Preclinical Non-human Models to Combat Dementia

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ABSTRACT

Dementia is characterized by a certain degree of memory loss with disabled intellectual functioning, which mostly presents as Alzheimer's disease. The underlying causes range from gene mutations, lifestyle factors, and other environmental influences to brain injuries and normal aging. Although there have been many rodent and non-human primate models created by various drugs, neurotoxins and genetic ablation but the current scenario does not exhibit a well characterized animal model to evaluate novel compounds and various treatment strategies for dementia. Therefore, a comprehensive model exhibiting the pathologies and neuro-behavioral parameters close to this syndrome is very much needed. This report discusses the various experimental strategies to create animal models of dementia.

KEYWORDS: Dementia, Alzheimer's disease, Memory loss, Spatial memory, Animal model

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Introduction

Dementia, one of the major medical illnesses at older age, where the patient's language, attention and memory are compromised. Based on the etiology it can be reversible or irreversible; the onset could be sudden or gradual and the effect could be short term or long term. Amnesia is one of the characteristic feature of dementia and could be anterograde or retrograde depending on the forgotten events which are recently stored or from distant past.[1] Dementia is not a mere consequence of normal aging, rather an acquired impairment of cognition leading to person's inability to deal with activities in daily living compromising social activities, occupational functioning and relationships without affecting the consciousness.[2] Around 7% of the 65 year old population is affected by dementia and this incidence reaches 30 to 50% by the age of 85.[3] As of 2009 report of Alzheimer's Disease International, it is estimated that as many as 35.6 million people are living with dementia worldwide and this number is expected to be double by 2030 and will reach 115.4 million by 2050. Much of those living in developing countries are estimated to be 58% and it may rise to 71% by 2050.[4] In India more than 3 million people are estimated to be suffering from this and by 2030 this estimate is expected to be double.[5]

Alzheimer's disease (AD) is the major cause of dementia whereas, vascular dementia, dementia with Lewy bodies, fronto-temporal dementia etc also lead to memory deficits.[6] The diagnosis for dementia is based on clinical criterion related to memory, attention, orientation, judgment, language, motor and spatial skills. In last two decades the research efforts have focused on the multiple causes for the pathogenesis of the disease, leading to the emergence of robust functional and morphological biomarkers that can be evaluated in patients non-invasively through neuroimaging techniques and that have largely increased the sensitivity and specificity of its diagnosis.[7,8] Although there is a huge treatment gap as more than 75% of the patients suffering from dementia have not been diagnosed and therefore do not posses access to treatment and supportive cares.[4]

With the monumental impact of this disease on our socio-economic status the need to focus on the scientific evaluation of the disease on non-human models to validate the disease diagnosis, pathophysiology and neurobehavioral outcomes has heightened. This has led to the development of several disease model organisms for AD ranging from *Drosophila,* vertebrates like Zebrafish to several rodents and non-human primates. Several transgenic animals are also created for AD by manipulating a single or multiple genes at their expression level to mimic the pathological symptoms of the disease. Here, we have attempted to summarize various strategies to create the model animals for dementia and AD and this effort would give us a comprehensive overview on the scientific approaches taken together for understanding the disease at the molecular and physiological context and further for developing various therapeutic strategies.

Animal models for Dementia

The recent strategies in the development of animal models for dementia have paved the way to validate the efficacy, safety and protectiveness of several anti-dementia drugs before they could reach the clinical trials. A reliable animal model of memory loss with certain characteristics have been established in multiple ways by exposing the animals to a predetermined brain injury[9] or intracranial infusion of certain neurotoxins.[10] Approaches have been adopted to create some suitable transgenic rodent models of Alzheimer's disease by genetically introducing certain mutant genes associated with the disease. A number of behavioral parameters are analyzed in multiple assessments tasks ranging from their normal exploratory locomotor activities to motor coordination and memory analysis in spatial mazes with varying degree of difficulties offered to the animals.[11] Contrary to this, even the lower animals like zebrafish,[12] snails[13] are effectively studied to understand the underlying mechanisms involved in cellular and molecular conservations for memory disorders. There have been certain mutations also studied in *Drosophila* to evaluate their roles in pharmacological and genetic basis of cognition.[14]

