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Animal Models and Their Utility in Parkinson's Disease Research: A Review.

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Abstract

Parkinson's Disease (PD) is a common heterogeneous neurodegenerative disorder in which symptoms include bradykinesia, stiffness, tremors, and eventually dementia and speech issues. PD neuropathology is characterized by the progressive neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta and the presence of a-synuclein protein aggregates known as Lewy bodies in affected cells. Whilst what may cause neurodegeneration in PD is still not understood, research using animal models suggest oxidative stress and mitochondrial respiration dysfunction may play important roles.

Animal models are essential in improving our understanding of PD, the most used of which is rodent models due to the behavioural tests available to evaluate motor functionality. Neurotoxin-based approaches apply known toxins such as MPTP and 6-OHDA to model neurodegeneration and motor deficits in mice and rats. Rotenone is another toxin found in pesticides that has been associated with Parkinson's-like pathology, suggesting the role of environmental toxins as a risk factor in PD development . Genetic models create transgenic

and AAV rodents using mutant forms of a-synuclein, such as A53T, A30P, and E45K. These models are important in understanding how Lewy body pathology contributes towards Parkinson's pathophysiology. Neurotoxin and genetic-based approaches have assisted in the development of therapeutics for PD, including levodopa, rasagiline, and ongoing research into possible AAV-mediated gene therapies. Rodent models have proven themselves highly useful in investigating the complexities of PD, understanding the strengths and limitations of varying types allows optimal application of rodent models in the field of PD research.

Introduction

Parkinson's disease (PD) is a complex progressive movement disorder (1). The commonality of PD as a neurodegenerative disease, is second to only Alzheimer's disease (1). Characteristics of PD include the progressive death of dopaminergic neurons located in the substantia nigra pars compacta (SNpc), a region of the brain found in the basal ganglia and the formation of abnormal protein aggregates known as Lewy bodies (1,2). Neuronal loss and Lewy pathology spreads to other regions of the brain as the disease progresses in the later stages (2). Loss of basal ganglia dopaminergic neurons results in dopamine deficiency, associated motor symptoms such as bradykinesia, muscular rigidity, instability of posture, and tremors. Non-motor symptoms have also been associated with PD, becoming more severe as the disease progresses, these include dementia, depression, issues with olfaction, and bladder disturbances (1,3,4).

Despite over two centuries of research, the definitive aetiology of PD remains poorly understood (5). Existing complex interactions between genetic and environmental risk factors makes it difficult to clearly understand causative mechanisms of an already phenotypically heterogeneous disease (1,6). Post-mortem examinations on brain tissue is the only current way to confirm brain pathology in PD patients (6), making models for experimentation extremely important for expanding our knowledge of PD. The heterogeneous nature of the disease means that animal models must also vary to account for the differing facets of PD (1,6). Many animal models have been developed, for both the environmental and genetic factors that contribute to PD (7–11). These models can be generally divided into two main categories: neurotoxin-based, or genetic-based models (11).

Toxin based, due to their cost-effectivity and ease of production, are more commonplace than genetic models (11), and can model environmentally associated neurodegeneration (12). Whilst motor deficits and dopaminergic neurodegeneration are seen in these models, they usually lack the presence of Lewy bodies (10,11). Genetic models on the other hand, are a relatively newer approach to modelling PD that uses known gene mutations associated with PD (11,13–16). Genetic models vary from transgenic animals expressing human mutations in these genes (7,17,18) or viral vectors used to elicit overexpression of alpha-synuclein, a major component of Lewy bodies (19), both result in PD models that express Lewy pathology (7,11,17).

Whilst a range of animal species are used to create PD models, the majority of studies use rodent models (11), which will be the main focus of this literature review. This review will discuss and critically analyse the use of neurotoxin and genetic models in PD research, with a particular focus on rodent models. Understanding the utility of different rodent PD models will allow for the use of appropriate models by researchers when designing experiments, optimising future research into PD pathology, aetiology, and therapeutics.

