Pathogenesis of Parkinson's disease: oxidative stress, environmental impact factors and inflammatory processes

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Abstract: Current hypothesis of neuronal degeneration in Parkinson's disease (PD) have been proposed, including formation of free radicals and oxidative stress, mitochondrial dysfunction, excitotoxicity, trophic factor deficiency, inflammatory processes, genetic factors, environmental impact factors, toxic action of nitric oxide, apoptosis, and so on. This review mainly discussed oxidative stress, environmental impact factors, and inflammatory processes in PD.

Keywords: pathogenesis; Parkinson's disease; oxidative stress; neurogenic inflammation; environmental impact

1 Introduction

Various mechanisms of neuronal degeneration in Parkinson's disease (PD) have been proposed. These include formation of free radicals and oxidative stress, mitochondrial dysfunction, excitotoxicity, calcium cytotoxicity, trophic factor deficiency, inflammatory processes, genetic factors, environmental impact factors, toxic action of nitric oxide and apoptosis—all of which may interact and amplify each other in a vicious cycle of toxicity leading to neuronal dysfunction, atrophy, and finally cell death (Fig. 1)^[1-4]. In this review we mainly discussed the oxidative stress, environmental impact factors, and inflammatory processes in PD.

2 Oxidative stress

The "oxidative stress" hypothesis infers an imbalance between the formation of cellular oxidants and the antioxidative processes (Fig. 2). Oxidative stress, due to the excessive formation of hydrogen peroxide and oxygen-derived free radicals, such as hydroxyl (OH·) and super-

oxide (O₂·) radicals, can cause cell damage due to chain reaction of membrane lipid peroxidation and/or alterations in membrane fluidity^[5] (Fig. 3).

In dopaminergic neurons, dopamine (DA) breakdown can occur spontaneously in the presence of iron, or can be catalysed by monoamine oxidase (MAO) in a reaction that generates hydrogen peroxide (H₂O₂). Even though H₂O₂ does not damage cells, the formation of hydroxyl radicals by the Fenton reaction can lead to cytotoxicity. Normally, cells scavenge these deleterious molecules using several antioxidant systems. For instance, glutathione (GSH) peroxidase detoxifies H₂O₂ using reduced GSH. Oxidized glutathione (GSSG) can be reduced by GSSG reductase and reused. GSH-S-transferase converts electrophilic centres of various potentially toxic compounds to thioether bonds. Superoxide dismutase (SOD) converts superoxide to H₂O₂. Catalase, in turn, converts H₂O₂ to molecular oxygen and water (Fig. 2).

Compared with the rest of the brain, the substantia nigra pars compacta (SNpc) is exposed to higher level of oxidative stress and a high rate of reactive oxygen species (ROS) formation. The reason for this is not clear, but may be related to the energy metabolism of these cells or to their high content of DA. Post-mortem studies in the parkinsonian brain indicate that DA neurons may be deficient in handling oxidative stress^[6]. This is believed to reflect both increased generation of free radicals and impairments in

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Fig. 1 Current hypothesis for the neurodegeneration cascade of events of Parkinson's disease. Oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammation processes, neurotoxins, nitric oxide, impaired cellular respiration and apoptosis contribute to cell death and enhance each other in a cycle of toxicity. The dashed lines represent potential targets for neuroprotection^[1].

the mechanisms for scavenging them: a 30%–60% decrease in GSSG in the SN of parkinsonian patients, in conjunction with increased levels of iron. Also, various markers of lipid peroxidation and protein oxidation damage to DNA are increased in the SN. Oxidative stress may also account for the nigral defect of complex I activity, in that complex I is highly vulnerable to oxidative damage and inhibition of complex I leads to increased ROS formation. Toxic products of oxidative changes may be important contributors to disease progression^[7].

Although post-mortem investigations and experimental impact studies showed that oxidative stress has relevance to PD, it is not known how this process relates to the time course of neuronal degeneration in SN or how oxidative stress relates to the other processes known to be involved in the cascade of events leading to dopaminergic cell death (which comes first, the chicken or the egg?). This situation has so far proved impossible to be resolved^[9].

In addition, Oxidative stress may contribute to impairment of the ubiquitin-proteasome system (UPS)^[10], and in turn, impairment of the UPS may cause oxidative stress.

3 Environmental impact factors

Epidemiological studies have shown that environmental impact factors may play roles in the PD process (Tab. 1).

