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Animal Models Of Parkinson's Disease: A Review

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Abstract

Disease modeling in non-human subjects is an essential part of any clinical research. To gain proper understanding of the etiology and pathophysiology of any disease, experimental models are required to replicate the disease process. Due to the huge diversity in pathophysiology and prognosis in different diseases, animal modeling is customized and specific accordingly. As in other neurodegenerative diseases, Parkinson's disease is a progressive disorder coupled with varying forms of physical and mental disabilities.

Keywords: Animal model, dopaminergic neurons, Parkinson's disease

Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder that affects motor functions of patients while causing several non-motor symptoms ranging from cognitive impairment to gastrointestinal issues. Its pathological hallmarks include neurodegeneration of dopaminergic neurons in the substantia nigra (SN) pars compacta and the presence of pathogenic neuronal alpha-synuclein (asyn) aggregates, also known as Lewy bodies and Lewy neurites. The brain pathology however, is not limited to the SN and asyn accumulates in many other areas throughout the brain. Remarkably, asyn accumulation does not occur simultaneously in these brain regions. The groundbreaking findings of Braak and colleagues have described that asyn pathology is dynamic and spreads during the course of the disease from one brain region to another in a stereotypical pattern. Based on these extensive post-mortem studies investigating brains from PD patients and control subjects, asyn pathology first appears in the olfactory bulb (OB) and the dorsal motor nucleus of the vagus nerve (DMV) then spreads towards the pontine tegmentum specifically affecting neurons in the locus coeruleus (LC) and lower raphe nuclei and thereafter reaches the SN and amygdala. Later on, during the final stages of the disease the pathology reaches to cortical areas. Importantly, these predilection sites that are affected by Lewy pathology throughout the disease progression are synaptically connected to each other. The spread of these asyn aggregates through synaptically coupled networks is likely to be a crucial pathogenic factor in PD and has led to the hypothesis that the disease may be initiated in the nerve terminals of the enteric nervous system (ENS), after which pathology spreads via parasympathetic and sympathetic connections to the DMV and intermediolateral cell columns of the spinal cord (IML), respectively. This is often referred to as Braak's gut-first hypothesis and in contrast to what has been believed for over a century, i.e. PD is not just a brain disease but a systemic disease. Indeed, several evidence has supported this view and illustrated that Lewy pathology and neurodegeneration not only occurs in the central nervous system (CNS), but in multiple peripheral organs as well.

The classical motor symptoms of Parkinson's disease (PD) (akinesia, bradykinesia, rigidity, tremor and postural abnormalities) are associated with the loss of nigral dopaminergic cells and a decline in caudate-putamen dopamine content that led to the introduction of dopamine replacement therapy. As a consequence,

there has been a key role for animal models of PD in devising novel pharmacological approaches to therapy, in developing new treatment strategies and in understanding the nature of the pathogenic processes involved in neuronal loss. The discovery that administration of reserpine or haloperidol to rodents and rabbits led to a transient parkinsonian-like state was rapidly followed by the key discovery that these symptoms were reversed by the administration of L-DOPA. This opened the door to an era where animal models of PD were used to investigate the basis of symptomatic treatment. More success followed when it was discovered that the unilateral stereotaxic injection of 6-hydroxydopamine (6-OHDA) in to the substantia nigra or the medial forebrain bundle caused the destruction of the nigro-striatal pathway and so loss of dopaminergic input to the striatum. This led to the introduction of the 'circling' rat model of PD that dominated research for many years and started the era of toxin use for producing animal models of PD. Through these advances came novel approaches to treatment such as the introduction of peripherally acting decarboxylase inhibitors, carbidopa and benserazide, that limited the peripheral side effects of L-DOPA and allowed a lowering of dose as more drug entered the brain. More recently came the introduction of selective monoamine oxidase-B (MAO-B) inhibitors, selegiline and rasagiline, that slow the degradation of dopamine formed from L-DOPA and prolong its duration of effect and latterly catechol-*O*-methyl-transferase (COMT) inhibitors, entacapone and tolcapone, that stop either the peripheral or central metabolism of L-DOPA to 3-*O*methyldopa so again prolonging its duration of effect and further increasing brain penetration of the drug. Parkinson's disease (PD) is a chronic and progressive movement disorder and the second most common neurodegenerative disease. Although many studies have been conducted, there is an unmet clinical need to develop new treatments because, currently, only symptomatic therapies are available. To achieve this goal, clarification of the pathology is required. Attempts have been made to emulate human PD and various animal models have been developed over the decades. Neurotoxin models have been commonly used for PD research. Recently, advances in transgenic technology have enabled the development of genetic models that help to identify new approaches in PD research. However, PD animal model trends have not been investigated. Revealing the trends for PD research will be valuable for increasing our understanding of the positive and negative aspects of each model.

