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Therapeutic Interventions in Alzheimer Disease

Analava Mitra and Baishakhi Dey

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1. Introduction

Alzheimer disease (AD), was first recognized in the early 1900's by Alois Alzheimer, a German psychiatrist and neuro pathologist and named after him (Fig.1). Auguste Deter, in 1902 is a reported patient of Dr. Alois (Fig.2). AD is the most common form of dementia affecting millions of the geriatric population worldwide, mostly those above 65-85 yrs of age. Women are more commonly affected than man [1]. Alzheimer currently afflicts about 5.2 million Americans and with the rapid escalation of the prevalence of the disease, the figure is expected to double by 2020. According to WHO, there are about 18 million people worldwide with AD, the figure will be projected to nearly double by 2025 to 34 million. Developing countries like India and China will be among the countries worst hit by AD due to ageing of the population and likely some genetic factors. In 2000, India had 3.5 million Alzheimer patients, however with the fast graying of population and growth rate being fastest in the 80+ segment of the society, the number of Alzheimer patients have been growing at a phenomenal rate [2]. This neurodegenerative fatal brain disorder generally begins in late life and disease progression is gradual and continuous, the longevity of a patient is about 8-10 yrs after symptoms appear. The disease conditions range from mild, moderate to severe; in mild conditions patients have some functional impairments, in moderate conditions there's a dependence on care givers for some important daily activities, in severe conditions there is complete neuronal and memory loss, motor impairment making the patient absolutely dependent on care givers. Age related behavioral changes and symptoms of Alzheimer should not be confused.

Typical clinical symptoms of Alzheimer include: signs of progressive memory loss disturbing daily activities, difficulty in completing daily activities, poor judgment, vision problems, sudden changes in mood and personality, self withdrawal from hobbies or social contacts, loss of cognition, loss of coordination, etc. Ageing is the greatest risk factor of AD though Alzheimer is not a normal part of aging since people below 65yrs of age can also develop AD referred to as 'younger or early onset' [1,2]. The differences between a normal aged brain and the brain of an
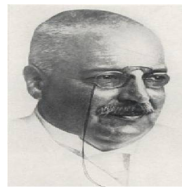
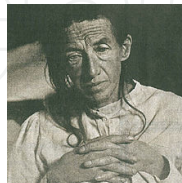**Figure 1.** Dr. Alois Alzheimer(1864-1915)

Figure 2. Auguste Deter (1902), patient of Dr. Alois

Alzheimer patient have been depicted in Fig.3. Other prominent risk factors in AD include family history, heredity (genetics), environmental factors. A genetic factor in late onset AD is ApoE ε4. The gene for apolipoprotein E (ApoE) on chromosome 19 has gained much recent attention in the pathogenesis of AD. ApoE is a protein modulator of phospholipid transport that might have a role in synaptic remodeling. ApoE has three common alleles, ApoE ε2, ε3, and ε4, which are expressed in varying amounts in the normal person. It is the ApoE ε4 genotype that is associated with the risk of AD. Everyone inherits one form of APoE gene from each parent; those who receive ApoE ε4 gene are at the risk of developing AD than those who receive ApoE ε2, ApoE ε3. Individuals who inherit two ApoE ε4 genes are at even higher risk; however inheriting one or two copies of genes does not gurantee that the individual will develop Alzheimer [3,4,5]. Moderate and severe head trauma, traumatic brain injuries are associated with increased risk of AD. Head injury resulting in loss of consciousness or post traumatic amnesia lasting about 30mins is associated with twice the risk of developing AD; severe head injuries have about 4.5 fold risks. Mild cognitive impairment (MCI) has an established link with AD in which a person has problems with memory, language, and some essential cognitive ability severe enough to be noticeable to others and shown upon cognitive tests but not severe enough to interfere with the daily life. However there is no clear explanation on the fact that why some people with MCI develops dementia and in some cases it is not. The overall health of the heart and blood vessels shows a close linkage with the brain health since a brain is nourished by the rich network of blood vessels and a healthy heart pumps nutrient and oxygen rich blood to these vessels. Cardiovascular diseases, high blood pressure, hypertensions, type 2 diabetes, cholesterolemia, obesity, smoking habits, and physical inactivity potentially increases the risk of AD [6-9].

2. Patho physiology of Alzheimer

The human brain consists of 100 millions of neurons connected to each other through synapses forming communication network; each cells entitled to perform their own duties relating to
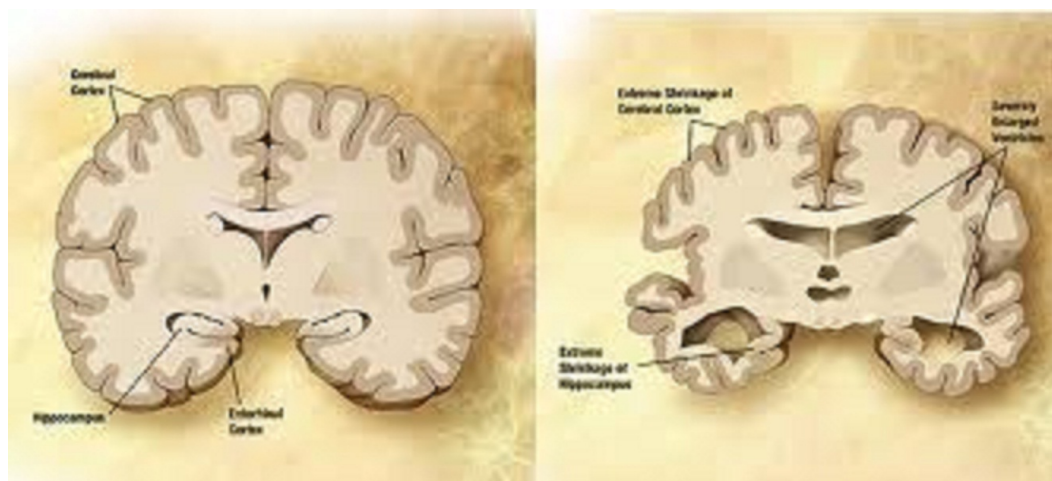
Figure 3. Alzheimer disease diagram, normal aged brain (left), Alzheimer brain (right)
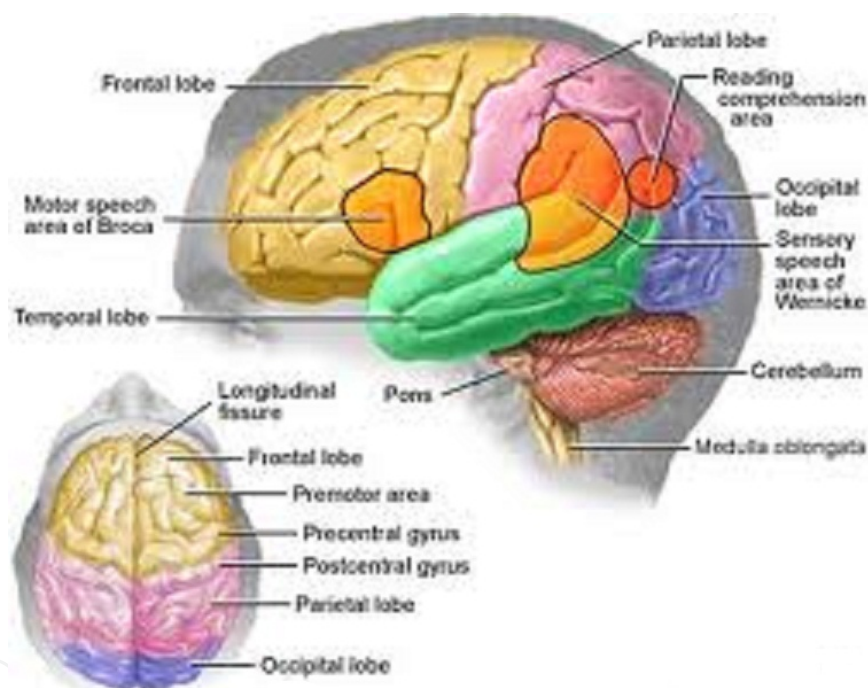

Figure 4. Shrinkage of Brain tissue in Alzheimer disease

memory, thinking, smell, taste, emotions etc. In case of AD these brain cells can't perform their duties. Patho physiology of Alzheimer disease being complex and multi factorial shows important pathological changes in brain like accumulation of amyloid cerebral plaques and neurofibrillary tangles of abnormal insoluble 'tau' protein (Fig.6,8,9). AD is also considered a 'tauopathy' due to abnormal aggregation of the tau protein. Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubules. These micro-tubules act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back. A protein called *tau* stabilizes the microtubules when phosphorylated, and is therefore called a microtubule-associated protein. In AD, tau undergoes chemical
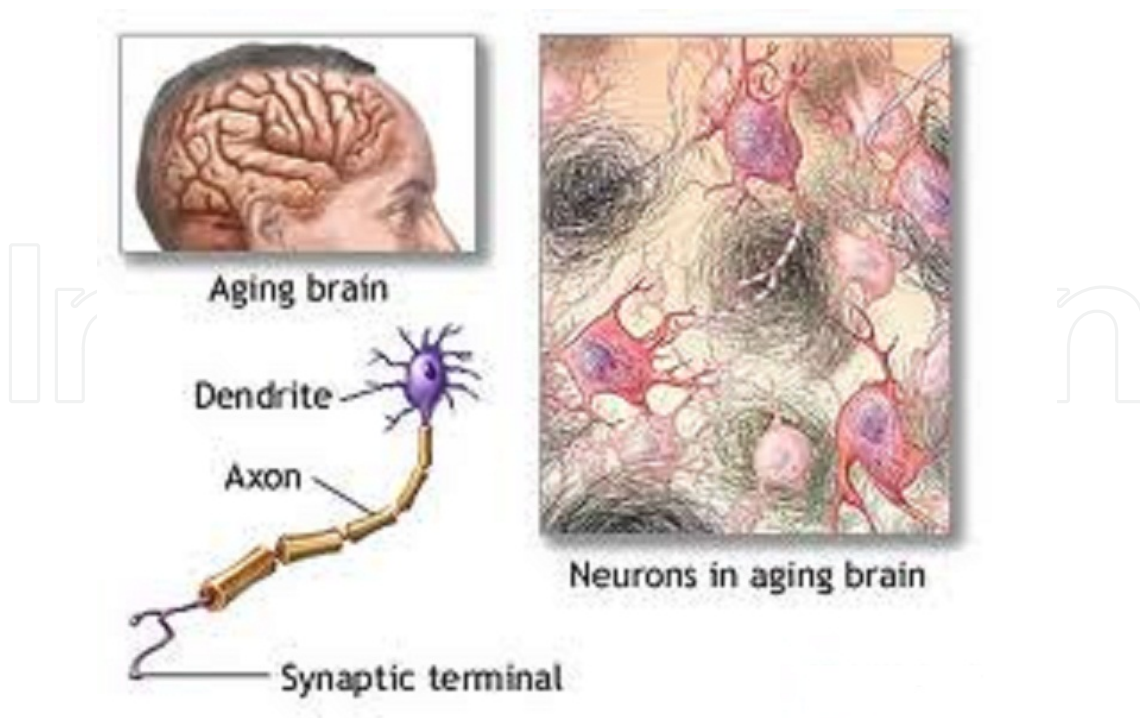
Figure 5. Normal homeostasis of Alzheimer Disease

changes, becoming hyperphosphorylated; it then begins to pair with other threads, creating neurofibrillary tangles and disintegrating the neuron's transport system [10,11].

