Chapter 9
Role of Alkoxyglycerol to Pause Tau-Induced Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is a common form of brain disorder and proper dysfunctionality which affect our thinking, learning, decision-making ability, results into inability to perform tasks efficiently. Dementia was studied and brought into light long since, from the pieces of evidences by Greek philosophers. But AD which is a common form of dementia appeared in 1906 in a 50-year-old woman suffering from common mental disorders. With passing time, the percentage increase in number of cases of AD and lack of proper diagnosis and treatment made it one of the most researched chronic mental disorder within scientific community. A lot of scientific studies and research have revealed that the hyperphosphorylated microtubule associated tau protein can be the cause of many neurodegenerative diseases in which tau mutations may be the cause for the hyperphosphorylated tau formation which effect neurons harshly results into neurodegeneration in brain. Many drugs are invented and used for the AD but they are not found to be much suitable cure for the disorder due to cost benefits and availability at right time everywhere. Later on, it is found that the AD and related dementia is the decline of plasmalogens, so a key glycerophospholipid may help in normal neuron function. With dietary supplementation of alkoxyglycerols (AKG) selective levels of plasmalogens can be restored and augmented in human body. AKG are ether lipids which is abundantly found in shark liver oil. Hence, AKG extracted from liver oil prove to be the suitable cure for AD and other types of neurodegenerative diseases. The researches are going on which is paving the way for invention of more effective and suitable cures.

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Abbreviations

A β	β-Amyloid
AD	Alzheimer's disease
AKG	Alkyl glycerol and /or alkoxy glycerol
Alkyl-Gro	1-*O*-alkylglycerols
ARTAG	Aging-related tau astrogliopathy
BBB	Blood Brain Barrier
CAA	Cerebral amyloid angiopathy
CNS	Central nervous System
CSF	Cerebrospinal Fluid
DHA	Docosahexaenoic acid
FDA	Food and Drug Administration
NFTs	Neurofibrillary tangles
PART	Primary age-related tauopathy
PHFs	Paired helical filaments
PlsEtns	ethanolamine plasmalogens
PNS	Peripheral Nervous System
ROS	reactive oxygen species
SLO	shark liver oil

9.1 Introduction

Alzheimer's disease is a common form of dementia which is the chronic and persistent mental disorder. The initial symptom of disease is like the mild memory loss and having inability to carry on conversation and environment respond (Mucke 2009; Goedert and Spillantini 2006). In scientific studies it has been found that risk of having AD and other types of dementia increases with increasing age. Increasing age can not only be the reason for the risk of having AD and other types of dementia. Studying the risk factor by comparing individuals of 65 to 85 years old revealed that individuals of 65 years old and above have a double chance of AD risk while individuals of 85 years and above only have a one-third chance of having AD (Keller 2006; Bartzokis 2004; Bell et al. 2019) (Fig. 9.1). The possible cause of AD can be genetic mutation. Other than genetic mutation, environmental impact and lifestyle factors can also be the possible cause of AD. The risk of having AD because of any of the above factors may vary from person to person (Purandare et al. 2006; Bush 2003; Drachman 2014). Tau mutation can cause neurodegeneration through tau hyperphosphorylation that results into formation of neurofibrillary tangle in brain. There is self-assembly of PHF/SF in AD brain due to tau mutation. Thus, a promising therapeutic treatment of AD can be offered by inhibition of abnormal hypophosphorylation of tau (Kandimalla

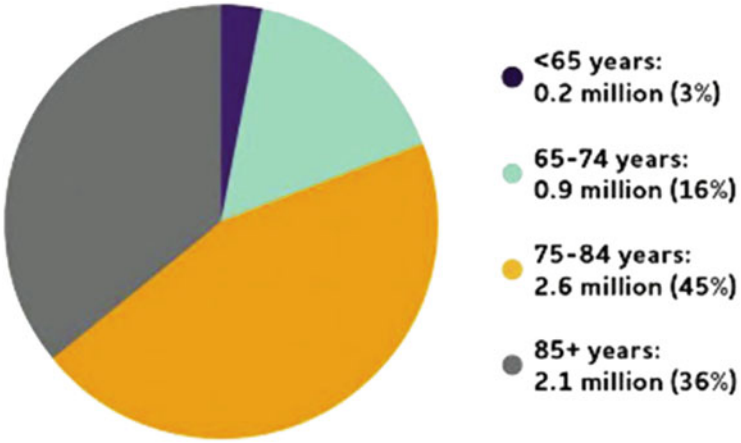

Fig. 9.1 Diagrammatic representation of ages of people with AD. (Adapted from Alzheimer's Association (2019))

et al. 2018). Hence there is a subsequent surge in healthcare costs due to unprecedented increase in number of people having this disorder. Clinically it is found that only four drugs are available for the treatment of AD symptoms, but they are unable to modify the disease. Consequently, having suitable cure is urgent demand of the time (Hung and Fu 2017). One emerging cure is alkoxyglycerol extracted from shark liver oil, found to have potential to cure AD (Poleschuk et al. 2020) In this chapter, various aspects related to AD will be summarised.

9.2 Dementia

Dementia is a group of symptoms which consistently occur together or a syndrome which shows a persistent nature and a combination of different states which are characterised by deterioration of activities of brain such as obliviousness, loss of capability for discernment along with reduced potential in social interactions and capacity to think. The people with dementia face impacts physically, psychologically, socially and economically, which significantly affects not only on their personal life but also on their related sectors of life including their walk of life, families, household and society at a large extent (Masika et al. 2020). Worldwide with nearly 60% people living in economically developing countries, 50 million people often suffers from dementia. In general population among the people aged 60 and higher, the people suffering with dementia at a specific period of time comes in between 5 and 8%. The total number of people who are suffering from dementia is estimated to come across about 82 million by 2030 and by 2050 it will be 152 million (Masika et al. 2020).

