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Animal models of early-stage Parkinson's disease and acute dopamine deficiency to study compensatory neurodegenerative mechanisms

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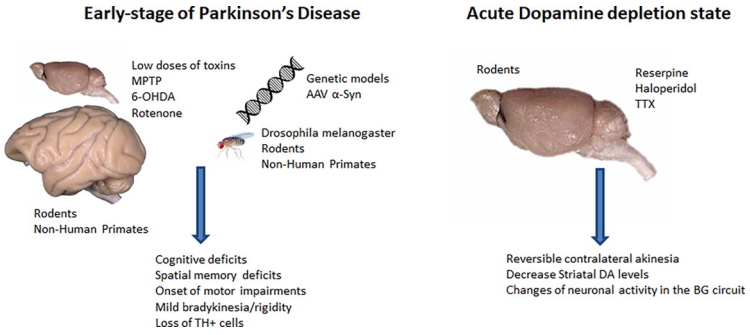
GRAPHICAL ABSTRACT



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ABSTRACT

Parkinson's disease is a common neurodegenerative disease characterized by a widely variety of motor and non-motor symptoms. While the motor deficits are only visible following a severe dopamine depletion, neurodegenerative process and some non-motor symptoms are manifested years before the motor deficits. Importantly, chronic degeneration of dopaminergic neurons leads to the development of compensatory mechanisms that play roles in the progression of the disease and the response to anti-parkinsonian therapies. The identification of these mechanisms will be of great importance for improving our understanding of factors with important contributions to the disease course and the underlying adaptive process. To date, most of the data obtained from animal models reflect the late, chronic, dopamine-depleted states, when compensatory mechanisms have already been established. Thus, adequate animal models with which researchers are able to dissect early- and late-phase mechanisms are necessary.

Here, we reviewed the literature related to animal models of early-stage PD and pharmacological treatments capable of inducing acute dopamine impairments and/or depletion, such as reserpine, haloperidol and tetrodotoxin. We highlighted the advantages, limitations and the future prospective uses of these models, as well as their applications in the identification of novel agents for treating this neurological disorder.

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1. Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disease (Mhyre et al., 2012). Although 200 years have passed since James Parkinson first described the disease as *Shaking Palsy* in 1817 (Parkinson, 2002), the mechanisms of its pathogenesis have not been completely elucidated. The cardinal features of PD include tremor, rigidity and bradykinesia. The neuropathological hallmarks of the PD include i) the progressive neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), ii) a lack of dopamine (DA) (Ehringer and Hornykiewicz, 1960) and iii) the contextual formation of Lewy bodies (LB), which are mainly composed of α-synuclein (α-SYN; Spillantini et al., 1998; Esposito et al., 2007a). According to the multiple hits hypothesis (Sulzer, 2007), these pathological changes appear to be caused by a chain of events, including oxidation (Di Giovanni et al., 2012; Di Matteo et al., 2009; Pierucci et al., 2011) and inflammation (Esposito et al., 2007b), leading to the emergence of characteristic motor and non-motor symptoms rather than a single symptom. Interestingly, several lines of evidence suggest that these events occur even years before motor symptoms are manifested and the patient is diagnosed (Galati and Di Giovanni, 2010). Among non-motor deficits, the REM sleep behaviour disorder (RBD) might appear even 25 years before the motor symptoms (Claassen et al., 2010). Therefore, the pre-motor phase of the disease lasts several years, during which the irreversible DA depletion within different brain areas leads to several neuronal adaptations and the appearance of a constellation of prodromal symptoms (Caverzasio et al., 2018).

Currently, a cure for PD is not available, and therapies are only meant to control motor symptoms by reversing the DA deficiency. For instance, the gold standard PD treatment is still L-dihydroxyphenylalanine (L-DOPA), a precursor of DA, which was introduced in the 1960s (Birkmayer and Hornykiewicz, 1961). However, its effects have been limited by the emergence of L-DOPA-induced dyskinesia (LID), a motor side effect that often worsens the patients' quality of life (Pèchevis et al., 2005).

Although, deep brain stimulation (DBS) of specific brain areas, such as the subthalamic nucleus (STN) or the globus pallidus (GP), is able to reduce LID and motor fluctuations observed in response to DA therapies, these treatments are not effective against axial motor problems or cognitive deficits (Galati and Stefani, 2015).

