



## Why We Cannot Translate Successful Results to New Therapies in Parkinson's Disease

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**Abstract:** There is a sense of total frustration in the field of Parkinson's disease due to the inability to translate successful results obtained with preclinical models to clinical studies and new therapies. The discovery that GDNF preserved the nigrostriatal circuit and reversed motor disability induced in animals by exogenous neurotoxins raised huge hopes of developing a regenerative therapy for Parkinson's disease. However, clinical studies failed to translate the successful results obtained from preclinical studies with exogenous neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or 6-hydroxydopamine. Potential reasons as to why it has not been possible to translate successful results obtained with preclinical models to clinical studies and therapies are discussed.

### Parkinson's disease

Parkinson's disease begins with pre-motor symptoms and takes years to develop motor symptoms, by which time the patient has lost more than 60-70% of their dopaminergic neurons, which contain neuromelanin [1]. In 1957, Parkinson's disease was linked to the loss of dopaminergic neurons containing neuromelanin, resulting in a significant decrease in their dopamine levels [2]. In 1967, L-dopa was introduced into the pharmacological treatment of the disease and now, 50 years later, L-dopa continues to be the most effective and useful drug despite the severe side effects observed after four to six years of use [3, 4, 5]. All the drugs used in the pharmacological treatment of the disease are only palliative, since the progression of the disease continues [6]. It is important to remark that both the degenerative process before motor symptoms, and the progression of the disease, is very slow [7].

The majority of patients with Parkinson's disease can be classified as suffering from an idiopathic form of the disease (70%), where the cause of the disease is unknown. The remaining patients (30%) are classified as having parkinsonism cases with a known cause for the disease, such as genetic mutations (5-10%), pesticides (paraquat), metals (manganese, copper), multisystem atrophies, pallidal atrophy, traumatic brain injury, side effects of drugs (chlorpromazine, haloperidol, thiethylperazine, metoclopramide, methylodopa, flunarizine, cinnarizine, lithium, reserpine), Wilson's disease and juvenile Huntington's disease. For a long time, environmental factors have been suggested as having a possible role to play in the idiopathic form of the disease. An umbrella review of meta-analyses related to environmental risk factors and Parkinson's disease classified the evidence obtained into four categories: convincing evidence (Class I),

highly suggestive evidence (Class II), suggestive evidence (Class III) and weak evidence (Class IV). Only one of 75 environmental factors (constipation) was classified as Class I evidence of risk/association to Parkinson's disease, but it can be an early premorbid manifestation of the disease. Head injury, anxiety or depression and beta-blockers were considered as class II risk factors. Head injury is considered as a type of parkinsonism and depression is a premotor symptom. However, a risk factor with Class I or II evidence for association does not prove causation of the disease. Pesticides and welding are only categorized as Class III evidence [8] and they can be classified in the groups of parkinsonism with known reason.

The discovery that certain genes were associated with familial forms of Parkinson's disease provided an important input into the basic research into understanding the role of these proteins in the disease [9-14]. There is a general consensus in the scientific community that the degeneration of dopaminergic neurons containing neuromelanin involves mitochondrial dysfunction, the aggregation of alpha-synuclein to neurotoxic oligomers, protein degradation and dysfunction of both the lysosomal and proteasomal systems, oxidative stress, neuroinflammation and endoplasmic reticulum stress [15-36]. In the familial form of Parkinson's disease, we know that genetic mutations trigger these mechanisms, while in the sporadic form of Parkinson's disease, the trigger for these mechanisms is still unknown.