Animal models of PD

In contrast with the situation for many other neurodegenerative diseases, PD benefits from of a wide range of available animal models, the different classes of which (pharmacological, toxin, genetic and α-synuclein) are briefly summarized below. We have focused here on the mammalian models; readers interested in the various non-mammalian models such as those in *Drosophilamelanogaster* or *Caenorhabditis elegans* are directed towards existing reviews The pharmacological models of PD were the first ones developed and contributed to an extent in the discovery of symptomatic drugs, such as the gold standard, levodopa (L-DOPA). Reserpine, an inhibitor of the vesicular monoamine transporters (VMATs), is administered peripherally. When given in a single dose, reserpine induces depletion of all monoamines including noradrenaline and serotonin alongside the critical one, dopamine which renders rodents severely, but transiently, akinetic. More recently, repeated low-dose administration of reserpine has been used to produce a progressive model with additional relevant characteristics for interrogation. It will be interesting to see how well-replicated and widely adopted this particular model becomes in the future. A second, less commonly used pharmacological model is induced by peripheral administration of haloperidol, an antagonist of dopamine D2 and, to a lesser extent, D1 receptors. Post-treatment, haloperidol induces a transient catalepsy with animals unable to right their posture. Although transient, the pharmacological models are certainly the easiest to generate as they require no specialist stereotaxic equipment, surgical skills, or adapted housing for example, unlike most of the models outlined below. For more permanent effects, toxin models have been developed. These toxins can be broadly subcategorised into neurotoxins (6-hydroxydopamine; 6-OHDA and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPTP), pesticides (rotenone, paraquat and permethrin) and endotoxins (lipopolysaccharide; LPS). The mechanism for how each of these toxins cause their degenerative effects is reviewed in detail elsewhere. In brief, when administered intracranially into the nigrostriatal tract (for 6-OHDA and LPS) or systemically (for MPTP, rotenone, paraquat and permethrin), theymostly cause disruption ofmitochondrial complexes involved in oxidative phosphorylation, alongside an increase in reactive oxidative species and ultimately nigral cell death. LPS, on the other hand, is thought to induce a PD-like phenotype through enhancingmicrogliosis and local iron and ferritin levels at the site of injection. Typically, these toxin

models induce a rapid loss of dopaminergic cells that gives rise to motor dysfunction and further behavioural deficits.

Animal models of brain-first and body-first Parkinson's disease (Nathalie Van Den Berge and Ayse Ulusoy)

Alpha-synuclein aggregates are the hallmark pathology of Parkinson's disease, which can propagate in a stereotypical pattern along the brain-body axis. Parkinson's disease patients not only display heterogeneous symptoms but also show variable patterns of alpha-synuclein pathology and affected neuronal systems during the disease course, complicating early and accurate diagnosis. Emerging data from post-mortem and imaging studies strongly suggest that disease heterogeneity could, at least in part, be explained by variable disease onset site, i.e. brain or body. This has led to the recently hypothesized formulation of two Parkinson's disease-subtypes, a body-first subtype where pathogenic alpha-synuclein arises in the body and spreads to the brain, and a brain-first subtype where pathogenic alpha-synuclein arises in the brain and spreads to the body. From a preclinical perspective, several animal models have been adapted or developed to reproduce Parkinson's disease-like pathology in the brain or periphery aiming to address the site of disease onset. Here, we review the current rodent and primate models that aim to reproduce Parkinson's disease pathology development and spreading in the brain and/or body and discuss the value and shortcomings of these models for the development of potential future applications in clinical trials and personalized medicine.

