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Review Article

Animal Models of Neurodegenerative Disorders

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Abstract

Neurodegenerative diseases are neurological disorders of the central and peripheral nervous systems increasingly observed in older animals. These diseases result in progressive loss of neuronal function and behavioral changes are the most common cause of dementia in older animals as well as humans. For the advancement of basic understanding of these diseases, various in-vitro and in-vivo models have been used. Animal models are living organisms, which mimic the pathophysiology of the original animals in a very precise manner. Such models are designed to replicate the underlying causes, pathological lesions, symptoms, and potential therapeutic options for the disorders being studied. Selection of an appropriate model with respect to a particular aspect of the neurodegenerative diseases in the most scientific, ethical and legal way is crucial. Various natural, induced, negative, transgenic and orphan models of commonly occurring neurodegenerative diseases developed so far are discussed in this review.

Keywords: Animal Models; Neurodegenerative Diseases; Transgenic, Alzheimer's; Prions; Spinal Muscular Atrophy; Mice; Rats

Introduction

Neurological disorders are affections of central and peripheral nervous system including cerebrovascular (brain stroke/tumour), neuro-degenerative, neuro-inflammatory and neuro-infectious conditions which lead to anxiety, depression, convulsion in animals and psychiatric disorders in humans. There are more than 600 nervous disorders, majority of which are incurable and create social and economic burden worldwide. Neurodegenerative diseases consist of a group of disorders characterized by a progressive loss of neurological function, either by cell death or dysfunction resulting into behavioral and cognitive deficits [25]. They are hereditary and breed or species-specific syndromes reported in variety of domestic animals resulting into degeneration of neuronal cell body, axons or both. The neuropathological lesions most commonly occur in aged mammals. For instance, cerebral β-amyloidosis and neurofibrillary tangles spontaneously occur in aged non-human primates, bears, sheep and dogs that are comparable to the lesions developing in human Alzheimer's disease [18].

Among neurodegenerative diseases, Alzheimer's disease is the most common form of dementia accounting approximately 50-60% of all cases and representing a major public health concern with significant social and economic impact [23]. The advanced studies on neurodegenerative diseases form the basis to explore the exact etiology, genetic predisposition, pathology especially at molecular level, potential sequelae and appropriate treatment. For this purpose, various types of models have been developed. A model is an object that precisely resembles any other object appearing to be its exact copy. The models in research can be either *in vivo* or *in vitro*. *In vitro* models include studies outside the living organism, for example primary cell cultures, cell lines etc. While, *in vivo* models are those in which research is conducted with or within the living organisms like animal/human clinical trials and laboratory animals as models.

Wessler (1976) [32] defined "an animal model as a living organism with an inherited, naturally acquired or induced pathological process that closely resembles the same phenomenon in humans in one or more respect". Held (1979) [13] also defined animal models more accurately as "a living organism in which normative biology or behavior can be studied or in which a spontaneous or induced pathological process can be investigated and in which the phenomenon in one or more respect resembles the same phenomenon in humans or other species of animal".

For advanced studies in the field of neurodegeneration, use of various animal models is preferred over *in vitro* cell culture. Because firstly, *in vitro* systems cannot simulate the complex response of innate and adaptive immunity of a living host and secondly, the behavioral alterations produced due to neuropathies cannot be studied using *in vitro* models. The aim of such models is to reproduce the causes, pathological lesions, symptoms and potential treatment options for the conditions under study. However, selection of appropriate model with respect to a particular aspect of these diseases is of utmost importance [25].

History of animal modelling

The concept of using animals as models began in ancient Greece (over 2,400 years ago) by prominent scientists like Galen of Pergamon (2^{nd}–3^{rd} century BC), Aristotle (4^{th} century BC), Erasistratus and Herophilus (4^{th}–3^{rd} century BC) and Alcmaeon of Croton (6^{th}–5^{th} century BC). They formulated concepts of human anatomy and physiology using animals as models because of the taboos regarding the dissection of humans. This influenced other scientists around the globe resulting into important discoveries and advances in science. One of them was the founders of modern science, William Harvey, who studied and compared the anatomic and functional properties of the heart and vasculature in multiple species including eels and other fish, chicks and pigeons [5].

The careful selection of the most informative species for an animal model is very important and challenging task for investigators. A comparative method for this selection was stated by August Krogh, 1920 winner of the Nobel Prize in Physiology and Medicine. With the beginning of the twentieth century, the use of animal modeling had increased dramatically and had become the de rigeur (meaning, trending) method of demonstrating biological significance. Initially, the researchers used outbred animals but later started inbreeding of laboratory animals to the point that genetically identical "strains" became available for experimental use [8].

