International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2013): 4.438

Parkinson Disease Research: Distinct Animal Models and Therapeutic Approach

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Abstract: ***Recently, the treatment of Parkinson's disease has seen a considerable progress; nevertheless, due the numerous sides' effects of drug treatment, as well as the difficulty of neurosurgical therapy, it is important to multiply the researches in order to better understand the pathogenic mechanisms of this disorder and to identify new therapeutic strategies. Fortunately for us, animal models represent an important aid in the experimental medical sciences because they enable us to gain insight into the different mechanisms underlying the human's diseases, once validated, animal models may also help to test the therapeutic effects of some molecules, develop new drugs and eventually, identify new therapeutic pathway. However, it is slightly difficult to model neurodegenerative disease because of their variability and the ambiguity of their etiology; therefore, there is a real need to ameliorate the current animal models and to develop new ones. The aim of this paper is to review the different animal model of Parkinson's disease which have been developed over the years, and critically discuss their advantages and their limits. We will also suggest a possible new therapeutic approach for Parkinson's disease focusing on the involvement of the non-dopaminergic system in the occurrence of the disease.***

Keywords: Animal models, Parkinson's disease, Neurotoxines, Genetics, therapeutic approach

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorder characterized by the classical features of trumor, rigidity, bradykinesia, hypokinesia/akinesia and postural instability (Calne 2005; Woolters and braak 2006; Wolters and Bosboom 2007; Erbas et al. 2012). These symptoms are caused by a selective and progressive degeneration of dopamine neuron in the substancia nigra pars compacta, which project to the striatum via the nigrostriatal pathway. Another characteristic of PD is the presence of Lewy bodies in the substancia nigra zona compacta,(Calne 2005) as well as in other brain regions including the cortex (Betarbet et al. 2002).

We do not yet know the cause of these degenerations, but the previous studies suggest that a combination of both genetic and environmental factors including pesticides and neurotoxins may play an important role in the pathogenesis of Parkinson disease.

Given the high prevalence of neurodegenerative diseases, (in particular Parkinson's disease) as well as the severity of their impact, it is important to intensify research aimed at elucidating the mechanisms and to identify new therapeutic strategies. For this, different types of animal models have been used for over 30 years and have been continually improved over the years.

Animal models are an important tool in experimental medical sciences because they enable us to elucidate the pathogenic mechanism of the human diseases. The understanding of the causative mechanisms may also lead to develop new therapeutic and protective approaches. Thus, an animal model should, ideally, mimic the exact pathological, histological, biochemical, and symptomatic feature of the disease. The aim of this paper is to review the different (genetic and neuro-toxic) models of Parkinson's disease and discuss their advantage and their limits.

2. Classical Neurotoxin Animal Models

2.1 MPTP Animal Model

The MPTP was first discovered in the early 1980s when four persons developed Parkinsonism after using an illicit drug intravenously. Analysis of this substance reported that these patients had self-administrated synthetic meperidine contaminated with MPTP (Langston et al. 1983).

The MPTP itself is not toxic; it becomes toxic when converted to MPP^+ by monoamine oxidase-B (MAO-B) in the astrocytes and the serotonin neurons. Thereafter, the MPP^+ reach the extracellular space where is will be transported by the dopamine transporters to the dopaminergic nerves terminals. (Sian et al. 1999) **(Figure 1).**

MPP^+ acts by inhibiting the complex I site and initiating other intracellular reaction (Sian et al. 1999; Jackson-Lewis et al. 2012); (**Figure 1**). This blockade of mitochondrial respiration results in an impairment of ATP formation and an elevation of intracellular Ca2+ leading to the activation of calcium dependent enzymes which disturbs the normal cell functions leading to cellular death (Sian et al. 1999). MPP+ also supports the occurrence of oxidative stress which is strongly implicated in the pathogenesis of numerous neurodegenerative disorders.

