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Is GDNF beneficial in Parkinson disease?

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Abstract

Glial cell line-derived neurotrophic factor (GDNF) has proved efficacious in treatment of neurodegeneration in toxin-induced models of Parkinson disease (PD), but clinical trials have been equivocal. Do the results of a recent study—suggesting that GDNF is ineffective in an α -synuclein-overexpression PD model—exclude GDNF as a therapy for PD?

Neurorestorative effects of glial cell line-derived neurotrophic factor (GDNF) have been shown in gene therapy studies in animal models. Several different viral vectors, including adeno-associated viral vectors (AAV) or lentiviruses, have been used to administer GDNF in neurotoxin-induced rat and nonhuman primate models of Parkinson disease (PD).¹ Although GDNF was found to be promising in toxin-induced animal models of PD, the results from clinical trials have been mixed. Why, despite positive data from animal models, do clinical trials of GDNF in PD fail? Histological examination has shown that overexpression and aggregation of α -synuclein—a protein that is involved in dopamine transport and is naturally expressed in presynaptic terminals—is characteristic of patients with Parkinson disease (PD); however, aggregation of α -synuclein does not occur in many toxin-based models of PD. In a paper by Decressac *et al.*,² published in *Brain*, researchers have investigated whether GDNF can protect against the neurodegenerative changes and cellular stress caused by the overexpression of α -synuclein.

“GDNF does not have a neuroprotective effect in this α -synuclein-induced toxicity model of PD”

Clinical trials investigating the neuroprotective effect of GDNF in patients with PD have produced mixed results. In one trial, where a single patient was given monthly intracerebroventricular injections of GDNF, the individual showed no improvement in motor function and reported several adverse effects of the treatment.³ However, in a small nonrandomized study in which GDNF was delivered directly into the putamen of five individuals with PD, the patients showed improvement in motor functions, as well as increased dopamine uptake (measured by PET), without any reported adverse effects.⁴ In a larger randomized trial that included 34 PD patients, none of the participants showed improvement in motor function, but an increase in dopamine uptake was seen in the putamen of some patients after GDNF infusion.⁵

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In the paper by Decressac *et al.*,² the authors questioned the relevance and predictability of toxin-based animal models for human disease. The researchers investigated whether GDNF

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Competing interests

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had neuroprotective effects in an α -synuclein-overexpression model of PD, which mimics many features of human disease. They found that viral vector-mediated delivery of GDNF into the substantia nigra and/or striatum did not prevent the loss of dopaminergic neurons and terminals in rats that overexpressed human α -synuclein. In addition, overexpression of GDNF did not reverse the behavioral changes seen in these animals. Measurement of striatal α -synuclein-positive aggregates showed that lentiviral expression of GDNF had no effect on α -synuclein aggregation. The authors conclude that GDNF does not have a neuroprotective effect in this α -synuclein-induced toxicity model of PD.

The study included an extensive series of well-executed experiments that involved administration of GDNF and α -synuclein using lentiviral and adeno-associated viral vectors. The paper documents the immunocytochemical and biochemical expression of GDNF, immunocytochemical measurements of midbrain dopamine circuitry in both the substantia nigra and striatum, and behavioral analysis of the transfected animals. Nonetheless, as with all 'negative' studies, a number of caveats should be considered.

After viral vector-mediated delivery of GDNF to the striatum or the substantia nigra, Decressac *et al.* showed larger areas of immunoreactivity in the brains of rats that received viruses containing GDNF than in those that received comparable titers of viruses containing green fluorescent protein (as a control vector). This finding suggests that GDNF was indeed secreted from the transfected neurons; however, a demonstration that the virally expressed GDNF was secreted in an active form would have been useful to confirm that the lack of efficacy of GDNF was not a result of the limited availability of the protein. GDNF activity cannot be ascertained by analyzing data from immunocytochemical studies or ELISAs. Evidence that the GDNF-expressing neurons can provide trophic support for midbrain dopaminergic neurons by paracrine or autocrine release of GDNF is needed to confirm the neurotrophic 'potency' of the expressed protein. Demonstration that viral delivery leads to production of bioactive GDNF, as indicated by neurite outgrowth *in vitro*⁶ or fiber sprouting *in vivo*,⁷ would confirm that GDNF provided neurotrophic activity to the region. In addition, immunocytochemical or biochemical evidence of upregulation of downstream signaling molecules, such as phosphorylated extracellular signal-regulated kinase (pERK), would verify the bioactivity of GDNF.

GDNF exerts its neurotrophic activity through binding to GDNF family receptor α -1 (GFR- α -1) and subsequent activation of the receptor tyrosine kinase RET, or through an interaction with neural cell adhesion molecule. The inability of GDNF to exert neurotrophic activity in Decressac *et al.*'s PD model could be attributable to loss of receptor expression in the α -synuclein-overexpressing cells, although the authors did not examine the effects of α -synuclein overexpression on the expression of GDNF receptor molecules.

"...further clinical trials with neurotrophic factors in PD seem to be warranted"

The relevance of this model of α -synuclein overexpression to human PD is also unclear. Postmortem analysis of brains from PD patients indicates that RET immunoreactivity in the substantia nigra is similar to that in the brains of patients without PD.⁸ No changes in RET or GFR- α -1 mRNA expression have been observed in the putamen in patients with PD.⁹ Characterization of the effects of viral-vector-based α -synuclein overexpression on GDNF receptors in the substantia nigra and striatum would be important in understanding the inability of GDNF to confer protection. Strong over-expression of a transgenic protein may alter the expression of receptors or other cellular proteins by interfering with cellular proteostasis. Overexpression of α -synuclein is associated with endoplasmic reticulum stress and activation of the unfolded protein response. As viral-vector-mediated delivery was not targeted solely to dopaminergic neurons, the unfolded protein response may also occur in

cells that are not normally affected in PD, and this may cause further degenerative changes.¹⁰

The possibility also exists that transcriptional competition occurred between the two vectors, at least when both the α -synuclein-containing and GDNF-containing viruses were injected into the same site (that is, in the substantia nigra). If the viruses were injected into the brain on the basis of volume and not titers, the numbers of viral particles that contained α -synuclein would be an order of magnitude higher than the numbers that contained GDNF. In this scenario, as the two vectors use similar cellular promoters, the competition for transcriptional factors would be heavily weighted towards α -synuclein expression. This could result in α -synuclein outcompeting the production of GDNF, thereby decreasing the effective dose of the latter protein. The levels of GDNF in the animals that were injected with both vectors are unknown, as assessment of the levels of GDNF was done only in the animals that were injected with vectors expressing GDNF. Measurements of GDNF production and signaling in animals injected with both GDNF-expressing and α -synuclein-expressing vectors are needed.

Future studies should explore whether the effects of viral-vector-based overexpression of α -synuclein on proteostasis are comparable to the changes in proteostasis observed in the brains of patients with PD. These studies may provide insight into the advantages and limitations of the model for evaluating GDNF or other neurotrophic factors as potential therapeutics for PD. Although a number of issues remain unresolved, further clinical trials with neurotrophic factors in PD seem to be warranted. The caveats described above notwithstanding, the study by Decressac *et al.* presents some interesting findings that stress the importance of studying potential PD therapies in more than just toxin-induced models.

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