INTRODUCTION

Neurotrophic factors (NTs) are secreted proteins that regulate survival and differentiation of nerve cells. Nerve growth factor (NGF), the first discovered NT, together with brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5), form the classical family of NTs. However, many other growth factors, which are effective also outside the nervous system, such as glial cell line-derived neurotrophic factor (GDNF), insulin-like growth factor (IGF I), ciliary neurotrophic factor (CNTF), basic fibroblast growth factor (bFGF) and members of the tumor growth factor-beta (TGF-beta) superfamily, fulfill the functional definition of “neurotrophic factors”. NTs were originally identified as target-derived compounds regulating neuronal survival, growth and differentiation during development. In the adult brain, NTs are necessary to maintain neuronal function and phenotype. Increased expression of NTs is a common response to brain damage (1) that may have a neuroprotective role given the ability of NTs to protect neurons against free radical damage, excitotoxicity and apoptosis (2).

Idiopathic Parkinson’s disease (PD) is a neurodegenerative disorder pathologically de-
fined by a selective loss of dopaminergic (DA) neurons in the pars compacta of the substantia nigra (SNc). Despite the great research efforts of the last decade, the etiopathogenesis of PD is still unknown. L-dopa and DA agonists are currently used to alleviate symptoms of PD, but most treated patients still develop a progressive functional disability that severely affects their quality of life. Given the progressive nature of nigrostriatal degeneration in PD, therapeutic agents capable of slowing down or blocking this process could be clinically significant.

It has been postulated that loss of DA neurons in PD may be accompanied by insufficient trophic support leading to neuronal apoptosis. However, it is not clear whether neuronal death is predominantly apoptotic in PD, or whether a reduced neurotrophic support is involved in the neuronal loss accompanying the disease in humans. Regardless of the causes of PD, NTs, by promoting DA neuronal growth and function and by interfering with neurotoxic processes, could be of therapeutic value.

THE GDNF FAMILY

Glial cell line-derived neurotrophic factor was the first identified member of a family of factors, which includes neurturin (NTN), enovin and artemin (ART), all of which are distant members of the transforming growth factor-beta (TGF-beta) superfamily. GDNF was purified and cloned from a rat glial cell line as a released trophic factor specific for cultured primary DA neurons (3). In addition, GDNF family proteins are potent survival factors for several populations of central and peripheral neurons. At present, GDNF appears to be the most promising trophic factor in the therapy of PD.

Glial cell line-derived neurotrophic factor family members (GFMs) bind to a receptor complex formed by a binding component, the glycosyl-phosphatidylinositol (GPI)-anchored GDNF family receptor (GFR), and a signalling component, the receptor tyrosine kinase Ret (for a review, see 4). According to one model of GDNF signalling, GFR would appear to be involved in GDNF binding with no intrinsic signalling ability, whereas Ret would appear to be responsible for the intracellular signalling, but unable to bind the factor in the absence of GFR.

The importance of GFMs and their receptors in the nigrostriatal circuit is well reflected by their expression in that area. GDNF and NTN are both present in developing striatal neurons and GDNF mRNA has been detected in both cholinergic and GABAergic interneurons of the striatum (5). In the SNc, GDNF mRNA is detectable in the majority of DA neurons. The mRNA for the Ret receptor has also been found in nigral DA neurons, whereas there is no clear indication of its presence in the striatum. GFR receptors show a distinct, albeit overlapping distribution, being expressed both by nigral DA neurons and, to some extent, also in the ventral striatum (6).

Effects of GDNF on DA neurons in culture

Glial cell line-derived neurotrophic factor has the ability, in combination with other factors, to convert rat fetal (E14.5) mesencephalic progenitor cells into tyrosine hydroxylase (TH)-immunoreactive neurons in vitro (7). In embryonic midbrain cultures, GDNF promotes the survival and inhibits the apoptosis of DA neurons (8). It also promotes the biochemical and morphological differentiation of cultured ventral mesencephalic neurons by producing a significant increase in the number of neurite-bearing cells as well as in the extent of their fiber network (9). These effects are specific as GDNF does not increase total neuron or astrocyte numbers nor does it increase transmitter uptake by GABA-containing and serotonergic neurons (3). In addition, GDNF protects cultured DA neurons from the neurotoxic effects of 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine (MPTP) (9), and 6-hydroxydopamine (6-OHDA) (10). As exemplified in Table I, GDNF robustly promotes the survival
and differentiation of midbrain DA neurons in culture providing thereby the rationale for its application in animal models of PD.

