Prostaglandins & other Lipid Mediators xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators

EETs and HO-1 cross-talk

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ARTICLE INFO

Article history:
Received 3 April 2016
Received in revised form 3 June 2016
Accepted 20 June 2016
Available online xxx

Keywords:
Epoxyeicosatrienoic acid
EET
Heme oxygenase
HO-1
Carbon monoxide
CO
Arachidonic acid
AA
Hypertension
Diabetes
NAFLD
Myocardial infarction

ABSTRACT

Epoxygenase-dependent metabolites of arachidonc acid, EETs and the heme-oxygenase (HO)-1/carbon monoxide/bilverdin system share similarities in their activity and mediators. They control endothelial function, dilating small arterial vessels, decrease blood pressure, protect the heart from ischemic and hypertensive cardiopathy, control renal circulation and function, promote angiogenesis and organ regeneration, oppose oxidative stress and inflammation, improve diabetes and obesity, have protective effects on the liver, and participate in portal hypertension. Furthermore, EETs induce HO-1, and inhibition of HO-1 abolishes most of the effects of EETs. Thus, a close interaction between the two systems exists, and is relevant in view of their therapeutic potential.

Contents

1. Introduction

Heme-oxygenase (HO), originally identified by Tenhunen et al. [1], is the enzyme that catalyzes the degradation of heme yielding equimolar quantities of biliverdin (BV), carbon monoxide (CO), and iron [2]. BV is converted to bilirubin (BR) through the action of BV reductase (BVR), and iron is sequestered into ferritin. HO has two main isoforms: HO-1, a 32-kDa heat-shock protein, inducible by numerous stimuli, and HO-2, a constitutively synthesized 36-kDa protein, generally unresponsive to any of the inducers of HO-1 and constitutively expressed and abundantly found in brain, testis, liver and endothelium [3].

The findings that HO is expressed in so many tissues and its natural substrate, heme, as well as various metals, xenobiotics, endocrine factors, and synthetic metalloporphyrins, increase HO-1 activity in whole animal tissues and coltured cells, suggest that HO has broader roles other than just hemoglobin degradation. This is confirmed by the phenotype of the first patient with HO-1 deficiency showing endothelial cell damage, iron accumulation in the liver and kidney, and increasing cell susceptibility to heme overloading in vivo [4]. Induction of HO-1 is an essential event for some

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http://dx.doi.org/10.1016/j.prostaglandins.2016.06.002
1098-8823/