As per the amyloid hypothesis, the neuropathologic hallmarks of AD are neuritic plaques and neurofibrillary tangles, consisting of hyper-phosphorylated microtubule-associated protein called 'tau' and extracellular amyloid plaques. The main component of amyloid plaques in AD is amyloid β (Aβ) peptide (38–43 amino acids) which is a proteolytic by-product from the amyloid precursor protein (APP) generated by the sequential β-secretase and γ-secretase cleavage (Fig.7). Research data have been shown that oligomeric Aβ species (smallest of which are dimers) isolated from AD brains are the most synaptotoxic forms. Aggregated amyloid fibrils, which are believed to be the toxic form of the protein disrupts the cell's calcium ion homeostasis, induces programmed cell death or apoptosis (Fig.7). It is also known that Aβ selectively builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilization of glucose by neurons [3,11-13].

The brain of a Alzheimer patient shows marked histo-pathophysiological changes like, widened sulci and shrinkage of the gyri (Fig.10). In the great majority of cases, every part of the cerebral cortex is involved; however, the occipital pole is often relatively spared. The cortical ribbon may be thinned and ventricular dilatation apparent, especially in the temporal horn, due to atrophy of the amygdala and hippocampus. Microscopically, there is significant loss of neurons, in addition to shrinkage of large cortical neurons, synapses, in association with shrinkage of the dendritic arbor of large neurons, is thought to be the critical pathological substrate (Fig.4). Neurofibrillary tangles are the other characteristic neurohistopathologic hallmarks seen in AD. These tangles found inside the neurons, concentrated in vulnerable
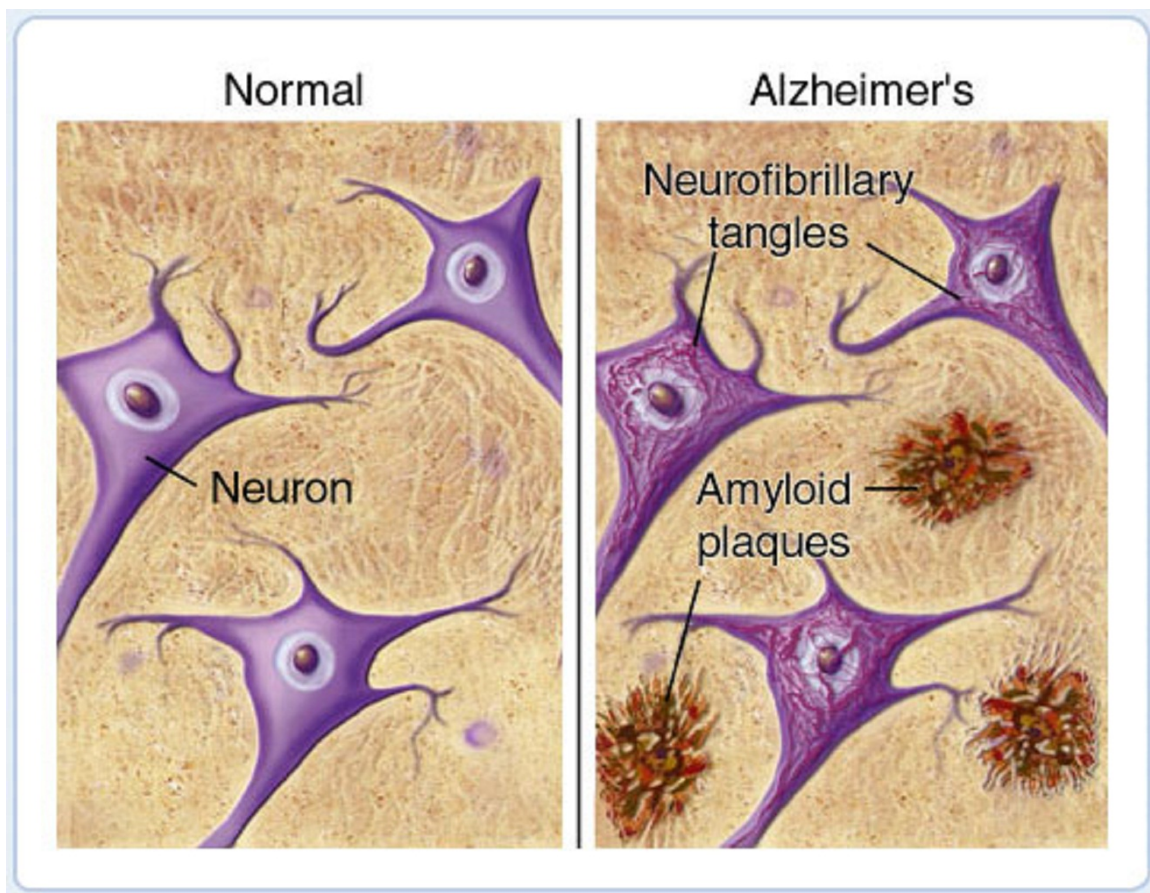
Figure 6. Normal Neuron (left), Neurofibrillary tangles, Amyloid plaques in Alzheimer (right)
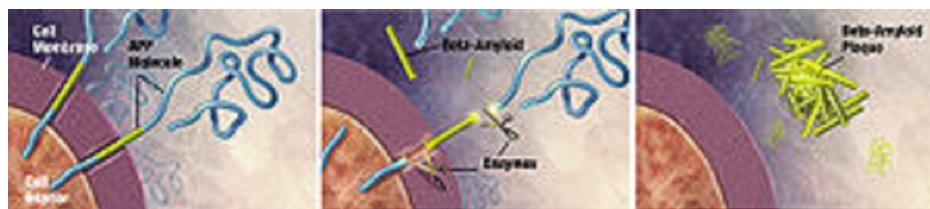

Figure 7. Enzyme action on APP (Amyloid precursor protein) and its fragmentation

neural systems and composed of paired helical filaments of hyperphosphorylated micro-tubule-associated tau protein that may cause disruption of normal cytoskeletal architecture with subsequent neuronal cell death. Other pathological alterations commonly seen in the brains of AD patients include neuropil threads, granulovacuolar degeneration, and amyloid angiopathy. Amyloid angiopathy is a distinct vascular lesion found in many AD brains, consisting of amyloid deposition in the walls of small-to medium-sized cortical and leptome-ningeal arteries. As a result of the deposits, the involved vessels may become compromised with resultant hemorrhage [14-17].

Inflammatory processes and cytokines play a controversial role in the pathology of Alzheimer's disease. Inflammation is a general marker of tissue damage in any disease, and may be either

secondary to tissue damage in AD or a marker of an immunological response. Some studies have demonstrated the presence of activated microglia, a marker of the brain's immune response. Alterations in the distribution of different neurotrophic factors and in the expression of their receptors such as the brain derived neurotrophic factor (BDNF) have been found in AD. Microglia have been shown to be significantly activated in AD brains and localized at sites of amyloid deposition. Early activation of microglia in early AD pathogenesis has been shown to be beneficial in scavenging and clearing toxic Aβ from the brain. Peri vascular macrophages like CD163 (hemoglobin-haptoglobin scavenger receptor) and CD206 (mannose receptor) are antigen-presenting phagocytic cells located in outer aspects of blood vessels within the brain, have shown to respond to CNS inflammation. Results of clinical trials have shown that, blood-derived macrophages from AD patients were shown to be less effective at phagocytosing Aβ compared with cells derived from non-demented control patients. Microglial and peri vascular macrophages may play role in clearing Aβ from the brain and in enhancing AD-related inflammation [18-20].
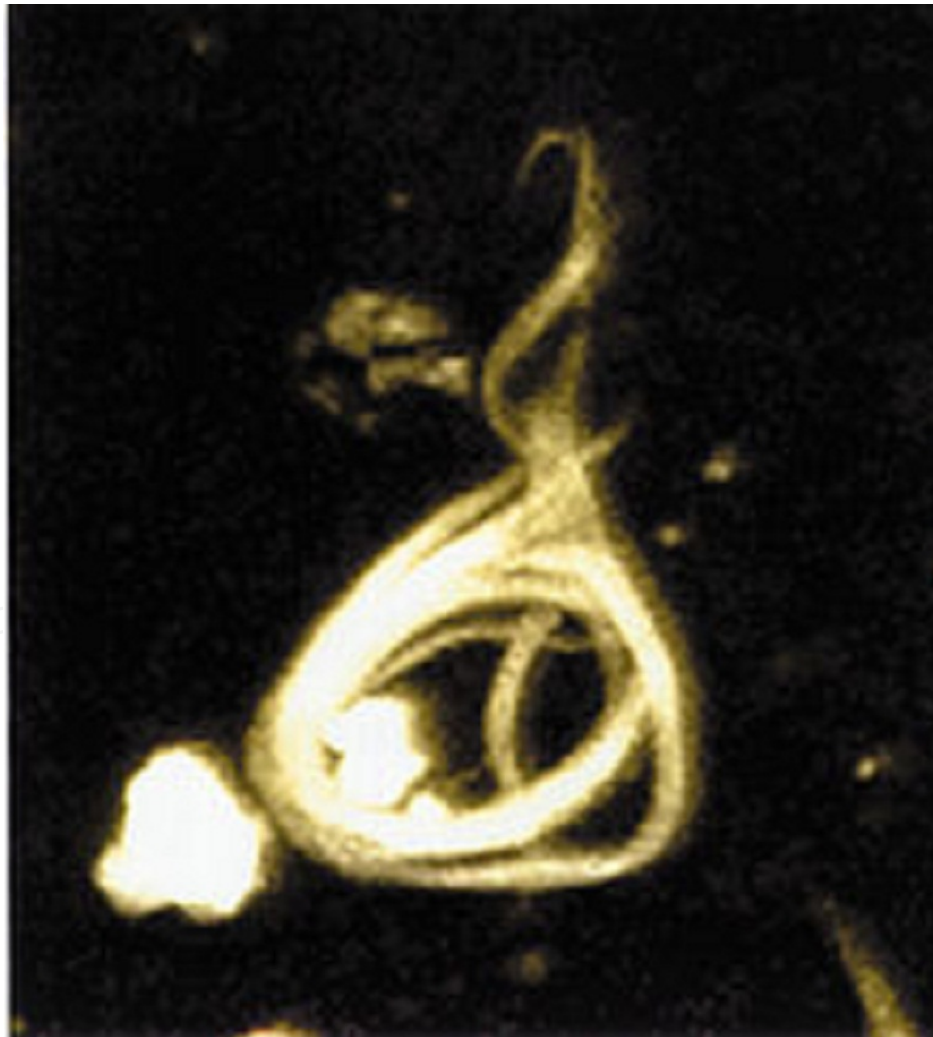

