Parkinson’s Disease as a Consequence of Impaired Redox Homeostasis in the Brain*

Choroba Parkinsona jako rezultat zaburzenia homeostazy red-ox mózgu

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Abstract

Parkinson’s disease (PD) is one of the most frequent neurodegenerative disorders of advanced age. Clinically, PD is characterized by akinesia, resting tremor, and rigidity. A characteristic feature of PD is loss of pigmented neurons in the substantia nigra. A review of available data on PD shows that multiple factors are involved in maintaining the redox state of the brain, and impairment of any of these components may result in PD. This includes changes in the neuromelanin level, iron level, mitochondrial function, dopamine and tyrosine metabolism, and inflammation. This mini-review presents some new aspects of the relationship between impairment of brain redox homeostasis and PD (Adv Clin Exp Med 2006, 15, 4, 705–709).

Key words: Parkinson’s disease, free radicals, neuromelanin, mitochondria, iron.

Streszczenie


Słowa kluczowe: choroba Parkinsona, wolne rodniki, neuromelanina, mitochondria, żelazo.

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spinal fluid and peripheral blood samples of PD patients, malondialdehyde content was elevated and the activities of antioxidative enzymes (glutathione reductase, Cu, and Zn superoxide-dismutase) were increased. This indicates the presence of a chronic oxidative stress state in the brain of PD patients [4].

**Neuromelanin in Parkinson’s Disease**

Neuromelanin (NM) is a true melanin, containing bound metal ions *in situ* [5]. NM is an insoluble pigment found in the neurons of specific brain regions [5], e.g. the substantia nigra (SN) and locus coeruleus [6]. It appears in humans at 2–3 years of age and accumulates with aging. Because tyrosinase is not present in the brain tissue, other mechanisms are suspected to be involved in NM formation. NM accumulates normally through the autoxidation of catecholamines and binds tightly to the redox-active metal ions, processes which would accelerate under conditions of intracellular or extracellular oxidative stress [7]. An inverse relationship was observed between the percentage of surviving neurons in PD and the amount of neuromelanin they contain, suggesting that the vulnerability of the dopaminergic neurons is related to their NM content. The NM level in PD subjects was less than 50% of that of controls.

The function of NM remains unclear, but at physiological pH, NM is an efficient antioxidant [8] and hence has a cytoprotective function in the sequestration of redox-active metal ions under normal conditions [5]. It is well known that iron levels are increased in the substantia nigra of PD patients, and the absence of a simultaneous increase in neuronal ferritin suggests that iron may be redox active and thus able to catalyze the Fenton reaction in the presence of H$_2$O. Increased tissue iron may saturate the iron-chelating sites on NM, and NM may thus cause increased, rather than decreased, production of reactive oxygen species (ROS). One possible trigger for this mechanism is suggested by the increased nigral iron content in postmortem PD brains and the correlation of this disease with urban living, where exposure to heavy metal ions is high, i.e. saturation of neuromelanin with redox-active metal ions. PD may therefore be a form of accelerated aging in the substantia nigra associated with environmental toxins in which neuromelanin has an active central role. Synthetic neuromelanin showed its toxic properties in dopaminergic cell cultures [9], but other data failed to support the hypothesis of neurotoxicity of melanin as a cause of PD.

**Dopamine and Parkinson’s Disease**

The etiology of neuronal death in PD is still unclear, but several lines of evidence support the involvement of dopamine-induced apoptotic striatal neuron death [10]. Apoptosis has been reported in *post mortem* nigral tissue of parkinsonic patients. A possible mechanism of dopamine-related toxicity may involve the oxidation of dopamine (DA) [11], the formation of reactive oxygen species (ROS), inhibition of mitochondrial respiration, lipid peroxidation, and neuronal death. The levels of DA, 3,4-dihydroxyphenylacetic acid, and 3,4-dihydroxyphenylalanine decreased with the degree of depigmentation and degeneration in the putamen, nucleus caudatus, and substantia nigra. Thus depigmentation and degeneration of dopaminergic SN neurons seem to be correlated to enhanced rates of autoxidation, possibly due to an impaired antioxidant capacity.

