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Mini review

Neurotrophic factors for the treatment of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative disorder caused by the progressive degeneration of the nigrostriatal dopaminergic pathway. The resulting loss of dopamine neurotransmission is responsible for the symptoms of the disease. Available treatments are initially successful in treating PD symptoms; however, their long-term use is associated with complications and they cannot stop the neurodegeneration. Current research aims at developing new therapies to halt/reverse the neurodegenerative process, rather than treating symptoms. Neurotrophic factors are proteins critical for maintenance and protection of neurones in the developing and adult brain. Several neurotrophic factors have been investigated for their protective effects on dopaminergic neurones. Here we review some of the most promising factors and provide an update on their status in clinical trials.

1. Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, with an incidence of 1.5–2% in the population over 60 years of age, which increases significantly with advancing age. As life expectancy is significantly increasing in the Western world, the incidence of PD is steadily escalating. Consequently, the financial and economical burden of the treatment and care of PD patients is substantial and increasing [1]. Thus, research on the causes of this debilitating disease is critical, as is the development of new treatments.

PD is caused by the progressive degeneration of the nigrostriatal (A9) dopaminergic pathway, which projects from the substantia nigra in the midbrain to the caudate-putamen (striatum) in the forebrain [2,3]. The resulting loss of dopamine neurotransmission in the striatum causes the cardinal symptoms of the disease: tremor at rest, rigidity and bradykinesia. Approximately 5% of PD cases are caused by heritable genetic mutations. The remaining cases are sporadic and of unknown origin, although many theories have been proposed to explain the cause of dopaminergic neuronal death which occurs in PD, such as environmental toxins, mitochondrial dysfunction with resulting oxidative stress, and inflammatory mechanisms [4,5].

The therapies presently available for PD are not effective in the long-term and cannot stop the ongoing neurodegeneration. The most commonly used treatment is the dopamine precursor, levodopa, which replaces lost dopamine in the denervated striatum and relieves motor symptoms. Levodopa is generally administered in conjunction with an inhibitor of peripheral decarboxylyase (carbidopa, benserazide), which has the effect of enhancing the central activity of levodopa. Levodopa is initially successful, however about 50% of patients develop complications within the first five years of treatment, primarily severe motor fluctuations and dyskinesias. Other drug treatments include inhibitors of the dopamine breakdown enzymes catechol-O-methyl-transferase (tolcapone, entacapone) or monoamine oxidase-B (selegiline, rasagiline), and dopamine receptor agonists (bromocriptine, pergolide, pramipexole, ropinirole). Surgical methods involving ablation of deep brain structures or deep brain stimulation have also been used with good success, but these procedures are not widely available or applicable for all patients. In summary, none of the current treatments provide safe and long-lasting relief from the symptoms and have little or no effect on the progression of the disease [1]. Current research is aimed at developing therapies that will halt the neurodegenerative process, rather than simply treat the symptoms. These include the use of antioxidants, anti-apoptotic agents, cell-based therapies and neuroprotective agents such as neurotrophic factors (NTF).

2. Neurotrophic factors for dopaminergic neurones

NTF are secreted proteins that play critical roles in the induction, specification, survival and maturation of developing neurones. Certain NTF also act in the adult brain, to support and protect mature neuronal populations. As PD is primarily caused by the degeneration of a single neuronal population, several factors have been investigated for their neurotrophic and protective effects on dopaminergic neurones. The goal of this therapeutic approach is to apply a factor(s) which can halt or reverse the progressive degeneration of nigrostriatal dopaminergic neurones,

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and which can be administered to patients in a safe, targeted and long-lasting manner. NTF that have selective effects on dopaminergic neurones represent good targets for this approach. These include glial cell line-derived neurotrophic factor (GDNF), neurturin, growth/differentiation factor (GDF) 5, mesencephalic astrocyte-derived neurotrophic factor (MANF) and cerebral dopaminergic neurotrophic factor (CDNF).

2.1. GDNF family of ligands (GFL)

2.1.1. Effects of GDNF in vitro

The GFL family is composed of four factors – GDNF, neurturin, persephin and artemin. GDNF, its prototypical member, was isolated from a glial cell line due to its neurotrophic effects on cultured dopaminergic neurones [6]. Subsequent studies have shown that it can also act on other neuronal types (see [7]). GDNF has been shown to induce the dopamine synthetic enzyme, tyrosine hydroxylase (TH), in fetal human and rat cortical cultures (Table 1) [8]. GDNF has been consistently shown to promote the survival and differentiation of dopaminergic neurones *in vitro* [6,9,10] and to protect these cells from the dopaminergic toxins, 1-methyl-4-phenylpyridinium ion (MPP+) and 6-hydroxydopamine (6-OHDA) [11–13]. GDNF treatment has also been reported to reduce apoptosis in dopaminergic neurones cultured from embryonic rat [14,15] and human [16] midbrain. GDNF can also protect cultured dopaminergic neurones from lipopolysaccharide-induced degeneration, a model of neuroinflammation [17]. Most of the above studies were conducted on embryonic day 14 (E14) rat midbrain, the time point at which dopaminergic neurones are undergoing their terminal mitotic divisions and are beginning to differentiate. An *in vitro* study showed that GDNF can also support these neurones during their postnatal period of natural developmental death [18]. Midbrain cultures may contain dopaminergic neurones of two origins, the nigrostriatal pathway (A9), which degenerates in PD and the mesolimbic pathway (A10), which is largely spared in this disease. Differential effects of GDNF treatment on A9 and A10 dopaminergic neurones *in vitro* have been reported, whereby a single dose of GDNF selectively enhanced the survival of A9 cells, while repeated exposure to this factor only increased the survival of A10 cells [19].

