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Oxidative Stress in Parkinson's Disease

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Abstract: ***Dopamine required for neuronal signaling is vesicle bound and redox inert. When it is released from the vesicles into the cytoplasm it is able to influence iron metabolism and undergo redox reactions that result in the formation of neuromelanin and ROS. Neuromelanin in turn will also influence iron metabolism and lead to the production of ROS. The equilibrium between vesicle bound dopamine and cytoplasmic dopamine is regulated by alpha-synuclein. Mutations in this protein shift the dopamine equilibrium in favour of the cytoplasm. In the presence of iron and under conditions of oxidative stress alpha-synuclem will aggregate and form deposits.***

Keywords: Oxidative stress, Parkinson's disease

1. Introduction

Current concepts on the development of Parkinson's disease have shown genetic predisposition to the environment or endogenous toxic causes of oxidative damage of nigral cells for several reasons. The level of reduced glutathione in substantia nigra decreases. Its depletion in Parkinson's disease may be due to neuronal loss. A positive correlation between neuronal loss and depletion of glutathione has been shown (Riederer P, Sofic E, Rausch W et al, 1989). The reduction of the reduced glutathione amount impairs the ability of neurons to detoxify hydrogen peroxide and increases the risk of free radicals formation and lipid peroxidation. Indeed, substantia nigra contains increased levels of malondialdehyde and hydroperoxides. The increase in the activity of mitochondrial superoxide dismutase in substantia nigra in Parkinson's disease is a compensatory mechanism to reduce oxidative stress (Saggu H, Cooksey J, Dexter D, 1989).

Another factor indicating increased oxidative stress is the accumulation of iron and progressive siderosis of substantia nigra (Dexter D, Wells F, Lees A et al, 1989). Also the level of ferritin, which is an iron-binding protein, is reduced in substantia nigra and thereby the iron-induced lipid peroxidation mediated by hydroxyl radicals is worsened (Dexter D, Carayon A, Javoy-Agid F, 1991).

Free radicals are believed to contribute to neuronal loss in cerebral ischemia, seizure disorders, schizophrenia, aging, Parkinson's disease and Alzheimer's disease (Barnham K et al. 2004, Abraham S et al. 2005, Ciccone C et al 1998, Halliwell B 1990, Gutteridge J 2000, Yoshikawa T, 1993, Youdin M 1994). Besides, the levels of glutathione and Vitamin E in patients with Parkinson's disease are increased as a compensatory mechanism to manage oxidative stress (Adams J, Klaidman L, Odunze I et al 1991). Free radicals are generated by electromagnetic excitation of molecular oxygen, reduction of reactive oxygen species, atmospheric pollutants and non-oxygen containing compounds such as carbon tetrachloride or chloroform. They are released during normal biochemical reactions in living tissue. The unbound electron makes these compounds highly reactive and they may initiate destructive reactions of peroxidation with various substrates important for cell survival such as proteins, lipids, and nucleic acids. There is a complex system of protection of living tissues from free radicals. Neurons are particularly susceptible to excessive free radicals, which may lead to neuronal death (Bonorden W, Pariza M, 1994). Receptor lipids containing polyunsaturated fatty acids are particularly sensitive to oxidative stress (Molina J et al. 1992, Sanya J et al.2009). Reactive oxygen metabolites affect the binding of ligands to membrane receptors such as alpha- and beta-adrenergic receptors, muscarinic, cholinergic, adenosine, histamine, and serotonergic receptors (Van Der Vliet A, Bast A, 1992). Peroxidation of membrane lipids may lead to reduction in the density of receptors and change the viscosity of plasma membrane thereby affecting the receptor-binding mechanism. ROS may also interact with thiol-disulfide portions of receptor proteins or other factors in the receptor system. Lipid peroxidation may also indirectly influence the receptor function.

Oxidative stress may lead to a breakdown in cellular Ca2+ homeostasis. Finally, reactive oxygen species interfere with the effects of nitric oxide and thus affect other signal transduction system. Hydroxyl radicals (OH) are the most damaging of all free radicals. Although they exist for a fraction of a second only they are able to destroy vital enzymes, cause DNA binding, release proteolytic enzymes, break polysaccharides and cause lipid peroxidation altering membrane permeability and the associated functions. There are at least nine different levels in which free radicals may be generated. The two most important reactions involved in Parkinson's disease are: Haber-Weiss reaction and Fenton reaction.

