

Primates and Rodent Models for Dementia: A Review

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ABSTRACT

Memory and cognitive functions are some of the most important and complex functions performed by the human brain. Any disorders which affect our memory will very much affect our lifestyle. Dementia and other cognitive dysfunctions are progressively emerging in the human race. To uncover newer drugs to cure such disorders we need better medium to understand the pathophysiological events occur during such disorders, so that we can make better approaches toward the cure. For such purpose different animal models are there. This review will uncover the most significant animal models. A thorough and critical evaluation of present rodent and primate models, their possible mechanism to cause such disorders and their role in drug discovery has been carried out. There are many possible pathological events that occur during cognitive disorders; in this

review, we try to cover them all. This review will give a complete in-site of prognosis, progression, and evaluation of newer drugs has been made.

Key words: Dementia, Animal models, Cognitive dysfunctions, Neurological dysfunction, Transgenic animal model.

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DOI: 10.5530/ijpi.2021.3.45

INTRODUCTION

Dementia is a cognitive disorder that affects cognitive areas of the brain, which leads to impaired thinking ability, impaired memory, forgetfulness, and certain other neurological dysfunction like anxiety, depression, and other personality disorders.¹ Combined all these functions affect one's social life, personal and professional life to a certain extent. A previous study estimated that currently 4.5 million people are suffering from dementia in the United States alone and the count will reach up to 15 million.

There are two kinds of event occurs in body which can lead to dementia and memory defects. First are the events which occur inside the brain and second are the events that occur outside the brain. In the brain, there are certain neurodegenerative events that will further lead to dementia, like the formation of neurofibrillary tangles and β amyloid plaques which affect the cognitive areas directly or indirectly by blocking the neurotransmission to these areas and leads to dementia.² Outside the brain, there will be certain an event that actually occurs outside the brain but ultimately affect the cognitive and memory areas of the brain which will further lead to memory defects. These events may include certain vascular disorders which lead to impaired blood supply either to the whole brain or to certain areas; this decreased blood flow will further lead to cognitive disorders if areas that lack blood flow are cognitive areas.³

Choosing the correct animal model for evaluating drug effects is also a very crucial decision to make. There are several laboratory animals that are used for evaluating the benefits of drugs under disease conditions, but we should select animal models that mimic human disease.⁴ The ideal animal model for dementia is that it exhibits the same histopathological, behavioral, and biochemical up and downs as humans with dementia should have.⁵ So far many animals are used for evaluating drugs for their beneficial effect in dementia and other cognitive disorders such as Primates (Apes and Monkeys), Rodents (Rats and Mice), worms, and flies.⁶ Every animal model will have their advantages over other and disadvantages from other like mice and rats are easy to handle but they do not develop plaques and tangles normally with age as humans do.

Primates are expensive to maintain but they have the exact physiology as human's have.⁴

In this review, we will study various models of dementia in primates and rodents Table 1. We are specifically focusing on these animals because they have the almost same physiology as humans do normally as well as in disease conditions, it is easy to induce dementia in such animals, they are easy to maintain and they can be molded into laboratory conditions.

SPONTANEOUS METHODS

Age associated models

As age increases, memory and other cognitive impairments increase with it. This decrease in memory and cognitive abilities can also be seen in various aged experimental animals.⁶ These animal models can serve as an excellent tool for the study of various pathophysiological events associated with memory disorders. These models associated with older age mimics almost the same neurochemical as well as morphological alterations in the brain of Alzheimer's patient.³ As the individual grows older, the level of amyloid precursor protein and tau protein increases in cerebrospinal fluid, both of which have different neurotoxic properties. This increased level is also observed in animals as age increases. These models also have certain advantages over other models like these are natural, no chemical or surgical procedure in required for induction. Aged rats are most commonly utilized for this experimental purposes.⁷ Apart from rats aged monkeys.⁸

CHEMICAL INDUCED MODELS

Scopolamine induced

Scopolamine (Hyoscine), is an alkaloid drug, which is isolated from Belladonna plant. It is used as an anti-muscarinic drug over a long time. Amnesia induced by scopolamine is senile amnesia.⁹ Cholinergic neurons play a very critical role in the cognitive functions of brain. In senile dementia (amnesia) there is reduction in level of cholinergic neurons in

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Table 1: Animal Models of dementia.

