

Lipid Integration in Neurodegeneration: An Overview of Alzheimer's Disease

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Abstract Various types of lipids and their metabolic products associated with the biological membrane play a crucial role in signal transduction, modulation, and activation of receptors and as precursors of bioactive lipid mediators. Dysfunction in the lipid homeostasis in the brain could be a risk factor for the many types of neurodegenerative disorders, including Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis. These neurodegenerative disorders are marked by extensive neuronal apoptosis, gliosis, and alteration in the differentiation, proliferation, and development of neurons. Sphingomyelin, a constituent of plasma membrane, as well as its primary metabolite ceramide acts as a potential lipid second messenger molecule linked with the modulation of various cellular signaling pathways. Excessive production of reactive oxygen species associated with enhanced oxidative stress has been implicated with these molecules and involved in the regulation of a variety of different neurodegenerative and neuroinflammatory disorders. Studies have shown that alterations in the levels of plasma lipid/cholesterol concentration may result to neurodegenerative diseases. Alteration in the levels of inflammatory cytokines and mediators in the brain has also been found to be implicated in the pathophysiology of neurodegenerative diseases. Although several mechanisms involved in neuronal apoptosis have been described, the molecular mechanisms underlying the correlation between lipid metabolism and the

neurological deficits are not clearly understood. In the present review, an attempt has been made to provide detailed information about the association of lipids in neurodegeneration especially in Alzheimer's disease.

Keywords Neurodegeneration · Alzheimer's disease · Oxidative stress · Lipid rafts · Ceramide · Sphingomyelin

Introduction

Lipids are considered as a group of naturally occurring hydrophobic or amphiphilic small molecules including fats, waxes, sterols, monoglycerides, diglycerides, triglycerides, phospholipids, and others [1]. Biosynthesis of lipid started with the conversion of carbohydrate into triglycerides through the process of lipogenesis in the endoplasmic reticulum. These synthesis processes further give rise to steroids including cholesterol and ergosterol [2, 3]. Fatty acids are considered as important components of biological lipids which are linked with the function of making building blocks of more structurally complex lipids. They also participate in the maintenance of the structure and function of cell membranes. Lipids are involved in a number of biological functions including energy storage, signaling, and acting as structural components of cell membranes [4, 5]. They can be divided into several categories depending on their origin from biological molecules like fatty acids, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, and prenol lipids [4]. Glycerolipids comprise the bulk of storage fat in animal tissues and function as energy storage. These lipids are mainly composed of mono-, di-, and tri-substituted glycerols, the most well known being the fatty acid triesters of glycerol, called triglycerides [6]. The initial steps involved in the metabolization of fats are the hydrolysis of the ester bonds of triglycerides and the release of glycerol and fatty acids from adipose tissue. A phospholipid is

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composed of two fatty acids, a glycerol unit, a phosphate group, and a polar molecule. It constitutes a major component of cell membranes and forms a semipermeable lipid bilayer that allows only certain molecules to diffuse across the membrane to enter or exit the cell [7].

The glycerophospholipids are usually referred as phospholipids and constitute the main structural component of biological membranes, like the plasma membrane, intracellular membranes of organelles, and neural cell membranes [8]. As glycerophospholipids are involved in the generation of second messengers including arachidonic acid, eicosanoids, platelet-activating factor, and diacylglycerol, they are considered as a reservoir for second messengers. They are also involved in metabolism, cell signaling, signal transduction, apoptosis, and modulation of activities of transporters and membrane-bound enzymes [8, 9]. Past studies reported that a slight alteration in the composition of glycerophospholipids in the brain may lead to various functional neurological disorders [8]. Likewise, glycerophospholipids, sphingomyelins, and sterol lipids including cholesterol and its derivatives are also an important component of membrane lipids that imparts various biological roles including hormone secretion and signal transduction [10].

