Egyptian Journal of Nutrition
Official journal of the Egyptian Nutrition Society
Print ISSN: 1687-1235
Online ISSN: 2090-2514
Vol. 40 (1): 14 – 23 (2025)
https://ejn.journals.ekb.eg/

Factors impacting Alzheimer's disease: new biological insights, promising diagnostic methods and treatments: an article review

Sahar S Atrees[1]; Mosaad Negam[2]

[1] chemistry department-science faculty fayoum university
[2] inorganic chemistry department-science faculty fayoum university

ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia and a prevalent neurodegenerative disease Alzheimer's disease is thought to be caused by the **abnormal build-up of proteins in and around brain cells**. One of the proteins involved is called amyloid, deposits of which form plaques around brain cells. The other pro tein is called tau, deposits of which form tangles within brain cells. In recent years, studies have provided a better understanding of Alzheimer's disease, but until recently, the combination of age-related changes in the brain with genetics, the environment, and lifestyle has not been fully understood. Many studies have investigated the preceding factors, including changes in brain tangles and plaques, and other biological features as metabolism of formaldehyde and metalloenzymes involved. In this study, factors associated with Alzheimer's disease, especially biological pathways such as tangles and plaque proteins (amyloid and tau), were identified. Metalloenzymes and chemicals such as formaldehyde (HCHO) will be studied in detail, with the goal of identifying new markers and treatments.

Keywords: Alzheimer disease, Amyloid protein, tau plaque, metalloenzymes and formaldehyde

Received: 5-2-2025 ***Accepted: 5-3-2025*** ***Published: 3-2025***

INTRODUCTION

Signs and symptoms of AlZheimer

Each charity is rated on many aspects of their operations including accountability, transparency, and fiscal responsibility. For seven consecutive rating periods, Cure Alzheimer's Fund has received 4-stars, the highest level possible.

People with memory problems have mild cognitive impairment (MCI), greater memory loss, wandering and repeated questions. People with more memory problems than normal for their age (**Vos , et al .2011**), but their symptoms do not interfere with their daily lives; they differ in

movement and become difficult, resulting in problems with sense and smell. This stage is called moderate Alzheimer's disease (**Ma t , 2014**). Damage occurs in areas of their brain that control language and consciousness, and they are unable to learn new things or dress or cope with situations. They may have paranoia and behave impulsively. Severe Alzheimer's disease occurs when brain tissue hurts, shrinks significantly, and cannot communicate and become completely dependent on others for care.

Alzheimer's disease is the biological process that begins with the appearance of a buildup of proteins in the form of amyloid plaques and neurofibrillary tangles in the brain. This causes brain cells to die over time and the brain to shrink

How the brain affects Alzheimer's disease

Toxic changes take place as abnormal build-up of proteins that form amyloid plaques and tau tangles (**Hippius and Neumdorfer**,**2003**). These changes cause healthy neurons to stop working, lose connections with other neurons and die. Damage to the hippocampus and entorhinal cortex, which are parts of the brain that are essential for forming memories, is essential. Age-related changes in the brain, including harm to neurons and other parts of brain cells that contribute to Alzheimer's disease, shrinkage, inflammation, and blood vessel damage (**Kametani , 2018**), and interference with free radicals and mitochondrial dysfunction that damage the brain, as well as multiple genes in combination with lifestyle and environmental factors, cause Alzheimer's disease.

Diagnosis of Alzheimer's disease

the diagnosis revealed a connection between cognitive decline and the presence of neurotic plaques and neurofibrillary tangles, confirming that AD is a complex disease with externally visible symptoms.

After these discoveries about the disease, the diagnosis takes two different directions: physical and biological: the first direction involves asking questions about people, family members, and friends about overall health, diet, and past mental problems; the second direction involves overcountermed medication; the second direction involves the ability to carry out daily activities and change behavior; the second direction involves conducting tests of memory; and the second direction involves problem-solving accounting, which can be used for diagnosis, including experiences with sleep, depression, anxiety, and agitation. Exploring new medication and nondrug strategies to manage these symptoms makes patients with AD more comfortable and helps their caregivers conduct the right drug for the disease (**Roblinson , et al , 2012**).

