BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, September 2022. Vol. **19**(3), p. 579-587

A Review on Neurodegenerative Diseases with their Suitable Animal Models

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http://dx.doi.org/10.13005/bbra/3011

(Received: 10 April 2022; accepted: 09 September 2022)

Neurodegeneration is one of the common disease conditions globally. The animal models give resemblance to these disease conditions. By using various animal models it can be easy to study the disease in detail with their pathology, history, mechanism of drug. Animal models are crucial for researchers to find out preventing measures of neurodegenerative diseases. The intention of writing this review paper is to give a brief idea about neurodegenerative disorder and the possible animal models that are recently in use with their short introduction. This paper also explains the future expected animal model that should overcome the previous model's lacuna. Neurodegeneration is a global health concern now. So to study disease pathology and finding advanced therapy is a challenge. For thorough understanding of this condition there are various animal models that provide deep information at molecular and cellular level. The genetic models are also present that mainly concern for mutation and studying the factors that contribute to the happening of disease conditions. It will be fruitful to study such factors that are responsible for causing disease, so that one can treat conditions by preventing or stopping the genetic risk factors by various drug mechanisms. Studying the neurodegeneration process using animal models is quite interesting.

Keywords: Animal models; Cognitive impairment; Gene therapy; Neurodegenerative disorder; Oxidative stress.

The neurodegenerative disease is a global concern, the tremendous population have affected by this disease. Treatment to this condition is considered as a financial burden[1]. Only Alzheimer's patient number is around 46 million globally. And this number expected to go beyond 132.5 million by 2050[2]. The number of pathogenic condition ruinous to neurodegeneration and progression of such condition result into disability and death of patient. These ruinous condition involve Parkinson's disease, Frontotemporal dementia, Alzheimer's and ALS i.e., amyotrophic lateral sclerosis. Most of patient with neurodegenerative disorder have no direct link with genetic cause. But there are some genetic risk factors that influences these conditions[3]. The animal models are used to study the pathophysiology of disease and their treatment. But issues with these models are they are not exactly similar to that of human diseases. The pathological symptoms they were showing rightly but there is missing the chain of complete step by step occurrence of pathophysiologic changes. However, developing new animal models allow brief understanding of disease at cellular

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and molecular level. Mouse as animal model gave weak estimation to drug efficacy. This is not the limitation to animal models. Instead of this give scope to discover more animal models using different rodent and non-rodent. The demonstration of human cellular model of neuron degeneration are having disadvantages like missing of maturation process, missing of neuronal circuit and absence of cellular, neuronal components, absence of glia cells[4]. Using naturally found animals as an animal model was discovered 100 years ago and now there is great improvement in health science [5, 6]. More than 100 of diseases that found in dogs and cats having likeness to humans[7]. The cancer etiologies are also similar to humans that are described by their genetic characteristics and environment[8]. Some reports suggest that pathophysiology of human and disease etiology are similar to dogs and cats. This facilitates knowing possible preventive majors, identifying risk factors and understanding disease etiology[9]. Duration of life of canine and feline are short compared to humans hence it does not cover full history, etiology of disease in their short life cycle.

In the veterinary clinical sector the animals are often managed with drug therapies which are likeness to humans. In present days veterinary sciences applied their scope to veterinary neurology and their practice. That facilitates brief study of clinical characterization of diseases. This review gives a detailed idea about animals in neurological study[8].

Barriers to use animal models in neurological research

Other than the edge over the experimental animals have some disadvantages[6]. Though there are some anatomical and physiological similarities found in animals there are some differences also exist like their effects on drug metabolism, drug action, and its toxicity. Anesthesia is required to study and examine the animals. The anesthetics affect the blood flow to the cerebral region, and O_2 requirement. This is necessary in oxygen dependent MRI. Immobility required for neuroimaging. There is species- species diversity observed in case of disease[10]. In the past year the translational science in experimental animals gives knowledge about human subjects in clinical trials, but it has limitations in statistical results and lacks standard medical therapy. The animal models are considered to be expensive and approved through ethical regulations[11]. These factors do not prohibit the use of animals for neurological research purposes. Instead, these problems give rise to search for more advanced methods to avoid such conflict and improve research work by using animal models. This would add value to preclinical research.

