*Available online*www.ijpras.com

International Journal of Pharmaceutical Research&Allied Sciences, 2019, 8(1):1-16

Research Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Modern Approaches and Strategies for Prevention and Therapeutic Influence of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is a chronic progressive polypathogenic neurodegenerative disease in which the combination of various mechanisms and risk factors and the appearance of amyloid plaques and neurofibrillary tangles cause anatomic, cellular and molecular changes, leading to a disorder of cortical functions, memory deficits, behavioral and functional disorders and total disintegration of intellectual and psychic activities.The up-to-date necessity of application of new effective drugs has been associated with an increase of the rate of the disease, a large number of risk factors and a variety of pathogenic mechanisms of neuronal degeneration. The therapeutic trends for Alzheimer's disease have been related to the symptomatic response and prevention of delay in the neuronal degeneration by the use of cholinergic, antiamyloid, antineurofibrillary, antiinflammatory, antioxidant, neurotrophic, neuroprotective and vasoactive agents.The classic therapeutic approach has been a compensatory therapy by the application of reversible acetylcholinesterase inhibitors. New trends have been connected to the elimination of amyloid plaques, formed by the action of γ-secretase enzyme. A perspective therapeutic trend is a multitarget therapy through compounds with potential properties for a simultaneous response to the pathogenetic mechanisms of the disease. In this regard, Galantamine and products with properties to inhibit acetylcholinesterase and γ-secretase and to possess radical-scavenging activity have been of interest. One of the most promising approaches to alternative prevention has been the antioxidant therapy with phytocompounds with antioxidant, antiamyloidogenic, antiinflammatory and antiapoptotic properties.The more effective trend for therapy of Alzheimer's disease is the combined therapy, involving both pathological mechanisms. The studies to increase the pharmacological effect by using the combination of acetylcholinesterase inhibitors with potential synergists have been ongoing.

Key words: *Alzheimer's disease, Therapy, Prevention, Trends, Galantamine*

INTRODUCTION

It is a progressive polypathogenic neurodegenerative disease [1], which is characterized with memory, learning, behavioral and cortical disorders and total disintegration of the intellect and mental activity as a result of the combination of various risk factors and mechanisms [2]. The disease is mainly associated with the presence of senile or amyloid plaques and neurofibrillary degenerations in connection with the impaired cholinergic mediation, neuronal loss and damage of dendrites, axones and synapses. Amyloid-activated microglial cells release proliferative cytokines and free radicals, that cause mitochondrial dysfunction, L-Glutamate release and neuronal death [3].

Pathogenetic hypotheses.

Pathogenetic hypotheses in Alzheimer's disease are: cholinergic, β-amyloid, neurofibrillary, mitochondrial, inflammatory and oxidative [4].

I. Cholinergic hypothesis.

In the cholinergic system, the neurotransmitter acetylcholine is synthesized by choline and acetylcoenzyme C, with the participation of the enzyme acetylcholinetransferase. During the action potential, acetylcholine is released from presynaptic vesicles in the synaptic space. Acetylcholine is destructed by the enzyme acetylcholinesterase, that is bound to the cytoplasmic membrane by glycopeptide molecules. In accordance with

the cholinergic theory, the behavioral and functional disorders are associated with a significant decrease in cerebral acetylcholinetransferase activity, reduction of synthesis, inhibition of acetylcholine release, reduction of cholinergic neurons, and alterations in presynaptic acetylcholine receptors [3].

II. β-amyloid hypothesis.

The basis of the pathogenesis of Alzheimer's disease is the progressive accumulation of intranuclear Aβ-peptides [5] and extraneuronal Aβ-oligomers in amyloid plaques. As the disease progresses, the neurodegenerative changes extend in a regular manner into discrete cortical regions and specific subcortical structures [6], affecting the cortex and hippocampus, which correlates with the progressive development of cognitive disorders [4]. Plaque formation follows the process of myelinization. Their number is the highest in the temporal and occipital part, and the smallest in the frontal and limbic cortex [7].

