



Review Article

Inducing Agents for Alzheimer's Disease in Animal Models



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Abstract

The most prevalent form of dementia, Alzheimer's disease (AD), is a neurological disorder that causes gradual memory loss. AD is characterized by amyloid-beta plaques, neurofibrillary tangles, and neuron loss. While preclinical and clinical trials are underway to reduce the generation and overall brain disease load, current treatment focuses on alleviating symptoms. Animal studies are essential for advancing our understanding of AD, identifying potential drug targets, and testing experimental therapies. An ideal animal model not only exhibits the same symptoms and pathological changes as a human disease but also follows the same sequence of pathological events. This review highlights the various inducing agents used to model AD in animals, such as streptozotocin, aluminium chloride, trimethyltin, lipopolysaccharide, scopolamine, and others, along with their underlying mechanisms. The outcomes of some studies that used such inducing agents to develop AD are discussed briefly. Among chemically induced models, streptozotocin and amyloid-beta are the most frequently used, while d-galactose, scopolamine, and aluminium-induced models are being used because they are non-invasive, reproducible, and compatible. However, none of the chemical/drug-induced models fully capture the scope of AD pathology and cognitive impairment. Overall, further research is necessary to establish the stability of the models in terms of consistency and reproducibility.

Introduction

Alzheimer's disease (AD) is widely recognized as the most prevalent form of dementia, accounting for 60–70% of cases globally. Its incidence is projected to increase due to the aging demographic trends worldwide.¹ AD is a debilitating neurological condition characterized by a gradual decline in cognitive abilities, including memory loss and decreased logical reasoning skills. Over 55 million individuals worldwide have dementia, with more than 60% living in low- and middle-income countries.² Every year, about 10 million new cases are reported. The deposition of amyloid-beta (A β) plaques and neurofibrillary tangles (NFTs) of hyperphosphorylated tau are hypothesized as the underlying pathologies of AD.^{3–5} Deposition of A β plaques results from the cleavage of a protein termed amyloid precursor protein (APP), with A β 42 identified as potentially hazardous.^{6,7} Abnormal amounts of this naturally occurring protein gather between neurons in Alzheimer's patients' brains, forming plaques that damage cell function.^{8,9} Hy-

perphosphorylated tau detaches from microtubules and sticks to other tau molecules, generating threads that eventually unite to create tangles inside neurons, known as NFTs.^{10,11} These tangles impair synaptic transmission between neurons by interfering with the transport system inside the neuron.¹²

The International Classification of Diseases-10 identifies different types of AD-related dementia: early onset (familial AD), late-onset (sporadic AD), mixed or atypical, and unspecified. Familial AD is characterized by rapid disease progression, while sporadic AD progresses more gradually.¹³ The cut-off age for familial AD and sporadic AD is usually 65 years. The genetic component of familial AD is well understood and heritable, unlike sporadic AD, which affects more than 95% of AD patients and remains poorly understood.¹⁴ This lack of understanding contributes to the poor prognosis and therapeutic challenges associated with sporadic AD.

While there was no cure for AD, several non-medical approaches aimed to support individuals with AD and potentially slow disease progression. These approaches focus on enhancing cognitive function, promoting overall well-being, and improving quality of life.^{15,16} For example, cognitive stimulation can be achieved by engaging in mentally stimulating activities such as puzzles, games, brain exercises or encouraging reading, storytelling, and discussions. Regular physical activity walking, swimming, and gentle exercises can improve overall health and well-being. Another approach is encouraging a balanced and nutritious diet rich in antioxidants, omega-3 fatty acids, and vitamins. Lifestyle changes,

