Sustainability, Agri, Food and Environmental Research, (ISSN: 0719-3726), 11(X), 2023:
http://dx.doi.org/10.7770/safer.v11i1.2371

Alzheimer's disease: metallobiology and its counteraction by utilizing characteristic inhibitors

La enfermedad de Alzheimer: la metalo-biología y su contrarresto mediante la utilización de inhibidores característicos

Deepti N. Chaudhari, Anupama N. Devkatte, Prerna D. Shere and Mahesh M. Shinde

MIT School of Food Technology, MIT Art, Design and Technology University, Pune

ABSTRACT

Alzheimer's sickness (AD) is an irreversible, reformist neurodegenerative problem which is driving reason for dementia in the senior individual's causes passing generally inside 7-10 years after determination. Neurodegeneration is surprising characteristics of Alzheimer's patients happens as a result of neuron harm and dysfunctioning of synaptic transmission. Primarily the cortical zones of mind get influenced which is liable for memory and other mental capacities at last prompts intellectual decrease. Misfolding of Aβ peptide because of oligomerization advanced by Cu2+, Zn2+, Fe2+ions brings about age of oxidative pressure. To forestall age of oxidative pressure by utilizing metal chelators or utilization of bioactive particles of characteristic cause to restrain aggravation of (Aβ) peptide the viable method to forestall Alzheimer's illness.

Key words: dementia, neurodegeneration, chelators, oxidative stress.

RESUMEN

La enfermedad de Alzheimer (EA) es un problema irreversible y neurodegenerativo reformista, la cuál es la razón que conduce a la demencia en las causas del individuo mayor y que toma lugar generalmente dentro de 7 a 10 años posteriores a la determinación médica. La neurodegeneración es una característica sorprendente de los pacientes con Alzheimer que se produce como resultado de un daño neuronal y una disfunción de la transmisión sináptica. Principalmente, las áreas corticales del cerebro son las que sufren alteraciones, las cuales son las responsables de la memoria y otras capacidades mentales, lo que finalmente provoca una disminución intelectual. El desdoblamiento del péptido Aβ debido a la oligomerización que se desarrolló como Cu2+, Zn2+, Fe2+iones, conlleva al envejecimiento por estrés oxidativo. El método viable para prevenir la enfermedad de Alzheimer y detener la exacerbación del péptido Aβ, es mediante el uso de quelantes de metales o partículas bioactivas correspondiente a la causa característica de la enfermedad, con el propósito de prevenir el envejecimiento por estrés oxidativo.

Palabras clave: demencia, neurodegeneración, quelantes, estrés oxidativo.

INTRODUCTION

A progressive neurological disorder named Alzheimer's disease characterised by loss of memory as well as lowering of thinking abilities and language skills .In US about 13% of peoples over the age of 65 are afflicted and over 85 years of age about 40%. After diagnosis of this disease the survival period is only up to 8 years only. In Alzheimer's disease (AD), neuronal damage due to disruption of synaptic function begins in the hippocampus, an area of cortex and then further throughout of brain. AD results due to formation of plaques and tangles in the brain which disturbs the transmission through the nerves. Clevage of the amyloid precursor protein (APP) by secretase enzymes further forms plaques due to aggregation of amyloid β peptide. Tangles formed due to the defect in tau proteins and detaches from microtubules thus skeleton get dissociate. The defective tau proteins get formed filaments in neuron[4]. Metal mainly iron, zinc, copper have associated with Aβ aggregation. Copper ion is mainly responsible for the amyloid aggregation [14]. Formation of the plaque by Aβ is inhibited by the thiosemicarbazone compound which reduces the activities of metal ions [11]. Natural inhibitors for the AD is curcumin extract [21], ginkgo biloba [10], grapes seed polyphenolic extract (GSPE) [12], cinnamon extract [21], aged garlic extract [20], sage [1], azaphilones [23].

