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INVITED REVIEW

Alzheimer disease and neuroplasticity: New approaches and new targets in pharmacotherapy

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ABSTRACT: Alzheimer disease (AD) is the major cause of dementia in the aged individuals. It is a neurodegenerative disorder characterized by apoptosis and loss of neurons resulting in synaptic dysfunction in central pathways involved in learning and memory. Neuroplasticity can simply be defined as changes in the brain neurons, and structural and functional changes in synapses formed by these neurons. If the changes are not confined to a single neuron but reach the level of a synapse the adaptive response formed may also be called "synaptic plasticity". Brain is adapted to all exogenous and endogenous stimulations (i.e. environmental or emotional stresses) by neuroplasticity. The most essential statement on AD pathology is that it assault the processes associated with neuroplasticity in central nervous system (CNS). Directly focusing on the causes of damages of synaptic elements and development of new therapeutic approaches devoted to reverse impaired neuroplasticity induced by the disorder may be a more effective strategy and provide more consistent solutions in the treatment of AD. The main objective of this review article is to update our knowledge on AD in the light of the present literature and discuss the new approaches and targets such as neuroplasticity hypothesis of AD and new candidate drugs.

KEYWORDS: Alzheimer disease; neuroplasticity; central nervous system (CNS); pharmacotherapy

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INTRODUCTION

Alzheimer's disease (AD) was first identified in 1906 by Alois Alzheimer, a German psychiatrist and neuropathologist (Figure 1). AD is the major cause of dementia in the middle-to old-aged individuals and is a chronic and progressive disorder with an average disease progression of approximately ten years (1). Currently, almost 35 million people worldwide are suffering from AD. According to the investigators, the incidence of AD will increase throughout the world, with projections that it will quadruple over the next 35 years to affect 1 in every 85 people on earth: over 100 million people by 2050 (2). With this aspect, the disorder will cause a big economical problem and discomfort in aged population.

Aging is a multifactorial process determined by genetic and epigenetic factors resulting in a wide functional decline including endocrine, immunological and cognitive functions. Thus, a large amount of aging individuals demonstrate progressive impairment of cognitive functions which are related to hippocampus or cortical alterations, two brain regions associated with learning and memory (3). The great majority of AD is sporadic and is not related to genetic factors. The familial form of AD comprises <1% of all cases (1). The risk increases by environmental and social factors such as head trauma, overeating, a sedentary life style and severe adverse stress. Chronic stresses may also cause memory impairments and increase vulnerability to AD (4-6).

As will be discussed below, AD is a neurodegenerative disorder characterized by apoptosis and loss of neurons resulting in synaptic dysfunction in central pathways involved in learning and

FIGURE 1- Alois Alzheimer (1864-1915), German psychiatrist and neuropathologist.

FIGURE 2- Santiago Ramón y Cajal (1852-1934), Spanish pathologist, histologist, neuroscientist, and Nobel laureate.

memory (7, 8). Although neurobiological, genetic and pathological causes of the synaptic dysfunction in AD are well known, unfortunately, our knowledge on how the disease can be averted or how we can provide an exact remission in the treatment of AD is very limited. At present, there is no rational or radical solution for AD by pharmacotherapy or any other medical method. The presently available drugs that are used in the treatment of AD are limited and they do not provide satisfactory results, beyond slowing down the progress of the disorder. Preventive effects of some new drugs are also debated. Although animal models have provided valuable information in understanding the etiopathogenesis of AD and in the development of new effective molecules in the treatment of the disorder, these models are still empiric and they do not provide together all three criterion; predictive, face and constructive validities yet (9,10). Development of more qualified animal models in AD is also required. Eventually, all over the world, AD is one of the most important problems awaiting rational solution. New drug designs and development of new molecules for the treatment of AD seems to be the most important investment area in central nervous system (CNS) disorders.

The most essential statement on AD pathology is that it assaults neuroplastic processes in CNS. At biological, psychological and social levels, it is the capacity to store new information that is affected by AD. Tracing memory mechanisms to their most basic levels leads to the loci at which AD pathology affects CNS mechanisms. Although this hypothesis was proposed in 1985 by Ashford and Jarvik (11), its origin goes back to 1911. Santiago Ramón y Cajal, a Spanish pathologist, histologist, neuroscientist, and Nobel laureate (see Figure 2) made several major contributions to neuroanatomy. He discovered the axonal growth cone, and provided the definitive evidence for what would later be known as "neuron theory", experimentally demonstrating that the relationship between nerve cells was not one of continuity, but rather of contiguity (12). "Neuron theory" stands as the foundation of modern neuroscience. When Cajal pointed out "*One also might imagine that amnesia, a paucity of thought associations, retardation, and dementia could result when synapses between neurons are weakened as a result of a more or less pathological condition, that is, when processes atrophy and no longer form contacts, when cortical mnemonic or association areas suffer partial disorganization*" (13), he was probably the first to realize that dementia results from a dysfunction of synaptic contacts (7).

Presently, concerning the pathological mechanism, the neuroplasticity hypothesis of CNS disorders including AD are again gaining importance (14,15). Directly focusing on the causes of the damage of synaptic elements, and development of new therapeutic approaches devoted to reverse the impaired neuroplasticity induced by the disorder may be a more effective strategy, and provide more consistent solutions in the treatment of AD. Hence, understanding the neuroplasticity basis of AD is important to develop new strategies. Thus, the main objective of this review article is to update our knowledge on AD and discuss the possible new approaches and targets such as neuroplasticity hypothesis of AD and new candidate drugs.

