Review Article

Alzheimer's Disease- Pharmacotherapeutic Interventions

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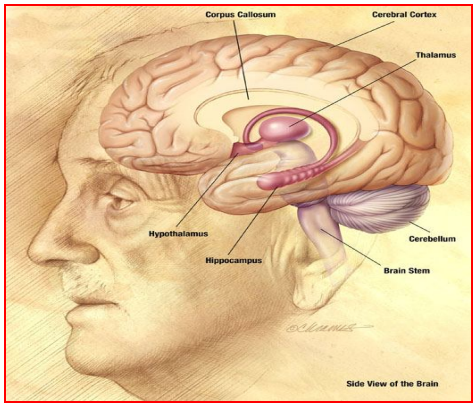
ABSTRACT

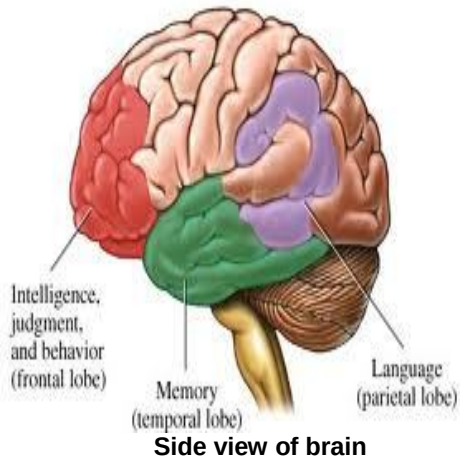
Alzheimer's disease (AD) is a neurodegenerative disorder. Neurodegeneration is defined as a progressive loss of structure or functioning of neurons including the death of neurons. Risk factors for AD are Hypertension, Elevated low density lipoprotein cholesterol, Low high density lipoproteins and Diabetes. Two microscopic features are characteristic of the disease namely Extracellular amyloid plaques and Intraneuronal neurofibrillary tangles (NFTs). The definitive diagnosis of AD is made by examining the brain tissue. Patients with suspected AD should have a history and physical examination with appropriate neurologic and psychiatric examinations. The primary goal of treatment in AD is to maintain patient functioning as long as possible. Secondary goals are to treat the psychiatric and behavioral sequelae. Current pharmacotherapeutic interventions are primarily symptomatic attempts to improve or maintain cognition.

Keywords: Alzheimer's disease, Intraneuronal neurofibrillary tangles, Neurodegeneration.

INTRODUCTION

It is a neurodegenerative disorder. Neurodegeneration is defined as a progressive loss of structure or functioning of neurons including the death of neurons[1].The neurodegenerative disorders include, Alzheimer's disease (AD) - cholinergic neurons degeneration, Parkinsonism disease- dopaminergic neurons degeneration, Huntington's disease- dopaminergic neurons over activity[2]. AD is characterized by dementia (loss of memory) AD was first described in 1907 by Alois Alzheimer[1]. AD is a progressive dementia which is characterized by the degeneration of cholinergic neurons in the basal forebrain nuclei[3]. ***Neuronal plasticity-*** memory retention which is handled by the cholinergic neurons.So as there is a loss of cholinergic neurons no neuronal plasticity [4].



