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GDNF and PD: Less Common Points of View

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1. Introduction

Glial cell line-derived neurotrophic factor (GDNF) was identified in 1993 (Lin et al., 1993), and since then it has been considered a strong survival factor for dopaminergic neurons of the nigrostriatal pathway that degenerate in Parkinson's disease (PD). This has led to the proposal of GDNF as a potential therapy to slow down, halt or reverse neurodegeneration in PD. Thus, the link GDNF-PD is quite instantaneous, and difficult to keep away from. In this chapter we want to explore less common perspectives in this relationship, and we propose to look at this association from unconventional/emerging points of view, one might say, beyond the typical top10. We will discuss some aspects of PD pathophysiology and alternative therapeutic approaches in PD from a GDNF point of view.

Epidemiological studies show a greater prevalence of PD in men than in women, and there are also gender differences in the progression of the symptoms and responses to L-DOPA treatment (Miller & Cronin-Golomb, 2010). Although the reasons for these gender differences in PD remain to be elucidated, there is growing evidence that estrogen may play a role in this phenomenon. We will present evidences that GDNF may account for the neuroprotection of dopaminergic neurons promoted by estrogen and thereby help to explain the lower incidence of PD in women.

Neuroinflammation is recognized as a major factor in PD pathogenesis, and increasing evidence suggest that microglia is the main source of inflammation contributing to dopaminergic degeneration (Tansey & Goldberg, 2009). Astrocytes, on the other hand, can act as physiological regulators preventing excessive microglial responses (Lynch, 2009). We propose that GDNF can be a key player in astrocytes modulation of microglia activation in the *substantia nigra*. Therefore, a GDNF therapy to PD may not only act directly on dopaminergic neurons themselves, but also indirectly through the modulation of glial crosstalk and neuroinflammation.

Several attempts have been made to increase GDNF at lesion sites aiming at neuroprotection/neuroregeneration. However, the delivery of GDNF to the central nervous

system (CNS) is challenging because GDNF is unable to cross the blood–brain barrier. One possibility to overcome this limitation is to conjugate or fuse GDNF with viral proteins, antibodies for transferrin or insulin receptors, or with a fragment of the tetanus toxin, which enable it to cross the blood–brain barrier. Another option is to use molecules that induce GDNF expression or enhance its signaling, and we will emphasize natural compounds. These molecules may prove to be an alternative therapeutic option for PD as herbal extracts are increasingly being reported to be neuroprotective in animal models of PD. Unconventional ways to increase GDNF levels in the brain include dietary manipulations, physical exercise, cognitive stimulation or acupuncture, and these may represent novel drug-free and non-invasive approaches for disease prevention and treatment, an issue that will also be addressed.

Neurodegenerative diseases are puzzling and there is still a long way before we can have answers to all our questions and concerns. In this chapter we hope to disclose new links between GDNF and the pathophysiology of PD, and bring together data that enable a new view on the protective actions of several compounds and lifestyles capable of modulating GDNF levels, which may have therapeutic implications. We believe that this chapter may help in some way to draw attention to new directions of research, and to explore the GDNF-PD route with new eyes.

2. Gender differences in PD

Epidemiological studies have suggested gender differences in PD risk, symptom severity, and treatment outcome (Miller & Cronin-Golomb, 2010). A higher prevalence of PD in men (Baldereschi et al., 2000; Kurtzke & Goldberg, 1988; Marder et al., 1996; Mayeux et al., 1992; Wooten et al., 2004), with a two-fold greater relative risk of PD in men than women (Gillies & McArthur, 2010b), were also reported. In what concerns symptom severity, males present worse rigidity, more frequent symptoms such as writing difficulties, fumblingness, speech and gait problems, whereas women exhibit more levodopa-induced dyskinesia (Miller & Cronin-Golomb, 2010). In addition, sex differences in response to anti-parkinsonism medications have also been reported (Brann et al., 2007). There is greater levodopa bioavailability in women, with higher plasma concentration, so the mean levodopa dosage is lower for women than for men (reviewed by Shulman, 2007). Furthermore, the treatment with levodopa promotes more significant improvements of motor function in women than in men (reviewed by Brann et al., 2007).

While the reason for the sex differences in PD remains to be elucidated, there is growing evidence that estrogen may play a neuroprotective role. This hypothesis is also supported by data showing that shorter exposures to estrogen during life, including fertile life length shorter than 36 years, and cumulative length of pregnancies longer than 30 months, are associated with younger age at onset of PD. In contrast, the use of postmenopausal estrogen replacement therapy seems to reduce the risk of developing the disease (Currie et al., 2004). Also supportive of the protective role of estrogen are data showing that situations corresponding to low endogenous estrogen levels, such onset of menses and menopause or withdrawal of hormone replacement therapy, result in a worsening of parkinsonian symptoms (Gillies & McArthur, 2010b). In contrast, the results obtained in gonadectomized adult male rats and mice exposed to testosterone and dihydrotestosterone indicate that androgens repress the expression of a midbrain dopaminergic phenotype (M.L. Johnson et al., 2010).

In addition to the pro-dopaminergic action of estrogen, an increasing amount of evidence suggests an inherent sex dimorphism in the nigrostriatal pathway. *In vivo* real-time imaging techniques in healthy humans showed greater amphetamine-stimulated striatal dopamine release in men than in women (Munro et al., 2006), and significantly higher striatal 18F-fluorodopa uptake in women (Laakso et al., 2002). Moreover, it has been shown that the activation of estrogen receptors induces differentiation of human neural stem cells, giving rise to dopaminergic neurons (Diaz et al., 2009), a process that may facilitate the replacement of neurons in the course of the disease progression. In addition, the healthy male nigrostriatal dopaminergic pathway expresses higher levels of genes implicated in PD pathogenesis such as α-synuclein and PTEN-induced putative kinase 1 (PINK-1) (Cantuti-Castelvetri et al., 2007).

2.1 Estrogen-mediated neuroprotection in PD models

17β-estradiol, the estrogen stereoisomer with female hormone activity and with high affinity to estrogen receptors, has been shown, both *in vitro* and *in vivo*, at least in female rodents, to protect dopaminergic neurons from different toxic insults such as 6-hydroxydopamine (6-OHDA) (Murray et al., 2003), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or methamphetamine (Bourque et al., 2009). In MPTP mouse models of PD, 17β-estradiol prevents the depletion of striatal dopamine, the reduction of dopamine transporter (DAT) binding and expression, and the decrease of tyrosine hydroxylase (TH)-immunoreactive cells (Callier et al., 2001; D'Astous et al., 2004; Dluzen et al., 1996; Jourdain et al., 2005; Ramirez et al., 2003). Moreover, male mice have been reported to be more sensitive to the toxicity induced by MPTP or methamphetamine than female mice (Bourque et al., 2009). In addition, 17β-estradiol was also shown to be protective against superoxide-, H_2O_2- or glutamate-induced neurotoxicity in primary neuronal mesencephalic cultures (Sawada et al., 1998).

Most studies on the neuroprotective effects of 17β-estradiol have been developed in female rodents, and the results on the protective effects of estrogen in male rodents are still controverse (Bourque et al., 2009; Murray et al., 2003). Both the dose of the hormone and the time of administration in relation to the lesion induction seem to be determinant to the results achieved. Although there are reports showing that 17β-estradiol therapy reduces dopaminergic lesion in females but not in males (Bourque et al., 2009; B. Liu & Dluzen, 2007), recent results from our group show that 17β-estradiol, administered to male rats at a dose regimen that mimics the female physiological levels of the steroid protects dopaminergic cells from a mild lesion induced by intrastriatal administration of 6-OHDA (De Campos et al., 2010). The discrepancies between the results obtained in different studies may also be influenced by differences in the lesion model/volume, or the use of intact or gonadectomized animals, thus altering the contribution of androgens.

2.2 Estrogen receptors involved in the neuroprotection of dopaminergic neurons

The expression of estrogen receptors (ERs) in the *substantia nigra* and striatum, as assessed by *in situ* hybridization, autoradiography, immunohistochemistry or Western blot analysis, has been reported as sparse or absent (Gillies & McArthur, 2010a). ERβ has been reported to be absent from the male mouse *substantia nigra*, and ERα expression was shown not to colocalize with TH (Gillies & McArthur, 2010a). Moreover, in rodents the striatum seems to lack ERβ, whereas ERα is present at low levels, although possibly at higher levels in female

compared with male mice (Rodriguez-Navarro et al., 2008). Nevertheless, the modulation of dopamine D2 receptors and DAT by 17β-estradiol has been suggested to involve ERβ, whereas studies using selective ER ligands favor a role for ERα over ERβ in mediating estrogenic neuroprotection (Morissette et al., 2008). Taken together, the results may also suggest that the effect of 17β-estradiol on the nigrostriatal pathway could involve alternative targets (Dluzen, 2005).

It is now well documented that estrogen produces its effects by classic (also called genomic) and non-classic (or non-genomic) actions. The classic pathway involves the activation of intracellular receptors and the regulation of gene transcription. The non-classical pathway is generally associated with more rapid effects (from seconds to minutes) and is initiated by the interaction of 17β-estradiol with receptors in the plasma membrane (Bourque et al., 2009). In the brain, the actions of 17β-estradiol mediated through membrane-associated receptors involve the activation of two different signaling pathways, the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol-3 kinase (PI3-K)/Akt pathway (Morissette et al., 2008).

