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Oxidative Changes and Possible Effects of Polymorphism of Antioxidant Enzymes in Neurodegenerative Disease

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1. Introduction

Frequency of neurodegenerative diseases increase significantly with the age. In the present, average age is increasing and the number of people over 60 years increases as well. Ageing is a physiological process; however it seems to be linked with an increasing risk of origin and development of several diseases including neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. Exact mechanisms of ageing are still unclear but experimental evidences support a hypothesis that ageing changes are consequences of increasing oxidative damage of organs, tissues, cells and all biomolecules. Oxidative damage is elevated when production of reactive oxygen species is increased compared to the physiological condition or a defence ability of organism against attacks of reactive oxygen species is decreased. Oxidation of specific proteins could play a key role in age associated damage. A relationship between protein aggregation, oxidative stress and neurodegeneration remains unclear although neurodegenerative diseases are connected with an origin of protein deposits. It assumes that protein oxidation and generation of protein aggregates generate a base for a loss of cell function and a reduced ability aged organisms to resist to physiological stress. Accumulation of modified proteins, disturbance of ion homeostasis, lipid and DNA modifications, and impairment of energy production are some of the crucial mechanisms linking ageing to neurodegeneration. In addition mitochondrial dysfunction plays a key role in neurology. Damage of mitochondrial electron transport may be an important factor in the pathogenesis of neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases.

Oxygen is vital for all aerobic organisms and reactive oxygen species (ROS) are formed in cells as a consequence of aerobic metabolism. Moreover mitochondrial respiration is associated with inevitable electron leak, resulting in a non-stop production of reactive oxygen species, such as superoxide anion radical, hydrogen peroxide and hydrogen radical. Universal nature of reactive oxygen species is underlined by the presence of superoxide dismutase in all aerobic organisms. Genes involved in detoxification of reactive oxygen species are highly conserved among eukaryotes and their deficiency could be limit of several diseases and life span. Oxidative stress is a unique pathophysiological condition resulting from the disrupted balance between oxidants and antioxidants. Increased level of reactive oxygen species may cause oxidative damage of all four biomolecules: nucleic acids, proteins, lipids, saccharides. A progressive grow of oxidative damage is the result of increasing production of reactive oxygen species and this damage may contribute to the origin and development of several diseases including neurodegenerative diseases, but on the other hand oxidative damage can be the consequence of them as well (fig. 1). Cells possess defence systems: enzymatic and non-enzymatic against ROS. The most important enzymatic antioxidants are: superoxide dismutase, catalase and glutathione peroxidase but many others enzymes have antioxidant potential.
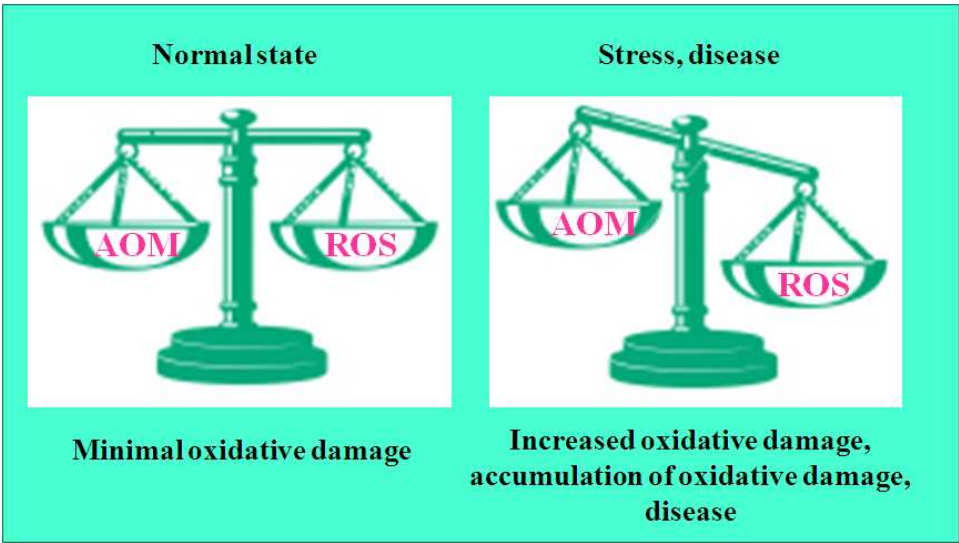

Figure 1. Reactive oxygen species in the development of disease. As a consequence of imbalance between reactive oxygen species (ROS) and antioxidant mechanisms (AOM) on the side of reactive oxygen species, oxidative stress is increasing. Increased level of reactive oxygen species causes increased oxidative damage of biomolecules, an accumulation of damage, and the development of many diseases.

2. Oxidative damage

Reactive oxygen species (ROS) are necessary for human life. The main characteristics of ROS are their high effectiveness in a small concentration and their extremely highly reactivity. ROS are oxidants which can be produced endogenously and exogenously. Potential harmful ROS

generate in cells under normal physiological conditions in different metabolic pathways and cell compartments (fig. 2).
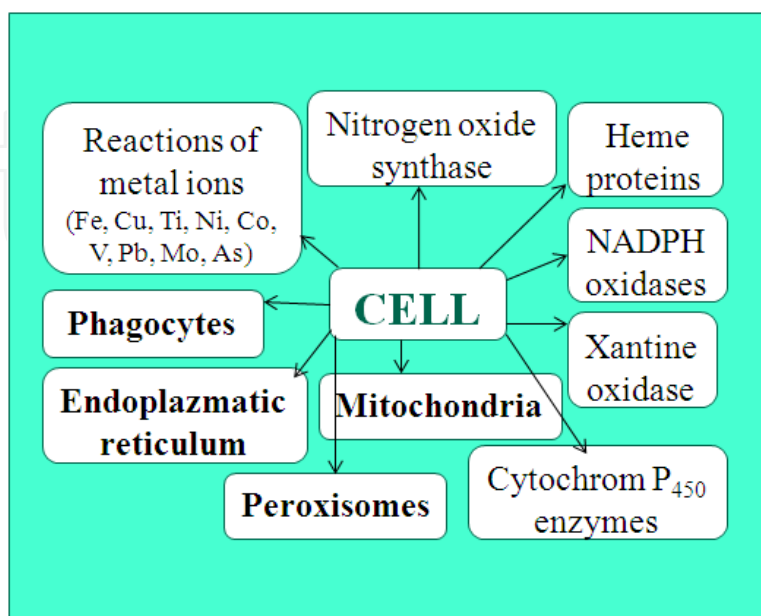

Figure 2. The main endogenous sources of reactive oxygen species (ROS) in cell. Organelles such as mitochondria, peroxisomes, phagocytes and endoplasmic reticulum and enzymes produce ROS during a pursuance their physiologic roles in cell and during metabolism of several components.