Sphingolipids are the complicated family of compounds that derived from the aliphatic amino alcohol sphingosine. The sphingosine backbone is O-linked to amino acid serine and a long-chain fatty acyl CoA and then converted into ceramides, phosphosphingolipids, glycosphingolipids, and other compounds [11]. In the central nervous system, the composition of sphingolipids is quite high and involved in the structural maintenance. Additionally, their metabolites function as second messengers to modulate a wide variety of signaling cascade [11, 12]. Ceramides, a precursor to sphingomyelin, are the simplest sphingolipids that engaged in the formation of lipid rafts essential in the regulation of sphingomyelin pathway of signal transduction, proliferation, differentiation, programmed cell death, and senescence. They also act as the regulator of synaptic function and have been implicated in synapse formation, transmitter release, and plasticity [11, 13, 14]. The occurrence of signaling cascade at cellular level has been found to be linked with lipid signaling [15, 16]. It could occur with the activation of G protein-coupled or nuclear receptors, and also some specific lipids act as signaling molecules and cellular messengers [17]. These signaling molecules include sphingosine-1-phosphate, which is involved in the regulation of signal transmission, cellular growth, and apoptosis [18, 19]. Besides, other signaling molecules including diacylglycerol and the phosphatidylinositol phosphates are involved in the calcium-mediated activation of protein kinase C, and prostaglandins are involved in inflammation and immunity [20, 21].

There are growing evidences that cholesterol is of particular importance in the development and progression of the

disease. Studies have reported that elevated cholesterol levels increase A β in cellular and animal models which further associated with the increased risk of Alzheimer's disease [12, 22]. Neurodegenerative disorders and other CNS diseases have immense clinical importance, and in the present scenario, there is no effective cure for these diseases and disorders, resulting in an increase economic burden on the society and negative impact on the quality of life. The crucial role of lipids in tissue physiology and cell signaling is demonstrated in many neurological disorders that are associated with deregulated lipid metabolism [13, 23] (Fig. 1). The role of lipids in neurodegenerative diseases and disorders including Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and other CNS injuries has been suggested by a number of investigators, but the exact molecular mechanism involved behind this is still unclear. In the present review, we focused on how lipid metabolism is involved in amyloid processing, β -amyloid segregation, and impairment of synaptic transmission, leading to the pathophysiology of Alzheimer's disease.

Lipid Rafts and Neurodegeneration

Lipid rafts are plasma membrane microdomains loaded with cholesterol, sphingolipids, sphingomyelin, gangliosides, and glycosylphosphatidylinositol-anchored proteins, which provide a particularly ordered lipid environment and make them resistant to non-ionic detergent extraction using Triton X-100 [12, 24, 25]. It contains around 50 % elevated sphingomyelin and decreased phosphatidylcholine levels as compared to the plasma membrane [26]. In these rafts, cholesterol acts as a dynamic glue that cleaves the raft together and serves as a molecular spacer [27]. Lipid rafts include receptors, channels, recognition molecules, coupling factors, and enzymes which are involved in signal transduction and intracellular trafficking of proteins, lipids, secretory and endocytic pathways, and inflammation and in cell surface proteolysis [28, 29]. In neurons, lipid rafts act as platforms for the signal transduction initiated by several classes of neurotrophic factors and hence are implicated in various physiological and pathological processes [30–32]. Studies also reported that lipid rafts are essential for neuronal cell adhesion, axonal guidance, and synapse communication [33]. Thus, in brain lipid, rafts play a very crucial role as these are structurally unique components of plasma membranes which are involved in the neural development and function and certain neurodegenerative diseases [34–36].

