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A survey from 2012 of evidence for the role of neuroinflammation in neurotoxin animal models of Parkinson's Disease and potential molecular targets

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Abstract

Parkinson's disease (PD) is a neurodegenerative movement disorder that results from the progressive loss of dopaminergic neurons in the midbrain substantia nigra pars compacta (SNpc). The specific molecular events that cause PD are currently not known; however, progress to better understand PD pathogenesis has been made using various animal models of the disease. In this review, we have highlighted reports from 2012 in which neurochemical/neurotoxins have been used in rodents to specifically address the role of neuroinflammation in the development and/or progression of PD-like pathology and in particular nigral degeneration. A number of studies have been summarized in which plausible pro-inflammatory, anti-inflammatory, or therapeutic agents targeting inflammatory pathways were introduced and/or investigated by various groups for neuroprotective effects. From these studies, it is clear that neuroinflammation acts to exacerbate the toxic outcomes that are set in motion within neurons following exposure to neurotoxins. Additionally, it is noted that future work is still needed to better understand the underlying mechanisms mediating the neuroinflammatory and neurotoxic phenotypes reported in rodent models of PD-like pathology to maximize the translation potential of these interventions to the clinic to prevent and/or delay PD onset and/or progression in humans.

Keywords

neuroinflammation; neurotoxin; nigrostriatal; neurodegeneration; dopaminergic; microglia; 6-OHDA; MPTP; LPS; paraquat; Parkinson's disease

Introduction

Parkinson's disease (PD) is a neurodegenerative movement disorder that results from the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) in the midbrain (Jankovic, 2008). Nigral DA neurons project to the striatum where they normally release dopamine at their terminals; however, the progressive degeneration of

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the nigrostriatal pathway can eventually deplete the striatum of adequate levels of dopamine, resulting in cardinal motor deficits (Sanchetee, 2008). To date, the molecular mechanisms underlying PD etiology have yet to be fully elucidated; however, progress to better understand PD pathogenesis has been made using various animal models of the disease. The purpose of the review herein is to highlight reports from 2012 in which neurochemical animal models of PD were used to specifically investigate the role of neuroinflammation in the development and/or progression of PD-like pathology.

Neuroinflammation occurs when brain microglia are activated and subsequently release cytokines, chemokines, reactive oxygen species (ROS), and reactive nitrogen species (RNS) in response to various stressful stimuli (Graeber et al, 2011; Innamorato et al, 2009; Tansey and Goldberg, 2010). Since microglia are the resident brain macrophages, it is thought that microglial activation may be necessary to help neurons recover from acute insults. However, it is generally accepted that the effects of chronic microglial activation are neurotoxic (Czeh et al, 2011). Thus, proper regulation of central nervous system (CNS) inflammatory mechanisms may be essential to prevent neurotoxicity, especially as it relates to PD. The latter idea is supported by studies of neuroinflammation in rodent neurochemical models of PD including: the mitochondrial inhibitor model, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP);, the reactive oxygen species models, 6-hydroxydopamine (6-OHDA) and paraquat; and the inflammation model, lipopolysaccharide (LPS). The findings from the most recent studies using these models will be discussed here.

Neuroinflammation and MPTP neurotoxicity

MPTP is a synthetic compound that upon entry into the brain, can be converted by the monoamine oxidase (MAO)-B enzyme, expressed mostly in astrocytes, into a toxic metabolite known as MPP (+) (Westlund et al, 1988; Westlund et al, 1985; Przedborski and Jackson-Lewis, 1998). Once it is converted, MPP (+) is selectively taken up by catecholaminergic neurons, including the DA neurons of the SNpc. Once it enters neurons, MPP (+) targets mitochondria where it acts to inhibit the function of mitochondrial complex I and leads to cell death (Przedborski and Jackson-Lewis, 1998). Since MPTP exposure leads to the death of DA neurons, including those in the SNpc, MPTP is an effective model of nigrostriatal dopamine depletion similar to that which occurs in PD. Therefore, it is of interest to determine the extent to which neuroinflammation is involved in the events of DA cell death that occur in response to MPTP exposure in animals.

