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Alzheimer's Disease:
Definition, Molecular and Genetic Factors

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1. Introduction

Frequency of neurodegenerative diseases increase significantly with the age. One of the most frightening and devastating of all neurological disorders is the dementia that occurs in the elderly. Dementia is a common name for progressive degenerative brain syndromes which affect memory, thinking, behaviour and emotions. Dementia mainly affects older people, although there is a growing incidence of the cases that start before the age of 65. After age 65, the likelihood of developing dementia roughly doubles every five years. Dementia affects 1 – 6% of human population over 65 years and 10 – 20% over 80 years. In the present, average age is increasing and the number of people over 60 years increases as well. Although 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. Dementia is characterised by the loss of or decline in memory and other cognitive abilities. It is caused by various diseases and conditions resulting in damaging brain cells. Different types of dementia (Alzheimer`s disease, vascular dementia or post-stroke dementia, mixed dementia, dementia with Lewy bodies, Parkinson`s disease, frontotemporal dementia, Creutzfeld-Jacob disease, normal pressure hydrocephalus) have been associated with distinct symptom patterns and distinguishing microscopic brain abnormalities. Alzheimer's disease (AD) is the most common cause of dementia and this disease represents 60 – 80% of all dementia. Alzheimer's disease is age-related disease and it is characterized by a range of changes in brain anatomy, biochemistry, genetic, and function. According to Alzheimer`s disease International in 2010, there were an estimated 35.6 million people with dementia worldwide. This means a 10 percent increase over previous global dementia prevalence reported in 2005 in The Lancet. Number of people with dementia will be increasing to 65.7 million by 2030 and 115.4 million by 2050.

Hallmark abnormalities of Alzheimer`s disease are deposits of the protein fragment β-amyloid (plaques) and twisted strands of the protein tau (tangles). Protein oxidation and generation of protein aggregates may be caused by loss of cell function alike a decreased ability of old organisms to resist the physiological stresses and oxidative damage. The relationship between protein aggregation, oxidative damage and neurodegenerative

diseases is still unclear. Study of the ageing process is very important because this process is a cause of onset of many neurodegenerative diseases which occurrence is raising with increasing age. Epidemiological studies have indicated that several genetic and environmental risk factors are associated with AD. Neuropathological, genetic and molecular biologic data suggest central roles for age-related changes in the metabolism of amyloid precursor protein and tau protein.

Ageing is a universal process which started with a life origin billions years ago and in the present we still did not find the way how to defeat our own ageing. Nobody can say when and where ageing is starting. Biologic, epidemiological and demographic data represent base for a lot of theories which try to identify a cause of ageing or to explain the ageing process and its consequence death. 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 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 an attack of reactive oxygen species is decreased. Oxidation of specific proteins can play a key role in age associated damage. A relationship between protein aggregation, oxidative stress and neurodegeneration remains unclear. One of the basic problems is the analysis of mechanisms that are base of damage. Both localisation and kind of damage are necessary for understanding of neurodegeneration. Neurodegenerative diseases are connected with an origin of protein deposits. It assumes that protein oxidation and generation of protein aggregates generates a base for a loss of cell function and a reduced ability aged organisms to resist to physiological stress.

2. Alzheimer's disease

Ageing is the main risk factor of neurodegenerative disorders such as Alzheimer`s disease and Parkinson`s disease. Approximately 5% of people in age 65 years have 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 chenges 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.

AD is the most wide-spread progressive neurological disorder in men after 65 years of age and it becomes very serious all-society problem in consequence of increasing of average age. 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. Risk factors for AD are:

• age,
• gender,
• gene polymorphism,
• hypercholesterolemia,

- diabetes mellitus,
- stroke,
- brain injuries,
- education,
- alcohol and smoking.

The greatest risk factor for Alzheimer's disease is advancing age, but AD is not a normal part of ageing. There is none available effective treatment or a preventive therapy of AD today and a definitive diagnosis is still established *post mortem* through the histopatological analyse of patient's brain.

Alois Alzheimer in 1906 described neuropsychiatric disorder affecting older people (Alzheimer, 1907). Nowadays this disorder is called Alzheimer`s disease. He did *post mortem* analysis of 51 years old woman (Auguste D.) who suffered from progressive pre-senile dementia (rapid loss of memory, disorientation in time and space) and she died four and half years after beginning of the disease. Alois Alzheimer observed brain atrophy with obvious neurofibrillar pathology and unusual deposits. 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 (fig. 1.) and by formation of **two main protein clusters** in extracellular 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) (Glenner and Wong, 1984). **Intracellular deposits** represent neurofibrillar tangles which are generated from filaments of microtubullar hyperphosphorylated tau protein (Alonso et al., 2008; Grundke-Iqbal et al., 1986; Lee et al., 1991). **Tau protein** is a neuronal microtubullar associated protein which is primary localized in axons. It is assumed that microtubullar associated proteins play a major role in conserve shape of cells and in a axonal transport (Buée et al., 2000). Tau induces *in vivo* packing and stabilization of cell microtubules, tightens and keeps polarity of neuronal cells. Amyloid plaques are example of a specific damage that is characteristic for AD while neurofibrillar tangles are present in different neurodegenerative pathological situations (Robert & Mathuranath, 2007). 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**". This event is the major causative factor in AD.

Pathogenesis of AD is complex and involves many molecular, cellular, biochemical and physiological pathologies. 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. Intranerve clusters were estimated by electron microscopy and it was shown that they are made by paired spiral fibres (thin fibres, diameter 10 nm) (Kurt et al., 1997). A protein component core of paired spiral fibres was identified as a microtubular protein tau (Grundke-Iqbal et al., 1986).

