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Review

An update on the rotenone models of Parkinson's disease: Their ability to reproduce the features of clinical disease and model gene–environment interactions

Michaela E. Johnson, Larisa Bobrovskaya *

School of Pharmacy and Medical Sciences, Sansom Institute for Health Research, University of South Australia, Adelaide, SA 5000, Australia

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder that is characterized by two major neuropathological hallmarks: the degeneration of dopaminergic neurons in the substantia nigra (SN) and the presence of Lewy bodies in the surviving SN neurons, as well as other regions of the central and peripheral nervous system. Animal models have been invaluable tools for investigating the underlying mechanisms of the pathogenesis of PD and testing new potential symptomatic, neuroprotective and neurorestorative therapies. However, the usefulness of these models is dependent on how precisely they replicate the features of clinical PD with some studies now employing combined gene–environment models to replicate more of the affected pathways. The rotenone model of PD has become of great interest following the seminal paper by the Greenamyre group in 2000 (Betarbet et al., 2000). This paper reported for the first time that systemic rotenone was able to reproduce the two pathological hallmarks of PD as well as certain parkinsonian motor deficits. Since 2000, many research groups have actively used the rotenone model worldwide. This paper will review rotenone models, focusing upon their ability to reproduce the two pathological hallmarks of PD, motor deficits, extranigral pathology and non-motor symptoms. We will also summarize the recent advances in neuroprotective therapies, focusing on those that investigated non-motor symptoms and review rotenone models used in combination with PD genetic models to investigate gene–environment interactions.

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* Corresponding author. Tel.: +61 8 830 21218; fax: +61 8 830 22389.
E-mail address: Larisa.Bobrovskaya@unisa.edu.au (L. Bobrovskaya).

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1. Introduction

Parkinson's disease (PD) is a chronic, incurable condition, which affects 1–3% of the elderly population worldwide (de Rijk et al., 2000). Majority of PD cases (90–95%) are sporadic with no apparent genetic linkage, while the remaining 5–10% of patients have the inherited form of the disease (Olanow and Tatton, 1999). PD has two major neuropathological hallmarks: the degeneration of dopaminergic neurons in the substantia nigra (SN) and the formation of Lewy bodies and Lewy neurites in surviving dopaminergic neurons (Lewy, 1912; Savitt et al., 2006). Lewy bodies are cytoplasmic inclusions, consisting of aggregated proteins; the major contributing protein is α-synuclein, a presynaptic protein whose exact function is unknown (Shulman et al., 2011). Although the etiology of PD is yet to be elucidated, increasing evidence supports the 'multi-hit' hypothesis encompassing both environmental and genetic factors such as, insecticide exposure and α-synuclein mutations, respectively. Studies investigating gene–environment interactions therefore could provide a superior understanding of this condition.

In 2007, Braak and colleagues proposed a dual-hit hypothesis for PD progression, suggesting that an external factor might initiate PD pathogenesis by inducing α-synuclein pathology, which moves along two potential paths to the midbrain. One such pathway begins subsequent to exposure in the olfactory bulb, while the other follows exposure in the gastrointestinal (GI) tract, both eventuating in damage to the SN (Hawkes et al., 2007). Mounting evidence that the early symptoms of hyposmia and GI dysfunction are frequently encountered in PD patients before motor symptoms supports this theory, although some researchers remain skeptical.

While Parkinson's disease was initially considered purely a motor disorder, recognition of a broad spectrum of non-motor symptoms, has led to its re-classification as a multicentric neurodegenerative condition (Braak and Del Tredici, 2008). The underlying causes of the PD non-motor symptoms are not well understood, but appear to be complex and related to widespread Lewy body pathology (Jellinger, 2011). PD patients report non-motor symptoms to have a greater impact on quality of life than the typical motor symptoms (Martinez-Martin, 2011); furthermore, some non-motor symptoms such as delayed gastric emptying can interfere with therapeutic drug actions (Pfeiffer, 2011). Therefore pre-clinical and clinical research into the underlying pathophysiology of such symptoms is vital to facilitate development of efficacious non-motor symptom treatments.

Difficulties associated with studying the early biological changes of PD arise as samples of the main organ affected, the brain, can only be investigated post-mortem. This limitation has led to the development of many animal models of PD, which can be broadly categorized into: (1) toxin models induced by 1-methyl-4-phenyl-1,2,4,5-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA) and rotenone, (2) inflammatory models induced by lipopolysaccharide, (3) pharmacological models induced by reserpine and haloperidol and (4) genetic models created by genetic modifications of α-synuclein, LRRK2, parkin, PINK1 and DJ-1. However, at present no model perfectly captures all aspects of the clinical presentation. In animals PD must be artificially induced for scientific research, as this disease has not yet been detected in any species other than humans (Natale et al., 2010). Animal models thus far have been invaluable tools for testing new potential symptomatic, neuroprotective and neurorestorative therapies and investigating the underlying mechanisms of PD pathogenesis, allowing a better understanding of the disease.

The value of pre-clinical studies is dependent on how precisely the model used replicates features of the disease under investigation. The key features of PD that animal models should recapitulate include: progressive degeneration of dopaminergic neurons in the SN, formation of Lewy body-like cytoplasmic inclusions in surviving dopaminergic neurons and behavioral motor symptoms that respond to dopamine (DA) therapy (Cicchetti et al., 2009). An additional desirable feature is the development of the commonly encountered non-motor symptoms, such as hyposmia, constipation and sleep disturbances. Initial PD animal models have focused solely upon replicating classical motor symptoms, however recently some studies have broadened behavioral assessments to include non-motor symptoms, subsequent to the discovery of their high prevalence and morbidity. Recently, combined gene–environment models have also become of interest in an attempt to replicate more of the pathways hypothesized to contribute to PD pathogenesis. In this paper we will focus on the toxin model induced by rotenone, which has been used in many animals such as rodents, *Caenorhabditis elegans* (*C. elegans*), *Drosophila*, zebrafish and *Lymnaea stagnalis* (*L. stagnalis*) (Betarbet et al., 2000; Bretaud et al., 2004; Ray et al., 2014; St Laurent et al., 2013).

Rotenone was first used in PD research in the 1980s after the discovery that MPTP, a toxin used to induce one of the most well-established PD models, was an inhibitor of mitochondrial complex I (Heikkila et al., 1985). Rotenone is a naturally occurring insecticide and pesticide that is extracted from the roots of plants within the *Lonchocarpus* and *Derris* genera (Soloway, 1976). It has been applied as an insecticide in vegetable gardens and for the control of nuisance fish populations, although recently rotenone exposure has been linked to an increased risk of PD (Martinez and Greenamyre, 2012; Tanner et al., 2011). Rotenone is highly lipophilic and therefore easily crosses all biological membranes