In case of neurological injury such as ischemia and early reperfusion, ceramide has been found to be overexpressed as a result of sphingomyelin metabolism. The overexpression of ceramide leads to the activation of mitochondria-dependent pathways including inhibition of anti-apoptotic proteins and

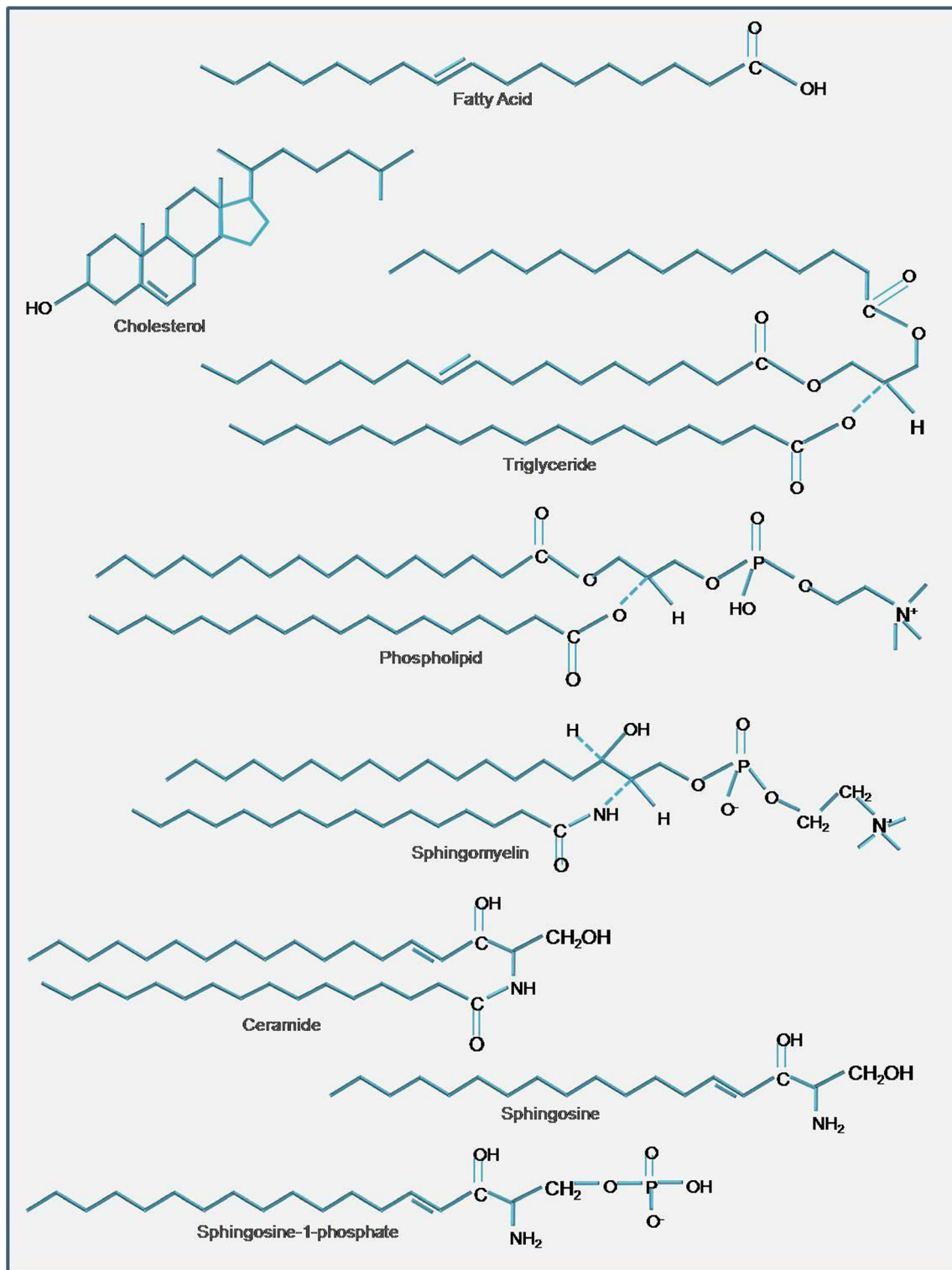


Fig. 1 Structure of some common lipids (fatty acids, cholesterol, triglyceride, phospholipids) and their components (sphingomyelin, ceramide, sphingosine, sphingosine-1-phosphate) commonly involved in the normal cell physiology and pathophysiology of neurodegeneration

electron transport chain, increase generation of reactive oxygen species (ROS), release of cytochrome c, and activation of caspase-3 and caspase-9, bax, SAPK, and cJNK that are associated with neuronal apoptosis (Fig. 2). In clinical and

experimental studies, increased levels of ceramide have also been reported in Alzheimer's disease [11, 12, 37]. Tau overphosphorylation and β -amyloid peptide accumulation have been found to be associated with the increased levels