The extracellular senile plaques [8] in brain are spherical structures constructed from an amorphous core of toxic Aβ-peptide oligomers consisting of 39-42 amino acids. Aβ-peptides are surrounded by activated astrocytes, proliferatied microglial cells, Hirano bodies, abnormal dystrophic neuritis and axones [9].

The study of the aminoacid sequence in the $A\beta_{42}$-peptides allow the determination of their precursor – APP. An aberrant degradation of APP results in the formation of $A\beta_{42}$-peptides involved in amyloidogenesis. The transmembrane APP is proteolytically desctucted by intramammary enzymes – proteases: α-, β- and γ-secretase. α-Secretase is activated by protein kinase C. In the non-amyloidogenic metabolism, APP is cleaved from α-secretase to a carboxy terminal fragment (C87), from which γ-secretase cleaves shorter, soluble non-toxic peptides. In pathological β-γ- heterogeneous proteolysis in vivo, β-secretase causes N-terminal cleavage of APP to an extracellular N-terminal fragment and a transmembrane intracellular C-terminal fragment (C99), which is subjected to γ-secretase degradation to neurotoxic amyloid peptides: 90 % $A\beta_{40}$-peptides and 10 % $A\beta_{42}$-peptides [10].

The increased levels of toxic soluble $A\beta_{1\text{-}42}$ oligomers cause disruption of the membrane lipid biosynthesis, change of ion transport across cell membranes [11], oxidative modification, denaturation and inactivation of cellular proteins, resulting in the acceleration of aggregation of the Aβ-peptides [12]. As a result of oxidation, soluble Aβ-peptides are converted into aggregates [13]. $A\beta_{42}$-oligomers are most aggregated in amyloid plaques and are more toxic than $A\beta_{40}$-peptides [10, 14]. The oxidation of the aminoacid L-Methionine is the most important factor for the neurotoxicity of Aβ-peptides [15]. The phosphorylation of APP residues is associated with the accumulation of intranuclear neurotoxic Aβ-peptides [6]. Acetylcholinesterase through peripheral centers accelerates the accumulation and aggregation of $A\beta_{1\text{-}42}$-oligomers, therefore amyloid plaques, containing a high concentration of acetylcholineesterase in the nucleus are much more toxic than plaques in which the enzyme is not involved [16].

The enhancement of synthesis, oligomerization and aggregation of neurotoxic $A\beta_{42}$-oligomers in senile plaques leads to the following cascade of pathological neurodegenerative changes [17]: 1) neuroinflammatory reactions and neuroimmune dysfunction; 2) amyloid angiopathy – deposition of Aβ-peptides in the superficial cortical vasculars, resulting in changes in cerebral hemodynamics and endothelial cerebrovascular dysfunction; 3) neurotransmitter disorders [18]: damage of neurotransmitter systems: noradrenergic, dopaminergic, glutamatergic, adenosinergic, and decreased concentrations of noradrenaline, serotonin, somatostatin, γ-aminobutyric acid, neuropeptide Y and substance P3.

Amyloid aggregates cause the following pathological changes [19]: 1) stimulate tau-protein hyperphosphorylation [20] and formation of neurofibrillary tangles [21], destruct microtubules [22]; 2) increase mitochondrial dysfunction [23]; 3) potentiate microglial proliferation [24] and enhance inflammatory processes; 4) induce the synthesis of hydrogen peroxide which, under the influence of copper ions (Cu^{2+}), leads to the synthesis of Aβ-peptides and free radicals and to the oxidation of proteins and DNA [25]; 5) induce the expression of nitric oxide synthetase [19] and increase the levels of superoxide radicals, that cause lipid peroxidation [12, 25].

Neurodegenerative changes lead to neuronal dystrophy and apoptotosis of cells. The initial stage is caused by the disruption of the phospholipid membrane bilayer by the action of Aβ-peptides, acrolein and 4-hydroxy-2-nonenal. Apoptosis of neurons in brain is induced by the following mechanism: dopamine deficiency causes hyperactivity of the excitatory glutamatergic neurons in the subthalamic nucleus and influx into the neuron through the mitochondrial channels of calcium ions, proapoptotic factors and cytochrome C [26]. The neurodegenerative changes under the action of Aβ-aggregates are spread progressively to near nerve cells and

cause: 1) anomalies in the cytoskeleton; 2) damage to axones; 3) dysfunction of synapses [27] and dendrites; 4) loss of synapses [28] (80 times faster than normal aging [23], loss of dendrites [3] and axones [6]. Neurodegeneration leads to an increase in memory deficit [21], behavioral disorders, and dementia [8].