Some enzymes (antioxidants) prevent oxidative damage by reactive oxygen products that are produced during normal metabolism. These are superoxide dismutase and glutathione peroxidase. Antioxidants are substances which may inhibit oxidation. They prolong the initiation phase or suppress the

propagation phase of autoxidation but cannot prevent it completely. Antioxidants are classified into two main categories: preventive inhibitors which slow down the initiation phase and free radical chains - breaking antioxidants that effectively remove free radicals from a system. Catalases, glutathione peroxidases, glutathione-transferase, superoxide dismutase, alpha-tocopherol, ferritin, and metallothionein are preventive or chain-breaking antioxidants (Ebadi M et al. 1996, Schulz J et al. 2000, Gilgun-Sherki Y et al. 2001). A defect in mitochondrial oxidative phosphorylation in the striatum of patients with Parkinson's disease has been reported. Similar effects have also been found in the platelets but not in the muscles in Parkinson's disease. Therefore, the specificity of mitochondrial damage may play a role in the degeneration of nigrostriatal dopaminergic neurons.

Endogenously produced neurotoxins have long been suspected of being involved in the pathogenesis of Parkinson's disease, however, there is little evidence to support this idea. Recently, the neurotoxic effects of MPTP have been found to induce a Parkinsonian syndrome. Dopaminergic cell death mediated by MPTP is caused by oxidative stress followed by lipid peroxidation caused by inhibition of mitochondrial enzymes involved in ATP synthesis.

Active oxygen radicals are continuously produced in the tissues under the influence of the mitochondrial electron transport system and reduced nicotinamide adenine and dinucleotide phosphate oxidase. Several antioxidant protection systems prevent tissue damage by oxygen radicals. These systems include a number of specific antioxidants such as catalase for hydrogen peroxide, superoxide dismutase for superoxides and glutathione peroxidases for hydrogen peroxide and lipid peroxides and nonspecific antioxidants such as reduced glutathione, ceruloplasmin, transferrin, and metalogionein (Sato M, Bremner I, 1993).

The results of the experiments conducted have provided further evidence that zinc or zinc metallothionein change during oxidative stress (Shiraga H, Pfeiffer R, Ebadi M, 1993). Some brain areas such as the striatum containing a high concentration of iron but low metaltionein levels are particularly susceptible to oxidative stress (Rojas-Castaneda P, Cerutis D, Blaxall H et al, 1994). Nigrostriatal dopaminergic neurons are lost with age and this phenomenon is sharply accelerated in Parkinson's disease. Although the reasons for this are not well understood the age-dependent oxidative stress may worsen the condition for several reasons. MAO-B activity in the human brain increases with age which is probably due to the proliferation of glial cells causing a decrease in dopamine concentration. This in turn may increase the dopamine turnover and metabolism generating higher levels of H202 and hydroxyl radicals. Furthermore, substantia nigra contains very low levels of glutathione, alpha-tocopherol, and zinc metallothionein which are known antioxidants thereby enhancing iron-mediated oxidation reactions. Substantia nigra also contains the highest level of malondialdehyde which is an indication of peroxidative damage. The process of increased dopamine synthesis in the other dopaminergic neurons preserved in the process of degeneration may be responsible for the oxidative stress on the cells. Another source of free radicals in substantia nigra is the oxidative degradation of dopamine through MAO-B which is highly concentrated in this structure. A distinctive feature of Parkinsonism is the serious decrease in dopamine in all components of basal ganglia. In early Parkinsonism it seems there is a compensatory increase in dopamine receptors to manage the initial loss of dopamine neurons. Since the disease progresses the number of dopamine receptors decreases, apparently due to the simultaneous degeneration of dopamine attachment sites on striatal neurons. In the other neurons in patients with Parkinson's disease dopamine exchange appears to be substantially increased judging by the concentration of the metabolite homovanillic acid in nerve endings in striatum, cell bodies and dendrites in substantia nigra as well as the subsequently increased production of radicals. If this increase because of the increased dopamine exchange is not buffered by scavenging enzymes (superoxide dismutase, catalase, and glutathione peroxidase), then the compensatory hypoactivity of dopaminergic neurons may become self-destructive.Continuous administration of L-DOPA would only increase the production of damaging free radicals (Mena M et al. 1993) Administration of L-DOPA is believed to increase accumulation of free radicals. Using electron spin resonance spectroscopy it has been shown that 10 mM L-DOPA is inactive but produces hydroxyl radicals in the presence of 10 rnM Fe-diethylenetriamine-pentaacetic acid and this effect is blocked by selegiline, a MAO-B inhibitor which is considered to be symptomatic and protective therapy in Parkinson's disease. Changes in production or elimination of potentially toxic oxygen radicals may play a role in dopaminergic cell death. In patients with Parkinson's disease the neuron-localized superoxide dismutase or the activity of glial-localized glutathione peroxidase does not seem to be significantly abnormal (Ceballos I, Sinet P, Nicole A, 1990), although the activity of the mitochondrial fraction of the latter is increased and the concentration of glutathione, which is the main substrate of glutathione peroxidase, is reduced. Although dopaminergic neurons that die in Parkinson's disease are found in areas where the density of glutathione peroxidase-containing glial cells is low the density of glial cells containing this enzyme grows with the coming on destruction of dopaminergic cells. This suggests that gliosis may progressively counteract the oxidative stress and increase the survival probability of the other neurons.

