Review Article

Lipids and Stress: A Correlation in Neurodegenerative Disorders

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ABSTRACT

The significance of lipids in cell signaling and tissue physiology is demonstrated by many CNS disorders and injuries that involve deregulated metabolism of lipids as the brain is having high concentration of lipids. This review attempts to provide an overview of the lipid imbalances associated with various neurological disorders. As oxygen is essential for energy metabolism for the survival and normal functions of most eukaryotic organisms, it also partially reduced, into superoxide, a basic free radical that can be ultimately converted into other forms of reactive oxygen species (ROS) along the respiratory chain. Cell metabolism could generate other free radicals from nitrogen, classified into reactive nitrogen species (RNS). The various normal functions, such as regulation of signal transduction, induction of mitogenic response, and involvement in defense against infectious agents, etc have recently been demonstrated by ROS and RNS at physiological concentrations. In living organisms, ROS are balanced with antioxidant systems to keep their level constant. Over production of ROS and/or reduction of antioxidants can be deleterious, and is termed oxidative stress. Under these conditions, excessive free radicals could freely pass through the plasma membrane, damaging the cell membrane via lipid peroxidation, modifying signal and structural proteins to lead to misfolding and aggregation. Amongst the different organs in the body, the brain is particularly susceptible to oxidative stress due to its high oxygen utilization, weaker antioxidant enzymes, high content of easily oxidized polyunsaturated fatty acids, and the terminal-differentiation characteristic of neurons. Thus, this review also focuses on the role of oxidative stress on various neurodegenerative diseases.

Keywords: Oxidative stress, lipids, Stress, CNS disorders.

INTRODUCTION

Lipids have an obligatory role in normal physiological function of the neurons and structural development of the brain. The mood, perception and emotional behaviour of the subject is highly governed by lipid composition of the brain. It is very difficult to classify lipids. There are eight different classes of lipids that form the central nervous system.[1] Fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids and polyketides.

The functions of lipids include formation of lipid bilayers that form the structure and provide necessary channel for protein function, function as an energy reservoir (for example triglycerides) and serve as precursors for various secondary messengers such as arachidonic acid (ArAc), docosahexaenoic acid (DHA), ceramide, 1,2-diacylglycerol (DAG), phosphatidic acid and lysophosphatidic acid. The overall normal physiology of the brain is governed by these normal functions of the lipids. Any anomalous incongruity from the normal function of brain, either due to any mechanical injury or due to pathological changes in neurons, leads to different types of neurodegenerative diseases, mental disorders, stroke and CNS traumas. Currently there exists no cure for these CNS injuries and disorders, resulting in a huge impact on quality of life. In many neurological disorders, the lipids play a crucial role in tissue physiology and cell signalling. Both, neurological disorders and neurodegenerative diseases involve unregulated lipid metabolism.[2]

Stress is an adaptive response that prepares the organism for a threatening situation. It affects an individual both emotionally and physically. It is a threat, real or implied to homeostasis.[3,4] Stressors and related stress reactions are eminent.[5,6] When stressors challenge an organism's integrity, a set of physiological reactions is evoked to counteract a possible threat and adapt the organism (the physiological setting) to the new situation: The 'stress response'.[5-9] Thereby, one stress-responsive neuroendocrine effector system that has been studied extensively over the past decades is the sympathetic-adrenal-medullary (SAM) system, which is under the control of central neural pathways.[9-11] Another component of the stress response (i.e., the physiological system that regulates the biological reactions elicited in response to stressful/challenging stimuli or stressors) is the hypothalamic-pituitary-adrenal (HPA) axis.[10,12]

Neurodegenerative diseases, are characterized by progressive loss of structure or function of neurons, including death of neurons.[1,2] The increased oxidative stress has been suggested to involve in etiology of various neurodegenerative diseases. Cumulative oxidative stress may induce cellular damage, impairment of the DNA repair system[3], and mitochondrial dysfunction, all of which have been known as key factors in hastening of aging process

and the development of neurodegenerative disorders.[2,4,5] For these reasons, there have been continuing efforts to find the agents that can protect against oxidative damage and potentially treat neurodegenerative diseases.