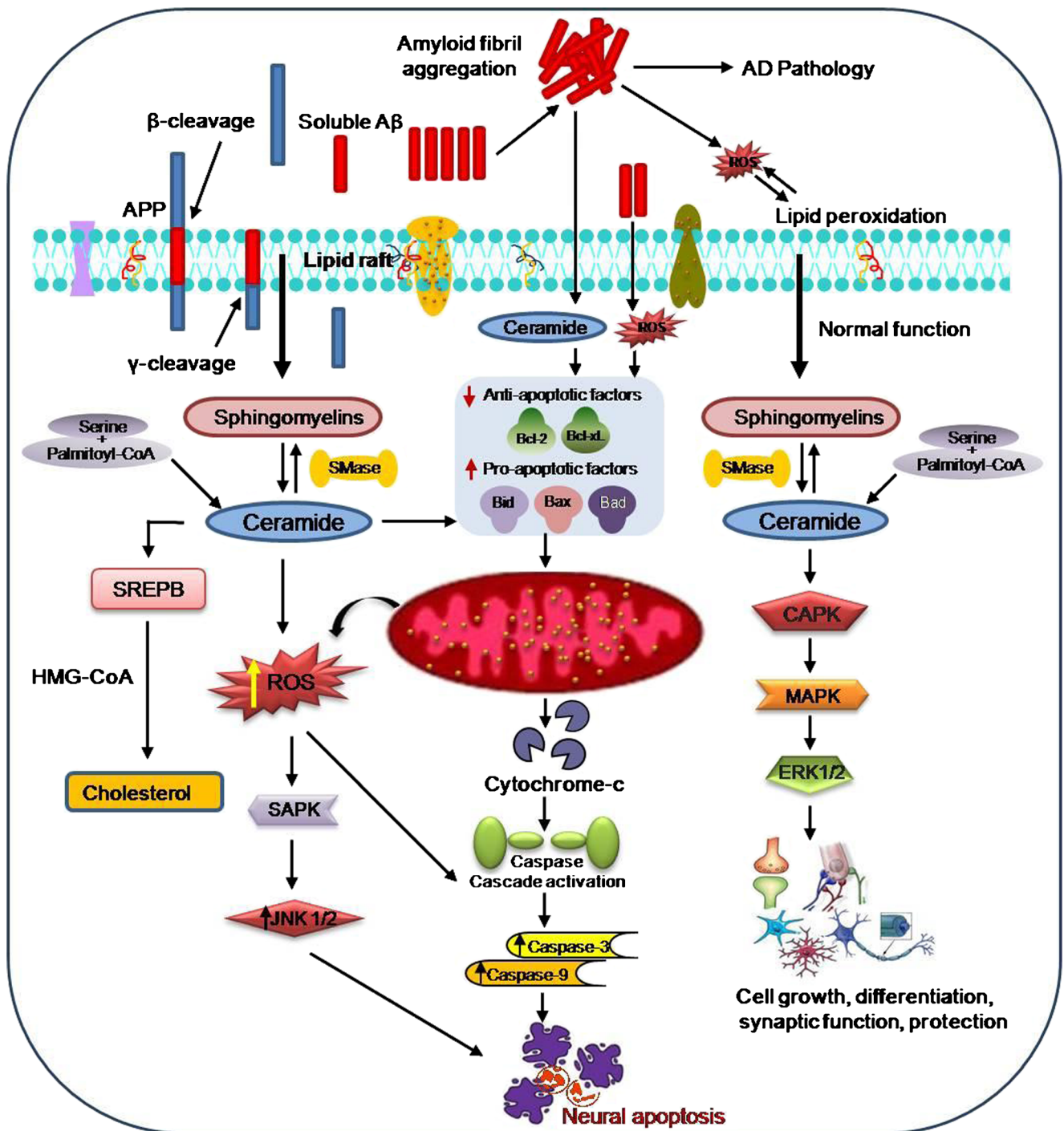


Fig. 2 Lipid raft-mediated signaling of sphingomyelin and ceramide allied with normal functions and apoptosis. Sphingomyelin and its secondary messengers are implicated in the regulation of cell survival and neural apoptosis. Amyloid fibril aggregation alters the ceramide concentration, resulting in the mitochondrial dysfunctions, enhanced generation of reactive oxygen species (ROS), and activation of cytochrome c. Increased level of ceramide as a result of sphingomyelin hydrolysis is also associated with the activation of proapoptotic factors and generation

of ROS that further activate SAPK kinase, Jun N-terminal kinases (JNKs 1/2), and caspase cascade, including the activation of caspase-3 and caspase-9. The outflow signaling through the JNKs and caspases ultimately triggers the onset of neuronal apoptosis, while the ceramide-induced activation of CAPK also activates MAPK kinase and extracellular signal-regulated kinases (ERKs 1/2). MAPK cascade strongly stimulates ERK but weakly inhibits JNK and therefore is involved in cell growth, differentiation, and the protective mechanism [49, 51]

of ceramide in the brain. Further, its high concentration in the blood may also be associated with the biochemical changes in the brain in the preclinical stage [38].

The deregulation of lipid metabolism affects the tissue physiology and cell signaling which leads to the various neurological disorders, including bipolar disorders,

schizophrenia, and neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's diseases [39].

Lipid Integration in Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disorder associated with loss of neurons. It is characterized by the presence of excessive amounts of neuritic plaques containing amyloid β protein and abnormal tau protein filaments in the form of neurofibrillary tangles [40–42]. Amyloid β protein has been associated to induce oxidative stress as a result of increased levels of lipid peroxidation products including hydroxynonenal (HNE), which can react further with various amino acids of associated proteins