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Review

Inflammation and infection in Parkinson's disease

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Summary. The hallmark of Parkinson's disease (PD) is a specific degeneration of dopaminergic neurons in the substantia nigra (SN). The cause of nigral dopaminergic neuronal cell death in PD and its underlying mechanisms remain elusive, however, involvement of inflammatory events has been postulated because inflammatory features have been described in the brain of PD patients. Some evidence also suggest that a possible deleterious effects of neuroinflammatory processes by infection in experimental models of neurodegenerative disease. In this review, we summarize and discuss the latest findings regarding inflammation in PD. Especially, we focused on the relationship between infection and PD.

Key words: Parkinson's disease, Inflammation, Infection, Substantia nigra, Dopaminergic neurons, LPS, Caspase-11, Interleukin-1ß

Introduction

Parkinson's disease (PD) is one of the most common chronic progressive neurodegenerative disorders, although its underlying disease mechanisms remain poorly understood. Exogenous agents, herbicide, infection, inflammatory response and oxidative stress have been suggested as the most probable causes of dopaminergic neurodegeneration in the substantia nigra (Ritz and Yu, 2000; Nguyen et al., 2002; Orr et al., 2002; Ischiropoulos and Beckman, 2003; Gorell et al., 2004). Some cases of PD are associated with head trauma, suggesting that an inflammatory component participates in PD (Herrera et al., 2005). Several works describing many case of PD are accompanied by brain inflammation with a dramatic proliferation of reactive microglial cells (McGeer et al., 1988a,b). Moreover, in patients with PD, high levels of interleukin-1ß (IL-1ß) were detected in the striatum and cerebrospinal fluid (Mogi et al., 1994, 1996). These findings suggest inflammatory reaction and infection can potentially participate in the pathogenesis of PD.

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Infection and neurodegenerative disorders

The innate immune response is a rapid and coordinated cascade of reactions by cells of the host to pathogens and insults (Nguyen et al., 2004). In the central nervous system (CNS), the accuracy of this innate immune response can protect neurons by favoring remyelination and trophic support afforded by glial cells. Conversely, its deregulation might be harmful for neuronal integrity and might trigger neurodegeneration (Nguyen et al., 2002; Wyss-Coray and Mucke, 2002). Endotoxin lipopolysaccharide (LPS), a component of Gram-negative bacterial cell wall is a potent inducer of innate immune response. Intraperitoneal injection of LPS induces a strong and transient increase in expression of the gene encoding Toll-like receptor 2, IκB-α, COX-2, IL-6 and IL-6 receptor in the circumventricular organs (Vallieres and Rivest, 1997; Laflamme et al., 1999, 2001; Rivest, 2003). Systemic injection of LPS leads to breakdown of the blood-brain barrier (BBB) and invasion of granulocytes or soluble molecules (Bohatschek et al., 2001). These findings suggest that systemic injection of LPS can potentially affect neurons in the brain. In fact, repeated intraperitoneal injection of LPS exacerbates motor axon degeneration in a mouse model of amyotrophic lateral sclerosis (ALS; Nguyen et al., 2004). Ling et al. (2002) suggested that prenatal LPS exposure caused loss of dopamine neurons in the postnatal rat midbrain, and prenatal infections may represent a risk factor for PD. Systemically administered LPS is known to enter the chorioamniotic environment and is potentially relevant to dopaminergic neuron development, as it is elevated in humans as a result of a common condition of pregnancy called bacterial vaginosis (BV) which is associated with the overgrowth of Gram-negative bacteria (Thorsen et al., 1998; Haefner, 1999). BV is associated with increased levels of LPS and IL-1ß in the chorioamniotic environment, and has been linked to numerous neurological disorders including white matter damage, intraventricular hemorrhage and cerebral palsy (Ando et al., 1988; Dammann and Leviton, 1997; Ling et al., 2002). Thus, examination of the mechanism of neurodegeneration by LPS is very important for the understanding of pathogenesis of neurodegenerative

disorders.

The substantia nigra (SN) is far more sensitive to LPS than other regions. The special susceptibility of SN could be due to special structural differences between SN and the other region. For instance, SN has the highest concentration of microglia in the brain (Lawson et al., 1990). LPS is a potent inducer of microglial activation, so density of microglial cells seems to contribute to the special susceptibility of SN against LPS.