III. Neurofibrillary hypothesis.

The accumulation of Aβ-peptides in amyloid plaques induces the formation of neurofibrillary degenerations, which are lesions [29], constructed from an aggregated in spiral-bound pairs [30] hyperphosphorylated microtubule-related tau-proteine [31, 32]. Neurofibrillary strands fill the entire neuron, and are surrounded by the activated microglial, astrocytic cells and Hirano bodies [33].

Neurofibrillary tangles are intracellularly located in the large pyramidal neurons in the neocortex, and appear at the earliest layer II of the temporal coronary cortex, then progressively spread to the hippocampus, the amygdala and some subcutaneous structures, such as the cholinergic basal nucleus of Meinert, and the primary sensory areas of the cortex. This progression correlates with the increase of the severity of dementia, and the clinical manifestation is connected with the massive involvement of the lower temporal cortex [4].

Factors contributing to the accumulation of aggregates from tau-proteine (τ) are: the increased production of Aβ-peptides [21], mitochondrial oxidative stress [34], the reduced activity of antioxidant systems and the enhancement of inflammatory processes [31]. Tau-proteine stabilizes microtubules, but their structure is disturbed by phosphorylation of residues of the aminoacids L-Serine (Ser), L-Tyrosine (Tyr) and L-Threonine (Thr) [35].

Hyperphosphorylation of τ-proteine is due to: 1) the elevation (under the influence of Aβ-peptides) of activity of glycogen synthase kinase 3β [36], Fyn-kinase [37], cyclic-dependent proteinkinase 5, stress activating proteinkinases, mitotic proteinkinase 1A [38]; 2) reduction of phosphatase activity: PP1, PP2A, PP2B and PP5, which dephosphorylate τ-proteine at Ser 199, Ser 202, Thr 205, Thr 212, Ser 214, Ser 235, Ser 262, Ser 396, Ser 404 and Ser 409 [39]. The structure of τ-protein is phosphorylated at 45 sites: residues 172-251 at the proline end and residues 368-441. L-Tyrosinekinase Abl phosphorylates Tyr 394 [35] and from glycogensynthase kinase 3β are phosphorylated: Ser 199, Ser 202, Ser 396, Ser 404 [40].

The phosphorylation of different amino acids causes different effects. The stabilization of microtubules is selectively disturbed by the phosphorylation of Ser 262 from phosphorylated L-Tyrosine kinase 1A [41].

The phosphorylation of Ser 202 enhances the polymerization of τ- protein, and the phosphorylation of Ser 202-Thr 205 leads to the formation of filaments, aggregating in neurofibrillary tangles [42], in which accumulate acrolein, 4-hydroxy-2-nonenal, Nitrotyrosine [25] and products of modifications [29] of resistant to proteolytic degradation hyperphosphorylated τ-protein: oxidation [43], carbonylation [29], glycosylation [42]. Soluble oligomers cause loss of synapses [44]. The non-soluble aggregates of τ-protein cause neuronal apoptosis and memory disorders [42].

IV. Mitochondrialhypothesis.

Under the influence of heavy metal ions and oxidative stress [13, 34], Aβ-aggregates elicit mitochondrial dysfunction [45] by the activation of pathological processes [46]: 1) the reduction of the activity of mitochondrial enzymes: pyruvate dehydrogenase, ketoglutarate dehydrogenase and cytochrome C-oxidase [47]; 2) the impairment of glucose exchange; 3) the suppression of oxidative phosphorylation processes due to the reduced adenosinetriphosphate (ATP) formation; 4) the change of ionic membrane equilibrium and electronic transport in mitochondria; 5) the induction of the release from astrocytes of extracellular glutamate [48] by the activation of N-methyl-D-Aspartate (NMDA)-glutamate receptors in neurons [49] which causes intracellular accumulation of calcium ions [48]; 6) the decrease of the concentration of antiapoptotic proteins Bcl-2, Bcl-x, Bcl-x1; 7) the increase of the levels of proapoptotic proteins p53, Bad, Bax and Bid and of caspases 3, 6, 7, 8, 9, 12 [50], which depolarize the mitochondrial membrane and induce the opening of mitochondrial channels and release the stored calcium ions and cytochrome C from mitochondria in cytosol [51, 52].

