International Journal of Biology, Pharmacy
and Allied Sciences (IJBPAS)
'A Bridge Between Laboratory and Reader'

www.ijbpas.com

EXPERIMENTAL ALZHEIMER'S DISEASE IN DIFFERENT ANIMAL MODELS

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ABSTRACT

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by progressive cognitive decline and neuropathological changes, including the accumulation of beta-amyloid plaques and tau tangles in the brain. Preclinical animal models play a crucial role in advancing our understanding of AD pathogenesis and in the development of potential therapeutic interventions. This review explores various preclinical animal models utilized in Alzheimer's disease research, encompassing Streptozotocin Induced Model, Amyloid-Induced Model, Colchicine-Induced Model, Okadaic acid-induced neuroinflammation, Scopolamine-Induced Model and many others will see in detailed manner. These models will elucidate the disease mechanisms and testing novel therapeutic strategies. Additionally, methodological considerations, limitations, and recent advancements in refining these models for improved fidelity are discussed. A comprehensive understanding of the strengths and limitations of preclinical animal models is imperative for bridging the gap between basic research and clinical translation in the pursuit of effective treatments for Alzheimer's disease.

Keywords: Alzheimer's disease, preclinical models, animal models, neurodegeneration, beta-amyloid, tau pathology

1. INTRODUCTION

Alzheimer's disease is a degenerative brain condition that impairs thinking, actions, and remembering. It is a brain condition that gradually impairs ability to think and remember as well as the capacity to complete tasks that are as basic as possible. Amongst elderly persons, it is the most frequent cause of dementia. Alzheimer's disease does not occur naturally as people age. It is caused by intricate brain alterations that begin years before symptoms show and ultimately lead to the loss of cells in the brain and the connections that connect them. Although the exact origins of Alzheimer's disease are not yet known, a mix of factors related to genetics, the environment, and lifestyle are likely to be involved. A prolonged preliminary stage that lacks clinical indications, a time of moderate cognitive impairment, and a disease phase are some of the phases of Alzheimer's disease. Depending on the phase of the disease, there are different warning signs and symptoms of Alzheimer's. The symptoms often include progressive declines in memory, reasoning, and behaviour [1].

Amyloid-beta (Aβ) plaques and neurofibrillary tangles build up in the brain as a result of Alzheimer's disease, and interconnections across the neurons (nerve cells) in the brain are damaged. Transgenic mice, rat models, and non-human primates are only a few of the preclinical animals that are employed to investigate Alzheimer's disease. For those with mild to moderate stages of Alzheimer's disease, most medications are most effective. In order to postpone or prevent the disease as well as cure its clinical signs, experts are looking at alternative medical treatments and non-drug approaches. Ethics issues, including as animal care, rationale, reduction, substitution, and transparency, ought to be addressed whenever employing animals as study subjects for Alzheimer's disease. Memory, reasoning, even personality is all impacted by the complicated brain condition known as Alzheimer's disease. It entails the breakdown of synapses across neurons as well as the buildup of beta-amyloid plaque and tangles of neurofibrillary cells which is caused by the hyperphosphorylation of tau protein in the brain. To investigate Alzheimer's disease, several preclinical animal experiments are employed [1, 2].

Preclinical animal models are essential for the research of Alzheimer's disease because they provide understanding on the illness's pathophysiology and facilitate the development of new therapies. The primary characteristics and course of the disease as it

exhibits in humans are mimicked by these animal models [3].

Preclinical animal models of Alzheimer's disease have substantially contributed to the discovery of possible treatments and enhanced our perception of the illness. While applying new approaches to clinical studies on humans, they give investigators an opportunity to investigate the underlying mechanisms, test out innovative strategies, and assess the efficacy as well as the safety of those interventions. These models represent an efficient foundation for research into the many stages of Alzheimer's disease, from the preclinical stage without any clinical signs through the stage of moderate cognitive impairment and the illness [3, 4].

Preclinical animal models are useful for gathering knowledge, but it is essential to remember that they do not exactly mirror the complexity and severity of Alzheimer's disease as seen in people. For the purpose to strengthen the results from these models, clinical investigations should be conducted. Nevertheless, preclinical animal experiments continue to be essential resources in the study of Alzheimer's disease, advancing knowledge and enabling the establishment of novel treatment approaches [3, 4].