Discussion

Neurotoxin-based models

Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a neurotoxin that leads to neuronal death of dopaminergic neurons in the SNpc, and has been seen to generate parkinsonism in humans and animals (10,20–22). MPTP initially crosses the blood-brain barrier (BBB), it is then metabolised by monoamine oxidase B (MOA-B) inside glial cells and oxidised into the toxin 1-methyl-4-phenylpyridine (MPP+) (10,23). MPP+ is then released by the glial cell and enters the dopaminergic neuron via dopamine transporter (DAT) proteins, where it is either stored in synaptic vesicles or enters mitochondria (23) (Fig 1). The inhibition of mitochondrial complex I, a protein in the electron transport chain, by toxin MPP+ leads to an impairment of mitochondrial respiration, oxidative stress, and eventually cellular death (23). MPTP's selective toxicity of dopaminergic neurons mirrors the cellular loss that is seen in PD patients; parallels may also be drawn between observable motor deficits (10,23,24).

MPTP rodent models have played an important role in screening possible therapeutics for PD, for example levodopa (25). Levodopa is now used for treatment of severe motor symptoms and disability in PD patients (1). Research in the early 1990's found levodopa's ability to reverse the severe motor deficits caused by MPTP (25).

Whilst a handful of rat models do exist for MPTP (26), the relative sensitivity of mice to MPTP toxicity make them preferred candidates for models (11,27). The reason why rats seem generally insensitive to MPTP is not yet fully understood, one explanation is that it's due to differences between metabolic pathways inside the brain, with rats metabolising MPTP into MPP+ before the BBB (27). This resistance seen in some rats, limits the amount of possible rodent models that can be produced using MPTP, instead 6-hydroxydopamine (6-OHDA) may be used to create rat models of PD (8,11).

6-hydroxydopamine

6-hydroxydopamine (6-OHDA) is another known neurotoxin used to create models of PD in research into both disease pathogenesis and possible therapeutics (8,28). 6-OHDA has a dopamine-like structure and can use DAT, allowing for the selective neurotoxicity of dopaminergic cells (28). Findings suggest autooxidation of 6-OHDA into reactive oxygen species (ROS) and inhibition of mitochondrial complex I, leads to oxidative stress and eventual cell death (Fig. 1) (28). Unlike MPTP, 6-OHDA cannot pass the BBB, and is instead administered via intracerebral infusion (29). With the use of rat models, recent findings however suggest that 6-OHDA may also disrupt the permeability of the BBB, leading to an accumulation of iron in the brain (29). Iron accumulation was also associated with an increase in microglia activity which, similarly to PD, can cause further neurodegeneration (29).

Similarly to MPTP, reduced coordination and abnormal locomotor activity is seen in 6-OHDA models (8). 6-OHDA rat models have been used to improve our understanding of potential therapeutics for

PD, for example, ambroxol (8). Ambroxol significantly improved performance on motor behavioural tests in 6-OHDA rats and increased activity of mitochondrial complex I, previously inhibited by 6-OHDA, suggesting possible use of ambroxol in the treatment of PD (8). 6-OHDA rat models were also used to support the safety of rasagiline, a monoamine oxidase inhibitor, for use as a therapeutic for PD (30). The research suggested that rasagiline significantly increased the chance of survival of dopaminergic cells in the PD rat model, it also showed low doses improved abnormal motor behaviours in 6-OHDA rat models (30). Findings like these, alongside others, were significantly useful for the progression of rasagiline into clinical trials, and subsequent approval of rasagiline by the European Medicines Agency, as a therapeutic for PD (31).

6-OHDA is usually injected unilaterally, because unlike MPTP, bilateral injection has an extremely high mortality (32) limiting the use of 6-OHDA as a model of bilateral parkinsonism. However, asymmetry of motor symptoms at onset is a supportive criteria for the diagnosis of PD (1); unilateral models of PD are not only useful in observing the aetiology of the disease, but also allow for the use of side bias behavioural tests, in which performance differences between a lesioned and control side of the animal are used to assess motor impairments (32).

