Neuroinflammation in Parkinson's Disease Animal Models: A Cell Stress Response or a Step in Neurodegeneration?

Carolina Cebrián, John D. Loike and David Sulzer

Abstract The motor symptoms of Parkinson's disease are due to the progressive degeneration of dopaminergic neurons in the substantia nigra. Multiple neuroinflammatory processes are exacerbated in Parkinson's disease, including glial-mediated reactions, increased expression of proinflammatory substances, and lymphocytic infiltration, particularly in the substantia nigra. Neuroinflammation is also implicated in the neurodegeneration and consequent behavioral symptoms of many Parkinson's disease animal models, although it is not clear whether these features emulate pathogenic steps in the genuine disorder or if some inflammatory features provide protective stress responses. Here, we compare and summarize findings on neuroinflammatory responses and effects on behavior in a wide range of toxin-based, inflammatory and genetic Parkinson's disease animal models.

Keywords Parkinson's disease · Neuroinflammation · Neurodegeneration · Animal models · Microglia · Proinflammatory cytokines · Lymphocytes

Contents

C. Cebrián · D. Sulzer
Department of Neurology, Columbia University Medical Center,
New York, NY 10032, USA

J.D. Loike
Department of Physiology and Cellular Biophysics,
Columbia University Medical Center, New York, NY 10032, USA

D. Sulzer (✉)
Departments of Psychiatry and Pharmacology, Columbia University Medical Center,
New York, NY 10032, USA
e-mail: ds43@columbia.edu

Curr Topics Behav Neurosci
DOI 10.1007/7854_2014_356

1 Introduction

Parkinson's disease (PD), the most common movement disorder (Lee et al. 2009), is characterized by a progressive loss of dopamine (DA) releasing neurons in the substantia nigra (SN) pars compacta (SNc), resulting in slowness of movement, rigidity, and tremor (Jankovic 2008), as well as the death of neurons in other catecholaminergic and cholinergic nuclei (Sulzer and Surmeier 2013). A central feature of PD is the presence of neuronal intracellular proteinaceous inclusions that contain alpha-synuclein (α-syn) known as Lewy bodies or Lewy neurites (Braak and Del Tredici 2010; Del Tredici and Braak 2012; Sekiyama et al. 2012).

Extensive microgliosis as a feature of the SNc of PD patients has been well documented since the initial report by Charles Foix in 1925 (Foix and Nicolesco 1925), who drew outstanding illustrations of activated microglia, which they labeled *neuroglia,* in PD brain, along with extracellular remnants of neuromelanin and Lewy bodies. This discovery was ignored for decades, in part as a peripheral immune response in the central nervous system (CNS) requires peripheral immune cells to traverse the blood-brain barrier (BBB), which was thought to be a rare event due to the "immune-privileged" nature of the brain (Engelhardt and Coisne 2011). This assumption was superseded as more recent studies described how cellular BBB permeability is regulated as a stress response (Franzén et al. 2003; Ransohoff and Perry 2009; Rezai-Zadeh et al. 2009).

The contemporary revival of interest in inflammatory processes associated with PD occurred when McGeer et al. (1988a, b) confirmed Foix's results by demonstrating activated microglia in the SN of patients postmortem. This topic has since become a major focus of PD research as covered in multiple reviews (Mena and García de Yébenes 2008; Tufekci et al. 2012; Blandini 2013; Sanchez-Guajardo et al. 2013a). Evidence supporting neuroinflammation in PD includes postmortem studies of brain, analyses of pro-inflammatory cytokines in serum and cerebrospinal fluid (CSF), PD risk factor associations with cytokine and major histocompatibility complex (MHC) class II (MHC-II) polymorphisms, and epidemiological studies of nonsteroidal anti-inflammatory use (Frank-Cannon et al. 2009; Hirsch and Hunot 2009; Lee et al. 2009; Tansey and Goldberg 2010). Whether neuroinflammation is a cause of PD pathogenesis or a secondary stress response remains, however, remains an elusive issue.

There is in our opinion no clear evidence that neuroinflammation is a primary trigger of PD, but there have long been hints that viral infection could be involved

in some cases, most famously a parkinsonism in patients who survived the Spanish flu outbreaks and von Economo's encephalitis during World War I (Henry et al. 2010). It has been suggested that systemic infection/inflammation exaggerates pathogenic events associated with PD and intensifies symptoms (Kortekaas et al. 2005; Collins et al. 2012) or exacerbates neuronal dysfunction during the prodromal stage (Lee et al. 2009). Another hypothesis is that stressed neurons activate microglia that release factors that further damage neurons (Frank-Cannon et al. 2009; Hirsch and Hunot 2009; Tansey and Goldberg 2010; Zhang et al. 2011a) causing a "vicious cycle" of neuroinflammation and neurodegeneration (Tansey and Goldberg 2010; Hoban et al. 2013). Such studies have led to exploration of anti-inflammatory therapies in PD, although to date these have shown limited success. It is important to emphasize that inflammatory steps are stress responses and may in some instances provide neuroprotection.

In this chapter, we review the literature on how animal models have been used to examine neuroinflammatory processes in PD. For each, we highlight the immune cells elicited, the inflammatory markers that are upregulated, the effects on neurodegeneration, and the behavioral manifestations that may be related to neuroinflammation. There is a very extensive and often contradictory literature on these responses, and as to our knowledge these have not been summarized in a single review, we hope that this chapter will assist the interpretation and design of future research. While evidence for neuroinflammation in most models is clear, the understanding of its role in pathogenesis, protection, and changes in behavior for the most part remains limited.

2 Neuroinflammation in Animal Models of PD

2.1 Toxin-based Models

2.1.1 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)

This toxin appeared in an initial report of a chemistry graduate student who injected himself intravenously with a synthetic heroin substitute and exhibited a long-lasting motor disorder within a few days (Davis et al. 1979) due to MPTP as a impurity (Kopin 1987). Postmortem examinations after a second appearance of MPTP as an impurity in a synthetic opiate revealed the presence of activated microglia that apparently persisted years after drug exposure (Langston et al. 1999).

MPTP was adapted as a PD model in rodents and primates. These studies showed that this compound acts as a lipophilic protoxin that crosses the BBB and is converted to the toxic metabolite 1-methyl-4-phenylpyridinium (MPP^+) by astrocytes and serotonergic neurons (Riachi et al. 1989) by monoamine oxidase-B (Ransom et al. 1987). MPP^+ is then released into the extracellular space and accumulated by the DA transporter (DAT) into DA neurons, causing a bilateral degeneration of the nigrostriatal tract (Taylor et al. 2013). MPP^+ produces

neurodegeneration through the blockade of electron transport chain enzyme complexes I, III, and IV (Desai et al. 1996). Additional factors modulate MPTP toxicity including iron, expression of the vesicular monoamine transporter, reactive oxygen species (ROS), and apoptosis (Salama and Arias-Carrion 2011).

Cellular Response

In mice, MPTP induces a rapid microglial activation that peaks prior to the loss of the DA neurons (Czlonkowska et al. 1996), a response particularly severe in the SAMP8 mouse line that has been used as a model of senility (Liu et al. 2010). Activation of the adaptive immune system by MPTP is shown by increased lymphocyte infiltration (Kurkowska Jastrzebska et al. 1999), primarily by T cells (Hirsch and Hunot 2009). Consistently, results with T-cell-receptor (TCR)-β-chain-deficient, immunodeficient and RAG1 knockout mice demonstrate that T-cell-deficiency attenuates MPTP-induced neurodegeneration (Brochard et al. 2009; Reynolds et al. 2010). Mice-deficient for inflammatory genes, including apoptosis signal-regulating kinase 1 (Lee et al. 2012a) and dynorphin (Wang et al. 2012), show attenuated microglial and astrocyte activation and are protected from MPTP toxicity. It has been suggested that D3 DA receptors on CD4+ T cells regulate their response to MPTP (González et al. 2013).

In non-human primates, HLA-DR-reactive microglia are found in SN following MPTP administration (McGeer et al. 2003). This activation is triggered early and persists for at least 35 months (Vázquez-Claverie et al. 2009).

Cytokine Response

Mice lacking gamma interferon (IFN-γ) or tumor necrosis factor-alpha (TNF-α) receptors displayed attenuated MPTP degeneration (Mount et al. 2007; Sriram et al. 2002; Barcia et al. 2011). In mouse striatum and SN, MPTP increases expression of the cytokines interleukin (IL)-1-beta (IL-1β), IL-6, IL-7, IL-10, the cytokine receptors IL-1R, IL-3R, IL-4R, IL-10R, the inflammation-related transcription factor NFκB (Grünblatt et al. 2001), the chemokine receptor CXCR4 and the chemokine ligand CXCL12 (Shimoji et al. 2009). In CSF of C57BL/6 but not BALB/C mice, MPTP increased the cytokines IL-10, IL-12, IL-13, IFN-γ, TNF-α and the monocyte chemotactic protein 1 (MCP-1) (Yasuda et al. 2008): this differences may be because the peripheral immune system in the C57BL/6 strain is more prone to a proinflammatory Th1 (T helper 1) phenotype that produces IFN-γ, while Balb/c mice tend to mount an anti-inflammatory Th2 (T helper 2) response (Sanchez-Guajardo et al. 2013a).

In monkeys, MPTP activates IFN-γ and TNF-α in SN microglia and astrocytes, and IFN-γ receptor signaling is increased in SN glia (Barcia et al. 2011). Microarray analysis of MPTP treated monkeys confirmed an increased expression of inflammation-related genes, including IL-11, chemokines, and complement system genes (Ohnuki et al. 2010).

In Vivo and Behavioral Features Related to Inflammation

Most studies on neuroinflammation and motor symptoms induced by MPTP have been performed in mice (Chung et al. 2010; L'Episcopo et al. 2010; Gupta et al. 2011; Lee et al. 2012b; Wang et al. 2012; Roy et al. 2012; Esposito et al. 2012; Ghosh et al. 2012). Together, these studies indicate that drugs that block inflammation are protective against MPTP alterations in behavior, including the antidepressant paroxetine (Chung et al. 2010), nitric oxide-donating nonsteroidal anti-inflammatory drugs (L'Episcopo et al. 2010), selective cyclooxygenase (COX)-2-inhibitors (Gupta et al. 2011), sodium phenylbutyrate (Roy et al. 2012), the fatty acid amide palmitoylethanolamide (Esposito et al. 2012), the antioxidant diapocynin (Ghosh et al. 2012), the partial of N-methyl-D-aspartate (NMDA) receptor agonist D-cycloserine (Wang et al. 2010), and the anti-inflammatory aescin (Selvakumar et al. 2014).

In monkeys that received a single intracarotid arterial injection of MPTP, activation of the peroxisome proliferator-activated receptor gamma (PPAR-γ) attenuated neuroinflammation, as measured by decreased CD68+ cells. Monkeys treated with PPAR-γ also displayed improved motor skills (Swanson et al. 2011).

2.1.2 6-hydroxydopamine (6-OHDA)

6-OHDA is a widely used catecholaminergic neurotoxin (Bové and Perier 2012), which in contrast to the typical systemic administration of MPTP to mice, is usually delivered directly to the medial forebrain bundle, SNc, or the striatum by stereotaxy in rats (Fulceri et al. 2006).

DA neuronal degeneration by 6-OHDA is due to its uptake by DAT. 6-OHDA is readily oxidized in the cytosol to produce ROS, including hydrogen peroxide and its corresponding *p*-quinone (von Coelln et al. 2001; Mazzio et al. 2004), which produces oxidative stress and mitochondrial respiration dysfunction (Barnum and Tansey 2010). The toxin further decreases striatal glutathione and superoxide dismutase (Perumal et al. 1992; Kunikowska and Jenner 2001), increases iron in SN (Oestreicher et al. 1994), and directly inhibits electron transport (Glinka et al. 1997).

Cellular Response

6-OHDA causes neuroinflammatory responses (Schober 2004; Tufekcy et al. 2012; Taylor et al. 2013) including reactive astrocytosis (Gomide et al. 2005; Wachter et al. 2010) and microglial activation (Akiyama and McGeer 1989; Marinova-Mutafchieva et al. 2009; Cicchetti et al. 2002). The microglial activation can be blocked by minocycline (He et al. 2001) or the COX-2 inhibitor celecoxib, which can delay DA cell loss (Sanchez-Pernaute et al. 2004).

The inflammatory profile observed in 6-OHDA-lesioned animals can depend on timing and the site of injection. For example, when 6-OHDA was injected into the striatum, microglial activation was more robust in striatum than SN (Armentero et al. 2006). Na et al. (2010), however, suggest that this is time-dependent as intrastriatal 6-OHDA increased inflammatory gene expression in striatum 3 days after the injection, but SN showed a similar inflammatory response after a week.

Cytokine Response

6-OHDA activates inflammatory features including NF-κB-mediated responses accompanied by inhibition of antioxidant systems regulated by Nrf2 (Tobón-Velasco et al. 2013), TNF-α (Mogi et al. 2000) and complement component 1q subcomponent-binding protein (Park et al. 2010).

Neuroprotection from 6-OHDA is provided by inhibiting inflammation with a peroxisome proliferator-activated receptor gamma agonist (Sadeghian et al. 2012), silencing the enzyme inducible nitric oxide synthase (iNOS) (Li et al. 2012) or blocking TNF-α (McCoy et al. 2006; Harms et al. 2011; Pabon et al. 2011; Zhang et al. 2011b).

In Vivo and Behavioral Features Related to Inflammation

As 6-OHDA can be delivered into one side of the brain, it provides a means to measure effects of DA depletion by studying rotational behavior (Pycock 1980), often activated by amphetamine. Blockade of soluble TNF-α signaling in vivo provided neuroprotection to DA neurons from 6-OHDA-induced death and attenuated rotational behavior (McCoy et al. 2006).

