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Altered Lipid Metabolism in Brain Injury and Disorders

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Abstract

Deregulated lipid metabolism may be of particular importance for CNS injuries and disorders, as this organ has the highest lipid concentration next to adipose tissue. Atherosclerosis (a risk factor for ischemic stroke) results from accumulation of LDL-derived lipids in the arterial wall. Pro-inflammatory cytokines (TNF- α and IL-1), secretory phospholipase A₂ IIA and lipoprotein-PLA₂ are implicated in vascular inflammation. These inflammatory responses promote atherosclerotic plaques, formation and release of the blood clot that can induce ischemic stroke. TNF- α and IL-1 alter lipid metabolism and stimulate production of eicosanoids, ceramide, and reactive oxygen species that potentiate CNS injuries and certain neurological disorders. Cholesterol is an important regulator of lipid organization and the precursor for neurosteroid biosynthesis. Low levels of neurosteroids were related to poor outcome in many brain pathologies. Apolipoprotein E is the principal cholesterol carrier protein in the brain, and the gene encoding the variant Apolipoprotein E4 is a significant risk factor for Alzheimer's disease. Parkinson's disease is to some degree caused by lipid peroxidation due to phospholipases activation. Niemann-Pick diseases A and B are due to acidic sphingomyelinase deficiency, resulting in sphingomyelin accumulation, while Niemann-Pick disease C is due to mutations in either the *NPC1* or *NPC2* genes, resulting in defective cholesterol transport and cholesterol accumulation. Multiple sclerosis is an autoimmune inflammatory demyelinating condition of the CNS. Inhibiting phospholipase A₂ attenuated the onset and progression of experimental autoimmune encephalomyelitis. The endocannabinoid system is hypoactive in Huntington's disease. Ethyl-eicosapentaenoate showed promise in clinical trials. Amyotrophic lateral sclerosis causes loss of motorneurons. Cyclooxygenase-2 inhibition reduced spinal neurodegeneration in amyotrophic lateral sclerosis transgenic mice. Eicosapentaenoic acid supplementation provided improvement in schizophrenia patients, while the combination of (eicosapentaenoic acid + docosahexaenoic acid) provided benefit in bipolar disorders. The ketogenic diet where >90% of calories are derived from fat is an effective treatment for epilepsy. Understanding cytokine-induced changes in lipid metabolism will promote novel concepts and steer towards bench-to-bedside transition for therapies.

Keywords

Atherosclerosis; Cholesterol; Inflammation; Neurodegenerative diseases; Stroke

1. INTRODUCTION

1.1. The Biological Membrane Structure and Function

Cellular membranes are composed of glycerophospholipids [phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS) and phosphatidylinositol (PI)], sphingolipids [sphingomyelin (SM), ceramide and gangliosides], cholesterol and cholesterol esters, acylglycerols, and fatty acids. The phospholipid bilayer and associated lipids provide not only a permeability barrier but also a structured environment that is essential for the proper functioning of membrane-bound proteins (Maxfield and Tabas, 2005). Cholesterol is one of the most important regulators of lipid organization as its structure allows it to fill interstitial spaces between hydrophobic fatty acid chains of phospholipids. The neutral lipids such as PC and SM predominantly reside on the outer or exofacial leaflet, whereas anionic phospholipids PS (exclusively inner leaflet), PE, and PI reside on the inner or cytofacial leaflet of the biological membrane. The transbilayer distribution of cholesterol between the leaflets determines membrane fluidity and can alter the membrane function. Cardiolipin is a phospholipid that is exclusively limited to the mitochondrial membrane and is essential for proper assembly and functioning of the mitochondrial respiratory chain and oxidative phosphorylation.

In addition to their role as structural components of the cell membrane, phospholipids serve as precursors for various second messengers such as arachidonic acid (ArAc), docosahexaenoic acid (DHA), ceramide, 1,2-diacylglycerol, phosphatidic acid, and lyso-phosphatidic acid. Lipids comprise a large number of chemically distinct molecules arising from combinations of fatty acids with various backbone structures. Overall, mammalian cells may contain 1,000–2,000 lipid species. Lipid metabolism may be of particular importance for the CNS, as this organ has the highest concentration of lipids next to adipose tissue.

1.2. Lipids and the Central Nervous System (CNS)

Neurodegenerative diseases, mental disorders, stroke and CNS traumas are problems of vast clinical importance. The crucial role of lipids in tissue physiology and cell signaling is demonstrated by the many neurological disorders, including bipolar disorders and schizophrenia, and neurodegenerative diseases such as Alzheimer's, Parkinson's, Niemann-Pick and Huntington diseases, that involve deregulated lipid metabolism (Fig. 1) (Adibhatla and Hatcher, 2007, and references cited therein). Altered lipid metabolism is also believed to be a key event which contributes to CNS injuries such as stroke (Adibhatla and Hatcher, 2008, and references cited therein; Adibhatla, et al., 2006a).

2. STROKE, TRAUMATIC BRAIN AND SPINAL CORD INJURIES

2.1. Stroke or “brain attack”: a problem of vast clinical importance

Stroke generally refers to a local interruption of blood flow to the brain and is the leading cause of long-term disability, third leading cause of death (Young, et al., 2007). Approximately 12% of strokes are hemorrhagic (rupture of a cerebral blood vessel), whereas the remaining 88% are ischemic and result from occlusion of a cerebral artery (either thrombotic or embolic). Blockage of a cerebral artery results in interruption of the blood flow and supply of nutrients, glucose and oxygen to the brain. The energy needs of the brain are supplied by metabolism of glucose and oxygen for the phosphorylation of ADP to ATP. Most of the ATP generated in

the brain is utilized to maintain intracellular homeostasis and transmembrane ion gradients of sodium, potassium, and calcium. Energy failure results in collapse of ion gradients, and excessive release of neurotransmitters such as dopamine and glutamate (Adibhatla and Hatcher, 2006), ultimately leading to neuronal death and development of an infarction. Excess glutamate release and stimulation of its receptors results in activation of phospholipases/sphingomyelinases (Adibhatla and Hatcher, 2006; Adibhatla, et al., 2006a), phospholipid hydrolysis and release of second messengers ArAc and ceramide (Adibhatla and Hatcher, 2006; Adibhatla, et al., 2006b; Mehta, et al., 2007). Ultimately these processes lead to apoptotic or necrotic cell death.

Focal cerebral ischemia or 'ischemic stroke' is caused by a local blockage of a cerebral artery that results in loss of blood flow to a portion of the brain. Stroke is characterized by an ischemic core (infarct) surrounded by a "penumbra" (peri-infarct) region that has partial reduction in blood flow due to presence of collateral arteries. The ischemic core is generally considered unsalvageable, whereas the penumbra may be rescued by timely intervention and is a target for the development of therapeutic treatment. Local arterial blockage can be caused by either a thrombus (a clot that forms at the site of the arterial occlusion) or an embolus (a clot that forms peripherally, dislodges into the arterial circulation and is transported to the brain). Atherosclerosis, discussed in the next section, is the main risk factor for development of these embolisms (Fig. 2). Inflammation poses as one of the high risk factors for stroke for its role in the initiation, progression and maturation of atherosclerosis.

