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Review Article

Classic and New Animal Models of Parkinson's Disease

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Neurological disorders can be modeled in animals so as to recreate specific pathogenic events and behavioral outcomes. Parkinson's Disease (PD) is the second most common neurodegenerative disease of an aging population, and although there have been several significant findings about the PD disease process, much of this process still remains a mystery. Breakthroughs in the last two decades using animal models have offered insights into the understanding of the PD disease process, its etiology, pathology, and molecular mechanisms. Furthermore, while cellular models have helped to identify specific events, animal models, both toxic and genetic, have replicated almost all of the hallmarks of PD and are useful for testing new neuroprotective or neurorestorative strategies. Moreover, significant advances in the modeling of additional PD features have come to light in both classic and newer models. In this review, we try to provide an updated summary of the main characteristics of these models as well as the strengths and weaknesses of what we believe to be the most popular PD animal models. These models include those produced by 6-hydroxydopamine (6-OHDA), 1-methyl-1,2,3,6-tetrahydropiridine (MPTP), rotenone, and paraquat, as well as several genetic models like those related to alpha-synuclein, PINK1, Parkin and LRRK2 alterations.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting 1% of the population over 55 years of age [1]. This disease is characterized by the loss of ~50–70% of the dopaminergic neurons in the substantia nigra pars compacta (SNc), a profound loss of dopamine (DA) in the striatum, and the presence of intracytoplasmic inclusions called Lewy bodies (LB), which are composed mainly of α-synuclein and ubiquitin. Although mutations in the α-synuclein gene have thus far been associated only with rare familial cases of PD, α-synuclein is found in all LBs [2]. Therefore, this protein may play an important role in the pathogenesis of this disease. The main features of PD are tremor, rigidity, bradykinesia, and postural instability; however, these motor manifestations can be accompanied by nonmotor symptoms such as olfactory deficits, sleep impairments, and neuropsychiatric disorders [3–5]. Although the complete PD disease process is not yet understood, we have gained a better understanding of its etiology, pathology, and molecular mechanisms, thanks to various animal models [6]. For example, reserpine administration in animals was found to produce a profound depletion of monoamines, including DA, in the brains of injected animals resulting in reserpine syndrome. The symptoms of this syndrome consisted of slowness of movement and rigidity [7] now commonly associated with PD. Interestingly, it was found that L-DOPA was able to reverse many of the symptoms associated with reserpine administration [8], furthering the hypothesis that DA depletion was at the root of PD symptomatology.

For the past several decades, animal models of PD have come in a variety of forms. Typically, they can be divided into those using environmental or synthetic neurotoxins or those utilizing the in vivo expression of PD-related mutations (genetic).

Of the neurotoxic models, compounds that produce both reversible (reserpine) and irreversible (MPTP, 6-OHDA, paraquat, rotenone) effects have been used effectively; however recent studies have focused more on irreversible toxins to produce PD-related pathology and symptomatology. Therefore, the neurotoxins covered in this paper will focus on those that produce an irreversible effect. Neurotoxin-based

models produced by 6-hydroxydopamine (6-OHDA) and 1-methyl-1,2,3,6-tetrahydropyridine (MPTP) administration are the most widely used toxic models, while paraquat and rotenone are more recent additions to the stable of toxic agents used to model PD [6, 9]. A common feature of all toxin-induced models is their ability to produce an oxidative stress and to cause cell death in DA neuronal populations that reflect what is seen in PD. Oxidative stress results from increased production of extremely reactive free radicals, including reactive oxidative species (ROS) and peroxynitrite. ROS may be formed during a number of cellular processes, including mitochondrial oxidative respiration and metabolism. There are some drawbacks to the use of these models such as the time factor in these models versus the time factor in the human condition, but these do not negate the value of neurotoxin-based animal models in the study of PD.

Recently, the identification of different genetic mutations (α-synuclein, parkin, LRKK2, PINK1, DJ-1) has led to the development of genetic models of PD [10]. It is important to remember that, at best, only ~10% of PD cases are due to genetic mutations [6], while the vast majority of PD cases arise as sporadic, that is, from unknown origins. Although the above-mentioned genes are mutated in PD and are not overexpressed or knocked out, nonetheless, these animal models are important in that they may reveal specific molecular events that lead to the death of the DA neurons and potential therapeutic targets. In this paper, we try to describe the advantages and disadvantages of all of these animal models and their potential roles in revealing the mechanisms for PD pathogenesis and in testing experimental therapeutics (Table 1).