NK1, a substance P receptor antagonist, administered immediately after 6-OHDA injection, protected DA neurons, preserved barrier integrity, reduced neuroinflammation, and significantly improved motor function (Thornton and Vink 2012). A CD200R-blocking antibody injected into striatum of rats treated with 6-OHDA showed a significant increase in contralateral rotation and a significant decrease in DA SN neurons with remarkably increased activation of microglia and proinflammatory cytokines (Zhang et al. 2011c).

Interestingly, human IL-10 gene transfer in rats unilaterally injected with 6-OHDA inhibited forelimb akinesia (Johnston et al. 2008). An antagonist of metabotropic receptor mGluR5 immediately ameliorated 6-OHDA-induced akinesia, although it did not modify neuronal survival or neuroinflammation (Ambrosi et al. 2010).

A recent study in mice reports that swimming is effective in attenuating behavior impairments and signs of inflammation including increased IL-1β levels (Goes et al. 2014) from 6-OHDA and alters glutathione peroxidase, glutathione reductase, and glutathione S-transferase activities. The authors conclude that protective effects induced by exercise on PD are due to the induction of antioxidant and anti-inflammatory responses.

2.1.3 Rotenone and Paraquat

Exposure to the herbicide paraquat and the pesticide rotenone is linked to an increased risk of PD in epidemiological studies (Kamel et al. 2007; Baldereschi et al. 2008; Hancock et al. 2008), and both have been adapted for PD models. Rotenone is highly lipophilic and crosses the BBB to diffuse into neurons where it inhibits complex I of the mitochondrial respiratory chain and causes neurodegeneration of SN neurons; however, reports of its selectivity for neurotoxicity are variable (Betarbet et al. 2000; Cicchetti et al. 2009). Paraquat is a charged molecule that does not cross the BBB and requires a neutral amino acid transporter for neuronal accumulation (Shimizu et al. 2001). In the cytosol, paraquat generates superoxide and impairs recycling of oxidized glutathione.

Cellular and Cytokine Responses

Rotenone toxicity is linked to increased ROS production with oxidative damage in the midbrain and striatum and microglial activation (OX-42 immunoreactivity) in SN and striatum with minimal astrocytosis (Sherer et al. 2003a, b, c) prior to DA cell loss. Microglia may mediate rotenone-induced neuronal degeneration through IFN-γ (Mount et al. 2007) or nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-generated superoxide production (Gao et al. 2003). Inhibition of microglia by minocycline in vitro provides protection from rotenone (Casarejos et al. 2006). Rotenone does not directly activate microglia in vitro (Gao et al. 2002b, 2003; Shaikh and Nicholson 2009; Klintworth et al. 2009), and so its toxicity has been suggested to result from disturbing CD200R-CD200L microglia-DA neuron cross talk (Wang et al. 2011).

Intracerebral injection of paraquat induces loss of DA neurons (Liou et al. 1996), activates microglia (Purisai et al. 2007), elevates expression of TNF-α, IL-1β, and NF-κB (Yadav et al. 2012), iNOS (Cicchetti et al. 2005; Gupta et al. 2010), and produces α-syn-containing inclusion bodies (Manning-Bog et al. 2002). IFN-γ knockout mice injected with paraquat displayed reduced cell death and microglial activation, decreased proinflammatory enzymes (iNOS and COX-2) and cytokines (TNF-α, IL-1β), and increased trophic factors (Mangano et al. 2012). It has been suggested that elevation of cytosolic DA induced by paraquat participates in the neurotoxicity via quinone formation (Izumi et al. 2014).

In Vivo and Behavioral Features Related to Inflammation

Sindhu et al. (2005) observed that Sprague-Dawley rats infused intranigrally with rotenone exhibited spontaneous contralateral rotations immediately after recovery from anesthesia. In rats treated subcutaneously with rotenone, an adenosine triphosphate-sensitive potassium channel opener, iptakalim, normalized rotenone-induced

behavioral symptoms, degeneration of SNc DA neurons, microglial activation, and mRNA levels of TNF-α and COX-2 (Zhou et al. 2007a, 2008).

Intraperitoneal injection of paraquat in mice causes DA neurotoxicity in SN, frontal cortex and hippocampus, motor impairment assessed by curling and footprint tests, brain-specific ROS generation, and microgliosis with increased levels of TNF-α and IL-1β (Mitra et al. 2011).

2.2 Inflammatory Models

2.2.1 LPS (lipopolysaccharide)

LPS, an endotoxin in the outer membrane of Gram-negative bacteria, is widely used to trigger immune response in animals (Liu and Bing 2011). It activates Toll-like receptor (TLR) 4, which is highly expressed in microglia (Sanchez-Guajardo et al. 2013a). While no reports have indicated that septic individuals with high LPS develop PD (Fang et al. 2012), it has been used to initiate DA neuronal death and examine neuroinflammation in animal models (Lee et al. 2009).

In neuronal culture, DA neurons are twice as sensitive to LPS as non-DA neurons, and LPS toxicity occurs via microglial activation (Bronstein et al. 1995; Gayle et al. 2002; Dutta et al. 2008). In vivo, LPS inflammation also causes selective toxicity of DA neurons (Qin et al. 2007; Hunter et al. 2009; Machado et al. 2011; Tufekci et al. 2011) that apparently lack TLR4 receptor (Sanchez-Guajardo et al. 2013a).

Chronic low-dose intranigral LPS infusion in rats induced delayed, chronic, and progressive loss of DA SNc neurons (Gao et al. 2002a), while intrauterine exposure to LPS causes a degeneration of SNc neurons in offspring (Carvey et al. 2003). Chronic low-dose intraperitoneal LPS acted in concert with parkin deficiency to induce nigral DA neuron loss (Frank-Cannon et al. 2008), suggesting that a non-specific immunogenic stimulus in concert with a permissive genetic mutation could cause parkinsonism.

Cellular and Cytokine Responses

Intranigral LPS triggers activation of astrocytes and microglia; damages SN DA neurons (Castaño et al. 1998; Iravani et al. 2005; Qin et al. 2007; Pott Godoy et al. 2008), releases proinflammatory factors including IL-1α, TNF-α, IL-1β, and inducible nitric oxide synthase (iNOS, Qin et al. 2007; Tomás-Camardiel et al. 2004; Hernández-Romero et al. 2008), and increases COX-2 (de Meira Santos Lima et al. 2006; Geng et al. 2011), ROS and matrix metalloproteinase-3 (MMP-3) (Qin et al. 2004; McClain et al. 2009).

In aged mice, LPS caused progressive loss of DA neurons, whereas younger mice or aged mice treated with the anti-inflammatory nonsteroid drug HCT1026 were resistant (L'Episcopo et al. 2011). A sustained elevation of TNF-α has been observed in striatum and mesencephalon of rats prenatally exposed to LPS (Ling et al. 2004).

Several studies support a central role for TNF-α in LPS neurodegeneration. LPS-induced nigral DA damage is inhibited by dexamethasone or soluble TNF-α inhibitors (Castaño et al. 2002) or neutralizing antibodies against TNF-α or IL-1 that block microglial activation (Dutta et al. 2008; McCoy and Tansey 2008). An IL-1 receptor antagonist reduced LPS-induced TNF-α and IFN-γ release and loss of DA neurons (Koprich et al. 2008). LPS did not release IL-1β and NFκB p65, or kill SN neurons in mice deficient for TNF-α receptors (Qin et al. 2007).

A role for DA in response to LPS was indicated since alpha-methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase (TH), prevented LPS-induced nigral DA death (De Pablos et al. 2005). The iron chelator desferrioxamine was also protective against LPS-induced SN neuronal degeneration (Zhang et al. 2012), consistent with a role for iron-mediated oxidative stress, which again may be related to DA oxidation or mitochondrial stress.

In Vivo and Behavioral Features Related to Inflammation

Similar to the 6-OHDA model above, four weeks of running exercise prior to LPS prevented the loss of DA neurons and motor dysfunction. Running did not change the LPS-induced status of microglia activation or the levels of cytokines/chemokines, but restored normal brain-derived neurotrophic factor (BDNF)-TrkB signaling. Blocking BDNF with a TrkB receptor antagonist abolished running's protective effect, while intrastriatal perfusion of BDNF alone blocked LPS-induced DA neuron loss (Wu et al. 2011).

Multiple in vivo studies confirm the role for TNF in LPS neurotoxicity that was suggested in cellular studies. Subacute LPS injection into SN induces PD-like symptoms in mice including aggregation of α-syn. Behavioral deficits were observed in wild-type (WT) and TNF-α knockout (KO) mice, but IL-1 KO mice behaved normally. TH gene expression was attenuated by LPS in WT and TNF-α KO, but not in IL-1 KO mice (Tanaka et al. 2013). Chronic in vivo co-infusion of a TNF blocker with LPS into the SNc of rats attenuated amphetamine-induced rotation, (McCoy et al. 2006), as did a glucagon-like peptide 1 receptor agonist (Harkavyi et al. 2008).

LPS injection in the striatum causes intracytoplasmic accumulation of α-syn and ubiquitin, defects in the mitochondrial respiratory chain, and extensive S-nitrosylation/nitration of mitochondrial complex I. The mitochondrial injury was prevented by treatment with L-N(6)-(l-iminoethyl)-lysine, an iNOS inhibitor. These results implicate neuroinflammation-induced S-nitrosylation/nitration of mitochondrial complex I in LPS-induced mitochondrial malfunction and degeneration of SN neurons (Choi et al. 2009). In another study, striatal LPS caused microgliosis

but not nigrostriatal neurodegeneration, with only a transient motor dysfunction (Hoban et al. 2013). The administration of a peptide antagonist of IL-1 signaling to rats after receiving LPS blocked inflammation as well as deficits in social activity and memory (Klementiev et al. 2014).

In mice, both neuroinflammation and motor impairment were exacerbated when LPS bilateral striatal injections were followed by the administration of methamphetamine (Jung et al. 2010), further indicating a role for DA itself in LPS damage.

2.2.2 Polyinosinic:polycytidylic Acid [poly(I:C)]

Introduction and Cellular and Cytokine Responses

Polyinosinic:polycytidylic acid [poly(I:C)] is structurally similar to double-stranded RNA and widely used to study antiviral responses such as production of type I interferons (Liu et al. 2012). Poly(I:C) is an agonist for TLR3, which is found in CNS microglia and is upregulated by LPS and IFN-γ (Olson and Miller 2004).

Single poly(I:C) injections to the rat SN do not cause SN neurodegeneration, but increase the susceptibility of DA neurons to a subsequent low dose of 6-OHDA (Deleidi et al. 2010). This induced long-lasting inflammation in SN and dorsolateral striatum involving microglia, astrocytes, and perivascular and parenchymal CD68+ macrophages and the chemokines, MCP-1, and RANTES (CCL5) in the SN, and IL-1β, IL-6, TNF-α, MCP-1, and transforming growth factor beta 1 (TGF-β1). IL-1R antagonist treatment rescued neurons from poly(I:C) and 6-OHDA toxicity (Deleidi et al. 2010).

In Vivo and Behavioral Features Related to Inflammation

In mice, pretreatment with poly(I:C) enhanced DA neuron loss in SN elicited by subsequent paraquat treatment. The neuronal loss was accompanied by robust signs of microglial activation, and increased expression of the catalytic subunit (gp91) of the NADPH oxidase oxidative stress enzyme. These findings suggest that viral agents can sensitize microglial-dependent inflammatory responses, rendering nigral DA neurons vulnerable to environmental toxin exposure (Bobyn et al. 2012).

2.2.3 Prostaglandin J2

Introduction and Cellular and Cytokine Responses

The major prostaglandin in mammalian brain is prostaglandin D2, which undergoes spontaneous dehydration to generate the bioactive cyclopentenone prostaglandins

of the J2 series. J2 prostaglandins are highly reactive and neurotoxic products of inflammation that impair ubiquitin/proteasome function and cause accumulation of ubiquitinated proteins (Li et al. 2004). A single report that we are aware of indicates that prostaglandin D2 administration into the SN activates microglia and astrocytes and produces neurodegeneration with α-syn aggregation (Pierre et al. 2009).

2.3 Genetic Models

2.3.1 α-Synuclein (SNCA)

Introduction

Over 20 loci and 15 disease-causing genes for parkinsonism have been identified (Deng and Yuan 2014). Mutations in seven genes are robustly associated with autosomal dominant (SNCA, LRRK2, EIF4G1, VPS35) or recessive (parkin/PARK2, PINK1, DJ1/PARK7) PD or parkinsonism. Of these, α-syn has received particular attention as aggregation of this protein is a neuropathological feature of the vast majority of PD cases. SNCA was also the first PD gene identified (Polymeropoulos et al. 1997), and encodes a 140 amino acid synaptic vesicle-associated protein that regulates synaptic vesicle exocytosis (Abeliovich et al. 2000; Fortin et al. 2005; Larsen et al. 2006; Nemani et al. 2010). Shortly thereafter, α-syn was identified as the main component of Lewy bodies and Lewy neurites in PD patients (Spillantini et al. 1997). At least five-point SNCA mutations have been linked to familial PD (Krüger et al. 1998; Zarranz et al. 2004) as well as gene duplications and triplication (Singleton et al. 2003; Ross et al. 2008), indicating that excessive levels of the normal protein also cause PD. SNCA triplication carriers display an approximately 10-year earlier onset and a more rapid disease course than duplication carriers, who more closely resemble patients with idiopathic PD (Kasten and Klein 2013).