A battery of genes may be involved in regulating inflammatory responses following MPTP exposure. Neuron-restrictive silencer factor (NRSF)/neuronal repressor element-1 silencing transcription factor (REST) is a ubiquitously expressed transcriptional repressor that acts to turn-off neuron-specific genes in non-neuronal cells (Schoenherr and Anderson, 1995). Interestingly, while the function of NRSF/REST may vary in different cell types, in a study by Yu et al, when NRSF/REST was conditionally depleted in the nigrostriatal brain region, NRSF/REST conditional knockout (cKO) mice were found to be more vulnerable to MPTP induced-DA neurotoxicity in comparison to wild-type (WT) littermates. Increased MPTP vulnerability in cKO mice was also associated with elevated nigral astrogliosis following insult. Further, higher expression of the pro-inflammatory cytokine, Interleukin-1 beta

(IL-1β) was observed in NRSF/REST cKO striatum tissues following MPTP treatments. These findings implicate NRSF/REST as an important regulator of neuroinflammatory responses; however, Yu and colleagues did not determine the extent to which microglial activation may have modulated these results. The authors postulated that astroglial activation and prolonged inflammatory conditions may partially explain the aggravated degeneration of DA neurons in the NRSF/REST cKO animals. This novel report provides compelling rationale to define the NRSF/REST target genes that mediate the observed protective effects against MPTP toxicity *in vivo.* In the study, Yu et al measured the mRNA expression levels of the dopamine receptor 2 (DRD2) and were found to be elevated in the striatum of saline-treated NRSF/REST cKO mice in comparison to WT littermates. Additionally, IL-1β mRNA levels were diminished in saline-treated NRSF/REST cKO mice; however, there were no differences noted in other genes analyzed (inducible Nitric Oxide Synthase, ubiquitin carboxyl-terminal esterase L1, neurotrophic tyrosine kinase receptor type 3, and Parkin) (Yu et al, 2012). While the observed altered expression of DRD2 and IL-1β genes in saline-treated NRSF/REST cKO mice was an interesting finding, the functional relevance of these changes was not addressed in the study. Thus, more work must be done to understand the role of NRSF/REST to alter gene transcription and related neurotoxicity phenotypes in animal models of PD-like pathology.

In relation to this concept, it is possible that NRSF/REST may act to modulate the expression of the gene, Prodynorphin. The Prodynorphin (Dyn) gene encodes the naturally occurring opioid neuropeptide, dynorphin, which is widely distributed throughout the brain to exert a variety of CNS effects (Fallon et al, 1985; Schwarzer, 2009; Tejeda et al, 2012). A recent study by Wang and colleagues suggested that dynorphin has anti-inflammatory and neuroprotective properties against MPTP toxicity in mice (Wang et al, 2012). Prior to that study, dynorphin had been shown to regulate striatal DA release (You et al, 1999) and was also shown to protect against inflammation-induced neurotoxicity (Liu et al, 2001). However, the ability of dynorphin to directly modulate neuroinflammation in the MPTP model had not been explored. In the study by Wang et al, it was found that Dyn ablation in mice resulted in exacerbated motor deficits and enhanced nigral DA neurotoxicity in response to MPTP in comparison to WT controls. *Dyn*-null animals were also reported to have higher numbers of Iba1-positive microglia in the midbrain following MPTP treatment compared to WT mice. Furthermore, the authors discovered that *Dyn*-null mice exhibited enhanced expression of pro-inflammatory genes (including CD16, CD32, and CD86) with a concomitant decreased expression of anti-inflammatory genes (CD206 and arginase) measured in the striatum following MPTP exposure. Thus, the authors concluded that dynorphin acts to prevent MPTP-induced neurotoxicity by exerting dual functions: inhibiting the activation of pro-inflammatory microglia while simultaneously promoting the activation of microglial anti-inflammatory factors. (Wang et al, 2012). Future studies to better understand the role of the dynorphin neuropeptide in mitigating inflammatory responses following neurotoxic insults will be needed.

Angiotensin II is another peptide with neuroinflammatory effects. The angiotensin II peptide hormone circulates in the blood and controls blood pressure and fluid balance as a part of the classic renin-angiotensin hormone system regulated predominantly by renal and hepatic