Agricultural pesticides (Rotenone)

Pesticide exposure in humans has been associated with an increased risk of developing PD, the most common of which is rotenone (12). The hydrophobic nature of rotenone allows it to cross the cellular membrane, allowing direct access into dopaminergic neurons without the use of DATs (Fig. 1) (12). Once inside the cell, rotenone inhibits mitochondrial complex I, similarly to MPTP and 6-OHDA's mechanism of action, leading to oxidative damage and eventual death of the cell (12). Research has shown that chronic infusions of rotenone into rats (Sprague-Dawley and Lewis strains) can reproduce the neuropathological and behavioural characteristics of PD, presenting with a-synuclein aggregates (12,33). These studies, however, are limited in their ability to evaluate environmental risks, as the method of administration does not parallel natural exposure routes such as inhalation, oral or dermal contact. The main positive findings of these papers is a neurotoxin model filling the gaps left by MPTP and 6-OHDA models: Progressive neurodegeneration and the presence of a-synuclein aggregates, key pathology of PD (1,12,33).

The utility of rotenone-based models is due to its ability to study the risk of exposure to environmental toxins, such as pesticides. To evaluate this risk, Liu et al. simulates environmental contact with rotenone in rats (34). In doing so, dopamine depletion, motor deficits, neural degeneration, and the presence of a-synuclein were all apparent in the rotenone exposed rats, all characteristics seen in PD patients (34). Gastrointestinal (GI) tract dysfunction was also present in the exposed rats (34), this is an important finding as GI motility deficits are a known symptom of PD, it also acts as a portal for external toxins to enter (1). GI dysfunction was also seen in a MPTP mice study by Lai et al., this study however is limited, as the means of toxin administration is via intraperitoneal injection, Liu et al. improves on

this limitation using a rotenone environment-based model. These rodent model findings suggest toxins in the environment may contribute to GI dysfunction and development of PD symptoms.

Alongside rotenone-based rodent models used to evaluate environmental risks in the development of PD, they have also been used to research possible therapeutics for the disease (35,36). Progressive PD rotenone rat models were used to study possible neuroprotective effects of caffeine (36) and naringin, a natural flavonoids in citrus fruits (35). Both agents were found to have neuroprotective effects on dopaminergic neurons in the rodent models, possibly due their antioxidant properties, reversing rotenone-induced decrease in antioxidative enzyme activity (35,36).

Genetic-based models

Transgenic rodent models

Genetic animal models are a newer form of evaluating PD, and have been becoming more prevalent in research in the past 10 years (11). In 1997, Polymeropoulos et al. published findings of a point mutation in the a-synuclein gene (SNCA) identified in patients suffering from familial PD, Ala53Thr (A53T) (14). The A53T mutation encodes for a mutant form of the a-synuclein protein that aggregates, causing Lewy bodies, an essential pathology and a biomarker for the different Braak stages of PD (2,14). Two other point mutations at the same SNCA gene were also found: E46K AND A30P (15,16). Transgenic models of PD were developed after the discovery of specific mutations linked to the disease's pathology (11,16).

Transgenic models can be made by implanting the mutated variants of human SNCA (A30P, A53T, E46K) in rodents with aid of a promoter to drive expression, this is possible due to rodent and human SNCA being homologous in nature (37). The transgene alongside the promoter is then transplanted into an embryonic cell and implanted into female mice, the offspring of the mice then carry the expressed transgene (37).

SNCA transgenic models of mice offer great utility, as they can allow us to understand exactly how a-synuclein aggregates and forms Lewy bodies in PD. A53T mutant mice models have exhibited a-synuclein inclusions and motor deficits (38). Similar to PD, fine motor and sensorimotor deficits came before gross motor and cognitive dysfunction in the mice (38). This model however was limited as the onset of motor impairments was abrupt and not progressive, it also did not show the dopaminergic neurodegeneration seen in PD (38).

Knockout transgenic models, a more recent phenomenon (11), have also been used to evaluate other mutations linked to PD, an example being the parkin gene (13). These knockout models are created by producing rodents lacking the target gene, simulating loss-of-function mutations in human PD (39). Parkin mutations have been shown to be present in some familial PD cases (13), Goldberg et al. investigated the role of these mutations in PD pathology by creating parkin knockout mice (39). Their finding showed parkin knockout induced behavioural deficits and reduced dopaminergic neural activity, suggesting wild type parkin to play a role in dopamine regulation. This model did not elicit

dopaminergic neurodegeneration and a-synuclein aggregation seen in PD, limiting its utility in modelling PD. Knockout rodent models of other PD-linked genes have also been made, for example in: PINK1 (40), LRRK2 (41), and DJ-1 (42) genes, giving insights into PD pathology. Future research should aim to refine these models to better capture the full complexity seen in PD and accelerate therapeutic development.