2.1.1. Atherosclerosis is a risk factor for stroke—Atherosclerosis is believed to be predominantly an inflammatory condition produced as a response to injury (Elkind, 2006). Atherosclerosis is defined by the accumulation in the arterial intima of mainly low-density lipoprotein (LDL)-derived lipids along with apolipoprotein B-100 (apoB100). LDL is the major carrier of cholesterol in the circulation and is composed of one apoB-100 together with phosphatidylcholine (PC), sphingomyelin (SM) and unesterified cholesterol (500:200:400 molecules respectively) constituting a surface film surrounding a core of cholesteryl esters and triacylglycerols.

The traditional view of atherosclerosis has been simply the deposition and accumulation of cholesterol, other lipids, and cellular debris within the wall of medium to large arteries, resulting in plaque formation and disturbance of blood flow (Fig. 2). The role of cholesterol in atherosclerosis is well established and has been elegantly reviewed (Maxfield and Tabas, 2005). It is now believed that a complex endothelial injury and dysfunction induced by a variety of factors such as homocysteine, toxins (smoking), mechanical forces (shear stress), infections agents (*Chlamydia pneumoniae*) and oxidized LDL results in an inflammatory response that is instrumental in the formation and rupture of plaques, one of the greatest risk factors for ischemic stroke (Emsley and Tyrrell, 2002; Hansson and Libby, 2006).

Two critical events involved in atherogenesis involve accumulation and oxidation of LDL in the arterial intima and recruitment of monocytes to the developing lesion. After diffusion through the endothelial cell junctions into the arterial intima, LDL can be retained through interaction of apoB100 and matrix proteoglycans. LDL accumulates in the arterial intima when its rate of influx exceeds the rate of efflux. While the exact mechanisms governing LDL accumulation remain to be elucidated (Nicolo, et al., 2007), evidence indicates that LDL uptake and retention are increased at plaque sites, which may involve degradation or binding to cellular and matrix components. Once in the arterial intima, LDL can be oxidized to OxLDL through oxidation of polyunsaturated fatty acids (PUFA) of LDL lipids, particularly PC of LDL to form OxPC.

A second critical event in atherosclerosis is an inflammatory response that triggers expression of adhesion molecules (selectins and integrins) in the arterial endothelium, stimulating adhesion of monocytes to the endothelium. Monocytes penetrate into the arterial intima, differentiate into macrophages and eventually become foam cells by binding and endocytosing OxLDL through CD36 scavenging receptors (Fig. 2). Studies showed that oxidized phospholipids bearing the PC headgroup as a ligand on OxLDL mediate uptake by macrophage scavenging receptors such as CD36 (Boullier, et al., 2005). The macrophage foam cells generate ROS, produce tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1), and matrix metalloproteinase 9 (MMP-9) that promote atherosclerosis, degrade the fibrous cap, and eventually lead to plaque rupture.

Increased levels of TNF- α and IL-1 up-regulate expression of adhesion molecules and promote further monocyte recruitment into developing atherosclerotic lesions. Macrophage MMP-9 degrades extracellular matrix components including the fibrous cap of atheromatous plaques. Rupture of the fibrous cap exposes the blood to the inner components of the plaque, particularly tissue factor released from apoptotic macrophages. Tissue factor binds to activated coagulation factor VII and triggers the coagulation cascade, resulting in formation of a blood clot. Destabilization of this clot results in release of an embolus into the blood stream, which can be transported to the brain, where it can lodge in a cerebral artery and induce an ischemic stroke (Fig. 2) (Elkind, 2006; Emsley and Tyrrell, 2002; Hansson and Libby, 2006; Stoll and Bendzus, 2006).

2.1.2. Lipoprotein-PLA₂ (Lp-PLA₂), also known as platelet activating factor (PAF) acetylhydrolase—

Lp-PLA₂, a 45 kDa protein, is a member of PLA₂ family classified as group VIIA PLA₂ and is also known as plasma PAF acetylhydrolase (Adibhatla and Hatcher, 2008, and references cited therein). This enzyme is found in blood circulation in most animals, and in humans is associated with apoB-100 of LDL and is also found in atherosclerotic plaques (Lavi, et al., 2007). Higher levels of Lp-PLA₂ are also associated with coronary heart disease, stroke and dementia (Lavi, et al., 2007; Oei, et al., 2005). Lp-PLA₂ is produced and secreted by cells of monocyte-macrophage series, T-lymphocytes and mast cells. In addition to PAF acetylhydrolase activity, Lp-PLA₂ also hydrolyzes oxidized PC of LDL to generate oxidized fatty acids and lyso-phosphatidylcholine (lyso-PC) (Zalewski, et al., 2006). Local coronary lyso-PC formation is also associated with endothelial dysfunction and supports the role of this enzyme in vascular inflammation and atherosclerosis in humans. Lp-PLA₂ also has an anti-inflammatory function arising from hydrolysis of PAF, which is known to activate platelets, monocytes and macrophages.

2.1.3. Atherosclerosis and group IIA secretory PLA₂ (inflammatory PLA₂)—

Group IIA phospholipase A₂ (secretory PLA₂, also known as inflammatory PLA₂) has been found in human atherosclerotic lesions. sPLA₂ IIA is implicated in chronic inflammatory conditions such as arthritis and may also contribute to atherosclerosis. sPLA₂ IIA is a pro-atherogenic factor and has been suggested to regulate collagen deposition in the plaque and fibrotic cap development (Ghesquiere, et al., 2005, and references cited therein). sPLA₂ is one of the enzymes responsible for the release of lyso-PC *via* its catalytic action and these two play a crucial role in the development of atherosclerosis (Kougiass, et al., 2006). Non-catalytic (non-enzymatic) atherogenic effects of sPLA₂ II are thought to involve binding to a muscular-type (M-type) sPLA₂ receptor.

2.1.4. Sphingomyelinase (SMase): A link between atherosclerosis and ceramide

—LDL possesses SMase activity, which may be intrinsic to apoB-100. SMase hydrolyzes SM to release ceramide, which is elevated in atherosclerotic plaques as well as in LDL isolated from these lesions. Ceramide is believed to play an important role in aggregation of LDL within

the arterial wall, a critical step in the initiation of atherosclerosis (Kinnunen and Holopainen, 2002).

2.2. Reactive Oxygen Species (ROS), Lipid Metabolism and Stroke

The study of ROS and oxidative stress is difficult due to the transient nature of ROS, the number of complex ongoing processes, direct and reverse interactions between these processes, and the capacity of ROS to alter a large number of cellular components.