Table 1: Comparison of Animal models and experimental conditions used in previous study

Sr. No.	Inducers	Animals	Dose and route of administration	Duration of study
1.	**Streptozotocin Induced Model [7]**	**Rat or mice**	**Intracerebroventricular *(ICV)* (2 mg/kg)**	**30 Days**
2.	**Amyloid-Induced Model [4,10]**	**Rat or Mice**	**Intracerebroventricular *(ICV)* (5 µl)**	**5-7 Days**
3.	**Colchicine-Induced Model [4]**	**Rat or mice**	***Po* (15 µg in a 5 µl vehicle) and (15 µg, ICV)**	**21 Days**
4.	**Okadaic acid-induced neuroinflammation [14,15]**	**Rat or mice**	**Intracerebroventricular *(ICV)* (200 ng) and intrahippocampal**	**15 Days**
5.	**Scopolamine-Induced Model [4,20]**	**Rat or mice**	***Ip (2 mg/kg) or Ip (1 mg/kg)***	**7 Days**
6.	**Atropine-Induced Model [4,21]**	**Rat or mice**	***Ip 5 mg/kg***	**21 Days**
7.	**Aluminium Chloride-Induced Model [4,24]**	**Rat or mice**	***Ip* (4 mg/kg or 40 mL/kg) Or *Po* (100 mg/kg)**	**40 Days Or 28 Days**
8.	**Aluminium salt [4,26]**	**Rat**	***Ip* (100 mg) Or *Ip* (20 mg)**	**1 Day Or 5 Days**
9.	**AlCl3+D-gal induced [27]**	**Rat**	***Ip* (150 mg/kg + 300 mg/kg)**	**1 Day**

2. Animal models of Alzheimer's diseases

2.1 Streptozotocin Induced Model

The spontaneous Alzheimer's disease involving insulin resistance in the brain is being investigated employing an ICV-STZ-

induced model, a chemically stimulated animal model. This model has been employed for preclinical testing of pharmaceutical treatments for Alzheimer's disease and triggers a variety of consequences resembling the molecular, pathological, and behavioural characteristics of the condition [5].

2.1.1 Principle

The ICV-STZ model's basic concept is that rodents are given smaller doses of streptozotocin (STZ) intracerebroventricularly in order to cause abnormalities resembling Alzheimer's disease. The ICV-STZ model includes delivering STZ directly into the brain's lateral ventricle, which causes an onset of dementia resembling Alzheimer's disease. Insulin resistance, which is known to play a significant role in the progression of Alzheimer's disease, is brought on by the STZ injection in the brain. It has several side effects, including as forgetfulness, cholinergic dysfunction that worsens with time, and neurodegeneration, and that are like the molecular, clinical, and psychological characteristics5. In primate species experiencing spontaneous cognitive impairment, the expression of genes involved in the APP pathway and tau phosphorylation has been examined using the ICV-STZ model. In male animals, the ICV-STZ model has been used to produce a sporadic Alzheimer's disease model [6, 7].

2.1.2 Procedure

In the ICV-STZ model, rats are frequently applied and male rats are frequently used. Low dosages of STZ are administered intracerebroventricularly right into the brain's lateral ventricle. The rat's brain's two lateral ventricles are primarily injected with (2 mg/kg, 2 μl/ventricle) or vehicle (2 μl/ventricle). The healing process of the animal after surgery should be assessed in the initial week. The mice are examined for the early stages of disease like Alzheimer's after one month, including memory loss, increasing cholinergic dysfunction, and degeneration. In various brain areas of ICV-STZ-injected rats, there is an increase in the production of the β-amyloid protein and hyperphosphorylation of Tau protein [7].

2.1.3 Advantages

The Streptozotocin-induced model has several advantages, including cost-effectiveness [9, 11], technical simplicity [8, 11], versatility [9], relevance to human diabetes [12] as well as established model [10, 12].

2.1.4 Disadvantages

The Streptozotocin-induced model has several disadvantages, including a lack of insulin resistance [13], high mortality rate [14], limited duration of diabetes [9], variability in

response **[8, 9]**, and off-target effects **[15]**. These limitations should be considered when using the model in diabetes research.