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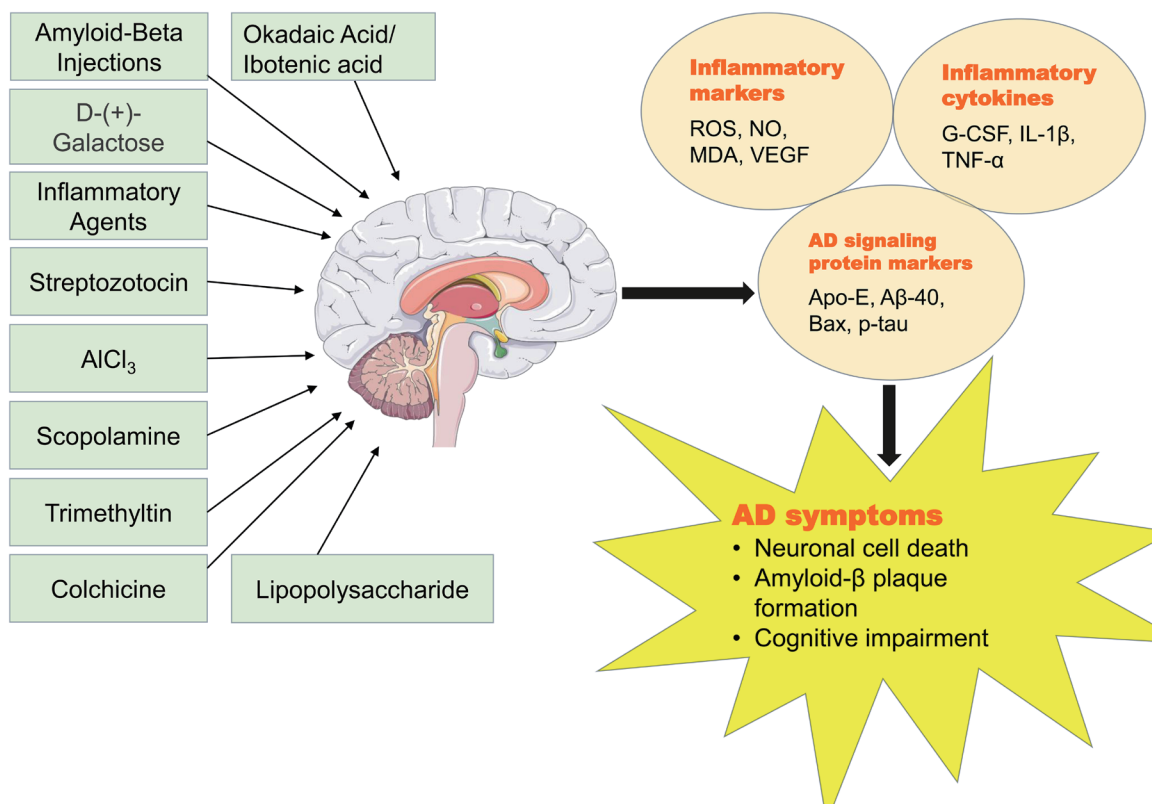


Fig. 1. Various approaches and agents used in animal studies to induce AD. AlCl₃: Aluminium chloride; Apo-E: Apolipoprotein E; Aβ-40: amyloid β-40; Bax: Bcl-2-associated X protein; G-CSF: granulocyte-colony stimulating factor; IL-1β: Interleukin-1 beta; MDA: malondialdehyde; NO: nitric oxide; p-tau: phosphorylated tau; ROS: reactive oxygen species; TNF-α: Tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor.

such as maintaining social connections, engaging in music therapy and creative activities such as painting, crafting, ensuring a regular sleep routine and addressing any sleep-related issues, and creating a safe and supportive environment, may help manage the behavioral and psychological symptoms associated with AD.

Researchers conducted various studies on animal models to better understand AD and develop potential treatments or interventions. These studies used substances to induce specific pathological features associated with AD rather than inducing the disease as it naturally occurs in humans. Instead, researchers aimed to replicate certain aspects of the disease process to study its mechanisms and test potential therapeutic approaches. Various approaches and agents are used in animal studies related to AD (Fig. 1). Transgenic mouse models in which researchers often use genetically modified mice that express human genes associated with AD, such as mutant forms of the APP or presenilin genes.^{13,17-19} These mice can develop amyloid plaques and other pathological features of Alzheimer's disease. Another approach is the Aβ injections, where synthetic or purified Aβ protein is injected into the brains of animals, usually rodents,²⁰⁻²³ leading to amyloid plaque formation and neuroinflammation, mimicking aspects of Alzheimer's pathology. Tau protein abnormalities are another hallmark of AD. Researchers may also use animal models that overexpress abnormal tau proteins or inject tau aggregates to study their role in the disease.²⁴⁻²⁶ Some studies investigate the effects of environmental toxins or chemicals, such as aluminium or certain pesticides, on the development or progression of Alzheimer's-like pathology in animal models.^{27,28} Along with Aβ and NFTs, chronic inflammation is a critical under-

lying factor in the pathogenesis of AD,²⁹ and researchers have used agents to induce neuroinflammation in animals to study its impact on the brain and cognitive function.

This review provided an overview of the several inducing agents employed in animal models to simulate AD, including streptozotocin, aluminium chloride, trimethyltin, lipopolysaccharide, and scopolamine, along with their underlying mechanisms. The discussion briefly encompassed the outcomes of several investigations that employed these inducing approaches in AD development.