α-syn is a natively unfolded soluble protein that can aggregate to form oligomers or protofibrils, and eventually insoluble polymers or fibrils (Conway et al. 2000a, b). The toxic contribution from different α-syn forms is a major area of investigation (Bungeroth et al. 2014). Both unfolded and aggregated might be neurotoxic via a variety of pathways including inhibition of protein degradation by chaperone-mediated autophagy (Cuervo et al. 2004) and membrane permeabilization (Rochet et al. 2004; Mosharov et al. 2006; Staal et al. 2008). Oligomeric α-syn may mediate neurodegeneration by disrupting synaptic vesicles (Rockenstein et al. 2014). α-syn fibrils, like prions, have been shown to seed new α-syn reactions (Miake et al. 2002; Masuda-Suzukake et al. 2013). Anti-aggregation compounds may help address these questions by inhibiting α-syn aggregate formation (Herva et al. 2014).

In animal studies, α-syn overexpression in combination with MPTP or rotenone increased neurodegeneration (Dauer et al. 2002; Mulcahy et al. 2013). LPS causes neuronal death in transgenic mice that express normal or mutant (A53T) α-syn

(Gao et al. 2008, 2011). Proteomic analysis of brains from mice overexpressing the human A30P mutation identified increased oxidized metabolic proteins (Poon et al. 2005), while mutant A53T mice displayed mitochondrial damage and degeneration (Martin et al. 2006).

An alternate model that emulates Lewy body pathology, synaptic dysfunction, and neuronal death in PD is to use fibrils generated from full-length and truncated recombinant α-syn (Volpicelli-Daley et al. 2011). In young asymptomatic α-syn transgenic mice, intracerebral injections of brain homogenates derived from older transgenic mice exhibiting α-syn pathology induced intracellular Lewy bodies/Lewy neurites-like inclusions and neurological symptoms (Luk et al. 2012a). In WT non-transgenic mice, a single intrastriatal inoculation of synthetic α-syn fibrils led to the cell-to-cell transmission of pathologic α-syn and PD-like Lewy pathology in anatomically interconnected regions in the SN but not in the adjacent ventral tegmental area, which is relatively spared in PD (Luk et al. 2012b). It is possible that this spread of pathology occurs via an inflammatory mechanism.

Cellular and Cytokine Responses

A number of SCNA mouse models (KO, overexpressors, and transgenics) have been generated (Chesselet 2008) although few exhibit DA cell loss (for exceptions, see Lin et al. 2012 and Janezic et al. 2013). Some of these models, however, display α-syn aggregation, gliosis, mitochondrial abnormalities, and functional abnormalities in the nigrostriatal system (Dawson et al. 2010).

The initial α-syn transgenic mouse introduced by Masliah et al. (2000) using a platelet-derived growth factor subunit B promoter exhibited human α-syn-immunoreactive inclusions most frequently seen in neurons in the deeper layers of the neocortex, the CA3 region of the hippocampus, olfactory bulb and occasionally in the SN. The mice also displayed lower TH^+ levels within the striatum than non-transgenic littermates. A transgenic mice harboring a SCNA transgene with a Thy1 promoter (Rockenstein et al. 2002) showed astroglial and microglial activation, elevated levels of TNF-α in the striatum, and increased levels of TNF-α, TLR1, TLR4, and TLR8 in the SN (Watson et al. 2012). Microglial activation and high levels of TNF-α were found in the SN of mice expressing human α-syn under control of the mouse TH promoter (Su et al. 2008). Expression of truncated human α-syn increased CD11b-positive microglia in the SN of transgenic mice (Tofaris et al. 2006). Transgenic mice that express A53T α-syn displayed astrogliosis in the spinal cord (Giasson et al. 2002).

It has been suggested that in α-syn transgenic models, microglia are not extensively activated unless the mice are treated with LPS or possess further genetic modifications (Sekiyama et al. 2012). Microgliosis was found in cortex and hippocampus of A30P overexpressing mice under the prion protein (PrP) promoter along with truncated and oligomeric α-syn (Gomez-Isla et al. 2003). α-syn pathological accumulation has been associated with microgliosis in the E46K α-syn transgenic under the PrP (Emmer et al. 2011). An A53T α-syn transgenic mouse

line under the PrP promoter and the A30P+A53T α-syn line under the TH promoter featured changes in microglia cell numbers and altered expression patterns in multiple genes related to the inflammatory responses (Lee et al. 2002; Miller et al. 2007).

Mice and DA neuronal cultures derived from mice with WT and mutant A53T α-syn in an α-syn-null background exposed to LPS, displayed neuroinflammation DA neuronal death and accumulation of cytoplasmic α-syn inclusions (Gao et al. 2008). Inhibition of nitric oxide and superoxide produced by microglia provided substantial neuroprotection.

To date, the few α-syn transgenic mouse models to display neuronal death are as follows: (1) a line of tetracycline-regulated inducible transgenic mice that overexpressed A53T α-syn in DA neurons; these developed motor disabilities, decreased DA release, fragmentation of Golgi apparatus, and impairment of autophagy/lysosome degradation pathways (Lin et al. 2012); (2) a line of bacterial artificial chromosome (BAC) mice overexpressing WT hSNCA140 generated by injection of BAC DNA containing WT hSNCA (Janezic et al. 2013).

In contrast to transgenic models, overexpression of α-syn by means of viral vectors has produced significant SN neuronal death (Ulusoy et al. 2010). In mice, overexpression of WT human α-syn can lead to slow degeneration of DA neurons (Theodore et al. 2008; Harms et al. 2013). Four weeks after injection, there was a marked increase in CD68-positive microglia and greater infiltration of B and T lymphocytes in the SNc of the rAAV2-SYN group than in controls. At 12 weeks, CD68 staining declined, but B- and T-cell infiltration persisted. Expression of proinflammatory cytokines was enhanced, whereas markers of alternative activation (i.e., arginase I, IL-4 and IL-13) were not altered. Increased immunoreactivity for mouse immunoglobulin was detected at all time points in the rAAV2-SYN animals. Thus, overexpression of α-syn is sufficient to trigger neuroinflammation featuring microglial activation and stimulation of adaptive immunity (Theodore et al. 2008). Overexpression of full-length human α-syn in mouse SNc induced extensive MHC-II expression by microglia, while mice lacking of MHC-II were protected from α-syn-induced microglial activation and DA neuron degeneration (Harms et al. 2013).

In rats, transgenic α-syn overexpression produced α-syn-positive cytoplasmic inclusions and swollen, dystrophic neurites selectively in the nigral DA neurons with a loss of 30–80 % of the nigral DA neurons by 8 weeks (Kirik et al. 2002). T-lymphocyte infiltration was related to the degree of neurodegeneration (Sanchez-Guajardo et al. 2010).

In monkeys, neuropathology following WT α-syn overexpression was confined to caudate putamen DA fibers with a limited cell loss in the SN, whereas overexpression of A53T α-syn resulted in robust degeneration of DA cells in SNc within one year (Eslamboli et al. 2007). Overexpression of A53T α-syn produced a long-term increase in microglia, while WT α-syn overexpression increased microglia for more than a year (Barkholt et al. 2012).

Injection of monomeric or oligomeric α-syn into SN induced microgliosis (Wilms et al. 2009; Couch et al. 2011). The use of HA-TAT internalization signal peptide to introduce nitrated α-syn into cells confirmed that microgliosis correlated

with α-syn-induced neurodegeneration (Yu et al. 2010). Distinct strains of α-syn may differentially promote tau inclusions and help explain the heterogeneity of synucleinopathies (Guo et al. 2013).

In Vivo and Behavioral Features Related to Inflammation

Mice overexpressing WT human α-syn under the Thy1 promoter exhibited impairments in sensorimotor function and non-motor symptoms at a young age, including deficits in olfaction, autonomic, digestive, and cognitive function (Fleming et al. 2004). Homozygous mice expressing the A53T mutant human α-syn under the control of the mouse prion promoter developed and displayed severe motor impairments with accumulation of α-syn in brain (Giasson et al. 2002). Homozygous A53T mutant mice exhibited decreased anxiety in 2-month-old animals (George et al. 2008) and increased locomotor activity and altered DA neurotransmission at 7–19-months, while mice expressing human WT or A30P α-syn showed no locomotor changes (Unger et al. 2006). Mice expressing the A53T mutant form of human α-syn exhibited hyperactivity and reduced anxiety-like behavior (Graham and Sidhu 2010). No neuroinflammatory parameters were reported in these transgenic α-syn overexpressor models.

Rats transduced with rAAV-α-syn displayed significant motor impairment when DA neuronal cell loss exceeded 50–60 % (Kirik et al. 2002). When α-syn induced neuronal pathology but not cell death, there was a long-term induction of MHC-II$^+$ microglia. In contrast, when α-syn induced both neuronal pathology and cell death, there was a delayed increase in microglia, which correlated with long-lasting CD68 expression and the reminiscent morphology of peripheral macrophages. A recent study from the same group found that when rats were vaccinated with recombinant α-syn prior receiving the transgenesis of α-syn; this resulted in (a) a high-titer anti-α-syn antibody response on α-syn overexpression, (b) the accumulation of CD4-positive T cells, (c) MHC-II-positive ramified microglia in the SN, (d) long-lasting infiltration of CD4-positive T cells, (e) Foxp3-positive cells throughout the nigrostriatal system, and (f) fewer pathologic aggregates in the striatum versus control animals that had received a mock vaccine. A long-term increase in striatal glial cell-derived neurotrophic factor in striatum and IgG deposition in α-syn-overexpressing cells and neurites in the SN was also observed. These results suggest that a protective vaccination strategy may induce regulatory T cells and activated microglia, and consequently immune tolerance against α-syn (Sanchez-Guajardo et al. 2013b). In rats injected in SN with rAAV-α-syn, functional impairment in the cylinder test and the adjusting steps task was observed after 8 week (Gombash et al. 2013).

rAAV-α-syn-treated monkeys, both WT and mutants, developed motor impairment, including head position bias, compatible with this magnitude of nigrostriatal damage (Kirik et al. 2003). Animals overexpressing the A53T α-syn showed a gradual worsening of motor performance (Eslamboli et al. 2007).

2.3.2 Leucine-rich Repeat Kinase 2 (LRRK2)

LRRK2 is a 2527 amino acid protein that contains functional kinase and GTPase domains, and leucine-rich repeat and WD40 protein-interaction domains (Paisan-Ruiz et al. 2004; Zimprich et al. 2004). It is expressed throughout various brain regions, including SN, basal ganglia, cortex, hippocampus, and cerebellum (Biskup et al. 2006; Healy et al. 2008). Multiple functions for LRRK2 have been suggested, including protein scaffolding, substrate binding, and protein phosphorylation (Drolet et al. 2011) and modulation of chaperone-mediated autophagy (Orenstein et al. 2013), a mechanism that may cause α-syn aggregation.

Mutations in LRRK2 are the most common cause of familial PD and are linked to both autosomal dominant and sporadic forms (Correia Guedes et al. 2010). The most prevalent modification of LRRK2 is the amino acid substitution G2019S in the kinase domain, generating a gain of function. Overexpression of G2019S has been linked to enhanced LRRK2 autophosphorylation and kinase activity (Greggio et al. 2006; Li et al. 2010a, b). A genome-wide study has also identified LRRK2 as a susceptibility locus for Crohn's disease (Danoy et al. 2010).

LRRK2 knockout rats are resistant to DA neurodegeneration from intracranial administration of LPS or adeno-associated virus-mediated transduction of human α-syn, and this resistance correlates with reduced proinflammatory myeloid cells recruited to the brain. These data suggest that knocking down LRRK2 may protect against SN neuronal loss by inhibiting recruitment of proinflammatory myeloid cells (Daher et al. 2014).

Cellular and Cytokine Responses

A role for LRRK2 in immune response was first proposed due to its expression in B-lymphocytes, dendritic cells, and macrophages (Gardet et al. 2010) and isolated mouse microglial cells (Gillardon et al. 2012). LRRK2 levels in microglia were upregulated by LPS, with LRRK2 (1441G) transgenic microglia secreting higher levels of TNF-α, IL-1β, and IL-6 and lower amounts of anti-inflammatory IL-10 than controls. Neurotoxic effects were confirmed when culture medium from LPS-stimulated cells was added to cultured cortical neurons (Gillardon et al. 2012). Knockdown of LRRK2 in microglia reduced LPS-induced TNF-α and iNOS production and decreased the activation of the p38 and NF-κB pathways (Kim et al. 2012). Additional studies confirmed a link between the G2109S LRRK2 mutation and an elevated LPS-induced-inflammatory response that includes TNF-α, IL-1β, IL-6, NF-κβ, and iNOS secretion (Kim et al. 2012; Moehle et al. 2012). Recently, phosphorylation of LRRK2 was shown to involve a TLR-mediated pathway involving Myd88, suggesting a role for LRRK2 in innate immune response (Dzamko et al. 2012).

In Vivo and Behavioral Features Related to Inflammation

Multiple behavioral features have been noted in animal models of LRRK2 mutation. Temporary but not constitutive overexpression of LRRK2 in adult rats impaired DA reuptake by DAT and consequently enhanced locomotor activity (Zhou et al. 2011). Transgenic mice expressing human LRRK2 with an I2020T mutation in the kinase domain exhibited impaired locomotion, reduced striatal DA, fragmented Golgi apparatus in DA neurons, and increased microtubule polymerization, while TH primary neurons derived from the transgenic mouse showed increased frequency of apoptosis and neurites with fewer branches and decreased outgrowth (Maekawa et al. 2012).

Mice lacking LRRK2 exon 41, which encodes the activation hinge of the kinase domain, displayed abnormal behavior (Hinkle et al. 2012). LRRK2 (R1441G) BAC transgenic mice displayed gastrointestinal dysfunction at an early stage (Bichler et al. 2013). These studies did not analyze neuroinflammatory parameters.