2. Neurotoxic Models

2.1. 6-Hydroxydopamine. 6-OHDA is the classic and oft utilized toxin-based animal model of PD [11–13]. A lot of information on the behavioral, biochemical, and physiological effects of dopamine in the CNS has been derived from this model. 6-OHDA was first isolated in the 1950s [14]. Ungersted [15] first used this neurotoxin to lesion the nigro-striatal dopaminergic pathway in the rat nearly 50 years ago, and the use of 6-OHDA remains widespread today for both *in vitro* and *in vivo* investigations. Mice, cats, dogs, and monkeys are all sensitive to 6-OHDA; however it is used much more frequently in rats [16–19]. Even though 6-OHDA exhibits a high affinity for several catecholaminergic transporters such as the dopamine transporter (DAT) and norepinephrine transporter (NET) [20], it is often used in conjunction with a selective noradrenaline reuptake inhibitor such as desipramine in order to spare the noradrenergic neurons from damage in animal models of PD [21].

Although the structure of 6-OHDA is similar to that of dopamine, the presence of an additional hydroxyl group makes it toxic to dopaminergic neurons. This compound does not cross the blood-brain barrier, which necessitates its direct injection into the SNpc, medial forebrain bundle (MFB), or the striatum [22, 23]. It is well known that 6-OHDA destroys catecholaminergic neurons by a combined

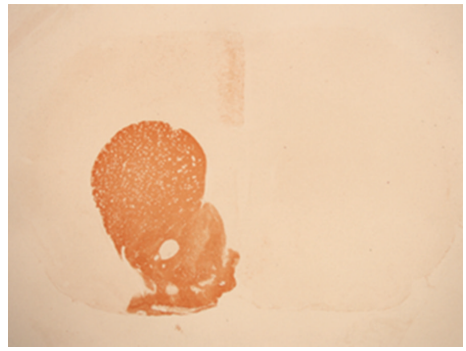


Figure 1: Photomicrograph of a 6-OHDA lesioned rat striatum immunostained for tyrosine hydroxylase (TH). Densities of TH-immunoreactivity striatal fibers are clearly reduced after the 6-OHDA injection (right side) as compared to the densities of striatal TH-immunoreactivity fibers in control rat (left side).

effect of ROS and quinones [24], and it can induce inflammation in the brain which tends to wane over time. The most common use of 6-OHDA is via unilateral injection into the rat medial forebrain bundle. Injection of 6-OHDA into the SNpc kills approximately 60% of the tyrosine hydroxylase- (TH-) containing neurons in this area of the rodent brain with subsequent loss of TH-positive terminals in the striatum [25] (Figure 1). Several studies have injected this compound directly into the striatum in order to test the hypothesis of retrograde degeneration, explicitly, that TH-positive terminals in the striatum die prior to TH-positive neurons in the SNpc, seemingly a replicate of PD in humans [23, 26, 27]. The magnitude of the lesion depends on the amount of 6-OHDA injected, the site of injection, and the animal species used. This model does not mimic all of the clinical features of PD. Dopamine depletion, nigral dopamine cell loss, and neurobehavioral deficits have been successfully achieved using this model, but it does not seem to affect other brain regions, such as olfactory structures, lower brain stem areas, or locus coeruleus. Although 6-OHDA does not produce or induce proteinaceous aggregates or Lewy-like inclusions like those seen in PD, it has been reported that 6-OHDA does interact with α-synuclein [25]. 6-OHDA is frequently used as a unilateral model because the bilateral injection of this compound into the striatum produces severe adipsia, aphagia, and also death [28, 29] due to the animal's inability to care for itself. One of the most attractive features of the unilateral 6-OHDA model is the fact that each animal can serve as its own control as there is a lesioned and an unlesioned hemisphere. This is particularly useful in behavioral analyses [15] as turning behavior to amphetamine or apomorphine following the unilateral application of 6-OHDA gauges the extent of the induced SNpc or striatal lesion and the efficacy of potential PD therapeutic agents and gene therapies [11, 30].