Oxidative stress results when production of ROS such as superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals exceeds a biological system's ability to detoxify these reactive intermediates. Superoxide anion radicals can combine with reactive nitrogen species such as nitric oxide to generate the strong pro-oxidant peroxynitrite. ROS are produced by a number of cellular oxidative metabolic processes including oxidative phosphorylation by the mitochondrial respiratory chain, xanthine oxidase, NAD(P)H oxidases, monoamine oxidases, and metabolism of ArAc by lipoxygenases (LOX) (Adibhatla and Hatcher, 2006). It has been generally accepted that ArAc metabolism by cyclooxygenases (COX) also generates ROS, but recent literature shows that COX-2 does not directly produce ROS but does form carbon-centered radicals on ArAc (Kunz, et al., 2007; Simmons, et al., 2004). Most ROS are produced at low levels and any damage they cause to cells is constantly repaired. Low levels of ROS are used in *redox* (reduction/oxidation) cell signaling and may be important in prevention of aging by induction of mitochondrial *hormesis* (*hormesis*: a beneficial response to low dose exposure to toxins). Generation of ROS is also used by the immune system to destroy invading pathogens. Although there are intracellular defenses against ROS, increased production of ROS or loss of antioxidant defenses leads to progressive cell damage and decline in physiological function. Over-production of these free radicals can damage all components of the cell, including proteins, carbohydrates, nucleic acids, and lipids, leading to progressive decline in physiological function and ultimately cell death.

Beyond the initial damage to membranes, reaction of these radicals with double bonds of fatty acids in lipids produces peroxides that give rise to α,β -unsaturated aldehydes including malondialdehyde (MDA), 4-hydroxynonenal (HNE) and acrolein. These aldehydes covalently bind to proteins through reaction with thiol groups and alter their function. We have previously shown that CA₁ hippocampal neurons were HNE positive by immunohistochemistry after transient cerebral ischemia (Adibhatla and Hatcher, 2006). Recently, elevated levels of an acrolein-protein conjugate were demonstrated in plasma of stroke patients (Adibhatla and Hatcher, 2007, and references cited therein).

The brain is believed to be particularly vulnerable to oxidative stress as it contains high concentrations of PUFA that are susceptible to lipid peroxidation, consumes relatively large amounts of oxygen for energy production, and has lower antioxidant defenses compared to other organs. Of all the brain cells, neurons are particularly vulnerable to oxidative insults due to low levels of reduced glutathione (Dringen, 2000). In addition to atherosclerosis, oxidative stress has been shown to be a component of many neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, Multiple Sclerosis, and Amyotrophic Lateral Sclerosis.

Cessation of blood flow to the brain leads to energy loss and necrotic cell death. This initiates the immune response, activating inflammatory cells including microglia/macrophages and generating ROS. ROS can further stimulate release of cytokines that cause up-regulation of adhesion molecules, mobilization and activation of leukocytes, platelets and endothelium. These activated inflammatory cells also release cytokines, MMPs, nitric oxide and additional ROS in a feed-back fashion (Wang, et al., 2007b). ArAc metabolites, synthesized by and liberated from astrocytes, microglial cells and macrophages, are intimately involved in the

inflammatory process by enhancing vascular permeability and modulating inflammatory cell activities and ROS generation. The role of ROS in activation of various signaling pathways such as p38, JNK, p53, ERK1/2, Akt, NF- κ B (Crack and Taylor, 2005), MMPs (Liu and Rosenberg, 2005) and stroke injury (Adibhatla and Hatcher, 2006; Margail, et al., 2005) have been recently reviewed.

2.2.1. Cytokines and Stroke—There are substantial data from both animal models and clinical studies that cytokines including TNF- α , IL-1 and IL-6 are up-regulated after stroke. Although the roles of cytokines in stroke pathology remain controversial, the majority of studies support their deleterious effects, at least in the early phase of stroke injury. Whether cytokines mediate pro-survival or pro-apoptotic signaling appears to depend on their concentration, the target cell, the activating signal, and the timing and sequence of action (Adibhatla and Hatcher, 2008). A number of studies have demonstrated that TNF- α and IL-1 modulate phospholipid and sphingolipid metabolism by up-regulating phospholipases and SMases and down-regulating enzymes of phospholipid/sphingolipid synthesis, although most of these studies were conducted in cell lines not of CNS origin. The release of ArAc during ischemia may be one of the initial events that up-regulate cytokine expression. Ceramide released by SMases triggers the MAP kinase cascade and can up-regulate cytokine expression through activation of NF- κ B. Thus phospholipid metabolism and cytokine expression (the inflammatory response) may function through a feedback mechanism. The integration of cytokine biology and lipid metabolism in stroke is less explored and was recently reviewed (Adibhatla and Hatcher, 2008).

A systemic inflammatory response involving up-regulation of TNF- α and IL-1 is believed to be instrumental in the formation and destabilization of plaques, one of the risk factors for ischemic stroke (Emsley and Tyrrell, 2002; Hansson and Libby, 2006). There is considerable clinical data indicating that this systemic inflammation is associated with unfavorable outcome in stroke patients (McColl, et al., 2007). However, this inter-relationship of systemic inflammation with stroke pathology has not been well studied.

2.2.2 Inflammation and resolution—A critical aspect of the inflammatory response is the ability to stop the inflammation, referred to as the resolution phase, an active process involving expression of anti-inflammatory agents. Activation of PLA₂s release ArAc, eicosapentaenoic acid, and DHA. ArAc is metabolized to eicosanoids (prostaglandins, leukotrienes, and thromboxanes) through the COX/LOX pathways, a major pathway mediating inflammation, but is also metabolized to anti-inflammatory lipoxins through the LOX pathway. Chemical mediators such as aspirin can acetylate COX-2; prostaglandin synthesis is inhibited and metabolism is shifted by acetylated COX-2/LOX pathway to generate pro-resolution lipoxins. Eicosapentaenoic acid and DHA, ω -3 fatty acids, are metabolized to resolvins and protectins such as neuroprotectin D1 that have important roles in resolution of inflammation (Serhan, 2007). For further reading refer to JX Kang's chapter on "Modulation of Cytokines by ω -3 Fatty Acid".

2.2.3. Oxidized PC (OxPC) is an inflammatory marker—We have previously shown that PC loss, either due to activation of phospholipases or inhibition of its synthesis *via* CTP:phosphocholine cytidyltransferase (CCT), may be a significant factor contributing to stroke injury that was attenuated by treatment with CDP-choline (a phase III clinical trial drug for stroke treatment) (Adibhatla and Hatcher, 2005; 2006; 2007; Adibhatla, et al., 2006b). Another contributing factor for PC loss could be conversion to OxPC. Peroxidation of fatty acids in phospholipids results in an oxidized phospholipid. Scission of the peroxidized fatty acid results in formation of a phospholipid such as OxPC (Kadl, et al., 2004) with a fatty acid containing an aldehyde residue, and the aldehyde cleavage fragments MDA, HNE, or acrolein discussed above. These reactive phospholipid aldehydes exhibit cytotoxicity by binding to

lysine residues of cellular proteins. OxPC itself also changes the membrane properties, resulting in alterations in ion transport and membrane protein function. The presence of OxPC on the apoptotic cell surface has been characterized by EO6 monoclonal antibodies that exclusively bind to OxPC (Qin, et al., 2007). In addition to OxPC, EO6 antibodies also recognize OxPC bound to lysine residues of proteins. OxPC on apoptotic cells may enhance pro-inflammatory signals and also serve as a marker of inflammation and apoptosis (Bratton and Henson, 2005; Chang, et al., 2004; Kadl, et al., 2004). The presence of OxPC has been demonstrated in multiple sclerosis brain using EO6 monoclonal antibodies (Qin, et al., 2007). Formation of OxPC species were also shown after permanent focal ischemia in mice (Gao, et al., 2006). For additional details, please refer to chapters on “Role of Oxidized Phospholipids in Inflammation” by Norbert Leitinger and “Mediation of Apoptosis by Oxidized Phospholipids” by Albin Hermetter.