Two groups have reported viral LRRK-2-based PD models using adeno- or herpes simplex virus (Lee et al. 2010; Dusonchet et al. 2011). During the first three weeks after injection, LRRK-2 G2019S virus induced a greater loss of TH-positive neurons in the SNc than WT LRRK-2 or EGFP expressing viruses. G2019S LRRK-2 expressing mice, but not WT LRRK2 or EGFP expressing mice, displayed microglia activation in the SNc and striatum (Lee et al. 2010). In the second study, WT or G2019S mutant human LRRK-2 were delivered in adenovirus type 5 vectors and expressed under control of the neuron specific synapsin-1 promoter. Mutant G2019S LRRK-2 caused progressive loss of DA neurons in the SNc with the majority of transduced neurons killed after 6 weeks. Transient inflammation was observed in the striatum at 10 days (Dusonchet et al. 2011). Neuroinflammation and behavior were not analyzed in depth.

2.3.3 Parkin (PARK2), PTEN-induced Putative Kinase 1 (PINK1), and DJ-1

These genes are implicated in mitochondrial function, particularly in stress response pathways. PARK2 acts as a regulator of protein breakdown (Miklya et al. 2014). Mutations in the *parkin* gene, which encodes for an E3 ubiquitin ligase, are the leading cause of early-onset, autosomal recessive parkinsonism (Kitada et al. 1998; Hattori et al. 1998; Lücking et al. 2000). Parkin levels in neurons are associated with protection from cellular stress and cell-cycle regulation (Tran et al. 2011).

PINK1 gene mutations represent the second most common cause of autosomal recessive PD. The gene encodes a 581-amino acid protein with a predicted N-terminal mitochondrial targeting sequence and a conserved serine/threonine kinase domain (Valente et al. 2004). More than 40 PINK1 mutations have been identified in PD patients (Corti et al. 2013). The homozygous form of G309D

PINK1 has been linked to mitochondrial dysfunction and peroxidation damage (Hoepken et al. 2007).

Point mutations (L166P, D149A) in DJ-1 cause rare autosomal recessive PD with early onset. DJ-1 is a redox-sensitive cytosolic chaperone protein that associates with mitochondria and the nucleus upon oxidation. Mutations cause a loss of function of DJ-1 by inducing instability of the dimeric, functional form of the protein, or lack of expression. Mutations also affect the serine protease activity of DJ-1, another crucial function of this protein (Alberio et al. 2012).

Cellular and Cytokine Responses

A role for parkin in glial cells with possible neuroinflammatory consequences has been proposed by in vitro studies. Casarejos et al. (2006) discovered that midbrain neurons cultured from parkin KO mice are more sensitive to rotenone and that the addition of parkin KO microglia to WT neurons increased sensitivity to rotenone. Aged parkin KO mice display fewer astrocytes, more microglia, reduced glial proliferation, and increased pro-apoptotic protein expression (Solano et al. 2008). Parkin levels are regulated by inflammatory signaling: LPS and TNF-α down-regulate parkin expression in macrophages, microglia, and neurons from WT mice blocked by inhibitors of nuclear factor-kappa β, and macrophages isolated from parkin KO mice display increased TNF-α, IL-1α, and iNOS mRNA expressions (Tran et al. 2011).

PINK1 stimulates IL-1β-mediated inflammatory signaling via enhanced TRAF6 and TAK1 (Lee et al. 2012a) and IL-1β-mediated signaling through Tollip and IRAK1 modulation (Lee and Chung 2012).

DJ-1 seems to be an important redox-reactive signaling intermediate controlling oxidative stress associated with ischemia, neuroinflammation, and age-related neurodegeneration (Kahle et al. 2009).

In Vivo and Behavioral Features Related to Inflammation

Parkin. Several groups have generated parkin KO mice (Goldberg et al. 2003; Itier et al. 2003; Von Coelln et al. 2004). Initial characterization failed to note nigral DA neuronal death, although abnormal DA metabolism was noted. Interestingly, catecholaminergic neurons in locus coeruleus of mice with parkin catalytic domain deletion degenerated with an accompanying deficit in the startle response (Von Coelln et al. 2004).

Proteomic studies using parkin-null mice showed marked reduction of mitochondrial respiratory chain proteins and stress response proteins, while several parkin substrates (AIMP2, FBP1, and PARIS) accumulate in the ventral midbrain of parkin-null mice (Ko et al. 2005; Shin et al. 2011). These cellular changes may be responsible for subtle deficits in DA metabolism and behavior. MPTP intoxication in parkin-null mice caused a similar level of DA neuronal toxicity as in

WT mice, although parkin overexpression protects against MPTP (Perez et al. 2005; Paterna et al. 2007; Thomas et al. 2007). Lentiviral-Cre nigral injection into adult parkinflox/flox mice causes acute parkin deletion and progressive nigral neuron death 10 months after the gene deletion. This model also showed pathogenic events caused by accumulation of PARIS including PGC1-α downregulation, and ultimately mitochondrial dysfunction (Shin et al. 2011).

PINK1. PINK1-targeted KOs (Kitada et al. 2007; Gispert et al. 2009) and shRNA-mediated knockdown models (Zhou et al. 2007b) did not replicate robust degenerative phenotypes and mitochondrial defects reported in fly models (Clark et al. 2006). Nevertheless, subtle deficits of nigrostriatal DA transmission and accompanying mild mitochondrial abnormalities were observed. One PINK1 KO model shows that a *Oryzias latipes* fish (known as medaka or Japanese rice fish) model deficient in PINK1 and parkin exhibited late-onset locomotor dysfunction, decreased DA levels, selective degeneration of DA neurons, and defects in mitochondrial activity death (Matsui et al. 2013).

DJ-1. LPS produced similar neuroinflammatory responses in of DJ-1-/- mice and WT mice, and the administration of soluble TNF did not appear to induce neuroinflammatory responses in LPS-treated wild-type or DJ-1-/- mice. Peripheral macrophages from WT and DJ-1-/- mice also displayed similar LPS-induced inflammatory and oxidative stress markers in vitro. The authors concluded that DJ-1 does not play a critical role in protecting DA neurons against inflammation-induced oxidative stress and/or there is compensatory gene expression in the midbrain of DJ-1-/- mice that renders them resistant to the cytotoxic effects triggered by peripheral inflammation (Nguyen et al. 2013).

Mice deficient for both parkin and DJ-1 were crossed with mice deficient for glutathione peroxidase 1, which is reduced in PD brains (Damier et al. 1993). These animals showed higher than normal striatal DA levels in the absence of nigral cell loss than wild-type, glutathione peroxidase 1 (-/-), and Parkin (-/-)DJ-1(-/-) mutant mice. Parkin(-/-)DJ-1(-/-) mice exhibit improved rotarod performance and increased serotonin in the striatum and hippocampus (Hennis et al. 2014).

There has been little analysis of the effects neuroinflammation on specific behavioral features for the genetic models of Parkin, PINK1, or DJ-1.

3 Discussion

3.1 Toxin-based Models

Parkinsonism in patients may develop after exposure to neurotoxins over decades, a feature that cannot be replicated in useable animal models (Nagatsu 1997). Traditional animal models of PD rather rely on toxins that selectively accumulate in SN DA neurons. The extent to which they effectively and reproducibly mimic the entirety of the human condition is controversial. As neurotoxin-induced models of

PD use a single or few injections over a short period and are followed by rapid onset of symptoms, their applicability for studying chronic neuroinflammation is limited (Potashkin et al. 2011) and these models may be best at emulating very late stages of the disease when neurons have died rather than the steps that cause neuronal death.

There is nevertheless clear evidence of neuroinflammation following injection of each commonly used neurotoxin to emulate PD, including MPTP, 6-OHDA, rotenone, and paraquat. While these compounds can cause acute parkinsonism in patients, they each appear to destroy DA neurons in manners different than PD and are likely to trigger stress responses including cytokine release and activation of glial cell types that do not resemble genuine PD. Importantly, each of these toxins are also quite effective at killing cultured DA neurons rapidly in the absence of neuroinflammatory cell types. It may be that the acute toxic effects of these compounds indicate inflammatory responses due to generalized stress responses and do not reveal steps that participate in the loss of neurons in PD.

3.2 Inflammatory Models

Neuroinflammation has been increasingly associated with the development of PD, but a direct cause–effect relationship has not been formally established for bacterial or viral infection-induced development of PD in humans. While inflammatory models, especially LPS, are potent stimulators of microglia and have introduced possible roles for inflammation-mediated DA neurodegeneration, these may not model valid pathogenic steps of the genuine disease. They may, however, provide useful insights into combinatorial models that emulate "multiple hits" that may better model the disorder.

3.3 Genetic Models

Although the majority of PD remains sporadic, specific genetic defects in rare familial cases have provided unique insights into the pathogenesis of PD. Models using PD pathogenic mutations seem more likely to reveal immunological responses involved in pathogenesis. These models, however, have mostly been disappointing in that they do not replicate degenerative features PD, including death of the analogous neuronal populations, and so their use is limited to date.

Our recent work suggests that antigen presentation to T cells might be involved in neuronal death in PD (Cebrián et al. 2014), consistent with studies suggesting that MHC molecules play a role in PD animal models where α-syn is overexpressed by viral transduction (Harms et al. 2013). As treatments that interact with specific T-cell populations already exist for immunological disorders such as multiple sclerosis, perhaps such therapies could be successfully extended to treat PD.

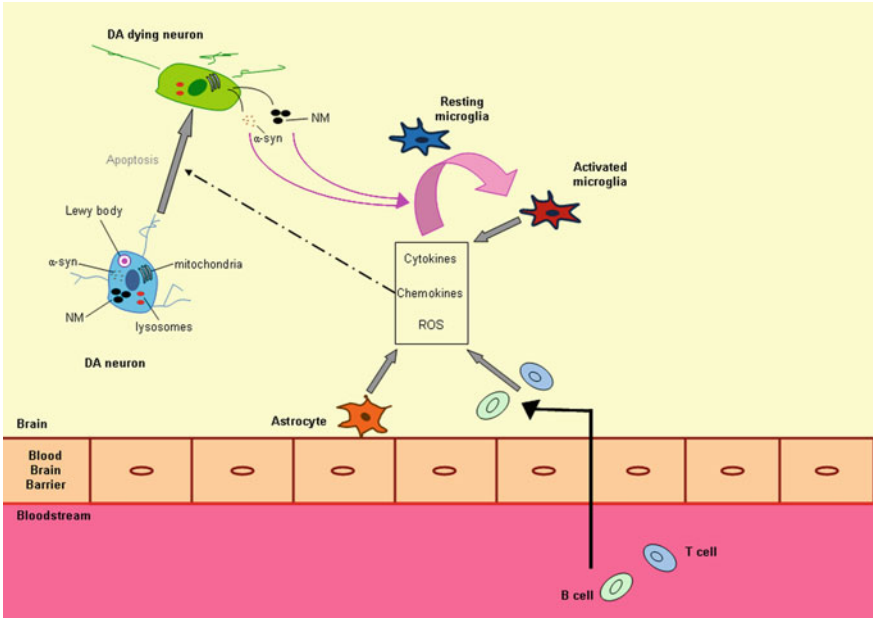

Fig. 1 A neuroinflammatory vicious cycle that may take place in PD. Lymphocytes cross the BBB and penetrate the brain, where they release a variety of proinflammatory factors including cytokines, chemokines, and ROS. Activated glia including astrocytes and microglia also release these substances, which may trigger the cell death of DA neuron through a variety of mechanisms discussed throughout the review. The resulting dying DA neurons produce extracellular α-syn and NM, which in turn further activates astrocytes and microglia, resulting in further tropic signaling for local inflammatory invasion and proliferation, thus providing an ongoing cycle of neurodegeneration.

Alternate approaches including viral-mediated expression of pathogenic mutations, direct injection of disease proteins, or combinatorial genetic and inflammatory substance treatments appear promising and may better characterize the roles of neuroimmune responses.

4 Conclusion

We leave the question posed in our title unanswered: while evidence for nearly a century clearly indicates that neuroinflammation is prominent during PD progression, and many studies show that manipulating inflammatory steps can alter progression in a variety of animal models of PD (Fig. 1; Tufekci et al. 2012; Blandini 2013), it remains unclear which if any steps are required for pathogenesis, or which are stress response mechanisms that provide neuroprotection. Of course, a particular inflammatory cascade could play both roles.

In our opinion, the most fruitful avenue to elucidate these roles is to develop improved PD models that better emulate pathogenesis. Models using PD genetic mutations including viral-mediated expression are to date poor at emulating central features of the PD, such as death of the neurons in the SN, but this technology is still relatively new and improved models will doubtless arrive. In the meantime, combinatorial efforts, such as the combination of an infective agent with mutations, appear promising.

We think that the field needs to keep in focus the genuine complexity of PD. There are now nearly 20 genetic "causes" of PD, and still most patients do not express these mutations, meaning that there is syndrome with multiple etiologies. There are further multiple "hits" that must occur, including aging which features a long list of alterations in protein and organelle turnover; factors that make particular neurons susceptible, likely including pacemaking activity and long axons; a particular targeting of monoaminergic and some cholinergic neurons; and in nearly all cases a synucleinopathy indicating the aggregation of a particular protein, in addition to inflammatory responses. The hopeful news about the requirement of multiple hits in PD pathogenesis is that there may be multiple means to interfere with disease progression.

