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Are rodent models of Parkinson's disease behaving as they should?

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Abstract

In recent years our understanding of Parkinson's disease has expanded both in terms of pathological hallmarks as well as relevant genetic influences. In parallel with the aetiological discoveries a multitude of PD animal models have been established. The vast majority of these are rodent models based on environmental, genetic and mechanistic insight. A major challenge in many of these models is their ability to only recapitulate some of the complex disease features seen in humans. Although symptom alleviation and clinical signs are of utmost importance in therapeutic research many of these models lack comprehensive behavioural testing. While non-motor symptoms become increasingly important as early diagnostic markers in PD, they are poorly characterized in rodents. In this review we look at well-established and more recent animal models of PD in terms of behavioural characterization and discuss how they can best contribute to progression in Parkinson's research.

Introduction

200 hundred years have passed since James Parkinson first described Parkinson's Disease (PD); a progressive neurodegenerative disorder that affects approximately 2-3% of people aged over 65 [1, 2]. The disease is normally diagnosed on the clinical presentation of bradykinesia as well as one of the other cardinal symptoms; resting tremor, rigidity and postural instability. Although PD is primarily considered to be a motor disorder, it is evident that there are numerous non-motor symptoms such as hyposmia, constipation, sleep disorders and depression [3]. The main symptoms of PD arise due to the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which causes imbalance of the nigrostriatal pathway. However, pathology across the rest of the brain is thought to be responsible for some of the non-motor symptoms. Importantly, Lewy bodies, one of the hallmarks of PD, are highly enriched in the brains of affected individuals [4]. These are proteinaceous inclusions that are primarily formed of aggregated forms of α-synuclein [5], but also contain a variety of different proteins and membranous components [6].

Many different genes have been associated with PD, either through pedigree genotyping, linkage or genome-wide association studies [7]. Mutations in these genes cause familiar variants of PD or are, along with others, considered risk factors in sporadic disease. The majority of Parkinson's cases, however, remain idiopathic. This shows a combination of genetic and environmental contribution to PD pathology, which along with the diverse array of symptoms and key pathological hallmarks, makes PD a difficult disease to fully recapitulate in animal models. An ideal PD model is thought to reflect a progressive and age-dependent disease presentation with key motor and non-motor symptoms. Pathologically the model should include loss of dopaminergic neurons in the SNpc and reduced dopamine content in the striatum as well as neuroinflammation and aggregation pathology reminiscent of Lewy bodies. These criteria are rarely fully met, yet a plethora of different PD models exists, ranging from Drosophila to non-human primates. Rodents are however, often preferred due to their relative rapid breeding cycle and mammalian genome.

The rodent models of PD can be broadly divided into environmental models, including the widely used MPTP mouse and 6-OHDA rat models, and genetic models with knock-in and knock-out rodents based on known PD-associated genes. The induced aggregation models represent a middle ground