The involvement of pesticides exposure (paraquat, organochlorines, carbamates, etc.) has been strongly implicated in the development of sporadic PD^[13,14]. Rural living is usually associated with the agricultural industry, and work in this environment also has been suggested to increase the risk of developing PD. Rotenone is a widely available and commonly used pesticide, often used to control fish stocks in reservoirs, that is a potent complex I inhibitor. A recent report notes that the systemic infusion of rotenone into rats induces selective dopaminergic cell death, intraneuronal ubiquitin rich protein inclusions (Lewy bodies) and a motor deficit. These findings add to the idea that environmental impact factors may cause or contribute to PD^[15].

Metals have recently been shown to interact with α -synuclein and to promote its fibrillation *in vitro*^[16]. Long-term and combined (*e.g.* lead with iron, iron with copper, manganese) exposures increase the risk of PD^[12,17]. Overall, however, epidemiological evidence in support on a relation between metal exposure and PD remains inconclusive^[18].

Epidemiological studies have indicated that certain factors, such as caffeine consumption, may decrease the risk of PD^[19]. They have also identified one undisputed factor that is inversely associated with PD: cigarette smoking. The effect of smoking has been estimated to de-

Fig. 2 Oxidative stress hypothesis and the antioxidative processes. **A:** Formation of free radicals from (dopamine) DA by MAO or auto-oxidation. In the presence of transition metals, H₂O₂ is converted to hydroxyl radical. **B:** Reactive oxygen species and the pathogenesis of neurodegenerative disorders. An imbalance between the production and elimination of reactive oxygen species could contribute to the pathogenesis of Parkinson's disease and other neurodegenerative disorders. Metabolism of DA leads to the formation of several cytotoxic molecules, including superoxide anions (O₂^{•-}), dopamine-quinone species (SQ[•]) and hydroxyl radicals (OH[•]). In PD, however, an abnormal increase in the production of reactive oxygen species might tilt the balance between production and elimination, leading to enhanced oxidative stress. DOPAC, 3,4-dihydroxyphenylacetic acid^[8]; MAO, monoamine oxidase.

Fig. 3 Oxidative stress in Parkinson's disease. Dopamine (DA) required for neuronal signalling is vesicle bound and redox inert; when DA is released from the vesicle into the cytoplasm it is able to coordinate Fe and undergo redox reactions that result in the formation of neuromelanin (NM) and reactive oxygen species (ROS). Neuromelanin will also coordinate Fe and produce ROS. The equilibrium between vesicle bound DA and cytoplasmic DA is regulated by α -synuclein; mutations in this protein shift the DA equilibrium in favour of the cytoplasm. In the presence of Fe and under conditions of oxidative stress α -synuclein will aggregate and form deposits. MPP, 1-methyl-4-phenyl pyridine^[5].

Tab. 1 Environmental impact factors and PD: epidemiological clues^[2,11,12]

Risk factor	Putative agent
Increased risk	
Pesticide exposure	Paraquat, organochlorines, carbamates
Metal exposure	Lead with iron, iron with copper, manganese
Decreased risk	
Smoking	Nicotine, MAO-B, CYP2D6
Coffee consumption	Caffeine

Fig. 4 Inflammatory-related changes in the brain suffered from Parkinson's disease^[24]

crease risk of PD by up to 50%, is dependent on lifetime dose, and cannot be simply explained by selective mortality^[20]. An important goal of future research will be to identify the specific compounds (such as nicotine), or mixture of compounds, that mediate the protective effects of smoking.

4 Neuroinflammatory processes

The hypothesis that neuroinflammation occurs in PD is supported by several lines of evidence (summarized in Fig. 4)^[21]. One of the first features of the inflammatory-associated modifications described in PD is the upregulated expression of major histocompatibility complex (MHC) molecules in the striatum and SNpc of mice intoxicated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Secondly, a marked increase in cytokine levels in the striatum and cerebrospinal fluid (CSF) of parkinsonian patients compared with control subjects has been observed^[22,23]. These cytokines include: proinflammatory cytokines [tumor necrosis factor α (TNF- α), interleukin (IL)-1 β , IL-6], T-cell activation-associated cytokine (IL-2), anti-inflammatory cytokine (IL-4), and several growth factors [Epidermal growth factor (EGF), transforming growth factor α (TGF- α), basic fibroblast growth factor (bFGF), TGF- β 1]. Because an increase in the level of cytokines was specific to the

nigrostriatal pathway and is not observed in cortical regions, it has been suggested that cytokine production may be strictly confined to the sites of injury^[24]. There is recent evidence that inhibition of the ubiquitin-proteasome system can induce a proinflammatory response, manifested by upregulation of cyclo-oxygenase-2 (COX-2)^[25].

