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Therapies Targeting Lipid Peroxidation in Traumatic Brain Injury

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Abstract

Lipid peroxidation can be broadly defined as the process of inserting a hydroperoxy group into a lipid. Polyunsaturated fatty acids present in the phospholipids are often the targets for peroxidation. Phospholipids are indispensable for normal structure of membranes. The other important function of phospholipids stems from their role as a source of lipid mediators – oxygenated free fatty acids that are derived from lipid peroxidation. In the CNS, excessive accumulation of either oxidized phospholipids or oxygenated free fatty acids may be associated with damage occurring during acute brain injury and subsequent inflammatory responses. There is a growing body of evidence that lipid peroxidation occurs after severe traumatic brain injury in humans and correlates with the injury severity and mortality. Identification of the products and sources of lipid peroxidation and its enzymatic or non-enzymatic nature is essential for the design of mechanism-based therapies. Recent progress in mass spectrometry-based lipidomics/oxidative lipidomics offers remarkable opportunities for quantitative characterization of lipid peroxidation products, providing guidance for targeted development of specific therapeutic modalities. In this review, we critically evaluate previous attempts to use non-specific antioxidants as neuroprotectors and emphasize new approaches based on recent breakthroughs in understanding of enzymatic mechanisms of lipid peroxidation associated with specific death pathways, particularly apoptosis. We also emphasize the role of different phospholipases (calcium-dependent and -independent) in hydrolysis of peroxidized phospholipids and generation of pro- and anti-inflammatory lipid mediators.

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1. Introduction

Oxygenated lipid mediators and reactive oxygen species play important roles in maintaining homeostatic balance under normal conditions (Halliwell, 1991; Niki, 2009). However excessive generation of reactive oxygen species with depletion of antioxidant reserves resulting in lipid peroxidation have been implicated in programmed cell death pathways and inflammation (Niki, 2009). After the identification of soybean lipoxygenase, lipid peroxidation has been studied extensively to understand its mechanisms, dynamics and effects on biological systems (Bergstrom, 1945; Halliwell and Chirico, 1993; Khan, 1955). Apart from producing local effects such as altering membrane structure, integrity, fluidity, permeability and functionality, the products of lipid peroxidation are effective in initiating secondary cellular responses (Ernster et al., 1968; Sevanian and Hochstein, 1985).

The central nervous system (CNS) is particularly vulnerable to uncontrolled lipid peroxidation upon injury for several reasons. First, the brain exhibits high metabolic activity receiving 20% of the oxygen despite accounting for 2% of the body weight (Pratico et al., 2002). With high rates of oxidative metabolic activity, the brain generates large quantities of reactive oxygen metabolites (Ames et al., 1993). Second, neurons lack the capacity to regenerate. Third, neurons exhibit a high membrane-to-cytoplasm ratio (Evans, 1993). Fourth, the brain has high levels of redox transition metals such as iron that can catalyze reactive metabolite generation (Halliwell, 1992). While catalytically-active iron is typically sequestered intracellularly by ferritin and extracellularly by transferrin, low pH conditions observed after traumatic brain injury (TBI) might facilitate iron release for oxidative reactions (Hall et al., 2010). Furthermore, disruption of the vasculature by mechanical forces can lead to release of free hemoglobin into the brain parenchyma providing an additional source of redox-active iron. Finally, despite high oxidative metabolic activity, the brain has a relatively low antioxidant capacity compared to other tissues (Markesbery and Lovell, 2007). Generation of lipid mediators from lipid hydroperoxides has important functions in normal CNS physiology (Niki, 2009). However their uncontrolled and excessive production plays an important role in secondary injury mechanisms that are set into motion after TBI (Kasprzak et al., 2001).

Lipid peroxidation can be broadly defined as the process of inserting a hydroperoxy group into a lipid. Polyunsaturated fatty acids (PUFA) present in the glycerolipids, phospholipids and cholesterols are often the targets for peroxidation, where the peroxyl groups are derived from an oxygen molecule or from hydrogen peroxide. PUFAs are fatty acids containing two or more double bonds each separated by a methylene bridge (-CH_2-) at their aliphatic carbon back bone. The bis-allelic hydrogen or the hydrogen attached to the methylene bridge are very easy to remove, thus making these lipids highly susceptible to lipid peroxidation (Gardner, 1989). Due to their ability to form a flexible membrane structure (Feller et al., 2002), PUFAs are an important and major fatty acid class accounting for approximately 50%

of total membrane fatty acids (Tinoco, 1982). Among the PUFAs, various species are observed in different locations. For example, the major ω-6 fatty acids linoleic acid and arachidonic acid are seen across the membrane systems, whereas the ω-3 fatty acid docosahexaenoic acid is concentrated in the brain cortex and organelles such as synaptosomes, synaptic vesicles, mitochondria and microsomes (Bradbury, 2011; Tinoco, 1982). The omnipresence, high abundance and sensitivity towards oxidation makes PUFAs one of the major targets of oxidative stress through lipid peroxidation in the cellular system.

In TBI, lipid peroxidation is marked by two major pathways: enzymatic and non-enzymatic. The enzymatic pathways involve activation of phospholipase A2 (PLA2) (Bazan et al., 1995), cyclooxygenases (COX) (Dash et al., 2000), lipoxygenases (LOX) (Zhang et al., 2006), cytochrome c and other peroxidases (Ji et al., 2012a; Mendes Arent et al., 2014). Non-enzymatic pathways primarily involve interaction of transition metals with reactive oxygen species (ROS) (Bayir et al., 2006). Moreover, the cellular defense system against lipid peroxidation is also compromised with TBI. This defense system includes various free radical removal enzymes such as catalase, superoxide distmutases (SOD) and glutathione peroxidases(Ansari et al., 2008) as well as sacrificial antioxidants such as Vitamin C and E (Bayir et al., 2006). Accumulation of many of the lipid peroxidation products are known to be toxic for the cells. Lipid mediators generated from oxidation of free or esterified PUFA have been implicated in dysregulation of cerebral blood flow, blood brain barrier damage, activation of inflammatory response and programmed cell death pathways (Williams and Higgs, 1988); (Kagan et al., 2009a; Friedmann Angeli et al., 2014). On the other hand some of the lipid mediators generated from multistage enzymatic oxidation of PUFA support the resolution of inflammatory process (Serhan, 2014).

In the following sections, we will describe the mechanisms of lipid peroxidation; summarize detection of lipid peroxidation in clinical TBI, and we will review previous attempts to use non-specific antioxidants as neuroprotectors and emphasize new approaches based on recent breakthroughs in understanding of enzymatic mechanisms of lipid peroxidation.

2. Mechanism of Lipid peroxidation

Classic description of the chain reaction of lipid peroxidation involves three main steps: initiation, prolongation and termination as shown in Figure 1. Initiation is the removal of a hydrogen atom from the PUFA to form a carbon-centered lipid free radical (Pederson and Aust, 1975). After the hydrogen is removed, the unpaired electron is rearranged to form a more stable radical containing conjugated dienes. The lipid radical then attracts molecular oxygen from the available dissolved oxygen pool to form lipid peroxyl radicals. The lipid peroxyl radical initiates a new cycle by extracting a hydrogen, thereby perpetuating the peroxidation reaction. The final step, or termination, is the formation of a non-radical from the combination of two radicals (Halliwell and Chirico, 1993; Porter et al., 1995; Wills, 1966; Witting, 1965). Apart from hydroperoxides, lipid peroxidation produces many products which include: lipid hydroxides, isoprostanes, neuroprostanes, aldehydes (such as 4-hydroxy-2-nonenal or 4-HNE), ketones, alkanes, lyso-phospholipids and aldehyde modified proteins (Gueraud et al., 2010; Porter, 1984). In this section, we will primarily review the peroxidation of phospholipids since phospholipids constitute 25% of brain’s dry

weight (Yusuf, 1992) and have high PUFA content. The majority of brain phospholipids contain PUFAs in their sn-2 position and some of them also contain PUFA in their sn-1 position making them vulnerable to oxidation (Bayir et al., 2007b; Ji et al., 2012a; Sparvero et al., 2010).