PATHOPHYSIOLOGICAL BASIS OF AD

Role of the two basic neurotransmitter systems in the pathophysiology of AD has been clarified. They are acetylcholine and glutamate. Other neurotransmitters such as monoamines and GABA are also related to AD in symptomatical level. In this review article, we will focus on acetylcholine and glutamate because of their direct relationship to the pathology of the disease.

"Septo-hippocampal pathway", originating from the cholinergic neurons in the septum and projecting to the hippocampus (Figure 3), is related to learning, and regulation and management of short-term memory functions. Many studies on human and animals conclude that hippocampus is an important brain region involved in memory formation (17,18). The amy-

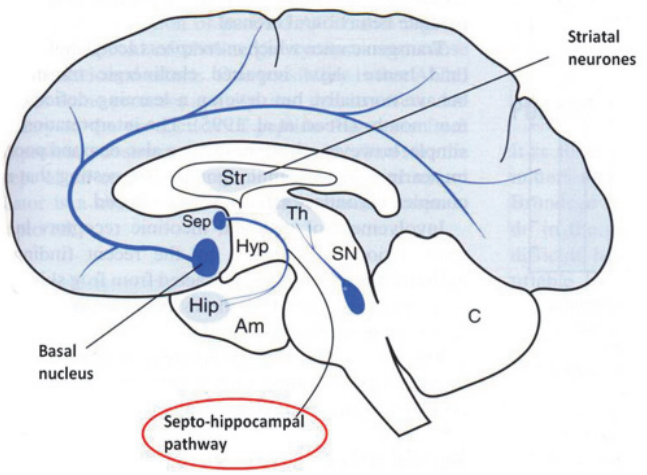

FIGURE 3- Septo-hippocampal pathway. C: Cerebellum, Hip: Hippocampus, Str: Striatum, SN: Substantia nigra, Am: Amygdale, Hyp: Hypothalamus, Th: Thalamus, Sep: Septum (from Uzbay, 2004, see ref. 16).

gdala and the orbitofrontal cortex are important contributors of information processing and formation of declarative memory (19,20). It is known that, emotional memory is formed in the amygdala (21), and declarative memory formation, including cases with verbal expression occurs in hippocampus (22). Hippocampus is also important in "memory consolidation" which is the process of conversion of short-term memory to long-term memory in the neocortex. Here, hippocampus plays a critical role in supplying the first input necessary for the long-term memory, conversion of these to long-term memories, and formation and strenghtening of the synaptic connections necessary for the maintenance of long-term memory (18,23). Extensive degenerative changes have been reported in the hippocampus and cortex of patients with AD. As the disease progresses, these changes progressively, but constantly, spread across the brain. In particular, there is a clear cholinergic cell loss (24,25). The gradual loss of cholinergic neurons, and the resulting decline in levels of the neurotransmitter acetylcholine, has been shown to correlate with the cognitive deficits in AD.

Glutamate, an excitatory neurotransmitter of the brain, is also associated with the pathophysiology of AD (25,26). Glutamate is implicated in almost all CNS functions, from primary sensory perception to cognition. All excitatory projection pathways to, from and within the hippocampus use glutamate as a neurotransmitter (27). However, as well as being a critical mediator of contact between neurons, under certain circumstances glutamate can kill neurons by a process called "excitotoxicity" (25). Glutamate activates several receptors, including the N-methyl-D-aspartate (NMDA) receptors, which are coupled to high conductance channels permeable to sodium, calcium and potassium. In the normal brain, the NMDA receptors are mediators of synaptic plasticity such as learning and memory (28). In the brain of patients suffering from AD there is an enhanced activation of NMDA receptors. This might lead to the hypothesis that an improvement of cognitive functions should be observed, but this is clearly not the case. In fact, temporally uncoordinated, continuous stimulation of NMDA receptors, i.e. energy deficits, prolonged membrane polarization and abnormal glutamate levels, leads to excessive calcium access, triggering a cascade of biochemical events that causes further excessive activation of the receptors. This excessive activation causes functional impairment and damages and kills neurons, which are unable to cope with the continuous releasing of neurochemical messages (29). Numerous evidences support the suggestion that NMDA receptor-induced excitotoxicity is critical in neurodegenerative statements including AD. Glutamate receptors, particularly NMDAs, also contribute to the neuronal toxicity induced by amyloid plaques which is one of the key pathological features of AD (25).

Nitric oxide (NO) is an unusual neurotransmitter in CNS. It is synthesized from the precursor L-arginine by the enzyme nitric oxide synthase. In CNS, it is synthesized in the postsynaptic area, and then diffuses back to the presynaptic neuron where it activates guanylate cyclase-cGMP cascade to release glutamate as retrograde. Thereby, it indirectly causes stimulation of postsynaptic NMDA receptors by glutamate (30). NO, at low physiological concentrations, may have an action as an anti-apoptotic/prosurvival factor in the CNS. However, at high concentrations, NO acts as a free radical and it can be toxic causing DNA damage and neuronal death in the brain. In AD, excessive NO production causes oxidative stress and damage of proteins, lipids and finally, mitochondrial dysfunction in the brain. Oxidative stress also damages DNA, which leads to alterations of nuclear regulatory factors, activation of proapoptotic genes, and cell death. However, current data suggest no significant changes in cGMP levels in patients with AD in comparison to the age-matched controls (31).