2.3 Contribution of GDNF to estrogen-mediated neuroprotection

The interactions between 17β-estradiol and neurotrophic factors, namely the ability of the former to regulate the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-I (IGF-I), artemin, their receptors or signaling pathways, are well documented (Dittrich et al., 1999; Garcia-Segura et al., 2007; Ivanova et al., 2001; J. Kang et al., 2010; Pan et al., 2010; Pietranera et al., 2010; J. Zhou et al., 2005). The expression of GDNF is also modulated by estrogens. As mentioned above, 17β-estradiol, through membrane-associated receptors, can activate the PI3-K/Akt pathway and regulate transcription factors such as NF-kB and cAMP response element binding protein (CREB) (Bourque et al., 2009), which are known to be involved in the control of GDNF expression (Saavedra et al., 2008). 17β-estradiol induces the expression of GDNF in spinal cord astrocyte cultures, and this increase in GDNF rescues spinal motoneurons from AMPA-induced toxicity (Platania et al., 2005). In hypothalamic cultures, 17β-estradiol up-regulates the expression of GDNF in neurons but not in astrocytes (Ivanova et al., 2002). These observations suggest a region-dependent effect on the cell type responsible for GDNF production in response to 17β-estradiol, which may be related to the presence/absence of estrogen receptors in different cell types depending on their location.

The induction of GDNF expression by 17β-estradiol in hypothalamic cell cultures is not prevented by the nuclear receptor antagonist ICI 182,780, indicating that it is mediated by non-classical estrogen signaling. In contrast, it is inhibited by cAMP/PKA and calcium signaling antagonists, suggesting that intracellular calcium and cAMP/PKA signaling are required for GDNF increase in neuronal cells in response to 17β-estradiol. GDNF regulation by 17β-estradiol was also investigated in neonatal astroglial and embryonic mesencephalic neuronal cultures (Kipp et al., 2006). In this case, the up-regulation of GDNF transcription occurs in astrocytes but not in neurons, and the effect is not prevented by ICI 182,780, but is abrogated by interrupting the intracellular calcium signaling or the MAPK signal transduction system (Kipp et al., 2006). In addition, unpublished results from our group show that 17β-estradiol up-regulates GDNF levels in neuron-glia ventral midbrain postnatal cultures, and potentiates the reported L-DOPA- or H_2O_2-induced GDNF up-regulation in the same model (Saavedra et al., 2005, 2006). Estradiol-induced increase of GDNF levels is

not blocked by ICI 182,780, and can be induced by estradiol-BSA, a membrane impermeable form, thus supporting the idea that 17β-estradiol is acting through a non-classical pathway (Fig. 1). Although GDNF up-regulation occurs in astrocytes, it is dependent on the presence of neurons indicating that neurons play a crucial role in the signaling process. GDNF neutralization and siRNA-mediated GDNF knockdown experiments clearly demonstrate the participation of this GDNF up-regulation in the neuroprotection provided by 17β-estradiol in 6-OHDA-challenged cultures (De Campos et al., 2010).

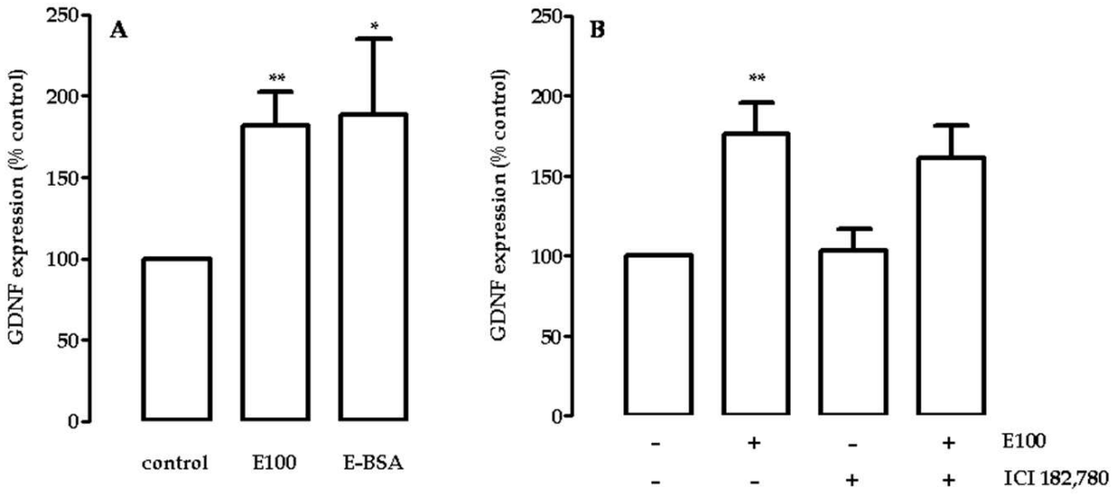

Fig. 1. Contribution of membrane and intracellular estrogen receptors to 17β-estradiol-induced GDNF expression in *substantia nigra* cultures. Cells were incubated for 48 h with 100 nM 17β-estradiol (E100) or with 10 nM membrane-impermeable conjugate estradiol-BSA (E-BSA) **(A)**, or with 100 nM 17β-estradiol in the absence (-) or presence (+) of 10 mM ICI 182,780, a specific blocker of intracellular estrogen receptors **(B)**. Cell extracts were prepared for Western blot analysis of GDNF levels. Data shown are the mean ± S.E.M. of up to nine independent experiments performed in triplicate. Statistical analysis was performed using one-way ANOVA followed by Dunnett's (A) or Bonferroni's test (B). *$P < 0.05$ and **$P < 0.01$ as compared to control.

2.4 Does GDNF contribute to the antioxidant actions of estrogen?

Oxidative stress is considered an important contributor to the neurodegeneration associated with PD, and several markers of oxidative damage are increased in the *substantia nigra pars compacta* of PD patients (Jenner, 2003; Przedborski & Ischiropoulos, 2005). The antioxidant properties of estradiol have long been recognized (Mooradian, 1993), and have been related with the hydroxyl group in the C3 position on the A ring of the steroid structure (Behl et al., 1997). The ability of estrogen to potently restrain free radical production provides an additional mechanism for estrogen-mediated neuroprotection in PD. Accordingly, estradiol suppresses oxidative stress and protects neuronal cells from death induced by oxidant agents (Behl et al., 1997; Mooradian, 1993; Sawada et al., 1998). Interestingly, the ability of GDNF to protect dopaminergic neurons has also been related with antioxidant properties involving the up-regulation of the antioxidant enzymes glutathione peroxidase, superoxide dismutase and catalase (Chao & Lee, 1999; Cheng et al., 2004). Since one of the mechanisms

responsible for the neuroprotective effects of estradiol is a reduction in oxidative stress, and the protective effects of GDNF involve a decrease in oxidative stress (M.P. Smith & Cass, 2007), it is tempting to speculate that GDNF may contribute to 17β-estradiol-induced reduction of oxidative stress. Indeed, in a recent work from our group we demonstrate that pre-treatment with 17β-estradiol, which increases GDNF expression, completely prevents the increase of 4-hydroxynonenal levels induced by 6-OHDA in the *substantia nigra* (De Campos et al., 2010).

2.5 Anti-apoptotic role of estrogen

Oxidative stress can cause neuronal apoptosis (Ratan et al., 1994; Tan et al., 1998) and has been considered as one of the major causes of dopaminergic degeneration (Mochizuki et al., 1996; Przedborski & Ischiropoulos, 2005). The neuroprotection mediated by estrogen involves the modulation of apoptosis-related genes (Garcia-Segura et al., 1998; Singer et al., 1998; Vegeto et al., 1999). Sawada and colleagues (2000) studied the anti-apoptotic mechanism induced by estradiol on nigral dopaminergic neurons. They show that estradiol suppresses gene transcription through the AP-1 element, inhibits the transcription of pro-apoptotic genes, and up-regulates the anti-apoptotic Bcl-2, with the consequent reduction of caspase activation. Interestingly, GDNF is able to support the viability of postnatal nigral dopaminergic neurons and embryonic human mesencephalic neurons by inhibiting apoptotic cell death naturally occurring *in vitro* (Burke et al., 1998; Clarkson et al., 1997). Moreover, GDNF also attenuates 6-OHDA- (Ding et al., 2004), bleomycin sulfate- and L-buthionine-[S,R]-sulfoximine-induced apoptosis in cultured dopaminergic neurons (Sawada et al., 2000b). Recent results from our group show a reduction in the number of annexin V-positive dopaminergic neurons in the *substantia nigra* of animals treated with 17β-estradiol before 6-OHDA injection compared with animals injected with 6-OHDA alone (De Campos et al., 2010). Since 17β-estradiol treatment increases GDNF levels in these animals, one may hypothesize that GDNF up-regulation contributes to the anti-apoptotic effect of 17β-estradiol treatment upon a 6-OHDA challenge.