In the last years, two main hypothesis explaining a cause of AD development were proposed: **hypothesis of amyloid cascade** – a neurodegenerative process is a serie of events started by an abnormal processing of amyloid precursor protein (APP) (Hardy & Higgins,

1992), and hypothesis of **neuronal cytoskeletal degeneration** (Braak & Braak, 1991) – cytoskeletal changes are the starting events of AD.
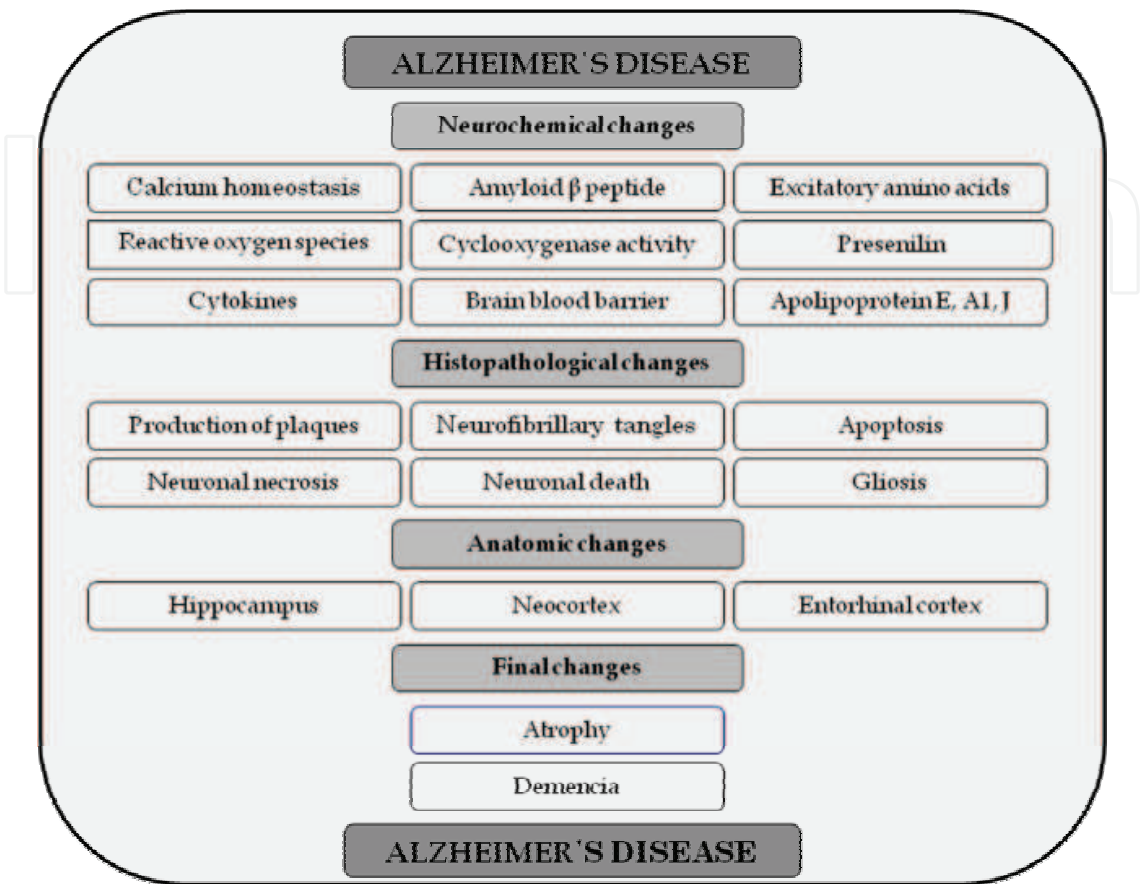

Fig. 1. Typical changes in patients with Alzheimer`s disease

2.1 Amyloid precursor protein

Amyloid precursor protein (APP) is an integral type I transmembrane family of glycoproteins (Kang et al., 1987) and it is expressed under normal physiological condition in brain but its function is unknown so far. It is expressed in several kinds of cells. Gene for amyloid precursor protein contains 18 exons (170 kb) (Yoshikai et al., 1990). N-terminus of amyloid precursor protein is localized toward to extracellular domain or may be localized in the lumen of intracellular vesicles, such as endoplasmic reticulum, Golgi apparatus or intracellular endosomes (Neve & McPhie, 2000). C-terminal of APP lies in cytoplasmic domain (Kang et al., 1987). There are known three different forms of APP mRNA: APP695, APP751 and APP770 that code three isoforms of APP with 695, 751 or 770 amino acids in the chain. The dominant form of APP is APP with 770 amino acids. It is encoded by 18 exons, where exon 17 resembles the membrane-spanning domain. APP695 lacking exon 7 and exon 8 is primarily expressed by neurons and it is the most abundant APP transcript in the brain (Neve et al., 1988). APP751 is lacking exon 8. A part coding of Aβ sequence contain a fraction of exon 16 and exon 17 and contains 40- to 42-amino acids residues that extend from ecto domain to transmembrane domain of protein. N-terminal part of Aβ originates by cleaving of bound between Met-Asp at the position 671-672. This process is catalysed by protease known as β-secretase.

Amyloid precursor protein is sensitive to proteolysis and *in vivo* can be processed by two different pathways: **amyloid** and **non-amyloid processing**, with the contribution of three kinds of proteases (α-, β-, γ-secretase) (fig. 2.). Beta and γ secretase are responsible for the amyloid processing and production of $A\beta_{40}$ or $A\beta_{42}$ variant with significantly higher ability of self-aggregate (Citron et al., 1996) and carboxyl-terminal fragments of amyloid precursor protein which are included in the pathogenesis of AD (Selkoe, 1999; Suh, 1997). Alpha secretase is responsible for non-amyloid processing of amyloid precursor protein.

In dominant non-amyloid processing APP is cleaved first by α-secretase within Aβ domain. There are produced two fragments: soluble extracellular fragment (sAPPα) and 83-residue COOH-terminal fragment (C83). Later C83 can be cleaved by γ-secretase. It is unusual hydrolysis in the middle of transmembrane domain and produces small 3 kDa peptid called p3 and C57-59 (amyloid intracellular domain – AICD).

Cleaving of amyloid precursor protein starts by β-secretase in amyloid processing of APP and soluble extracellular fragment (sAPPβ) and 99-residue COOH-terminal fragmet (C99) are produced. C99 is still membrane-bounded and it is substrate for γ-secretase which releases 4 kDa amyloid β peptide and AICD. Proteolysis by γ-secretase is heterogeneous. It can be produced 40-residue peptide ($A\beta_{40}$) (main product) but also a small part of 42-residue COOH-terminal variant ($A\beta_{42}$). Longer and more hydrofobic $A\beta_{42}$ peptide is much more prone to the production of plaques than $A\beta_{40}$ (Jarret et al., 1993). It is assumed that $A\beta_{42}$ is a minority form of amyloid β peptide and it is a main form of amyloid β peptide found in cerebral plaques (Iwatsubo a kol., 1994). Both pathways of APP processing occurr during physiological conditions and therefore it is supposed that all APP fragments including Aβ may be a part of current unknown normal processes.