Dementia is acknowledged by World Health Organization as something which have gained a good priority in public health and endorsed a global agenda on public

health response in 2017–2025 to dementia which furnishes a blueprint for action in addressing dementia as a public health property, by establishing dementia friendly initiatives, which includes detection, therapy, consideration, research and innovation (Masika et al. 2020).

9.2.1 Alzheimer's Disease

Alzheimer's disease acts as seed or foundation to instigate chronic or persistent dementia. It is considered as a neurodegenerative disease and is also an important protein conformation disease, which is predominantly engendered by the adherent polymerisation and processing of commonly soluble neuronal proteins (Tiwari et al. 2019). When misfolded, soluble neuronal protein attains altered conformation, which happens due to external factors, genetic mutation, ageing and aggregate, and leads to abnormality in neural functionalities. The discovery of AD titled as a neurodegenerative disease has been accredited to Alois Alzheimer, who was a German neurologist. He examined an old woman aged 50 years, who was named as Auguste Deter. She was suffering from loss of memory, difficulty in speaking especially in areas of language, confusions and hallucinations. Her autopsy has revealed the existence of divulged tangles and plaques in the cerebral cortex, which has persuaded him that this has gone yonder the tangles of dementia. This discovery of Sir Alois Alzheimer has paved way to further research which has disclosed certain facts like the existence of neuritic Amyloid β plaques in people who are suffering from this particular disease (Tiwari et al. 2019).

The symptoms of AD and related changes in the brain are usually noticed after 20 years of an individual in dementia patients. All these symptoms will happen when nerve cells in various sites of brain which are involved in various activities like learning, thinking and memory are destroyed. The advancement of Alzheimer's disease from brain that are concealed to the individual affected starts with problems in memory and finally leads to physical disability, which is termed as the Alzheimer's disease continuum. This continuum has been broadly classified into three broad phases termed as (1) pre-clinical, (2) mild cognitive impairment and finally (3) dementia from AD (Dubois et al. 2016) (Fig. 9.2).

The pathogenesis of AD has been assigned to intracellular neurofibrillary tangles made with tau-protein which is hyperphosphorylated and found at human brain's cortical- limbic areas. The aggregates of amyloid beta plaques are found as extra-cellular aggregate matters. Upon identifying and interpreting the important causative factors and mechanism of pathogenesis of AD, it seems to be essential to come across the fields such as pathogenesis, different mechanisms, diagnosis and finally various ways that help to develop best therapeutics.

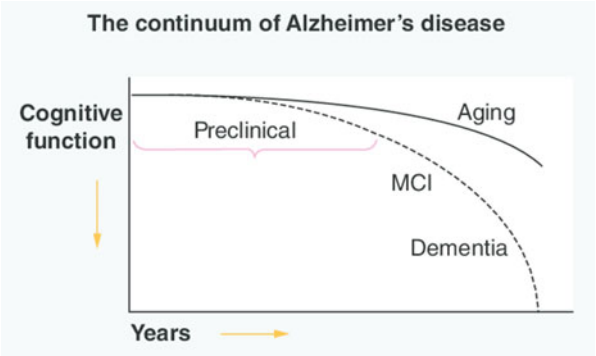

Fig. 9.2 The continuum of AD (Adapted from Sultan et al. 2018)

9.2.2 Neurological and Pathological Changes in AD

AD is a neurodegenerative disease. It results from a person's conditions like his/her genetic makeup, their age, enlightenment and society. Many postulates are there that set down the bedrock to attain the idea behind the examination of AD, from the most primitives like the cholinergic hypothesis. This cholinergic hypothesis is according to certain facts like AD patients usually exhibit abatement in action of acetyl cholinesterase and choline acetyltransferase in the cerebral cortex of their brain in comparison to the ordinary human brain. The post-mortem brain tissue from patients who had suffered from AD has established the sunken neurotransmitter pathway activity, which reveals the loss of cholinergic neurotransmission which mainly hand out to the cognitive impairment found in people with AD (McGirr et al. 2020).

The macroscopic features of AD include a brain often with at least moderate cortical atrophy that is usually marked in brain's limbic lobe structures. The temporal and frontal cortices usually have atrophy of the gyri, with inflated sulcal spaces, while the somatosensory cortices and primary motor are usually found undisturbed. Finally, due to this, there is usually an inflammation of the temporal and frontal horns of the lateral ventricle, and the brain weight is found to be reduced in most affected individuals (Fig. 9.3) (DeTure and Dickson 2019).

The area of study towards perceptiveness of Alzheimer's disease pathogenesis is wide. The reported histopathological characteristics of AD revealed that they are extracellular aggregates of neurofibrillary tangles which seem to be intracellular aggregations. Aβ plaques are composed of hyperphosphorylated microtubules associated tau (Tiwari et al. 2019). The development of Aβ plaques is initiated in temporal region, then at basal portion and finally at neocortex region's orbitofrontal portion. In later stages it progresses throughout the neocortex, amygdale, hippocampus and diencephalon. In serious cases Aβ progresses throughout the mesencephalon, cerebellar cortex and lower brain stem (Tiwari et al. 2019).

The important neuropathological hallmarks of Alzheimer disease (AD) consist of positive bruises such as cerebral amyloid angiopathy, amyloid plaques, and

