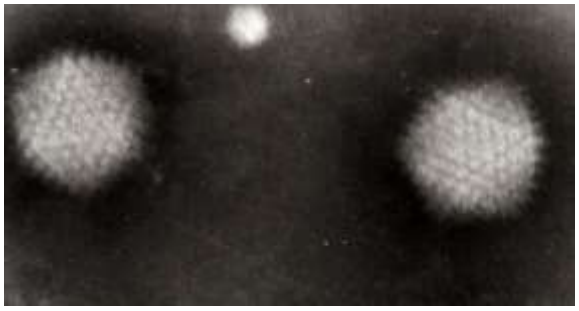
Perceiving Parkinson's

The Neurotrophic Factor Saga (Day 91)

In theory, neurotrophic factors may be the most promising of all potential therapies for Parkinson's. The neurotrophic factor saga is full of exhilarating highs and crushing lows.

Neurotrophic factors are proteins that direct and support the survival, growth, specification, and maturation of various populations of neurons, including the dopaminergic neurons of the substantia nigra that are heavily damaged in Parkinson's. Given how they work, many researchers believe that neurotrophic factors could protect or even regenerate the neurons that fall prey to the pathological neuron-killing process in Parkinson's.

Neurotrophic factors can be delivered to the human brain by direct infusion or by viral vectors. In the method of **direct infusion**, a catheter is inserted deep into the brain and periodic infusions of neurotrophic factors are administered for several months or years. In the method of **viral vectors**, genes that produce neurotrophic factors are inserted into a virus, which is then used to infect the neurons of interest, thus conferring the infected neurons with a permanent ability to synthesize their own neurotrophic factors.



Neurotrophic factors can be delivered to the brain using a virus, like these adenoviruses.

To date, two dopaminergic neurotrophic factors have been studied in humans - **glial cell line-derived neurotrophic factor (GDNF)** and **neurturin (NRTN)**. Let's have a look at the major studies involving GDNF and NRTN in humans.

Initial Uncontrolled Studies - Exhilarating Highs

The earliest studies on neurotrophic factors were performed in animals and showed great promise for protecting and regenerating dopaminergic neurons. The surge of enthusiasm that ensued from these animal studies led to two important studies in humans.

In the first study, a small 2003 British study, GDNF was directly infused into the basal nuclei (into a region called the putamen) of five people with Parkinson's. By 12 months, the participants collectively experienced a **39%** improvement in motor symptoms, a **61%** improvement in their activities of daily living score, and a **64%** reduction in dyskinesias. Side-effects were minimal.

The second study occurred in 2005, this time in the United States, in which GDNF was directly infused into the putamen of ten people with advanced Parkinson's. By six months, the participants collectively experienced an impressive **30-35%** improvement in their combined motor and nonmotor symptoms scores. Once again, side-effects were minimal.

In human studies, neurotrophic factors are often infused into the putamen (coloured red).

The positive results from these earlier human studies fostered much enthusiasm for neurotrophic factor therapy in Parkinson's. However, these studies had a weak design - both were **uncontrolled** studies, meaning that all the participants in each study received the same treatment. There was no control arm, no participants who were given an alternate or placebo treatment. Still, the uncontrolled studies generated a lot of excitement over neurotrophic factor therapies.

Later Randomized Controlled Studies - Crushing Lows

The excitement fostered by the uncontrolled studies above led to several better-designed randomized controlled studies on the effects of neurotrophic factors in people with Parkinson's.

In a 2006 Canadian study, 34 people with Parkinson's were randomized to receive a direct infusion of GDNF into the putamen, or a placebo. By six months, both groups showed a **slight decline** in their motor symptoms, with **no significant difference** noted between each group. Moreover, there were three serious events that required repositioning or removal of the infusion delivery catheter.

In 2010, a study performed in the United States randomized 58 people with Parkinson's to receive NRTN into the putamen via a viral vector called adeno-associated type-2 vector (AAV2), or a placebo. By 12 months, there was **no significant improvement** in motor symptoms in either group, and **no significant difference** in motor symptoms between each group. Moreover, serious events occurred in 17 participants, with five of them developing tumours. The sole bright point to this study was that by 18 months, a subgroup of patients did experience improvements in their motor symptoms.

Finally, in a recent 2015 study conducted in the United States, 51 patients with advanced Parkinson's were randomized to receive NRTN into both the putamen as well as the substantia nigra via AAV2, or a placebo. By 15-24 months, there was **no significant improvement** in motor symptoms in either group, and **no significant difference** in motor symptoms between each group. However, side-effects were minimal, with two participants suffering from minor brain bleeds.

Collectively, the negative results from these **randomized controlled** human studies produced a huge blow to the field of neurotrophic factor therapy; it appeared that the positive results from the earlier uncontrolled studies were likely due to a placebo effect. This is how the situation stands today.

Yet some researchers maintain that the randomized controlled human studies contained several flaws in their design, and that all is not yet lost. First, they argue that **AAV2 is not the best viral vector** for delivery of neurotrophic factors, and that the AAV5 viral vector is superior. Second, they argue that **different basal nuclei regions should have been targeted** for neurotrophic factor delivery, not the putamen. Third, they argue that all the randomized controlled studies **used the wrong dose of neurotrophic factor**. Thus, these researchers argue that a poor viral vector, an inappropriate brain target, or the wrong dose of neurotrophic factor may explain the collective failure of the randomized controlled human studies to show beneficial effects from neurotrophic factor therapy in Parkinson's.

Perhaps these pundits are right, and perhaps they are not. Regardless, while neurotrophic factors remain tantalizing as a potential therapy for people with Parkinson's, they have yet to live up to their initial promise, if they ever do.

Time will tell.

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References

(1) Sullivan and O'Keeffe. 2016. Neurotrophic factor therapy for Parkinson's disease: past, present, and future. Neural Regeneration Research 11(2), 205-207.

(2) Gill et al. 2003. Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nature Medicine9(5), 589-595.

(3) Slevin et al. 2005. Improvement of bilateral motor functions in patients with Parkinson disease through the unilateral intraputaminal infusion of glial cell line-derived neurotrophic factor. Journal of Neurosurgery 102(2), 216-222.

(4) Lang et al. 2006. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. Annals of Neurology 59(3), 459-466.

(5) Marks et al. 2010. Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. Lancet Neurology 9(12), 1164-1172.

(6) Olanow et al. 2015. Gene delivery of neurturin to putamen and substantia nigra in Parkinson disease: A double-blind, randomized, controlled trial. Annals of Neurology 78(2), 248-257.

(7) Domanskyi et al. 2015. Prospects of Neurotrophic Factors for Parkinson's Disease: Comparison of Protein and Gene Therapy. Human Gene Therapy 26(8), 550-559.