The effects of GDNF in animal models of PD

Protection of midbrain DA neurons by GDNF administration has been reported both in rodent and in non-human primate animal models of PD. In rats, the neuroprotective and/or behavioral effects of GDNF have been observed following: i) intranigral injections of 6-OHDA (11), ii) intrastriatal injection of 6-OHDA (12), iii) neurotoxic doses of methamphetamine and MPTP (13) and iv) axotomy-induced degeneration of the medial forebrain bundle (14). Appropriate administration appears the crucial issue in order to achieve maximal survival and trophic effects on nigrostriatal DA pathway and long-term behavioral motor recovery.

Rats that receive unilateral 6-OHDA lesions can be induced to turn repetitively in circles in a direction either ipsilateral or contralateral to the lesion using amphetamine or apomorphine, respectively. Glial cell line-derived neurotrophic factor, when intracerebroventricularly injected, can access basal ganglia structures and have beneficial, although transient, effects on drug-induced rotational behavior (15). In the MPTP-lesioned rhesus monkey, GDNF intracerebrally injected, either alone or in combination with L-dopa and carbidopa, improves bradykinesia, rigidity and postural instability (16).

Intrastriatal GDNF treatment in parkinsonian rats preserves the nigrostriatal DA system and increases axonal sprouting and reinnervation of deafferented striatum to a degree sufficient to reverse spontaneous motor deficits (17). On the other hand, intranigral GDNF administration increases nigral DA neuron survival but does not prevent striatal terminal degeneration in 6-OHDA-lesioned rats (12,15). Repeated nigral GDNF injections lead neither to significant reinnervation of the lesioned striatal target nor to a behavioral recovery (12). Taken together, these results indicate that the striatum is a more suitable site for GDNF administration than the SNc in order to prevent DA terminals from degeneration and/or to facilitate behavioral recovery from motor asymmetry.

Table I - Overview of the effects of various neurotrophic factors on ventral mesencephalic neurons in culture

<table>
<thead>
<tr>
<th>NTs</th>
<th>Survival</th>
<th>Neuritogenesis</th>
<th>Dopaminergic phenotype</th>
<th>Neuroprotection</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDNF</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>3, 8-10</td>
</tr>
<tr>
<td>NTN</td>
<td>+++</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>26</td>
</tr>
<tr>
<td>BDNF</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>50</td>
</tr>
<tr>
<td>NT-3</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>NR</td>
<td>29</td>
</tr>
<tr>
<td>NT-4/5</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
<td>NR</td>
<td>29</td>
</tr>
<tr>
<td>NGF</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NR</td>
<td>51</td>
</tr>
<tr>
<td>bFGF*</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>39</td>
</tr>
</tbody>
</table>

The degree of efficacy in promoting survival, neuritogenesis, dopaminergic phenotype and neuroprotection is expressed in arbitrary units where +++ = highest efficacy, and – = no efficacy.

Abbreviations and symbols: * = effect largely mediated via stimulation of astroglia; NTs = neurotrophic factors; GDNF = glial cell line-derived neurotrophic factor; NTN = neurturin; BDNF = brain-derived neurotrophic factor; NT-3 = neurotrophin-3; NT-4/5 = neurotrophin-4/5; NGF = nerve growth factor; bFGF = basic fibroblast growth factor; NR = not reported.
As exemplified in Table II, GDNF can have potent effects on DA survival, phenotype and motor behavioral recovery in animal models of PD. Despite these results, the main concern as regards the applicability of GDNF in PD is the need to inject repeatedly large amounts of the peptide directly into the brain in order to obtain clinically significant effects.