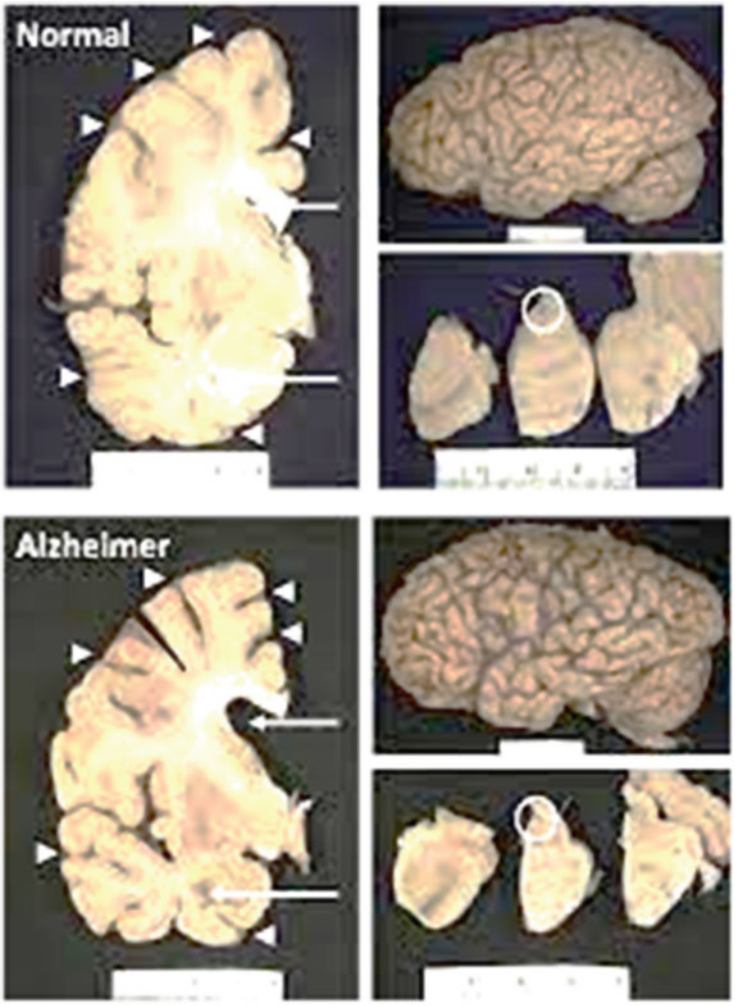

Fig. 9.3 Gross Anatomy of Alzheimer's Brain. (Adapted from DeTure and Dickson 2019)

neurofibrillary tangles and the negative bruises such as synaptic and neuronal damage (Serrano-Pozo et al. 2011).

Synapse and neuronal loss pave a great way for the tangle formation (Gómez-Isla et al. 1997; Arnold et al. 1991). This neurodegenerative process is distinguished by primordial impairment of synapses with retreating deterioration of axons which finally results in the atrophy of the perikaryon and dendritic tree. The synaptic loss at the limbic system and neocortex strongly correlate the cognitive deterioration seen in patients suffering from AD. The trans-synaptic delivery of Aβ promotes neurodegeneration characterised by synapsis loss. The Aβ oligomers secreted by

cultured neurons have the potential to damage spines and interfere with activity of regulated cytoskeleton associated protein distribution (Serrano-Pozo et al. 2011).

The pathology of AD is evidently simplistic and deceitfully multiplex. It is outwardly facile since it is composed of only two main bruises each and everything with a dominant singular protein, derived from well-circumscribed metabolic pathways. Both of these bruises occur with age and are the results of normal cellular metabolism from embryonic life to senescence (Castellani et al. 2006).

9.3 Physiological Function of Tau

As a microtubule allied protein, tau stabilises neuronal tubulins in turn stimulating axonal outgrowth. This intrinsically unfurled protein is soluble and has chance for aggregation (Wang and Mandelkow 2016). Tau protein regulates axonal transport, myelination, microtubule dynamics, neuronal excitability, iron equipoise, neurogenesis, learning and memory motor function, glucose metabolism, and DNA conservation (Fig. 9.4) (Kent et al. 2020). Sporadically tau protein happens to undergo alteration, mainly through phosphorylation that leads to certain pathological situations which are toxic to neuron. This results in several neurological disorders collectively called tauopathies, among which Alzheimer's disease is most common (Avila et al. 2004) (Fig. 9.5).

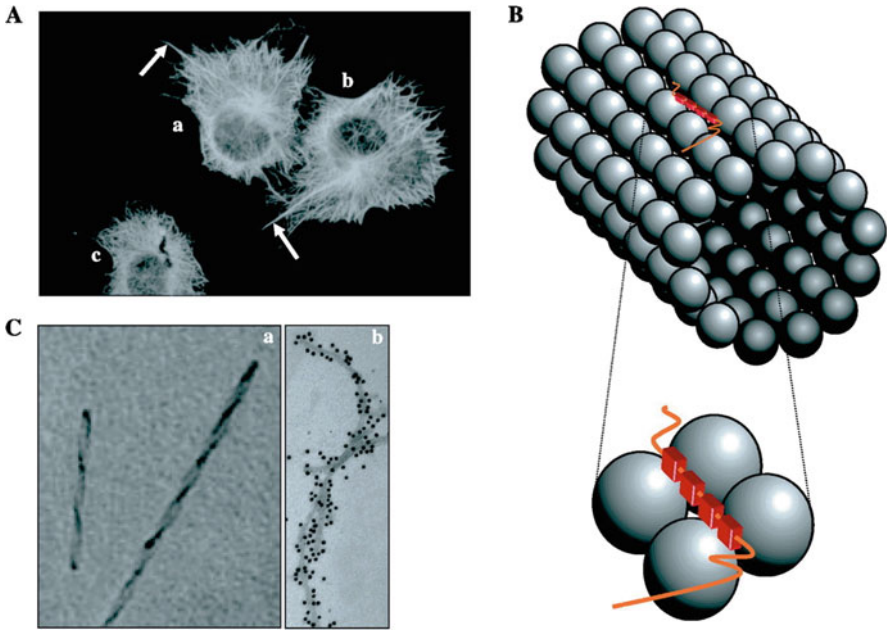

Fig. 9.4 Schematic representation of tau protein. (Adapted from Avila et al. 2004)

