

Review article

Role of advanced glycation end products in Alzheimer's disease

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Abstract

Population ageing, particularly in developed countries, is accompanied with an increased incidence of chronic degenerative diseases, including those affecting the central nervous system, such as dementia and Alzheimer's disease (AD). AD is a serious disease that follows a progressive course, but can be difficult to recognize initially due to a variable onset time. AD gradually becomes more evident and destructive, leading to decreased immune resistance and the development of comorbidities, and eventually to total incapacity and death. In addition, because the cost associated with the medical treatment and care of AD patients is becoming an enormous financial burden of health care systems, there is considerable interest in determining the causes underlying the onset and progression of AD, which have not yet been clearly defined. Genetic predisposition has been identified as a crucial factor; however, recent evidence suggests that reactive oxygen species and the activity of advanced glycation end products (AGEs) also substantially contribute to AD. Although a few studies have suggested that AGEs have minimal importance in AD, an increasing number of scientists believe that AGEs play a central role in the development of this disease due to the significant accumulation of these compounds in senile plaques and neurofibrillary tangles, which are the key indicators of AD. Evidence suggests that AGEs activate receptors of AGEs (RAGE) on neurons, astrocytes and glia, leading to oxidative stress and a cascade of biochemical activities that severely damage neuronal cells. In the present review, recent findings on AGEs in AD, as well as advances in therapeutic approaches related to this disease,

KEY WORDS: population ageing, chronic degenerative diseases, Alzheimer's disease, oxidative stress, glycative stress, advanced glycation end products (AGEs)

Introduction

Accompanied with the dramatic rise in the proportion of elderly people (≥ 65 years of age) in economically developed countries, the prevalence and incidence of chronic degenerative diseases, primarily cardiovascular, osteomuscular and neurodegenerative disorders, has markedly increased. Among neurodegenerative disorders, the increased incidence of dementias, particularly Alzheimer's disease (AD), is of particular concern.

AD is characterized by a progressive deterioration in mental, cognitive, and body function that leads to a complete inability to respond to the environment or control movement, eventually leading to death¹⁻⁶. It starts by mild cognitive disturbances even a few years before the exact diagnosis. It occurs with the decline in the ability to remember recent events and to learn new informations and skills. AD is generally expressed in two main forms: early onset familial AD (autosomal dominant familial AD, which comprises $< 1\sim 5\%$ of all cases, and late-onset AD (sporadic AD), which comprises 95% of all cases. There are no data about the other types of AD ([Table 1](#)). Studies indicate that early-

onset AD is associated with mutations in the amyloid precursor (*APP*) gene (chr.21q21), presenilin 1 (*PSEN-1*; chr.14) and 2 (*PSEN-2*; chr.1) genes, and beta-secretase 1 (*BACE1*; chr.11q23.3) gene. Presenilin is a component of γ secretase and mutations of its gene are a strong risk factor for early-onset AD. Gamma (γ) and β secretases cleave APP and generate $A\beta$; PSEN1 chr.14; PSEN2 chr.1; BACE1 chr11, β -secretase. Although the late-onset form of AD is attributable to several causes, it is also associated with several identified gene mutations, including the *APOE* $\epsilon 4$ allele (chr.19), *TREM 2* gene (chr. 6p21.1), and *ADAM 10* gene (chr. 15q21.3) ([Table 2](#))^{5,6}.

What is the cause of AD? Although the exact cause is unknown, evidence to date suggests that there are several contributing factors. The aim of this review is to present recent findings about the involvement of beta amyloid ($A\beta$) protein in the onset and course of AD. In addition, a number of studies have investigated the contribution of advanced glycation end products (AGEs) in the etiology of AD, as knowledge necessary for understanding the pathology and pathophysiology of disease, and possibly lead to the development of effective therapies.

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Pathology of AD

Two types of characteristic fibrous lesions are associated with AD: extracellular senile plaques (SPs) and intracellular neurofibrillary tangles (NFTs). The critical component of SP are A β peptides, while tau protein is the main component of NFT. A β peptide is derived from the cleavage of amyloid precursor protein (APP) and is subsequently glycosylated with reducing sugars, including glucose, lactose, and galactose, in AGE compounds, which are toxic compounds for the body (*Fig. 1*).

Both A β peptides and A β -AGEs are ligands for the receptor for AGEs (RAGE), which is a transmembrane protein located in the brain on neurons, astrocytes, microglia, and vascular endothelial cell membranes. Activation of RAGE induces a strong biochemical cascade mediated by the glycogen synthase kinase-3 (GSK-3) pathway, leading to atherogenic gene activation. A β -AGEs are formed during the nonenzymatic glycosylation or glycation of A β peptides with reducing sugars, such as glucose, lactose, and galactose. The characteristic SP and NFT lesions of AD are primarily located in the cortical gray matter, hippocampus and amygdaloid nuclei. The quantity of A β and A β -AGEs in SPs is directly associated with the intensity of AD symptoms (*Figs. 1-4*)⁷⁻¹⁴. AGE compounds damage neuronal cells in two ways: through the crosslinking essential protein molecules and by interaction with RAGE and its associated ligands.

Elevated A β peptide concentrations generated via positive biofeedback mechanisms induce RAGE expression. Two important enzymes, β and γ secretase, induce the intramembranous cleavage of APP and A β peptide formation. Importantly, the activities of these two enzymes are elevated in AD patients. RAGE expression is also greatly elevated in AD brains, leading to increased A β peptide transport through the blood brain barrier (BBB)⁷.

AGEs are formed through the Maillard reaction in a series of slow spontaneous nonenzymatic biochemical reactions. During the Maillard reaction, which is also known as glycation or the browning reaction (*Fig. 2*), the carbonyl group (C=O) of a reducing sugar binds with the amino group (NH₂) of a protein molecule side chain⁷⁻¹⁴.

AD manifests in two forms: autosomal dominant familial AD (early-onset familial AD), which comprises only 1%~5% cases), and a more common sporadic form (late-onset AD [LOAD]), which represents 95% cases (*Table 1*). Early-onset AD is relatively rare and is strongly associated with mutations in the genes encoding presenilin, which is a component of the γ secretase enzyme that cleave APP and generates A β peptide. In contrast, the sporadic form of AD represents the majority of cases and is typically observed in patients over 65 years of age

This form of AD is associated with mutations in the *ADAM 10* gene (MGH-MIND Genetics and Aging Research Unit, Massachusetts) *TREM 2* gene (chromosome 6p21.1), which leads to a 3 to 5-fold greater risk for AD. Two mutations have been identified in *ADAM 10* that lower its α -secretase activity,

Table 1. Forms of Alzheimer's disease (AD) according to the onset and cause.

Disease form	Characteristics/features
Autosomal-dominant familial AD (Early-onset genetic form of familial AD)	<ul style="list-style-type: none"> Accounts for $\leq 5\%$ of AD cases onset before 65 years of age primarily due to mutations in APP, PSEN1 (presenilin 1; chr.14) or PSEN2 (presenilin 2; chr.1) genes
Sporadic AD (Late-onset AD)	<ul style="list-style-type: none"> most cases of AD autosomal dominant heredity not indicated dominance of apolipoprotein E (APOE) associated with mutations in <i>ADAM10</i>, <i>TREM2</i>

A. Autosomal-dominant familial Alzheimer's disease

(Early-onset genetic form of familial AD)
Accounts for $\leq 5\%$ of AD cases – onset before 65 years;
primarily due to mutations in
APP, PSEN1 (presenilin 1) or PSEN2 (presenilin 2);

B. Sporadic form of AD

(Late-onset AD [LOAD]) most cases of AD;
autosomal dominant heredity not indicated;
dominance of apolipoprotein E (APOE)
ADAM 10 gene (published 2013. - MGH-MIND Genetics and Aging Research Unit, Massachusetts);

TREM 2 gene (mutations associated with a 3 to 5-fold greater risk for AD);

mutations in 13 GWAS genes (genome-wide association studies) – intensive multicentric investigations about the possible genetic inclination to LOAD; studies are conducted by Alzheimer's Disease Genetics Consortium granted by the National Institute on Aging (USA);

leading to reduced cleavage of the A β region of APP and decreased production of protective protein (sAPP α) (Tanzi and Suh, 2013). TREM2 is a microglial receptor-triggering receptor expressed on myeloid cells 2 that plays an important role in controlling the quantity of A β peptide in the brain.