NMDA receptor antagonism

The neurotransmitters and their receptors, which are actively involved in memory pathways, are widely targeted by their antagonists to impair learning and memory in animal models. NMDA (N-methyl-D-aspartic acid) receptor antagonists play

significant role in producing reversible or irreversible transient cognitive impairment in many experimental models to understand the molecular pathways involved in memory mechanisms and further to evaluate the screening of several anti-dementia drugs on these model animals.[15] There is a strong evidence that blocking the NMDA receptors at an early stage of neonatal life results in severe neurodegeneration due to lack of stimulation in the neurons.[16] Continuous NMDA antagonism results in irreversible damages in synaptic formations, more specifically blocks the induction of long term potentiation (LTP) through CA1 hippocampal pathway.[17] This in turn induces the abnormalities in hemispheric communications. Even constant administration at higher doses, these NMDAR antagonists develop permanent damage in the rodent brains termed as "Olney's Lesions".[18] A number of experimental NMDAR antagonists such as AP5 (D,L-2-amino-5-phosphonopentanoic acid), MK-801 (Dizocilpine maleate), NPC 12626 (2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid), PCP (1-(1-phenylcyclohexyl) piperidine), Ketamine have been used successfully to create the rodent models of memory loss to further investigate their molecular mechanisms involved[19] (Table 1). A series of cognitive parameters are analysed on these models using different behavioral apparatus viz., Morris water maze, radial arm maze, plus maze, active avoidance and passive avoidance tests. Even though blockade of NMDA transmission may be helpful to set up an animal model for the study of memory dysfunction, memantine, an NMDA channel blocker, is currently used for the treatment of AD. Hence the relationship between NMDA transmission and AD pathophysiology is not linear and simple, and needs further investigation.

Neurodegeneration by site specific delivery of neurotoxins

Selective neurodegeneration by various neurotoxins has also been tried in primates and rodents to elucidate the pathogenic mechanisms involved in Alzheimer's disease. Kainic acid, Domoic acid and Ibotenic acid are widely used neurotoxins, delivered through intracranial injections for specific neuron loss in hippocampal or other cortical areas (Table 2).[20,21] Mostly, these toxins induce glutamic acid mediated neuro-excitotoxicity by altering the calcium homeostasis in brain leading to inactivation of Ca2+ and CaM-mediated adenylate cyclase pathway, which in turn leads to neurdegeneration and loss of memory.[22,10] *In-vitro* treatment of kainic acid (KA) in primary striatal neurons induces excitotoxicity through p53 mediated mitochondrial dysfunction, production of reactive oxygen species, and apoptosis of neurons.[23] These findings are further validated with the impaired cognitive functions in rats when intra hippocampally administered.[24] Domoic acid (DA), the harmful neurotoxin extracted from algal blooms, can also cause severe anterograde amnesia when microinjected into the rat hippocampus.[21] Ibotenic

Table 1: Neuropathological and behavioral features of NMDAR antagonists induced animal models of memory loss

NMDAR antagonists	Site of Delivery	Subjects	Experimental outcome	References
AP5	Chronic intraventricular infusion	Male Lister rats	Spatial memory impairment in Morris water maze task	[43]
AP5	Basolateral Amygdala	Male Wistar rats	Impairment of inhibition effect in taste memory trace	[44]
AP5	Hippocampal CA3 region	Male & Female C57BL/6 mice	Attenuation of acquisition and long-term memory retrieval in spatial pattern completion task	[45]
MK-801	Intraperitoneal administration	Harlan Wistar rats	spatial cognition deficits in the cone field test	[46]
MK-801	Exposed to water, containing drug	Male Zebrafish	Cognitive impairment in inhibitory avoidance test and social interaction task	[47]
PCP	Subcutaneous administration	Male and female Sprague-Dawley rats on postnatal days of 7, 9 and 11	At adulthood impaired cognition in spatial reference and working memory task	[48]
PCP	Subcutaneous administration	Male mice of C57BL/6N, C57BL/6J, ddY, and ICR	Strain differences in enhanced immobility in the forced swim test (ddY>>C57BL/6N and 6J>ICR). Impairment of recognition memory but no strain difference in the novel object recognition test	[49]
Ketamine	Intraperitoneal administration	Male hooded Lister rats	dose-dependent working memory impairment in odor span task	[50]
Ketamine	Intravenous administration on postnatal days 5-6	Rhesus monkeys	At 10 months of age impairment in learning, motivation, color discrimination, and short-term memory tasks. Cognitive impairment persistant over 3 and one-half years of age	[51]
NPC 12626	Intraperitoneal administration	Male Sprague Dawley rats	At higher dose, the choice accuracy at all retention intervals is disrupted	[52]
NPC 12626	Mantle cavity, into the hemocoel	Land snail (*Cepaea nemoralis*)	Reduction in the pronociceptive effects evaluated Thermal response latency test	[53]

Table 2: Neuropathological and behavioral features of toxins induced animal models for memory loss

