International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 804-810 www.ijprajournal.com ISSN: 2249-7781

Alzheimer's disease: A review

Sampada Mahadeshwar[1], Harshada Modak[2]
[1]Student, Shree Saraswati Institute of Pharmacy, Tondavli, Sindhudurg;
[2]Student, Shree Saraswati Institute of Pharmacy, Tondavli, Sindhudurg.
Corresponding Author : Sampada Ashok Mahadeshwar

Date Of Submission: 01-06-2021 Date Of Acceptance: 14-06-2021

ABSTRACT: Alzheimer's disease (AD) is chronic neurodegenerative disorder in which the death of brain cells causes memory loss and it is the most common type of dementia.AD is currently present one of the biggest healthcare issue in the developed countries. It affects 10%of people over the age of 65 and 50% over the age of 85 years .more than5 million Americans have Alzheimer's disease. Recognised factors in Alzheimer's disease includes acetylcholine defeciency, free radicals and inflammation of the brain tissue .There is no cure for Alzheimer's disease but drugs designed to slow disease progression are available as well as some herbs are helpful in AD. In the recent years the main focus of research is on novel pharmacotherapies was based on the amyloidogenic hypothesis

KEYWORDS: Alzheimer's disease, Dementia, Tau protein, Cholinesterase inhibitors, Delusion.

I. INTRODUCTION

Alzheimer's disease is currently uncurable neurodegenerative condition which is the highly prevalent in old age. It was first described in 1906 by Alois Alzheimer who analysed brain tissue from patient who had died from unknown mental illness[1]. According to WHO(world health organization) estimates,the over all projected prevalence in global population will quadruple in the next decades, reaching 114 million patients by 2050[2]. AD is characterized by three primary groups of symptoms the first group is cognitive dysfunction which includes memory loss , language difficulties and executive dysfunction(that is, loss of higher level of planning and intellectual coordination skills).The second group comprises psychiatric symptoms and behavioral disturbance includes depression, hallucination ,delusions , agitation-collectivaly termed non cognitive symptoms.The third group comprises difficulties with performing activities of daily living (deemed "instrumental" for more complex activities such as driving and "basic" for dressing and eating unaided)[3].

Alzheimer's pathophysiology shows several biochemical alterations including changes in amyloid precursor protein metabolism, phosphorylation of tau protein, impaired energetics, mitochondrial dysfunction, cholinergic hypothesis, dendritic hypothesis[4]. Right now, there's no exact or proven way to prevent Alzheimer's disease. The strongest evidence so far suggests that you may be able to lower your risk of Alzheimer's disease by decreasing your risk of heart diseases. Some important factors which affect AD include Cardiovascular disease , hypertension, obesity, type2 diabetes traumatic injury, smoking, physical activity etc. Alzheimer's disease is complex, and it is unlikely that any perticular drug or other intervention can successfully lead to its proper treatment. Treatment approaches focus on management of behavioral symptoms, maintain mental function, and slow or delay the symptoms of disease. Researchers hope to develop therapies targeting specific genetic, molecular, and cellular mechanisms so that the actual underlying cause of the disease can be stopped or prevented[5].

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 804-810 www.ijprajournal.com ISSN: 2249-7781

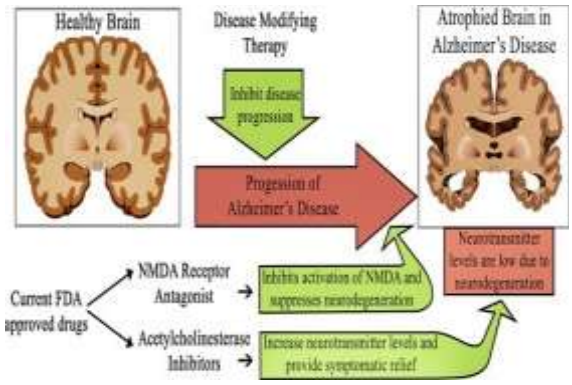

Figure I : Basic representation of AD[6]

Sign and symptoms :

Memory impairment is the main symptoms of AD and usually involves memory loss(Repetition of statements, forget events, conversations , improper use of words); Difficulty in thinking (difficulty in concentrating especially about concepts such as numbers); difficulties in making judgements and decisions; Mood change ; Confusion. ADis also recognised by insomnia, anxiety, depression, hallucinations[7].

