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Review article

Novel tactics for neuroprotection in Parkinson's disease: Role of antibiotics, polyphenols and neuropeptides

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ABSTRACT

Parkinson's disease is a progressive neurodegenerative disorder characterized by the degeneration of midbrain nigral dopaminergic neurons. Although its etiology remains unknown, the pathological role of several factors has been highlighted, namely oxidative stress, neuroinflammation, protein misfolding, and mitochondrial dysfunction, in addition to genetic predispositions. The current therapy is mainly symptomatic with L-DOPA aiming to replace dopamine. Novel therapeutic approaches are being investigated with the intention of influencing pathways leading to neuronal death and dysfunction. The present review summarizes three novel approaches, the use of which is promising in pre-clinical studies. Polyphenols have been shown to possess neuroprotective properties on account of their well-established antioxidative and anti-inflammatory actions but also due to their influence on protein misfolding and mitochondrial homeostasis. Within the amazing ancillary effects of antibiotics, their neuroprotective properties against neurodegenerative and neuroinflammatory processes are of great interest for the development of effective therapies against Parkinson's disease. Experimental evidence supports the potential of antibiotics as neuroprotective agents, being useful not only to prevent the formation of toxic α-synuclein oligomers but also to ameliorate mitochondrial dysfunction and neuroinflammation. Neuropeptides offer another approach with their diverse effects in the nervous system. Among them, pituitary adenylate cyclase-activating polypeptide, a member of the secretin/glucagon superfamily, has several advantageous effects in models of neurodegeneration, namely anti-apoptotic, anti-inflammatory and antioxidant actions, the combination of which offers a potent protective effect in dopaminergic neurons. Owing to their pleiotropic modes of action, these novel therapeutic candidates have potential in tackling the multidimensional features of Parkinson's disease.

Abbreviations: Aβ, β-amyloid; AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CAT, catalase; CNS, central nervous system; COX-2, cyclooxygenase-2; CREB, cyclic-AMP response-element binding protein; DA, dopamine; DAergic, dopaminergic; DCS, D-cycloserine; Dox, Doxycycline; ($\Delta\Psi$m, mitochondrial transmembrane potential; ERK, extracellular signal-regulated kinase; γ-GCS, γ-glutamylcysteine synthetase; GFAP, glial fibrillary acidic protein; GIRK2, G-protein coupled inwardly rectifying K channel 2; GPCR, G-protein-coupled receptor; GRP78, glucose-regulated protein 78; GSH, glutathione; GST, glutathione *S*-transferase; HEK-293, human embryonic kidney-293; HO-1, heme oxygenase-1; Iba1, ionized calcium binding adaptor molecule 1; IL-1β, interleukin-1 beta; K-ATP, ATP-sensitive K+ channels; LC3, light chain 3; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LAMP2a, lysosome-associated membrane protein 2a; L-DOPA, L-3,4-dihydroxyphenylalanine; LPS, lipopolysaccharide; LRRK2, leucine-rich repeat kinase 2; MAPK, Mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MMP9, matrix metalloproteinase 9; MPO, myeloperoxidase; MPP+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrimidine; mTOR, mammalian target of Rapamycin; NGF, nerve growth factor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NQO-1, NAD(P)H:quinone oxidoreductase-1; NTFs, Neurotrophic factors; 6-OHDA, 6-hydroxydopamine; PACAP, pituitary adenylate cyclase-activating peptide; PG, prostaglandin; PINK1, PTEN-induced putative kinase 1; PD, Parkinson's disease; ROS, reactive oxygen species; SN, substantia nigra; SNc, substantia nigra pars compacta; SOCS1, suppressor of cytokine signaling 1; SOD, superoxide dismutase; TH, tyrosine hydroxylase; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; VIP, vasoactive intestinal peptide.

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Contents

1. Introduction

Parkinson's disease (PD) is the second most common human neurodegenerative disorder after Alzheimer's disease (AD) and is characterized by progressive motor disability and cognitive dysfunction. PD is generally recognized by dopaminergic (DAergic) neuron loss in the *substantia nigra pars compacta* (SNc) (Damier et al., 1999) and by abnormal accumulation of cytoplasmic α-synuclein protein inclusions, called Lewy bodies, in surviving neurons (Braak et al., 2003). Despite intensive research conducted in the field of PD, the etiology of this neurodegenerative disease remains elusive. Although genetic elements and exposure to environmental toxins, such as pesticides, are thought to play a crucial role in disease onset, aging remains the predominant risk factor (Abdullah et al., 2015; Reeve et al., 2014). As such, PD has become a major concern regarding public health due to its disabling nature and high prevalence in the aging population. Characteristic clinical signs of PD include motor symptoms (such as tremor, bradykinesia, rigidity, and postural instability) and mild neuropsychiatric problems (such as abnormalities in speech, behavior, mood, cognition, and thought process) (Kakkar and Dahiya, 2015). Among the proposed underlying pathophysiological mechanisms, oxidative stress, neuroinflammation, protein misfolding, and mitochondrial dysfunction have been credited as major pathways of neurodegeneration (Gandhi and Wood, 2005).

Accumulating evidence suggests that oxidative stress is among the prominent risk factors underlying nigral degeneration (Hwang, 2013; Tsang and Chung, 2009). Indeed, DAergic neurons in this region of the CNS are particularly susceptible to oxidative stress owing to (1) elevated oxidative activity of monoamine oxidase B (Chen and Ly, 2006), which ensures high dopamine (DA) turnover rates, (2) high levels of iron ions known to participate in deleterious Fenton chemistry (Hirsch and Faucheux, 1998), and (3) relatively low levels of the antioxidant molecule glutathione (GSH) (Riederer et al., 1989), all of which lead to increased exposure to reactive oxygen species (ROS).

Neuroinflammation is also recognized as a key factor in the initiation and progression of PD pathology (More et al., 2013; Russo et al., 2014) and primarily manifests itself as the excessive activation and proliferation of microglia (microgliosis) as first discovered by pioneer post-mortem studies on PD patient brains (McGeer et al., 1988). Since then, it has been shown that microglia are abundant in the SNc in comparison to other brain regions (Kim et al., 2000; Lawson et al., 1990). Interestingly, as ROS are both an activator and by-product of microglia, oxidative stress and neuroinflammation are therefore intricately entwined in PD pathology.

PD is the second most frequent protein misfolding disease and the most common synucleinopathy. Lewy bodies and neurites, respectively found in the soma and processes of nerve cells, are

composed of a complex mixture of proteins, primarily the presynaptic protein α-synuclein, and to a lesser extent ubiquitin, tau, and β-amyloid, among several others. Research on the implication of α-synuclein in PD pathology exploded when a single point mutation (Ala53Thr) of SNCA, the gene encoding α-synuclein, was uncovered in a dominantly inherited form of early onset familial PD in a large Italian pedigree and in three unrelated Greek families (Polymeropoulos et al., 1997). As is the case for many other amyloidogenic proteins, experts have not identified the exact α-synuclein fibrillar structures responsible for cellular toxicity, although there is growing concensus that the process of fibrillization rather than the end product may be cytotoxic (Winner et al., 2011; Avila et al., 2014). α-Synuclein fibrillization is also intimately linked with oxidative stress and neuroinflammation as the process generates ROS and activates microglia. Finally, interplay between α-synuclein monomers or fibrils and clearance pathways cannot be overlooked in the pathophysiology of PD.

On account of their high energy requirement, SNc neurons are particularly vulnerable to mitochondrial dysfunction. Correlation between mitochondrial dysfunction and idiopathic PD was first established upon observing a deficiency in complex I of the electron transport chain in the SNc of patients (Schapira et al., 1989). Likewise, studies demonstrating a sizeable contribution for genes that cause familial forms of PD in mitochondrial homeostasis have reinforced this hypothesis. Indeed, leucine-rich repeat kinase 2 (LRRK2), DJ-1, α-synuclein, and the duo PTEN-induced putative kinase 1 (PINK1) and Parkin have been shown to act in fission/fusion dynamics, mitophagy, or mitochondrial ROS sensing (Chaturvedi and Beal, 2013). Additionally, the development of parkinsonian-like features in models making use of toxins targeting the electron transport chain, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrimidine (MPTP), its active metabolite 1-methyl-4-phenylpyridinium (MPP+), rotenone, 6-hydroxydopamine (6-OHDA), and paraquat, further strengthens a pathophysiological role for mitochondrial dysfunction in PD.

Although several pharmacological compounds improving the function of the nigrostriatal pathway can alleviate motor and non-motor symptoms of PD, these drugs are unable to hinder disease progression (Schapira, 2005). Indeed, the long standing gold standard in PD therapy, the DA precursor L-3,4-dihydroxyphenylalanine (L-DOPA), aims to relieve PD motor symptoms by replacing the deficient neurotransmitter. However, the therapeutic efficacy of L-DOPA tends to fade with time and is attended by motor and/or psychiatric side effects that are extremely discomforting for the patient. Unfortunately, an ideal therapy without long-term debilitating side effects is not currently available for PD patients. It is therefore of the utmost importance that future drug research and development bears the purpose of slowing DAergic neurodegeneration and impeding illness progression (LeWitt, 2004; Schapira et al., 2006). Future drug elaboration strategies in PD are thus likely to focus on the concept of neuroprotection that seeks to prevent DAergic cell death and, hence, slow or halt disease progression (Schapira, 1999). There is an ongoing search for substances that exert protective effects on DAergic neurons and aimed at retarding their degeneration (Lu et al., 2010; Reglodi et al., 2011; Song et al., 2012; Stayte and Vissel, 2014). In this sense, polyphenols, antibiotics, and the pituitary adenylate cyclase-activating peptide (PACAP) have gained renewed interest as the reports of their neuroprotective properties accumulate, especially pertaining to their ability to improve oxidative stress, neuroinflammation, protein misfolding, and mitochondrial dysfunction. The aim of the present paper is not only to carefully review these aspects but also to present original results laying forth the potential effects of these drugs in experimental PD.

2. Protective effects of polyphenols in Parkinson's disease

An ever-expanding number of studies have addressed the potential protective effects of dietary polyphenols in the CNS (see for review Ebrahimi and Schluesener, 2012). In the most recent reports, polyphenols were found to improve cognitive functions in mouse models of AD (Wang et al., 2012), downregulate matrix metalloproteinases in a mouse model of cerebral ischemia (Park et al., 2010), and exert a neuroprotective effect in a chronic mouse model of multiple sclerosis (Fonseca-Kelly et al., 2012). In humans, epidemiological studies found a negative correlation between the consumption of green tea (Kuriyama et al., 2006) or specific polyphenols (Kesse-Guyot et al., 2012) and loss of cognitive function, whereas clinical studies reported beneficial effects of the flavonoid-enriched extract of Ginkgo biloba, EGb 761, on memory impairment in a range of cognitive disorders (Le Bars et al., 1997). Alongside AD, PD is one of the most intensively studied neurological disorders on which the neuroprotective efficacy of polyphenols has been tried, both at the pre-clinical and clinical levels.

2.1. Polyphenols in models of Parkinson's disease

In light of centuries of use in traditional medicine, edible medicinal herbs and plants rich in polyphenols have attracted much attention for their use in human health. Mounting anecdotal evidence, especially from traditional medical systems in India, China, Japan, and Korea, lends these medicinal plant-based treatments significant beneficial effects in PD (Song et al., 2012). The three main avenues for drug development strategies in PD currently focus on (1) improving DAergic therapies and preventing motor complications, (2) identifying non-DAergic drugs for symptomatic improvement, and (3) discovering disease-modifying or neuroprotective compounds (Schapira et al., 2006). Elucidating the pharmacologically valuable role of polyphenols in PD falls under the second and third strategic ambitions. The following section reviews the neuroprotective properties of polyphenols with a particular focus on the main pathophysiological features of PD: oxidative stress, neuroinflammation, protein fibrillization, and mitochondrial dysfunction. Fig. 1 presents the main polyphenols studied in the context of PD and Table 1 synthesizes the most recent reports of neuroprotection exerted by polyphenols in pre-clinical models reviewed herein.

2.1.1. Oxidative stress

Although there have been an overwhelming number of studies reporting the antioxidative properties of polyphenols in neurons, only in recent years has research focused on the mechanisms by which polyphenols reduce intracellular ROS levels (Kong et al., 2001). *In vitro* PD models using these pro-oxidant toxins (*e.g.*: 6-OHDA, rotenone, paraquat, MPP+) are an important tool in clarifying these mechanisms, while *in vivo* paradigms offer further valuable insight into behavioral ameliorations conferred by polyphenol treatment in parallel to improved oxidative status.

Research on the implication of the Keap1/Nrf2/ARE axis underlying polyphenols' antioxidative actions has drastically lifted off in recent years (Kong et al., 2001). In human neuroblastoma SH-SY5Y, a DAergic cell line, challenged with 6-OHDA, pretreatment with the flavonoids pinocembrin (Jin et al., 2015) or naringenin (Lou et al., 2014) were found to reduce the formation of ROS, at least partly by inducing an increase in Nrf2 protein levels, subsequently activating ARE pathway genes. Interestingly, in the case of naringenin, silencing Nrf2 mitigated the observed beneficial effects (Lou et al., 2014). In fact, in the MDA-MB-231-ARE-Luc stable cell line, naringenin was able to activate Nrf2's transcriptional activity as shown by a dose-dependent increase in

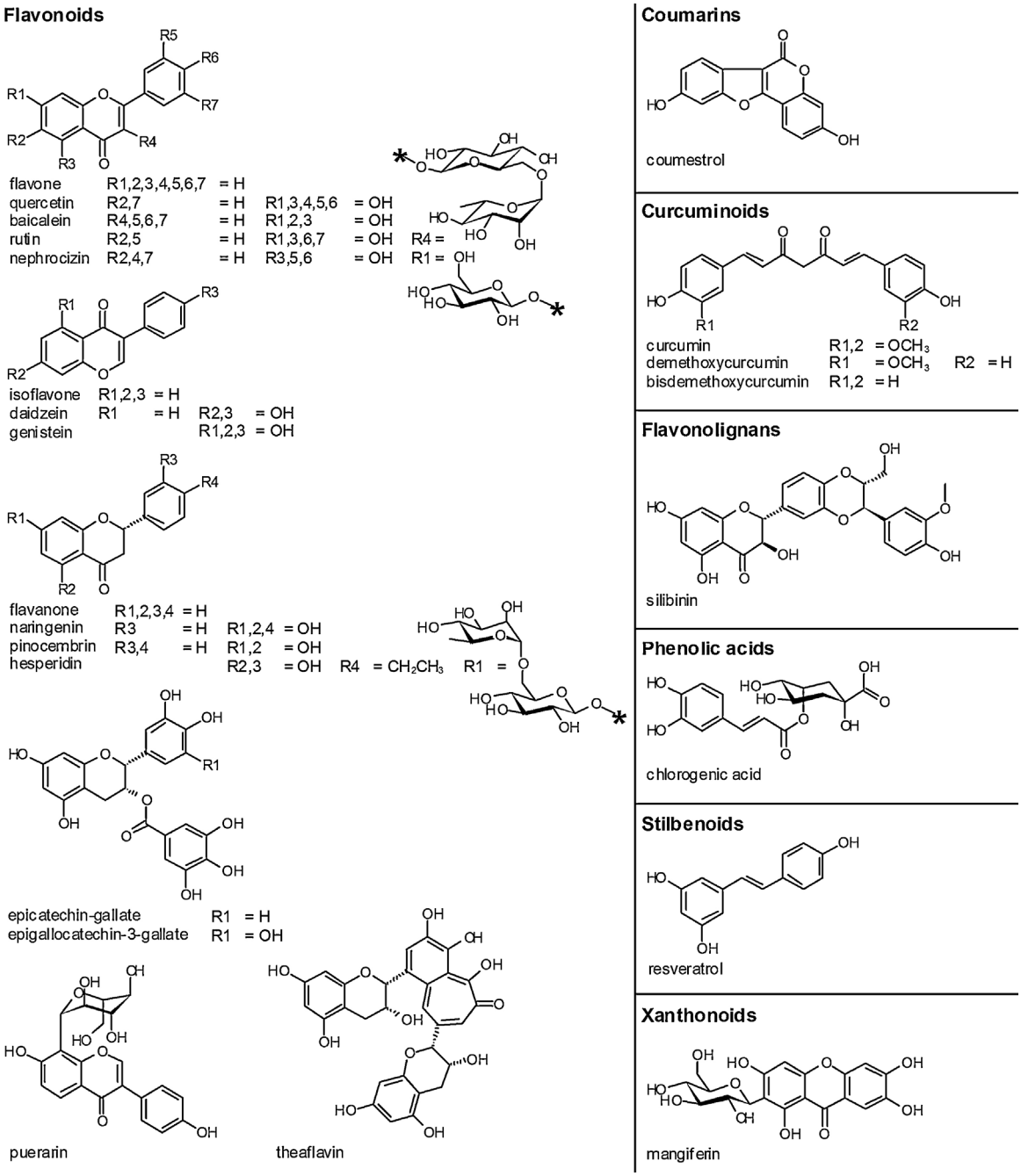


Fig. 1. Molecular representation of the most widely studied polyphenols in Parkinson's disease.

the activity of the ARE-dependent luciferase gene. The same group showed in 6-OHDA-lesioned mice given naringenin orally that the Keap1/Nrf2/ARE axis was readily activated and that oxidative stress was tapered (Lou et al., 2014). This was observed concurrently to the recovery of levels of striatal tyrosine hydroxylase (TH), a key enzyme in DA synthesis. Levels of DA and its metabolites were thus increased and, as a result, apomorphine-induced rotations were markedly reduced. Furthermore, another group showed that, when orally administered to 6-OHDA-lesioned rats, puerarin also reduces apomorphine-induced rotations while increasing levels of DA and its metabolites in the SN (Li et al., 2013a). Yet again, the expression levels of Nrf2 and Keap1 were increased by polyphenol treatment.