Mechanism of aβ peptide synthesis

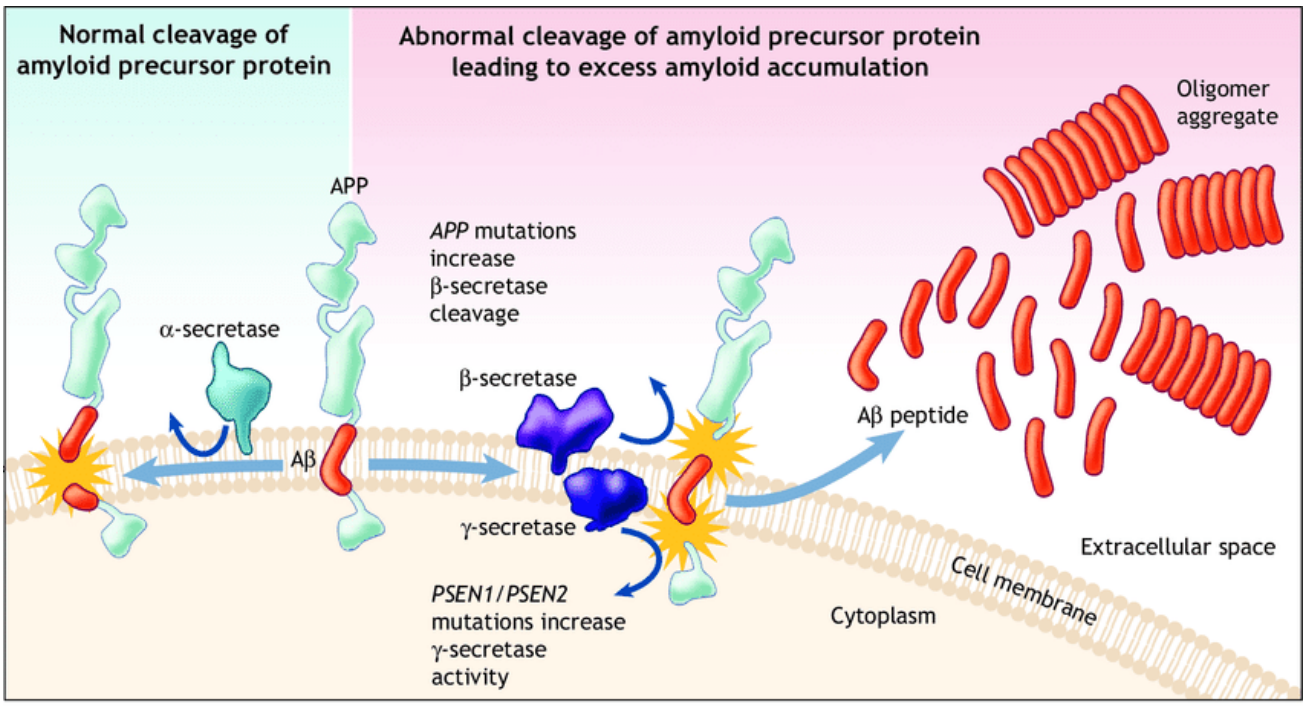
The Alzheimer's disease associated with injury and death of neurons initiating within the hippocampus in cortex region. Amyloid beta (Aβ) could be a short peptide. That is an abnormal proteolytic by-product of the transmembrane amyloid precursor protein (APP).

Amyloid β monomers are soluble and contain short region of β sheet at sufficiently high concentration. They undergo dramatic change to create a β-sheet rich tertiary structure that aggregates to create amyloid fibrils. This fibrils deposit outside neuron in dense formation called senile plaque [22] or neuritic plaques, in less dense aggregate within the wall of small blood vessels within the brain, this process is termed as amyloid angiopathy [2].

In AD abnormal aggregation of the tau protein also occur. Tau protein mainly present in the microtubules, major hallmarks of Alzheimer's disease. Properties of tau can be explain by its natural structure as a natively unfolded protein. Example are the large number of structural conformation and biochemical modification (phosphorylation, proteolysis) is part of mainly microtubules but also other cytoskeletal proteins kinase and membrane proteins. can be suppressing expression by aggregation. Allsop London and Kidd in 1983 reported a method for isolating intact plaque core from post mortem AD brain and found them to be insoluble in various denaturants.