S. No.	Model name	Animals utilized
1.	Spontaneous Models a) Age associated models	Rats, Monkeys
2.	Chemical induced Scopolamine induced Alcohol induced MPTP- induced Lipopolysaccharide induced Sodium Azide induced Heavy metal induced	Rats, Mice, Monkeys Rats Rats, Monkeys Mice Rats Rats
3.	Surgical methods ICV models Ischemic models	Rats Rats, Mice, Monkeys
4.	Transgenic Animal models of Dementia A β -tau Axis Secretase Model APoE Model Axonal Transport model	Rats Mice

forebrain (basal) and there is reduction in level of cholineacetyltransferase in cortical and limbic areas of brain.¹⁰

This reduction in cholinergic neurons functions can be mimicked by administering anti-cholinergic agents like scopolamine in various laboratory animals. These cholinergic agents can induce memory loss by blocking central cholinergic receptors involved in following animals:

- Rodents are very convenient experimental animals. Rats are commonly used in this model. Scopolamine can be given intraperitoneally (0.3 or 0.5 mg/kg) to reduce learning and memory.⁶
- Mice can also serve as a novel model to understand cholinergic changes in the brain during dementia. Scopolamine (0.01 to 0.1 mg/kg) subcutaneously is given 1hr prior to experimentation to induce a temporary reduction in memory as well as learning. Scopolamine (2 mg/kg) subcutaneously can be given for 10 days for a reduction in memory as well as learning.¹¹
- Monkeys or primates are used because of their anatomical and physiological similarities with humans. Scopolamine given at a dose of 0.01-0.04 mg/kg intramuscular can induce dose-dependent memory deficit in rhesus monkey study.¹²

Alcohol induced dementia

Alcohol is the world's highly consumed drug, can act as a psychoactive drug, but has a toxic profile, consumption of alcohol can lead to temporary or permanent organ damage or death in a dose-dependent manner. Ethanol consumption can lead to peripheral as well as central nervous system toxicity, which can further result in cognitive deficits such as learning and memory impairment. The proper mechanism of alcohol-induced neurotoxicity is still uncovered, but several explanations have been proposed. Among these is excitotoxicity which can be caused by excessive neurotransmitter release, oxidative stress which further leads to free radical generation which will result in neuronal damage.¹³

In a first rat model of alcohol-induced dementia, Alcohol given by oral gavage of 10 g/kg of 35% (v/v) ethanol (b.i.d) in distilled water for 10 weeks, can induce cognitive dysfunctions.¹⁴

In a second rat model, increasing concentrations of alcohol in drinking water until a 20% solution reached can be administered to rats to induce

dementia. After 8 weeks of administration of alcohol as the only source of fluid, rats should be given access to water for 1 h/day, and 20% alcohol for the remaining 23 hr. The solution of alcohol should be sweetened with sucrose (8.75 mg/ml) to mask its bitterness, so that stable consumption (average 20 ml/rat/day) of alcohol can be maintained for the rest of the 28 weeks treatment period, with an average intake of 4.0-8.5 g/kg/day.¹⁵

MPTP Induced Dementia

1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) is a neurotoxin which is specialized in selective damage to dopaminergic cells in the substantia nigra pars compacta. It is considered as a most reliable animal model of Parkinson's disease in rodents and primates. Administration of MPTP into the substantia nigra pars compacta results in induction of similar pathophysiological events that are seen in Parkinson's disease. Like, degeneration of Dopaminergic neurons, neuroinflammation, and motor dysfunctioning, it will also lead to glutamate-induced excitotoxicity. Cognitive impairment can often be seen in MPTP-lesioned rats as well as in monkeys, thus both rodents and primates can serve as models of Parkinson's disease Dementia.¹⁶

MPTP model of dementia in monkeys

MPTP can successfully affect cognitive functions in monkeys. MPTP can be administered intravenously in doses ranging from 0.05 mg/kg at the start of the study to 0.20 mg/kg. Animals receive cumulative doses of up to 60 mg over periods up to one year should be evaluated for Parkinson's Disease Dementia.¹⁷

