Chapter 10

Animal Models of Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, the consequent dopamine deficit in the striatum and the accumulation of aggregated α-synuclein (α-syn) in specific brain regions. The underlying pathophysiology of PD remains poorly understood. Animal models are the best tools to study the pathogenesis of PD. Most studies in PD animal models have focused on the motor features associated with dopamine depletion but still the molecular basis of PD and the molecular pathways of cell death remain unknown. While cellular models have helped to identify specific events, in vivo animal models have simulated most, although not all, of the hallmarks of PD and are useful for testing new neuroprotective approaches. In this chapter, we provide a summary of the most used PD animal models, including their advantages and limitations. Classically, in vivo PD animal models can be divided into those using environmental or synthetic neurotoxins (toxin-based models) or those utilizing the in vivo expression of PD-related mutations (genetic models). These models include 6-hydroxydopamine (6-OHDA), 1-methyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, and paraquat, as well as genetic models such as those related to α-syn, PINK1, Parkin, DJ-1, and LRRK2.

Keywords: MPTP, 6-OHDA, Rotenone, Paraquat, α-syn, LRRK2, Parkin, DJ1

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by the classical motor symptoms: resting tremor, bradykinesia, akinesia, rigidity, and postural instability. PD

is characterized by the loss of ~50–70% of the dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the consequent loss of dopamine (DA) in the striatum, and the presence of intracytoplasmic inclusions called Lewy bodies (LB) that are composed mainly of α-synuclein (α-syn) and ubiquitin [1]. Although the complete PD pathogenesis is not well understood, thanks to the use of animal models, we have gained a better understanding of its etiology, pathology, and molecular mechanisms. Importantly, none of the current available models is able to fully recapitulate PD symptoms and pathology [2].

The use of animal models in PD (both in vitro and in vivo) has greatly augmented thanks to new strategies for producing sophisticated models, such as the temporal- and/or cell-specific expression of mutated genes in vertebrates [3], human pluripotent cells coaxed into a specific type of neurons [4], and a host of different invertebrate organisms such as Drosophila [5], Medaka fish [6], or *Caenorhabditis elegans* [7]. Current PD experimental models can still be categorized into two main groups: toxic and genetic (or both of them combined). Over the years, a collection of strategies have been used to produce other animal models to model PD. Some of them included those based neither on neurotoxins nor on genetic mutations that are directly linked to familial PD. Some of these models lack transcription factors that are required for the survival of dopaminergic neurons, such as sonic hedgehog [8], nuclear receptor related protein-1 (Nurr1) [9], pituitary homeobox 3 (Pitx3) [10], or engrailed 1 [11]. Even so, the reproducibility and reliability of most of these new models are still under debate.

Therefore, the neurotoxins covered in this chapter focus on models produced by 6-hydroxydopamine (6-OHDA) and 1-methyl-1,2,3,6-tetrahydropyridine (MPTP) administration, and paraquat and rotenone which are more recent additions to the stable of toxic agents used to model PD. The recent identification of different genetic mutations related to PD (mainly SNCA (α-syn, PARK1, and 4), PRKN (parkin RBR E3 ubiquitin protein ligase, PARK2), PINK1 (PTEN-induced putative kinase 1, PARK6), DJ-1 (PARK7), and LRRK2 (leucine-rich repeat kinase 2, PARK8) has led to the development of a range of genetic models [12]. Although the expression of all these proteins in invertebrate models offers experimental advantages and can potentially address some important questions regarding the cellular processes underlying PD, in this chapter, we focus on the different expression of these proteins in mammalian models. Also, although the aforementioned genes are mutated in PD and are not overexpressed or knocked out (KO), these animal models are relevant in the way that may reveal specific molecular events that lead to the death of dopaminergic neurons.

In this chapter, we describe the classical and the most useful animal models to model PD. Readers with minimal knowledge of PD will eventually find out the different possibilities offered by each of these models, and their strengths and limitations.