The advances in genetics took animal modeling to further levels by providing ability to alter the genome of laboratory animal species allowing creation of animals exclusively susceptible or resistant to the factors under study especially for the cases where natural model were either not available or unfeasible. Genetically modified mice; rats; guinea pig; rabbit; ferret; zebra fish; worms etc. are now used increasingly, changing the face of biomedical research [5].

Classification of animal models

A wide variety of animal models have been used and developed for diverse pathophysiological and biomedical researches. Various scientists have classified these models on different basis since years. Hau and Schapiro (2011) [12] classified animal models into three main groups- exploratory, explanatory and predictive The exploratory models are those used to develop basic understanding of any fundamental or abnormal biological mechanism. The model is called explanatory when it is used to provide understanding of complex biological mechanisms. Such models are not necessarily based on use of animals rather they can be any physical or mathematical model. The predictive models are those, which are used for discovering, verifying or quantifying the effect of new treatment

for any disease or disorder. These models are also used to assess the toxic effects produced by any chemical compound [7].

The animal models have also been classified based on the species of the animal as rodent models, fish models, invertebrate models, non-human primate models and miscellaneous models [14]. Depending upon their background and mechanism of development, Schonecker (2014) [26] further classified the animal models into following five types.

Induced models

As the name suggests, induced or experimental models are healthy animals in which the condition under study is experimentally induced using surgical procedures, chemical injections or exposure to other types of stresses [6]. For example, use of partial hepatectomized animals to study liver regeneration, use of electrical stimulation to elicit seizures in animals for studying anticonvulsant drug efficiency, ligation of coronary artery or stroke induction to produced myocardial infarction models and use of laboratory animals with brain lesions to study of Parkinson's disease [15].

Spontaneous or natural models

Spontaneous models include laboratory animals that are born with naturally occurring spontaneous and random genetic mutations resulting in conditions similar to disorders of humans or target species. For example, athymic nude (hairless) mice have been extensively used as models to study natural killer cells, development of cancers, transfer of xenographs, etc. [11]. The Snell's dwarf mice having a non-functional pituitary and the curly-tail mouse, in which fetuses develop a whole range of neural-tube defects, are also popular among this type of model. Furthermore, BALB/c mice, C57BL/6 mice, SHR rats, ob/db mice and NOD mice are some other examples of spontaneous models [12].

Transgenic models

With advancement in genetic engineering, various transgenic models have been made available for specific disorder. These models are produced either by insertion or by deletion of specific gene in the genome of the animal. This process is called transgenesis. This model may be considered as a type of induced animal model. The transgenic animal models can be produced by various methods like microinjection of recombinant DNA, use of viruses (such retrovirus) as vectors to transfer gene into sperms/unfertilized ova/early embryos, genetically modified sperms and microarray DNA chip techniques [7]. The transgenic models are further divided into "knock-out" and "knock-in" subtypes. "Knock-out" models are produced by gene deletion or inactivation of gene expression whereas "Knock-in" models are produced by insertion of a gene at specific target locus in the host genome. For instance, *tau*-knock-out mice, 3xTg mouse and Trp53 mouse are some of the extensively used transgenic models [22].

Negative models

Negative models are those species, strains or breeds in which a certain disease does not develop. They have significant application in understanding the mechanism behind the resistance against any disease. Use of diabetes-resistant sublines of the diabetes prone BB-rats for studying diabetes susceptibility is an example of negative model [26].

Orphan models

The term "orphan model" includes those non-human species in which a functional disorder occurs naturally but has not yet been identified in humans. These species are used as models when a similar disease is identified in humans. Sheep and goats with scrapie's were considered as examples of orphan models until it was discovered that they can be used as models to study the "Creutzfeldt-Jakob disease" in humans, Bovine Spongiform Encephalopathies ("mad cow disease") in cattle as well as Chronic Wasting Disease (CWD) in deer and elk [26].

Animal models of common neurodegenerative disorders

The molecular mechanisms of the neurodegenerative conditions are not completely known and still, have no cure. In this regard, experimental studies need to be conducted using appropriate animal models to understand the structural, functional, and molecular features of these diseases and to propose better therapeutic methods [34]. Various animal models found naturally and induced so far for studies related to common neurodegenerative diseases are discussed below.