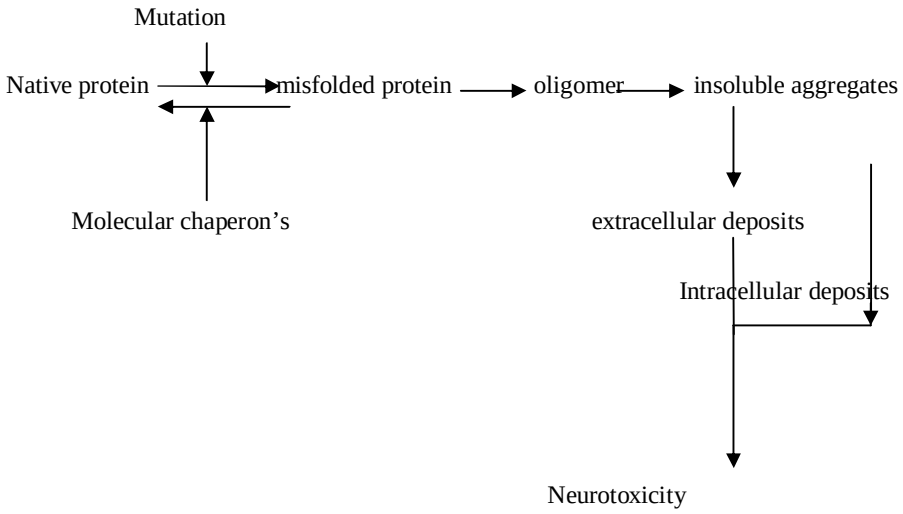


Side view of brain

Effect of protein misfolding in neurodegenerative disorders

Misfolding means the adoption of abnormal conformations by certain normally expressed proteins such that they tend to form large insoluble aggregates. The misfolded molecules are nonfunctional with respect to the normal function of the protein but can nonetheless make mischief within the cell. Misfolding conformations can be generated spontaneously at a low rate throughout life, so that aggregates gradually accumulate with age. In nervous system, the aggregates often forms distinct structures, generally known as amyloid deposits, that are visible under microscope and are characteristic of neurodegenerative disease[5].

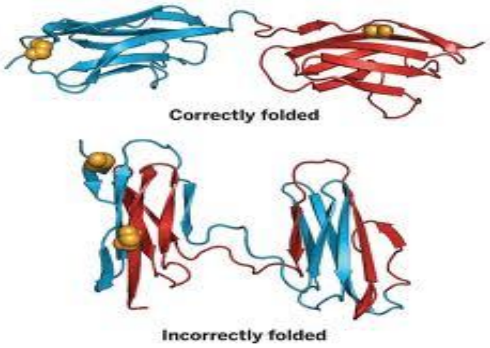
Protein misfolding: a process involved in many chronic neurodegenerative disorders



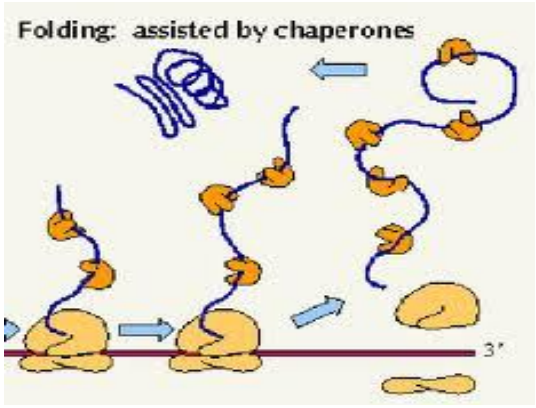
Examples of neurodegenerative diseases that are caused by such protein misfolding and aggregation are[5]

	Disease	protein
1.	Alzheimer's disease	β-Amyloid (Aβ)
2.	Parkinson's disease	α-synuclein
3.	Huntington's disease	Huntingtin

Misfolding of proteins



The brain possess a variety of protective mechanism that limit the accumulation of such protein aggregates. The main ones are the production of "Chaperone proteins" which bind to newly synthesized or misfolded proteins and encourage them to fold correctly and the ubiquitination reaction which prepares proteins for destruction within the cell[5].



Stages of Alzheimer's disease[3]

1. Mild stage

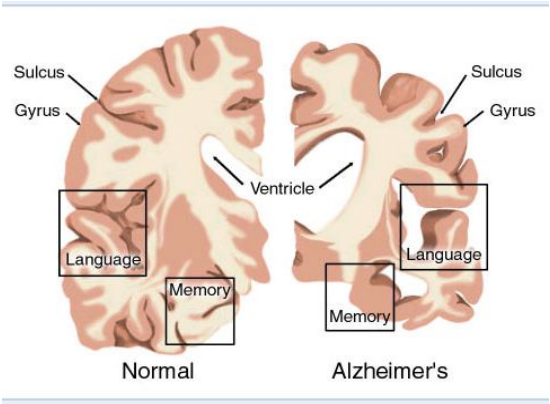
Patient has difficulty in remembering recent events,ability to manage finances, Household activities declines,begin to withdraw from difficult tasks and to give up hobbies.