2. Neurotoxic models

2.1. 6-OHDA (2,4,5-trihydroxyphenethylamine)

The classic and more often used neurotoxic in animal models of PD is 6-OHDA [13, 14]. Most animals are sensitive to 6-OHDA intoxication, including monkeys, cats, dogs, and rats. The

rats were the more frequently used [15, 16]. Its effect was first described in the 1950s during the study of central nervous system; 6-OHDA caused a noradrenaline depletion for several months and a selective loss of noradrenergic terminals [17, 18] and was firstly isolated by Ungersted to lesion the nigrostriatal pathway in the rat decades ago [19].

Although 6-OHDA is structurally similar to DA (and noradrenaline), the presence of an additional hydroxyl group makes it toxic to dopaminergic neurons. Also, this compound does not cross the blood-brain barrier, and it makes necessary the direct injection in the brain, normally in subtantia nigra pars compacta, medium forebrain bundle, or striatum [17, 20, 21]. Lesion size depends on the amount of 6-OHDA, site of injection, and species. Typically, 6-OHDA is administered in a unilateral manner and its results are very attractive since the intact side can be used as control. Furthermore, even if there is success rate in ventricular administration [22], the bilateral administration normally leads to severe adipsia, aphagia, and also death [23, 24]. When administered intrastriatally, the 6-OHDA provokes a progressive and retrograde neuronal loss in SNpc and ventral tegmental area (VTA). Actually, in animals with full lesions (>90%) it is also observed the typical pattern seen in PD patients, with a greater loss in SNpc compared to VTA [21, 25]. Although 6-OHDA interacts with α-syn, it does not induce the formation of LB inclusions [17, 26]. The motor evaluation in these animal models is usually performed after the administration of drugs such as apomorphine which induces rotational behavior, but novel tests lacking the use of any drug have also been developed in rodents [27]. One use of this model is to ascertain whether the nigrostriatal degeneration is retrograde, i.e., tyrosine hydroxylase (TH) terminals die before the TH-neurons in SNpc as it happens in patients [21, 28] (**Figure 1**).

This model is a good model on the base that it can replicate parkinsonian features as DA depletion, nigral DA cell loss, and behavior deficits. Nevertheless, it does not affect other regions in the brain as olfactory bulbs, lower brainstem areas, or locus coeruleus.

2.2. MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine)

Even if the discovery of MPTP in 1982 due to an error in drug synthesis process could cause some mayhem in certain circles, for PD researchers it was an invaluable gift. Its toxicity was discovered after some young addicts developed idiopathic PD when they injected the compound intravenously. MPTP can be considered a gold standard for toxin-based animal models since it mimics some of the hallmarks of PD such as damage to the nigrostriatal DA pathway with a profound loss of DA in the striatum and SNpc, oxidative stress, reactive oxygen species, energy failure, and inflammation [29, 30]. However, MPTP does not induce the formation of LB, definitive characteristic of PD [31, 32]. Some studies have attempted to demonstrate the production of LB-like inclusions after MPTP administration, but those findings are not easy to replicate and make necessary to play with different dosing and timing schedules [33, 34].

MPTP is not a dopaminergic toxin, but its high lipophilia makes it to cross the blood-brain barrier after systemic administration. Once astrocytes enter the brain, they are metabolized to MPP+ by monoamine oxidase-B (MAO-B). MPP+ enters the dopaminergic neurons through the DA transporter (DAT), and once in the cytoplasm it binds to VMAT2 or it is stored in the