Animal models of cognitive dysfunction syndrome and Alzheimer's disease

The most commonly seen neurodegenerative disease in humans is Alzheimer's disease (AD). It is clinically characterized by cogni-

tive impairments such as memory deficits and irreversible decline in the number of basal forebrain cholinergic neurons and synaptic losses mainly in the hippocampus and cerebral cortex of brain. The neuropathological components of this disorder include the presence of extracellular amyloid beta (Aβ) aggregates that precipitate as amyloid plaques and formation of neurofibrillary tangles. These tangles are formed by precipitation of hyperphosphorylated tau-protein resulting into progressive brain atrophy (mainly of hippocampus), neuronal death, synaptic dysfunction and astrogliosis. The pathogenesis of amyloid plaque formation starts with amyloidogenic metabolism of amyloid precursor protein (APP) by enzymes called secretases (β and γ secretases). During this metabolism, Aβ are formed which gradually start forming oligomers that acts as toxin ultimately resulting in amyloid plaques deposition, neurodegeneration and consequently, cognitive impairments and blood brain barrier (BBB) leakage [28].

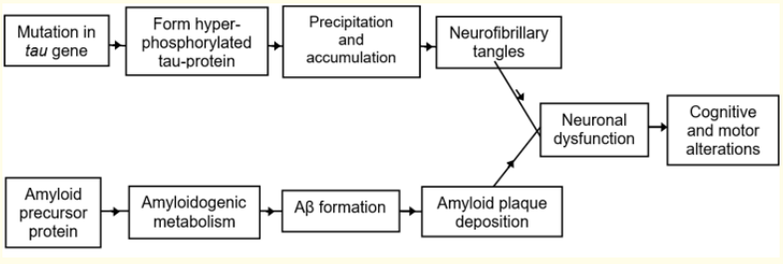

Figure 1: Pathogenesis of Alzheimer's disease.

Cognitive dysfunction syndrome (CDS) is a slow but progressive age-related neurodegenerative disorder of animals characterized by altered mentation and dementia. It is commonly seen in older dogs and cats, particularly of more than 8 years of age. The canine cognitive dysfunction (CCD) is commonly considered as canine analog of human Alzheimer's disease. The pathophysiology of CDS involves brain vascular disease and accumulation of beta-amyloid (Aβ) protein. Aβ is a neurotoxic protein that accumulates in the brains of dogs and cats with CDS and forms plaques within the brain parenchyma. Additional pathological processes that contribute to cognitive impairment in CDS include oxidative brain damage, neuronal mitochondrial dysfunction, glutamate-mediated excitotoxic neuronal damage, impaired neuronal glucose metabolism and abnormal microglial and astrocyte functions [4].

CDS cannot be cured at present but deterioration and clinical signs may be slowed and improved with mental stimulating practices and suitable diet. Behavioral support and environmental enrichment in the form of training, play, exercise and novel toys can help to maintain and improve cognitive functions. Nutritional and dietary interventions can improve antioxidant defense thereby reducing the negative effects of free radicals on the affected brain [10].

Although animal models have greatly advanced the understanding of AD and CDS pathogenesis, the lack of knowledge concerning its causes makes it difficult to develop a model exhibiting all the features, which hinder the discovery and characterization of effective drugs. Currently, the most employed animal models were developed based on known genetic mutations associated with these disorders [23]. Some commonly used animal models for AD and CDS studies are as follows.

- **Rodent Models:** For studying these conditions, transgenic and pharmacologically induced rodent models have been developed. Commonly, transgenic models, namely, BACE1 mice, tau-knockout mice, Tg2576 mice and APP mice have been used more extensively than the induced models. Tg2576 mice models are developed by overexpression of mutant form of *APP* gene resulting into elevated levels of Aβ and ultimately, increased formation of amyloid plaques. *BACE1* gene appears to be a potential target for AD treatment. Thus, crossing of the APP Tg mice and Tg2576 mice with the *BACE1* knockout mice may result in a better mouse model that exhibits cognitive decline, cholinergic dysfunction and high levels of Aβ [16].

- In pharmacologically induced rodent models, ICV-STZ models and AF64A rat models are commonly used. ICV-STZ model is a streptozotocin-induced model used to study the sporadic form of AD, which is caused by insulin resistance in the brain. This model is formed by administration of streptozotocin (a diabetes inducing drug) into the ventricles of the brain. The AF64A models are induced by withdrawal of cholinergic function by injecting AF64A neurotoxin into hippocampus of rats. They show changes in the function of neurotransmitters similar to those produced in AD and CDS [2].

