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Review Article

A review of animal models of Alzheimer's disease: a brief insight into pharmacologic and genetic models

Sajjad Salari[1,2], Maryam Bagheri[1,2]*

1. Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, Iran
2. Department of Physiology, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran

Abstract

Alzheimer's disease (AD) is the most common form of neurodegenerative disorders. Memory loss in an alert person and impairment in the function of language, attention, perception, judgment or problem solving can occur in patients with AD. However, there are some medications in order to delay the debilitating aspects of the disease; but unfortunately, scientists could not found approaches to cure this progressive problem. Hence, in order to investigate the exact mechanisms underlying the disease and to discover novel drugs that can slow the progress or alleviate the clinical symptoms of AD, producing a model which can express the most pathophysiologic and behavioral features of the disease is a desire. Nowadays, there are different animal models developed by use of pharmacologic agents and/or genetic manipulations. In this paper, we aimed to describe different animal models of AD, genetic and pharmacologic, that are mostly used by researchers.

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***Correspondence to:**
M. Bagheri
Tel/Fax: +98-84 32240404
Email:
Maryam.bagheri@medilam.ac.ir

Introduction

Alzheimer's disease (AD) was firstly described by Alois Alzheimer more than a century ago in Germany. It is estimated that almost 80% of individuals with dementia suffer from AD (Bi, 2010; Jellinger and Attems, 2010). AD is a severe progressive neurodegenerative brain disorder that affects approximately 5% of the population older than 65 years (Shah et al., 2008). Furthermore, AD is a debilitating complex disease which can interfere with social and occupational activities.

Presence of at least two clinical abnormalities are credential for diagnosis of AD. Memory loss in an alert person and impairment of one or more of the following functions: language, attention, perception, judgment or problem solving (Forstl and Kurz, 1999).

Genetic and environmental factors are involved in the progression of AD. Around 0.1% of the AD cases are familial forms with autosomal dominant inheritance and with early onset before age 65 (Wilson et al., 2011). Three genes are involved in developing familial form of the disease including the genes encoding amyloid precursor protein (APP) and presenilins 1 and 2 (Dorszewska et al., 2016).

Most cases of AD are termed sporadic AD with non-autosomal inheritance. However, environmental and genetic factors may contribute to the progression of the disease (Waring and Rosenberg, 2008). APOE gene is responsible in the sporadic form of the disease (Dorszewska et al., 2016).

US Centers for Disease Control and Prevention revealed that the number of dementia cases will reach around 14 million in Europe (Mura et al., 2010). The quality of life and life expectancy are decreased in AD. At the societal level, patients need long-term care in nursing homes which could lead to economic challenges in Western countries. In short, it can be

said that AD is one of the major public health problems in the world.

Hallmarks of Alzheimer's disease

The specific histopathological hallmarks of AD are amyloid beta (Aβ) plaques, neurofibrillary tangles (NFTs), hyperphosphorylated tau protein, and neuronal loss in the brain tissue (Skaper, 2012). The Aβ plaque, which is also known as senile plaque, is composed of the fibrillar form of Aβ peptides, mostly 38 to 43 amino acids in length, and is deposited extracellularly (Oliveira et al., 2015). NFTs inside the affected neurons contain hyperphosphorylated tau protein filaments (Haass and Selkoe, 2007). NFTs are the most common alteration in cytoskeleton. These abnormal inclusions are made up of poorly soluble isoforms of tau that is a microtubule binding protein and is typically soluble. Disturbances of the cytoskeleton may impair axonal transport and consequently affect neurons. As these neurons die, the synaptic inputs in the affected regions of the brain that are critical for normal cognitive and memory are lost (Kandel et al., 1991).

Glenner and Wong in 1984 discovered the Aβ peptide for the first time and later the Aβ peptide was introduced as the main component of senile plaques as a product of proteolytic cleavage of APP (Wilquet and De Strooper, 2004). Two proteolytic directions, the amyloidogenic and non-amyloidogenic pathways, have been suggested to be responsible for the cleavage of APP. Depending on the position of cleavage, two products will be expected; Aβ x or Aβ1–x, where x represents the number of residues in the peptide (Krone et al., 2008). The Aβ plaques observed in the brain of AD patients consist predominantly of $A\beta_{1–40}$ and $A\beta_{1–42}$, in which the C terminus ends with the 40^{th} and the 42^{nd} amino acid, respectively (Miller et al., 1993; Roher et al., 1993; Iwatsubo et al., 1994).