Biochemical diagnosis is considered more important because, given the biological steps of brain damage leading to AD, interference in the early stages and treatment are possible. These strategies are based on biological factors, such as proteins of neurons damaged as amyloid and tau (**Sang and Jackson , 2005**), other methods based on metalloenzymes that influence neuron firing, and chemicals that affect neurons and their enzymes, such as formaldehyde.

Chemicals and Alzheimer disease:

Age is the biggest risk factor for Alzheimer's, as it is for most types of dementia. This meansthat a person is more likely to get Alzheimer's as they get older. Above the age of 65, a person's risk of developing Alzheimer's doubles about every five years. formaldehyde is highly

reactive and is considered a CAS registry number (50 – 00- 0). It is found in paints, clothes and medical and industrial products (**Tulpule and Dirngen ,2013**), not only as an environmental pollutant but

also in substantial amounts in the human body via enzyme-catalyzed reactions.The formaline solution used in pathology results in 35% HCHO, whereas the fixation of tissue or culture cells results in 4% HCHO; thus (Cloose,et al. , 2008). An increase in HCHO leads to enzyme activity or acute exposure to high amounts of exogenous The balance between the formaldehyde disposal process and generation leads to a normal blood formaldehyde concentration of 0.1 mM, whereas in the brain, it is approximately 0.2 mM, and in the hippocampus and cortex, it is approximately 0.4 mM (Tong , et al. , 2013a). Table 1 shows that formaldehyde generates enzymes and related diseases. AD-aging and MS are associated with oxidative stress in the brain, confirming that formaldehyde has a role in neurodegenerative damage Alzheimer's disease makes it hard to make sensible decisions and judgments. People with Alzheimer's disease may make poor choices in social settings or wear clothes for the wrong type of weather. Everyday problems may be hard to solve. Someone with Alzheimer's disease may not know how to handle food burning on the stove or how to make decisions when driving. However, there may be ways to promote better brain health and reduce your risk of Alzheimer's by addressing certain lifestyle factors, including:Unmanaged chronic health issues, such as high blood pressure or hearing loss,Physical inactivity,Unhealthy diet,Alcohol misuse.Smoking. These diseases impair mitochondrial function together with brain lactate content as a consequence of an adequate supply of lactate to neurons to foster memory formation, while glutathione depletion in the brain has been demonstrated to cause behavioral changes; thus, formaldehyde-induced alterations in glucose and glutathione (GSH) metabolism contribute to deficits in behavior, cognition, and learning. These signs are observed in formaldehyde-exposed animals (Tong , et al. , 2013 b).

Table .1: formaldehyde endogenous enzymes metabolism and related disease.

Endogenous enzymes	disorder disease	reference
- Methylamine SSAO VAP1	AlZheimer multiple scierosis heart disease Diabetic mellitus	**Tulpule , et al ., 2013** **Tulpule , et al ., 2013** **Tulpule , et al ., 2013**
- Histone demethylation LSD1 JHDM	breast cancer sarcoma Bladder cancer	**Schild house , et al .,201** **Schild house , et al .,2011** **Schild house , et al .,2011**
- Methanol oxidation ADH1 Catalase	negligible	

Abbreviations: SSAO: semicarbazide-sensitive amine oxidase; VAP1:vascular adhesion protein; LSD1:lysine-specific demethylase; JHDM: domain containing histone demethylase; ADH1:alchol dehydrogenase.

Formaldehyde metabolism and brain health. GSH is an antioxidant involved in the oxidation of HCHO by ADH3, and formaldehyde generation processes include methanol oxidation–methyl amine deamination and histone demethylase. However, formaldehyde can be disposed of by reduction to methanol via the cytosolic alcohol dehydrogenase ADH (**Tulpule , et al . , 2013**) or oxidation to formate by the glycolytic enzyme ADH3 or by the mitochondrial aldehyde dehydrogenase ALDH 2 (**Unzeta , et al ., 2007**). The resultant formate that accumulates within cells has the potential to affect ATP production, as formate inhibits cytochrome C oxidase, which in turn induces glycolysis (**Schild house , et al ., 2011**).