2.2 Amyloid-Induced Model

An animal model developed for studying Alzheimer's disease is the chemically induced centrally administration of amyloid-induced model. The method entails injecting Aβ directly into the brain of animals to cause pathology resembling Alzheimer's disease. The model has been used to research cognitive impairments and adult hippocampal neurogenesis changes, as well as the pathogenic consequences of Aβ in Alzheimer's disease and the impacts of potential therapeutic medical treatments **[16]**.

2.2.1 Principle

Studies of changes in mature hippocampus neurogenesis and memory loss in mice have been conducted using the Aβ-induced model. It is used to provide an animal model for pharmacologically causing inflammation in rodents **[17]**. The effects of bis(heptyl)-cognition on Aβ oligomer-induced neuronal and deficits in memory in vitro have been studied using the Aβ-induced model. The excessive accumulation and settling of the Aβ protein, a hydrophobic peptide that tends to organise into long-lasting polymers, is thought to be the cause of the chain of occurrences that eventually results in the

breakdown of cells in Alzheimer's disease. It serves for investigating the pathogenic consequences of Aβ in dementia, such as the impairment of glutamatergic and cholinergic receptor-mediated neuronal transmission **[18]**.

2.2.2 Procedure

In the amyloid-induced model, mice are often used. In order to cause Alzheimer's-like disease in animals, the amyloid-induced model includes administering amyloid-beta (A) directly into the brain through intracerebral or intracerebroventricular injection. The majority of amyloid (5 μl) is given via ICV, and during the next 5-7 days, the mice's mobility and health are monitored for any signs of infection or sickness **[4, 18]**.

2.2.3 Advantages

This model involves the administration of Aβ oligomers to induce Alzheimer's-like pathology in animals, and it has several advantages, including relevance to human Alzheimer's disease **[19, 20]**, replication of pathological hallmarks **[20, 22]**, established model **[19, 21]**, versatility **[22]**, and potential for therapeutic interventions **[19, 21]**.

2.2.4 Disadvantages

The amyloid-induced model has potential disadvantages, including controversy surrounding the amyloid hypothesis **[24]**, limited success of Aβ-targeted clinical trials **[19, 21]**, focus on Aβ accumulation **[23, 25]**,

limited duration of Aβ accumulation **[19, 23]**, and variability in response **[25]**.

2.3 Colchicine-Induced Model

A possible animal model for studying Alzheimer's disease has been the colchicine-induced model. A plant alkaloid called colchicine prevents the formation of polymers of microtubules, which is necessary for collagen production. With cognitive decline and behavioural impairments like Alzheimer's disease, high-dose colchicine injection can cause pathology that is associated with Alzheimer's disease **[4]**.

2.3.1 Principle

In rats, Alzheimer's-like pathology, such as dementia and behavioural changes symptomatic of the disease, has been developed via the colchicine-induced model in Alzheimer's disease studies. Colchicine may disrupt cognition and inflict severe harm to the granule cells and mossy fibres in the hippocampus, leading to death of neurons. It can also inhibit axoplasmic transport **[4]**.

2.3.2 Procedure

Colchicine administered intravenously (ICV) to rats may cause pathology such as AD, which would lead to intellectual and behavioural alterations resembling AD. Colchicine was injected intra-hippocampally into rats, and dentate gyrus granule cell COX-2 mRNA levels were increased. This was accompanied by alterations in morphology associated with apoptosis. The rats that received colchicine injections (15 μg, ICV) had substantially increased levels of TNF- in the hippocampus. It is often given orally as a therapy and induces the breakdown of microtubules. In rats, however, a dosage of 15 μg in a 5 μL vehicle causes cognitive damage like that brought on by distilled water. The inflammatory reaction that occurs in the colchicine-induced model might be triggered by cycloxygenase-2 (COX-2), prostaglandin E2 (PGE2), interleukin-β (IL-1β), and tumor necrosis factor-α (TNF-α) **[4]**.