Adeno-associated virus rodent models

Adeno-associated virus (AAV) models of PD use AAV vectors to cause localised expression of a target gene inside the rodent (43). These models are highly useful in researching PD, as the genetic mutation can be localised in the SNpc, and has been used to produce models expressing both progressive neurodegeneration and a-synuclein aggregates (43).

AAV rat models overexpressing a-synuclein have been used as a model of PD (19,44). These models present with a reduction in locomotor activity, but do not present any non-motor symptoms or neurodegeneration (44). A study also expressed the A30P SNCA gene using AAV vectors in the rat SNpc, inducing significant neurodegeneration and a-synuclein accumulation (45). Models such as these could be used for research into pathophysiology of PD in humans.

A novel therapeutic being researched using AAV models is the possibility of gene therapy as treatment for PD (46). Björklund et al. investigated the safety of using AAV vectors to deliver glial cell line-derived neurotrophic factor (GDNF) genes into 6-OHDA rodent models (46). GDNF is known to protect nigral dopaminergic neurons against 6-OHDA and MPTP-induced neurotoxicity (46). In the study, Björklund et al. found that in 6-OHDA rodents injected with AAV-GDNF, neuron survivability was at 92-97% compared to the 45-51% of the control group, suggesting efficient rescuing of dopamine neurons (46). GDNF gene expression also elicited axonal sprouting and regeneration of damaged fibres in the striatum (46). These findings are highly significant, as gene therapy may offer long term treatment for a progressive disease such as PD (46).

Conclusion

To conclude, rodent models are extremely useful for researching PD. Living models of the disease are essential for understanding the progression and pathology of the disease, as current ways confirming brain pathology in humans is highly limited (6).

Rodent models have a large variety of behavioural tests that exist to evaluate motor symptoms, an example of one of these tests is the rotarod test (24,26,47). The rotarod test measures muscle coordination in rodents (47). Tests for other behavioural symptoms also exist, such as the open-field test for general locomotion activity and forced swim test for depressive behaviour (26). Further advantages in the use of rodent models include their ease to breed and handle, they also share essential anatomy and homologous genes for PD research (11,37).

Toxin-based approaches elicit both neurodegeneration and motor deficits in rodents (20,21,22–29, 31–35). Due to these characteristics, neurotoxin models are extremely useful in investigating possible therapeutics for PD, such as L-DOPA (25), Rasagiline (30), Ambroxol (8), Caffeine (36), and naringin (35). A disadvantage is the lack of a-synuclein aggregates present in toxin-based models (10). Genetic approaches to rodent models can elicit a plethora of symptoms dependent on what transgene is used (11). Transgenic mice and AAV models have high utility in investigating how a-synuclein aggregations are involved in PD (38,45). These models however can often lack nigral pathology and neurodegeneration (37).

There is no perfect model of PD, however the heterogeneity of PD models parallels the multifaceted nature of the disease itself, model variations are needed to investigate the many parts of the complex disease. Some combined approaches between neurotoxic and genetic models have been proposed to encompass how environmental risk factors alongside genetic susceptibility are involved in progression and pathogenesis of the PD (11). Further research into these models is needed to understand their effectiveness.