A number of hypotheses to explain the underlying biochemical mechanisms of AD have been proposed and include the cholinergic hypothesis, tau hypothesis, mitochondrial AD cascade hypothesis (Fig. 7), and amyloid hypothesis. In addition, the following factors may be involved in the development of AD: Herpes simplex virus type 1, age, sex, Down syndrome (trisomy 21), trauma, stress, diet rich with AGE compounds, aluminium in diet, and heart disease, particularly atrial fibrillation. However, the exact cause(s) of AD have yet to be conclusively demonstrated.

Formation of SPs and NFTs

Two hallmark pathologies of AD, SPs and NFTs, are found in the brain tissues of patients, particularly in the cerebral cortex, hippocampus, and amygdaloid nuclei. Both SPs, which are primarily located near synapses, and NFTs are mainly composed of A β peptide, tau protein, and A β -AGE glycation-derived compounds. Experimental evidence suggests that the formation of these lesions is strongly dependent on the nonenzymatic glycosylation of APP-derived A β peptides. A β peptides are typically 39~42 amino acids in length, and accumulate in the brain, leading to the onset and progression of AD (Figs. 1-4). The proteolysis of APP is induced by β and γ secretases results in the fragmentation of APP and formation of A β peptide the transmembrane domain of APP. In AD, the proteolytic activity of β and γ secretases is elevated,

Table 2. Presentation of elementary symptoms in the four stages of AD.

AD Stage	Characteristics/features
1. Predementia	<ul style="list-style-type: none"> Decline in directed attention and abstract thinking Reduced ability to comprehend reason-consequence Apathy and depression are frequent comorbidities Agitation and irritability
2. Early stage of defined disease	<ul style="list-style-type: none"> Clear decrease in ability to learn new content Drop in spectrum of used words and fluidity of speaking Marked decrease in memory, particularly new data
3. Middle stage	<ul style="list-style-type: none"> Decline in reading and writing ability Reduced ability to recollect words necessary for conversation Drop in motor activity Decreased short-term memory Frequent inability to recognize friends and family Frequent episodes of agitation, aggressiveness, and tearfulness Urinary incontinence may occur
4. Advanced stage	<ul style="list-style-type: none"> Complete dependency on caregivers Speech indiscernible or lacking Frequently aggressive and/or extremely apathetic Strong decline in muscular strength (inability to stand or walk) Strong decline in immunity and increased incidence of acute infections (pneumonia or other infective diseases), which are often fatal

1. Stage: Predementia

Decline in directed attention
 Decline in abstract thinking
 Reduced ability to comprehend composed links – type reason-consequence is greatly reduced
 Apathy and depression are frequent comorbidities
 Agitation and irritability are frequent

2. Stage: Early symptoms of already defined disease

Clear decrease in ability to learn new content
 Marked decrease in memory, particularly new data
 Drop in spectrum of used words and fluidity of speaking

3. Stage: Decline in ability in dealing with common daily jobs

Reduced ability to recollect words necessary for conversation
 Decline in reading and writing ability
 Drop in motor activity
 Decreased short-term memory
 Frequent inability for recognition of friends and members of household
 Frequent episodes of agitation, aggressiveness and tearfulness
 Urinary incontinence may occur

4. Stage: Advanced stage of the disease

Complete dependency on caregivers
 Speaking extremely poor with the possibility of complete drop
 Frequent aggressivity or extreme apathy
 Strong decline in muscular strength-inability to stand and walk
 Strong decline in immunity and increased incidence of acute infections (pneumonia or other infective diseases), which are often fatal

*According to other literature there are seven stages of AD

leading to the accumulation of A β peptide. The 240-kb gene encoding APP contains 18 exons and is located on the long arm of chromosome 21. APP is predominantly expressed in the vicinity of synapses and plays an essential role in synapse formation and repair (Figs. 3,4)¹⁴⁻¹⁷.

A β protein is a polyfunctional molecule that protects cells from oxidative stress and is involved in cholesterol transport regulation. In AD, the production of A β protein is markedly elevated, particularly in SPs. SPs are an average of 50 μ m (range: 10~160 μ m) and are composed of helical filaments of individual A β monomers. Located in the vicinity of SPs are many small astrocytes (10~20 μ m with 20~30 μ m projections) and microglia, in addition to other proteins and metallic ions (Fe³⁺ and Fe²⁺).

NFTs are formed intracellularly from hyperphosphorylated tau protein bound to microtubules. The activation of GSK-3 by RAGE has a crucial role in NFT formation. Following these events, microtubules are destabilised and undergo disintegration, thereby reducing their transport function (Fig. 5).

The interaction between RAGE and AGEs, particularly in conjunction with N^ε-(carboxymethyl)-lysine (CML), strongly induces protein kinase C (PKC), NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) oxidase, and I κ B (IKK) activation, leading to I κ B protein (NF- κ B blocker) degradation and liberation, and activation of transcription factor NF- κ B. Thus, AD is also characterized a NF- κ B cascade with the induction of strong atherogenic response^{11,15}).

