European Journal of Pharmacology 785 (2016) 70–76

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Hydroxyoctadecadienoic acids: Oxidised derivatives of linoleic acid and their role in inflammation associated with metabolic syndrome and cancer

Venkat N. Vangaveti [a,*], Holger Jansen [a], Richard Lee Kennedy [b], Usman H. Malabu [a,c]

[a] College of Medicine and Dentistry, James Cook University, Queensland 4811, Australia
[b] Faculty of Health, Deakin University, Waurn Ponds Campus, Geelong, VIC 3220, Australia
[c] Townsville Hospital, Department of Diabetes & Endocrinology, 100 Angus Smith Drive, Townsville, Queensland 4814, Australia

ARTICLE INFO

Article history:
Received 22 January 2015
Received in revised form
25 February 2015
Accepted 16 March 2015
Available online 15 May 2015

Keywords:
Linoleic acid
Hydroxyoctadecadienoic acids
Inflammation
Metabolic syndrome
Cancer

ABSTRACT

Linoleic acid (LA) is a major constituent of low-density lipoproteins. An essential fatty acid, LA is a polyunsaturated fatty acid, which is oxidised by endogenous enzymes and reactive oxygen species in the circulation. Increased levels of low-density lipoproteins coupled with oxidative stress and lack of antioxidants drive the oxidative processes. This results in synthesis of a range of oxidised derivatives, which play a vital role in regulation of inflammatory processes. The derivatives of LA include, hydroxyoctadecadienoic acids, oxo-octadecadienoic acids, epoxy octadecadecenoic acid and epoxy-keto-octadecenoic acids. In this review, we examine the role of LA derivatives and their actions on regulation of inflammation relevant to metabolic processes associated with atherogenesis and cancer. The processes affected by LA derivatives include, alteration of airway smooth muscles and vascular wall, affecting sensitivity to pain, and regulating endogenous steroid hormones associated with metabolic syndrome. LA derivatives alter cell adhesion molecules, this initial step, is pivotal in regulating inflammatory processes involving transcription factor peroxisome proliferator-activated receptor pathways, thus, leading to alteration of metabolic processes. The derivatives are known to elicit pleiotropic effects that are either beneficial or detrimental in nature hence making it difficult to determine the exact role of these derivatives in the progress of an assumed target disorder. The key may lie in understanding the role of these derivatives at various stages of development of a disorder. Novel pharmacological approaches in altering the synthesis or introduction of synthesised LA derivatives could possibly help drive processes that could regulate inflammation in a beneficial manner.

Chemical Compounds: Linoleic acid (PubChem CID: 5280450), 9- hydroxyoctadecadienoic acid (PubChem CID: 5312830), 13- hydroxyoctadecadienoic acid (PubChem CID: 6443013), 9-oxo-octadecadienoic acid (PubChem CID: 3083831), 13-oxo-octadecadienoic acid (PubChem CID: 4163990), 9,10-epoxy-12-octadecenoate (PubChem CID: 5283018), 12,13-epoxy-9-keto-10- trans -octadecenoic acid (PubChem CID: 53394018), Pioglitazone (PubChem CID: 4829).

1. Introduction

Linoleic acid (c18:2 n-6) is the most abundant of polyunsaturated fatty acids. As an essential nutrient, linoleic acid is a major constituent of low-density lipoproteins (LDLs) (Wang et al., 2009) . LA and its derivatives are known to exert a variety of biological effects and are involved in metabolic disorders and cancer (Mathieu et al., 2006; Niki, 2009; Tavakoli Yaraki and Karami Tehrani, 2013; Vangaveti et al., 2010; Yuan et al., 2010). LA cannot be synthesised endogenously in animals and hence its sole source is through dietary intake (Cunnane and Guesnet, 2011). Derivatives of LA are produced as a result of oxidation by the action of endogenous enzymes. The resulting derivatives of LA include hydroxy, peroxy, oxo, epoxy and epoxy-keto products (Goodfriend et al., 2002; Hayakawa et al., 1986; Kühn et al., 1993; Ramsden et al., 2012). In this review, we describe derivatives of LA namely, hydroxyoctadecadienoic acids (HODEs), oxo-octadecadienoic acids (oxo-ODE), epoxy octadecadecenoic acid and epoxy-keto-octadecenoic acid (EKODE). Furthermore, we review the role of these derivatives, focusing mainly on HODEs, in regulation of inflammation associated with metabolic syndrome and cancer.