2.3. Cholesterol is the precursor for neurosteroid synthesis

The vast majority of cholesterol in the brain is derived from *de novo* synthesis as virtually no cholesterol is transported from the plasma; cholesterol is synthesized in the neurons, glia (astrocytes), oligodendrocytes. In the adult brain, the predominant synthesis is by astrocytes; cholesterol is then secreted *via* transport molecules such as ATP binding cassette protein (ABCA1), taken up by lipoprotein receptors on neurons and internalized to the endosome/lysosome (E/L) system (Fig. 3). Cholesterol will be transported to mitochondria by Niemann-Pick C1 (NPC1) protein where the neurosteroids such as dehydroepiandrosterone (DHEA) and allopregnanolone are synthesized *via* the rate-limiting intermediate, pregnenolone. These neurosteroids act on nuclear and NMDA/GABA_A receptors to promote neurogenesis and modulate neurotransmission. While both provided benefit, allopregnanolone was more effective than progesterone in reducing infarction after stroke (Sayeed, et al., 2006). DHEA and allopregnanolone also stimulated neurogenesis (Karishma and Herbert, 2002; Suzuki, et al., 2004; Wang, et al., 2005).

2.4. Traumatic Brain Injury (TBI)

TBI is associated with significant neuropsychological deficits, primarily in the domains of attention, executive functioning and memory. In TBI, the initial traumatic event is shearing, laceration, and/or contusion of brain tissue resulting from a physical impact. Secondary injury after the initial trauma results from ischemia, alterations in ion and neuromodular levels, oxidative stress caused by ROS, edema and axonal swelling (Rigg and Zafonte, 2006). The neurosteroids such as DHEA and allopregnanolone reduced cell death, astrogliosis and functional deficits in rats after TBI (Djebaili, et al., 2005). Corticosteroids have been proposed as therapies to reduce secondary injuries following TBI. Corticosteroids inhibit the PLA₂/COX/LOX pathways, thus limiting ArAc release and metabolism, down-regulating pro-inflammatory cytokines and attenuating inflammatory responses. However, large scale clinical trials of corticosteroids and lazaroids (21-aminosteroids) for treatment of TBI have either failed to demonstrate efficacy or found increased risk of mortality (Rigg and Zafonte, 2006).

TBI and ApoE—ApoE is an important mediator of cholesterol and lipid transport in the brain and is encoded by the polymorphic gene APOE. While it may be reasonable to relate effects of ApoE to cholesterol transport, the mechanism whereby ApoE elicits these effects has not been elucidated. ApoE has been shown to reduce glial activation and CNS inflammatory response. This action is isoform-specific with the ApoE4 isoform being less effective at down-regulating inflammatory cytokines (Lynch, et al., 2005). A small peptide, apoE(133–149) was created from the receptor binding region that retains the ability of the native protein in down-regulating inflammatory responses. Administration of apoE(133–149) was shown to significantly improve histological and functional outcome after experimental TBI (Lynch, et al., 2005).

While the APOE $\epsilon 4$ allele was first implicated as a significant risk factor for Alzheimer's Disease (see later section on Alzheimer's Disease), a number of clinical studies have indicated that performance on neuropsychological tasks is worse in TBI patients with the APOE $\epsilon 4$ allele than those without it (Ariza, et al., 2006). While other clinical studies did not find an association of APOE $\epsilon 4$ allele with poorer outcome after TBI, these differences could be due to the severity of the TBI (no association in some studies with predominantly mild TBI), the neurological evaluation methods that assess the involvement of different brain regions, and the evaluation time post injury (up to 25 years after TBI). In other studies, the presence of the APOE $\epsilon 4$ allele has been associated with poorer outcome after cardiopulmonary resuscitation and intracerebral hemorrhage, but not after ischemic stroke (Smith, et al., 2006).

Both human postmortem and experimental studies have shown A β deposition and tau pathology after TBI (Jellinger, 2004). Statins have shown benefit in experimental TBI (Mahmood, et al., 2007), but it is unknown if statin treatment affected A β levels. The development of AD-like neuropathological and biochemical changes after severe TBI suggested that TBI may be a risk factor for subsequent development of dementia. Epidemiological studies have provided discrepant findings, thus the relationship between TBI and dementia remains a topic for further investigation.

2.5. Spinal Cord Injury (SCI)

Similar to TBI, SCI is the result of an initial physical trauma followed by a secondary degenerative process. The majority of SCIs result from contusive, compressive, or stretch injury rather than physical transection of the spinal cord. The initial event after SCI is depolarization and opening of voltage-dependent ion channels, and consequent massive release of neurotransmitters including glutamate. This leads to accumulation of intracellular calcium, initiating a number of damaging events: mitochondrial dysfunction, activation of nitric oxide synthase (NOS) and PLA $_2$. PLA $_2$ releases ArAc into the COX/LOX pathways to generate eicosanoids. One consequence of mitochondrial dysfunction, activation of NOS, and COX/LOX activity is generation of free radicals (comprised of different species including reactive nitrogen species, ROS and other radicals) and subsequent lipid peroxidation, which is considered a major pathway of secondary injury in SCI (Hall and Springer, 2004).

The glucocorticoid steroids dexamethasone and methylprednisolone have been extensively used in clinical treatment of SCI. In animal studies, it was demonstrated that high dose methylprednisolone inhibited post-traumatic lipid peroxidation in spinal cord tissue. Beneficial effects secondary to inhibition of lipid peroxidation included preservation of ion homeostasis, mitochondrial energy metabolism, and attenuation of delayed glutamate release (Hall and Springer, 2004). It is believed that inhibition of lipid peroxidation is the principle neuroprotective mechanism of high-dose methylprednisolone and that glucocorticoid receptor-mediated anti-inflammatory effects have only a minor role (Hall and Springer, 2004).

Another agent that has undergone Phase III clinical trials for SCI is GM1 ganglioside. Since high-dose methylprednisolone had become widely accepted for treatment of SCI, GM1 was administered only after the completion of the 24 hr methylprednisolone dosing protocol. The results indicated that GM1 did not provide greater functional improvement compared to methylprednisolone alone (Hall and Springer, 2004). The neurosteroid, DHEA sulfate offered neuroprotection in a spinal cord ischemia model, which was believed to be mediated through GABA $_A$ receptors (Lapchak, et al., 2000).

3. LIPIDS IN CNS DISORDERS

3.1. Alzheimer's Disease (AD)

AD is a progressive brain disorder affecting regions that control memory and cognitive functions, gradually destroying a person's memory and ability to learn, reason, communicate and carry out daily activities. One of the hallmarks of AD is overproduction of amyloid β -peptide ($A\beta$), resulting in the formation of plaques. A two-step cleavage of the neuronal membrane protein amyloid precursor protein (APP) (Ehehalt, et al., 2003) results in two products, $A\beta$ 40 and $A\beta$ 42. Strong evidence for the role of $A\beta$ in the pathogenesis of AD was provided by the observation that mutations in APP or the enzymes that cleave it lead to overproduction of $A\beta$ 42 and rapid progression of the disease (Mandavilli, 2006). The second hallmark of AD is formation of neurofibrillary tangles due to hyperphosphorylation of tau protein.