2.1. Enzymatic lipid peroxidation

Phospholipid hydroperoxides are the primary product of phospholipid oxidation and are mainly generated by enzymatic pathways in the cells. Enzymes containing iron in either the heme or non-heme form can catalyze the peroxidation of phospholipids. Cyclooxygenases (prostaglandin-endoperoxide synthase or COX) are the major phospholipid-oxidizing enzymes and produce prostanoids such as prostaglandins, prostacyclin and thromboxane (Bergstroem et al., 1964; Dubois et al., 1998; Samuelsson, 1979). COX primarily acts on free arachidonic acid to produce various prostanoids; however there is evidence that it can also act on a variety of other PUFAs including linoleic acid, gamma-linolenic acid, eicosadienoic acid, eicosatrienoic acid, eicosapentanoic acid, adrenic acid and docosahexaenoic acid (Laneuville et al., 1995; Wada et al., 2007; Yuan et al., 2009). The enzymatic activity of COX was originally described to utilize free fatty acids as substrates, but recent studies report COX oxidizes fatty acids esterified to phospholipids (Hammond and O'Donnell, 2012). The mechanism underlying the production of such esterified prostaglandins is not clearly understood (Aldrovandi et al., 2013). There are three types of COX enzymes present in the mammalian system: COX1, COX2 and COX3. COX1 is constitutively expressed, whereas the others are expressed upon induction (Chandrasekharan et al., 2002; Crofford, 1997).

Another major class of lipid peroxidation enzymes are the LOX. While COX generates cyclic lipid peroxidation byproducts, LOX produce linear peroxidation products (Kuhn et al., 2015). Lipoxygenases form positional, stereo- and enantio-specific lipid peroxidation products. Lipoxygenases are responsible for the production of hydroperoxy, hydroxy, epoxy and ketoxy fatty acids, leukotrienes (Hammarstrom, 1983), hepoxilins (Nigam et al., 2007) and lipoxins (Serhan et al., 1984). Lipoxygenases can effectively oxidize both free and esterified fatty acid chains (Clark et al., 2011; Maskrey et al., 2007; O'Donnell and Murphy, 2012). Based on the peroxide attachment position on the fatty acid chain, the mammalian lipoxygenases are classified as LOX3, LOX5, LOX8, LOX12 and LOX15. LOX3 mainly acts as an isomerase, while the others are primarily involved in peroxidation of phospholipids (Kuhn et al., 2015).

While COX and LOX play a primary role in phospholipid oxidation, other enzymes such as the major xenobiotic-metabolizing cytochrome p-450 family can also oxidize phospholipids (Serbinova et al., 1989). Cytochrome p-450 enzymes belong to the class of ω-hydroxylases (Kawashima et al., 1997), epoxygenases (Wang et al., 2004) and bisallylic hydroxylases (Brash et al., 1995) which generate terminal hydroxylated fatty acids, epoxy fatty acids and HETEs, respectively. The cytochrome p-450 family consists of 500 genes and 78 different membrane-bound, heme-containing, NADPH-dependent oxidases (Roman, 2002).

Aside from COX, LOX and cytochrome p-450, various iron-containing proteins can gain lipid peroxidase activity. One such protein that has gained attention in the field of lipid

peroxidation is the mitochondrial electron transport chain complex protein, cytochrome c. Upon pro-apoptotic stimulation, cytochrome c selectively oxidizes the anionic phospholipid cardiolipin in mitochondria and phosphatidylserine in the plasma membrane (Bayir et al., 2007b; Ji et al., 2012b; Kagan et al., 2005a; Tyurina et al., 2006). Similar to cytochrome c, a number of other membrane proteins with heme catalytic centers have been implicated in lipid peroxidation: myeloperoxidase (Davidenkova et al., 1982; Goldman et al., 1999), cytoglobin (Reeder et al., 2011), myoglobin (Grisham, 1985) and hemoglobin (Szebeni et al., 1984).

2.2. Non-enzymatic lipid peroxidation

Non-enzymatic lipid peroxidation is primarily derived from free radical reactions. Hydroxyl radical formed from the interaction of transition metals with reactive oxygen species (ROS) is the major radical involved in this process (Kappus, 1987). ROS are derived from molecular oxygen, hydrogen peroxide (Fridovich and Porter, 1981) and organic peroxides (Girotti, 1985). Although molecular oxygen is thought to be a powerful oxidizing agent, it is not directly involved in free radical-mediated lipid peroxidation reactions. Acceptance of a single electron by molecular oxygen forms a superoxide anion radical ($O_2^{\bullet -}$) (Kellogg and Fridovich, 1975). Under normal conditions, superoxide is reduced by SOD to form hydrogen peroxide (Fridovich, 1989). Hydrogen peroxide in turn reacts with ferrous ion via Fenton reaction to form hydroxyl radical, hydroxyl anion and ferric ions (Repetto et al., 2010) (Figure 2). Superoxide can also be utilized for the reduction of ferric ion to ferrous ion as the first step of Haber–Weiss reaction (Thomas et al., 1985).

In addition to ferrous iron, other transition metal ions such as Cu^{2+}, Co^{2+}, Ni^{2+} can generate hydroxyl radicals through Fenton-like reaction, albeit with much slower reaction rates. Both iron and copper ions are also involved in the degradation of organic hydroperoxides into organic peroxyl radicals and hydroxyl radicals (Repetto et al., 2010). While the amount of free ionic iron or copper is extremely low under normal conditions due to effective handling of these transition metals within and outside of the cellular environment (MacKenzie et al., 2008), there are conditions where transition metals are elevated as a result of disturbed handling. In disorders characterized by disturbed handling of transition metals, such as hemochromatosis (Papanikolaou and Pantopoulos, 2005) and neurodegenerative conditions (Lee et al., 2006), free transition metals may play a significant role in the generation of lipid hydroperoxides.

Another pathway that can generate hydroxyl radicals is the decomposition of peroxynitrous acid (Beckman et al., 1990). Reaction of superoxide anion radical with nitric oxide (NO) radical forms peroxynitrite anion (Robak and Gryglewski, 1993). The hydroxyl radicals produced by this pathway can act as the initiation step of the lipid peroxidation reaction (Beckman et al., 1990; Beckman et al., 1994; Pryor and Squadrito, 1995). Overall, the non-enzymatic generation of lipid hyrodperoxides is difficult to target therapeutically due to the high reaction rates and non-specific nature of generated products.

3. Detection of lipid peroxidation in clinical TBI

Oxidative stress and lipid peroxidation have been widely studied in experimental TBI (Bazan, 1976; Bazan et al., 2005; Chan, 1996; Hall, 1989; Hall, 1993; Hall et al., 1996). In this section we will briefly review detection of lipid peroxidation in clinical TBI. Lipid peroxidation end products such as malondialdehyde, 4-HNE and isoprostanes have been shown to increase in bio-fluids and brain tissue samples from TBI patients (Al Nimer et al., 2013; Cristofori et al., 2001; Cristofori et al., 2005; Kasprzak et al., 2001; Lin et al., 2014b; Lorente et al., 2015; Niki, 2014). Despite criticism for lack of specificity and artefactual production during analytical processing, malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS) remain the most commonly used markers of lipid peroxidation in clinical TBI, and their increase in cerebrospinal fluid (CSF) and serum have been associated with severity of injury and mortality (Cristofori et al., 2001; Cristofori et al., 2005; Kasprzak et al., 2001; Lin et al., 2014b; Lorente et al., 2015). Thiobarbituric acid (TBA) is not specific for MDA but can react with other aldehydes and decomposition products of hydroperoxides (Yoshida et al., 2010). In a heated sample at low pH, interaction of MDA and TBA generates pink chromogen that can be measured by spectrophotometry or spectrofluorophotometry (Niki, 2014) . In order to improve the specificity for lipid oxidation measurements, High Performance Liquid Chromatography (HPLC) methods have been developed and applied to CSF (Cristofori et al., 2001; Cristofori et al., 2005). Another lipid oxidation marker, 4- HNE, is an aldehyde end product of lipid hydroperoxide break down. It forms covalent adducts with proteins and can be detected by immunohistochemistry (Niki, 2014). A recent study reported that 4-HNE-conjugates are present in neurons in human TBI but were not detected in CSF (Al Nimer et al., 2013).