2.3.3 Advantages

The colchicine-induced model in Alzheimer's disease research offers advantages such as the induction of cognitive impairment **[26]**, oxidative stress **[26]**, relevance to human pathology **[27]**, potential for drug screening **[26]**, and its established use in research **[27]**. These advantages make it a valuable tool for investigating Alzheimer's disease mechanisms and testing potential therapeutic interventions.

2.3.4 Disadvantages

The colchicine-induced model has potential disadvantages, including neurotoxicity **[26, 28]**, non-specific effects, limited relevance to human pathology **[26]**, potential side effects **[28]**, and limited use in drug screening **[26]**.

2.4   Okadaic acid-induced neuroinflammation

The okadaic acid-induced neuroinflammation paradigm includes giving okadaic acid to animals to cause pathology resembling Alzheimer's disease. The model has been shown to arise Alzheimer's disease-associated pathology along with intellectual decline and behavioural alterations that are similar to those of Alzheimer's disease. It is used to examine the function of oxidative-nitrosative stress and neurological inflammation in Alzheimer's disease. Using the model, experts have investigated the cellular and biochemical causes of okadaic acid-induced neurotoxicity and tested possible treatments [29].

2.4.1   Principle

Okadaic acid causes neurological inflammation in Alzheimer's disease by inhibiting protein phosphatases 1 and 2A, which in turn promotes tau to become hyperphosphorylated and activates essential kinases including MAPK and GSK3β. Protein phosphatases, in particular PP2A, have been associated to decreased activity in Alzheimer's disease. Oxidative stress, mitochondrial malfunction, cholinergic dysfunction, altered NMDAR function, neurotoxicity, and apoptotic cell death are also linked to okadaic acid-induced neurotoxicity [30, 31].

2.4.2   Procedure

In the okadaic acid-induced neuroinflammation model, okadaic acid is injected intraventricularly or intrahippocampally into rats to produce pathologies resembling Alzheimer's disease. Through the intracerebroventricular (ICV) route, 200 ng of okadaic acid (forming a dosage of 100 ng for each ventricle) was bilaterally administered. Following the okadaic acid injection, the animals undergo surveillance for an onset of pathology that resembles Alzheimer's disease, including as dementia and alterations in behaviour [32, 33].

2.4.3   Advantages

The Okadaic acid-induced neuroinflammation model offers advantages such as relevance to neuroinflammation, induction of memory impairment, replication of pathological features [27], potential for therapeutic intervention studies [34], and its established use in research [27, 34].

2.4.4   Disadvantages

The Okadaic acid-induced neuroinflammation model has potential disadvantages, including non-specific effects, limited relevance to human pathology [32], potential neurotoxicity [33, 35], limited use in long-term studies, and variability in response [36].

2.5 Scopolamine-Induced Model

The scopolamine-induced model is a pharmacological simulation of Alzheimer's that involves injecting scopolamine to rodents to cause dementia that resembles Alzheimer's. The model is used to examine how scopolamine affects the functional connectivity of the brain and to explore forward-looking treatment approaches. The model, which has been employed for investigating the neuroprotective benefits of possible methods of therapy, generates Alzheimer's disease-associated pathology together with dementia-related cognitive and behavioural changes typical of the condition [37, 38].

2.5.1 Principle

As a muscarinic receptor antagonist, scopolamine causes the muscarinic acetylcholine receptor to switch from active to inactive, resulting in temporary forgetfulness and electrophysiological abnormalities that are similar to those seen in Alzheimer's disease (AD). The scopolamine-induced model is used to examine how scopolamine affects the functional interconnections of the brain and to determine whether these alterations are comparable to those seen in AD [39, 40].

2.5.2 Procedure

The injection of 1 mg/kg (i.p.) of scopolamine throughout a week caused deficits in memory.

The T-maze and novel object recognition task were used in behavioural studies to evaluate memory and cognition, while the open field test was used to examine mobility. To assess the central cholinergic system, the activity of the acetylcholinesterase enzyme (AChE) in the brain was measured [4, 41]. To assess the degree of oxidative stress, the levels of MDA, glutathione, and catalase activity were examined. In behavioural experiments, the administration of scopolamine causes a reduction in the improvement of memory and cognition. The amount of time spent in the favoured arm of the T-maze, the amount of time spent exploring the unfamiliar object, and the discriminating index of the familiar object were all shown to have significantly decreased [41].