### The failure to translate preclinical results to clinical studies

There is a real sense of frustration in the scientific community due to the difficulties of translating successful results from preclinical studies to clinical studies and new pharmacological therapies. There is a long list of clinical studies that have failed to translate successful results obtained from preclinical models for Parkinson's disease based on 6-hydroxydopamine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone to clinical studies [37-46]. The role of oxidative stress in Parkinson's disease and the potential neuroprotective role of antioxidants have been being suggested for a

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long time. One of the classical antioxidants is coenzyme Q10, which was shown to have a protective effect in preclinical studies based on the MPTP neurotoxic model [47, 48]. A clinical study using high-dosage coenzyme Q10 to treat early Parkinson's disease at 67 sites in North America and with 600 participants showed no evidence of clinical benefit [48, 49]. Is the failure of coenzyme Q10 a consequence of its inability to reach the place where the neurodegeneration of dopaminergic neurons occurs in the patient, or is the problem that coenzyme Q10 protects against the neurotoxic effects of MPTP in animals but that this neurotoxin is not present in the patient's brain? A single clinical study showed that taking the reduced form of coenzyme Q10 improved the wearing off phase in Parkinson's patients [50]. The role of mitochondrial dysfunction was proposed a long time ago, and creatine was shown to have protective effects in preclinical studies performed with 6-hydroxydopamine and MPTP by improving mitochondrial function [51-53]. However, clinical studies using creatine showed no clear evidence of having an effect on motor function [54, 55]. The adenosine 2A receptor antagonist preladenant improved motor ability in MPTP-treated monkeys [56]. Preladenant significantly prevented or reduced dyskinetic-like behavior in 6-hydroxydopamine and MPTP [57]. However, preladenant did not significantly reduce off time compared with a placebo in a phase 3 clinical study [58]. The peroxisome proliferator-activated receptor-gamma agonist pioglitazone demonstrates protective abilities in MPTP-treated animals by inhibiting monoamine oxidase-B [59-61]. A clinical study with pioglitazone demonstrated that this compound does not alter the progression of early Parkinson's disease in patients [62].

The discovery that glial cell-derived neurotrophic factor (GDNF) protects dopaminergic neurons offered hope for a regenerative therapy to treat Parkinson's disease. GDNF reversed motor disability and preserved dopaminergic neurons both in MPTP- and 6-hydroxydopamine-treated mice and rats, respectively [63-69]. The GDNF analog neurturin was used in gene therapy due to difficulties in obtaining the rights to employ GDNF from the patent holder. Neurturin is from the same family as GDNF and has similar effects on preclinical models to those observed with GDNF [70]. However, AAV2-neurturin gene therapy effect was not superior to sham surgery [71].

Several drugs that have had successful preclinical results, based on exogenous neurotoxins, are currently under clinical studies but the outcome of these studies is still not known [72]. Isradipine is a calcium channel blocker that protects substantia nigra pars compacta neurons from 6-hydroxydopamine-induced neurodegeneration [73]. A phase II safety, tolerability and dose selection study has been done (Parkinson Study Group, 2013). Adenosine A2A receptor antagonist, improved motor deficiencies induced by 6-hydroxydopamine [74, 75]. A phase I study using antibodies against alpha-synuclein (PRX002) showed that the use of these antibodies is safe for future phase II and III studies [76].

### **Possible factors involved in the failure to translate preclinical results to clinical studies**

One possible factor for the failure to translate successful preclinical results to clinical studies is the selection of patients in the clinical studies. The diagnosis of Parkinson's disease is carried out through clinical examination due to the lack of biomarkers.

Normally, the disease is diagnosed when the motor symptoms become evident after years of degeneration of the nigrostriatal system. Pre-motor symptoms have been proposed [1], but more research is required to be sure of performing the diagnosis correctly. Selecting patients who have been diagnosed early seems to be important because they have more preserved dopaminergic neurons containing neuromelanin, but it is possible to include misdiagnosed patients or patients with different forms of parkinsonism. Potential protective drugs for Parkinson's disease have to account for the fact that the majority of dopaminergic neurons containing neuromelanin have already been lost. However, protective drugs are intended to halt the progression of the disease by preventing the degeneration of the surviving dopaminergic neurons in the nigrostriatal system. The symptoms of Parkinson's disease in the initial phase allow the patient to have a relatively "normal and independent" life. Therefore, a protective therapy in the initial stages of the disease, which halts its progression, will provide a relatively "acceptable" quality of life. The discovery of biomarkers will facilitate the discovery of neuroprotective therapies that prevent the degeneration of the nigrostriatal system in the early stages.