6-OHDA is an attractive candidate as a possible endogenous toxin for the initiation of the PD neurodegenerative process as it is a product of dopamine metabolism [31], and it is the result of hydroxyl radical attack with the presence of

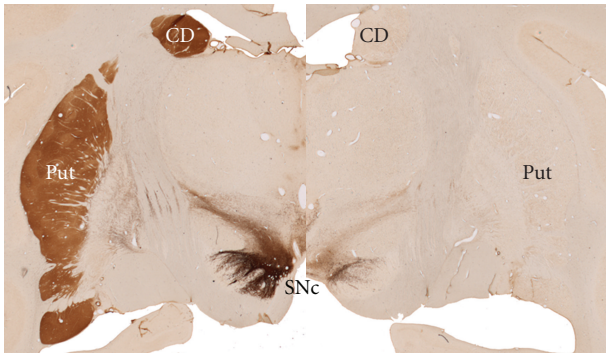
Table 1

Model	Behavioral symptoms	Nigrostriatal damage	Synuclein aggregation/Lewy body formation	Uses of the model	Disadvantages
6-OHDA	Rotational behavior after unilateral injection	Loss of DA innervation at injection site (striatum)	No inclusions	Screen therapies that may improve PD symptoms. Study mechanisms of cell death	Requires intracerebral injection, very little synuclein involvement.
MPTP	Motor impairments in primates Less obvious motor impairments in acute rodent models	Loss of DA neurons dependent on dosing regimen, reaching 95% in acute high-dose conditions. Reduced DA levels in striatum concurrent with midbrain DA neuron loss	Inclusions not prevalent. Few cases of synuclein aggregation in nonhuman primates, as well as increased synuclein immunoreactivity in rodents.	Screen therapies that may improve PD symptoms. Study mechanisms of cell death	Nonprogressive model of cell death. Inclusiones are rare.
Rotenone	Reports of decreased motor activity in rodents	Loss of DA neurons accompanied by reduced DA innervation in striatum	Synuclein aggregation in DA neurons.	Test neuroprotective compounds	Substantial morbidity and mortality. Labor and time intensive.
Paraquat	No clear motor deficits	Decreased striatal TH immunoreactivity	No inclusions present, but increased synuclein immunoreactivity in DA neurons of the SN	Test neuroprotective strategies	Not extensively tested. Effects in other neurotransmitter systems.
α-synuclein	Severe motor deficits in the A53T model, less in the A30P model	Generally no DA neuron degeneration observed	Synuclein aggregation found in DA neurons, generally restricted to A53T model	Study the role of synuclein aggregation in PD, as well as the normal role of synuclein	Generally no DA neuron death observed with synuclein models
LRRK2	Few behavioral deficits seen in Drosophila mutation models	No effect on DA development or maintenance in knockouts, minimal levels of degeneration in mutation models	Generally not observed	Study the role of LRRK2 mutations related to PD	General lack of degeneration and general lack of synuclein aggregation.

excess dopamine; as a neurotoxin, it does produce lesions in the nigrostriatal DA pathway. However, although it has been measured in the brains of levodopa-treated rats subjected to MPTP treatment, 6-OHDA has yet to be recovered from the PD brain. Despite its limitations, this model has contributed enormously to our understanding of PD pathology. 6-OHDA will continue to afford PD researchers a useful animal model for PD research for long time.

2.2. MPTP. In 1982, MPTP was accidentally discovered in a synthesis process gone awry, and, although it may have caused some mayhem in certain circles, today it represents the most important and most frequently used parkinsonian toxin applied in animal models. Young drug addicts developed an idiopathic parkinsonian syndrome after intravenous injection of this compound. After investigating the etiology of their condition, it was found that MPTP was the neurotoxic contaminant responsible for the parkinsonian effect [32]. Oxidative stress, ROS, energy failure, and inflammation have consistently been pointed to as hallmarks of PD. It has been repeatedly demonstrated that MPTP is indeed the gold standard for toxin-based animal models of PD among PD researchers for replicating almost all of these hallmarks [32]. Unfortunately, lacking in this list is the definitive characteristic of PD, LB formation [33, 34]. Interestingly, some studies have demonstrated the production of Lewy body-like inclusions after MPTP administration [35, 36] although these studies have been difficult to replicate. These studies suggest that, under the right circumstances, we may be able to reproduce the majority of hallmarks found in PD.