and alter their structure and function in the brain. The disease rapidly progresses to complete loss of mental powers, particularly loss of memory and normal emotional behavior. Dementia is a characteristic feature of Alzheimer's disease associated with loss of intellectual ability, leading to disruption of multiple higher cortical functions including memory, reasoning, orientation, learning capacity, and emotional stability [43, 44]. Degeneration of cholinergic neurons, particularly in the basal forebrain, has been found to be associated with loss of the neurotransmitter acetylcholine [45, 46]. Depletion of acetylcholine level in Alzheimer's disease patients appears to be a critical element in producing dementia [47]. In addition, direct association of lipid with Alzheimer's disease and the role of inflammatory mediators in the production and accumulation of β -amyloid protein, ROS, and lipid peroxide have also been reported [48, 49]. A lot of evidence on roles of lipids in Alzheimer's disease suggest that the alterations in the composition of brain lipid profile including phospholipid, sphingomyelin, ceramide, and ganglioside could be a causative factor in neuropathological or neurological disorders [11, 12, 50]. Lipids are involved in a variety of signaling events and functions; alterations in the levels of their composition in brain cells could modulate the signaling cascade and ultimately affect the neural function which further leads to Alzheimer's disease [23, 50, 51]. Lukiw and Bazan [52] reported the role of docosahexaenoic acid (DHA), a dietary essential polyunsaturated fatty acid (PUFA) enriched in fish oil, in maintaining the cell structure and function in the nervous system. They further suggested that the decline in the level of DHA leads to the oxidative stress, apoptosis, and cognitive and neuronal dysfunctions in Alzheimer's disease. Studies also reported that neuroprotection D1 (NPD1), the first identified DHA-derived mediator, significantly allied with cell survival and repair through the activation of anti-apoptotic and anti-inflammatory signaling [53].