Transgenic mouse models of AD require two or more mutations to reproduce all the physical features of AD ($A\beta$ plaques and tau tangles), however these models have not provided any leads to the relationship between $A\beta$ plaques and tau tangles. Most mouse models of AD are considered limited or incomplete: several models develop amyloid deposition but fail to develop neurofibrillary tangles that are an essential hallmark of AD. Neuritic atrophy is found in some transgenics, but of nearly one dozen mouse models, only one has reported loss of neurons that is characteristic of AD (Herrup, et al., 2004). Some tau models develop severe memory deficits associated with AD but express little amyloid protein (Mandavilli, 2006). These shortfalls limit the usefulness of these models for developing therapeutic strategies for AD (Schwab, et al., 2004).

There is growing evidence that cholesterol is of particular importance in development and progression of AD. ApoE is one of the major apolipoproteins in plasma and the principal cholesterol carrier protein in the brain. Identification of the gene encoding the variant ApoE4 (APOE ϵ 4 allele) as a significant risk factor for AD provided evidence for a role of cholesterol in the pathogenesis of AD (Puglielli, 2007). Elevated cholesterol levels increase $A\beta$ in cellular and animal models, and drugs such as statins and BM15.766 that inhibit cholesterol synthesis lower $A\beta$ levels (Hartmann, et al., 2007; Puglielli, 2007; Whitfield, 2006). Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase that initiates cholesterol and isoprenoid lipid synthesis while BM15.766 inhibits cholesterol synthesis at the ultimate step (Hartmann, et al., 2007). Prospective trials evaluating statin therapy, however, did not demonstrate improvement in cognitive function in AD patients (Caballero and Nahata, 2004).

Cholesterol is needed to make the cellular membrane micro-domains referred to as lipid rafts. APP, β -secretase, γ -secretase complex, and neutral sphingomyelinase (NSMase) are present in the lipid rafts that are rich in cholesterol and SM. Genetic mutations in APP or presenilins (part of the γ -secretase complex) increase production of $A\beta$ 42. Recent studies suggest that $A\beta$ 40 inhibits HMG-CoA reductase while $A\beta$ 42 activates NSMase and increases ceramide production, which can accelerate the neurodegenerative process (Grimm, et al., 2005; Mattson, et al., 2005). It is unclear what regulates the cleavage of APP to $A\beta$ 42 vs $A\beta$ 40.

Cholesterol is the precursor for biosynthesis of neurosteroids. In AD brains, a general trend was observed towards decreased levels of all steroids, with significantly lower amounts of pregnenolone and dehydroepiandrosterone. These lower levels correlated with increased amounts of β -amyloid peptides and phosphorylated tau proteins. It is not known whether these neurosteroid deficiencies contribute to or result from AD pathology, but since many neurosteroids have neuroprotective actions, their lower levels may contribute to $A\beta$ neurotoxicity (Wang, et al., 2007a). Studies have indicated that allopregnanolone is the most effective neurosteroid for neuroprotection. Allopregnanolone also stimulated neurogenesis by

increasing expression of genes that promote mitosis and inhibiting expression of those that repress cell proliferation, and may be a promising therapy for promoting cellular regeneration in AD and other neurodegenerative disorders (Wang, et al., 2007a).

AD, oxidative stress and lipid peroxidation—mRNA expression of pro-inflammatory sPLA₂ IIA was up-regulated in AD brains compared to non-dementia elderly brains. sPLA₂ IIA immunoreactive astrocytes in AD hippocampus were associated with A β plaques (Moses, et al., 2006). sPLA₂ could contribute to lipid peroxidation through the release of ArAc. Studies demonstrating increased lipid peroxidation in AD support a role for oxidative damage in this disorder (Williams, et al., 2006). HNE and acrolein levels were increased in the brain tissue from patients with mild cognitive disorder and early AD, indicating that lipid peroxidation occurs early in the pathogenesis of AD (Williams, et al., 2006). Acrolein, by far the strongest electrophile among all α,β -unsaturated aldehydes, reacts with DNA bases to form cyclic adducts, the major exocyclic adduct being acrolein-deoxyguanosine, which was elevated in brain tissue from AD patients (Liu, et al., 2005). ROS may also play a role in amyloid deposition in AD as oxidizing conditions cause protein cross-linking and aggregation of A β peptides, and also contribute to tau protein aggregation (Mariani, et al., 2005). A β aggregation stimulates ROS production, which may lead to cyclic or self-propagating oxidative damage. The DHA metabolite neuroprotectin D1 promoted neuronal survival and anti-apoptotic pathways that attenuated A β 42 neurotoxicity (Lukiw, et al., 2005). AD and mild cognitive disorder subjects also showed lower levels of antioxidant defense systems.

A number of questions remain unanswered regarding development of therapies for AD. Are the familiar and sporadic forms of AD distinct? Are the animal models good enough to provide clear answers? Mouse models are based on familial AD (the rare form of the disease) and may not model the common sporadic form. Furthermore, most models do not exhibit the extent of neurodegeneration seen in AD patients (Mandavilli, 2006). The triple transgenic mouse (APP/PS1/tau) studies raise the possibility that a multi-targeted approach (i.e. simultaneously targeting A β and tau) may provide the most significant clinical benefit for the treatment of AD (Oddo, et al., 2004).

3.2. Parkinson's Disease (PD)

PD is characterized by selective degeneration of dopaminergic neurons of the substantia nigra, resulting in bradykinesia, tremor and rigidity. Free radical generation and lipid peroxidation play a significant role in PD. One of the factors responsible for this is believed to be phospholipases activation in substantia nigra, supported by the fact that cPLA₂ deficient mice are resistant to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced neurotoxicity (Farooqui, et al., 2006). The MPTP metabolite MPP⁺ is taken up by nigrostriatal neurons where it inhibits mitochondrial oxidative phosphorylation and causes neuronal death. MPTP neurotoxicity has been used as an animal model for PD. Although MPTP produces virtually all the symptoms of PD, strictly it is not PD.

3.2.1. Treatment of PD—The dopamine prodrug levodopa remains the treatment option for PD, however, long-term levodopa therapy leads to dyskinesia. Alternatives for early PD therapy include monoamine oxidase B inhibitors, dopamine agonists, catechol-*O*-methyltransferase (COMT) inhibitors, and amantadine (Hauser and Zesiewicz, 2007). The mechanism of action of amantadine remains unknown; however, it has been suggested to have anticholinergic properties in addition to acting as an NMDA receptor antagonist to increase dopamine release and inhibit its reuptake. COMT inhibitors are used in combination with levodopa, and act peripherally to increase the pool of available levodopa, optimize its transport to CNS, and decrease the side effects of levodopa by allowing lower doses (Bonifacio, et al., 2007). CDP-choline increases tyrosine hydroxylase activity and has been used in combination

with levodopa for PD treatment. CDP-choline showed functional improvements and allowed levodopa to be administered at lower doses, decreasing its side effects (Adibhatla and Hatcher, 2005). The neurosteroid pregnenolone enhances neuronal dopamine release and may provide a therapeutic option for PD.