Four from the endogenous sources (mitochondria, phagocytes, peroxisomes, and cytochrome P_{450} enzymes) are responsible for origin of the majority of oxidants produced by cells [5]. The main endogenous sources of reactive oxygen species are mitochondria which produce reactive oxygen species continuously. Mitochondria serve mainly as producers of energy. In normal aerobic respiration mitochondria utilize oxygen that is reduced by serial steps whereby is produced water. Mitochondria are the major producer of reactive oxygen species via incomplete reduction of oxygen by electrons leaked out of the respiratory chain in the animal and human cells. Mitochondrial oxidative damage can lead to the release of greater amount of reactive oxygen species and cause increased oxidative damage of mitochondrial, cytoplasmic and nuclear components what subsequently may lead to dysfunctional mitochondria. Damage of mitochondrial electron transport may be an important factor in the pathogenesis of many diseases.

Phagocyting cells are another important endogenous source of oxidants. The main function of phagocytosis is the defence of host organisms against pathogens. Neutrophils and another phagocytes attack pathogens by mixture of reactive oxygen species: singlet oxygen ($O_2^{\bullet-}$), nitric oxide ($^{\bullet}NO$), hydrogen peroxide (H_2O_2), hypochlorous acid (HClO) [129]. Chronic virus, bacterial or parasite infection results in chronic increased phagocyting activity and finally chronic inflammation, which is a main risk factor for development of several diseases [5], and raising oxidative damage.

Peroxisomes are organelles from the microbody family and are present in almost all eukaryotic cells. They participate in the β-oxidation of fatty acids and in the metabolism of many others metabolites. Certain enzymes within peroxisome, by using molecular oxygen, remove hydrogen atoms from specific organic substrates, in an oxidative reaction, producing hydrogen peroxide. Hydrogen peroxide is degraded by catalase, another enzyme in peroxisome. Peroxisomes contain also xanthine oxidase which produces singlet oxygen and hydrogen peroxide.

Microsomal cytochrome P_{450} enzymes are a very large and diverse superfamily of hemoproteins identified from all lineages of life including humans, mammals, birds, fish, plants, bacteria. They form one of the primary defence system against xenobiotic compounds usually plant origin. Human cytochrome P_{450} enzymes are primarily membrane-associated proteins, located in the inner mitochondrial membrane or in the endoplasmic reticulum of cells. They modify thousands of endogenous and exogenous compounds by univalent oxidation or reduction. Induction of these enzymes protects before acute oxidative effects of foreign compounds or chemicals but also results in production of oxidants.

Although cells possess complex net of antioxidant defence, defence is not completely effective. Small fractions of pro-oxidants escape from elimination and cause molecular damage. Some of these damages are irreversible therefore they are accumulated in time and they make base of functional decline associated with age. Disruption of a balance between the level of reactive species generated during normal cellular metabolism and the level of endogenous antioxidant, either due to increased generation of ROS or decreased level of antioxidants, leads to oxidative damage and to several pathological conditions, including accelerated ageing and neurodegenerative disorders.

Exact mechanisms of reasons for origin of some neurodegenerative diseases are still unclear but experimental evidences support a hypothesis that ageing is a major risk and ageing changes are consequences of increasing oxidative damage. One of the basic problems is the analysis of mechanisms that are base of damage. ROS are effective in a very small concentrations and their half-life is very short. We still do not have sensitive instruments for measurement ROS (concentration and localisation) in living systems. Usually effects of ROS are determined indirect, by several markers of oxidative damage (fig. 3). Both localisation and kind of damage are necessary for understanding of neurodegeneration. Oxidative damage may by the most important contribution to ageing and age-related diseases. Literature is full of controversy results. Oxidative modification of proteins, saccharides, nucleic acid (nuclear and mitochondrial) and lipid peroxidation were observed in different tissues, cells, compartments, including mitochondria with advancing of age. There is no detail information how the higher availability of reactive oxygen species could be translated to an accumulation of oxidized biomolecules so far.

An accumulation of oxidized proteins, disturbance of ion homeostasis, modifications of lipids, saccharides, proteins and nucleic acids, and impairment of energy production are some of the crucial mechanisms linking ageing to neurodegeneration. Brain is particularly sensitive to reactive oxygen species attack and to oxidative damage consequence of several factors:

- Brain has a high content of unsaturated fatty acid (especially 20:4 and 22:6 fatty acids).

- Brain has high oxygen consumption (20% of using oxygen is consumed by brain).

- In the brain is high concentration of iron and ascorbate (key elements responsible for membrane lipid peroxidation).

- Brain is to poor of antioxidants and defence mechanisms.

PROTEINS	LIPIDS	DNA
-SH groups	malondialdehyde	2,6-diamino-4-hydroxy-5-formamidopyrimidine
GSH/GSSG	8-isoprostaglandin	4,6-diamino-5-formamidopyrimidine
3-nitrotyrosine	F_2-isoprostane	8-hydroxyadenine
3-chlorotyrosine	TBARS	8-hydroxydeoxyguanosine
dityrosine	conjugated dienes	8-hydroxyguanosine
carbonylated proteins	4-hydroxy-2-nonenal	5-hydroxycytosine

Figure 3. Markers of oxidative damage. Proteins, lipids and DNA are main targets of reactive oxygen species (ROS). These molecules generate a spectrum of molecules in the condition of oxidative stress which may be estimated for example in plasma, serum, bronchoalveolar lavage fluid, tissues and in exhaled breath condensate and reflect a danger of ROS for a subject in consequence of origin and development of several diseases.

Exclusive using of glucose as a source of energy by brain is responsible for high oxygen concentrations which are necessary for normal brain function. A predominant quantity of reactive oxygen species (90-95%) is generated during aerobic metabolism as a by-product in an electron transport chain of mitochondria. Mitochondrial dysfunction plays a key role in neurology [8]. A decline in respiratory chain Complex I and Complex IV activity is associated with ageing [38]. Damage of mitochondrial electron transport may be an important factor in the pathogenesis of neurodegenerative. Increased oxidative stress in consequence of unproportional ROS production is considered a main feature in the pathogenesis of neurodegenerative diseases [16, 141]. Apoptosis is an important mechanism of neuronal loss in age-related neurodegenerative diseases [38, 141]. Neuronal apoptosis in age-associated neurodegenerative disorders can be triggered by oxidative damage of proteins, lipids and DNA, metabolic compromise resulting from impaired glucose metabolism and mitochondrial dysfunction, and over activation of glutamate receptors resulting in disruption of neuronal calcium homeostasis. Several different kind of oxidative protein and lipid damages were observed in brain during ageing as well as increased generation of reactive oxygen species [59, 138, 144, 153, 154]. Increasing protein oxidation and lipid peroxidation can participate on the age-related brain

cell dysfunction. There are many studies demonstrated elevated concentration of different ROS and decreased antioxidant status during ageing and in neurodegenerative disorders but majority of them are determined on animal models or cell lines. We are still limited in human studies especially in the case of neurodegenerative disorders; and ethnicity, environment and life style may be responsible for controversial results.

