Neuroscience

The Complex Cascade of Parkinson's Disease: Sniffing out a Therapy?

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A suitable therapy for combating Parkinson's disease (PD) neurodegeneration has not been forthcoming and although treatments are available to slow progression, there is no cure and no medical repair procedures.

Of great interest to neurologists and neurology researchers have been the new findings with neurotrophic factors such as glial-cell derived neurotrophic factor and brain-derived neurotrophic factor, the neurotrophins being shown to have the ability to slow neurodegeneration and, in certain instances, rescue neurons. Unfortunately, outcomes of treatments using these proteins have been disappointing or inconclusive at best, and this includes direct infusion into areas of the brain. There is a consensus that once this disease starts there is little chance of halting its progress.

One of the first indications that PD is a future possibility in a patient is a loss of olfaction. We have taken this as a starting point, maybe the earliest indication that neurotrophin treatment should be initiated with the possibility that if this isn't a cure, it is a potent retardant of inevitable neuron loss and attenuating at least some of the many associated problems. Our work showed in cell cultures and an endotoxin animal model that synthesis of GDNF lagged behind inflammatory cell invasion, release of cytokines, protein folding problems and microglial activation.

Our hypothesis is, that early interventions with neurotrophins might delay devastating neuronal loss and overcome some of the inflammatory effects, and that this treatment could begin at the time of loss of olfaction, together with prescribing anti-inflammatories. Couple this with blocking nitric oxide synthase increases and a reasonably early starting point for treatment might well be found.

Parkinson's disease | neurotrophins | olfaction | neurodegeneration

Introduction and Background

Parkinson's disease is devastating in so many ways. It is a chronic illness and a patient's gradual decline can last for many years. The website Everyday Health has a figure of an individual using a walking stick, then a frame, then a wheelchair, and supports this illustration with the following:- *Parkinson's disease is progressive: It gets worse over time. The primary Parkinson's disease symptoms — tremors, rigid muscles, slow movement (bradykinesia), and difficulty balancing — may be mild at first but will gradually become more intense and debilitating. Parkinson's symptoms can become more severe over a period of 20 years or even longer. How fast the symptoms intensify varies from person to person*. (1). The cost in quality of life and dollars and cents (2) is tremendous, not only on the caregivers and medical professionals, but inevitably on loved ones, family and friends (3). Current treatments are largely based on dopamine replacement therapy and halting the loss of neurons with Levodopa, dopamine, Monoamine oxidase-B inhibitors (MAO-B inhibitors), an alternative to levodopa, and some surgical interventions particularly Deep Brain Stimulation (DBS; 4) but neurodegeneration continues despite periods of hope and occasional glimpses of a slowing of deterioration.

Unfortunately, newer treatment options have been slow to appear, and a recent post on the Parkinson's disease Foundation site (5) states, "To date, despite *decades of intensive study*, the causes of Parkinson's remain unknown" and, "The chemical or genetic trigger that starts the cell death process in dopamine neurons is the subject of intense study". It is the initiation and beginning of the problem that has many scientists looking at an inflammatory event, as inflammation appears to have strong links to the loss of neurons (6) and associated cellular problems, a list which now includes integrity of the blood brain barrier (7) and involvement of monocytes (8), to go along with the multiple, well-known factors which include mitochondrial dysfunction, protein misfolding, oxidative stress and many more (9).

Recently, the loss of olfaction has come more to the fore in studies of neurodegeneration (10), following earlier reports of the recognition of the potential of olfaction, or the loss of it, having an important role in disease staging and as a 'pre-clinical' marker (11).

So what scientists and physicians don't have, is a known, defined stimulus and a starting point, because the overt signs of Parkinson's disease, such as tremor and gait problems, only appear many years after the disease has begun its destructive onslaught of signaling mechanisms and pathways which do not appear in all patients, adding yet more problems to an already convoluted puzzle (12).

One of the first, teasing, pieces of evidence that there is something awry with neuro-signaling, is a loss of olfaction which has been reported as "an early 'pre-clinical' sign" (13) of neurodegeneration and an important addition to the understanding of PD disease as it becomes more and more accepted as being not just a motor disease (14), but a more complex problem with impaired sense of smell being a characteristic early feature (15). There is an interesting article in (14) of a man who had suffered from a loss of smell sense for more than a decade and was now, in addition, becoming confused with accompanying vision problems.

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This type of information gives us some idea of the timeline of PD from early signs to more severe problems, twelve years in this case from loss of being able to smell to more serious physical consequences. This indicates olfaction loss as something of a reliable diagnostic landmark (16), and maybe that's where we should start, since it is difficult, if not impossible, to get brain tissue from patients, especially as autopsy specimens are already at the point of massive neuronal loss and degeneration.

Neurodegenerative disease(s) has very visible and measurable markers from Lewy bodies to changes in content of specific proteins. From these findings we can theorize as to how things came to be that way, but we do not know the sequence of events, and we must make educated guesses and form hypotheses based on findings as to when the problems started and, tentatively, how it started.