DA neurotoxicity is enhanced under the conditions induced by cyanide and involves both ROS and nitric oxide-mediated oxidative stress as an initiator of apoptosis [12]. DA during *in vitro* oxidation induced cross-linking of membrane proteins in the mitochondria-synaptosomal fraction of rat brain. The process was inhibited at low glutathione (GSH) level, but was not affected by the presence of scavengers, metal chelators, or catalase. This indicates that dopamine-induced protein damage is related rather to quinones than to ROS formation [11]. DA has a neurotoxic potential in the substantia nigra, and it is counterbalanced by the cytoprotective status of these neurons at any particular time. In contrast, in the target field of the substantia nigra, namely the neostriatum, DA has a neuroprotective role [13]. An increased DA turnover, observed in PD, may not only reduce the intermediate symptoms of the disease, but also contribute to its progression.

**The Role of Mitochondria in Parkinson’s Disease**

Mitochondria are the major source of ROS, which appear to be released into both the matrix and intermembrane space [14]. Neurodegeneration may be caused by disrupted mitochondrial function and/or an excessive production of ROS. The main mitochondrial defect observed in PD concerns complex I (nicotinamide adenine dinucleotide coenzyme Q reductase) of the mitochondrial respiratory chain [15]. Disturbed mitochondrial function results in uncoupling of the respiratory chain,
excessive ROS formation, outflow of matrix calcium and GSH, change in the mitochondrial transmembrane potential, release of intermembrane proteins, and necrosis with or without caspases activation and activation of endonuclease [16].

The signaling pathway leading to apoptosis via mitochondria is triggered by the binding of proteins of the Bcl-2 family. This interaction forms large pores in the mitochondrial membrane through which cytochrome c is released. Premkumar and Simantov showed that the mitochondrial voltage-dependent anion channel (VDAC) is involved in DA-induced apoptosis, but whether the VDAC plays a role in mitochondrial dysfunction in Parkinson’s disease is still worth examination. Abnormal accumulation of presynaptic protein alpha-synuclein, which has recently been implicated in PD etiology, could lead to mitochondrial alterations that may result in oxidative stress [14].

**Glutathione and Parkinson’s Disease**

Oxidative stress has been implicated in playing a major role in the neuronal death in PD. One of the indices of oxidative stress is GSH depletion. In neural cells, redox maintains a balance between the level of ROS and thiol buffers such as GSH, which protect cells from oxidative stress. The increase in ROS formation, exceeding the compensatory actions of the level of thiol buffers, may result in the activation of signaling pathways and the expression of genes that induce apoptosis in affected neural cells [17]. An early event following GSH depletion is phospholipase A2-dependend release of arachidonic acid, which can cause damage to the GSH-depleted cells through its metabolism by lipoxygenase. The generation of superoxide radicals seems to play an important role in the toxic events that follow GSH depletion [18]. GSH depletion has been shown to effect mitochondrial function, probably via selective inhibition of mitochondrial complex I.

GSH and glutathione-dependent enzymes represent the major mechanism and a multifaceted detoxification system of endogenous antioxidant. GSH-biosynthesis, glutathione peroxidases, glutathione S-transferases, and glutathione S-conjugate efflux pumps protect the neural cells against an excess of ROS [19]. The antioxidant responsive element (ARE) was found recently in the gene promoters inducible by ROS. Recently it was concluded that Bcl-2, and antiapoptotic protein located in the outer mitochondrial membrane, affects the cellular level of ROS, which can include either their overproduction or an endogenous antioxidant pathway [20], but its mode of action is still uncertain.

**Iron and Parkinson’s Disease**

Several studies implicate iron in the pathomechanism of PD. One of the defining characteristics of neurodegeneration, including the cases of PD, is abnormal elevation of iron. The high concentration of iron in the melanin/glycidic-lipid matrix of neuromelanin suggests that most of the iron is chelated by NM [22]. A relatively selective lesion of DA-neurons, similar to PD, following injection of iron into rats’ brains was described by Sengstock. These observations indicate that Fe(II)-mediated generation of ROS, via the Fenton reaction, might be a contributing factor in the etiology of PD. Moreover, production of DA from phenylalanine by tyrosine hydroxylase is facilitated by Fe(II) [23].

