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Targeting delivery in Parkinson's disease

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Disease-modifying therapies for Parkinson's disease (PD), with the potential to halt the neurodegenerative process and to stimulate the protection, repair, and regeneration of dopaminergic neurons, remain a vital but unmet clinical need. Targeting the delivery of current and new therapeutics directly to the diseased brain region (in particular the nigrostriatal pathway) could result in greater improvements in the motor functions that characterise PD. Here, we highlight some of the opportunities and challenges facing the development of the next generation of therapies for patients with PD.

Introduction

Age-related neurodegenerative diseases are a group of conditions that affect patient motor and/or mental independence, and lead to a general lowering of quality of life. After Alzheimer's disease, PD is the second most prevalent of these neurological disorders, with an incidence of 8.6–19.0 per 100 000 inhabitants [1]. PD was first described by the English doctor, James Parkinson, in his 1817 essay 'An Essay on the Shaking Palsy' [2], and it has since been further characterised by a progressive loss of midbrain dopaminergic neurons as well as the presence of α-synuclein protein aggregates forming intracellular Lewy bodies in affected areas. First introduced over half a century ago [3], replacement of the neurotransmitter dopamine with the precursor levodopa (L-DOPA) remains the backbone therapeutic for standard PD therapy. However, L-DOPA (as well as all other pharmacological therapies for PD) is limited in that it only treats the motor symptoms of the disease; it does not alter the relentless degeneration of the affected neurons as the disease progresses, and it is associated with significant adverse effects in advanced disease. Therefore, it is imperative that novel disease-modifying therapies that have the potential to halt the neurodegenerative process itself, and to stimulate the protection, repair, and regeneration of dopaminergic neurons, are developed sooner rather than later.

When considering the hurdle of designing new targeted therapeutic interventions for PD, it is interesting to place the challenge in context with other neurodegenerative diseases. In comparison to other such diseases, PD offers both specific challenges as well as specific opportunities for targeted therapies. One of the challenges is that, unlike Huntington's disease (which is caused by mutations in one specific gene), the cause of sporadic PD (which accounts for most cases) remains unknown. Having said that, in recent years, linkage analysis and genome-wide association studies have revealed a potential genetic basis for at least some cases of 'sporadic' PD [4,5]. One of the opportunities afforded by the nature of the PD pathology is that it is primarily restricted to a specific location within the brain (namely the nigrostriatal pathway), which is undoubtedly less of a challenge for targeting therapies than the widespread areas affected in many other neurodegenerative conditions, such as multiple sclerosis or Alzheimer's disease. Moreover, because PD results in the relatively specific loss of dopaminergic neurons, there is also a specific population of target neurons for neuroprotection and replacement, in contrast to most other neurodegenerative conditions with diverse patterns of cell loss, such as traumatic brain injury or stroke. The long time period over which the disease progresses also presents both challenges and opportunities. Unlike amyotrophic lateral sclerosis, which typically progresses rapidly over 3 years or so, the disability of PD is typically extended over 2 decades or more. This gives a large window-of-opportunity for therapeutic intervention and, perhaps