MPTP is highly lipophilic and after systemic administration rapidly crosses the blood-brain barrier. Once in the brain, MPTP enters astrocytes and is metabolized into MPP+, its active metabolite, by monoamine oxidase-B (MAO-B). Recent findings show that once released from the astrocytes into the extracellular space via the OCT-3



(a) (b)

Figure 2: Photomicrographs of nonhuman primate immunostained for tyrosine hydroxylase (TH). Dopaminergic neurons located in the substantia nigra compacta (SNc) project to the caudate (CD) and putamen (PUT). Note the markedly reduced TH immunoreactivity in the substantia nigra and striatum (CD and PUT) in the MPTP-treated monkey (b) compared to control (a).

transporter [37], MPP+ is taken up into the neuron by the dopamine transporter (DAT) and can be stored in vesicles via uptake by the vesicular monoamine transporter (VMAT2) [38]. Consequently, mice lacking the DAT are protected from MPTP toxicity [39]. Once inside the neuron, MPP+ is able to inhibit complex 1 of the mitochondrial electron transport chain, resulting in the release of ROS as well as reduced ATP production. Storing into vesicles can decrease MPP+ toxicity [40–42]. Additionally, MPP+ stored in vesicles is thought to expel DA out into the intercellular space where it can be metabolized into a number of compounds, including toxic metabolites, such as DOPAL and where it is can be subjected to superoxide radical (5-cysteinyl-DA) and hydroxyl radical (6-OHDA) attack [43, 44].

MPTP is used mainly in nonhuman primates and mice but has also been used in many other species such as dogs and cats [45]. For unknown reasons, rats are resistant to MPTP and mouse strains vary widely in their sensitivity to the toxin [46]. MPTP can be administered by a variety of regimens, but the most common and reproducible form is still systemic injection (subcutaneous, intravenous) [47]. When MPTP is administered to nonhuman primates, they exhibit behavioral and neuroanatomical similarities to the human condition showing a bilateral parkinsonian syndrome [48] (Figure 2). Another commonly used route is the unilateral intracarotid injection. This causes mostly a unilateral parkinsonism, whose benefits as an animal model were described earlier, but is technically more complicated to perform [49].

Usually monkeys are treated with high doses of MPTP for a short time (acute model). Recently, however, new schedules have introduced lower doses of the neurotoxin for longer periods of time (subacute to chronic) to replicate more closely the human pathology [50]. There are recent studies attempting to develop a more progressive model of PD. In addition, models are being developed to study compensatory mechanisms or recovery. These models use low to intermittent doses administered once or twice per week [51–54]. It is well known that monkeys exhibit variability in MPTP susceptibility and that older primates are often more susceptible to MPTP [55]. MPTP-treated monkeys respond well to antiparkinsonian treatments like L-DOPA or apomorphine and, like human pathology, after the treatment develop dyskinesias. Recently, some studies have been taken in order to study and evaluate the nonmotor symptoms of the disease using this model [56–61]. This model has also been used for electrophysiological studies, leading to important findings, including the emergence of deep brain stimulation, which is currently the best surgical method to ameliorate symptoms in PD patients [62, 63].

Currently, the MPTP model is used more in mice than in monkeys. Aside from the obvious financial benefits, the mouse model is employed to test theories about cell death in PD, to work out events in the neuronal death process, and to study other pathological effects of PD. It is also extremely useful as an initial screening tool to test potential treatments for PD. On the other hand, the MPTP monkey model is mainly used to discern behavioral and symptomatic components of PD, as mice do not develop a level of impairment equal to the human condition. Monkeys also represent the last level of PD treatment research prior to any treatment being administered to humans [64]. However, the data generated by mouse models has led to a better understanding of molecular mechanisms involved in PD, and its utility has proven invaluable. One of the most important aspects of the MPTP mouse model is the possibility to work with genetically modified mice [65, 66]. This model can be useful for testing neuroprotective therapies. Currently, MPTP is the standard bearer for toxin-based PD animal models.

3. Pesticide/Herbicide Models

3.1. Paraquat. Paraquat (N,N′-dimethyl-4-4-4′-bypiridinium) (PQ) is a herbicide widely used in agriculture that exhibits a structural resemblance to MPP+, and, because of this structural similarity, it was reasoned that PQ should behave like MPP+. Epidemiological reports suggest that pesticide use increases the risk of developing PD, but, in the case of PQ, there have been only 95 cases of PD linked to its toxicity in humans [67]. PQ exerts its deleterious effects through oxidative stress mediated by redox cycling, which generates ROS. In particular, the superoxide radical, hydrogen peroxide, and hydroxyl radicals lead to the damage of lipids, proteins, DNA and RNA [68, 69]. Recent evidence on the effects of PQ in the nigrostriatal DA system is somewhat ambiguous as some researchers report that, following the systemic application of this herbicide to mice, animals exhibit reduced motor activity and a dose-dependent loss of striatal TH-positive striatal fibers and midbrain SNpc neurons [70, 71]. Other researchers claim that no PQ-induced changes occur in the nigrostriatal DA system [72, 73]. However, in a newer recent study, Rappold et al. [74] demonstrate that PQ, in high doses, employs the organic cationic transporter-3 (OCT-3) and the dopamine transporter (DAT) and is toxic to the DA neurons in the SN. Furthermore, they suggest that the damage done by PQ is caused by radicalized PQ and

facilitated by the glial cells. This means that PQ behaves like MPP+ in exerting its toxic effects. Although this study increases our understanding of how PQ may work, it does not end the controversy about PQ and PD.