The binding of hydrophobic Aβ assemblies in to soluble oligomers leads to fibrillar deposition (amyloid plaques) that can bind to different components of neuronal and non-neuronal plasma membrane results in the disfunctioning [15].The enzyme α-secretase enzyme cleaves amyloid precursor protein (APP) at K687 and L688 residue in extracellular domain in the middle segment.[5].

The enzyme β- secretase cleaves APP at extracellular region between residue M671 and D672 [5]. The carboxyterminal fragments (CTF) generated by α- and β-secretase are named as CTF83 and CTF99 [29]. The enzyme β-secretase generate C-terminal fragments which further cleaved by the gamma secretase form Aβ [19]. Gamma secretase produces two fragments Aβ (1-40) and Aβ (1-42) and enhance aggregation and form senile plaque [5].



Ref: https://www.researchgate.net

Metallobiology

The metal ions mainly iron, zinc, copper (Fe, Zn, and Cu) have long been associated with the aggregation of β-amyloid (Aβ) plaque in Alzheimer's disease promotes increased oxidation stress and neuronal dysfunction. Concentration of Fe, Cu, and Zn were increased in plaque compare to the surrounding neuropil (network of nerve [14]. Copper is an essential trace element involve in the function of numerous enzymes. Free copper in cell causes the oxidative damage. Cu (II) ions binds with high affinity to β- amyloid peptides at its N-terminal Asp1 and His 13, increases the proportion of β-sheet and α-helix structure in amyloid peptide which can be responsible for β-amyloid aggregation. Other copper Cu (I) ion bind at His13 and His14 [20].Reactive oxygen species (ROS) production results due to β-amyloid toxicity towards neuron dependent on metal ion redox properties.Copper ion complex with β amyloid fibrils produces hydrogen peroxides (H_2O_2) in presence of biological reducing agents.When the ratio of copper to peptide binding increases results in high H_2O_2 level and the production of hydroxyl radicals increases [6]. The produced hydroxyl radicals reacts with all amino acids mainly tyrosine, tryptophan, histidine and cysteine being the most reactive. Tyrosine is a more sensitive residue in peptide that undergoes in oxidized state and formed protein dimer linked by di-tyrosine [20].

$$TyrOH + OH^* \dashrightarrow TyrO^* + H_2O$$

$$2TyrO^* \dashrightarrow di\ Tyr$$

The brain is a highly oxidative organ consuming 20% of the body's oxygen despite accounting for only 2% of the body weight [9].

Tau protein acts to stabilize microtubule in cell cytoskeleton. Tau is regulates by phosphorylation, tau hypersecretion maintained by a failure of activation of phosphates like protein phosphatase-2A.

Hyperphosphorylated tau aggregate into neurofibrillar tangles. Zn^{+}, Cu^{2+}, Fe^{3+}, Mg^{2+}, Pb^{2}, Cd^{2+}, Hg^{2+} and Al^{3+} promotes tau hyperphosphorylation and induces tau aggregation [4].

Small molecules can be designed to prevent transition metal-induced amyloid deposition and oxidative stress within the AD brain refered as Therapeutic Chelation evolved from the metal hypothesis [24].

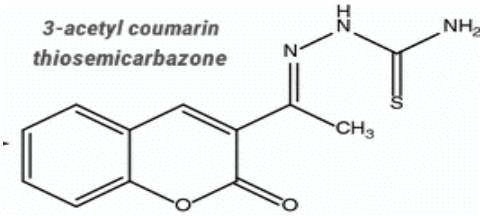
Inhibitors

Acetylcholinesterase (AChE) inhibitors helps to improve memory function and concentration in AD patients by interfering with breakdown of acetylcholine which results in increasing the level of the neurotransmitter at the synapse. There are currently three FDA-approved cholinesterase inhibitors such as galantamine (for mild to moderate AD), rivas tigmine, and donepezil (for all stage of AD[13]. Acetylcholine esterase function in neurotransmission, rapidly hydrolyses acetylcholine into acetate and choline in cholinergic synapse.