9.3.1 Role of tau in Neurodegenerative Diseases

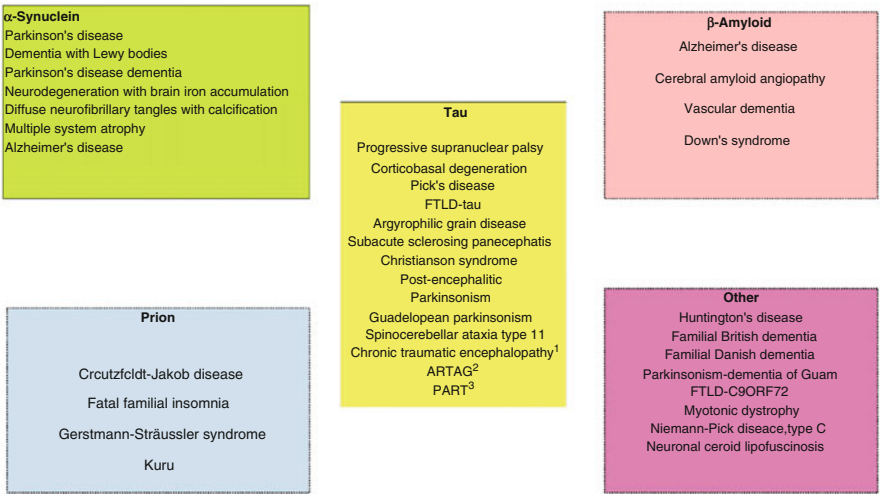

Fig. 9.5 Diagrammatic representation of tau pathology expressive in various neuropathological conditions where the middle box dictates the principal pathological feature of tau. The criss-crossing panels depict tau incorporation succeeded by disease associated auxiliary proteins.1. Chronic traumatic encephalopathy includes dementia pugilistica and traumatic brain injury; 2. ARTAG (Aging-Related Tau Astrogliopathy) that embraces Globular Glial Tauopathy; 3. PART (Primary Age-Related Tauopathy) and it involves clinically asymptomatic cases and tangle-predominant dementia; 4. FTLD, fronto-temporal lobar degeneration. (Adapted from Avila et al. 2004)

9.3.2 Tau Phosphorylation

Of the post-translational modification undergone by tau, phosphorylation is the most popular. A total of 85 putative phosphorylation sites are observed in tau, including 5 tyrosine residues, 35 threonines, and 45 serine which comprise 6, 41, and 53% of the phosphorylable remnants, respectively, on tau. These 85 acknowledged sites are categorised into two major categories: sites that are modified by kinases directed by proline such as tau protein kinase I (glycogen synthase kinase 3, GSK3), MAP kinase (p38), JNK, tau protein kinase II (cdk5), and other stress kinases like cdc2. The latter group is sites that can be modified by kinase directed by non-proline, like protein kinase A & C (PKA and PKC), calmodulin (CaM) kinase II, MARK kinases (23, 49, 65, 86, 117, 146, 199, 251), or CKII which alter residues abreast of acidic residues principally in exons 2 and 3 (49) (Fig. 9.6) (Guo et al. 2017).

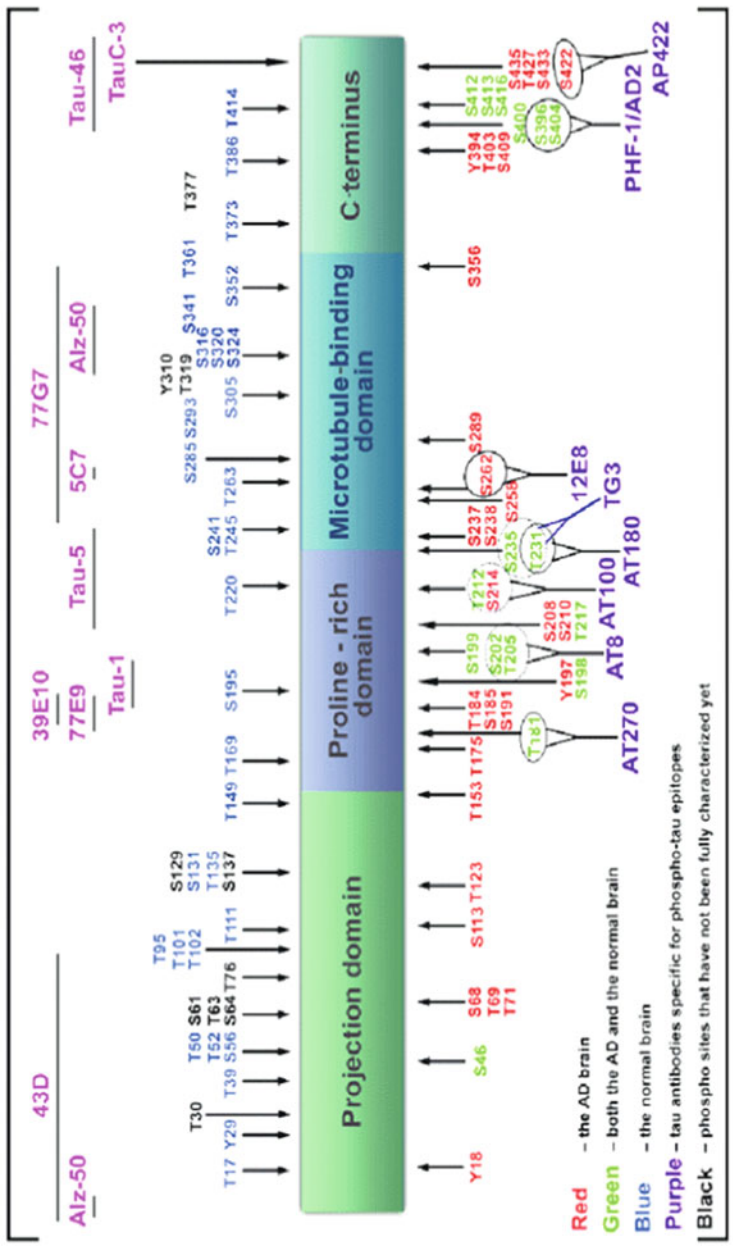

Fig. 9.6 Putative phosphorylation sites on tau (Adapted from Šimić et al. 2016)

9.3.3 Tau Toxicity in Neurodegenerative Disease

Hyperphosphorylation and formation of aggregates could be the leading cause of cytotoxicity mediated by tau in neurodegenerative diseases. In AD, it has been found that neurofibrillary lesions lead to an abate number of survivors, suggesting that degenerative processes may be involved in the development of extracellular tangles. In contrast, they are found in neurons having intracellular NFT. Accordingly, intracellular insertion occurs prior to apoptosis, the ligature of tau on extracellular matrix constituent like sGAGs(235) induces extracellular NFT to cell lysis. Thus tau aggregates appearing as sticky structure are toxic that could cohere and bereave off from cell (Avila et al. 2004).