Inducing approaches for Alzheimer's disease

Aluminium chloride (AlCl₃)

Prolonged exposure or chronic administration of heavy metals to mice has been observed to induce significant toxicity, leading to the development of many diseases, including neurotoxicity. Most studies have focused on the effects of aluminium, among other heavy metals, on biological systems.^{30,31} Abnormally high quantities of aluminium are found in the brains of Alzheimer's patients, which has toxicological consequences, including encephalopathy, bone disease, and anemia.³² It was documented that oxidative stress, cholinergic insufficiency, and the accumulation of Aβ and NFTs occurred in the brains of rats following oral administration of aluminium at a dosage of 300 mg/kg body weight.³³ Oxidative stress and mitochondrial malfunction are the major causes in an AlCl₃ model, manifested by blocking the NADH dehydrogenase enzyme in the electron transport chain of the cortical and hip-

pocampal regions.³⁴ In addition, neurodegeneration results from changes in neuroinflammatory mediators and proinflammatory cytokines in an AlCl_3 model.

Neuronal cell death may result from aluminium ion-induced calcium homeostasis dysregulation, which causes an aberrant increase of Ca^{2+} in mitochondria and disrupts normal cellular physiological processes. Aluminium ions can lead to the accumulation of $\text{A}\beta$ and hyperphosphorylation of Tau proteins, resulting in neuronal death in the brain.³⁵

Z. Firdaus *et al.*³⁶ examined the impact of *Centella asiatica* ethanolic extract on AlCl_3 -induced neurological disorders in rats. The study's findings demonstrated that AlCl_3 causes cognitive impairment (memory and learning deficits, anxiety, and reduced locomotion) as well as oxidative stress, cholinergic impairment, and histological changes in the brains of rats.³⁶ Similarly, Zhao Y *et al.*³⁷ 2020 studied the neuroprotective potential of syringic acid on AlCl_3 -stimulated behavioral deficits and neuroinflammation in rat AD models. The results showed that AD rats displayed reduced memory and learning impairments, augmented short-term memory loss, and diminished locomotion activity.³⁷ The syringic acid supplementation appreciably stabilized the AD rats' neurobehavioral impairments. Furthermore, Chen X. *et al.*³⁸ induced AD in Sprague Dawley rats by oral administration of 175 mg/kg of AlCl_3 for 25 days to study the protective effect of ononin treatment on AD (Table 1).³⁶⁻⁵⁷ The result showed that ononin treatment effectively modulated the AlCl_3 -triggered behavioral alterations in AD animals. The levels of interleukin-1 β (IL-1 β), tumor necrosis factor alpha (TNF- α), p38 mitogen-activated protein kinases (p38MAPK), acetylcholine esterase, malondialdehyde (MDA), and nuclear factor kappa B (NF- κ B) were suppressed, while the brain-derived neurotrophic factor (BDNF) and peroxisome proliferator-activated receptor- γ (PPAR- γ) contents were elevated in the brain tissues of AD animals.³⁸ Other studies used AlCl_3 in doses of 17 mg/kg for four successive weeks and 50 mg/kg/day in rats to induce AD.^{58,59} Taken together, the variation in AlCl_3 dose and duration of administration to induce AD necessitate further studies to determine the most suitable dose and route of administration.

Streptozotocin (STZ)

Streptozotocin (STZ), or 2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose), is a naturally occurring antibiotic produced by *Streptomyces achromogenes* and derived from glucosamine nitrosourea.⁶⁰ The most widely used model for sporadic AD in rodents is based on the effects of STZ, which matches the sporadic form in humans.⁶¹ The intracerebroventricular (ICV) administration of STZ elicits a distinct influence on the central nervous system (CNS) without noticeable effects on peripheral regions.⁶² Brain biochemistry, metabolism, and functions, including glucose uptake and energy consumption, oxidative tissue stress, cholinergic deficiency, and cognitive capacities, are severely and persistently impacted by ICV treatment with STZ. These effects lead to hippocampus-dependent cognitive loss, including difficulties with spatial learning and memory, as well as neurodegeneration, inflammation, and synaptic malfunction.⁶³ Moreover, STZ induces neuronal injury and hyperphosphorylation of tau, leading to the release of reactive oxygen species (ROS) and reactive nitrogen species.⁶⁴ In addition, the neuroinflammation associated with sporadic AD is related to changes in the number and shape of astrocytes and microglia in particular brain areas following STZ injection.^{65,66} Overall, these features validate the relevance of animal models of Alzheimer's disease, as loss of spatial memory and disorientation are fundamental markers of the progressive cognitive de-

