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Review Article

Animal Models in Drug Discovery of Alzheimer's Disease: A Mini Review

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Abstract

Alzheimer's disease is a progressive neurodegenerative disorder. The major pathological hallmarks include deposition of senile plaques and neurofibrillary tangles. A major obstacle to understand the pathogenesis of Alzheimer's disease is the lack of adequate suitable and reliable animal models. Various animal models have been used for decades to understand the etiology and complex pathophysiology of Alzheimer's disease. Animal models on various hypothesis have been developed that mimic different aspects of this problem that further substantially contributed to its advancement. Although these models have been utilized frequently in testing novel therapeutic drug candidates, large variability still exists in terms of methodology and their reliability in terms of clinical significance. None of the experimental model has yet predicted successfully for disease-modifying therapy for Alzheimer's disease. In this manuscript, author has made an attempt to discuss various widely accepted transgenic as well as nontransgenic animal models of Alzheimer's disease, highlighting their pathological and behavioural characteristics in comparison.

Keywords: *Alzheimer's disease; Animal models; Transgenic; Nontransgenic; Memory impairment*

Abbreviations: AD- Alzheimer's Disease; ACh- Acetylcholine; AChE- Acetylcholinesterase; AChT- Acetylcholine Transferase; NMDA- N-methyl-D-aspartate; NSAIDS- Non steroid Anti-Inflammatory Drugs; Aβ- Amyloid Beta; APP- Amyloid Precursor Protein; BACE- Beta-Site APP Cleaving Enzyme; PS- Presenilin; ROS- Reactive Oxygen Species; RNS- Reactive Nitrogen Species; STZ- Streptozotocin; IDE- Insulin Degrading Enzyme; GSK- Glycogen Synthase Kinase; NF- Neurotrophic Factor; BDNF- Brain Derived Neurotrophic Factor; L-NAME- Nω-Nitro-l-Arginine Methylester

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease, characterized by a complex muster of neuropathological, behavioural and biochemical ramification and a progressive loss of brain neurons in the areas of cortex and especially hippocampus [1]. It is one of the most common causes of dementia underlying the brain pathologies. AD usually begins with difficulty in remembering names, recent confabulation and events including apathy and depression as early symptoms. Later results an impaired communication, confusion, behaviour changes and ultimately difficulty in speaking, swallowing and walking [2].

There is a necessity for deeper understanding of this neurological disease. The socio-economic problem accounts for approximately two-thirds of all dementia cases and afflicts more than 36.5 million individuals worldwide, including more than 5.2 million Americans and this number is expected to triple by 2050 [2].

In 1906, a German physician, Dr. Alois Alzheimer reported the presence of pathological abnormalities (senile plaques and neurofibrillary tangles) in the autopsied brain of a woman affected by AD. These senile plaques and neurofibrillary tangles have been recognised to be the two major pathological hallmarks of AD [1,2].

Strategy for the treatment of AD involves augmentation of cholinergic functions of brain by the use of acetylcholinesterase (AChEs) inhibitors such as rivastigmine (Exelon), galantamine (Razadyne) etc. Alternative strategy includes use of N-methyl-D-aspartate (NMDA) glutamate-receptors antagonist viz; memantine (Namenda), vitamins, antioxidants and non steroid anti-inflammatory drugs (NSAIDs) [3,4]. Presently current therapies are modestly effective and producing partial improvement, hence there is a need of identification of newer drugs that slow down the AD degeneration process. Therefore, there is an urgent need to develop tools that help in early and differential diagnosis of AD. Also there is imperative demand of variety of animal models to elucidate suitable drugs for AD and related complications.

A brief overview of AD

AD is characterized by early memory loss, followed by gradual erosion of other cognitive functions particularly in the hippocampus, cortical and sub cortical regions including amygdala and nucleus basalis of Meynert [2,3,5]. Neuropathologically it is characterised by massive neuronal cell and synapse loss at specific sites as well as β-amyloid plaques accumulation and neurofibrillary lesions [3]. The plaques mainly consist of peptide Aβ derived from amyloid precursor protein (APP) and neurofibrillary tangles consist of hyperphosphorylated aggregates of the microtubules associated protein tau (Figure 1) [3]. It has been reported that familial AD (FAD) accounts for less than 1% of the total number of cases including autosomal dominant mutations in three genes: APP, presenilin 1 (PSEN1) and presenilin 2 (PSEN2) [4]. The presenilins are components of the proteolytic γ-secretase that together with β-secretase, generates Aβ. So, the genome-wide analysis showed that FAD is caused by pathogenic mutations in PSEN1 and PSEN2 whereas sporadic AD (SAD) consists of various susceptible genes including apolipoprotein E (APOE) [3].

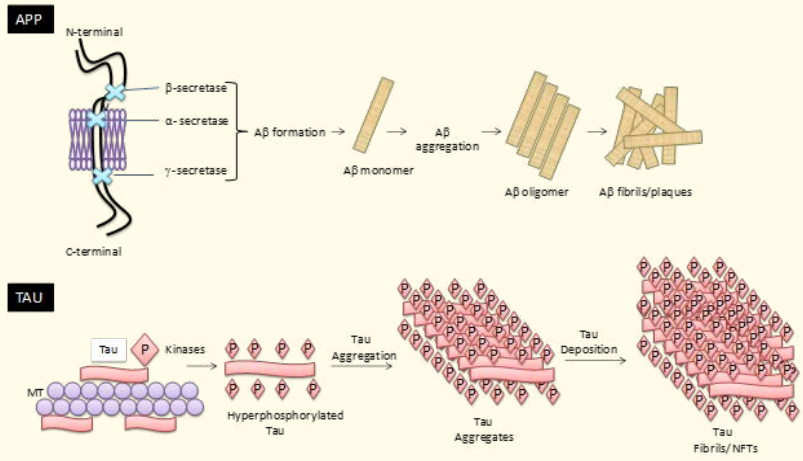

Figure 1: *The major neuropathological hallmarks Amyloid β (Aβ) plaques and neurofibrillary tangles (NFTs) of Alzheimer's disease. The major protein component of plaque is Aβ derived from amyloid precursor protein (APP) by proteolytic cleavage from α, β and γ-secretase. Aβ monomers aggregates to forms toxic oligomers and eventually deposits as plaques. Neurofibrillary tangles consist of aggregates of microtubule (MT) associated proteins known as tau. Under pathological conditions, tau is hyperphosphorylated and dissociates from MTs further deposited in aggregates known as NFTs.*