vesicles in the mitochondria, where it inhibits the complex I of the mitochondrial electron transport chain leading to neuronal death by oxidative stress [35–37]. Thus, in mice lacking DAT, MPTP is not toxic [38]. Since the storage vesicles have a limited capacity, MPP+ most likely pushes DA out into the intercellular space where it can be metabolized to a number of compounds some of which are toxic, such as DOPAL [39] and where it can be subjected to superoxide radical (5-cysteinyl-DA) and hydroxyl radical attack (6-OHDA) (**Figure 1**). Principally, MPTP is used in primates and mice, and it is still unknown why it is not toxic in rats [40, 41]. And in primates, the resemblance with human PD features goes beyond the loss of dopaminergic neurons in the SNpc. In these animals, it also causes a greater loss of DA in SNpc than in VTA or retrorubral field [42, 43]. The classic way of administration is intravenous and systematic [44]. Some researchers also use an alternative route and they inject unilaterally in the internal carotid. This technique presents the same benefits as described before but it's more difficult to perform [45]. In primates, traditionally, the animals have been treated with high doses of MPTP, and acute models were obtained. However, in the recent years, researchers have introduced new administration protocols in order to obtain more progressive models, which would mimic more exactly the pathology in PD patients. These progressive models would give a chance to study the compensatory mechanism which takes place before the onset of the symptoms [43, 46, 47]. Additionally, in primates treated with low doses of MPTP, a greater degeneration of dopaminergic nerve terminals has been observed in the putamen than in the caudate nucleus [43, 48]. Interestingly, in primates, there is a high variability in the animal's susceptibility to MPTP and normally older animals are the most susceptible ones [49]. Also, primates treated with MPTP usually respond well to anti-parkinsonian treatments such as L-DOPA or apomorphine, and they also develop dyskinesias after long-term treatment.

The MPTP model in primates can be used in order to study other features of the PD as the nonmotor symptoms, which have recently become a target for researchers since mice do not develop a level of impairment similar to the humans [50, 51]. In the electrophysiological field, this model has also contributed to many advances including deep brain stimulation, currently the major surgical method to alleviate PD symptoms in patients [52, 53]. In the present, MPTP is more often used in mice than monkeys, mainly because of economic and practical reasons. Mice allow researchers to understand better the molecular mechanisms involved in cell death, to explore the neuronal death process or other pathological effects of PD. One remarkable aspect of the research in mice is the possibility of working with genetically modified animals [54, 55]. In sum, MPTP can be considered as the standard bearer for toxin-based PD animal models.

2.3. Rotenone

Rotenone is the most intoxicating member of the rotenoid family and is typically found in tropical plants. It is both an herbicide and insecticide having a half-life of 3–5 days depending on light conditions and degrades quickly in soil and water [56]. The toxicity of rotenone comes from its high lipophilia, and it can easily cross the blood-brain barrier (**Figure 1**). It is mainly used in rats since, so far, the studies attempting to lesion in mice or monkeys have not

been successful [57, 58]. Recently, some studies have tested the toxicity of rotenone when administrated intragastric [59] or directly in the brain [60]. The administration of rotenone can be done via different routes. The most commonly used regime has typically been the systemic administration using osmotic pumps in rats, especially in Lewis rats which present a higher susceptibility to the toxic than other strains [61]. Oral administration is considered the least effective one [61, 62]. Intraperitoneal injections might induce behavioral and neurochemical deficits, and it also presents a high mortality [60]. In the case of intravenous administration, rotenone may lead to loss of nigrostriatal DA neurons and it is able to induce α-syn aggregation and LB formation, apart from other features such as oxidative stress or gastrointestinal problems [63]. It is the last aspect that makes this model so attractive, since it seems to replicate almost all of the hallmarks of PD [64]. Similar to what happens in PD, rotenone intoxication is associated with 35% reduction in serotonin, 26% in noradrenergic, and 29% in cholinergic neurons [65].

On the contrary, there is some controversy about the use of rotenone as a model of PD since in spite of the DA oxidation there is not much evidence of depletion of DA in the nigrostriatal system [66], and there are no well-documented cases of PD patients from rotenone intoxication. This makes the model not very advantageous compared to other toxic-based ones, such as 6-OHDA and MPTP.