enzymes. The discovery of an independent local brain renin-angiontensin system (RAS) and related production of brain angiotensin II peptide has gained the attention of many investigators who desire to elucidate the role of angiotensin II neuropeptide in the CNS (Wright and Harding, 2011). Among many other functions, the brain RAS may have a role in the etiology of PD. To test this hypothesis, in a recent paper, the Labandeira-Garcia group investigated the role of the angiontensin type 1 receptor (AT1) in the murine neuroinflammatory response to MPTP (Garrido-Gil et al, 2012). AT1 receptors normally bind angiontensin II peptide and are expressed in various brain regions including striatum and substantia nigra (Lenkei et al, 1997; Joglar et al, 2009; Wright and Harding, 2011). It had been shown in a previous study by the Labandeira-Garcia group that activation of AT1 receptors with angiotensin II could exacerbate microglial inflammatory responses to MPTP (Joglar et al, 2009). To investigate this phenomenon further, Garrido-Gil and colleagues generated AT1 knockout (KO) mice and in comparison to WT controls, the AT1 KO mice showed less nigral DA neurotoxicity in response to MPTP. This suggests that stimulation of the AT1 receptor may normally have neurotoxic effects within the MPTP paradigm. Additionally, Garrido-Gil et al reported that AT1 null mice exhibited reduced microglial activation and reduced microgliosis in response to MPTP treatment in comparison to WT mice. Interestingly, the authors found that in order to observe the anti-inflammatory and neuroprotective effects of AT1 gene ablation in MPTP-treated mice, activation of peroxisome proliferator-activation receptor gamma (PPAR-γ) was required. PPAR-γ is a nuclear receptor that is expressed in neurons and to a lesser extent in glia within various brain regions including the striatum and SNpc (Moreno et al, 2004). Prior to the Garrido-Gil study, PPAR-γ had been shown to be involved in a variety of cellular processes and to be activated by AT1 receptor antagonists (Erbe et al, 2006). Further, activation of PPAR-γ attenuated activation of microglia in culture following inflammatory stimuli (Bernardo et al, 2000). However, prior to the study by Garrido-Gil and colleagues, the association between brain AT1 receptor-dependent PPAR-γ activation and neuroinflammation had not been explored. Interestingly, Garrido-Gil et al demonstated that pharmacologic inhibition of PPAR-γ in concert with AT1 ablation eradicated the protective effects of AT1 gene ablation against MPTP toxicity. Thus, it was concluded that inhibition of the AT1 receptor activates PPAR-γ, which can then result in downstream anti-inflammatory and neuroprotective effects against MPTP (Garrido-Gil et al, 2012). The specific molecular mechanisms that are employed by PPAR-γ to exert these anti-inflammatory effects are not yet fully elucidated. Nurr1, another member of the nuclear receptor family has been shown to recruit the CoREST complex to inhibit inflammatory gene transcription (Saijo et al, 2009). Nevertheless, the reported interplay between the activation of brain AT1 and PPAR-γ receptors in modulating neuroinflammation and neurotoxicity presents a novel story that is worthy of additional investigation.

The Wingless-type MMTV integration site (Wnt)/β-catenin pathway is an additional signaling cascade that may be involved in modulating the inflammatory responses induced by MPTP. Wnt is a glycoprotein that is secreted from cells in response to specific extracellular stimuli that modulates a variety of cellular processes (reviewed by (MacDonald et al, 2009)). β-catenin is a transcriptional co-activator protein sequestered in the cytoplasm in the absence of an extracellular Wnt stimulus and subjected to continuous cytoplasmic

proteolytic degradation. The latter event inhibits β-catenin transcriptional function. However, in response to the extracellular binding of specific Wnt ligands, Wnt is secreted from the cell and subsequently forms a Wnt-receptor complex on the cell surface. The formation of the Wnt-receptor complex disrupts the proteolytic degradation of cytoplasmic β-catenin, allowing β-catenin to translocate to the nucleus and stimulate the expression of specific Wnt target genes therein (MacDonald et al, 2009). It had been shown in a previous study by L'Episcopo et al that expression of Wnt1 and activation of the Wnt/ β-catenin pathway in astrocytes served to protect DA neurons from MPTP-induced neurotoxicity in primary mesencephalic astrocyte-neuron co-cultures (L'Episcopo et al, 2011). In a more recent study, the same group reported that activation of Wnt/ β-catenin signaling was able to differentially modulate inflammatory effects in astrocytes compared to microglia in response to MPTP. In the latter study, in primary astrocyte-neuron co-cultures treated with MPP(+) *in vitro*, the effects of astrocyte activation were neuroprotective in part through stimulation of the Wnt/ β-catenin pathway. Conversely, when microglia were isolated *ex vivo* following treatment of mice with MPTP *in vivo*, the effects of microglial activation were found to be deleterious via suppression of the Wnt/ β-catenin pathway. In these *ex vivo* microglial cultures, microglial activation and associated Wnt/ β-catenin pathway suppression resulted in increased microglial production of ROS and RNS. Further, in *ex-vivo* microglial-neuronal co-cultures, microglial activation resulted in the activation of the cell death initiator, Caspase 3 in neural cells. It was also found that activation of Wnt/β-catenin signaling via pharmacologic stimulation or via siRNA down-regulation of a known β-catenin inhibitor (GSK-3β) could partially mitigate neuronal vulnerability to MPP(+) in microglial-neuronal co-cultures, confirming the causal effects between microglial Wnt/ β-catenin signal suppression and microglia-induced neurotoxicity using the MPTP paradigm. Further, *in vivo* treatment of mice with MPTP was discovered to down-regulate endogenous neuronal β-catenin, the loss of which could be blocked by use of the synthetic anti-inflammatory microglial regulatory drug, HCT1026. Together, these findings implicate the Wnt/β-catenin signaling pathway as an important mediator of neuroinflammatory responses induced by MPTP and suggests that microglia antagonize the protective effects of Wnt/β-catenin signal stimulation (L'Episcopo et al, 2012).

