

# Chronic microglial activation and progressive dopaminergic neurotoxicity

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## Abstract

PD (Parkinson's disease) is characterized by the selective and progressive loss of DA neurons (dopaminergic neurons) in the substantia nigra. Inflammation and activation of microglia, the resident innate immune cell in the brain, have been strongly linked to neurodegenerative diseases, such as PD. Microglia can respond to immunological stimuli and neuronal death to produce a host of toxic factors, including cytokines and ROS (reactive oxygen species). Microglia can also become persistently activated after a single stimulus and maintain the elevated production of both cytokines and ROS, long after the instigating stimulus is gone. Current reports suggest that this chronic microglial activation may be fuelled by either dying/damaged neurons or autocrine and paracrine signals from local glial cells, such as cytokines. Here, we review proposed mechanisms responsible for chronic neuroinflammation and explain the interconnected relationship between deleterious microglial activation, DA neuron damage and neurodegenerative disease.

## Introduction

Microglia, the resident innate immune cells in the brain, are activated in response to neuronal damage and several environmental stimuli/toxins. While most of the microglial functions are beneficial, it has become increasingly evident that microglia can become unregulated to both initiate and exacerbate neuron damage to drive disease. Recent studies suggest that neurotoxic microglia are chronically and excessively activated to serve as a regenerating source of cytokines and ROS (reactive oxygen species). In the present review, we will focus on PD (Parkinson's disease) and DA neuron (dopaminergic neuron) damage and discuss current hypotheses on how microglia become detrimental and chronically activated to fuel progressive neuron damage.

## PD

PD is the second most prevalent neurodegenerative disease and affects approx. 1–1.5% of the North American population. Degeneration of DA neuron cell bodies in the SN (substantia nigra) and the nerve terminals in the striatum results in resting tremor, rigidity, bradykinesia and gait disturbance in the PD patient [1]. While single gene mutations have been identified [2], most of the PD results from unknown aetiology, suggesting a prevalent role for the influence of environmental factors. Among the environmental

toxins, infectious agents [3–5], pesticides [6–8], MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [9], protease inhibitors [10,11] and heavy metals [12,13] have been implicated in the development of PD.

Currently, the mechanisms driving the progressive loss of DA neurons in PD are unknown. Available treatments only temporarily address PD symptoms and fail to alter the progression of PD. Here, we focus on the role of microglia and inflammation in this process.

## Microglia and DA neuron damage

As the resident innate immune cells in the brain, microglia are a predominant source of pro-inflammatory factors [TNF $\alpha$  (tumour necrosis factor  $\alpha$ ), PGE<sub>2</sub> (prostaglandin E<sub>2</sub>) and IFN- $\gamma$  (interferon- $\gamma$ )] and oxidative stress (\*NO, H<sub>2</sub>O<sub>2</sub>, O<sub>2</sub><sup>•-</sup> and ONOO<sup>-</sup>/ONOOH) which are toxic to neurons [14]. Although microglia are necessary for normal function, uncontrolled and overactivated microglia can result in disastrous neurotoxic consequences [14]. Interestingly, DA neurons are particularly sensitive to microglial activation, where they are selectively lost in response to pro-inflammatory stimuli in the brain, such as LPS (lipopolysaccharide) [15]. While DA neurons are the first cell type to be affected, greater levels of microglial activation do damage other neuronal cell types [16].

Several studies have confirmed that microglia can play a causal role in DA neuron death. For example, LPS, the polysaccharide component of the cell walls of Gram-negative bacteria, is toxic to neurons only in the presence of microglia [15,17]. Additionally, LPS activation of microglia both *in vivo* and *in vitro* causes progressive and cumulative loss of DA neurons over time [15,18,19]. Several other

**Key words:** dopaminergic neuron, microglia, NADPH oxidase, neuroinflammation, Parkinson's disease, reactive oxygen species.

**Abbreviations used:** DA neuron, dopaminergic neuron; ECM, extracellular matrix; ICAM-1, intercellular adhesion molecule 1; LFA-1, lymphocyte function-associated antigen 1; LPS, lipopolysaccharide; MMP-3, matrix metalloproteinase-3; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; ROS, reactive oxygen species; SN, substantia nigra; TNF $\alpha$ , tumour necrosis factor  $\alpha$ .

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endogenous peptides and environmental triggers such as paraquat [20], substance P [21], maneb [22], diesel exhaust particles [16] and rotenone [23] also directly activate microglia to cause neurotoxicity. Further, inflammation is also a noted contributor to direct neuron damage, as MPTP toxicity is significantly reduced in mutant mice deficient in pro-inflammatory factors, such as superoxide [24,25], myeloperoxidase [26], prostaglandins [27–30], NO (nitric oxide) [31] and TNF $\alpha$  [32–34].