Alpha-secretase shows characteristics of membrane-bound metalloproteinases. Non-amyloid processing of APP is the main pathway of APP processing which cleaves end part of 16 amyloid β sequence generating C83 (fig. 2.) (Esch et al., 1990). Gamma-secretase subsequently releases a small peptide (p3) which contains C-terminus of Aβ (fig. 2.). A biological importance of p3 and its role, if there is any, in the amylogenesis is still mystery. Sequence of Aβ is disturbed by non-amyloid processing of APP. It is assumed that α-secretase pathway reduces production of amyloid plaques however it has not been yet clearly demonstrated. In addition sAPPα, which is released by α-secretase, has trophic effects (Esch et al., 1990) which can act against neurotoxic effects of aggregated Aβ (Mok et al., 2000). The localisation of α-secretase is unknown. However trans-Golgi (Kuentzel et al., 1993) was suggested as a place of α-cleaving. It has been found that membrane-bound endoprotease on the cell surface has similar activity as α-secretase. Obscurity for α-secretase localisation can be explained by possibility that this enzyme can be made more by than one protein and enzyme. Activity of α-secretase has constitutive and inducible components. A constitutive activity was not identified but an inducible α-secretase activity is probably controlled by protein kinase C (Sinha and Lieberburg, 1999). It is shown that several proteases are responsible for α-secretase activity – member of ADAM (a disintegrin and metalloprotease) family ADAM9, ADAM10, ADAM 17/tumor necrotic factor-α (TNF-α)-converting enzyme (TACE) and pro-protein convertase PC7 (Brou et al., 2000; Fahrenholz & Postina, 2006; Lopez-Perez et al., 2001).

Beta-site amyloid precursor protein cleaving enzyme – **β-secretase** – (BACE1, Asp2) was identified in 1999 as an unusual member of pepsine family of the transmembrane aspartic proteases (Hussain et al., 1999; Lin et al., 2000; Sinha & Lieberburg, 1999; Yan et al., 1999).
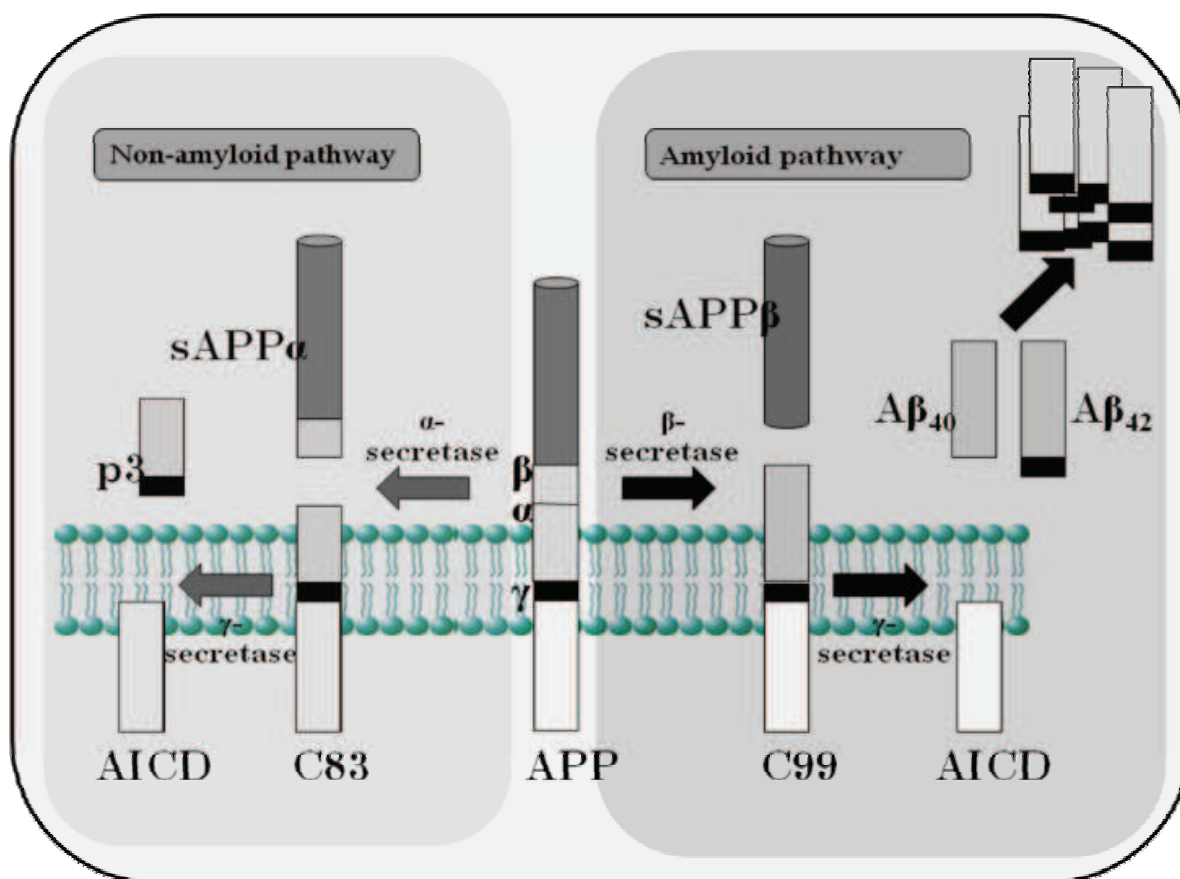
Fig. 2. Processing of amyloid precursor protein (APP). Non-amyloid processing of APP starts by α-secretase cleavage and continues by γ-secretase. A soluble fragment of amyloid precursor protein (sAPPα), a small peptide (p3) and amyloid intracellular domain (ACID) are produced. Amyloid pathway of APP starts with β–secretase cleavage and after that it continues by γ–secretase. A soluble fragment of amyloid precursor protein (sAPPβ), amyloid β peptide and amyloid intracellular domain are generated. Amyloid β peptide can be degradated or accumulated and therefore can be responsible for generation of amyloid plaques

BACE1 has N-terminal catalytic domain containing two important aspartate residues which are bounded to 17-residue transmembrane domain and a short C-terminal cytoplasmic end (Lin et al., 2000; Yan et al., 1999). Beta-secretase activity is present in most of the cells and tissues (Haass et al., 1992) and the highest activity was found in the neural tissue and in the neural cell lines (Seubert et al., 1993). This enzyme contains four potentially N-bond glycosylation sites and peptide sequence at N-terminal. It is phosphorylated inside its cytoplasmic domain at serine residue 498 by casein kinase 1 and phosphorylation is happened exclusively after BACE1 maturation by pro-peptide cleaving and N-glycosylation (Walter et al., 2001). Gene for β-secretase is localised on chromosome 11. BACE1 is an authentical β-secretase (Hussain et al., 1999; Yan et al., 1999). Related transmembrane aspartyl protease (BACE2 or Asp1) (Yan et al., 1999) has similar substrate specificity (Farzan et al., 2000) but it is not very expressed in the brain (Bennett et al., 2000). Beta-secretase is expressed with APP in several regions of the brain. Recent studies demonstrate that BACE1 levels and activity are increased in *post mortem* AD brains (Fukumoto et al., 2002; Harada et al., 2006), suggesting a role of this enzyme in AD.