Figure 8. Neuro-fibrillary tangle with hyperphosphorylated Tau Protein(high resolution)
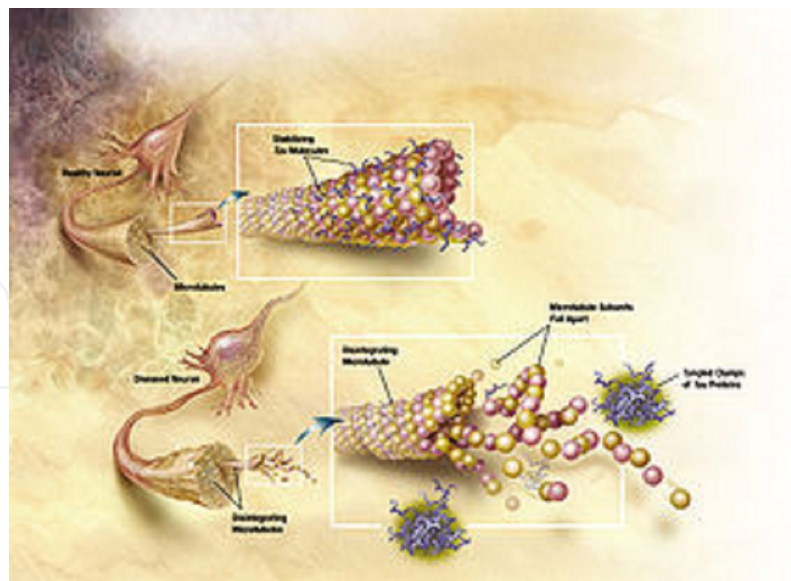
Figure 9. Changes in Tau protein & disintegration of microtubules in brain cells
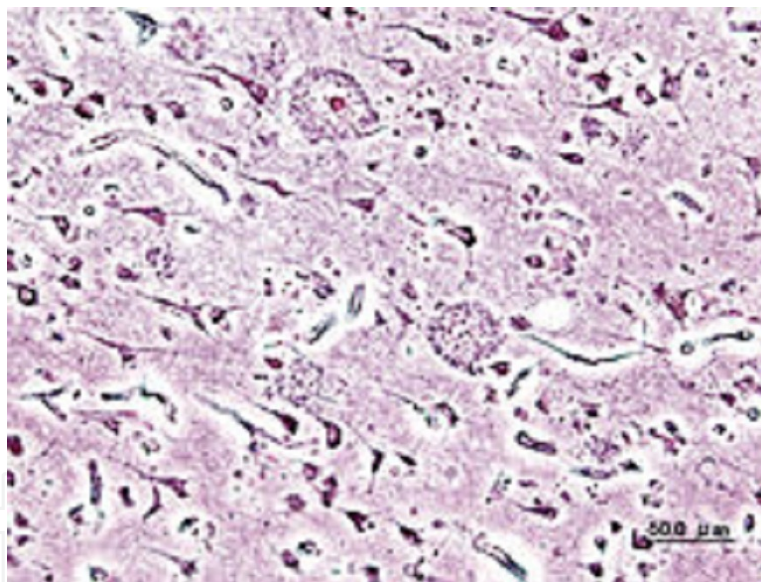

Figure 10. Histopathologic image of senile plaques in Alzheimer Brain

Vascular dysfunction has a critical role in AD. Results of epidemiological and pathological studies have demonstrated positive links between cerebro vascular disorders and AD. For example a person with severe atherosclerosis is at a threefold increased risk of developing AD or vascular dementia. Due to reduced cerebral blood flow in AD there are abnormal cholinergic innervations of intra cerebral blood vessels leading to brain hypo perfusion. Results of recent investigations have shown that, the upregulation of two transcription factors myocardin (MYOCD) and serum response factor (SRF) in AD lead to arterial hypercontractility potenti‐ating reduced cerebral blood flow. Other vascular anatomical defects observed in AD include

atrophy and irregularities of arterioles and capillaries, increase in collagen IV, heparin sulfate proteoglycans and laminin deposition in the basement membrane, disruption of the basement membrane, reduced total micro vascular density, occasional swelling of astrocytic endfeets, and extensive degeneration of the endothelium during the disease progression [21-24].

Decreased cerebral blood flow (CBF) has a negative impact on the protein synthesis necessary for memory and learning, and may eventually lead to neuritic injury and neuronal death. Moreover due to cerebral hypo perfusion amyloid β-peptide (Aβ) clearance across the blood–brain barrier (BBB) will be impaired leading to accumulation of Aβ on cerebral blood vessels and brain parenchyma causing cerebral amyloid angiopathy (CAA), which is associated with cognitive decline and is another significant factor in the pathogenesis of AD. CAA can severely disrupt the integrity of the blood vessel wall resulting in micro or macro intra cerebral bleedings that exacerbates neurodegenerative process and inflammatory response and may lead to hemorrhagic stroke. Cerebral amyloid angiopathy (CAA) with Aβ deposits in the vascular smooth muscle cell layer is a major pathological threat to the neurovascular unit in AD [13,17,20,21].

Research evidences have suggested that imbalances between Aβ production and clearance from the brain cause accumulation of Aβ in the wall of cerebral vessels and in the brains of AD individuals. Aβ that is produced both in the brain and periphery by a number of different cell types is transported across the BBB via receptor-mediated transcytosis; the key receptors being involved are: RAGE (Receptor for Advanced Glycation End products) that transports Aβ from the blood into the brain and LRP (low-density lipoprotein receptor related protein-1) that is the major cell surface Aβ clearance receptor that transports Aβ out of the brain across the BBB and promotes Aβ clearance on VSMC. Aβ is not only cleared from the brain interstitial fluid (ISF) as a soluble peptide, but can also be transported by its chaperone proteins in the ISF, such as apolipoprotein E (apoE), apolipoprotein J, and α2-macroglobulin. Apart from direct Aβ clearance into the blood, alternative perivascular route for the clearance of Aβ in the human brain also exists. The pulsation force of cerebral blood vessels has been proposed to drive an Aβ drainage route along the perivascular spaces. Vessel constriction or stiffening reduces the pulsatile blood flow which in turn reduces Aβ clearance along the perivascular spaces leading to increase in Aβ deposition in the arterial wall of AD patients [20-24].

ApoE is a reactive apolipoprotein that exists in 3 iso forms (apoE2, apoE3, and apoE4) in humans has a major function in the transport of lipids and cholesterol in our body. Individuals who carry at least one apoE4 allele have great chances to develop AD. ApoE, an Aβ chaperone protein is found to be associated with impaired transport of Aβ across the BBB. Free Aβ can be rapidly cleared from the brain mainly via LRP or RAGE receptor mediated transcytosis, but Aβ-ApoE complexes (mostly apoE4-Aβ complexes in contrast to apoE2-Aβ and apoE3-Aβ complexes) are cleared by the very low-density lipoprotein receptor at a much slower rate, causing Aβ retention in the brain. Transport of Aβ via the receptor for advanced glycation endproducts (RAGE) across the BBB provides a major source of Aβ that can deposit in the brain and can directly lead to neuroinflammation by activating nuclear factor-κB mediated secretion of pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin 6 that may reduce the BBB potency [13,17,24-29].

Figure 11. Cascade of events in Alzheimer Disease

From the genetic point of view it has been found that the distribution of cerebrovascular amyloid in AD varies with apoE genotype and specifically the increasing dose of apoE4 alleles has been associated with increased CAA. Understanding the cellular and molecular mechanism by which apoE genotype influences the pathogenicity of the disease process in AD individuals can act as important targets in developing new therapeutic interventions and diagnostic aids for AD.

Interactions of Aβ with human Vascular Smooth Muscle Cells has been found to significantly increase the activation of matrix metalloproteinase 2 (MMP2) via increasing the mRNA expression of membrane type 1 (MT1)-MMP, the primary MMP2 activator at the cell surface. MMP9 specifically has been found in postmortem AD tissue in significant amounts. Activated MMP9 can degrade basement membranes, extracellular matrix proteins and tight junction proteins subsequently damaging the integrity of the BBB and potentially leading to spontaneous cerebral hemorrhages. Similarly high levels of ROS in AD may damage proteins essentials for important neurovascular mechanisms. The breakdown of the BBB may in turn disrupt the normal transport of nutrients, vitamins and electrolytes across the BBB, which are essential for proper neuronal functioning. Therefore, therapies that reduce ROS, MMP2, and MMP9, or that block RAGE-Aβ interaction may offer potentially useful strategies to correct BBB dysfunction in AD [12,25,27-30].