Need of animal model in Alzheimer's research

Animal models plays central role in AD research. These animal models might not accurately procreate the anatomical conditions of the disease in human brain, but biochemically they are very similar [5]. In comparison mouse models are considered to be far better than the invertebrate in terms of memory and motor functions, neuroanatomy and the endocrine system. To follow a single animal model is inappropriate because one model cannot explain all the cognitive, biochemical, behavioural and histopathological abnormalities [6]. An effective and acceptable model is the one which mimics the disease pathology, can reproduce complexity of human behaviour in rodents and leads to the development of safer and effective therapy [4]. As major neuropathological hallmarks of AD are extracellular deposition of senile plaques, widespread formation of neurofibrillary tangles, chronic neuroinflammation and loss of cholinergic neurons. So, these pathogenic situations are required to be mimicked by the different animal models of AD [7,8].

Background

Over the last decades, plenty of research has been carried out, primarily in transgenic animal models (rodents), in an attempt to quantify the onset and course of AD [5]. For example, senescence accelerated mouse model and thiamine deficiency induced model were first to be developed in 1980. Then in 1990, chemical induced models were come into existence where chemicals like streptozotocin, scopolamine, Aβ, excitotoxin, neurotoxin, clonidine etc., were used. Transgenic model and brain injury induced model for AD were first used in 1990 [4,5,9]. Later in 2000 other AD inducing chemicals were introduced such as benzodiazepine, colchicines, okadaic acid, heavy metal etc., and other transgenic animals were produced [6,9]. A number of candidate therapeutics has shown great promise in theses animal models. Unfortunately, these studies have rarely translated into clinical benefits for patients.

Classification of Animal Models

Animal models for AD can be classified into spontaneous, chemical induced, transgenic, and other miscellaneous models [9]. Spontaneous animal model includes AID and SAM model. This model is advantageous in identifying the mechanism of aged related defects in learning and cognition [10]. Transgenic model utilizes the genetic mutation associated with familial AD but is invaluable in determining the molecular mechanism underlying the disease, also expensive to develop [5]. Chemically induced AD model includes disease development after administering a suitable chemical compound such as streptozotocin, colchicine, Aβ protein, alcohol, scopolamine, etc. But their major drawback is disease progression cannot be occurred at single administration. Time consumption and invasive nature make this model tedious (Figure 2) [11].

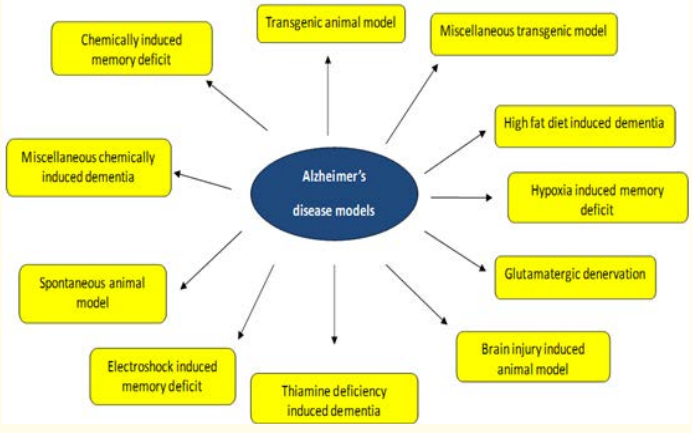

Figure 2: *Different animal models of Alzheimer's disease.*

Transgenic animal models

As said earlier, numbers of genetic mutations have been associated with the pathological changes that occur in the brain during the course of AD (FAD). But in order to understand the disease progression of AD, researchers have developed transgenic animals basically mice which can express these mutated proteins [12]. By the help of both transgenic and natural models, it will be helpful to extrapolate the information regarding development and progression of AD like disease in animals to what actually occurs in humans [13]. Transgenic model for AD uses animals that are genetically altered to have traits that mimic symptoms of AD. They are generated either by genetic modification of existing genetic makeup or by gene alteration on specific chromosomal position [12,13]. AD can easily be transgenically modelled in the mouse. Transgenic rat model is not developed and also not accepted widely. Mice is the better used species or transgenic modelling as it is low of cost, can be studied easily, short life span and not very tedious to work on [13]. Various transgenic models are:

Amyloid β (Aβ) peptide related model

Pathogenesis of AD has shown that Aβ fibril and tau hyperphosphorylation leads to senile plaque formation and recent advances suggested that Aβ oligomers, rather than Aβ fibrils are casual molecules in AD [14]. The development of transgenic mouse with three distinct mutations in AβPP has been associated with development of FAD. These types of mutations were named by the places in which they were discovered: Swedish (K670N/ M671L), London (V717I) and Indiana (V717F) [15-17]. These types of transgenic mouse showed intraneuronal accumulation of Aβ oligomers, synaptic loss, memory impairment [18,19] (Table 1). In such animal model extracellular deposits of Aβ develops at various time during the lifetime of animals. Moreover, it is evidenced that inflammation occurs brain and the animals displayed cognitive and behavioral deficits compared to wild-type animals [20].