Other studies show the inhibition of complex I causes increases in 3,4-dihydroxyphenylacetaldehyde (DOPAL) levels which is a toxic metabolite of dopamine, and death of DA neurons in vivo and in vitro. (Burke 2003)

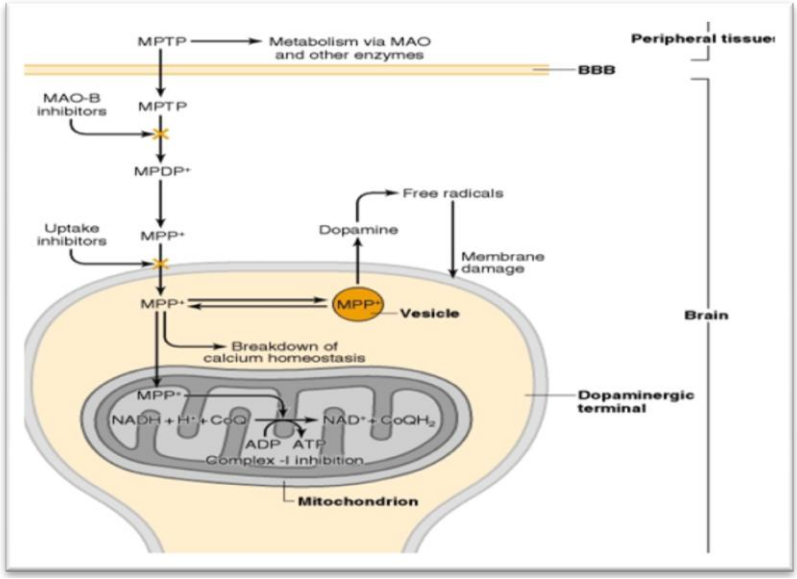

Figure 1: Schematic representation of the mechanisms involved in toxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). (Sian et al. 1999)
From: MPTP-Induced Parkinsonian Syndrome
Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 6th edition.
Siegel GJ, Agranoff BW, Albers RW, et al., editors.
Philadelphia: Lippincott-Raven; 1999

The most important drawback of MPTP animal model is that most protocols use acute administration and fail to mimic the progressive neurodegeneration that characterize PD (Betarbet et al. 2002).

Furthermore, there has been no evidence of the occurrence of Lewy bodies in some non-human primates and rodents MPTP models. Moreover, the resting tremor, which represents one of the most important clinical features of PD, is not always reproduced in MPTP-induced Parkinsonism (Sian et al. 1999)

2.2- 6-Hydroxidopamine (6-OHDA) animal model:

The 6-OHDA is a structural analogue of catecholamines, dopamine and noradrenaline (Simola et al. 2007). Since its first description by Senoh and Witkop, in 1959, this neurotoxin play an important role in the comprehension of the pathogenesis of PD as well as in the preclinical researches by developing animal models of this disease.

Ungerstedt was the first to use 6-OHDA in order to model PD in vivo (Simola et al. 2007), he demonstrated that an intracerebral injection of 6-OHDA into the substancia nigra pars compacta and the caudate putamen caused degeneration of DA and noradrenaline neurons, he also showed that injection of the toxin into the substancia nigra pars compacta produced motor asymmetry in the animals with an anterograde degeneration of the whole nigrostriatal pathway (Ungerstedt 1968).

The neuronal lesion induced by 6-OHDA is mainly due to oxidative stress and mitochondrial inhibition (Glinka et al. 1997, Blum et al. 2001). Once in the brain, 6-OHDA is recognized by the dopamine and Noradrenaline transporters (DAT and NAT) due to their structural similarity (Simola et al. 2007), when it enter into dopamine neurons, the 6-OHDA accumulates in the cytosol and quickly undergoes auto-oxidation phenomenon which results in the formation of high levels of free radicals.

The studies suggest that the 6-OHDA induces cell death of dopaminergic neurons by different mechanisms: The first one is the generation of reactive oxygen species (ROS) which involves two distinct mechanisms, the non-enzymatic self auto-oxidation, or the diamination by monoamines oxidase resulting in a generation of hydrogen peroxide (H2O2) which triggers the production of oxygen radicals. The production of ROS is initiated or amplified by iron via the Fenton reaction (Blum et al. 2001). The second mechanism underlying the 6-OHDA induced neurotoxicity is inhibition of the activity of the respiratory chain by blocking the complex I (Glinka and Youdim 1995).

These data show the implication of both the free radicals and the mitochondrial deficit; however, these two mechanisms are biochemically independent although they may act synergistically in vivo (Glinka et al. 1997).

6-OHDA is incapable to cross the blood brain barrier, which requires its direct administration into the brain using the stereotaxic surgery, this remain one of the major limitations of this model compared to other neuro-toxin model which can produce all the hallmarks of the disease by their solely peripheral injection.