2.4. Paraquat (N,N-dimethyl-4-4-4-bypiridinium)

Paraquat (PQ) is an herbicide that exhibits similar structure to MPP+, and this is the reason why it was suggested that it could have a parkinsonian toxic effect. However, so far, only 95 cases of PD patients linked to PQ have been reported [67] even if being widely used in agriculture. Typically, PQ exerts its deleterious effect through oxidative stress mediated by redox cycling and generating reactive oxygen species, more exactly, superoxide radical, hydrogen peroxide, and the hydroxyl radical, which in turn would lead to the damage of lipids, proteins, RNA, and DNA [68, 69]. The evidence of PQ toxicity in the nigrostriatal DA system is somehow ambiguous. Some studies carried out in mice have been able to demonstrate that systemic administration can reduce motor activity, and there is a dose-dependent loss of TH-positive striatal fibers and SNc neurons [70, 71]. In contrast, other researchers claimed that there are no PQ-induced changes after administration [72]. Interestingly, in a recent study, Rappold et al. [73] could evidence that when administered in high doses, PQ can employ the organic cationic transporter-3 (OCT-3) and the DAT becomes toxic to neurons in SNpc. They also suggest that PQ damages are caused by radicalized PQ and facilitated by glial cells, as it does MPP+. One of the most striking aspects of PQ with respect to PD is its ability to induce LB-like structures in dopaminergic neurons of the SNpc [74] mimicking the PD-like pathology. Nevertheless, how oxidative stress and cell death are linked because of PQ remains unknown, limiting the research to the study of the process of LB formation in dopaminergic neurons (**Figure 1**).

Additionally, PQ is not the only pesticide or agricultural chemical known to provoke damage in the dopaminergic system. Maneb (manganese ethylenebisdithiocarbamate) or ziram are other examples of compounds that when exposed to them have a greater risk of developing

PD [75, 76]. In any case, results from studies using pesticides give credence to the theory that environmental pesticides can cause PD [77, 78]. However, further studies are required to determine the precise involvement of these compounds in the etiology of PD.