Major brain Lipids and their importance

Phospholipids are essential components of all mammalian cells and have a variety of biological functions: (1) by forming lipid bilayers they provide structural integrity necessary for protein function, (2) they function as an energy reservoir (eg, triglycerides), and (3) they serve as precursors for various second messengers such as arachidonic acid, docosahexaenoic acid, ceramide, 1,2-diacylglycerol, phosphatidic acid, and lyso-phosphatidic acid. A deeper knowledge of the complexity of phospholipid metabolism will elevate our understanding of the role of lipids in maintaining normal cell physiology and how alterations in lipid metabolism contribute to various disease states.[2]

The essential function of lipids in cell signaling and tissue physiology is established by the large number of diseases and neurological disorders in which lipid metabolism is altered.[13] Lipid metabolism may be of particular importance for the nervous system, as this organ has the second highest concentration of lipids, exceeded only by adipose tissue. Many neurological disorders, including bipolar disorders and schizophrenia, and neurodegenerative diseases such as Alzheimer's, Parkinson's and Niemann-Pick diseases, involve deregulated lipid metabolism.[13]

Lipids and neurodegenerative disorders

Alzheimer's disease (AD)

It is the foremost common kind of dementedness, a progressive neurological disorder affecting regions of the brain that management memory and cognitive functions, step by step destroying an individual's memory and skill to learn reason, communicate and perform daily activities. AD is broadly divided into irregular or late onset AD (90-95% of AD) and early onset (occurring in persons below age sixty five, 5-10% of AD). Biochemically, cholesterol plays a awfully vital role within the aetiology of the disease. Apolipoprotein E, the most copiously found Apolipoprotein in plasma is the principal carrier protein of cholesterol in brain. Identification of the sequence secret writing the variant ApoE4 (APOE e4 allele) as a big risk issue for AD provided proof for a role of cholesterol within the pathological process of AD.[1,2, 14-16] It has been supposed that AD is characterized by overproduction of a protein named Amyloid-β protein that has a pair of subunits; Aβ42 and Aβ40. This protein ends up in the formation of plaques within the brain inflicting neuritic atrophy. Aβ40 inhibits HMG-CoA reductase, an enzyme important for cholesterol and lipid synthesis whereas Aβ42 activates neutral sphingomyelinase (N-SMase) and will increase ceramide production which might accelerate the neurodegenerative method. On these grounds, it's going to be plausible that if lipide made dietary supplement together with Aβ40 and Aβ42antagonist primarily based approach is designed for palliative treatment of Alzheimer's it's going to prove efficacious.[17-25]

Parkinson's disease (PD)

This malady is characterised by selective degeneration of dopaminergic neurons present within the neural structure, a basal ganglia structure set within the neural structure that plays a crucial role in movement, resulting in symptoms like bradykinesia, tremor and rigidity. The level of dopamine in brain falls due to hyperactivity of an enzyme Monoamine oxidase-B. This ends up in build of oxidative stress caused by radical generation and lipid peroxidation. One among the factors chargeable for this stress is believed to be phospholipases activation in neural structure. Some recent research suggests that PD is also associated with formation of Lewy bodies in brain, which are small agglomerates of protein named α-synuclein. These lewy bodies stay soluble in brain, however few aggregates that were related to polyunsaturated fatty acids (PUFA) remained insoluble, making them asymptomatic.[26-28] Although, there's a line of treatment for PD which incorporates use of medication like Levodopa, Carbidopa and MAO inhibitors however their extra pyramidal side effects (like, bradykinesia) remains a loophole of these drug therapy. A fatty acid named docosahexaenoic acid has been reported to stimulate oligomerization of α-synuclein. Recent studies have shown exaggerated levels of docosahexaenoic acid (DHA) in PD brains compared to controls, suggesting that DHA might have a task in formation of insoluble α-synuclein aggregates that don't show PD symptoms. Apparently, DHA cut reduced levodopa-induced dyskinesia indicating that DHA will reduce the severity or delay the event of levodopa-induced dyskinesia. Hence, it might be ended that DHA might represent a replacement approach to enhance the standard of lifetime of brain disease patients.[29-31]

Multiple Sclerosis (MS)

Multiple sclerosis (MS) is an inflammatory demyelinating disease affecting the CNS, however its underlying cause remains indefinable. Symptoms vary from comparatively benign to severely disabling, during which communication between the brain and alternative components of the body is discontinuous, rendering someone unable to write down, speak, or walk. In MS, the system attacks the medullary sheath of nerve cell fibers within the brain and spinal cord. MS is predominantly a T-lymphocyte mediated disorder, and cytokines could so have a key role within the pathological process of the disease. MS is that the solely neurological disorder where therapeutic manipulation of the cytokine system influences development of the disease.[32] Thiobarbituric acid reactive substances and F2-isoprostane levels were shown to be elevated in CSF of MS patients, and HNE was related to MS lesions, indicative that lipid peroxidation additionally happens in MS.[33]