2.6 Anti-inflammatory role of estrogen and dopaminergic neuroprotection

Estrogens control glial activation and the expression of inflammatory mediators implicated in neuroinflammation and neurodegeneration, such as cytokines and chemokines (reviewed by Morale et al., 2006). 17β-estradiol down-regulates glial activation promoted by MPTP in the *substantia nigra* and striatum (Tripanichkul et al., 2006), and it is also able to prevent the increase in the levels of inflammatory mediators, such as the inducible form of nitric oxide synthase (NOS) in response to lipopolysaccharide (LPS), a component of the cell wall of gram-negative bacteria (Vegeto et al., 2001). Activation of ERs in microglial cells blocks nitric oxide (NO) production (Vegeto et al., 2001) and prevents toxicity in mesencephalic neuronal cultures exposed to conditioned medium from LPS-activated microglia (Block & Hong, 2005). In mesencephalic cultures, 17β-estradiol inhibits microglial activation and promotes neuroprotective effects through the activation of both ERα and ERβ (X. Liu et al., 2005). Therefore, estrogens were suggested to promote the switch of microglia from a neurotoxic to a neuroprotective state (Morale et al., 2006). GDNF may also contribute to the anti-inflammatory activity of estrogen. Indeed, we have shown the effectiveness of GDNF in maintaining microglia in a resting state (Rocha et al., 2010). Moreover, Xing and collegues (2010), using midbrain slice cultures, demonstrated that GDNF can inhibit both LPS-induced microglia activation and dopaminergic cell death (see more details in the next section).

3. The vigilant glia

Microglia are the surveillance cells in the CNS, exquisitely sensitive to brain injury and disease, altering their morphology and phenotype to adopt an activated state in response to pathophysiological brain insults. In the adult healthy brain, the majority of microglia is in a "resting" state, monitoring for pathogens and changes in the surrounding microenvironment. Neurons express cell-surface ligands that interact with receptors on the surface of microglia to induce these highly specialized cells to adopt a resting phenotype. For example, CD200 expressed by neurons binds to its receptor CD200R on the microglial cell surface. The regulatory role of CD200-CD200R signaling has been compared to a "break" on innate immunity (X.J. Wang et al., 2007). Moderately activated microglia plays a homeostatic role in the CNS by scavenging neurotoxins, removing dying cells and cellular debris, and promoting collateral sprouting through the release of trophic factors (Block et al., 2007). The designation "activated microglia" comprises highly plastic cells with numerous functionally distinct phenotypes that are not readily apparent from either their morphology or from a limited number of cell-surface antigens that they are known to express (Perry et al., 2010).

3.1 Protective microglia

In the nigrostriatal system, activated microglia and macrophages promote axonal growth and sprouting of dopaminergic neurons after a mechanical lesion to the striatum (Batchelor et al., 1999). After striatal injury, sprouting dopaminergic fibers grow towards and surround macrophages expressing GDNF and BDNF mRNA (Batchelor et al., 1999). The dopaminergic sprouting after striatal injury was shown to involve the production of GDNF by macrophages at the wound site, since preventing GDNF expression with antisense oligonucleotides resulted in a marked decrease in the intensity of the periwound sprouting as revealed by immunohistochemistry and activity of DAT (Batchelor et al., 2000). Moreover, dopaminergic sprouting was related to a gradient of GDNF (Batchelor et al., 2002). These data clearly show that activated microglia and macrophages induce dopaminergic sprouting through synthesis of neurotrophic factors. Interleukin-1 (IL-1) is also involved in dopaminergic sprouting since IL-1 receptor knockout mice do not show neuronal sprouting after a 6-OHDA lesion (Parish et al., 2002). IL-1, produced by reactive microglia and macrophages, induces astrogliosis. Therefore, activated microglia and macrophages appear to stimulate dopaminergic sprouting both directly, by the secretion of neurotrophic factors, and indirectly by the secretion of IL-1 and the stimulation of reactive astrocytosis (Ho & Blum, 1998; Parish et al., 2002). Furthermore, a protective role of microglia in the dopaminergic system was also suggested by results showing that striatal injection of 6-OHDA increases the number of neuron/glial 2 (NG2) cells coexpressing the microglia marker Iba1 and GDNF, both in the striatum and *substantia nigra*. Morevover, 64% of the surviving TH-positive cells are localized in the vicinity of NG2/Iba1/GDNF-positive cells (Kitamura et al., 2010). In addition to the production of GDNF by activated microglia and macrophages upon a mechanical injury to the striatum (Batchelor et al., 1999; Liberatore et al., 1997), it was also described to occur in the injured spinal cord (Satake et al., 2000; Widenfalk et al., 2001), and in cultured macrophages (Hashimoto et al., 2005). Ischemia also induces microglia in cerebral cortex to express GDNF (Wei et al., 2000a). Besides, blockade of ischemia-induced microglia activation leads to a decrease in GDNF production and, in parallel, to a decrease in the expression of the neuronal plasticity proteins

synaptophysin and GAP-43, which may indicate a contribution of microglia to brain plasticity (Madinier et al., 2009). Similarly, increased expression of BDNF by microglial cells may contribute to the axonal regeneration after mesencephalic trigeminal nerve injury (Ichikawa et al., 2011). A neuroprotective role of microglia against excitotoxic stimuli was also suggested by results showing that stimulation of microglia with glutamate receptor agonists induces the expression of GDNF, BDNF and nerve growth factor (NGF) (J. Liang et al., 2010).

3.2 PD and neuroinflammation: a toxic version of microglia

Neuroinflammation is a pathological hallmark in patients and experimental models of PD. Both present the classical features of inflammation, with evidence of an uncontrolled process. Moreover, microglia may become activated early in the disease process and remain primed, responding strongly to subsequent stimuli, and thereby enhancing inflammation-induced oxidative stress and cytokine-dependent toxicity in vulnerable neuronal populations (Halliday & Stevens, 2011). In PD, for unknown reasons microglia become persistently overactivated, leading to the overproduction of cytokines (e.g. tumour necrosis factor (TNF)-α, IL-1β and IL-6), and other pro-inflammatory mediators, as well as the release of reactive oxygen species (ROS) (Y.S. Kim & Joh, 2006). A high number of activated microglia has been found in the *substantia nigra pars compacta* of post-mortem PD patients, in the vicinity of the degenerating dopaminergic neurons (Tansey & Goldberg, 2009). Additionally, elevated concentrations of IL-2, IL-6 and TNF-α in the serum, and of IL-6 and IL-1β in the cerebrospinal fluid have been reported in PD patients (E.C. Hirsch & Hunot, 2009). These observations, together with positron emission tomography (PET) imaging studies, support a role for neuroinflammation in PD that appears early and persists throughout the disease course (Tansey & Goldberg, 2009). However, microglial activation in PD is not limited to the *substantia nigra*, and is also found in the putamen, hippocampus, transenthorinal cortex, cingulate cortex and temporal cortex (Block et al., 2007). The selective loss of dopaminergic neurons from the *substantia nigra* might be due to their glutathione deficiency, high content of dopamine, elevated iron concentrations and increased number of microglia in the *substantia nigra* compared with other regions. Therefore, dopaminergic neurons in the *substantia nigra* might be particularly vulnerable to inflammatory insults owing to their precarious redox equilibrium and the large neighboring population of microglia (Block et al., 2007). Indeed, a great body of evidence supports the role of microglia in the degeneration of dopaminergic neurons. In the MPTP mouse model, inhibition of microglial activation with minocycline decreases dopaminergic death (Y. He et al., 2001; D.C. Wu et al., 2002), and neuronal death is greatly diminished in mutant mice deficient in NOS (Dehmer et al., 2000; Liberatore et al., 1999), or deficient in NADPH-oxidase, the enzyme that catalyzes the production of superoxide (D.C. Wu et al., 2003). Moreover, a model of PD was created by infusing LPS in the *substantia nigra*, which activates microglial cells and selectively kills dopaminergic neurons (Block & Hong, 2005). In cell culture models, dopaminergic cell death induced by 1-methyl-4-phenylpyridinium (MPP^+) is greatly reduced in neuron-enriched cultures as compared to neuron-glia cultures, and the addition of microglia to neuron-enriched cultures restablishes MPP^+-induced dopaminergic death (Block & Hong, 2005). The detrimental role of microglia in PD has lead to an attempt of using anti-inflammatory therapies in the treatment of PD (E.C. Hirsch & Hunot, 2009).