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Figures

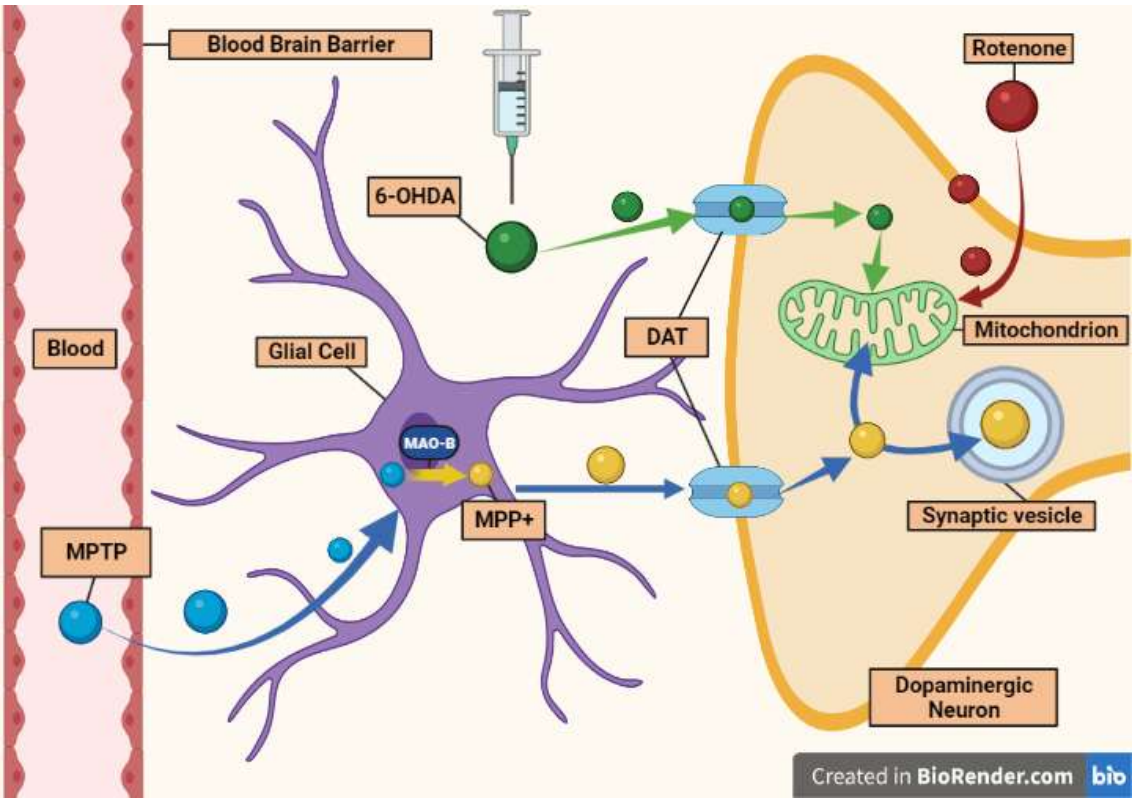

Figure 1 – Neurotoxin molecular pathways. All three discussed neurotoxins, Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-Hydroxydopamine (6-OHDA), and rotenone, elicit their effects similarly once inside the dopaminergic neuron: via the inhibition of mitochondrial complex I, which significantly impairs cellular respiration and stimulates the production of reactive oxygen species (ROS) (12,23,29). The increase of ROS and lack of optimal respiration leads to oxidative damage and stress, and eventual death of the cell (12,23,29). Their neurotoxic effect may be similar in nature, but how they enter the cell differs between the toxins. Lipophilic MPTP passes through the blood-brain barrier easily and is taken up by nearby glial cells (23). Inside the glial cell, MPTP is converted into 1-methyl-4-phenyl-2,3-dihydropyridinium (MPDP+) via the enzyme monoamine oxidase-B (MOA-B), MPDP+ is then oxidised into the toxin 1-methyl-4-phenylpyridinium (MPP+) (23). MPP+ then leaves the glial cell and is actively taken up by dopamine transporters (DATs), entering the dopaminergic neuron. MPP+ is then either transferred into synaptic vesicles by vesicle transporters (VATs) or enters the mitochondria (23). 6-OHDA does not pass through the blood brain barrier and needs to be administered directly into the brain to induce neurodegeneration (29). After being applied to the brain, 6-OHDA is taken in by DAT into dopaminergic neurons, inhibiting complex I (28). Rotenone is also highly hydrophobic crossing both the blood brain barrier and dopaminergic cell membrane easily, once inside it enters mitochondria and inhibits complex I (12,33). Diagram adapted from (12,23,29), created using www.biorender.com.