BIOCHEMICAL PHARMACOLOGY 72 (2006) 1516–1528

available at www.sciencedirect.com

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

15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 as a potential endogenous regulator of redox-sensitive transcription factors

Eun-Hee Kim, Young-Joon Surh *

National Research Laboratory of Molecular Carcinogenesis and Chemoprevention, College of Pharmacy, Seoul National University, Shinlim-dong, Kwanak-ku, Seoul 151-742, South Korea

ARTICLE INFO

Article history:
Received 11 May 2006
Accepted 28 July 2006

Keywords:
15-Deoxy-$\Delta^{12,14}$-prostaglandin
Redox regulation
Thiol modification
Transcription factors
PPARγ
NF-κB
AP-1
Nrf2

Abbreviations:
AP-1, activator protein-1
ARE/EpRE, antioxidant/electrophile response element
COX, cyclooxygenase
cyPGs, cyclopentenone prostaglandins
15d-PGJ_2, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2
γ-GCL, γ-glutamate cysteine ligase
GSTs, glutathione S-transferases
HIF, hypoxia inducible factor
HO-1, heme oxygenase-1
HRE, hypoxia response element
iNOS, inducible nitric oxide synthase
Keap1, Kelch-like ECH-associated protein 1

ABSTRACT

15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) has been known to display multifaceted cellular functions, including anti-inflammatory and cytoprotective effects. However, depending on the concentrations and intracellular microenvironment, this cyclopentenone prostaglandin can exert opposite effects. Because of the α,β-unsaturated carbonyl moiety present in its cyclopentenone ring structure, 15d-PGJ_2 can act as a Michael reaction acceptor and readily interacts with critical cellular nucleophiles, such as cysteine thiol groups in proteins. Many of the biological effects induced by 15d-PGJ_2 involve redox-transcription factors as the potential targets. Thus, 15d-PGJ_2 can modulate the transcriptional activities of nuclear factor-κB (NF-κB), activator protein-1 (AP-1), nuclear factor-erythroid 2p45 (NF-E2)-related factors (Nrf2), hypoxia inducible factor (HIF), etc. 15d-PGJ_2 is also well known as an endogenous ligand of peroxisome proliferator-activated receptor γ (PPARγ). However, the regulation of the aforementioned redox-sensitive transcription factors by 15d-PGJ_2 is not necessarily mediated via PPARγ activation, but rather involves covalent modification or oxidation of their critical cysteine residues acting as a redox-sensor. This commentary describes the biological and physiological functions of 15d-PGJ_2 and underlying biochemical and molecular mechanisms with emphasis on the modulation of redox-sensitive transcription factors and their regulators.

* *Corresponding author*. Tel.: +82 2 880 7845; fax: +82 2 874 9775.
E-mail address: surh@plaza.snu.ac.kr (Y.-J. Surh).
0006-2952/$ – see front matter
doi:10.1016/j.bcp.2006.07.030

MAPKs, mitogen-activated protein kinases
NF-κB, nuclear factor-κB
NQO1, NAD(P)H: quinone oxidoreductase 1
Nrf2, nuclear factor-erythroid 2p45 (NF-E2)-related factors
PPARγ, peroxisome proliferator-activated receptor γ
PPRE, PPAR response elements
RXR, receptor for 9 cis-retinoid
STAT, signal transducer and activator of transcription
TPA, 12-O-tetradecanoylphorbol-13-acetate

1. Introduction

Prostaglandins (PGs) are a family of biologically active autacoids synthesized from 20 carbon-containing polyunsaturated fatty acids, principally arachidonic acid generated from membrane phospholipids [1], and exert a vast variety of physiological functions [2]. Members of the J_2 series cyclopentenone PGs (cyPGs), characterized by the presence of an electrophilic carbonyl moiety in their cyclopentenone ring, have a unique spectrum of biological effects. 15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), one of the most-well defined cyPGs, functions as an endogenous ligand of peroxisome proliferator-activated receptor γ (PPARγ) and has not only anti-inflammatory and cytoprotective activities, but also pro-apoptotic and anti-proliferative properties depending on cell types and concentrations [2]. 15d-PGJ_2 is a dehydration derivative of PGD_2, and its synthesis initially depends upon the enzymatic machinery for PGD_2 generation [3]. Due to its electrophilic α,β-unsaturated carbonyl group in the cyclopentenone ring, 15d-PGJ_2 can form covalent adducts with cysteine thiols via Michael addition [4]. This may result in the alteration of cellular redox status and/or functions of target proteins, many of which play pivotal roles in fine-tuning of cellular signaling network.

A wide array of intracellular signal transduction cascades converge with distinct sets of transcription factors. Abnormal activation or improper silencing of transcription factors is implicated in many disorders, such as cancer [5]. Pro-oxidants and electrophiles can modulate redox-sensitive transcription factors, such as peroxisome proliferator-activated receptor (PPAR), nuclear factor-κB (NF-κB), activator protein-1 (AP-1), p53 and nuclear factor-erythroid 2p45 (NF-E2)-related factors (Nrf2). It is conceivable that 15d-PGJ_2 with both electrophilic and pro-oxidant properties can directly or indirectly interact with the aforementioned redox-sensitive transcription factors, thereby modulating their transcriptional activities. The purpose of this review is to summarize recent findings on the cellular functions of 15d-PGJ_2, particularly those exerted by targeting redox-sensitive transcription factors or their modulators.

2. Formation and chemical properties of 15d-PGJ_2

The first step in PG synthesis is the release of arachidonic acid from membrane phospholipids by phospholipase A_2. Arachidonic acid is then converted by cyclooxygenase (COX; also known as PGH synthase) to PGH_2. This unstable intermediate is converted enzymatically to a series of biologically active prostanoids, including PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2, each of which has its own specific receptor. Among these, PGD_2 spontaneously undergoes chemical dehydration to form PGJ_2. PGJ_2 can undergo further dehydration by loss of the 15-hydroxyl group, which, coupled with migration of the 13,14-double bond, results in the formation of 15d-PGJ_2 (Fig. 1). These reactions are promoted by albumin but proceed at a relatively slow rate compared to the very rapid formation of PGs from PGH_2 by prostanoid synthases [4]. Recently, Brummond et al. [6] reported the total synthesis of 15d-PGJ_2 by utilizing an allenic Pauson-Khand-type reaction.

15d-PGJ_2 has multifaceted biological properties that are uniquely different from other components of the PG family. These include anti-neoplastic, anti-inflammatory, and anti-viral activities that are likely to be mediated by interaction with cellular signaling molecules, such as transcription factors [2]. Due to its characteristic α,β-unsaturated carbonyl moiety, 15d-PGJ_2 can readily react with cellular nucleophiles, such as cysteinyl thiol groups of proteins. Such reactions are termed Michael addition reactions and may occur in one or both of two electrophilic centers of 15d-PGJ_2 (Fig. 1; box). Several studies have shown that 15d-PGJ_2 has the most potent biological activity among cyPGs [7–9]. Kondo et al. [7] reported that the intracellular production of reactive oxygen species (ROS) was strongly induced by 15d-PGJ_2 in neuroblastoma cells. In addition, the reduced glutathione (GSH) levels and GSH peroxidase activity were significantly lowered by treatment with 15d-PGJ_2. Likewise, 15d-PGJ_2 has been reported to be the most potent inducer of endothelial apoptosis, which is attributed to its electrophilic cyclopentenone moiety [8]. Moreover, 15d-PGJ_2 induced the expression of heme oxygenase-1 (HO-1) to a greater extent than did PGA_2 and a simple