3.3 Role of GDNF in controlling microglia activation

Consistent with the role of microglia in the pathogenesis and progression of PD, it has been demonstrated that an attenuation of dopaminergic neurodegeneration may be achieved by regulating microglial activation. There is a good deal of evidence suggesting that astrocytes are capable of reducing the potentially damaging effects of microglia. One of the mechanisms may be through the regulation of microglial expression of the antioxidant enzyme heme oxygenase-1 (HO-1) (Min et al., 2006). Astrocytes are also able to reduce LPS-induced NOS expression and NO production by microglia (Lynch, 2009). Besides, coculture with astrocytes or exposure to astrocyte conditioned media has been shown to reduce microglial phagocytic activity, and the production of IL-12 induced by LPS or interferon (IFN)-γ (Lynch, 2009). Astrocyte-derived transforming growth factor (TGF)-β and IL-10 are known to suppress microglial activation (Y.S. Kim & Joh, 2006). Recent work from our group has shown that soluble mediators released by cultured ventral midbrain astrocytes are able to prevent microglial activation induced by the pro-inflammatory agent Zymosan A (Rocha et al., 2010). We have found that low molecular weight (< 10 kDa) astrocyte-derived soluble mediators, including metallothionein-I/II, a small astrocytic protein with protective roles in the CNS, are able to suppress microglial activation induced by 0.5 μg/mL Zymosan A (Fig. 2). However, when a higher concentration of Zymosan A was used (5 μg/mL), these low molecular weight mediators were insufficient to prevent microglial activation. Under these conditions, we found that among three neurotrophic factors expressed by midbrain astrocytes (GDNF, cerebral dopamine neurotrophic factor (CDNF) and BDNF), only GDNF was able to modulate microglial activation induced by 5 μg/mL Zymosan A. This result was confirmed using several approaches, namely GDNF neutralization experiments, GDNF silencing in astrocyte cultures, and exogenous addition of GDNF to non-conditioned astrocyte culture media. Our results also show that the action of GDNF in microglial cells depends on GDNF family receptor (GFR)α1 (Rocha et al., 2010), a component of the receptor complex that can comprise also the transmembrane Ret tyrosine kinase or the neural cell adhesion molecule (NCAM) (Ibanez, 2010). Thus, the binding of astrocyte-derived GDNF to microglial GFRα1 receptors activates intracellular signaling cascade(s) responsible for inhibiting microglial activation. Our results are in accordance with the finding that exogenous GDNF inhibits LPS-induced increase of NO production and in the number of OX-6-positive cells in the *substantia nigra* in a cortex-striatum-midbrain organotypic culture (Xing et al., 2010), and also with the increased microglial activation observed in the *substantia nigra*, but not in the striatum, of GDNF heterozygous mice (Boger et al., 2010). It was also shown that the anticonvulsant and mood stabilizer valproate, and other histone deacetylase inhibitors, which increase the expression of GDNF and BDNF in astrocytes (P.S. Chen et al., 2006), are capable of reducing microglial activation (Peng et al., 2005; X. Wu et al., 2008).

This regulation of microglial activation by GDNF is of particular interest since GDNF is a potent neurotrophic factor for dopaminergic neurons in the nigrostriatal pathway (Duarte et al., 2007). Previous studies from our group have shown that upon neuronal injury, astrocytic expression of GDNF is increased as a neuroprotective strategy (Saavedra et al., 2006). Astrocytic GDNF up-regulation was found to involve the release of soluble mediators, namely IL-1β, that signal ventral midbrain astrocytes to increase GDNF expression (Saavedra et al., 2007). Furthermore, we have found that injured nigral neurons trigger GDNF up-regulation in striatal cells (Fig. 3), a mechanism that can be relevant to the

neuroprotection of dopaminergic terminals in the striatum. Altogether, these data raise the hypothesis that the neuroprotective effect of GDNF in the nigrostriatal system can result not only from a direct effect on dopaminergic neurons, but also from an indirect action through the modulation of glial crosstalk and the neuroinflammatory cascade occurring in PD.

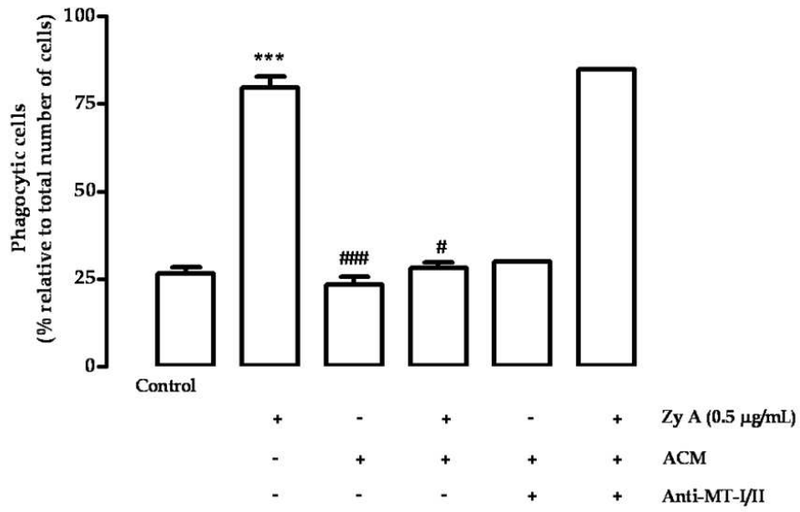

Fig. 2. Quantification of the number of phagocytic cells in *substantia nigra* microglia control cultures and in cultures incubated for 24 h with a low molecular weight fraction (< 10 kDa) of ventral midbrain astrocyte conditioned media (ACM), prior to exposure to 0.5 mg/mL Zymosan A (ZyA) for an additional period of 24 h. The effects of blocking the action of metalothionein (MT)-I/II present in ACM using a specific antibody (anti-MT-I/II; 1:1000; Dako), prior to exposure to 0.5 mg/mL ZyA, are presented. Data shown are the mean ± S.E.M. of up to four independent experiments performed in triplicate. Statistical analysis was performed using one-way ANOVA followed by Bonferroni's test. *** $P < 0.001$ as compared to control; # $P < 0.05$ and ### $P < 0.001$ as compared to ZyA.

Interestingly, inflammatory stimuli are among the candidate signals involved in the intercellular talk that induces glial GDNF expression after injury. Indeed, elevated GDNF expression is observed in response to LPS and to the pro-inflammatory cytokines IL-1β, IL-6, TNF-α and TNF-β in C6 cells (Appel et al., 1997; Verity et al., 1998), and in U-87MG glioblastoma cells (Verity et al., 1999). In cultured astrocytes both exogenous TNF-α, via TNF receptors, and endogenously produced TNF-α induce GDNF expression suggesting that an autocrine loop contributes to the production of neurotrophic factors in response to inflammation (Kuno et al., 2006). In contrast, TNF-α, TNF-β, IL-1β and LPS repress GDNF release in SK-N-AS neuroblastoma cells (Verity et al., 1999). Therefore, it has been proposed that GDNF synthesis and release in response to inflammatory molecules may be differentially regulated in cells of glial and neuronal phenotype (Verity et al., 1999). LPS also increases GDNF secretion (McNaught & Jenner, 2000) as well as GDNF mRNA expression in rodent primary astrocyte cultures (Kuno et al., 2006; Remy et al., 2003). *In vivo*, a high-dose of LPS, rather than a low dose, improves locomotor function after spinal cord injury in rats consistent with GDNF expression in microglia/macrophages (Hashimoto et al., 2005). This

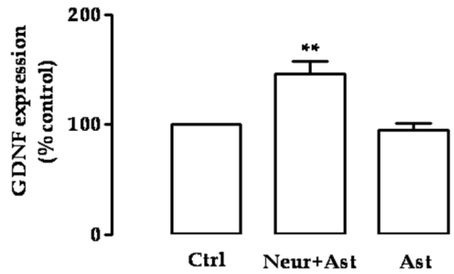

Fig. 3. GDNF expression in striatal cultures exposed to conditioned media from H_2O_2-challenged nigral mixed cultures (Neur+Ast) or ventral midbrain astrocyte cultures (Ast). Ventral midbrain astrocytes or nigral neuron-glial cells were exposed to 50 mM H_2O_2 or vehicle (control – Ctrl) for 1 h. The conditioned media were transferred to striatal cultures for 24 h and cell extracts were prepared for Western blot analysis of GDNF levels. Data shown are the mean ± S.E.M. of up to seven independent experiments performed in triplicate. Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. $^{**}P < 0.01$ as compared to control.

suggests that repair of CNS injuries can occur through GDNF produced by activated microglia/macrophages. Summarizing, growing evidence indicates that microglial activation promotes GDNF expression, and more recent data indicate that GDNF in turn inhibits microglia reactivity which may indicate that GDNF is involved in a process that self-limits microglial neurotoxicity, thus avoiding neuronal injury. These observations lead us to propose that this process to control microglia activation via GDNF fails in PD, and highlight the importance of better understanding the mechanisms implicated in the control of microglia activation by GDNF, and whether changes in these processes occur during the progression of PD.

4. Treating PD with neurotrophic factors: the GDNF candidate

Neurotrophic factors have emerged as key factors in the survival and phenotypic differentiation of neuronal cells during development, in the maintenance of mature neurons in the adult, as well as in their protection/repair upon injury (Benn & Woolf, 2004). It was proposed that changes in the levels of neurotrophic factors, due to alterations in the synthesis, release or activity associated with aging or genetic factors, might be involved in the neuronal loss observed in neurodegenerative diseases as PD (Mattson & Magnus, 2006; Siegel & Chauhan, 2000). The last years have registered increasing interest in the application of neurotrophic factors to the therapeutic field, and PD is a neurodegenerative disease whose treatment with trophic factors has been the focus of extensive research. The potential of GDNF, the prototypical neurotrophic factor for dopaminergic neurons, as a neuroprotective and neurorestorative agent to slow down or halt PD progression, has been vastly debated in the last years (e.g. Aron & Klein, 2011; Evans & Barker, 2008; Hong et al., 2008; Peterson & Nutt, 2008; Ramaswamy et al., 2009; Vastag, 2010).