Model	Description
PDAPP Mouse model	• It has Indiana V717F mutation under the control of PDGF mutation showing tenfold increase in hAPP level and Aβ level, diffused plaques accumulates at 6-9 months of age in cortex [18]. • It is an advantageous model as thioflavin-S positive plaque is deposited, neuritic plaues, synaptic loss, microgliosis, astrocytosis also occur (Neha *et al*. 2014).
Tg2576 Mouse model	• It expresses human APP695 containing double mutation K670N/M671L controlled by the hamster PeP promoter, diffuse local deposits occur around age of 11-13 months(Neha *et al*., 2014). • Two fold increment in mutated APP expression, 5.5 times increased Aβ '40 and 14 times increased Aβ 42. Effects produced are same as that in PDAPP mouse model (Elder *et al*., 2010).
APP23 Mouse model	• It carries Swedish double mutation at position 670/671 under the control of Thy-1 promoter (Richardson and burns, 2002). • Fibrillar amyloid plaques seen in neocortex and hippocampus surrounded by dystrophic neuritis at the age of 6 months (Neha *et al*., 2014).

Table 1: *Different types of Amyloid β (Aβ) peptide related models.*

Neurofibrillary and tau related model

In order to study the role of tau protein hyperphosphorylation and NFT in the pathogenesis of AD several animal models have been developed that over express either wild type or mutated human tau protein. It has been evidenced that tau protein mutations are associated with frontotemporal dementia not AD [21]. Tau related models mimics the neurofibrillary degenerative process by expressing mutated form of human tau. In these transgenic rats the hyperphosphorylated tau was only observed in the cortex and hippocampus region, no such tangles were observed in other brain parts [13]. Tau protein containing both G272V and P301S mutations resulted in both NFT formation and severe cognitive deficits [22]. In an effort to model NFT pathology which is relevant to AD rather than FTD, tau knockout

mice were crossed with mice expressing human genomic tau protein, resulting in mice expressing human (htau). However, these mice express minimal NFT pathology [23-25] (Table 2). Evidence suggests that in an attempt to replicate both neuropathological aspects of AD (both Aβ plaques and NFT) - a triple transgenic mouse model was developed [26]. This triple transgenic mouse expresses human AβPP with the Swedish mutation, PSEN (M146V) and tau protein (P301L). Such animal model also develops other pathological and behavioral characteristics similar to AD are gliosis, synaptic damage and memory impairment [26].

Model	Description
JNLP3	NFTs can be seen not only in the area of cortex and hippocampus but also in brain stem and spinal cord. The uniqueness of this model is it doesn't show amyloid plaque deposition but hyperphosphorylated tau protein (Richardson and Burns, 2002).
R406W	This model expresses R406W mutation driven by calcium-calmodilin- dependent-kinase II promoter leading to tau hyperphosphorylation and NFT generation (Kemper *et al*., 2011).

Table 2: *Different types of Neurofibrillary and tau related models.*

Neurofibrillary and tau related model

ApoE alleles determine age-adjusted relative risk factor for AD. In the pathogenesis of AD, ApoE promotes deposition of Aβ peptide and its conversion to oligomeric form [27]. However the role of ApoE is complex in the AD pathogenesis as it is involved in amyloid deposition as well as in Aβ clearance [14] (Table 3). It has been reported that study on ATP-binding cassette transporter A1 (ABCA1; a protein that removes cholesterol and phospholipids from cells) showed that ABCA1-/- mice have lower cerebral ApoE levels. Also it has been reported that transgenic ABCA1 over expression in PDAPP mice significantly reduced Aβ levels and plaque burden [12].

Model	Description
Tg2576 X ApoE mouse model	• It includes crossing of tg2576 mice with murine knock out ApoE mice causing lack of amyloid plaque deposition but there is parenchymal amyloid tissue deposition (Bales *et al*., 1999 and 2009). • There is an 60 % increase in ApoE protein leading to the formation of thioflavin-S positive neuritic plaques (Neha *et al*., 2014).
PDAPP X ApoE mouse model	• In this model PDAPP transgenic mice are crossed with the knockout ApoE3 and ApoE4 mice and ApoE4 mice have shown higher deposits of parenchymal amyloid tissue as that of ApoE3 (Fryer and Holtzman, 2005).

Table 3: *Different types of Apolipoprotein E (ApoE) mouse models.*

Secretase transgenic mouse model

In these animal models focus has been given on the secretase activity as in the AD secretase activity is altered which causes the amyloid plaque deposition. Hence Aβ can be deposited by genetically altering the activity of β-secretase and γ-secretase leading to memory impairment [9]. β-secretase activity has been modulated by crossing the beta-site APP cleaving enzyme (BACE) APP transgenic mice onto a BACE knock out background to reduce Aβ formation and deposition in APP/ BACE mice [28], whereas γ-secretase activity altered by expression of M146L presenilin 1 (PS1) in an APP transgenes causing Aβ deposition [29].

Presenilin transgenic mouse model

From the pathophysiology of AD it has been cleared that mutation in PSEN1 with locus on chromosome 14 is major cause of familial AD. Also mutations in PSEN proteins are associated with development of early-onset AD in humans. PS transgenic mouse models associat-

ed with plaque formation, synaptic dysfunction and loss of memory which are the major symptoms of AD [30]. However, mutated PSEN1 or 2 transgenic mouse do not show formation of amyloid plaques and neuronal loss. Moreover, doubly transgenic mouse expressing both mutated AβPP and PSEN1 develop Aβ plaques and AD related symptoms like neuroinflammation and cognitive decline. PSEN1 'knock in' mouse are generated by exchanging an exon encoding for AD linked human PSEN1 mutation for the homologous exon in the mouse PS1 gene generating a mouse producing only mutant PS1 and no wild type PSEN1 [9].

Axonal transport model

In the pathology of AD axonal transport deficit has been observed in tau hyperphosphorylation and APP transgenic mice [31]. As evidenced that both tau and APP might be directly involved in axonal transport: where tau regulates motor-protein binding to microtubules and APP links motor proteins to cargos. It has also been seen that kinesin and dynein proteins are responsible for the axonal transport [9]. In klc +/- mice increased axonal defects has been observed because of the decreased kinesin light chain. Also it has been reported that tau interacts directly with proteins of the motor complex, thereby altering axonal transport [32].

Knock out animal model

In addition to the overproduction of Aβ and tau hyperphosphorylation this model has been proved to be useful in detection of the molecular mechanism and some other pathways [5,9] (Table 4).