cline exhibited in AD patients. Various studies have used STZ to induce AD in rodents (Table 1).³⁹⁻⁴² For example, A. Gáspár *et al.* demonstrated the effect of a high dose of STZ (4.5mg/kg) on the learning and memory of Long-Evans rats (23 and 10 months old)³⁹ using the 5-choice serial reaction time task, the Morris water-maze, and the "pot-jumping" exercise. The 5-choice serial reaction time task (attention) and the pot jumping test (procedural learning) showed significant changes in young STZ-treated rats, while the phospho-tau/tau protein ratio in the hippocampus of aged rats showed a substantial increase. In contrast, cooperative (social) and competitive (visual) memory tests and $\text{A}\beta$ levels in the hippocampus were not significantly different. Alvei M. *et al.*⁴⁰ studied the pharmacological effect of three doses of levetiracetam (50, 100, and 150mg/kg) on STZ-induced AD rats (3 mg/kg). The results of the passive avoidance and Morris water-maze tasks demonstrated that levetiracetam (100 and 150 mg/kg) considerably reduced STZ-induced learning and memory deficits.

Trimethyltin (TMT)

Trimethyltin (TMT) is an organometallic potent neurotoxic compound that promotes considerable neurodegeneration and neuronal cell death in the central nervous system in the cerebral cortex and hippocampus.^{42,43} TMT has been detected in a variety of water sources, including those used for human consumption, as well as in marine ecosystems and aquatic organisms. Environmental exposures during plastic production and other industrial activities where plastic is heated account for most reported cases of TMT poisoning.⁶⁷ Neuronal cell death results from TMT's ability to disrupt neuronal membranes. TMT-induction induces intracellular Ca^{2+} overload, mitochondrial damage, and oxidative stress. In addition, TMT exposure can trigger neuroinflammatory responses, characterized by increased levels of pro-inflammatory cytokines such as TNF- α , IL-1 β , and nitric oxide, and increased gene expression of the glial fibrillary acidic protein and activated microglia in the brain.⁶⁸ Furthermore, TMT signals the development of several components critical to the pathophysiology of AD, including APP, presenilin 1, and others.⁴³

However, it's essential to clarify that while TMT can lead to cognitive impairments and neurodegeneration in animal models, it is not considered a direct causative agent for AD in humans. While TMT-induced neurotoxicity and cognitive impairments in animal models can provide insights into certain aspects of neurodegeneration and memory deficits, AD is a complex and multifactorial disease with genetic, environmental, and age-related factors playing significant roles. TMT-induced damage does not replicate the full spectrum of AD pathology, including the aggregation of $\text{A}\beta$ and tau proteins, hallmark AD features in humans.

Lipopolysaccharide (LPS)

LPS is a common non-genetically manipulated neuroinflammation model for AD. LPS is an endotoxin found in the cell walls of Gram-negative bacteria, which can cause systemic inflammation, amyloidogenesis, and neuronal cell death.⁶⁹ It was hypothesized that LPS elevates $\text{A}\beta$ levels, damages oligodendrocytes, and causes myelin destruction in the AD brain by acting on leukocyte and microglial TLR4-CD14/TLR2 receptors, triggering an NF- κ B-mediated rise in cytokines.⁷⁰ A dose-dependent response of activated microglia and astrocytes was seen following direct LPS infusion into the fourth ventricle of the brains of male rats.⁷¹ Neuroglial activation could be induced at dosages as low as 0.05 ng/h of LPS infusion, while the loss of choline acetyltransferase-positive cells in the basal forebrain was induced only at doses of 50 ng/h or higher.⁷²

Table 1. AD studies were conducted in animal models using various inducing agents