Isoprostanes are a series of prostaglandin-like compounds produced by free radical-mediated lipid peroxidation of arachidonic acid and can be quantified with Enzyme Linked Immunosorbent Assay (ELISA), Radio Immuno Assay (RIA), HPLC, Gas Chromatography-Mass Spectrometry (GC-MS) or Liquid Chromatography-Mass Spectrometry LC-MS (Roberts and Morrow, 2002). Isoprostanes can be formed by cyclooxygenase-catalyzed oxidation of arachidonic acid, however the enzyme does not normally utilize arachidonyl phospholipids as substrates (Bayir et al., 2006). Increases in F2 isoprostane or 8-epi prostaglandin F2α generation have been observed in the CSF of adult TBI patients (Bayir et al., 2004; Wagner et al., 2004). Interestingly, F2-isoprostane levels were two-fold higher in males than females on day 1 post-injury and were reduced with therapeutic hypothermia in the male TBI population (Bayir et al., 2004). Studies in the infant and child TBI population also demonstrated elevation of CSF F2 isoprostane concurrent with other biomarkers of oxidative stress (Bayir et al., 2002). Assessment of end product of lipid hydroperoxides can give a general idea about the involvement of lipid peroxidation in TBI; however, it does not identify the origin and identity of oxidized phospholipids. The latter is important for identification of causal links between lipid peroxidation and mechanisms of secondary injury after TBI.

The primary product of lipid peroxidation is phospholipid hydroperoxides (Niki, 2014). Their short half-life makes them difficult to detect in biological samples. Nevertheless, recent developments in mass spectrometry-based oxidative lipidomics approaches make it

possible to detect phospholipid hydroperoxides in plasma and tissue samples (Ji et al., 2012a); (Tyurin et al., 2010; Tyurina et al., 2015). Using this oxidative lipidomics approach, we have shown that lipid peroxidation is a nonrandom event after experimental and clinical TBI, and it is most prominent in the mitochondria early after injury as cytochrome c-catalyzed cardiolipin oxidation (Bayir et al., 2007b; Ji et al., 2012a). Accumulation of cardiolipin oxidation products is essential for the release of pro-apoptotic factors such as cytochrome c into cytosol (Kagan et al., 2005b; Tyurin et al., 2010). Furthermore, cytochrome c-mediated oxidation of cardiolipin is involved in the synthesis of various lipid mediators through hydrolysis by calcium independent iPLA2γ (Tyurina et al., 2014). Overall there is accumulating evidence demonstrating that lipid peroxidation occurs after severe TBI in humans and correlates with injury severity and mortality. Thus the secondary injury cascades leading to lipid peroxidation, particularly enzyme-mediated lipid peroxidation, constitute viable therapeutic targets for neuroprotection.

4. Therapeutic strategies targeting lipid peroxidation

In this section we will briefly review therapies targeting specific enzymatic pathways of lipid peroxidation including mitochondria-targeted electron scavengers and general antioxidant strategies in TBI. For the therapeutic strategies with limited data in TBI, we will also present available information from other acute CNS insults such as stroke and spinal cord injury.

4.1. Phospholipase A_2

Phospholipase A_2 (PLA2) is an esterase that specifically cleaves the fatty acyl group attached to the sn-2 position in phospholipids. PLA2 enzymes are grouped into four classes based on their activity and subcellular localization, namely secretory PLA2 (sPLA2), cytoplasmic PLA2 (cPLA2), plasmalogen-selective PLA2 (Pls-PLA2) and calcium-independent PLA2 (iPLA2) (Dennis, 1994). Even though PLA2 is not directly involved in the peroxidation of lipids, it is the first rate-limiting step in the production of multiple oxygenated lipid mediators (Farooqui and Horrocks, 2006).

PLA2 activity has been shown to increase after TBI (Shohami et al., 1987), stroke (Yagami et al., 2014) , and SCI (Horrocks et al., 1985). PLA2 generates lysophospholipid and free fatty acid, primarily arachidonic acid. Accordingly, the increase in arachidonic acid and its oxidized derivatives such as eicosanoids and leukotrienes observed after closed head injury were shown to be due to increased cPLA2 activity (Shohami et al., 1989). On the other hand increased activities of both cPLA2 and Pls-PLA2 contribute to increased free fatty acid content after cerebral ischemia (Bazan et al., 1993) (Farooqui and Horrocks, 1994). It was shown that cPLA2 elevation initiate the neural injury and Pls-PLA2 triggers secondary injury (Farooqui et al., 2003; Farooqui and Horrocks, 2004; Fujishima et al., 1999; Sapirstein and Bonventre, 2000). Activation of Pls-PLA2 as well as loss of plasmalogen-containing phospholipids were also reported after compression and sheer stress spinal cord injury (Lukacova et al., 1996).

A number of experimental studies utilizing PLA2 inhibitors have shown benefit in acute CNS injury models. Examples include Cytidine-5'-diphosphocholine (CDP-choline) in TBI

and stroke (Hurtado et al., 2007; Jacotte-Simancas et al., 2015; Secades and Frontera, 1995), quinacrine in middle cerebral artery occlusion (MCAO) (Estevez and Phillis, 1997), and arachidonyl trifluoromethyl ketone in SCI (Huang et al., 2009). CDP-choline is also investigated for its neuroprotective potential in clinical TBI (Adibhatla, 2013; Zafonte et al., 2009). Apart from inhibition of PLA2 activity, CDP-choline also stimulates synthesis of phosphatidylcholine (Grieb, 2014). Despite promising results in TBI and stroke models and in small clinical studies (Calatayud Maldonado et al., 1991; Clark et al., 1997; Clark et al., 1999; Clark et al., 2001; Davalos et al., 2002; Tazaki et al., 1988) two recent large clinical trials showed no benefit in TBI and ischemic stroke (Zafonte et al., 2012; Davalos et al., 2012). It is worth mentioning that glycosphingolipids, primarily gangliosides, strongly inhibit PLA2 activity *ex vivo* (Bianco et al., 1989), thus they have been tested for their neuroprotective potential in a number of CNS injury models (Sabel et al., 1984) (Toffano et al., 1984) as well as in patients with spinal cord injury. Although the results of the initial single center randomized control trial (RCT) with GM1 ganglioside were protective (Geisler et al., 1991) subsequent multicenter RCT failed to show a significant difference between GM1 treatment and placebo (Geisler et al., 2001). Nevertheless, there was a trend favoring treatment in the subgroup analysis of those with ASIA Impairment Scale-B (AIS B) classification.

4.2. Cyclooxygenase

Cyclooxygenase or prostaglandin-endoperoxide synthase catalyzes the production of prostaglandin H2 (PGH2), which is a precursor of many prostanoids and thromboxanes formed from arachidonic acid (DeWitt, 1991). Among the COX enzymes, COX1 is widely expressed in neurons and microglia, whereas COX2 is expressed constitutively in hippocampal and cortical neurons (Yermakova and O'Banion, 2000). A number of studies reported increased COX2 activity after TBI (Hickey et al., 2007; Morrison et al., 2000; Strauss et al., 2000). Higher levels of COX2 expression are associated with functional deficit and worse outcome after TBI.

Table 1 summarizes experimental studies evaluating COX inhibitors in TBI models. Overall the studies in TBI models suggest that selective inhibitors of COX-2 are not effective in improving outcome. Nonselective COX inhibitors on the other hand might be beneficial depending on the model and timing of the therapy after TBI. But the antiplatelet effects of nonselective COX inhibitors might overweigh the benefit that can be obtained from them in TBI. Notably long-term use of selective COX-2 inhibitors has been associated with an increase in ischemic cerebrovascular events (Bresalier et al., 2005). In contrast, inhibition of COX1 by aspirin has been associated with a reduction in adverse cardiovascular events (Berger et al., 2006; Bhatt et al., 2006). Evidence suggests that beneficial effects of aspirin, particularly low dose aspirin (72–162 mg/day), could be in part related to acetylation of COX2. COX2 acetylation triggers synthesis of novel specialized pro-resolving lipid mediators (SPMs) with anti-inflammatory actions such as 15-epi-lipoxin A4 (Serhan et al., 2000). In agreement with this concept, a recent study in fluid percussion injury model showed improved motor and cognitive function when rats were pretreated with aspirin-triggered SMP, 17(R)-Resolvin D1 (Harrison et al., 2015). Although aspirin may have beneficial effects by preventing secondary injury from ischemia in subarachnoid hemorrhage

(Dorhout Mees et al., 2003), pre-injury intake of aspirin was shown to increase the risk of lesion progression and unfavorable outcome after TBI in a recent large multicenter study (Fabbri et al., 2013).