2. Moderate stage
Patient requires assistance with activities of daily living,may forget some details of past life, names of family and friends, may become suspicious and tearful, Loses ability to drive safely.

3. Severe stage
Looks into mirrors and talks with their own image,patient loses ability to speak, walk and feed self, incontinent of urine and feces, requires 24 hours care.]

Risk factors for AD:
Hypertension, Elevated low density lipoprotein cholesterol, Low high density lipoproteins and Diabetes
The onset of AD is almost imperceptible, but deficits progress overtime. Cognitive decline is gradual, and behavioral disturbances may be present in moderate stages. Emotional outbursts and disturbing behavior, such as wandering and agitation, begin to happen and become more and more frequent as the disease runs its course.

Images represent a cross-section of the brain as seen from the front. The cross-section on the left represents a normal brain and the one on the right represents a brain with Alzheimer's disease.

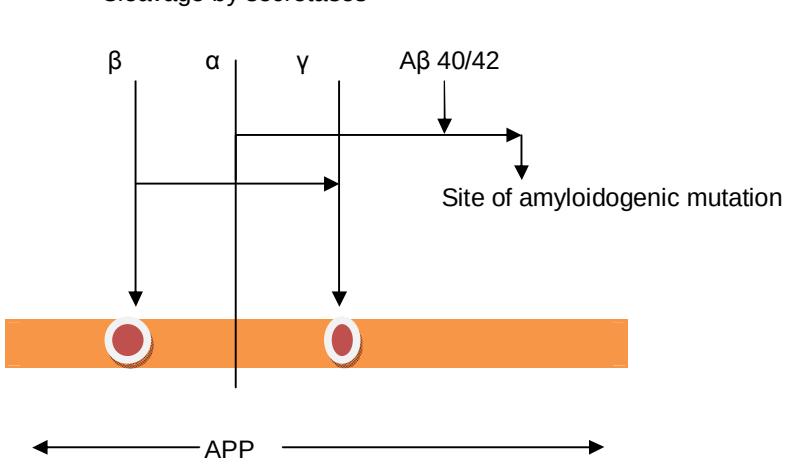


PATHOPHYSIOLOGY[5]
Two microscopic features are characteristic of the disease namely
Extracellular amyloid plaques
Intraneuronal neurofibrillary tangles (NFTs)
I Mutation
II Hyperphosphorylation of Ƭ(Tau protein)
III Excitotoxicity
IV Accumulation of inflammatory free radicals
V Oxidative free radicals

I MUTATION
1. Mutation in amyloid precursor protein(APP)
2. Mutation in APOE gene.

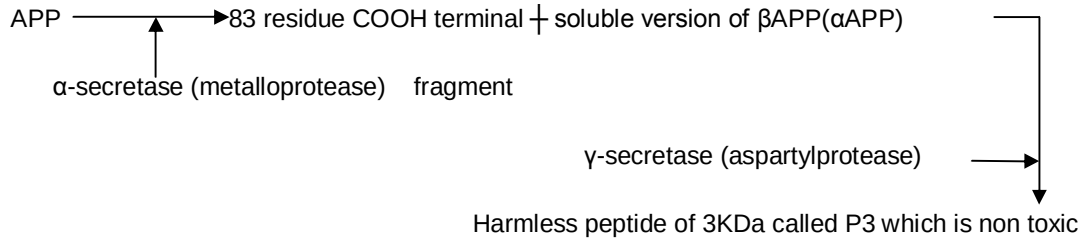
Amyloid precursor protein
APP a transmembrane protein present in the CNS that act as a nutrient for the survival of neurons. After eliciting its function, the APP will be degraded by the proteolytic enzymes namely secretases. The mutation in the amyloidogenic sites of APP will result in the formation of amyloid plaques or deposits.