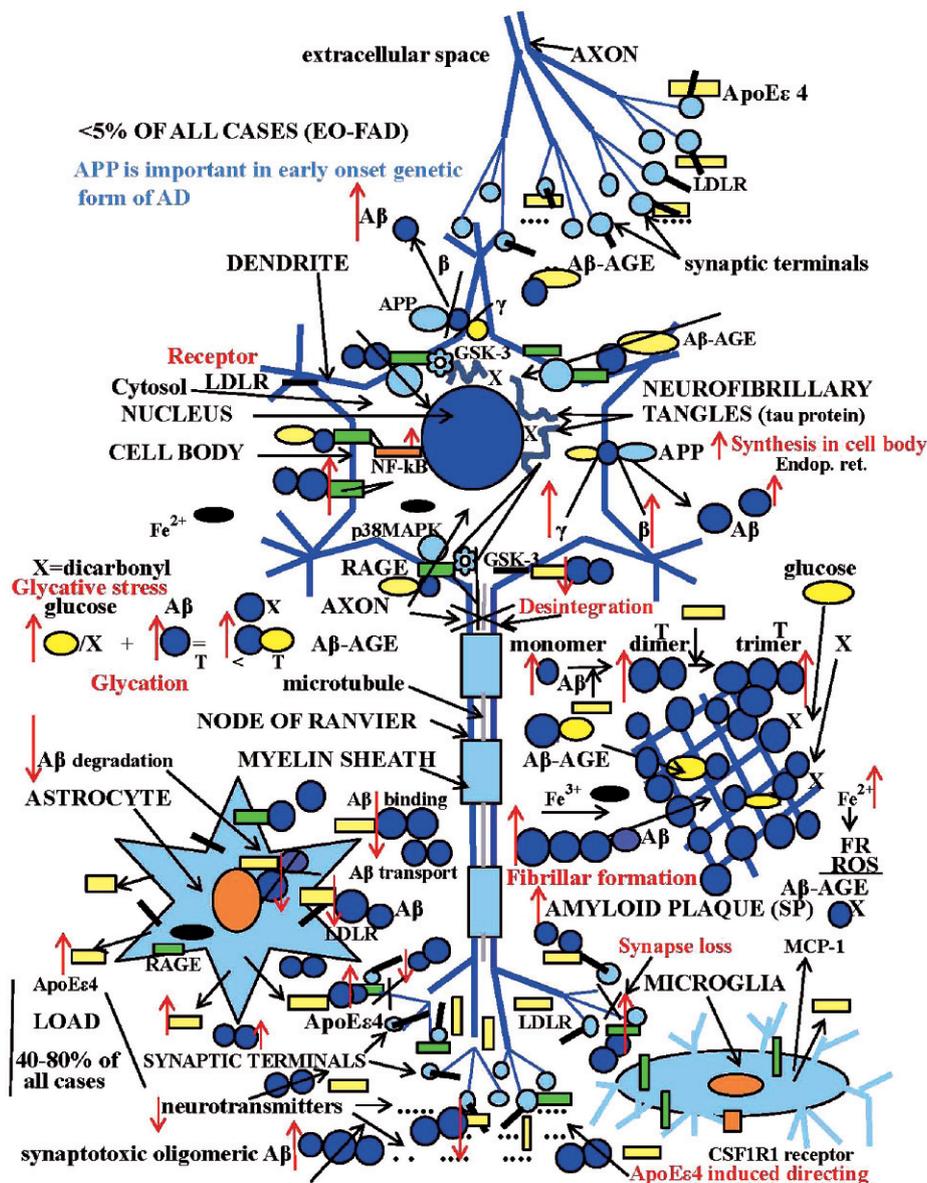


Fig.1. Schematic diagram of a neuronal cell and amyloid plaques in AD.

AD, Alzheimer's disease; EO-fAD, early onset-familial AD; LOAD, late onset AD; A β , amyloid beta (reductant); AGE, advanced glycation end product; RAGE, receptor for AGE; APP, amyloid precursor protein; LDL, low-density lipoprotein; LDLR, LDL receptor; MCP, monocyte chemoattractant protein; CSF, colony-stimulating factor; ApoE, apolipoprotein E. The red arrow indicates the increase (↑) or decrease (↓) of the quantity or activity of the appropriate symbol next to the arrow.

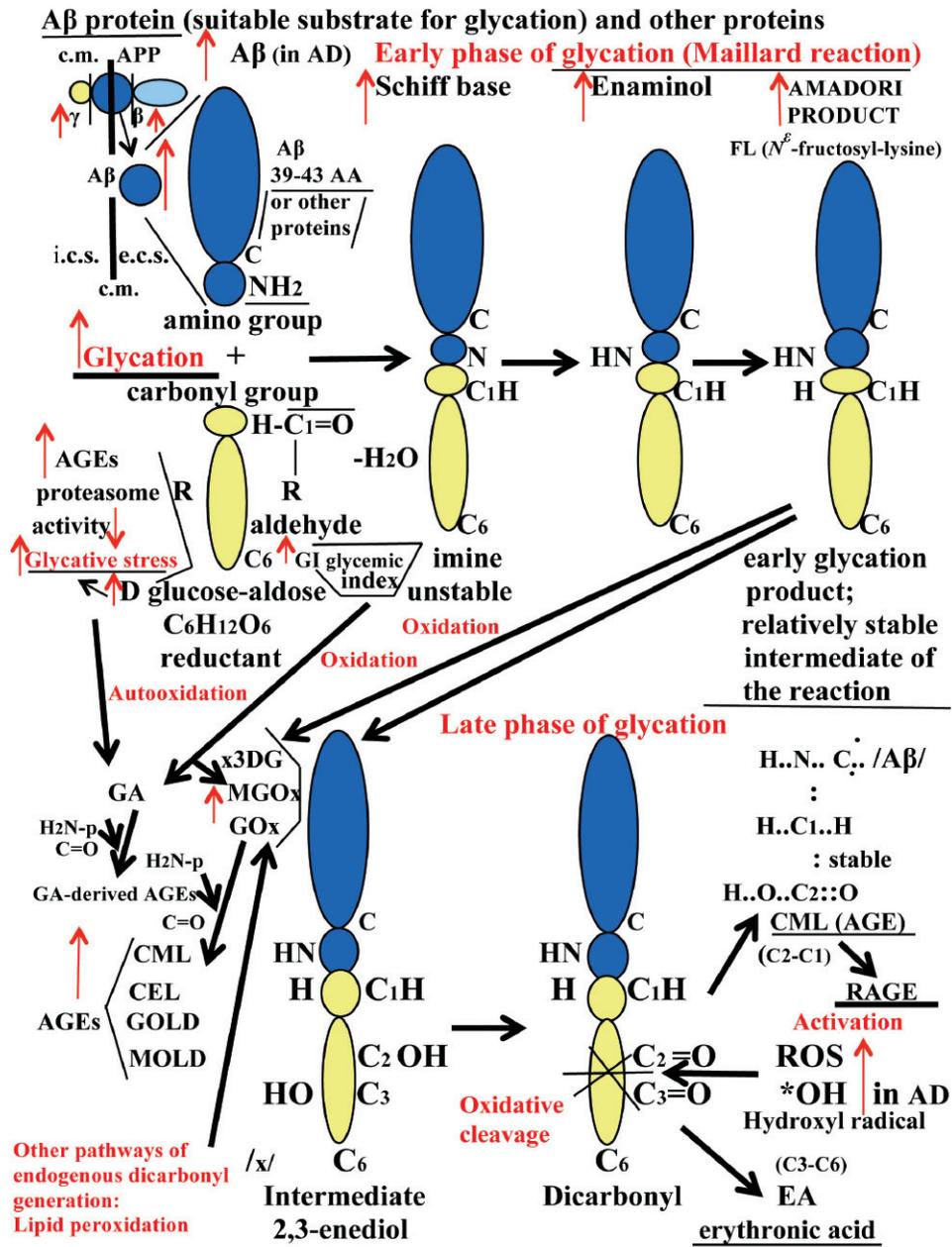


Fig.2. Schematic diagram of the glycation (nonenzymatic glycosylation) of amyloid beta (Aβ)

AD, Alzheimer's disease; c.m., cell membrane; i.c.s., intra cellular space; e.c.s., extra cellular space; AA, amino acid; Aβ, amyloid beta; AGEs, advanced glycation end products; RAGE, receptor for AGE; APP, amyloid precursor protein; ROS, reactive oxygen species; 3DG, 3-deoxyglucosone; GO, glyoxal; MGO, methylglyoxal; GA, glyceraldehyde; FL, N^ε-fructosyl-lysine; CML, N^ε-(carboxymethyl)-lysine; CEL, N^ε-carboxy(ethyl)-lysine; GOLD, glyoxal-lysine dimer; MOLD, methyl-glyoxal-lysine dimer; EA, erythronic acid; GI, glycemic index. The red arrow indicates the increase (↑) or decrease (↓) of the quantity or activity of the appropriate symbol next to the arrow.