2.1. Protein oxidation

One of the important targets of oxidative damage can be proteins which play elementary roles such as biological accelerators, gene regulators, receptors, transport proteins and structural components of cells. Oxidative modification of proteins by reactive oxygen species or by other reactive molecules (e.g. products of lipid peroxidation) is implicated in aetiology or development of many diseases and it can also contribute to secondary damage of other molecules. Damage of DNA repair enzymes could raise levels of DNA oxidative damage and increase of mutation frequency. DNA polymerase damage might result in decreasing of fidelity in replicating DNA. Endogenous proteins are very sensitive to free radical modification as by by-products of normal metabolic processes or after exposition to oxidative stress *in vivo* or *in vitro* [48, 64, 86]. ROS-associated protein modification can lead to loss of biological functions and to the change of protein forms. Modified proteins have increased sensitivity to intracellular proteolysis [176] and they are quickly degraded by endogenous proteases, particularly by multi-catalytic system [45]. Reactive oxygen species can react directly with proteins or they can react with molecules such as saccharides and lipids forming reactive products, which consecutively attack proteins. Reactions are often influenced by redox cycle of metal cations, particularly by iron and copper. Proteins can go through many covalent changes after exposing to oxidants [98]. Some of this alternations result from direct attacks of ROS on protein molecule; meanwhile another changes are produced indirectly [110]. Protein oxidation can lead to the amino acid side chain residues oxidation. All protein amino acid residues are sensitive to oxidative damage by hydroxyl radical that is generated by radiation but no all products generated during oxidation of some amino acid residues were absolutely characterised. However, tyrosine, phenylalanine, tryptophan, histidine, methionine and cysteine are preferred target of $^\bullet$OH attack [38]. In consequence of $^\bullet$OH attack of side chains in presence of oxygen can form hydroperoxides, alcohols and carbonyl compounds [39]. Proteins can contain after ROS attack new functional groups (hydroxyl and carbonyl groups) [22]. Protein oxidation can lead to the breaking of peptide bounds (formation of products with lower molecular weight) and to the formation of protein-protein cross-links (formation of products with higher molecular weight) and to the protein netting. These changes can result in different secondary effects including protein fragmentation, aggregation and unfolding. These processes are ordinarily connected with loss or change of protein activity and function [11, 102]. Increased oxidative damage of proteins result in:

• an increased production of reactive oxygen species [77],

• a decreased capacity to scavenge reactive oxygen species,

- an increased sensitivity of damaged proteins to become oxidized as a consequence of transcriptional and translational errors [1],

- a decreased levels or activities of the proteasome or proteases which degrade oxidized proteins [24].

2.2. Lipid peroxidation

Lipid peroxidation is an example of oxidative damage of cell membranes, lipoproteins and other lipid containing structures. This oxidative damage is degenerative process, which affects cellular membranes under conditions of oxidative stress [136]. Membranes are particularly sensitive to oxidative damage because they are rich on two or more carbon-carbon double bonds -C=C- [148]. During lipid peroxidation, polyunsaturated higher fatty acids are damaged in auto-catalytic, uncontrolled process which result is production of hydroperoxides of membrane lipids and wide spectrum of secondary metabolites including different aldehydes. Aldehyde products of lipoperoxidation may interact with mitochondrial membrane lipids and can change physiochemical state of membrane [150]. The major components of biological membranes are lipids and proteins. The amount of proteins is increasing with the number of functions that are on membranes performed. Lipid peroxidation can therefore cause damage of membrane proteins as well as lipids. Lipoproteins are also target of oxidative damage. Lipid hydroperoxides are primary products of lipid peroxidation. Dissociation of hydroperoxides is important from toxicological point of view for two reasons:

- new radicals are generated and ramify radical reactions,

- non-radical products are produced which can be also biologically active.

It was found, that lipid peroxidation produces: unsaturated aldehydes, malondialdehyde, 4-hydroxy-2-nonenal (HNE) and other products that are cytotoxic and mutagenic and can damaged other biomolecules [91]. Malondialdehyde arises largely from peroxidation of polyunsaturated fatty acids with more than two double bonds and it can also arise enzymatically during eicosanoid metabolism. 4-hydroxy-2-nonenal has toxic property like cell growth inhibition, genotoxicity, chemotaxic activity and able ability to modify lipoproteins and promote atherosclerosis [51]. It is able react with nucleofil components largely with metabolites and proteins contained thiol groups [50]. Effect of HNE is depending on its concentration. Lipid peroxidation can be overly destructive process in living system. It damages biological membrane thereby are changed their biophysiological properties. Aldehyde products of lipoperoxidation reacted with mitochondria membrane lipids and can change physiochemical state of membrane [28]. Peroxidation of membrane phospholipids is accompanied by change structural and functional characteristics of membranes. Lipid peroxidation impacts also function of proteins that are component of biological membranes. Consequence of near physiological junction lipids and proteins can lead oxidative damage of mitochondrial proteins to form proteins cross linkage, protein degradation or to lose of their function [166]. Oxidative damage can be established into proteins with reaction with aldehydes arisen during lipid peroxidation. For example HNE or malondialdehyde can react with ε-amino group of lysine, with thiol group of cysteine and with imidazol group of histidine [16].

2.3. Oxidative damage of DNA

Nucleic acids are particularly sensitive to oxidative damage. There is increasing evidence that ROS are involved in the development of cancer, not only by direct effects on DNA but also by affecting signal transduction, cell proliferation, cell death and intracellular communication. ROS can damage DNA by direct chemical attack of purine and pyrimidine bases and deoxyribose sugars and also by indirect mechanisms. There is a known more than 20 product of oxidative damage of the nucleic acids.

Superoxide, nitric oxide or hydrogen peroxide at physiologically relevant levels do not react with any of DNA or RNA bases or with the ribose or deoxyribose sugars at significant rates. Particularly hydroxyl radical is known to cause chemical modifications of DNA through the formation of one strand and two strands breaks and cross linkages with other molecules. Different saccharides radicals of DNA can arise by abstraction of a hydrogen atom from 2`deoxyribose because all positions in saccharides are susceptible to oxidative damage. Hydroxyl radical reacts with aromatic rings therefore also nitrogen bases of nucleic acids are modified. C5-C6 double bonds of pyrimidines and carbon atoms C4, C5, and C8 of purines are the most sensitive position to oxidative effect of hydroxyl radical and hydroxyl radical abstract electron and no hydrogen atom [169]. In consequence of ROS attack to nuclear proteins are generated protein radicals and radicals of base react under formation of DNA-protein cross-linking.

Mitochondrial DNA (mtDNA) is excessively sensitive on an oxidative damage because mtDNA is situated near inner mitochondrial membrane, where are formed ROS. Mitochondrial DNA is small and is not protected by histones like nuclear DNA. Mitochondria are able repair an oxidative damage of mtDNA and that base excise repair pathway plays a dominant role in mtDNA repair [36]. Damage of mtDNA can be potentially more important like damage of nuclear DNA because all mitochondrial genome code genes which are expressed whereas nuclear DNA includes great number of untranscribed sequences [166]. Linnane and co-workers [101] assume that accumulation of somatic mutations mtDNA is the main origin of human ageing and degenerative diseases.

3. Antioxidant defence

In consequence, imbalance between pro-oxidant and antioxidant in favour of pro-oxidants and their harmful effects, oxidative stress is increased. Cells possess antioxidant defence systems: enzymatic and non-enzymatic [15]. Antioxidants can work at various levels:

- protection the organism from the formation of reactive oxygen species,
- elimination of reactive oxygen species by conversion to un-radical molecules or to less reactive ROS,
- reparation of damaged molecules and cell structures,
- removing of oxidised molecules.