**GDNF in gene therapy**

The possibility of expressing NTs locally in specific brain areas may avoid potential side effects related to the activation of other brain structures. The introduction of specific therapeutic genes into target brain areas is possible by means of viral vector-mediated direct transfer. This genetic approach obviates the need for high doses and repeated administrations. Therefore, gene transfer based on viral vectors expressing NTs is currently under extensive investigation in animal models of PD.

Striatal injection of adenovirus (Ad) vector-expressing GDNF significantly prevents degeneration of the nigrostriatal DA pathway and reduces amphetamine-induced turning behavior in 6-OHDA- or MPTP-lesioned rats (18). The differential effects of injecting Ad-GDNF near either nigrostriatal DA cell bodies or DA terminals has been compared in aged rats. While similar protection of nigral DA neurons is observed, only striatal GDNF injection protects striatal DA nerve terminals against 6-OHDA-induced damage and prevents behavioral deficits characteristic of unilateral DA depletion (19). Taken together, these reports provide support for a potential therapeutic value of GDNF expression driven by adenoviral vectors in the attempt to prevent further cell death and/or enhance the DA tone of surviving neurons in PD. However, lack of sustained transgene expression, high immunogenicity and potential toxicity may limit the use of adenoviral vectors, at least those of the first generation, for clinical purposes.

Recent developments in lentiviral and recombinant adeno-associated viral vectors (rAAV) have resulted in transgene expression within the CNS detectable for more than 6 months after injection without cytotoxicity (20). A single administration of rAAV-expressing GDNF enhances nigral DA survival both before and after a striatal 6-OHDA lesion (21). Protection of nigral DA neurons in medial forebrain bundle (MFB)-axotomized rats is also obtained after nigral injection of self-inactivating modified lentiviral vector-expressing GDNF (22). Hence, GDNF gene therapy based on novel viral vectors could, potentially, fulfill most of the requirements to qualify as therapeutically relevant for PD: i) biological efficacy; ii) long-

<table>
<thead>
<tr>
<th>NTs</th>
<th>Survival</th>
<th>Neuritogenesis</th>
<th>Dopaminergic phenotype</th>
<th>Behavioral recovery</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDNF</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>17</td>
</tr>
<tr>
<td>NTN</td>
<td>+/++++</td>
<td>–</td>
<td>+/-</td>
<td>4/-</td>
<td>26, 51–53</td>
</tr>
<tr>
<td>NBN/ART</td>
<td>++</td>
<td>NR</td>
<td>++</td>
<td>NR</td>
<td>27</td>
</tr>
<tr>
<td>BDNF</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>++</td>
<td>23, 36</td>
</tr>
<tr>
<td>NT-3</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>24, 38</td>
</tr>
<tr>
<td>NT-4/5</td>
<td>++</td>
<td>++</td>
<td>NR</td>
<td>++</td>
<td>38</td>
</tr>
<tr>
<td>aFGF</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>54, 55</td>
</tr>
<tr>
<td>bFGF</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>+</td>
<td>56</td>
</tr>
</tbody>
</table>

The degree of efficacy in promoting survival, neuritogenesis, dopaminergic phenotype and behavioral recovery is expressed in arbitrary units, where +++ = highest efficacy and – = no efficacy.

Abbreviations: NTs = neurotrophic factors; GDNF = glial cell line-derived neurotrophic factor; NTN = neurturin; NBN/ART = neublastin/artemin; BDNF = brain-derived neurotrophic factor; NT-3 = neurotrophin-3; NT-4/5 = neurotrophin-4/5; aFGF = acidic fibroblast growth factor; bFGF = basic fibroblast growth factor; NR: not reported.
term expression; iii) lack of toxicity coupled with a wide therapeutic window. However, further studies are still necessary to evaluate long-term safety.