Residual carboxyl fragments C83 and C99 which are generated after APP cleaving by α- and β-secretase undergo proteolysis inside their domain in a cytoplasmatic membrane. It is regulated intramembrane proteolysis. An intracellular part goes to the nucleus where can influence transcription of several genes. Cleaving of C99 fragment by **γ-secretase** is a final step in the production of Aβ. The right position of cleaving by γ-secretase is determining for development of AD. Gamma-secretase which catalyses secondary cleavage of APP has pharmacological characteristics of aspartyl protease and a specific uncertain sequential specificity for its substrate because many mutations in APP near γ-secretase place are responsible for the production of Aβ in transfected cells (Lichtenthaler et al., 1997; Maruyama et al., 1996). It indicates that γ-secretase represents a multimer enzyme complex and contains at least four proteins: presenilin 1 (PS1), presenilin 2 (PS2), anterior pharynx defective 1 (Aph-1) and nicastrin.

2.1.1 Gene family of amyloid precursor protein

Amyloid precursor protein belongs to the family of genes which has three members in mammals: **amyloid precursor protein** (APP), **amyloid precursor-like protein 1** (APLP1) and **amyloid precursor-like protein 2** (APLP2). Homologues of amyloid precursor protein were found in *Drosophila melanogaster* and *Caenorhabditis elegans* – amyloid like protein (APL1) (de Strooper & Annaert, 2000). All the three proteins are type of I transmembrane proteins with a large extracellular domain (~ 624-700 amino acids), one transmembrane domain (~ 25 amino acids) and a short intracellular domain (~ 46 amino acids). Proteins have similar sequences but the main difference is in an absence of Aβ sequence in two APP similar proteins (fig. 3). No mutations associated with AD were observed in *APLP1* and *APLP2* genes and it supports a hypothesis that Aβ is connected with AD.

The physiological function of APP and its homologues remains unclear. It has been suggested that APP plays a trophic role in neuronal cells (Neve & McPhie, 2000; Qiu et al., 1995). Gene for amyloid precursor protein undergoes a complex alternative exon splicing (Selkoe, 2001a, 2001b; Tanaka et al., 1988). Other heterogenity of APP is reached by series of controlled posttranslational modifications such as N- and O-glycosylation, phosphorylation and sulfation. N-terminal domain shows a homology with Kunitz-type of serine protease inhibitors (KPI) (Kitaguchi et al., 1988; Ponte et al., 1988). Amyloid precursor protein may also participate in cell adhesion, cell proliferation, and synaptogenesis and could have neurotrophic and neuroprotective properties (Caillé et al., 2004; Coulson et al., 2000; Kirazov et al., 2001). Kamal et al. (2000) suggested that APP may serve as a membrane axonal transport receptor for kinesin 1. This hypothesis is interesting because several studies suggest that abnormal processing of APP may play a role in the pathogenesis of AD (Selkoe, 1999; Sinha & Lieberburg, 1999). It assumes that amyloid precursor protein could modulate signal transduction connected with G protein (Nishimoto et al., 1993).

Amyloid precursor protein maps to chromosome 21 in humans. Pathological mutations in sequence which is for amyloid β peptide and for *APP* gene are responsible for increasing production of Aβ and grow in amyloid β peptide self aggregation and production of plaques deposits (Seubert et al., 1993). Deletion of *APP* gene in mouse is without any significant impact to their life and no higher morbidity was revealed. Nevertheless small changes were observed in mobility and in old animals gliosis was found (Zheng et al., 1995). Amyloid β peptide is accumulated in some regions of brain such as *cerebellum*, *striatum* and *thalamus* and it is clearly contained in clinical signs of Alzheimer`s disease (Selkoe, 2001b).

Domain	Present in	Location
Amyloid β peptide	APP	Exons 16, 17
AICD	APP, APLP-1, APLP-2	Exons 16, 17, 18
Signal peptide	APP, APLP-1, APLP-2	Exon 1
Transmembrane	APP, APLP-1, APLP-2	
Heparin-binding I	APP, APLP-2	Exon 3
Cu^{2+}-binding	APP, APLP-2	Exon 4
Zn^{2+}-binding	APP, APLP-1, APLP-2	Exon 5
KPI	APP, APLP-2	Exon 7
OX-2	APP	Exon 8
Heparin-binding II	APP, APLP-1, APLP-2	Exon 9
Growth-promoting	APP	Exon 9
Collagen-binding	APP, APLP-2	Exon 13
Chondroitin (SO_4)-binding	APP, APLP-2	Exon 15
G0 binding	APP, APLP-1, APLP-2	Exon 17
Clarithin	APP, APLP-1, APLP-2	Exon 18

Fig. 3. Functional domains in amyloid precursor protein superfamily (Adapted by Marks & Berg, 2008). APP – amyloid precursor protein, APLP – amyloid precursor protein-like protein, AICD – amyloid intracellular domain, KPI – Kunitz protease inhibitor, OX-2 – thymocyte MRC antigen

2.1.2 Amyloid β peptide

Amyloid β peptide which is produced in amyloid pathway during APP processing preserves and accumulates whereby generates amyloid plaques in AD (fig. 4). Amyloid β peptide contains 40 ($A\beta_{40}$) or 42 amino acids ($A\beta_{42}$) (Younkin, 1998). It is physiological peptide which is produced in the brain continuosly. Its level is determined by balance between anabolic and catabolic activities (Saido, 1998; Selkoe, 1993). Amyloid β peptide is toxic for the cells in cell lines (Yankner et al., 1989) by different pathways and its toxicity correlates with the level of its aggregation. This peptide is able to influence a lot of metabolic pathways in brain. It is able to activate caspases, effectors of apoptosis, to affect calcium homeostasis by increasing intracellular calcium concentration (Mattson et al., 1993), and to induce neuron death.