9.3.4 Human tau Gene Expression

With 16 exons on chromosome 17q21, tau in humans is enciphered at MAPT, a microtubule associated protein tau gene (Wang and Mandelkow 2016). Tau protein has six isoforms of 37–46 kDa in the human nervous system resulting from differential splicing of the mRNA transcript of 6 kb. In the cerebral cortex, the 3R and 4R isoforms of tau are found in approximately identical quantities in healthy adults (Guo et al. 2017). By omitting exon 10, tau will have 3 microtubule-binding domains (3R), while from including it, tau will have 4 microtubule-binding domains (4R) (Fig. 9.7). Additionally by regulating exons 2 and 3, tau can incorporate (2 N or 1 N) or exclude (0 N) insertion of amino-terminals. Exons 4A, 6, and 8 can be translated in the PNS, producing larger tau proteins. Human tau expression changes with developmental stage, as foetal brains express only 0N3R tau, while adults express all isoforms (Kent et al. 2020).

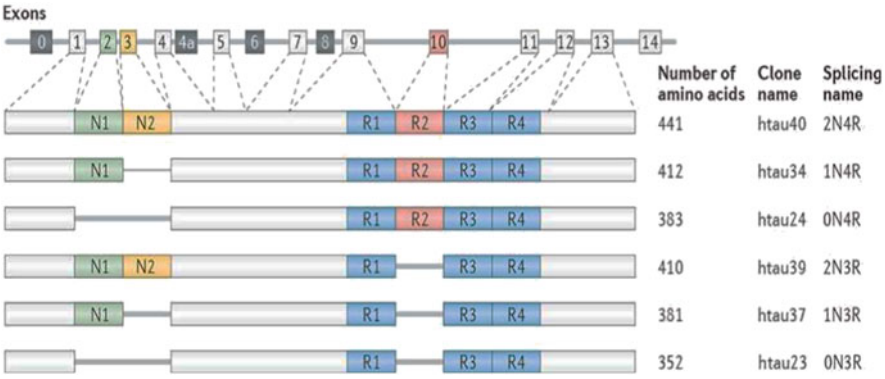

Fig. 9.7 Diagrammatic representation of the splice isoforms of tau in the human brain and MAPT gene. (Adapted from Wang and Mandelkow 2016)

9.3.5 *Immune Histochemical Localisation of tau in AD*

From various studies, it is established that tau is predominantly a neuronal protein yet its existence in distinct kind of glia cells is described to create neural disease. Tau can be modulated by phosphorylation in neural cells which are associated with the plasma membrane or as previously mentioned they can also be bound with microtubules. Evidence indicate the existence of nuclear antigen in proliferating cell that reacts with many tau antibodies. Furthermore, tau seems to be phosphorylated in the cytosol prior to transport into the nucleus (Avila et al. 2004).

In the developing neurons, the distribution of tau is affected by the phosphorylation. It is prominent in proline-rich region present in the somatodendritic region whereas in the distal part of the axon they are dephosphorylated. Phosphorylated tau in the distal axonal region seems to have carboxy-terminal domain (Avila et al. 2004).

9.3.6 *Pathological Alteration of tau in AD*

According to Mandelkow and Mandelkow (1998), these are the properties of tau that change in several ways during AD.

- Abnormal 'hyperphosphorylation' has been shown in AD at many sites such as 13, 14, and 26. Some of the enhancement is also seen in the tissue of foetal and mitotic cells and it prompts the theory where 'mitotic signals' gained by evolved neurons trigger tau hyperphosphorylation and, ultimately, apoptotic death. Most of the aberrant phosphorylation plots are Thr-Pro or Ser-Pro patterns, which shows why antibodies react with such phosphorylated epitopes mainly produced against AD-tau and are currently utilised to diagnose Alzheimer's brain tissue or to develop cell models. This research discovered that anomalous tau phosphorylation occurs before to aggregation.
- Microtubule binding is also lost in AD-tau, which is likely due to hyperphosphorylation at locations that release tau from microtubules (such as S262 or S214). This could explain the absence of microtubules, which would result in the breakdown of intracellular traffic, causing axons to die back.
- Tau is not being directed into the proper compartment in Alzheimer's disease, as evidenced by its reallocation from an axonal to a somatodendritic pattern. Various causes, such as increasing mRNA levels and tau synthesis, could lead the cell to become overburdened, causing the sorting system to malfunction.
- Tau agglomeration is primarily studied because of its unique solubility and unexplained behaviour. The aggregates are known as 'paired helical filaments (PHFs)' because of their two-stranded appearance. Their widths range from 10 to 20 nm, with 80 nm crossover repeats. PHFs clump together to form 'neuropil threads' or 'neurofibrillary tangles'. PHF accumulates in an ineffective amount in

in vitro, although it can be enlarged through oxidation, which triggers tau dimerisation, and interaction with polyanions like RNA or heparin.
- Proteolysis along with ubiquitination are the two post-translational modifications of AD-tau that are most likely cellular endeavour to reduce the abnormal protein (via the proteasome or the calpain pathway); although a few proteolytic fragments are detected early in the process, this could also lead to the nucleation of PHFs.
- Crosslinking and oxidative impairment elicit glycation and build up tangles.
- The amount of tau in the CSF has increased from 200 pg ml^{-1} to 600 pg ml^{-1}, indicating that withering neurons 34 are to blame. This feature has the potential to be used as a screening tool for early diagnostic test.

9.4 Alkoxy Glycerol

9.4.1 Definition

Alkoxy glycerol are naturally present ether lipids that present in haematopoietic or blood forming organ like bone marrow, liver and spleen. They are also found in cow's milk and various organs of human.