Impulsive neurological disease conditions in experimental animal models

Epilepsy

This is one of the common and widespread diseases. This commonly occurs 0.6 to 1 percent in dogs and in humans, its prevalence is 1 to 3 percent [12, 13]. Induction of an epilepsy in animal models like canine, allows brief observation about symptoms, etiology that is exactly the same with humans. The strokes, injury to the brain, tumors that mainly cause brain region are the main cause of the disease [14, 15, 16, 17]. "A robust body of seven literature" have mentioned the disease's occurrence, history, pharmacological changes and many more things that are exactly like human beings and dog species. This also represents that there is ECG data and genetic traits of disease are similar with humans. The diseased dog and the human with the same disease show similar behavioral and general problems [18, 19]. However, very little info is known about neuropathy, and salient features of neuron death, BBB and glial cell activation. In case of humans as well as experimental animal models, epilepsy is characterized by long term disability, early death, negative effect on social life, unusual behavior [20, 21]. About more than 50 % of dog species had 1 -2 status epilepticus during their life period [16]. This is the most severe disease in humans and dogs with mortality cases about 25%. Whereas in refractory seizure 33% mortality case in both. Hence the dog model is the most preferred animal model to study epilepsy and their therapeutic measure[22].

Stroke

According to the global burden of disease study 2010, stroke is the general reason for death and 3rd common factor for disability worldwide[23]. In dog breed stroke experimentally induced and it is used as an experimental model for stroke. Dogs have anatomical and functional similarity of brain with humans like they possess gray and white matter, and their distribution and occurrence are similar to human brain. The

cerebral fluid and anatomical features of cerebra is likeness to humans. This allows studying both disease induction and therapeutic measure in a wide descriptive way[24]. The cerebrovascular accidents are increasing in case of dogs. The common occurrence of CVA is found to resemble that of human CVA, because of this it is the best animal model to evaluate drug efficacy and toxicity. Ischemic stroke is common in both humans and dogs, it can be observed through MRI. Hemorrhagic stroke is rare in both. The parameters that are assessed by using the canine model are-oxidative metabolism, recent radio tracing agents, blood flow to cerebral area, stroke pathology and preventive pharmacological measure etc[25]. In the age of 8-10 dogs often experience strokes, this is similar in old age humans. The risk factors included are high B.P, long term kidney related diseases, atherosclerosis, DM. The national institute of health stroke provided the various evaluation instruments that can be applied in dog model[25].

Cognitive impairment and AD

In animals and in humans the increasing age is the major risk factor for causing Alzheimer's disorder. Another reason for AD is development of dementia and chronic conditions that led to AD. Cognitive dysfunction syndrome is a neurodegenerative disease condition that affects not only humans but also in animals such as cats and dogs. It occurs in sequence like progression of memory loss then impairment in daily activity, change in behavioral pattern. The characteristic features of AD are plaque formation, neuron fibril tangles occurrence, hippocampus neurodegeneration. Amyloid beta is the major fibrillary tangles in AD, which has a principal component known as tau protein. This protein is found in various neuron related disorders [26]. Hence based on tau protein occurrence and amyloid the animal models are tested to study AD.