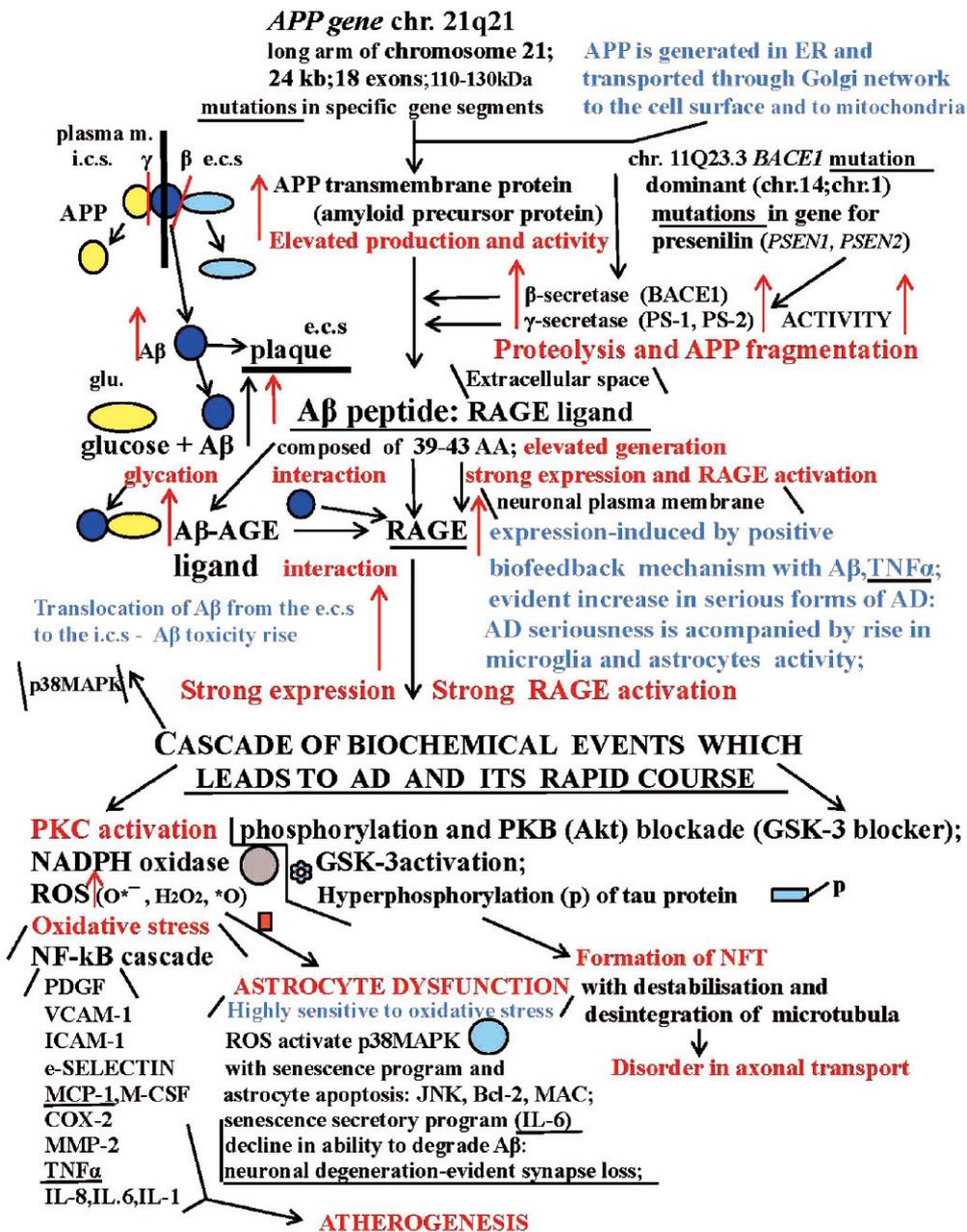


Fig.3. Schematic diagram of the molecular events related to AD (early-onset genetic form of AD).

AD, Alzheimer's disease; plasma m., plasma membrane; i.c.s., intra cellular space; e.c.s., extra cellular space; glu., glucose; AA, amino acid; A β , amyloid beta; AGEs, advanced glycation end products; RAGE, receptor for AGE; APP, amyloid precursor protein; TNF, tumor necrosis factor; NFT, neurofibrillary tangle; ROS, reactive oxygen species; NF- κ B, nuclear factor kappa-B; PDGF, platelet-derived growth factor; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; MCP, monocyte chemoattractant protein; M-CSF, macrophage colony-stimulating factor; COX, cyclooxygenase; MMP, matrix metalloproteinase; IL, interleukin; PK, protein kinase; MAPK, mitogen-activated protein kinase; GSK, glycogen synthase kinase; NADPH, reduced form of nicotinamide adenine dinucleotide phosphate; JNK, *c-jun* N-terminal kinase; BCL, B-cell lymphoma; MAC, mitochondrial apoptosis-induced channel. The red arrow indicates the increase (\uparrow) or decrease (\downarrow) of the quantity or activity of the appropriate symbol next to the arrow.

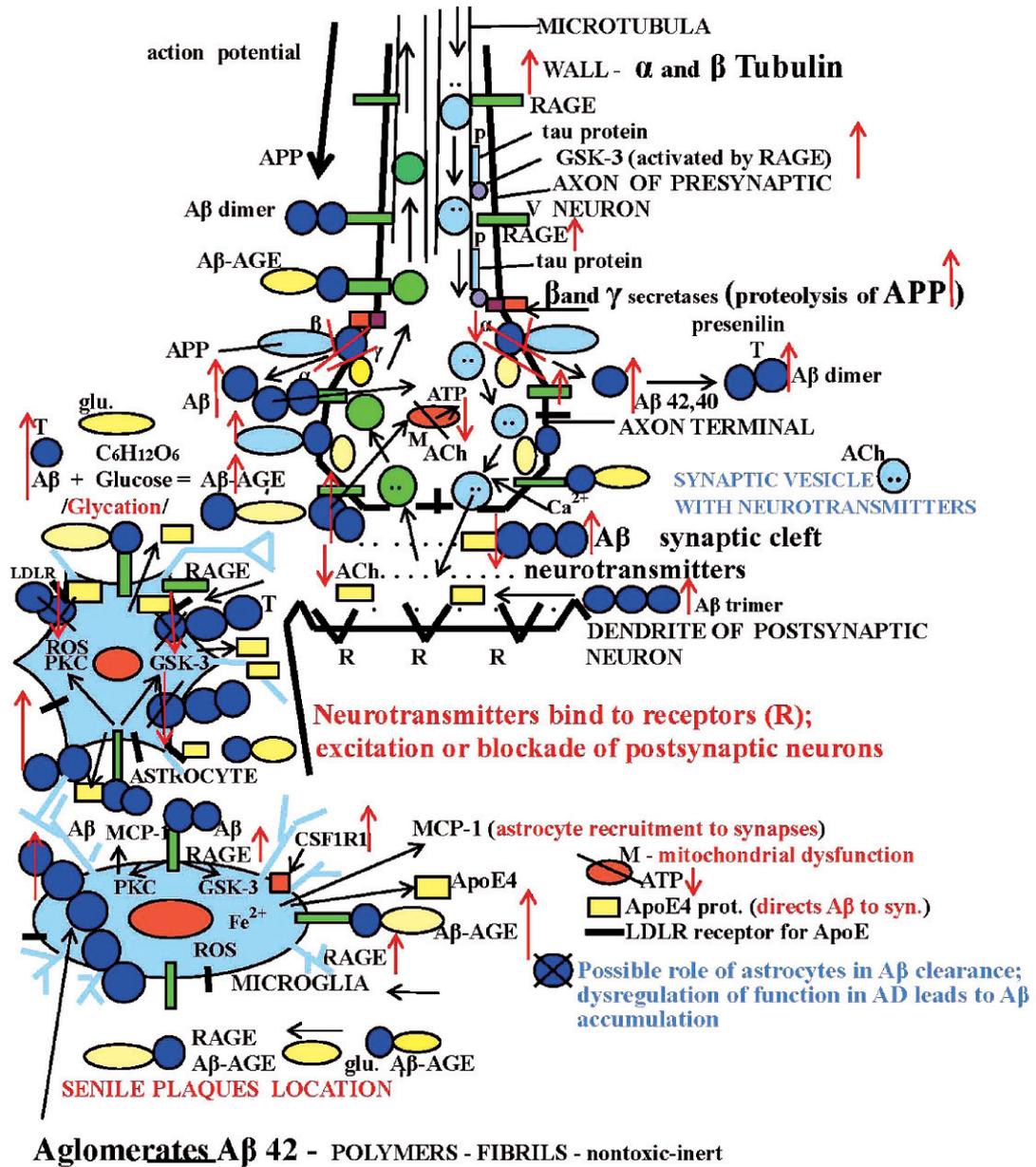


Fig.4. Schematic diagram of synaptic events potentially associated with the onset of AD

Mutations in *ADAM 10* (in LOAD) lead to reduced α -secretase activity. Mutations in ApoE (in LOAD) induce poor binding and degradation of A β in astroglia. RAGE mediates A β translocation from the extracellular to intracellular space.

