制乙酰胆碱酯酶活性、增加神经递质水平,降低氧化应激 Inhibits acetylcholinesterase activity, increases neurotransmitter levels, and reduces oxidative stress
雄性 SD 大鼠[76] Male SD rats	AlCl3, p. o.	100	15 周龄 15-week-old	葡萄细粉 Vitis vinifera fine powder	减少了氧化应激、神经炎症,改善胆碱能作用 Reduces oxidative stress, neuroinflammation, and improves cholinergic effects
雄性 SD 大鼠[77] Male SD rats	AlCl3, i. p.	10	未提及 Not mentioned	红辣椒(辣椒)甲醇提取物 Red hot pepper (*Capsicum annuum*) methanolic extract	缓解氧化应激和神经炎症,发挥神经保护作用 Relieves oxidative stress and neuroinflammation and exerts neuroprotective effects
雄性 白化小鼠[78] Male albino mice	AlCl3, s. c.	50	4 月龄 4-month-old	人参皂甙 Rb1 Ginsenoside Rb1	抑制氧化应激导致的神经毒性,抑制小胶质细胞和星形胶质细胞的激活 Inhibits neurotoxicity caused by oxidative stress, inhibits the activation of microglia and astrocytes

表 7 OA 诱导啮齿类 AD 动物模型
Table 7 OA-induced rodent AD models

造模动物品系 Model animal strains	造模方式 Modeling method	药物剂量 Drug dosage	年龄 Age	已应用评价的中药组分 Traditional Chinese medicine components that have been evaluated	中药组分的药效机制 Pharmacodynamic mechanisms of Chinese herbal medicine components
雄性 Wistar 大鼠[82] Male Wistar rats	OA, i. c. v.	200 ng/5 μL	成年 Adult	鞣花酸 Ellagic acid	减轻脑氧化应激,抗凋亡,调节神经胶质细胞和炎症因子 Relieves cerebral oxidative stress, anti-apoptosis, regulates glial cells and inflammatory factors
雄性 Wistar 大鼠[83] Male Wistar rats	OA, i. c. v.	200 ng/4 μL	未提及 Not mention	印度蜂王浆 Indian Royal Jelly	抑制氧化应激和神经炎症,改善胆碱能功能障碍 Inhibits oxidative stress and neuroinflammation and improves cholinergic dysfunction
雌性 SD 大鼠[84] Female SD rats	OA, i. c. v.	200 ng/kg	15 周龄 15-week-old	葫芦素 E Cucurbitacin E	改善氧化代谢和调节炎症 Improves oxidative metabolism and regulates inflammation
雄性 Wistar 大鼠[85] Male Wistar rats	OA, i. c. v.	200 ng	12~13 周龄 12~13-week-old	Kolaviron	抑制氧化应激、神经炎症,减轻细胞凋亡、焦亡,改善线粒体功能 Inhibits oxidative stress and neuroinflammation, reduces apoptosis and pyroptosis, and improves mitochondrial function
雄性 SD 大鼠[86] Male SD rats	OA, i. c. v.	200 ng/kg	8~9 周龄 8~9-week-old	黄芩茎叶黄酮 *Scutellaria baicalensis* georgi stem and leaf flavonoids	调节神经递质,抗氧化、调节炎性细胞因子 Regulates neurotransmitters, antioxidants, and regulates inflammatory cytokines
雄性 ICR 小鼠[87] Male ICR mice	OA, i. c. v.	100 ng/μL	6 周龄 6-week-old	吴茱萸碱 Evodiamine	下调大脑中的 tau 磷酸化 Downregulation of tau phosphorylation in the brain

表 8 SCOP 诱导啮齿类 AD 动物模型
Table 8 SCOP-induced rodent models

造模动物品系 Model animal strains	造模方式 Modeling method	药物剂量/(mg/kg) Drug dosage	年龄 Age	已应用评价的中药组分 Traditional Chinese medicine components that have been evaluated	中药组分的药效机制 Pharmacodynamic mechanisms of Chinese herbal medicine components
雄性 C57B/L6 小鼠[91] Male C57B/L6 mice	SCOP, i. p.	3	未提及 Not mention	青藤碱 Sinomenine	改善胆碱能系统失调、肠道及神经炎症、生物屏障损伤以及肠道菌群紊乱 Improve cholinergic system disorders, intestinal and neuroinflammation, biological barrier damage, and intestinal flora disorders
雄性 Wistar 大鼠[92] Male Wistar rats	SCOP, i. p.	3	8 周龄 8-week-old	球松素 Pinostrobin	调节氧化应激、胆碱能和谷氨酸能系统 Regulates oxidative stress, cholinergic, and glutamatergic systems
雄性 SD 大鼠[93] Male SD rats	SCOP, i. p.	1.5	未提及 Not mention	香草酸 Vanillic acid	调节胆碱能系统损伤,减少氧化应激,防止神经元损伤和突触功能障碍 Regulates cholinergic system damage, reduces oxidative stress, and prevents neuronal damage and synaptic dysfunction