In addition to identifying gene targets, there is a growing interest in discovering therapeutic agents that can prevent or reduce MPTP-induced neuroinflammation and associated neurotoxicity. A number of recent manuscripts have attempted to address this charge. Luchtman et al sought to determine the ability for the omega-3 fatty acid, eicosapentanoic acid (EPA), to exert a protective function against MPTP (Luchtman et al, 2012). EPA was previously known to inhibit inflammation via interaction with the cyclooxygenase 2 (COX2) enzyme, which promotes inflammation when bound to fatty acids other than the omega-3 fatty acids (Simopoulos, 2002). Interestingly, in the study by Luchtman and colleagues, EPA was found to reduce striatal pro-inflammatory cytokine production but was not able to prevent striatal dopamine depletion following MPTP treatment. Furthermore, the inhibitory effects of EPA on pro-inflammatory cytokine production during MPTP exposure occurred without coordinated inhibition of COX2 expression under the same conditions, suggesting that EPA may act on yet unidentified cellular targets to minimize MPTP-induced neuroinflammation (Luchtman et al, 2012). In a different study, the plant root extract

napthazarin was investigated for its therapeutic potential following MPTP exposure in mice. Napthazarin was found to reduce astrogliosis and microglial activation in addition to ameliorating DA neuron loss (Choi et al, 2012). However, in the same study by Choi et al, napthazarin was not shown to have direct neuroprotective function, suggesting that the reduction of astrogliosis and microglial activation by napthazarin was sufficient to protect against MPTP-induced DA neurotoxicity. A different set of plant root derivatives known as curcuminoids have also been recently tested for neuroprotective and anti-inflammatory properties in MPTP-treated mice in a study by Ojha and colleagues (Ojha et al, 2012). Prior to the study by Ojha, curcuminoids had been shown to inhibit numerous inflammatory mediators including COX2, TNFα, and IL-1β (Yang et al, 2008; Tohda et al, 2006). However, efforts to determine the ability for curcuminoids to protect against neuroinflammation and DA neurotoxicity using the MPTP model had not been reported. Thus, in the study by Ojha et al MPTP-treated mice received oral curcuminoids or a control diet. The authors reported that curcuminoids significantly reduced the striatal levels of pro-inflammatory cytokines IL-1β and TNFα following MPTP exposure. Additionally, curcuminoids ameliorated the effects of MPTP on motor deficits and prevented striatal DA depletion (Ojha et al, 2012). Notwithstanding, while all of the aforementioned putative therapeutic agents show promise as it relates to reducing neuroinflammation and preventing neurotoxicity in the MPTP model, a more thorough understanding of the molecular targets and sequential events that promote these effects is warranted before these approaches can be tested in the clinic.

The studies using the MPTP animal model of PD reported in 2012 provide novel insights into various gene products and cellular pathways that may be involved in PD-like neuropathology. Together, these reports suggest that neuroinflammation, and specifically that which results in microglial activation, may be key mechanisms required for MPTP-induced DA neurotoxicity. Of course it is essential to discuss whether the latter phenomenon is unique to the MPTP animal model or whether similar conclusions can be drawn from studies of other neurotoxic animal models of PD. Thus, to address this point, the next section of this review will highlight studies from 2012 that have used another oxidative neurotoxin *in vivo* in order to address the role of neuroinflammation in promoting neurotoxicity within the context of nigrostriatal degeneration and PD-like pathology.

6-OHDA: A different neurotoxin story with similar neuroinflammatory consequences

6-hydroxydopamine (6-OHDA) is a synthetic dopamine derivate which has strong oxidizing properties (Cohen and Heikkila, 1974). Due to its similar structure to the catecholamines, dopamine and norepinephrine, 6-OHDA is selectively taken up by catecholaminergic neurons (Simola et al, 2007). When 6-OHDA enters DA neurons, it generates reactive oxygen species (ROS) that form quinones and paraquinones and are effectively neurotoxic (Cohen and Heikkila, 1974; Simola et al, 2007). Thus, 6-OHDA is often used to model PD since its use results in retrograde degeneration of striatal dopaminergic DA terminals, DA depletion and death of DA neurons in the SNpc (Simola et al, 2007). One important difference between MPTP and 6-OHDA is that the latter cannot cross the blood brain

