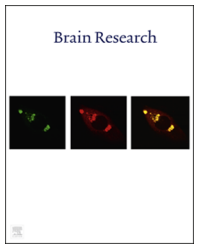
BRAIN RESEARCH 1640 (2016) 57–76

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research



Review

Therapies targeting lipid peroxidation in traumatic brain injury

Tamil Selvan Anthonymuthu[a,c,d], *Elizabeth Megan Kenny*[a,c,d], *Hülya Bayır*[a,b,c,d,e,*]

[a]*Department of Critical Care Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15213, USA*
[b]*Department of Environmental and Occupational Health, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15219, USA*
[c]*Center for Free Radical and Antioxidant Health, University of Pittsburgh, Pittsburgh, PA 15219, USA*
[d]*Safar Center for Resuscitation Research, University of Pittsburgh, Pittsburgh, PA 15260, USA*
[e]*Childrens's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, PA 15224, USA*

ARTICLE INFO

Article history:
Accepted 2 February 2016
Available online 10 February 2016

Keywords:
Phospholipase A2
Cyclooxygenase
Lipoxygenase
Cytochrome c
Cardiolipin
Glutathione

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.

This article is part of a Special Issue entitled SI:Brain injury and recovery.

*Corresponding author at: University of Pittsburgh, Department of Critical Care Medicine, Safar Center for Resuscitation Research,3434 Fifth Ave, Pittsburgh, PA 15260, USA.
E-mail address: bayihx@ccm.upmc.edu (H. Bayır).

http://dx.doi.org/10.1016/j.brainres.2016.02.006
0006-8993/

Contents

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