Formaldehyde treatment also stimulates GSH export from glial cells in the brain (**Tulpule and Dringer , 2012**). Thus, GSH may act as a neurotransmitter and neuromodulator at glutamate receptors, which play a role in memory and learning. Figure 1 shows that GSH is involved in formaldehyde metabolism(**Davis , et al ., 2013**).

Figure.1. Exogenous source of formaldehyde (HCHO) and pathway involve metabolism.

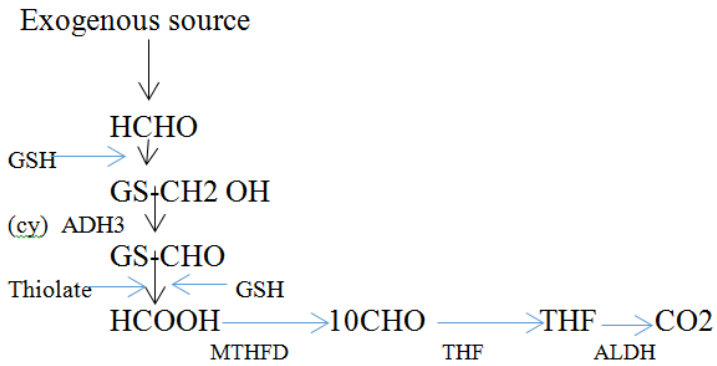

Fig. 1: formaldehyde (HCHO) oxidation product formate HCOOH is generated by mediate cytosolic ADH (cyto alcoholic dehydrogenase), along with glutathione GSH, conjugate S-formyl GSH hydrolyzed by thiolate to formate and GSH, the forming formate is further oxidized to CO2 by metabolic pathway involving tetra hydrofolate (THF) and mitochondrial tetrahydrofolate dehydrogenase (mit THFD).

The increase in oxidative damage contributes to the aging process and damaged mitochondria, which become less efficient, leading to a vicious cycle of increased reactive oxygen species (ROS) production. Healthy mitochondria are considered tools for preventing the progression of disease during aging, so the use of substances such as trehalose (**Atrees , 2024**) will improve their function, and this improvement will be related to oxidative enzymes, leading to an overall decrease in the spread of Alzheimer's disease and providing new treatments. Finally, measuring the exact concentration of formaldehyde in the early stage of disease or after the age of 40 regularly may provide new indicators for early detection of Alzheimer's disease. The metabolism of formaldehyde itself, as an enzyme involved in the generation of enzymes involved in disposing of these enzymes, is well known, and many studies on the activation or inhibition of these enzymes and the measurement of LDH and pyruvate dehydrogenase in the blood and CSF are needed for early diagnosis (**Davis , et al ., 2013**).

Metals and Alzheimer:

Neurometals are trace elements such as FE, Zn, Cu, and Mn that exist in the brain at different levels and with different distributions. Coper and zinc are essential for normal brain functions and are both localized in presynaptic vesicles and secreted into synaptic clefts during neural excitation. They play roles in the maintenance of brain structure and normal function (**Kawahara , et al ., 2022**). Zn overload or deficiency contributes to brain injury and exacerbates neurological conditions. Zn is associated with the activity of many matrix metalloproteins (MMPSs), cofactors of 300 metalloenzymes, polymerases and insulin.Alzheimer's disease is the biological process that begins with the appearance of a buildup of proteins in the form of amyloid plaques and neurofibrillary tangles in the brain. This causes brain cells to die over time and the brain to shrink.

Zn overload or deficiency contributes to neuronal injury. ZN deficiency in children results in dwarfism, delayed mental and physical development, and learning disabilities. Disorders of smell and taste occur in adults.

