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Review Article

Isoprostanes in fetal and neonatal health and disease

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ABSTRACT

Isoprostanes are prostaglandin-like bioactive molecules generated via nonenzymatic peroxidation of lipid membrane-derived arachidonic acid by free radicals and reactive oxygen species. Their cognate receptors, biological actions, and signaling pathways are poorly understood. Aside from being sensitive and specific biomarkers of oxidative stress, E- and F-ring isoprostanes have important biological functions and likely mediate many of the disease-related pathological changes for which they are used as indicators. The biochemical pathways involved in isoprostane formation, their pathogenetic relevance to adult disease states, and their biological function are addressed. Developmentally, plasma and tissue content data show that isoprostane levels are highest during fetal and early neonatal life, when compared with adults. As such, the available data suggesting that isoprostanes play an important biological role, as well as possibly actively participate in the regulation of pulmonary vascular tone and the transition from fetal to postnatal life, are here reviewed. Lastly, the association between isoprostanes and certain neonatal clinical conditions is addressed. Although its existence has been recognized for almost 20 years, little is known about the critical importance of isoprostanes during fetal life and immediate neonatal period. This review is an attempt to bridge this knowledge gap.

Contents

Abbreviations: BPD, bronchopulmonary dysplasia; COX, cyclooxygenase; EETs, epoxyeicosatrienoic acids; ET-1, endothelin-1; GM-CSF, granulocyte/macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; HETEs, hydroxyeicosatetraenoic acids; IsoP, isoprostane; MAPK, mitogen-activated protein kinase; MLC phos, myosin light chain phosphorylation; NB, newborn; PG, prostaglandin; ROCK, Rho kinase; ROS, reactive oxygen species; RNS, reactive nitrogen species; TK, tyrosine kinase; TP, TXA_2-PGH_2 receptor; TX, thromboxane.

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Introduction

The long-standing paradigm that only enzymatically formed compounds have important biological functions changed when Morrow et al. discovered that racemic prostaglandin (PG) diastereoisomers, later named isoprostanes (IsoPs), were produced in large amounts *in vivo* [1–3]. IsoPs are nonenzymatic, free radical-catalyzed isomers of cyclooxygenase (COX)-derived enzymatic products of arachidonic acid [1,2,4].

Under physiological conditions, IsoPs are present at nanomolar concentrations in biological fluids [2]. The development of reproducible and highly sensitive techniques, such as gas chromatography coupled to tandem mass spectrometry, to accurately measure IsoP levels [5] led to its acceptance as one of the most reliable indicators of *in vivo* free radical-induced oxidative stress.

IsoP body fluid levels have been extensively used as clinical markers of oxidative stress in many disease states such as atherosclerosis, diabetes, systemic hypertension, and cystic fibrosis [6–8]. Yet, members of the IsoP family are also biologically active and likely contribute to the pathogenesis of oxidant-induced injury and may mediate clinical features of diseases for which they are used as indicators.

Oxidative stress, a term originally coined by Helmut Sies [9], results from an imbalance between production of reactive oxygen and nitrogen species (ROS and RNS) and endogenous antioxidant defense mechanisms. Superoxide anion, hydrogen peroxide, and hydroxyl radicals are the main ROS involved in oxidative stress-mediated damage. Peroxynitrite, formed when nitric oxide interacts with superoxide, is one of the most important RNS compounds and their generation associated with vascular changes and tissue damage [10].

The transition from fetal to postnatal life imposes a significant stress on the newborn by virtue of a 3- to 4-fold increase in arterial oxygen tension. This “physiologic" oxidative stress activates specific metabolic pathways enabling an adequate adaptation to the extrauterine environment [11–15]. Although possibly better suited than adults to withstand the rapid increase in blood oxygen tension occurring at birth, the newborn IsoP levels are significantly higher than later in life [16,17]. Increased IsoP body fluid levels have also been reported in preeclampsia, intrauterine growth retardation, asphyxia, intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia [18], pulmonary hypertension, and retinopathy of prematurity [19–22]. Common to all these fetal and/or neonatal conditions is the presence of ROS-induced oxidative stress.