* Correspondence to: College of Medicine and Dentistry, James Cook University, Townsville, Room 109A, Building 47, Qld 4814, Australia. Fax: +07 47813652.
E-mail address: venkat.vangaveti@jcu.edu.au (V.N. Vangaveti).

http://dx.doi.org/10.1016/j.ejphar.2015.03.096
0014-2999/

2. Derivatives of Linoleic acid

Linoleic acid acts as one of the main substrates for formation of various cyclooxygenase (COXs) and lipoxygenase (LOXs) products (Kaduce et al., 1989) via its oxidation. Enzymes involved in oxidation of LA include lipoxygenases, cyclooxygenases and the cytochrome p450 family enzymes (Reinaud et al., 1989; Engels et al., 1986) (Fig. 1). Lipoxygenases oxidises LA at C9 or C13 resulting in formation of 9-*S*-hydroperoxy-10*E*, 12Z-octadecadienoic acid (9*S*-HpODE) and 13-*S*-hydroperoxy-9*Z*, 11E-octadecadienoic acid (13*S*-HpODE). These peroxy products are unstable and are reduced to the hydroxyl form by glutathione peroxidise forming 9*S*- or 13*S*-hydroxyoctadecadienoic acid (HODE) respectively (Kühn et al., 1993; Yuan et al., 2013). 9- and 13-HODE are important oxidised derivatives of linoleic acid both appearing in two enantiomeric forms, 9/13-S[inister]-HODE and 9/13-R[ectus]-HODE. While 9- and 13-S-HODE are the primary products of two types of lipoxygenases, namely 12- and 15-lypoxigenase (12-LOX and 15-LOX-1 but not 15-LOX-2) respectively (Jiang et al., 2003; Cabral et al., 2014), at least 13-R-HODE is produced via several lipoxygenase and cyclooxygenase pathways (Cabral et al., 2014). Non-enzymatically, HODEs are produced from LA by action of reactive oxygen species (Niki, 2009). The ratio of 9 and 13-HODE synthesised have been shown to differ in varied conditions and cell types. For example, 9-HODE has been shown to form more than 13-HODE in human umbilical vein endothelial cells (Kaduce et al., 1989). Oxygenation of LA yields 80% 9-HODE and 20% 13-HODE in vesicular glands (Hamberg and Samuelsson, 1967). In epithelial