Additional loss or degeneration in basic monoaminergic neurons (serotonine, dopamine and noradrenaline) may occur during AD. Thus, these degenerations or loss of neurons could be related to motivational failure, major depression, psychotic reactions and some Parkinson like symptoms that develop within process.

AD pathology may be divided into three broad chapters: accumulation related positive lesions, negative lesions related to the losses and reactive processes such as inflammation. Positive lesions are robust, easy to detect and constitute the basis of the diagnosis. Detecting or evaluating the loss of neurons and synapses are not easy and they are more directly related to cognitive deficits (32).

A summary of risk factors and histopathological hallmarks in AD are shown in Figure 4. As can be seen in Figure 4, neurodegeneration is related to two factors: production of extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles (1). Amyloid precursor protein (APP) is a membrane protein that has a role in the protection of synaptic integrity. Aβs is formed as a result of enzymatic breakdown of some peptide components from APP. They convert to highly insoluble and proteolysis-resistant fibrils called senile plaques by accumulation of toxic Aβ42 forms.

The human APP gene was first identified at the end of the 80s by various laboratories (33-35). Autosomal dominant mutations in APP, presenilin 1(PS1) and presenilin 2 (PS2) account for about 5% of the patients, commonly characterized by an early onset (before 65 years old). Only APP, but not its homologues, amyloid precursor-like protein 1 (APLP1) and APLP2, contain se-

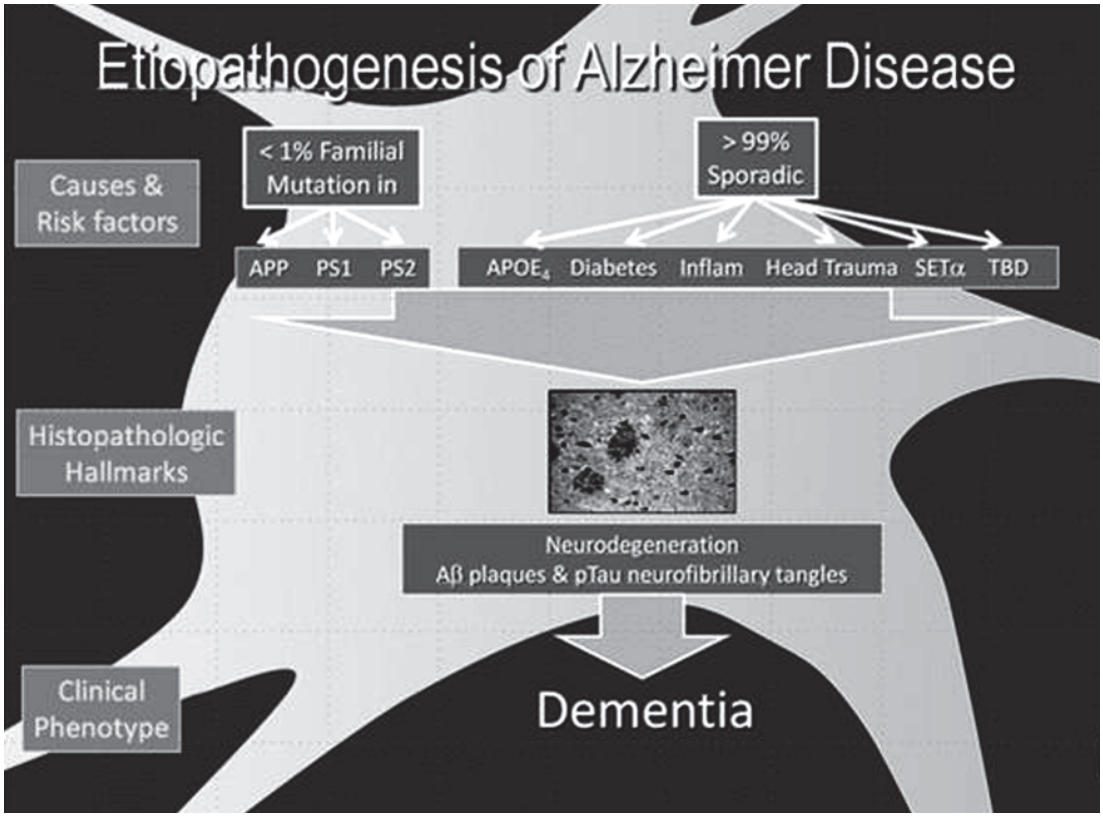

FIGURE 4- Risk factors and histopathological hallmarks of AD (from Iqbal and Grundke-Iqbal, 2011, see ref. 1).

quences encoding the Aβ domain. The first mutations demonstrated to be causative of inherited forms of familial AD were identified in the APP gene, providing evidence that APP plays a central role in AD pathogenesis. Mutation of APP, PS1 and PS2 genes increases to produce Aβ42 formation (36). PS1 is necessary for normal neurogenezis and survival, and localizes to synaptic membranes and neurite growth cones. Presenilins are related to intracellular trafficking, developmental signaling pathways and Ca^{2+} homeostasis (15,37-39).

Notch proteins are a group of large cell-surface membrane receptors that mediate complex cell fate decisions during development. For example, during neurogenesis in flies, the Delta protein signals from prospective neuroblasts through the Notch receptor on adjacent cells to prevent the latter from becoming neuroblasts and neurons. PS1 are necessary components of the machinery that carries out Aβ production and signal transduction within the Notch pathway (40). Mutations of PS1 and PS2 also disrupt constructive interaction and signaling in Nocth pathway and increases diathesis to produce Aβ42 formation (41).