Ruthenium polypyridyl complexes are inhibitor of acetyl choline esterase and aggregates. $[Ru (phen) 3]^{2+}$ and $[Ru(phen)2(bxbg)]^{2+}$. The inhibitory action of these two complexes investigated using Thioflavin T (ThT) fluorescence and transmission electron microscopy [18]. Natural inhibitors of AChE is huperzine A, is a alkaloid isolated from Chinese medicinal herb *Huperzia serata* use for memory enhancement.

Nelumbo nucifera is an aquatic plant contain compounds having numerous medicinal properties and possible choline esterase inhibitory action [17].

Resource:



https://encrypted-tbn0.gstatic.com/image

Resource

The thiosemicarbazone compounds are used to reduce redox activity of metal ions and acts as an inhibitors against Aβ aggregation. Thiosemicarbazone modification of 3-acetyl coumarin inhibits Aβ peptide aggregation and its efficiency mainly toward inhibition of Aβ (1-42). Novel 3-acetyl coumarin thiosemicarbazone modification causes Aβ (1-42) peptide aggregation proved by several techniques such as ThT fluorescence assay, turbidity assay, ANS fluorescence assay and native gel electrophoresis.

It inhibits Aβ (1-42) peptide aggregation upto 80% as compare to 3-acetyl coumarin which inhibits 52%. [11]. Also Ru (II)-P-Cymene thiosemicarbazone complexes are inhibitors of amyloid β peptide aggregation [18].

The α-d-mannosylglycerate is a natural extremolyte identified in microorganism growing under extremely high temperature upto 100°C had been shown to protect against various stress condition such as heat, freezing and thawing. This also have property of suppression of Aβ aggregation and neurotoxicity to human neuroblast cell studied by using thioflavin –T induced fluorescence [23]. AD patients have defect in phagocytosis of amyloid β (1-42).

Macrophage plays important role in immune system help the body to fight against foreign protein. Curcumin treated with macrophage in blood, improve uptake and ingestion of the plaques. Curcumin acts as anti-inflammatory agent in Alzheimer's that decrease the main chemicals for inflammation and transcription of inflammatory cytokines [21].

4

Ginkgo biloba protects the brains against age related losses of cholinergic neurons and increases the intake of acetylcholine in the hippocampus. Ginkgo improves antioxidant activity as 12mg/day of extract [10].

Asperbenzaldehyde is one of the tau aggregation inhibitor is identified from *Aspergillus nidulans,* an intermediate azophilones biosynthesis. Addition of these derivative compounds to the tau aggregates reduced both the total length and number of tau polymer, they plays role in the stabilizing microtubules [27].

Grapes seeds are rich source of polyphenolic compounds, with proanthocyanidins has antioxidant properties. Phenolic compound in grapes is greater about 90% by weight determined by the Folin-Ciocalteu method. Grapes seed polyphenolic extract inhibits aggregation of Aβ peptide and blocks Aβ fibril formation by interfering with protofibril formation, pre-protofibrilar oligomerization and initial coil to α-helix β shweet [12].

Extract of cinnamon inhibits the tau aggregation by inhibiting the assembly of free tubulin into microtubules and filaments formation in AD disease. The cinnamon extract A-linked proanthocyanidin was purified and it acts as a significant role in inhibitory activity [21].

Microglia may promotes the neurodegenerative process, by forming proinflammatory cytokines such as interleukin and tumor necrosis factor α (TNF- α) which leads neural damage. Aged garlic extract (AGE) has multiple activity including anti-inflammatory effect. AGE improves short term recognition memory in cognitive by altering of microglia cells [20].

Genus salvia, commonly known as sage of Lamiaceae family. *Salvia miltiorrhiza* has been shown inhibition activity against Aβ induced neurotoxicity by inhibiting increase in tumor necrosis factor α (TNF- α) and acetylcholinesterase (AChE) activity [1].

