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Exenatide as a potential treatment for patients with Parkinson's disease: First steps into the clinic

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Abstract

Background: There is an increasing number of approaches to try and relieve the motor symptoms of Parkinson's disease (PD) that focus predominantly on strategies of dopaminergic replacement or deep brain stimulation. There remains, however, a major need to slow down or reverse the relentless progression of the disease to prevent the evolution of disabling motor and nonmotor features that continue to cause disability despite the existing symptomatic approaches. Data emerging from the laboratory suggest that agonists for the glucagonlike peptide 1 (GLP-1) receptor may have biological properties relevant to PD pathogenesis and progression.

Methods: Future progress in the evaluation of GLP-1 agonists such as exenatide as potential disease-modifying treatments in PD can be facilitated by collection of proof-of-concept data to mitigate against the risk associated with major financial investments into these agents. There are, nevertheless, multiple issues that must be considered in the planning, setup, and conduct of pilot trials of potential disease-modifying drugs.

Results: Open-label proof-of-concept data have been collected in a small cohort of patients with moderate severity PD that suggest that this agent is well tolerated. Patients randomized to receive exenatide showed advantages on validated motor and nonmotor scales of PD that persisted after a 2-month drug washout period.

Conclusions: Although data must be interpreted with caution, given the strong possibility of placebo effects, the clinical evaluation of these patients supports additional investment into double-blind trials of the GLP-1 agonists in PD.

Keywords: Exenatide; Exendin 4; GLP-1; Parkinson's disease; Clinical trial design

1. Introduction

In the early stages of Parkinson's disease (PD), many symptoms can be relieved effectively with the use of dopamine replacement therapy. However, some symptoms can cause persistent disability despite even high doses of levodopa (L-dopa), likely related to degeneration of nondopaminergic cell types [1]. Additional troublesome problems emerge later in the disease because of complications resulting from chronic L-dopa use—fluctuations in motor control accompanied by involuntary movements known as dyskinesias [2]. The need for a neuroprotective agent therefore arises because of those symptoms that do not respond to L-dopa or that emerge later despite the beneficial effects of L-dopa. Specifically, these include dopa-refractory tremor, postural instability, gait freezing, psychiatric disturbance, and cognitive dysfunction/dementia.

Great effort and resources have been invested into a search for a neuroprotective drug for PD. Nevertheless, there are still no agents that have been licensed for this use. The reasons behind this failure to date include inappropriate selection of potential candidate agents, poor animal models of PD relied on to provide the basis on which agents are selected, difficulty in distinguishing symptomatic from neuroprotective effects, and the consequent difficulty in convincing regulatory authorities that any candidate drug may indeed fulfill such a neuroprotective role, acting as a deterrent for major commercial investment [3].

The difficulties experienced in this field are most recently highlighted with the failure of Cogane (PYM50028), an

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orally administered agent that crosses the blood–brain barrier and protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-associated neurodegeneration in the nonhuman primate model of PD, through induction of endogenous neurotrophic factor release. The promising laboratory data prompted a double-blind, randomized trial among more than 400 patients with PD. Initial press releases from Phytopharm (the commercial company sponsoring the trial) have suggested that there was no signal of biological effect after 12 months of exposure to the drug.

This disappointing news confirms that, unless and until we have improved laboratory models that mimic the neurodegenerative processes of PD accurately, the data emerging from the laboratory cannot be solely relied on when deciding on making major financial investments in the development of a potential neuroprotective agent. Nevertheless, this does not diminish the urgency of the need to test the most encouraging candidate neuroprotective therapies to avoid adding to the already long process of drug development and licensing.

To this end, the strategy that we have adopted for further exploration of exenatide is to collect proof-of-concept data, in a timely and highly cost-efficient fashion, from patients with PD in the hope of gaining preliminary insights into whether the data emerging from the laboratory may be, to some extent, replicated in patients with the disease, while ensuring that major resources are not unnecessarily devoted toward agents that ultimately do not fulfill their potential indicated from the laboratory.