barrier, and thus, it must be introduced by direct injection into the brain. Multiple laboratories have experimentally addressed the contribution of neuroinflammation in 6-OHDA-induced neurotoxicity, and not surprisingly, many similar trends have been observed when comparing the effects of 6-OHDA to those previously noted for the MPTP neurotoxin. For instance, one study by Sadeghian and colleagues sought to address the anti-inflammatory properties of the previously mentioned nuclear receptor, PPAR-γ, against 6-OHDA-induced toxicity in rats. The Sadeghian group found that when PPAR-γ agonists were given to rats prior to and following 6-OHDA administration, they effectively mitigated DA neuron loss and prevented striatal DA depletion. Furthermore, PPAR-γ agonists were reported to reduce the numbers of 6-OHDA-induced OX-6- and CD68-positive activated microglia in rats in comparison to control rats that did not receive PPAR-γ agonist. One important observation made by the authors was that following 6-OHDA administration, continuous exposure to PPAR-γ agonists was necessary in order to observe the neuroprotective effects. Moreover, while stimulation of PPAR-δ, another member of the PPAR receptor family, could effectively reduce striatal microglial activation following 6-OHDA administration, it was not able to prevent DA neurotoxicity or striatal DA depletion. Thus, the neuroprotective mechanisms that were observed following PPAR-γ activation may be unique to this nuclear receptor (Sadeghian et al, 2012). Additionally, since PPAR-γ is predominantly expressed in neurons (Moreno et al, 2004), it is reasonable to conclude that PPAR-γ agonists act on neurons directly to ameliorate toxicity and inhibitory effects on microglial activation and neuroinflammation may be secondary. Additional studies will be necessary to test this hypothesis. In summary, the study by Sadeghian and colleagues supported an anti-inflammatory and neuroprotective role for PPAR-γ in the 6-OHDA rat model similar to that described for PPARγ by Garrido-Gil and colleagues in the MPTP neurotoxin (Garrido-Gil et al, 2012).

Similar to the previously described pro-inflammatory effects of AT1 receptor stimulation in the MPTP model (Garrido-Gil et al, 2012), Villar-Cheda et al reported that AT1 receptor activation also mediated pro-inflammatory effects in the 6-OHDA rat model. The authors observed that aged rats (24 months of age) were more vulnerable to 6-OHDA-induced neurotoxicity in comparison to young rats (10 weeks of age) due to increased levels of the AT1 receptor and associated increases in the pro-inflammatory cytokines IL-1β and TNFα in the SNpc of aging rat brains. However, when aged rats were treated with the AT1 receptor antagonist candesartan, it attenuated 6-OHDA-induced DA neurotoxicity and diminished pro-inflammatory cytokine levels. This study implicated AT1 receptor activation in the vulnerability of TH neurons to 6-OHDA-induced toxicity and indicated that inflammation may be involved in mediating its neurotoxic effects (Villar-Cheda et al, 2012).

In an aforementioned study by Wang and colleagues, dynorphin was shown to have anti-inflammatory and neuroprotective effects against MPTP (Wang et al, 2012). However, another study by Thornton and Vink revealed an opposing role for the medium spiny neuron peptide Substance P (SP) in the 6-OHDA rat model (Thornton and Vink, 2012). Prior to the study by Thornton and Vink, SP was known to modulate DA neurotransmission; but its ability to regulate neuroinflammation had not been investigated. However, in the Thornton and Vink study, SP receptor antagonists administered by direct right lateral ventricle injection exacerbated 6-OHDA-induced DA neurotoxcity, while SP receptor antagonists

were marginally protective. Furthermore, SP receptor antagonists were able to reduce astrogliosis and also decrease the number of nigral Iba1-positive, activated microglia following intrastriatal 6-OHDA injection. SP receptors, designated neurokinin 1 (NK-1), are widely expressed throughout the mammalian brain (Rigby et al, 2005). NK-1 receptors are expressed at high levels in neurons but expression has also been detected in astrocytes while it is reported to be absent in microglia (Vinet-Oliphant et al, 2010; Stumm et al, 2001). In the Thornton and Vink study, it was not investigated which cell types NK-1 antagonists most predominantly affect; however, the report provided evidence to support a role for SP in potentiating the neurotoxic effects of 6-OHDA via a pro-inflammatory mechanisms (Thornton and Vink, 2012).