The first reports of alterations in glycolipids including levels of gangliosides, cerebroside, and cerebroside sulfatide in Alzheimer's disease came out in the late 1960s [50, 54].

Further, in the 1990s, brain phospholipid content was also reported to be decreased in Alzheimer's disease [55]. Decreased phospholipid species in specific brain regions including the hippocampus and parahippocampal gyrus of Alzheimer's disease brains were suggested due to increases in phospholipid turnover as evidenced by increase in the phospholipid catabolite glycerophosphocholine [55]. Bassett and Montine [56] reported that apolipoprotein E present in the central nervous system is principally involved in the regulation of lipid transport and its metabolism through known receptor-mediated processes; hence, it is more vulnerable to oxidation than other lipoproteins which may contribute to neurodegeneration in the Alzheimer's disease brain. A number of other studies consistently reported the decreased levels of sphingomyelins and increased levels of ceramides in Alzheimer's disease brains as a result of sphingomyelin hydrolysis [37, 57, 58].

Oxidative Stress Markers and Alzheimer's Disease

Oxidative stress refers to the impairment in the antioxidant defense mechanisms as a result of excessive production of free radicals including superoxide radical, hydrogen peroxide, hydroxyl radical, nitric oxide, and peroxynitrite [59]. These are associated with the increased levels of lipid peroxidation, DNA, and protein oxidation products in brains and lead to neurodegenerative diseases including Alzheimer's disease [60–62]. The presence of a high content of PUFA in the brain makes it a highly oxidative organ consuming 20 % oxygen of the body instead of only 2 % of the total body weight; therefore, lipid peroxidation is thought to be a major cause of oxidative damage in Alzheimer's disease [23, 55, 63]. Brain cells are more vulnerable toward oxidative damage than any other cells due to their low activity of antioxidant enzymes and high number of mitochondria. Mitochondrial dysfunction and oxidative metabolism play an important role in the pathogenesis of Alzheimer's disease and other neurodegenerative diseases. Transition metals have been found to be accumulated in the brain and hence increase the susceptibility to free radical generations through the process of Fenton's reaction. PUFA is involved in the modulation of iron transporters that facilitate iron uptake and thus induce neuronal apoptosis [64, 65]. The increased levels of ROS cause oxidative damage to nucleic acids, proteins, carbohydrates, and lipids and are linked with the accumulation of oxidized products. These oxidized products such as lipid peroxides give rise to reactive α - and β -unsaturated aldehydes such as malondialdehyde, 4-HNE, and acrolein [60, 66]. High levels of HNE, an oxidative product formed as a result of enhanced lipid peroxidation, have been found in the Alzheimer's brain tissue [67–69]. DHA, another primary lipid peroxidation target in oxidative damage, has been found to oxidize non-enzymatically into various neuroprostanes and

may be involved in the generation of ROS and enhanced oxidative stress linked with cognitive decline and neuronal dysfunction [52]. The presence of acrolein, an α - and β -unsaturated aldehydic product of lipid peroxidation in neurofibrillary tangles in the Alzheimer's disease brain, has also been reported [60]. Increased levels of reactive oxygen and nitrogen species as a result of oxidative events in Alzheimer's brain may initiate the apoptotic cascade that significantly leads to cellular dysfunction and ultimately death [70, 71]. Autopsied brain from Alzheimer's disease patients indicated an increase in the level of protein oxidation, lipid peroxidation, and its toxic metabolite HNE and a decrease in the levels of PUFA. The levels of antioxidant enzymes including glutamine synthetase, creatinine kinase, and glutathione peroxidase were also found to be decreased in the brain in Alzheimer's disease [61]. The role of A β in the production of free radicals and in the pathophysiology of Alzheimer's disease has also been demonstrated by various investigators [41, 45].