Ascorbic acid serves as an electron donor for dopamine beta-hydroxylase in chromaffin vesicles and probably for peptide amidating monoxygenase in neurohypophyseal secretory vesicles. It appears that the semidehydroascorbate that is produced is reduced by cytochrome b561 to regenerate intravesicular ascorbate. Cytochrome b561, a transmembrane protein, is reduced in turn by an extravesicular electron donor, probably cytosolic ascorbic acid [24]. The human gene product stromal cell-derived receptor 2 is a homologue of cytochrome b-561 and duodenal cytochrome b and is thus predicted to be active as a ferric reductase. This protein also contains a domain homologous to the N-terminal regulatory region of dopamine beta-hydroxylase. These findings from sequence analysis lead to the prediction that stromal cell-derived receptor 2 is a catecholamine-regulated ferric reductase active in the brain. Dysfunction of cytochrome b-561 or stromal cell-derived receptor 2, therefore, might predispose individuals to abnormal accumulation of Fe(III) and/or generation of cytotoxic free radicals as a consequence of a rapid cycling between Fe(III) and Fe(II) [25]. Generation of ROS might result in neurodegeneration and thus cause PD.

**Tyrosine and Parkinson’s Disease**

The DA content in the brain is directly related to DA synthesis from tyrosine. It is clear that oxidation of tyrosine (leading to TyrO• formation) cannot be omitted as a possible cause of PD. Aduction of nitric oxide to TyrO• results in TyrONO and 3-nitrotyrosine (3-NT) formation [26]. 3-NT may act as a promoter of repetitive redox cycling by its reduction to the corresponding nitroanion ra-
dical, which can be oxidized by molecular O2 and regenerate to maternal 3-NT and superoxide anion radical [27].

The mechanism of oxidation and nitration of proteins (including enzymes) still remains unclear, but recent experimental data suggest involvement of tyrosine radical (TyrO•) [26]. The nitration reaction with TyrO• involvement might result in DA synthesis depletion by inactivation of tyrosine hydroxylase [28]. Scavenging free radicals, such as NO•, NO2−, and CO2−, and ONOO− may also be depleted by reducing superoxide radical anion formation and reductive stress.

**Inflammation in Parkinson’s Disease**

Recent findings suggest that inflammatory processes are associated with neurodegeneration, including PD. In the MPTP model of PD, an immune reaction was shown in regions of impaired neurons as infiltration of CD4- and CD8-positive cells in the substantia nigra and MHC class I and II antigen expression on microglia [29]. Treatment with an anti-inflammatory drug (dexomethasone) resulted in a decrease in the inflammatory reaction and thus neuronal impairment [29]. Sirram proved that the proinflammatory cytokine TNF-α is an obligatory component of DA-neuron degeneration, and because TNF-α is synthesized predominantly by microglia and astrocytes, these findings support the hypothesis of an inflammatory origin of PD. Inflammation-induced dopaminergic neurodegeneration may be nitric-oxide mediated.

An in vitro model of nigral injury in which lipopolysaccharide-induced microglial activation leads to injury of DA cell lines suggested that only nitric oxide and H2O2 appear to mediate the microgila-induced DA injury [29]. The postmortem study of PD brains revealed a significantly higher percentage of DA neurons displaying caspase-8 activation. But its activation in the MPTP PD model showed that activation of caspase-8 precedes and is not the consequence of cell death. In an in vitro study, co-treating DA cell cultures with MPTP and caspase-8 inhibitors did not result in neuroprotection, but instead seemed to trigger a switch from apoptosis to necrosis. This effect is probably a consequence of ATP depletion, and the same mechanism may be in effect in PD [31].

Parkinson’s disease is a neurodegenerative process in which post-mortem studies have provided evidence that many connected factors are implicated in its etiology. Moreover, disturbances in an individual factor immediately results in dysfunction of the others. Thus it is unlikely that the single components (e.g. oxidative stress, reductive stress, tyrosine stress etc) are a part of the primary pathogenic process in which same mechanism may be in effect in PD [31].


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