Toxins	Pathogenic Mechanisms	Subjects	Experimental outcome	References
Kainic Acid	Overproduction of reactive oxygen species, mitochondrial dysfunction	Rats	Impairment in learning and memory in Y maze task	[24]
Kainic Acid	Decreased expression of NMDA receptor subunit 2B in hippocampus	Rats	No hippocampal neuronal loss, spatial memory inpairment	[54]
Domoic Acid	Degeneration of CA3 and CA1 pyramidal cells and dentate gyrus granule cells through loss of $Ca2^{+}$ homeostasis	Rats	Severe anterograde amnesia analysed by Morris water maze task	[21]
Domoic Acid	Increased conc. of intracellular Ca2+ led to reduced level of cyclic AMP, inducing cytotoxicity	Rats	Neurodegeneration and Memory impairment	[10]
Domoic Acid	Mild neuropathologic changes (I.P) Lesions in hippocampus (I.V); hippocampus and cerebral cortex (oral) Neuronal degeneration (I.P/I.C) Lesion in the hippocampus and cerebral cortex (oral)	Monkeys administered I.P/I.V /Orally Rats administered I.P/I.C /Orally	No behavioral impairments Memory deficit in Morris water maze test (I.P) Learning impairment in radial arm maze (I.C) No behavioral impairments (oral)	[55]
Ibotenic Acid	Reduction of choline acetyltransferase and acetylcholine esterase in the hippocampus	Rats	Memory impairment in maze tests	[67]
Ibotenic Acid	Lesion in the nucleus basalis of Meynert	C57BL/6 mice	Working memory impairment in 8-arm radial maze	[56]

I.P: Intraperitoneal; I.V: Intravenous; I.C: Intracranial

acid, synthesized by mushrooms *Amanita muscaria* and *Amanita pantherina,* has been reported to disrupt the cholinergic network when delivered in rat brain and further impairs cognitive performance in water maze.[11] Together these neurotoxins provide methods to induce memory loss resulting in validation of novel therapeutics.

Memory impairment by mechanical brain injury

Animal models for Traumatic brain injury (TBI) have a profuse clinical significance to understanding the pathophysiology of injured neurons and how they combat in response to trauma. TBI is often associated with memory impairment characterized by primary or secondary neuronal loss leading to alterations in synaptic plasticity.[25] The recent strategies in development of this model target site specific injury to the brain parenchyma or hippocampal/parahippocampal regions of rodents[26,27] and also primates.[28,29] Gao *et al.* have reported the moderate parasagittal fluid percussion method to induce TBI in rats leading to memory loss in Morris water maze tests.[30] Other studies reported in the 90s demonstrate that formation of lesion in specific region of the brain, such as dorsal hippocampus compromises about 40% of the total hippocampus volume leading to significant learning and memory impairment.[31,32] Recently, several modified approaches have been tested upon on rodents to induce the brain injury such as, pellet shot from a modified air rifle for penetrating injury to the brain parenchyma[33] or, detonation of an open field explosive to create a low level blast trauma without systemic injuries to the brain.[34] All these models showed significant cognitive and behavioral impairments along with neuropathological characteristics found acutely in the brain injury.

Transgenic mice

Transgenic models of Alzheimer's disease in mice have been successfully produced by targeting multiple genes closely related to the disease pathologies and several symptoms associated with the disease. This is the most useful system in exist to understand the pathophysiology of the disease and investigate new promising drugs for AD. In last two decades there have been several successful attempts made to create transgenic models with similar signs and symptoms very close to the disease. The clinical implications of these models are enormous and by using them in experimental trials a number of effective molecules have been identified and vigorously tested upon to come out with the most suitable therapeutic composition which could reduce the pathological burden of the disease rather than the symptomatic relief. A number of mutations associated with FAD targeting APP, PS1 and PS2 genes responsible for the pathogenesis of AD, have been identified till date and they are successfully captured in mice to develop the extracellular deposition of insoluble β-amyloid plaques, a pathological hallmark of AD (**Table 3**).

One of the mostly targeted molecules, APP (amyloid β precursor protein) with desired mutation could produce toxic amyloid plaques in the brain leading to cognitive impairment. These mutations in APP are widely investigated to understand the underlying mechanisms in Aβ metabolism, aggregation, and deposition.[35] The PDAPP mice were the first transgenics for AD that expressed several neuropathological features of the disease. It could successfully develop Aβ deposition in temporal and hippocampal regions, leading to amyloid angiopathy, microgliosis and astrocytosis and further behavioral impairments. All these properties have paved the way to make PDAPP one of the attractive models to

Table 3: Neuropathological and behavioral features of several transgenic mice models of Alzheimer's disease