Research data of epidemiological studies have shown controversial results as regards the association between APOE polymorphism and the rate of progression of cognitive decline in AD after onset. Some reports have suggested that homozygous APOE ε4 patients have more rapid cognitive and functional decline following clinical disease onset, but an MRI study on a large cognitively normal population showed rate of volume decrease of entorhinal cortex and hippocampus suggesting potential development. Thus though the role of APOE in the predisposition of AD is well established, still further studies are needed to understand the possible association of APOE with rate of AD progression. The cascade of events in Alzheimer disease is depicted in Fig.11.

3. Diagnosis of Alzheimer

Alzheimer's disease is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological

and neuropsychological features and the absence of alternative conditions. Advanced medical imaging technologies like computed tomography (CT) or magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to study the cerebral histo pathophysiological conditions of Alzheimer's disease. The Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association) have set up certain criteria for AD diagnosis which points to eight cognitive domains that are most commonly impaired in AD—memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities. The presence of such symptoms should be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD. A histopathologic confirmation including a microscopic examination of brain tissue is required for a definitive diagnosis. In addition to histopathologic confirmation, definite AD requires the clinical finding of dementia as determined by the Mini-Mental State Examination (MMSE) or other standardized neuropsychological testing; the examination must demonstrate deficits in two or more areas of cognition, with progressive memory loss in the absence of delirium. Assessment of intellectual functioning including memory testing can further characterize the state of the disease. The diagnosis can be confirmed with very high accuracy post-mortem when brain material is available and can be examined histologically. Neuropsychological screening tests can help in the diagnosis of AD. In the tests, people are instructed to copy drawings similar to the one shown in the picture, remember words, read, and subtract serial numbers. Neuropsychological tests such as the mini-mental state examination (MMSE), are widely used to evaluate the cognitive impairments needed for diagnosis. More comprehensive test arrays are necessary for high reliability of results, particularly in the earliest stages of the disease. Neurological examination in early AD will usually provide normal results, except for obvious cognitive impairment, which may not differ from that resulting from other diseases processes, including other causes of dementia. Interviews of family members and informations from caregivers about the patient's daily living abilities, the person's mental function are very important in this regard. Psychological tests for depression are also employed, since depression can either be concurrent with AD, an early sign of cognitive impairment, or even the cause [3,4,22].

With the advancements in imaging technology, computed tomography (CT) and magnetic resonance imaging (MRI) can be used to study the cortical atrophy, disproportionate volume loss in the medial temporal lobe structures and also normal age related changes that may be present at the early onset of disease. Functional imaging studies like the positron emission tomography (PET) and single-photon emission computed tomography (SPECT) scans, can be used as a diagnostic tool, which demonstrate hypometabolism and hypoperfusion, respectively, in the temporal-parietal regions bilaterally; for neuro imaging to confirm a diagnosis of Alzheimer's in conjunction with evaluations involving mental status examination (Fig.12). In a person already having dementia, SPECT appears to be superior in differentiating Alzheimer's disease from other possible causes, compared with the usual attempts employing mental testing and medical history analysis. Amyloid burden imaging compounds are under development. A new technique known as PiB PET has been developed that uses carbon-11 PET scanning for directly and clearly imaging beta-amyloid deposits in vivo using a tracer that binds selectively to the A-beta deposits with high levels of accuracy in predicting which people

with mild cognitive impairment will develop Alzheimer's disease within two years. Volumetric MRI can detect changes in the size of brain regions and measure the atropy in those regions in order to study the progress of AD. Amyloid imaging used in conjunction with other markers can serve as an important diagnostic tool [3,4].
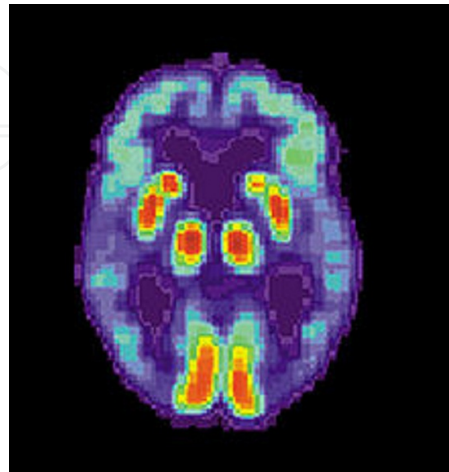

Figure 12. PET scan in the brain of Alzheimer patient (loss of function in temporal lobe)

Results of routine laboratory tests on chemistry panels, blood counts, metabolic panels (e.g., TSH) spinal fluid analyses, and inflammatory markers are all found to be within normal limits in patients with AD. Electroencephalographic (EEG) recordings are usually normal or show diffuse slowing in later stages of the disease. However it has been found that in AD patients it have been found that the levels of glutamate, creatinine, myo-inositol, N-acetyl aspartate are decreased as compared to normal people. Both decrease in N-acetyl aspartate/Creatinine ratio and decrease in hippocampal glutamate may be an early indicator of AD. Monitoring the level of blood dehydroepiandrosterone (DHEA) variations in response to an oxidative stress could be a useful proxy test for AD since experimental research data have shown that the subjects with Mild Cognitive Impairment did not have a DHEA variation, while the healthy controls did [3,4,8].

Another important marker of the disease is the analysis of cerebrospinal fluid for amyloid beta or tau proteins, both total tau protein and phosphorylated tau$_{181P}$ protein concentrations which predicts the onset of AD with a sensitivity of 94-100%. When used in conjunction with existing neuro imaging techniques, doctors can identify people with significant memory loss who are already developing the disease. Spinal fluid tests are commercially available, unlike the latest neuro imaging technology.

The differential diagnosis for AD is extensive and includes a multitude of neurodegenerative diseases that are associated with the development of dementia including Pick's disease, Lewy body disease, and other diseases such as vascular dementia and Creutzfeldt-Jakob disease. Most of these entities can be differentiated from AD by the clinical history and a careful examination. However, the challenge lies to test new hypotheses and not just to continue descriptive studies using better tools, technologies, increased parameters in CSF analysis and routine lab testing's, and more descriptions about the amount of amyloid in the brain [3,4].

4. Therapeutic interventions in Alzheimer

Virtually there are no proven modalities for cure of Alzheimer's disease; however there are treatment regimens that may improve symptoms and may even delay their progression in the early and middle stages of the disease, allowing patients to maintain certain daily functions for longer. Various country- or region-specific, evidence-based guidelines have been developed for the treatment of Alzheimer's disease. These make recommendations that vary according to available resources, funding practices, and local practice. In general, however, the guidelines provide recommendations regarding psychiatric management, psychosocial treatments, and the treatment of specific target symptoms. There are relatively few diseases that have been successfully prevented or even controlled without an understanding of specific etiology of the disease. Apart from the first line and second line FDA recommended synthetic drugs of choice in treating AD, some of the preventive strategies proved to be beneficial in AD include treatment of hypertension, omega fatty acid supplementation, physical activity and cognitive engagement.

5. Conventional therapeutic regimen in Alzheimer

From the point of conventional approach, major six classes of drugs are included in the treatment of AD: Acetylcholinesterase inhibitors (AChE-I), N-methyl-D-aspartate (NMDA) receptor antagonists, monoamine oxidase (MAO) inhibitors, antioxidants, metal chelators, anti-inflammatory drugs. AChE inhibitors are the first line agents for the treatment of mild to moderate AD. FDA approved five prescription drugs to control the symptoms of AD include: Donepezil, Galantamine, Rivastigmine, Tacrine among the AChE inhibitors and Memantine coming under NMDA receptor antagonists. However tacrine have been withdrawn due to the hepato toxicity effects. AChE inhibitors are prescribed to treat symptoms relating to memory, thinking, language, judgment and other thought processes. Cholinesterase inhibitors primarily act by increasing the levels of acetylcholine, the chemical messenger involved in memory, judgment and other thought processes. In AD the cells producing or using ACh are destroyed and thus less amount of ACh is available to carry messages. ACh is produced from acetyl-CoA and choline by cholineacetyltransferase which is released into the synaptic cleft and hydrolyzed by the actions of AChE to choline and acetic acid. This choline is reutilized in ACh synthesis. In the early stages of AD, the activity of AChE is found to be increased in the neuritic plaques and neurofibrillary tangles that accelerate aggregations of beta-amyloid. AChE inhibitors reversibly bind and block the activity of the enzyme acetyl cholinesterase that degrades ACh. AChE inhibitors block the actions of AChE thereby facilitating ACh neuro-transmission and reducing beta-amyloid burden [31-34].

Basing on the cholinergic theory, different classes of drugs have been developed to enhance cholinergic deficit in AD patients. Amongst them, AChE inhibitors block the activity of AChE enzyme to improve cognitive function, choline precursors like phosphatidylcholine improves the bioavailability of choline, ACh releasers enhance the release of ACh, M1 and M3 receptor

agonists mimic ACh on postsynaptic end terminal receptors, M2 and M3 receptor antagonists regulate ACh release via negative feedback, nicotinic agonists which would enhance ACh release.