PQ's importance to PD researchers is its ability to induce increases in α-synuclein in individual DA neurons in the SNpc and its ability to induce LB-like structures in DA neurons of the SNpc [75]. The relation of dopaminergic neuron loss with α-synuclein upregulation and aggregation suggests that this model could be valuable for capturing a PD-like pathology. However, the molecular link between oxidative stress and cell death in this model is still unknown. Thus, the significance of PQ in PD research is often limited to the study of the process of LB formation in DA neurons as well as the role of α-synuclein in PD. PQ is only one of the many agricultural chemicals known to cause damage to the dopaminergic system. Maneb (manganese ethylenebisdithiocarbamate) has been shown to decrease locomotor activity and potentiate both the MPTP and the PQ effects [73, 76, 77]. Moreover, the combination of PQ and maneb produced greater effects on the dopaminergic system than either of these chemicals alone. These compounds give credence to the theory that environmental pesticides can cause PD [67, 78–80]. In fact, recent studies have demonstrated that those exposed to PQ or fungicides like maneb or ziram experience a greater risk of developing PD [81, 82]. Further investigations using these models are needed to determine the involvement of environmental exposures in the etiology of PD.

3.2. Rotenone. Unlike PQ, which is a pure herbicide rotenone, is both a herbicide and an insecticide [83]. It is the most potent member of the rotenoid family of neurotoxins found naturally in tropical plants. The half-life of rotenone is 3–5 days depending on its exposure to sunlight, and it is rapidly broken down in soil and in water [83]. For these reasons, rotenone is not considered to be a groundwater pollutant. Rotenone is highly lipophilic and readily crosses the blood-brain barrier. Chronic exposure to low doses of rotenone results in inhibition of the mitochondrial electron transport chain in the rat brain. In animals, rotenone has been administered by different routes. Oral administration appears to cause little neurotoxicity [84, 85]. Chronic systemic administration using osmotic pumps has been the most common delivery regimen, especially in the Lewis rat, which may be more sensitive to rotenone than other strains of rats [86]. Intraperitoneal injections have been reported to elicit behavioral and neurochemical deficits, although mortality is very high [87]. Intravenous administration is able to cause damage to nigrostriatal DA neurons that is accompanied by α-synuclein aggregation, Lewy-like body formation, oxidative stress, and gastrointestinal problems [88]. The apparent beauty of this model is that, like paraquat, it seems to replicate almost all of the hallmarks of PD including causing α-synuclein aggregation and Lewy-like body formation [89, 90]. Interestingly, a subsequent study has found that rotenone is not specific to the DA system and has deleterious effects on other neuronal populations. Likewise, in PD in which neurodegeneration extends beyond the dopaminergic system, rotenone is associated with 35% reduction in serotonin, 26% in noradrenergic, and 29% in cholinergic neurons [89]. However, when rotenone was administered chronically at lower doses to achieve complex I inhibition similar to that observed in patients, it seems to produce a highly selective nigrostriatal degeneration [86] although only about 50% of the treated rats exhibit nigrostriatal lesions. The controversy about the use of rotenone as a model of PD is that although it does augment DA oxidation, evidence is slim on depletion of DA in the nigrostriatal system [91]. Attempts to lesion other animal species such as mice or monkeys have not been successful at all [72, 92]. However, recent studies by two groups have demonstrated that oral administration of rotenone to mice causes nigral degeneration, a decrease of striatal dopamine levels, and motor dysfunction [85, 93, 94]. They also demonstrated α-synuclein aggregation in different areas of the brain [95]. Furthermore, there are no documented cases of rotenone-induced PD in humans. Thus, it is not clear that this model offers any advantage over other toxic models, such as that of 6-OHDA or MPTP.