The degeneration underlying the histological changes leads to important changes at level of neuronal activity at different sites in the basal ganglia (BG) circuit, the main central network involved in PD pathological mechanisms. For example, aberrant oscillatory activity in β band frequencies is a peculiar hallmark of PD that has been observed in different locations in the BG circuit in both patients with PD and animal models (Alavi et al., 2013; Brown, 2006; Little and Brown, 2014). The β band is strongly associated with modulations in motor function, and alterations in its activity in subjects with PD are attenuated by L-DOPA therapy (George et al., 2013).

Another frequency band associated with movement modulation is the γ band, a frequency that was postulated to be associated with the development of LID in a PD animal model (Salvadè et al., 2016). In addition to their association with dyskinesia, γ oscillations are decrease during treatment with anti-PD therapies, similar to the β band (Litvak et al., 2012; Joundi et al., 2012; Halje et al., 2012).

2. Modelling Parkinson's disease

Despite the unquestionable recent advances, the efficacy of therapies must be improved by dissecting the pathological changes from the compensatory mechanisms; however, gaps in our understanding of the molecular and cellular biology of PD pathogenesis remain. Available animal models of human disorders have allowed researchers to investigate new therapeutic strategies (Cenci et al., 2002). The use of different PD animal models has proven to be of fundamental utility, although each model reflects different symptoms and stages of PD. Unfortunately, an experimental animal model that reproduces all the phenotypic and pathological features of PD is still unavailable. The ideal PD animal model would be able to replicate human PD from the early stage of degeneration. Importantly, it would reflect a progressive deterioration of motor and non-motor symptoms (Beal, 2001), offering researchers the opportunity to test novel therapies at a period when neuronal degeneration may be still reversible (Imbriani et al., 2017). Moreover, another important point is the necessity of a PD model that does not display confounding compensatory effects to study the "pure" changes induced by DA deficiency. Acute and reversible pharmacological DA-impairment models induced by reserpine, haloperidol and tetrodotoxin (TTX) have been developed to address this point.

Since the specific aetiology of PD is heterogeneous and unknown, with genetic factors predominating in some cases and environmental factors in others, different PD models have been created, ranging from genetic to toxin-based, in a variety of animals, including *Drosophila melanogaster* (*D. melanogaster*), rodents and non-human primates (NHP). Nevertheless, none of these models completely recapitulate the disease. Each available model has its own strengths and limitations that are important to consider when designing a study (Vingill et al., 2017) and selecting the optimal model depending on the specific objectives to address the questions to be investigated (Bové et al., 2005; Imbriani et al., 2017). In addition, because each of the models recapitulates some but not all pathological features of PD and represents a piece of the same puzzle, combinatorial studies with multiple models could be useful and might provide a wider view of PD pathogenesis (Dawson and Dawson, 2002). To date, experimental models have been based on inducing PD via the administration of neurotoxins or genetic manipulations. For example, transgenic mouse and *D. melanogaster* models of α-SYN mutations and wild-type overexpression have been generated, while the most popular and used neurotoxic models are obtained by injecting 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP; Berg et al., 2014; Guo, 2012; Chege and McColl, 2014). Recently, a very robust and accurate PD model showing all symptoms of PD has been created using a microRNA (miRNA) or short interfering RNA (siRNA) cocktail (Jagmag et al., 2015).

The models are continually evolving, but better models are clearly needed. In this review, we will initially focus on models of early-stage PD and compare them with chronic toxin-lesioned models. We then provide an overview the acute model obtained by TTX-mediate blockade of the medial forebrain bundle (MFB) that is able to produce a sudden acute and reversible DA depletion in rats (Commissiong et al., 1990; Miu et al., 1992), which has recently been readapted and extensively used by our group (Galati et al., 2009, 2010; Prosperetti et al., 2013; Grandi et al., 2018).

3. Compensatory mechanisms in Parkinson's disease

The importance of the early PD models arises from the necessity of obtaining a deeper understanding of the compensatory mechanisms that occur during the initial phase of disease. Indeed, when the typical motor deficits develop, 70–80% of the DA terminals are destroyed and progressive DAergic neuron loss has occurred (Bernheimer et al., 1973; Riederer and Wuketich, 1976, Bezard et al., 2001). Therefore, compensatory mechanisms exist that compensate for the lack of DA and subsequent degeneration to maintain the physiological neuronal activity. Nevertheless, when these mechanisms are overwhelmed, motor symptoms appear. In the period that precedes the onset of motor symptoms, in which some prodromal symptoms appear, compensatory mechanisms are activated to compensate for the DA deficiency and to maintain the physiological neuronal activity. Importantly, the compensatory nature of any hypothetical mechanism should be considered in relation to its impact on modulating PD symptoms to ensure that the mechanism is actually compensatory.

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