AChE inhibitors are mostly well tolerated by the patients; however common side effects include nausea, vomiting, loss of appetite, increased frequency of bowel movements etc. Tacrine, the first FDA approved AD-drug, which inhibits AChE reversibly in a non-competitive manner is no longer in use due to severe side effects (hepatotoxicity) and short biological half life. Donepezil hydrochloride is the second drug of choice approved by USFDA for treatment of mild to moderate AD. This drug is a centrally acting, reversible and non-competitive AChE inhibitor having an N-benzylpiperidine and an indanone moiety which shows longer and more selective action. However it also suffers from the side effects of GI disturbances, nausea, vomiting, headache etc [31,33].
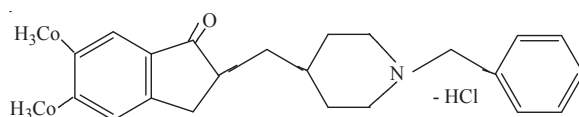

Figure 13. Donepezil hydrochloride

Galantamine reversibly inhibits AChE in a competitive manner and also acts on nicotinic acetylcholine receptors, beneficial for cognitive and non-cognitive AD symptoms. Results of clinical trials have reported this drug to be 50 times more potent against human AChE than butyrylcholinesterase at therapeutic doses. With escalations in drug doses some of the notable adverse effects include vomiting, nausea, diarrhoea etc. Rivastigmine is a reversible carbamate AChE inhibitor that interacts preferentially with acetylcholinesterase G1 with high brain selectivity; this drug has been approved in at least 40 countries around the world. Rivastigmine has the ability to inhibit the activity of butyrylcholinesterase. It binds to both the esteratic and ionic locations of AChE but dissociates at a much slower rate than AChE. Metrifonate, a precursor to the active pseudo irreversible AChE inhibitor DDVP (2,2-dichlorovinyl dimethyl phosphate) rapidly enters the brain with a longer plasma half life than donepezil but shows side effects of diarrhea and muscular cramps and hence could not achieve the market due to muscular weakness. There are certain AChE inhibitors of natural origin finding its use in AD. Physostigmine, a parasympathomimetic plant alkaloid isolated from the seeds of *Physostigma venenosum* have the ability to cross the BBB, having role in cholinergic transmission, can stimulate indirectly both nicotinic and muscarinic receptors. However physostigmine also inhibits another enzyme butyrylcholinesterase which has a role in AD and some of the adverse effects of this drug like nausea, vomiting, headache, diarrhea are attributed to its inhibitory actions on butyrylcholinesterase. Despite of the advantage to cross the BBB, the short half life, narrow margin of therapeutic index has restricted its potentiality. Galanthamine is an alkaloid isolated from *Galanthus nivalis* with competitive reversible AChE inhibitory activity. Galanthamine shows dual mechanism of action, AChE inhibition and allosteric modulation of nicotinic acetyl choline receptors. This drug has 10 fold selectivity for AChE than butyrylcholinesterase. Alpha-7 nicotinic acetylcholine receptors have a role in beta-amyloid mediated neurotoxiciy

and since galanthamine can modulate nicotinic acetylcholine receptors it is suggested to prevent beta-amyloid mediated neurotoxicity. Huperzine A, an alkaloid drug isolated from club moss (*Huperzia serrata*) is claimed to show neuroprotective properties with significant improvements in cognitive function and results of clinical trials have shown this drug to be free from unexpected toxicities. This drug has attracted the attention of the scientists due to its strong AChE activities; (-)-huperzine A, a natural isomer have shown strongest dose dependent inhibitory activity against AChE, in comparison to commercially available synthetic drugs like donepezil, tacrine etc [31-33].

Memantine is an uncompetitive low-to-moderate affinity *N*-methyl-D-aspartate (NMDA) receptor antagonist that regulates glutamate activity. Glutamate plays an essential role in learning and memory by triggering NMDA receptors to let a controlled amount of calcium into the nerve cell. This calcium creates the chemical environment required for information storage. Excess glutamate on the other hand, over stimulates NMDA receptors so that they allow too much calcium into nerve cells leading to disruption and death of these cells. Memantine protects cells against excess glutamate by partially blocking NMDA receptors. It's a recently FDA approved NMDA antagonist for the treatment of cognition in moderate to severe Alzheimer's disease, having a half life period between 3-7 h and free from harsh adverse side effects. Memantine can be administered with AChE inhibitors. However FDA did not approve Memantine for mild AD. Results of clinical trials have shown small but statistically significant improvements in mental functions and ability to perform daily activities in AD patients [34,35].
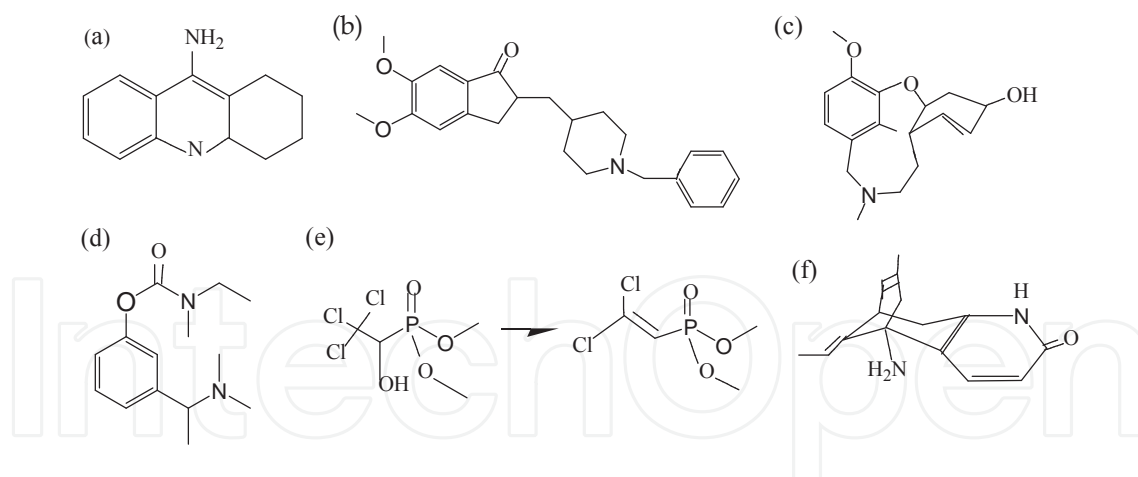

Figure 14. AChE inhibitors (a) Tacrine (b) Donepezil (c) Galantamine (d) Rivastigmine (e) Metrifonate (f) Huperzine

Several metal species like iron, zinc, copper, aluminum are reported to induce beta amyloid aggregation and neurotoxicity in the brain of AD patients; results of structural evidences showing interrelations between aluminum and Abeta, presence of iron and zinc in abnormal high concentrations in AD patients have triggered the idea of using metal chelators as therapeutic targets in the treatment of AD. Desferrioxamine (DFO) and Clioquinol are clinically proven metal chelators used to treat AD patients. DFO chelates with metal ions or aluminium and reduces its neocortical concentrations thereby delaying the progression of
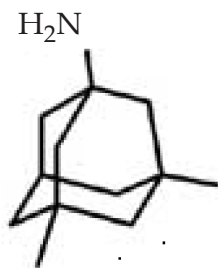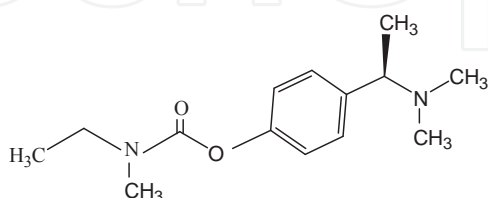
Figure 15. Memantine
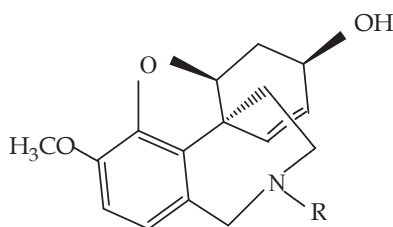

Figure 16. Rivastigmine

Figure 17. Galanthamine

dementia associated with AD and shows behavioral improvements. However the proper mechanism of action is not yet revealed. Transition metals like copper and zinc are found to be in high concentrations in the neo-cortical regions of the AD patients and these metals are mostly aggregated in the neurotic plaques potentiating beta amyloid aggregation and neuro-toxicity. Clioquinol chelates with these metals and reduces the beta amyloid aggregation in the brain, thus finding use as a therapeutic target in treating Alzheimer [35].

From the pathology of Alzheimer it is clear that several neurotransmitter systems, especially those regulating dopamine, serotonin, acetylcholine has a role in it. With the dysfunction of the dopaminergic system, there is increase in activity of type B monoamine oxidase, the enzyme responsible for degradation of dopamine. The increase in monoamine oxidase level is prominent in the brain platelets contributing to the severity of dementia. The drug Selegiline reversibly inhibits MAO-B; moreover it has a potent anti oxidative effect over the neurons of the brain and also protect against glutamate-receptor-mediated toxicity. Apart from MAO inhibition selegiline has a potent action in the recovery of damaged neurons involving a number of mechanisms like stimulation of neurite outgrowth, stimulation of gene expression in pre apoptotic neurons or stimulation of cytokine biosynthesis. Rasagiline, structurally similar to selegiline also shows neuro protective activities and is found to be ten times more
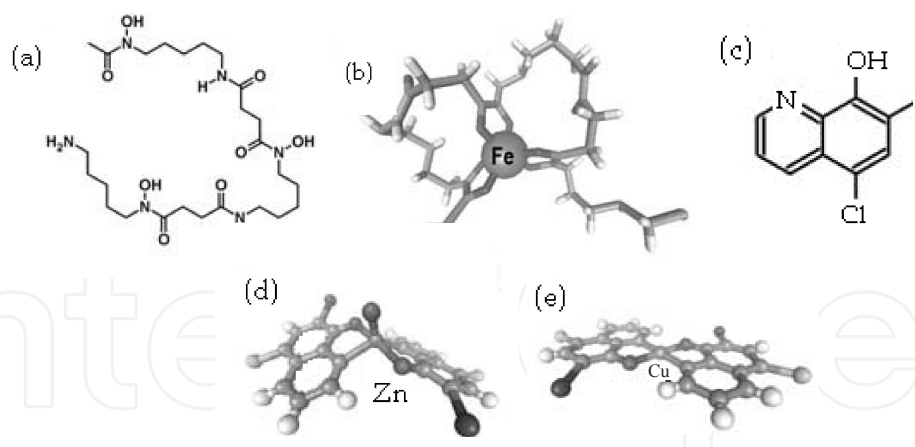
Figure 18. (a) Desferrioxamine (b) Ferrioxamine B (c) Clioquinol (d) Clioquinol Zn complex (e) Clioquinol Cu complex

active in inhibition of MAO-B. The propargylamine moiety in rasagiline is responsible for neuro protective activities. The drug Ladostigil, is the result of combination of active compounds from rasagiline (MAO-B inhibitor, neuroprotector) and rivastigmine (AChE inhibitor) thus finding application as a effective therapeutic agent in treating AD [33-35].
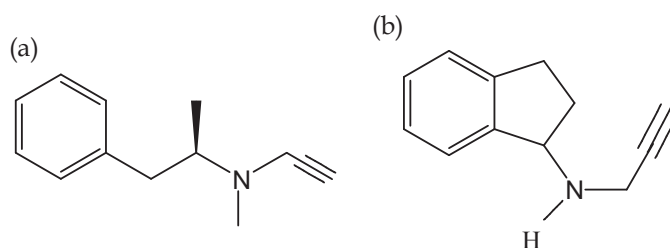