Prevention :

prevention in the preclinical stage is likely the mosteffective way to decrease the incidence of this age-associated neurodegenerative condition, and There is great interest in prevention studies as a way to reducethe incidence and prevalence of dementias[8]. There have been numerous difficulties in conducting pri-mary prevention trials in AD because of the unclear pathophysiological mechanism of AD, the difficulty in ac-curate selection of the target population, the need for a large sample size, long duration of follow up, the high costof the prevention study, adverse events of the preventiondrugs being studied and the related ethical issues[9]. Aims in prevention studies for AD includes delaying biomarkers changes, delaying cognitive decline, delaying dementia.The prevention of AD require large investment of timeand money, but the return on investment may be huge, considering the projections of costs for patients with dementia in the near future[10].

Diagnosis :

In clinical settings, the diagnosis of AD is mainly based on medical history, physical and neurological examinations, and neuropsychological evaluation, as well as the exclusion of other etiologies using selective ancillary testing. The clinical diagnosis of AD has an accuracy of 70_90% relative to the pathological diagnosis, with greater accuracies being achieved in specialty settings such as memory disorder clinics[11].

Establishing the diagnosis of Alzheimer disease relies on clinical-neuropathologic assessment. Neuropathologic findings on autopsy examination remain the gold standard for diagnosis of AD. The clinical diagnosis of AD (prior to autopsy confirmation) is correct approximately 80%-90% of the time.

Clinical sign : Slowly progressive dementia

Neuroimaging : Gross cerebral cortical atrophy on CT or MRI.Diffuse cerebral hypometabolism on PET.

Neuropathologic findings : Microscopic β-amyloid neuritic plaques, intraneuronal neurofibrillary tangles (containing tau protein), and amyloid angiopathy at postmortem examination. The plaques should stain positively with β-amyloid antibodies and negative for prion antibodies, which are diagnostic of prion diseases. The numbers of plaques and tangles must exceed those found in age-matched controls without dementia. Guidelines for the quantitative assessment of these changes exist. Aggregation of alpha-synuclein in the form of Lewy bodies may also be found in neurons in the amygdala.

Cerebrospinal fluid (CSF) : Decreased Aβ amyloid 42 and increased tau[12].

Stages of Alzheimer's disease :

- ✓ Stage I (Normal)-

Mentally healthy person

- ✓ Stage II(Normal age forgetfulness)-

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 804-810 www.ijprajournal.com ISSN: 2249-7781

Person over the age 65 experience subjective complaints of cognitive and /or functional difficulties.

✓ Stage III (Mild cognitive impairment)

Complaints of memory loss, intact activities of daily living ,no evidence of Alzheimer's disease

✓ Stage IV (Mild Alzheimer's)

Forgetfulness,short term memory loss, repetitive questions, hobbies,interst loss , impaired activities of daily living.

✓ Stage V (Moderate Alzheimer's disease)

Progression of cognitive dificits , dysexecutive symptoms, further impaired activities of daily living, transition in care, emergence of behavioral and psychological symptoms of dementia.

✓ Stage VI(Severe Alzheimer's disease)

Agitation altered sleep patterns , assistance required in dressing, feeding, bathing established behavioral and psychological symptoms of dementia.

✓ Stage VII(Very severe Alzheimer's disease)

Bedbound, no speech, incontinent, basic psychomotor skills loss[13,14].

Risk factors :

Age: The most cases of AD are seen in older adults ages 65 years or above.For those over 85 the risk increase to 50%[15].

Genetics: In sporadic Alzheimer's disease, there is no appearance of a genetic pattern of inheritance. A connection has been found between a gene called Apolipoprotein E (ApoE) and the development of Alzheimer's disease. This gene is supposed to be responsible for the protein that carries cholesterol in the blood vessels. One form of the gene, ApoE4, has been shown to increase the chances of developing the disease to a greater extent. However, the ApoE2 form protects from the disease[16].

Disease condition: Cardiovascular diseases (heart problems), hypertension,typeII diabetes, Obesity,Traumatic head injury [12], Depression, are important risk factors for Alzheimer's disease.

Habbits : Smoking [12](it affects cerebrovascular system), Improper diet etc[13].

Education : It is observed that there is a connection between educational level and the risk of developing Alzheimer's disease. People with fewer years of education seem to be at a higher risk as they are unaware of the prevalent causes. The exact cause for this relationship is unknown, but it is theorized that a higher education level leads to the formation of more synaptic connections in the brain. This creates a "synaptic reserve" in the brain, enabling patients to compensate for the loss of neurons as the disease progresses[5].