The mitochondrial degeneration in the frontal, parietal and temporal areas of brain, by initiating the free radical formation, stimulates the synthesis of Aβ-peptides, the phosphorylation of the τ-proteine and the oxidation of DNA, resulting in a change in the structure and function of synapses [46].

V. Inflammatoryhypothesis.

Aβ-peptides activate the microglial cells by: 1) stimulating NMDA-receptors [49]; 2) the potentiation of L-Tyrosine kinases Abl, Fau, Fyn, Lyn, PYK2, Src, in which there are phosphorylate L- Tyrosine residues in the multireceptor microglial complex [24]. The activated microglial cells and astrocytes [53] stimulate

immunoimmflamation [54] by secreting inflammation factors: interleukin 1β, interleukin 6 and tumor necrosis factor α [55], resulting in the increased glutamate-induced apoptosis. Interleukin 1β elevates Aβ-oligomer toxicity, interleukin 6 stumulates Aβ-peptides synthesis [54].

Therapeutic approaches in Alzheimer's disease

The therapeutic approaches in Alzheimer's disease (Table 1., Table 2. and Table 3.) are related to the symptomatic response in varying degrees and for a varying length of time, depending on the form, extent and progression of the disease. Neuronal degeneration can be improved by: the early diagnosis and early onset of treatment [55], long-term administration, the combination of cholinergic, anti-amyloid, anti-neurofibrillary, anti-inflammatory, antioxidant [56], neurotrophic, neuroprotective and vasoactive agents.

Table 1. Cholinergic agents

1.	Reversible inhibitors of acetylcholinesterase [57]	Galantamine (Nivalin) [58], Donepezil (Aricept) [59], Rivastigmine (Exelon) [60]
2.	Butyrylcholinesterase inhibitors	Bisnorcymserine, Phenethylcymserine, MF-8622
3.	Cholinergic modulators	Eptastigmine, Zanapezil
4.	Allosteric modulators of nicotinic acetylcholine receptors	Galantamine [58]
5.	Nicotinic acetylcholine receptor agonists	Nefiracetam, iGT 521, SB1553A
6.	Acetylcholine transferase activators	Dehydrolipoic acid [61]
7.	Precursors of acetylcholine	Cholinealfoscerate [62]
8.	NMDA (N-Methyl-D-Aspartate) receptor antagonists [63]	Memantine,Tenocyclidine, Dimebon, LY235959, WIN634802, LY354740, LIGA20, LY274614 701252
9.	Muscarinic receptor agonist	Cevimeline (AF102),Talsaclidine, AF 267B, AF 150 S

Table 2. Antiamyloid agents

I.	**Inhibitors of Aβ-peptide synthesis**	
1.	β-secretase inhibitors [64]	Ibuprofen [65], Indomethacin [66]
2.	γ-secretase inhibitors	Avagacestat [67], Begacestat [68], Semagacestat [69]
3.	γ-secretase modulators [70]	R-Flurbiprofen (Tarenflurbil) [71, 72], Imatinib (Gleevec) [73]
4.	Inhibitors of γ-secretase-activating proteine	Imatinib (Gleevec) [73]
5.	Inhibitors of amyloid precursor proteine synthesis	Phenserine [74]
6.	α-Secretase activators	Atorvastatin, Lovastatin, Simvastatin [75], 17β-Estradiol [76], Etazolate [77]
II.	**Inhibitors of Aβ-aggregation**	Tramiprosate (Alzhemed) [78]
III.	**Stimulators of degradation of Aβ-peptides**	
1.	Stimulators of Aβ-degradation from enzyme Neprilisine	Imatinib (Gleevec) [72]
2.	Agonists of γ-PPAR (peroxisome proliferator-activating receptor)	Pioglitazone, Rosiglitazone [79]
IV.	**Immunotherapy [80]**	
1.	Vaccines against Aβ-peptides [81]	AN1792-8 [82]
2.	Monoclonal antibodies [83]	Bapineuzumab [84], Gantenerumab [85], Ponezumab [86], Solanezumab [87]