In addition, **neurogenesis and Zn and** Zn play critical roles in neural proliferation and differentiation, neural migration and axonal growth during neurodevelopment in the embryonic and neonatal periods (**Kawahara , et al ., 2022**;**Poshwat , et al ., 2015**). Free zinc, as an ion or a sustained fraction, loses its ability to bind mainly to metalloenzymes stored in presynaptic vesicles of excitatory glutamatergic neurons, is secreted in the cleft, binds to various N-methyl–D- aspartate type (NMDA)-glutamate receptors and other receptors, modulates dendritic functions, and inhibits AMPA–type glutamate receptors. Zinc also affects synapse plasticity, which appears to impact future memory and learning processes and even neurological abnormalities.Cu functions as a cofactor of many enzymes, such as uricase and dopamine hydroxylase. Cu plays a role in the synthesis of neurotransmitters, myelination and neuroprotection against reactive oxygen species. Cu, as a Zn, is located in synapses and is secreted in the synaptic cleft during neural firing. Secreted Cu in synapses regulates neural excitability (**Kawahara , et al ., 2022**) by binding to NMDA-type and AMPA-type glutamate receptors and GABA receptors, and loosely bound copper in synapses may bind to organic acids or ATP in excess, resulting in toxic effects.

Because CUs/Zn are important in neural functions, their levels are too high for normal healthy brains

The Cu/Zn concentrations in synapses are much higher than those in CSF, whereas the concentration of glutamate in the cleft is in the milligolar range. However, the Zn concentration increases to 10 nanomoles in CSF under ischemic conditions, whereas the Zn concentration in synapses is estimated to be 1–100 micromoles in Zn spike hippocampal synapses in neurons, which are long with Ca ion spikes; in this case, the Zn concentration increases (**Ross , et al ., 2013).**

Several factors regulate Zn/Cu homeostasis in the brain, mainly through the use of metalotransporters and metallothionsthey act as antioxidants via the accelerated action of ZN/cu superoxide dismutase and maintain the membrane structure and synthesis of metallothione. Figure 2. shows the effects of Zn on pathology and related diseases. By a variety of processes, Zn helps maintain redox equilibrium, as shown in Figure 2. Dietary intake of Zn is 11.5 mg/dl, and Zn deficiency of less than 56 micrograms/dl in women impedes the

growth of neurons, increases the risk of dwarfism, and impairs memory function. Thus, measuring the amount of ZN/cu in CSF regularly after 40 years of age may be an early sign of

Figure.2. zn physiology and diseases contributing

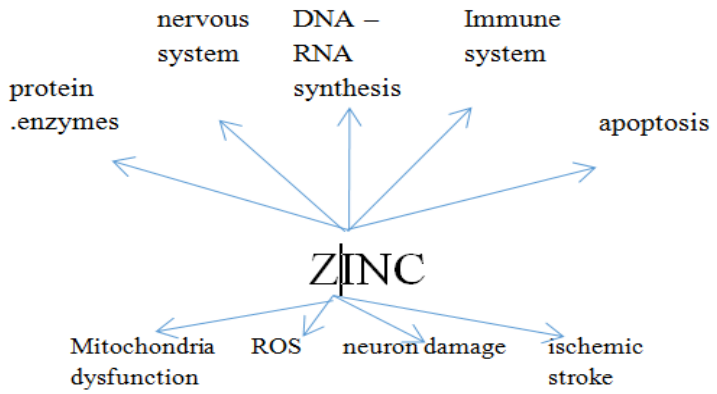

Fig.2: upward direction arrows: Zn as a trace metal involve in activity of numerous proteins and enzymes, deoxyribonucleic acids (DNA) and ribonucleic acids (RNA). Function of immune systems. Zn homeostasis is crucial for normal healthy brain neurons. Downwards arrows directions: Zn release in synaptic vesicles leads to neural disorders ,neuron damage, Zn is a redox –inert metal involve in redox regulation signals, Zn elaborate redox oxygen species (ROX) through action on mitochondria leads to ischemic stroke.

Metals and Proteins of Alzheimer's disease:

Brain changes that occur in Alzheimer's disease can affect moods and behaviors. Symptoms may include: Depression, Loss of interest in activities, Social withdrawal, Mood swings, not trusting others, Anger or aggression, Changes in sleeping habits Wandering, Loss of inhibitions Delusions, such as believing something has been stolen when it hasn't Alzheimer's disease tends to develop slowly and gradually worsens over several years. Eventually, Alzheimer's disease affects most areas of your brain. Memory, thinking, judgment, language, problem-solving, personality and movement can all be affected by the disease The five Alzheimer's stages can help you understand what might happen. But it's important to know that these stages are only rough generalizations. The disease is a continuous process. Each person has a different experience with Alzheimer's and its symptoms APP, a precursor protein of β–amyloid protein (AβP), which accumulates in the brains of AD patients and accumulates this protein, is believed to be involved in the pathogenesis of Alzheimer's disease (**Kawahara , et al ., 2022**).