4.3. Lipoxygenases

Lipoxygenases catalyze the di-oxygenation of PUFA containing a 1, 4 diene structure. Lipoxygenases are involved in the production of octanoids, eicosanoids and docosanoids (Brash, 1999; Kuhn et al., 2015). Among several LOX enzymes, 5 LOX protein levels were reported to increase in glial cells and neutrophils after TBI (Zhang et. al, 2006). Following fluid percussion injury, plasma levels of 12-HETEand PGE-2 were found to increase during the first hour after injury with peak levels at 5 minutes (Ellis et al., 1989). Among these products 12-HETE is produced from Arachidonic acid by 12-LOX and PGE-2 by COX2. Corroborating the findings in experimental TBI, 12-HETE and 5-HETE levels in the CSF of patients with head injury were found to increase 10–17 fold vs. control (Farias et al., 2011). The source of increased 12-HETE and 5-HETE production after TBI is likely glia, neutrophils and to a lesser extent neurons (Hariri et al., 1989; Zhang et al., 2006). Among several LOX enzymes 12/15 LOX protein levels were reported to increase primarily in neurons in the peri-infarct area after transient MCAO in mice (van Leyen et al., 2006). Furthermore baicalein, a nonspecific 12/15 LOX inhibitor, ameliorated brain edema and improved neurological deficits after transient focal ischemia (Cui et al., 2010) (Jin et al., 2008; Moskowitz et al., 1984). Leukotriene synthesis indicative of 5 LOX activity was also reported during ischemia and reperfusion and was thought to play an important role in the development of cerebral edema (Ban et al., 1989; Moskowitz et al., 1984). The lipid mediators generated by LOX activity have strong effects on neutrophil recruitment and vascular permeability, thus LOX are thought be important therapeutic targets. Table 2 summarizes the studies evaluating therapeutic potential of LOX inhibition in TBI and other CNS injuries. Recent studies utilized more specific inhibitors of LOX, whereas earlier studies used less selective inhibitors with activity against both COX and LOX.

Interestingly several lipid mediators generated by LOX from arachidonic, eicosapentaenoic and docosahexaenoic acids called SPMs (Figure 3) play an important role in the resolution of inflammation primarily by attenuating neutrophil infiltration and enhancing phagocyte efferocytosis (Dennis and Norris, 2015). Among the SPMs generated as depicted in the figure 3., the arachidonic acid derivative, lipoxin A4, and its derivatives, ATLA4 (aspirin-triggered lipoxin A4) and BMA-11, were shown to exert neuroprotective effects in stroke models (Hawkins et al., 2014; Wu et al., 2010; Wu et al., 2012; Ye et al., 2010). Intracerebroventricular administration of lipoxin A4 10 minutes after weight drop model of experimental TBI was reported to decrease BBB breakdown and brain edema and attenuate brain levels of TNFα, IL1β and IL6 mRNA (Luo et al., 2013). Similarly, lipid mediators derived from ω3-fatty acids docosahexaenoic acid and eicosapentanoic acid, namely resolvins and neuroprotectins, were also shown to exert beneficial effects in cerebral ischemia reperfusion injury (Bazan, 2005; Marcheselli et al., 2003; Serhan et al., 2004). Figure 4. Summarizes all the LOX and COX dependent mediators and its role in inflammation. Taken together, the beneficial vs. detrimental effects of LOX may depend on

the spatial (including subcellular localization) and temporal profiles of the lipid mediators they generate after injury.

4.4. Mitochondrial targeted lipid peroxidation inhibitors

The classic pathway of lipid mediator synthesis includes (Figures 3 and 4) hydrolysis of esterified PUFA by one of the Ca^{2+}-dependent PLA2, followed by oxygenation of the released free PUFA by COX, LOX and P450 enzymes. Recently an alternative Ca^{2+}-independent pathway was described whereby oxygenation of *esterified* PUFA within the phospholipid molecule is followed by Ca^{2+}-*independent* PLA2-mediated hydrolysis to yield lipid mediators (Figure 5) (Tyurina et al., 2014). It has been shown that peroxidized cardiolipin can be hydrolyzed by mitochondrial Ca^{2+}-independent iPLA2γ to release linoleic- and arachidonic acid-derived lipid mediators (HODE and HETE) after controlled cortical impact (CCI) and global cerebral ischemia (Ji et al., 2015; Tyurina et al., 2014). Cardiolipin oxidation is catalyzed by cytochrome c, an electron transport protein in mitochondria (Kagan et al., 2005b). Normally all six of the coordination positions in the heme iron of cytochrome c are occupied, thus preventing its interactions with small ligands such as hydrogen peroxide (Stellwagen, 1968). Upon interaction with cardiolipin, cytochrome c loses its tertiary structure resulting in loss of ability to participate in electron transfer and gain peroxidase function (Kapralov et al., 2007); (Basova et al., 2007). The resultant cytochrome c/cardiolipin complex leads to cardiolipin oxidation (Kagan et al., 2005b). It has been shown that in addition to being a source for lipid mediator synthesis, cardiolipin peroxidation is essential for the release of pro-apoptotic factors, including cytochrome c, from mitochondria into the cytosol (Ji et al., 2012a; Kagan et al., 2005b). Subsequently, the released cytochrome c participates in apoptosome formation and catalysis of phosphatidylserine oxidation ultimately leading to externalization of phosphatidylserine, a recognition signal for phagocytosis of apoptotic cells by microglia (Fadeel et al., 2010).

Several different mitochondria-targeted inhibitors of the cardiolipin oxidation pathway have been developed based on: i) inhibition of production of hydrogen peroxide, which is utilized as an oxidizing equivalent in the peroxidase reaction; ii) inhibition of the peroxidase activity of cytochrome c in the complex (Kagan et al., 2009b). Among the first category, mitochondria-targeted electron acceptor XJB-5-131 was shown to concentrate >500-fold in neuronal mitochondria. Mitochondrial accumulation of XJB-5-131 prevents formation of superoxide and thus hydrogen peroxide, resulting in improved neurocognitive outcome after TBI and asphyxial cardiac arrest in PND17 rats (Ji et al., 2012a; Ji et al., 2015). Among the second category, triphenylphosphonium conjugated imidazole oleic acid (TPP-IOA) and stearic acid (TPP-ISA) block peroxidase activity of cytochrome c/cardiolipin complex by specifically binding to its heme-iron. Both compounds inhibit pro-apoptotic oxidative events, suppress cytochrome c release and prevent cell death (Atkinson et al., 2011). Another target in the cardiolipin oxidation pathway is Ca^{2+}-independent iPLA2γ. Inhibition of Ca^{2+}-independent iPLA2γ by its selective inhibitor R-BEL (R)-(E)-6-(bromomethylene)-3-(1-naphthalenyl)-2H-tetrahydropyran-2-one prevents generation of lipid mediators from oxidized cardiolipin in the intestine (Tyurina et al., 2014). There has not been a study evaluating the neuroprotective potential of R-BEL administration after TBI. It is possible that the lipid mediators generated upon cardiolipin oxidation during apoptosis,

such as 9-HODE and 13-HODE, are modulating the inflammatory process after injury. It is possible that timing of therapy could be important after injury, as constitutive genetic ablation of Ca^{2+}-independent iPLA2γ was shown to alter hippocampal cardiolipin content and molecular species and lead to mitochondrial degeneration, autophagy and cognitive dysfunction (Mancuso et al., 2009).

4.5. General inhibitors of lipid peroxidation

Apart from specific inhibitors of enzymatic lipid oxidation, a number of therapies can attenuate lipid peroxidation and have shown neuroprotective potential in experimental studies after TBI. These therapies generally fall under the following categories; a) general, nonspecific antioxidants that act as a free radical scavengers in the biological system including endogenous antioxidants and b) antioxidant enzymes. In this section we will briefly discuss therapies in these two categories.

