Available online at www.sciencedirect.com
ScienceDirect
Pharmacology & Therapeutics 115 (2007) 13–24
Pharmacology & Therapeutics
www.elsevier.com/locate/pharmthera

Associate editor: R.M. Wadsworth

Reactive carbonyls and oxidative stress: Potential for therapeutic intervention

Elizabeth M. Ellis *

Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 204 George Street, Glasgow, G1 1XW, United Kingdom

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

* Tel.: +44 141 548 2122; fax: +44 141 553 4124.
E-mail address: Elizabeth.ellis@strath.ac.uk.

0163-7258/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2007.03.015

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

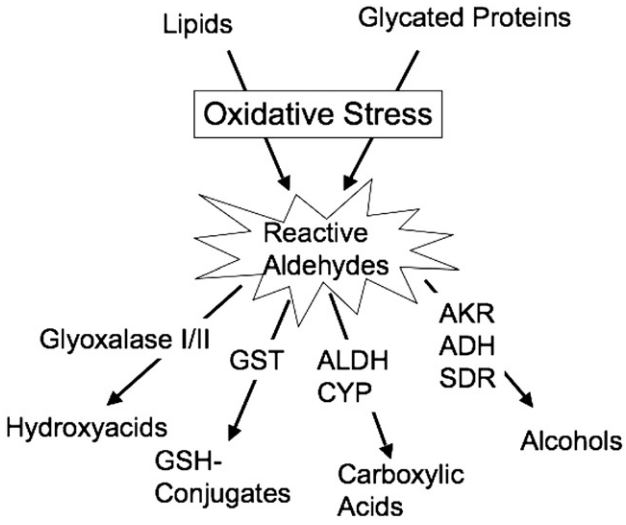
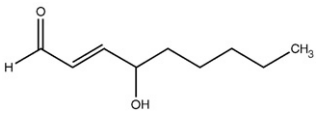
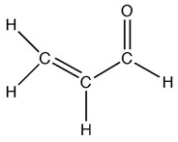
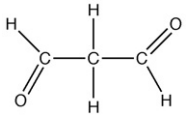
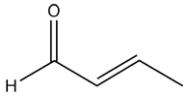
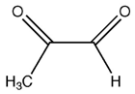
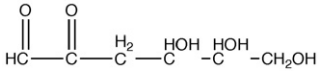


Fig. 1. Metabolism of reactive aldehydes produced as a consequence of oxidative stress. Reactive aldehydes produced through either lipid peroxidation or glycoxidation can be converted to hydroxyacids through the action of glyoxalase I/II, oxidized to carboxylic acids by ALDH and CYP, reduced to alcohols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

Table 1
Some reactive aldehydes as products of oxidative stress

Structure	Name	Product of	Examples of diseases in which elevated	References
	4-hydroxynonenal	Lipid peroxidation	AD, hypertension, atherosclerosis, diabetes	Toyokuni et al., 2000; Leonarduzzi et al., 2005; Williams et al., 2006; Asselin et al., 2006
	Acrolein	Lipid peroxidation; Glycoxidation	AD	Lovell et al., 2001
	MDA	Lipid peroxidation	AD, atherosclerosis	Smith et al., 1995; Holvoet & Collen, 1998
	Crotonaldehyde	Lipid peroxidation	AD	Kawaguchi-Niida et al., 2006
	MG	Glycoxidation	Diabetes, AD, hypertension	Bourajjaj et al., 2003; Kuhla et al., 2005; Wu, 2006
	3-Deoxyglucosone	Glycoxidation	Diabetes	Beisswenger et al., 2001

of hypertension, levels of HNE-protein adducts are significantly increased in plasma (Asselin et al., 2006). HNE is also detected in fibrotic plaques and in oxidized LDL, supporting its role in the pathogenesis of atherosclerosis (Leonarduzzi et al., 2005). In Type II diabetes, there is an elevation in the levels of HNE-albumin adducts in serum (Toyokuni et al., 2000; Table 1).

2.2. Carbonyls produced via glycoxidation

Reducing sugars such as glucose can form Schiff bases with amino groups on the amino acids lysine and arginine, a reaction know as the Maillard reaction. This can, through a series of rearrangements, give rise to advanced glycation endproducts (AGE; Munch et al., 1998; Thornalley et al., 1999). Oxidation of these glycation products can release dicarbonyls, such as the α-oxoaldehydes methyl glyoxal (MG), glyoxal, and 3-deoxyglucosone, as well as short-chain aldehydes, such diacetyl, acetol, and pyruvaldehyde, and also acrolein (Thornalley et al., 1999; Thornalley, 2005). This process of glycoxidation occurs when there is an excess of glucose coupled with high levels of oxidants (Abordo et al., 1999), and so is a particular problem in diabetes (McLellan et al., 1992). MG and glyoxal levels can rise through other mechanisms, such as increased glycolytic flux; and as these compounds can also react with proteins, this greatly increases the rate of AGE formation, in turn leading to increased α-oxoaldehyde production.