AD, Alzheimer's disease; LOAD, late onset AD; T, neurotoxic; R, receptor; M, mitochondria; A β , amyloid beta; AGEs, advanced glycation end products; RAGE, receptor for AGE; APP, amyloid precursor protein; glu., glucose; syn., synthesis; ATP, adenosine triphosphate; ACh, acetylcholine; LDL, low-density lipoprotein; LDLR, LDL receptor; ROS, reactive oxygen species; PKC, protein kinase C; GSK, glycogen synthase kinase; MCP, monocyte chemoattractant protein; ApoE, apolipoprotein E. The red arrow indicates the increase (\uparrow) or decrease (\downarrow) of the quantity or activity of the appropriate symbol next to the arrow.

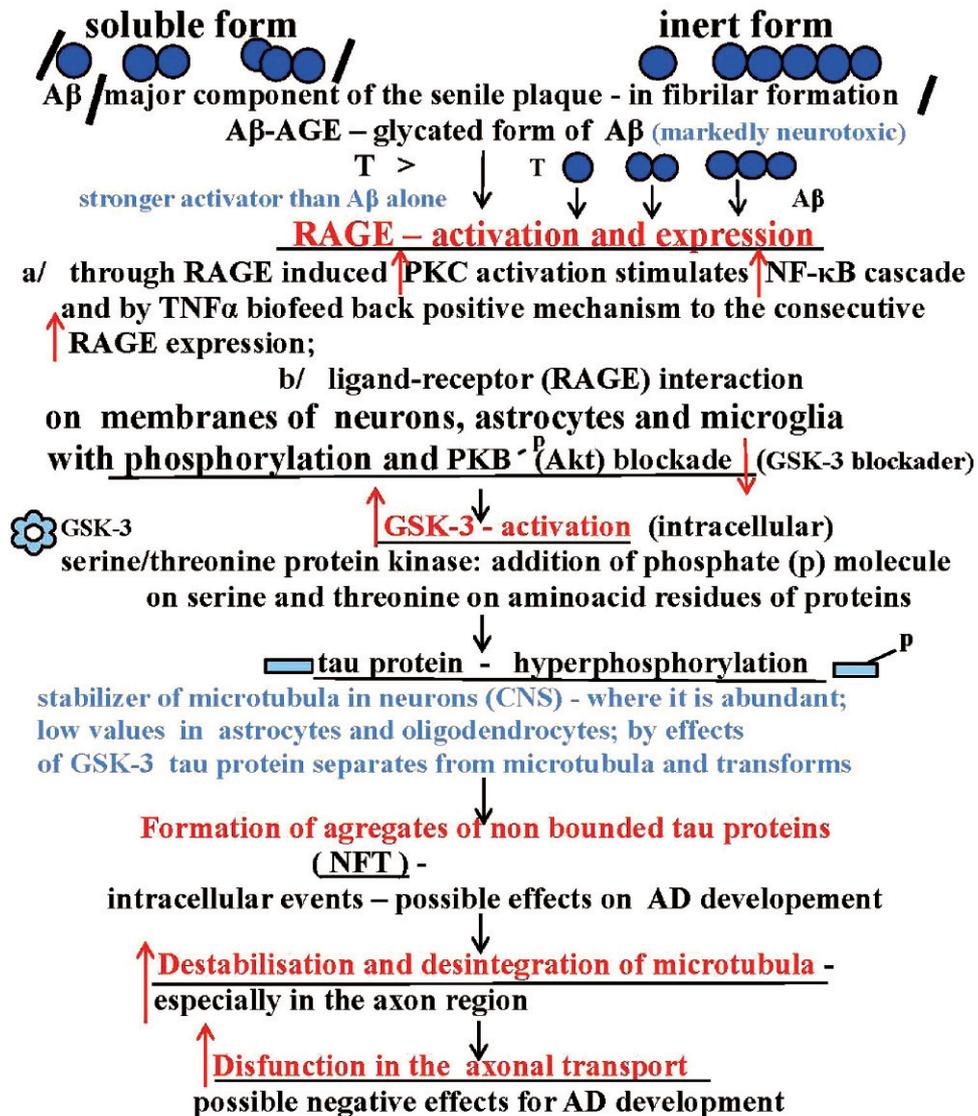


Fig.5. Cascade of events induced by GSK-3 activation.

AD, Alzheimer's disease; Aβ, amyloid beta; AGEs, advanced glycation end products; RAGE, receptor for AGE; GSK, glycogen synthase kinase; PK, protein kinase; TNF, tumor necrosis factor; CNS, central nervous system; NFT, neurofibrillary tangle; NF-κB, nuclear factor kappa-B. The red arrow indicates the increase (↑) or decrease (↓) of the quantity or activity of the appropriate symbol next to the arrow.

Glycation of β amyloid

The involvement of the nonenzymatic glycation of A β and the generation of A β -AGE compounds in the onset and development of AD, has been confirmed in a number of recent investigations^{11,14,18}. Glycation is considered to confer stability and increase the half-life of proteins, including A β protein. AD patients display marked elevation of the glycation process in the brain. In addition, a dramatic increase in early glycation Amadori products and AGEs is also typically observed^{8,14,18}.

Many scientists speculate that AGEs are strongly associated with the onset and course of AD. In fact, nearly all recently proposed theories concerning the etiology and course of AD involve the interference of AGEs compounds at different stages of the underlying pathophysiologic events. In particular, the role of AGEs compounds in the function of RAGE has attracted attention. In addition, the importance of tau protein, β and γ secretases, APP, GSK-3, microtubule-based axon transport, and neuronal cortical, hippocampal, and amygdaloidal destruction in AD has also been proposed.

Shuvaev et al.¹⁸ investigated glycation levels in the cerebrospinal fluid (CSF) and plasma of AD patients and that the glycation rate corresponds to the severity of AD. In AD brains, the level of AGEs is significantly higher than that found in normal brains²⁴. Srikanth et al.⁸ also proposed that RAGE and AGEs have important roles in AD pathogenesis. Although the accumulation of AGEs in cells and tissues is a normal sign of ageing, AGE levels are significantly increased in AD. AGEs are also components of SPs and NFTs and play a role in the cross-linking of proteins, oxidative stress, and deterioration of neurons¹⁴. Fawver et al.¹⁴ found that glycation and accumulation of SPs is accelerated in the brains of patients with Down syndrome, and also speculated that glycation influences the pathology and progression of AD²⁰. Li et al.¹¹ analysed the glycation process in AD brains, particularly A β -AGE complex generation, A β and A β -AGE interaction with RAGE, and GSK-3 signal cascade activation, and found that incubation of A β peptides with methylglyoxal induced the production of A β -AGE, which, induced the formation of large lesions in hippocampal neurons. Based on these findings, GSK-3 activation, PKB (Akt) blockade, and tau protein hyperphosphorylation was proposed to induce NFTs formation and microtubular destabilisation, leading to decreased microtubular transport. Thus, A β and A β -AGE are highly neurotoxic compounds whose accumulation appears to be critical for the onset and progression of AD¹⁷.

AGEs are found at high concentrations in SPs, which are located near astrocytes and microglia plasma membranes, and RAGE. RAGE activation induces a biochemical cascade of harmful molecular events that cause functional aberrations, followed by the destruction and death of cells. Together, these events induce the global destruction of important brain functions^{19,25}.

The participation of AGEs in AD pathogenesis has been proposed by a number of investigators. For example, Takeuchi et al.²⁶ speculated that AGEs are involved in the onset and course of AD as AGEs were found in both SP and NFT lesions. Glyceraldehyde-combined AGE (Glycer-AGE) has a special importance in AD pathogenesis^{14,20,24,25-32}. The role of reactive oxygen species (ROS) in AD etiology as also

been proposed. In addition, Sato et al.²⁷ also proposed that AGEs and RAGE have important roles in the pathogenesis of AD. These researchers identified that AGE-2 derived from glyceraldehyde is found in the hippocampus and parahippocampal gyrus of AD patients³³.