4.5.1. Vitamin E—Vitamin E family is composed of 8 compounds (4 tocopherols (d-α, d-β, d-γ, d-δ) and 4 tocotrienols (d-α, d-β, d-γ, d-δ)) that exhibit the biological activity of naturally occurring vitamin E, d-α-tocopherol. Tocopherols are lipid-soluble and scavenge lipid peroxyl radicals, inhibiting the chain reaction of lipid peroxidation (Figure 1). The resultant tocopherol radical is reduced back to tocopherol by ascorbic acid and lipoic acid via the vitamin E recycling process (Chan, 1993). Vitamin E levels have been shown to decrease concomitant with enhanced accumulation of MDA in jugular venous blood samples of patients with TBI (Paolin et al., 2002). Interestingly, there was no change in the peripheral venous blood levels of vitamin E and MDA in these patients. Experimental studies have shown beneficial effects of Vitamin E treatment in TBI. Dietary vitamin E supplementation attenuated elevated brain free fatty acid levels induced by sudden decompression-mediated vasogenic cerebral edema (Yoshida et al., 1985) and improved cerebral blood flow in the cortex after epidural compression injury (Busto et al., 1984). Furthermore, improvement in functional outcome has been reported with Vitamin E post-treatment after fluid percussion injury (Clifton et al., 1989) and with Vitamin E pre-treatment after repetitive mild TBI (Conte et al., 2004). Accumulating evidence in experimental stroke suggests that the neuroprotective potential of tocotrienols may be greater than tocopherols (Patel et al., 2011), but no studies in TBI have evaluated the effect of tocotrienols.

The only published RCT of Vitamin E (at a dose of 400 IU/d IM for 7 days) in severe TBI showed decreased hospital mortality and improved 6 month Glasgow Outcome Scale Score (GOS) vs. placebo in adults (Razmkon et al., 2011). Due to the small size of this trial (n = 23–27 patients/group), known antiplatelet effects of Vitamin E, and associated risk of hemorrhagic stroke with Vitamin E supplementation (Schurks et al., 2010), a multicenter RCT is necessary before Vitamin E can be recommended for routine use in severe TBI .

4.5.2. Vitamin C—Ascorbate or Vitamin C acts as a primary defense against aqueous oxygen, nitrogen and sulfhydryl radicals in the blood. Vitamin C is very effective in trapping free radicals, preventing formation of lipid hydroperoxyides and reducing membrane damage (Frei et al., 1989; Frei, 1991). There is a high concentration of ascorbate in both gray and white matter of the brain Additionally, the choroid plexus has a specific active

transport system that increases the ascorbate concentrations in CSF to a level approximately 10-times higher than in the plasma (Spector and Eells, 1984). Ascorbate level in the brain is decreased after traumatic brain injury (Awasthi et al., 1997; Tyurin et al., 2000) , however the extracellular ascorbate increases after ischemia (Hillered et al., 1988) and trauma (Hillered et al., 1990).

A 2–3-fold decrease in CSF ascorbate levels was reported in clinical TBI in infants, children and adults (Bayir et al., 2002) (Cristofori et al., 2001). Similarly, plasma ascorbate levels are decreased after stroke (Yokoyama et al., 2000), intracranial hemorrhage and head trauma (Polidori et al., 2001). Razmkon and colleagues (Razmkon et al., 2011) compared treatment with low-dose (500 mg/d IV for 7 days) and high-dose Vitamin C (10 g IV on the 1st and 4th days followed by 4 g/d IV for 3 days) with placebo after severe TBI in adults. While high-dose Vitamin C decreased the diameter of perilesional hypodense region on head CT (defined as edema), low-dose Vitamin C increased the diameter of this region compared with placebo. There was no effect of either dose of Vitamin C on mortality or 6 month GOS scores. Unfortunately the effect of Vitamin C or E supplementation on plasma, CSF or interstitial fluid ascorbate and Vitamin E levels was not evaluated in this trial. The results of this placebo-controlled randomized single center trial are interesting and further studies should evaluate the safety and efficacy of high-dose Vitamin C in severe TBI patients.

4.5.3. Glutathione (GSH)—GSH is the most abundant intracellular non-protein thiol. Along with Vitamin E and C, GSH completes the major elements of endogenous antioxidant reserve. GSH is a co-substrate in the reduction of hydrogen peroxide and lipid hydroperoxides by glutathione peroxidase (GPx). When it is involved in direct scavenging of free radicals, the antioxidant function of GSH is largely achieved as thiyl radicals are formed. Decrease in GSH is implicated in TBI (Xiong et al., 1999), SCI (Azbill et al., 1997) and cerebral infarction (Frithz et al., 1982). Brain tissue GSH levels decrease at 6–24 h after controlled cortical impact (CCI) with restoration of normal levels at 72 h in adult rats (Tyurin et al., 2000). In contrast, GSH levels increase in CSF on day 1 after injury with normalization by day 7 in infants and children with severe TBI compared to controls (Bayir et al., 2002).

GSH is synthesized from glutamate, glycine, and cysteine. N-acetylcysteine (NAC) is a cysteine donor, and when administered within 1 h of CCI in rats, it was shown to restore brain and mitochondrial GSH levels and improve mitochondrial function (Xiong et al, 1999). NAC has limited permeability through the intact BBB. A novel cell-permeable amide form of NAC has better bioavailability and was shown to decrease lesion volume and improve cognitive function compared to NAC or vehicle treatment when given 30 minutes after CCI in rats (Pandya et al., 2014). Another GSH-replenishing compound, gamma-glutamylcysteinyl ethyl ester (GCEE) provides glutamate and cysteine and bypasses the rate-limiting step in the GSH synthesis. Treatment with GCEE 10 minutes after CCI in mice reduced autophagy and led to partial improvement in behavioral and histologic outcome compared to vehicle (Lai et al., 2008). NAC has been evaluated in a double-blind, placebo-controlled randomized study after blast-induced mild TBI. The results of this trial showed that supplementation of standard therapy with oral NAC decreased number of symptoms such as dizziness, hearing loss, headache, memory loss, sleep disturbances, and

neurocognitive dysfunction ,assessed during the first 7 days after injury in the combat setting (Hoffer et al., 2013). To date, there has not been a clinical study evaluating the efficacy of NAC in severe TBI.

4.5.4. Other antioxidants—A number of other antioxidants have also been evaluated in experimental studies for their neuroprotective role in TBI, including curcumin(Wu et al., 2011; Zhu et al., 2014), epigallocatechin gallate (Itoh et al., 2011), 2-methylaminochromans (Hall, 1995), resveratrol (Lin et al., 2014a), melatonin (Ding et al., 2015) and alpha lipoic acid (Ozbal et al., 2015) . Although the multicenter trial with tirilizad showed no overall benefit (Marshall et al., 1998), subgroup analysis suggested that it may be effective in reducing mortality in male patients suffering from severe TBI with accompanying traumatic subarachnoid hemorrhage. Progesterone, a pleiotropic agent, was shown to be neuroprotective in part through attenuation of lipid peroxidation in experimental TBI (Djebaili et al., 2005; Roof et al., 1997). Despite initial promising results in single center studies, multicenter clinical trials of progesterone failed to show benefit relative to placebo in severe, moderate-to-severe, or moderate acute TBI (Skolnick et al., 2014; Wright et al., 2014).

4.5.5. Superoxide Dismutase (SOD)—Similar to the biological antioxidant reserve, some of the endogenous enzymes also play an important role in removing ROS and the associated lipid peroxidation and toxic effects. One such enzyme is SOD, which converts superoxide into hydrogen peroxide. Although small fluctuations in the steady state concentrations of superoxide play an important role in learning and memory, its enhanced production after injury is deleterious (Knapp and Klann, 2002; Thiels et al., 2000). Numerous sources including the mitochondrial electron transport chain and NADPH oxidase generate excess superoxide after injury (Brennan et al., 2009). Excess superoxide production combined with the decreased SOD activity (both cytosolic CuZnSOD and mitochondrial MnSOD (Bayir et al., 2007a; Wang et al., 2015) results in elevated superoxide levels following TBI.

The reaction rate for formation of peroxynitrite from superoxide and nitric oxide is comparable to the reaction rate of SOD (Gray and Carmichael, 1992; Kissner et al., 2003), thus it is important to maintain high activity of SOD. In agreement with this, mice expressing 50% of the normal complement of MnSOD display worse outcome after CCI (Gray and Carmichael, 1992; Kissner et al., 2003). Similarly, treatment with SOD or overexpression of CuZnSOD was associated with beneficial effects including decreased brain edema and improved motor function after diffuse TBI (Kontos and Wei, 1986; Mikawa et al., 1996). However the beneficial effects of increasing SOD activity may depend on the SOD variant, injury type and age. Beni et al., has shown that CuZnSOD knock out mice but not CuZnSOD transgenics showed better neurological scores than the wild type mice after contusion head injury (Beni et al., 2006). Similarly, immature CuZnSOD transgenic mice sustain worse injury than their wild type littermates after hypoxia-ischemia (Ditelberg et al., 1996). It is likely that increasing SOD activity without a concomitant increase in the activities of catalase or GPx will result in enhanced hydrogen peroxide accumulation, which can activate apoptotic death pathways (Kagan et al., 2005a) as well as NFκB-mediated

inflammation (Beni et al., 2006). Administration of SOD-mimics has been evaluated in clinical TBI. A large clinical trial with polyethylene glycol (PEG)-conjugated SOD showed no improvement in survival or neurological outcome after moderate to severe TBI (Young et al., 1996), although an earlier small phase II study reported a positive trend (Muizelaar, 1993).