Parkinson disease

This disease cause due to the injury to Nigrostriatal pathway. To study the history, etiology, and treatment therapy there are number of animal models available. The pros and cons of animal models are making choices to decide specific animal model for study. There are present animal models that used to assess PD drug action, safety and another model that are used for inducing disease called neurotoxic murine; they cause injury to the nigrostriatal dopaminergic area. This model is important to learn about structure, etiology and functioning of the Nigrostriatal pathway. The animal model for PD must involve dopamine neuron system as well as non dopamine neuron system, additionally central, motor and peripheral system. The age related risk factor should be expressed through models. But disadvantage is that

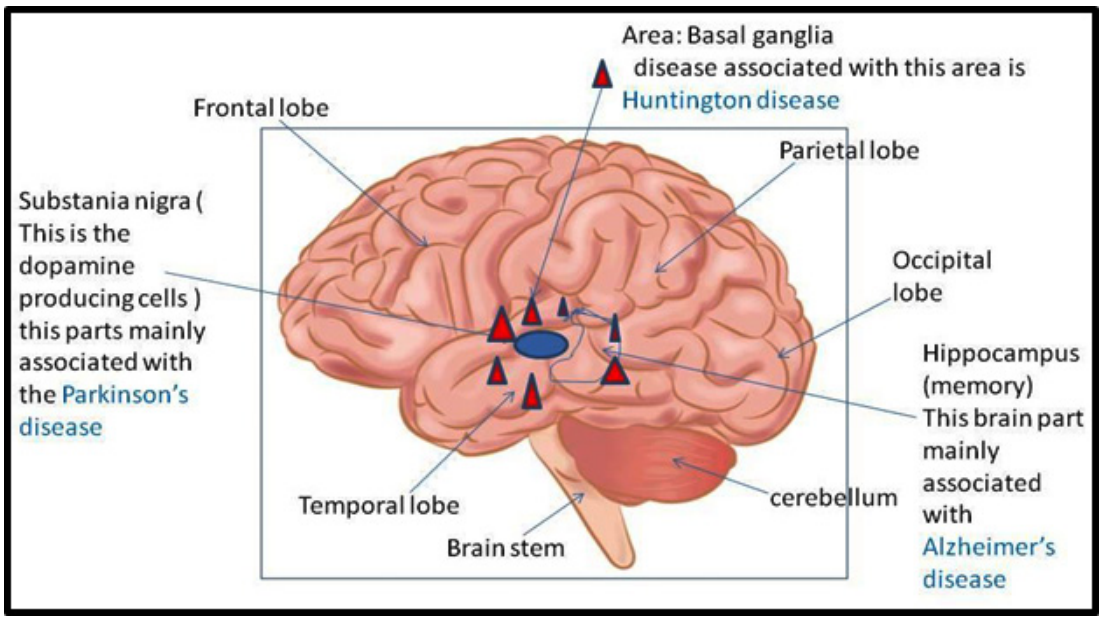

Fig. 1. Human brain showing different brain regions and diseases that are associated with it

Table 1. Different animal models are used to study the neurodegenerative diseases