Using specific antibodies against AGEs, Yan et al.²⁸ established that AGEs are closely associated with paired helical filaments in NFTs in the neurons of patients with the sporadic form of AD. In these neurons, signs of oxidative stress, which is known to play a role in neuronal destruction, were also observed²⁰⁻²⁵. These findings indicate that tau protein and A β peptide in environments rich in aldose easily enter the glycation process, leading to Schiff base, Amadori product, and AGEs formation, which may be critical for genesis of AD³⁴.

The close connection between AGE accumulation and NFT generation was also demonstrated by Luth et al.¹⁶, who analysed the relationship between neuronal AGEs accumulation, NFT formation, and cell death. Histochemical analyses revealed that RAGE stimulation induces GSK-3, leading to the hyperphosphorylation and fragmentation of tau protein, and its disassociation with microtubules. AGE complexes bind tau protein fragments and form NFT particles with a high AGE content. These findings also emphasize the close association between AGE-positive neurons and AD severity²².

Takeuchi et al.²⁹ used an immunohistochemical-based approach to demonstrate that SP and NFTs contain a high proportion of AGEs. In addition, these authors speculated that diabetes mellitus is a strong risk factor for AD. In addition, the interaction of AGEs derived from glyceraldehyde with RAGE, and the role of oxidative stress in the development and progression of AD was also proposed^{32,35,36}.

The importance of GSK-3 in the genesis and progression AD has also been proposed³¹. In particular, the kinase GSK-3 β has been shown to promote the agglomeration of tau protein (paired helical filament -tau component of NFTs). The GSK-3 β /phosphatidylinositol-3 P13/Akt and A β /AGE/RAGE/Akt / GSK-3 signaling cascades were confirmed to play a role in this process³⁷.

Two mutations in the *ADAM 10* gene, located on the long arm of chr.15 (chr.15q22) have recently been identified (Tanzi and Suh, 2013). These mutations, Q170H and R181G, impair the α secretase activity of ADAM 10, leading to reduced cleavage of the A β fragment from APP. In normal cells (without AD changes), following the cleavage of APP by β and γ secretases, complete A β peptide is released into synapses. Thus, these mutations in *ADAM 10* have an important role in the development of LOAD (**Fig. 6**)³⁸.

In a great number of LOAD there is a dominance of apolipoprotein E (APOE), especially allele *ApoE ϵ 4* - 40-80%. *ApoE ϵ 4* is important for directing amyloid beta peptide to synapses and its low binding and transport to astrocytes where it is insufficiently degraded. Thus, its A β concentration is elevated. The toxicity of A β rises, and the result is exacerbated synapse loss around the plaques³⁹.

TREM2 gene (mutations associated with a 3 to 5-fold greater risk for AD). It is important for controlling the quantity

of Aβ in the brain. It codes one microglial receptor-triggering receptor expressed on myeloid cells; chromosome 6p21.1; anti-inflammatory role in the brain ⁴⁰).

A potential connection between the level of free iron (ferrous iron- and non-transferrin bound iron [NBTI]) and AD has been proposed ²⁴). The H₂O₂-induced oxidation of free iron through the Fenton reaction generates ferric iron (Fe³⁺), hydroxyl ion, and (⁻OH) hydroxyl radical (*OH), which is a strong oxidant and is especially toxic for neurons. RAGE /Aβ/Aβ-AGE interaction impairs astrocyte iron transport, leading to iron accumulation, particularly ferrous iron (Fe²⁺) ^{14,20,25,26-31}).

Mitochondrial dysfunction

In addition to their involvement in SP formation, Aβ peptides have strong toxic effects on mitochondria (Fig. 7). Aβ affects nearly all mitochondrial structures and functions, including the ETC, Krebs cycle, membranes, DNA, proteins, receptors, and transmembrane channels. Aβ induces the production ROS that disrupt the ETC, and activation of the transcription factor JNK, leading to expression of the apoptotic genes *Bax* and *MAC*, which encode channels that control *Cyt-c* and *Smac* efflux from mitochondria into the cytosol. This efflux leads to caspase activation and induction of the apoptotic cascade in astrocytes and neurons (Fig. 7).

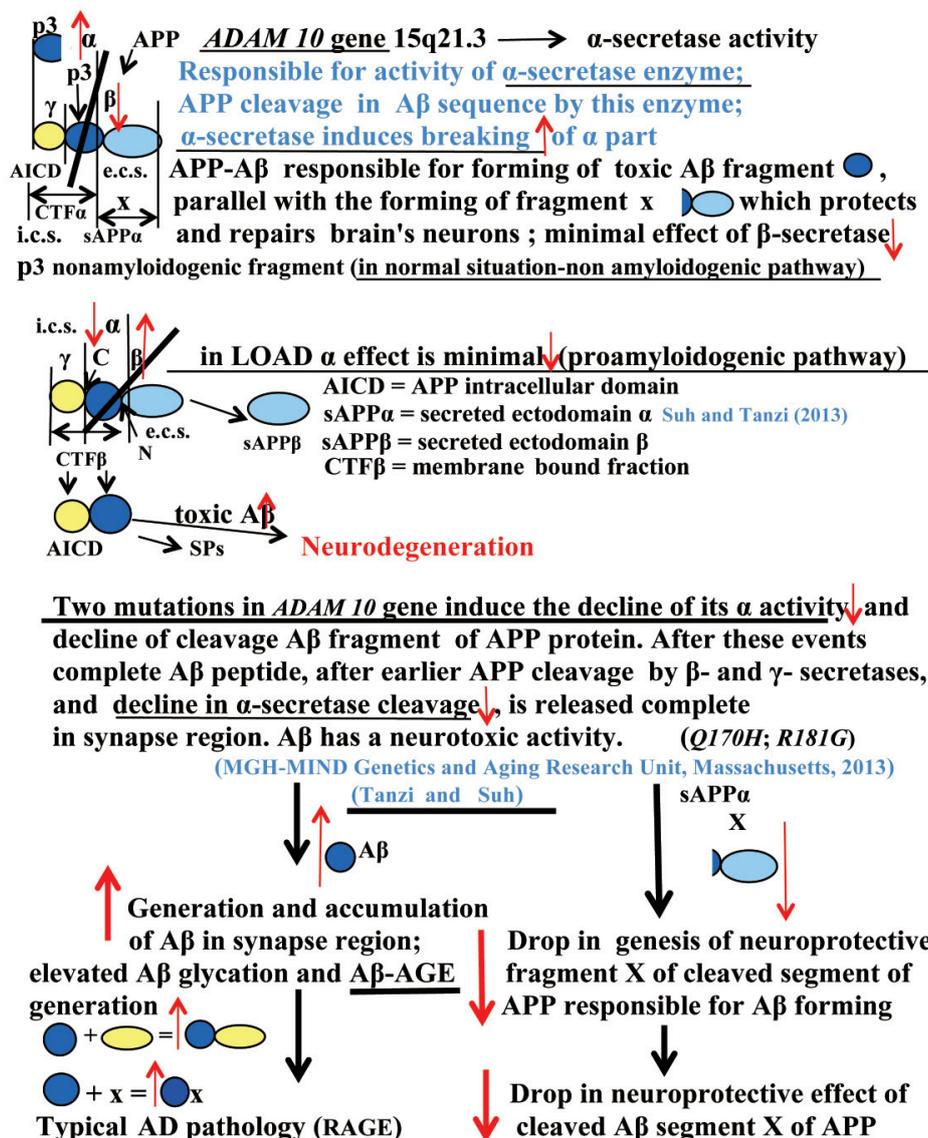


Fig.6. Involvement of two mutations in the ADAM 10 gene on late-onset AD (LOAD).