4.5.6. Catalase—Catalase converts hydrogen peroxide into water and molecular oxygen. It has a low affinity for hydrogen peroxide, thus it is only effective in eliminating hydrogen peroxide at high concentrations. Catalase activity was shown to increase after TBI (Goss et al., 1997). The increase in catalase activity is region specific after controlled cortical impact, with hippocampus having a higher increase vs. cortex (DeKosky et al., 2004; Miller et al., 2014). Pre-treatment with polyethylene glycol SOD/catalase restored opioid-induced vasodilation and cyclic GMP production after fluid percussion injury, suggesting that both superoxide and hydrogen peroxide might have a causal role in decreased cerebral blood flow observed after injury (Thorogood and Armstead, 1996). Hypothermia treatment decreased catalase activity in the hippocampus after controlled cortical impact (DeKosky et al., 2004; Miller et al., 2014). In patients, this is likely secondary to attenuated endogenous antioxidant consumption and lipid peroxidation with hypothermia (Bayir et al., 2009).

4.5.7. Glutathione peroxidase (GPx)—GPx are selenoenzymes involved in the conversion of peroxides into hydroxides. There are 8 different classes of GPx enzymes that can metabolize hydrogen peroxide or lipid hydroperoxides. Among these, Gpx4 is the only GPx that accepts phospholipid hyroperoxides in membranes as substrate using GSH as hydrogen donor (Roveri et al., 1994). The critical importance of this enzyme is evident from the studies demonstrating embryonic lethality of GPx4 deficient mice (Yant et al., 2003). Gpx4 ablation in adult mice reportedly results in delayed death accompanied by neuronal loss in hippocampus and reactive gliosis (A Khan and JT Gowder, 2014). GPx4 plays an important role in apoptotic and ferroptotic cell death pathways (Friedmann Angeli et al., 2014; Yang et al., 2014). Conditions of cysteine and glutathione depletion favor ferroptosis and lead to oxidation of PUFAs in membrane phospholipids (Friedmann Angeli et al., 2014; Yang et al., 2014). GPx4 is expressed in all neuronal layers of the immature brain (Savaskan et al., 2007). In the adult brain, GPx4 expression becomes more restricted to neurons of the cerebral cortex, hippocampus and cerebellum, whereas glial cells are devoid of GPx4 (Savaskan et al., 2007). Following bilateral entorhinal cortex lesion, GPx4 expression is upregulated in reactive astrocytes of lesioned areas but not in neurons. The GPx mimic, Ebselen [2-phenyl-1,2-benzisoselenazol-3(2H)-one], is reported to reduce NO levels and modulate the TL4-mediated p38-MAPK pathway after weight drop injury in rats (Wei et al., 2014).

5. Concluding remarks and Future Directions

Lipids are indispensable for normal structure of organelles and cells. Furthermore, lipid mediators derived from oxidized phospholipids and free fatty acids play important signaling functions to maintain homeostasis (Balasubramanian et al., 2015; Chu et al., 2013; Fadeel et al., 2010). Increased ROS generation, enhanced activity of lipid peroxidation enzymes, and

decreases in reductants and activity of antioxidant enzymes result in uncontrolled oxidation of phospholipids that contributes to secondary injury after TBI.

Lipid peroxidation inhibitors such as free radical scavengers have been used numerous times in TBI, but clinical trials of these agents in TBI and other free radical diseases have largely failed. The reasons for to the negative results are multiple and include: 1) limited CNS penetration of the drugs tested; 2) complex actions of mediators formed from peroxidized lipids depending on the time and the extracellular milieu after injury; and 3) inadequate understanding and identification of the sources and mechanisms of redox imbalance after TBI. Unless the true sources and mechanisms of TBI redox imbalance are identified, the use of sacrificial antioxidants and free radical scavengers will fail.

Recent improvements in LC-MS based lipidomics and oxidative lipidomics approaches offer remarkable opportunities for identification, characterization and quantification of lipid oxidation products and their source. This information is critical for targeted therapy development. Future experimental studies evaluating therapies targeting lipid peroxidation should consider assessment of therapeutic target specificity and CNS penetration of the compounds being tested in diverse experimental models of TBI. In addition, the effect of the targeted therapies on lipid peroxidation should be evaluated using contemporary methods in experimental and clinical TBI. Combined these approaches might improve the likelihood of successful translation of promising therapies targeting lipid peroxidation to clinical TBI.

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Highlights

- Description of attempts to use non-specific antioxidants as neuroprotectors
- Enzymatic lipid peroxidation in specific death pathways - particularly apoptosis
- Generation of lipid mediators from peroxidized phospholipids by phospholipases

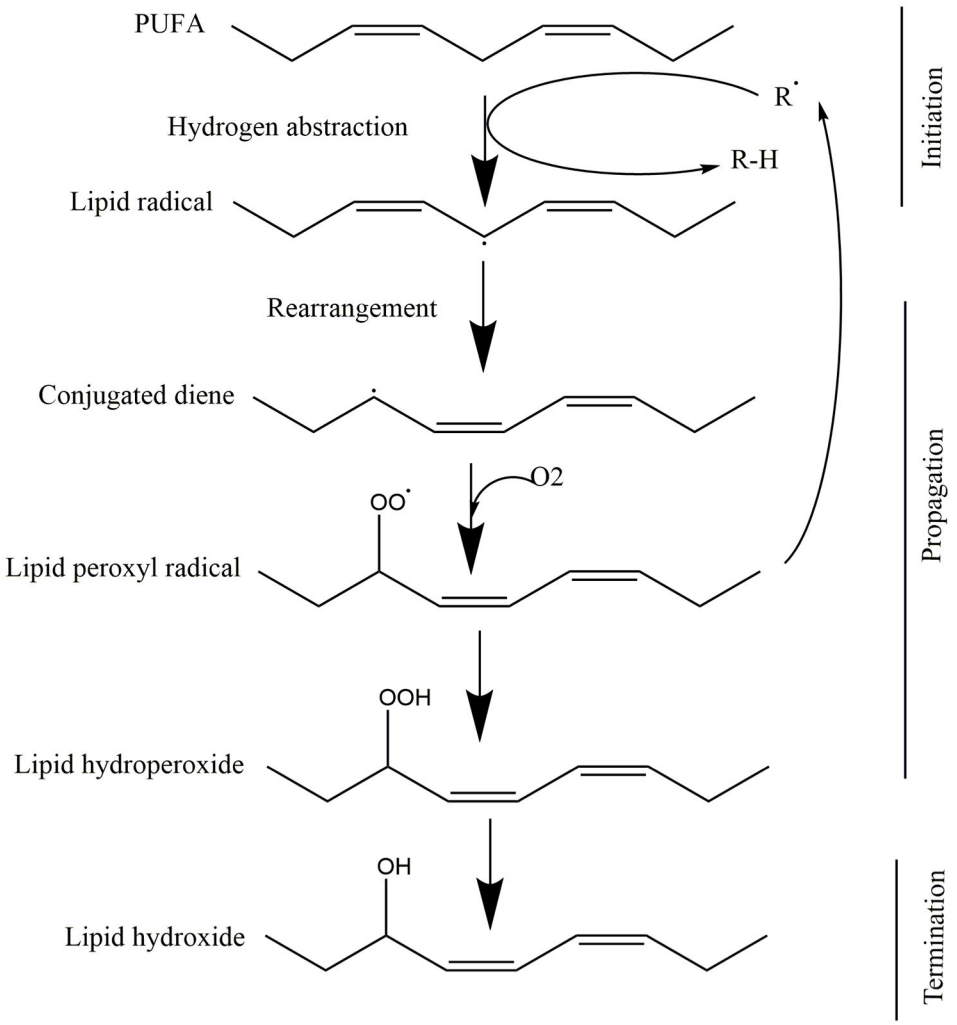

Figure 1. Chain reaction of lipid peroxidation

Chain reaction of lipid peroxidation involves a three step pathway: 1) initiation - removal of a hydrogen from PUFAs to form a carbon-centered lipid radical; 2) propagation - attachment of a peroxy group to the lipid radical to form a lipid peroxyl radical. This lipid peroxyl radical initiates a new cycle by extracting a hydrogen, thereby perpetuating the peroxidation reaction; and 3) termination - disappearance of free radical by forming a non-radical such as hydroxide.