Polyphenols may also act by increasing the expression or activity of endogenous antioxidative enzymes. One of the most important inbuilt antioxidative machineries is the GSH system whose functions are improved by polyphenols in several reports. *In vitro*, EGCG (Ye et al., 2012), baicalein (Jung and Lee, 2014), and nephrocizin (Lin et al., 2012) were shown to improve GSH levels and/or glutathione peroxidase (GPx) activity following an oxidative insult. Similar results were obtained in rodent models for several polyphenols alongside reduced DAergic degeneration and improvements in behavior, such as motor deficits (Agrawal et al., 2012; Haleagrahara et al., 2013; Kavitha et al., 2013; Khan et al., 2013; Zhu et al., 2014) and apomorphine- or amphetamine-induced turns (Karuppagounder et al., 2013; Li et al., 2013a,b; Lou et al., 2014). Interestingly, an aqueous extract of the plant *Selaginella delicatula*, whose key polyphenolic constituents are biflavanoids, was shown to not only improve GSH levels but also to enhance the activity of glutathione *S*-transferase (GST), which

Table 1
Most recent and significant reports of neuroprotection exerted by polyphenols in PD models.

Chemical classification	Compound, route and dosage	*In vitro*		*In vivo*		Main biological effects	References
		Toxic treatment	Model	Toxic treatment	Model		
Coumarins	Coumestrol 1 μM 1 h pretreatment	LPS	HAPI rat microglial cell line			↓NO ↓iNOS proteins and mRNA ↓IRF-1 expression and STAT1 phosphorylation ↓IL-6 and MCP-1	Jantaratnotai et al. (2013)
Flavonoids	Baicalein 0.1–10 μM 1 h pretreatment	6-OHDA 6-OHDA	SH-SY5Y or Rat brain mitochondria			↑Cell survival ↓ROS, lipid peroxidation ↑DJ-1 Recovery of $\Delta\Psi m$	Wang et al. (2013)
	Baicalein 1–15 μM up to 24 h cotreatment	Proteasome inhibitors MG132 or MG115	Differentiated PC12			↓ROS ↑GSH ↓Apoptosis Recovery of $\Delta\Psi m$	Jung and Lee (2014)
	Baicalein *in vitro*: 10 μM 6 h pretreatment and up to 24 h cotreatment *in vivo*: 1–10 mg/kg daily *i.p.* 7 d pretreatment	MPP+	Primary rat astrocytes	MPTP	Mice	↑Motor coordination ↓DAergic neuron death ↓Microglia and astrocyte activation ↓NF-κB nuclear translocation ↓COX-2 ↓JNK and ERK phosphorylation	Lee et al. (2014)
	Baicalein 10 mg/kg daily *i.p.* 5 d cotreatment and 9 d post-treatment			MPTP	Mice	↑Motor balance and coordination ↓TNF-α and IL-1β ↓Basal presynaptic Glu release Recovery of postsynaptic GluR1 insertion	Xue et al. (2014)
	Daidzein 0.1 μM 1 h pretreatment	LPS	HAPI rat microglial cell line			↓NO ↓iNOS proteins and mRNA ↓IRF-1, IL-6 and MCP-1 ↓STAT1 phosphorylation	Jantaratnotai et al. (2013)
	Epicatechin-gallate 0.25–1.0 μg/mL mixed in diet *p.o.* 24 d				Transgenic *Drosophila* expressing wild-type human α-synuclein	Recovery of climbing activity ↑Survival rate ↓Brain cell death ↓Lipid peroxidation	Siddique et al. (2014a)
	EGCG 2–10 mg/kg daily *p.o.* 10 doses as pretreatment and 5 just before MPTP injection			MPTP	Mice	↑TH-positive neurons ↓Bax/Bcl-2 ratio ↓α-Synuclein ↑PKCα	Mandel et al. (2004)
	EGCG treatment on α-synuclein monomers, incubated for 2–3 d with PC12	α-Synuclein aggregates	PC12			Suppression of toxic effect	Ehrnhoefer et al. (2008)
	EGCG treatment on preformed α-synuclein aggregates, incubated for 3 d with PC12	α-Synuclein aggregates	PC12			Suppression of toxic effect	Bieschke et al. (2010)
	EGCG 10 min pretreatment on preformed α-synuclein aggregates	α-Synuclein aggregates	Lipid vesicles			↓Lipid membrane permeabilization	Caruana et al. (2012)
	EGCG 10 μM 30 min or 1 h pretreatment	MPP+	Differentiated PC12			↑Cell survival ↓ROS ↑CuZnSOD, GPx-1, SIRT1 and PGC-1α	Ye et al. (2012)
	EGCG 10 min pretreatment on preformed α-synuclein aggregates	α-Synuclein aggregates	Respiring mitochondria isolated from SH-SY5Y or Lipid vesicles			↓Cytochrome *c* release ↓Lipid membrane permeabilization	Camilleri et al. (2013)

Genistein 1 μM 1 h pretreatment	LPS	HAPI rat microglial cell line			↓NO ↓iNOS proteins and mRNA ↓IRF-1, IL-6 and MCP-1 ↓STAT1 phosphorylation	Jantaratnotai et al. (2013)
Green tea polyphenol mixture* *in vitro*: 20 μM 22 h post-treatment *in vivo*: 40 mg/kg daily *p.o.* 80 d	α-Synuclein monomers and oligomers with or without MPP+	MES23.5	MPTP	Cynomolgus monkeys	↓Motor deficits ↑DA and its metabolites ↑TH-positive neurons ↓α-Synuclein oligomers	Chen et al. (2014)
Hesperidin 20 μg 4 h pretreatment	Rotenone	SK-N-SH			Recovery of cell proliferation ↓ROS ↑GSH ↑GPx, SOD and CAT activities ↓Apoptosis Recovery of $\Delta\Psi m$	Tamilselvam et al. (2013)
Naringenin *in vitro*: 20–80 μM 2 h pretreatment and 24 h cotreatment *in vivo*: 70 mg/kg daily *p.o.* 4 d pretreatment	6-OHDA	SH-SY5Y	6-OHDA	Mice	↓Apomorphine-induced rotations ↑Cell survival ↓ROS ↑GSH ↑Nrf2, HO-1, GCLC and GCLM ↓JNK and p38 phosphorylation	Lou et al. (2014)
Nephrocizin 12.5–100 μM 6 h pretreatment	6-OHDA or H_2O_2 or *p*-Quinone	Differentiated PC12			↑Cell survival ↓ROS ↑GSH ↓Caspase-3 and -8 activation Hydroxyl radical scavenger	Lin et al. (2012)
Pinocembrin 1–25 μM 4 h pretreatment	6-OHDA	SH-SY5Y			↓Apoptosis ↓ROS and MDA ↑Nrf2, HO-1 and γ-GCS	Jin et al. (2015)
Puerarin 60–120 mg/kg daily *p.o.* 30 d post-lesion			6-OHDA	Rats	↓Apomorphine-induced rotations ↑DA and its metabolites ↑BDNF-positive cells ↑Keap1 and Nrf2 ↑γ-GCS, GSH and CAT activities ↑COX mRNA	Li et al. (2013a)
Puerarin 10–40 mg/kg daily *p.o.* 30 d post-lesion			6-OHDA	Rats	↑Survival rate ↓Apomorphine-induced rotations ↑GPx and SOD activities ↑NQO-1 mRNA ↓HO-1 mRNA ↑MnSOD and DJ-1	Li et al. (2013b)
Puerarin 0.04–0.12 mg/kg daily *i.p.* 3 d cotreatment and 7 d post-treatment			MPTP	Mice	↓Motor deficits ↑TH-positive neurons ↓ROS ↑GSH, Lamp2A and GDNF ↑Akt phosphorylation	Zhu et al. (2014)
Quercetin 0.1 μM 3 h pretreatment	MPP+ on microglia	N9 + differentiated PC12 insert co-cultures			↓Microglial IL-6, TNF-α and IL-1β mRNA ↓Supernatant IL-6, TNF-α and IL-1β protein ↓Microglial iNOS ↓Microglial mitochondrial superoxide anion ↓Neuronal apoptosis	Bournival et al. (2012)

Table 1 (*Continued*)

Chemical classification	Compound, route and dosage	*In vitro*		*In vivo*		Main biological effects	References
		Toxic treatment	Model	Toxic treatment	Model		
	Quercetin 50 mg/kg daily *p.o.* 14 d post-lesion			6-OHDA	Rats	↑Body weight and food intake ↓Motor deficits ↑Neuronal density ↓Protein carbonylation ↑GSH ↑SOD activity Benefits enhanced by iron chelator desferrioxamine	Haleagrahara et al. (2013)
	Quercetin 25–75 mg/kg twice daily *i.p.* 4 d post-lesion			Rotenone	Rats	↓Apomorphine- or amphetamine-induced rotations ↑DA and TH ↑GSH and GSSG ↑CuZnSOD, MnSOD, CAT, complex-I activities ↓NADPH diaphorase activity ↓DNA fragmentation	Karuppagounder et al. (2013)
	Quercetin and oxidized metabolites treatment on α-synuclein monomers or preformed aggregates					↓Aggregation of α-synuclein monomers ↑Disaggregation of preformed aggregates	Zhu et al. (2013)
	Rutin (quercetin 3-O-rutinoside) 1–10 μM 30 min pretreatment and 24 h cotreatment	Rotenone	SH-5YSY			↓ROS and intracellular Ca2+ ↓JNK and p38 phosphorylation ↓Apoptosis Recovery of $\Delta\Psi$m	Park et al. (2014)
	Selaginella delicatula aqueous extract* 25–100 mg/kg daily *p.o.* 21 d cotreatment			Rotenone	Mice	↓Motor deficits ↑DA ↓ROS, MDA, protein carbonylation and nitration ↓SOD, TR and GST activities ↑GPx, complex-I, -II and citrate synthase activities ↑Mitochondrial ATPases Recovery of $\Delta\Psi$m	Chandran and Muralidhara (2013)
	Theaflavin 10 mg/kg biweekly *p.o.* 5 w cotreatment			MPTP with probenecid	Mice	↓Motor deficits ↓COX-2, GFAP, IL-4, IL-6, IL-10, TNF-α and IL-1β ↓Bax/Bcl-2 ratio	Anandhan et al. (2013)

Lignans	Silibinin 50–200 mg/kg daily *p.o.* 1 d cotreatment and 6 d post-lesion			MPP+	Rats	↑Memory consolidation ↓Motor deficits ↑DA ↑SOD, lipid peroxidase, complex-II, -IV, -V activities ↓Nitrites Recovery of $\Delta\Psi m$	Geed et al. (2014)
	Silibinin 10–100 mg/kg daily *i.p.* 1 d pretreatment and up to 6 d post-lesion			MPP+	Rats	↑TH ↓TNF-α, IL-1β and iNOS	Jung et al. (2014)
	Silymarin* 100–300 mg/kg daily *i.p.* 5 d pretreatment			6-OHDA	Rats	↓Catalepsy ↓MPO activity ↓TNF-α and IL-6	Haddadi et al. (2013)
	Silymarin* 100–300 mg/kg daily *i.p.* 5 d pretreatment			6-OHDA	Rats	↑Motor coordination ↓MDA and IL-1β	Haddadi et al. (2014)
	Silymarin* 25–400 mg/kg daily *i.p.* 5 d cotreatment			MPTP	Mice	↑DA ↑TH-positive neurons ↓Apoptosis	Pérez-H et al. (2014)
Phenolic acids and derivatives	Chlorogenic acid 0–100 μM 10–20 h cotreatment	DA or L-DOPA	Differentiated PC12-α-syn-Tet Off system			Suppression of toxic effect ↓Oxidation of DA and L-DOPA ↓Binding of DA and α-synuclein ↓DA- and L-DOPA -induced α-synuclein aggregation	Teraoka et al. (2012)
	Curcumin 3–30 μM 24 h treatment		SH-SY5Y transfected with wild-type α-syn-flag or A53T α-syn-flag plasmid			↓mTOR and p70S6K phosphorylation ↓α-Synuclein ↑Autophagy	Jiang et al. (2013a,b)
	Curcumin 1–20 μM 30 min pretreatment	6-OHDA	SH-SY5Y			↑Cell survival ↑TH phosphorylation ↓Quinone-bound proteins, cleaved caspase-3 ↓p38 phosphorylation	Meesarapee et al. (2014)
	Curcumin 25–100 μM mixed in diet *p.o.* 24 d				Transgenic *Drosophila* expressing wild-type human α-synuclein	Recovery of activity pattern ↑Survival rate ↓Brain cell death ↓Lipid peroxidation and protein carbonylation	Siddique et al. (2014b)
	Curcumin, demethoxycurcumin or bisdemethoxycurcumin 60 mg/kg daily *p.o.* 3 w pretreatment			6-OHDA	Rats	↓Motor deficits ↑DA and its metabolites, TH-positive neurons ↓ROS ↑GSH, D_2 receptors ↑GR, GPx, SOD and CAT activities	Agrawal et al. (2012)
	Curcumin metabolites 40 μM 20 min pretreatment	MPP+ or H_2O_2 or $MnCl_2$	PC12			↑Cell survival ↓α-Synuclein aggregation α-Synuclein binding Free radical scavenging	Marchiani et al. (2013)
	Gallic acid 0.1 mM mixed in diet *p.o.* 15 d cotreatment			Paraquat	*Drosophila*	↑Survival rate ↑Climbing performance	Ortega-Arellano et al. (2013)

Table 1 (*Continued*)

Chemical classification	Compound, route and dosage	*In vitro*		*In vivo*		Main biological effects	References
		Toxic treatment	Model	Toxic treatment	Model		
Proanthocyanidins	Pycnogenol* 5–20 mg/kg daily *i.p.* 7 d cotreatment and 7 d post-treatment			MPTP	Mice	↓Motor deficits ↑TH, DA, GSH ↓ROS ↑GPx, SOD and GR activities ↓Astroglia and microglia activation ↓NF-κB, iNOS, COX-2, TNF-α α□□□ IL-1β	Khan et al. (2013)
Stilbenoids	Resveratrol 0.1 μM 3 h pretreatment	LPS on microglia	N9 + differentiated PC12 insert co-cultures			↓Microglial TNF-α and IL-1α mRNA ↓Neuronal caspase-3 activation ↓Neuronal apoptosis	Bureau et al. (2008)
	Resveratrol 5–20 μM various time points as pre-, co- and post-treatments	Rotenone or MPO Rotenone MPP+ or rotenone	Primary rat microglia/ astrocytes or Mesencephalic neurons + microglia insert co-cultures or Mixed glial cells from *Mpo*$^{-/-}$ mice BV2			↑Cell survival ↓Nitrites, ROS, MPO, phagocytic activity ↓iNOS, COX-2, TNF-α and IL-1β mRNA ↓gp91phox subunit of NADPH oxidase	Chang et al. (2013)
	Resveratrol 25 μM 8–48 h treatment		Primary skin fibroblasts from 2 early-onset PD patients with different Park2 mutations			↑Mitochondrial oxidative capacity ↓ROS ↑AMPK and SIRT1 activities ↑NAD + /NADH ↑Transcriptional activity of PGC-1α ↑Autophagic flux	Ferretta et al. (2014)
	Resveratrol 20 μM 24 h pretreatment	Rotenone	SH-SY5Y			↑Cell survival ↑HO-1 expression ↑Autophagic flux	Lin et al. (2014)
	Resveratrol 50 mg/kg daily *p.o.* 8 d pretreatment and 13 d post-treatment			MPTP	Mice	↑TH proteins and mRNA ↓GFAP and CD11B proteins and mRNA ↑SOCS1 proteins and mRNA ↓TNF-α, IL-1β and IL-6 proteins and mRNA ↓TNF-αR1, IL-1βR1 and IL-6Rα mRNA	Lofrumento et al. (2014)
Xanthonoids	Mangiferin 10–40 mg/kg daily *p.o.* 9 d pretreatment and 5 d cotreatment			MPTP	Mice	↓Motor deficits ↑DA ↑TH- and DAT-positive neurons ↓ROS ↑GSH ↑SOD, CAT, GPx and MAO-B activities ↓Bax/Bcl-2 ratio	Kavitha et al. (2013)

The term "cotreatment" in animal models signifies that administration of polyphenol was performed on the same day as the lesion.