AD, Alzheimer's disease; i.c.s., intra cellular space; e.c.s., extra cellular space; N, nucleus; Aβ, amyloid beta; AGEs, advanced glycation end products; RAGE, receptor for AGE; APP, amyloid precursor protein; AICD, APP intracellular domain; sAPPα, secreted ectodomain α; sAPPβ, secreted ectodomain β; CTF, C terminal fragment; SPs, senile plaques. The red arrow indicates the increase (↑) or decrease (↓) of the quantity or activity of the appropriate symbol next to the arrow.

Treatment of AD

Elevated intake of AGEs in foods or the inadequate processing of AGEs are suggested to leads to earlier onset of AD and a more rapid course, particularly individuals with genetic predisposition (*Figs. 8 and 10*)⁴¹⁻⁴³.

Although the direct cause of AD remains unclear, several theories, including those described above, have been proposed. Understanding the underlying cause(s) of AD is necessary for the development of preventative measures and effective therapies. Currently, two groups of medications are available: cholinesterase inhibitors and antagonists of N-methyl-D-aspartate (NMDA) receptors (*Table 3*). The former group includes donepezil hydrochloride (Aricept), rivastigmine (Exelon), and galantamine hydrobromide (Reminyl), while the latter group includes memantine (Ebixa). Cholinesterase inhibitors function by blocking acetylcholine (Ach) esterase, which is an Ach breaker. The crucial effects of memantine are connected with NMDA receptors (NMDAR, N-methyl-

D-aspartate receptor, glutamate receptor). By binding to NMDAR, memantine protects the brain cells from harmful effects of, in AD elevated concentrations of released glutamate (N-Methyl-D-aspartate, NMDA) from damaged brain cells. Memantine is the glutamate antagonist and by binding to NMDAR suppresses the harmful glutamate effect. Chemistry name for memantine is 1-amino-3,5-dimethyladamantane hydrochloride^{32-35,39-41}.

A number of other compounds with possible beneficial effects for AD treatment have been evaluated, including antioxidants, AGE breakers, RAGE blockers, and antiglycation compounds (*Fig. 9*). In addition, several novel compounds are under experimental and clinical investigation, and include alagebrium (ALT-711), aminoguanidine, 4,5-dimethyl-3-phenacylthiazolium chloride (DPTC), benfotiamine, tiamine, and piridoxamine. The analysis of the efficacy of these compounds for AD therapy, and other methods of AD therapy, are beyond the scope of this study, but have been discussed elsewhere (*Figs. 9-11, Table 3*)^{34-37,41-43}.

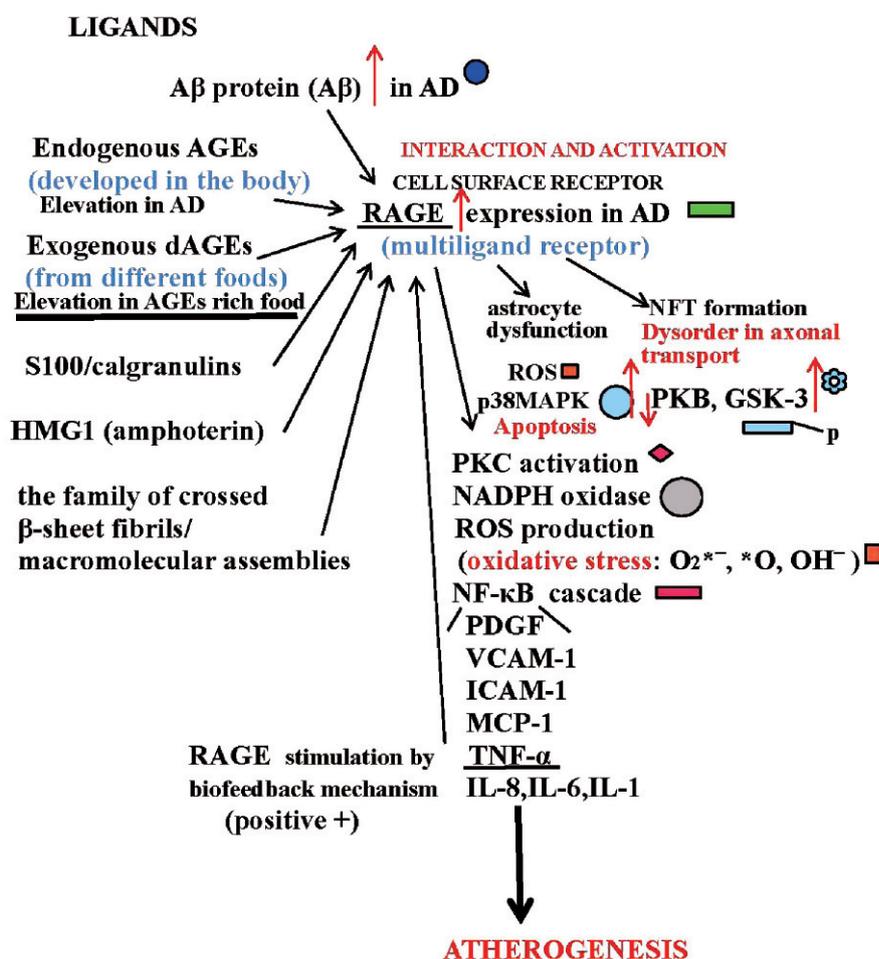


Fig. 8. Exogenous AGEs and their influence on the progression of Alzheimer's disease.

Consumption of low quality, inadequately processed foods leads to earlier and a more rapid onset and progression of this deteriorative disease in genetically predisposed individuals.

AD, Alzheimer's disease; Aβ, amyloid beta; AGEs, advanced glycation end products; dAGEs, dietary AGEs; RAGE, receptor for AGE; APP, amyloid precursor protein; NFT, neurofibrillary tangle; HMG1, high-mobility group protein 1; ROS, reactive oxygen species; PK, protein kinase; MAPK, mitogen-activated protein kinase; GSK, glycogen synthase kinase; NADPH, reduced form of nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-B; PDGF, platelet-derived growth factor; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; MCP, monocyte chemoattractant protein; TNF, tumor necrosis factor; IL, interleukin. The red arrow indicates the increase (↑) or decrease (↓) of the quantity or activity of the appropriate symbol next to the arrow.