Causes :

Causes of AD can be explained with help of three hypothesis-

Amyloid hypothesis: Amyloidosis is the abnormal deposition of amyloid proteins in the tissues, with the altered amyloid proteins forming an insoluble ß-pleated sheet. Reduced tissue and cellular clearance is observed in amyloid protein deposits. The membrane protein amyloid-ß precursor protein (APP) is proteolysed to form Aß, and it is the amyloid form of A that makes up the amyloid plaques (neuritic plaques) found in the brains of Alzheimer's disease sufferers[17].

Tau hypothesis : Tau is a microtubule-associated protein found in most tissues and highly expressedin the peripheral nervous system. In neurons, it is an important component of the cytoskeleton[18]. Tau is widely expressed in the central and peripheral nervous system, and therefore may be regarded as a neuronal phosphoprotein. In addition to the involvement ofTau in the maintenance of neuronal structure and in synaptic plasticity, microtubulesare essential for axonal transport of organelles (mitochondria, ER, lysosomes) andvesicles containing proteins and neurotransmitters, which are displaced from the cell body (soma) to distal synapses. There is a phosphorylation gradient along the axon and in different brain regions. Hyperphosphorylated Tau impairs axonal. transport and synaptic metabolism, causing dysfunctions that result in loss of cell viability and ultimately lead to the collapse of microtubular cytoskeleton and neuronaldeath. The phosphorylation and dephosphorylation of Tau at serine and threoninephosphoepitopes are critical regulatory events inneuronal homeostasis[19].

Cholinergic hypothesis : The cholinergic hypothesis of Alzheimer's disease came about due to the combined observations of deficits in choline acetyltransferase and acetylcho-line (ACh) and the fact that ACh is important in memory and learning. It was thought that reduction in cholinergic neurons as well as cholinergic neuro transmission led to the decline in cognitive and noncognitive functions. Cholinergic function loss correlated to cognitive decline, but no causal relationship was established [20].

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 804-810 www.ijprajournal.com ISSN: 2249-7781

Drug treatment :

Cholinesterase inhibitors: Cholinesterase inhibitors are the mainstay of drug treatment for moderate Alzheimer's disease. Donezepil(5-10mg),Rivastigmine(6-12mg), Galantamine(8-24mg)[5].

Glutamatergic partial antagonist:(for moderately severe disease) - Memantine(10-20mg)[21].

Some ayurvedic herbs like Guduchi, Yashtimadhuk,Padma (Nelumbo nucifera), Vacha, Convolvulus pluricaulis,Shankhpushpi, Pancha-Tikta-Ghruta Gugguli, Amalaki,Musta Arjun, Amalaki, Ashwagandha, Galo Satva, Kutaj, and others are excellent herbs for slowing down the brain cell degeneration caused by Alzheimer's. They enhance the brain's ability to function, and therefore, provide stability when used consistently[7].

Treatment strategies or therapies according to number of existing hypothesis :

A] Amyloid cascade hypothesis : " This hypothesis is that deposition of amyloid β protein (AβP), the main component of the plaques, is the causative agent of Alzheimer's pathology and that the neurofibrillary tangles, vascular damage, and dementia follow as a direct result of this deposition". These words represents the amyloid cascade hypothesis[22]. The amyloid cascade hypothesis suggests that the aggregation, and deposition of AD peptides, andespecially A□(1-42), are a primary event in AD pathogenesiswhich triggers neurotoxicity and neurodegeneration[23]. A huge body of evidence has accumulated over these last 25 years showing that different forms of Aβ, from insoluble aggregates to soluble dimers/oligomers, either synthetic or derived from AD brains, can cause synaptotoxic effects and neuronal death in a variety of in vitro and in vivo models. However, with respect to the original premise, soluble Aβ peptides, rather than their insoluble fibrillar aggregates, are now thought to be the main responsible of the neurodegenerative disorder, as they seem to better correlate with AD symptoms and severity[24,22].