The most important enzymatic antioxidants are: superoxide dismutase, catalase and gluta-thione peroxidase. Superoxide dismutase (SOD, EC 1.15.1.1) is universal enzymatic antioxi-dant. This enzyme is extremely efficient and catalyses the neutralization of superoxide anion to oxygen and hydrogen peroxide. There are three major families of superoxide dismutase, depending on the metal cofactor: Cu/Zn (which binds both copper and zinc), Fe and Mn types (which bind either iron or manganese), and the Ni type, which binds nickel. In humans three form of SOD are present: cytoplasmic Cu/Zn-SOD (SOD1), mitochondrial Mn-SOD (SOD2), and extracellular Cu/Zn-SOD (ECSOD, SOD3). Catalase (CAT, EC 1.11.1.6) is a common antioxidant enzyme responsible for controlling hydrogen peroxide concentrations in cells. Catalase as an intracellular antioxidant enzyme catalyzes the decomposition of two molecules of hydrogen peroxide into one molecule of oxygen and two of water and its activity is genetically determined. Glutathione peroxidases (GPXs, EC 1.11.1.9) are family of enzymes ubiquitously distributed which have peroxidase activity whose main biological role is to protect the organism from oxidative damage. Glutathione peroxidases reduce hydrogen peroxide to water and reduced glutathione and lipid hydroperoxides to their corresponding alcohols, water and reduced glutathione. Four types of GPXs have been identified: cellular GPX, gastrointestinal GPX, extracellular GPX, and phospholipid hydroperoxide GPX [161]. Other an essential part of defence mechanism is a super-family of enzymes called glutathione transferases (GSTs, EC 2.5.1.18). These enzymes are involved in the cellular detoxification of various electrophilic xenobiotic substances such as chemical carcinogens, environmental pollutants, drugs and antitumor agents. These enzymes also inactivate endogenous α,β-unsaturated aldehydes, quinone, epoxides, and hydroperoxides formed as secondary metab-olites during oxidative damage. GSTs may reduce reactive oxygen species to less reactive metabolites and protect organism against consequences of lipid peroxidation. Heme oxygen-ase (heat shock protein 32, HO; EC 1.14.99.3) plays an important role in organism defence to oxidative stress [114] and inflammation [111]. There are known three isoforms of HO: HO-1, HO-2, and HO-3. HO-1 is activated by a lot of inflammatory mediators, reactive oxygen species and by other stimuli [109, 135]. Upregulation of HO-1 is accepted as a sensitive marker of oxidative stress. Oxidative modified DNA can be repaired by several enzymes such as glycosylases: 8-oxoguanine-DNA-glysocylase (OGG1, EC 4.2.99.18), Nei-like protein 1 and 2 (NEIL, EC 4.2.99.18); Apurinic/apyrimidinic endonuclease 1 (APE 1, EC 4.2.99.18), X ray repair cross-complementing group 1 (XRCC 1, EC 4.2.99.18) and poly(ADP-ribose) polymerase-1 (PARP 1, EC 2.4.2.30). OGG1 removes 8-oxoguanine paired with a cytosine. Human *OGG1* gene consists of eight exons which can be alternatively spliced to produce different isoforms. The most abundant mRNAs of OGG1 are type 1a and 2a. These two isoforms are ubiquitously expressed in human tissues.

4. Alzheimer`s disease

Ageing is the main risk factor of neurodegenerative disorders. Approximately 5% of people in age 65 years have Alzheimer`s disease (AD) and the prevalence of this disease increases with increasing age from 19% to 30% after 75 years of age. Overall, 90-95% of Alzheimer`s

disease represents a sporadic form and 5-10% represents familiar form. Alzheimer`s disease is neurodegenerative disorder characterised by cognitive failures, impairment of memory and by dramatic changes in behaviour. AD symptoms may include:

- loss of memory,
- difficulty in finding the right words or understanding what people are saying,
- difficulty in performing previously routine tasks, and activities,
- problems with language,
- personality and mood changes.

Although the cause or causes of Alzheimer's disease are not yet known, most experts agree that AD, like other common chronic conditions, probably develops as a result of multiple factors rather than a single cause.
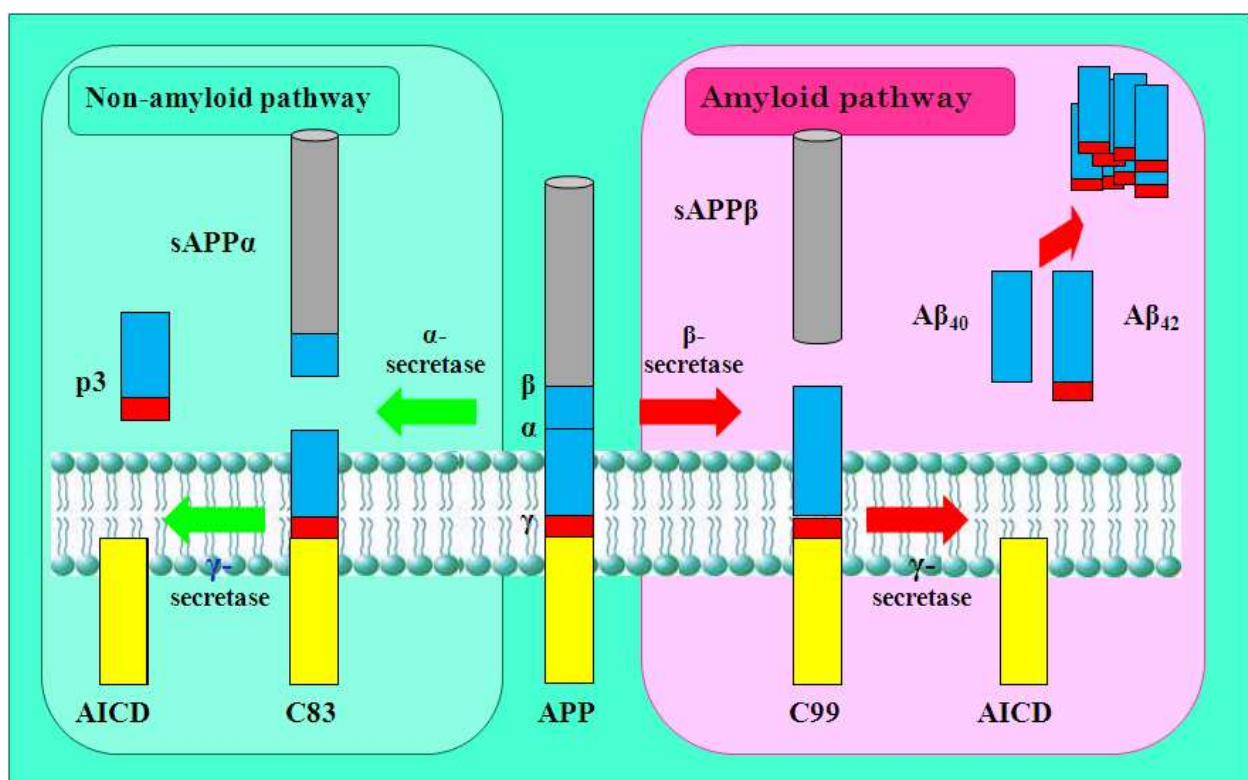

Figure 4. Processing of amyloid precursor protein (APP). Non-amyloid pathway of APP starts by α-secretase cleavage and continues by γ-secretase. Non toxic a soluble fragment of amyloid precursor protein (sAPPα), a small peptide (p3) and an amyloid intracellular domain (ACID) are produced. Amyloid pathway starts with β–secretase cleavage and after that it continues by γ–secretase. A soluble fragment of amyloid precursor protein (sAPPβ), a toxic amyloid β peptide (Aβ) and an amyloid intracellular domain are generated. Amyloid β peptide can be degradated or accumulated and therefore can be responsible for generation of amyloid plaques.

