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Review

Neuroinflammatory mechanisms in Parkinson's disease: Potential environmental triggers, pathways, and targets for early therapeutic intervention

Malú G. Tansey *, Melissa K. McCoy, Tamy C. Frank-Cannon

Department of Physiology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, USA

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Abstract

Most acute and chronic neurodegenerative conditions are accompanied by neuroinflammation; yet the exact nature of the inflammatory processes and whether they modify disease progression is not well understood. In this review, we discuss the key epidemiological, clinical, and experimental evidence implicating inflammatory processes in the progressive degeneration of the dopaminergic (DA) nigrostriatal pathway and their potential contribution to the pathophysiology of Parkinson's disease (PD). Given that interplay between genetics and environment are likely to contribute to risk for development of idiopathic PD, recent data showing interactions between products of genes linked to heritable PD that function to protect DA neurons against oxidative or proteolytic stress and inflammation pathways will be discussed. Cellular mechanisms activated or enhanced by inflammatory processes that may contribute to mitochondrial dysfunction, oxidative stress, or apoptosis of dopaminergic (DA) neurons will be reviewed, with special emphasis on tumor necrosis factor (TNF) and interleukin-1-beta (IL-1β) signaling pathways. Epigenetic factors which have the potential to trigger neuroinflammation, including environmental exposures and age-associated chronic inflammatory conditions, will be discussed as possible 'second-hit' triggers that may affect disease onset or progression of idiopathic PD. If inflammatory processes have an active role in nigrostriatal pathway degeneration, then evidence should exist to indicate that such processes begin in the early stages of disease and that they contribute to neuronal dysfunction and/or hasten neurodegeneration of the nigrostriatal pathway. Therapeutically, if anti-inflammatory interventions can be shown to rescue nigral DA neurons from degeneration and lower PD risk, then timely use of anti-inflammatory therapies should be investigated further in well-designed clinical trials for their ability to prevent or delay the progressive loss of nigral DA neurons in genetically susceptible populations.

Keywords: Parkinson's disease; Neuroinflammation; Microglia activation; Cytokines; Neurodegeneration; Oxidative stress; Dopamine neuron death; Anti-inflammatory therapy; TNF; IL-1β

Contents

* Corresponding author. Fax: +1 214 645 6049.
E-mail address: malu.tansey@utsouthwestern.edu (M.G. Tansey).

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Overview

Although the etiology of idiopathic Parkinson's disease (PD) is unknown, this neurodegenerative disease is characterized by the loss of dopamine (DA)-producing neurons in the ventral midbrain with cell bodies in the substantia nigra pars compacta (SNpc) that project to the striatum (nigrostriatal pathway), with a lesser effect on DA neurons in the ventral tegmental area (VTA) (Uhl et al., 1985; Moore et al., 2005). PD prevalence is age-associated, with approximately 1% of the population being affected at 65–70 years of age, increasing to 4–5% in 85-year-olds (Fahn, 2003). Epidemiological studies and pathological analyses demonstrate a mean age of onset of 70 in sporadic PD, which accounts for about 95% of patients (Tanner, 2003; Farrer, 2006); but familial forms of the disease linked to mutations in a restricted number of genes account for 4% and these patients develop early-onset disease before the age of 50 (Mizuno et al., 2001; Van Den Eeden et al., 2003). Over the past decade, a definitive link has been demonstrated between mutations in specific genes and heritable forms of PD (for an in-depth review see Farrer, 2006). Mutations in Parkin, DJ-1 and PINK1 have been linked to recessively inherited parkinsonism (Kitada et al., 1998; Bonifati et al., 2003a,b; Valente et al., 2004b,a) whereas mutations in α-synuclein and LRRK2 (also known as Dardarin) have been linked to dominantly inherited parkinsonism (Polymeropoulos et al., 1997; Paisan-Ruiz et al., 2004; Zimprich et al., 2004). Although some of these mutations can be found in higher frequency among certain ethnic populations, together they account for only a small percentage (perhaps up to 15%) of all PD cases.

For the idiopathic or non-familial forms of PD, the prevailing view is that the causes are multifactorial and genetic predispositions, environmental toxins, and aging are likely to be important factors in disease initiation and progression (Nagatsu and Sawada, 2006). The finding that the single greatest risk factor for developing PD is age, implicates cumulative CNS damage as a causative mechanism. However, nigral lesions in PD and aged individuals vary considerably, raising the possibility that aging and the disease process underlying PD may be occurring independently. At the cellular level, cumulative evidence supports an "oxidative stress hypothesis" for initiation of nigral dopamine neuron loss (for in-depth reviews see Owen et al., 1996, 1997; Jenner and Olanow, 1998; Beal, 2005; Lin and Beal, 2006). Oxidative stress occurs when there is an intracellular accumulation of reactive oxygen and nitrogen species (ROS/RNS) due to reduced endogenous anti-oxidant capacity and/or overproduction of ROS within the cell. Clearly, all aerobic organisms are susceptible to oxidative stress because ROS (primarily superoxide and hydrogen peroxide) are produced by mitochondria during respiration. However, the brain is considered to be abnormally sensitive to oxidative damage in part because oxygen consumption by the brain constitutes 20% of the total oxygen consumption in the body; and the brain is enriched in the more easily peroxidizable fatty acids (20:4 and 22:6) while its anti-oxidant defenses (such as catalase, superoxide dismutase, glutathione, and glutathione peroxidase) are relatively sparse (Floyd, 1999). Within the midbrain, the SN appears to be among the most vulnerable regions primarily because it operates under a pro-oxidative state relative to other parts of the brain even in healthy individuals. Specifically, the substantia nigra has a high metabolic rate combined with a high content of oxidizable species, including DA, DA-derived ROS, neuromelanin, polyunsaturated fatty acids, iron, and a low content of antioxidants (glutathione in particular) all of which render this brain region highly vulnerable to the effects of peroxynitrite and sulfite (Marshall et al., 1999); when combined with the high levels of ascorbate in the brain, the iron/ascorbate mixture is a potent pro-oxidant for brain membranes (Floyd, 1999). Further support for this claim is the finding that carbonyl modifications (indicative of protein oxidation) in the SN of normal individuals are present at twice the level present in the basal ganglia and prefrontal cortex (Floor and Wetzel, 1998). The extent of oxidative damage measured by the presence of the nucleoside oxidation product 8-hydroxyguanosine is approximately 16-fold greater and that of the aldehyde 4-hydroxy-2,3-nonenal (HNE) is about 6-fold greater in SN of PD brains compared to that of healthy control subjects (Yoritaka et al., 1996; Zhang et al., 1999). Biochemical studies indicate HNE can covalently modify proteins, block mitochondrial respiration (Picklo et al., 1999), and induce caspase-dependent apoptosis (Liu et al., 2000b). In summary, evidence of enhanced oxidative stress in the brains of PD patients includes increased oxidation of lipids, DNA and proteins and has been documented in a large number of studies