Another drawback of this model is the necessity to inject noradrenaline transporter inhibitor before the injection of 6-OHDA as it shows high affinity to both dopamine and noradrenaline transporters.

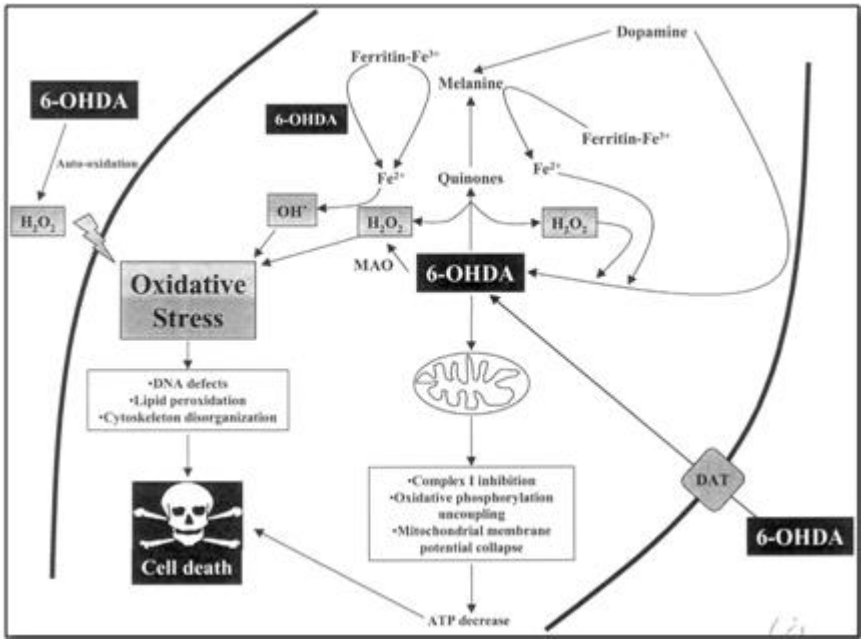

Figure 2: Hypothetical mechanism of 6-OHDA toxicity. (Blum et al. 2001)

6-OHDA could exert its neurotoxicity by three main mechanisms:

- The generation of ROS by intra or extra-cellular auto-oxidation
- The formation of hydrogen Peroxide by MAO activity
- The blockade of the mitochondrial respiratory chain.

Despites their limitations, the classical MPTP-treated mice and the 6-OHDA treated rat remain the most widely used models of PD; and the most widely employed for the screening of antiparkinsonnian drugs and development of new therapeutic strategies like the cell transplantation.

3. Pesticides Animal Models

Previous epidemiological surveys have shown that exposure to pesticides, rural residences and drinking of water from wells are one of the major Parkinson's disease risk factor, these finding have opened the route to development of new animal models.

Indeed, different animal models have been developed based on the exposure of the animals to pesticides such as rotenone, paraquat, and maneb. These models have allowed us to understand some aspect of the mechanism underlying the dopaminergic neural death opening up new horizons to therapeutic preclinical researches.

Paraquat

Paraquat (1,1-dimethyl-4,4-bipyridinium dichloride) is a quaternary nitrogen herbicide widely used in agriculture for broadleaf weed control. Because of its close structural similarity to MPP+ which is the toxic metabolite of MPTP (**Figure 3**), it was suggested that paraquat (PQ^{++}) should have the same neurotoxic effect as MPP^+; Indeed, epidemiological studies in agriculture communities have shown a correlation between the occurrence of PD and the use of Paraquat, in the other hand, a research carried by Brooks et al. 1999 suggested that paraquat cause destruction of dopamine neurons in the substancia nigra eliciting a neurobehavioral syndrome similar to that caused by MPTP toxin. However, it seems that Paraquat and MPP^+ exert their neurotoxicity via different mechanisms, actually, PQ^{++} seems to generates ROS within the cells by redox cycling, while MPP^+-induced neurodegeneration involve additional mechanisms (Di Monte et al. 1986).

The ability of Paraquat to cross the blood brain barrier is controversial, Li et al. 2005 claimed that Paraquat is charged molecule with hydrophilic proprieties; therefore, its ability to reach the brain is limited. However, other studies suggest that a membrane transporter –possibility the transporter of neutral amino acids- would allow PQ^{++} to cross the BBB (Brown et al. 2006).