续表8

造模动物品系 Model animal strains	造模方式 Modeling method	药物剂量/(mg/kg) Drug dosage	年龄 Age	已应用评价的中药组分 Traditional Chinese medicine components that have been evaluated	中药组分的药效机制 Pharmacodynamic mechanisms of Chinese herbal medicine components
雄性 BALB/C 小鼠[94] Male BALB/C mice	SCOP, i. p.	1	7~8 周龄 7~8-week-old	毛茛苷 Ranuncoside	降低血糖和血脂,减少氧化应激和神经炎症 Lowers blood sugar and blood lipids, reduces oxidative stress and neuroinflammation
雄性 Wistar 大鼠[95] Male Wistar rats	SCOP, i. p.	1	60 日龄 60-day-old	黑莓果提取物 Blackberry fruit extract	调节氧化应激和胆碱能信号传导 Regulates oxidative stress and cholinergic signaling
C57BL/6 小鼠[96] C57BL/6 mice	SCOP, i. p.	3	8~10 周龄 8 ~ 10-week-old	芝麻酚 Sesamol	平衡胆碱能系统,减少神经炎症和氧化应激,改善线粒体功能障碍 Balances the cholinergic system, reduces neuroinflammation and oxidative stress, and improves mitochondrial dysfunction

3 小结

AD 作为当前老年病医学研究领域的热点问题,其重要性和关注度日益倍增。现有的治疗大多是对症治疗为主,虽在一定程度上缓解了 AD 的认知和行为,但无法改变疾病的进程。靶向药物的研发基本以失败告终,其可能原因是由于目前使用的 AD 动物模型存在一定局限性。本研究对现有的常见 AD 动物模型进行了分类总结,介绍了相关动物品系、药物剂量、造模方式等内容,并对不同模型的优缺点进行了评价,认为现有的 AD 动物模型虽种类较多,但与自然发展的人类 AD 患者的病理过程和特点方面还存在着一定的差异。从全文来看,现有的中药组分研究大多建立在单一的动物模型中,并不能表示这些药效机制会发生在其他动物模型中。目前使用的动物模型存在一定局限性,影响了研究成果的临床转化。例如,无法完全模拟人类 AD 的所有临床表现和病理过程,多通过引入特定的因素来模仿一些 AD 的特征;大多数的 AD 动物模型与人类 AD 患者的发病年龄和病程不匹配,通常发生在相对较短的时间内,且缺乏与老年人群体相关的交互因素的影响,AD 的进程变化可能有差异;实验动物与人类在生理、基因、代谢等方面存在显著差异;现有的评估方法不能全面反映病理和认知功能的变化,某些早期的轻微变化可能无法通过现有的测试被捕捉到。本文所述各类 AD 模型的优缺点(见表 9)。未来需要不断改进动物模型,开发具有更高的转化性、能够模拟人类 AD 疾病复杂性和多样性的动物模型。建立能够反映不同发病阶段(如早期、轻度、重度)的动物模型。通过引入衰老模型或合并其他疾病(如糖尿病、高血压等)的动物模型,模拟临床 AD 患者的复杂生理状况,研究这些因素如何影响 AD 的进展。在实验设计中,除了常规的行为学测试(如迷宫测试)外,还可以增加更多的认知和生理指标,结合神经影像学技术、神经生物学标志物(如血浆或脑脊液中的淀粉样蛋白、tau 蛋白等)进行综合评估。开发新型的生物标志物(如用于早期诊断的脑电图、磁共振成像等)和可穿戴设备,提升模型对临床症状和治疗反应的敏感度。通过跨物种和跨学科的合作,结合小鼠模型、非人灵长类动物模型、人类细胞模型、脑器官等多层次、多模型的方法,增强研究的转化性。应用精准医学的思路,基于个体的遗传背景、环境因素和生理特征来设计和优化 AD 动物模型。在进行临床前实验时,与临床研究人员保持紧密合作,确保实验设计能够直接反映临床需求和临床结果。通过早期的临床数据反馈,修正动物模型中的设计缺陷和不足之处,从而提高模型的临床相关性。关注中医药相关的证候研究模型开发,探索中药活性成分在中医证候模型中的应用。在今后的实验研究中应依据研究机制选择不同动物品系,为 AD 治疗药物的研究开发及作用机制探讨提供可行的依据,力求做到全面、系统、合理、科学评价药物的疗效与作用机制,更好地为临床服务。