Neuropath logical level of Alzheimer's disease:

Amyloid plaques are composed of amyloid–beta peptide (Aβ) (**Wong ,et al ., 2014**); when a transmembrane protein called amyloid precursor protein (APP) is cleaved by β-secretase, it yields two parts: SAPβ and C99; the C99 component is cleaved by alpha-secretase into AICD and different forms of Aβ, one of which is called Aβ42, which is considered toxic (**Liu , et al., 2019**); and Aβ42 Amyloid formation is a transition between a dilute solution phase and a

particular solid β-sheet.Both Zn and Cu ions are involved in dimerization, trafficking and expression of APP and the production of ABp.PrP, a 30-35 KA cell surface glycoprotein widely distributed in the brain, is a conformational change from a normal prion protein (PrPc) to a normal scrapei form (PrPsc) involved in the pathogenesis of prion disease in sheep, encephalopathy in cows, and Kurs in humans **(Singh , et al ., 2013**). ZN/Cu participates in the conformational change of PrP by binding four CUs to the N-terminus and two other CUs to the histidine amino acid at positions 96 and 111. Table (2) shows the toxic form of the brain protein.

Table .2. Alzheimer related proteins with enzyme involved and their toxic froms .

Protein name	**Toxic form**	**Enzyme involve**	**Reference**
Prp^{c}	Prp^{sc}	ZIP-type Transporters	**Singh , et al ., 2013**
α – synuclein	NAC	ferric reductase Ferri reductase	**Singh , et al ., 2013**
APP	AβP	Iron transporter	**Davies , et al ., 2011**
Tau monomer	Tau dimer Beta sheet Proline II helix	Cu- oxidase	**Barbier , et al ., 2019**

Abbreviations: Prp^{c} :prion protein; NAC :non-amyloid component; APP: precursor protein of β-amyloid protein; AβP: AlZhemier β- amyloid protein.

Frail peptide alpha–synuclein, termed the nonamyloidal component (NAC), participates in ABP plaques in AD. This protein binds Cu and Zn ions and other metals such as Mn ++ at its N-terminal end (**Davies , et al ., 2011**).

The tau protein is 352–441 amino acids long, acidic with an N-terminal region (1–165), a proline-rich middle region, a neutral C-terminal region, a transient second structure of alpha helices and beta-pleated sheets, and a polyproline 11 helix (166–242) that is highly soluble in nature and expressed in neurons in monomeric form. Metallthionine binding to tau (243--367) stabilizes soluble microtubules in neurons, which is essential for the stability of neurons and axonal nutrients (**Barbier , et al ., 2019**). Figure 3 shows the structure of the tau protein.