In this review we will address the biochemical pathways involved in IsoP formation, their pathogenetic relevance in disease states and biological function. We will specifically focus on IsoPs as markers of oxidative stress during gestation and the perinatal period. In addition we will review the limited available data relative to the involvement of IsoPs on the developmental-dependent regulation of pulmonary and systemic vascular resistance and their associated clinical implications. A better understanding of the factors accounting for IsoP generation and their biological effects may open new therapeutic and preventive avenues in dealing with disease states from fetal to adult life.

Biochemistry of isoprostanes

The isolation of PG diastereomer compounds from human plasma and urine [1,2] led to the recognition that PGs and IsoPs are generated

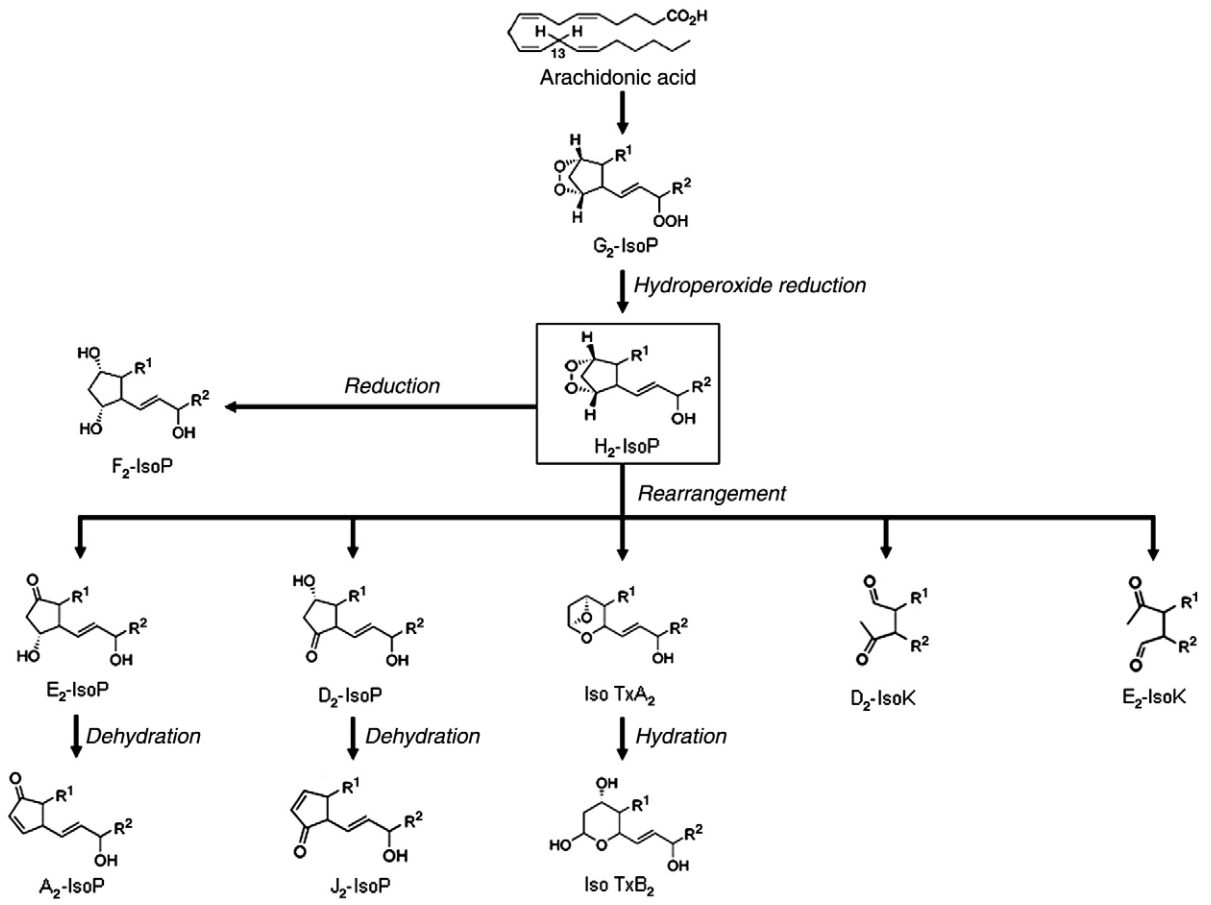

Fig. 1. Generation and structure of isoPs, isothromboxanes, and isoketals.