9.4.2 Chemical Composition

The principal alkoxyglycerol consists of batyl (octadecyl),chimyl (hexadecyl),and selachyl (octadecyl) ethers. Hallgren and Larsson (1962) conclude that glycerol ethers present as a form of diesters inside the tissue and also as alkyl acyl phosphatides (Fig. 9.8). 1-*O*-(2-methoxyalkyl) form of glycerol. Alkylglycerols were separated from the phospholipids and neutral lipids of milk of human, cow and sheep, human's colostrum, and also in the blood component like red bone marrow of human, uterine carcinoma, red blood cells, and blood's plasma.

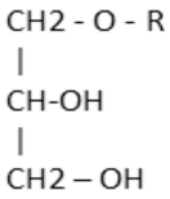

Fig. 9.8 Chemical Structure of Alkyloxy glycerol

Table 9.1 Percentage of AKG in the liver oil of shark and human milk and its bone marrow

Alkylglycerols	Milk (Human)	Liver oil (Greenland shark)	Bone marrow (Human)
14:0		2.0	
15		0.7	
16:0	23.9	9.1	29.4
16:1	Trace	10.8	
17	3.6	3.6	7.6
18:0	22.8	2.8	24.6
18:1	33.8	59.4	16.7
18:2	1.4	1.6	
18:3			
19	2.4	1.5	6.1
20:0	1.6		2.9
20:1	2.3	6.2	3.2
22:0	0.7		0.7
22:1	3.4	2.2	5.1
24	2.1		

(Fully adapted from Iannitti and Palmieri 2010)

9.4.3 Sources

AKG is found naturally in the milk of human, cow and sheep, and majorly found in shark liver oil (Table 9.1). The concentration of glycerol ethers in unsubstituted form is 10 times more in human milk when compared to cow's milk and it is double when compared to sheep's milk. The principal constituents of 2-methoxy-substituted glycerol ethers are the glycerol ethers having the long hydrocarbon chains of 16 and 18 carbon atoms. In some shark species or rat fish (elasmobranch fishes) liver oil is the major marine sources of alkyloxy glycerol (Iannitti and Palmieri 2010)

9.4.4 AKG and Blood Brain Barrier

In 1913, a researcher Edwin Goldman inserted a dye into the animal brain directly and concluded that injected dye into the brain was unable to spread and finally suggested that some types of barrier are halting the dye and discovered the blood brain barrier (BBB) (Iannitti and Palmieri 2010). Blood brain barrier is a major difficult path for delivery of the drugs into central nervous system (CNS) of human brain. It consists of several barriers in parallel and consists of two vascular BBB, namely the capillary bed and the barrier of blood-cerebrospinal fluid that consist mainly of the choroid plexus (Neuwelt et al. 2008). A single layer of cells in the brain paved together by close-fitting junction and formed BBB and this layer also prevents or controls the plasma seepage into the CNS. The BBB plays various roles such as: it blocks the entry of circulating substances present nearby CNS; it facilitates the

movement of critical substances necessary for the CNS function; and it also facilitates the movement of critical substances from the blood to the CNS and vice versa. So, it maintains the immune environments, nutritive and homeostatic of the CNS, and it controls the interchange of some informational components between blood and the CNS (Banks 2009).

Iannitti and Palmieri (2010) concluded about the opening of BBB and showed that intracarotid short-chain AKG shows low toxic and effective strategy against temporary BBB opening. It help to overcome a problem associated with the narrow admittance of various drugs such as cytotoxic drug to the brain. It has been noticed that AKG also transfers the methotrexate to the brain and lots of instruments and techniques have been illustrated for increasing barrier permeability by controlling the AKG movement. It has been proved that there are no toxic effects of BBB opening at therapeutics level. So, a new therapeutic procedure is represented by intracarotid AKG that helps in overcoming the narrow access of therapeutic agents and various drugs to the CNS.

9.4.5 Health Beneficiaries of Alkyl Glycerols from Shark Liver Oil

Various types of glycerols are present in the cells and fluid of body as bioactive ether lipids and are also known as Natural 1-*O*-alkylglycerols or alkyl-Gro. Alkyl-Gro are the precursors of phospholipids ether and contribute in the structure and function of specific cells membrane such as white blood cells (WBC) and macrophages. These compounds can also be extracted from milk and bone marrow lipids of human (Hallgren and Larsson 1962). High levels of alkylglycerol are associated with the liver oil in some species of shark and combination of these compounds is differed by the length and unsaturation of chain in the alkyl-glycerol group (Bordier et al. 1996a, b).

Some research shows that alkyl-Gro stimulates antibody production and haematopoiesis and found in the milk and other body fluids (Linman et al. 1959). It has been noticed that newborn offspring gets beneficial effects during oral treatment of pregnant animals. Oral treatment of shark liver oil (SLO) in the pregnant sows raise the particular immunoglobulins in the serum of sows used for treatment (Mitre et al. 2005). Oral supplement of SLO and natural purified alkyl-Gro shows the anti-tumour effects. The development of grafted tumour can be reduced and compaction of the number of pulmonary metastases can be done by the supplement of these two components (Pedrono et al. 2004; Deniau et al. 2010).

9.5 Relation of Plasmalogens, AKG and Alzheimer's Diseases

Plasmalogens are a type of glycerol-phospholipids that contain an alkenyl chain mainly in as O-16:0, O-18:0 or O-18:1 and an acyl chain present at the position of sn1 and the sn2, respectively, and primarily an ethanolamine head or choline group at the position of sn3 (Paul et al. 2021). These specific phospholipids are necessary components of cell's plasma membranes and are considered as endogenous form of antioxidant phospholipids (Lee 1998). They play vital roles in additional cellular process such as regulation of cholesterol, transport of cholesterol regulator and efflux of high-density lipoprotein-mediated cholesterol (Paul et al. 2021). All mammalian tissues contain plasmalogens but concentration is highly variable between tissues (Table 9.2). The concentration of plasmalogens is moderately high in brain, skeletal muscle, kidney and some immune cells types and low in liver.

