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Prospects for polymer therapeutics in Parkinson's disease and other neurodegenerative disorders

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ABSTRACT

Parkinson's disease (PD) is characterized by a progressive loss of dopaminergic neurons and represents a growing health burden to western societies. Like many neurodegenerative disorders the cause is unknown, however, as the pathogenesis becomes ever more elucidated, it is becoming clear that effective delivery is a key issue for new therapeutics. The versatility of today's polymerization techniques allows the synthesis of a wide range of polymer materials which hold great potential to aid in the delivery of small molecules, proteins, genetic material or cells. In this review, we capture the recent advances in polymer based therapeutics of the central nervous system (CNS). We place the advances in historical context and, furthermore, provide future prospects in line with newly discovered advancements in the understanding of PD and other neurodegenerative disorders. This review provides researchers in the field of polymer chemistry and materials science an up-to-date understanding of the requirements placed upon materials designed for use in the CNS aiding the focus of polymer therapeutic design.

Contents

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BBB, blood brain barrier; DMAEMA, 2-dimethylaminoethyl methacrylate; HD, Huntington's disease; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; 6-OHDA, 6-hydroxydopamine; PAMAM, poly(amido amide); PD, Parkinson's disease; PEG, polyethylene glycol; PEI, polyethylene imine; PLGA, poly(lactic-co-glycolic acid); PLL, poly-L-lysine; SCI, spinal cord injury.

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1. Introduction

Parkinson's disease (PD) is a movement disorder that was described in 1817 by James Parkinson in his famous text *"An Essay on the Shaking Palsy"*. PD is a progressive neurodegenerative disorder which can give rise to a range of symptoms including the well-known triad of bradykinesia, rigidity and tremor. Parkinson's disease (PD) and many neurodegenerative disorders (such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and multiple sclerosis (MS)), exhibit complex pathological features. While these pathologies are being ever further elucidated, the causes (with the exception of genetic predispositions such as huntingtin gene mutations for HD) are more ambiguous. Many neurodegenerative disorders (including PD) are age related disorders and represent a growing healthcare burden to aging populations, and as of yet, lack disease modifying intervention. Medications such as the gold standard levodopa for PD, result in a marked improvement in patient quality of life, but for a limited period [1]. They treat the symptoms of the disease not the underlying progression of the disease which, in the case of PD, is the dying back of the dopaminergic neurons in the midbrain. Disease modifying interventions are being sought based on gene therapies, new drug formulations, stem cells and other techniques, for which polymers of a variety of chemistries and structures are being considered for increasingly important roles.

PD patients can exhibit a variety of phenotypic features, which can differ in severity from patient to patient depending on the underlying pathology, and can be accompanied by dementia and/or depression. Its cause can be divided into sporadic PD or familial PD where a genetic risk factor is known, and the age of onset can vary. In short, the pathology is complex and not consistent between patients, a matter that must be born in mind when discussing the merits of different medications, or during the design of future therapies. However, several inherent features of PD could be considered to offer relatively more straightforward opportunities for intervention than some other neurological disorders, which for the purpose of this review, makes PD an attractive example to address. The first of these features is the generally slow progressive nature of the disease. Unlike diseases such as ALS, which typically displays a rapid progression with 50% or patients dying within 2.5 years [2], PD usually progresses at a much slower rate [3] giving a longer period for potential intervention. The second feature, which sets PD (and other progressive diseases) apart from acute conditions such as traumatic brain injury (TBI), stroke, or spinal cord injury (SCI), is that at the time of diagnosis there is a modest window of opportunity within which, if the disease progression could be halted, a reasonable quality of life could be maintained. Clinical symptoms present after an approximate 50% loss of nigral neurons and an approximate striatal dopamine loss of 80% [4], providing a rationale for developing neuroprotective therapies to preserve these remaining neurons. Another key feature of PD for therapeutic intervention is the relatively select area of the brain that is affected. While AD affects the hippocampus and cortex, and MS can affect any region of the CNS, PD predominantly affects the nigrostriatal pathway: the substantia nigra (where the cell bodies reside) and the striatum (where the neurons project). In summary, a therapeutic intervention aimed at treating Parkinson's disease optimally could have an effect lasting years, and be targeted to the nigrostriatal pathway, either through direct stereotactic injection, or translocation across the blood brain barrier (BBB). This is clearly a formidable task, and while progress is being sought via clinical trials in gene therapies, direct protein infusions and cell therapies, there is an emerging field of polymer therapeutic research, for neurodegenerative diseases as a whole [5]. Growth factors such as glial cell line derived neurotrophic factor (GDNF), neurturin (NTRN), brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) all show promise as a means of achieving neuronal protection or re-innervation [6–10], and polymer therapeutics are likely to play a significant role in overcoming the problem of effective delivery [11,12]. Although the field is in its infancy in terms of clinical translation, polymer science research is being developed in many areas (as

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