* Indicates extracts composed of several polyphenols and phytochemicals.

catalyzes the addition of GSH onto potentially harmful xenobiotic substrates as a means of detoxification (Chandran and Muralidhara, 2013). Noteworthy, puerarin was shown to improve levels of GSH in the brains of 6-OHDA-treated rats, which could be explained by the concomitant increase in γ-glutamylcysteine synthetase (γ-GCS), the enzyme that synthesizes GSH (Li et al., 2013a). Other antioxidative enzymes that have been studied following polyphenol treatment are catalase (CAT), which detoxifies H_2O_2, superoxide dismutase (SOD), which dismutes superoxide anion in the mitochondria (MnSOD) or in the cytosol (CuZnSOD), and NAD(P)H:quinone oxidoreductase-1 (NQO-1), which prevents the one-electron reduction of quinones that results in the production of radical species. Substantial amelioration of the activities of these enzymes, complemented by dampened motor deficits, were shown for puerarin (Li et al., 2013b), curcuminoids (Agrawal et al., 2012), and pycnogenol (Khan et al., 2013), an extract of Pinus maritime bark whose main polyphenolic constituents are proanthocyanidins.

Since ROS production and mitochondrial homeostasis are closely linked, as it will be discussed further, several papers have investigated the role of proteins involved in mitochondrial function, such as the silent mating type information regulation 2 homolog 1-peroxisome proliferator/activated receptor gamma coactivator 1-alpha (SIRT1/PGC-1α) axis, with regards to oxidative stress. Exemplarily, Ye and coworkers (2012) found that the flavanol EGCG administered to MPP+-treated differentiated DAergic PC12 (rat pheochromocytoma cells) improved the expression of SIRT1 and PGC-1α, concomitantly improving the latter's transcriptional activity.

6-OHDA is known to auto-oxidize in cell culture medium, yielding the cytotoxic by-products H_2O_2 and *p*-quinone, which, respectively, promotes ROS production and is conjugated with cysteine residues to form noxious quinoproteins. Nephrocizin (luteolin-7-*O*-β-d-glucopyranoside) treatment on differentiated DAergic PC12 prevents cell death from exposure to either H_2O_2 or *p*-quinone (Lin et al., 2012). However, nephrocizin has no effect on 6-OHDA auto-oxidation and formation of H_2O_2 in the absence of cells, suggesting that its neuroprotective mechanisms operate downstream. In that respect, nephrocizin was shown to act by suppressing the production of intracellular ROS generated by H_2O_2, but that are not induced by *p*-quinone. Moreover, nephrocizin inhibited activation of pro-apoptotic players, caspase-3 and caspase-8, as mediated primarily by H_2O_2 and *p*-quinone, respectively. Further assays demonstrated that nephrocizin was able to cross cell membranes and to directly scavenge the hydroxyl radical. In like manner, another study found that curcumin pretreatment of human neuroblastoma SH-SY5Y cells exposed to 6-OHDA is effective in protecting against cell death while diminishing levels of quinone-bound proteins (Meesarapee et al., 2014).

Mitogen-activated protein kinase (MAPK) pathways involved in cell survival and apoptosis are modulated by polyphenols and may have a role to play in the protection against oxidative stress. In human neuroblastoma SH-SY5Y cells exposed to 6-OHDA, phosphorylation of MAPKs and levels of cleaved caspase-3 were reduced by curcumin (Meesarapee et al., 2014) and naringenin (Lou et al., 2014). Rutin (quercetin 3-*O*-rutinoside) prevented ROS production and intracellular Ca^{2+} increase, while decreasing apoptosis through mitigation of the expression and activity of pro-apoptotic factors (Park et al., 2014). Rutin repressed c-Jun N-terminal kinase (JNK) and p38 phosphorylation, while administration of either JNK or p38 inhibitors mimicked its neuroprotective action and potentiated its effect in cotreatment. In a different paradigm consisting in primary astrocytes treated with MPP+, the flavone baicalein also inhibited the phosphorylation of JNK and extracellular signal-regulated kinase (ERK) (Lee et al., 2014). Finally, another important kinase perhaps involved in neuroprotection conferred by polyphenols is Akt. Indeed, Akt phosphorylation was increased by puerarin administration in MPTP-treated mice (Zhu et al., 2014). This observation was accompanied by reduced ROS, increased GSH, and improved motor deficits.

2.1.2. Neuroinflammation

Numerous *in vitro* models of neuroinflammation have been established in response to a need for investigating the anti-inflammatory potential of therapeutic molecules such as polyphenols and for exploring immunomodulatory dysfunction that attends PD pathophysiology. The most widespread paradigm involves glia challenged with lipopolysaccharide (LPS), a component of Gram-negative bacteria outer membranes that, upon activating toll-like receptor 4 (TLR4), elicits a robust inflammatory response in a wide variety of immune effector cells (Qureshi et al., 1999; Sabroe et al., 2002). In PD research, MPP+, rotenone, and 6-OHDA also trigger neuroinflammatory transformations in glial cells.

Neuroinflammatory features, such as gliosis and cytokine dysregulation, as seen in brains of PD patients, are often observed in rodent models of the disease. Several polyphenols were shown to diminish the expression or transcription of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6 (Anandhan et al., 2013; Jung et al., 2014; Khan et al., 2013; Lofrumento et al., 2014). Of interest, the expression of anti-inflammatory cytokines IL-4 and IL-10, which increases as a compensatory mechanism in MPTP/probenecid mice, was diminished by theaflavin treatment, suggesting a general effect in dampening the inflammatory response. Moreover, a role for modulation of the suppressor of cytokine signaling 1 (SOCS1) may underlie polyphenols' anti-inflammatory potential. The protein encoded by this gene functions downstream of cytokine receptors and takes part in a negative feedback loop to attenuate cytokine signaling. In this respect, orally administered resveratrol was successful in reducing glial activation, rescuing DAergic neurons, and decreasing the production of IL-6, IL-1β, and TNF-α as well as their receptors in the SN of MPTP-treated mice (Lofrumento et al., 2014). Noteworthy, the transcription and expression of SOCS1 were upregulated by resveratrol in the striatum and SN, which could explain the restrained release of pro-inflammatory cytokines.

Since the CNS houses glia as well as neurons, studying their crosstalk is imperative in elucidating underlying mechanisms of neuroinflammation. Unlike mixed cultures, insert co-culture systems without cell-cell contact enable the investigator to identify which cell culture is generating the toxic effects and which one is being affected. In that respect, quercetin or resveratrol administered to MPP+- or LPS-activated N9 microglia, a murine cell line, co-cultured in inserts with differentiated DAergic PC12 prevented pro-inflammatory cytokine expression and transcription, and further prevented neuronal cell apoptosis (Bournival et al., 2012; Bureau et al., 2008). In a similar insert co-culture system of rotenone-treated primary mesencephalic neurons with primary microglia, resveratrol improved cell survival (Chang et al., 2013). Remarkably, these beneficial effects were not achieved when neurons were cultivated without microglia, suggesting a neuroprotective effect mediated by the glial population.

In addition to cytokines, other key pro-inflammatory players include the inducible prostaglandin (PG)-synthesizing enzyme cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and markers of astrogliosis or microgliosis, such as glial fibrillary acidic protein (GFAP), integrin alpha M (CD11b), and ionized calcium binding adaptor molecule 1 (Iba1). Reduced levels of these proteins or their mRNA were shown in parallel to DAergic neuroprotection and behavioral improvements for multiple

polyphenols such as theaflavin (Anandhan et al., 2013), baicalein (Lee et al., 2014), resveratrol (Lofrumento et al., 2014), puerarin (Li et al., 2013b), and pycnogenol (Khan et al., 2013). Furthermore, the activity of NADPH diaphorase expressed in neurons, which like iNOS catalyzes the production of the inflammatory mediator nitric oxide (NO), was decreased by quercetin in 6-OHDA-treated rats (Karuppagounder et al., 2013).

One study in particular showed the multidimensional anti-inflammatory effects of resveratrol in various rotenone-challenged cultures and the intimate implication of myeloperoxidase (MPO), an enzyme that produces hypochlorous acid and tyrosyl radical during microglial respiratory burst. Hypochlorous acid and tyrosyl radical are cytotoxic not only to pathogens but also to the cells that produce them and, as such, link neuroinflammation with oxidative stress. Briefly, resveratrol administered to rotenone-treated BV2 (a murine microglial cell line) or primary microglia was shown to reduce expression of MPO and levels of nitrite, a NO metabolite (Chang et al., 2013). MPO acts as a positive feedback element and is able to increase its own expression and activity in both microglia and astrocytes. However, resveratrol mitigated the increase in MPO expression and activity induced by MPO treatment on primary microglia or astrocytes, which was not achieved with other representative anti-inflammatory drugs, namely ethyl pyruvate and 15-deoxy-Δ-12,14-prostaglandin J2. Furthermore, in MPO-deficient primary glial cells, resveratrol significantly attenuated the rotenone-induced production of nitrite and transcriptional up-regulation of IL-1β, COX-2, TNF-α, and iNOS. Finally, to further support their findings, the authors examined whether MPO levels could be rescued in a different neurotoxic model, that of BV2 microglia treated with MPP+, and found that resveratrol also diminished expression of MPO and production of ROS. Resveratrol's anti-inflammatory role is without a doubt one of the most explored and is reviewed in greater detail elsewhere (Renaud and Martinoli, 2014).

An increasingly popular polyphenol mixture tested for its anti-inflammatory properties is the milk thistle extract silymarin composed of various flavonolignans. In 6-OHDA-challenged rats, intraperitoneal injections of silymarin promoted the improvement of bar catalepsy scores (Haddadi et al., 2013) and motor coordination (Haddadi et al., 2014). In addition, silymarin decreased striatal MPO activity, much like resveratrol, and caused levels of pro-inflammatory cytokines to drop in the cerebrospinal fluid (Haddadi et al., 2013, 2014). Furthermore, the principal flavonolignan of silymarin, silibinin, was investigated for its individual anti-inflammatory properties. When administered in MPP+-treated mice, silibinin was found to recover TH levels and to diminish the expression of both iNOS and pro-inflammatory cytokines in the SN (Jung et al., 2014). Suggestively, silibinin is responsible for at least part of silymarin's potent anti-inflammatory action.

Perhaps the most acknowledged effect of estrogen-like polyphenols, or phytoestrogens, is their anti-inflammatory action. The isoflavones daidzein and genistein, and the coumarin coumestrol – three soy phytoestrogens – were tested on LPS-activated HAPI cells (a rat microglial cell line) for their anti-inflammatory properties in comparison with 17β-estradiol (Jantaratnotai et al., 2013). Interestingly, all three phytoestrogens successfully reduced the transcription and expression of iNOS as well as the production of NO through an antioxidative-independent mechanism, as shown by a sodium nitroprusside assay. Moreover, the expression of the pro-inflammatory cytokine IL-6 and chemokine monocyte chemoattractant protein-1 (MCP-1) was mitigated by phytoestrogen treatment. Results obtained with these polyphenolic phytoestrogens were similar to those yielded by 17β-estradiol, which hints toward a probable binding effect of ERs explaining the ROS scavenging-independent mechanism of neuroprotection at the low concentrations used (low micromolar).

Only very few studies have delved deeper in unraveling the cellular mechanisms underlying the anti-inflammatory effects of polyphenols. One team used baicalein administered to primary astrocytes treated with MPP+ to show that it in fact inhibited the nuclear translocation of the pro-inflammatory power player nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Lee et al., 2014). They further showed that reducing the nuclear localization of this transcription factor mitigated the expression of the downstream target COX-2, suggesting a role for the NF-κB pathway in this polyphenol's anti-inflammatory actions. NF-κB's transcriptional activity also prompts the expression of most pro-inflammatory cytokines and enzymes. In like manner, the Pinus maritime bark extract pycnogenol was found to decrease the expression of NF-κB as well as its downstream targets (Khan et al., 2013). Further studies are warranted to understand the signalization pathways by which polyphenols act to offset neuroinflammation.

2.1.3. Protein fibrillization

Indisputably, the green tea flavanol EGCG has been one of the most expansively studied polyphenols pertaining to its fibril-destabilizing properties, not only in PD but also in AD (Bieschke et al., 2010) and type 2 diabetes (Meng et al., 2010). EGCG was shown to impede toxic aggregation of amyloidogenic α-synuclein in a variety of *in vitro* models (Bieschke et al., 2010; Camilleri et al., 2013; Caruana et al., 2012). It is thought that EGCG may promote the formation of new kinds of oligomers that were found to be nontoxic to mammalian cells lines such as rat PC12 and human embryonic kidney-293 (HEK-293) cells (Bieschke et al., 2010), probably by redirecting them to "off-pathway" fibrillization (Ehrnhoefer et al., 2008). In addition, EGCG was able to impair the membrane destabilizing capacities of preformed fibrils (Camilleri et al., 2013).

In vivo, EGCG's fibril-destabilizing effects were tested in MPTP-treated mice following oral administration of the compound and, indeed, the flavanol was able to prevent α-synuclein accumulation (Mandel et al., 2004). Furthermore, a mixture of green tea polyphenols containing several catechins, although mainly EGCG, orally administered to MPTP-lesioned cynomolgus monkeys was found to reduce motor deficits, while improving the number of nigral TH-positive neurons and DA levels in the striatum (Chen et al., 2014). In addition, green tea polyphenols were able to reduce levels of α-synuclein oligomers in the striatum and hippocampus. In parallel, the authors conducted experiments in a DAergic substantia nigra/neuroblastoma hybrid cell line, MES23.5 cells, treated with α-synuclein monomers or oligomers in combination with MPP+, and found that tea polyphenols diminished levels of oligomers while improving cell viability.