3.2.2. PD, oxidative stress and lipid peroxidation—In PD, the accelerated metabolism of dopamine by monoamine-oxidase-B may result in excessive ROS formation. A role for oxidative stress in PD was demonstrated by marked increases in 8-hydroxy-2'-deoxyguanosine, a hydroxyl radical-damaged guanine nucleotide. Several markers of lipid peroxidation were also found to be significantly increased in PD brain regions (Mariani, et al., 2005).

3.2.3. PD and α -synuclein—PD is associated with the presence of Lewy bodies containing insoluble aggregates of α -synuclein in association with other proteins. Recently the presence of PUFA was linked to the appearance of soluble oligomers of α -synuclein that ultimately promote the formation of insoluble α -synuclein aggregates (Welch and Yuan, 2003). DHA was shown to stimulate oligomerization of α -synuclein, and DHA levels were elevated in PD brains (Sharon, et al., 2003), suggesting that DHA could have a role in formation of α -synuclein aggregates. On the other hand, DHA reduced levodopa-induced dyskinesias in MPTP-treated monkeys (Samadi, et al., 2006). This discrepancy for the role of DHA in PD warrants further investigation.

3.3. Niemann-Pick Diseases (NPD)

NPD are genetic pediatric neurodegenerative conditions characterized by specific disorders in lipid metabolism and are categorized as types A, B and C. NP Types A and B (NPA and NPB) are caused by deficiencies in acidic sphingomyelinase (ASMase) (Schuchman, 2007, and references cited therein). NPA, the most common type, is caused by a nearly complete lack of ASMase and is characterized by jaundice, an enlarged liver, and profound brain damage. Since ASMase is localized to the lysosomes, NPA results in accumulation of SM and is classified as a lysosomal storage disorder (Futerman and van Meer, 2004). People with NPB have approximately 10% of the normal level of ASMase, generally have little or no neurologic involvement. Tricyclodecan-9-yl potassium xanthate (D609), a widely known PC-phospholipase C inhibitor, also inhibits SM synthase (Larsen, et al., 2007) and may help prevent accumulation of SM in NPB, a possibility not yet tested.

NP type C (NPC) is always fatal but it differs from NPA and NPB at the biochemical and genetic level. NPC is caused by mutations in either the *NPC1* or *NPC2* genes (Vance, 2006). While the precise functions of the NPC1 and NPC2 proteins are not clear, these are involved in transport of lipids, particularly cholesterol, from the late endosomes/lysosomes (Maxfield and Tabas, 2005). Deficiencies in these proteins result in lysosomal accumulation of cholesterol and other lipids. In NPC, cholesterol accumulates in all tissues except the brain, where cholesterol levels decrease with age (Vance, 2006; Xie, et al., 2000). Since 70–80% of cholesterol in the brain is contained in myelin, the extensive demyelination that occurs in NPC probably accounts for the net loss of cholesterol in the brain, which would likely mask accumulation of cholesterol in neurons or astrocytes. In a mouse model of NPC, significant neuronal accumulation of cholesterol was shown by post-natal day 9 when only mild signs of neurodegeneration were detectable (Reid, et al., 2004).

Currently there are no treatments for NPC. Ezetimibe (Garcia-Calvo, et al., 2005; Temel, et al., 2007) is a novel cholesterol-lowering drug that acts at the brush border of the small intestine where it inhibits the absorption of cholesterol from the diet. Specifically, it appears to bind to a critical mediator of cholesterol absorption, the Niemann-Pick C1-Like 1 (NPC1L1) protein

on the gastrointestinal tract epithelial cells as well as in hepatocytes. Despite the accumulation of cholesterol in late endosomes/lysosomes, neither cholesterol lowering agents nor dietary measures slowed the progression of the disease. These studies suggest that cholesterol accumulation *per se* is not the major contributor to the pathogenesis of NPC, but that disrupted cholesterol transport within the cell to the endoplasmic reticulum and mitochondria for cholesterol esterification and synthesis of neurosteroids may be the critical factor. Neurosteroids and enzymes involved in steroid synthesis were significantly reduced in NPC1-deficient mice. Administration of the neurosteroid allopregnanolone alleviated progression of the disease (Vance, 2006), suggesting that neurosteroid therapy might be a treatment option for NPC (Burns and Duff, 2004; Griffin, et al., 2004).

In addition to accumulating cholesterol, NPC1-deficient cells also accumulate gangliosides and other glycosphingolipids, and neuropathological abnormalities in NPC disease closely resemble those seen in primary gangliosidoses. Treatment of NPC mice with N-butyldeoxynojirimycin, an inhibitor of glycosphingolipid synthesis, increased the average life span, and reduced ganglioside accumulation and neuropathological changes (Vance, 2006).

3.4. Multiple Sclerosis (MS)

MS is an inflammatory demyelinating autoimmune disease affecting the CNS. In MS, the immune system attacks the myelin sheath of nerve cell fibers in the brain and spinal cord. MS is predominantly a T-lymphocyte mediated disorder, and cytokines may therefore have a key role in the pathogenesis of the disease. MS is the only neurological disorder where therapeutic manipulation of the cytokine system influences development of the disease (Adibhatla and Hatcher, 2007). Thiobarbituric acid reactive substances and F₂-isoprostane levels were shown to be elevated in CSF of MS patients, and HNE was associated with MS lesions, indicative that lipid peroxidation also occurs in MS (Carlson and Rose, 2006).

Experimental autoimmune encephalomyelitis (EAE)—EAE is the immune response to immunization with myelin antigens (Marusic, et al., 2005) and is an animal model for MS. Recent studies demonstrated a key role for cPLA₂ in EAE (Marusic, et al., 2005, and references cited therein). cPLA₂, which can be induced by TNF- α (Kronke and Adam-Klages, 2002), was highly expressed in EAE lesions. Blocking cPLA₂ showed a remarkable decrease in both the onset and progression of the disease (Marusic, et al., 2005), indicating that cPLA₂ has a significant role in both the induction and effector phases of EAE. A second study showed that cPLA₂ null mice were resistant to EAE (Marusic, et al., 2005). It should be noted that these studies were conducted using C57BL/6 or SV127 mouse strains which are naturally deficient in inflammatory PLA₂/sPLA₂ IIA (Adibhatla and Hatcher, 2006). Treatment of EAE rats with sPLA₂ inhibitor CHEC-9 (CHEASAAQC) significantly attenuated sPLA₂ activity, EAE symptoms, and ED-1 positive microglia/macrophages (Cunningham, et al., 2006). Recently, MS patients were shown to have elevated sPLA₂ activity. These studies suggest that both cPLA₂ as well as sPLA₂ inhibition may be treatment options for MS.