**GDNF in cell replacement therapy**

The ability of GDNF to regulate developmental neuron survival and differentiation of DA neurons may be used to enhance the success of cerebral grafts and to induce stem cells to phenotypically differentiate into DA neurons. GDNF administration adjacent to the embryonic DA graft not only increases graft survival but also restores the nigrostriatal DA pathway in unilateral 6-OHDA-lesioned rats, thus leading to a lasting decrease in drug-induced rotational behavior (23). Pre-treatment with GDNF is also effective in increasing graft-derived fiber outgrowth and improving contralateral forelimb function and amphetamine-induced rotational behavior in unilateral 6-OHDA-lesioned rats (24). Co-graft of a GDNF-secreting Schwann cell line with embryonic ventral mesencephalic cells improves graft survival and promotes neurite outgrowth into the host neuropil as well as axonal growth in the striatum (25). Taken together, these reports suggest that GDNF could be effectively used in conjunction with cell replacement therapies.

**GDNF-related NTs**

Neurturin is expressed in the nigrostriatal system, and it exerts potent effects on survival and function of midbrain DA neurons. NTN mRNA is sequentially expressed in the ventral midbrain and striatum during development and supports survival of cultured embryonic DA neurons (6). The structural homology and the similar potency and efficacy of NTN and GDNF in promoting DA neuron survival (Tables I and II) suggest that GDNF and NTN may exert redundant trophic influences on nigral DA neurons (26). To date, there are contrasting reports on the effectiveness of NTN in PD animal models, probably due to the different experimental conditions adopted (Table II). Recently, new GDNF-family members, such as neublastin (NBN) (27), identical to ART, have been cloned. As with GDNF, protection of nigral DA neurons has been reported both in vitro and in vivo (27). However, further investigations are necessary to clarify whether NTN and NBN/ART might be considered potential therapeutic agents in PD.

**CLASSICAL NTs**

All the NTs belonging to the NGF family bind to the p75NTR low-affinity receptor, but their ligand specificity is determined by binding activating transmembrane receptor tyrosine kinases, the trks. NGF acts through trkA; BDNF and NT 4/5 act through trkB whereas NT-3 acts through trkC and, less potently, through trkA and trkB. In adult CNS, p75NTR receptor, which is related to proteins belonging to the tumor necrosis receptor-alpha family, appears to be mainly co-expressed with trkA. When not associated with trk receptors, p75NTR can mediate neuronal death (28). mRNAs encoding trkB and trkC, the functional high-affinity receptors for BDNF, NT-4/5 and NT-3 respectively, are expressed in the SN of the adult rat brain, as well as in cultures of developing ventral mesencephalon. The NGF receptor trkA is not expressed in ventral mesencephalic DA neurons and NGF appears to be only a weak trophic factor for DA neurons, most likely acting through indirect mechanisms.

**BDNF**

Among the NTs, BDNF is considered an interesting candidate for the development of therapeutic strategies applicable in PD (Table II). BDNF promotes the survival, morphological and biochemical differentiation of DA neurons in fetal midbrain cultures (29). In addition, BDNF protects DA neurons from the neurotoxic effects of MPP⁺ and 6-OHDA (30).

The distribution of BDNF and its high-affinity receptor, trkB, in the nigrostriatal system suggests a critical role of this neurotrophin in the survival of different resident neuronal populations.
TrkB mRNA has been found in both cholinergic and GABAergic striatal interneurons (31). The expression pattern of BDNF and trkB in the striatum has suggested that BDNF could act both as a target-derived trophic factor for DA neurons projecting from the SNc, and as an autocrine factor affecting the survival of neurons within the striatum itself. In the SNc, the mRNAs of both BDNF and trkB have been detected in DA neurons (32). The co-expression in nigral DA neurons of BDNF and trkB supports the idea that BDNF can affect neuronal survival by both paracrine and autocrine mechanisms.