Oligomeric acylated aminopyrazoles with a donor-acceptor-donor (DAD) forms hydrogen bond pattern complementary to that of a beta-sheet efficiently block the solvent-exposed beta-sheet portions in Aβ(1-40) and thereby prevent formation of insoluble protein aggregates [24].

Tau aggregation inhibitors (TAIs) also provide the therapeutic means for treating AD [8]. Cannbinoid are neuroprotective agent against excitotoxicity in brain damage. Synthetic cannabinoid prevents microbial activation, cognitive impairment and losses of neuronal markers [7].

CONCLUSION AND FUTURE PERSPECTIVES

Alzheimer's illness (AD), a main purpose for dementia inside the older, is an irreversible, reformist neurodegenerative problem clinically described by heart misfortune and intellectual decay that winds up in death for the most part inside 7-10 years after conclusion. Age is that the prevailing danger think about Alzheimer's infection, the reformist idea of neurodegeneration recommends an age subordinate cycle that eventually winds up in synaptic brokenness and neuronal harm in cortical regions of mind fundamental for memory and better mental capacities. The loss of synaptic capacities is by all accounts the basic think about intellectual decrease. Aβ could be a metal restricting protein Cu2+, Zn2+, Fe2+ advances Aβ oligomer formation.Cu2+ and Fe2+ are redox dynamic, generateROS. The medications right now accessible to treat Alzheimer's sickness address just its manifestations and with restricted adequacy. there's need to grow new remedial modalities like manufactured metal chelators or present bioactive particles to beat oxidative pressure and to repress collection of amyloid beta (Aβ) peptide which assumes a urgent function inside the pathogenesis of illness.

REFERENCES

Adrian L. Lopresti. Salvia (Sage): A Review of its Potential Cognitive-Enhancing and Protective Effects. Drugs R D. 2017 Mar; 17(1): 53–64.

Alessandro Biffi , and Steven M. Greenberg , Cerebral Amyloid Angiopathy: A Systematic Review J Clin Neurol. 2011 Mar; 7(1): 1–9.

Allsop D, Landon M, Kidd M. The isolation and amino acid composition of senile plaque core protein. Brain Res. 1983 Jan 24; 259 (2) 48-54)

Arvi Rauk. The chemistry of Alzheimer's disease. Chem. Soc. Rev. 2009 Sep; 38(9):2698-715

Bagheri S[1], Squitti R[2], Haertlé T [3,4,5], Siotto M[6], Saboury AA[3].. Role of Copper in the Onset of Alzheimer's disease Compared to Other Metals. Front Aging Neurosci. 2018 Jan 23; 9: 446.

Belen G. Ramirez, Cristina Blazquez, Teresa Gomez Del Pulgar, Manuel Guzman and Maria L. de Ceballos. Prevention of Alzheimer's disease Pathology by Cannabinoids: Neuroprotection Mediated by Blockade of Microglial Activation. Journal of Neuroscience 23 February 2005, 25 (8) 1904-1913

C.M. Wischik, J.M.D. Storey, D.J. Wischik, C.R. Harrington. Chapter 15 – Inhibition of Tau Aggregation as a Basis for Treatment and Prevention of Alzheimer's disease. Developing Therapeutics for Alzheimer's disease Progress and Challenges 2016, Pages 385–436

Danielle G.Smith, Roberto Cappai and Kevin J.Barnham. The redox chemistry of the Alzheimer's disease amyloid β peptide. Biochimica e t Biophysica Acta (BBA) - Biomembranes Volume 1768, Issue 8, August 2007, Pages 1976-1990

Dr. Edward R. Rosick. *Ginkgo biloba* has Multiple Effects on Alzheimer's disease. Life Enhancement May 2002

Dnyanesh S Ranade, Archika M Bapat, Shefali N Ramteke, Bimba N Joshi, Pascal Roussel, Alain Tomas, Patrick Deschamps, Prasad P Kulkarni. Thiosemicarbazone modification of 3-acetyl coumarin inhibits Aβ peptide aggregation and protect against Aβ-induced cytotoxicity. *European Journal of Medicinal Chemistry 2016 October 4, 121: 803-809*