It has been proposed that those neurons more vulnerable in PD *substantia nigra* (ventral tier *versus* dorsal tier) display an increased expression of proteins that may contribute to vulnerability, together with a deficient expression of neuroprotective molecules. Interestingly, GDNF is among the neurotrophic factors whose differential pattern of expression between the ventral and the dorsal tiers of the *substantia nigra* might account for

their distinct vulnerability in PD (Double et al., 2010). GDNF mRNA levels are significantly higher in the ventral striatum, the target region of the ventral tegmental area (VTA) and rostromedial *substantia nigra* cells, than in the dorsal striatum, the target region of dopaminergic neurons from the caudoventral *substantia nigra* (Barroso-Chinea et al., 2005). This correlates with VTA and rostromedial *substantia nigra* cells being more resistant to 6-OHDA toxicity than dopaminergic neurons from the caudoventral *substantia nigra* as occurs in PD (Barroso-Chinea et al., 2005), and supports the idea that the heterogeneous expression of GDNF is a factor involved in the differential vulnerability of midbrain dopaminergic neurons in PD.

Post-mortem studies investigating GDNF distribution in the human parkinsonian brain have yielded conflicting results (Saavedra et al., 2008), and clinical trials performed in advanced PD patients have generated quite disappointing outcomes (see below, 4.1 Clinical trials using GDNF), but many studies in animal models show that GDNF delivery can have trophic effects and restore motor function (Soderstrom et al., 2006). Additionally, GDNF is essential for the maintenance of adult nigrostriatal dopaminergic neurons and other central and peripheral nuclei affected in PD (Pascual et al., 2008). Therefore, the idea of using GDNF as a neuroprotective/neurorestorative therapy for PD is still being pursuited.

Mesencephalic astrocyte-derived neurotrophic factor (MANF), identified as selectively trophic for dopaminergic neurons *in vitro* (Petrova et al., 2003), and CDNF, which exhibits trophic and neurorestorative effects as potent as GDNF both *in vitro* and *in vivo* (Lindholm et al., 2007), might also be relevant targets for the development of alternative or complementary therapeutic approaches for PD.

4.1 Clinical trials using GDNF

Several clinical trials have been performed using the direct intracerebral infusion of GDNF. Despite the extensive literature supporting the neuroprotective role of GDNF on the nigrostriatal pathway most of the clinical trials performed in advanced PD patients have generated rather disappointing results (Aron & Klein, 2011).

The first clinical trial consisted in a randomized controlled trial using recombinant GDNF (r-metHuGDNF, Liatermin®, Amgen) and placebo delivered monthly as bolus via an intraventricular (ICV) catheter to patients with idiopathic PD (Nutt et al., 2003). No clinical benefits were registered at doses sufficient to induce side effects, and the post-mortem analysis of one patient revelead no evidence of rescue of dopaminergic fibers in the striatum or cells in the *substantia nigra* suggesting that insufficient GDNF reached its targets after ICV injection (Nutt et al., 2003). The following clinical trials addressed this issue by using continuous intraputaminal GDNF infusion. In an open-label clinical trial performed on five PD patients, Gill et al. (2003) reported excellent tolerance, few side effects, a significant decrease in total Unified Parkinson's Disease Rating Score (UPDRS) in the 'off' state, elimination of severe akinetic episodes, significant reduction of dyskinesias and improvements in quality of life. 18F-dopa PET scanning showed a significant increase in the uptake around the infusion site and in the *substantia nigra.* A report on one patient autopsied 43 months later showed evident increased TH-positive nerve fibers in the infused putamen indicating that GDNF stimulated axonal sprouting (Love et al., 2005). An independent open-label clinical trial using a different delivery protocol performed unilaterally on ten PD patients also reported positive results at six months and minimal side effects (Slevin et al., 2005). These promising results lead to the design of a randomized placebo-controlled trial involving 34 PD patients. Nevertheless, no significant clinical differences were detected at

six months between patients receiving GDNF or placebo (Lang et al., 2006), and the open-label extension of the study was interrupted because three patients developed neutralizing antibodies, which could potentially cross-react with endogenous GDNF (Tatarewicz et al., 2007). Moreover, a parallel toxicologic study showed that infusion of GDNF into the putamen induced cerebellar damage in some monkeys (Hovland et al., 2007).
The overall discouraging results from these clinical trials may be related to poor diffusion of GDNF, the development of anti-GDNF antibodies, or other unindentified effects, while the different outcomes have been proposed to rely on differences in GDNF doses or catheter properties, patient cohort selection, or the choice of unsuitable endpoints, with suboptimal brain delivery of GDNF considered the major limiting factor (Aron & Klein, 2011; Sherer et al., 2006).
A phase I trial involving the delivery of neurturin, another member of the GDNF family, to the striatum of PD patients via adeno-associated virus (AAV) vector showed tolerability, safety, and also potential efficacy (Marks et al., 2008), and a phase II trial was carried out. In this clinical trial there was no significant difference in the UPDRS motor score at 12 months between patients treated with AAV2-neurturin compared with control individuals, and some patients developed tumours (Marks et al., 2010). Currently, a new trial involving the delivery of a four-fold higher dose of AAV2-neurturin to both the putamen and *substantia nigra* is ongoing (Vastag, 2010).

4.2 The ups and downs of GDNF

Although GDNF overexpression is neuroprotective, uncontrolled GDNF levels could lead to unexpected side effects. High doses of exogenously delivered GDNF induce dyskinesias and weight loss in monkeys (Z. Zhang et al., 1997). Additionally, compensatory down-regulation of TH in response to GDNF overexpression in the nigrostriatal system has been reported, both in intact (Georgievska et al., 2004; Rosenblad et al., 2003) and lesioned (Georgievska et al., 2002) rats. An important issue with possible functional consequences that was not addressed in these studies is whether prolonged GDNF infusion alters GDNF receptors Ret, GFRα1 and/or NCAM levels. There is evidence that BDNF infusion into the hippocampus for 6 days (Frank et al., 1996), or prolonged BDNF treatment of primary cortical (Knusel et al., 1997) or hippocampal (Haapasalo et al., 2002) cultures can down-regulate TrkB receptor levels. However, more recent studies in cultured hippocampal slices argue against the possibility that sustained periods of increased BDNF levels will initiate compensatory responses at the receptor level, and suggest that chronic up-regulation of BDNF is accompanied by increased activation of the neurotrophin receptor at spine synapses (Lauterborn et al., 2009). Thus, it is relevant to assess the effect of sustained high levels of GDNF in the nigrostriatal system on GDNF receptor levels as a possible compensatory down-regulation can limit GDNF-mediated neuroprotection. A potential approach to prevent the negative consequences of chronic GDNF infusion in the brain might be to use a regulated viral vector system (Manfredsson et al., 2009). Once optimized, such a system will offer the possibility to fine-tune the therapeutic dose to each PD patient, and to quickly stop GDNF overexpression in case toxicity emerges by adjusting the administration of the controlling agent (Manfredsson et al., 2009).
Several efforts are being made to solve the problems associated with the delivery, targeting, safety, and distribution of trophic factors to the CNS, which need to be overcome before GDNF therapy for PD becomes a reality (Sherer et al., 2006). The delivery of GDNF to the

CNS is challenging because GDNF is unable to cross the blood-brain barrier (Kastin et al., 2003; Kirik et al., 2004). A possibility to overcome this limitation is to conjugate or fuse GDNF with other molecules that enable it to cross the blood-brain barrier. Fusion with viral proteins (Dietz et al., 2006), conjugation with antibodies for transferrin (Albeck et al., 1997; Xia et al., 2008; Q.H. Zhou et al., 2010) or insulin (Boado & Pardridge, 2009; Boado et al., 2007) receptors, or with a fragment of the tetanus toxin (Larsen et al., 2006) provides an efficient way of delivering GDNF to the CNS. Recently, GDNF delivery to the CNS using bone marrow stem cell-derived macrophages, which are able to pass the blood-brain barrier, was proven to ameliorate MPTP-induced degeneration of TH-positive neurons and terminals, stimulate axon regeneration, and reverse hypoactivity in the open field test (Biju et al., 2010).

4.3 Inducing endogenous GDNF expression/signaling

Molecules that induce the endogenous expression of trophic factors or enhance their signaling are receiving increasing attention as alternative therapeutic options for PD. Therefore, in addition to a therapeutic tool itself, GDNF constitutes also a target for the development of new therapeutics. Interestingly, it was suggested that XIB4035, a non-peptidyl small molecule that acts as a GFRα1 agonist and mimics the neurotrophic effects of GDNF in Neuro-2A cells, might have beneficial effects for the treatment of PD (Tokugawa et al., 2003). Leucine-isoleucine (Leu-Ile), a hydrophobic dipeptide that partially resembles the site on FK506 that binds to immunophilin (Schreiber, 1991), significantly increases GDNF and BDNF levels in the conditioned medium from cultured hippocampal neurons, and protects both dopaminergic and non-dopaminergic neurons from natural cell death in low density cultures (Nitta et al., 2004). Interestingly, the effect is lost when cultures are prepared from mice lacking the *GDNF* or *BDNF* gene (Nitta et al., 2004). Moreover, Leu-Ile increases GDNF and BDNF striatal content in mice, inhibits 6-OHDA-induced dopaminergic denervation, and reduces rotational behavior after methamphetamine challenge (Nitta et al., 2004). The ability of Leu-Ile to cross the blood-brain barrier, and to promote GDNF expression without exhibiting immunosuppressive properties, makes it a novel tool for the treatment of PD or other neurodegenerative diseases. More recently, incubation with PYM50028 (Cogane™; common name smilagenin), a novel non-peptide neurotrophic factor inducer, was shown to protect cultured dopaminergic neurons from the toxic effect of MPP^+, an effect almost completely lost in the presence of anti-GDNF and/or anti-GFRα1 antibody. Moreover, GDNF mRNA expression was markedly increased by smilagenin treatment (Y. Zhang et al., 2008). Oral administration of smilagenin to MPTP-lesioned mice resulted in a significant elevation of striatal GDNF levels and attenuated the loss of dopaminergic neurons from the *substantia nigra* (Visanji et al., 2008). Interestingly, smilagenin is now undergoing phase I clinical testing (Aron & Klein, 2011). Finding molecules like XIB4035, Leu-Ile or smilagenin, capable of stimulating GDNF expression/signaling may prove beneficial to the treatment of PD, and would overcome most of the problems associated with the delivery of GDNF protein into the brain, with GDNF expression induced by viral vectors, or with the use of encapsulated GDNF producing cells (Bespalov & Saarma, 2007).

