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Promising rodent models in Parkinson's disease

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ABSTRACT

Background: In the past decade, the study of the pathogenic mechanisms underlying neurodegeneration in Parkinson's disease (PD) has revealed a genetic component, often associated with a number of environmental risk factors. Animal models have improved our understanding of disease pathogenesis, providing significant insights into the understanding of novel molecular pathways. Each model has its own specific features and limitations, and the choice of the most appropriate one depends on the specific question that has to be answered.

Aim: To provide an overview of some of the models supporting the hypothesis that early synaptic dysfunction represents a central event in the course of the disease.

Development: Along with "classical" models, based on the administration of neurotoxins and capable of replicating the neuropathological hallmarks of the disease, a number of genetic models, reproducing the disease-causing mutations of monogenic forms of familial PD, have been generated. More recently, novel models have been developed, based on the combination of a toxic insult together with PD mutations, allowing for the identification of dysfunction at a prodromal disease stage.

Conclusions: The development and characterization of new models is crucial for a better understanding of PD related-synaptopathy, and hold promise for the identification of novel therapeutics.

1. Introduction

Parkinson's disease (PD) is recognized as the second most common neurodegenerative disorder. Its neuropathological hallmarks are neuronal loss in the substantia nigra pars compacta (SNpc) and intracellular inclusions of α-synuclein, the major component of Lewy bodies [1]. Cardinal motor features (resting tremor, rigidity, bradykinesia, and postural instability) are related to striatal dopamine deficiency [2], although the symptomatology is often accompanied by multiple non-motor complaints, including dysautonomia, cognitive dysfunction, pain and mood disorders, whose origin is associated with different neurotransmitters than dopamine [3].

In the last decade, the identification of several gene mutations, responsible for inherited PD, has contributed to the generation of multiple animal models of monogenic PD, allowing for improved understanding of molecular pathways and mechanisms, and providing an unbiased route into dissecting out the mechanisms of a disease where traditional approaches did not offer sufficient insight [4]. Additionally, the well-established role of environmental factors has favoured the generation of different animal models, based on the combination of a toxic insult in addition to a background of genetic mutations, thereby allowing for the identification of early dysfunction at a prodromal disease stage [5].

Overall, basic research has encouraged the development of models which are able to replicate different pathogenic aspects of the disease, mimicking the human condition. However, it is important to remark that this is not necessarily the correct approach. Indeed, the choice of the most appropriate model depends on which hypothesis has to be tested.

Most recently, growing evidence supports the notion that a disruption of synaptic activity, occurring at terminal levels, represents the primary event in disease pathogenesis, with subsequently retrograde cell body degeneration [6]. Keeping in mind the concept of "synaptopathy" as a key event in PD pathogenesis, here we focused on those experimental models supporting such a working

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hypothesis. Thus, our aim was not to exhaustively summarize the data derived from all currently available animal models, and we refer to other recent reviews for comprehensive descriptions.

2. Neurotoxin-based models

In neurotoxin-based models, generally rodents or nonhuman primates, a pharmacological agent (neurotoxin) is systemically or locally administered to induce selective degeneration of nigrostriatal neurons. Toxin models have been widely used over the years, since they represent a valid tool to replicate most of the pathological and phenotypic features of the disease. However, the acutely induced neurodegeneration induces a massive loss of nearly 70% - 80% of dopaminergic neurons, making it difficult to explore early dysfunction and progression, thereby highlighting the main limitation of this approach. In order to overcome this problem, novel neurotoxin models with distinct degrees of dopamine denervation have been created. It is known that massive denervation of the dopaminergic nigrostriatal terminal causes presynaptic changes at corticostriatal level, leading to an increase in glutamatergic transmission and, as a consequence, impairments in synaptic plasticity [7]. It has also been demonstrated that partial dopamine denervation is able to differentially alter striatal synaptic plasticity, at a level that correlates to the extent of deafferentation [8]. Specifically, in a 6-OHDA model of early PD, with partial denervation and mild motor alterations, the decreased levels of dopamine were sufficient to selectively impair long-term potentiation (LTP) but not long-term depression (LTD) [8] (Fig. 1). This finding supports the hypothesis that the expression and maintenance of LTP requires high levels of striatal dopamine, and that only further reduction prevents the induction of LTD. Furthermore, 6-OHDA and MPTP models show that progressive striatal dopamine denervation leads to loss of dendritic spines on striatal medium spiny neurons (MSNs), suggesting a significant role of dopaminergic tone in regulating spine morphogenesis in this neuronal population. In asymptomatic MTPT-treated nonhuman primates, the degree of dopaminergic deafferentation correlated with the extent of MSN spine loss, suggesting that striatal spine loss is a marker of early pathological changes [9].