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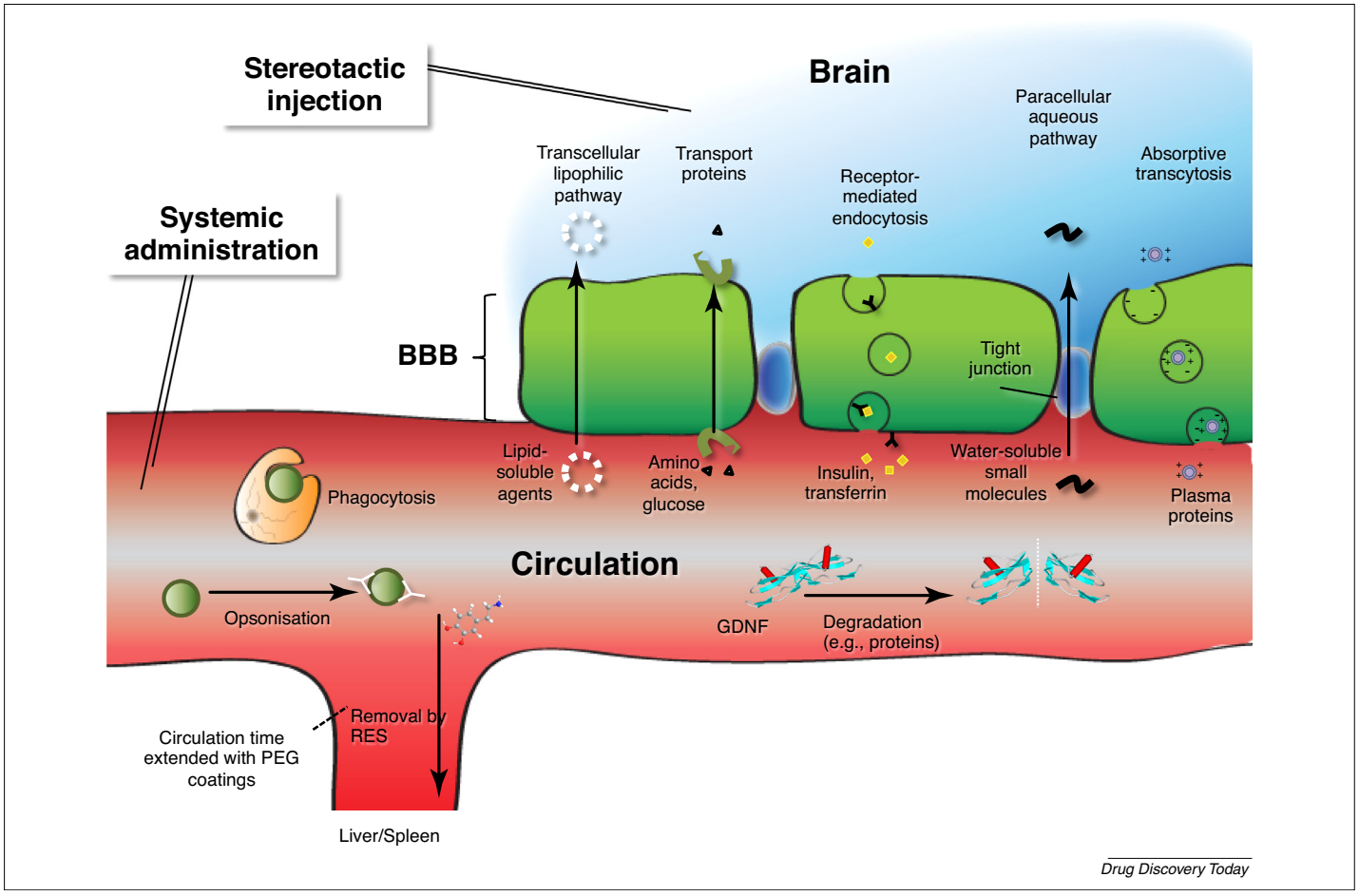

FIGURE 1

Schematic depiction of the barriers to targeting systemically administered therapies to the brain as opposed to direct stereotactic injection. Many of the barriers to effective delivery via systemic administration [such as phagocytosis, removal by the reticuloendothelial system (RES), degradation and crossing the blood brain barrier (BBB)] can be overcome by stereotactic injection. The advantages and disadvantages of both routes are discussed in the main text. Abbreviations: GNDF, glial cell line-derived neurotrophic factor; PEG, poly(ethylene glycol).

in the future, will allow time for 'personalised medicine' approaches (e.g., reprogramming of fibroblasts into functional midbrain dopaminergic neurons for transplantation) [6].

Several trophic factors have been investigated for their neuroprotective properties, such as glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), brain-derived growth factor (BDNF), neurotrophin-3 (NT-3), neurturin, and, more recently, cerebral dopamine neurotrophic factor (CDNF) [7,8]. Of these, GDNF and neurturin show strong promise for protecting the remaining dopaminergic neurons in patients with PD [9]. However, the long timescale of PD progression also presents a challenge for growth factor therapies, which, because of the short protein half-life, will require sophisticated controlled-release systems, continual infusion devices, or gene therapy interventions. Moreover, because large molecules, such as growth factors, do not readily cross the blood–brain barrier (BBB; a selective permeability barrier separating blood flow from the extracellular fluid of the brain; Fig. 1), these requiring targeted, typically surgical, central delivery to the required site of action.

Thus, PD has certain features that give firm rationale for the development of targeted therapies, in particular gene and growth factor therapies. To summarise, these include the selectivity of neuron loss in a particular brain region, an array of potential therapeutic agents, and a suitable time period for neuroprotection. However, challenges include the unknown etiology, patient-to-patient variability in Parkinsonian pathology and symptoms, and the length of time over which the therapy needs to remain active to be effective.

A range of animal models of PD have been developed that enable researchers to analyse the efficacy of new therapeutics and also determine the host response to them. Given that most studies so far have used neurotoxin 'pathogenic' models of PD, one must be careful when extrapolating findings to the human condition. The relative merits and problems of current animal models of PD are summarised elsewhere [10], but the dawn of patient-derived cell culture models should also provide more relevant testing conditions [11].

Route to the target area

When designing a targeted therapy for any disease, it is essential to consider by which means it is expected to reach the target site. Currently, PD drugs containing L-DOPA are typically administered orally, which results in system-wide distribution via the bloodstream despite an effect being desired in the nigrostriatal pathway