- **Fish Models:** Besides rodent models, zebra fish have been increasingly recognized as a model organism for studying cognitive disorders. Presentation of complex behaviors in memory and conditioned response tasks are some of the characters that make zebra fish interesting model for central nervous system diseases. Transgenic zebra fish models are also developed now for investigating the neurodegeneration associated with taupathy [23].
- **Invertebrate Models**: Invertebrate animals, namely, *Caenorhabditis elegans* and *Drosophila* are also suitable to study AD, as they are able to express the genes of interest and allow rapid construction of different transgenic models. Transgenic *Drosophila* expressing genetically modified tau-protein and APP *Drosophila* models producing Aβ peptide, neurodegeneration and memory decline. Furthermore, *Drosophila* overexpressing the *BACE* gene has been used for drug testing [16].

- *C. elegans* is a nematode having only about 302 neurons thus, greatly facilitating the study of neuronal morphology and pathophysiology. Although *C. elegans* are not able to process APP to form Aβ peptide, transgenic *C. elegans* expressing Aβ42 peptide intracellularly in muscle cells exhibit aggregation and muscle dysfunction (paralysis). The nematode tau-pathy models are created by introduction of either wild type or mutated *tau* genes in neurons of *C. elegans* inducing age-dependent motor neuron dysfunction, neurodegeneration and locomotor deficits due to impaired neurotransmission in them. Hence, this model provides important insights into Aβ toxicity, but does not allow screening of genetic or chemical modifiers of APP processing [33].

- **Primate Models**: Primates mostly those that are maintained in captivity are known to show Alzheimer's disease like age-related cognitive deficits. Such animals are used as spontaneous/natural models, mainly for studies related to human Alzheimer's disease. Commonly, rhesus monkeys (*Macaca mulattas*), stump-tailed macaques (*Macaca arctoides*) and crab-eating macaques (*Macaca fascicularis*) are used as natural model. Induced primate models are produced by injecting neurotoxin such as ibotenic acid that causes destruction of basal forebrain cholinergic neurons resulting into cognitive and behavioral impairment. However, the insufficient performance of above mentioned models necessitated the development of more effective primate models for AD [19].

Animal models of bovine spongiform encephalopathy and scrapie

Prions are heavily glycosylated proteinaceous infectious agents that cause a number of diseases collectively called as "transmissible spongiform encephalopathies". These prion diseases are transmissible, fatal and progressively neurodegenerative diseases of animals and humans including scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle, feline spongiform encephalopathy (FSE) in cats, the transmissible mink encephalopathy (TME), chronic wasting disease (CWD) in deer and Creutzfeldt Jakob's disease in humans [3].

After entering into a host, the prion proteins (PrP) undergo replication followed by conformational changes to form protease-resistant β-sheet-containing isoform (PrP^{res}) which accumulates in the tissue and acts as neurotoxin. This accumulation of resistant prion proteins results into vacuolation of nerve cells, neuronal loss and astrocytosis in various areas of CNS. The destruction of neurons results into formation of tiny holes in brain tissue that appears as sponge-like under microscope and gives rise to the term spongiform disease [3].

A major problem in prion pathology is that recognizable symptoms are observed long after development of severe neuropathological lesions of the disease. Thus, studies related to the transmission and pathological mechanisms of these diseases are usually suggested in animal models of prion diseases.

Rodent models

Both induced and transgenic rodent models have been developed for understanding the accurate mechanism of transmission and pathogenesis of BSE. The induced mice models are produced by injecting BSE brain extracts through intracerebral route in healthy wild type mice. The incubation period in such models is approximately 250 days. Moreover, BSE and Scrapie infected hamsters and guinea pigs are used as models of BSE and Scrapie, respectively. According to some studies, the mechanism of serotonin (5-Hydroxytryptamine/ 5-HT) neurotransmission in brain, which regulates mood and pain sensitivity is also affected in prions diseases. Thus, 5-HT-depleted mice models have been developed by intracranial injection of the neurotoxin 5,7- dihydroxytryptamine (5,7- DHT) and are widely used for neurodegenerative research [30].

Apart from induced models, various types of transgenic models have also been made available for studies related to BSE, such as PrP^{106}-Tg mice models, BoPrP-Tg mice models and PrPc-depleted mice ($Prnp^{0/0}$) models. BoPrP-Tg mice models are generated by expression of five or six octarepeats of bovine prion proteins (Brun., *et al*. 2007). These models develop BSE-like neuropathology. Apart from transgenic mouse models, transgenic cattle models have also been developed to study the physiological role of prion proteins in cattle after sequencing of prion protein homologues in cattle, bear, dogs, fish and birds [1,24,27].

Scott., *et al*. (2000) [27] observed that a portion of prion protein containing only 106 amino acids (PrP106) was able to replicate despite two large deletions. They were called as "miniprions" and were later found to accelerate the co-expression of full-length PrP. Nowadays, these miniprions are used to develop transgenic PrP (Sc) 106 mice models. Such unique features of miniprions offer new insights into the mechanism of prion replication and suggest a new approach to the development of even more efficient animal models for prion diseases [27].