Haber-Weiss Reaction

$$Fe^{3+} + O_2^{\bullet -} \longrightarrow Fe^{2+} + O_2$$

Fenton Reaction

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH^\bullet$$

Fenton-like Reaction

$$Me^{n+} + H_2O_2 \longrightarrow Me^{(n+1)+} + OH^- + OH^\bullet$$

Free radical formation by transition metals

$$ROOH + Me^{n+} \longrightarrow RO^\bullet + Me^{(n-1)+}$$

$$ROOH + Me^{n+} \longrightarrow ROO^\bullet + Me^{(n+1)+}$$

Free radical from nitric oxide

$$NO + O_2^{\bullet -} \longrightarrow ONOO^-$$

$$ONOO^- + H^+ \longrightarrow ONOOH$$

$$ONOOH \longrightarrow OH^\bullet + NO_2^\bullet$$

Figure 2.
Reactions involved in the production of free radicals.

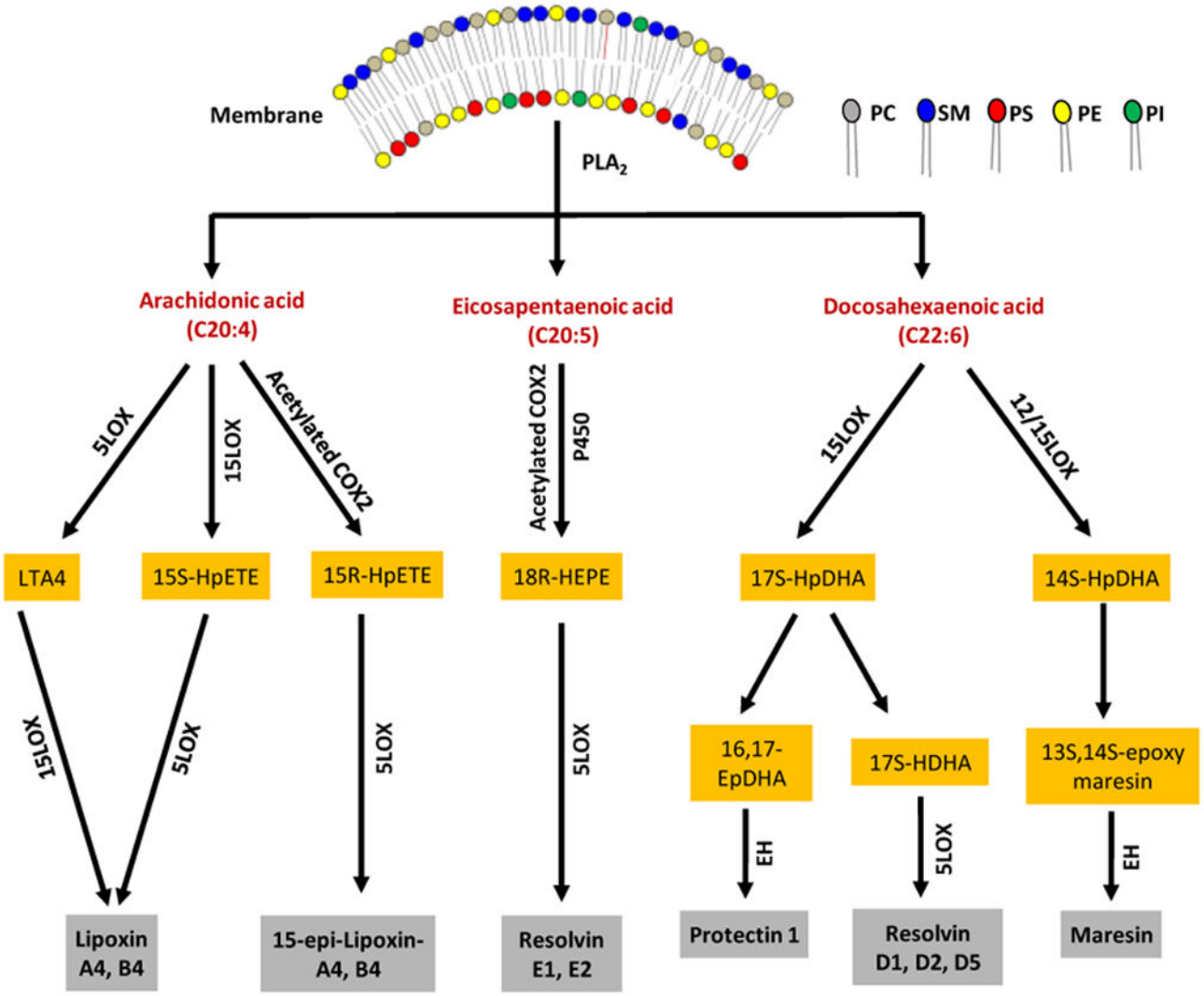

Figure 3. Biosynthetic pathways of specialized pro-resolving lipid mediators (SPMs)

Free fatty acids produced after the hydrolysis of phospholipids such as phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylethanolamine (PE) and phosphatidylinositol (PI) are modified by either LOX or acetylated COX to produce the hydroperoxy fatty acids. Hydroperoxy arachidonic acids are directly converted into lipoxin and epi lipoxin by the LOX enzyme, and Hydroperoxy EPA is converted into Resolvin E1, and E2. In the case of hydroperoxy DHA, further conversion to epoxy products and consequently into maresins and resolvin D1, D2 occurs.