It is interesting to note that 6-OHDA administration may result in nigrostriatal neuroinflammation that is not uniform across different brain regions. In an imaging study, Maia and colleagues used a microglial activation-specific tracer *in vivo* to image inflammation in rat SNpc and striatum 3, 7, 14, 21, 28, and 56 days after a unilateral 6-OHDA intrastriatal lesion. They reported that the inflammatory response was delayed in the nigral region in comparison to the striatal region up to 14 days post lesion. However, similar extents of inflammation were evident in both brain areas by day 14 post-lesion. This is indicative of a retrograde inflammatory response that spreads from the initial site of 6-OHDA toxicity in the striatum and then extends in a retrograde manner towards the SNpc region. It is possible that striatal inflammation may occur as a result of DA neuron axonal degeneration in the striatum and eventually results in death of the DA neuron cell bodies and subsequent inflammation in the SNpc. These findings by Maia et al suggest that there may be a window during which administration of therapeutic agents could be used in response to neurotoxic stimuli in efforts to potentially prevent the retrograde spread of neuroinflammation that may occur in the nigrostriatal pathway (Maia et al, 2012).

Statins are a class of drugs that are normally prescribed to lower cholesterol production by the liver. According to the Mishra lab, statins are suggested to be one potential therapeutic agent for PD patients (Kumar et al, 2012). A putative neuroprotective role for statins has been postulated by others as well. Thus, the Mishra group sought to address the ability for the statin drugs atorvastatin and simvastatin to exert neuroprotective properties in the 6-OHDA rat model. Low and high doses of the respective statin drugs were administered orally for 14 days following unilateral intrastriatal 6-OHDA injections. Atorvastatin and simvastatin showed similar beneficial effects in a dose-dependent manner. Both statin drugs reduced the motor deficits that occurred following 6-OHDA administration. In addition, the statin drugs effectively reduced reactine nitrogen species (RNS) production and minimized striatal oxidative stress in response to 6-OHDA. Furthermore, levels of the cytokines, TNFα and IL-6, were reduced in the striatum when using atorvastatin and simvastatin after 6-OHDA administration. Thus, these studies indicated that atorvastatin and simvastatin have potential neuroprotective properties by exerting anti-inflammatory functions. While a direct effect of atorvastatin and simvastatin on DA neuron health was not investigated in the study by the Mishra group, future studies to evaluate this will be required to fully assess the potential of statins as neuroprotective drugs in early PD (Kumar et al, 2012).

Paraquat: A potent inducer of oxidative stress and related neuroinflammatory outcomes

Paraquat is a chemical within a class known as bipyridyl derivatives and has a similar structure to the MPTP metabolite, 1-methyl-4-phenylpyridinium(MPP+); however, it is clear that paraquat and MPTP exert different effects when exposed to cells (Berry et al, 2010). Reduction-oxidation cycling of paraquat leads to the production of superoxide radicals (Przedborski and Ischiropoulos, 2005; Bove et al, 2005; Berry et al, 2010). Paraquat can also oxidize iron which can then subsequently react with hydrogen peroxide to form hydroxdyl radicals (Przedborski and Ischiropoulos, 2005). Thus, it is clear that paraquat can act as an oxidizing agent. Of interest to PD studies, paraquat exposure in rodents results in nigral dopamine neuron degeneration ; however, it is not fully understood why these cell types are particularly vulnerable to paraquat insult (Berry et al, 2010).

Recently, the Singh group sought to address this question by investigating the role of the murine enzyme, Cyp2d22 (orthologue to human Cytochrome P450 2D6, a member of the cytochrome P450 superfamily of oxidases), to modulate paraquat-induced nigral dopaminergic degeneration (Srivastava et al, 2012). In the study by the Singh group, nine weeks of daily intraperitoneal paraquat injections in mice was found to significantly reduce striatal dopamine levels, and this phenomenon was exacerbated in the presence of the Cyp2d22 inhibitor, ketoconazole. Nigral dopaminergic neurodegeneration was also reported following exposure to paraquat and was further enhanced following co-administration of paraquat with ketoconazole. These effects were associated with increased SNpc microglial activation. Additionally, TNF protein levels were markedly increased in nigrostriatal tissues. It is likely that these effects are due to paraquat-induced increases in oxidative stress, an idea which is supported by the observation that the antioxidant, resveratrol, was able to prevent the inflammatory and neurotoxic effects of paraquat and/or of co-administration of paraquat with ketoconazole in the described Singh study (Srivastava et al, 2012). Furthermore, observed increases in the levels of the oxidative stress responsive enzymes, heme oxygenase-1 (HO-1), apoptosis signaling-regulating kinase -1 (ASK1), and p38 mitogen-activated protein kinase (MAPK) following paraquat administration or co-administration of paraquat and ketoconazole were also reported. Together, these data suggest that oxidative stress may be the mechanism by which paraquat induces its deleterious effects in the nigrostiatal region and may implicate Cyp2d22 as a potential therapeutic target to partially protect against this phenomenon. However, it is still of interest to gain additional insight into how Cyp2d22 may be regulating cellular oxidation responses as it relates to PD phenotypes. In summary, recent studies in neurochemical animal models of PD that involve paraquat, 6-OHDA and MPTP support a role for neuroinflammation in mediating the toxicity of these oxidative neurotoxins *in vivo*; but it may very well be that neuroinflammation merely acts to exacerbate the toxic outcomes that have already been set in motion within neurons following exposure to MPTP, 6-OHDA, or paraquat. Thus, to determine a direct role for inflammatory stimuli in initiating neuronal cell death, several recent studies have utilized the LPS animal model of PD-like pathology. The findings from LPS animal model studies from 2012 will be highlighted in the next section of this review.