Another possible factor contributing to the failure to translate successful preclinical results to clinical studies are the preclinical models. The most used preclinical model for Parkinson's disease over the last 50 years has been exogenous neurotoxins such as 6-hydroxydopamine, MPTP and rotenone. The first preclinical model to induce the loss of nigrostriatal neurons was 6-hydroxydopamine, a derivative of dopamine that does not exist in vivo. 6-hydroxydopamine is not entirely specific to the dopaminergic neurons, since it also affects adrenergic neurons and pre-treatment with desipramine is required to improve its specificity. However, only 3% of 6-hydroxydopamine lesions were carried out in the presence of desipramine, according to PubMed. 6-hydroxydopamine induces mitochondrial dysfunction [77-91] due to its ability to autoxidize in the presence of oxygen to dopamine o-quinone and neuroinflammation [92-96]. The role played by 6-hydroxydopamine on the proteasomal system is controversial, since some reports show that this neurotoxin induces proteasomal dysfunction [97], while others show an increase in proteasomal activity [98]. It has been suggested that 6-hydroxydopamine induces autophagy, and later apoptosis, inhibiting autophagy flux [99, 100]. MPTP is also one of the most used preclinical models, since it induces parkinsonism in humans [101]. The neurotoxicity of MPTP for dopaminergic neurons depends on its conversion to MPP<sup>+</sup> in astrocytes, which has a very high affinity to dopamine transporter [102]. MPP<sup>+</sup> induces mitochondrial dysfunction by inhibiting complex I of the electron transport chain [103, 104]. MPTP also induces proteasomal [105, 106] and lysosomal [107] dysfunction, endoplasmic reticulum stress [108], neuroinflammation and oxidative stress [109-111]. Rotenone is a classic mitochondrial complex I inhibitor, which has been used as a preclinical model of Parkinson's disease. The difference between rotenone and 6-hydroxydopamine or MPTP is that rotenone does not require a specific transport. Rotenone inhibits the activity of mitochondrial complex I and induces a reduction in mitochondrial membrane potential, ATP depletion and the release of cytochrome C from mitochondria, as well as reactive oxygen species [112-115], alpha-synuclein aggregation [116], proteasomal inhibition [117], autophagic dysfunction [118], neuroinflammation [119-121] and oxidative stress [122, 123].

One possible problem with preclinical models based on exogenous neurotoxins is that they probably do not replicate the progression of the disease, since they do not exist in the human brain. The reason for which exogenous neurotoxins are used as preclinical models is that they induce neurotoxicity in dopaminergic neurons and the subsequent degeneration of the nigrostriatal system. The preclinical model probably requires there to be a complete sequence of neurotoxic events, including the neurotoxic agent that initiates the neurodegeneration. Therefore, it is possible that exogenous neurotoxins are unable to replicate these neurotoxic events which occur during the disease's progression, because they do not exist in the human brain. It is possible that potential drugs need to act on the first event that triggers neurodegeneration to halt the progression of the disease. Exogenous neurotoxins induce both a massive and very rapid degeneration of the nigrostriatal neurons. For example, MPTP induced a severe parkinsonism in drug abusers who used a synthetic drug contaminated with MPTP [101] after only three days. This extremely rapid action of MPTP contrasts with the very slow progression of Parkinson's disease. It takes years to degenerate 60-70% of the nigrostriatal neurons to get motor symptoms [1]. The extremely rapid effect of MPTP on the human brain suggests that the neurotoxin that triggers the degenerative process in Parkinson's disease has to be of endogenous origin. It is probable that the degenerative process in Parkinson's disease is focused on a single dopaminergic neuron, which generates motor symptoms after years of accumulation. The preclinical model must therefore induce a slow and progressive degeneration similar to what occurs during the disease's progression.