Using a state-of-the-art stereological technique to count dopaminergic neurons in the substancia nigra pars compacta of mice; (Di Monte 2001) has found a significant cell loss after a systemic subchronic exposure to Paraquat.

Besides the generation of free radicals, the studies have shown an in-vitro effects of paraquat on alpha-synucleine fibrillations, the same study demonstrated that Paraquat elicit the aggregation of alpha-synucleine in the substancia negra and the cortex of the mice brain suggesting that a direct interaction between the protein and environmental agents are potential mechanisms leading to synucleine pathologies in neurodegenerative diseases (Manning et al. 2002).

Glutamate excitotoxicity is also involved in Paraquat-induced neurotoxicity. Using the striatal microdialysis method in the freely moving rats, Shimizu et al. 2003 b reported that PQ stimulated glutamate efflux to initiate exitotoxicity resulting in evoked depolarization of NMDA receptors channels and calcium penetration into cells by activation of non-NMDA receptors.

A complimentary in vitro study of the midbrain culture supported that a constant exposure to low levels of PQ could lead to the vulnerability of dopaminergic neurons in the nigrostriatal system by the excitotoxic pathway. (Shimizu et al. 2003).

Taken together, these results show that Paraquat exerts its effect via different mechanisms including the oxidative stress, alpha-synuclein aggregation and finally, the glutamate exicitotoxicity.

Rotenone

Rotenone is a mitochondrial toxin, unlike Paraquat, which is a synthetic molecule, the rotenone is naturally occurring in the seeds and stems of some plant species. Originally, rotenone was employed by Indians as a fish poison (Uversky 2004), nowadays, this mitochondrial inhibitor is widely used as pesticides in vegetable gardens, and it is also used to kill or sample fish populations in lakes and reservoirs (Betarbet et al. 2000; Uversky 2004)

The first use of rotenone to model PD was in 1985 when Heikkila made a central injection of both rotenone and MPP+ using stereotaxic technique and found that this administration results in a degeneration of the dopaminergic nigrostriatal pathway (Heikkila et al. 1985).

In 2000, it was reported that chronic, systemic exposure to rotenone reproduces features of parkinson's disease including a selective nigrostriatal dopaminergic degeneration as well as a behavioral features like hypokinesia and rigidity. Furthermore, these degenerations were associated with fibrillar cytoplasmic inclusions that contain ubiquitin and alpha-synuclein (Betarbet et al. 2000).

Many later studies have confirmed the ability of rotenone to produce all hallmarks of Parkinson's disease either following a chronic subcutaneous exposure to low dose of rotenone (Sherer et al. 2003) or by a daily intraperitonial injection of the toxin (Cannon et al. 2009). Recently, it was reported that a systemic inhibition of complex I by rotenone induces depletion in Dopaminergic cells in the retina in a rotenone –rat model (Biehlmaier et al. 2007). **(Figure 4)**

Rotenone toxicity is caused by inhibition of complex I (Sherer et al. 2003b) being highly lipophilic, rotenone easily cross the blood brain barrier independently to any transporter, when it enters into the brain, the rotenone accumulates in the mitochondria where it inhibit the complex I of the electron-transport-chain.

The oxidative damage is reported to be strongly implicated in the rotenone-induced toxicity both in vitro and in vivo. This result was supported by the attenuation of neuronal death by antioxidant in different rotenone models (Sherer et al. 2003b).

In the other hand, Tada-Oikawa et al. 2003 demonstrated that, besides the inhibition of complex I, the generation of hydrogen peroxide and the change in mitochondrial membrane potential are also related to the rotenone induced-apoptosis.

Finally, it seems that the activation of astrocytes and microglial cells is also implicated in the rotenone-induced neurotoxicity, which is another hallmark of Parkinson's disease (Sherer et al. 2003c ; Norazit et al. 2010)