4. Genetic Models

The underlying principle for studying genetic mutations of a disease is the belief that the clinical similarities between the inherited and sporadic forms of the disease share a common mechanism that can lead to the identification of molecular and biochemical pathways involved in the disease pathogenesis. Genetic mutations in PD are rare and represent only about 10% of all PD cases [6]. And animal models of these mutations (α-synuclein and LRRK2, autosomal dominant PD) and (PINK1/Parkin and DJ-1, autosomal recessive PD) are important as they represent potential therapeutic targets. However, we must first understand the workings of these animal models because it is becoming clearer that there are many facets to PD disease.

Mutations to the α-synuclein gene, which is normally thought to play a role in the synaptic vesicle recycling, were the earliest evidence for genetic link to PD. Two mutations in the α-synuclein gene (A53T, A30P) cause a dominantly inherited form of PD [96] and have been used to create transgenic mice in an effort to recapitulate the pathophysiology of PD. Studies done using α-synuclein transgenic mice have yielded considerable progress, showing that A53T mutations in mice can result in a severe motor phenotype which can eventually lead to paralysis and death [97]. Additionally, mutations to the α-synuclein gene in mice produce inclusions that resemble LBs [98]. However this phenotype is generally restricted to the A53T mutation and not found in A30P transgenic mice. Indeed, it has been shown that knocking out α-synuclein does not affect DA neuron development or maintenance [99, 100] suggesting that the loss of α-synuclein probably plays no role in the degeneration of DA neurons that is seen in PD. Interestingly, studies done in *Drosophila* expressing mutant α-synuclein show dopaminergic cell loss, reduced TH expression in the SN, filamentous intraneuronal inclusions, and motor deficits [101]. Some of the α-synuclein transgenic mice have olfactory impairments and colonic dysfunction, and it seems

that there are other nonmotor abnormalities [102]. Understanding these nonmotor symptoms could offer new model for testing therapies focused on the nonmotor symptoms. However, since the function of α-synuclein has yet to be figured out, the actual role of α-synuclein in PD still remains elusive.

Mutations to the LRRK2 gene have been shown to cause a dominant form of PD [103]. Unlike α-synuclein which is ubiquitous, LRRK2 (leucine rich repeat kinase 2) is localized to membranes. However, similar to α-synuclein transgenic mice, it has been determined that knocking out LRRK2 has no effect on DA neuron development and maintenance [102]. Moreover, *Drosophila* models are limited in their translation to the human condition, and the LRRK2 mouse model is not particularly a strong model as it shows only minimal levels of neurodegeneration [104].

Mutations to parkin (which accounts for about 50% of the familial cases of PD and 20% of the young onset PD cases), DJ1 (a redox sensitive molecular chaperone and regulator of antioxidant gene expression), and PINK1 (phosphatase and tensin homolog—PTEN-induced novel kinase 1, which is localized to the mitochondrial intermembrane space) cause autosomal recessive forms of PD. Knock-out rodent models of these genes do not demonstrate any nigrostriatal degeneration, present with intranucelar inclusions, or displays any form of DA neuron loss that resembles idiopathic or inherited PD and fail to develope any type of behavioral or pathological phenotype (only PINK1 knockout mice display reduced DA release in the striatum) [105]. However, recently it has been shown that knocking out parkin in mice at adult age causes neurodegeneration in the SNc [106].

Overall, this genetic mouse models are able to recapitulate specific aspects of PD, although none produce the neuronal degeneration associated with PD; therefore these themselves may be defective and may require additional modulations or modifications, like for example the human environment [107].

5. Conclusions

Animal model systems are the closest to humans that we are able to study. A number of animal models of PD have been developed to understand the pathogenesis and test potential therapeutics of this disease. In this paper we have summarized the most prominent aspects characterizing the most popular toxic and genetic models of PD. Each model has advantages and disadvantages as we have discussed in this paper. Toxic models offer some of the hallmarks of PD while genetic models offer others. Meanwhile the toxic models are useful to screen drugs for symptomatic treatment of the disease; transgenic or knockout models are useful for evaluating the role of genetics in PD. The drawback of the toxin models is that most of them resemble PD at late stages, whereas genetic animal models use either overexpression or knock-out technology to model disease from early on. The choice of the model to be used depends on the questions being asked. With toxin models, we are working toward developing a progressive model by tempering the toxic doses used. With genetic models, we are trying to come up with the right balance of contributing components through knock-in or conditional technology. However, there is much progress to be made, because it seems unlikely that a single model, be it toxic or genetic, can fully recapitulate the complexity of human PD. Future models should involve a combination of neurotoxin-induced and genetically induced models ideally taking into account factors of aging and environmental insults.

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