2. Exenatide as a neuroprotective candidate: Scientific rationale

Exenatide is the synthetic version of exendin 4, confirmed to be an agonist for the glucagonlike peptide 1 (GLP-1) receptor, and resistant to the normal GLP-1 enzymatic degradation processes [4]. Evaluation of its possible role as a potential neuroprotective/disease modifying agent in PD needs careful consideration whether (*i*) the effects of exenatide in the laboratory are of relevance to PD pathogenesis; (*ii*) the biological effects are accompanied by behavioral improvements in a range of animal models of neurodegeneration not limited to the simple dopamine toxin animal model system; (*iii*) it has sufficient safety in humans based on its license for use in patients with type 2 diabetes; (*iv*) it can cross the blood–brain barrier in animals, indicating that peripheral administration may be possible in humans; (*v*) doses administered peripherally, in theory, may reach the brain concentrations required to show efficacy; and (*vi*) proof-of-concept data can be collected quickly and efficiently from patients with PD to provide preliminary support for its further study.

2.1. The effects of exenatide in the laboratory are of relevance to PD pathogenesis

Neurodegeneration in PD appears to have cell autonomous and noncell autonomous components [5]. Cell autonomous processes include (*i*) production of excessive levels or abnormal forms of α synuclein, (*ii*) dysfunction of the normal autophagy/lysosomal processes required to clear excess or abnormally folded proteins, and (*iii*) mitochondrial dysfunction. These processes can also interfere ultimately with microtubule function, and lead to abnormalities of vesicle storage at the synapse and elevation of intracellular calcium ions. Additional noncell autonomous processes include possible cell-to-cell transmission of abnormal or excessive levels of α synuclein, local inflammation and generation of toxic reactive oxygen species, and loss of neurotrophic support [6]. Some or all of these processes contribute to the neurodegenerative process of PD and may be manipulated potentially by exenatide or other GLP-1 agonists.

2.1.1. Neurotrophic properties

There is evidence to suggest that the progressive nature of PD may relate to loss of trophic support. Lower levels of brain-derived neurotrophic factor and nerve growth factor are seen in the substantia nigra of patients with PD, whereas levels of glial cell-derived neurotrophic factor are seemingly better maintained [7,8]. Neurotrophic factors are known to upregulate calcium buffering proteins, antioxidant enzymes, and antiapoptotic factors, and can protect against neurotoxicity in animal models [9].

Laboratory work has showed that exenatide has beneficial effects on neurons in vitro. In rat pheochromocytoma cells, exenatide induced neurite outgrowth, promoted neuronal differentiation, and rescued degenerating neuronal cells [10]. The effects of endogenous GLP-1 and exenatide were likened to the trophic effects of nerve growth factor, although it is clear that its effects are mediated through the GLP-1 receptor rather than the TrkB (tyrosine receptor kinase B) receptor. Exenatide was also shown to protect against excitotoxic damage and also to reverse the damage provoked by glutamate or ibotenic acid in in vitro or in vivo animal models [11].

2.1.2. Anti-inflammatory properties

The possible role of neuroinflammation in the pathogenesis of PD disease is gaining increasing evidence (reviewed in [12]), based broadly on epidemiologic data hinting at lower rates of PD among patients using nonsteroidal anti-inflammatory drugs [13], a consistent association between the human leukocyte antigen locus and PD risk from the meta-analyses of genomewide association studies [14], the presence of activated microglia seen in patients with PD using the PK11195 positron emission tomographic ligand [15], and the presence of proinflammatory mediators seen in the postmortem tissue of patients with PD [16].

Exenatide has been shown to attenuate toxicity in the MPTP mouse model, sparing neurons in the substantia nigra pars compacta and their striatal dopaminergic projections in association with reduced activation of microglia, and reduced expression of proinflammatory molecules: matrix metalloproteinase-3, tumor necrosis factor-α, and