Animal models of Parkinson's disease: a source of novel treatments and clues to the cause of the disease (Susan Duty and Peter Jenner)

Animal models of Parkinson's disease (PD) have proved highly effective in the discovery of novel treatments for motor symptoms of PD and in the search for clues to the underlying cause of the illness. Models based on specific pathogenic mechanisms may subsequently lead to the development of neuroprotective agents for PD that stop or slow disease progression. The array of available rodent models is large and ranges from acute pharmacological models, such as the reserpine- or haloperidol-treated rats that display one or more parkinsonian signs, to models exhibiting destruction of the dopaminergic nigro-striatal pathway, such as the classical 6 hydroxydopamine (6-OHDA) rat and 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP) mouse models. All of these have provided test beds in which new molecules for treating the motor symptoms of PD can be assessed. In addition, the emergence of abnormal involuntary movements (AIMs) with repeated treatment of 6-OHDA-lesioned rats with L-DOPA has allowed for examination of the mechanisms responsible for treatmentrelated dyskinesia in PD, and the detection of molecules able to prevent or reverse their appearance. Other toxin-based models of nigro-striatal tract degeneration include the systemic administration of the pesticides rotenone and paraquat, but whilst providing clues to disease pathogenesis, these are not so commonly used for drug development. The MPTP-treated primate model of PD, which closely mimics the clinical features of PD and in which all currently used anti-parkinsonian medications have been shown to be effective, is undoubtedly the most clinically-relevant of all available models. The MPTP treated primate develops clear dyskinesia when repeatedly exposed to L-DOPA, and these parkinsonian animals have shown responses to novel dopaminergic agents that are highly predictive of their effect in man. Whether non-dopaminergic drugs show the same degree of predictability of response is a matter of debate. As our understanding of the pathogenesis of PD has improved, so new rodent models produced by agents mimicking these mechanisms, including proteasome inhibitors such as PSI, lactacystin and epoximycin or inflammogens like lipopolysaccharide (LPS) have been developed. A further generation of models aimed at mimicking the genetic causes of PD has also sprung up. Whilst these newer models have provided further clues to the disease pathology, they have so far been less commonly used for drug development. There is little doubt that the availability of experimental animal models of PD has dramatically altered dopaminergic drug treatment of the illness and the prevention and reversal of drug-related side effects that emerge with disease progression and chronic medication. However, so far, we have made little progress in moving into other pharmacological areas for the treatment of PD, and we have not developed models that reflect the progressive nature of the illness and its complexity in terms of the extent of pathology and biochemical change. Only when this occurs are we likely to make progress in developing agents to stop or slow the disease progression. The overarching question that draws all of these models together in the quest for better drug treatments for PD is how well do they

recapitulate the human condition and how predictive are they of successful translation of drugs into the clinic? This article aims to clarify the current position and highlight the strengths and weaknesses of available models.

Animal Models for Parkinson's Disease Research:Trends in the 2000s (Kyohei Kin *et al.,)*

Parkinson's disease (PD) is a chronic and progressive movement disorder and the second most common neurodegenerative disease. Although many studies have been conducted, there is an unmet clinical need to develop new treatments because, currently, only symptomatic therapies are available. To achieve this goal, clarification of the pathology is required. Attempts have been made to emulate human PD and various animal models have been developed over the decades. Neurotoxin models have been commonly used for PD research. Recently, advances in transgenic technology have enabled the development of genetic models that help to identify new approaches in PD research. However, PD animal model trends have not been investigated. Revealing the trends for PD research will be valuable for increasing our understanding of the positive and negative aspects of each model. In this article, we clarified the trends for animal models that were used to research PD in the 2000s, and we discussed each model based on these trends.

Animal models of Parkinson's disease: a guide to selecting the optimal model for your research (Joana Lama *et al.,)*

Parkinson's disease (PD) is a complex, multisystem disorder characterised by α-synuclein (SNCA) pathology, degeneration of nigrostriatal dopaminergic neurons, multifactorial pathogenetic mechanisms and expression of a plethora of motor and non-motor symptoms. Animalmodels of PD have already been instructive in helping us unravel some of these aspects.
However, much remains to be discovered, requiring continued interrogation by the research community. In contrast with the situation for many neurological disorders, PD benefits from of a wide range of available animalmodels (pharmacological, toxin, genetic and α-synuclein) but this makes selection of the optimal one for a given study difficult. This is especially so when a study demands a model that displays a specific combination of features. While many excellent reviews of animalmodels already exist, this review takes a different approach with the intention of more readily informing this decision-making process. We have considered each feature of PD in turn – aetiology, pathology, pathogenesis, motor dysfunctions and non-motor symptoms (NMS) – highlighting those animal models that replicate each.