For Alzheimer`s disease many neurochemical and pathological changes are characteristic such as gliosis, tissue atrophy caused by loss of synapses which is the most striking in frontal and temporal parts of brain cortex and by formation of two main protein clusters in ex-

tracellular and intracellular region of brain. Extracellular deposits or senile amyloid plaques occur the most frequently in neocortex. Primary they are consisting of 4 kDa, 40-42 amino acid polypeptide chain called amyloid β peptide (Aβ) [66]. Intracellular deposits represent neurofibrillar tangles which are generated from filaments of microtubullar hyperphosphorylated tau protein [4, 70, 99]. Amyloid plaques are example of a specific damage that is characteristic for AD while neurofibrillar tangles are present in different neurodegenerative pathological situations [134]. Created aggregates are involved in a process which leads to progressive degeneration and to neuron death. In the past decade, a significant body of evidence has pointed the attention to the amyloid processing of amyloid precurcor protein - "amyloid cascade" (fig. 4). This event is the major causative factor in AD.

Pathogenesis of AD is complex and involves many molecular, cellular, biochemical and physiological pathologies [9]. Alzheimer`s disease is a characteristic process with identifiable clinical state which are in a continuity with normal ageing process. It is a multifactorial disease and genetic as well as environmental factors are included in its pathogenesis. Whereas majority of AD is sporadic 5% is caused by mutations (familiar AD). There was observed a large loss of synapses and a neuronal death in a part of brain which is crucial for cognitive function including cerebral cortex, entorhinal cartex and hippocampus. Senile plaques created by deposits of amyloid fibres were localized in the brain.

4.1. Oxidative damage and Alzheimer`s disease

Reactive oxygen species probably play an important role in the generation of amyloid plaques, the development of neurofibrillary tangles and the neurodegenerative process itself. Age-related accumulation of reactive oxygen species results in damage to nuclear and mitochondrial DNA, lipids (lipid peroxidation), proteins (protein oxidation), and sugars (advanced glycosylation end products). Oxidative damage caused by reactive oxygen species can account for the vastly heterogeneous nature of Alzheimer`s disease. Several different kind of oxidative protein and lipid damages were observed in brain during ageing as well as increased generation of reactive oxygen species [1, 24, 136, 147, 150]. We have found increased lipid peroxidation, accompanied by accumulation of conjugates of lipid peroxidation products with proteins, formation of dityrosines, loss of sulfhydryl groups and change in ANS (fluorescent probe 1-anilino-8-naphthalenesulfonate) in the ageing rat brain [7]. Keller et al. [91] observed that 4-hydroxy-2-nonenal damage a glutamate transport in synaptosome and mitochondrial function in brain. Increasing lipid peroxidation can participate on the age-related brain cell dysfunction. Recently, several reports have suggested that mitochondrial abnormalities and oxidative stress play a role in sporadic Alzheimer`s disease [26, 89, 132, 158, 181]. In brain tissue from Alzheimer`s disease patients, there are increased levels of markers of oxidative stress, including oxidized proteins, membrane lipids, and DNA [121, 127, 147, 148]. Oxidative modification of biomolecules is a marking process for the targeting of proteases. In the process of ageing there is a marked decrease in protease activity, damaged molecules can be cumulated with age and it may contribute to the age-related neurodegenerative diseases, including Alzheimer`s disease.

Brain and cerebral blood vessel deposits of amyloid β peptide are the main signs of Alzheimer`s disease. Experimental and clinical studies showed an causal relationship between an accumulation of amyloid β peptide and origin of Alzheimer`s disease [25, 63, 73]. An abnormal production of amyloid β peptide or disturbed amyloid β peptide degradation can cause a pathological accumulation of amyloid β peptide and subsequent production of amyloid plaques [182]. It is suggested hypothesis that amyloid β peptide cause neuronal damage and cognitive failure via the generation of reactive oxygen species, mitochondrial oxidative damage, synaptic failure, and by inflammation changing in the brains of Alzheimer`s disease patients [133, 140, 158, 160]. Several *in vitro* studies have shown that synthetic amyloid β peptide facilitates the production of reactive oxygen species [12, 78, 132]. It was observed increased levels of soluble amyloid precursor protein in plasma and cerebrospinal fluid with advancing age [88, 106]. Increased level of soluble amyloid precursor protein may be a sorce of amyloid β peptide in the brain and vessels. Pluta et al. [126] demonstrated a transit of amyloid β peptide through the blood brain barrier. Expression of amyloid precursor protein, α-secretase, β-secretase, enothelin-converting enzyme, neprilysin as well as insulin-degrading enzyme was demonstrated at the brain barrier system [35]. It is possible that 80% of amyloid plaques in transgenic models Alzheimer`s disease [44] and 90% of human amyloid plaques is in a contact with capillaries [87]. Transit of amyloid β peptide or fragments of amyloid precursor protein from blood to the endothelial cells and brain parenchyma can cause changes in the vascular elasticity [127, 162] or can have direct pathological implications in the brain tissue. Changes in the brain blood vessels after brain attack or during the ageing process can cooperate in the pathogenesis and development of Alzheimer`s disease. Beta-secretase (BACE1) expression and its mediated β-site amyloid precursor protein cleavage activity appear to be tightly coupled to mitochondrial function. Beta-secretase upregulation may be a common consequence in various potential Alzheimer`s disease-related etiological conditions that involve energy insufficiency and/or oxidative stress [174]. *Post mortem* analysis of Alzheimer`s disease patients showed increased level of β-secretase [100, 163] and it can be responsible for an accumulation of amyloid plaques [179] and amyloid cascade. Reactive oxygen species that are generated due to ageing can activate β-secretase and facilitate the cleavage of amyloid precursor protein. Amyloid β peptide can be toxic for organism not only for its accumulation and amyloid plaques generation but also for possibility to increase oxidative stress and oxidative damage, to inhibit complexes of respiratory chain in mitochondria, and to inhibit enzymes of Krebs cycle [117, 132, 133, 147, 148]. However clear and exact mechanisms interface between amyloid β peptide and increased oxidative damage are unknown. Oxidative damage of amyloid degrading enzymes can be result of pathological changes of Alzheimer`s disease as well as a contributing factor to amyloid β peptide accumulation and generation of amyloid plaques. During ageing we observed protein and lipid oxidative damage that was caused by increased production of reactive oxygen species and insufficient or inadequate antioxidant defence. Age-related increasing production of reactive oxygen species could be one of a key factor leading to the age-related diseases, including neurodegenerative disease. Elevated oxidative damage and accumulation of amyloid deposits can have repercussion on deepened oxidative damage, preference of amyloid processing of amyloid precursor protein and development of Alzheimer`s disease.