Huntington's disease (HD)

Huntington disease is a chromosome dominant nervous disorder characterised by behavioral abnormalities, psychological feature decline, and involuntary movements that cause a progressive decline in useful capability, independence, and ultimately death. The pathophysiology of Huntington disease is joined to an expanded trinucleotide repetition of cytosine-adenine-guanine (CAG) amino acids within the IT-15 gene on chromosome 4. There's no disease-modifying treatment for Huntington disease, and novel pathophysiological insights and therapeutic methods are required. Lipids are important to the health of the central nervous system, and analysis in animals and humans has disclosed that cholesterol metabolism is disrupted in Huntington disease. This lipid dysregulation has been joined to specific actions of the mutant huntingtin gene on steroid regulative element binding proteins. This leads to lower cholesterol levels in affected areas of the brain with proof that this depletion is pathologic. Huntington disease is additionally related to a pattern of insulin resistance characterised by a catabolic state leading to weight loss and a lower body mass index than people while not Huntington disease. Insulin resistance seems to act as a metabolic agent attending disease progression. The fish derived omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, are examined in clinical trials of Huntington disease patients. Medicine that combat the dysregulated lipid environment in Huntington disease, could facilitate treat this confusing and cataclysmic hereditary condition.[34-37]

Stress and neurodegenerative disorders

Role of oxidative stress and lipid peroxidation in Alzheimer's disease

A number of studies illustrate increased lipid peroxidation in AD. Lipid peroxidation ends up in formation of acrolein, the strongest electrophile among all α, β-unsaturated aldehydes.[38-42] It reacts with DNA bases together with guanine, adenine, cytosine and thymidine to make cyclic adducts, the major exocyclic adduct being acrolein-deoxyguanosine. Increased levels of acrolein deoxyguanosine adducts were recently incontestible in brain tissue from AD patients. Reactive oxygen species (ROS) may additionally play a role in amyloid deposition in AD as oxidizing conditions cause protein cross-linking and aggregation of Aβ peptides, Aβ aggregation has been shown to induce accumulation of ROS, which can cause cyclic or self-propagating oxidative damage. AD and gentle Cognitive Disorder subjects conjointly showed lower levels of antioxidant defence systems. Thus, this signifies that oxidative stress plays a pathologically vital role in disease progression.[43-46]

Role of oxidative stress and lipid peroxidation in Parskinson's disease

In PD, the accelerated metabolism of monoamine neurotransmitter by monoamine-oxidase-B might lead to excessive reactive oxygen species formation. The oxidative stress in PD is marked by increase in 8-hydroxy-20-deoxyguanosine, a hydroxyl group radical-damaged guanine nucleotide commonly used to evaluate oxidative damage to DNA. Many markers of lipid peroxidation were conjointly found to be considerably exaggerated in PD brain regions like the concentration of poly unsaturated fatty acids within the neural structure is diminished, whereas that of malondialdehyde, a marker of lipid oxidization, is exaggerated. Extra proof of lipid oxidization in PD is provided by the demonstration of a rise in 4-hydroxy-2-nonenal, lipophilic product of the peroxidation of membrane bound arachidonic acid. Thereby, this means that pathologic process of degenerative disorder involves peroxidation of lipids that accelerated the metabolism of dopamine.[47,48]

Recent developments in Lipids & Stress management

Neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's diseases and Multiple sclerosis compose a gaggle of pathologies characterised by a separated etiology with distinct morphological and pathophysiological features. These disorders are outlined by a complex nature and have common neuropathological hallmarks like (a) abnormal protein dynamics with defective protein degradation and aggregation; (b) oxidative stress and free radical formation; (c) impaired bioenergetics and mitochondrial dysfunctions; (d) neuroinflammatory processes.[49,50] It is difficult to ascertain the right sequence of these events, however it's been shown that the oxidative damage to the brains of affected people is one in every of the earliest pathological markers.[51] At low levels, ROS operate as communication intermediates for the modulation of cellular activities however, at higher concentrations, they contribute to neuronal membrane damage.