References

Abeliovich A, Schmitz Y, Fariñas I et al (2000) Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. Neuron 25(1):239–252

Akiyama H, McGeer PL (1989) Microglial response to 6-hydroxydopamine-induced substantia nigra lesions. Brain Res 489(2):247–253

Alberio T, Lopiano L and Fasano M (2012) Cellular models to investigate biochemical pathways in Parkinson's disease. FEBS J279. doi:10.1111/j.1742-4658.2012.08516.x

Ambrosi G, Armentero MT, Levandis G et al (2010) Effects of early and delayed treatment with an mGluR5 antagonist on motor impairment, nigrostriatal damage and neuroinflammation in a rodent model of Parkinson's disease. Brain Res Bull 82(1–2):29–38

Armentero MT, Levandis G, Nappi G et al (2006) Peripheral inflammation and neuroprotection: systemic pretreatment with complete Freund's adjuvant reduces 6-hydroxydopamine toxicity in a rodent model of Parkinson's disease. Neurobiol Dis 24(3):492–505

Baldereschi M, Inzitari M, Vanni P et al (2008) Pesticide exposure might be a strong risk factor for Parkinson's disease. Ann Neurol 63(1):128

Barcia C, Ros CM, Annese V et al (2011) IFN-γ signaling, with the synergistic contribution of TNF-α, mediates cell specific microglial and astroglial activation in experimental models of Parkinson's disease. Cell Death Dis 2:e142

Barkholt P, Sanchez-Guajardo V, Kirik D et al (2012) Long-term polarization of microglia upon α-synuclein overexpression in nonhuman primates. Neuroscience 208:85–96

Barnum CJ, Tansey MG (2010) Modeling neuroinflammatory pathogenesis of Parkinson's disease. Prog Brain Res 184:113–132

Betarbet R, Sherer TB, MacKenzie G et al (2000) Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nat Neurosci 3(12):1301–1306

Bichler Z, Lim HC, Zeng L, Tan EK (2013) Non-motor and motor features in LRRK2 transgenic mice. PLoS One 8(7):e70249

Biskup S, Moore DJ, Celsi F et al (2006) Localization of LRRK2 to membranous and vesicular structures in mammalian brain. Ann Neurol 60(5):557–569

Blandini F (2013) Neural and immune mechanisms in the pathogenesis of Parkinson's disease. Funct Neurol 28(1):5

Bobyn J, Mangano EN, Gandhi A et al (2012) Viral-toxin interactions and Parkinson's disease: poly I: C priming enhanced the neurodegenerative effects of paraquat. J Neuroinflammation 9:86

Bové J, Perier C (2012) Neurotoxin-based models of Parkinson's disease. Neuroscience 211:51–76

Braak H, Del Tredici K (2010) Pathophysiology of sporadic Parkinson's disease. Fortschr Neurol Psychiatr 78(Suppl 1):2–4

Brochard V, Combadière B, Prigent A et al (2009) Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. J Clin Invest 119 (1):182–192

Bronstein DM, Perez-Otano I, Sun V et al (1995) Glia-dependent neurotoxicity and neuroprotection in mesencephalic cultures. Brain Res 704(1):112–116

Bungeroth M, Appenzeller S, Regulin A, Völker W et al (2014) Differential aggregation properties of alpha-synuclein isoforms. Neurobiol Aging S0197–4580(14):00201–00202

Carvey PM, Chang Q, Lipton JW et al (2003) Prenatal exposure to the bacteriotoxin lipopolysaccharide leads to long-term losses of dopamine neurons in offspring: a potential, new model of Parkinson's disease. Front Biosci 8:826–837

Casarejos MJ, Menéndez J, Solano RM et al (2006) Susceptibility to rotenone is increased in neurons from parkin null mice and is reduced by minocycline. J Neurochem 97(4):934–946

Castaño A, Herrera AJ, Cano J et al (1998) Lipopolysaccharide intranigral injection induces inflammatory reaction and damage in nigrostriatal dopaminergic system. J Neurochem 70 (4):1584–1592

Castaño A, Herrera AJ, Cano J et al (2002) The degenerative effect of a single intranigral injection of LPS on the dopaminergic system is prevented by dexamethasone, and not mimicked by rh-TNF-alpha, IL-1beta and IFN-gamma. J Neurochem 81(1):150–157

Cebrián C, Zucca FA, Mauri P et al (2014) MHC-I expression renders catecholaminergic neurons susceptible to T-cell-mediated degeneration. Nat Commun 16(5):3633

Chesselet MF (2008) In vivo alpha-synuclein overexpression in rodents: a useful model of Parkinson's disease? Exp Neurol 209(1):22–27

Choi DY, Liu M, Hunter RL et al (2009) Striatal neuroinflammation promotes Parkinsonism in rats. PLoS One 4(5):e5482

Chung YC, Kim SR, Jin BK (2010) Paroxetine prevents loss of nigrostriatal dopaminergic neurons by inhibiting brain inflammation and oxidative stress in an experimental model of Parkinson's disease. J Immunol 185(2):1230–1237

Cicchetti F, Brownell AL, Williams K et al (2002) Neuroinflammation of the nigrostriatal pathway during progressive 6-OHDA dopamine degeneration in rats monitored by immunohistochemistry and PET imaging. Eur J Neurosci 15(6):991–998

Cicchetti F, Drouin-Ouellet J, Gross RE (2009) Environmental toxins and Parkinson's disease: what have we learned from pesticide-induced animal models? Trends Pharmacol Sci 30 (9):475–483

Cicchetti F, Lapointe N, Roberge-Tremblay A et al (2005) Systemic exposure to paraquat and maneb models early Parkinson's disease in young adult rats. Neurobiol Dis 20(2):360–371

Clark IE, Dodson MW, Jiang C et al (2006) Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. Nature 441:1162–1166

Collins LM, Toulouse A, Connor TJ et al (2012) Contributions of central and systemic inflammation to the pathophysiology of Parkinson's disease. Neuropharmacology 62 (7):2154–2168

Conway KA, Harper JD, Lansbury PT Jr (2000a) Fibrils formed in vitro from alpha-synuclein and two mutant forms linked to Parkinson's disease are typical amyloid. Biochemistry 39 (10):2552–2563

Conway KA, Lee SJ, Rochet JC et al (2000b) Acceleration of oligomerization, not fibrillization, is a shared property of both alpha-synuclein mutations linked to early-onset Parkinson's disease: implications for pathogenesis and therapy. Proc Natl Acad Sci USA 97(2):571–576

Correia Guedes L, Ferreira JJ, Rosa MM et al (2010) Worldwide frequency of G2019S LRRK2 mutation in Parkinson's disease: a systematic review. Parkinsonism Relat Disord 16 (4):237–242

Corti O, Brice A (2013) Mitochondrial quality control turns out to be the principal suspect in parkin and PINK1-related autosomal recessive Parkinson's disease. Curr Opin Neurobiol 23:100–108

Couch Y, Alvarez-Erviti L, Sibson NR et al (2011) The acute inflammatory response to intranigral α-synuclein differs significantly from intranigral lipopolysaccharide and is exacerbated by peripheral inflammation. J Neuroinflammation 8:166

Cuervo AM, Stefanis L, Fredenburg R et al (2004) Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy. Science 305(5688):1292–1295

Członkowska A, Kohutnicka M, Kurkowska-Jastrzebska I et al (1996) Microglial reaction in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced Parkinson's disease mice model. Neurodegeneration 5(2):137–143

Daher JP, Volpicelli-Daley LA1, Blackburn JP et al (2014) Abrogation of α-synuclein-mediated dopaminergic neurodegeneration in LRRK2-deficient rats. Proc Natl Acad Sci USA (in press)

Damier P, Hirsch EC, Zhang P et al (1993) Glutathione peroxidase, glial cells and Parkinson's disease. Neuroscience 52(1):1–6

Danoy P, Pryce K, Hadler J et al (2010) Association of variants at 1q32 and STAT3 with ankylosing spondylitis suggests genetic overlap with Crohn's disease. PLoS Genet 6(12): e1001195

Dauer W, Kholodilov N, Vila M et al (2002) Resistance of alpha-synuclein null mice to the parkinsonian neurotoxin MPTP. Proc Natl Acad Sci USA 99(22):14524–14529

Davis GC, Williams AC, Markey SP et al (1979) Chronic Parkinsonism secondary to intravenous injection of meperidine analogues. Psychiatry Res 1(3):249–254

Dawson TM, Ko HS, Dawson VL (2010) Genetic animal models of Parkinson's disease. Neuron 66(5):646–661

de Meira Santos Lima M, Braga Reksidler A, Marques Zanata S et al (2006) Different parkinsonism models produce a time-dependent induction of COX-2 in the substantia nigra of rats. Brain Res 1101(1):117–125

De Pablos RM, Herrera AJ, Villarán RF et al (2005) Dopamine-dependent neurotoxicity of lipopolysaccharide in substantia nigra. FASEB J 19(3):407–409

Del Tredici K, Braak H (2012) Lewy pathology and neurodegeneration in premotor Parkinson's disease. Mov Disord 27(5):597–607

Deleidi M, Hallett PJ, Koprich JB et al (2010) The Toll-like receptor-3 agonist polyinosinic: polycytidylic acid triggers nigrostriatal dopaminergic degeneration. J Neurosci 30 (48):16091–16101

Deng H, Yuan L (2014) Genetic variants and animal models in SNCA and Parkinson disease. Ageing Res Rev. 2014 Apr 21. pii: S1568–1637(14):00048–8

Desai VG, Feuers RJ, Hart RW et al (1996) MPP(+)-induced neurotoxicity in mouse is age-dependent: evidenced by the selective inhibition of complexes of electron transport. Brain Res 715(1–2):1–8

Drolet RE, Sanders JM, Kern JT (2011) Leucine-rich repeat kinase 2 (LRRK2) cellular biology: a review of recent advances in identifying physiological substrates and cellular functions. J Neurogenet 25(4):140–151

Dusonchet J, Kochubey O, Stafa K et al (2011) A rat model of progressive nigral neurodegeneration induced by the Parkinson's disease-associated G2019S mutation in LRRK2. J Neurosci 31(3):907–912

Dutta G, Zhang P, Liu B (2008) The lipopolysaccharide Parkinson's disease animal model: mechanistic studies and drug discovery. Fundam Clin Pharmacol 22(5):453–464

Dzamko N, Inesta-Vaquera F, Zhang J et al (2012) The IkappaB kinase family phosphorylates the Parkinson's disease kinase LRRK2 at Ser935 and Ser910 during Toll-like receptor signaling. PLoS One 7(6):e39132

Emmer KL, Waxman EA, Covy JP et al (2011) E46K human alpha-synuclein transgenic mice develop Lewy-like and tau pathology associated with age-dependent, detrimental motor impairment. J Biol Chem 286(40):35104–35118

Engelhardt B, Coisne C (2011) Fluids and barriers of the CNS establish immune privilege by confining immune surveillance to a two-walled castle moat surrounding the CNS castle. Fluids Barriers CNS 8(1):4

Eslamboli A, Romero-Ramos M, Burger C, Bjorklund T et al (2007) Long-term consequences of human alpha-synuclein overexpression in the primate ventral midbrain. Brain 130(Pt 3):799–815

Esposito E, Impellizzeri D, Mazzon E et al (2012) Neuroprotective activities of palmitoylethanolamide in an animal model of Parkinson's disease. PLoS One 7(8):e41880

Fang F, Wirdefeldt K, Jacks A et al (2012) CNS infections, sepsis and risk of Parkinson's disease. Int J Epidemiol 41(4):1042–1049

Fleming SM, Salcedo J, Fernagut PO et al (2004) Early and progressive sensorimotor anomalies in mice overexpressing wild-type human alpha-synuclein. J Neurosci 24(42):9434–9440

Foix C, Nicolesco J (1925) Anatomie cérébrale. Les noyaux gris centraux et la región Mésencéphalo-sous-optique., Suivi d'un apéndice sur l'anatomie pathologique de la maladie de Parkinson. Masson et Cie, eds (Paris), 508–538

Fortin DL, Nemani VM, Voglmaier SM et al (2005) Neural activity controls the synaptic accumulation of alpha-synuclein. J Neurosci 25(47):10913–10921

Franzén B, Duvefelt K, Jonsson C, Engelhardt B et al (2003) Gene and protein expression profiling of human cerebral endothelial cells activated with tumor necrosis factor-alpha. Brain Res Mol Brain Res 115(2):130–146

Frank-Cannon TC, Alto LT, McAlpine FE et al (2009) Does neuroinflammation fan the flame in neurodegenerative diseases? Mol Neurodegener 16(4):47

Frank-Cannon TC, Tran T, Ruhn KA et al (2008) Parkin deficiency increases vulnerability to inflammation-related nigral degeneration. J Neurosci 28(43):10825–10834

Fulceri F, Biagioni F, Lenzi P et al (2006) Nigrostriatal damage with 6-OHDA: validation of routinely applied procedures. Ann N Y Acad Sci 1074:344–348

Gao JJ, Diesl V, Wittmann T et al (2002a) Regulation of gene expression in mouse macrophages stimulated with bacterial CpG-DNA and lipopolysaccharide. J Leukoc Biol 72(6):1234–1245

Gao HM, Hong JS, Zhang W et al (2002b) Distinct role for microglia in rotenone-induced degeneration of dopaminergic neurons. J Neurosci 22(3):782–790

Gao HM, Kotzbauer PT, Uryu K et al (2008) Neuroinflammation and oxidation/nitration of alpha-synuclein linked to dopaminergic neurodegeneration. J Neurosci 28(30):7687–7698

Gao HM, Liu B, Hong JS (2003) Critical role for microglial NADPH oxidase in rotenone-induced degeneration of dopaminergic neurons. J Neurosci 23(15):6181–6187