Free radicals, namely superoxide, peroxide and hydroxyl radicals, are produced in the dopaminergic neurons of the midbrain (Agid Y, Ruberg M, Javoy-Agid F et al, 1993). Free radicals and quinones are produced in substantia nigra during degradation of dopamine by MAO-B. They are formed during the synthesis of neuromelanin, which is found in most of the dopaminergic neurons of mesencephalon. The third source of free radicals in substantia nigra is iron, which catalyses the formation of hydroxyl radicals such as H202, the decomposition of lipid peroxides and the acceleration of non-enzymatic oxidation of different molecules. Under normal conditions the continuous production of free radicals is compensated by powerful protective systems. These include cytosolic Zn2+ Cu2+ superoxide dismutase and

mitochondrial Zn2+ Cu2+ superoxide dismutase which protect against oxygen toxicity by catalyzing the dismutation of superoxide anions to oxygen and hydrogen peroxide. The fact that the gene of Zn2+ Cu2+ superoxide dismutase is highly expressed in neuromelanin- pigmented neurons, the subgroup of cells most susceptible to the degenerative process in substantia nigra in Parkinson's disease, may be indicative for having these highly reactive oxidative species produced in significant concentrations in those cells exactly. Glutathione peroxidase, one of the most powerful enzymes that protects against oxygen toxicity by scavenging H202 generated by cell metabolism, is found exclusively in the glial cells of the midbrain. The density of glutathione peroxidase contained in the glial cells identified through an immunohistochemical method varies among different groups of dopaminergic cells of normal mesencephalon. It is high in the central gray matter, which is preserved in Parkinson's disease, and is the lowest in the compact part of substantia nigra, which is the most affected in this condition. The strong relationship among the density of glutathione peroxidase, the positive cells in brain controls and the heavy loss of dopaminergic neurons in Parkinson's disease shows that the neurons most susceptible to this disease are surrounded by a lower density of glutathione positive cells and, therefore, are less protected from oxidative stress.

Circumstantial evidence in support of the formation of excessive free radicals in the striatum of patients with Parkinson's disease includes increased iron, reduced ferritin, reduced glutathione, reduced complex I and increased lipid peroxidation in substantia nigra of patients. Besides, patients with Parkinson's disease have been successfully treated with antioxidants (Fahn S 1991).

Free iron may generate free radicals and cause lipid peroxidation. It is an essential element necessary for the growth and development of all cells. The levels of iron and copper as well as the extent of lipid peroxidation are increased in globus pallidus and substantia nigra in patients with Parkinson's disease. The dietary iron deficiency causes reduced sensitivity of dopamine D2 receptor, given that intraventricular injection of iron salts causes the opposite effects. High levels of iron in normal substantia nigra and its accumulation in dopaminergic neurons in people with Parkinson's disease suggest that it is a contributing factor in the development of Parkinson's disease.