Nomenclature

List of abbreviations

18-aGA	18a-Glycyrrhetinic acid
20-HETE	20-Hydroxyeicosatetraenoic acid
AA	Arachidonic acid
ACC	Acetyl-CoA carboxylase
ACh	Acetylcholine
ASC	Adipose-derived mesenchymal stem cell
AKT	Protein kinase B
ALAS	δ-Aminolevulinic acid synthase
AMPKα	Adenosine monophosphate activated protein kinase-α
ANP	Atrial-natriuretic peptide
AP-1	Activator protein 1
ATP	Adenosine triphosphate
AUDA	12-(3-Adamantan-1-yl-ureido) dodecanoic acid
BH4	Tetrahydrobiopterin
BKCa	Big conductance calcium-activated potassium channels
BMDCs	Bone marrow dendritic cells
BNP	Brain natriuretic peptide
BR	Bilirubin
BV	Biliverdin
BVR	Biliverdin reductase
cGMP	Cyclic guanosine monophosphate
CO	Carbon monoxide
CoPP	Cobalt protoporphyrin IX
COX	Cyclooxygenase
CPT-1	Carnitine palmitoyltransferase
CYP450	Cytochrome P450
DHT	Dihydroxyeicosatrienoic acids
DNA	Deoxyribonucleic acid
EDHF	Endothelium-derived hyperpolarizing factor
EBP	Enhancer binding protein
ECNa	Epithelial sodium channel
EET	Epoxyeicosatrienoic acid
ESR-1	Estrogen receptor-1
ET-1	Endothelin-1
GC	Guanylyl cyclase
GCH-1	GTP-cyclohydrolase-1
HETE	Hydroxyeicosatrienoic acid
HFD	High fat diet
HGF	Hepatocyte growth factor
HIF-1α	Hypoxia-inducible factor alfa
HO	Heme oxygenase
HS	Hemorrhagic shock
IKK	Inhibitor of nuclear factor kappa-B kinase subunit
IL	Interleukin
KCa	Calcium-activated potassium channels
KCl	Potassium chloride
KO	Knockout
LAD	Left Anterior descending coronary artery
L-NAME	N-Nitro-L-Arginine methyl ester
MAPK	Mitogen activated protein kinase
MCD	Methionine-choline deficient
MCP-1	Macrophage chemoattractant protein-1
MSC	Mesenchimal stem cell
MI	Myocardial infarction
MIP-1α	Macrophage inflammatory protein-1 alpha
mRNA	Messenger ribonucleic acid
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NAFLD	Non-alcoholic fatty liver disease
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
eNOS	Endothelial nitric oxide synthase
Nrf2	Nuclear factor (erythroid-derived 2)-like
NSCLC	Non-small cell lung cancer
oxLDL	Oxidized low density lipoprotein
PDGF	Platelet derived growth factor
peNOS	Phospho endothelial-nitric oxide synthase
PGE2	Prostaglandin E2
PGI2	Prostacyclin
PHT	Partial hepatectomy
PI3K/AKT	Phosphatidylinsitol-3-kinase/AKT
PKC	Protein Kinase C
PPAR	Peroxisome proliferator activated receptor
ROS	Reactive oxygen species
SDF-1	Stromal cell-derived factor-1
sGC	Soluble guanylyl cyclase
sEH	Soluble epoxide hydrolase
SHR	Spontaneously hypertensive rats
SIRT-1	Sirtuin-1
SMC	Smooth muscle cell
SnCl2	Stannous chloride
SnMP	Stannous mesoporphirin
STZ	Streptozotocin
tAUCB	trans-4[4-(3-Adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid
TGFbeta	Transforming growth factor beta
TIMP-1	Metallopeptidase inhibitor 1
TNF-α	Tumor necrosis factor alpha
TRPV4	Transient receptor potential V4
VEGF	Vascular endothelial growth factor
WT	Wild type
ZnPP	Zinc protoporphirin IX

types of acute reactions and for cellular protection following injury. Induction of HO-1 removes the toxic molecule, heme, and generates CO, BV and iron, which mediate its pleyotropic effects: antioxidative, anti-apoptotic, pro-angiogenic, and anti-inflammatory.

CO, which was originally considered only a toxic gas, was then shown to have important cell signaling properties, and is implicated in a wide range of cellular responses and physiological/pathophysiological states [5] acting as anti-inflammatory, cytoprotective, maintenance of tissue homeostasis and, in some particular cases, anti-proliferative and vasodilator, through guanylyl cyclase (GC) and calcium-activated potassium channels (BKCa) activation [6], downregulating proinflammatory cytokines and upregulating the anti-inflammatory cytokines by interfering with mitogen activated protein kinase (MAPK) signaling [7]. CO mainly targets mitochondria: modulating mitochondrial membrane permeabilization and cell death control, improving mitochondrial metabolism (modulation of cytochrome *c* oxidase activity and mitochondrial biogenesis), reactive oxygen species (ROS) generation and signaling (redox adaptive cell responses, alert signals) with mild uncoupling effect [8].

BR is a potent endogenous anti-oxidant [9] with potential clinical implications [10]. Moreover, BVR contains a region with a leucine zipper deoxyribonucleic acid (DNA)-binding motif and binds to a region of the HO-1 promoter acting as transcriptional activatior of HO-1 [11].

Probably, BR (and/or BVR) and CO act synergistically in conferring antioxidant protection of endothelial cells. The antioxidant

Please cite this article in press as: D. Sacerdoti, et al., EETs and HO-1 cross-talk, Prostaglandins Other Lipid Mediat (2016), http://dx.doi.org/10.1016/j.prostaglandins.2016.06.002