Several groups have investigated the survival-promoting effects of BDNF on the nigrostriatal DA pathway and its capacity to prevent behavioral motor asymmetries in animal models of PD (Table II). In parkinsonian rats, prevention of nigral cell loss is observed both after supranigral injection of engineered BDNF secreting fibroblasts (33) and after three-week infusion of BDNF in the SNc (34). Intrastriatal grafts of engineered fibroblast- or astrocyte-expressing BDNF partially prevent nigrostriatal DA degeneration without affecting tyrosine hydroxylase-immunoreactive (TH-IR) nerve terminals of 6-OHDA-lesioned rats (35). The effects of BDNF appear to be more transient than those of GDNF, since decrease in rotational behavior and KCl-induced DA release is observed in rats 1-3 months after the administration of GDNF- but not of BDNF-bridged grafts (23). Administration of rAAV-expressing BDNF in the SN of 6-OHDA-lesioned rats reduces amphetamine-induced turning behavior but does not, in spite of long-term transgene expression, affect the number of nigral TH-labeled neurons (36). Thus, although BDNF is as effective as GDNF in promoting DA neuronal survival, it is not as effective as GDNF in inducing and maintaining the DA phenotype (Table II).

**NT-3 and NT-4/5**

NT-3, which acts through the trkC receptor, has broadly similar effects to BDNF in promoting the survival and differentiated phenotype of cultured DA neurons. Although BDNF and NT-4/5 are thought to act through the same high-affinity receptor (trkB), these two NTs have distinct as well as overlapping actions in vitro. For instance, NT-4/5 had no effect, in marked contrast to BDNF and NT-3, on the DA uptake capacity of cultured mesencephalic neurons (37). In addition, these factors appear less promising than GDNF (Table II) in experimental animal models of PD. While NT-3 and NT-4/5 are nearly as effective as GDNF in promoting DA neuronal survival, they are less effective than GDNF in promoting functional and behavioral recovery (24, 38).

**OTHER TROPHIC FACTORS**

In addition to GDNF and certain NTs belonging to the classical NT family, basic fibroblast growth factor (bFGF), transforming growth factor alpha (TGF-alpha), epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor-BB (PDGF-BB) and growth/differentiation factor 5 (GDF5), have proven to increase DA neuron survival in cultured mesencephalic neurons. As exemplified in Table II, in experimental animal models of PD, bFGF and acidic fibroblast growth factor (aFGF) appear to be moderately effective in promoting functional and behavioral recovery. However, bFGF, EGF, PDGF-BB, GDF5 and TGF-alpha effects are predominantly indirect, as they occur mainly through the stimulation of glial cell division and release of trophic factors (39).

**NTs in PD**

In spite of the bulk of preclinical research conducted so far, the few studies concerning NTs in human CNS are rather scattered and do not shed any light on the role of NTs and their receptors in PD (40, 41). A number of clinical trials have either been conducted or are ongoing to evaluate the safety and the therapeutic benefits of
NTs in clinical settings associated with loss of neuronal function, including neurodegenerative diseases (see Table III). So far, only GDNF has been tested in PD patients: more specifically, while a case report showed no benefit and severe side effects following intracerebroventricular injections of GDNF in a patient with PD (42), GDNF exposure of fetal DA cells, prior to putaminal implant, was reported to enhance graft survival in two patients with PD (43). These preliminary results raise the possibility that NTs may perhaps be employed to promote a better graft survival in the surgical approach to PD treatment.

CONCLUSIONS

Since certain NTs, in particular GDNF and BDNF, are neuroprotective in animal models of PD, the rationale for developing therapies involving the use of native or recombinant NTs is strong. However, it is not known how closely neurotoxin-induced lesions mimic the state of diseased neurons in human PD. While in experimental animals a PD-like syndrome is obtained through an acute chemical insult (MPTP or 6-OHDA), the naturally occurring disease is, in contrast, a slow and progressive process due to unknown causes. Thus, benefits observed in animal models with the use of NTs may not necessarily be reproduced in clinical trials. In addition, beneficial effects could be hampered by potentially occurring side effects consequent to a chronic treatment (e.g., aberrant neuritic outgrowth, increased function of other responsive neuronal populations, peripheral effects). Lastly, recent clinical trials with NTs in other neurodegenerative diseases have been disappointing; e.g., GDNF did not appear to be beneficial in amyotrophic lateral sclerosis (ALS) patients and, in