3. Genetic models

The advent of the 'genetic era' and genome-wide association studies have encouraged the development of new genetic models that have proven to be crucial for an improved understanding of disease mechanisms. We are aware of the existence of many transgenic rodent models, but we will report only on a few, again focusing on their role in the study of early synaptic dysfunction.

SNCA/PARK1 was the first gene to be linked to familial PD; it encodes α-synuclein, a protein mainly localized within presynaptic nerve terminals, where it is thought to play a role in synaptic vesicle recycling and neurotransmitter release [10]. Three missense mutations (A30P, E46K, A53T) as well as gene locus multiplications have been identified in some family members affected by autosomal dominant parkinsonism [11]. Interestingly, gene dosage correlates with the clinical phenotype, with individuals carrying *SNCA* duplications that appear clinically similar to patients with sporadic PD and, on the other hand, individuals with triplications presenting early-onset, severe form of the disease [12]. Growing evidence supports a role of α-synuclein in modulating synaptic transmission and plasticity, by regulating the vesicle pool size, mobilization, endocytosis and, consequently, the probability of vesicle release [13].

In support of the role of α-synuclein in synaptic transmission, recent evidence from both transgenic mice expressing truncated human α-synuclein (1–120), as well as from rats injected with the adeno-associated viral vector carrying wild-type human α-synuclein, showed a partial reduction of striatal dopamine levels. Of interest, a selective loss of long-term potentiation (LTP) in striatal cholinergic interneurons (ChIs) was found, with sparing of LTP in MSNs [14]. The selective alteration found in ChIs was dependent on α-synuclein-dependent modulation of the GluN2D subunit of NMDA receptors. These electrophysiological results were also associated with learning deficits and motor alterations [14]. A further study examined bacterial artificial chromosome (BAC) transgenic mice (SNCA-OVX) expressing wild-type α-synuclein, and demonstrated an impairment in dopamine release that appeared to be linked to elevated α-synuclein levels. Moreover, in aged mice this early phenotype was then followed by progressive loss of nigral dopaminergic neurons, behavioural motor deficits and an altered firing pattern in surviving dopaminergic neurons [15]. These two models significantly contribute to the identification of neurophysiological alterations in selective neuronal populations at early disease stages affecting synaptic neurotransmission and preceding neuronal loss.

LRRK2 mutations are responsible for another autosomal dominant form of PD, whose phenotype is similar to sporadic PD. The LRRK2 protein, also named dardarin, is a multidomain protein with GTPase and kinase functions involved in many cell activities, including neurotransmission, endocytosis and autophagy. Among LRRK2 pathogenic mutations, G2019S is one of the most commonly linked to PD and it causes an increase in kinase activity [16]. Several studies on animal models carrying mutations in the kinase domain support a role of *LRRK2* in synaptic transmission. *LRRK2* overexpressing mice show unaltered basal synaptic transmission in MSNs, but they have impairments in D2-receptor-mediated short-term synaptic plasticity associated with behavioral hypoactivity and impaired recognition memory, which is closely linked to decreased striatal dopamine levels. These data suggest that LRRK2 may play a crucial role in dopamine dependent striatal plasticity, acting at pre-synaptic terminals [17]. Furthermore, Chou et al. showed an impairment of corticostriatal synaptic plasticity in MSNs recorded from eight to nine-month-old (G2019S) LRRK2 transgenic mice, an age at which they did not observe degeneration of SNpc dopaminergic neurons or nigrostriatal terminals, but were able to identify early dysfunction of dopaminergic cells, with a decrease in spontaneous firing frequency and impaired evoked dopamine release in the striatum. Notably, such dopaminergic impairment was sufficient to prevent the induction of LTD in MSNs [18].

Overall, experimental evidence strongly supports the involvement of LRRK2 mutations in synaptic dysfunction. Moreover, there is likely to be an interplay between LRRK2 and α-synuclein: in an elegant genetic study by Lin et al. [19], overexpression of LRRK2 alone did not cause neurodegeneration, while the co-overexpression of either wild-type or G2019S LRRK2 with A53T α-synuclein dramatically accelerated the progression of neuropathological abnormalities in comparison with neurodegeneration observed in any of the single transgenic brains. Genetic ablation of LRRK2 prevented somatic accumulation and aggregation of α-synuclein. Surprisingly, the authors showed that the kinase domain of LRRK2 is not crucial in this interplay, since in double transgenic mice with LRRK2 lacking the kinase domain, extensive α-synuclein-mediated neuropathology could be still observed [19]. These findings are of relevance, in view of potential therapeutic strategies based on inhibition of LRRK2 expression aimed at counteracting α-synuclein-induced neurodegeneration.

Among the autosomal-recessive PD forms, interesting observations come from PINK1 knockout mice [20]. *PINK1* encodes a mitochondrially targeted Ser/Thr kinase involved in mitophagic