AD induction agents/ animal species	Dose of the in- ducing Agent	Drug/treatment model	Main findings	Refer- ence
AIC ₃ /Rat	i.p. injection of 100 mg/kg for 60 days	<i>Centella asiatica</i> ethanolic extract (CAE) (Oral Daily dose of 150 and 300 mg/kg for 60 days)	AIC ₃ causes cognitive impairment, oxidative stress, increased activity of the enzyme AChE, and changes in cellular architecture, although CAE significantly mitigates these effects	36
AIC ₃ /Rat	100 mg/kg i.p. for 60 days	Syringic acid (25 & 50 mg/kg/day for 30 days)	Syringic acid supplementation in AD rats attenuated the expression of NF-κB, IL-1β, IL-6, and TNF-α.	37
AIC ₃ /Rat	Oral dose of 175 mg/kg for 25 days.	Ononin (Ononin 30 mg/kg orally from day 25 to day 36)	In the brain tissues of AD rats, ononin significantly reduced acetylcholine esterase, Aβ1-42, and MDA while increasing SOD and overall antioxidant activity	38
Streptozotocin/ Aged and young rat	1.5 mg/kg/day for three days by ICV injection	–	Icv STZ generated impulsive-like behavior, but it did not affect fear learning/memory, visual discrimination, or social learning.	39
Streptozotocin/Rat	3mg/kg/day for three days by ICV injection	Levetiracetam (Treatment regimens of 50, 100, and 150 mg/kg i.p. for 28 days)	The death of neurons in the hippocampus caused by STZ was prevented. Hyperphosphorylation of tau was reversed, and oxidative stress markers such as lipid peroxides, glutathione, and AChE activity were all normalized	40
Streptozotocin/ Male Wistar rat	3 mg/kg/day by ICV injection	Galantamine plus methacrylated gelatin (10 mg/kg)	Loss of hippocampal neurons, oxidative stress, and neuroinflammatory alterations were observed in ICV-STZ-treated rat brains, as well as increases in AChE and LPO activity levels.	41
Trimethyltin/ Male Wistar rats	i.p. (8mg/kg)	Crocin (25 or 50 mg/kg)	Successful development of the model and analysis of the results revealed a protective benefit for crocin, as evidenced by an uptick in hippocampal neuronal density and a reduction in inflammatory mediators.	47
Trimethyltin/ Male and female C57BL/6 mice	–	Trans-anethole (10–50 μM dissolved in ethanol)	Trans-anethole inhibits TMT's effect on long-term potentiation (LTP).	43
Trimethyltin/ Male and female C57BL/6 mice	i.p. (2.6 mg/kg)	H ₂ gas (2% by inhalation)	TMT-treated mice that inhale 2% H ₂ gas show improved memory performance and a reduction in AD, OS, and inflammatory-related markers.	42
Scopolamine/ male Wistar rats.	2mg/kg/day, i.p. for 6 weeks	–	Impaired antioxidative defense systems, increased oxidative stress, mitochondrial dysfunction, apoptosis, and neuroinflammation are just some of the cellular changes induced by scopolamine.	44
Scopolamine/Rats.	0.4 mg/kg by i.p.	Rivastigmine (1.5 mg/kg)	These findings suggest that brain targeting using RT-loaded PLGA and PBCA NP could significantly improve Alzheimer's disease treatment.	48
Scopolamine/Rats.	1mg/kg for 9 days by i.p.	Embelin (0.6 mg/kg)	Embelin has nootropic and neuroprotective properties against scopolamine-induced amnesia in rats.	49
Scopolamine/Rats.	0.7 mg/kg by i.p.	Oleoresins and donepezil by oral (50 mg/kg and 0.5 mg/kg)	When compared to donepezil, oleoresins from spices are more effective at boosting antioxidant levels and decreasing lipid peroxidation caused by scopolamine.	50

(continued)

Table 1. (continued)

AD induction agents/ animal species	Dose of the in- ducing Agent	Drug/treatment model	Main findings	Refer- ence
D-galactose/Mice	1.25 mg/kg, s.c., once daily for 40 days.	Aerobic treadmill exercise (40 days)	D-galactose reduces the SOD and AChE activities. The number of EGF-positive cells and neurons in the CA1 and CA3 areas of the hippocampus was reduced.	51
D-galactose+ AICl ₃ /Rats	D-galactose (60 mg/kg i.p.) and AICl ₃ (200 mg/kg orally) OD for 10 weeks.	WIN55,212-2 (cannabinoid agonist; 0.5, 1 and 2 mg/kg/day)	Cognitive impairments and marked neuronal loss in the CA1. A decrease in the expressions of GFAP and Nestin, including increased levels of MDA and decreased levels of SOD and GSH.	52
D-galactose+ AICl ₃ /Mice	D-galactose (120 mg/kg) and AICl ₃ (20 mg/kg) by gavage for 8 weeks	Nervonic acid (10.95 and 43.93 mg/kg)	D-galactose+ AICl ₃ decline the locomotion and learning ability through decreased levels of neurotransmitters, such as dopamine, serotonin, and GABA.	45
Colchicine/Rats	–	Donepezil (1mg/kg) and Resveratrol (10mg/kg)	Microglia numbers increased whereas astrocyte count showed no change.	46
Colchicine/Rats	15 µg	Naproxen (10 mg/kg, orally)	Chromatolysis and Plaque formation in the hippocampus was observed. neurodegeneration is time-dependent and mediated by cyclooxygenase-induced neuroinflammation.	53
Okadaic Acid/Mice	100 ng/µL (ICV)	Evodiamine (50 or 100 mg/kg) intragastrically	Increased oxidative stress, is characterized by increased MDA and decreased GSH levels.	54
Okadaic Acid/Rats	100 ng/side (ICV)	India Royal jelly (100, 200, and 400 mg/kg, per oral dose)	Higher free radicals and cytokines that caused inflammation	55
Ibotenic acid/Rats	10 µg/5 µL (ICV)	flavonoids of <i>Herba Epimedii</i> (8 and 16 mg/kg)	Impaired learning and memory, neuronal injury and loss, and a pro-apoptotic response were all effects of injecting ibotenic acid into the hippocampus.	56
Ibotenic acid/Rats	5 µg/µL (ICV)	Thymoquinone (5 mg/kg)	Behavioral changes, Hyperplastic astrocytes, necrosis, and severe neuroinflammation induced by the ICV administration of ibotenic acid.	57