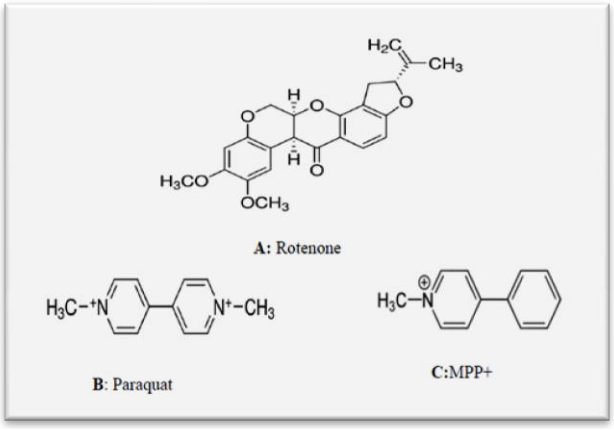

Figure 3: Chemical structure of rotenone (A), paraquat (B) and MPP+ (C)

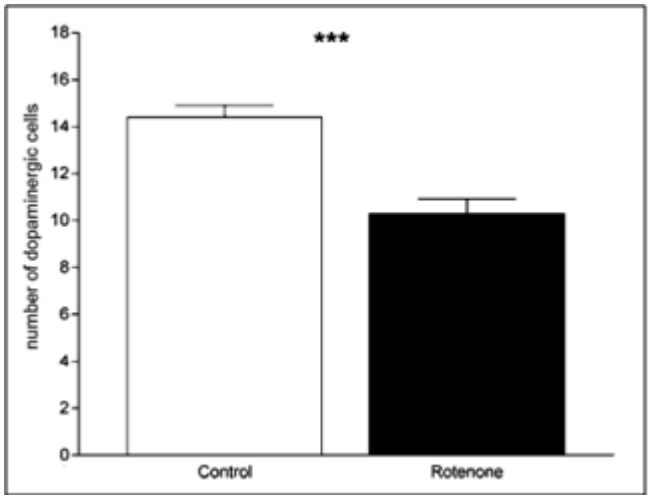

Figure 4: Quantitative analysis of the retinal density of dopaminergic neurons in control injected and rotenone injected rats. The numbers indicate the mean of labelled cells counted in adjacent 0.37 mm2 fields in the central retina ($P < 0.001$), Error bars represent S.E.M. (Biehlmaier et al. 2007).

4. Pharmacological Animal Models

Another group of animal models has also been used to induce neurotoxicity in the nigrostriatal pathway, the pharmacological models, however, they are not widely used currently.

Reserpine

In the late 1950s, carlsson et al. discovered that a systemic administration of reserpine to rodents resulted in a depletion of catecholamine in the brain as well as a parkinsonian-like symptom which has been successfully reversed by L-DOPA (Carlsson et al. 1957). Reserpine act by inhibiting the vesicular monoamine transporter (VMAT2) which leads to loss of storage capacity and then a depletion of brain monoamines and dopamine (Duty and Jenner 2011).

The major drawback of this model is that Reserpine does not induce any nigral dopaminergic cell degeneration and its effect is actually temporary. However, this model has been successfully used to investigate the effects of both dopaminergic (including L-DOPA) and non-dopaminergic drugs currently used to treat Parkinson's disease (Carlsson et al. 1957; Goldstein et al. 1975), besides its ability to mimic the biochemical and the behavioral component of this disorder.

Amphetamine

Amphetamine has also been used to model PD, a recent epidemiological study has shown that the use of methamphetamine drug or other amphetamine derivates may increase the risk of Parkinson's disease (Callaghan et al. 2012). However, experimentally, this model is not very reliable as it actually, destroys the dopaminergic nerve terminals in the striatum but doesn't affect the dopaminergic cell bodies in the substancia nigra (Krasnova and Cadet 2009), furthermore, amphetamine result in an increase in locomotor activity which doesn't really match with the Parkinson's disease's behavioral features.

5. Genetic Animal Models

Although only 10% -20% of Parkinson's disease cases are due to familial causes (Dawson et al. 2010, Cannon et al. 2009), it is so important to make genetic animal and cellular models as they represent potential therapeutic targets, and they help us have insight into the molecular mechanism of this disease. Previous studies have shown that mutations in a number of genes are robustly associated with autosomal dominant or recessive Parkinson's disease.

Mutations in several genes are implicated in autosomal dominant forms of PD or Parkinsonism such as alpha-synuclein (SNCA) and leucine rich repeat kinase 2 (LRRK2) (Wolters and Bosboom 2007; Puschmann 2013).Mutations in others genes like eukaryotic translation inhibition factor 4- gamma 1 (EIF4G1), vacuolar protein sorting 35 (VPS35) (Puschmann 2013), and UCHL1 and HTRA2 (wolters and Bosboom 2007) are also implicated with autosomal dominant PD.

