Mutation Research 711 (2011) 13–27

Contents lists available at ScienceDirect

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

journal homepage: www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Review

DNA damage induced by endogenous aldehydes: Current state of knowledge

Georgia-Persephoni Voulgaridou[a], Ioannis Anestopoulos[a], Rodrigo Franco[b], Mihalis I. Panayiotidis[c,d], Aglaia Pappa[a,*]

[a] Department of Molecular Biology and Genetics, Democritus University of Thrace, Alexandroupolis, 68100, Greece
[b] Redox Biology Center & School of Veterinary Medicine & Biomedical Sciences, University of Nebraska-Lincoln, Lincoln, NE 68583, USA
[c] School of Community Health Sciences, University of Nevada, Reno, NV 89557, USA
[d] Department of Pathology, Medical School, University of Ioannina, University Campus, Ioannina 45110, Greece

ARTICLE INFO

Article history:
Received 23 November 2010
Received in revised form 1 March 2011
Accepted 3 March 2011
Available online 16 March 2011

Keywords:
Aldehydes
Oxidative stress
DNA damage
4-Hydroxy-2-nonenal (4-HNE)
Acrolein
Malondialdehyde (MDA)
Crotonaldehyde (Cr)
4-Oxo-trans-2-nonenal (4-ONE)
Formaldehyde (FA)
Methylglyoxal (MG)
Glyoxal
Acetaldehyde (AA)
Glyceraldehyde (GA)

ABSTRACT

DNA damage plays a major role in various pathophysiological conditions including carcinogenesis, aging, inflammation, diabetes and neurodegenerative diseases. Oxidative stress and cell processes such as lipid peroxidation and glycation induce the formation of highly reactive endogenous aldehydes that react directly with DNA, form aldehyde-derived DNA adducts and lead to DNA damage. In occasion of persistent conditions that influence the formation and accumulation of aldehyde-derived DNA adducts the resulting unrepaired DNA damage causes deregulation of cell homeostasis and thus significantly contributes to disease phenotype. Some of the most highly reactive aldehydes produced endogenously are 4-hydroxy-2-nonenal, malondialdehyde, acrolein, crotonaldehyde and methylglyoxal. The mutagenic and carcinogenic effects associated with the elevated levels of these reactive aldehydes, especially, under conditions of stress, are attributed to their capability of causing directly modification of DNA bases or yielding promutagenic exocyclic adducts. In this review, we discuss the current knowledge on DNA damage induced by endogenously produced reactive aldehydes in relation to the pathophysiology of human diseases.

Contents

* Corresponding author at: Department of Molecular Biology and Genetics, Democritus University of Thrace, University Campus, Dragana, 68100 Alexandroupolis, Greece. Tel./Fax: +30 2551030625.
E-mail address: apappa@mbg.duth.gr (A. Pappa).

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doi:10.1016/j.mrfmmm.2011.03.006

1. Introduction

DNA damage plays a major role in mutagenesis, carcinogenesis, aging and various others pathophysiological conditions. DNA damage can be induced through hydrolysis, exposure to reactive oxygen species (ROS) and other reactive metabolites. The reactions often are activated by exposure to exogenous chemicals and environmental factors, but often result endogenously as a consequence of metabolic endogenous processes.

Aldehydes are highly reactive molecules that are intermediary or final products of metabolism involved in a wide spectrum of biochemical, physiological and pharmacological processes. Endogenous aldehydes are produced during the metabolism of amino acids, carbohydrates, lipids, biogenic amines, vitamins and steroids. Also the biotransformation of a large number of environmental agents and drugs leads to the generation of aldehydes. Aldehydes, being highly reactive electrophilic molecules, interact with phospholipids, proteins and DNA while their mediated effects vary from physiological and homeostatic to cytotoxic, mutagenic or carcinogenic [1,2].