4.2. Alzheimer`s disease and polymorphism in antioxidant enzymes

Oxidative damage is one of the mechanisms which results in stimulation of the amyloid pathway of APP processing therefore genes of antioxidant enzymes could present another group of candidate genes. Superoxide dismutase represents the most important part of an active antioxidant defence. The genes encoding SOD1, SOD2, SOD3 are located in different chromosomes and in all of them polymorphisms have been described. *SOD1* is encoded on 21q22.1, *SOD2* on 6q25.3, and *SOD3* on 4p16.3-q21. Regulation of *SOD* genes plays a crucial role in balancing the reactive oxygen species concentration. In *SOD1* has been observed substitution of A to C at the non-coding position 35. This polymorphism influence SOD1 activity [56]. Substitution T to C at position 24, resulting in a valine to alanine substitution at amino acid 16 has been identified in *SOD2*. In *SOD3* gene has been identified three single nucleotide polymorphism: alanine to threonine substitution at amino acid 40, phenylalanine to cysteine at amino acid 131, and finally the most studied polymorphism which represents substitution of arginine to glycine at amino acid 213. It has been observed no linkage between AD polymorphism in *SOD1* [37, 105]. It was observed that three polymorphisms in *SOD2* can be associated with development of AD [173].

Catalase is a common antioxidant enzyme responsible for controlling hydrogen peroxide concentrations in cells. The catalase gene is located on chromosome 11p13. There are known different polymorphisms of this enzyme in coding regions [67, 93] and in non-coding regions as well [27, 58, 68, 93, 164, 180]. A common polymorphism in the promoter region of the catalase gene consists of a C to T substitution at position -262 in the 5' region [58], which is thought to result in reduced activity. Catalase gene polymorphism does not confirm a protective role in AD patients.

Glutathione transferases have historically also been called glutathione-S-transferases, and it is this latter name that gives rise to the widely used abbrevation, GST. Three major families of proteins the cytosolic, mitochondrial and microsomal (membrane-associated proteins in eicosanoids and glutathione metabolism, MAPEG) are known. In some organisms expression of *GSTs* are upregulated by exposure to prooxidants [6, 41, 167]. Seven classes of cytosolic glutathione transferases are recognising in mammals (Alpha, Mu, Pi, Sigma, Theta, Omega, and Zeta) [76]. At least 16 cytosolic GST subunits exist in human and display polymorphisms, and this is probably to contribute to interindividual differences in responses to diseases and xenobiotics. *GSTM1* is one of the genes encoding the Mu class of enzymes. Gene for GSTM1 has been mapped to glutathione transferase mu gene cluster on chromosome 1p13.3. Three polymorphisms of *GSTM1* have been identified: a substitution (*GSTM1A* and *GSTM1B*) and a deletion [131, 175]. The alleles of the substitution variant differ by C to G transition at base position 534, resulting in a lysine to asparagine substitution at amino acid 172 [34, 75]. There is no evidence to date that *GSTM1A* and *GSTM1B* alleles are functionally different from one another; thus these alleles are typically categorized together as a single functional phenotype. Other polymorphism is a deletion – *GSTM1* null variant that results in a lack of functional gene product and null genotype of GSTM1 was shown as a risk factor in Italian AD patients. The *GSTT1* gene is located at 22q11.2. Absence of both alleles for this gene represents null variant analogous to *GSTM1*. Deletion of whole gene results in the lack of enzymatic activity [152].

Gene for GSTP1 is one of the most intensive studying genes of glutathione transferase family and has been mapped on chromosome 11q13 and comprising nine exons. There are known two polymorphisms of *GSTP1*: substitution of isoleucine to valine at amino acid 105 and alanine to valine at amino acid 114, demonstrating different catalytic efficiencies due to changes in the active site [3]. Polymorphism in *GSTP1* may represent risk factor for AD and with advancing age [125, 151]. Presence of gene for GSTM1 and GSTT1 could be a protective factor [125, 157].

The *GPX1* gene is located in the 3p21 locus; the pro198leu polymorphism involves a change of thymine (T) for cytosine (C), which leads to the substitution of leucine (leu) for proline (pro), whose recessive allele leu has been linked to 70% reduction of enzyme activity. The leucine allele of *GPX1* may be a possible risk factor [118].

Subjects carrying the *HO-1* (-413) TT genotype might show a higher AD risk due to their genetic inability to induce a more effective HO-1 protective response [83]. Authors showed that an AD risk effect of *HO-1* (−413) TT genotype is only apparent in the presence of liver X receptor (LXR) LXR-β (intron 2) TT, LXR-β (intron 5) AA, or LXR-β (intron 7) TT genotypes. No genetic association between AD and polymorphisms of heme oxygenase 1 and 2 were observed in a Japanese population [143]. A (GT)n repeat in the human HO-1 gene promoter region is highly polymorphic, although no particular alleles are associated with AD or PD [92].

The DNA base excision repair (BER) pathway is the major pathway responsible for removing oxidative DNA damage caused by oxidative reagents and alkylation and thus protects cells against the toxic effects of endogenous and exogenous agents and this pathway is of particular importance in postmitotic tissues such as brain. The first step in the BER pathway is recognition and removal of the damaged base by a DNA glycosylase. A variety of glycosylases have evolved to recognize oxidized bases, which are commonly formed by reactive oxygen species generated during cellular metabolism. One of them is 8-oxoguanine-DNA-glysocylase (OGG1). The most common polymorphism of *OGG1* is in this gene substitution of serine (Ser) for cysteine (Cys) at codon 326 in exon 7. The variant homozygote is associated with reduced enzymatic activity [94]. Allele and genotype frequencies of *OGG1* were equally distributed between AD patients and healthy subjects [32, 115]. The Arg46Gln polymorphism of *OGG1* is also not associated with the pathogenesis of AD [47]. Mao et al. [104] identified in AD patients deletion in *OGG1* and their results suggest that defects in OGG1 may be important in the pathogenesis of AD in a significant fraction of AD.

Apurinic/apyrimidinic endonuclease 1 (APE1) is an enzyme involved in BER pathway. Its main role in the repair of damaged or mismatched nucleotides in DNA is to create a nick in the phosphodiester backbone of the AP site created when DNA glycosylase removes the damaged base. There are four types of AP endonucleases that have been classified according to their sites of incision. Genetic polymorphism has been identified in *APE1* gene and associated with cancer risk. One of the most studied polymorphism is Asp148Glu. No association was found in AD patients [115].