AICl₃, Aluminium chloride; AChE, acetylcholinesterase; TMT, Trimethyltin; ROS, reactive oxygen species; NO, nitric oxide; MDA, malondialdehyde; VEGF, Vascular endothelial growth factor; OS, oxidative stress; G-CSF, granulocyte-colony stimulating factor; NF-κB, Nuclear factor kappa B; IL-1β, Interleukin-1 beta; TNF-α, Tumor necrosis factor alpha; Apo-E, Apolipoprotein E; Aβ-40, amyloid β-40; Bax, Bcl-2-associated X protein; p-tau, phosphorylated tau; SOD, Superoxide dismutase; CWS, Cold water stress; i.p., Intraperitoneal injection; ICV, intracerebroventricular; EGF, epidermal growth factor; OD, once daily; CA1, hippocampal conus ammonis 1; GFAP, glial fibrillary acidic protein; GSH, glutathione.

Scopolamine

Scopolamine is a compound that blocks acetylcholine receptors, leading to cholinergic dysfunction and resulting in cognitive impairments reminiscent of those seen in AD.⁷³ This drug interferes with the cholinergic pathways in brain regions involved in cognition and memory.⁷⁴ Recent research indicated that scopolamine causes the buildup of ROS, leading to oxidative stress and memory impairment. The cholinergic theory can be implemented through the intraperitoneal or ICV injection of scopolamine, which causes cognitive abnormalities similar to those seen in AD. Notably, rats show a twofold rise in A β protein levels and APP expression levels after six weeks of intraperitoneal administration of scopolamine. Additionally, the activity of tau kinase, which causes tau hyperphosphorylation, and the amount of pTau protein were increased.⁴⁴ The scopolamine-induced model has the advantage of not requiring complicated surgical procedures, unlike the ICV model.

A β Injections

The accumulation of external amyloid plaques, intracellular NFTs, and a cholinergic deficiency are the main features of AD. In rodent studies, A β peptide accumulation in the hippocampus has been linked to worse learning and memory due to alterations in hippocampal long-term potentiation. Dendritic spine and excitatory synapse loss have been related to A β oligomers and oxidative stress.^{75,76} Results from studies in which synthetic A β 1-42 species were injected into various regions of the brains of non-transgenic rats were often unreliable because of a lack of genuine characterization of the administered A β aggregates. Afterward, well-characterized hazardous soluble A β 1-42 species (oligomers, protofibrils, and fibrils) were ICV injected into the rat brain to create a more robust model. Studies of the distribution of fluorescently tagged A β 1-42 showed that soluble A β species spread to all areas of the rat brain. Spatial memory was impaired in the Morris water maze test, and long-term plasticity was damaged in acute hippocampal slices from A β -treated mice after seven days.⁷⁷ Shahidi S *et al.*⁷⁵ used behavioral and electrophysiological techniques to assess the protective effect of N-acetyl cysteine on learning and memory in an A β -induced AD model in adult male rats. Passive avoidance test step-through latency was shortened after intrahippocampal A β injections, and the amplitude and slope of excitatory postsynaptic potentials in the hippocampal neuron population were also reduced. If A β -treated rats were also given N-acetyl cysteine, the deficits caused by A β injection were reduced compared to the A β -only group.⁷⁵ Co-injection of A β with another inducing agent, such as ibotenic acid, has been reported,^{78,79} leading to significant neuronal death in the injection site and faraway regions, such as CA1, CA4, and the dentate gyrus compared to a single inducing approach.