Structure of APP

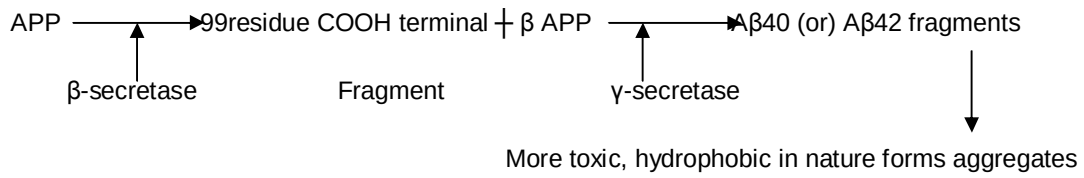


APP gene resides on chromosome 21. Amyloid deposits consists of aggregates of Aβ containing 40 or 42 residues which are produced by the proteolytic cleavage of APP. Both proteins aggregate to form amyloid plaque. Aβ 42 is more toxic in nature when compared with Aβ 40. Mutations in another gene, that for the lipid transport protein APOE4, also predisposes to AD, probably because of expression of abnormal APOE4 proteins that facilitate the aggregation of amyloid plaques. APOE4 gene is present on chromosome 19.

Proteolytic cleavage of amyloid precursor protein[1]



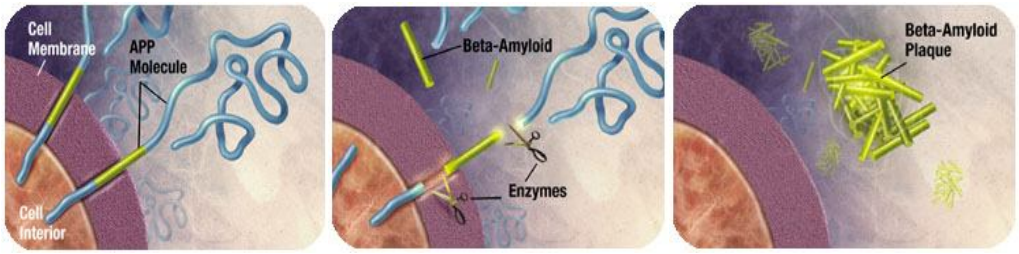
Amyloid plaque formation [1]



Beta-amyloid Plaques

Amyloid precursor protein (APP) is the precursor to amyloid plaque.

a) APP sticks through the neuron membrane.
d) disrupting the work of neurons. This affects the hippocampus and other areas of cerebral cortex.
b) Enzymes cut the APP into fragments of protein, including beta-amyloid.
c) Beta-amyloid fragments come together in clumps to form plaques In AD, many of these clumps form,

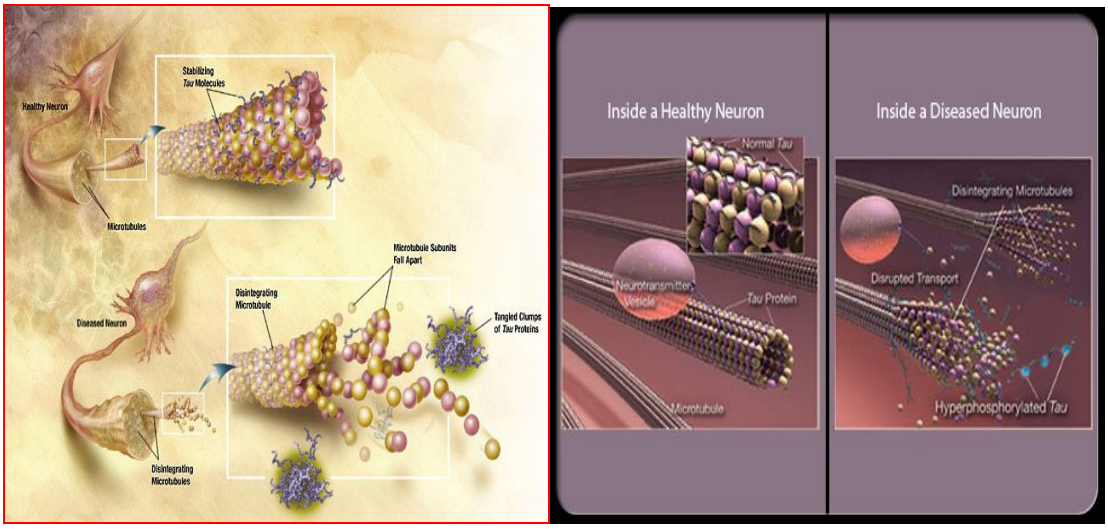


Formation of amyloid plaques by the cleavage of APP by secretases

II Hyperphosphorylation of Ƭ (Tau) protein

Ƭ protein is present in the cholinergic neurons and are essential for the survival of neurons[3]. These proteins have the ability to bind and stabilize the microtubules of the nerves. In AD it is abnormally phosphorylated and deposited