LPS: A purely inflammatory stimulus with sophisticated neurotoxic consequences

Lipopolysaccharide (LPS) is a bacterial endotoxin that was originally discovered as a component of the outer cell membrane of gram-negative bacteria. While the localization of LPS to the bacterial cell wall may serve a variety of functions for these unicellular organisms, it is known that binding of LPS to receptors in specific vertebrate immune system cell types elicits the secretion of pro-inflammatory cytokines (Elin and Wolff, 1976; Reed and Milton, 2001). The strong pro-inflammatory LPS-induced response in animals makes LPS an attractive stimulus to model inflammation in neurological disease.

In a recent study, Zhou and colleagues sought to determine whether the effects of a single LPS-induced inflammatory response can have long-term deleterious effects on the nigrostriatal pathway. A single low dose (25ug diluted into 20uL of saline) of LPS was injected into the rat lateral ventricles and the effects were assessed up to 48 weeks post injection. The authors reported the presence of more OX-42 and OX-6 positive, activated microglia in LPS-treated animals at 48 weeks post injection. The latter was observed specifically in the striatum and hippocampus brain regions and to a lesser extent in the SNpc. Interestingly, although the authors reported significant motor impairments in rats as early as 16 weeks post LPS injection, DA neurotoxicity was not assessed at that time point. However, at 24 weeks post LPS treatment, the authors reported a 22% reduction of SNpc DA neurons, which progressed to a 40% reduction by 48 weeks post injection. None of these effects were observed in saline-treated animals (Zhou et al, 2012). Thus, this study suggests that once inflammation is induced in the brain, its neurotoxic effects can be detected long afterwards.

It is of interest to determine what factors may be capable of mitigating the inflammatory response to LPS in the brain. In a short letter, Iravani and colleagues demonstrated that unilateral intranigral LPS administration results in nigral astrogliosis and an increase in the expression of the trophic factor, Glial Derived Neurotrophic Factor (GDNF) in astrocytes. While GDNF levels were undetectable under normal conditions, the increase in astroglial GDNF expression was postulated to serve as an astroglial-specific neuroprotective mechanism against inflammation. While this idea wasn't tested directly, the authors confirmed increased levels of the pro-inflammatory cytokine, IL-1β in the ipsilateral nigral region, while no changes in IL-1β were detected in the striatum following LPS administration. Interestingly, the authors also did not observe increased TNF levels in the nigra or striatum brain regions following LPS exposure (Iravani et al, 2012). Future reports to understand the role of astroglial GDNF and other glial-derived neurotrophic factors in LPS-induced neuroinflammation will be enlightening.

While it is well-established that intranigral injection of LPS in rodents results in a marked inflammatory response in the CNS, one study by Hernandez-Romero et al suggests that peripheral inflammation may exacerbate the neurotoxic effects of intranigral LPS exposure (Hernandez-Romero et al, 2012). Hernandez-Romero et al reported that inducing a peripheral inflammatory response in rats by single injection of carageenan (a polysaccharide extracted from raw seaweed (Tobacman, 2001; Cohen and Ito, 2002) bilaterally into two

paws enhanced an intranigral LPS-dependent increase in the mRNA levels of the inflammatory markers IL-1β and IL-6. Additionally, loss of nigral dopaminergic neurons was exacerbated following combinatorial induction of CNS and peripheral inflammation in comparison to LPS-induced inflammation in the CNS alone. Thus, it was concluded that peripheral inflammation may be a significant factor that enhances dopaminergic degenerative processes; however, a comprehensive picture of the molecular mechanisms involved in this process remains to be elucidated.