2.5.3 Advantages

The scopolamine-induced model in Alzheimer's disease research offers advantages such as cognitive impairment induction [42], relevance to human Alzheimer's disease [42], established use in research [42, 44], potential for therapeutic intervention studies [43, 44], and versatility [42].

2.5.4 Disadvantages

The scopolamine-induced model has potential disadvantages, including non-specific effects, limited relevance to human pathology [42],

short-term effects, variability in response [38], and limited use in drug screening [42].

2.6 Atropine induced model

The atropine-induced model is a pharmacological model of Alzheimer's disease that involves the administration of atropine to induce Alzheimer's-like pathology in animals.

2.6.1 Principle

Acetylcholine and other choline esters' actions are blocked by atropine, a muscarinic receptor antagonist that is competitive and reversible. It enters the cholinergic system, lowering the hypofunction of the muscarinic Ach receptor, and also partially inhibits the nicotinic receptor [45].

2.6.2 Procedure

Atropine has been demonstrated to cause amyloid plaques, a diagnostic sign of Alzheimer's disease, in rats when administered intraperitoneally (ip) in a dosage of 5 mg/kg for 21 days [4]. The scopolamine-induced model, similar to the atropine-induced model, gets into the cholinergic system and decreases the dysfunction of the muscarinic Ach receptor [4, 45].

2.6.3 Advantages

The atropine induced model in Alzheimer's disease research offers advantages such as cholinergic pathway modulation, impaired learning and memory, degeneration of cholinergic neurons, administration versatility (orally as well as ICV), and established use in research [4].

2.6.4 Disadvantages

The atropine induced model has potential disadvantages, including surgical skills required, limited impact on tau and Aβ accumulation, short-term effects, limited relevance to human pathology, and limited use in drug screening [4].

2.7 Aluminium Chloride-Induced Model

For examining the consequences of AD and alternative therapies, experts can employ the AlCl3-induced model of AD in rodents. The model includes giving rats AlCl3, which causes aluminium to build up in the brain, especially in the hippocampus and frontal cortex, areas that are known to be especially affected in AD [46].

2.7.1 Principle

A typical technique for examining the consequences of Alzheimer's disease (AD) in rats is the aluminium chloride (AlCl3)-induced model. Intellectual impairments, beta-amyloid pathology, and tau pathology are hallmarks of AD and are brought on by aluminium buildup in the cerebral cortex [47].

2.7.2 Procedure

Insufficient amounts of aluminium can lead to a variety of diseases. Aluminium chloride (AlCl3) may be injected intraperitoneally into

rodents to develop an AD model over a time frame of about 40 days [4]. For 28 days, the rats were given AlCl3 orally (100 mg/kg b.wt.) prepared in water. Aluminium builds up in the brain after AlCl3 treatment, especially in the frontal cortex and hippocampus, which are known to be especially at risk in AD. Aluminium buildup in the brain causes dementia, beta-amyloid pathology, and tau pathology, which are hallmarks of AD [48].

2.7.3   Advantages

The aluminium chloride-induced model in Alzheimer's disease research offers advantages such as relevance to aluminum-induced neurotoxicity [49], replication of pathological features, evaluation of neuroprotective interventions [46], established use in research [49, 50], and versatility [50].

2.7.4   Disadvantages

The aluminium chloride-induced model has potential disadvantages, including non-specific effects [49], limited relevance to human pathology, limited use in drug screening [46], potential neurotoxicity [49], and limited impact on tau and Aβ accumulation.

2.8   Aluminium salt

Aluminium salts have various applications and properties. They can be used as basic compounds with hydroxy groups attached to the aluminium atom, as coagulant agents in water treatment, as adjuvants in vaccines, and in the production of aluminium through molten salt electrolysis [51].

2.8.1   Principle

Although aluminium salts are being examined as they pertain to cause AD, their significance in the onset or induction of AD is still up for assertion in the field of science. Although several research have hinted to a possible connection between aluminium consumption and AD, the precise processes and causal links are still unclear [52].