Figure 19. Monoamine oxidase inhibitors (a) Selegiline (b) Rasagiline

Oxidative damage to neurons has a significant role in the pathogenesis of AD; hence antioxidant therapy to prevent oxidative injury can be effective in preventing or retarding the progress of AD. Extracts from *Ginko biloba* named as Egb761 have been found to show cognitive improvement in AD patients and in those with multi-infarct dementia. Similarly Melatonin is found to have antiamyloidogenic activities and is found to reduce neuronal damage caused by reactive oxygen species in AD patients. Antioxidant therapy with vitamin E though reported in some cases but it does not improve cognitive impairment and its therapeutic use has not been established. Clinical trials with Idebenone, a co-enzyme Q10 analog have been found to attenuate Abeta-induced neurotoxicity and cognitive impairments. Dehydroevodiamine hydrochloride (DHED), a compound extracted from *Evodia rutaecarpa* showed AChE inhibitory activities, DHED protects neurons against hydrogen peroxide and glutamate. Moreover DHED decreases reactive oxygen species production and cell death induced by Abeta and carboxyterminal peptides of amyloid precursor proteins, thus improving cognitive impairments in AD. Metalloporphyrin antioxidants have been found to delay neuronal death resulting from increased mitochondrial oxidative stress; Mn-salen complexes have been found to be efficacious against oxidative stress [35].
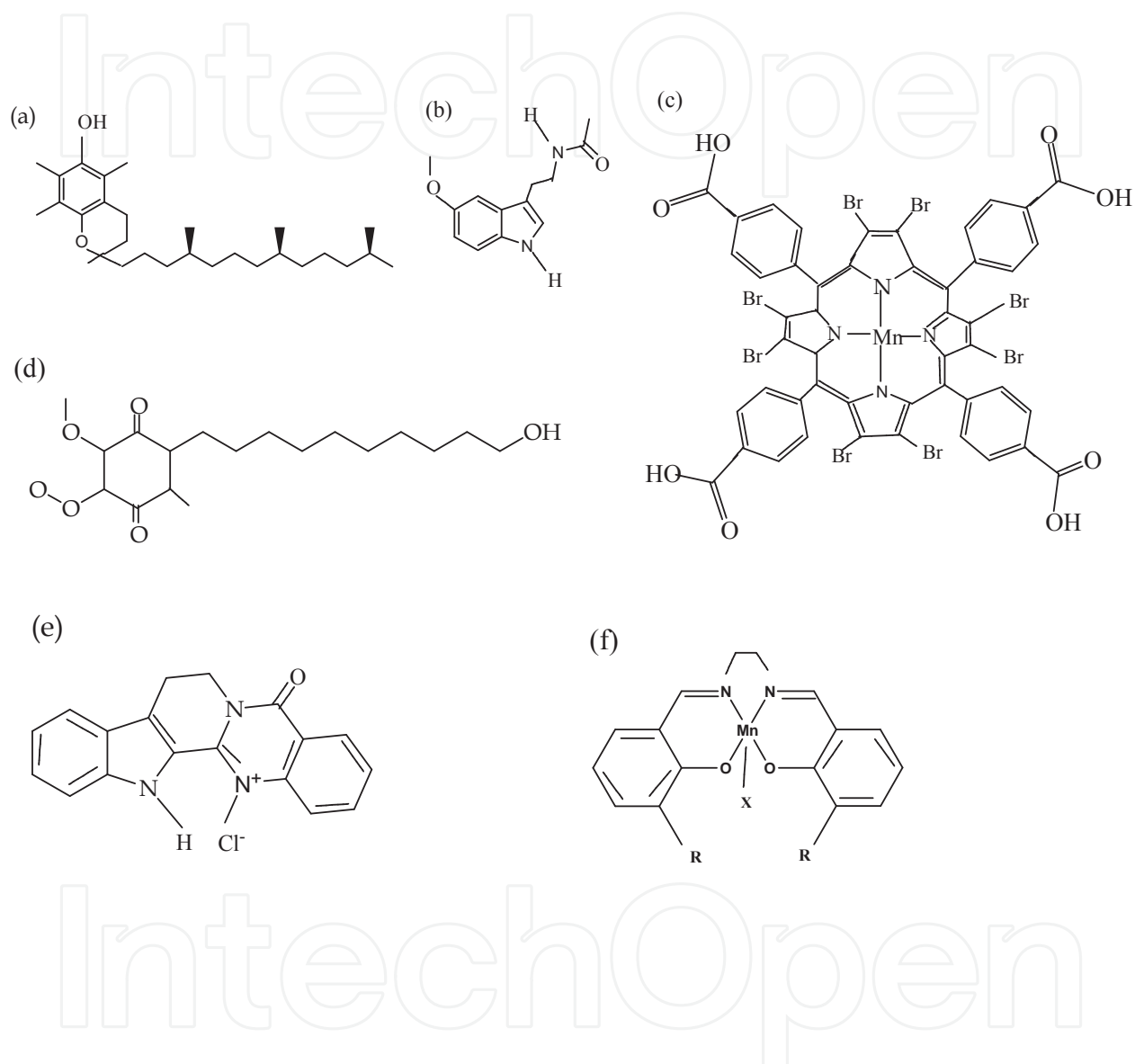
Figure 20. Antioxidants: (a)alpha tocopherol (b) Melatonin (c) Manganese (ш) beta-octabromo-meso tetrakis (4-carboxy phenyl) porphyrin (d) Idebenone (e) Dehydroevodiamine (f) Mn-salen

In AD, neuronal destruction is due to inflammation around Abeta plaques. Drugs under the NSAID groups have anti-inflammatory actions, and found to inhibit cyclooxygenase-1 and cyclooxygenase-2 which are responsible for the oxidation of arachidonic acids to prostaglandins; however due to adverse effects of some NSAIDs on cardiovascular systems, these group of drugs have not found routine use in AD treatment.

Figure 21. NSAIDs (a) Ibuprofen (b) Aspirin (c) Naproxen (d) Flubiprofen

6. Omega fatty acids in treating Alzheimer

Polyunsaturated fatty acids or PUFA have significant biological roles in cellular structure and function. PUFA are the key components of phospholipids, comprising cellular and intracellular membranes. They govern the growth and vitality th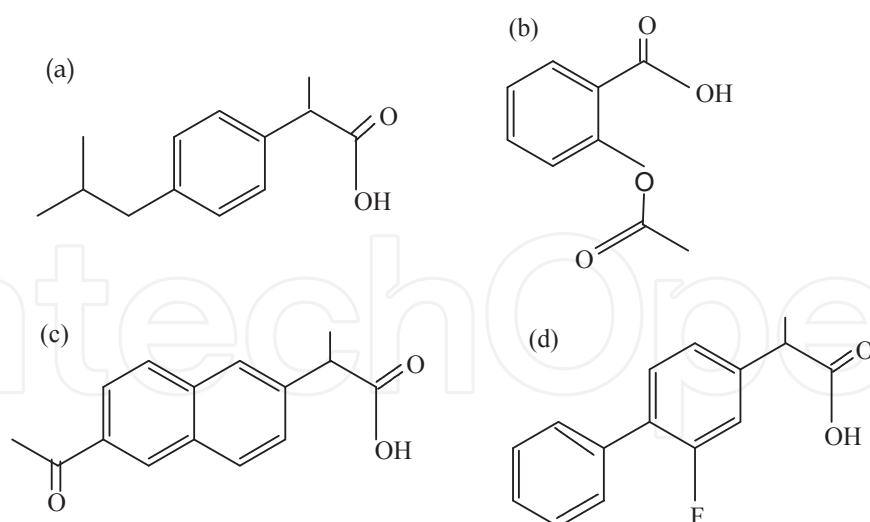rough oxidation (metabolism of food to produce energy required for cellular processes), chemical activities and transportation. In addition to being the structural materials for bio-membranes, PUFA are required for generating and propagating electrical impulses; synthesis of eicosanoids, important signaling hormones with numerous complex functions. Amongst its wide range of actions include anti-inflammatory, anti-thrombotic and vasodilatory properties, balancing and counteracting pro-inflammatory, vasoconstrictor actions of eicosanoids; the cardiovascular benefits of n-3 PUFA are largely attributed to these eicosanoid properties, and at the same time having significant roles in brain function. Polyunsaturated fatty acids like alpha linoleic acids (ALA), linolenic acids (LA), eicosapentaenoic acids (EPA) or docosahexaenoic acids (DHA) are not synthesized in the body and hence must be supplied in the diet [36].

Lipids constitute approximately sixty percent of the dry weight of the brain. DHA and Arachidonic acids (AA) are the most highly concentrated PUFAs present in neural phospholipids, including sub cellular membranes. DHA is particularly concentrated at neural synapses, retina, brain and nervous system. Though there is a predominance of omega-6 fatty acids in circulation, in contrast to omega-3 fatty acids, however DHA predominates in these vital structures. The amount of DHA levels in the neural phospholipids depend on the amount of dietary intake rich in omega-3 fatty acids. Clinical studies have shown that insufficient omega-3 PUFA during early neural development shows decreased DHA content in the brain.

The n-3 PUFAs have significant biological mechanisms in brain function. Neurotransmitters such as dopamine and serotonin have a role in mental illness, research data have focused on

associations between PUFA and central nervous system activity. Levels of n-3 PUFA have been associated with monoaminergic neurotransmitter levels. There are indications that PUFA are involved in the synthesis and activities of brain peptides, which are involved in modulating the activities of neurotransmitters. Evidence points to the role of eicosanoids in healthy brain functioning, and phospholipid membranes in neural cell signaling. Results of animal studies have shown that, n-3 deficiency is found to reduce phosphatidylserine (PS) levels in the brain, which is thought to play an important function in neural signaling activities. In alcoholics, DHA deficiency has predicted reduced 5-hydroxyindoleacetic acid (5-HIAA) concentrations in cerebrospinal fluid, an indicator of low serotonin turnover rate in the frontal cortex. Studies have further indicated that n-3 PUFA may affect receptor properties or activation of signal transduction by receptors. Electrical impulse conduction is dependent on the exchange of ions through the cell membrane, which relies on the fluidity and physiological structure of cell membranes. Furthermore, n-3 PUFA are also thought to influence gene expression of a range of enzymes required for important neural functions including synaptic transduction, ion channel formation, energy metabolism and formulation of proteins vital for brain development and function. Regular delivery of oxygen and nutrients via the blood is also vital for optimal brain function, and psychopathology is associated with both reduced cerebral blood flow and transportation of glucose, the brain's primary energy source, to brain regions as required. In this regard, n-3 PUFA are associated with production of nitric oxide, as well as anti-inflammatory and vasodilatory eicosanoids (notably PGI_2), and are known to assist in endothelial-dependent vasodilatation. They have also been associated with substantially increased transport of glucose across the blood-brain barrier. Therefore, it is also possible that their primary influence on brain function includes improved cerebral blood flow and blood-brain barrier integrity. This idea is supported by the fact that there's a high co-morbidity between cardiovascular disease and psychopathology, having a common underlying vascular pathology which can be mediated by lifestyle factors such as suboptimal levels of n-3 PUFA [36].