Giulio Maria Pasinetti[1, 2] and Lap Ho[1.] Role of grape seed polyphenols in Alzheimer's disease neuropathology. Nutr Diet Suppl. 2010 Aug 1; 2010(2): 97–103

Igor O. Korole. Alzheimer's disease: A Clinical and Basic Science Review. MSRJ - 2014 VOL: 0414

James SA[1,2], Churches QI[3], de Jonge MD[2], Birchall IE[1], Streltsov V[3], McColl G[1], Adlard PA[1], Hare DJ[1,4]. Iron, Copper, and Zinc Concentration in Aβ Plaques in the APP/PS1 Mouse Model of Alzheimer's disease Correlates with Metal Levels in the Surrounding Neuropil. ACS Chem Neurosci. 2017 Mar 15; 8(3):629-637

Lennart Mucke[1] and Dennis J. Selkoe[2.] Neurotoxicity of Amyloid β-Protein: Synaptic and Network Dysfunction. Cold Spring Harb Perspect Med. 2012 Jul; 2(7): a006338**.**

Mandelkow EM[1], Mandelkow E. Biochemistry and cell biology of tau protein in neurofibrillary degeneration. Cold Spring Harb Perspect Med. 2012 Jul; 2(7):a006247

Nunan J[1], Shearman MS, Checler F, Cappai R, Evin G, Beyreuther K, Masters CL, Small DH. The C-terminal fragment of the Alzheimer's disease amyloid protein precursor is degraded by a proteasome-dependent mechanism distinct from gamma-secretase. Eur J Biochem. 2001 Oct; 268(20):5329-36.

Nutchareeporn Nillert[1,2] Jariya Umka Welbat,[1,2,3] Wunnee Chaijaroonkhanarak,[1]Kittisak Sripanidkulchai,[1,2] and Bungorn Sripanidkulchai[2,] . Neuroprotective Effects of Aged Garlic Extract on Cognitive Dysfunction and Neuroinflammation Induced by β-Amyloid in Rats. Nutrients. 2017 Jan; 9(1)

Peterson D.W[1]George RC, Scaramozzino F, LaPointe NE,Anderson RA,Graves DJ, Lew J.Cinnamon extract inhibits tau aggregation associated with Alzheimer's disease in vitro.J Alzheimers Dis. 2009; 17(3):585-97

P Cras, M Kawai, D Lowery, P Gonzalez-DeWhitt, B Greenberg, and G Perry. Senile plaque neurites in Alzheimer disease accumulate amyloid precursor protein. Proc Natl Acad Sci U S A. 1991 Sep 1; 88(17): 7552–7556

Shefali N. Ramteke, Gulshan R. Walke, Bimba N. Joshi, Srikanth Rapole2 and Prasad P. Kulkarni*1. Effects of oxidation on redox and cytotoxic properties of copper complex of Aβ1-16 peptide. Free, Volume 48, 2014 1417-1425

Shrikant Mishra and Kalpana Palanivelu. The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Ann Indian Acad Neurol. 2008 Jan-Mar; 11(1): 13-19

Simon C. Drew . The Case for Abandoning Therapeutic Chelation of Copper Ions in Alzheimer's disease. Neurosci. 02 June 2017

Smita R. Paranjape*, Andrew P. Riley, Amber D. Somozas, C. Elizabeth Oakley, Clay C. C. Wangs, Thomas E. Prisinzano, Berl R. Oakley, and T. Chris Gamblin. Azaphilones Inhibit Tau Aggregation and Dissolve Tau Aggregates *in Vitro. ACS Chem. Neurosci.*, 2015, *6* (5), pp. 751–760.

Vivian W. Chow,[1] Mark P. Mattson,[2] Philip C. Wong,[1] and Marc Gleichmann[2] . An Overview of APP Processing Enzymes and Products. Neuromolecular Med. 2010 Mar; 12(1): 1–12.

Received: 10th January 2021; Accepted: 01th Jule 2021; First distribution: 07th December 2022.