2.8.2   Procedure

Additionally, it has been discovered that any aluminium salt might cause neurological damage linked with AD at dosages of 100 mg in a single day or 20 mg in five consecutive days. Al salts also impair cholinergic function and trigger oxidative stress, which triggers the process of apoptosis [4, 52].

2.8.3   Advantages

The aluminium chloride-induced model in Alzheimer's disease research offers advantages such as relevance to aluminum-induced neurotoxicity, replication of pathological features, evaluation of neuroprotective interventions [49, 50], established use in research, and versatility [53].

2.8.4   Disadvantages

The aluminium salt induced model has potential disadvantages, including non-specific effects, limited relevance to human pathology [50], limited use in drug screening, potential neurotoxicity, and limited impact on tau and Aβ accumulation [50].

2.9   AlCl3+D-gal

AlCl3+D-galactose is administered together to rodents in the AlCl3+D-gal induced model that causes symptomatic and deficits in cognition similar to AD. The model is designed to investigate prospective therapies and simulate the pathological changes seen in AD [54].

2.9.1   Principle

AlCl3 and D-galactose are co-administered to rats in the AlCl3+D-gal generated model of Alzheimer's disease (AD) in order to elicit signs and mental disorders similar to those of AD.

2.9.2   Procedure

The AlCl3+D-gal induced model frequently employs rodents, usually of the Sprague-Dawley or Wistar strains. Rats get both D-gal and AlCl3 at the same time. Experiments have found that dosages like D-gal 60 mg/kg.bwt and AlCl3 200 mg/kg.bwt are effective for generating AD-related dementia. However, the doses employed may vary. Depending on the research, combined administration may last for a different amount of time. From a few weeks to many months is possible. Across the experiment, numerous tests are conducted on the rodents in order to determine mental impairments and symptoms resembling AD. Behavioural exams, cognitive tests, metabolic investigations, histological examinations, and the measurement of oxidative stress indicators may all be a part of these evaluations. AlCl3+D-gal co-administration's results are contrasted with those of a control group that gets a vehicle or placebo. This enables scientists to pinpoint how the produced model specifically affects dementia [54].

2.9.3   Advantages

The AlCl3+D-gal induced model in Alzheimer's disease research offers advantages such as mimicking AD-like cognitive impairments, development of AD-like symptoms [56], evaluation of therapeutic interventions [55], replication of AD-associated pathologies [49], and established use in research [57].

2.9.4   Disadvantages

The AlCl3+D-gal induced model has potential disadvantages, including non-specific effects [55], limited relevance to human pathology, limited use in drug screening [55, 56], potential neurotoxicity [56], and limited impact on tau and Aβ accumulation [55, 49].

3. CONCLUSION

In conclusion, the utilization of preclinical animal models has significantly contributed to our understanding of Alzheimer's disease pathogenesis and potential therapeutic interventions. Through a comprehensive examination of various animal models, it becomes evident that these models have successfully replicated essential pathological features and behavioural phenotypes akin to human Alzheimer's disease. The insights gained from these models have not only elucidated key disease mechanisms involving beta-amyloid and tau pathology but have also facilitated the evaluation of novel treatment strategies.

Despite their undeniable utility, it is crucial to acknowledge the limitations inherent in preclinical animal models, including the simplification of the disease complexity, species differences, and the challenge of fully capturing the human cognitive spectrum. Advances in model refinement, incorporation of multiple disease-relevant factors, and innovative technologies hold promise in enhancing the translational relevance of these models.

Moving forward, the integration of preclinical findings with clinical observations remains pivotal for the successful translation of potential therapies from bench to bedside. A collaborative effort between researchers, clinicians, and pharmaceutical developers is essential to bridge the gap between preclinical studies and clinical trials. As our understanding of Alzheimer's disease continues to evolve, preclinical animal models will undoubtedly play an indispensable role in guiding therapeutic advancements and shaping the future of Alzheimer's disease research and treatment.

In summation, this comprehensive exploration of preclinical animal models underscores their invaluable contributions to advancing our knowledge of Alzheimer's disease, providing a foundation for targeted therapeutic strategies, and ultimately striving for improved quality of life for those affected by this debilitating condition.

4. Acknowledgements

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