Transgenics	Traget Site	Functional Outcome	References
Amyloid precursor protein (PDAPP)	Swedish, London, Indiana- isoforms of Human APP: V717F	Amyloid depotition in brain tissues and impaired performance in learning and memory tasks	[57]
Amyloid precursor protein (PDAPP)	Human APP770: V717F	Confocal and electron microscopy images show neuritic plaques with a dense amyloid core surrounded by astroglial cells. Abundant Extracellular amyloid fibrils also found	[58]
$APPs_w$ or Tg2576	Human APP695: double mutation K670N, M671L	Significant over expression of Aβ peptides and learning and memory deficit at 9-10 months of age	[59]
APP23	Human APP695: double mutation K670N, M671L	Aβ plaques at 6 months, hyperphosphorylated tau tangles and neuronal loss followed by cognitive impairment	[60]
Presenilin 1 (PS1)	Human PS: M146L or M146V	Increased production of beta-amyloid (Aβ) and hyper-phosphorylation of tau protein in hippocampus and decrease in level of presynaptic synaptophysin	[61]
Presenilin 2 (PS2)	Human PSEN2: N141I or M239V	Overexpression of Presenilin 2 and increased production of Abeta-42 leading to activation of caspase-3 and Cox-2. Also behavioral deficit in water maze task	[62]
APP/PS1	Human/mouse APPswe: double mutation K595N, M596L Human PS1: A246E	High levels of Aβ(1-40) and Aβ(1-42) detected among different brain regions and significant memory deficits in radial arm water maze test	[63]
3xTg: PS1/APP/Tau	PS1(M146V), APP(Swe), and tau(P301L)	Amyloid plaques and neurofibrillary tangles formed. Synaptic abnormalities and cognitive deficit	[41]
Beta site APP cleaving enzyme (BACE)	β-Secretase	Increased load of Aβ peptides deposition in the cortex, hippocampus and in brain vasculature. Also impaired spatial acquisition in water maze test	[64]
Apolipoprotein E (apoE7/apoE4)	Apo E4: C112R, or L28P and C112R ApoE7: Q244K or Q245K	Significant increase in levels of serum lipid and impaired memory performance in behavioral tasks	[65]
Tau	Microtubule-associated tau protein (T44): P301L	Increase in the level of phosphorylated tau at the surface of rough endoplasmic reticulum membranes in brain tissue	[66]

evaluate the valid mode of diagnosis and treatment of AD.[36] Interestingly another line of transgenic mice with double mutations in APP and Presenilin (PS1) have shown spatial memory deficits in water maze analysis followed by a higher extracellular amyloid-β deposition and intracellular deposition of hyperphosphorylated tau proteins.[37] The mutations only in the Presenilin gene do not exhibit Aβ deposition unless coupled with APP mutation.[38] However, functional reduction of Presenilin alone by 50% has led to significant cognitive impairment in *Drosophila,* demonstrate that Presenilin homeostasis is one of the important mechanisms involved in memory network.[14] Although most of these models engineered till date do not undergo significant cell loss but only a few of the selective transgenic models with very early and aggressive neuropathology sustain neuronal loss.

Several lines of evidence reveal that there is microglial activation prior to amyloid-β deposition in brain suggesting that the immunogenic reactions followed by production of cytokines and neurotoxin induced neurodegeneration preceed amyloid-β pathology in the brain.[39,40] There is a triple transgenic line created recently in an attempt to mimic the most symptomatic and neuropathological phenotypes of the disease by targeting PS1, APP and Tau protein together. The pathological findings suggest that there are synaptic abnormalities and deposition of both plaques and tangles, leading to cognitive deficits.[41] Beta site APP cleaving enzyme (BACE1), one of the important proteases, breaks down the APP into soluble amyloid peptide. The mutation in BACE1 may lead to abnormal break down of APP, forming insoluble plaques in the brain. The BACE1 knock-in along with APP transgene have shown the faster neural degradation in mice brain.[42]

Conclusions

50 years back biologists and psychologists were least likely to believe that various pathophysiological complications leading to dementia could be studied experimentally. But in last two decades there have been extensive analysis done on non-human models to uncover the neurophysiological and molecular events leading to dementia. There have been several strategies to establish these experimental animal models including intracranial delivery of certain neurotoxins, administration of antagonists for neurotransmitter receptors, site specific mechanical injury to the brain and transgenics. Fortunately, transgenic mice that are generated with specific mutations indicate the molecular pathways involved in dementia. Also, these models can mimic the neuro-pathological and behavioral symptoms of the disease. Considering the rapid progress in the field, these animal models have contributed tremendously in preclinical studies and paved way to bridge the gap for human translation. Therefore the clinical significance of these models is immense and selection of a validated

model organism for preclinical testing remains a real challenge.

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