Prostaglandins & other Lipid Mediators 107 (2013) 95–102

Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators

Review

Isoprostanes and neuroprostanes: Total synthesis, biological activity and biomarkers of oxidative stress in humans

Jean-Marie Galano[a], Emilie Mas[b], Anne Barden[b], Trevor A. Mori[b], Cinzia Signorini[c], Claudio De Felice[d], Aaron Barrett[e], Catherine Opere[e], Edith Pinot[a], Edzard Schwedhelm[f], Ralf Benndorf[h], Jérôme Roy[g], Jean-Yves Le Guennec[g], Camille Oger[a], Thierry Durand[a,*]

[a] Institut des Biomolécules Max Mousseron (IBMM), UMR 5247 – CNRS – University Montpellier I and II – ENSCM, Faculty of Pharmacy, Montpellier, France
[b] School of Medicine and Pharmacology, University of Western Australia and the Cardiovascular Research Centre, Perth, Australia
[c] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy
[d] Neonatal Intensive Care Unit, University Hospital, Azienda Ospedaliera Universitaria Senese (AOUS), Siena, Italy
[e] Department of Pharmacy Sciences, School of Pharmacy and Health Professions, Creighton University Medical Center, 2500 California Plaza, Omaha, NE, 68178, United States
[f] Institute of Clinical Pharmacology and Toxicology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[g] Inserm U1046 Physiologie & Médecine Expérimentale du Cœur et des Muscles, University Montpellier I and II, Montpellier, France
[h] Institute of Anatomy and Cell Biology, University of Würzburg, Würzburg, Germany

ARTICLE INFO

Article history:
Received 18 December 2012
Received in revised form 23 April 2013
Accepted 23 April 2013
Available online 2 May 2013

Keywords:
PUFAs
Metabolites
Isoprostanes
Neuroprostanes
Biomarkers
Bioactive lipids

ABSTRACT

Isoprostanes (IsoPs) and neuroprostanes (NeuroPs) are formed *in vivo* by a free radical non-enzymatic mechanism involving peroxidation of arachidonic acid (AA, C20:4 n-6) and docosahexaenoic acid (DHA, C22:6 n-3) respectively. This review summarises our research in the total synthesis of these lipid metabolites, as well as their biological activities and their utility as biomarkers of oxidative stress in humans.

Contents

* Corresponding author. Tel.: +33 411759558; fax: +33 411759553.
E-mail address: Thierry.Durand@univ-montp1.fr (T. Durand).

1098-8823/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.prostaglandins.2013.04.003

1. Introduction

Free radicals have been implicated in a wide variety of human disorders [1] and are known to oxidize biomolecules, including DNA, proteins and lipids. Polyunsaturated fatty acids (PUFAs) are unstable lipids, due to the presence of multiple double bonds that are subject to react with free radicals to form numerous oxygenated metabolites [2]. There has been considerable research in isoprostanes (IsoPs) [2] since their discovery by Morrow et al. in 1990 [3]. The F_2-IsoPs are formed *in vivo* predominantly by free radical non-enzymatic oxidation of arachidonic acid (AA, C20:4 n-6), although there is some evidence to suggest F_2-IsoPs can be derived, in part, *via* a cyclooxygenase-induced pathway [4]. There are numerous reports demonstrating IsoPs are the most reliable biomarkers of oxidative stress *in vitro* and in animal models [5], as well as in humans [6]. Additionally, several IsoPs have also been shown to be biologically active [2].