LPS and Parkinson's disease

Activation of microglia is believed to contribute to neurodegenerative processes through the release of proinflammatory cytotoxic factors, including interleukin-1ß, tumor necrosis factor-α (TNF-α), nitric oxide (NO), reactive oxygen species (ROS) and arachidonic acid metabolites (Orr et al., 2002; Teismann et al., 2003). Intranigral injection of LPS induces a strong microglial activation and degeneration of dopaminergic neuron in the SN and striatum (Herrera, et al., 2000). In their studies, only the dopaminergic neurons of the SN were affected, with no detectable damage to either the GABAergic or the serotonergic neurons. The damage to the dopaminergic neurons in the SN was permanent, as observed 1 year post-injection. In addition, Gao et al. (2002) reported that neurotoxicity by LPS was selective to dopaminergic neurons compared with GABA neurons and 5-HT neurons *in vitro*. Kim et al. (2000) also reported that neurons in the SN are most sensitive to LPS-induced neurotoxicity, whereas neurons in the hippocampus or cortex remain insensitive to treatment, even with high concentrations of LPS *in vitro* and *in vivo*. Therefore, the intranigral injection of LPS is an interesting model for studying the selective effects of inflammatory reaction on the dopaminergic system and also potentially useful for studying PD (Herrera et al., 2000; Kim et al., 2000; Liu et al., 2000; Castano et al., 2002; Gao et al., 2002; Iravani et al., 2002, 2005; Qin et al., 2004, Tomas-Camardiel et al., 2004; Iczkiewicz et al., 2005).

We studied the effects of the intranigral injection of LPS on dopaminergic system of the mice. Intranigral injection of LPS decreased tyrosine hydroxylase-positive neurons and increased microglial cells in the SN compared with the contralateral side injected with vehicle at days 7 and 14 post-injection (Arai et al., 2004). Moreover, intranigral injection of LPS induced the expression of caspase-11 mRNA at 6-12 hour post-injection and caspase-11 at 8-12 hour post-injection in the ventral midbrain. LPS increased interleukin-1ß content in the ventral midbrain at 12-24 hour post-injection. Conversely, LPS failed to elicit these responses in caspase-11 knockout mice. In our results, caspase-11 plays a crucial role in the LPS-induced dopaminergic neurotoxicity in mice. Furuya et al. (2004) reported that caspase-11 mediates the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced striatal-nigral dopaminergic neurotoxicity, suggesting that caspase-11 is involved in selective dopaminergic neurodegeneration in the SN in both MPTP and LPS models.

Caspase-11 and interleukin-1ß in LPS-induced dopaminergic neurotoxicity

Murine caspase-11 is a member of the caspase-1 subfamily (Wang et al., 1996) and expression of caspase-11 is regulated by NF-κB (Schauvliege et al., 2002). Caspase-1 is involved in processing pro-IL-1ß to mature IL-1ß, and the activation of caspase-1 is induced by caspase-11; therefore caspase-11 is essential for IL-1ß secretion (Wang et al., 1998). Caspase-11 knockout mice were resistant to LPS-induced septic shock (Wang et al., 1998), indicating that caspase-11 plays a major role in the inflammatory process by LPS. In addition, caspase-11 knockout mice were resistant to experimental autoimmune encephalomyelitis (EAE) as a mouse model of multiple sclerosis (Hisahara et al., 2001), and apoptosis induced by ischemic brain injury (Kang et al., 2000). These findings suggest that caspase-11 highly contributes to neurodegeneration in mice. In our study, caspase-11 knockout mice were resistant to LPS-induced increase in IL-1ß and microglial activation in the SN (Arai et al., 2004). Previous studies demonstrated the expression of caspase-11 in brain neuron and microglia by MPTP (Furuya et al., 2004) and hypoxia (Kim et al., 2003). Similarly, in their studies, expression of caspase-11 by LPS was observed in both microglial cells and neurons (Arai et al., 2004). Caspase-11 in microglial cells and neurons contribute to IL-1ß secretion (Kim et al., 2003) and apoptosis (Kang et al., 2000; Hisahara et al., 2003), respectively. Therefore both inflammatory process and apoptotic pathway seem to participate in LPS-induced SN dopaminergic neurotoxicity.