Several preclinical models, based on genetic mutations related to Parkinson's disease, have been developed. The expression of the mutated human alpha-synuclein gene (A30P) in rats has been reported to result in the reduction of dopaminergic neurons and the accumulation of alpha-synuclein in the substantia nigra, in addition to neuritic dystrophy in both the substantia nigra and striatum [124]. Both Pink1 and DJ-1 knockout rats showed progressive nigral neurodegeneration, with about a 50% dopaminergic cell loss observed at eight months of age [125]. A knock-in mouse model with the LRRK2 mutation G2019S revealed that this mutation impaired the extracellular release of dopamine [126] without any loss of dopaminergic neurons in the substantia nigra [127]. Transgenic mice with the LRRK2 R1441G mutation had reduced motor functions [128]. Parkin knockout mice are viable with normal brain morphology. However, despite having nigrostriatal deficits, they show no loss of dopaminergic neurons or any changes in the level of parkin substrates [129]. Therefore, genetic models which use a mutated form of a gene associated with the disease are not suitable for investigating the sporadic form of the disease, as they do not include the specific triggers leading to the degeneration of dopaminergic neurons. Interestingly, a genetic Parkinson model (MitoPark mice) with adult onset and a slow, progressive impairment of motor function has been created. The gene knockout for mitochondrial transcription factor A in dopaminergic neurons generates mice with respiratory chain deficiencies [130]. However, the agent that induces this mitochondrial dysfunction is a genetic mutation that is not present in the sporadic form of the disease.

Another possible factor for the failure to translate successful preclinical results to the preclinical models of clinical studies is an

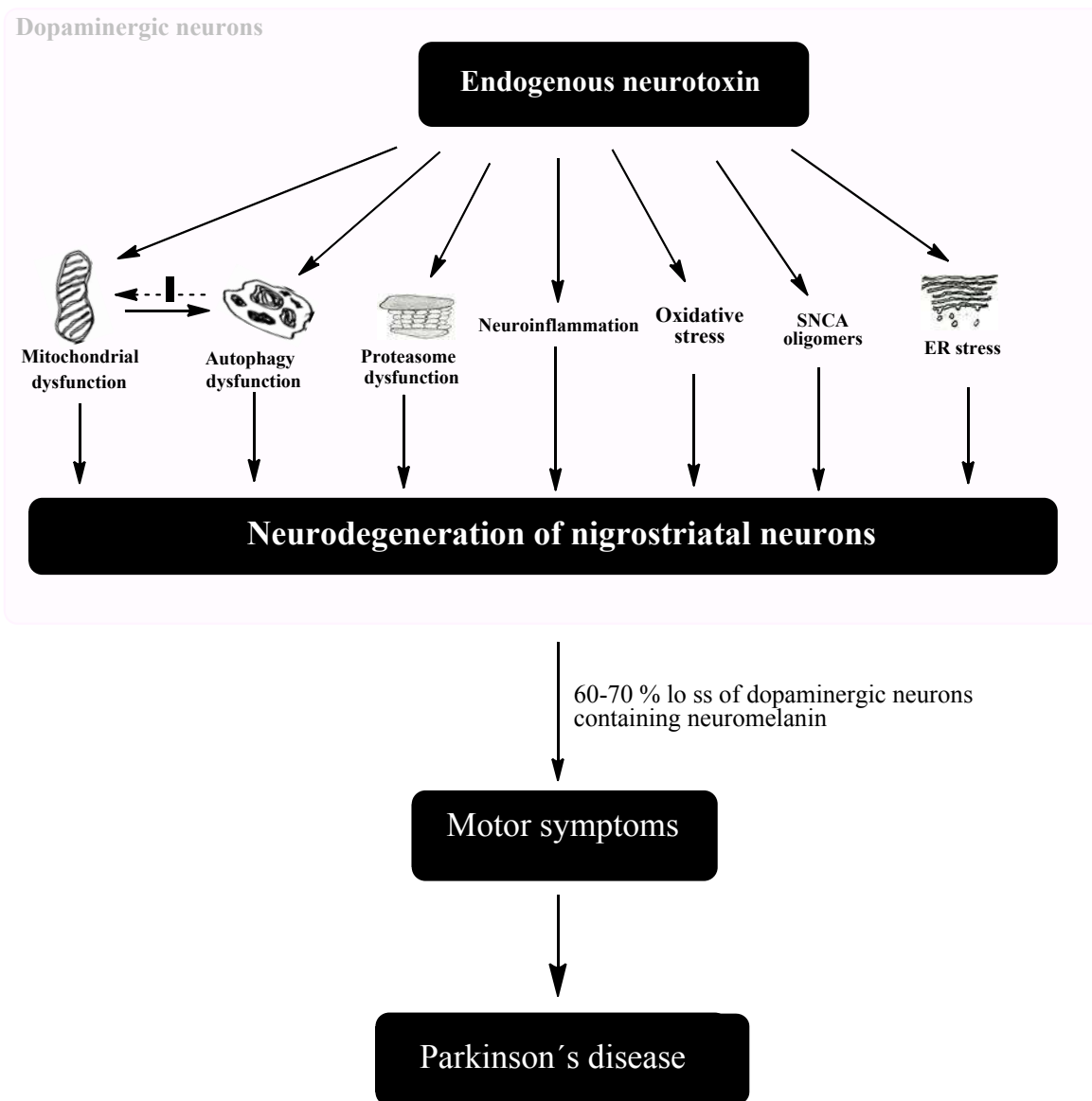
ignorance of the triggers for the neurodegeneration of dopaminergic neurons of the nigrostriatal system. We know that mitochondrial and protein degradation dysfunction, alpha-synuclein aggregation to neurotoxic oligomers, neuroinflammation and oxidative and endoplasmic reticulum stress are involved in the degeneration of the nigrostriatal neurons. The question is what triggers these mechanisms in the brain of the Parkinson's disease patient. In the familial form of Parkinson's disease, alpha-synuclein aggregates as a consequence of a mutation, but what induces its aggregation in the sporadic form of the disease? Exogenous neurotoxins such as MPTP, 6-hydroxydopamine and rotenone are not present in the dopaminergic neurons of Parkinson's disease. Therefore, the question is what triggers these mechanisms in the sporadic form of the disease?

