Movement Disorders
CLINICAL PRACTICE

VIEWPOINT

Glucagon-like Peptides (GLP-1) Perspectives in Synucleinopathies Treatment

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Repurposing Drugs for Parkinson's Disease

There is great interest in repurposing drugs (i.e. evaluating the potential of drugs known to be safe in humans with an existing licensed indication) to examine additional possible therapeutic effects in other conditions. This type of approach is being widely embraced in the search for disease-modifying drugs in Parkinson's disease (PD).[1] Agents that have been used as cancer treatments (Nilotinib),[2] anti-hypertensives (Isradipine),[3] health food supplements (Inosine),[4] as well as a number of diabetes drugs (including Pioglitazone and Exenatide)[5–8] have been proposed as potential disease-modifying drugs and have successfully secured funding for clinical trials to formally assess their value. In this paper, we will focus on how and why drugs influencing the GLP-1 receptor have become of increasing interest in PD and potentially other alpha synucleinopathies.

Links Between T2DM and PD

A meta-analysis of longitudinal cohort studies has shown that patients with diabetes mellitus (DM) are at a higher risk of developing PD than patients without diabetes. This appears to be independent of macro-vascular disease, given the persistence of the association when patients with vascular disease are excluded.[9] The risk is modest however (RR 1.34), as underlined by the inconsistency of the association when examined using less sensitive case-control methodology. The presence of diabetes also appears to increase the rate of progression of PD. Patients with both diagnoses appear to develop cognitive impairment as well as gait and balance difficulties far earlier than PD patients without DM, even after exclusion of those with vascular complications or peripheral neuropathy.[10,11]

Recent data suggest that an association between PD and rate of progression extends to those even with pre-diabetes. The rate of progression of PD, even in the early years, is faster among patients with PD with only slightly elevated HbA1c levels (far below those used to diagnose diabetes; Mollenhauer–DeNoPa cohort personal communication). These data might simply be explicable as a result of elevated blood glucose. Indeed glycation enhances alpha synuclein toxicity by reducing membrane binding, impairing clearance, and promoting the accumulation of toxic oligomers. Furthermore, these effects on alpha synuclein are reversible (in flies) in the presence of glycation inhibitors.[12]

An alternative hypothesis is that the same mechanisms that promote peripheral insulin resistance (causing elevations in HbA1c or diabetes) may also play a role centrally (causing neurodegeneration).[13] Indeed, it is possible to measure insulin resistance in post-mortem brain tissue by measuring the extent of serine phosphorylation of the insulin receptor substrate-1. The relationship between peripheral and central insulin resistance is unclear, however patients with Alzheimer's disease, multiple system atrophy, and PD all appear to have elevated levels of central insulin resistance based on this measure irrespective of a diagnosis of diabetes.[14–16] Whether these changes are related to the causes of, or are simply consequences of, neurodegeneration is unclear, however, there are now considerable data relating central insulin resistance to neuronal survival pathways.[17]

GLP1 Receptor Agonists + DPP4 Inhibitors

Among the newer licensed treatments for diabetes are drugs called the glucagon-like peptide 1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors.[18] GLP-1 is a gut hormone that is released from the cells of the large intestine following ingestion of food, which acts on GLP-1 receptors in the pancreas promoting insulin release from the beta islet cells and suppressing glucagon release, thus promoting blood glucose control.

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Endogenous GLP-1 is rapidly broken down by the enzyme DPP-4, however these effects on blood glucose can be enhanced either by using synthetic GLP-1 receptor agonists which are resistant to DPP-4 degradation, or by using agents which inhibit DPP-4 activity. These actions have led to the widespread use of these drugs in Type 2 diabetes patients and the discovery that their use may be associated with improved outcomes in terms of major adverse cardiovascular events.[19]

As well as influencing insulin release, GLP-1 receptor stimulation also increases beta islet cell mass.[21–23] GLP-1 receptors are present in multiple other body tissues (including brain, kidney, lung, heart, and blood vessels) and therefore there have been multiple studies evaluating the effects of GLP-1 receptor stimulation in diseases of these organs. In addition, there are increasing numbers of patients receiving these therapies as treatments for obesity[24] and for non-alcoholic fatty liver disease.[25] Previous concerns about the potential risk of pancreatitis with GLP-1 receptor agonists appear unfounded.[20]