5. Complementary and alternative ways of getting GDNF?

PD patients commonly use complementary and alternative therapies, including altered diet, dietary supplements, herbal supplements, caffeine, nicotine, exercise, physical and massage

therapy, melatonin, bright-light therapy and acupuncture (Lokk & Nilsson, 2010; Pecci et al., 2010; Zesiewicz & Evatt, 2009). What is the impact of these complementary and alternative therapies on GDNF levels?

5.1 Is there a GDNF diet?

Compelling evidence from epidemiological and animal studies highlights the importance of dietary factors in counteracting dopaminergic degeneration occurring in PD, so that healthy dietary choices might be relevant to reduce the risk of PD (Di Giovanni, 2009; Gao et al., 2007). Therefore, dietary intervention on PD has emerged as a new way to halt disease progression, or even prevent it.

Some studies show that caloric restriction and intermittent fasting diets are neuroprotective and improve functionality in animal models of stroke, Parkinson's, Huntington's (Mattson, 2005) and Alzheimer's (Halagappa et al., 2007) disease. Moreover, data from epidemiological studies suggest that individuals with low-calorie, low-fat diets may have reduced risk of PD (C.C. Johnson et al., 1999; Logroscino et al., 1996), while the potential association between obesity (Abbott et al., 2003; Hu et al., 2006; Ikeda et al., 2007), or cholesterol intake (Miyake et al., 2010) and the risk of PD have been shown. Accordingly, MPTP treatment produces greater striatal dopamine depletion in high-fat-fed than in control mice (J.Y. Choi et al., 2005). Likewise, rats under high-fat diet for 5 weeks before 6-OHDA infusion into the medial forebrain bundle exhibit greater dopamine depletion in the *substantia nigra* and striatum, and increased oxidative stress than control rats (Morris et al., 2010). Confirming the protective effect of caloric restriction, susceptibility to a neurotoxic insult to dopaminergic neurons is exacerbated in obese mice (Sriram et al., 2002). Conversely, dietary restriction protects adult mice against MPTP-induced dysfunction and degeneration of nigrostriatal dopaminergic neurons, and deficits in motor function decrease markedly in these animals (Duan & Mattson, 1999). Dietary restriction mimicked using a non-metabolizable analogue of glucose (2-deoxy-D-glucose) reduces damage to dopaminergic neurons in the *substantia nigra*, and improves the behavioral outcome following MPTP treatment (Duan & Mattson, 1999). Moreover, treatment with 2-deoxy-D-glucose protects cultured dopaminergic cells against oxidative and metabolic insults (Duan & Mattson, 1999). Surprisingly, caloric restriction was not neuroprotective against 6-OHDA toxicity in rats (Armentero et al., 2008). This lack of effect was likely due to the short duration of dietary restriction, and to a more pronounced neurotoxic insult compared with that registered in previous studies (Duan & Mattson, 1999; Maswood et al., 2004).

Caloric restriction and reduced meal frequency/intermittent fasting are dietary manipulations thought to prolong the health span of the nervous system by acting upon important metabolic and cellular signalling pathways to stimulate the production of protein chaperones, antioxidant enzymes, and neurotrophic factors that help cells to deal with stress and resist disease (Martin et al., 2006). The effect of dietary restriction on GDNF levels was not addressed by Duan & Mattson (1999), but an increase in GDNF levels in the nigrostriatal system may play a role in the positive effect of dietary restriction on MPTP-damaged dopaminergic neurons and motor impairment reported by these authors. In fact, more recent observations indicate that a low-calorie diet reduces the loss of dopaminergic neurons from the *substantia nigra*, the severity of neurochemical deficits, and motor dysfunction in a non-human primate model of PD (Maswood et al., 2004). Furthermore, monkeys maintained for 6 months on a 30% caloric restriction diet exhibit significantly higher levels of GDNF in

the caudate nucleus compared with control monkeys, suggesting that the protective effect of reduced calorie diet may result from up-regulation of GDNF expression and consequent activation of neuroprotective signal transduction pathways in dopaminergic neurons (Maswood et al., 2004).

Since caloric restriction increases the amount of endogenous GDNF in the brain of monkeys, it may be possible to ameliorate PD, at least partially, through dietary manipulations. It is also worthy to mention that, for instance, hippocampal BDNF levels are reduced in rats subjected to a saturated-fat diet (H.R. Park et al., 2010; D.C. Wu et al., 2003) which leads us to hypothesize that a similar reduction of GDNF levels might also occur under a high-fat diet. Consistent with the observation that caloric restriction attenuates MPTP-induced depletion of dopamine, the distance moved and speed of movement increased more than two-fold in caloric restricted monkeys compared with those on control diet (Maswood et al., 2004). From an evolutionary point of view, and based on experimental data, it was speculated that the neuroprotective effects of caloric restriction could be due to the induction of growth factors by increased motor activity (Finch, 2004). In fact, activation of the same cellular and molecular pathways that occur in response to mild dietary restriction and intermittent fasting-induced stress can occur in response to physical exercise and cognitive stimulation (Mattson et al., 2004).

Taken together, these evidences support the relevance that dietary intervention might assume as a non-invasive and drug-free strategy for PD management, and suggest that an amelioration of GDNF levels may be involved in the protective effects of a healthy diet and caloric restriction on the nigrostriatal pathway.

5.2 Exercising for GDNF expression?

Substantial evidence suggests a positive role of exercise in slowing the progression of PD (Crizzle & Newhouse, 2006; Falvo et al., 2008; Goodwin et al., 2008), and beneficial effects of exercise on motor and non-motor PD symptoms have been described (Gage & Storey, 2004; Lehman et al., 2005; Logroscino et al., 2006). In addition, epidemiological studies show a negative correlation between the regular practice of exercise and the prevalence of PD (H. Chen et al., 2005; Sasco et al., 1992; Tsai et al., 2002; Q. Xu et al., 2010). Interestingly, it has been recently reported that forced exercise is more beneficial for people with PD than voluntary exercise (Ridgel et al., 2009). Thus, exercise might constitute a non-pharmacological neuroprotective therapy for PD contributing to slow the progressive degeneration of dopaminergic neurons. However, there is a lack of consensus on the optimal delivery and extent of exercise (dosing, type, etc) appropriate at each stage of the disease (Dibble et al., 2009; Goodwin et al., 2008). The mechanisms implicated in the beneficial effect of exercise in PD patients are now being uncovered (M.A. Hirsch & Farley, 2009). In particular, several trophic factors might be involved in the beneficial effects of exercise (e.g. Cotman et al., 2007; Gomez-Pinilla et al., 1998; Widenfalk et al., 1999; Yasuhara et al., 2007).

The data from animal models parallel the observations in PD patients as increased physical activity is neuroprotective/neurorestorative in models of nigrostriatal injury. However, despite the findings supporting the view that exercise protects against the behavioral effects of 6-OHDA and MPTP, data on the protection of dopaminergic neurons from 6-OHDA- or MPTP-induced toxicity are mixed (Zigmond et al., 2009). It has been reported that running for 3 months prior to acute MPTP administration completly protects from TH cell loss

(Gerecke et al., 2010). On the other hand, exercise for 2 weeks after intrastriatal injection of 6-OHDA results in partial recovery of TH labeling and axonal fiber projection to the striatum (Yoon et al., 2007). Treadmill exercise starting the day after intrastriatal 6-OHDA infusion induces significant preservation of TH-positive fibers in the striatum and TH-positive neurons in the *substantia nigra pars compacta* as compared to the non-exercised group (Tajiri et al., 2010). An increase in TH labeling in the *substantia nigra pars compacta* of MPTP-treated mice receiving treadmill exercise was also recently reported (B.A. Smith et al., 2011). In contrast, other authors find no reduction in the loss of dopaminergic neurons in exercised animals (Fisher et al., 2004; O'Dell et al., 2007). Improvements in motor performance in animals undergoing exercise may not necessarily be accompanied by changes in total striatal dopamine levels after exercise (O'Dell et al., 2007; Petzinger et al., 2007). Compensatory changes in stimulus-evoked release and a decrease in dopamine decay might play a relevant role (Petzinger et al., 2007). Some studies show that exercise leads to DAT down-regulation in MPTP-treated mice (Fisher et al., 2004; Petzinger et al., 2007), suggesting that increased synaptic availability of dopamine may underlie behavioral improvements in response to exercise. In contrast, an increase in DAT protein expression has been recently reported in MPTP-treated mice receiving treadmill exercise (B.A. Smith et al., 2011). These discrepancies might be related to differences in the lesion regimen/extension and exercise paradigm.

