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Review

Non-steroidal anti-inflammatory drugs in Parkinson's disease

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Abstract

Parkinson's disease (PD) is known to be a chronic and progressive neurodegenerative disease caused by a selective degeneration of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNc). A large body of experimental evidence indicates that the factors involved in the pathogenesis of this disease are several, occurring inside and outside the DAergic neuron. Recently, the role of the neuron–glia interaction and the inflammatory process, in particular, has been the object of intense study by the research community. It seems to represent a new therapeutic approach opportunity for this neurological disorder. Indeed, it has been demonstrated that the cyclooxygenase type 2 (COX-2) is up-regulated in SNc DAergic neurons in both PD patients and animal models of PD and, furthermore, non-steroidal anti-inflammatory drugs (NSAIDs) pre-treatment protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6 hydroxydopamine (6-OHDA)-induced nigro-striatal dopamine degeneration. Moreover, recent epidemiological studies have revealed that the risk of developing PD is reduced in humans who make therapeutical use of NSAIDs. Consequently, it is hypothesized that they might delay or prevent the onset of PD. However, whether or not these common drugs may also be of benefit to those individuals who already have Parkinson's disease has not as yet been shown.

In this paper, evidence relating to the protective effects of aspirin or other NSAIDs on DAergic neurons in animal models of Parkinson's disease will be discussed. In addition, the pharmacological mechanisms by which these molecules can exert their neuroprotective effects will be reviewed. Finally, epidemiological data exploring the effectiveness of NSAIDs in the prevention of PD and their possible use as adjuvants in the therapy of this neurodegenerative disease will also be examined.

Keywords: Parkinson's disease; Aspirin; Cyclooxygenase inhibitors; Neuroprotection; Neurodegenerative disease; Inflammation; Hydroxyl radicals

Contents

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Introduction

Parkinson's disease (PD) is the most prevalent neurological disorder of the basal ganglia, and it is characterized by a progressive loss of dopaminergic (DAergic) neurons in the caudate nucleus, putamen and substantia nigra (SN) (Ehringer and Hornykiewicz, 1960; Riederer and Wuketich, 1976). The loss of DAergic neurons in the substantia nigra pars compacta (SNc) is the principal feature of PD (Bernheimer et al., 1973) and results in cardinal motor symptoms such as tremor at rest, bradykinesia, muscular rigidity, stooped posture and instability (Sian et al., 1999). Hitherto, despite the recent progress in understanding the etiopathogenesis of PD, the modalities whereby the neurodegenerative process begins and progresses are still unclear. The situation is further complicated by the large number of factors that seem to be involved in the onset of this disease, such as aging, genetic vulnerability, exogenous or endogenous toxins, hydroxyl radicals production, neuronal metabolic disturbances and inflammation (Hirsch et al., 1998; Sian et al., 1999; Jellinger, 2000; Gebicke-Haerter, 2001; Jenner and Warren, 2006). The consequent cumulative neuronal insults attributable to these metabolic stress factors may promote premature SNc DAergic degeneration through the activation of apoptotic programs (Hartmann and Hirsch, 2001; Novikova et al., 2006; Nair et al., 2006). However, the specifics and sequential neuroapoptotic events associated with premature, progressive SNc neuronal atrophy remain undefined.