Model	Description
Htau mouse model	Crossing of mouse expressing human tau transgene with tau knockout mouse results in generation of Htau mouse (Tucker *et al*., 2001)
Neprilysin knockout model	Eprilysin is a natural enzyme that causes degradation of amyloid β peptide and if Aβ is injected artificially it is degraded in 30 min in presence of neprilysin. Hence in neprilysin knockout mice amyloid is accumulated in cortex and hippocampus (Mohajeri and Wolfer, 2009; Grimm *et al*., 2013)
Insulin degrading enzyme knockout model	Genes for insulin degrading enzyme has been reported to produce late-onset AD, this is present on the chromosome 10q24 and degrade APP, hence in the IDE knockout mice there is an accumulation of amyloid peptide (Vepsalainen *et al*., 2007; Neha *et al*., 2014)

Table 4: *Different types of Knockout mouse models.*

Transgenic rat model

It is very well documented that the mostly commonly used animal in the field of neuroscience research is rat [5]. Similar to transgenic mouse models rats expressing transgenes have been developed, though few of them have actually been shown to develop Aβ deposition and/or NFT pathology [13,18]. Recently a transgenic rat model (TgF344 - AD) was developed which expresses human AβPP with the Swedish mutation and PSEN (PS1ΔE9) genes, leading to development of plaques and tau pathology [33,34]. In some another study targeting rat nerve growth factor receptor with a monoclonal antibody conjugated to saporin (192 IgG-saporin) results in loss of cholinergic neurons and some cognitive impairment [33]. There have been a correlation between AD and impaired brain insulin signalling that led to the development of a model in which rats are treated with streptozotocin (STZ), a drug that targets insulin-producing beta cells of the pancreas for destruction [35]. In such models rats treated with STZ develop memory and learning deficits, progressive loss of cholinergic neurons and neurodegeneration [25,35].

Miscellaneous transgenic animal models

Mutated human α-synuclein mouse model

This type of model shows same pathological changes as that in AD. This type of model expresses the mutant [A30P] α SYN under the

control of the pan - neuronal Thy1 promoter that shows interneuronal α-synuclein inclusion and motor impairment at 17 months of age [36].

Mouse model over expressing human Cox-2

In this type of model the over expression of Cox-2 by Thy1 promoter has been reported in cortex, hippocampus and amygdale of brain that develops the same cognitive defects as in AD [37].

Anti-nerve growth factor (NGF) mice

It has been studied that deprivation of NGF causes cholinergic defects as seen in AD. In this model animals showed a neurodegenerative symptoms associated with cholinergic atrophy, neuronal loss, tau hyperphosphorylation, Aβ plaques, APP and also defects in cortical synaptic plasticity [38,39].

A. High fat diet (HFD) induced dementia

The animals fed on high fat diet or cholesterol rich diet showed memory deficit in addition to the atherosclerosis and increases the risk of AD. HFD causing dementia includes lard, cholesterol, casein, sodium-cholate, yee-sac powder, NaCl, vitamins and minerals and is fed for 3 months [9]. It has been reported that high cholesterol level in diet causes increased Aβ deposits and impairment in learning and memory [32]. High cholesterol level causes plaque deposition which then interact with the brain inflammatory cells producing neuroinflammation and also oxidative and nitrostative stress, HFD also induces the glucose intolerance and insulin insensitivity [40]. It has been reported that serum cholesterol concentration is directly proportional to the brain cholesterol concentration [41]. This model is advantageous as it mimics the most of the pathology of AD but main problem with this model is that it is time consuming [9].

Hypoxia induced memory deficit

Hypoxia induced by chemicals

Chronic hypoxia causes vascular dementia which is a common neurodegenerative disease [42]. Hypoxia causing dementia reduces the blood supply to the brain producing the memory loss. Animals exposed to carbon dioxide, carbon monoxide, sodium nitrite and hydroxylamine cause memory and learning impairment [9]. Recently it has been studied that hypoxia is involved in Aβ accumulation as it affect the degradation and clearance of Aβ, hyperphosphorylation of tau, degeneration of neurons [43]. Hypoxia induces neuroinflammation and alters cerebral blood flow affecting the transport across BBB, therefore increases the accumulation of Aβ [44]. Major advantage of this model is its usefulness for screening of nootropics and free radical scavengers with memory improving effects [9].

Hypoxia induced by surgery

Global cerebral ischemia induced by bilateral carotid artery occlusion for 12 min, followed by prolonged reperfusion of 24h produces a significant impairment of memory [9,45]. Different cerebrovascular disease contributes to one third of Alzheimer's type of dementia [46].

Glutamatergic denervation

NMDA Glutamate receptor type1 in AD brains undergoes sustained low level of activation producing low level neurotransmission. This dysregulation is thought to play a major role in neuronal damage [7]. The outcomes of glutamate related neuronal toxicity are excessive synthesis of glutamate, excessive release of glutamate, deficient glutamate reuptake and diminished glutamate catabolism [6].

Brain injury induced animal model

There are two major areas in the brain diencephalons and medial temporal lobe the injury on which may cause memory impairment, also the injury to nucleus basalis magnocellularis produces memory impairment as in AD [9]. It is advantageous as it does not require

surgical manipulation but major limitation is its tediousness. Savage., *et al*. developed animal model by inducing radiofrequency lessioning of lateral and internal medullary lamina of thalamus to induce memory loss in rats [47].

Concussion like brain injury induced animal model

In this model approximately 21g weight, 10 mm in diameter is dropped from a height of 25 cm onto the mouse head. This impact produces the concussion like brain injury without the skull fracture leading to loss of memory within 1 to 3 weeks [48].

Electrolyte lesion induced memory deficit

In the medial septum of rat brain electrolyte lesion is developed by passing anodal current 2 mA for 20 sec, through a stereotaxically implanted steel electrode that causes impairment of learning and memory after 2 weeks [49].