Table 3. Antineurofibrillary, antiinflammatory, antioxidant, neurotrophic, neuroprotective, vasoactive agents.

I.	**Antineurofibrillary agents [88]**	
1.	Stabilizers on microtubules	Epothilone [89]
2.	Caspase inhibitors [90]	Pep 419 (caspase 6 inhibitor) [90]
3.	Inhibitors of tau-proteine phosphorylation	
3.1.	Inhibitors of L-Tyrosine kinases	Imatinib (Gleevec) [73], Dasatinib, Masitinib mesilate [41], Memantine [91], Valproic acid [92], litii salts [93]
3.2.	Stimulators of proteine-phosphatases	Sodium selenate [94]
4.	Inhibitors of τ-proteine aggregation	Methylthioninium chloride [95]
II.	**Mitochondrial protectors**	Latrepirdine (Dimeboline) [96]

III.	**Anti-inflammatory agents**	
1.	Non-steroidal anti-inflammatory agents	Ibuprofen [65], Diclofenac, Indomethacin, Nimesulide, Refecoxib [66]
2.	Agonists of γ-PPAR (peroxisome proliferator-activating receptor)	Pioglitazone, Rosiglitazone [79]
3.	Inhibitors of tumor necrosis factor α	Etanercept (Enbrel) [97]
4.	Antihyperlipidemic	Lovastatin, Simvastatin [75]
IV.	**Aantioxidants [41]**	Curcumine [98], Ginkgobiloba [99], Melatonine [100], CoenzymeQ$_{10}$ [101], Idebenone, Decylubiquinone, Mito Q [102], Vitamin E [103], Selegiline [104]
V.	**Neurotrophic agents**	Cerebrolysine [105]
VI.	**Neuroprotective agents.**	Piracetam [106]
VII.	**Vasoactive agents.**	Nicergoline (Sermion) [1]

I. Cholinergic agents

Classical therapy is compensatory with the reversible acetylcholinesterase inhibitors: Galantamine [107], Donepezil, Rivastigmine, which by inhibiting the degradation of the intrasynaptic acetylcholine, increase the possibility of conducting a signal to the postsynaptic cholinergic neuron. Rivastigmine with acetylcholinesterase forms a carbamoylated rather than acylated complex, that is hydrolysed much more slowly. Clinical trials have shown that acetylcholinesterase inhibitors affect mildly cognitive dysfunctions and behavioral disorders in patients with baseline and mean disease rates within 1 month of the onset of therapy [2].

Butyrylcholinesterase inhibitors are Bisnorcymserine, Phenethylcymserine, MF-8622. As cholinergic modulators are used including Eptastigmine and Zanapezil. Galantamine allostericaly modulates nicotinic acetylcholine receptors. Nefiracetam, iGT 521, and SB1553A are nicotinic acetylcholine receptor agonists, and enhance the nicotinic acetylcholine receptor activity through protein kinase C pathway.

Galantamine is anatural [108] long-acting specific centrally active cholinergic drug for the treatment of mild-to-moderate Alzheimer's disease [109-114]. The drug stimulates choline-acetyltransferaseactivity, and potentiates the release of neurotransmitter acethylcholine by its dual mode of action: I) by competitively (reversibly) inhibition [73] of brain, erythrocytic, muscle and serum enzyme acetylcholinesterase; regulates the cholinergic transmission and stimulates the muscarinic receptors, which leads to the decreasing of Aß-generation and aggregation [115] and to the reduction of plaque formation [116]. Galantamine possesses the antioxidants [117] and neuroprotective properties [118] by inhibiting reactive oxidant species [119]; II) The neuroprotective activity of Galantamine against oxidative stress, caused by a variety of cytotoxic agents (ß-amyloid) [120], glutamate [121], hydrogen peroxide [122] and ethanol [123], is mediated through the positive allosteric modulatory stimulation of α7-subtype sites-binding of neuronal pre- and postsynaptic nicotinic acethylcholine receptors by increasing the probability of channel opening and slowing down the desensitization of the receptors [124]. Galantamine possesses a synergistic neuroprotective effect in combination with Rofecoxib and Caffeic acid [125], Memantine [126], Melatonin, [127] and Choline alphoscerate [128].