B] Strategies focused on Tau protein : Alternative to amyloid cascade hypothesis, Tau protein centered treatments aim to inhibit the phosphorylation or aggregation of Tau protein. In addition,microtubule-stabilizing drugs could be used as a disease-modifying strategy in AD[25].Tau-targeted therapeutic strategies have been present in tau-transgenic animal models to ameliorate biochemical changes due to tau over-expression (such as insolubility and hyperphosphorylation), histological alterations (such as NFT formation and somatodendritic localization) as well as behavioural (both memory and motor) impairments. To combat AD rather than only targeting Ab, a combinatorial tau/Ab strategy is likely the better approach[26].

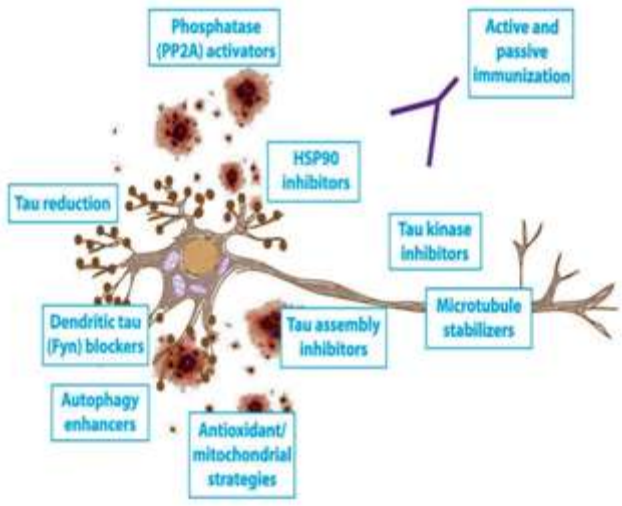

Figure I : Tau-targeted therapeutic strategies[26].

C] Cholinergic hypothesis : Many pharmacological studies have examined that the cholinomimetic drugs and cholinergic receptors plays important role in memory task.cholinergic

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 804-810 www.ijprajournal.com ISSN: 2249-7781

hypothesis is that drugs that potentiate central cholinergic function should improve cognition and per- haps even some of the behavioural problems. Clinical development of the cholinomimetic drugs for the symptomatic treatment of Alzheimer's are available, first and second generation of cholinesterase inhibitors (Donepezil, Tacrine, Rivastigmine etc)[27].

D] Dendritic hypothesis : Converging evidence which indicates that the processes occuring insodea d outside the neuronal dendrites are central to the pathogenesis of Alzheimer's disease. Dendritic hypothesis of AD closely related to existing synaptic hypothesis[28]. Soluble AD oligomers are the principle neurotoxic species responsible for dendritic pathology. AD oligomers may Causes N-methyl-D-aspartate receptor (NMDAR) activation post-synaptically by forming complexes with the cell-surface prion protein (PrPC). This protein interacts with Fyn tyrosine kinase-metabotropic glutamate receptor 5 complex (Fyn-mGluR5). Fyn activation occurs due to A is bound to PrPC-Fyn-mGluR5 complex. Fyn contributes in treatment of AD pathology. Saracatinib and masitinib are Fyn kinase inhibitors currently in clinical trials for mild-to-moderate AD[29].

E] Mitochondrial cascade hypothesis : Mitochondrial cascade hypothesis maintains the gene inheritance defines an individual's baseline mitochondrial function; inherited and environmental factors which determine rates at which mitochondrial function changes over the time; baseline mitochondrial function and mitochondrial change rates influence AD chronology[30].

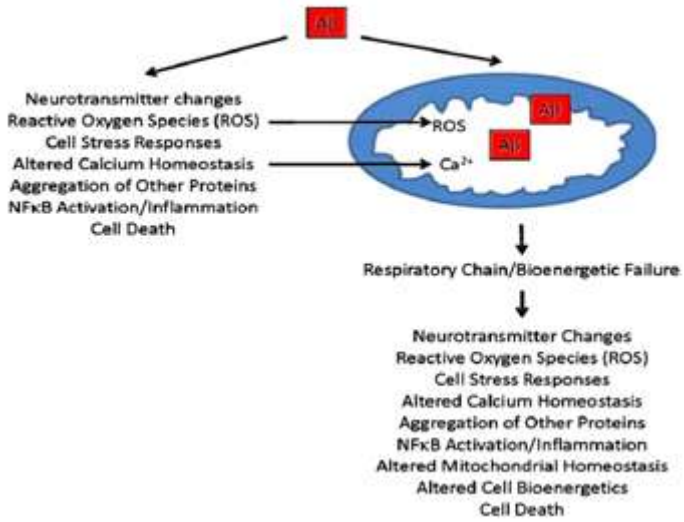

Figure III : Mitochondrial cascade hypothesis

This hypothesis States in sporadic, late - onset AD, mitochondrial function effect APP expression , or AD accumulation[31]. Mitochondrial cascades are compatible with the amyloid cascade hypothesis,and could mediate A-toxicity. As illustrated, A-can directly introduce various AD-associated functional changes and patholo-gies, and directly or indirectly cause mitochondrial dysfunction. A--induced mitochondrial dysfunction, in turn, could further con-tribute to or initiate additional AD-associated functional changes and pathologies[32].