2.1.2. Effects of GDNF in vivo

In normal adult rats, a single injection of GDNF into either the substantia nigra or striatum significantly increased the levels of dopamine and its metabolites in the striatum and nigra [20]. Several studies have reported neuroprotective and functional effects of GDNF in adult animal models of PD (see [21]). In one early study, repeated injections of recombinant rat GDNF protected against dopaminergic cell loss induced by transection of the adult rat medial forebrain bundle (MFB), the fibre bundle containing the dopaminergic projections from the substantia nigra to the striatum [22].

The most widely used laboratory model of PD involves unilateral injection of the selective dopaminergic toxin, 6-OHDA in the adult rat. This results in the degeneration of nigrostriatal dopaminergic neurones and consequent depletion of striatal dopamine transmission on one side of the brain. Stereotaxic injection of 6-OHDA into the MFB or substantia nigra induces a complete lesion of the nigrostriatal pathway, while intrastriatal injection induces progressive neurodegeneration. Several groups have examined the effects of intracerebral injection of recombinant GDNF in rats with 6-OHDA-lesions of the MFB. Injection of GDNF in or near the substantia nigra at four weeks after or just before a 6-OHDA lesion resulted in reduction of motor deficits, and preservation of nigral dopaminergic neurones and striatal dopamine release and uptake [23–25]. In adult rats with bilateral 6-OHDA lesions of the MFB, injection of high doses of GDNF into the lateral ventricles resulted in improved motor function and sparing of nigral dopaminergic neurones [26]. GDNF's effects may be dependent on host age, as one study found that young rats displayed significantly higher levels of neuroprotection than aged rats [27]. This may be relevant to clinical trials, where the age of the patient may determine the extent of neuroprotection that is achievable with GDNF treatment.

The intrastriatal lesion model has been used extensively since it is possible to administer the NTF while neurodegeneration is progressing. Administration of single or multiple doses of recombinant human GDNF near or in the substantia nigra starting at the day of, or the day before, a 6-OHDA-induced lesion, had protective effects on nigral dopaminergic cell bodies [28,29]. A series of four intrastriatal injections of GDNF was found to decrease drug-induced rotations and preserve nigrostriatal dopaminergic neurones in adult rats with 6-OHDA-induced lesions [30]. Long-term rescue of nigrostriatal dopaminergic neurones from 6-OHDA lesions was reported after short-term GDNF treatment [31]. Long-term protection against rotational asymmetry, reductions in striatal dopamine levels and uptake, and death of nigral dopaminergic cell bodies induced by 6-OHDA lesions of the MFB was conferred by a single dose of GDNF, divided between the lateral ventricle and substantia nigra [32]. GDNF injections into the striatum one week after an intrastriatal 6-OHDA lesion resulted in re-innervation of the striatum as well as recovery of motor function [33], indicating that the ability of intrastriatal GDNF injection to confer behavioural improvements may be due to its effects on the remaining striatal afferents in the partially denervated striatum.

For application to clinical studies, the optimal injection site for production of safe and effective results is obviously an important consideration. Some studies have directly compared the sites of administration of GDNF in 6-OHDA-lesioned rats. Kirik et al. found that intrastriatal GDNF delivery had protective effects on motor function and the integrity of the nigrostriatal pathway, intranigral GDNF protected nigral cell bodies but not striatal innervation or motor function, while intraventricular GDNF had no significant effects [34]. Another study found that intraventricular infusion of GDNF starting two weeks after an intrastriatal lesion had protective effects on the integrity and function of the nigrostriatal pathway, which lasted for six weeks after cessation of GDNF infusion, whereas the effects of intrastriatal infusion stopped upon withdrawal of GDNF [35]. Another group found that intrastriatal infusion of a high dose of GDNF four weeks after an intrastriatal lesion induced restorative effects on motor behaviour and the integrity of dopaminergic neurones and their terminals [36]. Thus, the intrastriatal route of administration appears to be the most efficacious in this progressive model of PD. Sequential application of GDNF over the nigra for two weeks, followed by injections of GDNF into the striatum for three weeks, in rats with intrastriatal 6-OHDA lesions, protected nigral dopaminergic cell bodies but did not prevent striatal denervation or improve motor function [37]. This suggests that the motor improvements observed in the other studies were dependent on an ability of GDNF to induce

Table 1
Effects of GDNF on dopaminergic neurones *in vitro*.

Effect	Reference
Increases tyrosine hydroxylase expression	[8]
Promotes survival of mesencephalic cultures	[6,9]
Promotes morphological differentiation	[10]
Protects from MPP+ neurotoxicity	[12,13]
Protects from 6-OHDA neurotoxicity	[11]
Decreases apoptosis	[14–16]
Protects from LPS neurotoxicity	[17]