In the brain, deposition of $A\beta_{1-40}$ is observed primarily in the cerebral vasculature (Iwatsubo et al., 1994; Suzuki et al., 1994), whereas $A\beta_{1–42}$ is found predominantly in the parenchyma. Compared to $A\beta_{1–40}$, $A\beta_{1–42}$ aggregates more easily (Jarrett et al., 1993) and also earlier in life (Iwatsubo et al., 1994; Lemere et al., 1996).

Pathogenesis in Alzheimer's disease

Synapses and neuronal loss that mostly found in neocortex, hippocampus and amygdala lead to cognitive impairments. In addition, high levels of oxidative stress and free radicals or low content of antioxidant and/ or free radical scavenging capacity play a role in the development of the disease (Bilbul and Schipper, 2011). Furthermore, astrocytes that have a pivotal role in brain development, blood flow regulation, synaptic function, pH hemostasis, and metabolism undergo functional and morphological remodeling in response to brain injury, infection and neurodegeneration (Sofroniew, 2009). These changes which are known as reactive astrogliosis are achieved through up-regulated expression of glial fibrillary acidic protein (GFAP) in astrocytes (Sofroniew and Vinters, 2010). Much evidence supports the contribution of reactive astrogliosis in the development of AD (Sofroniew, 2009; Czlonkowska and Kurkowska-Jastrzebska, 2011).

Animal models of Alzheimer's disease

Animals with a shorter lifespan can serve as suitable models for studying the mechanisms of normal aging and the pathological mechanisms of age-related diseases over a limited period of time. In addition, such animals have a short gestation period, which is useful for investigating the effect of interventions over different generations. Animals with short lifespan that have attracted much interest recently include the fruit fly Drosophila melanogaster, with only two to three months lifespan, and rabbits and rodents with comparatively short lifespans and gestation periods. Accordingly, these animals constitute good general research models, and they can also provide opportunities to investigate specific diseases such as AD and Parkinson's disease with relevant genetic backgrounds.

It was previously supposed that only humans develop all aspects of the pathological symptoms of familial and sporadic AD. However, this hypothesis was contested after some features of AD neuropathology were observed in non-human species. Amyloid deposits were found in aged bears, dogs, and primates. Furthermore, NFTs were also detected in sheep, bears, and baboons (Woodruff-Pak, 2008). In 2008 Woodruff-Pak (Woodruff-Pak, 2008), declared that the specific hallmarks of AD including extensive Aβ accumulation, hyperphosphorylated tau, cholinergic neuronal loss, and massive brain atrophy were observed in one of five old mouse lemurs.

Numerous different species ranging from worms and flies to polar bears and genetically designed mice have been used in different investigations to clarify the mechanisms underlying the development of AD, and to find a suitable approach for treatment of the mentioned diseases (Woodruff-Pak, 2008). However, todays, there is no perfect animal model that can express all the pathological deficits at the level of behavior, biochemistry, and anatomy associated with AD in humans. Pharmacological and/or genetic manipulation of different species can induce the animal models that only show some of the neuropathological and behavioral deficits (Yamada and Nabeshima, 2000) and are suitable for different investigations based on the researcher stated goals. Consequently, different types of these animal models including mouse models of Tg2576, APP-London, NFT-like neuropathology, tau/PS1/PS2, GFAP IL-6, and rat models of amyloid pathology and tau pathology as transgenic models, as well as Amyloid beta fragments, streptozotosin (STZ) injection and neurotransmitter manipulation as pharmacologic models, that are used more often by researchers are discussed here.

Transgenic animal models

Based on the identification of genes that involved in the progression of AD, amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2), mouse models with the mentioned mutations have been used since 1990s(Do Carmo and Cuello, 2013). Transgenic models are an important tool in testing the famous "Amyloid Hypothesis" theory, and are widely used in elucidating in mechanisms involved in AD. In addition, they may help in finding crucial biomarkers in order to detect AD cases at the very early stages.

Mice and fruit flies are used widely to induce different types of gene manipulations that are performed particularly to generate animal models with Aβ-associated neuropathological features. These models can express mutations associated with human APP, C-terminal fragment of APP (Martino Adami et al., 2015), Aβ, and familial form of AD (Skaper, 2012; Guzman et al., 2014; Reinert et al., 2014; Futai et al., 2016).

Mouse model of Tg2576

The human APP695 mutations which are widespread in Swedish families with early onset AD, can be overexpressed in a mice with double mutations. This mouse model is known as Tg2576, and displays most AD features including cognitive impairment and AD-like neuropathy (Wolf et al., 2016). In addition, Tg2576 mice exhibit abundant gliosis and neuritic dystrophy, along with Aβ deposition, but not neuronal loss in CA1 (Saydoff et al., 2013). In contrast to the Tg2576 animals (Puzzo et al., 2015), a significant decrease in the CA1 pyramidal neurons can be expressed in APP23 transgenic mice.