However, how and when neuroinflammation arises in the course of PD and where inflammation participates in the cascade of events leading to nerve cell death have not yet been fully resolved (Fig. 5)^[24].

To date, one of the best characterized cytotoxic mechanisms induced by pro-inflammatory cytokines in PD is the activation of inducible nitric oxide synthase (iNOS), which mediates the synthesis of high level of nitric oxide (NO), shown toxic to neurons^[26]. Of relevance to the potential role of iNOS in the pathogenesis of PD is the demonstration that the density of glial cells expressing iNOS is markedly increased in the SN of parkinsonian patients compared with control subjects^[27]. Other studies have shown pro-inflammatory cytokines [TNF- α , IL-1 β , and Interferon- γ (IFN- γ)] to be the most potent activators of iNOS in rodent glial cells. The hypothesis that this also might be the case in humans has been challenged. Recently, Hunot *et al.*^[24] identified such a pathway in glial cells, involving cytokine-stimulated expression of the low-affinity IgE receptor CD23

Fig. 5 Putative deleterious role of neuroinflammatory processes in Parkinson's disease (PD). The pathway represented in activated glial cell the neuroinflammatory reaction as observed in PD brain. Proinflammatory cytokines, including IL-1 β , TNF- α and IFN- γ , induce CD23 expression in glial cells whose engagement (by a ligand as yet to be identified) triggers iNOS expression and NO release. NO may amplify the production of cytokines within the glial cells but also diffuse to neighboring dopaminergic neurons. Of note, it is still debated whether infiltrated T lymphocytes could be the cellular source of IFN- γ in PD brain. The pathway shown in dopaminergic neuron possible inflammatory-associated cytotoxic mechanisms in dopaminergic neurons. NO produced by activated glial cells can react with superoxide (O₂⁻) to form peroxynitrite (ONOO⁻), which can damage proteins and other cell constituents. NO also may contribute to oxidative stress by releasing iron from ferritin. Alternatively, cytokines may activate receptors (*e.g.* TNFR1) coupled to death signaling pathways. These pathways may involve activation of caspases and/or an oxidant-mediated apoptogenic mechanism through the release of ceramide and the activation of the transcription factor NF κ B^[24].

whose activation induced iNOS expression and subsequent high release of NO.

Alternatively, cytokine-induced dopaminergic cell death may involve more direct cytotoxic mechanisms through direct activation of cytokine receptors localized in dopaminergic neurons and coupled to intracellular death-related signaling pathways. In PD, investigations primarily have been focused on TNF- α receptors (TNF-RI). Engagement of TNF-RI has been shown to activate, in a cascade fashion, a group of cysteine proteases known as caspases that are central to the apoptotic machinery in mammalian cells^[28,29]. They are known to activate the ceramide (a breakdown product of the major cellular membrane phospholipid sphingomyelin) pathway, which can amplify the caspase pathway but also activate the transcription factor NF κ B through an oxidative stress-dependent mechanism.

5 Summary

In conclusion, neuroinflammation is an indisputable neuropathological feature of PD. Probably, the first indication that neuroinflammatory processes in the PD brain most likely arise secondary to a primary insult and quite possibly participate in the propagation of the neurodegenerative process. If true, this statement could have major therapeutic implications, as targeting specific neuroinflammatory-associated deleterious mechanisms may prove effective in slowing or even halting the disease course^[21]. Although the ultimate quest is to develop preventive treatments for PD, our best hope for now is probably to target secondary deleterious mechanisms^[24].

In summary, the assertion that PD has a clinical and pathological end point common to a variety of different causes is now compelling. Inevitably, it is reasonable to hope that a clearer understanding of the cause and pathogenesis of PD will provide us with targets for treatments that provide modification and neuroprotection for the disease.

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帕金森病的发病机理：氧化应激，环境影响因素与神经炎症

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摘要：目前，帕金森病的发病机理存在各种假说，包括氧化应激与清除自由基能力下降、线粒体功能异常、兴奋性氨基酸的毒性作用、神经营养因子的缺乏、神经炎症机制、基因与环境影响因素、一氧化氮毒性作用和凋亡等。本文就帕金森病的氧化应激、环境影响因素、神经炎症机制作一综述。

关键词：发病机理；帕金森病；氧化应激；神经炎症；环境影响