Disease	Model	Description	Reference
Parkinson's disease	6-hydroxydopamine	6-hydroxydopamine is toxic to neurons and it was used to damage the nigro-striatal dopaminergic pathway in laboratory rats half a century ago. This is the oldest model of Parkinson's. The assessment of biochemical, behavioral and physiological parameters can be done by using this model. This is advantageous to study cause of cell death and evaluate therapy that enhance symptoms of Parkinson'sAnimals used: mice, cats, dogs, monkeys. however mostly in Rat	34, 35, 36
	MPTP	Parameters such as oxidative stress level, energy down, and occurrence of inflammation are the characteristic features of PD and this MPTP resembles the same characteristics.Animals used: primates and mice other species like dog and cats (Rat having resistance to this neurotoxin)	37, 38
	Paraquat	This is mostly used in farming as an herbicide. Due to its structural similarity to MPP+, it acts like MPP+. Mechanisms of action include seviour effect of oxidative stress through redox cycling and that result into generation of the reactive oxygen species which damages the lipid protein, deoxyribonucleic acid and ribonucleic acid.Animal : mouse	39
	LRRK2	This is Genetic model that involves genetic mutation that plays a role in generation of disease pathology. Genetic mutation in this disease is limited i.e., 10 % only. They show potential targets in PD.	40
Huntington's disease	Transgenic animal R6/2 mouse	This animal model expresses elongation of Htt R6/2. Advantage of this model is, it expresses behavioral and physiological characteristics that are similar to HD. This is the most widely used animal model for HD.	41
	Transgenic animal Pig mutant Htt	This animal's anatomical and physiological characteristics are similar to humans hence it is suitable to test all behavioral related and pathological related parameters. Drug pharmacokinetic study performed on this animal. Drug delivery mechanisms can be easily understandable through this model.Other animals used: fly, worm, zebra fish.	41
	Quinolinic c acid	This agent induced symptoms like hyperkinesia, apomorphine induced dystonia, memory impairment. etc. The animals used are: rat (Sprague- Dawley), mouse and primates.	41
Multiple sclerosis	EAE models (Experimental autoimmune encephalomyelitis)	In this model T- cell inflammation and weak antibody response are likeness to humans. This model is mostly preferred for therapy studies. For many years the rat and guinea are used as EAE models in autoimmune mediated inflammation to the central nervous system. Tissue, myelin protein that leads to occurrence of disease. The clinical sign is observed within 9 to 12 days. Myelin basic protein causes self limiting disease that leads to long term relapsing of condition. As myelins are components of both the central nervous system and peripheral system, hence it affects peripheral systems also.	42
	Murine EAE	This is used to evaluate genetic correlation of genetic factors to disease. This model was introduced in the year 1950, that time this model pros are very less due to rare occurrence of the disease. And it is a little different from that found in guinea pigs and rats. This hurdle was overcome by introducing pertussis toxin to augment disease.	42
	Toxin-induced demylination model	The introduction of The gliotoxin ex., ethidium bromide, lysolecithin directly into white matter induces demyelination foci. This model is helpful to understand Re-myelination step by step. This model has good reproducibility. Other agents that act as demyelinating agent's are-calcium ionophore, diphtheria toxin, 6-aminonicotinamide etc. These agents in animal models do not provide suitable information regarding remyelination. Second limitation of these models is that there is a lack of immune activity.	43, 44
	Antibody induced demyelination	Galactocerebrosides are biomarkers of not fully matured oligodendrocytes. The galactocerebrosides antibodies are used for inducing allergic neuritis. By this there was the appearance of a small area where demyelination is found in CNS at the dorsal root of the spinal cord.	43, 45
	Encephalomyelitis virus	The infectious agent that may lead to MS, plays a crucial role in starting and progression of this disease. The multiple	46, 47, 48

		sclerosis induced by the Theiler's virus and hepatitis virus (mouse). The Theiler's encephalomyelitis virus causes infection to mice that is helpful to demonstrate the model of neuron related viral infection of multiple sclerosis. The experimental report of the animal model is based on both viruses as well as on mice. C57BL/6J mice strain develops acute disease followed by rapid and great immune reaction that is necessary to clear virus and prohibit demyelination.	
Alzheimer's disease	Model based of amyloid pathology	The rodents that are transgenic and show Amyloid beta accumulation in senile plaques, another one is cerebrovascular amyloid AD model. These model likenesses to human mutations in APP, PSEN 1 and PSEN1/2 having the same function that in humans. An APP mutant causes an increase in total amyloid beta 42 and amyloid beta 43. This commences to neuritis that is symptomatically similar to AD. Astrocytosis, microgliosis and molecular changes are well assessed through this model.	49, 50
	Model based on tau pathology	These animal models are based on over-expression of mutations that result in FTD-MAPT. This gives excess changes in neurodegeneration. This model gives details of tauopathy. Mutations of P301L or P301S MAPT. Mouse MAPT knockout this model gives the same tau pathology to that found in humans.	50, 51

none on recent animal model would able to show these features. Besides this problem the animal models are very helpful to understand PD and its pathophysiology[27].

