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Reactive carbonyls and oxidative stress: Potential for therapeutic intervention

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Abstract

Reactive aldehydes and ketones are produced as a result of oxidative stress in several disease processes. Considerable evidence is now accumulating that these reactive carbonyl products are also involved in the progression of diseases, including neurodegenerative disorders, diabetes, atherosclerosis, diabetic complications, reperfusion after ischemic injury, hypertension, and inflammation. To counter carbonyl stress, cells possess enzymes that can decrease aldehyde load. These enzymes include aldehyde dehydrogenases (ALDH), aldo-keto reductases (AKR), carbonyl reductase (CBR), and glutathione *S*-transferases (GST). Some of these enzymes are inducible by chemoprotective compounds via Nrf2/ARE- or AhR/XRE-dependent mechanisms. This review describes the metabolism of reactive carbonyls and discusses the potential for manipulating levels of carbonyl-metabolizing enzymes through chemical intervention.

Keywords: Aldehyde metabolism; Oxidative stress; Chemoprotection

Contents

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1. Introduction

Oxidants, including reactive oxygen species (ROS), are constantly produced in cells through normal metabolic processes (Halliwell, 2001). Oxidative or oxidant stress occurs when the balance of oxidants within the cell exceeds the levels of antioxidants present (Sies, 1997). This imbalance can arise, and can potentially lead to damage, in a variety of disease conditions, including cardiovascular disease and atherosclerosis (Madamanchi et al., 2005), hypertension (Touyz, 2004), inflammatory-based diseases such as chronic obstructive pulmonary disease (MacNee, 2005), diabetic complications (Robertson, 2004), ischaemia/reperfusion (Warner et al., 2004), and neurodegenerative diseases such as Alzheimer's disease (AD; Markesbery, 1997). An increased level of ROS can lead to damage of macromolecules within the cell; and it is this damage to lipids, proteins, and DNA that can give rise to pathological consequences. There is considerable overlap not only in the pathology but also in the etiology and underlying molecular mechanisms of oxidant stress-dependent diseases, for example, between diabetes, atherosclerosis, and hypertension (King et al., 1998; Ceriello & Motz, 2004). In many cases, reactive carbonyls are produced as a consequence of oxidative stress, and considerable evidence is now emerging that it is the presence of these carbonyls rather than the initial oxidative insult that leads to the cellular damage observed.

2. Production of reactive carbonyls in oxidant-exposed cells

The main mechanisms of endogenous reactive carbonyl production as a result of oxidant stress include the oxidation of lipids or lipid peroxidation, and the oxidation of glycation products or glycoxidation (Fig. 1).

2.1. Carbonyls produced via lipid peroxidation

The peroxidation of membrane-derived lipid molecules is a well-studied consequence of increased intracellular oxidant levels (Esterbauer et al., 1982, 1991) This process is known to give rise to many products through a series of iterative oxidation and cleavage reactions (Esterbauer et al., 1982). The most commonly characterized products are aldehydes, derived from ω-6 polyunsaturated fatty acids, such as malondialdehyde (MDA), hexanal, acrolein, glyoxal, crotonaldehyde, *trans*-2-nonenal, 4-oxo-2-nonenal, and 4-hydroxy-2-nonenal (HNE; Esterbauer et al., 1982, 1991; Rindgen et al., 1999; Uchida et al., 1998). MDA is the most common aldehyde produced, comprising of 70% of the total produced by lipid peroxidation (Esterbauer et al., 1991). Hexanal contributes 15% and HNE contributes 5% of total aldehydes (Benedetti et al., 1980). Acrolein was identified as a lipid peroxidation product more recently through studies that examined the oxidation of low density lipoprotein (LDL) but was previously characterized as an environmental pollutant (Uchida et al., 1998).

Many lipid peroxidation products have been detected at high levels in diseased states, and in fact several have the potential to be used as biomarkers of oxidative damage and disease progression (Table 1). For example, in AD brain, there is an increase in levels of acrolein (Lovell et al., 2001) and studies have suggested that the levels of acrolein-modified proteins can be used as markers of the disease (Calingasan et al., 1999). Other reactive aldehydes, such as HNE, are also elevated in AD brains, up to 3 nmol/mg of cell protein (Williams et al., 2006), and protein adducts of some aldehydes, such as crotonaldehyde, have been specifically detected in reactive astrocytes and microglia around senile plaques from AD brain (Kawaguchi-Niida et al., 2006). In other diseases, for example in a rat model

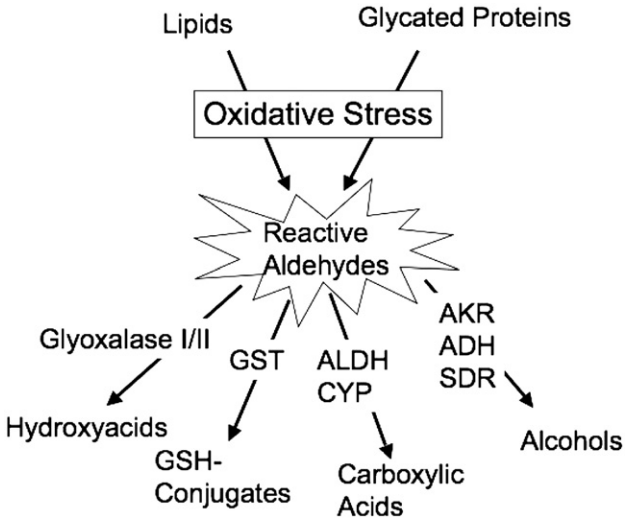

Fig. 1. Metabolism of reactive aldehydes produced as a consequence of oxidative stress. Reactive aldehydes produced through either lipid peroxidation or glycoxidation can be converted to hydroxyacids through the action of glyoxalase I/II, oxidized to carboxylic acids by ALDH and CYP, reduced to alcohols by ADH, AKR or SDR, or can be conjugated to GSH by GST.