Neurofibrillary tangles are composed of the tau proteins. In healthy individuals, tau is a component of microtubules. Microtubules stabilize growing axons and support structures for transport of nutrients, vesicles, mitochondria and chromosomes within the cell. In AD, tau protein is abnormally hyperphosphorylated and converts the structures to insoluble fibrils, originating deposits within the cell (36,42). It has been shown that tau pathology appears later than Aβ accumulation in AD (36,43).

Human apolipoprotein E (apoE) is a lipoprotein of 299 amino acids expressed in multiple organs with the highest expression in the liver followed by the brain. ApoE is one of the key lipoproteins of lipoprotein complexes that regulate the metabolism of lipids by directing their transport, delivery, and distribution from one tissue or cell type to another through apoE receptors and proteins associated with lipid transfer and lipolysis. Three common polymorphisms in the APOE gene, ε2, ε3, and ε4, result in single amino acid changes in the ApoE protein. The APOEε2, ε3, and ε4 alleles strongly and dose-dependently alter the likelihood of developing Alzheimer's disease (AD). In particular, APOE ε4 is associated with increased risk for AD, whereas APOEε2 is associated with decreased risk (44,45). Presence of APOEε4 disrupts synaptic integrity in neuronal pathways and break synaptic neurotransmission (46). Diabetes, inflammation and head trauma are other risk factors for AD (1) (Figure 4).

The most reliable biomarkers validated in the last few years include an abnormal cerebrospinal fluid Aβ and tau profile; the presence of hippocampal atrophy on magnetic resonance imaging (MRI), glucose hypometabolism on positron emission tomography (PET) scan, or presence of a known pathogenic mutation in genes encoding APP, PS1 and PS2. In light of striking evidence in 2007, new research criteria were proposed (47) and revised in 2010 (48). According to these new criteria, the diagnosis of AD is made when there is both clinical evidence of the disease phenotype and in vivo biological evidence of AD's pathology. The newly reported algorithm proposes that the diagnosis can be made in the presence of episodic memory impairment and a positive biomarker. Thus, Aβ accumulation

biomarkers are the first changes before the appearance of clinical symptoms. Later on during AD pathogenesis, biomarkers of synaptic dysfunctions (functional MRI) appear, followed by biomarkers of neuronal loss (structural MRI) (36,43).

WHAT IS NEUROPLASTICITY?

The CNS has the ability to adapt to both exogenous and endogenous stimuli. Many important central functions are executed with this adaptation, and insufficient adaptation causes the emergence of several diseases. Neuroplasticity can briefly be defined as changes in the brain's neurons, and structural and functional changes in synapses formed by these neurons. If the changes are not confined to a single neuron but reach the level of a synapse the adaptive response formed may also be called "synaptic plasticity". Variability of synaptic activity plays a role in the adaptation of the nervous system. Adaptation to environmental changes may only be accomplished by learning, and learning requires synaptic plasticity. Learning is the strongest and most important adaptive response of the central nervous system to endogenous and exogenous stimuli. Long term potentiation (LTP) formation in neurons is necessary for learning and it is an adaptive response associated with neuroplasticity and synaptic plasticity. Although chronic and severe stress causes negative neuroadaptive changes like depression, short term and limited stress is necessary for LTP, which forms the basis for learning. Thus, neuroplasticity can cause positive as well as negative changes (49)

Some physical changes may appear in the whole neuron or in a part like the dendrite due to neuroplasticity. In addition, new neuron formation, changes in neurons' resistance to negative factors like chronic severe stress and an increase or decrease in synaptic activity may appear. Changes in the central nervous system associated with neuroplastic responses are seen in Table 1. Depending on the strength and length of the stimulus and the properties of primary responding region, single, several or all of these changes may appear. The quality of the resulting neuroplasticity and remodeling due to it also depend on these factors. New neuron formation is called neurogenesis. Neurogenesis is observed most often in the hippocampus and olfactory region. Increases in hippocampal volume and neurogenesis are seen with every mental exercise and chronic stress causes decreases in hippocampal volume and neurogenesis of hippocampal neurons (49,50). Apoptosis can be defined briefly as cell death. In brain tissue apoptosis is physiologically the reverse of neurogenesis. Normally, apoptosis and neurogenesis work in concert to enable stability. An increase in one may trigger the other and vice versa. Environmental factors such as stress and endogen factors such as increases in free radicals and glucocorticoids not only decrease neurogenesis but also induce apoptosis. At any site in the brain an increase in apoptosis without accompanying neurogenesis or regression of neurogenesis with ongoing apoptosis results in degeneration and functional losses (49,51,52).

Neurotrophic factors are always released in very low concentrations and sometimes they change neurotransmitter-mediated central neurochemical transmission. Some psychotropic drugs may act on central neurotrophic factors besides neurochemical transmission (53). Some of the important neurotrophic factors known to be present in the central nervous system are seen in Table 2. Neurotrophic factors do not function as neurotransmitters in the central nervous system; their primary function is to help the development and regeneration of neurons, and they contribute to the important neuronal pathways for their structural health and for the maintenance of their function. They have important roles in the central nervous system for programming and execution of apoptosis. There may be a deficiency of certain neurotrophic factors due to endogenous or exogenous causes and this triggers a biological cascade resulting in the death of that neuron or group of neurons (53-55). Neurotrophic factors are essential for the structural and functional health of neuronal pathways.