Optic nerve diseases

This disease condition is a highly ruinous condition in ophthalmology that causes degradation of retinal ganglion cells, Loss of vision and lastly blindness occur to patients. Animal models are necessary to evaluate drug efficacy in treating this disease. This provides thorough information about the potential of new agents and their mechanism. Additionally help to understand the cause of axon nerve dies. The number of animal species can be used to study ophthalmic disease. The monkey's eye anatomy and physiology are similar to a human's eye. Monkeys have the same anatomical structure to the retinal and optic nerve. Limitation of using this model is that it is very expensive, difficult to handle; it requires an experienced person to deal with this, housing monkeys in laboratories requires a large area etc. Hence because of this limitation the mice and rats preferred to study optic nerve related diseases. Rats are inexpensive, easy to handle and their eyes and optic nerve are accessible. Optic nerve and retina structure have some differences with human's eye. They do not possess maculae, this is only found in monkeys hence it is used to study drug inducing macular degeneration. Animal models for optic related neurodegenerative diseases are- glaucoma, optic neuritis, anterior ischemic optic neuropathy[28].

Multiple sclerosis

This is the inflammatory disease of CNS that further deteriorates characteristics of neurodegenerative disorder such as axonal damage, synaptic damage, nerve cell damage etc. Effective therapies that prevent such damages are still missing[29]. The characteristic feature of this disease is there is wide plaque formation of white matter demyelination which correlates with oligodendrocyte degradation, gliosis and axonal degeneration. The content found in inflammatory infiltrate T- lymphocytes and macrophages[30]. The stimulated astrocytes and microglia cells are involved in lesion initiation, progression and resolution by secreting inflammatory mediators, Growth factor GF. The gray matter demyelination and white matter damage these both factors add value to causing multiple sclerosis[31].

Huntington's disease

This neurodegenerative disorder is complex in nature with their symptoms, motor activity, and cognitive function. The animal model in this disorder serves as a medium that explains disease conditions and mechanism of drugs and also evaluates newer drugs. This is basically a human condition hence researchers cannot expect that animal models would cover all the symptoms and pathology of this disease[32]. Huntington's

disease is caused by gene mutation i.e., expanded CAG repeat in HTT gene. This is a single gene disorder and occurs rarely. When researchers are able to know HD causes then it is helpful to treat other such diseases that are rarely found[33].

Troubles that are associated during selection of the model for disease in rodents

The models that are based on genetic changes are not showing proper expression of genetic variants and it makes it difficult to understand pathology and therapy. This type of model is very tedious to know the proper mechanism of a drug and not able to conduct gene specific therapy. One cannot predict the cellular & molecular level changes that occur during the period of neurodegeneration.

Innate limitations are the factors that are used to develop animal models. In transgenic and AAV related animal models the overexpression of protein is overcome by developing knock-in animals. Beside this, such a type of model is time consuming and shows moderate phenotyping. Some methods that give valuable reading by analysis such as automated behavioral analysis, in-vivo image, comics approaches, specific cellular and molecular defects. These readings are most relevant in humans.

Due to the short life span of rodents, they are not able to give full pathological events with characteristic features of neurodegeneration. This is the big disadvantage of this animal model. There are innate differences found in the development and working of rodents and mankind. Hence special attention should be given while assessing the cognitive impairment, emotional factor, language like characteristics in human disease condition [52].

While deciding a model to study disease conditions one should definitely know the thorough information about differences between human and rodent genome. Such as RNA binding proteins that play a crucial role in disease conditions. In mouse models this RNA based processing is not fully understandable. Another limitation is that there are species related amino acid changes.

Inbred animals do not possess genetic diversity. There are new methods that cover this problem are collaborative cross and diversity outbreeds animal set of mouse [53,54]. The gene editing system i.e., CRISPR-Cas9 is the virus mediated expression of genes that help to understand mutations and genetic background of different breeds [55].