Important new therapeutic approaches against Alzheimer's diseaseare directed to the search for the drugs to reduce the synthesis and aggregation of Aβ-peptides [129, 130] by γ-secretase inhibitors [67, 131] and modulators [70] and remove Aβ-peptides and amyloid plaques by stimulating their degradation or by immunotherapy including: 1) the immunization with DNA containing Aβ$_{42}$-peptides genes [82]; 2) active: immunization with Aβ$_{42}$-peptides; 3) passive: immunization with monoclonal Aβ-antibodies [83].

II. Approaches for reduction of Aβ-peptide synthesis

γ-Secretase inhibition or modulation leads to the prevention of the accumulation of amyloid plaques, and is the latest trend in the search for new drugs against Alzheimer's disease. γ-Secretase inhibitors are peptidomimetics that block the active site of γ-secretase. The first in vivoγ-secretase inhibitor tested has been the DAPT dipeptide: N-[N-(3,5-difluorophenylacetyl)-L-alanyl]-S-phenylglycine tertiary butylester, the disadvantage of which is that for oral administration in mice for obtaining 50% reduction in Aβ-peptide synthesis, very high doses are required: 100 mg/kg [67]. The suppression of γ-secretase prevents the proteolysis of the Notch receptor, leading to the toxicity that excludes the clinical use of γ-secretase inhibitors. Compounds that reduce the formation and oligomerisation of Aβ-peptides by the modulation of the enzyme, without affecting the Notch

receptor are more suitable for therapeutic use compared to γ-secretion inhibitors, due to the avoidance of toxicity [132].

Studies have shown that the protease complex has allosteric binding sites, that can modulate the sites of proteolysis of APP. Non-steroidal anti-inflammatory drugs (Ibuprofen, Indomethacin, Sulindac) reduce the production of $A\beta_{42}$-oligomers and increase the levels of $A\beta_{38}$-peptides [133]. The modulator R-Flurbiprofen is in the third phase of the clinical trials in the United States [71]. Allosteric modulators are also the inhibitors of kinases, such as the inhibitor of Abl-kinase: Imatinib (Gleevec), which inhibits γ-secretase without affecting the Notch receptor [134]. It was found that the nucleotide adenosine triphosphate binds toγ-secretase, and selectively increases the proteolysis of APP and the production of Aβ-peptides, without affecting the Notch-receptor. This fact proves that the γ-secretase complex contains a nucleotide-binding site, which makes it possible to search for new compounds for allosteric modulation of the enzyme [135].

Synthesis of $A\beta_{42}$-peptides is suppressed by the activation of α-secretase by Galantamine [136], 17β-Estradiol [76], Etazolate [77] and by lowering the cholesterol concentration from the inhibitors of 3-hydroxy-3-methylglutaryl coenzymeA (HMG-CoA) reductase: Atorvastatin, Lovastatin, Simvastatin [75]. Improved amyloidogenic APP metabolism by binding the lipid peroxidation product isoprostane to thromboxane A2 F2αIII receptors is suppressed by the inhibitors of these receptors [137].

III. Approaches enhancing degradation of Aβ-peptides.

γ-Peroxisome proliferator-receptor activating agonists Pioglitazone and Rosiglitazone inhibits β-secretase expression, and by increasing the sensitivity of insulin receptors, stimulates the degradation of serum glucose, and thereby potentiates the degradation of Aβ-peptides from insulin degradation enzyme [138].