X-ray repair cross-complementing-1 (XRCC) is a protein, which plays a coordinating role for consecutive stages of the BER system and interacts with several proteins of BER including

hOGG1, APE1, DNA polymerase β (pol β) and DNA ligase IIIα [115]. XRCC1 is recruited to the site of repair till the last stage of ligation, regulating and coordinating the whole process. More than 60 single nucleotide polymorphisms (SNPs) XRCC1 polymorphisms are known but the most common polymorphisms in *XRCC1* gene are: Arg149Trp, Arg280His, and Arg399Gln, and are associated with decreased function of XRCC1. It is unlikely that the XRCC1 Arg194Trp polymorphism plays a major role in the pathogenesis of late-onset AD in elderly Han Chinese [130] but positive association was found in Turkish population [46]. Arg280His, and Arg399Gln were not associated with AD [115].

5. Parkinson´s disease

Parkinson´s disease (PD) was firstly described by James Parkinson in 1817. It is the second most common neurodegenerative disease which affects approximately 1% of the human population aged 65 and more [80]. PD is slowly progressed disorder characterized by selective degeneration and loss of dopaminergic neurons in the *substantia nigra* (SN) *pars compacta* region of the midbrain, as well as with the appearance of intracytoplasmic inclusions known as Lewy bodies [30]. Among clinical symptoms of the disease belong rigidity, resting tremor, bradykinesia and postural imbalance [139]. Beside motor dysfunctions, as the major clinical features, non-motor symptoms, such as sleep disturbances, dementia and depression may be present as well [177].

Familiar PD represents only 5-10% of the total cases of PD. Recently, several gene mutations have been linked with rare familiar forms of PD (e.g. α-synuclein, parkin, nuclear receptor-related 1). The most important in early-onset familiar PD is the parkin gene [40]. So far no genetic changes are definitely connected with sporadic or idiopathic form of the disease. However, the prevalent form of PD appears to be multifactorial and a combination of environmental and genetic factors, together with ageing, may contribute to the development of the disease. Biochemical abnormalities that have been detected in sporadic PD include: oxidative stress [108, 124, 168], mitochondrial and proteasomal dysfunction [116, 142] and glutathione depletion [10, 177].

5.1. Oxidative damage and Parkinson´s disease

Although the primary cause of PD is still unknown, oxidative stress together with mitochondrial dysfunction are thought to be significantly implicated in the neurodegenerative process. Excessive formation of reactive oxygen and nitrogen species in PD may damage cellular components such as lipids, proteins and DNA. Increased lipid peroxidation, measured by increased amounts of malondialdehyde [42] and 4-hydroxynonenal, as well as increase in the extent of protein oxidation and elevated concentration of 8-hydroxy-2´-deoxyguanosine, a product of DNA oxidation [84], in SN provides direct evidence of oxidative damage [43].

Since majority of all oxygen is used in mitochondria, electron transport chain is major source of free radicals. Recent research confirmed that about 1-2% of total molecular oxygen is converted into reactive oxygen species [23]. Post-mortem studies on patients with

PD have revealed a specific decrease in the activity of NADPH dehydrogenase (complex I). The alterations in complex I activity were not detected in other regions of the brain, as well as in other neurodegenerative diseases [142]. Complex I deficiency could contribute to neurodegeneration in PD not only due to decreased ATP synthesis but also increased ROS production [11, 137]. Van der Walt et al. [165] also published that the 10398G polymorphism within NADH dehydrogenase 3 may provide significant protection against developing PD in Caucasian populations.

Alternatively, ROS may arise during metabolism of dopamine. Autooxidation of dopamine and its polymerization into neuromelanin produces electrophilic semiquinones and quinones, which can contribute to ROS production, especially superoxide anion radicals [60]. It is also known that dopamine is able to coordinate iron and generate Fe^{2+}, providing an important source of hydroxyl and superoxide radical production [13]. In generally, elevated iron levels were observed in *substantia nigra* in PD [149]. A major source of increased iron levels during PD is microglial activation which induces iron release and free radical production [123]. Free iron may promote already mentioned autooxidation of dopamine [14]. Oxidative stress induced by elevated levels of free iron also appears to promote α-synuclein (a prominent component of Lewy bodies) aggregation, the major histopathological hallmark of PD [75].

Important role in protection of dopaminergic neurons against oxidative stress plays the antioxidant molecule glutathione (GSH). GSH removes H_2O_2, which is produced during cellular metabolism. Perry et al. [121] firstly reported decreased levels of total GSH in autopsied brains from PD patients. Total GSH is reported to be decreased by 40-50% specifically in nigral dopaminergic neurons [119]. GSH depletion also appears to correlate with the severity of the disease and is the earliest known marker of oxidative stress and indicator of degeneration of nigral neurons [85]. On the other hand, Mythri et al. [108] observed 3-5 fold increase in total GSH levels in all the non-SN regions of tested PD brains compared to control samples. On the contrary, they found no significant changes in the levels of protein carbonyls, as markers of protein oxidation, or nitrosative stress markers. According to these results, they expected that specific signals from the degenerating dopaminergic SN neurons might induce elevated levels of GSH and such prevent oxidative damage [108]. Beside GSH, other antioxidant activities are altered in the SN. The levels of antioxidant enzymes, such as superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, were found to be changed in SN [168].

5.2. Parkinson´s disease and polymorphism in antioxidant enzymes

Current research shows that ROS and oxidative damage are part of pathological processes during PD, but it remains to be determined whether this is a primary event or a consequence of other cellular dysfunctions. Analysis of polymorphisms of detoxifying enzymes may help to clarify whether PD may be caused by a genetic predisposition to oxidative stress.

Among antioxidant enzymes, superoxide dismutase (SOD) represents the first line of defence. From three different SOD isoenzymes, SOD2 appears to be the most relevant in PD because of its mitochondrial localization. Several research groups confirmed that *SOD2* (Ala9Val) polymorphism is not significantly associated with PD in Caucasian population [52, 69, 146]. On the other hand, some studies, especially on Asian population, found higher Ala allele

frequency in the group of PD patients [57, 172]. Observed results might be explained by ethnic differences in genotypes frequencies.

Little is known about the association of catalase polymorphisms and PD. However, Parboosingh et al. [113] observed no connection between mutations of catalase gene and PD.

Glutathione transferases (GST) are the most studied phase II detoxification enzymes. Activity of GST was observed to be reduced in substantia nigra of PD [145]. Studies of *GST* polymorphisms and PD yielded mixed results. Several studies confirmed positive association between *GSTM1* and *GSTT1* null genotypes and higher risk of PD [120, 157]. On the other hand, other studies found no association [90, 171]. Similarly, *GSTP1* was detected to have only a minor role in PD [90,, 171]. However, Wahner et al. [90] noted a 32% risk reduction among Caucasian PD patients carrying at least one *GSTO1* and *GSTO2* variant allele.

Markedly elevated expression of heme oxygenase 1 was observed in PD and it has been shown that its overexpression may protect neurons against oxidative stress-induced toxicity [81]. However, Funke et al. [61] found no association of (GT)n fragment length polymorphism in the promoter region, as well as three other coding SNPs with PD.

Since increased 8-oxo-guanine levels have been observed in PD patients, still more attention is paid to analysis of genetic polymorphisms of oxoguanine DNA glycosylase (OGG1), which removes oxidized guanine from DNA. Coppede et al. [33] published that *hOGG1* Ser326Cys polymorphism is not associated with sporadic form of PD.