Mouse model of APP-London

Another model of transgenic animals is APP-London. Increased levels of $A\beta_{1–42}$ have been found in young APP-London animals, while neuritis plaques have been observed in old individuals in the APP-London mutations (Calhoun et al., 1998).

Mouse model of NFT-like neuropathology

NFT-like neuropathology can be generated by transgenic techniques as well. The first NFT-positive mouse model was called JNPL3. Interestingly, cross-breeding of this model with Tg2576 animals developed a new model displaying tau pathology without Aβ pathology (Lewis et al., 2001).

Mouse model of tau/PS1/PS2

A triple transgenic mouse model is available which co-expresses a wild type human tau protein, mutant APP and PS1. It is produced by crossing between animals expressing the wild-type tau isoform with mice carrying the London and Swedish APP mutations and PS1 mutations; the new line in this case showed only cytoskeletal alteration and somatodendritic accumulation of tau (Boutajangout et al., 2004; Perl, 2010) at the early 2.5 months.

Mouse model of PS1 and PS2

Researchers have tried to develop other types of mutations which led to transgenic mice that overexpressed human mutant PS1 or PS2. These models are not severely impaired compared to the Tg2576. In animals with over-expression of PS1, higher levels of $A\beta_{42}$ were found, however, with lack of plaque-like accumulation or behavioral alterations

(Futai et al., 2016), (Kobayashi and Chen, 2005).

Mouse model of GFAP-Interlukin 6

In this model, expression of IL-6 in astrocytes is triggered by chronic neuroinflammtion. Progressive neurodegeneration, cognitive and motor skills deficits are presented at the beginning of 6 months in these animals. Importantly, this model could serve as an excellent tool in drug discovery.

Although rats are physiologically, genetically and morphologically closer to humans than mice, but mice are preferred over rats due to technical reasons. Transgene injection in rat embryo is more difficult. Furthermore, following injection embryos have shorter survival time. However, rats enable a better evaluation of cognition through longitudinal studies (Do Carmo and Cuello, 2013).

Rat models of amyloid pathology devoid of plaques

UKUR25 and UKUR28 transgenic rats are two strains in this group with developing accumulation of intracellular Aβ in pyramidal neurons of neocortex and in CA2 and CA3 in the hippocampus. These models prove the role of intracellular Aβ in the amyloid pathology. Furthermore, these models express the important role of intracellular Aβ in initializing the steps of tau-phosphorylation cascade and cognitive impairments (Echeverria et al., 2004a; Echeverria et al., 2004b).

Rat models of amyloid pathology with mature plaques

Tg478/Tg1116 (also known as PSAPP) rats that have expression of hAPP695 and carry the Swedish and Swedish/ London mutations are the first model in this group. Increased level of APP, Aβ40 and Aβ42 accompanied with diffuse plaques can be found by 17–18 months of age (Flood et al., 2009). From the age of 9 months old, PSAPP rats display abundant diffuse plaques in the cortex, hippocampus, thalamus and hypothalamus. However, compact plaques are hardly detectable even at the age of 22 months in the hippocampus region (Do Carmo and Cuello, 2013).

Rat models of tau pathology

Rats contain 6 isoforms of tau as humans. Consequently, rat models of tau pathology have been produced with developing of NFTs (Cente et al., 2006; Mocanu et al., 2008; Filipcik et al., 2012). Overexpression of human non-mutated tau including 4 repeated domains (151–391, 4R) in neurons results in the production of hyperphosphorylated tau protein and ends to the neurofibrillary degeneration (Zilka et al., 2006). Progressive cognitive deficit as well as sensorimotor disturbances are represented in the mentioned models. These impairments correlate with the progressive accumulation of NFTs and insoluble tau complexes (Do Carmo and Cuello, 2013).

Pharmacologic animal models

Amyloid beta fragments

Many investigators have declared that acute or chronic infusion of various types of Aβ fragments into the specific regions of brain in rodents can induce neurodegeneration in some parts of the brain and learning and memory deficits (Bagheri et al., 2013; Ghofrani et al., 2015) .$A\beta_{1–40}$, $A\beta_{1–42}$, and $A\beta_{25–35}$ are the fragments used extensively in vivo by researchers.Accordingly, in 1991, Kowall and colleagues observed neuronal loss in rats with intracerebral injection of $A\beta_{1–40}$, and later on, in 1994 Nitta and coworkers found that rats given continuous infusion of $A\beta_{1–40}$ at a dose of 300 pmol/day in cerebroventricle showed significant impairment of spatial reference memory in the water maze and passive avoidance tests (Kowall et al., 1991; Nitta et al., 1994).