Currently, mutations in four genes associated with autosomal recessive P.D have been identified : Parkin gene, phosphatase and tesin homolog induced novel kinase 1 (PINK1), DJ1 and ATP 13A2(Dawson et al. 2010; Wolters and Bosboom 2007; pushmann 2013).

Genetic models of PD have focused on these genes mutations. In these models, we use either overexpression or knockout technology to model Parkinson's disease in animals (Jackson-Lewis et al. 2012). Historically, these models have been in mouse due to the ease of genetic manipulation in this species (Dawson et al 2010). Target genes in genetic models typically include alpha synuclein (Snca), leucine rich repeat kinase 2 (Lrrk2), for the autosomal dominant form and parkin (Park2), PTEN-induced putative kinase 1 (Pink1), and DJ-1 (Park7) for the autosomal recessive form of PD.

The advantages of the genetic animal models are that they possess defects in genes where dysfunctions have been linked to the disease in humans. Thus they may be useful in the comprehension of the mechanism by which gene mutations contributes to the pathogenesis of the disease. Furthermore, some Parkinson's disease genetic models, specially the Parkin, PINK 1 and DJ-1 knockouts might help us understand the earliest abnormalities in the nigrostriatal dopaminergic system that occur due to these mutations and to understand the molecular mechanisms of compensation (Dawson et al. 2010). Genetic models have never contributed to drug development; however, it is possible that, whit further amelioration, they will contribute in this way in the future.

Genetic animal models of Parkinson's disease also show some limitations, while a reasonable animal model should reproduce progressive loss of dopaminergic neurons, formation of Lewy bodies as well as the motor dysfunctions, to date, none of the current models has fulfilled this criteria (Dawson et al. 2010). The other major problem with the genetic mouse model of PD, is that mice have a short lifespan of 2 years which doesn't make it a good choice for modeling a neurodegenerative disease specially PD that take five to seven decades to manifest in humans (Dawson et al. 2010).

6. Implication of Other Systems and Hypothesis to Develop a New Therapeutic Approach

The dopaminergic system is not the only one to be involved in the pathogenesis of Parkinson's disease, actually, many studies has focused on the involvement of other neurotransmitters like glutamate (Blandini et al. 1996), GABA (Bartholini et al. 1987) noradrenaline (Delaville et al. 2011) and also acetylcholine (Liu et al. 2015). Hence, they are many non-dopaminergic drugs for Parkinson's disease such as the glutamate antagonist that act by slowing the processes of excitotoxicity, or the anticholinergic drugs that help restrict the action of acetylcholine in the brain.

Moreover, other studies have shown the involvement of serotonergic system in the locomotor activity, using an electrophysiological technique and an in vivo microdialysis, Di Giovanni et al. 1999 indicated that the central serotonergic system exerts a tonic inhibitory control on dopaminergic nigrostriatal pathways via the 5-HT2C / 2B receptor subtypes.

These data lead us to propose a new therapeutic approach for the treatment of Parkinson's disease by focusing on the interaction between the dopamine and the serotonin systems, this approach is based on the selective inhibition of these receptors using serotonin antagonists in normal rats as well as in animal models; this study may help us to elucidate the mechanism by which the serotonin system is involved in motor disorders, in another hand, it may help in the discovery of new drugs that may slow the degeneration process.

7. Conclusion

We can't deny that we learned a lot about the pathogenesis of Parkinson disease thanks to animal models, they also helped in the development and the screening of drugs. However, both toxin-based animal models and genetic models have their own drawbacks which must be taken into consideration when choosing the model. The neurotoxin models give insight about PD at the end-stage despite the progressive nature of the disease. Transgenic models may provide some piece of information about the genetic aspect of PD and the mechanism by which gene's mutations are involved, nevertheless, they don't reproduce all the hallmarks of the disease besides the fact that only 10 to 20% of PD cases are due to familial causes.

The recent hypothesis claimed that most neurodegenerataive diseases are caused by a combination of both genetic and environmental factors, thus, it could be ideal to develop models using both transgenic manipulation and neurotoxin. Indeed, a recent study has put both of them together in one model (Peng et al. 2010), but there is a real need to multiply the effort in order to ameliorate the current models or develop new ones.

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