Other polyphenols and polyphenol-rich extracts have been investigated for their fibril-destabilizing properties, including quercetin (Zhu et al., 2013), curcumin (Jiang et al., 2013a,b) and its metabolites (Marchiani et al., 2013), and chlorogenic acid (Teraoka et al., 2012), which were shown to inhibit initiation and/or growth of α-synuclein fibrils *in vitro*. Of interest, oxidized species of quercetin were more efficient in destabilizing human wild-type α-synuclein fibril formation and growth (Zhu et al., 2013). Both quercetin and its oxidized forms were able to disaggregate preformed fibrils. Authors suggested that oxidized quercetin might cause stronger inhibition than quercetin does because of its elevated polarity and hydrophilicity. In a physiological context, quercetin would likely scavenge ROS thereby adopting an oxidized form still useful to fibril-destabilization ends, which infers a possible double mandate of polyphenols *in vivo*.

Drosophila melanogaster expressing wild-type human α-synuclein have been very useful to study the synucleinopathic aspect of PD and to investigate prospective neuroprotective strategies. In

that respect, epicatechin-gallate, another green tea flavanol, or curcumin mixed in the diet of *Drosophila* expressing human α-synuclein were both found to increase life span, recover loss of climbing ability or activity pattern, reduce lipid peroxidation or protein carbonyl content, and mitigate death of brain cells (Siddique et al., 2014a,b).

Another avenue to consider in preventing protein fibrillization is the clearance of aggregates and oligomers mediated by autophagic pathways, which were found to be impaired in PD (Ghavami et al., 2014). Of interest, differentiated DAergic PC12 treated with proteasome inhibitors MG132 or MG115 underwent extensive cell death, apoptosis, and mitochondrial damage. Administration of the flavone baicalein was able to reverse the adverse effects following proteasome inhibition (Jung and Lee, 2014). Another study showed that resveratrol pretreatment on human neuroblastoma SH-SY5Y cells challenged with rotenone conferred protection against cell death (Lin et al., 2014). This effect was abolished by administration of bafilomycin A1, an autophagosome-lysosome fusion inhibitor, suggesting a role for autophagy in this process. Interestingly, pharmacological inhibition of heme oxygenase-1 (HO-1) abolished resveratrol-mediated autophagy and neuroprotection. In like manner, one study showed the capacity for puerarin to increase the expression of lysosome-associated membrane protein 2a (LAMP2a), a lysosomal membrane receptor that regulates clearance of cytosolic proteins by chaperone-mediated autophagy (Zhu et al., 2014). In fact, levels of LAMP2a at the lysosomal membrane are directly associated with the activity of the proteolytic pathway. Although none of these studies clearly demonstrate direct clearance of α-synuclein oligomers, quercetin was shown to inhibit β-amyloid-induced paralysis in *Caenorhabditis elegans* as a direct result of activation of protein degradation pathways (Regitz et al., 2014). Evidently, a role for modulating the misfolding of proteins and their clearance underlies the neuroprotective actions of some polyphenols.

2.1.4. Mitochondrial dysfunction

The development of parkinsonian-like features in models making use of toxins targeting the electron transport chain strengthens a pathophysiological role for mitochondrial dysfunction in PD. At first hand, it can be observed by the loss of mitochondrial transmembrane potential ($\Delta\Psi m$), which, among other events, triggers apoptosis of DAergic neurons. In that sense, several polyphenols were studied for their potential to recover $\Delta\Psi m$ after an oxidative insult and a concomitant dampening of the apoptotic cascade was often observed *in vitro* (Jung and Lee, 2014; Wang et al., 2013). Such observations were also made *in vivo* alongside reduced DAergic degeneration paralleled by the improvement of motor deficits (Chandran and Muralidhara, 2013; Geed et al., 2014). In particular, the aqueous extract of *S. delicatula* administered to rotenone-challenged mice was also found to enhance the activities of citrate synthase and complex I and II, as well as the expression levels of mitochondrial ATPases (Chandran and Muralidhara, 2013). Likewise, quercetin was also shown to improve the activity of complex I in the SN of 6-OHDA-treated rats concomitantly to reducing DNA fragmentation, which suggests a potent anti-apoptotic action (Karuppagounder et al., 2013), Moreover, silibinin administered orally to rats receiving a striatal injection of MPP+ ameliorated the activities of complex IV and V (ATP synthase) (Geed et al., 2014). However, it aggravated MPP+-induced decrease in complex I activity, which was probably compensated for by an enhancement of the activity of complex II, the second door of entry for electrons in the transport chain.

Direct administration of toxins and polyphenols on isolated brain mitochondria may also serve to better qualify neurotoxic and neuroprotective effects. In that respect, baicalein administered to isolated rat brain mitochondria treated with 6-OHDA diminished ROS production, whereas lipid peroxidation induced by $FeSO_4$-cysteine was prevented in parallel (Wang et al., 2013). Quercetin was also found to scavenge the hydroxyl radical in rat cortex mitochondria treated with rotenone *ex vivo*, which suggests a role for direct ROS depletion in this flavonoid's mitochondria-sparing actions (Karuppagounder et al., 2013).

Genes that cause familial forms of PD are often implicated in mitochondrial homeostasis. Indeed, LRRK2, DJ-1, and the duo PINK1-Parkin have been shown to act in fission/fusion dynamics, mitophagy, lysosomal-autophagic degradation, or mitochondrial ROS sensing (Chaturvedi and Beal, 2013). In light of this, one study showed that the flavone baicalein increases the expression of DJ-1 in 6-OHDA-challenged SH-SY5Y human neuroblastoma cells (Wang et al., 2013). Moreover, in Parkin-null or G2019 LRRK2-transgenic *Drosophila*, EGCG was shown to reverse DAergic neurodegeneration and to significantly improve climbing activity (Ng et al., 2012). Interestingly, the protective effects of EGCG were abolished when AMP-activated protein kinase (AMPK) was genetically inactivated, suggesting an implication for this mitochondrial metabolic power player in neuroprotection.

Another polyphenol whose action on AMPK has been extensively studied is resveratrol. One eloquent study showing resveratrol's potential in improving mitochondrial homeostasis used primary skin fibroblast cultures from two patients with early-onset PD caused by different Park2 mutations, the gene encoding Parkin (Ferretta et al., 2014). Treatment with resveratrol was found to increase mitochondrial function as illustrated by an increase in ATP production, complex I activity and oxygen consumption, as well as a decrease in lactate content and ROS production. Resveratrol also promoted the activation of AMPK and another mitochondrial homeostasis power player, SIRT1, alongside increasing the NAD+/NADH ratio. In addition, resveratrol modulated PGC-1α's transcriptional activity as observed by an increase in mRNA expression of several downstream target genes. Finally, resveratrol enhanced macro-autophagic flux in the skin fibroblast cultures through a microtubule-associated protein light chain 3 (LC3)-independent pathway, which is perhaps suggestive of a role in α-synuclein clearance.

2.1.5. Human studies: The case of epigallocatechin-3-gallate

Compelling epidemiological evidence affords a link between green or black tea intake and a reduced risk of developing PD (see for review Mandel et al., 2012). Based on these epidemiological data, a double-blind, randomized, placebo-controlled delayed study was launched to better define the protective effects of EGCG or green tea polyphenols in PD. This investigation, conducted by the Chinese Parkinson Study Group and supported by The Michael J. Fox Foundation, sought to determine the safety and efficacy of green tea polyphenols in patients with *de novo* PD (ClinicalTrials.gov identifier: NCT00461942, Efficacy and Safety of Green Tea Polyphenol in De Novo Parkinson's Disease Patients). This phase 2 study showed in over 400 untreated people with PD a significant improvement at 6 months in unified PD rating scale (UPDRS) scores for each dosage group (Chan et al., 2009). Noteworthy, no important safety issues were discerned in any group administered with green tea polyphenols. At 12 months, however, improvements made in comparison to the placebo-treated group were no longer significantly substantial, leading the authors to conclude that treatments with green tea polyphenols yielded no discernable disease-modifying outcomes, despite them providing symptomatic relief in early *de novo* PD. Suggestively, time of administration of EGCG or other polyphenols is apparently a central issue in translating pre-clinical findings to human-applied therapies.

2.2. Therapeutic considerations

It is apparent that polyphenols bear interesting neuroprotective properties in pre-clinical models of PD. Indeed, their beneficial effects in contexts pertaining to oxidative stress, neuroinflammation, protein misfolding, and mitochondrial dysfunction justify further investigations in patients with PD that, as of yet, have been restricted to the study of green tea polyphenols in *de novo* cases (Chan et al., 2009). These neuroprotective actions seem to arise from polyphenols' influence on cellular elements such as HO-1, MPO, α-synuclein misfolding, and multiple pathways, namely SIRT1/AMPK, MAPKs, and Keap1/Nrf2/ARE axes. Among the most intensively studied polyphenols in recent years, resveratrol, quercetin, EGCG, and curcumin remain prevalently investigated, while the extract silymarin, its main flavonolignan silibinin, and baicalein have considerably gained in popularity.

In spite of these encouraging observations, a few issues exist in pre-clinical designs that may render them less predictive for human applications than we would hope. In particular, the role of direct antioxidant effects of polyphenols in physiological environments is controversial. On the one hand, H-atom transfer must occur faster than at least one of the reactions of free-radical-production cascades (*e.g.*, the limiting propagation step in lipid peroxidation) (Di Meo et al., 2013). On the other hand, polyphenol concentrations, which rarely exceed micromolar concentrations in plasma or tissues at any given time (Del Rio et al., 2013), will be substantially inferior to those of endogenous antioxidants such as ascorbate (30–100 μM) and urate (140–200 μM). Consequently, it is argued that their contribution to plasma's total antioxidant capacity never exceeds 2% and may therefore be irrelevant in a physiological context (Hollman et al., 2011). This considered, biological effects that can occur at nanomolar concentrations through indirect mechanisms, for example by the activation of the Keap1/Nrf2/ARE axis, may better explain polyphenols' antioxidative actions. Directly linked to this dilemma, the most critical obstacle to the use of polyphenols in treating neurodegenerative diseases such as PD remains their bioavailability and ability to cross the blood–brain barrier (BBB).

2.2.1. Bioavailability and safety in humans

Most drugs marketed worldwide are administered *per os* for practical reasons, which renders development of pharmacological treatments dependent on oral bioavailability. The most important factors that dictate bioavailability and bioefficacy are (1) physicochemical properties, (2) interaction with food matrix, and (3) response to physiological conditions of the gastrointestinal tract. For this reason – and provided that phytochemicals elicit great interest for their potential in developing alternative drugs or even just for weighing their effect from nutritional intake – numerous studies report the pharmacokinetic profile of polyphenols following oral administration (Manach et al., 2005).

The bioavailability of polyphenols is without a doubt the most controversial aspect debated with respect to therapeutic administration. As of date, EGCG is the only known untransformed polyphenol abundantly available in human plasma (77–90%) in a free form (Ullmann et al., 2004), while most others are highly glucuronidated or sulfated. After gastric digestion, some polyphenols manage to remain stable, though most of them react with digestive enzymes under duodenal conditions yielding other molecules such as galloyl or methylated derivatives, which could possibly reduce their absorption. As an example, the pharmacokinetic profile of EGCG after a single-dose administration in humans higher than 1000 mg reveals maximal plasma levels of about 1 μM (Ullmann et al., 2004). Noteworthy, it has also been reported that the bioavailability of EGCG increases after chronic administration of 800 mg (Henning et al., 2005), suggesting that repetitive administration may be a more efficacious therapeutic option. In the case of resveratrol, this stilbenoid is readily metabolized into its glucoronide (*trans*-resveratrol-3-*O*-glucuronide) and sulfate (*trans*-resveratrol-3-sulfate) conjugates in the intestine and liver (Walle, 2011). In spite of this, recent lines of evidence provide that these metabolites may also possess significant beneficial properties (Marchiani et al., 2013). In addition, human expressed sulfatases may also transform resveratrol sulfates or other sulphated polyphenols back into their original chemical state (Andreadi et al., 2014). Finally, most polyphenols orally administered do not present any important safety issues. Minor problems reported are usually irritation of the gastrointestinal tract.

2.2.2. Blood–brain barrier

Perhaps the most important aspect to weigh when considering polyphenols as a potential treatment avenue for PD is the capability of these molecules to enter the CNS. This also encompasses their potential to accumulate in brain tissue in sufficient concentrations and in biologically active forms. The key obstacles polyphenols encounter on their way to the CNS are (1) BBB and (2) multidrug resistance-associated proteins. Still only a few years back, our knowledge of polyphenols' capacity to cross the BBB was quite limited. However, it is now quite clear that a very important number of polyphenols do cross the BBB and these data are extensively reviewed elsewhere (Campos-Bedolla et al., 2014).

2.2.3. Delivery systems

Perhaps one of the most promising new strategies to enhance CNS bioavailability is the development of novel delivery and encapsulation technologies. Indeed, pharmacological advances are persistently improving the bioavailability of polyphenols, whether by the use of lipid nanocapsules, nanoparticles, exosomes, nanocomposites, or emulsified formulations (for review see Fang and Bhandari, 2010). In addition, intranasal administration of polyphenols may offer better bioavailability, in light of successful tests with other CNS-borne drugs, such as apomorphine for PD or insulin for AD, reviewed in detail elsewhere (Chapman et al., 2013). In fact, intranasal curcumin administration was better incorporated in the brain than its oral form (Di Mauro and Di Mauro, 2008). However, nasal irritation must be considered as a risk factor and may be a roadblock in the development of intranasal polyphenol administration (Chapman et al., 2013).

2.2.4. Synergy

In the last 10 years, new methods in drug administration have arisen. Multidrug therapy is one of these new paradigms whose development was warranted to overcome hurdles in stand-alone treatments such as low efficacy, resistance, and undesirable side effects. The use of polyphenols and their combination in treating multiple aspects of diseases is a particularly interesting alternative to western medicine pertaining to their wide spectrum of activity. Their synergistic actions arise from mechanisms such as (1) regulation of either the same or different targets in various pathways, (2) regulation of transporter enzymes responsible for intestinal absorption or renal clearance, and (3) regulation of detoxifying enzymes in the liver leading to increased bioavailability (Yang et al., 2014). Lately, polyphenols have been used together or with other PD-relevant drugs as multidrug treatments and new interesting synergistic actions have emerged. Exemplarily, a mixture of resveratrol and quercetin was found to have synergistic inhibitory effects on inflammatory (Khandelwal et al., 2012), amyloid formation (Gazova et al., 2013), and oxidative (Kurin et al., 2012) processes. Lately, EGCG has been used together with rasagiline, an irreversible inhibitor of monoamine oxidase B that is responsible for metabolizing DA, as a multidrug treatment.

Subliminal doses of the duo acted synergistically to restore DAergic neurons of the nigrostriatal axis (Reznichenko et al., 2010). These recent findings may arouse future interest for investigating the clinical potential of polyphenols in combination with other polyphenols or already existing PD drugs.

2.2.5. Final considerations

As reviewed here, pre-clinical research is eloquent in delineating the multiple neuroprotective mechanisms by which polyphenols may exert a protective action in the multifaceted disease that is PD. Nonetheless, the rare clinical findings available as of date offer scarce and inconclusive data on the efficacy of polyphenols in preventing neurodegeneration. Still today, it remains unclear whether pre-clinical models have failed to be predictive or if clinical trials have been unsuccessful to detect these effects. Inasmuch as the observed negative outcomes are not sufficient to invalidate the putative health benefits of polyphenols in patients suffering from neurodegenerative diseases, there remains an imperative need for better-designed studies in humans. With the data available at present, it would appear that a shift in the clinical approach is warranted in the likes of stand-alone towards complementary paradigms, neurorescue towards prevention strategies, and oral towards other routes of administration, for example. At any rate, owing to their extensively verified safety, almost inexistent side effects in humans, chemical engineering-friendliness, generally inexpensive extraction or synthesis, and, most importantly, the absence of adverse symptoms that develop over time with the use of most PD drugs, namely L-DOPA, polyphenols remain an interesting prospect for the development of complementary or preventive therapies in view of tackling the multi-etiological foundations of PD. Long-term clinical success may reside in uncovering a way to improve the efficacy of current PD therapies using polyphenol co-administration, an approach which has yet to be tried in humans.