In fact, the premise of microglia overactivation in PD has been supported by analysis of post-mortem brains from PD patients, where there is clear evidence of microglia activation in the SN [35]. Further, cases of immunological insult to the brain are associated with PD, where fetal brain inflammation, viruses and infectious agents have been correlated with later onset of PD [36]. However, increasing evidence suggests that deleterious microglial activation may be triggered by neuron damage, causing a self-propelling cycle of neuron death, which is a proposed mechanism of chronic neuronal loss across diverse neurodegenerative diseases [14].

## Chronic microglial activation and progressive neurotoxicity

### Reactive microgliosis: the microglial response to neuron death

Evidence points to chronic microglial activation as a critical component of deleterious microglial activation. In response to neurodegeneration or brain injury, microglial activation was initially perceived as a transient event [37]. However, the microglial response to neuronal damage (reactive microgliosis) is now believed to be both long-lived and self-propelling [38–40]. In fact, the neurotoxic response of microglia to central nervous system injury is implicated as a critical component of microglia-mediated neurotoxicity across multiple diseases [14,41]. Damaged or dying neurons have the potential to activate microglia, regardless of the neurodegenerative disease in question or how the neurons are damaged (environmental toxin, endogenous disease protein, or reactive microgliosis) [14]. This repeating cycle of the neurotoxic activation of microglia in response to neuron injury is commonly referred to as reactive microgliosis [42] (Figure 1A). Thus microglial activation initiated by early toxic insult to DA neurons may be propagated and potentially amplified throughout the disease.

Recent work has begun to reveal how neuronal damage activates the chronic and deleterious microglial inflammatory response. For example, modifications to the ECM (extracellular matrix) may be a critical mechanism through which damaged neurons activate microglia to produce extracellular superoxide. Earlier work has shown that the lack of or interference with ICAM-1 (intercellular adhesion molecule 1) interactions between microglia and neurons is known to result in enhanced microglia activation and production of cytotoxic factors [43]. However, ICAM-1 overexpression in astrocytes paired with the overexpression of LFA-1 (lymphocyte function-associated antigen 1) in microglia is associated with

MPTP-induced reactive microgliosis, years after the toxin was administered [44]. Further, the ECM protein laminin has also been associated with reactive microgliosis and the production of extracellular superoxide in MPTP-induced DA neurotoxicity [45]. Thus it is possible that modifications to the ECM during neuronal damage provide the necessary environment for chronic neuroinflammation and progressive damage.

In addition, proteases known to modify the ECM are also released from damaged neurons. For example, MMP-3 (matrix metalloproteinase-3), a protease known to degrade ECM components such as laminin, is released upon DA cell damage with MPP<sup>+</sup> (1-methyl-4-phenylpyridinium) and is toxic to DA neurons [46]. Further, MMP-3 was shown to induce the production of superoxide in microglia, and MMP-3-knockout mice are less sensitive to MPTP [47]. Future efforts will focus on the identification of other proteases that modify the ECM to result in chronic neurodegeneration.