ALS is a progressive age-dependent disease involving degeneration of motor neurons in the brain, brainstem and spinal cord. In a transgenic mouse model of ALS, Friedlander et al. (1997) showed that a dominant negative inhibitor of a cell-death gene, the interleukin-1ß-converting enzyme (ICE), significantly slows the symptomatic progression of ALS. Mochizuki et al. (2001) suggested that a dominant negative inhibitor of Apaf-1, which is responsible for recruitment of procaspase-9, suppressed the mitochondrial apoptotic cascade in the chronic MPTP induced mouse model of Parkinson's disease. These results indicate that ICE-like proteases and pro-apoptotic caspases might affect disease progression in the ALS and Parkinson's disease models, and suggest ICE inhibitors or caspase inhibitors may be of value in the treatment of ALS or Parkinson's disease in humans.

In patients with PD, high levels of IL-1ß were detected in the striatum and cerebrospinal fluid (Mogi et al., 1994, 1996), therefore inhibition on the excessive effects of IL-1ß has potential to be a target for treatment of PD. Minocycline has neuroprotective effects on

MPTP, LPS and 6-OHDA-induced dopaminergic neurodegeneration via inhibition on microglial activation and IL-1ß release in midbrain (Du et al., 2001; He et al., 2001; Wu et al., 2002; Tomas-Camardiel et al., 2004). We identified that minocycline inhibits caspase-11 expression in LPS-induced mouse model of PD, suggesting that neuroprotective effects of minocycline on dopaminergic neurons are related to inhibition of caspase-11 expression (unpublished data). Chemically modified derivatives of tetracyclines, like minocycline, may prove effective in preventing or altering the progression of PD.

The pass through BBB of peripheral granulocyte into the neural parenchyma by LPS

The cerebral microvasculature of the brain, which forms the BBB, regulates the movement of substances from the blood to the brain. BBB damage has been reported during systemic infections, when pathogens activate various mediators leading to dysfunction of organs, including the brain (Herrera et al., 2005). In PD patients, dysfunction of BBB was observed (Kortekaas et al., 2005). Simard and Rivest (2004) suggest that microglia of blood origin could activate cells of the immune system and cause harm to the CNS. A septic encephalopathy is observed in 70% of patients suffering sepsis (Bolton et al., 1993). Bohatschek et al. (2001) reported that systemic injection of LPS induces breakdown of BBB and leads to invasion of granulocytes into the brain in mice. Thus, infection is a risk factor for PD (Perry et al., 2003). Herrera et al. (2005) suggests that external factors such as infection, stroke and trauma may disrupt the BBB with the consequent extravasation of substances that may activate microglial cells and leads to the formation of ROS. Kokovay and Cunningham (2005) also reported that bone-marrow-derived microglial cells contribute to the neuroinflammatory response and express iNOS in the brain of MPTP mouse model of Parkinson's disease. We also observed bone-marrow-derived microglia extravasated in SN of mice transplanted bone marrow from GFP transgenic mice (Furuya et al., 2003; unpublished data). In addition, activated microglial cells release several substances, such as proinflammatory cytokines, nitric oxide and ROS, which may lead to dopaminergic neuronal death (Fig. 1). From these findings, the protection against inflammatory signal transduction from periphery into the brain by infection may be important for the treatment of PD. Especially the treatment for Gram-negative bacterial infection may be the key for suppression on increase in LPS level in the body of PD patients.

The potential of anti-inflammatory drug as anti-Parkinson's disease drug

It is reported that nuclear translocation of NF-κB is increased in dopaminergic neurons of PD patients (Hunot et al., 1997) and it is considered that inflammation or infection increases the risk of PD (Nguyen et al., 2002; Chen et al., 2003). Dexamethasone, a potent anti-inflammatory drug prevented pro-inflammatory glial activation and the loss of dopaminergic neuron (Castano et al., 2002), suggesting that inhibition of NF-κB may be useful for treatment of PD. Minocycline has neuroprotective effects on dopaminergic neurons in MPTP, LPS and 6-OHDA-induced PD animal models (Du et al., 2001; He et al., 2001; Wu et al., 2002; Tomas-Camardiel et al., 2004). We also observed that minocycline shows neuroprotective effects on dopaminergic neurons via inhibition of caspase-11 expression in LPS-induced PD model in mice, however high dosage was required for the neuroprotective effects compared with clinical dose as anti-biotics (unpublished data). Chemical modification derivatives of tetracyclines, like minocycline using structure-activity relationship analysis, may lead to creation of the drug that has neuroprotective effects at low dose. We confirmed that anti-IL-1ß neutralizing antibody has neuroprotective effects on LPS-induced dopaminergic neurotoxicity by intranigral injection in mice (unpublished data); however this treatment using antibody has issue of drug delivery to targeting region for clinical use. Selective inducible nitric oxide synthase (iNOS) inhibitors also have