Electroshock induced memory deficit

Electroshock results in anterograde and retrograde amnesia by down regulation of muscarinic cholinergic receptors [50]. Monophase rectangular pulses with current intensity of 50 mA, single phase of 1 ms, stimulation frequency of 50 Hz and trial duration of 0.5s given by silver corneal electrode produce tonic-clonic seizures and memory impairment. Memory loss can be produced by ECS induced convulsions (10 mA current for 0.2s) applied through the ear clip or corneal electrode through an electro stimulator [9,51].

Thiamine deficiency induced memory deficits

If mouse is exposed to thiamine deficiency diet for 21-28 days, leads to thiamine deficiency in mouse [52]. Because of the thiamine deficiency there is a loss of cholinergic neurons in forebrain and loss of cholinergic fibres innervating hippocampus ultimately leading to the selective neuronal loss, neuroinflammation, oxidative stress, memory impairment [9,53].

Pyrithiamine induced thiamine deficiency induced memory deficits

Pyrithiamine is an inhibitor of thiamine absorption and metabolism as it affects thiamine pyrophosphokinase and thiamine triphosphate involved in its absorption and metabolism [54]. The main mechanism of memory loss in this model is glutamate excitotoxicity [55]. In this model pyrithiamine is co-administered along with thiamine deficient diet and produce significant memory loss [9].

Spontaneous animal models

The characteristic feature of old age is memory impairment, hence ageing can be a good and spontaneous model for AD [9].

Aged induced dementia (AID)

The pathophysiology of AD can be mimicked by age related cognitive dysfunction, behavioural alteration and cholinergic neurons loss [56,57]. It has been also studied and reported that dopaminergic and glutamatergic dysfunction may also contribute to age related dementia [9]. Being non-invasive and natural it is an advantageous model. Although aged rodents are commonly used animal models but it can also utilizes the bears, dogs and non-human primates [9].

Senescence accelerated mice model (SAMP)

Many salient features of AD can be mimicked by senescence accelerated prone 8 (SAMP8). SAMP were developed through selective breeding rather than transgenic technology. There are nine major SAMP sub-strains that undergo accelerated ageing and three SAMR sub-strains that undergo normal ageing process [10]. And among these strains it has been reported that SAMP8 strain is the most reliable rodent animal model [55]. There are alterations in various genes and proteins involved in ROS production, neuroprotection, signal

transduction, etc. Its approach at both gene and protein level it is an advantageous model for AD. These animal model develop Aβ plaques with cognitive impairment within 6 months of age [9,10].

Chemically induced animal models

Scopolamine induced memory deficit

Scopolamine is an anti-cholinergic drug commonly used experimental drug for cognition impairments. Scopolamine blocks the binding site of acetylcholine (Ach) muscarinic receptors in cortex and excessive ACh causes damage of hippocampus nerves. It causes memory and learning impairment in dose dependent manner [58]. Scopolamine induced memory deficit is widely used because of the non-involvement of any surgical procedures [9].

Colchicines induced memory impairment

Colchicine induces dementia by loss of cholinergic neurons either by destruction of cholinergic pathways or by decrease in cholinergic turnover [59]. It also causes decline in dopamine, nor-adrenaline, serotonin in cerebral cortex, caudate nucleus and hippocampus [60]. Increased level of protein carbonyls, lipid peroxidation leading to oxidative stress may also be a reason for memory loss by colchicine administration. Increased expression of cyclooxygenase [COX]-1 and 2 also contribute to the colchicine induced memory deficit [61]. Colchicine also elevates the glu/GABA ratio in brain cortex causing hyper-activation of NMDA receptors and increased calcium influx. Major advantage of this model is that it can mimic the characteristics of senile dementia of Alzheimer's type (SDAT) [59]. One of the study from our lab showed that intracerebroventricular (ICV) colchicine administration colchicine caused a significant decrease in the acetylcholinesterase activity which leads to memory deficits as shown in Figure 3 [90].

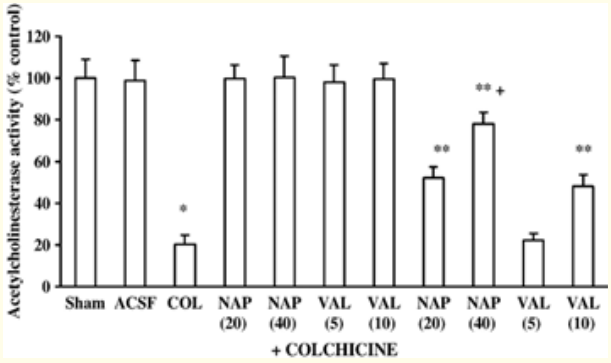

Figure 3: *Effect of Colchicine on animal model of Alzheimer's disease.*

Okadaic acid induced memory impairment

Colchicine induces dementia by loss of cholinergic neurons either by destruction of cholinergic pathways or by decrease in cholinergic turnover [59]. It also causes decline in dopamine, nor-adrenaline, serotonin in cerebral cortex, caudate nucleus and hippocampus [60]. Increased level of protein carbonyls, lipid peroxidation leading to oxidative stress may also be a reason for memory loss by colchicine administration. Increased expression of cyclooxygenase [COX]-1 and 2 also contribute to the colchicine induced memory deficit [61]. Colchicine also elevates the glu/GABA ratio in brain cortex causing hyper-activation of NMDA receptors and increased calcium influx. Major advantage of this model is that it can mimic the characteristics of senile dementia of Alzheimer's type (SDAT) [59]. One of the study from our lab showed that intracerebroventricular (ICV) colchicine administration colchicine caused a significant decrease in the acetylcholinesterase activity which leads to memory deficits as shown in Figure 3 [90].