Lipopolysaccharide induced dementia

Lipopolysaccharide is a cell wall component of gram -ve bacteria. Peripheral or central administration of LPS can induce neuroinflammation in animals.¹⁸ LPS will cause neuroinflammation by activating glial cells, which will lead to synthesis and secretion of neuro-active and neurotoxic molecules, including cytokines, like interleukins (IL-1 IL-2, IL-6), TNF- α , and IFN- γ .¹⁹ Among all the cytokines released due to glial cells. Interleukin-2 (IL-2) has been suggested to act as a neuromodulator in the brain.²⁰ IL-2 is also known to induce several behavioral changes, including memory impairment.²¹ LPS in addition will further lead to cause oxidative stress by initiating the formation of reactive oxygen intermediates and nitric oxide.²² These two are further responsible for the production of reactive oxygen as well as nitrogen species centrally.²³ All these pathophysiological changes in the brain can lead to neurotoxicity, which will further induce dementia in animals.²⁴

Mice can be challenged with a single dose of LPS (1 mg/kg; i.p.), followed by an equivalent volume of isotonic saline (vehicle of drug or drug) for 28 days for induction of dementia.²⁵

Sodium Azide induced dementia

Sodium azide is an inorganic compound with the formula NaN₃. Chronic (2-3 weeks) subcutaneous (s.c.) administration of sodium azide is supposed to induce chemical hypoxic situations and reduce the energy production in the mitochondria by causing oxidative stress by producing oxygen radicals. Chronic NaN₃ delivery is supposed to affect the cortical, hippocampal areas, mesencephalic reticular formation, and central amygdala regions of the brain. These regions are responsible for memory and learning functions. Damage to these areas will lead to learning and memory deficits.⁶ Rats treated with various doses of sodium azide (24- 51 mg/kg per day) will induce cognitive impairment.²⁶

Aluminium induced dementia

The presence of aluminum in the brain is supposed to be involved in various neurodegenerative disorders including Alzheimer's disease.

Previous studies suggest that the mechanism of aluminum-induced neuro-toxicity through oxidative stress and neuro-inflammatory events. Aluminum is widely present in our environment; it is a constituent of cooking utensils and various drugs (antacids and antiperspirants). From these mediums, it gets accumulated in our body through food, air, and water.²⁷

Animals administered with aluminum and its salts have developed AD-like neurodegenerative disorders because aluminum will increase the A β proteins, increase the hyper-phosphorylated tau-protein, degradation of cholinergic neurons in various brain regions, trigger the neuro-inflammation, and cause oxidative damage. Dementia in rats can be induced by the administration of AlCl₃ (10 mg/kg, i.p.) for 20 consecutive days.²⁸ AlCl₃ at a dose of 50 mg/kg/day in drinking water for 5 weeks can also induce dementia in rats.²⁹

SURGICAL MODELS

ICV models

Streptozocine-ICV model in rats

STZ is a drug which is selectively toxic for insulin producing and secreting cells. It effectively induces toxicity peripherally as well as centrally. Intracerebroventricular administration of STZ impairs the Insulin and Insulin receptor system. Previous research in AD pointed towards involvement of the impaired glucose utilization, mitochondrial dysfunction, reduced ATP production, and energy dysregulation. These pathophysiological events are key consideration of the hypothesis that these abnormalities are mediated by desensitization of the neuronal Insulin receptors (IRs).³⁰ Apart from impairment of insulin and insulin receptor system, ICV-STZ will produce neuronal damage by causing oxidative stress through production of ROS and RNS, abnormal phosphorylation of Tau- protein, and accumulation of A β in various areas of brain which are involved in memory and learning.⁶

Stereotaxic apparatus should be used to directly inject the STZ in brain. An experimental rat model should be developed using Streptozotocin (STZ) administered intracerebroventricularly (ICV) in dose 3 mg/kg. Rats should be anaesthetized with chloral hydrate (300 mg/kg, i.p.). The head should be positioned on the stereotaxic frame and mid line sagittal incision should be made in the scalp. Burr holes should be drilled in the skull on both the sides over the lateral ventricles using the coordinates, 0.8 mm posterior to bregma, 1.5 mm lateral to sagittal suture, 3.6 mm beneath the surface of the brain.³⁰

MPTP-ICV model in rats

Anaesthetize the rats using Zoletil (20 mg/kg, i.p.), then MPTP-HCl (1 μ mol in 2 μ l of saline) should be infused bilaterally into the SNc (Substantia Nigra compacta), using coordinates: AP: - 5.0 mm, ML: \pm 2.0 mm, DV: - 7.7 mm from the bregma, midline, and skull surface, respectively. Immediately after surgery, penicillin-G procaine (0.2 ml, 20,000 IU) should be injected intramuscularly to rats to avoid infection, then they will be housed individually in plastic cages for a week, afterwards they will be returned to their home cages. 10% sucrose solution should be provided *ad libitum* to prevent weight loss after surgery and reduce mortality for 5 days from surgery.³¹