Problems with olfactory function in PD have been known for many years (17), but there has been relatively little research using this potential marker, maybe the earliest marker we have been given, as studies of circulating factors have, so far, just provided us with the ability to say "we have a problem". However, there has been a fairly constant flow of evidence over the last twenty years of a link between olfaction and PD (17, 18), and maybe this warrants more detailed studies, coupled with both existing and emerging treatments. Linking such research with reliable markers (19), might give us a better chance of stopping chronic neurodegeneration, or slowing its development.

These findings do give us another spark of hope. Maybe make a sniff test part of getting a driver's license? Maybe at graduation? Who knows? For years many people involved in science, medicine and PD support groups have waited with fingers crossed to see if neurotrophic factors were the treatment we had hoped and prayed for, a treatment that could stop neurodegeneration in its path, and maybe reclaim ailing neurons. Unfortunately clinical trials have not yielded promising results (20) though there are still many things to be tried. Glial cell-derived neurotrophic factor (GDNF) and gene therapy (21, 22) are two weapons currently being employed, but outcomes of trials have been disappointing and these authors (21) conclude, "Although gene therapy approaches tested so far have been shown to be safe, none met their primary endpoints in phase II clinical trials…..". Direct infusion of GDNF also did not appear to be beneficial (22), though some neurotrophic factors in animal models have yielded positive outcomes, and GDNF and neurturin have been shown to be protective of, and able to repair, neurons and regenerate axons (23, 24, 25).

Parkinson's disease is a complex illness and shows itself in both motor and non-motor ways (26, 27). Promising results have been seen in cell culture and animal models, but moving the playing field to a human did not produce the resounding success people had hoped for. Animal models continue to produce interesting and confounding results (28). But we do know that neuro-protective factors exist. We also know that GDNF can protect and rescue neurons. What we don't know are the why's and the when's, but we do have some clues in that maybe problems with a sense of smell are an indicator that PD is, unfortunately, in an individual's future.

Cell destruction is underway from evidence of our own macrophages cleaning-up and digesting dead neurons (29). We are aware that GDNF and other factors can and do look after neurons. Work in an animal model has reported results which "suggest that the brain may promote neural axons regeneration in spinal cord via a more beneficial microenvironment which retains higher level(s) of GDNF and lower levels of nitric oxide synthase (NOS)" (30). Perhaps putting these all together will give us some exciting results regarding the stimulus and onset of neurodegeneration at a time conducive to overcoming the inevitability that we have right now (31) and only treating the symptoms (32).

Conclusion

Our research efforts have focused on this 'group' of problems and found that factors detrimental to cell survival, such as TNF-alpha (33, 34, 35), IL-6 (33), NOS (34) and specific lymphocyte types (35) are evident long before increases in tissue GDNF concentrations which, in our model (Figure 1), do not reach staggeringly high levels, even after 24 hours (36, 37).

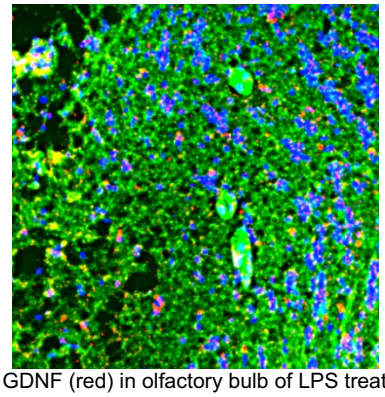

Figure 1. GDNF (red) in olfactory bulb of LPS treated rat

Perhaps the earliest time we should strike at PD is when there is a loss of olfaction and maybe that, together with anti-inflammatory medications and suitable amounts of GDNF, we could achieve a slowing of neurodegeneration and a rescuing of some cells (Figure 2).

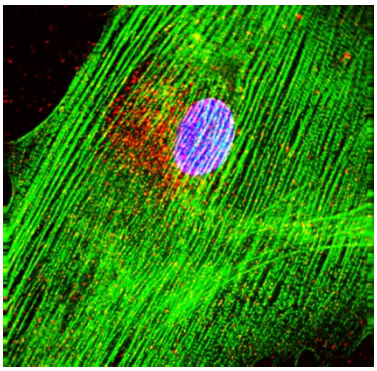

Figure 2. GDNF synthesis (red) in a cultured dopaminergic neuron

There are very few 'hits' when one looks for articles on when it is too late to treat PD. It is a continuous, long term, gradual trip to……. Well the piece in the Boston Globe by Bret Schulte might say it all (38). 'The beginning of the end. The race for a Parkinson's cure', and although this tells us about the toxicity of the protein α-synuclein, and the possibilities of chewing it up before it kills too many neurons, this too is a treatment long after the disease has a hold. The earliest sign we have is, maybe, a loss of ability to smell. At this time we can ask the question as to whether we can stop neurodegeneration, retard its progress, and even rescue neurons. Anything after that is too late and might just extend a horrible illness.

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