Fish models

The transmission of prion proteins is limited by "species barriers" and thus, fishes could not be infected with BoPrP. However, certain fishes such as Salmon, Trout, Carp, Tuna and Catfish have been found infected with other isoform of Prp. These PrP infected fishes have been used as models to study the mechanisms of PrP misfolding, prion replication and the cellular pathways through which prions induce neurodegeneration. In addition to mammals, PrP homologues have also been identified in birds, reptiles, amphibians and fish but not in invertebrates. Zebrafish possess two prion protein orthologs, *PrP-1 and PrP-2*, mapped to chromosomes 10 and 25, respectively. Thus, these genes were used to produce transgenic zebrafish models, such as *PrP-1* knockdown models, GFP-Tg zebrafish models, BoPrP/OvPrP-Tg zebrafish models, etc. [20].

Animal models of spinal muscular atrophy

These diseases are characterized clinically by severe muscular weakness and atrophy. These neurological signs are visible either due to degeneration and loss of motor neurons in ventral horns of the spinal cord or due to axonal degeneration in the ventral spinal nerve rootlets and peripheral nerves. The "shaker calf syndrome" of newborn calves is an example of spinal cord-motor neuron disease where all segments of the spinal cord are severely affected resulting into shaking of the head, body and tail of affected calves [21].

Another classical example of spinal cord-motor neuron degeneration is "spinal muscular atrophy (SMA)", commonly seen in dogs, calves and pigs. It is hereditary condition resulting in progressive neurogenic muscular atrophy. Certain breeds of dogs like Pointer, German shepherd and Doberman are found to be genetically predisposed to this condition [29]. For understanding the pathogenic mechanism and therapeutic efficacy of drugs for SMA, various natural, induced and transgenic models have been developed.

The strain of mice called "wobbler mouse" is an example of natural/spontaneous model for SMA. This strain was produced due to mutations in inbred C57B1/Fa mice strain. Among transgenic models, SMN mice model with mutant *SMN1* or *SMN2* gene and NAIP mice model with multiple copies of *NAIP* gene are widely used [21]. Induced models of SMA have been developed using following methods:

- Low calcium and magnesium containing diets in rats and rabbits,
- Heavy metals administration such as mercury, lead, aluminium etc. in mice and rats,
- Neurotoxins like iminodipropionitrile, vinblastine, podophyllotoxin etc. administered intrathecally in rats,
- Ascorbic acid deficit in guinea pig,
- Immunization of motor neurons in guinea pigs.

Animal models of Infectious neurodegenerative diseases

Rabies is a fatal zoonotic viral disease of mammals caused by *Lyssavirus* of *Rabdoviridae* family. Various animal models have been developed to achieve comprehensive perception of the neurovirulence, spread along the neurons and neurodegenerative mechanism of this deadly disease. Such as, induced rodent models of rabies are produced after intracerebral infection with high egg passage (HEP) strain of fixed virus in suckling or adult mice. In transgenic models, p75 neurotrophin receptor-deficient mice have been used in experimental studies of rabies [17].

Canine distemper is highly contagious viral disease of dogs and other canines caused by *Morbillivirus* of *Paramyxoviridae* family. For gaining insights in pathogenesis, neurovirulence, immunosuppression and drug efficacy of CDV, animal models have been developed. Of these, induced ferret models have been most widely used. These ferret models are infected with different strains of CDV, intranasally. These ferret models have also been used to evaluate efficiency of vaccines [31].

Conclusion

Neurodegenerative disorders are one of the most complex, lethal and difficult to diagnose conditions in animals with limited work in veterinary field. The behavioral changes and cognitive dysfunctions, observed as major signs in these conditions, cannot be studied using *in vitro* and *in silico* models available so far. Thus, animal models have been extensively used for research in the field of neuroscience. Animal models are animated copies of target species mimicking the condition under study. Various induced and transgenic, rodent and invertebrate animal models have been developed for this purpose.

Selection of appropriate animal model for a given problem is a complex process that involves consideration of both scientific and practical factors. Failure in choosing appropriate model may leads to waste of animals and resources, inaccurate results and duplicative experiments. With the limitation that no single animal model can mimic all the aspect of any disease, one may think of them being replaced by other type of models in future. However, the ongoing development and refinement in animal models by combining them with xenografting, 3D bioprinting, telemeterization and other advanced techniques, have led to more promising and foreseeable future of animal modeling.

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