3.5. Huntington's Disease (HD)

HD is a rare inherited neurological disorder characterized by abnormal body movements and lack of coordination; cognition may also be affected. HD is caused by a trinucleotide repeat expansion in the Huntingtin (*Htt*) gene. The normal gene has fewer than 36 repeats, whereas the mutated *Htt* gene has 40 or more CAG repeats. Since CAG is the codon for glutamine, HD is one of the polyglutamine disorders.

Endocannabinoids, endogenous agonists of cannabinoid receptors, are comprised of amides, esters and ethers of long chain PUFA. *N*-arachidonylethanolamine (AEA, anandamide) and 2-arachidonylethanolamine (2-AG) are well characterized lipid mediators of the endocannabinoid

system (Maccarrone, et al., 2007). The endocannabinoid system has been found to have an important neuroprotective role in CNS injury and neurodegenerative diseases; an extensive review of these studies was recently published (Pacher, et al., 2006).

Endocannabinoids act as retrograde messengers, and upon release from postsynaptic neurons, regulate further neurotransmitter release by activating presynaptic cannabinoid receptors (Degroot and Nomikos, 2007). The endocannabinoid system is *hypoactive* in HD (Maccarrone, et al., 2007), which may underlie the neurotransmission abnormalities of HD and may be the cause of the clinical manifestations of the disease. Inhibition of fatty acid amide hydrolase, monoacylglycerol lipase or the endocannabinoid membrane transporter can enhance endocannabinoid levels and counteract neurochemical deficits and the *hyperkinetic* effects of HD (Maccarrone, et al., 2007). Dietary supplementation with essential fatty acids protected against motor deficits in a transgenic mouse model of HD (Clifford, et al., 2002). Ethyl-eicosapentaenoate (Ethyl-EPA, LAX-101 or Miraxion) showed promise in clinical trials and its action is presumed to be through JNK pathway (Puri, et al., 2005). HD is associated with up-regulated transglutaminase activity in selectively vulnerable brain regions and transglutaminase-catalyzed cross-links co-localize with huntingtin (htt) protein aggregates (Muma, 2007). Combination therapy using minocycline and coenzyme Q₁₀ (CoQ₁₀) in R6/2 transgenic HD mouse model also provided synergistic benefit (minocycline attenuated microglia proliferation and CoQ₁₀ reduced htt protein aggregation) (Stack, et al., 2006).

HD and lipid peroxidation—In HD, one study reported no increase in 8-hydroxy-2'-deoxyguanosine or other markers of DNA oxidation, and no change in lipid peroxidation. In contrast, other studies have shown increases in the lipid peroxidation markers F₂-isoprostane and MDA in HD (Mariani, et al., 2005).

3.6. Amyotrophic Lateral Sclerosis (ALS)

ALS is an adult-onset neurodegenerative disease characterized by progressive loss of spinal cord and cortical motorneurons and is usually fatal within 2–5 years of diagnosis. Approximately 10% of ALS cases are familial (inherited), with the remaining 90% of cases being sporadic in origin (Kunst, 2004). Of the familial cases, approximately 20% (i.e., 2% of all ALS) are due to mutations in the gene for the cytosolic copper-zinc superoxide dismutase (SOD1), which detoxifies superoxide anion radicals to hydrogen peroxide. Expression of a mutant SOD1 protein, with or without residual SOD activity, is necessary to cause ALS phenotype, suggesting a dominant negative mechanism (Kunst, 2004). There is strong evidence that the toxicity of mutant SOD1 in ALS is not due to loss of activity, but to the gain of one or more toxic functions that are independent of SOD activity (Nirmalanathan and Greensmith, 2005, and references cited therein). It is believed that mutant SOD1 stimulates oxidative stress and induces mitochondrial dysfunction, excitotoxicity, inflammation, and protein aggregation.

The role of glutamate-mediated excitotoxicity in ALS was supported by the efficacy of riluzole, (a benzothiazole derivative that acts by reducing glutamate excitotoxicity) in slowing the progression of ALS (Kunst, 2004). Riluzole is the only available treatment for ALS, but is now known to have limited therapeutic benefits with minimal effects on survival (Nirmalanathan and Greensmith, 2005). Several inflammatory markers such as caspase 1, COX-2 and TNF- α are increased in spinal cord tissue in transgenic mouse models of ALS. Inhibition of COX-2 reduced spinal neurodegeneration and prolonged the survival of ALS transgenic mice (Minghetti, 2004). The role of COX-2 in ALS as well as the presence of TNF- α suggests that cPLA₂ and/or sPLA₂ may also be up-regulated in ALS to provide ArAc to the COX pathway. TNF- α induces cPLA₂, sPLA₂ as well as COX-2. This suggests that anti-TNF- α therapy could attenuate the progression of ALS, an option that has not been utilized yet.

ALS and lipid peroxidation—Evidence of increased oxidative DNA damage in ALS was indicated by elevated levels of 8-hydroxy-2'-deoxyguanosine in plasma, urine and CSF (Mariani, et al., 2005). Several studies have shown increased lipid peroxidation and DNA damage in transgenic mice expressing mutant SOD1 and in neural tissue or sera from ALS patients (Agar and Durham, 2003; Simpson, et al., 2004).

3.7. Schizophrenia and Bipolar disorders

Schizophrenia is marked by disturbances in thinking, emotional reactions, social behavior, with delusions and hallucinations. Drugs that block dopamine receptors alleviate symptoms of schizophrenia, indicative of excess dopaminergic function, while agents that block glutamate receptors induce some of the symptoms of schizophrenia in otherwise normal persons (Horrobin, 2002).

Recent theories on the neurological deficits of schizophrenia have focused on abnormalities in phospholipid metabolism, particularly increased activity of PLA₂ enzymes and reduced activity of the system which incorporates PUFA into phospholipids (a simultaneous increase in phospholipid hydrolysis and decrease in synthesis) (Berger, et al., 2006; Horrobin, 2002). Neither abnormality alone produces schizophrenia but the presence of both does. These abnormalities lead to changes in membrane structure and thus the function of membrane-bound proteins, availability of cell signaling molecules, and the behavior of neurotransmitter systems. This hypothesis is supported by animal studies demonstrating that application of PLA₂ into the brain produces alterations in the dopamine system (Horrobin, 2002). Also, since phospholipid metabolism has a crucial role in neuronal and synaptic growth and remodeling, it is plausible that defects in this system result in failure of normal neurodevelopment in schizophrenia. There is also evidence that schizophrenia is associated with alterations in lipid transport proteins and membrane phospholipid composition (increase in PS and decrease in PC and PE) (Berger, et al., 2006). Genome studies have found that several genes involved in myelination have decreased expression levels in schizophrenia (Berger, et al., 2006, and reference cited therein).

A number of reports indicate that at least a portion of schizophrenic patients have reduced levels of PUFA, particularly ArAc and DHA, in red cell phospholipids, with low levels particularly associated with negative symptoms (Horrobin, 2002). ArAc, DHA and EPA are important for monoaminergic neurotransmission, brain development, and synaptic functioning (Berger, et al., 2006). This suggests that supplementation with essential fatty acids could alleviate symptoms of schizophrenia. In preliminary studies, however, DHA essentially had no effect and ArAc appeared to worsen symptoms in some schizophrenia patients. Unexpectedly, EPA provided significant improvement, comparable in magnitude to that produced by new atypical antipsychotic drugs, without any of the side effects characteristic of drug treatment. The combination of EPA and DHA was also beneficial in bipolar disorder (Horrobin, 2002).