The brain is very at risk of free radical injury because of its high oxygen consumption rate, high content of lipids, and relative scarceness of inhibitor protein compared with different organs.[52] Significant biological changes, associated with a condition of oxidative stress, are found in brain tissue of people plagued by PD, AD, and other diseases.[53,54-57]

Neuroprotective antioxidants are thought of a promising approach to slow down the progression and limit the extent of neuronal cell loss in neurodegenerative disorders.[58-61] These agents were classified by Behl and Moosmann in keeping with their mode of action in (a) compounds that stop the formation of free radicals; (b) compounds that with chemicals interfere with shaped free radicals; (c) compounds that limit the injury extent to the cell by assuaging the secondary metabolic burden of exaggerated levels of free radicals[62]. N-acetylcysteine, lipoic acid, GSH, and its thiol derivatives belong to the last category of neuroprotective antioxidants. Medicinal-chemistry-based methods embrace analogues[63,64], as well as prodrugs and codrugs approaches.[65] The codrug

approach consists in linking, via a covalent chemical linkage, two completely different pharmacophores with similar or different medicine activities so as to boost physiochemical, biopharmaceutical, and drug delivery properties of therapeutic agents. The ensuing codrug needs to be stable at epithelial duct level and transported to the target website of action wherever it provides the two parent drug following hydrolysis.[66] The codrug approach has been used for the treatment of PD and AD joining antioxidant or chelating molecules with a therapeutic compound (antiparkinson or anti-alzheimer's drugs).[67-69] Particularly, codrugs containing inhibitor molecules like GSH, N-acetyl-cysteine, methionine, and cysteinyl derivatives are synthesized so as to allow a targeted delivery of inhibitor on to specific teams of neurons wherever cellular stress is related to PD and AD. L-Dopa-GSH codrugs (LD-GSH, 1-2), obtained via an amide bond between LD and the C- and N-terminal GSH, respectively, have been synthesized and evaluated as potential anti-Parkinson agents with antioxidant properties.[70]

Few data are available within the literature regarding GSH codrugs for the treatment of AD. Recently synthesized Ibuprofen-GSH (IBU-GSH, 8) obtained via organic compound bond between GSH and IBU, a nonsteroidal anti-inflammatory drug (NSAID).[71] NSAIDs treatment reduces AD risk, delays unwellness progression, and reduces neuroglia activation.[71] Particularly, Lim et al.[72] reported that six months of treatment of a transgenic animal model of AD with IBU resulted in a very vital reduction of amyloid protein plaque burden and total Aβ peptide levels. Moreover, IBU treatment led to a discount of plaque-associated neuroglia and a corresponding attenuation in pro-inflammatory protein levels in brain.[73] Codrug possessed sensible stability towards human plasma protein activity and displayed in vitro free radical scavenging activity in time and concentration-dependent manner. More importantly, it antagonizes the injurious and psychological feature effects of β- amyloid (1–40) in a rat model for AD, as conjointly confirmed by behavioural tests of long spatial memory. In conclusion, IBU-GSH might permit targeted delivery of IBU and GSH directly to neurons, where oxidative stress and inflammatory processes are associated with AD.[71]

The connection between psychosocial stress and also the course of MS has been investigated in many studies. Thereby, the impact of acute or short-run stressors appears to be relatively tiny, whereas chronic psychosocial stressors, like social conflicts, loss and sophisticated sorrow, low perceived social support, anxiety, and depressive episodes, are thought to be doable risk factors for the event of MS exacerbations.[8, 74, 75] Moreover, psychological, cognitive-behavioral, or stress management interventions might become progressively vital therapeutic tools within the future treatment of MS.[8,75]

In HD, one study reported no increase in 8-hydroxy-2'-deoxyguanosine or different markers of DNA oxidation, and no amendment in lipid peroxidation (as measured by thiobarbituric acid reactive substances, a comparatively non-specific marker for lipid peroxidation). In distinction, different studies have shown increase within the lipid peroxidation markers F2-isoprostane and malondialdehyde in HD.[76]

CONCLUSION

Environmental factors can cause metabolic changes in humans that either increase the production of ROS/RNS or decrease the antioxidant production with increased lipid peroxidation, protein and DNA oxidation. Oxidative stress induces the formation of lipid peroxidation leading to prolongation of oxidative stress via the propagating chain reaction. Oxidized proteins accumulate in cells via aggregations, protein aggregates cause more mitochondrial damage, and damaged mitochondria can further induce protein damage. Nowadays lots of research have been done in this field to improve the quality of life of patients by exploring the various neurodegenerative disorders in relation to lipids and stress management.

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