3. Role of antibiotics in neuroprotection

Antibiotics are any chemical compound that at low concentrations are able to kill or inhibit the growth of microorganisms. Since their introduction in human health, the widespread use of antibiotics radically changed the panorama of infectious diseases, enabling its control and leading to a drastic decrease in mortality rates. However, nowadays there is a renewed interest in antibiotics because of their surprising ancillary properties, not related to their antimicrobial activity. In this sense, it has been clearly demonstrated that at subinhibitory concentrations any antibiotic causes up- or down-expression of a large number of gene transcripts both in prokaryotic and eukaryotic cells (Rothstein et al., 2005; Yim et al., 2007; Ahler et al., 2013). Moreover, some antibiotics, especially tetracyclines and β-lactams, have remarkable anti-inflammatory effects (Gordon et al., 2012; Moon et al., 2012; Wei et al., 2012). Furthermore, MicrocinE492, a small antibiotic peptide, has cytotoxic effects on malignant human cell lines (Lagos et al., 2009). In like manner, macrolide antibiotics have been proven to induce gastrointestinal motility (Lam and Ng, 2011). Within these ancillary effects of antibiotics, their neuroprotective properties against neurodegenerative (Stoilova et al., 2013; Forloni et al., 2009; Noble et al., 2009; Ruzza et al., 2014) and neuroinflammatory (Sultan et al., 2013; Noble et al., 2009) processes are of great interest for the development of effective therapies against neurodegenerative diseases such as PD, AD, and human transmissible spongiform encephalopathies. In this respect, Rifampicin, a macrocyclic antibiotic, enhances brain β-amyloid (Aβ) clearance and fulfills many protective functions against chronic neurodegeneration and acute cerebral ischemia (Yulug et al., 2014). Tetracyclines in turn inhibit the conversion of prion protein PrP^{C} into PrP^{Sc} form and hinder prion aggregation (Tagliavini et al., 2000; Forloni et al., 2009; Stoilova et al., 2013). Furthermore, Minocycline, a semisynthetic tetracycline derivative, prevents Aβ and tau protein accumulation in AD models (Noble et al., 2009).

In the following sections, we will analyze the evidence and the potential of antibiotics as neuroprotective drugs to prevent and/or ameliorate the detrimental effects of PD on α-synuclein misfolding, mitochondrial function, DAergic neuronal death, and neuroinflammation, as reviewed in Table 2.

3.1. Antibiotics in α-synuclein misfolding

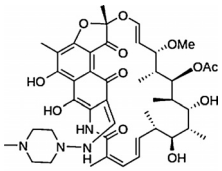
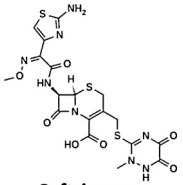
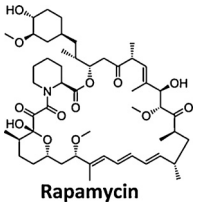
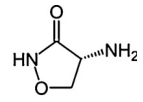
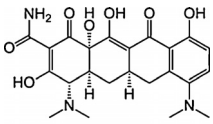
α-Synuclein is a 140 amino acid neuronal protein that has been related with many neurodegenerative disorders besides PD (Bennett, 2005; Baba et al., 1998; Arima et al., 1998). α-Synuclein is, as mentioned before, the main constituent of Lewy bodies in which it is found as a misfolded fibrillar aggregate (Ruzza et al., 2014; Bennett, 2005). It is thought that the aggregation of α-synuclein may be one of the first steps in a cascade of events leading to neuron degeneration and PD (Avila et al., 2014; Ruzza et al., 2014; Bennett, 2005). In this sense, several studies showed that the soluble oligomeric α-synuclein intermediates formed during the fibrillization process are the cytotoxic species responsible for neuronal death (Avila et al., 2014; Bennett, 2005; Cremades et al., 2012). Furthermore, it has been proposed that insoluble fibrillar aggregates, as those found in Lewy bodies, may result from a cellular detoxification mechanism that promotes the passage of toxic soluble α-synuclein oligomers into a non-toxic insoluble fibril, hence protecting cells from their deleterious effects (Avila et al., 2014; Cremades et al., 2012). Therefore, any compound that inhibits the formation or promotes the clearance of toxic α-synuclein oligomers may be useful for the development of therapeutic agents for PD.

In this sense, epidemiological studies showed that treatment with Rifampicin, a semi-synthetic macrocyclic antibiotic, decreased Aβ deposition and diminished the incidence of dementia in leprosy patients suggesting that this antibiotic has neuroprotective properties (Bi et al., 2013; Chui et al., 1994; Yulug et al., 2014). Furthermore, the inhibitory activity of Rifampicin on Aβ aggregation led to the study of its effects on other amyloidogenic, disease-causing, proteins such as α-synuclein, as a potential therapeutic molecule (Kapurniotu, 2004). In this respect, a study by Li et al. (2004) demonstrated that Rifampicin binds tightly to α-synuclein and blocks its fibrillation process and, even more, it is able to disaggregate preformed fibrils. Moreover, Xu et al. (2007) found that Rifampicin treatment protected PC12 cells against MPP+-induced toxicity by preventing the formation of α-synuclein oligomers.

Interestingly, in a recent study Jing et al. (2014) reported that Rifampicin upregulates the expression of the glucose-regulated protein 78 (GRP78), a key component of the cellular defense system dedicated to avoid the accumulation of misfolded proteins. Suggestively, a growing body of evidence indicates that GRP78 activation prevents neurons from undergoing apoptosis (Goldenberg-Cohen et al., 2012; Jiang et al., 2013a,b). Therefore, the inductor effect of Rifampicin on GRP78 and thus on misfolded α-synuclein accumulation may explain, at least partially, its protective properties against cell apoptosis (Jing et al., 2014).

Besides Rifampicin, mounting evidence supports a protective role of β-lactam antibiotics against neurodegenerative disorders (Cui et al., 2014; Rothstein et al., 2005; Leung et al., 2012; Ho et al., 2014). Interestingly, the neuroprotective properties of β-lactam antibiotics could be partially explained through their effects on the α-synuclein fibrillation process. In this respect, Ruzza et al. (2014) demonstrated that Ceftriaxone, a widely prescribed, well tolerated, β-lactam antibiotic able to cross the BBB, binds specifically to α-synuclein and

Table 2
Neuroprotective effects of antibiotics on pathological features of Parkinson's disease.

Antibiotic	α-Synuclein misfolding	Mitochondrial dysfunction and Oxidative stress	Neuroinflammation
 Rifampicin	• Blocks α-synuclein aggregation • Disaggregates preformed fibrils	• Prevents MPTP-induced neurodegeneration • Diminishes oxidative damage	• Blocks the release of proinflammatory factors
 Ceftriaxone	• Blocks α-synuclein aggregation	• Reduces oxidative stress and apoptosis in PD models • Reduces excitotoxicity damage	• Inhibits MPTP-induced microglial activation
 Rapamycin	Diminishes α-synuclein aggregation • Enhances aggregate clearance	• Diminishes MPTP/6-OHDA-induced mitochondrial dysfunction • Upregulates antioxidant enzymes	–
 D-Cycloserine	–	• Prevents MPTP-induced excitotoxicity	• Inhibits MPTP-induced microglial activation
 Minocycline	–	• Inhibits cytochrome c release and blocks apoptosis • Specific scavenger for peroxynitrite	• Inhibits MPTP/6-OHDA-induced microglial activation

inhibits its oligomerization process. Furthermore, through computational docking, the binding site for Cetriaxone has been proposed to be located within the C-terminal region of the protein (Ruzza et al., 2014). Interestingly, most α-synuclein (90%) found in Lewy bodies is phosphorylated at residue Ser129 (Fujiwara et al., 2002). In this respect, It has been shown that phosphorylation at Ser129 enhances toxic oligomer formation and thus, accelerates neurodegeneration (Sato et al., 2011). In this sense, it may be possible that binding of Ceftriaxone to the C-terminal region of α-synuclein blocks phosphorylation at Ser129 position and therefore prevents aggregation and its associated toxicity, although there is not yet experimental data supporting this hypothesis. Finally, Liu et al. (2013) demonstrated that Rapamycin, a BBB-crossing antibiotic with immunosuppressive activity, diminishes α-synuclein aggregation as well as enhances oligomer clearance through increase of autophagy and thus improves cell survival.

3.2. Antibiotics and mitochondrial dysfunction in Parkinson's disease

Compelling studies suggest a central role for mitochondrial function in PD (Gu et al., 2004; Esteves et al., 2011). Moreover, patients with PD present abnormal mitochondrial complex I activity (Schapira et al., 1990; Esteves et al., 2011). Furthermore, mutations in several genes linked to the pathogenesis of PD are involved in controlling mitochondrial function (Clark et al., 2006; Onyango, 2008). Suggestively, many neurotoxins which are able to induce a PD-like disorder in animal models, including paraquat, rotenone, and MPTP, act at a mitochondrial level, mainly through inhibition of complex I, further supporting mitochondrial dysfunction in the etiology of PD. Since these neurotoxins mimic PD features in animals and humans and cause selective death of DAergic neurons, they are extremely useful to study its etiopathogenesis (Onyango, 2008; Liberatore et al., 1999). In this respect, complex I inhibition by these toxins seems to enhance oxidative stress and the release of cytochrome *c*, which in turn leads to α-synuclein aggregation and neuronal death (Petrucelli and Dawson, 2004; Onyango, 2008). Likewise, Dawson (2010) demonstrated that oxidative stress and excitotoxicity, a process leading to cell death as a consequence of an increased accumulation of glutamate in the extracellular spaces (Kim et al., 2011; Selkirk et al., 2005; Bisht et al., 2014), are the main causes of DAergic neurodegeneration in the brain. Furthermore, it is though that mitochondrial dysfunction enhances oxidative stress and *vice versa*, in which propels a vicious circle with detrimental consequences for cell survival (Onyango, 2008; Jiang et al., 2013a,b).

On the other hand, compelling studies suggest that autophagy, a protein and organelle degradation mechanism, may play a protective role in neurodegenerative disorders since it not only recycles cellular material but also removes many deleterious agents including damaged mitochondria, pro-apoptotic molecules, and aggregated proteins from cells and, thus, improves neuron survival (Pan et al., 2009; Liu et al., 2013; Tolkovsky et al., 2002; Gu et al., 2004; Tolkovsky, 2009; Malagelada et al., 2008). In addition to its effects on α-synuclein aggregation, it was found that

Rifampicin is able to cross the BBB at concentrations high enough to prevent the MPTP-induced neurodegeneration in nigrostriatal DAergic neurons in a mouse model of PD (Oida et al., 2006). Moreover, animals treated with Rifampicin displayed diminished oxidative damage (Oida et al., 2006). Likewise, Chen et al. (2010) found that Rifampicin diminished oxidative stress and ameliorated mitochondrial dysfunction protecting PC12 cells against rotenone-induced apoptosis.

Besides Rifampicin, many other antibiotics, including Ceftriaxone, D-Cycloserine (DCS), Rapamycin, and Minocycline, have been proposed as potential therapeutic agents against mitochondrial impairment in PD. Since mitochondrial dysfunction is a primary event during excitotoxicity (Schinder et al., 1996), any compound that prevents glutamate accumulation would indirectly protect mitochondria and thus cells. In normal conditions, the bulk of glutamate uptake is carried out by the glutamate transporter GLT-1, which plays an essential role in avoiding increases of extracellular glutamate and associated neurotoxicity (Rothstein et al., 1996; Selkirk et al., 2005). However, in pathological conditions there is an imbalance of glutamate homeostasis as a consequence of the down-regulation of GLT-1, leading to excitotoxicity and oxidative stress (Sheldon and Robinson, 2007; Bisht et al., 2014).

Interestingly, the motor deficits and DAergic neuron damage observed in a 6-OHDA rat model of PD were ameliorated by Ceftriaxone treatment (Leung et al., 2012). Moreover, accumulating evidence demonstrated that Ceftriaxone upregulates the expression of GLT-1, which impedes the accumulation of glutamate and therefore prevents excitotoxicity (Bisht et al., 2014; Cui et al., 2014; Rothstein et al., 2005). In addition, a study by Leung et al. (2012) demonstrated that Ceftriaxone reduced oxidative stress and apoptosis in DAergic neurons. This is in agreement with recent data reporting that Ceftriaxone restores the diminished level of GSH and CAT activity in the MPTP model of PD (Bisht et al., 2014).

On the other hand, there is convincing evidence supporting a protective role of DCS, a broad spectrum antibiotic prescribed for the treatment of multidrug resistant *Mycobacterium tuberculosis* infections, against neurological disorders (Billard and Rouaud, 2007; Wu et al., 2008; Schneider et al., 2000). In this respect, it was found that DCS has a dual role in regulating the activity of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor, whose hyperactivation leads to excitotoxicity (Hood et al., 1989; Pawlak et al., 2012). In this sense, DCS may act as an antagonist of NMDA receptors when the glutamatergic system is hyperactivated, but when its activity diminishes DCS behaves as an agonist of NMDA receptor (Ho et al., 2011; Watson et al., 1990; Pawlak et al., 2012; Lanthorn, 1994). Moreover, Ho et al. (2011) found that *in vivo* DCS treatment reversed the biochemical and biological detrimental changes induced by MPTP, including cognitive and emotional disorders as well as impairments in motor function. Since treatment with NMDA antagonists ameliorates MPTP-induced degeneration and protects DAergic neurons, the antagonistic effect of DCS on NMDA receptors would be therefore essential to prevent the excitotoxicity damage induced by MPTP (Ho et al., 2011; Plaitakis and Shashidharan, 2000).

Regarding Rapamycin, a study by Tain et al. (2009) showed that Rapamycin treatment diminished mitochondrial dysfunction in cells from Parkin-mutant patients. Moreover, Rapamycin was able to ameliorate pathological phenotypes such as locomotor and mitochondrial dysfunctions, observed in PINK1/Parkin *Drosophila* mutants (Tain et al., 2009). Interestingly, these effects seem to be mediated by 4E-BP, a translation inhibitor involved in cellular response to stress and environmental changes (Tain et al., 2009; Clemens, 2001; Richter and Sonenberg, 2005), which is negatively regulated through phosphorylation by the mammalian target of Rapamycin (mTOR) (Gingras et al., 2001a,b; Beretta et al., 1996). Since Rapamycin is a TOR inhibitor (Beretta et al., 1996; Gingras et al., 2001a,b), treatment with this antibiotic leads to an increase of the active form of 4E-BP, which in turn suppresses the pathological phenotypes of PINK1/Parkin *Drosophila* mutants (Tain et al., 2009; Beretta et al., 1996).

In addition, increased autophagy rate is another consequence of mTOR inhibition by Rapamycin (Beretta et al., 1996). In this respect, Pan et al. (2009) found that Rapamycin protected against rotenone, a mitochondrial complex I inhibitor, in a neuroblastoma cell model. Furthermore, this protective effect seems to be due to increased mitochondrial autophagy, which allows cells to remove damaged mitochondria and pro-apoptotic molecules and, thus, protects them against rotenone-induced apoptosis (Pan et al., 2009). This is in agreement with recent data suggesting that Rapamycin enhanced behavioral improvements, ameliorated mitochondrial injuries, diminished the loss of L-DOPA, and prevented the death of DAergic neurons in both 6-OHDA and MPTP cell or animal models of PD (Malagelada et al., 2010; Liu et al., 2013; Jiang et al., 2013a,b). Furthermore, it was found that Rapamycin upregulated the expression of the neuronal survival promoting kinase Akt, antioxidant enzymes such as SOD and GPx as well as anti-apoptotic markers, while it also reduced pro-apoptotic factors (Malagelada et al., 2010; Dudek et al., 1997; Franke et al., 1997; Ries et al., 2006; Jiang et al., 2013a,b).