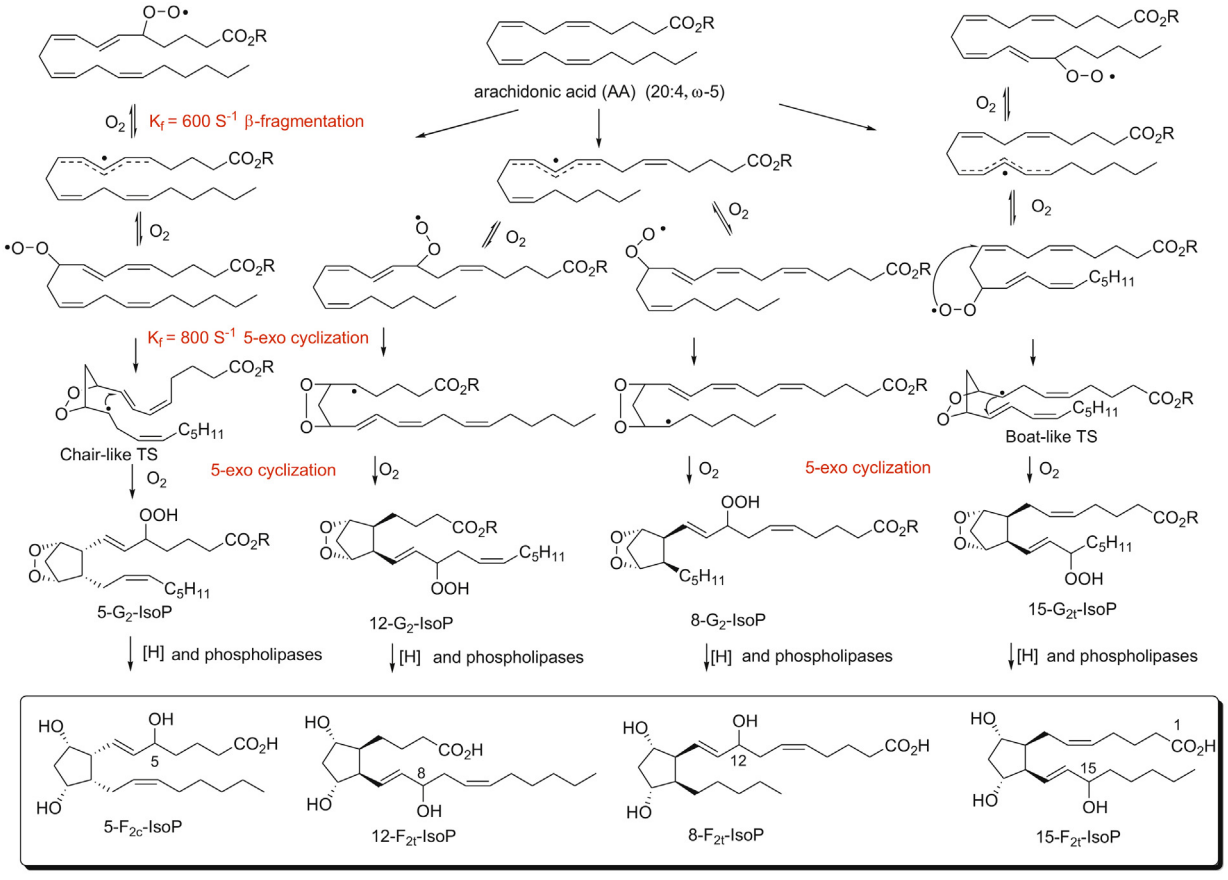
Subsequent to the reporting of F_2-IsoPs, others have described oxidation products of the n-3 fatty acids alpha-linolenic acid (ALA, C18:3 n-3), eicosapentaenoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3), yields the phytoprostanes [7], F_3-IsoPs [8] and F_4-IsoPs or neuroprostanes (NeuroPs) [9], respectively. More recently, dihomo-isoprostanes (Dihomo-IsoPs) derived from adrenic acid (AdA, C22:4 n-6) have been reported [10]. DHA is located mainly in brain grey matter and AdA in brain white matter. Other oxidative metabolites of these and other fatty acids, including A-, D-, E- and J-IsoPs, have been described in the literature [2]. More recently, the isofurans (IsoFs), formed from free radical-induced peroxidation of AA but under conditions of high oxygen tension, have been described [11,12].

This review describes strategies for the total synthesis of E-, D- and F-IsoPs, NeuroPs and Dihomo-IsoPs. It will focus on those IsoPs and NeuroPs that have been found *in vivo*, including their physiological activity and utility as biomarkers of oxidative stress in humans.

2. Biosynthesis

The biosynthesis of F-IsoPs (at the time referred as PG-like compounds) was first described in the mid 70s wile research was being carried out into the elucidation of the biosynthesis of prostaglandins [13,14]. Subsequent to this, Roberts, Morrow and co-workers in 1990 [3], proposed a pathway to account for the non-enzymatic peroxidation of arachidonic acid bound to phospholipids, leading to novel PG-like compounds which they named Isoprostanes (IsoPs) [5,15]. The F-IsoPs are released as free acids by the platelet-activating factor acetylhydrolase and possibly other phospholipases [16,17], circulate predominantly in high density lipoproteins [18] in plasma, and are excreted in urine where a significant proportion of F_2-IsoPs are conjugated as glucuronides [19].

The pathway for IsoP synthesis is initiated by hydrogen abstraction at one of the bis-allylic positions of the corresponding PUFA (Scheme 1). The transient pentadienyl radical is oxygenated at its terminal position to give pentadienyl peroxyl radicals. This oxygenated radical can have several fates leading to a number of metabolites, one of them involves irreversible O-C/C-C bicyclization (double 5-exo-trig cyclization) to available double bonds, followed by addition of oxygen and H-transfer yielding G-type IsoPs. Reduction of the hydroperoxide group is followed by the



Scheme 1. Isoprostanes (IsoPs) formation from arachidonic acid (AA).