Physical exercise increases the expression of GDNF in the nigrostriatal system, and this correlates with the protection of dopaminergic neurons against MPTP toxicity (Faherty et al., 2005), and amelioration of motor impairment due to a 6-OHDA lesion (Cohen et al., 2003; Tajiri et al., 2010). Exercise in the running-wheel markedly accelerates spontaneous recovery after a 6-OHDA lesion as animals exercised on the running-wheel prior or after a unilateral striatal 6-OHDA injection show a faster motor recovery compared to non-exercised animals (O'Dell et al., 2007). Recently, daily treadmill exercise similar to clinical settings (30 min/day, 5 days/week for 4 weeks) was shown to up-regulate both GDNF and BDNF in the lesioned and intact sides of the striatum (Tajiri et al., 2010). In a chronic MPTP mouse model with moderate neurodegeneration treadmill exercise during 18 weeks drastically increased GDNF levels in the striatum but not in the *substantia nigra*, and the opposite was observed for BDNF (Lau et al., 2011). The improvement of motor function observed in many studies of forced limb use, treadmill running or running-wheel exercise in both 6-OHDA (Mabandla et al., 2004; Tillerson et al., 2001; 2003; Yoon et al., 2007) and MPTP (Fisher et al., 2004; Tillerson et al., 2003) models of PD raised the hypothesis that up-regulation of GDNF might mediate, or at least contribute to, the protection of the nigrostriatal pathway observed in those reports (A.D. Smith & Zigmond, 2003). How does exercise increase GDNF expression? Since GDNF production is activity-dependent, dopamine is known to stimulate GDNF expression (Saavedra et al., 2008), and exercise increases dopamine in the striatum (Sutoo & Akiyama, 2003), one may envisage that increased dopamine levels during activity of the striatal circuitry may mediate increased GDNF expression in the nigrostriatal system upon physical exercise.

5.3 A stimulating GDNF lifestyle?

Environmental enrichment is characterized by housing conditions that facilitate sensory, motor and cognitive stimuli, accompanied by voluntary physical activity and social interactions. An enriched environment is neuroprotective in animal models of PD. Mice reared in an enriched environment are more resistant to MPTP compared with mice raised in a standard environment (Bezard et al., 2003; Faherty et al., 2005). Moreover,

environmental enrichement also improves motor function after unilateral 6-OHDA injection in rats (Jadavji et al., 2006; Steiner et al., 2006). More recently, continuous exposure to environmental enrichement during 3 weeks before and after 6-OHDA injection was reported to prevent dopaminergic neuronal death, protect the nigrostriatal pathway, and reduce motor impairment (Anastasia et al., 2009). The molecular mechanisms involved in the neuroprotective effect of environmental enrichement observed in several rodent models of brain disorders are not clear, but the synthesis and release of neurotrophic factors may play a crucial role (Nithianantharajah & Hannan, 2006). In fact, environmental enrichment increases GDNF mRNA in the *substantia nigra* and striatum, and totally protects against MPTP-induced parkinsonism (Faherty et al., 2005). Bezard et al. (2003) and Turner & Lewis (2003) showed that enriched environment also increases the expression of BDNF in the striatum but, unfortunately, the effect on GDNF levels was not addressed in these studies. In a previous work, an enriched environment was shown to induce the expression of GDNF and to increase the phosphorylation of the transcription factor CREB, while reducing the spontaneous apoptosis in the rat hippocampus by 45%, and protecting against kainate-induced seizures and excitotoxic injury (Young et al., 1999).

What is the relevance of the results obtained in animal models of PD to humans suffering the disease? Most individuals are exposed to a high degree of environmental complexity and novelty. However, the level of cognitive, social and physical stimulation can vary significantly from one person to another, so that correlative and epidemiological data shows that lifestyle, including occupation, leisure activities and physical exercise, has a direct effect on the risk of cognitive decline (Baroncelli et al., 2010). In fact, there is an association between higher educational accomplishment and reduced risk of PD-related dementia (Glatt et al., 1996). Since PD patients suffer from impaired cognitive functions (Jokinen et al., 2009 and references therein), and GDNF contributes to synaptic transmission (Saavedra et al., 2008). Thus, getting engaged in higher levels of mental and physical activity through education, occupation and recreation might constitute a non-invasive and drug-free approach to increase GDNF levels, which, in turn, might both protect the nigrostriatal pathway and reduce the cognitive impairment affecting PD patients.

5.4 Green GDNF?

Consistent with the considerable effort in identifying naturally occurring neuroprotective substances, growing evidence indicates that many oriental herbs and extracts attenuate the degeneration of dopaminergic neurons, and ameliorate the parkinsonism induced by MPTP and 6-OHDA (for a review see L.W. Chen et al., 2007). The number of reports supporting the neuroprotective action of several herbs and herbal extracts on PD models continues to rise, and here we briefly overview the most recent studies.

In vitro, protection against 6-OHDA toxicity was demonstrated using Cyperi rhizoma, the rhizome of *Cyperus rotundus* L. (Lee et al., 2010), while *Chrysanthemum morifolium* Ramat (I.S. Kim et al., 2009) and Yi-Gan San (Doo et al., 2010b) protect cells from MPP^+ toxicity. *In vivo*, Yi-Gan San (Doo et al., 2010b), *Withania somnifera* root extract/Ashwagandha/Indian ginseng (Rajasankar et al., 2009a,b), panaxatriol saponins, the main constituents extracted from *Panax notoginseng* (Luo et al., 2011), pycnogenol, an extract of *Pinus maritime* bark (Khan et al., 2010), *Gynostemma pentaphyllum* (H.S. Choi et al., 2010), and epigallocatechin-3-gallate, a green tea catechin (J.S. Kim et al., 2010), were shown to be neuroprotective in the MPTP model of PD.

Several mechanisms have been proposed to contribute to the neuroprotective effect of herbs and herbal extracts. These include their function as antioxidants to alleviate oxidative stress, inhibitors of monoamine oxidase B to decrease neurotoxicity, scavengers of free radicals, chelators of harmful metals, modulators of cell survival genes and apoptotic signals (L.W. Chen et al., 2007). As a result, herbs and herbal extracts are receiving increasing attention as therapeutic agents for the treatment of PD. The efficacy and safety of their use in adjunct or monotherapy in PD management is under consideration (Chung et al., 2006). Unfortunately, the effect on GDNF expression has not yet been addressed for many of them. It would be very interesting to investigate if these and other herbal extracts are able to increase GDNF expression, as well as whether their protective effects in PD models are mediated, or not, by the up-regulation of GDNF expression. The available data on GDNF induction by herbs or herbal compounds is reviewed below.

Rehmannia glutinosa, a traditional Chinese medicine herb frequently used in the therapy of dementia, induces GDNF gene expression in C6 cells and in primary cortical astrocytes (H. Yu et al., 2006). The stimulation of GDNF gene expression by *Rehmannia glutinosa* in C6 cells can be independently up-regulated through PKC and ERK1/2 pathways (H. Yu et al., 2006). Recently, the protective effect of catalpol, an active component extracted and purified from *Rehmannia glutinosa* was investigated in a chronic MPTP mouse model and in MPP^+-treated mesencephalic neurons. The oral administration of catalpol for 8 weeks dose-dependently improves locomotor ability, significantly elevates striatal dopamine levels and the number of TH-positive neurons in the *substantia nigra pars compacta*, and the striatal DAT density. Interestingly, catalpol treatment also increases GDNF striatal levels, and both the number of dopaminergic neurons and DAT density are positively correlated with GDNF levels (G. Xu et al., 2010). Moreover, catalpol protects cultured mesencephalic neurons against MPP^+ toxicity and up-regulates GDNF mRNA levels in neurons intoxicated with MPP^+, but not in control cultures. Importantly, the protective effect of catalpol against dopaminergic degeneration is abolished by the presence of the GDNF receptor tyrosine kinase Ret inhibitor 4-amino-5-(4-methyphenyl)-7-(t-butyl)-pyrazolo-[3,4-d]pyrimidine (G. Xu et al., 2010). Catalpol has antioxidant (Bi et al., 2008; Tian et al., 2007) and anti-apoptotic (Bi et al., 2009) effects, properties also displayed by GDNF (Saavedra et al., 2008), which suggest that GDNF up-regulation could be an essential step in catalpol-induced neuroprotection, but this is currently unknown.