Animal models of Parkinson's disease: bridging the gap between disease hallmarks and research questions (Axelle Dovonou *et al.,*)

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms. More than 200 years after its first clinical description, PD remains a serious affliction that affects a growing proportion of the population. Prevailing treatments only alleviate symptoms; there is still neither a cure that targets the neurodegenerative processes nor therapies that modify the course of the disease. Over the past decades, several animal models have been developed to study PD. Although no model precisely recapitulates the pathology, they still provide valuable information that contributes to our understanding of the disease and the limitations of our treatment options. This review comprehensively summarizes the different animal models available for Parkinson's research, with a focus on those induced by drugs, neurotoxins, pesticides, genetic alterations, α-synuclein inoculation, and viral vector injections. We highlight their characteristics and ability to reproduce PD-like phenotypes. It is essential to realize that the strengths and weaknesses of each model and the induction technique at our disposal are determined by the research question being asked. Our review, therefore, seeks to better aid researchers by ensuring a concrete discernment of classical and novel animal models in PD research.

Animal models (Fabio Blandini and Marie-Therese Armentero)

Animal models of Parkinson's disease (PD) have been widely used in the past four decades to investigate the pathogenesis and pathophysiology of this neurodegenerative disorder. These models have been classically based on the systemic or local (intracerebral) administration of neutoxins that are able to replicate most of the pathological and phenotypic features of PD in mammals (i.e. rodents or primates). In the last

decade, the advent of the 'genetic era' of PD has provided a phenomenal enrichment of the research possibilities in this field, with the development of various mammalian (mice and, more recently, rats) and non-mammalian transgenic models that replicate most of the disease-causing mutations identified for monogenic forms of familial PD. Both toxic and transgenic classes of animal PD models have their own specificities and limitations, which must be carefully taken into consideration when choosing the model to be used. If a substantial and reproducible nigrostriatal lesion is required (e.g. for testing therapeutic interventions aimed at counteracting PD-related cell death), a classic toxic
model such as one based on the administration of 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine or 6-hydroxydopamine will adequately serve the purpose. On the other hand, if selected molecular mechanisms of PD pathogenesis must be investigated, transgenic models will offer invaluable insights. Therefore, until the 'perfect' model is developed, indications to use one model or another will depend on the specific objectives that are being pursued.

Discussion and Conclusions

There is little doubt that the availability of experimental animal models of PD has dramatically altered dopaminergic drug treatment of the motor signs of the illness and in the prevention and reversal of drug related side effects that emerge with disease progression. However, so far, we have made little progress in moving in to other pharmacological areas for the treatment of PD, and we have not developed models that reflect the progressive nature of the illness and its complexity in terms of the extent of pathology and biochemical change. Only when this occurs are we likely to make progress in developing the next generation of drugs for PD that aim to stop or slow the disease progression.

Many methods have been developed and various animal species are used for PD animal models. Rodent models made using neurotoxin are most commonly used as PD animal models, and genetic models have been increasing in popularity. We believe that almost every PD model is essential for PD research as long as the appropriate model is selected for the hypothesis. Because it is impossible to replicate human PD completely in animals, we should keep paying attention to the validity of the animal models and the results from the experiments with these animal models. It is clear that researchers in the PD field have a wide array of animal models at their disposal and that many of these recapitulate multiple features of the disease from pathology and pathogenesis to the motor and non-motor symptoms. However, this extensive choice can make selecting the model for a given study a daunting prospect, especially so for one that aims to address multiple aspects of the disease simultaneously.

Several animal models have been developed to understand the pathogenesis and test new drug candidates against PD. However, PD is a highly heterogeneous disease involving several factors and pathways that may differ among clinical cases. Therefore, none of the existing and future models will replicate the entire spectrum of clinical features listed in PD. In this review, we tried to summarize the most relevant PD animal models, their respective advantages and disadvantages, as well as their ability to reproduce the main hallmarks of PD.