Ibotenic Acid-ICV model in rats

Bilateral injections of Ibotenic acid into basal forebrain leads to formation of lesions which will further cause memory impairment in rats. Rats should be anesthetized with sodium pentobarbital (45 mg/kg i.p.) and placed in a stereotaxic apparatus. Injection of Ibotenic acid should be given in basal forebrain with the help of an injection needle connected to a micro syringe, by following the coordinate's 1.5 mm posterior, 2.8 mm bilateral to the bregma, 7.3 mm below the dura. Ibotenic acid should be

dissolved in 50 mM Na phosphate buffer at a concentration, and then 0.5 ml (6 μ g per side) should be infused for 5 min. One week later, the contralateral side is treated in the same manner.¹⁷

Ischemic models

Various ischemic approaches can be used to induce vascular dementia in various experimental animals like rats and monkeys. Vascular dementia is a progressive disease that affects cognitive and learning abilities. Ischemia induce multiple pathophysiological events that lead to neurotoxicity such as excitotoxicity, increased calcium influx, oxidative and nitrate stress, inflammation and apoptosis.³² There are various ischemic models which can be utilised to induce vascular dementia. Some of them are following:

Bilateral Common Carotid Artery Occlusion model

Animals should be anaesthetized with chloral hydrate (400 mg/kg, i.p.) A midline incision will be made on neck. Separate the thymus gland which will be visible after making the incision. Both common carotid arteries should be identified and freed from surrounding tissue. A thread should be passed below each carotid artery. Do not tie the thread, apply the weight on the thread, so that it will occlude the arteries. Maintain it same to induce ischemic situation. After 10 min, weight on the thread should be removed to allow the reflow of blood through carotid arteries. The incision made should be sutured back in layer to layer. The sutured area should be cleaned afterwards with 70% ethanol and anti-biotic (Neosporin) dusting powder should be sprayed over the sutured area. Body temperature of mice should be maintained at 37°C by heated platform throughout surgical procedure 24 hr after the ischemia reperfusion injury animals will be evaluated for potency of drugs.³³

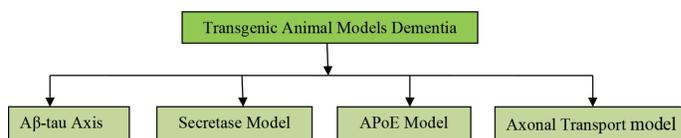
Vessel occlusion model

In four vessel occlusion model both common carotid arteries and both vertebral arteries should be occluded. In this model both vertebral arteries should be permanently occluded.³³ Now a days there are several modifications which are made with this model like, the vertebral arteries should be occluded permanently or for 15 min.³⁴

Unilateral common carotid artery occlusion model

In this model, one among the two common carotid artery should be permanently ligated using a suture.³⁵ A unilateral common carotid artery occlusion (UCCAO) in the rat causes minor changes in cerebral blood flow (CBF) in the ipsilateral hemisphere³⁶⁻³⁹ In rats, a combination of systemic hypoxia and UCCAO causes ischemic brain damage. This raises the possibility that the combination of HS (hemorrhagic shock) and UCCAO may also cause neurological damage.⁴⁰

TRANSGENIC ANIMAL MODELS OF DEMENTIA



A β -tau Axis model

The amyloid plaque has a major component in dementia which is 4 kDa polypeptide which is also called as A β -Protein that is a soluble product and secreted normally. There are two isoforms of A β - protein (A β 41 and A β 42). In the case of Dementia, there is an elevation in A β 42 levels.⁴¹ The abnormal APP process leads to excess insoluble isoforms of A β -protein mainly A β 42 causes the formation of aggregates having amyloid protein in the form of oligomers. Which are more toxic to neurons.^{42,43}

The first transgenic rat model of dementia resulted in intracellular A β accumulation but there is no senile plaque. According to the reports, animal models expressing human amyloid precursor protein (APP), amyloid β (A β) both of which carrying familial dementia gene mutation.⁴⁴ Transgenic mice harboring APP mutation generated as a model of dementia.⁴⁵ Animal models were critical in providing support for amyloid cascade hypothesis, which mainly claims that A β pathology causes tau pathology. Plaques and NFTs (Neurofibrillary Tangles) were the main players but the emphasis has shifted to oligomer form of A β and soluble forms of tau. The tau gene on chromosome 17 was the site of the first genetic mutation that causes FTD (Frontotemporal dementia) in humans and mutant tau gene mice have remained the primary animal model of FTD.⁴⁶⁻⁴⁹ The JNPL3 lines, which expressed human tau with the P301L mutation was one of its kind.⁵⁰ Progressive more deficits, neurofibrillary tau aggregates and neuro-degeneration occur in this mice.

