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Review article

Brain aging and Parkinson's disease: New therapeutic approaches using drug delivery systems

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ABSTRACT

The etiology and pathogenesis of Parkinson's disease (PD) is unknown, aging being the strongest risk factor for brain degeneration. Understanding PD pathogenesis and how aging increases the risk of disease would aid the development of therapies able to slow or prevent the progression of this neurodegenerative disorder. In this review we provide an overview of the most promising therapeutic targets and strategies to delay the loss of dopaminergic neurons observed both in PD and aging. Among them, handling alpha-synuclein toxicity, enhancing proteasome and lysosome clearance, ameliorating mitochondrial disruptions and modifying the glial environment are so far the most promising candidates. These new and conventional drugs may present problems related to their labile nature and to the difficulties in reaching the brain. Thus, we highlight the latest types of drug delivery system (DDS)-based strategies for PD treatment, including DDS for local and systemic drug delivery. Finally, the ongoing challenges for the discovery of new targets and the opportunities for DDS-based therapies to improve and efficacious PD therapy will be discussed.

Contents

Abbreviations: PD, Parkinson's disease; DAergic, dopaminergic; SNpc, substantia nigra pars compacta; DA, dopamine; LB, lewy body; α-syn, alpha synuclein; L-DOPA, levodopa; MAO, monoamine oxidase; CNS, central nervous system; DDS, drug delivery systems; MPs, microparticles; NPs, nanoparticles; SNCA, synucleinalpha non A4 component of amyloid precursor; PLK, Polo like kinase; LAMP, lysosomal associated membrane receptor protein; LRRK2, leucine-rich repeat kinase 2; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; GDNF, glial cell line-derived neurotrophic factor; BBB, blood–brain barrier; VEGF, vascular endothelial growth factor; PEG, polyethylen glycol; PLGA, poly(lactic-coglycolic acid).

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic (DAergic) neurons of the substantia nigra pars compacta (SNpc), especially the DAergic neurons of the ventrolateral tier that project to the striatum [1]. The differential vulnerability of DAergic neurons to degeneration is still a matter of debate, but it seems to be related to increased sensitivity to mitochondrial dysfunction and changes in protein degradation [2–4]. The consequent decrease in striatal dopamine (DA) is correlated with motor impairment symptoms such as tremor, bradikynesia and rigidity. Non-motor symptoms such as sleep disorders or depression are also present during the disease, just as neuronal loss may occur in other brain regions. Lewy bodies (LBs) and neurites are intracellular inclusions that constitute the neuropathological hallmark of PD due to an abnormal protein aggregation of alpha-synuclein (α-syn) predominantly [5].

The etiology of PD is unknown although researchers believe that it may be caused by a combination of environmental and genetic factors, aging being the strongest risk factor [6,7]. The rate of progression of PD yields evidence of the natural loss of compensatory mechanisms associated with aging. In this way early-onset PD leads to a slower deterioration over time than late-onset PD [8]. The link or difference between aging and PD may be the intensity or acceleration of the neurological damage processes [9]. This imbalance of compensatory resources has led specialists to seek novel knowledge about the aging process.

At present there is no cure for PD and current therapies are focused on DA replacement. Levodopa (L-DOPA) still remains the most effective drug for controlling PD symptoms [10,11]. However, as the disease progresses, many PD patients become severely disabled due to the appearance of non-DAergic symptoms, particularly in the advanced stage of the disease and to the occurrence of drug-induced side effects such as fluctuations [12]. In order to produce a marked benefit not only on motor symptoms but also on non-motor symptoms, non ergotic DA agonists such as pramipexol, ropinirol and rotigotine are now used [13]. Other adjuvant drugs block enzymes that break down L-DOPA/DA such as catechol-*O*-methyltransferase inhibitors and monoamine oxidase B (MAO-B) inhibitors inducing a longer duration of L-DOPA effect and decreasing fluctuations. Finally, the DA agonist apomorphine is used as a rescue therapy when unpredictable *off* periods appear along the day and the glutamate activity blocker amantadine is used as a potent antidyskinetic agent. Certain non-motor symptoms with a great impact on the quality of life do not respond to dopaminergic drugs and, consequently, new drugs that cover this gap are essential [14]. In addition, the development of a disease-modifying strategy has become a priority. In this regard, much has been learned in recent years about PD pathophysiology. Most of these discoveries have identified potential targets, which may lead to the development of novel PD therapies. Remarkably, most of the new drugs and potential therapies for PD are labile compounds that show short *in vivo* half-life and that come with the challenges of delivery to the central nervous system (CNS). Thus, innovative technologies able to extend the length of the treatment, release drugs in a controlled manner or enhance brain drug delivery are the key to developing more effective treatments. In this regard, drug delivery systems (DDS) such as liposomes, microparticles (MPs), nanoparticles (NPs) or hydrogels, as well as conventional transdermal patches or subcutaneous implants, have shown great potential for improving the outcome of new and conventional therapies for PD [15]. The aim of this paper is to review novel therapeutic targets that may detain DAergic neurodegeneration observed both in PD and aging. Then, recent advances in the use of DDS for PD are discussed. Finally, the ongoing challenges for the discovery of new targets and the opportunities for DDS-based therapies for an improved and efficacious PD therapy will be discussed.

2. Methods

2.1. Evaluation of the literature

A MEDLINE search was conducted using the keywords aging, therapeutic targets, alpha-synuclein, mitochondrial disruptions, neuroinflammation, glia and Parkinson disease. For the section "Drug delivery systems approaches" the literature search, from 2013 to 2015, included the keywords drug delivery systems; microparticles; nanoparticles; GDNF and Parkinson disease. All research papers and reviews with the mentioned contents were included in the review process.

3. New therapeutic targets

Recent knowledge of the basic mechanisms and pathophysiology of PD might support the search for targets for treating this disease. In this section we will review the most promising therapeutic targets and strategies to detain the loss of DAergic neurons (Fig. 1).

3.1. Alpha-synuclein toxicity. Phosphorylation and aggregation

This small peptide of 140 amino acids is the main LB component and it seems to be closely linked to PD pathogenesis [5] (Fig. 1A). However, the role of α-syn on disease onset and progression is not totally understood. Physiologically, α-syn regulates synaptic activity by interacting with synaptic vesicles and promotes a snare complex assembly [16]. Interestingly, α-syn expression is increased with aging [8].

The implication of synuclein in PD results from the identification of mutations in the SNCA gene (synuclein alpha non A4 component of amyloid precursor) in PD families. Duplication or triplication of SNCA (PARK4 locus) has also been implicated in PD, indicating that α-syn-wild type may trigger toxicity at high levels [7]. Point mutations in SNCA gene (PARK1 locus) affecting α-syn conformation are also associated with familial PD, thus targeting α-syn post translational modifications has also drawn the attention of various authors