TABLE 1. Neuroplasticity-induced changes in the brain (49)

Increase or decrease in dendritic branching
Breakage of dendrites
Increase in dendritic length
New synapse formation or disappearance of present synapses
Change in synaptic efficiency of present synapses (Increase or decrease)
Neurogenesis
Apoptosis
Changes in main brain metabolites
Changes in survival of present neurons (increase or decrease)
Increased resistance of neurons to breakage under stress
Changes in stimulus-induced postsynaptic potentials of present neurons
Changes in activities of neurotrophic factors (increase or decrease)

Inflammatory signaling pathways are also important. They involve upregulation of cytosolic phopholipase A_2 and the arachidonic acid cycle, the depletion of the brain-essential fatty acid docosahexaenoic acid (DHA) and DHA-derived neuroprotectin D1 (NPD1), and changes in the expression of key proapoptotic and antiapoptotic members of the Bcl-2 gene family. These are believed to be the major contributors to the pathogenic mechanisms in degeneration of the brain during AD. Lifelong impairment in the supply of DHA and NPD1 to the brain might be expected to result in a chronic loss of neurotrophic support for neuronal synapses and contribute to progressive disturbances in cognitive functions, memory and associated higher brain functions (56).

Finally, neuroplasticity is a flexible re-organization or adaptation of mammalian brain carried out by changes in synaptic formation and elements. Neuroplasticity of brain is affected by endogenous, exogenous and environmental stressful factors. It is a continuous process in reaction to neuronal activity and neuron injury, death, and genesis which involves modulation of structural and functional processes of axons, dendrites and synapses. The various structural elements that embody plasticity include LTP, synaptic efficacy, synaptic remodeling, synaptogenesis, neurite extension including axonal sprouting and dentritic remodeling, and neurogenesis and recruitment. In a more comprehensive logic, phenomenological processes that are apparent in plasticity are: synapses (electrical, biochemical, structural), neurite (axon, dendrite), neuron cell bodies, anterograde (toward distal neurites) and retrograde (from distal neurites) transport, cell interactions, neuronal networks or pathways, and behavioural, psychological and sociological activities (15). Unfavorable neuroplasticity is characterized by an adverse adaptation of the brain and appears in a number of CNS disorders.

NEUROPLASTICITY HYPOTHESIS OF ALZHEIMER'S DISEASE

As part of neuroplasticity, AD is defined as a pathological remodelling characterized by memory failures, retardation of cognitive functions, and accompanying behavioral defects that appear due to an unreliable neurotransmission between hippocampus or other related limbic system formations, and entorhinal and associative cortex because of neuronal loses of these areas. The neuroplasticity hypothesis also pulls together the tau and amyloid hypotheses with the consequence that there are two essential cellular memory mechanisms, each attacked by one of two types of pathology. Firstly, accumulation of amyloid (more closely linked to cause, affecting more distribute to cortical regions including the temporal and parietal lobes), results in senile plaque formation, then, once a critical point is reached, and secondly hyperphosphorylation of tau leads to the neurofibrillary pathology (correlated with dementia severity, initially affecting the hippocampus and medial temporal lobe). In each case, if the delicate balance between forming new connections and removing connections that are no longer required is disrupted, AD pathology may develop.

Which neuroplasticity changes take place in the brain during AD? In AD strongest associate of cognitive failure is in synapse loss (57-59), demonstrating the profound cognitive effects of loss of neuronal connectivity. Synaptic loss is an early event in AD and is a structural correlate of cognitive dysfunction. Memory loss in AD may result from synaptic dysfunction that precedes large scale neurodegeneration, where the synapse-to-neuron ratio is decreased about 50% (15,60-62). There is prominent neuronal loss in AD, especially in hippocampal area and enthorinal and association cortex (15,63,64), which disrupts memory-related circuitry in the brain, as mentioned above. Neuronal loss in these formations results in synapse loss due to deafferentation of target regions. More synapses are lost than can be accounted for by neuronal loss (65-67), signifying dysfunction and altered plasticity in remaining neurons (68).

In addition to neuronal and synapse losses, there are morphological disruption of neurites in AD, which further disrupt neuronal connectivity. Senile plaques, composed mainly of Aβ peptide, are space occupying lesions that disrupt the normal route of neurites (69,70). Modeling the effects of the altered neurite morphology around plaques in the brain of patients with AD on transmission of signal through neurites predicts a delay of several milliseconds around each plaque, which would severely disrupt the precise temporal firing of neuronal networks, thus possibly contributing to dementia (71).

Synapse and dendrite losses in AD exceed that seen with normal aging (72,73). Synaptic degeneration, like early AD, progresses slowly at first; perhaps reflecting attempts for compensatory plasticity, and as such could be initially reversible, but eventually becomes irreversible due to marked synapse loss (15,74).

Dendritic extent in the hippocampus can increase with age itself, possibly a compensatory response to loss of synaptic connections (68). Neocortex and hippocampus in AD also show massive somatodendritic sprouting (75,76), which may reflect unsuccessful remodeling in response to presynaptic or axonal damage (77). These dendritic changes therefore may be secondary to deafferation, signal transduction failures, or cytoskeletal abnormalities (15,73).