表 9 不同 AD 模型的优缺点

Table 9 Pros and cons of different AD models

分类 Category	造模方法 Modeling methods	优势 Advantage	存在问题 Problems and deficiencies
自然衰老动物模型 Animal models of natural aging	日常维持饲养 Daily maintenance feeding	操作简单,在模拟人类 AD 的自然发病过程和疾病机制上,更贴近临床的实际情况 Operation is simple, and it is closer to the actual clinical situation in simulating the natural pathogenesis process and disease mechanism of human AD	发病进程缓慢,实验周期长,投入成本较大,染病机率较高,低生殖率,个体差异大,控制变量困难 Pathogenesis process is slow, the experimental cycle is long, the input cost is large, the probability of infection is high, the reproductive rate is low, the individual differences are large, and the control variables are difficult
转基因动物模型 Transgenic animal models	基因编辑技术 Gene editing technology	基因突变可控性,病理症状已知,有利于 AD 遗传基础及发病机制研究 Controllability of gene mutations and the known pathological symptoms are conducive to the study of the genetic basis and pathogenesis of AD	部分再现 AD 病理特征,基因表达稳定性差,造模过程繁琐且成本高,寿命较短,出生率低 Some reproduce the pathological characteristics of AD, the gene expression stability is poor, the modeling process is cumbersome and costly, the life span is short, and the birth rate is low
	Aβ, i. c. v.	快速诱发 Aβ 沉积,注射剂量和部位的可控性,影响因素单一,造模时间短 Rapid induction of Aβ deposition, controllability of injection dose and site, single influencing factor, and short molding time	缺乏长期的病理特征,Aβ 在脑内分布不均,注射过程可能造成创伤或应激反应,无法全面反所有的 AD 病理变化 Lack of long-term pathological features, uneven distribution of Aβ in the brain, and the injection process may cause trauma or stress response, and it is impossible to comprehensively reverse all pathological changes of AD
	IBO, i. c. v.	具胆碱能神经毒性,可迅速损伤大脑中与 AD 相关的特定区域,效果稳定且可重复 Cholinergic neurotoxicity that rapidly damages specific areas of the brain associated with AD with stable and reproducible effects	损伤具非选择性,长期效应不足,不能完全模拟人类 AD 病理特征和病理过程 Lesion is non-selective, and the long-term effect is insufficient, which cannot fully mimic the pathological characteristics and pathological process of human AD
	STZ, i. c. v., i. p.	脑室内注射可精准控制注射剂量和部位,模拟 AD 脑内胰岛素代谢紊乱。腹腔注射操作简单,创伤较小,成本低 Intraventricular injection can accurately control the injection dose and site, simulating the insulin metabolism disorder in the brain of AD. Intraperitoneal injection is simple, less invasive, and less costly	脑室内注射操作技术要求高、对动物创伤较大,存活率低。腹腔注射药物的分布不够精准,可能影响模型的可靠性 Intraventricular injection is technically demanding, traumatic to animals, and has a low survival rate. The distribution of intraperitoneal drugs is not precise and may affect the reliability of the model
药物介入性动物模型 Drug-interventional animal models	D-gal, i. p., s. c.	简便易行,成本较低,周期短,重复性高,主要基于氧化应激和炎症机制 It is simple and easy to implement, low cost, short cycle time, and high reproducibility, mainly based on oxidative stress and inflammatory mechanisms	可引起局部的刺激反应或长期的免疫系统反应,不能完全模拟 AD 所有病理机制 It can cause local irritation or long-term immune system response, and cannot fully mimic all pathological mechanisms of AD
	$AlCl_3$, i. p., i. g., p. o., s. c.	操作简便、成本低、死亡率低、实验周期短。腹腔注射可快速且精准的给药。皮下注射适合缓慢释放药物。口服给药方式损伤小,贴近人类实际。灌胃对动物的应激较少 It is easy to operate, low cost, low mortality and short experimental cycle. Intraperitoneal injections allow for rapid and precise administration. Subcutaneous injections are suitable for slow-release medications. The oral administration method has little damage and is close to the actual human experience. Intragastric administration is less stressful for the animal	腹腔注射应激较大,引起腹腔的局部不良反应。灌胃操作难度大,药物吸收效果不一。口服药物生物利用度低,起效较慢。皮下注射吸收速度较慢,可能有局部反应 Intraperitoneal injection is stressful, causing local adverse reactions in the abdominal cavity. Gavage is difficult to operate, and the effect of drug absorption is varied. Oral drugs have low bioavailability and a slower onset of action. Subcutaneous injections are slower to absorb and may have local reactions

续表9

分类 Category	造模方法 Modeling methods	优势 Advantage	存在问题 Problems and deficiencies
	OA, i. c. v.	研究 tau 蛋白的磷酸化和神经细胞损伤,具有快速性和高特异性 Phosphorylation of tau protein and nerve cell damage are studied with rapidity and high specificity	不能完全模拟 AD 的所有病理,长期效果不明确,可能存在非特异性效应 It cannot completely mimic all pathologies of AD, the long-term effect is unclear, and there may be non-specific effects
	SCOP, i. p.	良好的可控性,可干扰乙酰胆碱系统,模拟早期认知障碍,快速建立模型,成本较低 It has good controllability, can interfere with the acetylcholine system, simulate early cognitive impairment, and quickly establish a model with low cost	作用是暂时性的,不完全代表阿尔茨海默病的病理特征,果量可引起毒性反应,引发的认知功能障碍是可逆的 Effect is transient and does not fully represent the pathological features of Alzheimer's disease, and the amount of fruit can cause toxic reactions, and the cognitive dysfunction caused by it is reversible

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