Active Aβ-immunotherapy uses synthetic proteins, which stimulates the production by the B cells of antibodies, which neutralizes Aβ peptides, and the complex is cleared out in the brain.The first representative for the active immunotherapy was AN1792-8, but was stopped in 2002 due to the induction of encephalitis inflammation by T-cell activation. In phase 2 of the clinical studies, there were CAD106, ACC001, ACI-24 UB-311 and Affitope vaccines, where the risk of inflammation is reduced [82].

Passive immunotherapy is the vaccination with polyclonal immunoglobulins containing antibodies against Aβ-oligomers [139] or with monoclonal antibodies (mAb) against Aβ-peptides [140]. Antibodies cross the blood-brain barrier and include the following mechanisms of action: 1) the connection of Aβ with mAb, resulting in the suppression of toxic aggregates. 2) the interaction of mAb with circulating Aβ-peptides in the peripheral blood and creating a concentration gradient, for the removal of the soluble Aβ-oligomers from the brain; 3) induced by Aβ-mAb complex activation of the complement-depend cytotoxicity, leading to the lysis of the target cell; 4) connecting Aβ-peptides from amyloid plaques in the brain and phagocytosis of the Aβ-mAb complexes by binding Fc-γ receptors in the microglial cells and mAb Fc domain [82].

Bapineuzemab binds to the N-terminal area of $A\beta_{1-5}$-aggregates in the brain [84], and Ponezumab (IgG2 antibody) reacts with the C-terminal part of Aβ-peptides [86]. Gantenerumab reduces with 30 % the Aβ-aggregates [85]. Solanezumab connects with the N-terminal portion of soluble $A\beta_{13-28}$-peptides [87]. Crenezumab is an IgG4 antibody and reacts with $A\beta_{12-23}$-oligomers [82]. An advantage of Crenezumab is that it has low affinity for antibody-binding leukocyte receptors, and reduces the risk of Fc-receptor mediated activation of the microglial cells, resulting in brain-inflammatory processes [140].

IV. Anti-neurofibrillary approaches.

An important therapeutic aspect against Alzheimer's disease is the study of agents against the formation of neurofibrillary rangles including: 1) the caspase inhibitors [90]; 2) the inhibitors of tau-proteine hyperphosphorylation; and 3) the passive immunotherapy with antibodies against tau-proteine [141]. Caspase 3 and caspase 6 stimulate the degradation of tau-protein [90], which facilitates the formation of neurofibrillary filaments [142]. Caspase inhibitors protect the destruction of tau-protein. The peptide Pep 419 is a selective allosteric caspase inhibitor 6 [90]. For blockade of caspase activity, investigations have reported the gene transfer by adenoviral vectors of antiapoptotic family Bcl: Bcl-w and Bcl-x1 [143]. Tau-proteine phosphorylation inhibitors are the inhibitors of L-tyrosine kinases: Imatinib (suppresses Abl) [73], Masitinib mesilate (inhibits Fak, Fyn, Lyn) and Dasatinib (suppresses Abl and Src) [41].

V. Anti-inflammatory approaches.

The approaches for reducing inflammatory processes resulting from Aβ-induced microglial proliferation have been associated with the application of: 1) Non-steroidal anti-inflammatory agents that inhibit the formation of

cytokines [66] by blocking the enzyme cyclooxygenase; 2) statins: Lovastatin, Simvastatin, which lower C-reactive protein levels and reduce the Aβ-stimulated increase of interleukin 1β and interleukin 6 [75]. The possibility of using products, containing plant extracts with anti-inflammatory and antimicrobial action has also been studied.

VI. Neurotrophic, neuroprotective and vasoactive approaches.

Cerebrolysine has a neurotrophic effect similar to that of nerve growth factor, and facilitates the transport of glucose through the hematoencephalic barrier [105]. Piracetam is a neuroprotector, and increases the viability of neurons [106]. The vasoactive effect of the semi-synthetic derivative of ergotamine Nicergoline (Sermion) is expressed in the improvement of cerebral blood flow, which results in an increase of energy metabolism, glucose uptake and protein synthesis. Nicergoline is an agonist of dopaminergic presynaptic receptors, which increases the concentration of dopamine in synapses, reduces the toxicity of L-Glutamate, blocks the entry of calcium ions into the cells, inhibits the platelet aggregation and increases the erythrocyte plasticity [1].