Okadaic acid induced memory impairment

STZ is a glucosamine nitrosourea compound present in the strain of Streptomyces achromogenes [9]. It is an alkylating agent mimicking some properties of nitrosourea, an anticancer agent and has hyperglycaemic effect independent of its role in memory impairment. STZ causes ROS and RNS production induces neuronal damage and tau hyperphosphorylation [35,64]. It has been studied that STZ impairs the glycolytic enzyme activity in brain which leads to decline in ATP and creatine phosphate level. This impaired energy system and reduced acetyl CoA synthesis leads to the defects in cholinergic transmission [9,65]. STZ rats have also shown the increased activity of AChE and lesser ACh. STZ also reported to induce Aβ peptide like aggregates by changing the GSK 3 α/β activity [41]. Expression of genes involved in formation of glial derived NF, BDNF and integrin-α-M is up-regulated by STZ, whereas it down-regulates the expression of genes for NGE-IB and methallothionein 1/2 and ultimately leads to the alteration in apoptosis and cell survival process [9]. It also mimics the characteristics of SDAT but mortality rate is high [9]. One study from our lab showed that ICV-STZ administration causes significant decline in the memory and learning ability of rats and also causes oxidative stress as shown in Figure 4 [95].

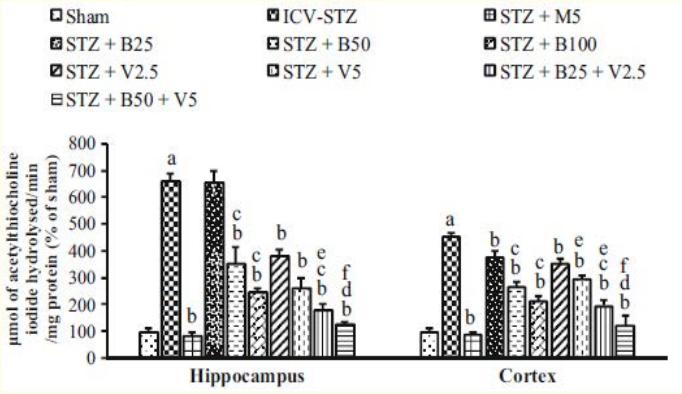

Figure 4: *Effect of ICV-STZ on animal model of Alzheimer's disease.*

Alcohol induced memory deficit

Ethanol has been reported to cause hippocampus and cholinergic neurons impairment, affect sensory-motor system, disrupts memory and learning [9]. Acute ethanol treatment produces NO excessively which impairs memory and learning, whereas higher doses of ethanol interfere with glutamatergic system and enhances GABAergic transmission in memory related areas of brain. It also increases the extracellular level of adenosine leading to memory impairment [9]. Neonatal model of ethanol has also been reported in which memory impairment is induced in pregnant animal feeding them on ethanol mixed diet. This model does not require any surgical procedure but it is very long and time consuming [66].

Aβ induced memory deficit

Aβ plaque is the major pathological hallmark in AD and direct injection or continuous infusion of Aβ into the brain causes brain dysfunction, neurodegeneration and learning and memory impairment. Aβ is infused for 14 days into the 3rd ventricle of rat brain causing its accumulation in hippocampus and cortex [9]. One study from our lab showed that intrahippocampal Aβ [1-42] administration in rat brain causes significant memory and learning loss as well as results in mitochondrial dysfunction and oxidative stress as shown in Table 5 [96].

Treatment group (mg/kg)	Brain Region	LPO (nmol MDA/mg of protein) (% of Sham)	Nitrite (µmol/mg of protein) (% of Sham)	GSH (nmol of GSH/mg Pr) (% of Sham)	Catalase (µM of H_2O_2/min/mgpr) (% of Sham)	SOD (Units/mg of protein) (% of Sham)
Naïve	**Cortex**	0.0184 ± 0.6 (97)	239.6 ± 2.1 (101)	0.61 ± 0.02 (105.1)	7.36 ± 0.52 (105.2)	0.49 ± 0.017 (102.8)
	Hippocampus	0.0246 ± 0.3 (95)	181.8 ± 4.5 (98)	0.69 ± 0.08 (97.1)	6.22 ± 0.08 (101)	0.593 ± 0.02 (106.0)
Sham (ACSF)	**Cortex**	0.019 ± 0.88 (100)	237.3 ± 1.4 (100)	0.58 ± 0.02 (100)	7 ± 0.25 (100)	0.48 ± 0.04 (100)
	Hippocampus	0.0259 ± 0.01(100)	285.6 ± 2.18 (100)	0.71 ± 0.03 (100)	6.16 ± 0.32 (100)	0.56 ± 0.02 (100)
Aβ (1-42) (1 µg/µl)	**Cortex**	0.0912 ± 0.3[a] (480)	643.08 ± 2.09[a] (341.4)	0.239 ± 0.21[a] (41.3)	2 ± 0.05[a] (28.5)	0.103 ± 0.0012[a] (21.5)
	Hippocampus	0.134 ± 0.25[a] (520)	828.2 ± 2.60[a] (290.7)	0.238 ± 0.08[a] (33.6)	2.20 ± 0.12[a] (35.8)	0.164 ± 0.88[a] (29.4)

Values are mean ± S.E.M.

aP<0.05 compared to sham group (Aβ (1-42): Amyloid beta (1-42)

Table 5: *Effect of Aβ (1-42) on animal model of Alzheimer's disease.*

L-Methionine induced dementia

Chronic homocysteine level causes changes in cerebral blood vessels producing impaired cerebral perfusion, oxidative stress and decrease in nitric oxide (NO) bioavailability [67]. Hyperhomocysteinemia also causes vascular dementia and also neurotoxicity by NMDA hyper-excitation leading to tau hyperphosphorylation and Aβ deposits [68].

Excitotoxins, neurotoxins, cholinotoxins induced memory deficit

Ibotenic acid is an excitotoxin as it is a NMDA receptor agonist causing calcium overload in neurons and neuronal toxicity. Lesion of NBM (unilateral) by ibotenic acid is a validated model for AD. Ibotenic acid also damages cholinergic neurons in NBM lesions [40]. Several other cholinotoxin and neurotoxin which produces AD like symptoms are kainic acid, intracerebroventricular (i.c.v) infusion of quinolinic acid, intraseptal infusion of anti-NGF, NMDA antagonist dizocilpine infusion, selective cholinergic toxin AF-64A (ethylcholine aziridinium ion), quisqualic acid, 3-nitropropionic acid as shown in Table 6 [94] and AMPA [9]. One study from our lab intrahippocampal kainic acid administration caused oxidative damage (as indicated by rise in lipid peroxidation, nitrite concentration, and depletion of SOD) in the hippocampus, suggesting kainic acid induced oxidative damage and memory deficits as shown in Table 7 [91].