6. Huntington`s disease

Huntington`s disease (HD) is an autosomal dominant inherited neurodegenerative disorder of the central nervous system. Worldwide prevalence of HD is 5 to 8 per 100,000 people with no gender preponderance [74]. HD is characterized by cognitive and memory dysfunctions, weight loss, and choreiform movements. It is caused by an expansion of a polymorphic three nucleotide repeat sequence CAG in the exon 1 of the gene coding for the protein huntingtin (htt) on chromosome 4 (4p16.3) [82]. Wild type htt may exert a variety of intracellular functions such as: protein trafficking, vesicle transport and anchoring to the cytoskeleton, clathrine-mediated endocytosis, postsynaptic signaling, transcriptional regulation, and anti-apoptotic function [65]. For instance, htt is involved in fast axonal transport, enhancing vesicular transport of brain-derived neurotrophic factor along microtubules [62, 159]. The protein htt consists of a series of CAG repeats coding for glutamine residues (polyQ) followed by two short stretches of prolines. Normally, the number of the polyglutamine repeats is 10-29 (median, 18). By contrast, HD patients have expanded numbers of CAG repeats, from 39 to 121 (median, 44). Expanded repeats cause a conformational change in the htt promoting the formation of intracellular aggregates, mainly in medium spiny neurons where the expression of huntingtin is elevated. The number of CAG repeats is inversely correlated with the age of disease onset, and disease progression is rapid in patients with more CAG expansion [96]. In brain, the most remarkable changes are found within the striatum, there is a gradual atrophy of the caudate nucleus and putamen [170].

6.1. Oxidative damage and Huntington`s disease

The generation of reactive oxygen species and the consequent oxidative stress is thought to play a pivotal role in the neurodegeneration observed in HD [53, 71] (Ferrante, Grunewald). Several lines of evidence suggest that not only increased oxidative stress, but also protein metabolism impairment, mitochondrial dysfunction, and they interplay contribute to neuronal dysfunction in HD [18, 19, 112, 128].

DNA fragmentation is significantly increased in human HD patients and correlates with the length of CAG repeats [20]. The oxidation of DNA leads to the formation of the metabolite 8-hydroxy-2`-deoxyguanosine (OHdG) which is a direct result of free radical activity [128]. Significant increases of OHdG levels, coming from nuclear DNA, occur in the caudate nucleus and parietal cortex in postmortem tissue of HD patients [18, 128]. In addition, increased oxidative damage to DNA is present in serum from HD patients [29, 79. Moreover, the improvement of elevated OHdG by creatine treatment suggests OHdG as a promising peripheral biomarker [79]. These findings are in consensus with the elevated levels of OHdG that occur in other neurodegenerative diseases in which oxidative stress is implicated as a pivotal pathogenic mechanism [55]. Nevertheless, some research groups have not confirmed changes in OHdG levels in HD patients [2].

Elevated levels of malondialdehyde (MDA), a marker of lipid peroxidation, have been documented in HD brain [72]. Elevated levels of MDA have also been shown in the peripheral blood of HD patients, and preliminary results suggest that the levels of lipid peroxidation (MDA level) appear to be correlated to disease severity [29, 155]. Reduced activities of erythrocyte glutathione peroxidase and Cu/Zn-superoxid dismutase in HD patients implicate that the defense mechanism is impaired in peripheral blood cells of HD. Because of ubiquitous expression of huntingtin, the peripheral abnormalities may reflect the same consequences to mutant huntingtin in the brain [29]. An abnormal accumulation of lipofuscin, product of unsaturated fatty acid lipid peroxidation, has been proven in HD patients [17]. Supplemental markers of oxidative damage, as for example inducible form of heme oxygenase, 3-nitrotyrosine, and above mentioned malondialdehyde, are elevated in human HD striatum and cortex compared with age-matched control brain specimens [19, 54].

The primary source of reactive oxygen species in neurons is mitochondria. Mitochondrial dysfunction in HD is closely associated with oxidative stress. In was first reflected that here was an energetic impairment in HD, because HD patients exhibit profound weight loss despite continual caloric intake [20, 21]. Lowered glucose utilization in striatum of HD patients early stages prior to pronounced striatal atrophy [97]. Mitochondrial functional abnormalities were observed, such is a defect in succinate dehydrogenase in the caudate of postmortem HD brains. Subsequent studies confirmed that there was a significant decrease in complex II activity in the caudate nucleus, in complex III activity in the caudate and putamen, and of complex IV in the putamen of HD brains [18, 72, 103].

Plasma lipid peroxide and lactate concentrations as indicators of oxidative stress and mitochondrial dysfunction, were significantly elevated in HD patients. On contrary, aspartate and

glutamate aminopeptidase activities were significantly reduced in HD patients. These changes may be related to the progression of the disease [49].

6.2. Polymorphisms and Huntington`s disease

Besides CAG repetition in huntingtin gene, there are 2 genetic polymorphisms in the full-length htt gene. One of them, named CCG polymorphism is located in the first proline-rich fragment, second one is delta 2642 glutamic acid polymorphism. Previous studies have shown that alleles with 7 or 10 repeats are predominant in CGG polymorphism, but the distribution from among ethnics is variable. In western population is strong association between the 7 repeat CCG allele and HD [156]. On contrary, in Japanese population has been shown association with the 10 repeat CCG allele and HD [107]. Latest study performed on Chinese population compared the clinical features between the 7 and 10 repeats CCG alleles, but did not find any statistical significant results [178].

It was proposed a model that somatic expansion of CAG repeats in HD cells might contribute to disease onset and progression of HD and is mediated by the DNA repair oxoguanine glycosylase 1 (OGG1) enzyme [95]. This enzyme removes 8-oxoguanine from the DNA. Study of the *hOGG1* Ser326Cys polymorphism performed on 91 patients showed that bearers of mutant Cys allele appear to have an increased number of the CAG repeats of the expanded HD allele. Since this is the first evidence of an association between the hOGG1 genotype and both CAG repeat length and age at onset of the HD, for confirmation, further studies are required [31].

7. Conclusions

Population ages therefore neurodegenerative diseases are in a centre of interest. Several studies showed that missing antioxidant genes may have negative effect on central nervous system and may represent a risk for development of neurodegenerative diseases. Unfortunately majority of results are from animals and cell tissue studies. Animal studies, in vitro and ex vivo studies are full of positive effects of single antioxidant gene overexpression such as superoxide dismutase, catalase and antioxidant therapy may represent promising treatment. Molecular and genetic analyses represent a new potential for neurodegenerative diseases studying. The role of gene polymorphisms and many others gene polymorphisms as risk factors for the occurrence of neurodegenerative diseases are still controversial. Moreover impact of gene polymorphisms can depend on several different factors, especially for neuro-degenerative diseases, such as ethnicity, social environment, life style. We need new studies for clear determination of antioxidant gene polymorphisms. Moreover multiple genotype analyses are necessary as well because a single gene polymorphism can be without relationship to increased risk of neurodegenerative disorders but the combination of gene polymorphisms may have significant effect, positive or negative.

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