intracellularly as paired helical fragments called neurofibrillary tangles finally causes neuronal cell death[5]. Neurofibrillary tangles is the 2nd hallmark of AD, consists of abnormal collections of twisted threads found inside the nerve cells. Ţ phosphorylation is enhanced by Aβ plaques. Whether hyperphosphorylation and intracellular deposition of tau harms the cell is not certain, although it is known that tau phosphorylation impairs fast axonal transport, a process that depends on microtubules. Neurofibrillary tangles comprise intracellular aggregates of a highly phosphorylated form of a neuronal protein (Tau) the relationship of these structures to neurodegeneration is not known[5] .

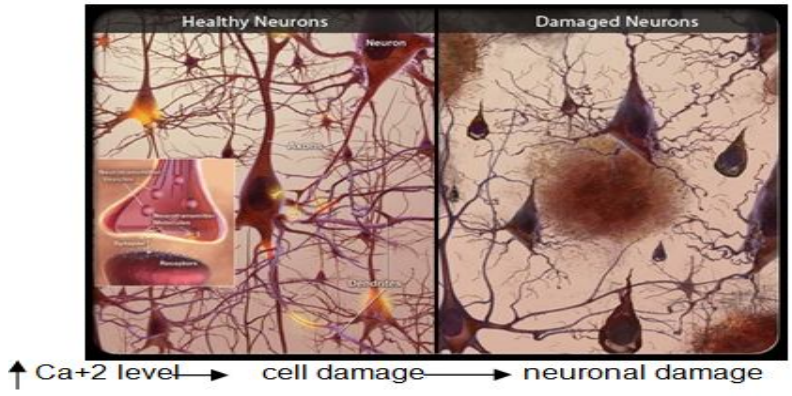


Formation of NFTs clumps

Neurons have an internal support structure partly made up of microtubules. A protein called *tau* helps stabilize microtubules. In AD, *tau* changes, causing microtubules to collapse, and *tau* proteins clump togetherto form neurofibrillary tangles.

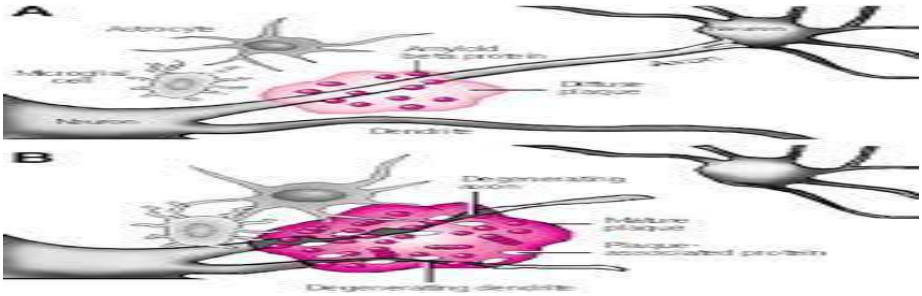
III Excitotoxicity

Toxicity due to diffusion of more levels of calcium.Calcium overload is the essential factor in excitotoxicity. Glutamate, a neurotransmitter is highly toxic to neurons. A low concentration of glutamate applied to neurons in culture kills the cells and the finding in the 1970s that glutamate given orally produces neurodegeneration in vivo caused considerable alarm because of the wide spread se of glutamate as taste enhancing food additive. Local injection of kainic acid is used experimentally to produce neurotoxic lesions. It acts by excitation of local glutamate releasing neurons, and the release of glutamate, acting on NMDA and also metabotropic receptors leads to neuronal death. Activity of glutamate on NMDA will enhance the influx the calcium into the cell. The increased levels of calcium inside the cells will lead to cell damage finally leading to neuronal damage[5].