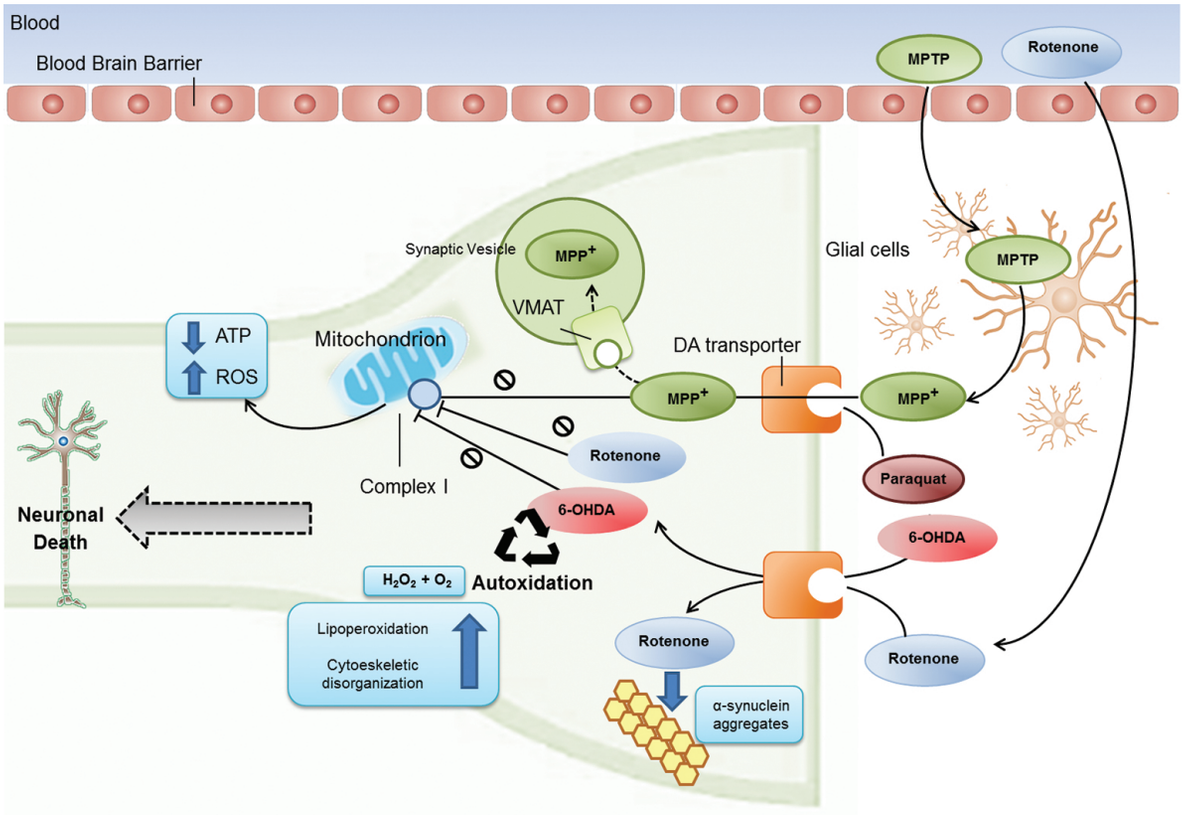

Figure 1. Pathogenesis of toxin-induced models. MPTP crosses the blood-brain barrier and is metabolized to 1-methyl-4-phenylpyridinium (MPP^+) by the enzyme monoamine oxidase B (MAO-B) in glial cells and then to the active toxic compound. MPP^+ is then taken up by dopamine transporter where it impairs mitochondrial respiration by inhibiting complex I of the electron transport chain, causing oxidative stress and activation of programmed cell death molecular pathways. Both paraquat and 6-hydroxydopamine (6-OHDA) easily cross cell membrane through the dopamine transporter and may also exert their toxicities, in part, by targeting mitochondria with the subsequent production of ROS and quinones causing the degeneration of the nigrostriatal dopaminergic neurons. Rotenone is extremely hydrophobic and penetrates easily the cellular membrane inducing the formation of α-synuclein aggregates and mitochondrial impairment with the subsequent production of ROS and quinones.

3. Genetic models

Although PD is mainly a sporadic disorder, about 10% of all PD cases are caused by genetic mutations [79]. Animal models of these mutations are important as they represent potential therapeutic targets. Having said that, the pathological and behavioral phenotypes of these genetic models are often quite different from the human condition [80]. For example, almost all of these genetic models failed to find significant loss of dopaminergic neurons, the main

pathological hallmark of PD [81–84]. Below, we describe different genetic models that reproduce the most known mutations observed in familial PD (**Figure 2**).