Secretase model

Transgenic mouse model of dementia that focus on secretase have also been developed. Transgenic mouse model have been created by some modification of γ and β secretase activity genetically which may result in the amyloid desposition and memory impairment.⁵¹ The expression of M146L PSEN1 is an amyloid precursor protein (APP) transgen that causes amyloid desposition can alter- secretase activity.⁵² It has been shown that β secretase activity can be modulated by crossing β amyloid converting Enzyme (BACE) APP transgene mice onto a BACE in order to reduce desposition and A β formation. In APP/ BACE mice, overexpression of BACE causes increase in A β formation and desposition.⁵³

ApoE model

(Apolipoprotein E)

ApoE is not a direct cause of dementia and this is by far the most powerful genetic risk factor for the diseases⁵⁴⁻⁵⁶ approximately half of all sporadic dementia patients have at least one $\epsilon 4$ allele.⁵⁷

Gila produce the majority of ApoE in the normal brain, but neuron produce ApoE after injury.⁵⁸ Female transgenic mice with ApoE expressing ApoE from a neuron specific promoter have learning and memory deficits.^{59,60} The two different types of ApoE models are as follow:

Tg2576 \times ApoE mouse model

Tg2567 mice were crossed with murine knockout ApoE mice, which may result in complete absence of the amyloid plaques as well as amyloid desposition in the parenchyma tissue.^{61,62} In Tg2576 transgenic mice accumulation of A β to the brain causes increase in the ApoE content by 60% when we compare it with control mice, resulting in accumulation of neutrtritic plaques positive for thioflavin s-plaque.⁶³

Pdapp \times ApoE mouse model

When ApoE₃ and ApoE₄ mice are knocked out and crossed with PDAPP, the ApoE₄ mice developed more parenchymal amyloid plaques than the ApoE₃ mice ApoE- positive PADPP mice have compact desposits scattered throughout the frontal cortex.⁶⁴ In transgenic APP mice lacking ATP-binding cassette transporter A1 (ABCA₁), the state of ApoE lipidation and solubility influences amyloidogenesis.⁶⁵

Axonal transport model: Axonal transport deficits in tau and amyloid precursor protein (APP) have been reported, and this deficit is implicated in the pathology of dementia.⁶⁶ Proteins such as kinesin and dynein have been found to mediate axonal transport.⁶⁷ Kinesin light chain deficiency causes increased axonal defects in Klc+/ mice and amyloidogenic APP processing when crossed with APP transgenic mice.⁶⁸

CONCLUSION

This review has covered age induced, chemically induced and surgically induced and transgenic models of dementia. We have covered all possible mechanism of action of all inducing models. In this review we have covered both rodents as well as primates, which can be possibly utilized for the experimental purpose. On one hand primates are related to human species and can possibly mirrorised the disease as it happens in humans, but experimentation with primates has some limitations like their maintenance is not easy, bigger storage facilities are required. On the other hand rodents are very much convenient option. They can mimic the disease as humans do and they are easy to maintain. Most of the work on dementia includes rodent now a days so we have a weight age toward rodents but we have also covered some important models in primates.

ACKNOWLEDGEMENT

We would like to thanks Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela (An Autonomous College), for providing us moral support for writing this critical review.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

MPTP: 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; **PDD:** Parkinson's Disease Dementia; **LPS:** Lipopolysaccharide; **STZ:** Streptozocine; **ICV:** Intracerebroventricular; **UCCAO:** Unilateral Common Carotid artery Occlusion; **APP:** Amyloid Precursor Protein; **BACE:** β Amyloid converting Enzyme; **ABCA1:** ATP Binding Cassette Transporter A1; **ApoE:** Apolipoprotein E.

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Article History: Submission Date : 10-06-2021; Revised Date : 30-06-2021; Acceptance Date : 25-07-2021.

Cite this article: Sharma RK, Singh H, Kaur D, Kumar Y. Primates and Rodent Models for Dementia: A Review. *Int. J. Pharm. Investigation.* 2021;11(3):254-9.