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Invited review

Neuroinflammation and oxidative stress: Co-conspirators in the pathology of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a complex disease, with genetics and environment contributing to the disease onset. Recent studies of causative PD genes have confirmed the involvement of cellular mechanisms engaged in mitochondrial and UPS dysfunction, oxidative stress and apoptosis in the progressive degeneration of the dopaminergic neurons in PD. In addition, clinical, epidemiological and experimental evidence has implicated neuroinflammation in the disease progression. This review will discuss neuroinflammation in PD, with particular focus on the genetic and toxin-based models of the disease. These studies have confirmed elevated oxidative stress and the pro-inflammatory response occurs early in the disease and these processes contribute to and/or exacerbate the nigro-striatal degeneration. In addition, the experimental models discussed here have also provided strong evidence that these pathways are an important link between the familial and sporadic causes of PD. The potential application of anti-inflammatory interventions in limiting the dopaminergic neuronal cell death in these models is discussed with evidence suggesting that the further investigation of their use as part of multi-targeted clinical trials is warranted.

1. Introduction

It has been over 50 years since the seminal observation from Arvid Carlsson that dopamine is used in the central nervous system as a neurotransmitter (Carlsson et al., 1957). During this time the death of dopaminergic nerves have been implicated as the central cause for the development of Parkinson's disease (PD). PD is the second most common neurodegenerative disorder worldwide, with a prevalence of approximately 1% in people over age 60 and rising to over 4% by age 85 (de Lau and Breteler, 2006). However, an estimated 3% of cases are identified in individuals younger than age 50 (Hawkes, 2008). Clinically, the disease is characterised by resting tremor, rigidity, bradykinesia and postural instability (Jankovic and Stacy, 2007; Smeyne and Jackson Lewis, 2005). The development of these classical motor symptoms can be attributed to the selective loss of dopaminergic (DA) neurons, primarily in the substantia nigra pars compacta (SN). This hallmark loss of neurons results in striatal dopamine depletion and a resultant dysfunction of the basal ganglia, a cluster of nuclei involved in the initiation and execution of movement (Rodriguez-Oroz et al., 2009). Pathologically, the disease is also characterised by the presence of proteinaceous cytoplasmic inclusions known as Lewy bodies (Lees et al., 2009). Although motor symptoms remain the major criteria for clinical diagnosis, non-motor symptoms including impaired olfaction, constipation, sleep disorders and various neuropsychiatric manifestations can become prominent both before and during PD onset and progression (Chaudhuri and Schapira, 2009).

To date, no effective therapies have been developed to cure PD; however, pharmaceutical treatments focusing on relief and management of symptoms are available. In the early stages of PD, motor symptoms respond well to dopamine replacement therapy, achieved by the administration of L-DOPA, a precursor in the synthesis of dopamine (Birkmayer and Hornykiewicz, 1962). The fact that a therapy first used in the 1960s remains the front line treatment choice for PD underscores our lack of understanding of the

Abbreviations: 6-OHDA, 6-hydroxy dopamine; AR-PD, autosomal recessive Parkinson's disease; BBB, blood-brain barrier; COX, cyclo-oxygenase; CR3/43, MHC Class II; DA, dopaminergic/dopamine; DAMPS, damage-associated molecular patterns; EBM11, anti CD-68; EGF, epidermal growth factor; FGF, fibroblast growth factor; GDNF, glial derived neurotrophic factor; GSH, glutathione; GPx, glutathione peroxidase; 4-HNE, 4-hydroxynonenal; IFN, interferon; ICAM-1, intercellular adhesion molecule 1; IL-, interleukin; LFA-1, lymphocyte function-associated antigen 1; LPS, lipopolysaccharide; LRRK2, Leucine-rich repeat kinase-2; MHC, major histocompatibility complex; MPTP, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; NO, nitric oxide; NOS, nitric oxide synthase; NSAIDS, non-steroidal anti-inflammatory drugs; PAMP, pathogen-associated molecular patterns; PD, Parkinson's disease; PINK1, PTEN-induced putative kinase-1; PRR, pattern recognition receptor; ROS, reactive oxygen species; SN, substantia nigra; SOD, superoxide dismutase; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumour necrosis factor.

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underlying causes of neuronal degeneration in this disease. This review will focus on the molecular mechanisms and interplay by which neuroinflammation and oxidative stress influence the aetiology of PD, with the aim to identify the molecular pathways that can be targeted to retard the progression of the DA cell death in PD.

2. Aetiology of PD

PD is considered to be a multi-factorial disorder with both genetic defects and exposure to environmental factors influencing disease progression (reviewed in Gao et al., 2011). The majority of PD cases are sporadic and idiopathic with only 10% of all cases linked to a genetic cause. To date, 16 PARK loci have been reported, with *SNCA* (PARK1/4) and *LRRK2* (PARK8) and *parkin* (PARK2) and *PINK1* (PARK6) being the most common causes of autosomal dominant (AD-PD) and autosomal-recessive (AR-PD) PD, respectively (reviewed in (Martin et al., 2011)). In addition, mutations in *parkin, SNCA and LRRK2* have also been reported in sporadic PD, suggesting an influence over progression and age of onset of the disease (reviewed in (Kumari and Tan, 2009; Moore et al., 2005). Monogenic and sporadic forms of PD display distinct clinical and pathological features. However, there are many overlapping features, specifically the nigral degeneration, advocating common disease mechanisms. Animal models of the disease support a critical interaction between genetics and the environment in PD pathogenesis. While genetic models of PD generally do not display any overt phenotype (loss of DA neurons or the presence of Lewy bodies), two-hit models involving the use of environmental toxins in these animals are often a better representation of the human pathology. These combined models are useful tools for understanding the underlying mechanisms leading to the neurodegeneration in PD. Indeed, alterations in protein processing, mitochondrial dysfunction and elevated oxidative stress have all been linked to the disease pathogenesis (Obeso et al., 2010). In addition, it is now well accepted that chronic neuroinflammation is pathological feature of the disease (Hirsch and Hunot, 2009; Lee et al., 2009) (Fig. 1).