The mechanisms by which ω-3 fatty acids could interfere in AD patho physiologic features are not clear, but since anti-inflammatory effects are an important property of these fish oils rich in PUFA, they are applicable for AD also. Epidemiologic evidences have shown that administration of ω-3 fatty acid in patients with mild to moderate AD did not delay the rate of cognitive decline according to the MMSE or the cognitive portion of the Alzheimer Disease Assessment Scale but, positive effects were observed in a small group of patients with very mild AD. Increased intake of the ω-3 polyunsaturated fatty acids (primarily eicosapentaenoic acid (EPA), 20:5ω-3, and docosahexaenoic acid (DHA), 22:6ω-3) may be beneficial in reducing risk for AD. Increased fish consumption and diets supplemented with omega-3 fatty acids are found to exhibit a protective effect, cognitive improvement and enhancement of learning abilities. Animal studies on transgenic mouse model of AD with DHA-enriched diets significantly reduced total β-amyloid by 70% when compared with diets low in DHA or control chow diets [ext-link ext-link-type="bibr" rid="REF-NOC60062-9 REF-NOC60062-10"/].

However these findings cannot serve as a basis for general recommendations for treatment of AD with dietary DHA-rich fish oil preparations. Rather, larger cohort's studies in patients with mild cognitive impairment, including those at risk for AD are needed to further explore the potentiality of the ω-3 fatty acids in halting initial progression of the disease [36].

7. In silico drug design in Alzheimer

Though a number of FDA approved drugs are currently available for the treatment of Alzheimer but there are no such effective treatments to stop the insidious nerve cell death process once the disease begins. Available drugs can manage and ease some of the symptoms of the disease but the progression of the disease can in no way be slowed down by these treatments. In AD patients there is very less production of neurotransmitter acetylcholine due to the progressive damage of the cells producing acetylcholine. Most of the FDA approved drugs aim to prevent the breakdown of acetylcholine by inhibiting the enzyme acetyl cholinesterase. But in AD due to rapid destruction of nerve cells, the acetylcholine produced even though protected from further breakdown but the amount produced is significantly insufficient to transmit messages between the brain cells. This fact necessitates further new drug development.

In contrast to traditional drug discovery, "Rational Drug Design'' has been found to be a more deterministic approach where the first necessary step is the identification of the molecular target critical to the disease process and then determine the molecular structure of the target molecule. In-silico drug design approach makes use of Computer Assisted Drug Design (CADD) tools to find a ligand (putative drug) that will interact with a receptor which represents the 'target site'. A ligand can bind to the receptor either by hydrophobic, electrostatic or hydrogen bonding interactions and solvation energies of the ligand and receptor sites are the important facts to be considered in this case.

The basics behind the pathology of AD is the presence of neuritic plaques containing amyloid-β-peptide (Aβ) and intra neuronal accumulation of tubule associated 'tau' protein. In order to target therapeutic strategies basing on molecular mechanisms for AD, new drug entities can be developed that will act directly on the Aβ or the amyloid precursor protein (APP) processing which may include vaccination with Aβ peptide, Aβ passive immunization. However clinical trials with a vaccine made of synthetic Aβ 1-42 showed the lateral development of encephalitis and hence the trial was put on hold though the concept exists. Passive immunization can be obtained by monoclonal antibodies against Aβ. New anti-amyloid agents to prevent fibrillizations can be designed by detailed characterizations of the proto fibrils and fibril formations. Another lucrative approach is to target the APP processing where the three major enzymes are to be targeted: alpha secretase, beta secretase and gamma secretase, the basic aim is to increase the alpha cleavage or to decrease the beta and gamma secretase activities. Nerve growth factors and neurotrophines can also act as important therapeutic targets. Growth factor gene therapy (though under clinical trial) where patient's fibroblasts transfected with NFG and transplanted to brain are expected to be effective in case of severe AD [37].

In in -silico drug design approach, computational docking techniques can be used to develop an effective drug to prevent the progression of Alzheimer disease. Here the 'TARGET' is the amyloid precursor protein (APP) and the 'LEAD COMPOUND' is the protease enzyme. By the aid of database search tools like FASTA, BLAST in Swissport, proteins having protease activity for b-APP can be identified. Next step is to identify the protease enzyme that cleaves the b-APP so as to prevent the formation of beta-amyloid peptide. Structural informations on

b-APP is available from PDB (Protein Data Bank) with ID 1RW6. Soft wares like PASS, CASTp provides information about the active site for b-APP. Enzyme modeling can be done using packages like Swiss Model, Modeller etc. Specific interactions of these lead compounds with the active site of b-APP can be studied by docking programs like DOCK, AUTODOCK etc. The most effective protease enzyme with minimum energy conformation can be identified by the above procedure which will act as the potential drug in treating Alzheimer. Use of computational docking techniques help to explore a large number of compounds, study the binding characteristics of 'hits' and is found to be effective in reducing the time and monetary expenditure as associated with traditional drug development techniques [38].

8. Non-pharmacological approach

Virtually at this point of time there is no cure for Alzheimer. But apart from therapeutic interventions, attempts can be done to manage the disease and treat the symptoms by the care givers in a non-pharmacologic manner. Along with medications, physical exercise, social involvement as well as proper nutrition are essential in treating the symptoms of AD. The goal of non-pharmacologic treatment in AD though sounds simple but clinically remains a challenge where the care giver has a vital role to play; first thing is to provide a calm structured environment where the comfort, dignity of the afflicted person is maintained and the patient remains functioning as long as possible [39-41]. For AD patients the environment should be so arranged that maximize use of cognitive capacities of AD patients that are intact and compensate for those cognitive capacities that decline. Treatment in a non-pharmacologic manner aims to improve the quality of life to treat the disease symptoms. It is not a simple task for a care giver to increase functional independence, reduce the need for psychoactive medications, prolong life, reduce the need for restraints, reduce acute hospital admissions, reduce depression and improve morale. Alzheimer begins in the medial temporal lobe and spreads to other parts of the brain slowly destroying parietal, temporal and frontal lobes, cingulated cortex, hippocampus, amygdale, damaging the tempero-parieto-occipital association cortex leading to memory dysfunction, emotional disturbances, personality changes, visual, language and movement disorders. Due to damages in the frontal lobes AD patients will have difficulty in performing daily tasks; with the gradual progression of the disease hallucinations, delusions, paranoia, agitation, panic and denial are seen among the afflicted. Among the non-pharmacologic treatment domains include: properly mapped physical environment that removes fear and promotes safety, induce a sense of positive attitude or emotion among the afflicted persons by the care giver while helping in daily activities by helping them to perform the task but not to do the total task for them and make them even more dependent; change negative emotions and promote feelings of purpose and accomplishment. While treating AD patients in non-pharmacologic manner one of the major corner stone is how we understand the afflicted person and help him to understand himself [42-44]. The care giver must change his/her behavior & environment in order to change the behavior of the patient. A person in middle stage of AD should never be attempted to bring back to the realistic world but reduce his fear in all possible stages and help him to move into his sense of the

world. Due to sensory impairment and lack of receptive and expressive language abilities non-verbal perceptual inputs which replace words like familiar music, known food smell, and known touch may be used and afflicted can be communicated with a look, tone or a hug to induce a feeling of care and safety. In case of negative behavior and aggression the triggering agent should be identified and eliminated. The ultimate outcome of such a treatment approach is to slow the rate of disease progression, delay institutionalization, improve the quality of life and reduce the need for medication [39]. Below in fig.22 a specially designed room is shown for sensory integration therapy.

Figure 22. Specially designed room for sensory integration therapy (Snoezelen); an emotion oriented psychosocial intervention for people with dementia

9. Conclusions

There is an increasing emergency in finding a prevention or treatment for AD and dementia because of the aging of the populations and realizing the severity and complications associated

with this deadly disease. Fortunately, AD and dementia research is now at a progressing stage. Availability of improved medical imaging technologies like CT scan, MRI, PET, use of biomarkers helps in early diagnosis of the disease, its progression and severity. Furthermore, pharmacological and non-pharmacological therapies could be directly tested both to prevent and delay the progression of amyloid in the brain and effects on brain morphology and cognitive decline. Pharmacological therapies that could delay the onset of dementia for several years could result in a substantial reduction in the prevalence of AD because the patients will die of another cause before they develop AD. A second and far more important approach will be the application of these new technologies to understand the etiology of AD. The identification of specific etiological factors is much more likely in the long term to have a major impact on the incidence, prevalence, and disability because of AD and dementia. Proper understanding the etiology of the disease is essential to develop hypothetical treatment approaches which can be further clinically established. Basing on in-silico drug design approaches it is essential to understand the molecular mechanisms of APP processing, role of folate and homocysteine in neuronal homeostasis. Main target should be to develop novel therapeutic agents via cost effective, eco-friendly methodologies. Along with specific drug therapy, lifestyle interventions and environmental variables are also to be targeted to reduce the incidence of AD. However in case of new drug research in Alzheimer, ability to utilize the technologies, clinical skills and financial resources to support research studies are of vital importance.

Author details

Analava Mitra* and Baishakhi Dey

*Address all correspondence to: analavamitra@gmail.com

School of Medical Science and Technology, IIT Kharagpur, India

References

[1] Basics of Alzheimer diseaseAlzheimer association (2011).

[2] Alzheimer Disease facts and FiguresAlzheimer's & Dementia. Alzheimer association (2011). , 7(2), 1-68.