Gao HM, Zhang F, Zhou H et al (2011) Neuroinflammation and α-synuclein dysfunction potentiate each other, driving chronic progression of neurodegeneration in a mouse model of Parkinson's disease. Environ Health Perspect 119(6):807–814

Gardet A, Benita Y, Li C et al (2010) LRRK2 is involved in the IFN-gamma response and host response to pathogens. J Immunol 185(9):5577–5585

Gayle DA, Ling Z, Tong C et al (2002) Lipopolysaccharide (LPS)-induced dopamine cell loss in culture: roles of tumor necrosis factor-alpha, interleukin-1beta, and nitric oxide. Brain Res Dev Brain Res 133(1):27–35

Geng Y, Fang M, Wang J et al (2011) Triptolide down-regulates COX-2 expression and PGE2 release by suppressing the activity of NF-κB and MAP kinases in lipopolysaccharide-treated PC12 cells. Phytother Res 26(3):337–343

George S, van den Buuse M, San Mok S, Masters CL et al (2008) Alpha-synuclein transgenic mice exhibit reduced anxiety-like behaviour. Exp Neurol 210(2):788–792

Ghosh A, Kanthasamy A, Joseph J et al (2012) Anti-inflammatory and neuroprotective effects of an orally active apocynin derivative in pre-clinical models of Parkinson's disease. J Neuroinflammation 9:241

Giasson BI, Duda JE, Quinn SM et al (2002) Neuronal alpha-synucleinopathy with severe movement disorder in mice expressing A53T human alpha-synuclein. Neuron 34(4):521–533

Gillardon F, Schmid R, Draheim H (2012) Parkinson's disease-linked leucine-rich repeat kinase 2 (R1441G) mutation increases proinflammatory cytokine release from activated primary microglial cells and resultant neurotoxicity. Neuroscience 208:41–48

Gispert S, Ricciardi F, Kurz A et al (2009) Parkinson phenotype in aged PINK1-deficient mice is accompanied by progressive mitochondrial dysfunction in absence of neurodegeneration. PloS ONE 4:e5777

Glinka Y, Gassen M, Youdim MB (1997) Mechanism of 6-hydroxydopamine neurotoxicity. J Neural Transm Suppl 50:55–66

Goes AT, Souza LC, Filho CB et al (2014) Neuroprotective effects of swimming training in a mouse model of Parkinson's disease induced by 6-hydroxydopamine. Neuroscience 256C:61–71

Goldberg MS, Fleming SM, Palacino JJ et al (2003) Parkin-deficient mice exhibit nigrostriatal deficits but not loss of dopaminergic neurons. J Biol Chem 278:43628–43635

Gombash SE, Manfredsson FP, Kemp CJ et al (2013) Morphological and behavioral impact of AAV2/5-mediated overexpression of human wildtype alpha-synuclein in the rat nigrostriatal system. PLoS One 8(11):e81426

Gomez-Isla T, Irizarry MC, Mariash A, Cheung B et al (2003) Motor dysfunction and gliosis with preserved dopaminergic markers in human alpha-synuclein A30P transgenic mice. Neurobiol Aging 24(2):245–258

Gomide V, Bibancos T, Chadi G (2005) Dopamine cell morphology and glial cell hypertrophy and process branching in the nigrostriatal system after striatal 6-OHDA analyzed by specific sterological tools. Int J Neurosci 115(4):557–582

González H, Contreras F, Prado C, Elgueta D et al (2013) Dopamine receptor D3 expressed on CD4+ T cells favors neurodegeneration of dopaminergic neurons during Parkinson's disease. J Immunol 190(10):5048–5056

Graham DR, Sidhu A (2010) Mice expressing the A53T mutant form of human alpha-synuclein exhibit hyperactivity and reduced anxiety-like behavior. J Neurosci Res 88 (8):1777–1783

Greggio E, Jain S, Kingsbury A et al (2006) Kinase activity is required for the toxic effects of mutant LRRK2/dardarin. Neurobiol Dis 23(2):329–341

Grünblatt E, Mandel S, Maor G et al (2001) Gene expression analysis in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mice model of Parkinson's disease using cDNA microarray: effect of R-apomorphine. J Neurochem 78(1):1–12

Guo JL, Covell DJ, Daniels JP et al (2013) Distinct α-synuclein strains differentially promote tau inclusions in neurons. Cell 154(1):103–117

Gupta A, Kumar A, Kulkarni SK (2011) Targeting oxidative stress, mitochondrial dysfunction and neuroinflammatory signaling by selective cyclooxygenase (COX)-2 inhibitors mitigates MPTP-induced neurotoxicity in mice. Prog Neuropsychopharmacol Biol Psychiatry 35 (4):974–981

Gupta SP, Patel S, Yadav S et al (2010) Involvement of nitric oxide in maneb- and paraquat-induced Parkinson's disease phenotype in mouse: is there any link with lipid peroxidation? Neurochem Res 35(8):1206–1213

Hancock DB, Martin ER, Mayhew GM et al (2008) Pesticide exposure and risk of Parkinson's disease: a family-based case-control study. BMC Neurol 8:6. doi:10.1186/1471-2377-8-6

Harkavyi A, Abuirmeileh A, Lever R et al (2008) Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease. J Neuroinflammation 5:19

Harms AS, Barnum CJ, Ruhn KA et al (2011) Delayed dominant-negative TNF gene therapy halts progressive loss of nigral dopaminergic neurons in a rat model of Parkinson's disease. Mol Ther 19(1):46–52

Harms AS, Cao S, Rowse AL et al (2013) MHCII is required for α-synuclein-induced activation of microglia, CD4 T cell proliferation, and dopaminergic neurodegeneration. J Neurosci 33 (23):9592–9600

Hattori N, Kitada T, Matsumine H et al (1998) Molecular genetic analysis of a novel Parkin gene in Japanese families with autosomal recessive juvenile parkinsonism: evidence for variable homozygous deletions in the Parkin gene in affected individuals. Ann Neurol 44(6):935–941

He Y, Appel S, Le W (2001) Minocycline inhibits microglial activation and protects nigral cells after 6-hydroxydopamine injection into mouse striatum. Brain Res 909(1–2):187–193

Healy DG, Falchi M, O'Sullivan SS et al (2008) Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol 7 (7):583–590

Hennis MR, Marvin MA, Taylor CM, Goldberg MS (2014) Surprising behavioral and neurochemical enhancements in mice with combined mutations linked to Parkinson's disease. Neurobiol Dis 62:113–123

Henry J, Smeyne RJ, Jang H et al (2010) Parkinsonism and neurological manifestations of influenza throughout the 20th and 21st centuries. Parkinsonism Relat Disord 16(9):566–571

Hernández-Romero MC, Argüelles S, Villarán RF et al (2008) Simvastatin prevents the inflammatory process and the dopaminergic degeneration induced by the intranigral injection of lipopolysaccharide. J Neurochem 105(2):445–459

Herva ME, Zibaee S, Fraser G, Barker RA et al (2014) Anti-amyloid compounds inhibit alpha-synuclein aggregation induced by Protein Misfolding Cyclic Amplification (PMCA). J Biol Chem (in press)

Hinkle KM, Yue M, Behrouz B et al (2012) LRRK2 knockout mice have an intact dopaminergic system but display alterations in exploratory and motor co-ordination behaviors. Mol Neurodegener 7:25

Hirsch EC, Hunot S (2009) Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol 8(4):382–397

Hoban DB, Connaughton E, Connaughton C et al (2013) Further characterisation of the LPS model of Parkinson's disease: a comparison of intra-nigral and intra-striatal lipopolysaccharide administration on motor function, microgliosis and nigrostriatal neurodegeneration in the rat. Brain Behav Immun 27(1):91–100

Hoepken HH, Gispert S, Morales B et al (2007) Mitochondrial dysfunction, peroxidation damage and changes in glutathione metabolism in PARK6. Neurobiol Dis 25:401–411

Hunter RL, Cheng B, Choi DY et al (2009) Intrastriatal lipopolysaccharide injection induces parkinsonism in C57/B6 mice. J Neurosci Res 87(8):1913–1921

Iravani MM, Leung CC, Sadeghian M et al (2005) The acute and the long-term effects of nigral lipopolysaccharide administration on dopaminergic dysfunction and glial cell activation. Eur J Neurosci 22(2):317–330

Itier JM, Ibanez P, Mena MA et al (2003) Parkin gene inactivation alters behaviour and dopamine neurotransmission in the mouse. Hum Mol Genet 12:2277–2291

Izumi Y, Ezumi M, Takada-Takatori Y, Akaike A et al (2014) Endogenous dopamine is involved in the herbicide paraquat-induced dopaminergic cell death. Toxicol Sci (in press)

Janezic S, Threlfell S, Dodson PD, Dowie MJ et al (2013) Deficits in dopaminergic transmission precede neuron loss and dysfunction in a new Parkinson model. Proc Natl Acad Sci USA 110 (42):E4016–E4025

Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 79(4):368–376

Johnston LC, Su X, Maguire-Zeiss K et al (2008) Human interleukin-10 gene transfer is protective in a rat model of Parkinson's disease. Mol Ther 16(8):1392–1399

Jung BD, Shin EJ, Nguyen XK et al (2010) Potentiation of methamphetamine neurotoxicity by intrastriatal lipopolysaccharide administration. Neurochem Int 56(2):229–244

Kahle PJ, Waak J, Gasser T (2009) DJ-1 and prevention of oxidative stress in Parkinson's disease and other age-related disorders. Free Radic Biol Med 47(10):1354–1361

Kamel F, Tanner C, Umbach D et al (2007) Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. Am J Epidemiol 165(4):364–374

Kasten M, Klein C (2013) The many faces of alpha-synuclein mutations. Mov Disord 28 (6):697–701

Kim B, Yang MS, Choi D et al (2012) Impaired inflammatory responses in murine Lrrk2-knockdown brain microglia. PLoS One 7(4):e34693

Kirik D, Annett LE, Burger C et al (2003) Nigrostriatal alpha-synucleinopathy induced by viral vector-mediated overexpression of human alpha-synuclein: a new primate model of Parkinson's disease. Proc Natl Acad Sci USA 100(5):2884–2889

Kirik D, Rosenblad C, Burger C et al (2002) Parkinson-like neurodegeneration induced by targeted overexpression of alpha-synuclein in the nigrostriatal system. J Neurosci 22(7):2780–2791

Kitada T, Asakawa S, Hattori N et al (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392(6676):605–608

Kitada T, Pisani A, Porter DR et al (2007) Impaired dopamine release and synaptic plasticity in the striatum of PINK1-deficient mice. Proc Natl Acad Sci 104:11441–11446

Klementiev B, Li S, Korshunova I et al (2014) Anti-inflammatory properties of a novel peptide interleukin 1 receptor antagonist. J Neuroinflammation 11:27

Klintworth H, Garden G, Xia Z (2009) Rotenone and paraquat do not directly activate microglia or induce inflammatory cytokine release. Neurosci Lett 462(1):1–5

Ko HS, von Coelln R, Sriram SR et al (2005) Accumulation of the authentic parkin substrate aminoacyl-tRNA synthetase cofactor, pp38/JTV-1, leads to catecholaminergic cell death. J Neurosci 25:7968–7978

Kopin IJ (1987) MPTP: an industrial chemical and contaminant of illicit narcotics stimulates a new era in research on Parkinson's disease. Environ Health Perspect 75:45–51

Koprich JB, Reske-Nielsen C, Mithal P et al (2008) Neuroinflammation mediated by IL-1beta increases susceptibility of dopamine neurons to degeneration in an animal model of Parkinson's disease. J Neuroinflammation 5:8

Kortekaas R, Leenders KL, van Oostrom JC et al (2005) Blood-brain barrier dysfunction in parkinsonian midbrain in vivo. Ann Neurol 57(2):176–179

Krüger R, Kuhn W, Müller T et al (1998) Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Ann Neurol 18(2):106–108

Kunikowska G, Jenner P (2001) 6-Hydroxydopamine-lesioning of the nigrostriatal pathway in rats alters basal ganglia mRNA for copper, zinc- and manganese-superoxide dismutase, but not glutathione peroxidase. Brain Res 922(1):51–64

Kurkowska-Jastrzebska I, Wrońska A, Kohutnicka M et al (1999) The inflammatory reaction following 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine intoxication in mouse. Exp Neurol 156(1):50–61

L'Episcopo F, Tirolo C, Caniglia S et al (2010) Combining nitric oxide release with anti-inflammatory activity preserves nigrostriatal dopaminergic innervation and prevents motor impairment in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. J Neuroinflammation. 7:83

L'Episcopo F, Tirolo C, Testa N et al (2011) Switching the microglial harmful phenotype promotes lifelong restoration of subtantia nigra dopaminergic neurons from inflammatory neurodegeneration in aged mice. Rejuvenation Res 14(4):411–424

Langston JW, Forno LS, Tetrud J et al (1999) Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure. Ann Neurol 46(4):598–605

Larsen KE, Schmitz Y, Troyer MD et al (2006) Alpha-synuclein overexpression in PC12 and chromaffin cells impairs catecholamine release by interfering with a late step in exocytosis. J Neurosci 26(46):11915–11922

Lee HJ, Chung KC (2012) PINK1 positively regulates IL-1β-mediated signaling through Tollip and IRAK1 modulation. J Neuroinflammation 9:271

Lee HJ, Jang SH, Kim H et al (2012a) PINK1 stimulates interleukin-1β-mediated inflammatory signaling via the positive regulation of TRAF6 and TAK1. Cell Mol Life Sci 69 (19):3301–3315

Lee BD, Shin JH, VanKampen J et al (2010) Inhibitors of leucine-rich repeat kinase-2 protect against models of Parkinson's disease. Nat Med 16(9):998–1000