It has been proposed that AD is a disorder of impaired morphological plasticity (78,79). The spatial and temporal progression of the disease flows from the areas of the brain which retain the highest degree of plasticity, such as hippocampal formation and association cortices, to those with less plasticity, including primary sensory cortices (80,81). In a recent study, Gengler et al. (82) reported age-dependent impairment of synaptic plasticity in the hippocampus of transgenic APP/PS1 mice. These mice are used in experimental studies as a model of AD. In this study, the authors observed increasing levels of β-amyloid and accumulation of plaques with the associated gliosis and synaptic loss resulting in progressive deterioration of synaptic plasticity, which correlates with age-dependent memory impairments in this transgenic mouse strain (83). What cellular or molecular mechanisms target neuroplasticity in AD? Mechanisms of cell death and the contribution of cell death pathways to alterations in plasticity have been investigated in AD. Caspase activation has been observed in the post mortem AD brains, along with caspase-cleaved APP and tau, indicating a possible role of apoptosis in neuronal death (79,83). Caspase activation local to the synapse could also contribute to neuronal dysfunction and loss of plasticity (84).

Ectopic cell cycle proteins are present in sites vulnerable to neuronal death in post mortem AD patients (85,86). Some of these proteins, such as proliferating cell nuclear antigen, are also involved in DNA repair, but convincing evidence from in situ hybridization studies suggests that DNA replication actually occurs in at-risk neurons, indicating true re-entry into the cell cycle (87). Aβ appears to drive this abnormal and ultimately fatal cell cycle entry. In primary neuronal culture, neurons treated with Aβ have increases in expression of cyclins, begin DNA replication, then undergo apoptosis in a cyclin-dependent manner (79,88).

In early AD, several growth-related proteins are upregulated, which may reflect attempts to stimulate plasticity, including growth-associated protein 43 (GAP-43), myristoylated alanine-rich C kinase substrate (MARCKS), spectrin, heparansulfate, laminin, neural cell adhesion molecule (NCAM), various cytokines and neurotrophic factors including nerve growth factor (NGF), fibroblast growth factor (bFGF), epidermal growth factor (EGF), interleukin (IL) 1, 2 and 6, insulin-like growth factor 1 (IGF-1), IGF-2, platelet-derived growth factor (PDGF), Hepatocyte growth factor (HGF), and several growth factor receptors (88). Deregulations of proteins involved in structural plasticity of axons and dendrites indicate a failure of plasticity mechanisms, and support a disruption of synapse turnover as a primary mechanism in AD (15,89). Synaptic remodeling in AD is detected also by elevation in the NCAM/SNAP-25 (neural cell adhesion molecule /synaptosomal-associated protein of 25 kDa) ratio (76,90).

Is there any protective role of neurotrophins in the development or progression of AD? Results from a number of studies indicate that neurotrophins and their receptors have a key function in protection of synaptic formation and reliable neurotransmission in CNS. Indeed, neurotrophic factors are key regulators not only for development, maintanence and survival, but also for cognition, formation and storage of normal

memory (91). The most prominent members of the mammalian neurotrophin family are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) (please see, Table 2). They activate various cell signaling pathways by activating two types of membrane-bound receptors, Tyrosine receptor kinases (Trk) and $p75^{NTR}$. Three subtypes of Trk receptors have been defined: TrkA, TrkB and TrkC. The neurotrophins are synthesized as proneurotrophins that all bind to the $p75^{NTR}$. In their active cleaved form, each neurotrophin selectively activates one of three types of Trk receptors. NGF activates TrkA, NT-3 activates TrkC, while BDNF and NT-4 activate Trk B receptors (91,92).

NGF has protective effect on cholinergic neurons. In the absence of NGF, cholinergic neurons exhibit cell shrinkage, reduction in fiber density and downregulation of transmitter associates enzymes such as choline acetyl transferase (ChAT) and acetyl choline esterase (AChE), resulting in a decrease of cholinergic transmission (92,93). In AD, reduction of ChAT and AchE activity was observed. Thus, classical AD treatment with AchE inhibitors enhances neuronal transmission by increasing the availability of acetylcholine at the receptors (91). The role of $p75^{NTR}$ is not clear. However, there is another interesting link between NGF and APP: neuronal cell cultures upregulate APP expression when treated with NGF (94,95). The interaction between NGF and tau in AD is less clear.

TABLE 2. Some of the important neurotrophic factors present in the central nervous system (49)

Nerve growth factor (NGF)
Brain-derived neurotrophic factor (BDNF)
Neurotrophin 3 (NT-3)
Neurotrophin 4/5 (NT-4/5)
Neurotrophin-6 (NT-6)
Neurotrophin-7 (NT-7)
Glia-derived neurotrophic factor (GDNF)
Ciliary neurotrophic factor (CNTF)
Cholinergic development factor (CDF)
Insulin-dependent growth factor (IDGF)
Epidermal growth factor (EGF)
Proapoptotic receptors (P75)
Antiapoptotic receptors (TrkA)

BDNF also regulates synaptic plasticity and plays an important role in memory formation and storage (3,96). Messenger RNA and protein levels of BDNF are found to be decreased in hippocampus and neocortex during AD (97). Not only is BDNF diminished, but also its full-length receptor TrkB is analoguously reduced in the hippocampus and frontal cortex in AD. Upregulation of truncated TrkB receptors has also been found in association with senile plaques (98,99). In addition, increase of full-length TrkB was observed in glial-like cells in hippocampus and increase of BDNF in dystrophic neurons surrounding senile plaques (99). Polymorphism of the BDNF has been implicated with higher risk for AD. Especially for non-ApoE4 carriers and specific ethnic groups, this effect is well documented (100,101). A very interesting link is the fact that during aging and in AD, tau pathology starts in the entorhinal cortex and proceeds along the retrograde transport pathways of BDNF to the subiculum and CA1 subfield and then to the basal forebrain, amygdale and finally to several cortical regions (90). BDNF regulation is maintained through cholinergic innervations and through NMDA receptors (102,103). The maintenance of normal BDNF mRNA levels appears to be mediated predominantly by NMDA receptors, whereas the increases in BDNF above normal levels are mediated by non-NMDA receptors. Interestingly, the NMDA receptor antagonist memantine used as treatment against AD increases the levels of BDNF and TrkB in rats (104). BDNF has also protective effects against β-amyloid-induced toxicity in brain (3).