. 3. tau structure of neuron in brain

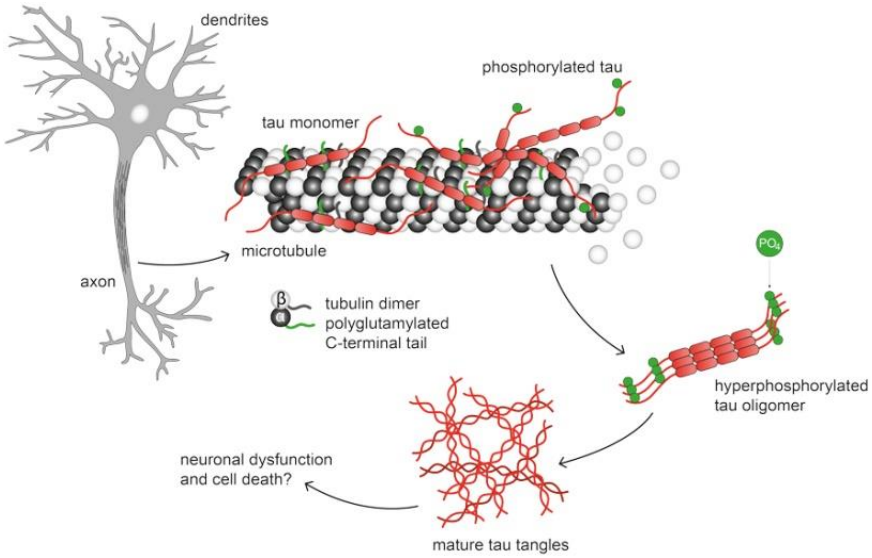

Fig.3: Human brain tau protein constitute a family of 6 isoforms with rang of 352-441 amino acids, truncated version of tau more likely to form the sticky filaments in brain of Alzheimer disease.

Abnormal chemical changes in tau lead to tau detaching from the microtubules of neurons, forming threads at joints and forming tangles inside neurons, and tangles block the neurotransporter system and transsynapic communication between neurons.

The findings of the present study suggest the following biological ways to regulate the progression of AD: First, the levels of several metals, especially copper/zinc, are regulated to normal conditions. Additionally, CU/Zn involves conformational changes in many neuroclump proteins; thus, the regulation of these two elements helps decrease AlZheimer because of their strong effects on metallothionine production, and these enzymes also affect Ad progression.

Copper consumption from drinking water, food sources such as nuts, meat, and fruits may increase excessive levels of Cu, which can create chemical imbalances, and toxic effects can lead to clumping of neuroproteins, leading to Alzheimer's disease. The second pathway involves the transformation of neuroproteins from the soluble phase to the solid phase, causing deposits and diseases in which solid beta sheets form amyloid and tau, which can form these plaques and tangles that are toxic to the brain. Additionally, a third pathway involves the study of enzymes involved in metallothionine metabolism in the brain, especially MT-3, which will provide information that can be used for early diagnosis and the use of these enzymes as new markers for diagnosis. Treatments.

The prevalence of AD increases from 5.3% in people aged 65--74 years to 34.6% in people aged 85 years and older. Neurodegenerative processes in neurons in AD are caused by many proteins, such as APP, alpha-synctein, PrP, and tau, which form tangles and plaques that are toxic to the brain. The ability of many biological pathways suggested in this review to manage brain cell toxicity and measure the OH proline content in tangles and plaques may be used as a new treatment for the inhibition of the prolyl hydroxylase enzyme, providing a new perspective for the diagnosis and treatment of AD.

Measurements of metal concentrations, especially those of Cu/Zn and related metallothionine enzymes, reveal that these metals bind to the above proteins and are strict in their conformation; thus, measuring their concentrations is promising, and chelators are used to decrease their degree of toxicity.

Finally, certain chemicals, especially formaldehyde, can be managed by balancing metabolism to normal conditions and may be used as measurement markers in the early stages of the disease in AlZheimer. All these suggestions need more study and research to be confirmed and directed in the right way of action**.**

.

REFERENCES

Atrees SS. 2024. Monoccacharide managements in diabetes : apathway to better health outs. An article review. Bultein of the nutritional institute of the arab repuplc of Egypt .64: 53-62.

Barbier P, Zejneli O, Martinho M, Lasorsa A. Belle R. et al. 2019.role of tau as a microtubule –associate protein .structure and function aspects:Frontiers in Aging NeuroScience.vol11; 204.https://doi.org/10.3389/Fnagi.2019.00204.

Cloos PA, Christensen J, Agger K,and Helin K.2008. erasing the methyl mark ,histone demethylase at the center of cellular differentiation and disease. Genes Dev .22,1115- 1140.

Davis MJ , Iancu OD, Acher FC,et al. 2013. Role of m GLUR 4 in acquisition of fear learning, and memory . Neuropharmacology ,66: 365-372.