Sodium azide induced dementia

Sodium azide is an inhibitor of mitochondrial respiratory chain, causing excitotoxicty due to generation of free radicals, inhibition of aerobic energy metabolism leading to neurodegeneration and APP dysfunctioning [9,69]. It affects the enzyme acetylcholine transferase (AChT) causing lesser cholinergic inputs but no loss of cholinergic neurons. It increases the AChT, GAP-43 and transferring receptors producing the memory and learning impairment [69].

Treatment group (mg/kg)	Brain Regions	Total Glutathione (µ mole of GSH/mg of protein) (% of Vehicle treated)	Reduced Glutathione (µ mole of GSH /mg of protein) (% of Vehicle treated)	Oxidized Glutathione (µ mole of GSH /mg of protein) (% of Vehicle treated)	Redox Ratio (GSH/GSSG)	Glutathione-S-transferase (nmol of CDNB/min/mg of protein) (% of Vehicle treated)
Vehicle	Striatum	100 ± 6.8	100 ± 4.99	100 ± 4	2.18 ± 0.05	100 ± 6.5
	Cortex	100 ± 4.4	100 ± 6.6	100 ± 4.6	1.76 ± 0.06	100 ± 9.7
	Hippocampus	100 ± 8.0	100 ± 5.3	100 ± 2.9	2.2 ± 0.066	100 ± 10.3
3-NP (10)	Striatum	55 ± 6.1[a]	49 ± 7.7[a]	68.6 ±6[a]	1.59 ± 0.07[a]	38 ± 7.1[a]
	Cortex	67 ± 6.1[a]	66 ± 5.8[a]	71 ± 4.6[a]	1.63 ± 0.056[a]	49 ± 9.4[a]
	Hippocampus	64 ± 5.5[a]	64 ± 5.0[a]	70 ± 4.5[a]	2.00 ± 0.067[a]	77 ± 110[a]

Values are mean ± S.E.M.

aP<0.05 compared to sham group (3-NP: 3- Nitropropionic acid)

Table 6: *Effect of 3- Nitropropionic acid on animal model of Alzheimer's disease.*

Treatment group (mg/kg)	MDA levels (nmol MDA/mg of protein) (% of Sham)	Nitrite levels (µmol/mg of protein) (% of Sham)	GSH (nmol of GSH/mg Pr) (% of Sham)	Total glutathione (nmol of GSH/mgpr) (% of Sham)	Oxidized glutathione (nmol of GSH/mgpr) (% of Sham)	SOD (Units/mg of protein) (% of Sham)	Redox ratio (% of Sham)
Naïve	3.31 ± 0.02 (98.81)	228 ± 3.2 (97.02)	79.51 ± 2.91(100.87)	112.01 ± 0.44 (100.54)	32.50 ± 2.63 (99.72)	27.00 ± 0.24 (111.94)	2.44 ± 0.17 (100.83)
Sham	3.35 ± 0.04 (100)	235 ± 7.64 (100)	78.82 ± 3.49 (100)	111.41 ± 0.28 (100)	32.59 ± 3.34 (100)	24.12 ± 0.12 (100)	2.42 ± 0.33 (100)
KA	9.40 ± 0.58[a] (280.61)	481.67 ± 2.28[a] (204.96)	48.55 ± 2.24[a] (61.59)	123.83 ± 1.86[a] (111.15)	75.28 ± 9.84[a] (231.02)	10.62 ± 1.04[a] (44.02)	0.66 ± 0.08[a] (26.72)

Values are mean ± S.E.M.

aP<0.05 compared to sham group (KA: Kainic acid)

Table 7: *Effect of on Kainic acid animal model of Alzheimer's disease.*

Heavy metal induced dementia

Heavy metals are reported to cause formation of reactive oxygen species (ROS) in brain leading to development of AD and other neurodegenerative disease. Heavy metals known to cause neurotoxicity by ROS generation are Aluminium (Al), Zinc, Cobalt, Chromium, Iron and Copper [9,70]. Heavy metals like cadmium, lead and arsenic causes depletion of glutathione by binding to the sulfhydryl group [71]. Zinc causes the dimerization of Aβ while Al interferes with the metabolism of Aβ peptide and insulin degrading enzyme (IDE). Al also causes tau hyperphosphorylation and apoptosis leading to neuronal toxicity in the hippocampus as in case of AD [72]. One study from our lab showed that chronic exposure of aluminum causes cognitive dysfunction and related oxidative damage as shown in the Table 8 [92].

Treatment group (mg/kg)	MDA levels (nmol MDA/mg of protein) (% of control)	Nitrite levels (µmol/mg of protein) (% of control)	Non protein (Thiol nmol/mg of protein) (% of control)	Catalase (µmol of H_2O_2 decomposed/min/mg of protein) (% of control)	SOD (Units/mg of protein) (% of control)	Glutathione-S-transferase (nmol of CDNB/min/mg of protein) (% of control)
Naive	0.1768 ± 0.04 (100)	216.8 ± 30.06 (100)	0.0653 ± 0.005 (100)	0.709 ± 0.04 (100)	48.252 ± 3.19 (100)	97.9 ± 5 (100)
D-gal (100)	0.5965 ± 0.05[a] (338.63)	605.83 ± 28.32[a] (279.44)	0.0256 ± 0.003[a] (39.203)	0.147 ± 0.018[a] (20.73)	13.873 ± 2.11[a] (28.75)	37.8 ± 5.3[a] (38.61)

Values are mean ± S.E.M.

aP<0.05 compared to sham group (D-gal: D-galactose)

Table 8: *Effect of D-galactose on animal model of Alzheimer's disease.*

Benzodiazipine induced memory deficit

Benzodiazepine has been reported to cause suppression of Long Term Potentiation (LTP) which is involved in maintaining learning and memory [9]. Benzodiazepine receptor agonists such as diazepam and lorazapam have been reported to produce anterograde amnesia [73], whereas tribenzodiazipine such as alprazolam and triazolam produce both anterograde and retrograde amnesia in mice [74].