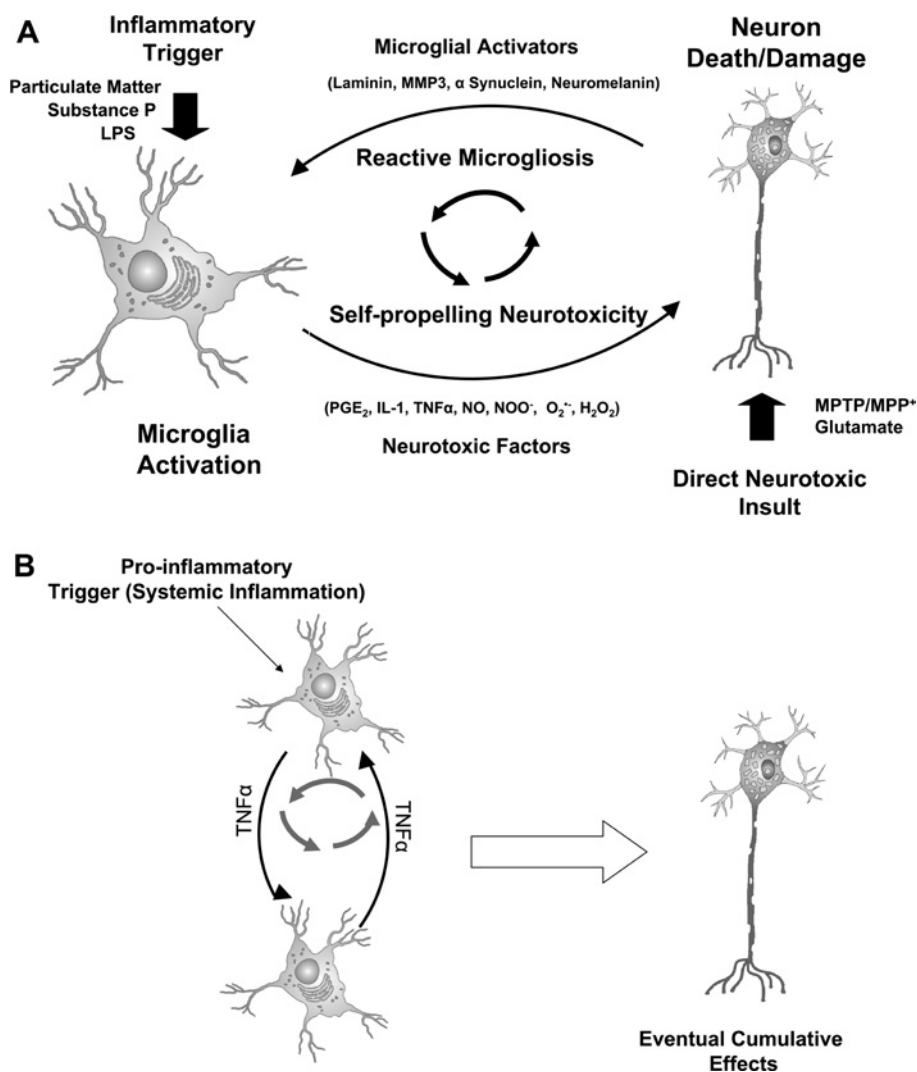
However, it is likely that several factors released from damaged neurons combined with multiple modifications to the ECM are likely to work together to result in reactive microgliosis and progressive DA neurotoxicity. Interestingly, in addition to common factors that may drive reactive microgliosis, such as the ECM and proteases, some factors may be more disease-specific to PD. For example,  $\alpha$ -synuclein, the hallmark protein of PD, has been identified as a soluble neuron injury factor where the aggregated extracellular form of  $\alpha$ -synuclein will activate microglia to cause the production of extracellular superoxide and selective DA neurotoxicity [48]. Further, neuromelanin, a neuropigment located in DA neurons in the human SN, has also been reported to be released by damaged DA neurons to activate microglia and exert DA neuron damage [49]. Further enquiry into these mechanisms of self-potentiating neuron damage is needed for the purpose of identifying definitive markers of neurodegenerative disease and developing therapeutic targets capable of halting disease progression.

### Chronic microglial activation in the absence of neuron damage

Interestingly, several studies have shown that microglia can be activated by a pro-inflammatory stimulus to produce chronic microglial activation without immediate neuron damage (Figure 1B). For example, during critical periods of embryonic development (embryonic day 10.5), maternal exposure to low concentrations of LPS in mice causes microglial activation that persists into adulthood to eventually affect neuronal survival in the adult [19,50]. Recently, we have shown that inflammation induced by a single systemic LPS injection (5 mg/kg, intraperitoneal) in the adult can (i) activate brain microglia to produce chronically elevated pro-inflammatory factors and (ii) induce delayed and progressive loss of DA neurons in the SN [51]. This animal model of microglia-mediated DA neurotoxicity shows a clear chronic activation of microglia, where activation is triggered in the SN at 1 h after LPS treatment and activation remains continuous for at least 10 months (Figure 2). However, the neuron damage in the SN does not begin until 7 months after microglial

### Figure 1 | Chronic microglial activation and progressive neurotoxicity

Evidence points to chronic activation as a critical component of the deleterious microglial response. Microglia can be persistently activated in the absence of a chronic stimulus to exert neurotoxicity through two mechanisms: **(A)** regardless of the initial toxic insult (immunological insult from microglia or direct neuronal toxicity), dying or damaged neurons activate microglia to produce neurotoxic factors, which are toxic to surrounding neurons, resulting in perpetuating toxicity. Modified with permission from Macmillan Publishers Ltd: *Nat. Rev. Neurosci.* [42]; © 2007; <http://www.nature.com/nrn>. **(B)** Autocrine and paracrine signals, such as cytokines, may chronically activate microglia without neuron damage. However, over time and possibly with aging, this chronic microglial activation also has the potential to culminate in DA neuron damage.



activation. This model provides an example of potentially benign microglial activation that progresses over 7 months to become deleterious and neurotoxic. The induction of DA neuron loss may be a product of aging, which is consistent with the fact that PD develops later in life. At present, the mechanisms driving this chronic neuroinflammation in the brain and why the microglial activation eventually becomes toxic are poorly understood. However, the findings that inflammation-mediated neuron damage tends to be delayed and progressive suggest that measures of neurotoxicity may be largely dependent on the timing of the analysis of neuron damage, where the probability of neurotoxicity may increase with the age of the subject.