Neurotoxicity of Aβ can be mediated through the ability of amyloid β peptide participate in the production of reactive oxygen species and increased oxidative damage of biomolecules (fig. 4). Methionine residue 35 plays an important role in this process. Damage induced by Aβ can be modulated by superoxide dismutase. Aβ induces production of superoxide anion radical by stimulation of NADPH oxidase. Hydrogen peroxide arises in the presence of amyloid β peptide through reduction of the copper and the iron. Neurotoxicity is caused also by binding to nicotine acetylcholine receptor, forming calcium and potassium channels in cell membranes, decreasing glucose transport and releasing of chemokines and cytokines.
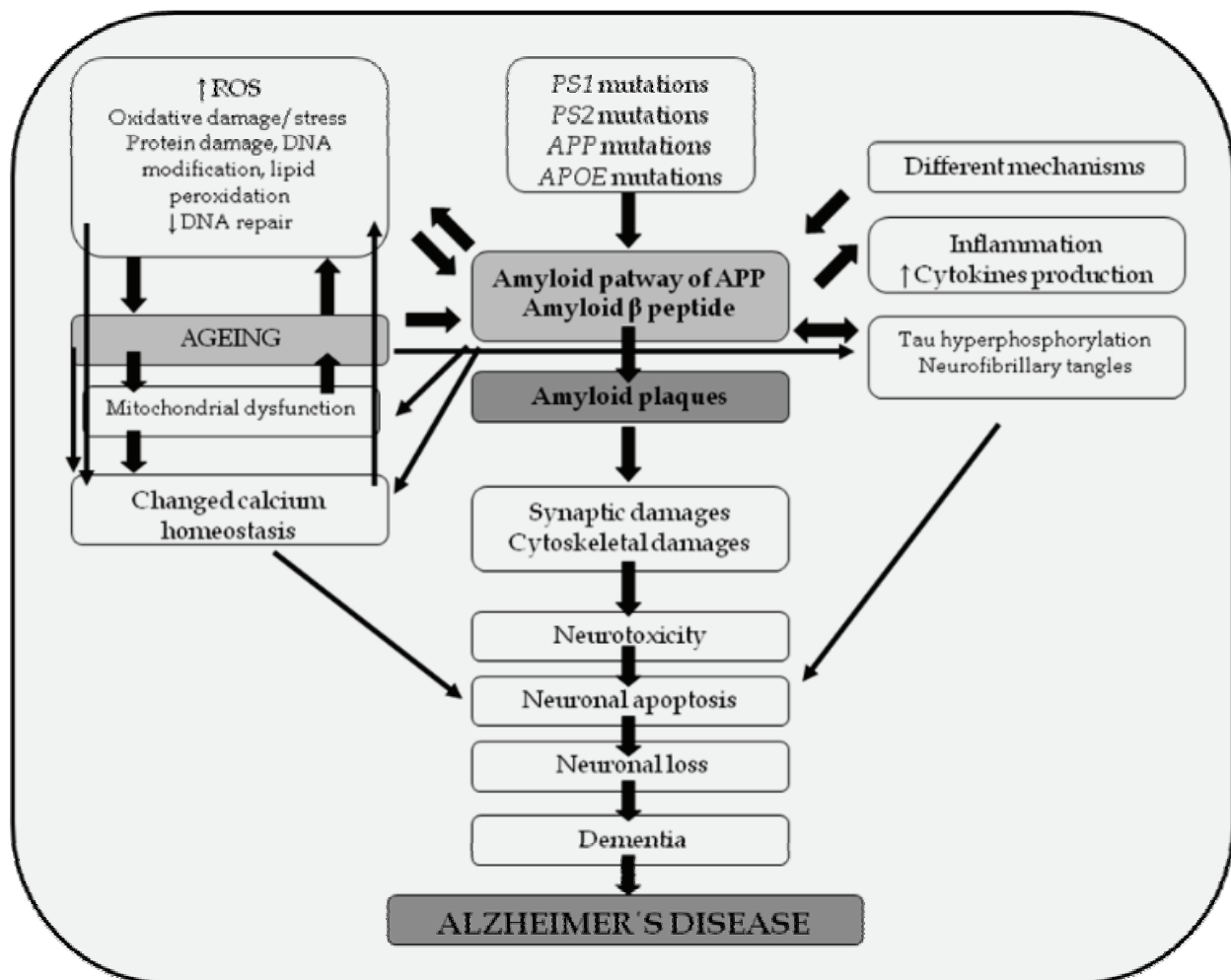
Fig. 4. Relationship between amyloid β peptide (Aβ), the ageing process, oxidative damage and Alzheimer's disease. ROS-reactive oxygen species, PS – presenilin, APP-amyloid precursor protein, APOE-apolipoprotein E

Oxidative modification of glutamate transporter and glutamate synthetase oxidation can be caused by Aβ as well. In AD patients was observed mitochondrial dysfunction and reduced energetic metabolism in brain. The main pathway of glucose oxidation is Krebs cycle in mitochondria. Oxidative decarboxylation of pyruvate (product of glycolysis) is catalysed by pyruvate dehydrogenase complex and offers acetyl CoA initiating Krebs cycle. Pyruvate dehydrogenase complex is formed by three enzymes: pyruvate dehydrogenase (EC 1.2.4.1, E1), dihydrolipoyl transacetylase (EC 2.3.1.12, E2) and dihydrolipoyl dehydrogenase (EC 18.1.4, E3). Rate limiting steps in Krebs cycle are reactions catalysed by pyruvate dehydrogenase complex and by oxoglutarate dehydrogenase complex. Oxoglutarate dehydrogenase complex is compact of three enzymes: oxoglutarate dehydrogenase (EC1.2.4.2), dihydrolipoyl succinyltransferase (EC 2.3.1.61) and dihydrolipoyl dehydrogenase (EC 1.8.1.4). AD patients had decreased concentration of these enzymes. Calcium modulates a lot of metabolic processes including synaptic plasticity and apoptosis. In the pathogenesis of AD play an important role dysregulation of intracellular calcium signalling. It is assumed that neurodegeneration induced by Aβ and protein tau can be mediated by changes in calcium homeostasis. Permanent changes in calcium homoeostasis are proximal reason of neurodegeneration in AD patients (Khachaturian, 1989).

Amyloid β peptide is metabolised very quickly in the brain. Its half time is 2 hours and 10 minutes in the plasma (Betaman et al., 2006) nevertheless it is resistant towards elimination (Jankowsky et al., 2005). Several proteases can participate in Aβ conversion. However one dominant protease is not known today. A lots of proteases cleave monomer Aβ in several positions (Eckman and Eckman, 2005; Rangan et al., 2003; Tucker et al., 2000).