F] metabolic hypothesis : In healthy human, the intranasal administration of insulin reduses the caloric intake, enhances memory function and mood acutely[33]. AD patients also show a beneficial effect on memory function from the acute as well as longer-term daily administration of insulin. In a pilot clinical trial, patients with AD benefited significantly from the daily intranasal administration of insulin on memory function after 4 months of daily treatment[34].

II. CONCLUSION

Alzheimer's disease is the most common form of dementia and it's prevalence is increasing worldwide. Neuropathological imagine, Neuropathologic findings can establish the diagnosis with high accuracy. Various risk factors

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 804-810 www.ijprajournal.com ISSN: 2249-7781

like age , genetics, cardiovascular disease smoking, obesity are associated with AD. The causes of AD can be mainly explained on amyloid and cholinergic hypothesis. The delay in neurodegeneration by targeting amyloid plaques is the potential mechanism for AD. Amyloid precursor protein (APP) and tau protein are the key players in pathophysiology of AD. A variety of interesting theories are emerging, including different perspective on hypothesis such as amyloid cascade hypothesis, tau Hyperphosphorylation, cholinergic hypothesis and various hypothesis related to AD . This article may help to understand basics of Alzheimer's disease.

REFERENCES

[1]. Folch J., Petrov D., Ettcheto M., Abad S., Sanchez-Lopez E., Garcia L.M., Olloquequi J. and Camins A.; "Current Research Therapeutic Strategies for Alzheimer's Disease Treatment " 2016, SAE paper no. 8501693

[2]. Alzheimer's Association Report. "Alzheimer's disease facts and figures Alzheimer's Association," Alzheimer's & Dementia. 2015; 11: 332-384.

[3]. Burns A, Jacoby R, Levy R. ,1990, "Psychiatric phenomena in Alzheimer's disease" Br J Psychiatry ; 1990, SAE paper no. 157.1.72.

[4]. R., Zhu H., Sharma S., Bogdanov M., Rozen S.G., Matson W. ,Oki N.O.,Motsinger-Reif A.A., Churchill E., Lei Z., Appleby D., Kling M.A., Trojanowski J.Q. , Doraiswamy P.M. , Arnold S.E. ;" Alterations in metabolic pathways and networks in Alzheimer's disease" , Transl Psychiatry,2013 (DOI: 10.1038/tp.2013.18)

[5]. Bhushan I., Kour M., Kour G., Gupta S., Sharma S., Yadav A. ; "Alzheimer's disease: Causes & treatment – A review" 2018, Ann Biotechnol. 2018; 1(1): 1002.

[6]. Abeysinghe A.A.D.T., Deshapriya R.D.U.S., Udawatte C., "Alzheimer's disease; a review of the pathophysiological basis and therapeutic interventions", 2020, Life Sciences 256(1):117996 .

[7]. Singhal A.K., Naithani V., Bangar O. P.; "Medicinal plants with a potential to treat Alzheimer and associated symptoms" , 2012 ; (DOI: 10.4103/2231-0738.95927)

[8]. Khachaturian ZS, Petersen RC, Gauthier S, Buckholtz N, Corey-Bloom JP,Evans B, "A roadmap for the prevention of dementia: the inaugural Leon Thal Symposium" , the journal of the Alzheimer's Association 2008, 4:156–163.

[9]. Thal LJ, "Prevention of Alzheimer disease" ,Alzheimer Dis Assoc Disord 2006, 20(Suppl 2):S97–S99.