Future expectation regarding animal models on neurodegenerative diseases

By knowing present model pros and cons there is scope to develop a newer animal model by eliminating the cons of the previous one. This would be beneficial in better understanding of various neurodegenerative disorders and their treating therapies. First point that might be taken

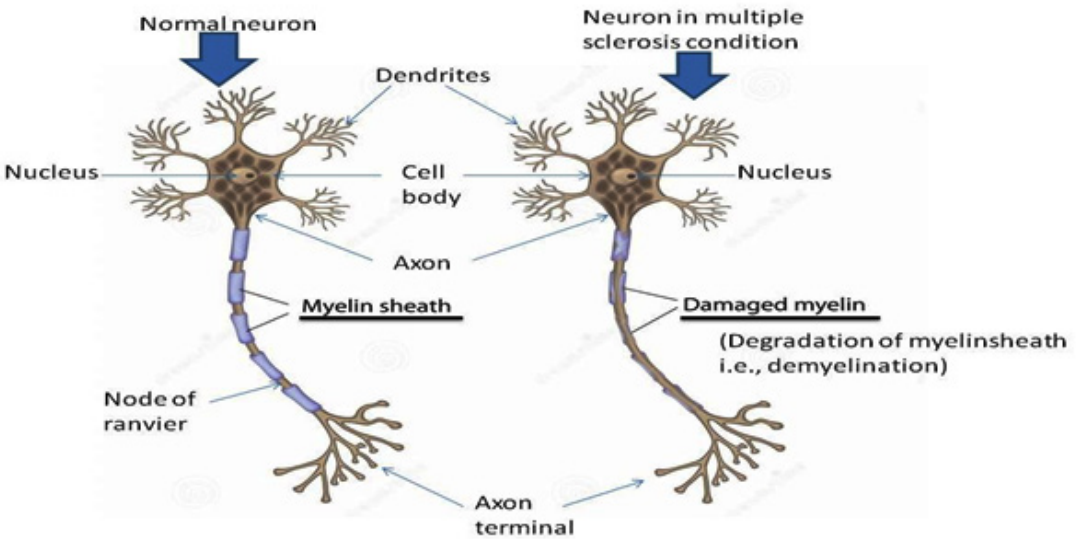

Fig. 2. Representation of normal neuron Vs multiple sclerosis neuron

into consideration while developing an advanced model is that it should be easily predictable in humans and have the same etiology of disease that happens in humans. Some drugs are showing the same efficacy on man and rodents also. So this is a great achievement in modeling the animal. There are a number of animal models present recently but still there is a need to modify them and give an advanced look to previous one by understanding disease pathology.

The two animal models that are very useful in understanding pathophysiology and treatment of AD are APP and tau animal models, the cons of this model are, they are not fully representing the diseases that cause to humans. But still they have the positive side that the APP animal model gives exact regulation of amyloid beta accumulation and hence it is fruitful to assess the factors that contribute to stop aggregation of tau and thus prevent future consequences. While designing the new model one thing kept in mind that which factors that expressing well and that completely likeness to humans. And which factors that do not represent the criteria to overcome these things. Many researchers are working on development of superior animal models in neurodegenerative disorders that are mostly based on genetic characteristics and some genetic factors that contribute for initiation of neurological related disorders. The phenotype similarities in models are suitable to compare directly with humans and easy to predict the exact cause of disease. Best and effective animal model development ,simply means , it should be economic, it should provide better evaluation ,easy to test all the parameters, overcome the previous hindrance and present a brief etiology of disease and provide a drug mechanism of action.

CONCLUSION

The conclusion of this paper is to give a brief idea about neurodegenerative health conditions and the diseases that are associated due to neurodegeneration. For understanding the disease thoroughly the animal models are the best thing which provide etiology of disease with drug mechanisms. The paper shortly summaries the animal models for various neurodegenerative disorders with brief insights on the diseases. Many models have been developed to understand the disease conditions but still there are some lacuna's present. So there is a need to overcome these lacuna's and modify the recent models that are future outcome of this paper.

ACKNOWLEDGEMENT

Authors are thankful to Dr. Sanjay J. Kshirsagar, principal MET Institute of Pharmacy, Bhujbal knowledge city for the support, motivation and facilities.

Conflict of interest

There is no conflict of interest.

Funding source

There is no funding source.

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