Given the presence of GLP-1 receptors throughout the brain, there has been great interest in the potential trophic effects of these drugs in neurodegeneration. Of relevance to this, it has been confirmed that the original GLP-1 receptor agonist, exenatide, can cross the blood brain barrier.[26] There is, however, frustratingly little evidence regarding the differential risk of developing PD among diabetes patients according to their diabetes treatment regime. Nevertheless one such paper from Sweden reported that diabetes patients on DPP-4 inhibitors had a lower risk of developing PD (OR 0.23) while patients on GLP-1 receptor agonists also had a lower risk of PD although the small number involved prevents these data being conclusive.[27]

GLP-1 Effects in Laboratory Models of PD

Neurotrophic properties of GLP-1 receptor agonists were first identified in 2002.[28] Since then, there have been multiple reports of the beneficial effects of GLP-1 receptor agonists in a wide range of toxin-based models of PD.[29,30] While the translational value of these models is somewhat limited, as they often do not exhibit the major neuropathological features or demonstrate the complex extra-dopaminergic involvement seen in human disease, they have allowed investigations into the potential mechanisms of action of GLP-1 agonists, which appear to have multiple effects relevant to the neurodegenerative processes of PD. They have been shown to have anti-inflammatory effects in some laboratories,[29] however, these properties may not be necessarily relevant to their therapeutic effects.[31] There are data indicating beneficial effects on mitochondrial function,[32] as well as through enhancing the actions of the neurotrophic factor BDNF.[33] It is likely that all of these actions are inter-related, possibly through an effect of GLP-1 receptor stimulation on insulin resistance and downstream Akt signaling.[13]

Clinical Trial Data

Many putative disease-modifying agents have had efficacy in laboratory models of PD and yet have failed when tested in the clinic. There have been two trials of exenatide in patients with PD, both of which had encouraging results although should still be viewed as preliminary. The first was an open label trial, necessarily so, in view of the difficulty in accessing placebo versions of the subcutaneous injections. This showed that patients with a mean of 10 years disease duration treated with exenatide had less decline in MDS UPDRS part 3 scores over a 1-year period than patients who did not receive exenatide. There was also less decline in cognitive performance.[6] Furthermore, when reassessed the next year, after stopping the exenatide, the previously observed advantages were maintained.[7]

These results, although open label and thus potentially vulnerable to placebo effects, were viewed as sufficiently encouraging by the manufacturer to allow access to placebo versions of exenatide to enable a small double-blind placebo controlled trial to be performed. Sixty patients with PD, of a shorter disease duration (mean 6.4 years), were recruited and randomly assigned to exenatide or placebo for 48 weeks, after which there was a 12-week washout period before comparing scores on the MDS UPDRS part 3. Patients treated with exenatide had a 3.5-point advantage in the severity of their PD compared with those treated on placebo.[8]

These results, while extremely encouraging, still have to be interpreted with caution. The second trial was again small, still constrained by the limited supplies of drug/placebo, and therefore there were differences, depsite randomisation, in the baseline severity of the patients between the exenatide and placebo groups. While there was appropriate adjustment for these differences in the statistical analysis, seasoned commentators have cautioned that these results must be replicated in confirmatory trials before influencing physician-prescribing habits.[34,35]

Furthermore, despite the existing laboratory data, it has to be convincingly demonstrated in people with PD whether any clinical effects relate to symptomatic effects on the dopamine system or disease-modifying actions on the underlying pathophysiological processes of PD. Careful consideration must be given to trial design to enable clarification of these possibilities.[36] There are further trials of exenatide as well as with lixisenatide and alogliptin in setup, and an ongoing trial of liraglutide (NCT02953665) in PD.

It is arguable that there is an even greater need to identify a disease-modifying therapy for patients with multiple system atrophy, given the lack of effective symptomatic agents for this condition. There is evidence not only of insulin resistance in the brains of patients with MSA, but also that transgenic MSA mice treated with exenatide showed improved insulin resistance, alpha synuclein load, and dopaminergic neuronal survival, thus strongly supporting the prospect of a trial in this cohort of patients. There is also an ongoing trial of liraglutide in Alzheimer's patients (NCT01843075).

Even if it can be shown unequivocally that the GLP-1 receptor agonists do slow down the rate of progression of PD, there

may be residual obstacles to getting one or more of these drugs licensed given that, for exenatide at least, the drug has become off-patent and therefore there is far less commercial interest in its development. Attempts to address this issue, and thus ensuring delays to accessing new repurposed treatments are minimized, are being discussed. Given that there are also many further drug candidates that may act on the same pathways promoting cell survival, as well as a wealth of immunotherapy, gene therapy and cell therapy trials in setup, we should be optimistic that the first disease modifying intervention for PD is not too far away from reach.

Author Roles

Professor Foltynie and Dr Athauda are responsible for conception, organization, and execution of the entire content.

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