Table III - Overview of the clinical effects of neurotrophic factors in neurodegenerative diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>NTs</th>
<th>Trials/clinical cases</th>
<th>Status/outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease (PD)</td>
<td>– GDNF (i.c.v.)</td>
<td>– Case report</td>
<td>– Severe side effects</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>– Human fetal nigra+GDNF</td>
<td>– 2 cases</td>
<td>– Enhanced graft survival</td>
<td>43</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
<td>– GDNF</td>
<td>– Phase II</td>
<td>– Discontinued</td>
<td><a href="http://www.amgen.com">http://www.amgen.com</a></td>
</tr>
<tr>
<td></td>
<td>– BDNF (s.c.)</td>
<td>– Phase III</td>
<td>– No efficacy</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>– BDNF (i.t.)</td>
<td>– Phase II</td>
<td>– Ongoing</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>– BDNF (s.c. high dose)</td>
<td>– Phase II</td>
<td>– Ongoing</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>– CNTF (s.c.)</td>
<td>– Phase II</td>
<td>– Discontinued (S.E.)</td>
<td>58</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>NGF (s.c.)</td>
<td>Phase III</td>
<td>No efficacy</td>
<td><a href="http://www.gene.com">http://www.gene.com</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>NGF</td>
<td>3 cases</td>
<td>? (Hyperalgesia)</td>
<td>60</td>
</tr>
<tr>
<td>Constipation (spinal cord injury)</td>
<td>NT-3</td>
<td>Phase II</td>
<td>Ongoing</td>
<td><a href="http://www.amgen.com">http://www.amgen.com</a></td>
</tr>
</tbody>
</table>

Abbreviations: NTs = neurotrophic factors; GDNF = glial cell line-derived neurotrophic factor; BDNF = brain-derived neurotrophic factor; CNTF = ciliary neurotrophic factor; NGF = nerve growth factor; NT-3 = neurotrophin-3; i.c.v. = intracerebral ventricular; s.c. = subcutaneous; i.t. = intrathecal; P.O. = per os.
fact, displayed an array of side effects, while trials conducted with BDNF have not been satisfactory. These failures may, at least in part, be the consequence of the poor pharmacological properties of NTs (e.g. short in vivo half-lives due to protein degradation, low blood brain barrier permeability) (44).

On the other hand, to improve CNS delivery and avoid some of the unwanted effects of systemic administration of NTs, gene therapy techniques have recently been developed and tested in animal models. The use of recombinant viruses to deliver GDNF or other NTs could avoid repeated invasive intracerebral procedures. Yet, several improvements are needed in current gene therapy technology: in safety, cell specificity, stability and possibility of regulation of gene expression.

Neurotrophic factors could also be used in combination with other therapeutic strategies such as, for instance, cell replacement interventions. In fact, one limitation of grafting fetal neural tissue or expanded populations of human CNS progenitor cells into the brain is the relatively poor survival of the implanted cells. The ability of GDNF and BDNF to regulate the survival and differentiation of developing DA neurons can be used to enhance the success of cerebral grafts and/or to induce stem cells to phenotypically differentiate into DA neurons. Additionally, GDNF can be delivered by inserting into the striatum cells engineered to produce GDNF (45).

A further way to overcome some of the problems linked to the therapeutic use of NTs might be the employment of low molecular weight compounds, either possessing intrinsic neurotrophic activity or capable of modulating the synthesis, release or signalling properties of endogenous NTs in the nigrostriatal system. Potential candidates include immunophilins (46), and NT mimetics. To date, however, no data is available on the possibility of producing low molecular weight compounds capable of mimicking the activity of GDNF or BDNF. Although this is due to the relatively poor information as regards the molecular details of their binding to receptors, the recent reports on NT mimicry strategies conducted in the field of NGF suggest that such an approach is feasible. For example, small cyclic peptides, capable of mimicking NGF β-turn structures that bind specifically to the trkA receptor, behave as trkA antagonists by competing with NGF for high affinity binding sites (47), while non-peptidic small molecule β-turn analogs of an anti-trkA monoclonal antibody have been reported to function as specific trkA agonists (48). To circumvent the problem of molecular instability, D-amino acid peptido-mimetics, more protease-resistant than L-amino acid peptides and with longer half-lives, may be soon available (49). In addition, the development of agents capable of specifically modulating p75NTNR receptor activity, without affecting the survival promoting functions of trks, may be relevant for the treatment of neurodegenerative disorders, in which uncontrolled apoptotic processes may be implicated. Thus, receptor or ligand modeling may give way, also in the case of BDNF or GDNF, to approaches similar to those mentioned above for NGF, with the aim of obtaining a fine tuning of neurotrophic activity in PD.