2.1.3 Amyloid β peptide degrading enzymes

Physiological peptide - amyloid β peptide is metabolised by several enzymes. **Neprilysin** (NEP; EC 3.4.24.11), **endothelin-converting enzyme** (ECE; EC 3.4.24.71), **insulin-degrading enzyme** (IDE; EC 3.4.24.56), and probably also **plasmin** (EC 3.4.21.7) which are expressed in the brain contribute to the proteolysis of Aβ in the brain (Eckman et al., 2003; Iwata et al., 2000; Shirotani et al., 2001). Decreased activity of any enzymes in consequence of genetic mutation or as a result of changes in gene expression and proteolytic activity during ageing and diseases may increase risk of AD. Insulin-degrading enzyme, neprilysin and endothelin-converting enzyme are not able to degrade amyloid β deposits. It assumes that amyloid β aggregates can be degraded only by plasmin (Tucker et al., 2000). **Plasmin** is an important enzyme present in blood where degrades a lot of blood plasma proteins. It is a serine proteinase derived from an inactive zymogen called plasminogen.

Neprilysin

Neprilysin (NEP) is a 90 to 110 kDa plasma membrane glycoprotein that is composed of a short N-terminal cytoplasmic region, a membrane-spanning domain and a large C-terminal extracellular, catalytic domain, which contains a HexxH zinc-binding motif (Turner et al., 2001). Originally neprilysin was identified as a main antigen of kidney membranes thirty years ago. Neprilysin together with endothelin-converting enzyme 1 (ECE-1) and endothelin-converting enzyme 2 (ECE-2) belongs to zinc metalloproteinases, II. type of integral membrane peptidase – M13 family.

Neprilysin has several roles in the central nervous system, liver, lungs, musles, and bones. It participates in cardiovascular regulation, inflammation, neuropeptide metabolism, cell migration, and proliferation (Harrison et al., 1995; Turner & Tanzawa, 1997). Neprilysin cleaves peptide bound of small regulatory peptides and degrades a variety of bioactive peptides (Turner & Tanzawa, 1997). Studies of Aβ catabolism using inhibitors of metalloproteinases and neprilysin knock out mice (Iwata et al., 2000) showed that neprilysin is enzyme degrading amyloid β peptide. Expression and activity of neprilysin is regulated by several factors that are related to AD, and age.

Recently a homologue of neprilysin was discovered and named neprilysin 2 (NEP2). Unlike neprilysin and endothelin-converting enzyme 1, which are expressed in the central nervous system and periphery, NEP2 was found to be almost exclusively expressed only in selected population of neurons and spinal cord (Turner at al., 2004). This enzyme may also degrade Aβ (Shirotani et al., 2001).

Endothelin-converting enzyme

Endothelin-converting enzyme (ECE) plays an important role in the metabolism of Aβ. Endothelin-converting enzyme is a homologue of neprilysin and it is a zinc metalloproteinase. The enzyme catalyses a change of inactive molecule of big endothelin (bET) to a very effective vasoconstrictor endothelin 1 (ET-1) (Xu et al., 1994). Endothelin-converting enzyme was discovered in neurons and glial cells in the brain and it is localised

both intra- and extra-cellularly (Barnes & Turner, 1997). The enzyme is able to hydrolyse some biological active peptides such as bradykinin, neurotesin, substantion P and oxidized chain of insulin B (Johnson et al., 1999). Ability of endothelin-converting enzyme to degrade amyloid β peptide has been discovered in experiments with a metallopreoteinase inhibitor – phosphoramid and then its positive effect was verified in human brain (Funalot et al., 2004).

Insulin-degrading enzyme

Insulin-degrading enzyme (IDE) is a zinc metalloproteinase. It is primarily located in the cytosol but it is also found in peroxisomes (Seta & Roth, 1997). A fraction of IDE can be found in the plasma membrane (Vekrellis et al., 2000). Insulin-degrading enzyme is able to cleave *in vitro* several physiological substrates, including insulin, glucagon, atriopoetin, amylin, Aβ. Insulin-degrading enzyme has physiological functions in insulin metabolism. It can degrade amyloid β peptide and it is selective for amyloid β peptide monomer (Farris et al., 2003; Vekrellis et al., 2000). Farris et al. (2003) and Miller at al. (2003) showed that endogenous levels of $A\beta_{40}$ and $A\beta_{42}$ were increased in the brain of IDE transgenic mice. Some *post mortem* analysis showed that decreased levels of insulin-degrading enzyme in patients with Alzheimer`s disease (Cook et al., 2003). Products that are produced by IDE cleaving of amyloid β peptide are not toxic.

2.2 Genetic risk factors for Alzheimer's disease

Alzheimer`s disease is a multifactorial disease and genetic as well as environmental factors are included in AD pathology. In the last decades, several genes involved in AD have been identified. There is no single gene responsible for an origin of Alzheimer`s disease. Mutations in amyloid precursor protein, presinilin 1 and presinilin 2 are liable for familiar AD. Mutations and polymorphisms in multiple genes contribute to sporadic AD.

2.2.1 Familiar form of Alzheimer's disease

Familiar form of Alzheimer`s disease is responsible for 5-10% of all cases of AD. It is characterized by early manifestation of dementia (sometimes in patients 40 years old) (Rosenberg, 2000). Mutations in three genes – gene for **amyloid precursor protein** on chromosome 21q21, gene for **presenilin 1** on chromosome 14q24.2 and gene for **presenilin 2** on chromosome 1q42.13 – increase production of $A\beta_{42}$ peptide and play a role in an autosomal dominant hereditary of Alzheimer`s disease (Goate et al., 1991; Levy-Lahad et al., 1995; Schellenberg et al., 1992). It is described 23 mutations of *APP* gene and 155 mutations of *PS1* gene and 9 mutations of *PS2* gene (www.alzforum.org). In familiar form of AD is increased level of amyloid β peptide years before any clinical symptoms of Alzheimer`s disease are observed. Interestingly, mutations in the tau gene are not associated with AD.

Amyloid precursor protein

Missense mutations in *APP* gene causing familiar form of AD are clustered around secretese cleavage sites. These mutations are responsible for increased production of Aβ which can cumulate and form amyloid plaques. Concentration of Aβ is increased in patients with Down syndrome. Most of these patients have neuritic plaques and tangles in their 40s. Gene for *APP* is located on chromosome 21 and patients with Down syndrome have trisomy 21, and this fact can be cause of AD development. Over 23 different *APP* mutations have been observed (Campion et al., 1999; Cruts & van Broeckhoven, 1998; de Jonghe et al., 2001).