Pertaining to Minocycline, it was found that this BBB-crossing, widely prescribed, and well tolerated semisynthetic antibiotic prevented the maneb/paraquat- induced inhibition of mitochondrial complex I and restored MnSOD to normal levels in mice models of PD (Dixit et al., 2013; Huang et al., 2012). In this respect, there is convincing evidence showing that tetracyclines confer neuroprotection by ameliorating the immunity response and blocking the apoptotic pathway (Domercq and Matute, 2004). In this sense, the anti-apoptotic properties of Minocycline are mainly due to its inhibitory effect on the release of cytochrome *c* from mitochondria, thereby preventing caspase-3 activation (Zhu et al., 2002; Teng et al., 2004; Kim and Suh, 2009; Domercq and Matute, 2004). Furthermore, Schildknecht et al. (2011) demonstrated that Minocycline may also act as a specific scavenger for peroxynitrite detoxification. Although peroxynitrite normally acts as an intracellular signaling molecule under neuropathologic conditions, its overproduction may be deleterious for cells (Schildknecht and Ullrich, 2009) leading to the release of cytochrome *c* and p38 MAPK pathway activation (Wilkins et al., 2004; Lin et al., 2001; Jope et al., 2000). Moreover, after tyrosine nitration by peroxynitrite, α-synuclein becomes more prone to aggregation, thereby increasing its toxicity. Therefore, under pathological conditions, the antioxidant peroxynitrite-removing property of Minocycline may be an essential contributor to diminish α-synuclein aggregation and its associated toxicity (Schildknecht et al., 2011).

3.3. Antibiotics and neuroinflammation in Parkinson's disease

There is mounting evidence suggesting that inflammation seems to play a crucial role in the etiology of PD (Pradhan and Andreasson, 2013; Gerhard et al., 2006; Wu et al., 2007). In this respect, although in some conditions activation of microglia, the resident immune system cells of the CNS, may be beneficial, chronic inflammation is detrimental for neuron survival (Pradhan and Andreasson, 2013; Zhang et al., 2005). Once activated, microglial cells produce and release a set of factors including pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 as well as ROS and reactive nitrogen species (RNS) that contribute to cell damage and finally to neuronal death (Phani et al., 2012; Pradhan and Andreasson, 2013).

Suggestively, growing data demonstrate the prevalence of an inflammatory component after exposition to neurotoxins such as MPTP, 6-OHDA, and rotenone in animal models of PD, further

supporting a crucial role for microglia activation during the development of the disease (Pradhan and Andreasson, 2013; Marinova-Mutafchieva et al., 2009; Sherer et al., 2003). Moreover, it was found that misfolded α-synuclein released from neurons may activate microglia, which in turn enhances neurodegeneration (Zhang et al., 2005; Alvarez-Erviti et al., 2011). Therefore, as proposed by Pradhan and Andreasson (2013), regulating inflammation may be useful in order to prevent the development and/or the progression of PD. In this respect, antibiotics constitute a promising strategy for inhibiting microglial activation and, therefore, to protect neurons from inflammation-induced degeneration.

Rifampicin's immunosuppressive properties have been known since the 1970s (Dajani et al., 1972). In this sense, Bi et al. (2011) found that Rifampicin blocked the release of pro-inflammatory mediators NO, PGE2, TNF-α, and IL-1β from LPS-stimulated BV2 microglial cells. In this respect, Rifampicin's anti-inflammatory effects on activated BV2 microglial cells seem to arise from its capability to inhibit key signaling molecules such as NF-κB, MAPKs, TLR2 and TLR4, which are essential for the secretion of pro-inflammatory mediators (Bi et al., 2011; Kim and Suh, 2009; Pahlevan et al., 2002). In addition, the potential of Rifampicin as a therapeutic agent against inflammation-induced neurodegeneration recently gained further support from a study by Bi et al. (2014) showing that Rifampicin treatment reduced the number of apoptotic cells and enhanced the viability of cortical neurons when co-cultured with LPS-stimulated BV2 microglia.

In addition to Rifampicin, Ho et al. (2014) found that Ceftriaxone treatment ameliorated MPTP-induced cognitive disabilities such as working memory and recognition function deficits in a rat model of PD. Interestingly, Ceftriaxone's neuroprotective properties seem to depend, in part, on its inhibitory effect on the MPTP-induced microglial activation (Ho et al., 2011; Wang et al., 2010; Ho et al., 2014). This is in agreement with previous data reported by Chu et al. (2007) indicating that Ceftriaxone has anti-inflammatory effects reducing the expression of matrix metalloproteinase 9 (MMP9) and TNF-α.

As previously mentioned, tetracyclines exert remarkable anti-inflammatory effects. In this respect, Minocycline was found to inhibited MPTP-induced microglial activation preventing the release of cytotoxic molecules and, thus, ameliorated the MPTP-induced loss of DAergic neurons (Wu et al., 2002). This is in agreement with data from He et al. (2001) showing that Minocycline protected DAergic neurons against 6-OHDA toxicity, through the inhibition of microglia activation. In this sense, a growing body of evidence suggests that Minocycline inhibits microglia activation through p38 MAPK signaling pathways, which regulate the release of pro-inflammatory factors from activated microglia (Kang et al., 2014; Stirling et al., 2005; Tikka et al., 2001; Tikka and Koistinaho, 2001).

In addition to Minocycline, it was found that Doxycycline, another tetracycline derivative, conferred neuroprotection *in vivo* against 6-OHDA. Doxycycline is also one of the tetracyclines most commonly used in conditional transgene expression systems (Furth et al., 1994; Gossen et al., 1995). Interestingly, a clinical trial with Doxycycline (ClinicalTrials.gov identifier: NCT00246324, Safety and Efficacy Study of Doxycycline in Combination with Interferon-B-1a to Treat Multiple Sclerosis) was effective, safe, and well tolerated (Minagar et al., 2008). The proven reliability and safety of Doxycycline support its potential prospect as an effective and cheap protective treatment for CNS neurodegenerative diseases. In this respect, Lazzarini et al. (2013) reported that, in the 6-OHDA mouse model of PD, Doxycycline in a dose that both induces/represses conditional transgene expression (1) mitigates the loss of DAergic cell bodies in the SNc and of nerve terminals in the striatum (Fig. 2), and (2) prevents glial activation in the SN with effects on the microglial response in the striatum.

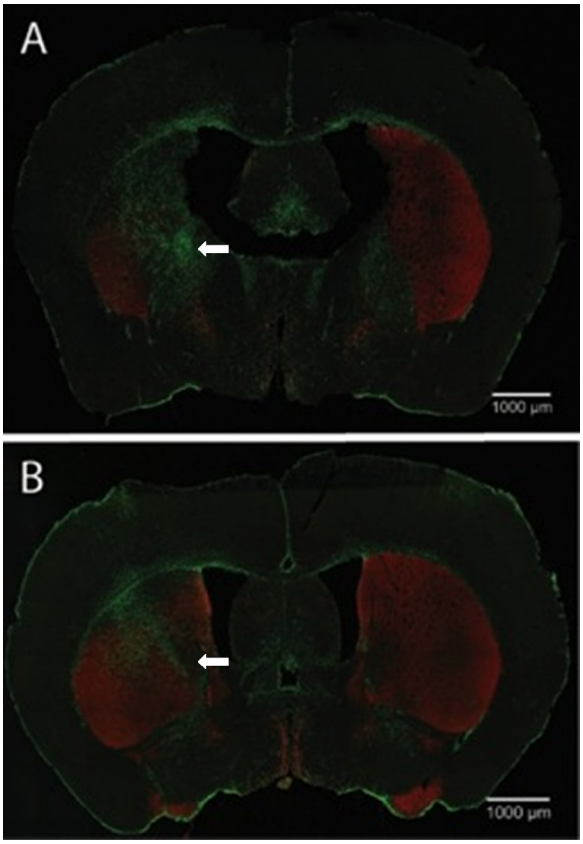


Fig. 2. Distribution pattern of astrocytes immunoreactive for GFAP (green) and neuron/axons immunoreactive for TH (red) in double-stained sections of the rat striatum of 6-OHDA lesioned animals treated or not with Doxycycline. Twenty five days after 6-OHDA microinjection we observed an increase of the density of GFAP-ir labeling in the lesioned striatum in the absent of Doxycyline (A) (arrow). Note also the reduction of the TH-ir (red) in the injured brain side in A. (B) Microphotography of striatal TH-ir and GFAP-ir of mice receiving 6-OHDA and Doxycycline (Dox, i.p.). See the increase in the area labeled with TH-immunoreactivity (red) and the decrease of glial cells in the lesioned side of the brain (arrow).

In addition, Cho et al. (2009) obtained evidence of *in vivo* neuroprotection of Doxycycline in nigral DAergic neurons following MPTP lesions in the mouse PD model suggesting that Doxycycline might provide protection by suppressing MMP induction. Accumulating evidence suggests that MMP3 is associated with DAergic neuronal death and neuroinflammation and, as a consequence, is involved in the pathogenesis of PD (Kim et al., 2011; Kim and Joh, 2006). MMP3 is a zinc-dependent proteolytic enzyme that is converted to active MMP3; the active form remodels the extracellular matrix complex (Kim and Hwang, 2011). Genetic ablation of MMP3 reduced nigrostriatal DAergic neuron loss and improved motor function. These data suggest that MMP3 could play a crucial role in neurodegenerative diseases such as PD. Moreover, MMP3 immunoreactivity was elevated in the SN of 6-OHDA-injected rats (Sung et al., 2005) and colocalized within Lewy bodies in post-mortem brains of PD patients (Choi et al., 2011).

As previously mentioned, α-synuclein is capable of inducing microglial activation (Zhang et al., 2005; Alvarez-Erviti et al., 2011). Furthermore, it was found that α-synuclein may also induce the expression of metalloproteinases MMP1, 3, 8, and 9 in rat primary cultured microglia (Lee et al., 2010). Suggestively, in addition to the harmful effects of MMP3, it was demonstrated that MMP9 is upregulated in MPTP mice models of PD and that ablation of MMP9 protected DAergic neurons from death (Lee et al., 2010; Lorenzl et al., 2004). Moreover, a study by Lee et al. (2010) demonstrated that inhibition of MMPs diminished microglial

activation and release of inflammatory factors including NO, ROS, and pro-inflammatory cytokines. In this respect, taking into account the deleterious effects of MMPs on neuron survival and compelling evidence suggesting that they may play a harmful role in PD by linking α-synuclein aggregation and microglial activation, therapies aimed to inhibit MMPs could constitute an interesting alternative to dampen the neuroinflammatory component of the disease. In this respect, our results showed that Doxycycline has a strong inhibitory effect on LPS-induced production of MMP3 and MMP9 in microglial cells and, therefore, it could be useful to prevent and/or diminish neuroinflammatory-associated neurodegeneration in PD (Fig. 3). Finally, a study by Ho et al. (2011) showed that DCS ameliorated the neurodegenerative processes induced by MPTP and that its inhibitory effect on microglial activation seems to be a crucial event for neuroprotection.

3.4. Therapeutic considerations

As a disabling disorder of high and increasing prevalence, PD is currently one of the most challenging threats concerning human health. In addition, to worsen the scenario, it is nowadays extremely difficult to achieve an early adequate diagnosis of the disease and, therefore, when the symptomatology becomes evident, a huge percentage of DAergic neurons is already lost. Moreover, since PD affects many cellular processes, pleiotropic therapeutic agents capable of dampening the progression of the disease at different

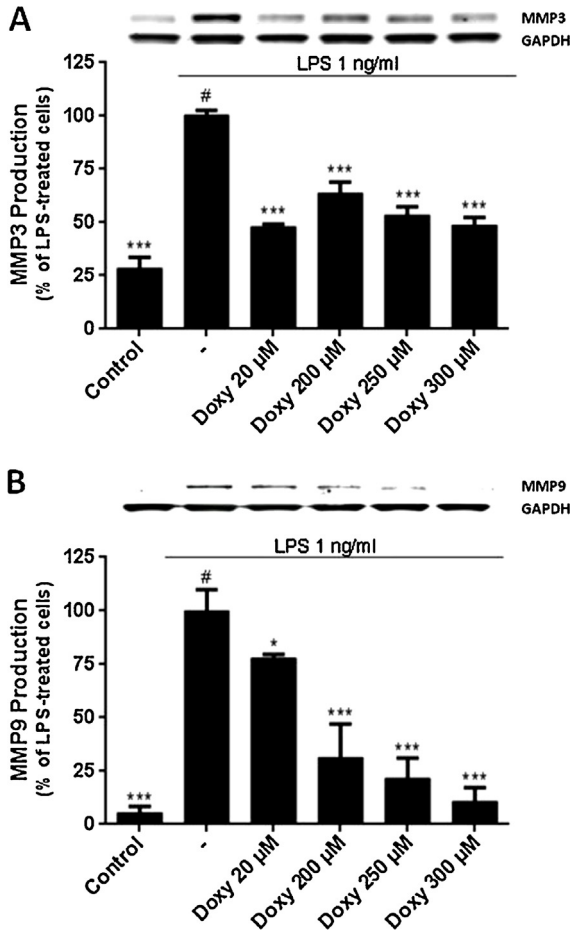


Fig. 3. Doxycycline blocks the LPS-induced MMP3 (A) and MMP9 (B) production. Cells were pretreated 4 h with doxycycline (20 μM, 200 μM, 250 μM, and 300 μM) and then exposed to LPS 1 ng/mL by 24 h. In the absent of Doxycycline LPS induced the production of MMP3 and MMP9 but in the present of the antibiotic theirs production was significantly blocked. * $P < 0.05$ vs LPS-treated cell and *** $P < 0.001$ vs LPS-treated cells, in the absent of doxycycline.

levels are required. In this respect, experimental evidence supports the potential of antibiotics as neuroprotective agents, being useful not only to prevent the formation of toxic α-synuclein oligomers but also to ameliorate mitochondrial dysfunction and neuroinflammation, key events in the etiology of PD.

One point that should be taken into account regarding their potential employment in clinical therapy is the time of administration of the drug. In this respect, it is plausible to think that antibiotics such as Rifampicin and Ceftriaxone that bind to monomeric α-synuclein and inhibit its aggregation would be more effective in preventive rather than in palliative therapy, although they may also be useful to ameliorate mitochondrial dysfunction and neuroinflammation. Conversely, antibiotics that block microglial activation could be more appropriate for treating chronic neuroinflammation in PD. Nonetheless, further experimental data is required to support this hypothesis. However, regarding the potential application of antibiotics as therapeutic agents for treating PD, few clinical trials have been performed and a few more are currently in development (ClinicalTrials.gov identifier: NCT00063193, A Multi-center, Double-blind, Pilot Study of Minocycline and Creatine in Subjects With Early Untreated Parkinson's Disease; ClinicalTrials.gov identifier: NCT02005029, Erythromycin in Parkinson's Disease: A Pilot Study of Its Effects on Levodopa Pharmacokinetics and Pharmacodynamics) but, at least to our knowledge, no results from these studies have been reported yet. However, indirect evidence supporting a protective role of antibiotic in human health as protective molecules for fighting neurodegenerative processes arise from epidemiological studies, which showed that leprosy patients undergoing antibiotic treatment presented a decreased Aβ deposition and lesser prevalence of dementia (Bi et al., 2013; Chui et al., 1994; Yulug et al., 2014). In addition, the antibacterial activity of antibiotics may also induce a positive effect on PD therapy since *Helicobacter pylori* eradication by antibiotic treatment leads to improved absorption and pharmacokinetics of L-DOPA, which would improve clinical response to medication (ClinicalTrials.gov identifier: NCT00664209, Treating *H. pylori* in Parkinson's Patients With Motor Fluctuations). Furthermore, from a clinical point of view, antibiotics have been prescribed in medicine for decades without serious secondary effects on human health, although some reports suggest that chronic treatments, especially with Minocycline, may be under certain conditions slightly harmful for the recipient (Porter and Harrison, 2003; Abe et al., 2003). However, antibiotic concentrations required for neuroprotection seem to be lower than those required when they are used as antimicrobial compounds. Therefore, antibiotics seem to be safe and they would not represent, *per se*, a risk to health.