The choice of the animal model must be based on the PD features addressed by the question the experimenter seeks to answer. Neurotoxin-induced animal models remain popular due to their cost-effectiveness in generating a PD-like phenotype in a relatively short time span. Thus, they are commonly used in drug validation for symptomatic treatment of PD or cell replacement therapy. On the other hand, to investigate the function of PDlinked genes in disease development, transgenic models should be considered. Other questions concerning the targeting of α-syn pathology can also be answered in animal models injected with PFFs or viral vectors encoding *SNCA* gene copies. In the absence of a suitable model fully recapitulating the targeted PD features of interest, a possible solution could be to complement the phenotypes by combining some of the listed models. The selection of animal species is equally as important. Although the translational results to humans are valuable in mammalian models, the use of rodents and primates for drug or gene screening is untenable. *C. elegans* and *Drosophila* could be considered to identify novel neuroprotective targets. However, the simplicity and lack of similarity with humans are limitations. Moreover, research in PD should not be limited to the use of *in vivo* models. Although animals offer a better pre-clinical prediction of a drug effect, *in vitro* models could provide complementary information on the underlying molecular mechanisms. Still, most *in vitro*-based models cannot reproduce the non-cell autonomous impact of the complex cell network in the brain. The near future could shed light on the use of human brain organoids to perform drug or gene

screenings, although additional characterization of these emerging models will be required The availability of an experimental model mimicking all the major pathological and phenotypic features of PD is a crucial need that remains to be addressed. Such a tool would be instrumental for a full understanding of PD pathogenesis, which would lead to the identification of disease-modifying therapies. Various toxic and transgenic models of PD are currently available, all with significant advantages and disadvantages. If we consider toxic models, substantial nigrostriatal degeneration is generally obtained, with good replication of PD motor symptoms (particularly in MPTP-treated monkeys), although no consistent

LB-like formation is detected, with the possible exception of rotenone. On the other hand, transgenic models offer astonishing insights into selected molecular aspects of PD pathogenesis, particularly for the familial forms, and LB-like inclusions can be observed, at least in a-synuclein over expressing animals. However, the absence of consistent neuronal damage in the nigrostriatal pathway remains a major limitation for these models. Thus, until a 'perfect' model is developed, any suitable research strategy will rely on the accurate selection of the model to be used based on the specific research needs. For example, if a neuroprotective treatment must be tested, a model granting a reproducible, toxin-induced nigrostriatal lesion will be used. By contrast, if the role of selected proteins involved in PD pathogenesis is to be investigated, then a specific transgenic model will be the right choice.

References

1. Nathalie Van Den Berge and Ayse Ulusoy.(2022). Animal models of brain-first and body-first Parkinson's disease. Neurobiology of Disease 163-105599
2. Susan Duty1 and Peter Jenner. (2010). Animal models of Parkinson's disease: a source of novel treatments and clues to the cause of the disease. British Journal of Pharmacology 164 1357–1391
3. Kyohei Kin , Takao Yasuhara, Masahiro Kameda and Isao Date. (2019). Int. J. Mol. Sci. 2019, 20, 5402; doi:10.3390/ijms20215402
4. Joana Lama, Yazead Buhidma, Edward J.R. Fletcher and Susan Duty. (2021). Animal models of Parkinson's disease: a guide to selecting the optimal model for your research. *Neuronal Signaling* (2021) 5 NS20210026
5. Axelle Dovonou1†, Cyril Bolduc1, Victoria Soto Linan1, Charles Gora, Modesto R. Peralta and Martin Levesque. (2023). Animal models of Parkinson's disease: bridging the gap between disease hallmarks and research questions. *Translational Neurodegeneration 12:36*
6. Fabio Blandini and Marie-Therese Armentero. (2011). Animal models of Parkinson's disease. FEBS Journal 279-1156–1166
7. Langston JW, Ballard P, Tetrud JW & Irwin I (1983) Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science 219, 979–980.
8. Fornai F, Lenzi P, Ferrucci M, Lazzeri G, di Poggio AB, Natale G, Busceti CL, Biagioni F, Giusiani M, Ruggieri S et al. (2005) Occurrence of neuronal inclusions combined with increased nigral expression of alpha-synuclein within dopaminergic neurons following treatment with amphetamine derivatives in mice. Brain Res Bull 65, 405–413.
9. Shimoji M, Zhang L, Mandir AS, Dawson VL & Dawson TM (2005) Absence of inclusion body formation in the MPTP mouse model of Parkinson's disease. Brain Res Mol Brain Res 134, 103–108.
10. Alvarez-Fischer D, Guerreiro S, Hunot S, Saurini F, Marien M, Sokoloff P, Hirsch EC, Hartmann A & Michel PP (2008) Modelling Parkinson-like neurodegeneration via osmotic minipump delivery of MPTP and probenecid. J Neurochem 107, 701–711.
11. Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV & Greenamyre JT (2000) Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nat Neurosci 3, 1301–1306.
12. Fei Q, McCormack AL, Di Monte DA & Ethell DW (2008) Paraquat neurotoxicity is mediated by a Bakdependent mechanism. J Biol Chem 283, 3357–3364.
13. Manning-Bog AB, McCormack AL, Li J, Uversky VN, Fink AL & Di Monte DA (2002) The herbicide paraquat causes up-regulation and aggregation of alphasynuclein in mice: paraquat and alpha-synuclein. J Biol Chem 277, 1641–1644.
14. Thiruchelvam M, Brockel BJ, Richfield EK, Baggs RB & Cory-Slechta DA (2000) Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease? Brain Res 873, 225–234.