In human, various diseases are associated with the deficiency of plasmalogens concentration in the organs. Due to some genetic disorders, broad deficit of plasmalogens can be detected in specific peroxisomal disorders because it affects the plasmalogens biosynthesis pathway (Steinberg et al. 2006). In some complex diseases, such as coronary artery disease, Alzheimer's disease, obesity and type 2 diabetes, reduced concentration of plasmalogens has been reported (Paul et al. 2021).

9.5.1 Plasmalogens and Alzheimer's Disease

On the basis of previous two decades' research, it has been concluded that there is a direct link of plasmalogens insufficiency with AD. It has been confirmed that concentration of ethanolamine plasmalogens (PlsEtns) decreased in the post-mortem samples of brain as well as in cerebrospinal fluid, plasma, RBCs and serum of patients diagnosed with AD (Rothhaar et al. 2012; Molina et al. 1998). The concentration of PlsEtns reduced during examination of the AD patient's brain (Onodera et al. 2015; Wood et al. 2010). It has been showed that high decrease in the concentration of PlsEtns was detected on the site of neurodegeneration in the brain such as temporal cortex, hippocampus and frontal cortex of AD brain.

Stress leads by the oxidation in the cells can lead to loss of PlsEtns in the AD brain and lastly leads to degradation of plasmalogen by reactive oxygen species (ROS) (Braverman and Moser 2012). It is the presence of vinyl ether bond by which plasmalogens become more vulnerable to oxidative stress (Mangold and Weber 1987). It shows that plasmalogens protect the other lipids from oxidative destruction and they act as scavengers (Reiss et al. 1997). Plasmalogens show antioxidant effects towards diverse range of ROS. The reduction of plasmalogens enhance the oxidative and membrane damage during AD (Su et al. 2019).

Table 9.2 Plasmalogen content in different human tissues

Tissue	PlsCho (%total PL)[a]	PlsEtn (%total PL)[a]	PlsCho (% GPCho)	Plasmalogen (%total PL)[a]	PlsEtn	Reference
Brain	0.8–0.9	20	1	22	58	Heymans et al. (1983), Panganamala et al. (1971)
Heart	11	15	26	–	53	
Kidney	4.7	14	5		46	
Skeletal muscle	6.5	14	19		48	
Liver	3.4	4.7	3		8	Han et al. (2001)
Grey matter						
Cerebellum					78	
Frontal cortex				54	57	
Temporal cortex					56	
Parietal cortex				51	58	
White matter						
Cerebellum					78	
Frontal cortex				76	84	
Temporal cortex					83	
Parietal cortex				100	81	
Neutrophils			3.6		68	Chabot et al. (1990)
Eosinophils			4		72	Ojima-Uchiyama et al. (1988)
Erythrocytes		20				Farquhar and Ahrens (1963)

[a]Overall phospholipid level comprises cardiolipin, PlsEtn, GPEtn, GPCho, GPIns, PlsCho, sphingomyelin, and GPser. (Fully adapted from Braverman and Moser 2012)

The level of antioxidant properties of plasmalogens is reduced significantly during oxidative stress and neuroinflammation (Katafuchi et al. 2012). It has been advised that there is correlation loop between ROS production, β-amyloid accumulation, neuroinflammation and plasmalogen deficiency (Su et al. 2019). The dilapidation of PlsEtns is mediated by the enzyme plasmalogen-selective phospholipase A2 which discharges arachidonic acid or DHA from glycerol. It leads to the loss of PlsEtns in the brain and is stimulated by ceramide which is produced during the inflammatory conditions (Farooqui and Horrocks 2001; Latorre et al. 2003). The

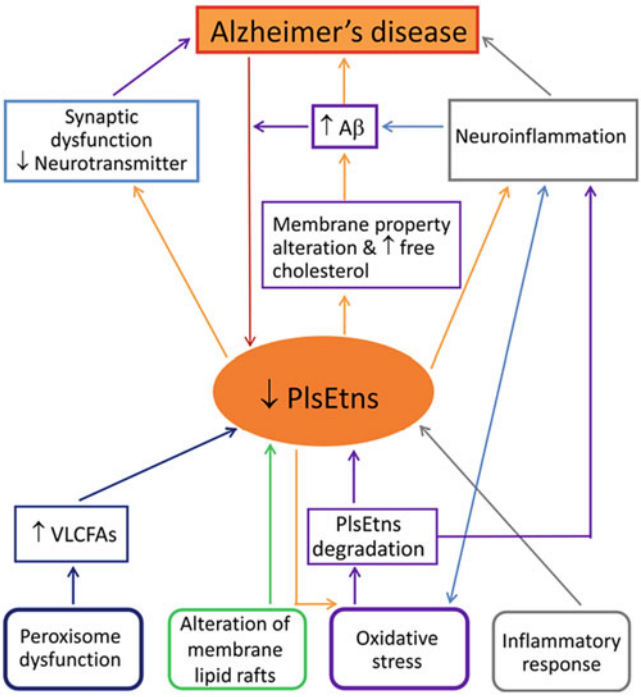

Fig. 9.9 Mechanism associated with ethanolamine plasmalogens insufficiency and Alzheimer's disease. (Fully adapted form Su et al. 2019)

synthesis of thromboxanes is done by DHA and it is also the precursor of leukotrienes and prostaglandins (Su et al. 2019). Metabolites such as maresins, docosatrienes, resolvins, and neuroproteins involved in anti-inflammatory process are derived from DHA. Arachidonic acid along with these derivatives control the pro- and anti-inflammatory processes (Su et al. 2019) (Fig. 9.9).