Miscellaneous animal models

Bioactive lipid lysophosphatidic acid (LPA) has been reported to cause neurite retraction in neuronal cells and produces tau hyperphosphorylation [9]. It has been studied that PAF receptor antagonists like BN 50730 and BN 52031 have produced significant amnesia in rats [75]. Nω-nitro-l-arginine methylester (L-NAME) and N-omega-nitro-L arginine are the nitric oxide inhibitors and have been reported to show memory impairment and cognitive loss as nitric oxide is involved in the regulation of learning and memory and through generation of reactive nitrogen species (RNS) [76]. One study from our lab showed that D-galactose induced neurotoxicity is well known model for studying aging and related oxidative damage that leads to memory impairment as shown in the Table 9 [93].

Animal models of AD and Clinical AD

Till date there are varieties of AD animal models available, but no single animal models have been known that exhibited both neuropathological and behavioral symptoms characterizing human AD. Also it evidenced that the use of these models has rarely been translated into clinical for humans with AD [15]. Reason may be due to imperfect replication and intrinsic genetic differences between animal models of AD and human AD as well as species-specific functions of structurally identical genes and responses to targeted therapies [15]. Artificial nature of transgenic technology is another major reason for this. However, a very high percentage of AD cases in humans are sporadic and not familial and transgenic animal models that have been developed to model AD research are related with human FAD. So, the transgenic animal models are not evidently relevant to the AD in humans [2,4-6,9]. Table 10 shows that there are fundamental differences between human AD and AD in animal models. Among these differences are characteristics of Aβ peptide itself and plaque formation, concurrent presence of Aβ and NFT, gross localization of pathology and properties of the resulting immune response [3,4]. So, the lack of clear understanding regarding the causes and complex pathophysiology of AD, make animal models tough for explaining the pathogenesis of this disease and also for the screening of new therapeutics for the benefit of human beings [3,9].

Characteristics	Human AD	Transgenic animal AD	References
Neuronal Loss	There is progressive loss of cholinergic neurons	Single-transgenic rodent models exhibit very little neuronal loss during the disease. Double or triple transgenic mouse models, exhibit severe loss of neurons mainly in the hippocampus.	(15, 77) (29, 78, 79)
Brain atrophy	Significant atrophy of the brain occurs mainly in the entorhinal cortex, hippocampus, and amygdala	Brain atrophy is a developmental defect occurs very early in life (by three months of age) and prior to accumulation of Aβ.	(15, 80, 81)
Localization of Aβ plaques and NFT	Aβ deposits begin exclusively in the neocortex. Pathology then extends into hippocampus then to the regions of diencephalon, where the thalamus and hypothalamus are located, as well as the striatum and cholinergic neurons of the basal forebrain. In the late stages of disease, Aβ pathology detected in regions of the brain stem and the cerebellum.	In mouse models of AD, the spatial distribution of pathology depends largely on the promoter used to drive expression of the transgenes.	(15, 82)
Physical nature of the Aβ peptide	In humans, Aβ peptides are the primary components of senile plaques. Multiple different isoforms of Aβ plaques are Aβ1-40 and Aβ1-42. These peptides undergo a number of post-translational modifications, such as isomerization, racemization, pyroglutamyl formation, oxidation, and covalent linkage of Aβ dimers.	Aβ deposits are compact and laminar, and the murine Aβ peptide is completely soluble in solutions containing the denaturing agent sodium dodecyl sulfate This is likely due to the lack of post-translational modification of Aβ in the mouse model	(15, 83) (84, 85)
Nature of the inflammatory response to Aβ	The presence of Aβ plaques provides stimuli to surrounding astrocytes and microglia, resulting in induction of localized immune responses in the human AD brain. Aβ is capable of activating complement and inducing expression of proinflammatory cytokines such as IL-1β, IL-6, TNF-α, and some chemokines.	In mouse models of AD, however, there have been conflicting reports regarding the nature of the inflammatory response to Aβ.	(86-89)

Table 9: *Fundamental Differences between AD in animal models and human.*

Treatment group (mg/kg)	TBARS levels (nmol MDA/mg of protein) (% of control)	Nitrite levels (µmol/mg of protein) (% of control)	GSH (nmol of GSH/mg of protein) (% of control)	Catalase (µmol of H_2O_2 decomposed/min/mg of protein) (% of control)	SOD (Units/mg of protein) (% of control)
Control	0.174 ± 0.010 (100)	264 ± 12 (100)	0.65 ± 0.01 (100)	6.75 ± 0.012 (100)	0.72 ± 0.14 (100)
$AlCl_3$	0.589 ± 0.021[a] (339)	606.32 ± 12[a] (229.67)	0.15 ± 0.06[a] (23.37)	1.1 ± 0.12[a] (16.43)	0.096 ± 0.05[a] (13.45)

Values are mean ± S.E.M.

aP<0.05 compared to sham group ($AlCl_3$: Aluminium Chloride)

Table 10: *Effect of on Aluminium Chloride animal model of Alzheimer's disease.*

Conclusion

Significant progress has been made during the last decade in understanding the neuropathological mechanism of the biochemical and cellular abnormalities in AD. In parallel, numerous kinds of transgenic and nontransgenic animal models for AD have been developed. Although the successful animal models develop Aβ deposition and plaques accompanied by cognitive impairment, other neuropathological changes such as NFT are barely detectable in the current animal models. Transgenic animal models are the most suitable for assessing the effects of drugs that inhibit Aβ synthesis, fibril formation and deposition in the brain. As dementia has multiple etiologies, so in this review we emphasize on different animal models of memory deficits that have been identified. Chemical induced animal models of memory deficits have been more commonly employed for understanding the pathogenesis and for management of dementia and other cognitive deficits. However, transgenic models have distinct advantages and are being employed more frequently nowadays.

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