IV Accumulation of inflammatory free radicals

Senile plaques is surrounded by neurites (axon/ dendrites)and invaded by microglia and astrocytes - the inflammatory cells of brain. These are found in the frontal cortex, hippocampus, thalamus, less frequently in basal ganglia and cerebellum. This inflammatory free radicals will cause cellular damage and finally to the neuronal damage leading to neuronal death[1].



Inflammatory process – neuronal damage

V Oxidative free radicals

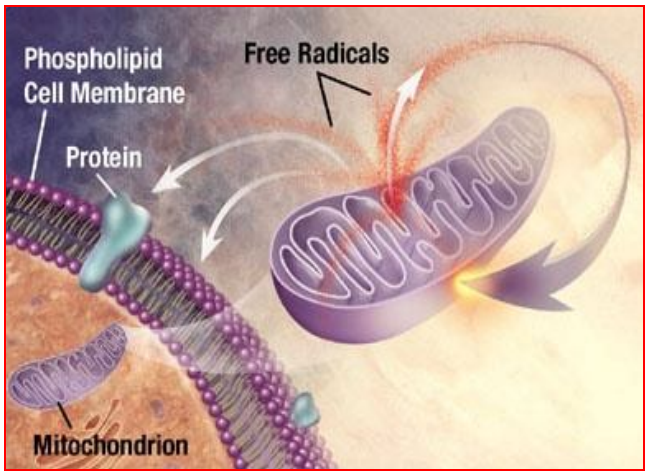
Due to oxidative free radical formation cellular damage occurs which leads to neuronal damage.

Endogenous factors

Dysfunction of the METS, auto oxidation of catecholamine's, Xanthine oxidase reaction etc

Exogenous factors

Exposure to radiation, cigarette smoking, polluted air etc.

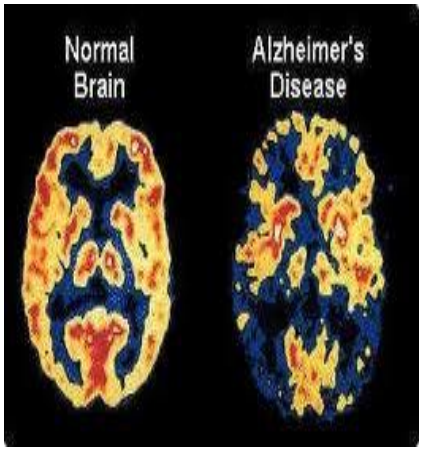


Formation of free radicals upon dysfunction of mitochondrial electron transport system

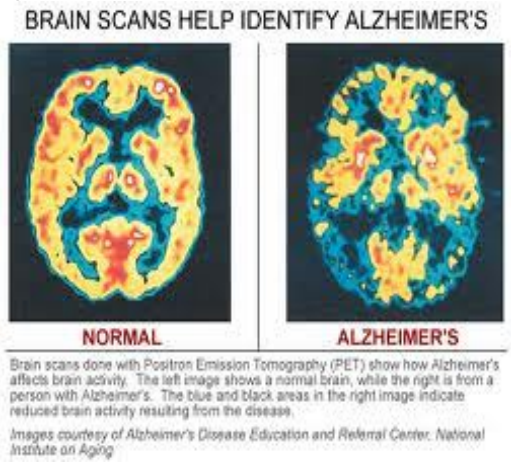
DIAGNOSIS

The definitive diagnosis of AD is made by examining the brain tissue. Patients with suspected AD should have a history and physical examination with appropriate neurologic and psychiatric examinations. Information about prescription drug use, family medical history.The Folstein Mini-Mental state examination (MMSE) can help to establish a history of deficits in two or more areas of cognition and establish a base line against which to evaluate change in severity. Diagnostic tests can be done through various scans like Magnetic resonance imaging(MRI), Positron Emssion Tomography(PET), Computed Tomography(CT)[3].