Presenilins

Presenilins are main candidates for γ-secretase and they are contained in amyloid processing of APP. The human *PS1* and *PS2* mutations are linked to early onset AD. Presenilin 1 occurs in a normal processing of APP. Many different *PS1* mutations have been identified in 390 families. Mutations of presenilin 1 may be responsible for missing cleaving of APP and production of Aβ$_{42}$ the most aggressive variant for generation of amyloid plaques in the human brain (Xia et al., 1997). Moreover presenilin 1 acts together with glycogen synthase kinase (GSK3b). Glycogen synthase kinase is one of the critical protein kinases included in tau phosphorylation. In some cases of familiar Alzheimer`s Disease mutations of presenilin 1 cause an unusual interaction of PS1 with GSK3b and it can lead to increased hyperphosphorylation of tau protein and this form of tau protein then does not play its physiological roles (Takashima et al., 1998). Mutations in *PS2* are a much rarer than in *PS1* mutations. *PS2* mutations have been already described in 6 families.

2.2.2 Sporadic form of Alzheimer's disease

Despite numerous efforts, our knowledge of the heredity of AD remains incomplete. No consensus exists about the involvement of gene polymorphisms in risk of AD sporadic form. Genes for alfa-2-macroglobulins (Blacker et al., 1998), apolipoprotein E (*ApoE* ε4 variant) (Poirier et al., 1996), component of oxoglutarate dehydrogenase complex (Ali a kol., 1994), glycogen synthase kinase (*GSK3B*) (Schaffer et al., 2008), and some mitochondrial genes may be involved in familiar AD as well. Genes of secretases and amyloid β peptide degrading enzymes have been suggested as candidate genes for AD because they play a crucial role in a process of formation of senile plaques. The *BACE1* promoter polymorphisms may contribute to sporadic AD (Wang & Jia, 2009). Polymorphisms in the neprilysin gene (Helisalmi et al., 2004), and insulin-degrading enzyme (Vepsäläinen et al., 2010) increase the risk for AD. Angiotensin-converting enzyme (ACE) gene insertion/deletion polymorphism is considered as a biomarker for AD. Insertion/deletion and other *ACE* polymorphisms have a statistically significant effect on the risk of AD (Helbecque et al., 2009; Yang & Li, 2008; Wang et al., 2006). 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. Catalase (EC 1.11.1.6) is a common antioxidant enzyme found in all organisms. Catalase gene polymorphism does not confirm a protective role in AD patients (Capurso et al., 2008). Glutathione transferases (GSTs, EC 2.5.1.18) may play an important role as risk factors for AD because GSTs detoxify products of oxidative damage. Polymorphisms of *GSTs* can be therefore implicated in AD (Pinhel et al., 2008; Spalletta et al., 2007).

Apolipoprotein E

The most important genetic risk factor for sporadic AD is the *ApoE* gene, its ε4 allele, and is linked to familial late onset AD as well. ApoE is essential for a normal metabolism of lipoproteins, cholesterol and triacylgylcerols. Gene for ApoE is located on chomosome 19q13.2-13.3 and consists of 4 exons and 3 introns and is approximately 3.7 kb in length. *ApoE* has three isoforms: *ApoE* ε2 variant, *ApoE* ε3 variant, and *ApoE* ε4 variant. *ApoE* ε4 variant increased the risk of AD compared to *ApoE* ε2 variant, and ε3 variant (Carter, 2005; Fernandez & Scheibe, 2005; Poirier et al., 1993). ApoE may be connected to Aβ production and to increased aggreagation of Aβ. Polymorphism in *ApoE* promoter may be a risk factor for AD as well (Bizzarro et al., 2009).

Cytokines

Cytokines are secretory proteins that mediate intracellular communication in the immune system. However, they regulate a variety of processes in the central nervous system and may be involved in AD because neurodegeneration is accompanied by inflammation (so-called neuroinflammation). Inflammatory mediators are overexpressed and present in AD lesions (Selkoe, 2001a). Polymorphims in the promoter of IL-6, IL-10, and TNFα gene were suggested to be a risk factors for AD (Candore et al., 2007; Gnjec et al., 2008; Vural et al., 2009).

Methylenetetrahydrofolate reductase

5, 10-Methylenetetrahydrofolate reductase (MTHFR, EC 1.5.1.20) is a pivotal enzyme for DNA synthesis and homocysteine remethylation. Increased plasma homocysteine level is a risk factor for the development of AD (Seshadri et al., 2002). Two common genetic polymorphisms in the *MTHFR* gene C677T (Kang et al., 1988) and A1298T (van der Put et al., 1998) were discovered. *MTHFR* polymorphism causes decreased enzymatic activity of MTHFR and increased of the plasma total homocysteine level. Mutation in *MTHFR* is slightly associated with the onset of senile dementia (Nishiyama et al., 2000). Genotypes and haplotypes of the MTHFR have important implication for the pathogenesis of AD (Bi et al., 2009; Dorszewska et al., 2007; Gorgone et al., 2009; Kim et al., 2008; Wakutani et al., 2004). The MTHFR is a component of one carbon metabolism therefore it may interact with dietary intake of methionine, vitamins B6, B12, and folic acid in associations with AD.

2.2.3 Epigenetics and Alzheimer's disease

Recent evidence has suggested that histone acetylation and DNA methylation are implicated in the etiology of AD. Changes in chromatin structure are a prominent pathological feature of neurodegenerative diseases. Gene-environment interactions underlie neuropsychiatric disorders and epigenetics is involved in human processes (Figure 5). Epigenetic mechanisms refer to the processes that modify gene expression without altering the genetic code itself. Important epigenetic mechanisms include covalent modifications of two core component of chromatin: histone proteins – posttranslational modifications: histone acetylation, methylation, phosphorylation and the DNA – methylation, nucleosome positioning, higher order chromatin remodeling, deployment of numerous classes of short and long non-protein-coding RNAs, RNA editing and DNA recoding. Epigenetic mechanisms may play a crucial role in the interplay of genetic and environmental factors in determining a subject's phenotype (Reichenberg at al., 2009). Epigenetics may represent a basic molecular genetic mechanism in the pathophysiology of AD. The most frequently studied epigenetic mechanisms are DNA methylation and histone modification. These phenomena have been recognized as important permissive and submissive factors in controlling the expressed genome via gene transcription.