Immunohistochemical and histopathological studies showed that the presence of oxidative stress products in neurofibrillary tangles and senile plaques as a result of oxidative stress is the important hallmark of Alzheimer's disease [71–73]. In addition to this, neuroinflammation was also found to be implicated in the pathogenesis of Alzheimer's disease. These inflammatory cytokines are activated as a result of enhanced oxidative stress and linked with neurodegeneration in Alzheimer's diseases [39, 74]. Recently, Bazan et al. [75] showed the protective role of DHA and its mediator NPD1 in the neuroinflammation and stroke-mediated brain damage through the discerning regulation of apoptotic and anti-apoptotic proteins. They further reported the protective role of NPD1 in Alzheimer's disease via the downregulation of amyloidogenic processing of the amyloid- β precursor protein and expression of pro-inflammatory genes.

Environmental factors including exposure to heavy metals and pesticides have also been found to be linked with enhanced vulnerability to the incidences of Alzheimer's disease in humans [76–79]. Studies demonstrated that exposure to arsenic activates the JNK3 and p38 MAPK associated with the formation of neurotic plaques and neurofibrillary tangles [80, 81], which may cause apoptosis in cortical neurons and contribute to Alzheimer's disease [82, 83]. We have also reported that arsenic accumulates in the brain regions and enhanced the levels of oxidative stress products and inhibition of antioxidant defense system in rats. Further, this enhanced oxidative stress leads to the death of neuronal cells in the hippocampal area and caused cholinergic dysfunctions [84]. In another study, enhanced oxidative stress as a measure of lipid peroxidation following exposure to lambda-cyhalothrin, a type II synthetic pyrethroid, and monocrotophos, an organophosphate pesticide in rats, and its association with cholinergic dysfunctions have also been reported [85, 86]. Besides toxicants, exposure to high levels of man-made electromagnetic radiations and their

adverse health effects has become a matter of concern for the health scientists. Some effects linked to electromagnetic pollution are decreased testosterone levels in men, miscarriages in pregnant women, birth defects in babies, Alzheimer's disease, cataracts, depression and suicides, chronic fatigue, and others [87]. In spite of that, a few studies have suggested that radiation emitted by a cell phone may interact with brain activity and behavior [88–90], gene expression and DNA, cell growth, proliferation and tumors [91, 92], hormones, proteins, and enzymes [93–95]. Recently, Kesari et al. [96] reported that exposure to electromagnetic radiation could be a risk factor childhood leukemia, brain tumors, genotoxic effects, immune system deregulation, allergic and inflammatory responses, infertility, cardiovascular and neurological effects, and neurodegenerative diseases. They further suggested that these deleterious health effects are associated with increased ROS, which may enhance the effect of microwave radiations and cause neurodegeneration.

Conclusion

The lack of neuronal repair in the central nervous system is the main basis of the severity of injury, functional deficits, and associated neurodegenerative disorders. The alterations in lipid metabolism and lipid rafts due to the enhanced oxidative stress and impaired enzymatic cascade are also associated with these diseases. These alterations result in the transformation of membrane flexibility and permeability which allow the accumulation of lipid peroxides and compromised energy metabolism that linked with the neurodegeneration. Deposition of amyloid plaques as a result of altered lipid rafts and generation of ROS to cause lipid peroxidation and damage to the biological membrane is found in Alzheimer's disease. The modulation in lipid raft synthesis and inhibitors against myelin inhibitory protein could be the constructive tool for neuronal loss therapy and may open new avenues for the treatment of neurological disorders and diseases. The present review has mainly focused on the involvement of lipids, their metabolites, and oxidative stress in the pathogenesis of neurodegeneration especially on Alzheimer's disease. As the production of amyloid precursor protein mainly regulated by the lipid rafts and its interaction with other molecules affects the signaling cascade, the review examined the mechanism underlying them. Further studies are required on lipid rafts to open new vistas in the regulation of signaling pathways and myelin inhibitory protein for the treatment of neurodegenerative diseases.

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