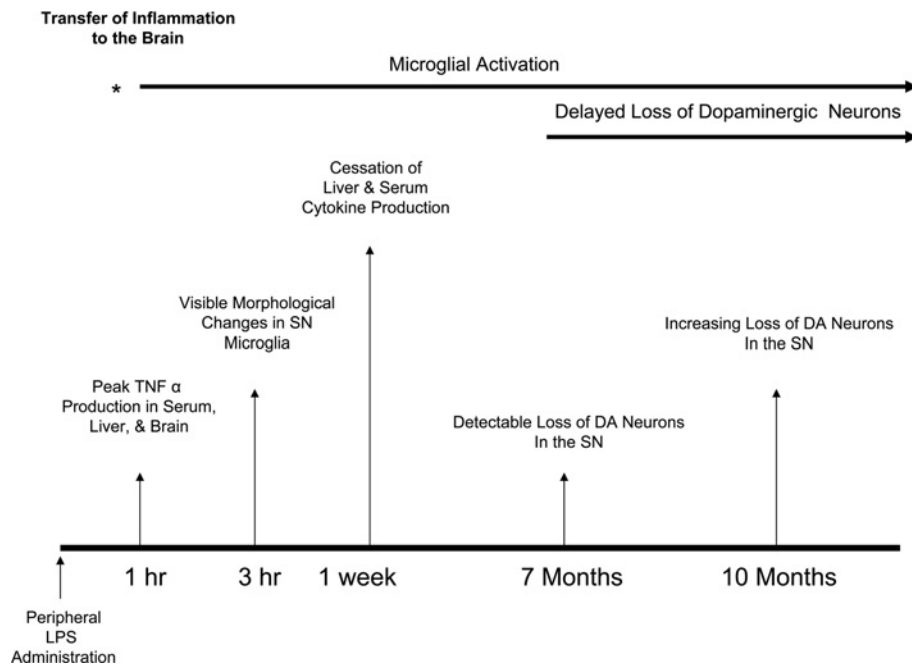
### 'Primed' microglia and neurotoxicity

Several studies suggest that in order for microglia to become deleterious and damage DA neurons, several homeostatic mechanisms have to either be surpassed or fail. One explanation is that microglia can be activated to such an excess with a potent stimulus that regulatory mechanisms are overwhelmed, allowing DA neuron damage to occur. Alternatively, increasing evidence suggests that some stimuli may predispose microglia to react robustly to previously innocuous stimuli, a process termed 'microglia priming'.

In fact, several pro-inflammatory stimuli have been shown to prime microglia. For example, the pesticide rotenone

**Figure 2 | Systemic LPS causes chronic microglial activation and progressive DA neurotoxicity**

This Figure chronologically depicts the pro-inflammatory profiles in the periphery and the brain in response to LPS and the consequences for DA neuron survival. Notably, microglial activation begins at 1 h after LPS treatment and continues for 10 months. DA neurons are lost beginning at 7 months and this damage progresses with time. Modified from *Glia*, vol. 55, no. 5, 2007, pp. 453–462. Copyright © 2007 Wiley-Liss, Inc. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.



primes microglia to result in synergistic microglial activation and associated DA neurotoxicity upon additional insult with LPS [52]. Additionally, aging is shown to provide a pro-inflammatory environment in the brain and is another factor that amplifies the microglial response [53]. Even neuronal death is a factor that primes microglia to become more sensitive to additional stimuli [54]. In fact, through immunological perturbation during critical periods of development [19] or aging and senescence [55], microglia can become primed, where additional stimuli result in an exaggerated and prolonged pro-inflammatory response that enhances neuron damage. Thus microglia can not only induce neuron damage, but also become highly sensitive to additional stimuli, which may predispose them to being persistently activated to produce continuous and uncontrolled neurotoxicity that fails to recede after the instigating stimulus has dissipated.