Smilagenin is a compound extracted from *Rhizoma anemarrhenae* and *Radix asparagi*, medicinal herbs frequently used in the traditional Chinese medicine. A recent work shows that smilagenin, added prior to MPP^+, protects cultured mesencephalic dopaminergic neurons against MPP^+-induced toxicity. GDNF mRNA levels, but not those of GFRα1 or Ret, are markedly elevated in the presence of smilagenin. Moreover, the neuroprotective effect is partially lost in the presence of GDNF and/or GFRα1 antibodies (Y. Zhang et al., 2008). Oral administration of smilagenin to MPTP-lesioned mice elevates striatal GDNF levels and attenuates the loss of dopaminergic neurons (Visanji et al., 2008). Since smilagenin can be taken orally, readily crosses the blood-brain barrier, stimulates GDNF expression, and has neuroprotective effects in the MPTP mouse model of PD, hopefully it is a good candidate for the treatment of PD.

Rhus verniciflua Stokes, commonly known as lacquer tree, has been used for centuries in Korea as a food supplement and a traditional herbal medicine. Recently, the detoxified extract of *Rhus verniciflua* was shown to induce GDNF mRNA and protein expression, both

in dopaminergic-like SH-SY5Y cells, and in the rat brain after oral administration (Sapkota et al., 2010). Moreover, GDNF immunoreactivity is markedly enhanced in the *substantia nigra* of rats treated with *Rhus verniciflua* extract. Interestingly, the neuroprotective effects of *Rhus verniciflua* against rotenone-induced toxicity in SH-SY5Y cells include the prevention of GDNF and BDNF down-regulation in rotenone-treated cells (Sapkota et al., 2011).

Ibogaine is a psychoactive compound extracted from *Tabernanthe iboga*, and used for decades in African folklore medicine and rituals. Many studies indicate that ibogaine reduces craving and withdrawal symptoms of several drugs of abuse (Ron & Janak, 2005). This anti-addiction drug increases GDNF levels in SH-SY5Y cells, and up-regulates the GDNF pathway as assessed by the phosphorylation of the GDNF receptor Ret and the downstream kinase ERK1 (D.Y. He et al., 2005). A MEK inhibitor impede ibogaine-induced GDNF up-regulation (D.Y. He & Ron, 2006). In addition, after systemic administration to rodents, ibogaine increases GDNF expression in the VTA (D.Y. He et al., 2005). Since GDNF has been implicated as a negative regulator of drug and alcohol addiction (Ron & Janak, 2005), the effect of ibogaine on GDNF expression likely contributes to its positive impact on the treatment of addiction. Despite its properties, ibogaine is not approved as an addiction treatment because it induces hallucinations, which will impede its use in PD therapeutics too.

Given the neuroprotective effect of some herbal extracts on animal and cellular models of PD, and the ability to induce GDNF expression reported for some of them, it may prove useful to screen traditional therapies for their effect on GDNF levels in the nigrostriatal system, as they might reveal to be valuable GDNF inducers and alternative therapeutic approaches to PD.

5.5 'GDNF-Acupuncture'?

Acupuncture is among the complementary and/or alternative therapies most widely used by PD patients (Lokk & Nilsson, 2010; Pecci et al., 2010). Interestingly, increasing evidence supports a beneficial effect of acupuncture on MPTP (Y.G. Choi et al., 2011; Doo et al., 2010a; Jeon et al., 2008; J.M. Kang et al., 2007), 6-OHDA (Y.K. Kim et al., 2005; H.J. Park et al., 2003; Y.P. Yu et al., 2010) and medial forebrain bundle transection (Jia et al., 2009, 2010; X.B. Liang et al., 2003) PD models, and also in PD patients (Chang et al., 2008; Zhuang & Wang, 2000). Acupuncture can enhance the therapeutic effects of western medicine and reduce the need of medication (Ren, 2008). Relevant in the context of the present sinopsis is the fact that acupuncture therapy increases various neuroprotective agents (Joh et al., 2010), namely GDNF. In medial forebrain bundle-transected rats, high frequency electroacupunture stimulation up-regulates GDNF mRNA levels in both sides of the globus pallidus, suggesting that the retrograde nourishment of GDNF to dopaminergic neurons may contribute to the behavioral improvement observed in these rats (X.B. Liang et al., 2003). Another study shows that the number of GDNF-positive cells and the content of Ret receptor increased significantly in 6-OHDA-injected rats subjected to electroacupuncture (Y.C. Wang et al., 2010). At this point it is also worthy to mention that acupuncture attenuates microglial activation and inflammatory events in MPTP-treated mice (J.M. Kang et al., 2007). Since acupuncture increases GDNF expression, and GDNF is an important inhibitor of microglia activation (see section 3.3 Role of GDNF in controlling microglia activation), it is tempting to speculate that acupuncture might reduce microglia activity through GDNF up-regulation. Interestingly, electroacupuncture increases GDNF signaling

in other disease models. Electroacupuncture activates the endogenous GDNF signaling system by increasing the mRNA and protein levels of GDNF and its receptor GFRα1 in dorsal root ganglions of neuropathic pain rats (Dong et al., 2005). In contrast, electroacupuncture-induced analgesia in a rat model of neuropathic pain is significantly attenuated by the down-regulation of GFRα1 expression with antisense oligodeoxynucleotides (Dong et al., 2006). Electroacupuncture also up-regulates GDNF expression in a model of transient focal cerebral ischemia, thereby extending the duration of the endogenous GDNF up-regulation, which may be one of the pathways involved in the protective effect of electroacupuncture against ischemic injury (Wei et al., 2000b). Since the stimulatory effects of electroacupuncture on GDNF/GFRα1 levels have been demonstrated in different models, it would be relevant to address whether they underlie the beneficial effects of electroacupuncture in PD animals models.

6. Conclusion

Male gender, together with the sex dimorphism in the nigrostriatal system, can contribute to the gender differences in PD. The estrogen 17β-estradiol plays a determinant protective role through its antioxidant, anti-inflammatory, and anti-apoptotic actions. Moreover, 17β-estradiol is capable of inducing the expression of neurotrophic factors, namely GDNF, which can have a determinant contribution to the aforementioned protective effects of 17β-estradiol. Although the protective effect of 17β-estradiol in females is consensual, the role of this hormone in males is still not broadly accepted.

Microglia plays a protective role by removing apoptotic neurons and by promoting neuronal survival through the release of neurotrophic factors. However, microglia activation can also play a particularly deleterious role in the nigrostriatal system, contributing to further enhance neuronal injury in PD. Substantial evidence suggests that microglial activation is capable of inducing GDNF expression, and more recent data indicate that GDNF in turn inhibits microglia activation. This may indicate that GDNF is involved in a process that self-limits microglial neurotoxicity thus preventing neuronal injury. The extensive neuroinflammation observed in PD brain indicates that this mechanism of control is no longer effective in the diseased brain. Although the results obtained so far with anti-inflammatory drugs were not conclusive, it would be important to determine what causes the disruption or alteration of this feedback mechanism in the course of PD.

The possibility of manipulating endogenous GDNF expression can have clinical implications for the management of PD, and prove to be useful as an alternative or a complement to pharmacological or more invasive approaches. Growing evidence shows the possibility of reducing the risk for age-related neurodegenerative disorders through dietary and behavioral changes inducing neuronal survival and plasticity. Thus, dietary manipulations, physical exercise and cognitive stimulation, which are known to induce GDNF up-regulation, represent novel drug-free and non-invasive approaches that may help preventing the onset of degeneration or, in combination with pharmacological treatments, reduce the severity of the motor symptoms through the modulation of GDNF levels. Moreover, the use of alternative therapies like herbal supplements and acupuncture might also prove to be neuroprotecive via GDNF up-regulation in the nigrostriatal system. Thus, these approaches to increase endogenous GDNF levels deserve further investigation. Likewise, the impact on GDNF levels of other complementary and alternative therapies

used by PD patients should also be addressed in the future. Moreover, given its involvement in synaptic plasticity and synaptogenesis, GDNF also plays a role in learning and memory. One may therefore speculate that increasing the endogenous GDNF expression would also contribute to fight the cognitive decline observed in PD patients. Additionally, it would be interesting to examine the effect of caloric restriction, physical exercise, enriched environment, herbal extracts or acupuncture, which increase GDNF expression in the nigrostriatal system and are neuroprotective in PD models, on the levels of MANF and CDNF, two other dopaminotrophic factors.

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8. References

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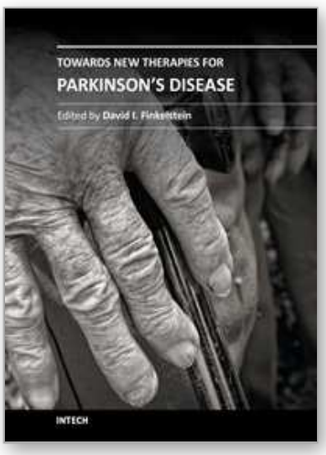

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Parkinson's disease (PD) is characterised clinically by various non-motor and progressive motor symptoms, pathologically by loss of dopamine producing cells and intraneuronal cytoplasmic inclusions composed primarily of ?-synuclein. By the time a patient first presents with symptoms of Parkinson's disease at the clinic, a significant proportion of the cells in the substantia nigra have already been destroyed. This degeneration progresses despite the current therapies until the cell loss is so great that the quality of normal life is compromised. The dopamine precursor levodopa is the most valuable drug currently available for the treatment of PD. However for most PD patients, the optimal clinical benefit from levodopa decreases around five to six years of treatment. The aim of the chapters of this book is to work towards an understanding in the mechanisms of degeneration and to develop disease modifying therapies.

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