A major source of endogenously produced aldehydes is the lipid peroxidation process. During lipid peroxidation (LPO) a variety of reactive oxygen/nitrogen species (ROS/RNS) oxidize lipids leading to free radical chain reactions and subsequent formation of byproducts, like lipid radicals, hydrocarbons and aldehydes [3,4]. These products further react and modify both proteins and DNA resulting in toxicity or even mutagenesis and therefore have been associated with aging, cardiovascular diseases, neurological disorders and cancer [3,5]. Aldehydes are well-studied products of LPO, with the α,β-unsaturated to be the most cytotoxic by reacting with phospholipids, proteins and DNA. However, their effects are not only toxic but rather homeostatic as they participate in signal transduction pathways [4,6,7]. There are multiple mechanisms for aldehydes formation during lipid peroxidation. One common mechanism begins with singlet oxygen and its reaction with unsaturated lipids, which produces hydrogen peroxide. Hydroperoxide reacts with the protein myeloperoxidase and leads to the formation of hypochlorous and hypobromous acid when chloride and bromide are present, respectively. The interaction of the acids with amines produces chloroamines and bromoamines and eventually aldehydes [3]. The major aldehyde products of LPO are 4-hydroxynonenal (4-HNE), acrolein, malondialdehyde (MDA) and crotonaldehyde (Cr). These are highly reactive molecules that damage DNA by the formation of exocyclic adducts most of which are anticipated to be highly mutagenic. MDA is considered to be the most mutagenic product of lipid peroxidation, whereas 4-HNE is the most toxic [8]. LPO, together with the glycation process often leads to the formation of reactive carbonyl species (RCS) which are potent mediators of cellular carbonyl stress [9]. Glycation is considered to be the major source of RCS such as glyoxal and methylglyoxal and together with oxidative stress are two important biochemical processes known to play a key role in complications of many disease states. Of the most biologically important carbonyl compounds are methylglyoxal (Mg) and glyoxal (Gx) which readily form DNA adducts generating potential promutagenic DNA lesions. In general, aldehydes can damage DNA either directly by reacting with DNA bases, by generating more reactive bifunctional intermediates, which form exocyclic DNA adducts or formation of ethenobases initiated by addition of an exocyclic aminogroup of a DNA base (reviewed in [10] (Scheme 1). Of these, 4-hydroxy-2-nonenal (HNE), malondialdehyde (MDA), acrolein, and crotonaldehyde have been most intensely studied with respect to their chemical and biological interactions with nucleic acids. The ability of these reactive electrophiles to modify DNA bases, yielding promutagenic lesions, is considered to contribute to the mutagenic and carcinogenic effects associated with the elevated levels of endogenously produced reactive aldehydes under stress conditions.

Herein, we present a review on the current knowledge of DNA adducts induced by endogenously produced aldehydes in relation to published adduct types and their significance in biology and pathophysiology of human diseases.

2. Types of aldehydes-induced DNA damage

2.1. 4-Hydroxynonenal (4-HNE)

4-HNE is a 9-carbon α,β unsaturated aldehyde (enal) formed when n-6 polyunsaturated fatty acids such as arachidonic and linoleic acid are attacked by peroxidative free radicals during LPO. 4-HNE is a highly chemically reactive molecule and is considered one of the major generators of oxidative stress, often used as a bioactive marker of the extent of oxidative stress and LPO in a variety of biological systems [11–13]. There are two different pathways that lead to 4-HNE production during LPO process, an enzymatic and a non-enzymatic one. While the enzymatic pathway for 4-HNE production appears to be more prominent in microsomes [14] the non-enzymatic pathway is less understood involving dimerized and oligomerized fatty acids derivatives as key intermediates [15]. Following the non-enzymatic pathway, the autoxidation of linoleic acid leads to the formation of 9-and 13-hydroperoxides (9-HPODE/13-HPODE), which further gives 3Z-nonenal. This is further non-enzymatically oxidized to give 4-HPNE [16]. The enzymatic pathway involves the enzymes lipoxygenase and hydroperoxide lyase. Briefly, linoleic acid is enzymatically cleaved to 3Z-nonenal, which subsequently oxygenates to 4-HPNE in a non-enzymatic way [15]. 4-HPNE is subsequently decomposed to 4-HNE or 4-oxo-nonenal (4-ONE).

Cells have many mechanisms to remove 4-HNE through several metabolic pathways with the most important one being the tripeptide glutathione (GSH). This reacts with 4-HNE (both enzymatically and non-enzymatically) to form a conjugate which can be a target for further enzymatic deactivation or cellular export by specific transporters (e.g. MRP2). The mitochondrial aldehyde dehydrogenase ALDH2, using NAD as a co-factor, also oxidizes 4-HNE to 4-hydroxynonenal-2 enoic acid (4-HNA). Other enzymes that could use as a substance 4-HNE are aldehyde reductase, aldose reductase and aldo-keto reductase, which reduce 4-HNE to 1,4-dihydroxy-2-nonene (DHN) in an NADPH-dependent manner [4].

4-HNE capability to form protein adducts (through interactions with Cys, His and Lys residues) could lead to mitochondrial malfunctions and inhibition of cell signaling and is believed to be one of the reasons for the elevated levels of HNE in various diseases like Alzheimer, Parkinson and arteriosclerosis [4,12,17,18]. Even though 4-HNE is best known for its apoptotic and cytotoxic effects, it also has the potential to create DNA adducts, which in some cases can lead to mutations. 4-HNE, like other enals, forms exocyclic adducts after reacting with DNA nucleobases. The principal reaction