Lee MK, Stirling W, Xu Y et al (2002) Human alpha-synuclein-harboring familial Parkinson's disease-linked Ala-53 –> Thr mutation causes neurodegenerative disease with alpha-synuclein aggregation in transgenic mice. Proc Natl Acad Sci U S A. 99(13):8968–8973

Lee JK, Tran T, Tansey MG (2009) Neuroinflammation in Parkinson's disease. J Neuroimmune Pharmacol 4(4):419–429

Lee KW, Zhao X, Im JY et al (2012b) Apoptosis signal-regulating kinase 1 mediates MPTP toxicity and regulates glial activation. PLoS One 7(1):e29935

Li Z, Arnaud L, Rockwell P et al (2004) A single amino acid substitution in a proteasome subunit triggers aggregation of ubiquitinated proteins in stressed neuronal cells. J Neurochem 90 (1):19–28

Li M, Dai FR, Du XP et al (2012) Neuroprotection by silencing Inos expression in a 6-OHDA model of Parkinson's disease. J Mol Neurosci 48(1):225–233

Li X, Moore DJ, Xiong Y et al (2010a) Reevaluation of phosphorylation sites in the Parkinson disease-associated leucine-rich repeat kinase 2. J Biol Chem 285(38):29569–29576

Li X, Patel JC, Wang J et al (2010b) Enhanced striatal dopamine transmission and motor performance with LRRK2 overexpression in mice is eliminated by familial Parkinson's disease mutation G2019S. J Neurosci 30(5):1788–1797

Lin X, Parisiadou L, Sgobio C et al (2012) Conditional expression of Parkinson's disease-related mutant α-synuclein in the midbrain dopaminergic neurons causes progressive neurodegeneration and degradation of transcription factor nuclear receptor related 1. J Neurosci 32 (27):9248–9264

Ling ZD, Chang Q, Lipton JW et al (2004) Combined toxicity of prenatal bacterial endotoxin exposure and postnatal 6-hydroxydopamine in the adult rat midbrain. Neuroscience 124 (3):619–628

Liou HH, Chen RC, Tsai YF (1996) Effects of paraquat on the substantia nigra of the Wistar rats: neurochemical, histological, and behavioral studies. Toxicol Appl Pharmacol 137(1):34–41

Liu M, Bing G (2011) Lipopolysaccharide animal models for Parkinson's disease. Parkinsons Dis 2011:327089

Liu J, Guo YM, Hirokawa M et al (2012) A synthetic double-stranded RNA, poly I:C, induces a rapid apoptosis of human CD34(+) cells. Exp Hematol 40(4):330–341

Liu J, Wang MW, Gu P et al (2010) Microglial activation and age-related dopaminergic neurodegeneration in MPTP-treated SAMP8 mice. Brain Res 1345:213–220

Lücking CB, Dürr A, Bonifati V et al (2000) Association between early-onset Parkinson's disease and mutations in the parkin gene. N Engl J Med 342(21):1560–1567

Luk KC, Kehm V, Carroll J et al (2012a) Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science 338(6109):949–953

Luk KC, Kehm VM, Zhang B et al (2012b) Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice. J Exp Med 209(5):975–986

Machado A, Herrera AJ, Venero JL et al (2011) Inflammatory animal model for Parkinson's disease: the intranigral injection of LPS induced the inflammatory process along with the selective degeneration of nigrostriatal dopaminergic neurons. ISRN Neurol 2011:476158

Maekawa T, Mori S, Sasaki Y et al (2012) The I2020T Leucine-rich repeat kinase 2 transgenic mouse exhibits impaired locomotive ability accompanied by dopaminergic neuron abnormalities. Mol Neurodegener 7:15

Mangano EN, Litteljohn D, So R et al (2012) Interferon-γ plays a role in paraquat-induced neurodegeneration involving oxidative and proinflammatory pathways. Neurobiol Aging 33 (7):1411–1426

Manning-Bog AB, McCormack AL, Li J et al (2002) The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein. J Biol Chem 277 (3):1641–1644

Marinova-Mutafchieva L, Sadeghian M, Broom L et al (2009) Relationship between microglial activation and dopaminergic neuronal loss in the substantia nigra: a time course study in a 6-hydroxydopamine model of Parkinson's disease. J Neurochem 110(3):966–975

Martin LJ, Pan Y, Price AC et al (2006) Parkinson's disease alpha-synuclein transgenic mice develop neuronal mitochondrial degeneration and cell death. J Neurosci 26(1):41–50

Masliah E, Rockenstein E, Veinbergs I et al (2000) Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. Science 287 (5456):1265–1269

Masuda-Suzukake M, Nonaka T, Hosokawa M, Oikawa T et al (2013) Prion-like spreading of pathological α-synuclein in brain. Brain 136(Pt 4):1128–1138

Matsui H, Gavinio R, Asano T et al (2013) PINK1 and Parkin complementarily protect dopaminergic neurons in vertebrates. Hum Mol Genet 22(12):2423–2434

Mazzio EA, Reams RR, Soliman KF (2004) The role of oxidative stress, impaired glycolysis and mitochondrial respiratory redox failure in the cytotoxic effects of 6-hydroxydopamine in vitro. Brain Res 1–2:24–29

McClain JA, Phillips LL, Fillmore HL et al (2009) Increased MMP-3 and CTGF expression during lipopolysaccharide-induced dopaminergic neurodegeneration. Neurosci Lett 460(1):27–31

McCoy MK, Martinez TN, Ruhn KA et al (2006) Blocking soluble tumor necrosis factor signaling with dominant-negative tumor necrosis factor inhibitor attenuates loss of dopaminergic neurons in models of Parkinson's disease. J Neurosci 26(37):9365–9375

McCoy MK, Tansey MG (2008) TNF signaling inhibition in the CNS: implications for normal brain function and neurodegenerative disease. J Neuroinflammation 5:45

McGeer PL, Itagaki S, Boyes BE et al (1988) Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 38(8):1285–1291

McGeer PL, McGeer EG (1998) Glial cell reactions in neurodegenerative diseases: pathophysiology and therapeutic interventions. Alzheimer Dis Assoc Disord 12(Suppl 2):S1–S6

McGeer PL, Schwab C, Parent A et al (2003) Presence of reactive microglia in monkey substantia nigra years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine administration. Ann Neurol 54 (5):599–604

Mena MA, García de Yébenes J (2008) Glial cells as players in parkinsonism: the "good," the "bad," and the "mysterious" glia. Neuroscientist 14(6):544–560

Miake H, Mizusawa H, Iwatsubo T, Hasegawa M (2002) Biochemical characterization of the core structure of alpha-synuclein filaments. J Biol Chem 277(21):19213–19219

Miklya I, Goltl P, Hafenscher F et al (2014) The role of parkin in Parkinson's disease. Neuropsychopharmacol Hung 16(2):67–76

Miller RM, Kiser GL, Kaysser-Kranich T et al (2007) Wild-type and mutant alpha-synuclein induce a multi-component gene expression profile consistent with shared pathophysiology in different transgenic mouse models of PD. Exp Neurol 204(1):421–432

Mitra S, Chakrabarti N, Bhattacharyya A (2011) Differential regional expression patterns of α-synuclein, TNF-α, and IL-1β; and variable status of dopaminergic neurotoxicity in mouse brain after Paraquat treatment. J Neuroinflammation 8:163

Moehle MS, Webber PJ, Tse T et al (2012) LRRK2 inhibition attenuates microglial inflammatory responses. J Neurosci 32(5):1602–1611

Mogi M, Togari A, Tanaka K et al (2000) Increase in level of tumor necrosis factor-alpha in 6-hydroxydopamine-lesioned striatum in rats is suppressed by immunosuppressant FK506. Neurosci Lett 289(3):165–168

Mosharov EV, Staal RG, Bové J et al (2006) Alpha-synuclein overexpression increases cytosolic catecholamine concentration. J Neurosci 26(36):9304–9311

Mount MP, Lira A, Grimes D et al (2007) Involvement of interferon-gamma in microglial-mediated loss of dopaminergic neurons. J Neurosci 27(12):3328–3337

Mulcahy P, O'Doherty A, Paucard A, O'Brien T et al (2013) The behavioural and neuropathological impact of intranigral AAV-α-synuclein is exacerbated by systemic infusion of the Parkinson's disease-associated pesticide, rotenone, in rats. Behav Brain Res 15 (243):6–15

Na SJ, DiLella AG, Lis EV et al (2010) Molecular profiling of a 6-hydroxydopamine model of Parkinson's disease. Neurochem Res 35(5):761–772

Nagatsu T (1997) Isoquinoline neurotoxins in the brain and Parkinson's disease. Neurosci Res 29 (2):99–111

Nemani VM, Lu W, Berge V et al (2010) Increased expression of alpha-synuclein reduces neurotransmitter release by inhibiting synaptic vesicle reclustering after endocytosis. Neuron 65(1):66–79

Nguyen TA, Frank-Cannon T, Martinez TN et al (2013) Analysis of inflammation-related nigral degeneration and locomotor function in DJ-1(-/-) mice. J Neuroinflammation 10:50

Oestreicher E, Sengstock GJ, Riederer P et al (1994) Degeneration of nigrostriatal dopaminergic neurons increases iron within the substantia nigra: a histochemical and neurochemical study. Brain Res 660(1):8–18

Ohnuki T, Nakamura A, Okuyama S et al (2010) Gene expression profiling in progressively MPTP-lesioned macaques reveals molecular pathways associated with sporadic Parkinson's disease. Brain Res 1346:26–42

Olson JK, Miller SD (2004) Microglia initiate central nervous system innate and adaptive immune responses through multiple TLRs. J Immunol 173(6):3916–3924

Orenstein SJ, Kuo SH, Tasset I et al (2013) Interplay of LRRK2 with chaperone-mediated autophagy. Nat Neurosci 16(4):394–406

Pabon MM, Bachstetter AD, Hudson CE et al (2011) CX3CL1 reduces neurotoxicity and microglial activation in a rat model of Parkinson's disease. J Neuroinflammation 8:9

Paisán-Ruíz C, Jain S, Evans EW et al (2004) Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 44(4):595–600

Park B, Yang J, Yun N et al (2010) Proteomic analysis of expression and protein interactions in a 6-hydroxydopamine-induced rat brain lesion model. Neurochem Int 57(1):16–32

Paterna JC, Leng A, Weber E et al (2007) DJ-1 and Parkin modulate dopamine-dependent behavior and inhibit MPTP-induced nigral dopamine neuron loss in mice. Mol Ther 15:698–704

Perez FA, Curtis WR, Palmiter RD (2005) Parkin-deficient mice are not more sensitive to 6-hydroxydopamine or methamphetamine neurotoxicity. BMC Neurosci 6:71

Perumal AS, Gopal VB, Tordzro WK et al (1992) Vitamin E attenuates the toxic effects of 6-hydroxydopamine on free radical scavenging systems in rat brain. Brain Res Bull 29 (5):699–701

Pierre SR, Lemmens MA, Figueiredo-Pereira ME (2009) Subchronic infusion of the product of inflammation prostaglandin J2 models sporadic Parkinson's disease in mice. J Neuroinflammation 6:18

Polymeropoulos MH, Lavedan C, Leroy E et al (1997) Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276(5321):2045–2047

Poon HF, Frasier M, Shreve N et al (2005) Mitochondrial associated metabolic proteins are selectively oxidized in A30P alpha-synuclein transgenic mice–a model of familial Parkinson's disease. Neurobiol Dis 18(3):492–498

Potashkin JA, Blume SR, Runkle NK (2011) Limitations of animal models of Parkinson's disease. Parkinsons Dis 2011:658083

Pott Godoy MC, Tarelli R, Ferrari CC et al (2008) Central and systemic IL-1 exacerbates neurodegeneration and motor symptoms in a model of Parkinson's disease. Brain 131(Pt 7):1880–1894

Purisai MG, McCormack AL, Cumine S et al (2007) Microglial activation as a priming event leading to paraquat-induced dopaminergic cell degeneration. Neurobiol Dis 25(2):392–400

Pycock CJ (1980) Turning behaviour in animals. Neuroscience 5(3):461–514

Qin L, Liu Y, Wang T et al (2004) NADPH oxidase mediates lipopolysaccharide-induced neurotoxicity and proinflammatory gene expression in activated microglia. J Biol Chem 279 (2):1415–1421

Qin L, Wu X, Block ML et al (2007) Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia 55(5):453–462

Ransohoff RM, Perry VH (2009) Microglial physiology: unique stimuli, specialized responses. Annu Rev Immunol 27:119–145

Ransom BR, Kunis DM, Irwin I et al (1987) Astrocytes convert the parkinsonism inducing neurotoxin, MPTP, to its active metabolite, MPP+. Neurosci Lett 75(3):323–328

Reynolds AD, Stone DK, Hutter JA, Benner EJ et al (2010) Regulatory T cells attenuate Th17 cell-mediated nigrostriatal dopaminergic neurodegeneration in a model of Parkinson's disease. J Immunol 184(5):2261–2271

Rezai-Zadeh K, Gate D, Town T (2009) CNS infiltration of peripheral immune cells: D-Day for neurodegenerative disease? J Neuroimmune Pharmacol 4(4):462–475

Riachi NJ, LaManna JC, Harik SI (1989) Entry of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine into the rat brain. J Pharmacol Exp Ther 249(3):744–748

Rochet JC, Outeiro TF, Conway KA et al (2004) Interactions among alpha-synuclein, dopamine, and biomembranes: some clues for understanding neurodegeneration in Parkinson's disease. J Mol Neurosci 23(1–2):23–34