[10]. Gauthier S., Wu L., Rosa P., Jia J., "Prevention strategies for Alzheimer's disease " ,Translational Neurodegeneration, 2012 (DOI: 10.1186/2047-9158-1-13)

[11]. Barnes DE, Yaffe K., "The projected effect of risk factor reduction on Alzheimer's disease prevalence", Lancet Neurol 2011; 10: 819-28

[12]. Khan M.M.,Ahsan F., Ahmad U.,Akhtar J., Badruddeen, Mujahid M. ;" ALZHEIMER DISEASE: A REVIEW" , World journal of pharmacy and pharmaceutical sciences,2016, (DOI: 10.20959/wjpps20166-7045)

[13]. Burns A., Iliffe S., "Alzheimer's disease : Clinical review" ;2009, volume 338,(DOI:10.1136/bmj.b158)

[14]. Giordani B., "The Latest in Alzheimer's Disease Research" ; 2018 ,Michigan Alzheimer's Disease Core Center.

[15]. "Alzheimer's Association", Alzheimer dement, 2010,(DOI 10.1016/j.jalz.2010.01.009)

[16]. Mayo Clinic Medical Information and Tools for Healthy Living. Mayo Foundation for Medical Education and Research. 2010.

[17]. Corbett A, Williams G and Ballart C. ,"Drug repositioning: an opportunity to develop novel treatments for Alzheimer's disease" ,Pharmaceuticals. 2013; 6: 1304-1321.

[18]. Kosik K .S., "The Molecular and Cellular Biology of Tau", Brain Pathol, 1993, (DOI :10.1111/j.1750-3639.1993.tb00724.x)

[19]. De-Paula V.J., Radanovic M., Diniz S.,Forlenza O.V., "Alzheimer's Disease", Sub-cellular Biochemistry, 2012, (DOI: 10.1007/978-94-007-5416-4_14)

[20]. Thies W and Bleiler L ,"Alzheimer's disease facts and figures", Alzheimer Dement.2013; 9: 208-245.

[21]. Areosa SA , Sherriff F., "Memantine for dementia", Cochrane Database Syst Rev 2003 ;(3): CD003154 .

[22]. Ricciarelli R., Fedele E., "The Amyloid Cascade Hypothesis in Alzheimer's Disease: It's Time to Change Our Mind", Current Neuropharmacology, 2017, 15, 926-935

[23]. Hardy J., Selkoe DJ, "The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics", Vol. 297, (DOI: 10.1126/science.1072994)
[24]. Mucke, L., Selkoe D.J., "Neurotoxicity of amylod β-protein: synaptic and network dysfunction" , Cold Spring Harb Perspect Med, 2012, (doi: 10.1101/cshperspect.a006338)
[25]. Carasso LS , Benhar I., "Antibody-targeted drugs and drug resistance-Challenges and solutions" ,Drug resistance updated, Vol. 18, 2015, (DOI:10.1016/j.drup.2014.11.001)
[26]. Götz J., Ittner A., Ittner L.M., "Tau-targeted treatment strategies in Alzheimer's disease", British Journal of Pharmacology (2012) 165 1246–1259.
[27]. Francis P.T., Palmer A.M., Snape M., Wilcock G.K., "The cholinergic hypothesis of Alzheimer's disease: a review of progress" , Neurol Neurosurg Psychiatry 1999;66:137–147.
[28]. Cochran N., Hall A.M., Roberson E.D., "The Dendritic Hypothesis for Alzheimer's Disease Pathophysiology",Brain Res Bull, 2014 ;103:18-28.
[29]. Yang K., Belrose J., Trepanier CH , Lei G., Jackson MF , "Fyn, a Potential Target for Alzheimer's Disease", 2011 , Journal of Alzheimer's disease: JAD 27(2):243-52
[30]. Swerdlowa R.H., Burnsa J.M., Khanb S.M., "The Alzheimer's Disease Mitochondrial Cascade Hypothesis: Progress and Perspectives", Biochim Biophys Acta. 2014 ; 1842(8): 1219–1231.
[31]. Swerdlow RH. Mitochondria and cell bioenergetics: increasingly recognized components and apossible etiologic cause of Alzheimer's disease. Antioxidants & redox signaling. 2012; 16:1434–1455. [PubMed: 21902597]
[32]. Swerdlow R.H., "Mitochondria and Mitochondrial Cascades in Alzheimer's Disease", 2017, (DOI 10.3233/JAD-170585)
[33]. Morgen K., Fro¨lich L., "The metabolism hypothesis of Alzheimer's disease: from the concept of central insulin resistance and associated consequences to insulin therapy", Journal of Neural Transmission,2015 (DOI: 10.1007/s00702-015-1377-5)
[34]. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A et al (2012) Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol 69(1):29–38