Glycoxidation products can exacerbate several pathological conditions. For example, in the lens of diabetics, MG and glyoxal levels are elevated and lead to protein carbonylation and the formation of protein aggregates which are thought to contribute to the formation of cataracts (Shamsi et al., 1998). MG is also thought to contribute to the development of vascular complications in diabetics (Bourajjaj et al., 2003). In addition, high levels of AGE and MG have also been detected in AD patients as a consequence of increased oxidative stress. MG is thought to be involved in the formation of amyloid plaques and neurofibrillary tangles (Munch et al., 1998; Abordo et al., 1999; Ahmed et al., 2005; Kuhla et al., 2005; Table 1).

2.3. Reactivity of carbonyls

Many of the carbonyls that are produced as a result of either lipid peroxidation or glycoxidation are extremely reactive (Table 1). Alkanals, such as hexanal, are the least reactive and have weaker effects than unsaturated aldehydes. Alkenals containing a C=C unsaturated bond, such as acrolein, are usually an order of magnitude more reactive than the alkanals. This is particularly the case if they contain an α,β-unsaturated (C2–C3) double bond, in addition to the C1 aldehyde. This makes the C3 carbon a strong electrophile that can undergo Michael addition by nucleophilic groups on proteins, DNA, and lipids (Marnett et al., 1985; Cooper et al., 1987), thereby causing damage to these molecules. The aldehyde group is also reactive and can form Schiff bases with amino acids. 4-hydroxy-2-alkenals, such as HNE, are extremely reactive because of the interaction between the electrophilic double bond, the aldehyde moiety, and the hydroxyl group (Witz, 1989). The reactivity of the α,β-unsaturated bond is increased by the

close proximity of the electron-withdrawing hydroxyl at C4 and the C1-carbonyl group. HNE is one of the most cytotoxic aldehydes known and can cause significant damage to macromolecules within the cell at micromolar concentrations (Brambilla et al., 1986).

2.4. Consequences of reactive carbonyls for the cell

Damage caused by aldehydes can disrupt the function of proteins and enzymes, can initiate further damage to lipids, and can lead to the formation of DNA adducts. In addition, some aldehydes can lower intracellular glutathione (GSH) levels, thereby leading to increased oxidant imbalance with the cell (White & Rees, 1984). These types of molecular perturbations can lead to cell death (Li et al., 2006a, 1996).

2.4.1. Cytotoxicity of reactive carbonyls

Cytotoxicity is generally measured by examining loss of viability. Reactive aldehydes, such as HNE, interact directly with proteins and membranes, causing significant loss of function to membrane transporters, enzymes, signalling components, transcription factors, microtubules, and other proteins, such as tau (Karlhuber et al., 1997; Picklo et al., 2002). Acrolein is also cytotoxic and, in neuronal cells, causes changes in Ca^{2+} concentrations, altering glucose transport and glutamate uptake (Li et al., 1997; Lovell et al., 2001). As described earlier, other aldehydes, such as MG, can rapidly form Schiff bases with amino acids, which leads to the production of AGE at a much faster rate than from sugars, such as glucose (Thornalley, 1996). MG therefore causes significant toxicity to a range of cell types, including neuronal cells (Suzuki et al., 1998).

2.4.2. Reactive carbonyls trigger apoptosis

Many aldehydes that cause necrotic cell death through direct damage to essential cell components have been shown to also trigger apoptotic pathways at lower concentrations. These pathways ultimately lead to cell death but via a mechanism that involves activation of caspases (Kruman et al., 1997; Ji et al., 2001; Li et al., 2006a). This has been demonstrated for a range of aldehydes, for example HNE, in alveolar macrophages (Li et al., 1996), acrolein-induced cell death in human alveolar macrophages (Li et al., 1997), and MG treatment of human leukaemia HL-60 cells (Kang et al., 1996).

This suggests that certain key cellular components are particularly sensitive to aldehyde damage, thereby triggering the apoptotic pathways.

2.4.3. Reactive carbonyls trigger signalling pathways

At sublethal doses where no cell death can be detected, reactive aldehydes can also cause perturbations in signalling pathways, and some such as HNE have been postulated to play a role as signalling molecules themselves (Echtay et al., 2003). For example, 0.1 μM HNE activates protein kinase C (PKC)-β (Chiarpotto et al., 1999). PKC-β is inhibited by higher levels of HNE (1–10 μM). However, HNE inhibits PKC-δ at 0.1 μM but at 1–10 μM HNE can activate PKC-δ (Chiarpotto et al., 1999) suggesting that different pathways are activated at different concentrations. Similarly, low concentrations of acrolein induce Hsp72 in human umbilical vein endothelial cells (HUVEC) via a PKC-δ/JNK pathway and calcium mechanism (Misonou et al., 2005). MG and glyoxal also trigger distinct signals for MAP family kinases as well as caspase activation in human endothelial cells (Akhand et al., 2001).

2.4.4. Genotoxicity of carbonyls

Some reactive aldehydes are not particularly cytotoxic but may cause genotoxicity by damaging DNA. Interactions with DNA can cause mutations or deletions. For example, the 4-hydroxyalkenals, including HNE (Eckl et al., 1993), acrolein (Marnett et al., 1985), and MG (Kasai et al., 1982) have all been shown to cause genetic damage. A consequence of such damage is an increased likelihood of the initiation of carcinogenesis.