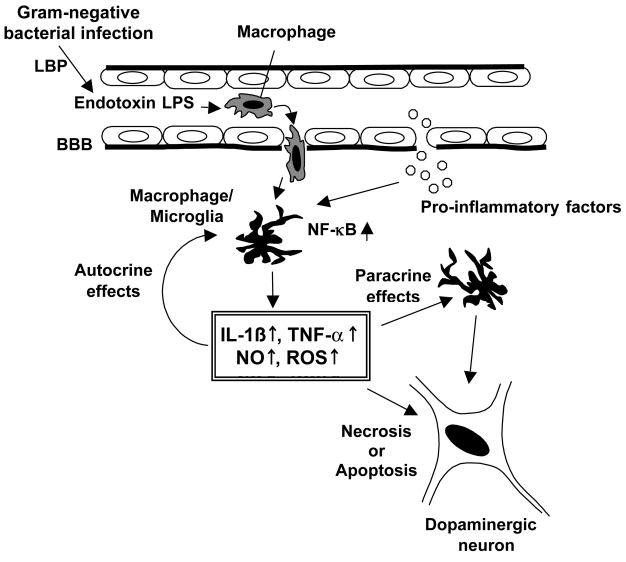

Fig. 1. Neuron-microglia/macrophage interactions that may lead to neuronal death. LPS may be released from Gram-negative bacterial cell wall by LPS-binding protein (LBP) in blood. LPS may disrupt the blood brain barrier (BBB) with consequent extravasation of pro-inflammatory factors and macrophage. Parenchymal microglia and macrophage/microglia derived from peripheral macrophage may be activated by LPS and pro-inflammatory factors. Activated microglia/macrophage release cytokines, nitric oxide (NO) and reactive oxygen species (ROS), which may lead to neuronal death. Inhibition of the microglial activation would be important for the prevention of the neurodegenerative process.

neuroprotecive effects on dopaminergic neurons in LPS-induced PD model in rats (Iravani et al., 2002; Arimoto and Bing, 2003). Oxidative stress and nitration may be associated with neurodegeneration (Ischiropoulos and Beckman, 2003), so radical scavengers or iNOS inhibitors may have potential to be effective against neurodegenerative disorders. Cop-1, copolymer-1 immunization has been used effectively in patients with chronic neuroinflammatory disease such as relapsing remitting multiple sclerosis (Benner et al., 2004). They suggested that Cop-1 immunization is effective in a mouse model of PD, therefore a vaccination strategy may represent a promising therapeutic avenue for PD.

Concluding comments and future directions

PD is a common neurodegenerative disorder characterized by the progressive loss of the dopaminergic neurons in the SN. The loss of dopamine neurons is associated with microglial activation and elevation of cytokines, ROS and NO. Overproduction of free radicals cause an imbalance in the oxidation/reduction capacity of cells and react with proteins and nucleic acids to alter their functions, or induce lipid peroxidation, leading to cell death (Orr et al., 2002). There is considerable evidence that NO could be pivotal to the pathogenesis of PD, and the increase in NO can be attributed to the activation of microglia (Hunot et al., 1996). The concentration of nitrites is increased in PD cerebrospinal fluid (Qureshi et al., 1995), and 3-nitrotyrosine, an index of protein nitrosylation induced by the NO-derived molecule peroxynitrite, has been detected in SN of PD patients (Good et al., 1998). Pro-inflammatory cytokines, such as IL-1ß and TNF-α stimulate unactivated microglia, propagating the microglial response and microglia-related injury to neurons. Cytokines may directly bind to their receptors on the cell surfaces on dopaminergic neurons (Hirsch and Hunot, 2000), and could trigger intracellular death related signaling pathways. Inflammation and infection are risk factors for PD, therefore selection of anti-biotics may be important for the control of LPS level in the body. Chronic activation of microglial cells and deregulated innate immunity has profound and detrimental effects on neuronal survival. Thus, inflammatory response and environmental factors such as infections may require more attention and revision, especially in sporadic case of PD evolving over extended periods of time.

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