On the other hand, microbial resistance to antibiotics is currently a major concern. Furthermore, pathogenic microorganisms have become resistant to drugs once effective and therefore diseases thought to be eradicated (*i.e.* tuberculosis) have reappeared. In this respect, chronic treatment with antibiotics may favor the emergence and dissemination of resistance genes between microbial populations and, thus, the effectiveness of antimicrobial compounds could be dramatically decreased. In this sense, it is imperative to develop derivative molecules from antibiotics, which conserve their neuroprotective properties but lack antimicrobial activity, prior to their clinical application in neurology. Although further research is needed, many features of antibiotics have positioned them as a promising alternative against PD and other neurodegenerative disorders. In this respect, the current challenges lie in developing antibiotic potential into effective therapies.

4. Effects of pituitary adenylate cyclase-activating polypeptide in models of Parkinson's disease

Neurotrophic factors (NTFs) and different growth factors are promising therapeutic agents for neurodegenerative disorders,

including PD. Neurotrophins, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3, and neurotrophin-4 are essential for neuronal development, growth, and differentiation. Each neurotrophin can signal through Trk receptors, the activation of which can also occur by G-protein-coupled receptor (GPCR) mechanisms. Two GPCR ligands, adenosine and pituitary adenylate cyclase activating polypeptide (PACAP), induce transactivation of Trk receptors through their respective GPCRs, A_{2A} receptor and PAC1 receptor, to promote cell survival. Transactivation of neurotrophic receptors by GPCR ligands enhance the possibility that small molecules may be used to elicit neurotrophic effects for the treatment of neurodegenerative diseases (Aron and Klein, 2011). If a molecule is strongly neuroprotective through its own receptors and, in addition, it transactivates neurotrophin receptors, it seems to be a good candidate in Parkinson's disease for its targeting multiple mechanisms. In the following chapter we discuss the neuroprotective potential of PACAP, a neuropeptide with highly potent cytoprotective effects (Somogyvari-Vigh and Reglodi, 2004; Lee and Seo, 2014; Eiden, 2012). The peptide was first isolated as a hypophyseotrope neuropeptide, but its diverse effects were recognized soon after its discovery. PACAP exerts its actions through GPCRs, PAC1 and VPAC receptors. PAC1 receptor is specific for PACAP, while VPAC1 and VPAC2 receptors also bind vasoactive intestinal peptide (VIP) with similar affinity (Vaudry et al., 2009). PAC1 receptor seems to be the main receptor involved in the neuroprotective actions of the peptide. *Via* PAC1 receptor, PACAP exerts strong anti-apoptotic effects in neurons and non-neuronal cells. The peptide also possesses anti-inflammatory and antioxidative effects, all playing a role in its potent cytoprotective efficacy. In addition to the triple protective mechanism of PACAP, it has numerous other functions that may be beneficial in cases of neuronal injuries.

In the present section, we summarize studies related to the neuroprotective efficacy of PACAP in models of PD both *in vivo* and *in vitro* (Table 3). We have published an extensive review on the protective effects of PACAP in models of neurodegenerative diseases in 2011 (Reglodi et al., 2011), therefore, in the present chapter we offer a brief summary of earlier data and focus on novel results published in the recent few years.

4.1. Neuroprotective effects of PACAP

The neuroprotective effects of PACAP were recognized soon after its discovery and hundreds of studies have proven this effect since the first reports that came from cortical and cerebellar neuronal cultures (reviewed in Somogyvari-Vigh and Reglodi, 2004). PACAP has been shown to be protective in different neuronal cultures against diverse harmful effects. Among others, PACAP treatment effectively decreased cell death induced by oxidative stress, ethanol in cerebellar granule neurons, glutamate in cortical neurons, and prion protein fragments in PC12 cells. These *in vitro* effects have been reviewed in several papers (Somogyvari-Vigh and Reglodi, 2004; Reglodi et al., 2011; Vaudry et al., 2009; Eiden, 2012; Lee and Seo, 2014).

The first *in vivo* results came from cerebral ischemia models where PACAP was proven to reduce the infarct size both in focal and global ischemia models in rats (Somogyvari-Vigh and Reglodi, 2004). Since these pioneer reports, numerous data have supported its *in vivo* neuroprotective effects. For example, additional data in stroke models have been published, supporting the original observations in cerebral ischemia models (Ohtaki et al., 2006; Dejda et al., 2011). These reports show that PACAP not only reduces infarct volume but also improves functional outcome *via* anti-apoptotic and anti-inflammatory mechanisms. Most recent data also demonstrate that functional recovery in a mouse stroke model can be enhanced by PACAP-producing stem cells (Brifault et al., 2015). The local PACAP delivery induces a microglial phenotype switch, which might explain the anti-inflammatory effects of PACAP in stroke models. PACAP is also protective in other types of ischemic lesions of the nervous system, like retinal hypoperfusion (Danyadi et al., 2014; Werling et al., 2014).

Table 3
Summary of the in vitro and in vivo neuroprotective effects of PACAP in models of Parkinson's disease.

Injury, treatment	Cell type/animal	Main effect of PACAP	Reference
In vitro			
Salsolinol	SH-SY5Y neuroblastoma cells	cell viability↑; apoptosis↓; BDNF↑; p-CREB↑; caspase-3↓	Brown et al. (2013)
LPS, inflammatory mediators	SH-SY5Y neuroblastoma cells	cell viability↑; apoptosis↓; BDNF↑; p-CREB↑; caspase-3↓	Brown et al. (2014)
LPS	Neuron-glia mixed culture	DA uptake↑; induced morphological changes↓ (loss of dendrites↓, axonal disintegration↓), loss of DAergic neurons↓ LPS-induced elevation of TNF-α↓; NO↓, superoxide↓, ROS↓	Yang et al. (2006)
6-OHDA	Mesencephalic embryonic dopaminergic neurons	number of TH-positive neurons↑; DA uptake↑; cell survival↑	Takei et al. (1998)
MPP+	α-Synuclein overexpressing PC12 cells	protection↑	Chung et al. (2005)
MPP+	Neuro-2a neuroblastoma cells	apoptosis↓; toxicity on protein of translational control↓; protein synthesis inhibition↓	Deguil et al. (2007)
MPP+	Neuron-glia mixed culture	protection↑	Yang et al. (2006)
MPP+	SH-SY5Y neuroblastoma cells	cell death↓, deleterious effect on mitochondrial membrane potential↓, cAMP↑	Lamine et al. (2015)
Rotenone	PC12 cells	apoptosis↓; caspase-3 activation↓; PKA/MAPK actication↑	Wang et al. (2005)
In vivo			
Intranigral 6-OHDA	Rat	nigral cell degeneration↓; hypokinesia↓, asymmetrical symptoms↓, behavioral recovery↑	Reglodi et al. (2004a,b, 2006a,b, 2011)
MPTP	Mouse	vesicular monoamine transporter 2 decrease↓, DOPAC decrease↓; D2 receptor expression↑	Wang et al. (2008)
MPTP	Mouse	protein synthesis dysregulation in striatum, frontal cortex and hippocampus↓; TH neuronal loss↓; performance in water maze↑	Deguil et al. (2010)
MPTP	Mouse	TH staining↑, whole brain TH density↑, caspase-3↓, IL-6↓, TNF-alpha↓	Lamine et al. (2015)
Metamphetamine	Mouse	striatal vesicular monoamine transporter 2 expression↑; striatal DA loss↓, oxidative stress↓	Guillot et al. (2008)
Prostaglandin-inflammation	Mouse	DAergic cell loss↓, motor deficits↓	Shivers et al. (2014)

Several studies have shown the neuroprotective efficacy of PACAP in other acute and chronic brain injury models. For example, the peptide has strong neuroprotective action in traumatic brain injury: it reduces axonal damage in both impact acceleration and fluid percussion models (Tamas et al., 2012). PACAP is also able to improve both functional and morphological symptoms in a model of spinal cord injury (Tsuchida et al., 2014; Tsuchikawa et al., 2012). Recent studies have further strengthened these original observations and have suggested that this action is due to the antioxidant and anti-inflammatory/immunomodulatory actions of PACAP (Hua et al., 2012; Mao et al., 2012; Miyamoto et al., 2014). Similarly to the attempts of alleviating symptoms in stroke by PACAP-expressing stem cells (Brifault et al., 2015), Fang et al. (2010) showed that delayed transplantation of human mesenchymal stem cells combined with PACAP provides trophic molecules to promote neuronal cell survival, which also fosters a beneficial microenvironment for endogenous glia to increase their neuroprotective effect on the repair of injured spinal cord tissue.

PACAP also shows protection in inflammatory disorders of the CNS, such as in models of multiple sclerosis. It has been shown that administration of PACAP suppresses experimental autoimmune encephalomyelitis, a model of multiple sclerosis (Kato et al., 2004). Studies in mice lacking PACAP have supported these observations by showing that knockout mice exhibit exacerbated encephalomyelitis, thus, the endogenous production of the peptide protects against multiple sclerosis, probably by modulating regulatory T cells (Tan et al., 2015; Tan and Waschek, 2011).

As far as neurodegenerative diseases are concerned, the protective effects of PACAP have been shown in different models of neurodegenerative diseases, namely kainate-induced rat models of Huntington chorea (Tamas et al., 2006), models of PD, and several *in vitro* and *in vivo* models of AD (Reglodi et al., 2011). Recent studies reveal that PACAP might be a promising therapeutic agent in neuronal loss observed in AD, as the peptide prevents tau cleavage (Metcalfe et al., 2012), improves learning in a mouse model of AD (Dogrukol-Ak et al., 2009), and protects against β-amyloid toxicity (Han et al., 2014a,b). Most experimental data are available on models of PD, the details of which are outlined below.

Human PACAP studies are mainly restricted to diagnostic investigations, and few data available so far indicate that PACAP levels change in several pathological conditions of the CNS including acute (traumatic brain injury, cerebral hemorrhage) as well as chronic (AD) conditions (Bukovics et al., 2014; Han et al., 2014a,b; Ma et al., 2015).

4.2. Presence of PACAP and its receptors in the mesencephalon and striatum and effects on dopamine synthesis

The distribution of PACAP and its receptors provide the anatomical basis for the potential efficacy of PACAP in PD (Vaudry et al., 2009). PACAP binding and receptor mRNA have been shown in the SN and ventral tegmental area, both during the embryonic period and in adults (Vaudry et al., 2009). PAC1 receptor is also present in the striatum, where the terminal fields of the nigrostriatal DA system are found (Vaudry et al., 2009). PACAP receptor mRNA is present in the SN, both in developing and adult mesencephalon (Takei et al., 1998; Hashimoto et al., 1996). PACAP expression has also been demonstrated in rodent and human mesencephalon, including the SN (Palkovits et al., 1995; Takei et al., 1998). Chung and coworkers have studied the gene expression differences between DAergic neurons in the SN and mesencephalic ventral tegmentum and have found that the expression of PACAP is one of the possible factors responsible for the lower vulnerability of the ventral tegmental area in contrast to the SN in PD, since the expression of the peptide is significantly higher in the ventral tegmental area (Chung et al., 2005). Age-related decline in the cerebral peptide expression have also been reported and some authors suggest that this can be partially related to the increased vulnerabiliy of the aging brain to neurodegenerative diseases, including PD (Tripathy et al., 2012; Banki et al., 2015; Vamos et al., 2014). Indeed, aging PACAP knockout animals show higher levels of oxidative stress than their wild type mates (Ohtaki et al., 2010). We have recently shown that knockdown of PACAP mimics aging phenotype in cerebromicrovascular endothelial cells, while overexpression of PACAP in aging cells mimics young angiogenic capacity (Banki et al., 2015).

PACAP is known to influence catecholamine synthesis. The peptide potentiates catecholamine release from various cell types, like adrenal chromaffin cells and sympathetic neurons (Dong et al., 2014). PACAP also increases DA release in several parts of the nervous system *via* TH activation, the rate limiting enzyme in DA synthesis (Moser et al., 1999; Rius et al., 1994; Takei et al., 1998). Western blot analyses prove that PACAP increases the amount of TH protein and DA uptake in mesencephalic cultures and the peptide increases the number of TH-immunopositive neurons in the mesencephalon of embryonic rats treated with 1–100 nM PACAP for 7 days (Takei et al., 1998). PACAP influences TH expression on gene transcriptional and posttranscriptional levels (Dong et al., 2014; Corbitt et al., 2002). A recent study has shown that PACAP increases quantal release of DA (Dong et al., 2014). The authors compared effects of PACAP on DA release to that of L-DOPA. They found release *via* the fusion pore prior to full exocytosis with the same frequency following treatments with both PACAP and L-DOPA. However, release events showed a shorter duration and higher average current after PACAP treatment and PACAP reduced the proportion of spikes having rapid decay time. The authors suggest that the different dynamic profiles of PACAP and L-DOPA may be beneficial in the treatment of Parkinson's disease (Dong et al., 2014). Taken together, these observations provide the anatomical and physiological basis for the potential efficacy of the endogenously present peptide and also the exogenously administered PACAP in the SN.

4.3. In vitro *neuroprotective effects of PACAP in cell culture models of Parkinson's disease*

4.3.1. 6-OHDA

The first proof for the neuroprotective potential of PACAP in *in vitro* models of PD came from cultured embryonic DAergic neurons of the mesencephalon, where PACAP increased the number of TH-immunopositive neurons and enhanced DA uptake as well as protected against 6-OHDA-induced toxicity (Takei et al., 1998).

4.3.2. MPTP

Using an α-synuclein overexpressing PC12 cell line, Chung and coworkers (2005) have shown that PACAP protects against MPP+ toxicity. The authors have also shown that PACAP protects both GIRK2-positive (G-protein coupled inwardly rectifying K channel 2) and -negative cell cultures against MPP+ toxicity in a dose-dependent manner (Chung et al., 2005). GIRK2 is known to be elevated in SN neurons and is linked to the degeneration of DAergic neurons. A9-like DAergic neurons (GIRK2 expressing) are more vulnerable to MPP+ toxicity and respond to lower PACAP concentrations than A10 (GIRK2 negative)-like neurons, showing that PACAP is related to the vulnerability of the DAergic neurons.

Several changes in the protein profile of the brain are induced by MPP+ (Deguil et al., 2007; Kadar et al., 2014). PACAP has been shown to effectively counteract several translational changes in the murine Neuro-2a neuroblastoma cell line (Deguil et al., 2007). PACAP is also able to protect these cells against the apoptotic process induced by MPP+ (Deguil et al., 2007). Another study has also reported that PACAP and a short fragment of the peptide can

prevent MPP+ toxicity in a mesencephalic mixed neuron-glia culture, but this protective effect could not be shown in the absence of microglial cells (Yang et al., 2006).

A recent paper has further confirmed the effifacy of PACAP27, PACAP38 and a stable analog (Ac-[Phe(pI)^{6}, Nle^{17}]PACAP(1-27)) in SH-SY5Y human neuroblastoma cells against MPP toxicity (Lamine et al., 2015). In cells exposed to MPP, PACAP and its analog increased cAMP, decreased cell death by 40-50% and maintained mitochondrial potential.

4.3.3. Rotenone

Rotenone causes inhibition of the mitochondrial complex I activity, resulting in ATP inhibition and loss of $\Delta\Psi$m, finally leading to death of nigral neurons and, thus, it is widely used in PD models (Zaminelli et al., 2014; Qualls et al., 2014). It has been found that PACAP27 dose-dependently inhibits apoptotic cell death in rotenone-induced toxicity of PC12 cells (Wang et al., 2005). This can be blocked by the PACAP receptor antagonist PACAP6-27. The protective effect observed in PC12 cells is linked with MAPK activation by PKA and involves caspase-3 inhibition (Wang et al., 2005).