3. Neuroinflammation

The immune responses within the brain are tightly regulated, a phenomenon first described by Sir Peter Medawar as ‘‘immune privilege’’ (Medawar, 1948). This regulation is partly dependent on the blood-brain barrier (BBB) but also the modulation of the response by the resident cells of the brain, the microglia and astrocytes (and to a lesser extent, neurons). Microglia are the major resident immune cells in the brain, providing innate immunity, however astrocytes and oligodendrocytes are also involved in the neuroinflammatory response (Tansey et al., 2007). Microglia maintain the homeostasis of the brain through the production of various neurotrophic (Brain-Derived Neurotrophic Factor (BDNF), Insulin-like Growth Factor-1 (IGF-1)) and anti-inflammatory factors (IL-10), influencing surrounding astrocytes and neurons. In the healthy brain, the resident microglia exhibit a resting phenotype. However, under stresses such as pathogen invasion, injury, or toxic protein accumulation, microglia become activated, initiating immune responses to instigate tissue repair by clearing debris and apoptotic cells and by releasing growth factors (reviewed in (Aloisi, 1999)). If controlled, the innate immune response will resolve once the initial stress has been eradicated. However, persistence or a failure in the resolution of the inflammatory stimuli will lead to the overproduction of neurotoxic factors including cytokines, chemokines, and prostaglandins. Pro-inflammatory cytokines such as Tumour Necrosis Factor-α (TNF-α) and Interleukin-1β (IL-1β) act on astrocytes, inducing the adaptive immune response while chemokines such as monocyte chemotactic protein-1 (MCP-1)/Chemokine (C-C motif) ligand 2 (CCL2) recruit additional immune cells. In addition, these inflammatory responses may potentiate neuronal cell damage through the generation of reactive oxygen and nitrogen species (ROS/RNS). The inflammatory response in the brain involves both the innate and adaptive immune systems to provide a balance between beneficial and deleterious effects.

3.1. Innate immune response

CNS cells can mount innate immune responses through conserved pattern-recognition receptors (PRRs). The Toll-like receptors (TLRs) bind highly conserved structural motifs either from pathogens (pathogen associated molecular patterns; PAMPs) or from damaged or stressed cells (damaged-associated molecular patterns; DAMPs). Therefore, not only can invading micro-organisms (bacteria, viruses) activate an innate immune response in the CNS, evidence suggests endogenous signals such as heat shock proteins, high mobility groups box chromosomal protein 1 (HMGB-1), DNA, Aβ, α-synuclein and tau can also (Arroyo et al., 2011). TLR expression is upregulated in a wide range of CNS disorders in microglia, astrocytes and neurons and is generally associated with increased production of pro-inflammatory cytokines to promote neuronal cell death (Carty and Bowie, 2011). The nucleotide-binding oligomerization domain-like receptors (NLRs) are another family of PRRs expressed in both microglia and astrocytes that recognise invading pathogens to initiate a pro-inflammatory response (Chauhan et al., 2009). The receptor for advanced glycation end-products (RAGE) has also been implicated in the release of pro-inflammatory cytokine and free radicals in neurological disorders through the ligand, HMGB-1. It is expressed on both neurons and astrocytes and is increased following oxidative stress and immune/inflammatory responses, thereby perpetuating the damaging cellular effects (Han et al., 2011).

3.2. Adaptive immune response

Growing evidence supports an association between neuropathologies of the CNS and immune changes in the periphery. Although the innate immune response in the CNS can influence the immune status of the organism as whole, we now know that immune activation in the periphery can also affect neuronal cell survival. Peripheral immune responses have been linked to many CNS disorders including PD, Alzheimer’s disease (AD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), stroke, traumatic brain injury (Beschorner et al., 2002; Brochard et al., 2009; Combrinck et al., 2002; Cunningham et al., 2005; Miklossy et al., 2006; Rentzos et al., 2012). In addition, aging has been reported to be a risk factor in a discordant link between the peripheral immune system and the CNS (Godbout et al., 2005). These studies all suggest that activated or primed microglia mount an exaggerated response to a secondary stimuli compared to resting microglia, thereby furthering contributing to the neuropathologies and their associated behavioural defects.

Under normal physiological conditions, activated T- and B-lymphocytes are not present in high numbers in the CNS. However, following infection or injury in the CNS and the subsequent induction of the innate immune response, the production of pro-inflammatory cytokines such as IL-1β and TNF-α by glial cells is increased. This increases the permeability of the BBB, leading to the upregulation in cellular adhesion molecules on microvascular endothelial cells. Activated T cells and B cells then migrate to the site of neuronal injury. In addition, there is an upregulation in chemokines within the brain leading to increased migration of peripheral leukocytes. It is widely considered that acute neuroinflammation is beneficial in the CNS after injury or infection by ensuring homeostasis. However, chronic neuroinflammation is known to be dam-