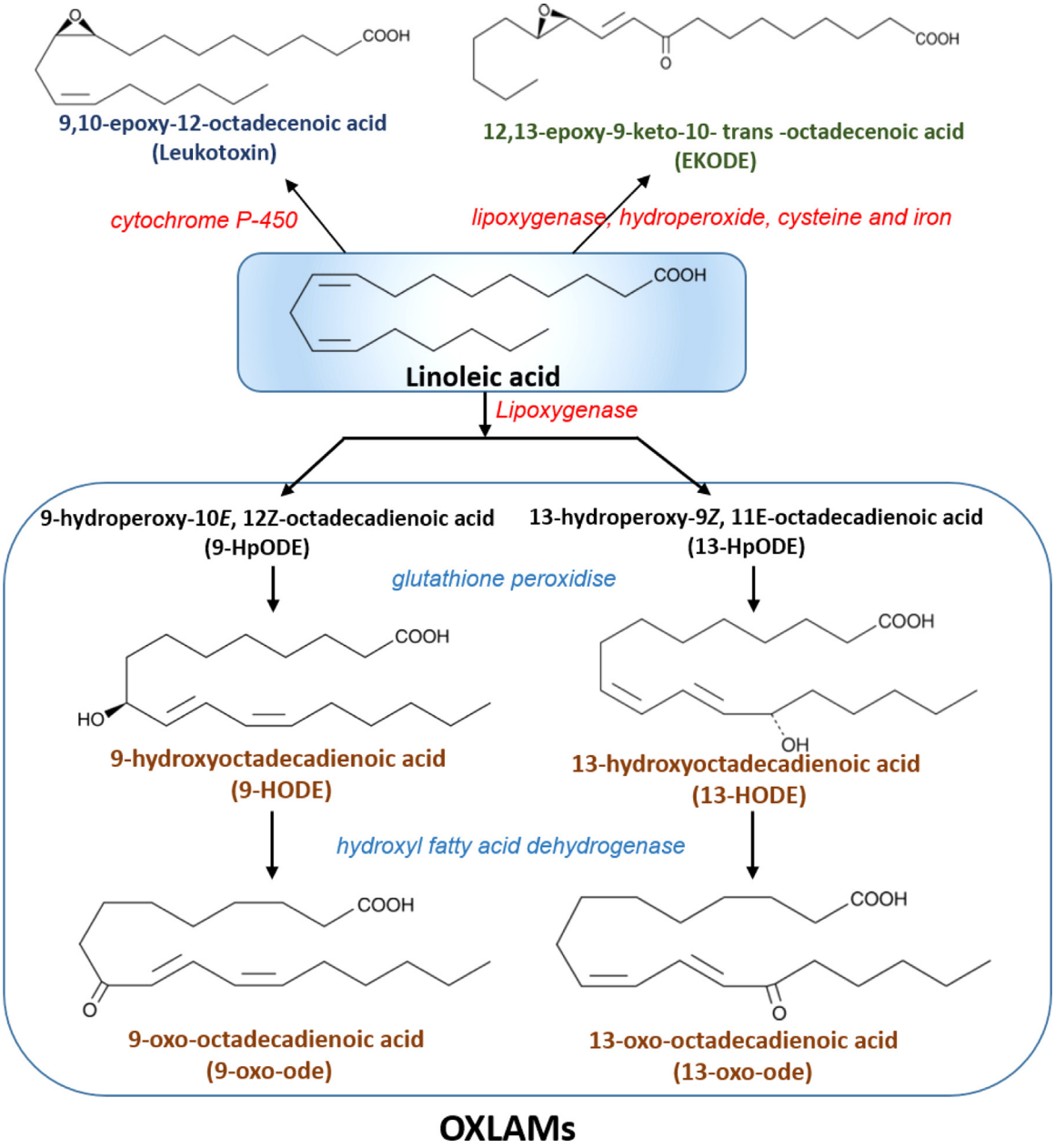

Fig. 1. Biosynthesis of linoleic acid derivatives. Action of llipoxygenase oxidises LA at C9 or C13 resulting in formation of hydroperoxy products 9-HpODE and 13-HpODE which are reduced by glutathione peroxidise forming 9- and 13-HODE, respectively. 9- and 13- oxo-odes are derived from HODEs by action of hydroxyl fatty acid dehydrogenase. These four are collectively called as OXLAMs. Leukotoxin (9, 10-epoxy-12-octadecenoate), is an epoxy derivative from linoleic acid by action of cytochrome p-450. EKODE is generated when LA is treated with lipoxygenase, hydroperoxide, cysteine and iron. LA – *linoleic acid*, 9-HpODE – *9-hydroperoxy-10E, 12Z-octadecadienoic acid*, 13S-HpODE – *13-hydroperoxy-9Z, 11E-octadecadienoic acid*, 9-HODE – *9-hydroxyoctadecadienoic acid*, 13-HODE – *13-hydroxyoctadecadienoic acid*, 9-oxo-ode – *9-oxo-octadecadienoic acid*, 13-oxo-ode – *13-oxo-octadecadienoic acid and* EKODE – *12,13-epoxy-9-keto-10- trans -octadecenoic acid*.