D-(+)-Galactose

D-galactose, a reducing sugar, is an aldohexose found in many foods, including dry figs, honey, and milk products. Naturally occurring amounts of aldohexose D-galactose are present in the brain and the rest of the body, with a maximum daily recommended amount of 50 g.⁸⁰ Nevertheless, it is well-established that exceeding the usual concentration of exogenous D-galactose can cause oxidative stress, apoptosis, and inflammation, producing aging effects in several organs, including the brain.⁸¹ Mitochondrial failure and elevated oxidative stress are significant indicators of brain aging. Long-term injections of D-galactose result in a rise in AGE, RAGE, AR, SDH, telomere length shortening, telomerase activity, BACE-1, and A β ₁₋₄₂.^{82,83} One of the underlying mechanisms pro-

posed is that when the amount of D-galactose rises, it is converted to H₂O₂ by the enzyme galactose oxidase, causing a drop in SOD. Subsequently, reduced Iron (Fe) reacts with the increased H₂O₂ to produce OH⁻.⁸⁴ These ROS can harm neurons by impairing redox equilibrium and causing lipid peroxidation in cell membranes.

Several recent studies used D-Galactose combined with another agent, such as AlCl₃ or A β ₂₅₋₃₅, to induce AD-like symptoms, including cognitive and memory impairments, oxidative damage, and inflammation.^{35,45,85,86} D-galactose can accelerate the overproduction of ROS, and AlCl₃ intervention can cause neurotoxicity.⁴⁵ The body's metabolism of D-galactose and AlCl₃ results in D-galactitol, which the organism fails to metabolize. This leads to an increase in osmotic pressure, disrupting the typical morphology of hippocampus neurons and causing a gradual decline in neurological function.^{45,87,88}

Colchicine

Colchicine is a medication commonly used to treat gout and arthritis. It works by reducing inflammation and pain. However, colchicine has been associated with neurological side effects, including cognitive impairment and memory loss, which can resemble symptoms seen in AD.⁸⁹ The exact mechanism by which colchicine might induce AD-like symptoms is not completely clear. However, proposed mechanisms include disruption of microtubule function, potential impact on inflammation in the brain, interference with mitochondrial function, contribution to oxidative stress, and possible disruption of the blood-brain barrier.^{46,90}

Colchicine has been used for the induction of AD in animal models in several research (Table 1).^{46,91-94} It has been proposed that the inflammatory action could be caused by cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), IL-1 β , and TNF- α . The expression of COX-2 mRNA in dentate gyrus granule cells is significantly upregulated, and morphological changes associated with cell death are observed in rats following intrahippocampal injection of colchicine.⁹⁵ It's important to note that no research has examined this model's specific sequence of pathogenic events and cognitive impairment. As a result, whether the observed alterations in the colchicine-induced model align with the inflammatory hypothesis of AD remains an open question.

Okadaic acid

Okadaic Acid (OA) is a marine toxin produced by certain types of dinoflagellates, and it is well-known for its inhibitory effect on protein phosphatases, particularly protein phosphatase 1 and protein phosphatase 2A.⁹⁶ The disruption of normal protein phosphorylation and dephosphorylation processes can have various cellular effects, including alterations in the cytoskeleton, cell cycle progression, and apoptosis. In neurodegenerative diseases, disruptions in protein phosphorylation are often associated with the formation of abnormal protein aggregates, such as tau tangles in AD. Research has shown that OA causes cellular death and tau phosphorylation, produces intracellular ROS, and activates MAPK signaling.⁹⁷ In addition, cultured hippocampus neuronal cells exposed to OA increased Ca²⁺ through ionotropic excitatory amino acid receptors, resulting in neuronal cell death.⁹⁸

To investigate the effect of IMM-H004 on OA-induced learning and memory deficits in rats, a prior study used 200 ng/5 μ L of OA administered unilaterally via ICV injection.⁹⁹ The results showed that OA-treated rats demonstrated substantial impairments in spatial memory in the Morris water maze test. In addition, the hippocampus showed considerable increases in tau phosphorylation, A β protein deposition, and cell death. Another study found

that rats that received a single ICV injection of OA (200 ng/10 μ L) on both sides exhibited notable behavioral impairments, including nesting behavior, short-term working, image discrimination, and spatial discrimination memory.¹⁰⁰ Moreover, the hippocampus and prefrontal cortex showed a substantial increase in the frequency of pT231-tau immunoreactive cells, along with other abnormalities such as an expanded cell body and highly stained cytoplasm. Furthermore, a significant increase in the protein expression of pS396-tau, pT231-tau, and pS202/205-tau and a decreased number of neurons in the hippocampus and prefrontal cortex were observed.

