

Alzheimer's Disease: Pathophysiology, Hypotheses and Treatment Strategies

Azza A Ali

Pharmacology and Toxicology Department,
Al-Azhar University, Cairo, Egypt

Received: May 25, 2016; **Accepted:** May 26, 2016; **Published:** May 31, 2016

Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative disorder. One new case of AD is expected to be developed every 33 seconds. So, about million new cases will be developed per year and the total estimated prevalence is expected to reach 13.8 million by 2050 [1]. AD is characterized by a group of symptoms classified as cognitive and non-cognitive dysfunctions. The cognitive dysfunction includes memory loss, executive dysfunction and language difficulties while non-cognitive dysfunction includes behavioral disturbances and psychiatric symptoms as hallucinations, delusion, agitation as well as depression [2]. In the late stage of the disease, cognitive performance of AD patients greatly declines to such an extent that they need complete support for all their daily activities [3, 4].

There are many hypotheses or theories for describing the pathophysiology of AD either still postulated or evidenced. Cholinergic hypothesis is the oldest one and based on cholinergic dysfunction [5]. Cholinesterase inhibitor such as donepezil is a piperidine derivative that has been approved for treatment of mild to moderate AD. It can inhibit acetylcholinesterase, the inhibition is reversibly and non-competitively [6]. Neuropathologically, AD is also defined by the presence of intraneuronal neurofibrillary lesions made up of tau proteins thus support the Tau hypothesis [7].

On the other hand, Genetic studies provided evidences for Amyloid cascade hypothesis which postulates that the neurodegeneration in AD caused by abnormal accumulation of amyloid beta ($A\beta$) plaques in various areas of the brain. Accordingly, accumulation of $A\beta$ plaques acts as a pathological trigger for a cascade that includes neuritic injury, formation of neurofibrillary tangles via tau protein leads to neuronal dysfunction and cell death in AD brain [8]. In amyloidogenic pathway, Amyloid precursor protein (APP) cleaved by β -secretase generates membrane bound C-terminal fragment which subsequently cleaved by γ -secretase and produces $A\beta$ peptide. The physiological functions of (APP) are poorly understood [9]. However, it have been established that, presenilins 1 and 2 are proteins predominantly present in neuron encoded by PSEN1 and PSEN2 genes. Specifically, PSEN1 gene mutation has been observed to altered cleavage pattern of γ -secretase which has resulted into higher $A\beta_{1-42}$ production and loss of PSEN dependent functions [10, 11]. Moreover, there are three major isoforms of Apolipoprotein E: ApoE2, ApoE3, and ApoE4. Animal studies as well as biochemical and cell biological studies suggest that ApoE4 can increase $A\beta$ peptide aggregation and impair its clearance in the brain thus, acts as driving force for pathogenesis of AD [12]. These represent a major risk factor associated with late onset AD [13].

Corresponding author: Azza A Ali

✉ azzamoro@gmail.com

Professor and Head of Pharmacology
and Toxicology Department, Faculty of
Pharmacy, Al-Azhar University, Cairo, Egypt.

Tel: +20 01061905439

Citation: Azza A Ali. Alzheimer's Disease: Pathophysiology, Hypotheses and Treatment Strategies. *Acta Psychopathol.* 2016, 2:3

In addition, neuropeptides are neuronal signaling molecules that work in CNS as messenger hormones, neurotransmitters or neuromodulators and play an important role in cognitive and behavioral functions. The role of neuropeptides in amyloid cascade hypothesis has been also established [14]. In this context, corticotrophin-releasing hormone (CRH) was found to exert neuroprotective role in AD. Previous studies showed that CRH has been found in reduced level in Cerebro Spinal Fluid (CSF) of AD patients as compared with the same sex and age matched healthy controls [15]. It has been also reported that, somatostatin influences learning and memory process and reduced level of somatostatin has been found in the brain and CSF of AD patients. The somatotrophin release inhibiting factor content declined significantly with cognitive deficits [16]. It is worthy to mention that, genetic deficiency of somatostatin resulted in alteration in the hippocampus and increased quantity of $A\beta$ peptide in AD brain [17, 18].

In the light of what was mentioned, novel strategies to modify the disease process have been developed. The major developing strategies are targeted to both $A\beta$ and tau based therapeutics which is the main key to unlock AD in the future. $A\beta$ based therapeutics or strategies may be achieved by targeting $A\beta$ protein, transport, aggregation and clearance as well as, by modulation of secretase enzymes in addition to, amyloid based vaccination therapy. However, tau based therapeutics or strategies may be achieved by targeting tau protein, Inhibition of tau phosphorylation, targeting microtubule stabilization, blocking

tau oligomerization and enhancing tau degradation as well as tau based vaccination therapy.

On the other hand, targeting intracellular signaling cascades and modulating levels of neurotransmitter are also of great importance. The role of adenosine as neuromodulator in neurodegenerative disorders has been also investigated. Adenosine receptors, especially adenosine A2A play pivotal role in modulation of neuronal function, linking the system to AD related cognitive deficits [19, 20]. Caffeine which is a natural methylxanthine with a non-selective adenosine A1 and A2A receptor antagonist is well known as a neuromodulator that has associative effect on cognitive function and information processing as well as on motor behaviors [21].

Targeting mitochondrial dysfunction also represents an effective and promising strategy to modify AD process especially in the high-risk individuals [22]. It is reported that Coenzyme Q10 (CoQ10) which is present primarily in the mitochondria is effective in improving cognitive disorders and has been used as anti-aging. It can suppress ROS production, minimized ROS injury and stabilize mitochondrial function [22, 23]. In addition, targeting oxidative stress play a central role in the treatment strategies of AD, some natural antioxidants including Vitamin E and Selenium can provide protection and have shown marked neuroprotective effect. Moreover, Epigallocatechin-3-gallate (EGCG); the most abundant and active compound of green tea is more effective as

neuroprotective than the antioxidants Vitamin E and Selenium. This may be attributed to its additional anti-inflammatory effect as well as to its ability to antagonize hippocampus A β aggregation in the experimental models of AD [24].

Finally it is noteworthy that; for the complexity of the mechanisms involved in AD thus, multi-target directed strategies either by using compounds with several potential targets or by using combined therapies perhaps represents the new promising strategy for the reduction of AD prevalence and incidence. It can also provide marked symptomatic and disease modifying benefits. For example, co-treatment with moderate doses of caffeine and nicotine has more pronounced protecting effect than each drug alone during induction of AD in rats [21]. Moreover, combination treatment using either EGCG & CoQ10 or EGCG & Vitamin E and Selenium has more pronounced effect than each one alone in minimizing the hazards of aluminum- induced AD in an experimental rat model of AD [22]. In other word, reducing oxidative stress together with inflammatory mediators as well as both A β and tau pathologies attenuate both biochemical and histopathological alterations as well as cognitive deterioration associated the incidence and the progression of AD [21-23]. However, more researches and clinical trials are needed to evaluate and improve the quality of evidence associated with these multi-target directed strategies in the reduction of AD prevalence and incidence.

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