It has been shown that brain NT-3 mRNA levels are unchanged in AD (105-107). In addition, cerebrospinal fluid levels of NT-3 are not changed either (108).

Although not belonging to the neurotrophin family, fibroblast growth factor-2 (FGF-2) is important in neuronal development and neuroprotection after neuronal loss (109). Interestingly, it also regulates BDNF. Increased levels and enhanced binding of FGF-2 were detected in senile plaques and neurofibrillary tangles in brain during AD (110,111). Moreover, it has been shown that FGF-2 increases the neurotic involvement of plaques (112). Incubation of neuronal cultures with FGF-2 results in increased tau phosphorilation (113) by increasing the levels of tau kinase glycogen synthase kinase 3β (GSK-3β) and tau itself (114,115).

In conclusion, neuronal plasticity is profoundly altered in brain during AD and that both amyloid and tau alterations as well as neuron and synapse loss contribute to these changes. Neurotrofins such as NGF and BDNF has also an essential role in the development of reliable synapses. A number of mechanisms underlying the loss of plasticity in AD, such as protein aggregation, synaptic dysfunction, and neuronal loss are also indicated in other neurodegenerative disorders.

CURRENT AND FUTURE PHARMACOTHERAPY OF AD

Current pharmacotherapy in AD

Current pharmacotherapy options of AD are very limited. Like in other serious CNS diseases, AD treatment is also symptomatic and does not provide a rational solution. Present drugs are intended for delaying progression of the disease rather than to provide a capable treatment. If these drugs are used in early periods of AD, they may serve to delay progression of the disease in some patients. However, patients and physicians are already hopefully waiting for more effective and convenient drugs for the treatment of AD.

Because neurotransmitter acetylcholine levels were found to be reduced in AD, early drug development studies were focused to increase the brain acetylcholine levels and AchE inhibitors (AchEIs) were developed as the first drugs for the treatment of AD. To date, four ACEIs were approved for the treatment of mild to moderate AD. They are tacrine, donepezil, rivastigmine, and galantamine. Donepezil is now approved also for severe AD. Although tacrine was the first drug approved for the treatment of AD, it is rarely used due to its hepatotoxicity (36).

According to meta-analysis of 13 randomized, double-blind, placebo-controlled trials with donepezil, rivastigmine and galantamine from the Cochrane Dementia and Cognitive Improvement Group's Specialized Register, all of these AChEIs were found to be efficacious for the treatment of mild to moderate AD. Donepezil also had less adverse effects compared with rivastigmine (36).

A further available therapeutic option for moderate to severe AD treatment is memantine. Memantine has a noncompetitive antagonistic activity on NMDA receptors. Thereby, it protects neurons from excitotoxicity involved in excessive glutamate action (25). A meta-analysis on the efficacy of AchEIs and memantine indicated that these drugs produced statistically significant but clinically marginal improvement in AD (116). Memantine is a newer drug and more controlled clinical studies are required to understand its clinical efficacy in AD.

Additional therapeutic approaches

Several additional therapeutic approaches have been proposed in the last few years (36,117). Epidemiological evidence suggests that long–term use of anti-inflammatory drugs, particularly non-sterodial anti-inflammatory drugs (NSAIDs) has protective effects against AD. However, results from prospective studies did not support to this approach. Results of the studies involved in NSAIDs such as nimesulide, hydroxychloroquine, celecoxib, diclofenac, naproxen and dapsone indicated that these drugs failed to slow progression of cognitive decline in patients with mild to moderate AD. Although indometacine, another NSAID, may delay cognitive decline in this subset of patients, gastrointestinal adverse effects induced by this drug treatment limits its use in the pharmacotherapy of AD (36).

Since reduction of homocysteine levels with high-dose folate, vitamin B6 and vitamin B12 supplementation can slow the cognitive decline in AD, these vitamins were tested and used in AD. However, a randomized controlled trial showed that high-dose vitamin supplement regimen did not have any significant beneficial effect in AD (118). Antioxidants such as vitamine E, Ginkgo bloba, green tea, wine, blueberries and curcumin, omega-3-fatty acids and estrogen therapy neither did exhibit any significant effect in patients with AD (2,36,119).

Drugs under investigation in treatment of AD

In the light of current findings on the pathogenesis of AD, new original treatments are under development. Basic strategy in many of these investigations attempt to block the course of the disease in early phases.