Neuromelanin is a pigment contained in the cell bodies of substantia nigra and locus coeruleus. It has been found that dopaminergic neurons containing neuromelanin are more susceptible to oxidative damage compared to non-melanin dopaminergic neurons. The specific loss of melanin dopaminergic neurons with an increased concentration of iron and copper is found in substantia nigra in Parkinson's disease. It is reported that in addition to iron other elements such as Zn, Cr, Se, Sr, Co, Sb, Ni, Hg, Ce, Au, Ta, Sc have been present in neuromelanin at much higher concentrations than in substantia nigra and putamen. These findings show that the latter two structures contain metals in higher concentrations than those observed in the blood and neuromelanin has a specific affinity thereto (Zecca L, Pietra R, Goj C, 1994). The observation that lipid peroxidation is selectively increased in substantia nigra in patients with Parkinson's disease suggests increased production of free radicals resulting from chronic local oxidative stress, which may lead to progressive degeneration of nigral dopaminergic neurons. The origin of this supposed overproduction of free radicals is not known but there are three possibilities for its explanation: the presence of dopamine, iron, and neuromelanin. The proportion of neuromelanin-pigmented neurons normally presented among dopaminergic cells correlates with the expected level of loss of cells in the different cell subgroups in Parkinson's disease, which suggests that melanin dopaminergic neurons are most susceptible to degeneration compared to those which do not contain a pigment. The susceptibility of these neurons depends not only on their location in the nigral complex but also on their neuromelanin content. The gradual accumulation of neuromelanin for several decades may contribute in more than one way to the pathological process determining cell death - either directly by the production of free radicals or indirectly by binding and release of toxins. Therefore, the pigment itself may be a contributing factor but is not enough to cause the death of the subpopulation of dopaminergic neurons affected by Parkinson's disease.

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Author Profile

Prof. Ivan Hristov Manchev, MD, PhD, DSc was born in the city of Plovdiv, Bulgaria. He graduated from the Medical Academy in Sofia in 1978 with higher medical education. From 1981 until 1990 he worked as intern at the Neurological Ward of of Primary District Hospital – Burgas. In 1983 he was awarded a Specialty in Neurology. Since 2006 he is a specialist in General Medicine. Within the frame of this dissertation for acknowledgment of PhD in Medical Science has been defended in 1989. In 2012 he has been awarded with scientific degree "Doctor of medical sciences". In 2010 he was nominated " British Doctor of Philisophy Degree" from UK NARIC. Since 1990 he has been Assistant in Neurology at the Department in Neurology and Neurosurgery of the Higher Medical Institute – Stara Zagora, and since 1991 he is Chief Assistant at the same department. In 1996 he was nominated Associate Professor and Head of the department in Neurology and Psychiatry at the Faculty of Medicine – Thracian University, Stara Zagora, where he still works. In 2011 he was nominated Professor of Neurology. Prof. I.Manchev is author and co-author of more than 135 scientific works in all basic aspects of Neurology, including of nine monographs and textbooks. His monograph "Epidemiology of the risk factors for cerebrovascular disease" has been published in Canada and USA and "Systemic hereditary degenerative and dystrophic diseases of the nervous and muscular system" has been published in United Kingdom and USA in 2007. A considerable part of his works is dedicated to the vascular diseases of the nervous system – Epidemiology, Clinics and Diagnostics. Others are connected with research on the multiple sclerosis, meningitis and encephalitis, myasthenia gravis, epilepsy, etc. Some his publications have been presented at international events and published in respected foreign editions. He is a member of the Union of Scientists in Bulgaria , of the Bulgarian Scientific Society in Neurology, of the Board of Managers of the Prevention of Brain Attacks Foundation, of the International Brain Research Organization and the European Federation of Neurological Societies. He is also a member of the editorial staff of the following magazines : Cerebral – Vascular Diseases, Bulgarian Neurology, Neurology and Psychiatry. Biographic notes for him are contained in the compendia of the American Biographical Institute and the International Biographical Center, Cambridge. He has been bestowed by the Cambridge Center with a diploma and a medal of renowned scientist. He is a member of the Faculty Council of the Faculty of Medicine – Stara Zagora. He is Vice Dean of the Faculty of Medicine – Stara Zagora. Prof. I.Manchev is a National consultant for Stara Zagora, Burgas, Sliven and Yambol districts.