4.3.4. Salsolinol

Salsolinol is an endogenous neuromodulator in DAergic cells formed during the metabolism of DA. Dysregulation of salsolinol, especially its (R) enantiomer in the brain, is thought to contribute to the development of PD (Możdżeń et al., 2014; Qualls et al., 2014). SH-SY5Y cells, derived from human neuroblastoma cells, bear high levels of DAergic activity and are used extensively as a cellular model to study mechanisms of toxicity and protection in nigral DAergic neurons (Cuevas et al., 2015; Qualls et al., 2014). We demonstrated that PACAP dose-dependently blocked the cytotoxicity induced by salsolinol, and that the PACAP receptor antagonist PACAP6-38 counteracted the effect of PACAP (Brown et al., 2013). Our results also confirmed reported apoptotic effects of salsolinol and extended those findings to include involvement of neurotrophic pathways in salsolinol-induced neurotoxicity. Thus, salsolinol caused a reduction in BDNF and its signal transduction through phosphorylated cyclic-AMP response-element binding protein (p-CREB), both of which were normalized by PACAP treatment. PACAP could also suppress caspase-3 activity. Since stimulation of BDNF/CREB signalling can lead to inhibition of neuronal apoptosis, it was suggested that PACAP's effects on this signaling pathway might be a major mechanism of its neuroprotection.

4.3.5. Inflammation

Inflammation is a key contributor to the deterioration of DAergic neurons in the SN and microglia or microglia-like cells are significant generators of inflammatory mediators (He et al., 2014). LPS is commonly used to activate the inflammatory response of microglia cells. LPS activation of microglia causes release of TNF-α, INF-γ, and NO along with a host of neurotoxic substances that result in DAergic neuronal death. LPS also decreases the number of TH-positive cells in primary mesencephalic cultures as well as increases cytokine output (Gayle et al., 2002). PACAP, similarly to its structurally related peptide, VIP, has been shown to inhibit several pro-inflammatory factors produced by activated microglial cells in culture. For example, PACAP treatment inhibits NF-κB's transcriptional activity in microglial cells induced by LPS or TNF-α (Delgado, 2002a,b; Delgado et al., 2002). Subsequent studies have shown that PACAP and VIP inhibit TNF-α, IL-1β, IL-6, and NO production by LPS-induced microglial cells (Delgado et al., 2003). Several chemokines released by activated microglia, such as microglia-derived CXC chemokines MIP-2 and KC, and CC chemokines, MIP-1α, -1β, MCP-1, and RANTES, are also inhibited by PACAP (Delgado, 2002b; Delgado et al., 2002). Furthermore, VIP/PACAP inhibit MEKK1 activity and the subsequent phosphorylation of MEK4, JNK, and c-Jun, which results in a decrease in binding of the transcription factor AP-1 and a marked changes in the composition of AP-1 complexes, from c-Jun/c-Fos to JunB/c-Fos (Delgado, 2002b; Delgado et al., 2002). These studies provide a strong basis for the *in vitro* efficacy of PACAP in inflammatory models of PD.

DA uptake has been shown to be reduced to 40% of normal values in mesencephalic neuron-glia cultures exposed to LPS (Yang et al., 2006). Pretreament with PACAP38, PACAP27, or with their 3 amino acid fragment, PACAP4-6, prevents the reduction of DA uptake at subpicomolar concentrations. Both PACAP and its short fragment have been shown to counteract the morphological changes induced by LPS in these cells: the loss of dendrites, axonal disintegration, along with the loss of DAergic neurons. This observation raises the possibility of PACAP acting *via* microglial inhibition in this *in vitro* model of PD. The authors have found that PACAP reduces the LPS-induced elevation in levels of TNF-α, NO, superoxide, and ROS.

In a recent study, we used human THP-1 microglia-like cells and subjected them to a combination of LPS and IFN-γ (Brown et al., 2014). We then used the media obtained from such exposure, containing inflammatory mediators, and applied it to SH-SY5Y cells. Such treatment resulted in approximately 54% cell death as well as a reduction in BDNF, p-CREB, and caspase-3 activity. Pretreatment of the SH-SY5Y cells with PACAP1-38 dose-dependently attenuated toxicity induced by the inflammatory mediators, which could be blocked by the antagonist PACAP 6-38. Taken together, it was suggested that the protective effects of PACAP against inflammatory-induced toxicity is likely mediated by enhancement of cell survival markers through activation of PACAP receptors, reinforcing the concept that PACAP or its agonists could be of therapeutic benefit in inflammatory-mediated PD (Brown et al., 2014).

4.4. In vivo *neuroprotective effects of PACAP in animal models of Parkinson's disease*

4.4.1. 6-OHDA

The *in vivo* neuroprotective effects of PACAP in models of PD were first established in a 6-OHDA-induced SN injury model in rats. Injecting 6-OHDA into the SN on one side leads to severe hypokinetic symptoms and the development of asymmetrical signs due to the unilateral lesion. In this model, intranigral PACAP treatment resulted in reduced or abolished hypokinetic signs, as shown by the ambulation time, distance covered, number of rearings, total inactivity time, and percentage of free rearings with no leaning against the wall. PACAP-treated rats had significantly better recovery in asymmetrical symptoms, such as turning, rearing, and thigmotaxis toward one side (Reglodi et al., 2004a,b). The behavioral signs were in accordance with reduced DAergic cell loss in the SN and ventral tegmental area (Reglodi et al., 2011). In aging animals, PACAP was also effective, although not as effective as in young animals (Reglodi et al., 2006a,b). The experiments were also repeated in females, which are less vulnerable to 6-OHDA-induced toxicity. It was found that PACAP could still ameliorate the behavioral signs in spite of the same cell loss (Reglodi et al., 2006a,b). In castrated males, where 6-OHDA does not induce such a severe cell loss, PACAP does not lead to decreased neuron loss, but it effectively ameliorates the behavioral symptoms in all male groups (Reglodi et al., 2006a,b).

4.4.2. Methamphetamine

The neurotoxicity of methamphetamine depends on the transporter proteins that package and recycle DA and its long-term

use in humans is associated with the loss of neurons in SN and development of PD later in life (Pitaksalee et al., 2015). Dysfunction of the DA transporter and vesicular monoamine transporter 2 caused by methamphetamine leads to a loss of DA, to oxidative stress, and to neuroinflammation (Reglodi et al., 2011). PACAP treatment effectively increased vesicular monoamine transporter 2 expression in the striatum in mouse methamphetamine-induced toxicity. This transporter is responsible for packaging DA into secretory vesicles. Mice treated with PACAP38 exhibited an attenuation of striatal DA loss after methamphetamine exposure as well as greatly reduced markers of oxidative stress. PACAP treatment also attenuated the significant DA loss induced by methamphetamine toxicity in the striatum (Guillot et al., 2008). It also led to reduced striatal overexpression of glial fibrillary acidic protein, an indicator of astrogliosis, and that of glucose transporter 5, an indicator of microgliosis. Interestingly, these effects are observed even when PACAP treatment precedes the toxic insult by 4 weeks. This effect cannot be due to the direct effect of PACAP on DA synthesis and release in the striatum, since 4 weeks after the PACAP infusion, alterations in the striatal DA content, TH activity or DA transporter were not observed in contrast to the increase in vesicular monoamine transporter 2. The relative changes in vesicular monoamine transporter 2 in relation to the plasmalemmal DA transporter is thought to determine the neuronal ability to resist the damaging effect of toxicants that affect DA sequestration. The long-term regulatory and protective effect of PACAP observed in this study suggests a potential preventive therapeutic use of PACAP with long-term efficacy (Guillot et al., 2008; Reglodi et al., 2011).

4.4.3. MPTP

PACAP has been shown to provide neuroprotection against MPTP-induced toxicity in a mouse model of PD, where intravenous injection of the peptide increased TH-positive neurons (Wang et al., 2008). The MPTP-induced decrease in levels of vesicular monoamine transporter 2, DA transporter protein, as well as the DA metabolite DOPAC could also be reversed by PACAP treatment. Furthermore, PACAP increased D2 receptor expression in the striatum. DAergic neurotransmission involves multiple systems, including ATP-sensitive K+ channels (K_{ATP}) that are closely associated with pre-synaptic DA neurons and densely-distributed D1 and D2 receptors on the post-synaptic membrane. It has been shown that PACAP selectively regulates K_{ATP} subunits and also D2 receptors in the striatum (Wang et al., 2008).

Deguil and coworkers have also studied the effects of PACAP in MPTP-induced toxicity. They have confirmed the protective effects of PACAP in a MPTP parkinsonian mouse model and have shown that PACAP prevented the MPTP-induced protein synthesis dysregulation in the striatum, frontal cortex, and hippocampus, and protected against TH neuronal loss (Deguil et al., 2010). The behavioral ameliorating effects of PACAP have also been confirmed in water-maze tests.

A recent study has confirmed these observations with PACAP38 and a stable analog (Ac-[Phe(pI)^6, Nle17]PACAP(1-27)) (Lamine et al., 2015). It was found that the markedly reduced TH staining of the SN in mice after MPTP injection was reversed after PACAP (or analog) treatment. This was also shown in the whole brain with densitometric analysis: the significant TH depletion was prevented by PACAP and its analog (Lamine et al., 2015). Furthermore, both treatments ameliorated the MPTP-induced increases in the inflammatory markers TNFalpha and IL-6 as well as the proapoptotic caspase-3.

4.4.4. Inflammation

Successive administration of PGJ2, a downstream target of COX-2, can mimic in part the chronic inflammation and progressive DAergic cell depletion in the nigrostriatal pathway (Shivers et al., 2014). A recent study has shown that PACAP27 can effectively reduce DAergic cell loss and motor deficits in an intermediate severity stage of the disease model (Shivers et al., 2014). However, the treatment was not effective in severe cases, where microglial activation could not be prevented by PACAP treatment.

4.4.5. Behavioral considerations

Several behavioral effects of PACAP may be beneficial *in vivo* in neurodegenerative diseases. For example, PACAP has been shown to increase locomotor activity in several studies, although this effect depends on several factors, as the opposite has also been reported (Masuo et al., 2004; Somogyvari-Vigh and Reglodi, 2004). The role of PACAP in memory formation and consolidation has also been established and this effect may be a very important additional beneficial effect not only in AD but also in memory impairment observed in PD (Borbely et al., 2013; Pirger et al., 2014). In addition, PACAP is involved in the complex pathways responsible for normal stress coping and is considered as a master regulator of central and peripheral stress responses (Kormos and Gaszner, 2013). Parkinson patients often suffer from depression as well (Grover et al., 2015), and PACAP is also known for its antidepressant activity (Reichenstein et al., 2008). However, the behavioral aspects of PACAP treatments are ambiguous, depending on several factors, and opposing effects have been reported for some behavioral functions. Thus, it is still under investigation what the long-term behavioral effects of PACAP might be in models of PD.

4.4.6. Mechanisms of action

As it has been mentioned above, the degeneration of the DAergic cells involves complex processes induced by inflammatory, apoptotic and oxidative stress-related processes. The potency of PACAP in counteracting neuronal cell death is mainly due to a combination of favorable effects. These mechanisms have been reviewed in several papers (Eiden, 2012; Vaudry et al., 2009; Reglodi et al., 2011, 2012; Somogyvari-Vigh and Reglodi, 2004). The main signaling route seems to be the protective pathways activated by the PAC1 receptor/PKA and PKC-mediated signaling, leading to the decrease of pro-apoptotic factors (caspases, cytochrome *c*, Bad, Bax, JNK, p38 MAPK, apoptosis inducing factor, etc.) and the increase of anti-apoptotic ones (Bcl-2, Bcl-xL, ERK, 14-3-3 protein, etc.). The accompanying effect on the anti-inflammatory pathways and antioxidative molecules help in its neuroprotective effect. Recent studies have confirmed these mechanisms and have also provided additional insight into the neuroprotective mechanism. Resch and coworkers have reported that PACAP is involved in the antioxidant GSH production by astrocytes (Resch et al., 2014). Another study has revealed the involvement of serpin1b in the neurotrophic effects of PACAP, and that this pathway is shared with NGF, a major neurotrophic factor (Seaborn et al., 2014). Whether the described neuroprotective efficacy of the peptide can be translated into human therapy awaits further investigation.

4.5. Studies in PACAP deficient mice—The role of endogenous PACAP

The effects of endogenous PACAP are extensively studied in PACAP knockout mice. Although the compensatory mechanisms are not well-known yet, defects present in PACAP deficient mice can still help us to elucidate developmental and protective roles of the neuropeptide. Under unchallenged circumstances, no major alterations have been described in PACAP knockout mice, although some developmental defects or alterations have been observed both in the nervous system and peripheral organs (Nemeth et al., 2014; Sandor et al., 2014; Yamada et al., 2010). In addition to structural changes, several behavioral abnormalities have also been described (Hazama et al., 2014; Gaszner et al., 2012). In

contrast to normal circumstances, major differences can be observed under challenged conditions. In accordance with the well-known neuroprotective effects of the peptide, PACAP deficient animals are more vulnerable to different harmful effects, indicating that endogenous PACAP is part of the self-protective machinery (Reglodi et al., 2012). Among others, PACAP knockout mice have an increased infarct volume in middle cerebral artery occlusion-induced focal cerebral ischemia (Ohtaki et al., 2006) and increased retinal lesion in models of retinal ischemia or excitotoxic lesions (Endo et al., 2011, Szabadfi et al., 2012).

Similarly, increased sensitivity of PACAP deficient mice to PD has been recently documented by Watson et al. (2013). The authors found that a low level exposure to paraquat, a pesticide known to increase the risk for PD, led to selective neuronal loss only in the SN of PACAP deficient mice. While the subthreshold dose of the pesticide did not cause any neuronal loss in wild type mice, it led to a 30% reduction of TH immunoreactive neuron loss in the SNc of PACAP knockout mice (Watson et al., 2013). Furthermore, PACAP knockout mice exhibited increased microglial activation and enhanced TNF-α expression along with impaired peripheral lymphocyte induction. These results clearly show that the loss of endogenous PACAP sensitizes the SN to toxic insults leading to PD (Watson et al., 2013).

In order to investigate possible reasons behind the increased vulnerability of PACAP deficient mice to neurotoxins, we have conducted a proteomics study of different brain areas of PACAP knockout mice using 2D gel electrophoresis and mass spectrometry analysis (Maasz et al., 2014). The most marked differences in the protein and peptide composition was observed in the diencephalon and mesencephalon. Several proteins were identified among the down- and up-regulated ones. Among the altered proteins, many are involved in metabolic processes, energy homeostasis and structural integrity. ATP synthase and tubulin beta-2A were expressed more strongly in PACAP knockout mice. In contrast, the expression of more peptides/proteins markedly decreased in knockout mice, like pyruvate-kinase, fructose biphosphate aldolase-A, GST, peptidyl propyl cis-trans isomerase-A, gamma enolase, and aspartate amino transferase. The altered expression of these enzymes might partially account for the decreased antioxidant and detoxifying capacity of PACAP deficient mice, in accordance with earlier observations that have showed that the antioxidant capacity decreases in aging knockout mice (Ohtaki et al., 2010). Our results also show that PACAP knockout mice might compensate this disturbed energy balance by increasing ATP synthase levels under intact or unstressed conditions, but this might not be sufficient under stressed conditions. These observations also suggest that endogenous PACAP is necessary for providing a favorable energy balance, in the lack of which this energy balance is disturbed, making the organism more vulnerable to noxious stimuli, like hypoxia, ischemia, aging, toxins, and neurodegenerative conditions.

5. Concluding remarks

As mentioned in the introductory part of the present paper, the current therapeutic approach to PD is of a symptomatic type. The use of L-DOPA, which is still considered the gold standard, aims to relieve PD motor symptoms by replacing the deficient neurotransmitter, DA. Up to now, no treatment has been found that could slow down the progression of the disease or that could prevent DAergic cell death. Since the pathology of the disease is very complex and several pathomechanisms are involved in the DAergic neuronal death, experimental therapeutic approaches should also involve several pathways. Neuroprotective therapy in PD aims to prevent DAergic cell death and, hence, slow or halt disease progression (Schapira, 1999). At present there are no proven neuroprotective therapies with only symptomatic treatments available. In this respect, of increasing importance is the issue of whether early treatment confers the potential for neuroprotection. In this review we summarized results of three novel candidates in the future treatment of PD. Polyphenols, antibiotics, and protective neuropeptides, or possibly their combination, could offer novel therapeutic approaches that act at multiple pathways leading to the degeneration of the DAergic neurons in the SN.

Conflict of interest statement

The authors have no conflicts of interest.

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