VII. Combined therapy.

The more effective approach is a combined therapy involving both pathological mechanisms [144]. A synergistic effect has been reported for the combinations of: Galantamine / Nicotine; Galantamine / Memantine; Donepezil / Memantine; Latrepirdine; Tacrine / Melatonin [145]; Cerebrolysine / Donepezil [146], Cerebrolysin / Cavintone [105].

CONCLUSION

Alzheimer disease is associated with synaptic injury and neuronal loss, and is accompanied by amylod plaques, neurofibrillary tangles of hyperphosphorylated tau protein, microglial cell proliferation and astrogliosis [147] leading to the progressive memory loss followed by complete dementia [148].

Current therapies have improved the cholinergic transmission within the central neural system, and have included: the inhibitors of acetylcholinesterase and butyrylcholinesterase, cholinergic modulator, nicotinic acetylcholine receptor agonists, acetylcholine transferase activators, precursors of acetylcholine, NMDA receptor antagonists, and muscarinic receptor agonists [149].

Memoquin, a drug under preclinical studies has offered the added advantage of being a free radical scavenger, an inhibitor of amyloid beta aggregation, tau hyper phosphorylation inhibitor, and an anti-oxidant [149].

The role of the biomarkers (toxic β-amyloid peptides in amyloid plaques and tau-proteine in neutofibrilary tangles) in the early diagnosis of Alzheimer's disease [150] is very important, as this first observable pathophysiologic event occurs in the brain, years before the earliest clinical symptoms [151]. Recently, there have been completed and ongoing novel modern investigational therapeutic strategies that seek the prevention and modification of Alzheimer's disease [152]. The major developments in this direction have been the amyloid and tau based therapeutics [153]. Very promising new trends in therapy of Alzheimer's disease include the antiamyloid agents: I) the inhibitors of Aβ-peptide synthesis: 1) β- and γ-secretase inhibitors; 2) γ-secretase modulators;3) the blockers ofγ-secretase-activating proteine;4) the inhibitors of the synthesis of amyloid precursor proteine; 5) α-secretase activators; II) the inhibitors of Aβ-aggregation;and III) the stimulators of degradationof Aβ-peptides. Many additional approaches targeting the Aβ-independent effects of apoE4 have been promising and have been at an early stage of development including:1) the reduction of apoE4 expression in neurons; 2) the specific apoE4-protease inhibitors; 3) the humanized monoclonal antibodies specific for the neurotoxic apoE fragments; 4) the modifying apoE levels or its Aβ binding property; 5) the synthetic apoE mimetic peptides [154].

One of the most promising approaches for the prevention has been an antioxidant therapy, which inhibits free radical action by the induction of endogenous antioxidant enzymes. In this respect, new alternatives have been perspective phytocompounds from the medicinal herbs [155, 156] with antioxidant, antiamyloidogenic, anti-inflammatory and antiapoptotic properties.

A new effective approach has been immunotherapy which includes: vaccines against Aβ-peptides and monoclonal antibodies (Aducanumab, Bapineuzumab, Crenezumab, Gantenerumab Ponezumab, Solanezumab [157].

New investigations have been connected with the application of the inhibitors of tau-proteine phosphorylation which included: the blockers of L-Tyrosine kinases and of tau-proteine oligomerization and aggregation, the stimulators of proteine-phosphatases, and tau degradation and tau iminotherapy with tau vaccine AADvac [158].

Other therapeutic approaches have been: nerve growth factor and somatostatin secretion stimulation, astrocyte and gamma aminobutyric acid receptor modulators [159].

The therapeutic trends in Alzheimer's disease have been connected with the improvement of the neuronal degeneration, long-term administration, combination of cholinergic, antiamyloid, antineurofibrillary, anti-inflammatory, antioxidant, neurotrophic, neuroprotective and vasoactive agents. The more effective approach has been a combined therapy involving both pathological mechanisms.

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