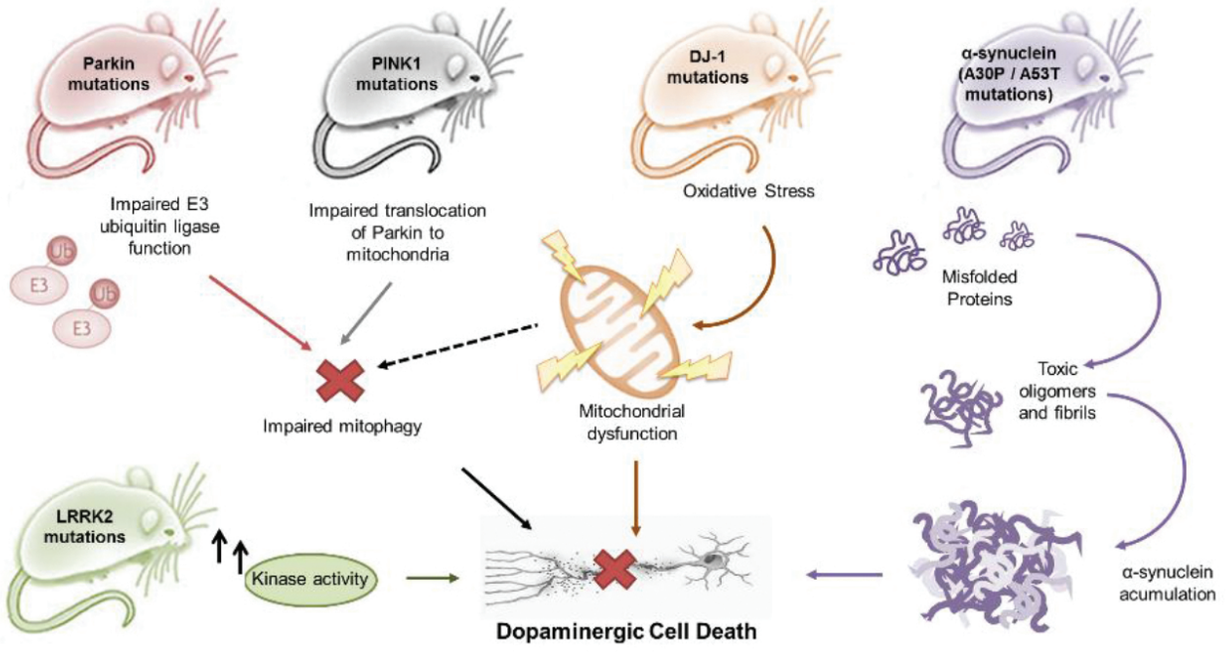

Figure 2. Genetic animal models in Parkinson disease (PD). Many genetic mouse models have been developed in order to understand PD pathogenesis and identify potential therapeutic targets. Genetic models are adjusted based on genetic mutations identified in the human disease. These genes are part of signaling pathways important for neuronal dopaminergic function. These models contribute to know mechanisms on disease onset or progression of PD or to understand the case and effect of these genetic mutations.

3.1. α-syn

SNCA (α-syn) was the first gene linked to a dominant-type, familial PD, called Park1 [85]. The duplication or triplication of α-syn is sufficient to cause PD, suggesting that the level of α-syn expression is a critical determinant of PD progression [86]. Three missense mutations of α-syn, encoding the substitutions A30P, A53T, and E46K, have been identified in familial PD so far [87, 88]. The pathological accumulation of misfolded α-syn plays an essential role in the pathogenesis of PD since α-syn is the main component of LB. While LBs are found principally in nigral neurons of PD patients, they are also found in other brain regions such as locus coeruleus, nucleus basalis of Meynert, hypothalamus, cerebral cortex, and cranial nerve motor nuclei [89]. Numerous animal models have been developed trying to replicate α-syn neurodegeneration and propagation. These include transgenic mice (KO and overexpression), grafting models, intracerebral protein injections, or virally induced expression of α-syn. The main handicap of these models is that no significant nigrostriatal degeneration has been found in most of them, although some of these mice showed decreased striatal levels of TH or DA and behavioral impairments [80].

In general, the models of α-syn overexpression in mice produced some behavioral alterations in both the A30P and A53T mice [90–92]. Also, depending on the promoter, some models showed loss of terminals and DA in the striatum [93–98] although almost of them failed to reproduce the dopaminergic cell loss characteristic of PD [2, 94, 99–101]. Only the TH promoter led to dopaminergic cell loss in a few studies [102, 103]. Janezic et al. [104] generated bacterial artificial chromosome (BAC) transgenic mice (SNCA-OVX) that express WT human α-syn and display an age-dependent loss of SNc DA neurons preceded by early deficits in DA release from terminals in the dorsal striatum, protein aggregation, and reduced firing of SNc DA neurons [104]. Regarding viral vectors injections, largely lentiviruses and adeno-associated viruses (AAVs), have been used to drive exogenous α-syn in mice, rats, and primates [105–109]. In this case, viral vector-mediated α-syn models display α-syn pathology and clear dopaminergic neurodegeneration. The injection of human mutant α-syn by AAVs into the SNpc of rats induces a progressive, age-dependent loss of DA neurons, motor impairment, α-syn cytoplasmic inclusions, and degenerative changes in striatal axons both in rats [110, 111] and mice [109, 112]. In the last years, the suggested prion-like behavior of α-syn has been examined in animal models of PD. These models not only explore the pathology and spreading of α-syn but the cell-to-cell transfer. Importantly, to date, numerous studies have demonstrated that α-syn may be transmissible from cell to cell in animal models in different ways using different approaches [33, 113–120].