One candidate is alpha-synuclein, since alpha-synuclein oligomers (i) induce mitochondrial dysfunction; (ii) induce disruption of the endoplasmic reticulum and Golgi traffic; (iii) inhibit proteasomal activity; (iv) increase oxidative stress; (v) inhibit autophagy and (vi) induce neuroinflammation by activating microglia and increasing proinflammatory cytokines and nitric oxide [131-146]. The question is what induces alpha-synuclein aggregation to neurotoxic oligomers in the sporadic form of Parkinson's disease. Aminochrome, formed inside of dopaminergic neurons containing neuromelanin, induces the formation of neurotoxic alpha-synuclein oligomers [147]. In addition, aminochrome induces mitochondrial dysfunction, oxidative stress, protein degradation dysfunction and endoplasmic reticulum stress [148-155].

## Conclusions

The difficulty of translating successful results from preclinical models for Parkinson's disease to clinical studies seems to be dependent on several factors: (i) the selection of patients in clinical studies, who have lost the majority of the dopaminergic neurons from their nigrostriatal systems; (ii) the use of exogenous neurotoxins that do not replicate the progression of the disease. The principal features of these preclinical models are that they induce a very rapid and massive degeneration of the nigrostriatal system, while the degeneration of the nigrostriatal neurons in Parkinson's disease is very slow and takes years; and (ii) an ignorance of what triggers the degenerative mechanism involved in the disease, such as mitochondrial dysfunction, the aggregation of alpha-synuclein to neurotoxic oligomers, both lysosomal and proteasomal protein degradation dysfunction, neuroinflammation and oxidative and endoplasmic reticulum stress [Figure 1]. A successful preclinical model must include the neurotoxin that triggers the degeneration of the nigrostriatal system.

**Figure 1.** Possible mechanisms involved in nigrostriatal degeneration in Parkinson's disease. It is in general accepted that the degeneration of dopaminergic neurons containing neuromelanin in the nigrostriatal system involves mitochondrial and protein degradation dysfunction, alpha-synuclein aggregation to neurotoxic oligomers, neuroinflammation, oxidative and endoplasmic reticulum stress. To obtain a preclinical model that replicates the neurotoxic events, which occur during the Parkinson's disease, requires include the first event that triggers these mechanism. In our opinion the first event is the formation of an endogenous neurotoxin that triggers all these mechanisms.



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