9.5.2 Plasmalogens and AKG

As per the study done by Destaillats et al. (2010), it has been found that some compounds from the group of alkyl glycerol and/or alkoxy glycerol enhance the plasmalogens in a mammal to a great extent than the endogenous level of plasmalogens in healthy mammal. These AKGs increased the levels of endogenous plasmalogens by avoiding the rate limiting peroxisomal stage of plasmalogen synthesis through several enzyme-catalysed reactions on the endoplasmic reticulum (Paul et al. 2021). They can be derived from natural biomass such as microorganism, animal by-products and natural products. Mostly these compounds are extracted

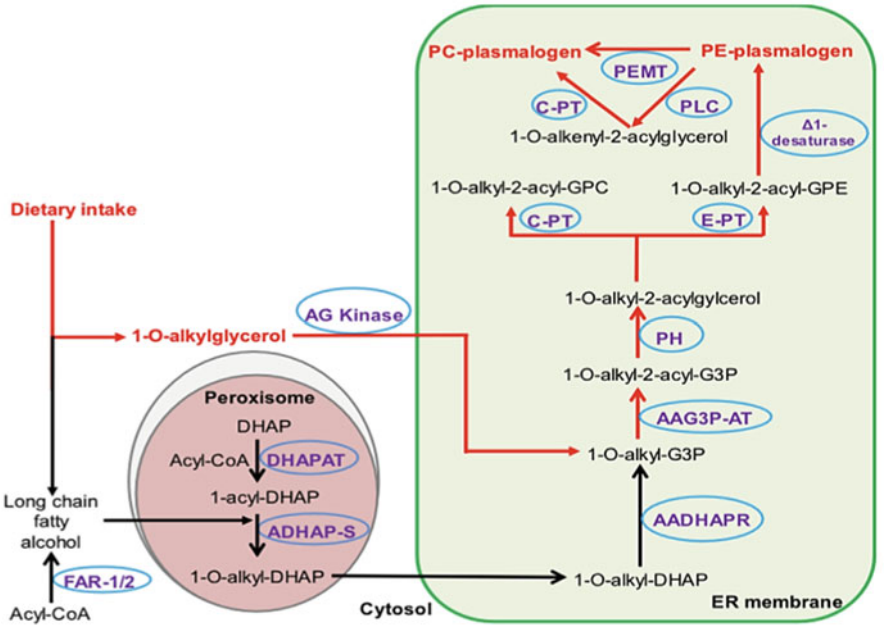

Fig. 9.10 Endogenous plasmalogen content can be modulated by AKGs. Red pathway indicating the bypass of rate- limiting peroxisomal biosynthetic steps by AKGs. Enzymes are shown in violet and metabolites are shown in red and black. (Fully adapted from Paul et al. 2021)

from marine oil such as fish oils and/ or egg lecithins. The major source of AKGs is shark liver oil (Destaillats et al. 2010).

Based on the research, it has been found that in initial stage AKGs metabolised into alkyl ether phospholipids and then change into alkenyl ether phospholipids or plasmalogens (Fig. 9.10) (Paul et al. 2021). So, increase in the concentration of alkyl ether phospholipids following AKG supplementation is a primary indicator of the integration of AKGs into the biosynthetic pathway of plasmalogens (Paul et al. 2021). AKG supplementation increases the level of alkyl-phosphatidylethanolamine (PE(O)) and alkyl-phosphatidylcholine (PC(O)) in liver, adipose tissue and skeletal muscle and typically reaching at peak after two-four weeks of AKG supplement treatment in mice. The level of alkenylphosphatidylethanolamine (PE(P)) and alkenylphosphatidylcholine (PC(P)) gradually increased in plasma of mice during the first 2 weeks of AKG treatment and the level of PE(P) progressively increased in the adipose tissue during 4 weeks treatment of AKG supplement (Paul et al. 2021). The increases in the level of PE (P) and PC (P) in the liver were most projecting after 12 weeks of duration during the AKG treatment (Paul et al. 2021). Additionally, the AKG supplement enhances the concentration of multiple plasma and adipose plasmalogen species that contain different alkenyl chains. It also increases the level of multiple hepatic plasmalogens but in smaller concentrations (Paul et al. 2021).

9.5.3 A Possible Therapy for AD: Plasmalogens

The promising result has been noticed by several researchers for preventing AD by applying plasmalogens replacement therapy in animals (Su et al. 2019) that intraperitoneal administration of purified form of plasmalogens in the hippocampus of adult male mice reduces the neuroinflammation by inducing lipopolysaccharide (Katafuchi et al. 2012). In the hippocampus accumulation of β-amyloid protein can be eliminated by plasmalogen treatment and it is mainly correlated with the decline in the concentration of plasmalogen content in the hippocampus (Katafuchi et al. 2012). Nishimukai et al. (2003) concluded that concentration of plasmalogen increases by the factor of 3 in blood plasma, and in the liver, it is increased by 25% after feeding a phospholipids (10 wt.%) containing test diet to rats for 7 days. Wood et al. (2011) showed that reduced level of PlsEtns can be restored in plasma and brain of adult mice by oral supplementation of plasmalogens precursor PPI-1011 dose @ 100 mg/kg/day and this restoration of plasmalogen is related with a triggered re-myelination of neuronal cells.

9.6 Conclusion

In the twenty-first century, development in bio science is touching the sky but still after lots of research we could not get the full treatment of Alzheimer's diseases. It takes millions of lives each year. Because the age-related complete treatment of this disease is very hard and with ageing our cells functioning degrade. In AD concentration of plasmalogens and some protein such as tau protein get fluctuated. But we can avoid this situation by using some natural compounds such as AKG. AKG is the best natural source that is obtained from shark liver oils majorly. It affects the concentration of plasmalogens and on the basis of research it has been proved that it helps in the curing process of AD. But the availability and purification of AKG affect a large number of shark's population. It affects the ocean ecosystem seriously. So, the main focus of scientist should be on production of AKG by some other organism such as microorganism like bacteria, fungi, etc. with the help of gene modification. Researchers should get the way of producing AKG synthetically so that there is no burden on our ecosystem. Even AKG also plays a vital role in other diseases such as cancer, opening of blood brain barrier and activating the immune system. AKG does not show any toxic effect on the opening of blood brain barrier. So, it has great importance for human life as it can avoid several diseases.

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