Thus far, among the various accepted experimental models of PD, neurotoxins still represent the most popular tools to produce selective death of DAergic neurons both in *in vitro* and *in vivo* systems. Even though recent genetic discoveries have lead to a number of different genetic models of PD, none of these shows the typical degeneration of DAergic neurons (Beal, 2001; Fleming et al., 2005). Among the neurotoxins, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a product of synthetic meperidine derivative, and 6-hydroxydopamine (6-OHDA), hydroxylated dopamine derivatives are the most used for inducing parkinsonian features in cells and animal species. MPTP is metabolized to the 1-methyl-4-phenylpyridinium ion (MPP^+) by monoamine oxidase-B (MAO-B) (Langston et al., 1984). This highly toxic metabolite is selectively taken up into DAergic neurons, via the dopamine (DA) transporter (Snyder and D'Amato, 1986), where it provokes an intracellular accumulation of Ca^{2+}, interfering with the function of nerve terminals in the striatum (Sun et al., 1988) and inhibiting complex 1 (NADH-ubiquinone oxidoreductase) of the respiratory chain causing progressive cell death (Cleeter et al., 1992). On the other hand, the neurotoxic effects of 6-OHDA are mediated by the generation of hydroxyl radicals, pro-inflammatory mediators or pro-apoptotic agents (Cohen, 1984; Jeon et al., 1995; Bové et al., 2005). The results of the administration of each neurotoxin, albeit by different mechanisms, is DA depletion in the nigro-striatal pathway of laboratory animals and molecular alterations comparable to those seen in PD's patients (Blum et al., 2001). Recently, it has been shown that 6-OHDA and MPTP like the bacterial lipopolysaccharide (LPS) induce the death of DA cells activating an immune response (Wang et al., 2005; Vijitruth et al., 2006; de Meira Santos Lima et al., 2006). These animal models have been crucial in the study of PD and have allowed the formulation of different hypotheses about its etiopathogenesis, and recently, they have been utilized to determine the role of inflammation in DA neuronal death. Moreover, toxin-based models have been useful in developing neuroprotective and neurorestorative strategies and in testing new drugs for the treatment of this disorder. In this review, experimental data regarding the role of neuroinflammation in the aetiology of PD, the effect of non-steroidal anti-inflammatory drugs (NSAIDs) and the possibility for their use as a new therapeutic approach for this neurodegenerative disease will be reviewed.

Inflammation in Parkinson's disease

Decades of research on the aetiology of Parkinson's disease have resulted in much information, but little has been gained in establishing the events causing the initiation and progression of the disease. Recently, the involvement of neuroinflammation and microglial activation in the pathogenesis of PD (Table 1) has been emphasized (Mogi et al., 1994a,b; Mogi et al., 1995; Blum-Degen et al., 1995; Rowe et al., 1998; Langston et al., 1999; Mirza et al., 2000; Knott et al., 2000, 2002; McGeer et al., 2001; McGeer et al., 2002; Imamura et al., 2003; Ouchi et al., 2005; Ishida et al., 2006; Kim and Joh, 2006). Results of neurotoxin models of PD, corroborating findings obtained in transgenic animal models and epidemiological studies, strongly

Table 1
Evidence of inflammation in PD-Human data

Study	Evidence from PD patients
McGeer et al., 1988	Up-regulation of MHC molecules in brains
Mogi et al., 1994a,b	Increased level TNF-α, in the striatum and CSF
Mogi et al., 1995	Increased levels of β2-microglobulin, the light chain of MHC, in striata
Blum-Degen et al., 1995	Increased levels of IL-1β and IL-6 in the CSF
Rowe et al., 1998	Presence of antibody reactivity to quinone-modified proteins
Langston et al., 1999	Presence of gliosis and clustering of microglia around nerve cells in MPTP-induced parkinsonism in humans
Mirza et al., 2000	Absence of reactive astrocytosis in the inflammatory process in PD autopsies.
Knott et al., 2000	Up-regulation of nitric oxide synthase- and cyclo-oxygenase-1- and -2-containing amoeboid microglia
Knott et al., 2002	Up-regulation of glial neurotrophins (BDNF, NT-3) in response to signals released from failing nigral neurons.
McGeer et al., 2002	Association of interleukin-1 beta polymorphisms with idiopathic PD
Imamura et al., 2003	The number of activated microglia is higher not only in the SN and putamen but also in the hippocampus, transentorhinal cortex, cingulate cortex and temporal cortex in PD.
Ouchi et al., 2005	Parallel changes in microglial activation and corresponding dopaminergic terminal loss in the affected nigrostriatal pathway in early PD.
Ishida et al., 2006	Increased expression of PAR-1 in astrocytes in SNpc of PD brain.