Anti-amyloid aggregation [glycosaminoglycan (GAG) mimetic drugs], vaccination, selective Aβ42-lowering, γ-secretase inhibition, α-secretase potentiation and modulation of tau deposition were the treatment strategies of the last decade and several agents were developed and premarketing clinical trials were done (36). Although some of them reached to phase II and III levels of the clinical trials, clinical trials were stopped either because of adverse effects or ineffectiveness. Some drugs used for other indications such as lithium (a mood disorder stabilizing agent), rosiglotazone (an antidiabetic/antiinflamatuar agent) and selegiline (a selective MAO-B inhibitory agent) show promise in AD treatment (2). These agents, their mechanism of action and current status are given in Table 3.

TABLE 3. The drugs under investigation for treatment of AD.

Action mechanism	Agents	Statement
Anti-amyloid aggregation	Tramiprosate	Not continued
	Colostrinin	Phase II
	AZD103	Phase II
Vaccination	Bapineuzumab	Phase III
	ACC-001	Phase I
	Solanezumab	Phase III
	PF-04360365	Phase I
SALA	Tarenflurbil	Not continued
γ-secretase inhibition	LY-450139	Not continued
	BMS-708163	Phase II
α-secretase potentiation	Etazolate	Phase II
Modulation of tau deposition	Methylene blue	Phase II
GSK inhibition	Lithium	in progress
PPAR gamma agonistic activity	Rosiglotazone	in progress
Selective MAO-B inhibition	Selegiline	in progress

SALA: Selective Aβ42-lowering agents; GSK: glycogen synthase kinase; PPAR: peroxisome proliferator activated receptor

CONCLUSION

How should be drugs of the future in AD treatment? All the drugs used in AD treatment, also including those under investigation, are either disease-modifying agents or the agents that slow progression of the disease. None of them bring a radical solution for AD. New trend in pharmacotherapy of AD may be based on reversing the negative neuroplasticity that cause the disease. There two major elements that have a role in adverse neuroplasticity during AD: heavy neurodegeneration and poor regeneration of the neurons regarding especially septo-hippocampal pathway. As seen in Figure 5, the agents that inhibit neurodegeneration and stimulate regeneration in this target may provide more radical solutions in the treatment of AD via reversing the adverse neuroplasticity.

Prevention of apoptosis and supporting neurogenezis or established balance of apoptosis/neurogenezis in critical brain areas such as hippocampus in elderly are very important to suppress the incidence of AD in population. Probably, prevention of AD may be easier than its pharmacotherapy. Thus, the investigations to develop an effective vaccine are going on and show some promise. Marketing the more effective drugs in AD treatment may not be far off.

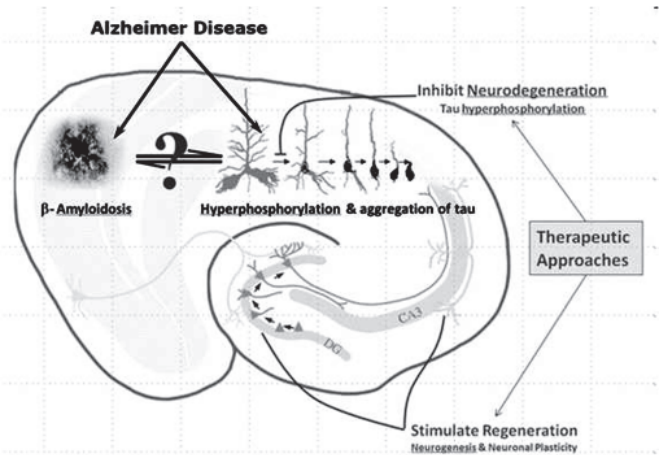

FIGURE 5- Pathogenesis of AD and neuroplasticity-based therapy (from Iqbal and Grundke-Iqbal, 2011, see ref. 1).

Alzheimer hastalığı ve nöroplastisite: Yeni yaklaşımlar ve farmakoterapide yeni hedefler

ÖZET: Alzheimer hastalığı (AH) yaşlı bireylerdeki demansların temel nedenidir. Öğrenme ve bellek ile ilişkili santral yolaklarda sinaptik işlev bozukluğuna neden olan apoptosis ve nöron kayıpları ile karakterizedir. Nöroplastisite kısaca beyinin nöronlarında ve bu nöronlar vasıtasıyla oluşturulan sinapslardaki yapısal ve işlevsel değişiklikler olarak tanımlanabilir. Eğer değişiklikler tek bir nöron ile sınırlı değilse ve sinaps düzeyine ulaşıyorsa, ortaya çıkan adaptif yanıt sinaptik plastisite olarak da adlandırılabilir. Beyin tüm endojen ve eksojen uyarılara (çevresel veya duyusal stresler gibi) nöroplastisite vasıtasıyla adapte olur. AH'nin patolojisindeki en temel durum santral sinir sistemindeki (SSS) nöroplasite ile ilişkili süreçlerin olumsuz yönde etkilenmesidir. Doğrudan sinaptik elemanların hasarlanma nedenlerine odaklanılması ve hastalığın neden olduğu bozulmuş veya olumsuz nöroplastisitenin tersine döndürülmesine yönelik yeni terapötik yaklaşımların geliştirilmesi daha etkili bir strateji olabilir ve hastalığın tedavisinde daha kalıcı çözümler sağlayabilir. Bu derlemenin ana amacı, AH hakkındaki bilgilerimizi mevcut literatür ışığında güncellemek ve AH'de nöroplastisite hipotezi ve yeni aday ilaçlar gibi yeni yaklaşımlar ve hedefler hakkında tartışmaktır.

ANAHTAR SÖZCÜKLER: Alzheimer hastalığı; nöroplastisite; santral sinir sistemi (SSS); farmakoterapi

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