### Microglia as a source of oxidative stress

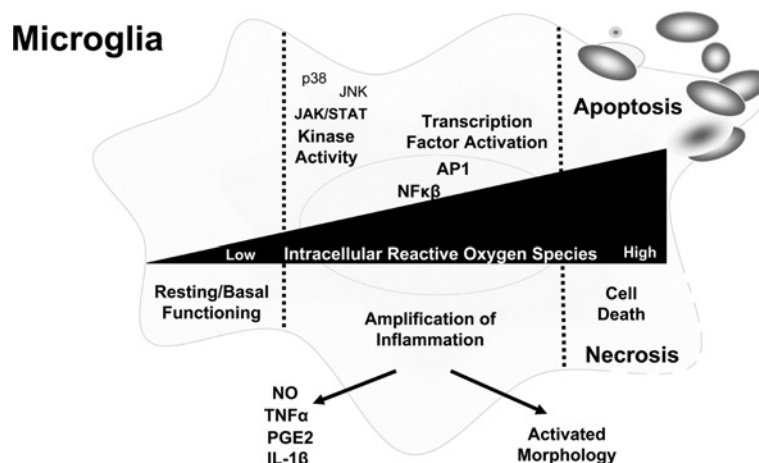
It is hypothesized that microglial activation results in selective DA neurotoxicity due to the inherent susceptibility of the DA neuron to oxidative stress [56]. Microglia are a robust source of oxidative stress in the brain, where extracellular ROS is predominantly generated from NADPH oxidase. NADPH oxidase is a multi-subunit enzyme complex in phagocytes, such as microglia, that is activated during host defence to catalyse the production of superoxide from oxygen. A variety of stimuli, including bacteria, inflammatory peptides

[57] and multiple neurotoxins [14] activate NADPH oxidase. In addition, this enzyme complex is associated with neurodegenerative disorders and neuronal damage. NADPH oxidase is activated in brains from AD (Alzheimer's disease) patients [58], and the catalytic subunit [gp91 (glycoprotein 91)] is up-regulated in PD [25]. Interestingly, NADPH oxidase mediates DA neuron damage across a diverse list of compounds that are toxic through microglial activation, such as LPS [59], rotenone [60], paraquat [20], MPTP [25,54],  $\beta$ -amyloid [61], substance P [21], air pollution [16] and  $\alpha$ -synuclein [48]. At present, most microglia-mediated, selective DA toxins that we have tested in our laboratory exert their toxic effect through NADPH oxidase.

In addition to the production of neurotoxic extracellular superoxide, NADPH oxidase is also thought to regulate microglial signalling (Figure 3). In fact, by altering concentrations of intracellular ROS, NADPH oxidase primes the microglial response to further insult. Triggers of microglia activation, such as rotenone [52] and neuronal death [62], are shown to prime microglia through NADPH oxidase and result in synergistic microglial activation that is associated with neurotoxicity upon additional insult with LPS. Thus microglial NADPH oxidase activation and the production of ROS have been implicated as critical regulators of microglial function and microglia-mediated neurotoxicity. In the case of PD and vulnerable DA neurons, NADPH oxidase and microglia-derived ROS may be a significant contributor to disease progression.

### Figure 3 | Intracellular ROS regulate microglial activation

Microglial activation can result in the production of both extracellular and intracellular ROS through NADPH oxidase. Intracellular ROS act as second messengers capable of modifying gene expression through effects on kinase cascades and transcription factor activation. Upon increasing the levels of intracellular ROS and depletion of the cells' antioxidant defence, ROS act as second messengers to amplify the pro-inflammatory function of microglia, which may contribute to overactivation and neurotoxic consequences. However, higher levels of intracellular ROS may result in microglia death (predominantly apoptosis-anti-inflammatory), similar to that which occurs in phagocytes in the periphery. Modified with permission from Macmillan Publishers Ltd: *Nat. Rev. Neurosci.* [42]; © 2007; <http://www.nature.com/nrn>.



## Conclusions and implications

In summary, inflammation-mediated DA neurodegeneration is commonly characterized by a delayed and progressive loss of DA neurons. Microglia can be chronically activated by either neuron damage and/or paracrine/autocrine cytokine signals to remain persistently activated long after the instigating stimulus has abated. This chronic microglial activation can serve as a regenerating source of cytokines and free radicals in the brain which can fuel progressive DA neurotoxicity. We propose that deleterious microglial activation that is progressively and selectively toxic to DA neurons is defined by the following characteristics: (i) DA neurotoxicity, (ii) NADPH oxidase activation, (iii) microglial priming for enhanced pro-inflammatory response and (iv) resistance to resolution of inflammation. Future efforts need to focus on the biochemical mechanisms that regulate these characteristics in an effort to identify novel therapeutic targets capable of slowing or halting the progression of neurodegenerative disease, particularly PD.

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