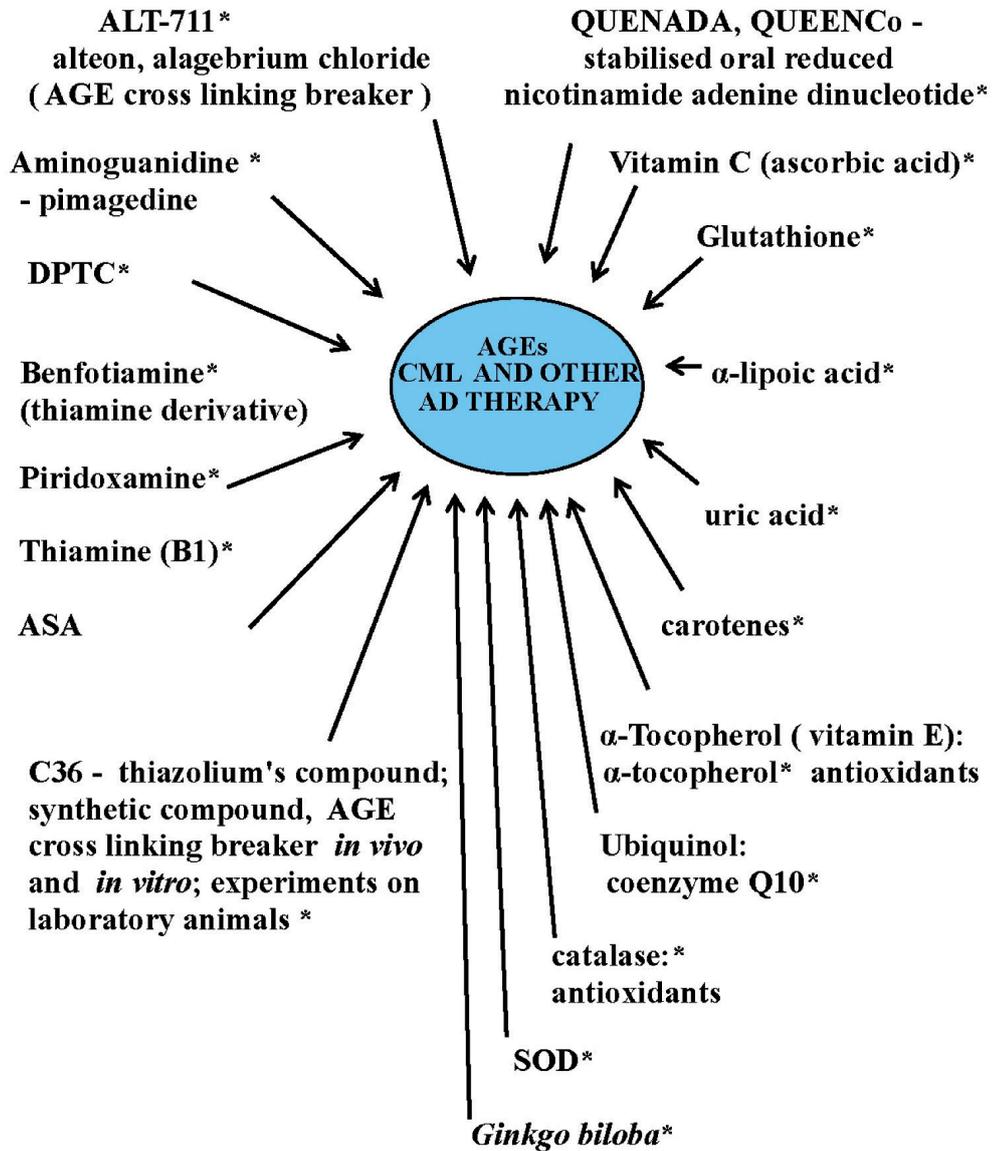


Fig.9. AD therapies.

Inhibitors and breakers of previously formed AGEs (left). Antioxidants and free radical (ROS) scavengers are likely involved in the onset and pathophysiology of AGEs (right).

* included in AD therapy, AD, Alzheimer's disease; ROS, reactive oxygen species; AGEs, advanced glycation end products; Aβ, amyloid beta; dAGEs, dietary AGEs; RAGE, receptor for AGE; CML, N^ε-(carboxymethyl)-lysine; AG, aminoguanidine; DPTC, 4, 5-dimethyl-3-phenacylthiazolium chloride; ASA, acetylsalicylic acid; LA, lipoic acid; SOD, superoxide dismutase.

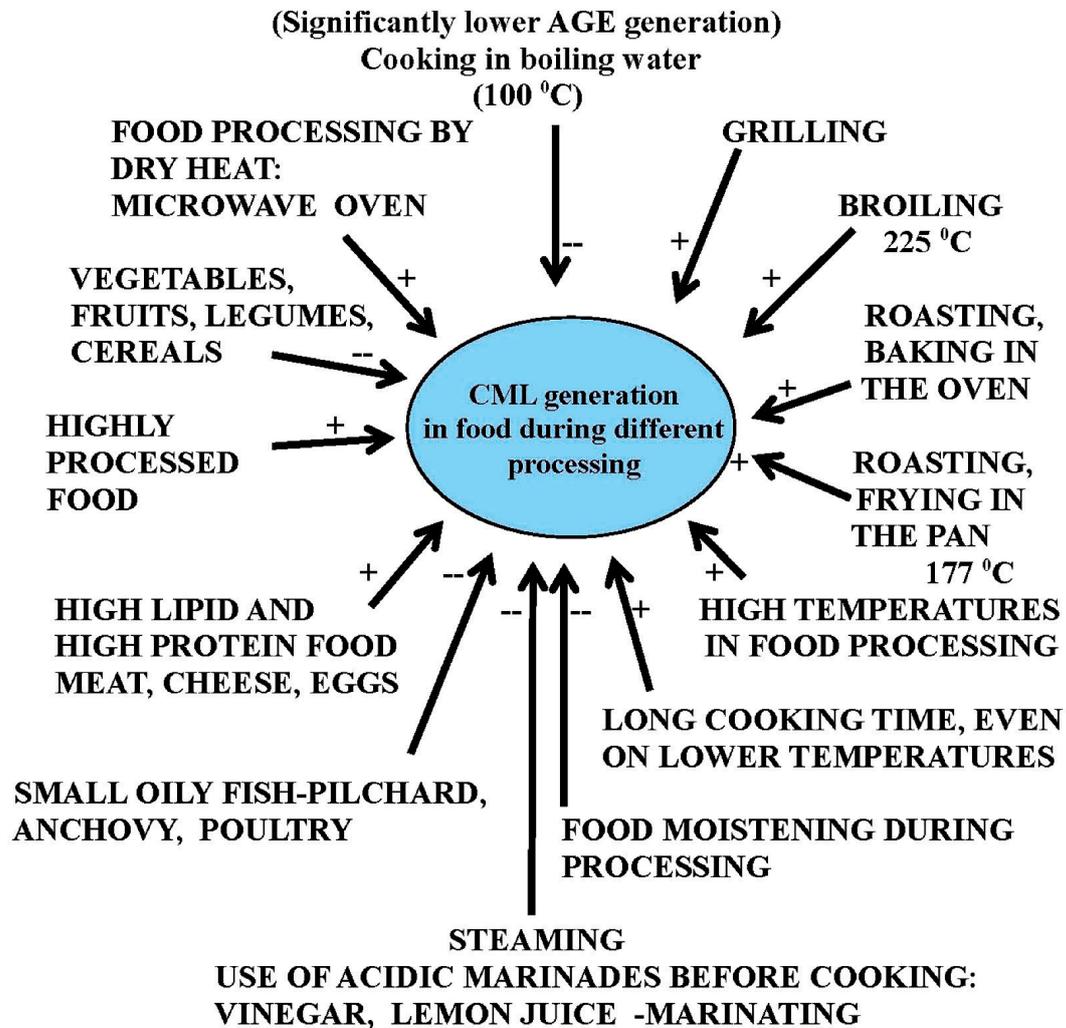


Fig.10. Causes of higher (+) and lower (-) AGE generation in food.

Food processing temperatures above 230°C (446°F) are critical for subsequent rise in dAGEs (d=dietary) formation. AGEs, advanced glycation end products; CML, N^ε-(carboxymethyl)-lysine.

Table 3. Important medications for AD.

Drug class	Compound	
Cholinesterase inhibitors	Aricept (donepezil hydrochloride)	
	Exelon (rivastigmine)	
	Reminyl (galantamine)*	* blocks acetylcholine (ACh) destruction
NMDA receptor antagonists	Ebixa (memantine)†	† blocks effects of glutamate

NMDA, N-methyl-D-aspartate.

Conclusion

The continued increase in the incidence of dementias, particularly AD, as life expectancy concomitantly rises is becoming a significant problem worldwide. As the incidence of AD is now greater than 10% in most populations, the costs associated with the care and treatment of affected individuals places an enormous financial burden on individual families, the health sector, as well as the overall society. Although the exact cause of AD remains elusive, the potential role of AGEs in the development and progression of AD has been recently recognized. This finding has prompted numerous biochemical, epidemiologic, and clinical studies aimed at deciphering the roles of AGEs in AD in the hope of developing an effective therapy in the near future.

Acknowledgements

Part of this research was presented at the 25th Summer Stroke School “Healthy Lifestyle and Prevention of Stroke” on June 10, 2014, at Dubrovnik, Croatia.

Conflicts of interest statement

The author has no conflicts of interest related to this study to declare.

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