Ibotenic acid

Ibotenic acid is a naturally occurring amino acid found in certain mushrooms, particularly in species of the *Amanita* genus. Researchers use ibotenic acid to create lesions or induce specific patterns of neural damage in laboratory animals, allowing them to study the effects on behavior, cognition, or cellular processes. Research has demonstrated that ibotenic acid causes considerable neuronal death in the cortex, substantia nigra, striatum, and hippocampus, as well as intense gliosis around the sites of neuronal death.¹⁰¹ Ibotenic acid shares structural similarities with glutamate, an excitatory neurotransmitter, and is a potent N-methyl-D-aspartate receptor agonist, resulting in sustained activation and excitotoxicity.¹⁰² The outcome is increased water entry into the neurons caused by osmotic lysis and an overabundance of chloride and calcium ions.¹⁰³ Additionally, ibotenic acid affects cholinergic cells in the ventral pallidum and substantia innominata complex and causes neuronal death throughout the nucleus basalis of the Meynert complex. Research has shown that rats can experience neuroinflammation and neurodegeneration due to cortical cholinergic dysfunction caused by ICV injections of ibotenic acid.^{102,104} The proposed mechanism for neuroinflammation and neuronal cell death involves influencing both local microglia and protoplasmic astrocytes. The advantage of this toxin model is the similarities between the pathophysiology in AD models in rodents and the cholinergic situation in human patients. However, the invasive method and high mortality rate are two drawbacks of this model.

Future directions

Scientists are continually refining and developing new animal models that better recapitulate the complexity of AD, including the genetic and environmental factors contributing to the disease's heterogeneity. It's important to highlight that these studies aim not to induce AD in animals but to create models that recapitulate specific aspects of the disease's pathology. Animal studies are essential for advancing our understanding of AD, identifying potential drug targets, and testing experimental treatments. However, findings from animal studies must be interpreted cautiously, as they may not always translate directly to humans.

The complicated pathophysiology of AD means that there are currently no reliable models of early-stage AD. In the intermediate to late stages of AD, most models show that pathogenic events and cognitive impairment emerge rapidly. Most people with AD first experience mild cognitive impairment and subjective cognitive decline before the disease progresses to definitive AD, which can take many years in humans. To better understand the early pathological changes associated with AD and to find potential treatments, further animal models of mild cognitive impairment and subjective cognitive decline are required since late-onset sporadic AD is the most prevalent form of AD. These animal models should not only display clinical episodes comparable to actual AD but also undergo

gradual cognitive deterioration over an extended period. Additionally, some limitations require to be addressed in future research. The surgical techniques, dosage of the inducing agent, and the efficacy of the therapeutic molecule can differ among researchers. Repeated administration of the therapeutic molecule within animal models may not consistently yield the anticipated outcomes. While amyloid infusion may benefit therapeutic research, it fails to elucidate the underlying causes and solely concentrates on the neurotoxic effects induced by amyloid oligomers. Furthermore, the utilization of excitotoxins is not exclusive to cholinergic neurons in the basal nuclear projections into the cortex, thus not adequately depicting the observed pathology in AD. Overall, further research is necessary to establish the stability of the models in terms of consistency and reproducibility.

Conclusion

AD is a progressive neurological condition, and its exact causes are still not fully understood. A β plaques and tau tangles are two aberrant proteins that accumulate in the brain of people with AD, causing cognitive decline and memory loss. While various studies and experiments have been conducted on animals to better understand the disease, these studies typically involve genetic manipulation or the administration of substances that mimic some of the pathological features of AD. These studies aim to gain insights into the disease's mechanisms and develop potential treatments. Thus, these AD-inducing agents are helpful pharmacological tools to study, to some extent, the cellular and molecular changes related to AD pathogenesis. Further research is required to optimize the inducing dose and to discover models that can cover the full scope of AD pathogenesis.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Concept and design (KK, YS), acquisition of data (KK, NAE), drafting of the manuscript (KK, NAE), critical revision of the manuscript for important intellectual content (KK, NAE, YS), and study supervision (YS). All authors have made significant contributions to this study and have approved the final manuscript.

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