15. Ungerstedt U, Ljungberg T & Steg G (1974) Behavioral, physiological, and neurochemical changes after 6-hydroxydopamine-induced degeneration of the nigrostriatal dopamine neurons. Adv Neurol 5, 421–426.
16. Sauer H & Oertel WH (1994) Progressive degeneration of nigrostriatal dopamine neurons following intrastriatal terminal lesions with 6-hydroxydopamine: a combined retrograde tracing and immunocytochemical study in the rat. Neuroscience 59, 401–415.
17. Blandini F, Levandis G, Bazzini E, Nappi G & Armentero MT (2007) Time-course of nigrostriatal damage, basal ganglia metabolic changes and behavioural alterations following intrastriatal injection of 6-hydroxydopamine in the rat: new clues from an old model. Eur J Neurosci 25, 397–405.
18. Hunter RL, Cheng B, Choi DY, Liu M, Liu S, Cass WA & Bing G (2009) Intrastriatal lipopolysaccharide injection induces parkinsonism in C57/B6 mice. J Neurosci Res 87, 1913–1921.
19. Alberio T, Lopiano L & Fasano M (2012) Cellular models to investigate biochemical pathways in Parkinson's disease. FEBS J 279, 1146–1155.
20. Chesselet MF (2008) In vivo alpha-synuclein overexpression in rodents: a useful model of Parkinson's disease? Exp Neurol 209, 22–27.
21. Lam HA, Wu N, Cely I, Kelly RL, Hean S, Richter F, Magen I, Cepeda C, Ackerson LC, Walwyn W et al. (2011) Elevated tonic extracellular dopamine concentration and altered dopamine modulation of synaptic activity precede dopamine loss in the striatum of mice overexpressing human alpha-synuclein. J Neurosci Res 89, 1091–1102.
22. Li X, Patel JC, Wang J, Avshalumov MV, Nicholson C, Buxbaum JD, Elder GA, Rice ME & Yue Z (2010) Enhanced striatal dopamine transmission and motor performance with LRRK2 overexpression in mice is eliminated by familial Parkinson's disease mutation G2019S. J Neurosci 30, 1788–1797.
23. Kumar A & Cookson MR (2011) Role of LRRK2 kinase dysfunction in Parkinson disease. Expert Rev Mol Med 13, e20.
24. Qing H, Wong W, McGeer EG & McGeer PL (2009) Lrrk2 phosphorylates alpha synuclein at serine 129: Parkinson disease implications. Biochem Biophys ResCommun 387, 149–152.
25. Gautier CA, Kitada T & Shen J (2008) Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. Proc Natl Acad Sci USA 105, 11364–11369.
26. Gispert S, Ricciardi F, Kurz A, Azizov M, Hoepken HH, Becker D, Voos W, Leuner K, Muller WE, Kudin AP et al. (2009) Parkinson phenotype in aged PINK1- deficient mice is accompanied by progressive mitochondrial dysfunction in absence of neurodegeneration. PLoS One 4, e5777.
27. Lu XH, Fleming SM, Meurers B, Ackerson LC, Mortazavi F, Lo V, Hernandez D, Sulzer D, Jackson GR, Maidment NT et al. (2009) Bacterial artificial chromosome transgenic mice expressing a truncated mutant parkin exhibit age-dependent hypokinetic motor deficits, dopaminergic neuron degeneration, and accumulation of proteinase K-resistant alpha-synuclein. J Neurosci 29, 1962–1976.
28. Paterna JC, Leng A, Weber E, Feldon J & Bueler H (2007) DJ-1 and Parkin modulate dopamine-dependent behavior and inhibit MPTP-induced nigral dopamine neuron loss in mice. Mol Ther 15, 698–704.