Thus, despite the limitations of these α-syn models, some of them could be useful to elucidate the role of a-α-syn in PD and the suggested prion-like mechanism of propagation of this protein [121].

3.2. LRKK2

Mutations in LRRK2 are known to cause a late-onset autosomal dominant form of PD [122]. The most frequent mutations are the G2019S and the R1441C [123]. Many different LRRK2 rodent models have been developed with different approaches but as it happens with α-syn, although they show α-syn or ubiquitin accumulation, progressive motor impairments, and slight reduction of striatal DA, they do not display functional disruption of the nigrostriatal dopaminergic neurons [82, 124–128]. Similarly, overexpression of G2019S or R1441C LRRK2 leads to none or slight loss of dopaminergic neurons in the SNpc and no alteration in striatal DA levels or locomotor activity in both mice and rats [129–131].

BAC transgenic mice expressing mutated LRKK2 have also been developed showing no nigrostriatal degeneration [132–134]. On the contrary, a rat LRRK2 model with neuron-specific, adenoviral mediated expression of LRRK2 G2019S in the nigrostriatal system has been produced, which develops a progressive degeneration of nigral dopaminergic neurons [135]. Additionally, using viral vector-based models, Lee and colleagues [28] reported that the expression of G2019S LRRK2 resulted in a 50% neuronal loss in the ipsilateral SNc associated with reduced striatal dopaminergic fibers [136]. In summary, we can conclude that the transgenic LRRK2 animal models are not a useful model for studying the pathology of PD.

3.3. Pink1 and Parkin

Homozygous mutations in the Parkin and PINK1 genes were discovered in families with autosomal recessive PD [137]. In fact, parkin mutations are the most common cause of autosomal recessive PD. Likewise, mutations in PINK1 are the second most common. Despite this early onset, patients with these mutations have an indistinguishable phenotype from that of sporadic patients. Many PINK1 and parkin KO mice have been generated, and the phenotypes of these mice are very similar. PINK1 and Parkin KO mice have an age-dependent, moderate reduction in striatal DA levels accompanied by low locomotor activity, but do not exhibit major abnormalities in the DA neurons or striatal DA levels, and they do not show LB formation either [81, 138–145]. A new approach consisting in overexpression of T240R-parkin and of human WT parkin in rats leads to progressive and dose-dependent DA cell death [146]. Noteworthy, the Parkin-Q311X-DAT-BAC mice exhibit multiple late onsets and progressive hypokinetic motor deficits, age-dependent DA neuron degeneration in the SNc, and a significant reduction in striatal DA and dopaminergic terminals in the striatum [147]. Overall, PINK1 and Parkin models do not produce functional disruption of the nigrostriatal pathway or other PD-related pathology, thus their usefulness is questionable.

3.4. DJ-1

Missense DJ-1 mutations are linked to autosomal recessive and early-onset PD. DJ-1 KO mice showed no loss of SNpc dopaminergic neurons but reduced striatal DA release and decreased locomotor activity [148, 149]. Recently, a new DJ-1 KO mouse, backcrossed on a C57/BL6 background, displayed an early-onset unilateral loss of DA neurons in the SNpc, progressing to bilateral degeneration with aging. Also, these mice exhibit age-dependent bilateral degeneration in the locus coeruleus and mild motor behavioral deficits [150]. If confirmed, this model could provide a possible tool to study the progression of PD.

4. Concluding remarks

Our current understanding of PD pathology greatly benefited from the use of animal models. However, despite these accomplishments, current PD animal models still have to be improved a lot. It seems difficult that a single model can fully recapitulate the complexity of the human PD in the short term. Because there is no perfect model to date, it is very important to choose the correct animal model for each experiment. By providing an overview of the different animal models available to modeling PD, readers would find that there are a lot of options addressing a specific experimental need.

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