Cui and colleagues have identified a polysaccharide known as fucoidan, which they reported to partially block the deleterious effects of intranigral LPS injection in rats. While the molecular basis for the action of fucoidan is not completely elucidated, prior to the study by Cui et al, fucoidan had been shown to inhibit the production of RNS in glial and microglial cell lines following stimulation with the proinflammatory cytokine, Interferon-γ (IFN-γ) (Do et al, 2010). In the same study, it was also discovered that fucoidan could modulate various signaling cascades including the JAK-STAT signaling pathway and p38-MAPK signaling cascade, both of which are known to be activated in response to the binding of IFN-γ (Do et al, 2010). However, little was known about the role of fucoidan to mitigate the effects of neuroinflammatory stimuli *in vivo*. Thus, to investigate this directly, Cui and colleagues administered LPS to rats by unilateral intranigral injection with or without intraperitoneal administration of fucoidan. While LPS resulted in a loss of nigral DA neurons, fucoidan reduced this loss by 25–30%. Additionally, the number of CD11-positive microglia in rat nigra was reduced in fucoidan-treated rats following LPS administration. Furthermore, when primary microglia were exposed to LPS in culture, fucoidan partially reduced TNF mRNA and protein levels in comparison to cells without only LPS addition. Fucoidan was also found to reduce ROS species in primary microglia in culture following LPS exposure (Cui et al, 2012). The ability for LPS to modulate IFN-γ, JAK-STAT, or p38-MAPK pathways was not investigated in the study by Cui and colleagues. Thus, it is unknown whether similar or alternative molecular mechanisms may be employed by fucoidan to mitigate LPS-induced neuroinflammation *in vivo*. Based on these findings, fucoidan may represent a potential therapeutic agent against the degenerating effects of neuroinflammation; however, future studies to explain the underlying molecular events that may promote the protective outcomes following fucoidan treatment are still needed.

Yuan et al also identified a neuroprotective role for the plant extract, Tenuingenin (TEN). The Yuan group had previously found TEN to be neuroprotective in 6-OHDA-treated DA (SH-SY5Y) cell lines and had also shown TEN to induce the up-regulation of the antioxidant enzyme superoxide dismutase and down-regulation of cleaved caspase 3 during 6-OHDA exposure using the same *in vitro* paradigm. However, Yuan and colleagues were interested in determining the ability for TEN to protect against LPS-induced neurotoxicity *in vivo*. To test this directly, LPS was administered by direct unilateral intranigral injection in rats, with or without the intragastric injection of TEN, 2 weeks prior and 12 weeks following LPS administration. Yuan et al reported TEN to have a number of beneficial effects. TEN was found to prevent LPS-induced movement impairments. TEN also minimized the loss of striatal DA and partially protected against the nigral DA neurotoxicity that occurred in response to LPS administration. Furthermore, TEN reduced the increased levels of the pro-

inflammatory cytokines, TNFα and IL-1β, that occurred in the SNpc brain region in response to LPS injection (Yuan et al, 2012). Taken together, these observations support an anti-inflammatory role for TEN that may explain its neuroprotective function against LPS-induced neurotoxicity. However, more work to identify the molecular targets of TEN *in vivo* should be pursued prior to advancing its use to the clinic.

Conclusion

This review highlighted the most recent findings from studies using various neurochemical models of PD-like pathology in rodents. The reports that were reviewed herein provide additional insights into the interplay between neuroinflammatory and neurotoxic mechanisms that may result in nigral degeneration. From these studies, it can be concluded that inflammation is capable of directly inducing nigral DA neuronal cell death. Further, it is clear that pro-inflammatory mechanisms can exacerbate the neurotoxic effects of various noxious stimuli which may occur in unhealthy DA neurons, including mitochondrial dysfunction and oxidative stress. However, it is not yet known which initial stimulus is causal of disease in humans: inflammation before toxicity or inflammation *in response* to toxicity? The answers to these questions are likely to be very complex. Nevertheless, as described in this report, a number of plausible pro-inflammatory, anti-inflammatory, and therapeutic agents (summarized in Table 1) were investigated in neurochemical animal models of PD-like in 2012. Future work to better understand the underlying mechanisms mediating the reported phenotypes *in vivo* will be enlightening and may inform additional studies to validate the targets reviewed herein for therapeutic drug development.

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Table 1

Summary of the neuromodulators and potential therapeutic agents postulated to be involved in nigral neurotoxicity *in vivo* in animal models of PD from publications in 2012

Pro-inflammatory	Anti-inflammatory	Potential Therapeutic Agents
Angiotensin II/AT1 Receptor	NRSF/REST	Eicosapentanoic Acid
Substance P/NK-1 Receptor	Dynorphin	Napthazarin
	Wnt/β-catenin	Curcuminoids
	PPAR-γ	Atorvastatin
	GDNF	Simvastatin
	Cyp2d22	Fucoidan
		Tenuingenin