- **Diagnostictests**



MRI- scan



PET- scan

Treatment for Alzheimer's disease

While there is a variety of neurotransmitter deficits loss of cholinergic activity is most prominent and correlates with AD severity. Managing blood pressure, cholesterol and blood sugar may reduce the risk of developing AD and may prevent the worsening of dementia in patients with AD[3]. Evidence of decrease in cholinergic mechanism lead to the use of cholinergic drugs.

1. Cholinergic drugs
   a) Precursor of acetylcholine synthesis- choline chloride lecithin
   b) Cholinergic receptor agonist- Bethanicol
   c) Anticholinesterases –Tacrine, Donepezil, Rivastigmine,Galantamine
2. NMDA blockers- Memantine
3. Secretase activity blockers- OM911, OM992
4. Phosphorylation inhibitors- Congo red
5. Antioxidants –vitamin C, vitamin D
6. Nootrophic agents- Piracetam, Aniracetam
7. Natural products- Brahmi, Shankapushpi
8. Anti-inflammatory drugs-Ibuprofen, Indomethacin

Cholinesterase inhibitors and memantine are first line therapy in early management of behavioral symptoms, modest improvement may be achieved.

Clinical pharmacology of cholinesterase inhibitors

	Donipezil	Rivastigmine	Galantamine
Brand name	Aricept	Exelon	Razadyne
Dosage forms	Tablet Oral disintegrating tablet	Capsule Oral solution patch	Tablet Oral solution Extended release capsule
Starting dose	5mg daily at bed time	1.5 mg twice a day(or)4.6mg/day(patch)	4mg twice a day or 8mg daily for ER
Maintaince dose	5-10mg daily	3-6mg twice a day (or) 9.5mg/day (patch)	8-12mg twice a day (16-24mg daily for ER)
meals	No effect of food	Take with food	Take with food
Half life	70 hours	1.5 hours	7 hours
Renal elimination	yes	Major pathway	yes

Memantine – NMDA blocker

Blocks glutamatergic neurotransmission by antagonizing NMDA receptors which may prevent excitotoxic reactions. Indicated for the treatment of moderate to severe AD. Side effects include constipation, confusion, dizziness, headache, cough, hypertension. Dose – initial dose of 5mg/day and increased

weekly by 5mg/day to the effective dose of 10mg twice daily. Dosing must be adjusted in patients with renal failure[3]

Recent work suggest that NSAIDs may reduce Aβ42 formation by regulating γ-secretase, an effect unrelated to cyclo-oxygenase inhibition, by which NSAIDs reduce inflammation. It may therefore possible to find compounds that target γ-secretase selectively without inhibiting cyclo-oxygenase, thus avoiding the side effects associated with current NSAIDs. Disappointingly, clinical trials with various NSAIDs have so far failed to show any effect on cognitive performance or disease progression in AD patients[5].

Future prospects

Researches also are looking at other treatments including

- ✓ Cholesterol lowering drugs called statins
- ✓ Antioxidants and folic acid
- ✓ Anti-inflammatory drugs
- ✓ Substances that prevent the formation of β amyloid plaques
- ✓ Nerve growth factor to keep the neurons healthy

CONCLUSION

The primary goal of treatment in AD is to maintain patient functioning as long as possible. Secondary goals are to treat the psychiatric and behavioral sequelae. Current pharmacotherapeutic interventions are primarily symptomatic attempts to improve or maintain cognition.Only four drugs are approved by USFDA namely Tacrine, Rivastigmine, Galantamine, Donepezil and the remaining drugs are under research.

REFERENCES

1. Derasari and Gandhi's – Elements of pharmacology Eighteenth edition-2008-2009 B.S.Shah Prakashan., 341-346
2. P Jagadish Prasad- conceptual pharmacology universities press (India) private limited 2010.
3. Barbara.G.Wells;JosephT.DIPIRO;TerryIL, Schwinghammer; CindyW.Hamilton., pharmacotherapy 5th edition 727-732
4. Available on www.hindawi.com/journals/np/-an open access journal
5. H.P.Rang, M.M.Dale, T.M. Ritter, R.J.Flower.,Rang and Dales pharmacology (2007) – 6th edition Elsevier limited., 508-517
6. Tripati KD, Essentials of medical pharmacology 5th edition jaypee, New Delhi., 471-474.