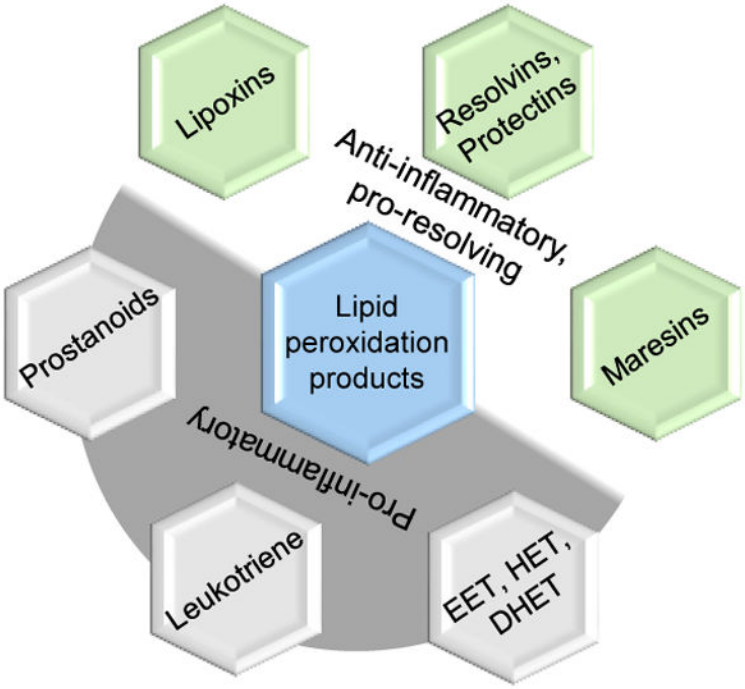

Figure 4.
Lipid mediators and their roles in inflammation

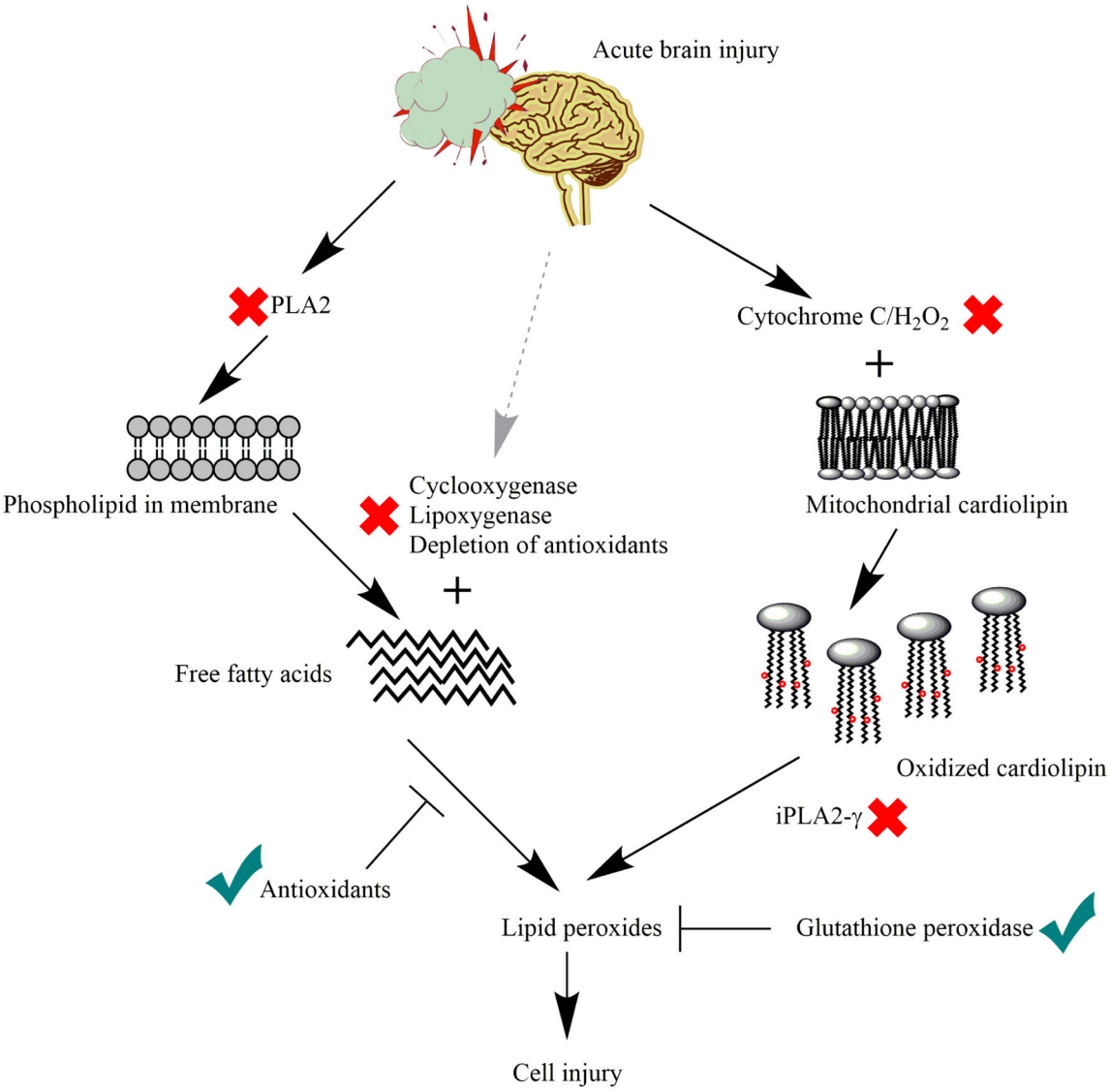

Figure 5. Lipid peroxidation mechanisms after TBI and possible therapeutic targets

Lipid peroxidation after TBI follows two main pathways: 1) Calcium-dependent pathway in which PUFAs are initially hydrolyzed from phospholipids by PLA2 and subsequently oxidized by various enzymes; 2) Calcium-independent mitochondrial pathway in which mitochondria specific phospholipid cardiolipin is oxidized by cytochrome c/H2O2 and further hydrolyzed by calcium independent PLA2 to form lipid peroxides. Inhibition or reduction of marked components or enhanced activity of marked components in lipid peroxidation pathways are possible therapeutic options after TBI.

Table 1

Cyclooxygenase inhibitors in acute brain injury

Sl. No	Compound	Species	Injury	Effect	Ref
1	Ibuprofen	Mice	TBI, Fluid percussion	No effect	(Harrison et al., 2014)
2	Indomethacin	Rats	TBI, Fluid percussion	Reduced mortality due to more rapid return to normal breathing after the apneic period post-TBI.	(Kim et al., 1989)
3	Nimesulide	Rat	TBI, impact acceleration diffuse TBI	Substantial improvement in cognitive function	(Cernak et al., 2002)
4	Meloxicam	Rat	TBI, Mild weight drop	Reduced MDA, cerebral edema, blood brain barrier (BBB) permeability, restored glutathione levels, improved neurological score at 48h.	(Hakan et al., 2010)
5	Indomethacin	Mice	TBI, Weight drop	Reduction in brain 6-Keto PGF1α levels (6 h) and neurodeficit, no effect on brain edema	(Girgis et al., 2013)
6	Carpofen	Mice	TBI, Weight Drop	Reduced lesion size; water content and number of microglia in the lesioned cortex; lowered the levels of proinflammatory cytokines and improved functional outcome	(Thau-Zuchman et al., 2012)
7	Celecoxib	Rat	TBI, Weight drop	No effect on the neurological score or the brain water content	(Girgis et al., 2013)
8	Meloxicam	Mice	TBI, Weight drop	No effect on the neurological score or the brain water content	(Girgis et al., 2013)
9	Lornoxicam	Rats	TBI, weight drop diffuse TBI	Reduced brain edema but did not affect BBB permeability	(Topcu et al., 2013)
10	Nimesulide	Rat	Trauma, Impact acceleration	Improved memory (Barnes maze) and motor (rotarod) performance after neurotrauma	(Cernak et al., 2001)
11	Roficoxib	Rat	TBI, FPI	No effect on hippocampal neuronal death	(Kunz et al., 2006)
12	Indomethacin	Human	TBI, Head-injured patients	Decreased ICP as well as cerebral blood flow and temperature	(Jensen et al., 1991)

Table 2

Lipoxygenase inhibitors in acute brain injury

Sl. No	Compound	Species	Injury	Effect	Ref
1	MK-886, Boscari ®	Rat	TBI, controlled cortical impact	Reduced lesion volume and neuronal death	(Voigt et al., 2012)
2	MK-886, Boscari ®	Rat	TBI, controlled cortical impact	Reduced inflammatory response in a region specific manner	(Hartig et al., 2013)
3	MK-886	Rat	TBI, unilateral moderate fluid percussion injury	Reduced brain edema, attenuated blood brain barrier	(Corser-Jensen et al., 2014)
4	SK&F 105809	Rat	TBI, weight drop	High dose attenuated brain edema	(Shohami et al., 1992)
5	LOXBlock-1,3	HT22 Cell, Rat primary neuron, Oligodendrog lial Cells	Cell, glutamate toxicity	Protection Against Oxidative Glutamate Toxicity	(van Leyen et al., 2008)
6	Baicalein	HT22	Cell, Iodoacetic acid toxicity	Attenuated cell death	(Lapchak et al., 2007)
7	MCI-186	Rat	Ischemia, permanent left internal carotid artery occlusion	Attenuated brain edema	(Nishi et al., 1989)
8	Baicalein	Rabbit	Ischemia, small clot embolic stroke model	Reduced behavioral deficits	(Lapchak et al., 2007)
9	Nordihydroguai aretic acid	Rat	Ischemia, transient 4- vessel occlusion	Reduced the post ischemic neuronal death , improved behavioral deficits	(Shishido et al., 2001)
10	Caffeic acid	Rat	Ischemia, transient MCAO	Attenuated brain atrophy, infarct volume, and astrocyte proliferation	(Zhou et al., 2006)
11	Baicalein	Mice, primary cortical neurons	Ischemia, transient MCAO	Reduced glutamate-induced death of primary neurons. Decreased infarct size in mice. ischemia	(van Leyen et al., 2006)
12	Baicalein	Rat	Ischemia,, permanent MCAO	Improved neurological deficit, reduced brain water content and infarct size	(Cui et al., 2010)
13	Baicalein, CDC, AA861	organotypic cultures of rat hippocam pal slices	Oxygen glucose deprivation	Attenuation of neuronal damage	(Arai et al., 2001)
14	BW755C	Rat	SCI	Improved neurological recovery	(Faden et al., 1988)
15	Phenidone	Rat	Stroke-prone spontaneously hypertensive rats	Prolonged stroke free survival	(Munsiff et al., 1992)