[3] Yamasaki, T, Muranaka, H, Kaseda, Y, Mimori, Y, & Tobimatsu, S. Understanding the pathophysiology of Alzheimer disease and mild cognitive impairment: A mini review on fMRI and ERP studies. Neurology Research International (2011). , 20(12), 1-10.

[4] Gary, S. W. Barry RPV, Buckholtz PP, Dekosky NS, Ferris ST et al. Diagnosis and treatment of Alzheimer disease and related disorders: consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer Association and the

American Geriatrics Society. Journal of the American Medical Association (1997). , 278(16), 1-9.

[5] Verghese, P. B, Castellano, J. M, & Holtzmann, D. M. Roles of Apolipoprotein E in Alzheimer's disease and Other Neurological Disorders. Lancet Neurology (2011). , 10(3), 241-252.

[6] Kuller, L. H, & Lopez, O. L. Dementia and Alzheimer's disease: A new direction. The 2010 Jay L. Foster Memorial Lecture. Alzheimer's Dement (2011). Doi:j.jalz. 2011.05.901, 7(5), 540-550.

[7] Guidelines for Alzheimer Disease ManagementCalifornia Workgroup on Guidelines for Alzheimer's disease Management (2008).

[8] Winslow, B. T, Onysko, M. K, Stob, C. M, & Hazlewood, K. A. Treatment of Alzheimer Disease. American Family Physician website www.aafp.org/afp.

[9] Alzheimer's disease and Dementia-A Growing ChallengeNational Academy on an Aging Society (2000).

[10] Bell, R. D, & Zloklovic, B. V. Neurovascular mechanisms and blood brain barrier disorder in Alzheimer's disease. Acta Neuropathologica (2009). Doi:s00401-009-0522-3, 118(1), 103-113.

[11] Alonzo, N. C, Hyman, B. T, Rebeck, G. W, & Greenberg, S. M. Progression of cerebral amyloid angiopathy: accumulation of amyloid-beta40 in affected vessels. Journal of Neuropathology and Experimental Neurology (1998). Doi:, 57, 353-359.

[12] Asahina, M, Yoshiyama, Y, & Hattori, T. Expression of matrix metalloproteinase-9 and urinary-type plasminogen activator in Alzheimer's disease brain. Clinical Neuropathology (2001). , 20, 60-63.

[13] Attems, J, Jellinger, K. A, & Lintner, F. Alzheimer's disease pathology influences severity and topographical distribution of cerebral amyloid angiopathy. Acta Neuropathologica (2005). Doi:s00401-005-1064-y., 110, 222-231.

[14] Attems, J, Quass, M, Jellinger, K. A, & Lintner, F. Topographical distribution of cerebral amyloid angiopathy and its effect on cognitive decline are influenced by Alzheimer disease pathology. Journal of Neurological Sciences (2007). Doi:10.1016/j.jns. 2007.01.013., 257, 49-55.

[15] Bailey, T. L, Rivara, C. B, Rocher, A. B, & Hof, P. R. The nature and effects of cortical microvascular pathology in aging and Alzheimer's disease. Neurological Research (2004). Doi:, 26, 573-578.

[16] Begley, D. J, & Brightman, M. W. Structural and functional aspects of the blood-brain barrier. Progress in Drug Research (2003). , 61, 39-78.

[17] Bell, R. D, Sagare, A. P, Friedman, A. E, et al. Transport pathways for clearance of human Alzheimer's amyloid beta-peptide and apolipoproteins E and J in the mouse

central nervous system. Journal of Cerebral Blood Flow and Metabolism (2007). , 27, 909-918.

[18] Corder, E. H, Saunders, A. M, Strittmatter, W. J, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. (1993). Doi:10.1126/science.8346443., 261, 921-923.

[19] Deane, R, Bell, R. D, Sagare, A, & Zlokovic, B. Z. Clearance of amyloid-beta peptide across the blood-brain barrier: implications for therapies in Alzheimer's disease. CNS and Neurological Disorders- Drug Targets (2009). Doi:

[20] Deane, R. Du Yan S, Submamaryan RK, et al. RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. Nature Medicine (2003). Doi:nm890., 9, 907-913.

[21] Deane, R, Wu, Z, Sagare, A, et al. LRP/amyloid beta-peptide interaction mediates differential brain efflux of Abeta isoforms. Neuron. (2004). Doi:10.1016/j.neuron. 2004.07.017., 43, 333-344.

[22] Drzezga, A, Lautenschlager, N, Siebner, H, et al. Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. European Journal of Nuclear Medicine and Molecular Imaging (2003). Doi:s00259-003-1194-1., 30, 1104-1113.

[23] Ervin, J. F, Pannell, C, Szymanski, M, Welsh-bohmer, K, Schmechel, D. E, & Hulette, C. M. Vascular smooth muscle actin is reduced in Alzheimer disease brain: a quantitative analysis. Journal of Neuropathology and Experimental Neurology (2004). , 63, 735-741.

[24] Grabowski, T. J, Cho, H. S, Vonsattel, J. P, Rebeck, G. W, & Greenberg, S. M. Novel amyloid precursor protein mutation in an Iowa family with dementia and severe cerebral amyloid angiopathy. Annals of Neurology (2001). Doi:10.1002/ana.1009., 49, 697-705.

[25] Jung, S. S, Zhang, W, & Van Nostrand, W. E. Pathogenic A beta induces the expression and activation of matrix metalloproteinase-2 in human cerebrovascular smooth muscle cells. Journal of Neurochemistry (2003). Doi:10.1046/j.1471-4159.2003.01745.x., 85, 1208-1215.

[26] Parks, J. K, Smith, T. S, Trimmer, P. A, & Bennett, J. P. Jr, Parker WD., Jr Neurotoxic Abeta peptides increase oxidative stress in vivo through NMDA-receptor and nitric-oxide-synthase mechanisms, and inhibit complex IV activity and induce a mitochondrial permeability transition in vitro. Journal of Neurochemistry (2001). Doi:10.1046/j. 1471-4159.2001.00112.x., 76, 1050-1056.

[27] Preston, S. D, Steart, P. V, Wilkinson, A, Nicoll, J. A, & Weller, R. O. Capillary and arterial cerebral amyloid angiopathy in Alzheimer's disease: defining the perivascu-

lar route for the elimination of amyloid beta from the human brain. Neuropathology and Applied Neurobiology (2003). Doi:10.1046/j.1365-2990.2003.00424.x., 29, 106-117.

[28]   Rosenberg, G. A. Matrix metalloproteinases and their multiple roles in neurodegenerative diseases. Lancet Neurology (2009). Doi:S1474-4422(09)70016-X., 8, 205-216.

[29]   Sagare, A, Deane, R, Bell, R. D, et al. Clearance of amyloid-beta by circulating lipoprotein receptors. Nature Medicine (2007). Doi:nm1635., 13, 1029-1031.

[30]   Ushijima, Y, Okuyama, C, Mori, S, Kubota, T, Nakai, T, & Nishimura, T. Regional cerebral blood flow in Alzheimer's disease: Comparison between short term and long term donepezil therapy. Annals of Nuclear Medicine (2006). , 20(6), 425-429.

[31]   Sugimoto, H, Yamanishi, Y, Limura, Y, & Kawakami, Y. Donepezil hydrochloride (E2020) and other Acetylcholinesterase Inhibitors. Current Medicinal Chemistry (2000). , 7-303.

[32]   Orhan, G, Orhan, I, Oztekin, N. S, Fikri, A. K, & Sener, B. Contemporary Anticholinesterase Pharmaceuticals of Natural Origin and their Synthetic Analogues for the Treatment of Alzheimer Disease. Recent Patents on CNS Drug Discovery (2009). , 4, 43-51.

[33]   Woodruff Pak DS, Vogel RW, Wenk GL. Mecamylamine Interactions with Galantamine and Donepezil: Effects on Learning, Acetylcholinesterase and Nicotinic Acetylcholine Receptors. Neuroscience (2003). , 117-439.

[34]   Sugimoto, H. Structure-activity relationships of acetylcholinesterase inhibitors: Donepezil hydrochloride for the treatment of Alzheimer's disease. Journal of Pure and Applied Chemistry (1999). , 71(11), 2031-2037.

[35]   Suh, W. H, Suslick, K. S, & Suh, Y. H. Therapeutic agents for Alzheimer Disease. Current Medicinal Chemistry-Central Nervous System Agents (2005). , 5-259.

[36]   Sinn, N, & Milte, C. Howe PRC. Oiling the Brain: A Review of Randomized Controlled Trials of Omega-3 Fatty Acids in Psychopathology across the Lifespan. Nutrients (2010). , 2(2), 128-170.

[37]   Religa, D, & Winblad, B. Therapeutic strategies for Alzheimer Disease based on new molecular mechanisms. Acta Neurobiol Express (2003). , 63-393.

[38]   Kandavelmani, A. Alzheimer Disease: In silico Drug Design-An Endeavour. Bioinformatics India (2005). , 3(2), 25-28.

[39]   Zeisel, J, & Raia, P. Non-pharmacological Treatment for Alzheimer Disease: A mind-brain approach. American Journal of Alzheimer Disease and Other Dementias (2000). , 15(6), 331-340.

[40]   Weiner, M. F, & Gray, K. F. Balancing Psychosocial and Psychopharmacologic measures in Alzheimer Disease. The American Journal of Alzheimer's Care and Related Disorders and Research (1994). , 9(4), 6-12.

[41] Martichuski, D. K, & Bell, P. A. Treating excess disabilities in special care units: A Review of interventions. The American Journal of Alzheimer's Care and related disorders and Research (1993). , 5-8.

[42] Reisberg, B, Kenowsky, S, & Franssen, E. Souren LEM, Shulman E, Steinberg G, Aronstein Z, Auer S. Slowing the progression of Alzheimer Disease: Towards a Science of Alzheimer Disease care. Caring (1996). , 2(2), 2-4.

[43] Morton, I, & Bleathman, C. The effectiveness of validation therapy in dementia: a pilot study. International Journal of Geriatric Psychiatry (1991). , 6-327.

[44] Sclan, S, Saillon, A, Franssen, E, et al. The Behavioral Pathology in Alzheimer's disease Rating Scales (BEHAVE-AD): Reliability and Analysis of symptom category scores. International journal of Geriatric Psychiatry (1996). , 11-819.