Davies P. Moualla D, Brown DR . 2011. Alpha –synuclein is a cellular ferrireductase . Plos One ; 6: e 15814 Vos SJ, Xiong C, VisserPJ, Jasielec MS, Hassenstab J ,Grant EA, Cairns

Hippius H and Neundorfer G.2003. the discovery of Alzheimer disease . dialogs in clinical

Kawahara M, Tanka K-I, and Kato- Negishi M .2022. cross talk of copper and Zink in the pathogenesis of vascular dementia .J. Clin .Biochem. Nutr. Vol71,No.1:7-15.

Kametani F, and Hasegawa M.2018. reconsideration of amyloid hypothesis and tau hypothesis in Azheimer disease . Frontiers in neuroscience .12., 25.https://doi.org/10.3389/Fnins. 2018.00025

Li Z, Liu Y, Wei R, Yong W, and Xue M. 2023. The importance role of Zn in neurological diseases.Biomolecules.13: 28. https://doi.org/10.3390/biom13010028.

Liu P-P, Xie Y, Meng X-Y, and Kang J-S.2019. history and progress of hypothesis and clinical trials for AlZheimer disease . Signal Transduction and Targeted Therapy . 4., (29). https://doi.org/10.1038/s 41392-019-0063-8.

Ma T. 2014. GSK3 in AlZheimer disease : mind the isoforms Journal of AlZheimer disease ,39: 707-710. https://doi .org/10.3233/JAD-131661.

NJ, et al., 2013.perclinical Alzheimer disease and its outcomes : the lancet neurology 12., 957-965. https://doi.org/10.1016/s1474-4422(13) 701947.

Poshwat B, Nowak G, Szewczy K-B. 2015. Relation between zink and glutamate receptors in the processes underlying neurodegeneration .Neural Plast . 591563.

Roos PM , Veslerberg O, Syversen T, Flaten TP,and Nordberg M.2013. metal concentration in cerebrospinal fluid and blood plasma from pateints with amyotrophic lateral sclerosis . Biol Trace .Elem. Res. 151:159-170.

Robinson P, Giorgi B, and Sirkka-Liisa E.2012.the lived experience of early –stage AlZheimer disease : A three –year longitudinal phenomenol ogical case study .Journal of phenomenological Psychology .43,216-238.https://doi.org/10.1163/15691624-12341236.

Sang T K, and Jackson G R. 2005. Drosophila models of neurodegenerative disease . NeuroRX.2: 438-446. https://doi.org/10.1602/neurrx.2.3.438.

Schildhaus HU, Riegel R, Hartmann W.et al. 2011.lysine –specific demethylase in high expressed in solitary fibrous tumor . Hum . Pathol.42: 1667-1675...

Singh A, Haldar S, horback K, et al. 2013. Prion proteins regulate iron transporters by functioning as ferri reductases. J. AlZheimer. Dis; 35: 541-552.

Tong Z, Han C, Luo W,Wang X, Li H, Luo H, Zhou J, Qi Jand He R.2013a. accumulated hippocampal formaldehyde induce age –dependent memory decline. Age (Dordr.(35. 583-596.

Tong Z, Han C, Luo W, et al.2013b .aging –associated excess formaldehyde leads to spatial memory deficits . SCi .Rep. 3., 1807.

Tulpule K, and Dringen R.2013. formaldehyde in brain an overlooked player in neurochemistry.Journal of neurochemistry .127: 7-21. Doi : 10.1111/jnc-12356.

Tulpule K, and Dringer R. 2012. Formate generate by cellular oxidation of formaldehyde accelerate the glycolytic flux in cultured astrocytes .Glia .60: 582-593.

Tulpule K, Hahnholt MC, Dringer R.2013. formaldehyde metabolism and formaldehyde induced stimulation of lactate production and glutathione export in culture neurons. Journal of Neurochemistry .125:260-272.

Unzeta M, Sole M, Boada M, and Hernandez M. 2007. Semicarbazide –sensitive amineoxidase SSAo and its possible contribution to vascular damage in AD . J. Neural. Transm.114: 857-862

Wong B X, Tsatsanis A, Lim L Q, , Adlard PA, Buch AI. In addition, Duce JA. 2014. B-amyloid precursor protein doesnot possess ferroxidase activity but dose stabilize the cell surface ferrous –iron exporter ferro portin . PloS One; 9: e114174.