In order to investigate the role of Aβ in the pathology of AD without overexpression of genes, infusion of Aβ into the brain of rats can be valuable (Bagheri et al., 2011; Ghofrani et al., 2015). In addition, studying the brain in different states such as astrogliosis will be possible through this model (Bagheri et al., 2015).One drawback is that the biochemical form of Aβ can be affected by the infusion time, and the temperature. In addition, the length of time the peptide is incubated in solution before the surgery can affect the toxicity of the peptide. However, there are clear advantages of this model; it is inexpensive and reproducible when carried out very carefully.

Rat model of ferrous amyloid buthionine (FAB)

In this model a solution containing amyloid peptide $A\beta_{1-42}$, the inhibitor of glutathione synthesis

buthionine sulfoximine, and ferrous sulfate is infused over 4 weeks to produce the disease phenotype (Lecanu and Papadopoulos, 2013).

Rat model of streptozotosin (STZ) injection

Some of AD's features such as phosphorylation of the tau protein, amyloid deposits, cognitive impairment, and neuronal degeneration can be induced following STZ injection. STZ that is toxic to pancreatic β cell has been used after postmortem histopathological studies of AD patients (Grunblatt et al., 2004; de la Monte and Tong, 2009). It showed decrease in the expression of insulin, insulin-like growth factor and the related receptors in the brain (Pilcher, 2006).Later on a hypothesis was developed and researchers proposed that AD may be a type 3 diabetes (Lecanu and Papadopoulos, 2013).

Neurotransmitter manipulation

Cholinergic degeneration is the earliest stage of AD pathology and occurs in the basal forebrain that leads to cognitive dysfunction (Winkler et al., 1998). In order to study the role of cholinergic system in learning and memory deficit in dementia, scientists have produced various animal models with cholinergic dysfunction. Electrocoagulation, excitotoxins, fimbria/fornix transection, and cholinotoxin are various tools to induce cholinergic lesions (Yamada and Nabeshima, 2000). It should be noted that the disadvantage of this model is that the animal models with cholinergic dysfunction do not exhibit the neuropathological features of AD, such as amyloid plaques and NFTs, so they have been used specifically to evaluate the efficacy of therapeutic interventions with cholinergic drugs (Laursen et al., 2014).

Conclusion

Here, we aimed to describe different genetic and pharmacologic models of Alzheimer's diseases. Different animal models represent different aspects of the disease. While pathophysiological pathways can be studied in the pharmacologic models, pivotal roles of genes can be investigated in the genetic forms of the disease. The pathological features induced in the pharmacologic models such as Aβ fragments infusion, mostly express neuronal loss and Aβ deposition while, with the genetic form, investigators may face the disease with the early and familial onset. However, in some genetic forms such as triple transgenic mouse, tau/ App/ PS1, only cytoskeletal alteration and somatodendritic accumulation of tau protein will be displayed.

However, because of the large discrepancy in the behavioral findings observed through the huge experiments using AD mouse models, a question that arises is whether we are really any closer today to determining the exact mechanisms involved in the disease than when the first model was developed (Buccafusco, 2000).

Most of the experiments are achieved using animal models that have increased Aβ levels. Aβ pathology is mimicked in these models, while other factors associated with AD pathology are not. For example, as described before, Tg2576 and PS1/APP mice, do not develop neuronal loss or larger ventricles, as represented in human AD (Hsiao et al., 1996; Westerman et al., 2002). Other transgenic mouse models may lack cognitive deficits. Furthermore, different types of behavioral tests, age of the animals, the genetic background, time of experiments and sleep cycle of animals may affect the results (Buccafusco, 2000).

On the other hand, another argument regarding use of transgenic models based on APP and/ or tau mutations is that other mechanisms and pathways may be at play during the disease. It is plausible that the production of Aβ or tau pathologies is a compensatory response of other pathogenic mechanisms including cell malfunction or disregulation which has not been excluded yet (Buccafusco, 2000).

Depends on the question that researchers wish to answer, evaluating a therapeutic approaches or investigating the detailed underlying mechanisms, different animals species can be selected. However, economical aspect and reproducibility of the models seem to be important in experiments. Overall, employing a genetic model in combination with pharmacologic agents may be an ideal model for future studies.

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Conflict of Interest

The authors have no conflict of interest.

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