DNA methylation

DNA methylation is performed by the addition of a methyl group from S-adenosyl methionine to CpG islands by DNA methyltransferases (Mehler, 2008). Usually are methylated CpG islands near promoter regions of genes and DNA methylation generally represses transcription and so is associated with gene silencing. DNA methylation is dependent on the methylation potential and is closely related to the one-carbon metabolism. Methylenetetrahydrofolate reductase is a key enzyme in the one-carbon metabolism. The

enzyme is coded by the gene *MTHFR* on chromosome 1 location p36.3 in humans (Goyette et al., 1994).
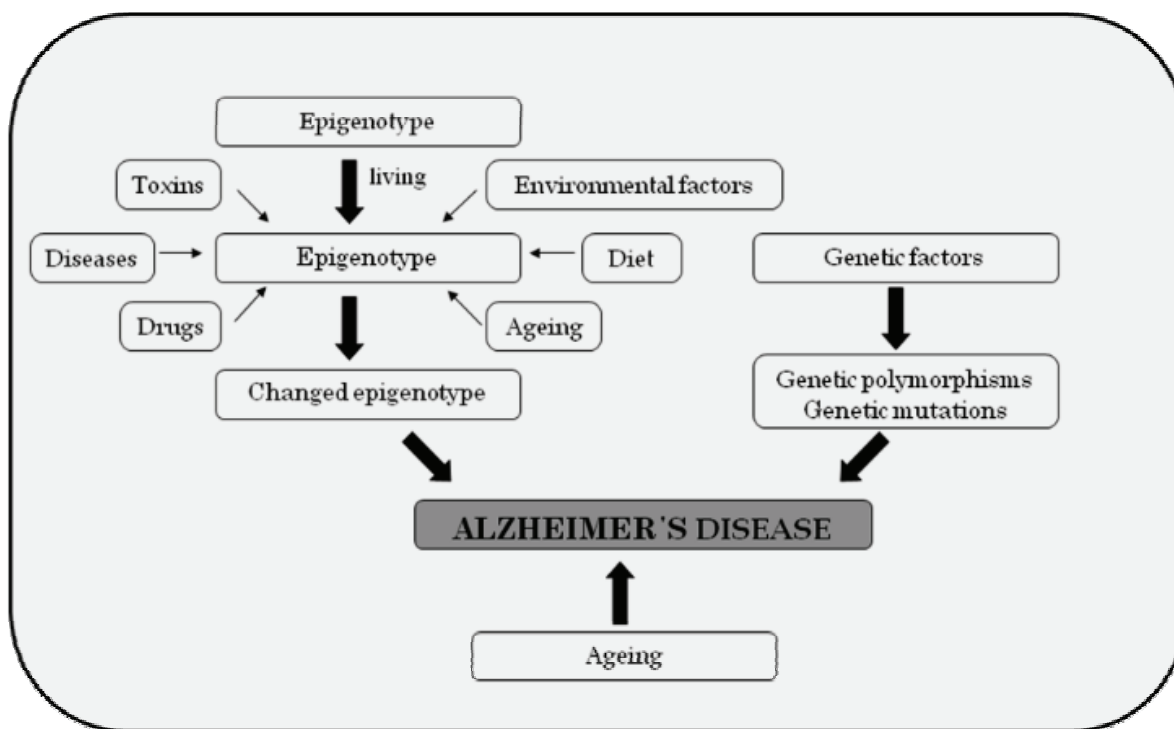

Fig. 5. Implication of epigenetic, genetic and environmental factors to Alzheimer`s disease origin

Histone modifications

The covalent modification of histones is happened at distinct amino acid residues on their amino terminal fails (Felsenfeld & Groudine, 2003). Histone acetylation, methylation, phosphorylation, ubiquitylation are the most common histone modifications. Histone acetylation is linked to transcriptional activation, while deacetylation is related to transcriptional repression (Berger, 2007).

Epigenetic modifications contribute to the phenotype's differences. DNA methylation was examined in monozygotic twins discordant for AD. In AD twin was observed decreased DNA methylation compared to non AD twin (Mastroeni et al., 2009). Amyloid precursor protein has been shown to be normally methylated, and hypomethylated with age (Tohgi at al., 1999) and in AD patients (West et al., 1995), which subsequently enhanced production of Aβ. Hypomethylation occurs with age and Aβ may be involved in the generation of amyloid β peptide itself. Amyloid β peptide causes global DNA hypomethylation and neprilysin hypermethylation, which consequently suppresses its expression in mRNA and protein level (Chen et al., 2009). In cell culture and in human post-mortem study, hypomethylation of the promoter region of *PS1* was found to increase presenilin expression, and enhance amyloid β generation (Scarpa et al., 2003, Wang et al., 2008). *PS1* and *BACE* are expressed at high levels in brain cells and both genes are unmethylated in brain (Fuso et al., 2005). AD may be associated with an increased in histone acetylation. Altered gene transcripton in AD has been associated with alterations in histone acetylation profiles (Kilgore et al., 2010). Amyloid intracellular domain (AICD) can interact *in vitro* with the histone acetyltransferase Tip60 and co-act as a transcriptional activator (Cao & Sudhof, 2001).

3. Conclusion

Neurological diseases, including AD are very serious medical problems. More than 150 million people suffer from neurodegenerative and neurological diseases. The average age of the world population is increased as a result of better knowledge, advances in diagnosis and treatment of various diseases. Unfortunately, age represents a key risk factor for development of age-related diseases, such as AD. Molecular and genetic analyses represent a new potential for AD studying. The role of mentioned gene polymorphisms and many others gene polymorphisms as risk factors for the occurrence of AD is still controversial. We still need new studies for clear determination gene polymorphisms which are related to AD. Moreover multiple genotype analyses are necessary as well because a single gene polymorphism can be without relationship to increased risk of AD but the combination of gene polymorphisms may have significant effect for AD development. Every person is unique and dementia affects people differently - no two people will have symptoms that develop in exactly the same way. An individual's personality, general health and social situation are all important factors in determining the impact of Alzheimer`s disease on him or her.

4. Acknowledgment

5. References

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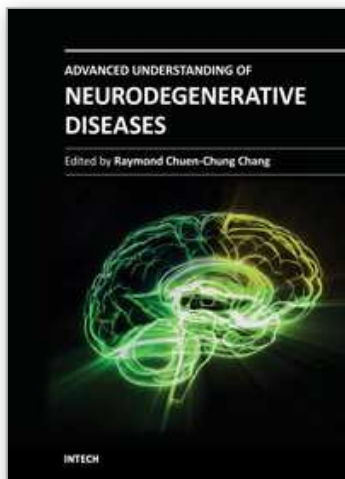
Advanced Understanding of Neurodegenerative Diseases

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Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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