Rockenstein E, Mallory M, Hashimoto M et al (2002) Differential neuropathological alterations in transgenic mice expressing alpha-synuclein from the platelet-derived growth factor and Thy-1 promoters. J Neurosci Res 68(5):568–578

Rockenstein E, Nuber S, Overk CR, Ubhi K et al (2014) Accumulation of oligomer-prone α-synuclein exacerbates synaptic and neuronal degeneration in vivo. Brain (in press)

Ross OA, Braithwaite AT, Skipper LM et al (2008) Genomic investigation of alpha-synuclein multiplication and parkinsonism. Ann Neurol 63(6):743–750

Roy A, Ghosh A, Jana A et al (2012) Sodium phenylbutyrate controls neuroinflammatory and antioxidant activities and protects dopaminergic neurons in mouse models of Parkinson's disease. PLoS One 7(6):e38113

Sadeghian M, Marinova-Mutafchieva L, Broom L et al (2012) Full and partial peroxisome proliferation-activated receptor-γ agonists, but not δ agonist, rescue of dopaminergic neurons in the 6-OHDA parkinsonian model is associated with inhibition of microglial activation and MMP expression. J Neuroimmunol 246(1–2):69–77

Salama M, Arias-Carrión O (2011) Natural toxins implicated in the development of Parkinson's disease. Ther Adv Neurol Disord 4(6):361–373

Sanchez-Guajardo V, Annibali A, Jensen PH et al (2013a) α-Synuclein vaccination prevents the accumulation of parkinson disease-like pathologic inclusions in striatum in association with regulatory t cell recruitment in a rat model. J Neuropathol Exp Neurol 72(7):624–645

Sanchez-Guajardo V, Barnum CJ, Tansey MG et al (2013b) Neuroimmunological processes in Parkinson's disease and their relation to α-synuclein: microglia as the referee between neuronal processes and peripheral immunity. ASN Neuro 5(2):113–139

Sanchez-Guajardo V, Febbraro F, Kirik D et al (2010) Microglia acquire distinct activation profiles depending on the degree of alpha-synuclein neuropathology in a rAAV based model of Parkinson's disease. PLoS One 5(1):e8784

Sánchez-Pernaute R, Ferree A, Cooper O et al (2004) Selective COX-2 inhibition prevents progressive dopamine neuron degeneration in a rat model of Parkinson's disease. J Neuroinflammation 1(1):6

Schober A (2004) Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP. Cell Tissue Res 318(1):215–224

Sekiyama K, Sugama S, Fujita M et al (2012) Neuroinflammation in Parkinson's disease and related disorders: a lesson from genetically manipulated mouse models of α-synucleinopathies. Parkinsons Dis. doi:10.1155/2012/271732

Selvakumar GP, Janakiraman U, Essa MM, Thenmozhi AJ et al (2014) Escin attenuates behavioral impairments, oxidative stress and inflammation in a chronic MPTP/probenecid mouse model of Parkinson′s disease. Brain Res S0006–8993(14):00358

Shaikh SB, Nicholson LF (2009) Effects of chronic low dose rotenone treatment on human microglial cells. Mol Neurodegener 4:55

Sherer TB, Betarbet R, Kim JH et al (2003a) Selective microglial activation in the rat rotenone model of Parkinson's disease. Neurosci Lett 341(2):87–90

Sherer TB, Betarbet R, Testa CM et al (2003b) Mechanism of toxicity in rotenone models of Parkinson's disease. J Neurosci 23(34):10756–10764

Sherer TB, Kim JH, Betarbet R et al (2003c) Subcutaneous rotenone exposure causes highly selective dopaminergic degeneration and alpha-synuclein aggregation. Exp Neurol 179 (1):9–16

Shimizu K, Ohtaki K, Matsubara K et al (2001) Carrier-mediated processes in blood–brain barrier penetration and neural uptake of paraquat. Brain Res 906(1–2):135–142

Shimoji M, Pagan F, Healton EB et al (2009) CXCR4 and CXCL12 expression is increased in the nigro-striatal system of Parkinson's disease. Neurotox Res 16(3):318–328

Shin JH, Ko HS, Kang H et al (2011) PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease. Cell 144:689–702

Sindhu KM, Saravanan KS, Mohanakumar KP (2005) Behavioral differences in a rotenone-induced hemiparkinsonian rat model developed following intranigral or median forebrain bundle infusion. Brain Res 1–2:25–34

Singleton AB, Farrer M, Johnson J et al (2003) Alpha-Synuclein locus triplication causes Parkinson's disease. Science 302(5646):841

Solano RM, Casarejos MJ, Menéndez-Cuervo J et al (2008) Glial dysfunction in parkin null mice: effects of aging. J Neurosci 28(3):598–611

Spillantini MG, Schmidt ML, Lee VM et al (1997) Alpha-synuclein in Lewy bodies. Nature 388 (6645):839–840

Sriram K, Matheson JM, Benkovic SA et al (2002) Mice deficient in TNF receptors are protected against dopaminergic neurotoxicity: implications for Parkinson's disease. FASEB J 16 (11):1474–1476

Staal RG, Hananiya A, Sulzer D (2008) PKC theta activity maintains normal quantal size in chromaffin cells. J Neurochem 105(5):1635–1641

Su X, Maguire-Zeiss KA, Giuliano R et al (2008) Synuclein activates microglia in a model of Parkinson's disease. Neurobiol Aging 29(11):1690–1701

Sulzer D, Surmeier DJ (2013) Neuronal vulnerability, pathogenesis, and Parkinson's disease. Mov Disord 28(1):41–50

Swanson CR, Joers V, Bondarenko V et al (2011) The PPAR-γ agonist pioglitazone modulates inflammation and induces neuroprotection in parkinsonian monkeys. J Neuroinflammation 8:91

Tanaka S, Ishii A, Ohtaki H et al (2013) Activation of microglia induces symptoms of Parkinson's disease in wild-type, but not in IL-1 knockout mice. J Neuroinflammation 10(1):143

Tansey MG, Goldberg MS (2010) Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention. Neurobiol Dis 37(3):510–518

Taylor JM, Main BS, Crack PJ (2013) Neuroinflammation and oxidative stress: co-conspirators in the pathology of Parkinson's disease. Neurochem Int 62(5):803–819

Theodore S, Cao S, McLean PJ et al (2008) Targeted overexpression of human alpha-synuclein triggers microglial activation and an adaptive immune response in a mouse model of Parkinson disease. J Neuropathol Exp Neurol 67(12):1149–1158

Thomas B, von Coelln R, Mandir AS et al (2007) MPTP and DSP-4 susceptibility of substantia nigra and locus coeruleus catecholaminergic neurons in mice is independent of parkin activity. Neurobiol Dis 26:312–322

Thornton E, Vink R (2012) Treatment with a substance P receptor antagonist is neuroprotective in the intrastriatal 6-hydroxydopamine model of early Parkinson's disease. PLoS One 7(4): e34138

Tobón-Velasco JC, Limón-Pacheco JH, Orozco-Ibarra M, Macías-Silva M et al (2013) 6-OHDA-induced apoptosis and mitochondrial dysfunction are mediated by early modulation of intracellular signals and interaction of Nrf2 and NF-κB factors. Toxicology 8(304):109–119

Tofaris GK, Garcia Reitböck P, Humby T et al (2006) Pathological changes in dopaminergic nerve cells of the substantia nigra and olfactory bulb in mice transgenic for truncated human alpha-synuclein(1-120): implications for Lewy body disorders. J Neurosci v26(15):3942–50

Tomás-Camardiel M, Venero JL, de Pablos RM et al (2004) In vivo expression of aquaporin-4 by reactive microglia. J Neurochem 91(4):891–899

Tran TA, Nguyen AD, Chang J et al (2011) Lipopolysaccharide and tumor necrosis factor regulate Parkin expression via nuclear factor-kappa B. PLoS One 6(8):e23660

Tufekci KU, Genc S, Genc K (2011) The endotoxin-induced neuroinflammation model of Parkinson's disease. Parkinsons Dis 2011:487450

Tufekci KU, Meuwissen R, Genc S et al (2012) Inflammation in Parkinson's disease. Adv Protein Chem Struct Biol. doi:10.1016/B978-0-12-398314-5.00004-0

Ulusoy A, Decressac M, Kirik D et al (2010) Viral vector-mediated overexpression of α-synuclein as a progressive model of Parkinson's disease. Prog Brain Res 184:89–111

Unger EL, Eve DJ, Perez XA et al (2006) Locomotor hyperactivity and alterations in dopamine neurotransmission are associated with overexpression of A53T mutant human alpha-synuclein in mice. Neurobiol Dis. 21(2):431–443

Valente EM, Abou-Sleiman PM, Caputo V et al (2004) Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science 304:1158–1160

Vázquez-Claverie M, Garrido-Gil P, San Sebastián W et al (2009) Acute and chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine administrations elicit similar microglial activation in the substantia nigra of monkeys. J Neuropathol Exp Neurol 68(9):977–984

Volpicelli-Daley LA, Luk KC, Patel TP et al (2011) Exogenous α-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. Neuron 72(1):57–71

von Coelln R, Kügler S, Bähr M, Weller M et al (2001) Rescue from death but not from functional impairment: caspase inhibition protects dopaminergic cells against 6-hydroxydopamine-induced apoptosis but not against the loss of their terminals. J Neurochem 77(1):263–273

Von Coelln R, Thomas B, Savitt JM et al (2004) Loss of locus coeruleus neurons and reduced startle in parkin null mice. Proc Natl Acad Sci 101:10744–10749

Wachter B, Schürger S, Rolinger J et al (2010) Effect of 6-hydroxydopamine (6-OHDA) on proliferation of glial cells in the rat cortex and striatum: evidence for de-differentiation of resident astrocytes. Cell Tissue Res. 342(2):147–160

Wang AL, Liou YM, Pawlak CR et al (2010) Involvement of NMDA receptors in both MPTP-induced neuroinflammation and deficits in episodic-like memory in Wistar rats. Behav Brain Res 208(1):38–46

Wang Q, Shin EJ, Nguyen XK et al (2012) Endogenous dynorphin protects against neurotoxin-elicited nigrostriatal dopaminergic neuron damage and motor deficits in mice. J Neuroinflammation 9:124

Wang XJ, Zhang S, Yan ZQ et al (2011) Impaired CD200-CD200R-mediated microglia silencing enhances midbrain dopaminergic neurodegeneration: roles of aging, superoxide, NADPH oxidase, and p38 MAPK. Free Radic Biol Med 50(9):1094–1106

Watson MB, Richter F, Lee SK et al (2012) Regionally-specific microglial activation in young mice over-expressing human wildtype alpha-synuclein. Exp Neurol 237(2):318–334

Wilms H, Rosenstiel P, Romero-Ramos M et al (2009) Suppression of MAP kinases inhibits microglial activation and attenuates neuronal cell death induced by alpha-synuclein protofibrils. Int J Immunopathol Pharmacol 22(4):897–909

Wu SY, Wang TF, Yu L et al (2011) Running exercise protects the substantia nigra dopaminergic neurons against inflammation-induced degeneration via the activation of BDNF signaling pathway. Brain Behav Immun 25(1):135–146

Yadav S, Gupta SP, Srivastava G et al (2012) Role of secondary mediators in caffeine-mediated neuroprotection in maneb- and paraquat-induced Parkinson's disease phenotype in the mouse. Neurochem Res 37(4):875–884

Yasuda Y, Shimoda T, Uno K et al (2008) The effects of MPTP on the activation of microglia/astrocytes and cytokine/chemokine levels in different mice strains. J Neuroimmunol 204 (1–2):43–51

Yu Z, Xu X, Xiang Z et al (2010) Nitrated alpha-synuclein induces the loss of dopaminergic neurons in the substantia nigra of rats. PLoS One 5(4):e9956

Zarranz JJ, Alegre J, Gómez-Esteban JC et al (2004) The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol 55(2):164–173

Zhang ZJ, Cheang LC, Wang MW et al (2011a) Ethanolic extract of fructus Alpinia oxyphylla protects against 6-hydroxydopamine-induced damage of PC12 cells in vitro and dopaminergic neurons in zebrafish. Cell Mol Neurobiol 32(1):27–40

Zhang S, Wang XJ, Tian LP et al (2011b) CD200-CD200R dysfunction exacerbates microglial activation and dopaminergic neurodegeneration in a rat model of Parkinson's disease. J Neuroinflammation 8:154

Zhang W, Phillips K, Wielgus et al (2011c) Neuromelanin activates microglia and induces degeneration of dopaminergic neurons: implications for progression of Parkinson's disease. Neurotox Res 19:63–72

Zhang Z, Zhang K, Du X et al (2012) Neuroprotection of desferrioxamine in lipopolysaccharide-induced nigrostriatal dopamine neuron degeneration. Mol Med Rep 5(2):562–566

Zhou H, Falkenburger BH, Schulz JB et al (2007a) Silencing of the Pink1 gene expression by conditional RNAi does not induce dopaminergic neuron death in mice. Int J Biol Sci 3:242–250

Zhou F, Wu JY, Sun XL et al (2007b) Iptakalim alleviates rotenone-induced degeneration of dopaminergic neurons through inhibiting microglia-mediated neuroinflammation. Neuropsychopharmacology 32(12):2570–2580

Zhou H, Huang C, Tong J et al (2011) Temporal expression of mutant LRRK2 in adult rats impairs dopamine reuptake. Int J Biol Sci 7(6):753–761

Zhou F, Yao HH, Wu JY et al (2008) Opening of microglial K(ATP) channels inhibits rotenone-induced neuroinflammation. J Cell Mol Med 12(5A):1559–1570

Zimprich A, Biskup S, Leitner P et al (2004) Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 44(4):601–607