Taken together, the experimental evidence here reviewed suggests that NTs and their receptors, in particular GDNF and BDNF, may be important therapeutic targets in PD. Unfortunately, to date, none of the identified NTs is specific for DA neurons and all of them, on the other hand, can elicit a wide variety of effects. Therefore, further knowledge regarding the potential consequences of prolonged exposure to “therapeutic” doses of NTs is needed. It will also be necessary to develop ways of efficiently delivering NTs to the brain and/or of locally stimulating their synthesis or of mimicking their activity. Hopefully, future research linking functional genomics with structural molecular chemistry may allow the design of drugs (e.g. small molecules, peptide mimetics) capable of modulating and/or mimicking specific functions of defined NTs in PD.
REFERENCES

10. Kramer BC, Goldman AD, Mytilineou C. Glial cell line derived neurotrophic factor promotes the recovery of dopamine neurons damaged by 6-hydroxydopamine in vitro. Brain Res 1999;851:221-227
17. Rosenblad C, Martinez-Serrano A, Bjork-
lund A. Intrastriatal glial cell line-derived neurotrophic factor promotes sprouting of spared nigrostriatal dopaminergic afferents and induces recovery of function in a rat model of Parkinson’s disease. Neuroscience 1998;82:129-137
24. Espejo M, Cutillas B, Arenas TE, Ambrosio S. Increased survival of dopaminergic neurons in striatal grafts of fetal ventral mesencephalic cells exposed to neurotrophin-3 or glial cell line-derived neurotrophic factor. Cell Transplant 2000;9:45-53
25. Wilby MJ, Sinclair SR, Muir EM et al. A glial cell line-derived neurotrophic factor-secreting clone of the Schwann cell line SCTM41 enhances survival and fiber outgrowth from embryonic nigral neurons grafted to the striatum and to the lesioned substantia nigra. J Neurosci 1999;19:2301-2312
33. Frim DM, Uhler TA, Galpern WR, Beal MF, Breakefield XO, Isacson O. Implanted fibroblasts genetically engineered to produce brain-derived neurotrophic factor prevent 1-methyl-4-phenylpyridinium toxicity to dopaminergic neurons in the rat. Proc Natl Acad Sci USA 1994;91:5104-5108

34. Volpe BT, Wildmann J, Altar CA. Brain-derived neurotrophic factor prevents the loss of nigral neurons induced by excitotoxic striatal-pallidal lesions. Neuroscience 1998;83:741-748


37. Hyman C, Juhasz M, Jackson C, Wright P, Ip NY, Lindsay RM. Overlapping and distinct actions of the neurotrophins BDNF, NT-3, and NT-4/5 on cultured dopaminergic and GABAergic neurons of the ventral mesencephalon. J Neurosci 1994;14:335-347


49. Chaiken IM, Williams WV. Identifying sturc-
51. Rosenblad C, Kirik D, Devaux B, Moffat B, Phillips HS, Bjorklund A. Protection and regeneration of nigral dopaminergic neurons by neurturin or GDNF in a partial lesion model of Parkinson’s disease after administration into the striatum or the lateral ventricle. Eur J Neurosci 1999;11:1554-1566
55. Jin BK, Iacovitti L. Dopamine differentiation factors increase striatal dopaminergic function in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mice J Neurosci Res 1996;43:331-334
57. No authors listed. A controlled trial of recombinant methionyl human BDNF in ALS: The BDNF Study Group (Phase III). Neurology 1999;52:1427-1433