Alterations in glutamatergic and GABAergic neurotransmitter systems have been implicated in various psychiatric disorders including schizophrenia and bipolar disorder. A number of neurosteroids exhibit the capacity to modulate excitatory and inhibitory neurotransmitter systems in the brain: allopregnanolone is a potent modulator of GABA_A receptors and demonstrates anticonvulsant actions in seizure paradigms. Pregnenolone sulfate and DHEA modulate GABA_A and NMDA receptors. In schizophrenia and bipolar disorder, pregnenolone and DHEA levels were elevated compared to control subjects, while allopregnanolone levels decreased in schizophrenia, suggesting alterations in pregnenolone metabolism. Thus neurosteroids may be modulators of the pathophysiology of schizophrenia and bipolar disorder, and relevant to treatment of these disorders (Marx, et al., 2006a).

3.8. Epilepsy

Epilepsy is a neurological disorder characterized by recurrent spontaneous seizures due to an imbalance between cerebral excitability and inhibition, with a tendency towards uncontrolled excitability (Papandreou, et al., 2006). Recurrent severe seizures can lead to death of brain cells. Phenytoin (Dilantin, Phenytek) is a widely used anti-seizure medicine (LaRoche, 2007). The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited, possibly by promoting sodium efflux from neurons. Phenytoin tends to stabilize the threshold against hyper-excitability caused by excessive stimulation. The current status of new (second generation) anti-epileptic drugs has been recently reviewed (Bialer, et al., 2007).

The ketogenic diet is an established and effective non-pharmacological symptomatic treatment for epilepsy that has been in clinical use for more than 80 years (Bough and Rho, 2007). The ketogenic diet is a high fat, low protein and low carbohydrate diet in which >90% of calories are derived from fat and dietary availability of glucose is minimal. The hallmark feature of the ketogenic diet is production of ketone bodies (β -hydroxybutyrate, acetoacetate, and acetone) in the liver with a concomitant rise in plasma levels. Since glucose (the preferred source of energy, particularly in the brain) is severely restricted, the ketone bodies are used as the energy source in extrahepatic tissues (Gasior, et al., 2006). Despite its many years of use, there is still considerable debate over how the ketogenic diet works; several hypotheses have been advanced, but none are widely accepted. One hypothesis, which arrived out of the Epilepsy and Brain Mapping's research, suggests that ketosis, dehydration and acidosis each appear to play a role, and that there are alterations in (1) acid-base balance; (2) water and electrolyte distribution; (3) lipid concentration (4) brain energy reserve or (5) a central action of ketones on the brain.

4. SUMMARY AND PERSPECTIVE

Historically, the lipid field has been less prominent in neuroscience. Recent advances have demonstrated that lipids have broad information carrying functions in the CNS as both ligands and substrates for proteins. Lipids alter the geometric properties of membranes and control protein traffic, and provide messenger molecules that mediate communication between cells, suggesting that advances in our understanding of lipid metabolism could have far reaching implications in other genomic, proteomic and metabolomic fields (Feng and Prestwich, 2006; Piomelli, et al., 2007). Lipidomic analyses together with RNA silencing (Aagaard and Rossi, 2007) may provide a powerful tool to elucidate the specific roles of lipid intermediates in cell signaling. A deeper knowledge of the complexity of lipid signaling will elevate our understanding of the role of lipid metabolism in various CNS disorders, opening new opportunities for drug development and therapies for neurological diseases.

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Abbreviations

ArAc, Arachidonic acid
 CDP-choline, Cytidine-5'-diphosphocholine
 CNS, Central nervous system
 COX/LOX, Cyclooxygenase/lipoxygenase
 DHA, Docosahexaenoic acid
 HNE, 4-Hydroxynonenal

IL-1 β , Interleukin 1 β
 Lp-PLA₂, Lipoprotein-PLA₂
 MMP, Matrix metalloprotease
 OxPC, Oxidized phosphatidylcholine
 PAF, Platelet activating factor
 PC, Phosphatidylcholine
 PE, phosphatidylethanolamine
 PI, phosphatidylinositol
 PLA₂, Phospholipase A₂
 sPLA₂, Secretory PLA₂ or inflammatory PLA₂
 PS, Phosphatidylserine
 PUFA, Polyunsaturated fatty acid
 ROS, Reactive oxygen species
 SM, Sphingomyelin
 SMase, Sphingomyelinase
 TNF- α , Tumor necrosis factor- α .

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Figure 1.

Lipid systems affected in CNS disorders (shaded) and injuries (clear). Neurosteroid synthesis in the brain is affected in various brain disorders and injuries and treatment with neurosteroids (pregnenolone, dehydroepiandrosterone and allopregnanolone) showed positive trend in these brain pathologies (Figure 3).

Figure 2.

Atherosclerosis, a major risk factor for ischemic stroke. Under inflammatory conditions (OxLDL, homocysteine, cigarette smoke, shear stress and infectious agents such as *Chlamydia pneumoniae*) endothelial cells of the artery express adhesion molecules that allow monocytes (1) to adhere to endothelial cells (2). Chemoattractants such as monocyte chemoattractant protein-1 (MCP-1) draw the monocytes through the endothelium into the arterial intima. Once resident in the intima, monocytes differentiate into macrophages (3) in response to locally produced agents such as monocyte colony stimulating factor. LDL (4) under oxidative stress gets oxidized to OxLDL. The macrophages increase expression of scavenging receptors such as CD36, SR-A and SR-B. These scavenger receptors then internalize specifically oxidized LDL (OxLDL, specifically OxPC) particles such that cholesteryl esters accumulate in cytoplasmic droplets, resulting in lipid-loaded macrophages (foam cells, 5). Foam cells produce ROS, which further propagate LDL oxidation, and secrete cytokines and matrix metalloproteinases (MMPs). The MMPs contribute to degradation of the fibrous cap surrounding the plaque, resulting in its rupture and formation of a blood clot (6). If the blood clot dislodges from the plaque, arterial blood flow can carry it to the brain, where it lodges in a cerebral artery (embolism) and causes an ischemic stroke (7).

Figure 3.

Synthesis of neurosteroids in the brain and their effects on various brain disorders and injuries. Niemann-Pick C protein transports cholesterol from endosome/lysosome system to mitochondria where the neurosteroid synthesis occurs. DHEA and allopregnanolone may provide beneficial effects based on the following studies: NPC (Griffin, et al., 2004), AD, Schizophrenia, bipolar disorders, epilepsy (Marx, et al., 2006a; Marx, et al., 2006b), PD (Wojtal, et al., 2006), stroke (Sayeed, et al., 2006), TBI (Djebaili, et al., 2005) and SCI (Lapchak, et al., 2000). Studies showed both DHEA and allopregnanolone stimulated neurogenesis in stroke. (Marx, et al., 2006b) and increased neuroprogenitor cells in AD models (Wang, et al., 2007a).