3. Carbonyl metabolizing enzymes and their roles

Despite their toxic effects, many aldehydic products of lipid peroxidation or glycoxidation can be successfully metabolized to less toxic compounds through the action of enzymes (Siems & Grune, 2003; Fig. 1). These reactions are either oxidation/reduction (phase I) or conjugation (phase II). Enzymes involved include glutathione *S*-transferases (GST), aldehyde dehydrogenases (ALDH), cytochromes P450 (CYP), aldo-keto reductases (AKR), alcohol dehydrogenases (ADH), and members of the short chain dehydrogenase/reductases (SDR), such as carbonyl reductase (CBR1; Fig. 1). For many aldehydes, such as acrolein and HNE, despite several studies that have examined metabolic fate *in vivo*, (Parent et al., 1998; Alary et al., 2003), the relative importance of these enzyme pathways is unknown.

3.1. Oxidation of aldehydes

3.1.1. Aldehyde dehydrogenases

ALDH can oxidize a range of toxic aldehydes to acids (Mitchell & Petersen, 1987; Vasiliou et al., 2004). ALDH are grouped into classes (ALDH1–7), and there are around 17 ALDH enzymes in human (Vasiliou et al., 2004). Of these, ALDH1 and ALDH3 members have been shown to be capable of oxidizing lipid-derived aldehydes, including MDA, hexanal, *trans*-2-octenal, and *trans*-2-nonenal, and acrolein (Lindahl & Petersen, 1991; Lindahl, 1992; Townsend et al., 2001). ALDH2 enzymes are mitochondrial and have been shown to be important in the metabolism of acetaldehyde (Ehrig et al., 1990). ALDH5A (succinic semialdehyde dehydrogenase) is also mitochondrial and has been shown to be capable of metabolizing HNE in vitro (Murphy et al., 2003).

An examination of the roles of these enzymes in protecting cells against reactive aldehydes revealed that ALDH1A1 overexpression provides only moderate protection against *trans*-2-nonenal and not against other lipid aldehydes (Townsend et al., 2001). ALDH3A1, on the other hand, could protect against these aldehydes and could completely block HNE-induced apoptosis. This indicates that ALDH3A1 has the potential to protect against aldehydes produced as a result of lipid peroxidation (Townsend

et al., 2001). Additional support for its protective role is derived from studies using human corneal epithelial cells where ALDH3A1 provides protection from HNE-induced damage (Pappa et al., 2003) and also against oxidative stress (Estey et al., 2007). Overexpression of ALDH3A2 (fatty ALDH) in adipocytes can protect against HNE but not against MG (Demozay et al., 2004). These types of experiments are invaluable in testing the roles of the enzymes in protection against aldehydes. Additional evidence has come from genetic studies. Individuals that have a genetic deficiency in ALDH2 have increased levels of oxidative stress markers and appear to be at greater risk from AD (Kamino et al., 2000), hypertension (Takagi et al., 2001), and myocardial infarction (Takagi et al., 2002) in some populations. In addition, ALDH2-deficient PC12 cells are more sensitive to HNE and oxidants (Ohsawa et al., 2003). This provides some evidence that one of the roles of ALDH2 is to protect against oxidative stress through the metabolism of lipid peroxidation products (Ohsawa et al., 2003).

Overall, the evidence to date suggests that ALDH2, ALDH3, and ALDH5 enzymes may contribute to the oxidation of oxidative stress-derived aldehydes.

3.1.2. Cytochrome P450

CYP are a large family of enzymes known to be involved in the oxidation of a range of substrates through hydroxylation of C–H bonds or the formation of epoxides. As monooxygenases, several CYP can catalyze the oxidation of aldehydes. In particular, members of the CYP3A and CYP4A families can oxidize lipid peroxidation products such as HNE (Gueraud et al., 1999; Amunom et al., 2005). There is some evidence that in the fruitfly *Drosophila melanogaster* a CYP can transform acrolein into glycidaldehyde after conjugation with GSH (Barros et al., 1994). Much more work is needed to uncover the role of this family of enzymes in aldehyde metabolism (Guengerich, 2001).

3.2. Reduction of reactive aldehydes

Three families of enzymes are known to reduce aldehydes to alcohols or reduce an unsaturated double bond in aldehydes. These are ADH, SDR, and AKR.

3.2.1. Alcohol dehydrogenases

ADH belong to the medium chain dehydrogenase reductase (MDR) family. Few studies to date have examined the role of ADH in aldehyde metabolism, as most previous work has focussed on their ability to oxidize alcohols. However, the reduction of HNE by a 4-methylpyrrazole-sensitive enzyme has been demonstrated, indicating that an ADH is involved in reactive aldehyde metabolism (Hartley et al., 1995). Recently ADH1 was identified as being involved in the metabolism of *trans*,*trans*-muconaldehyde, a toxic benzene metabolite in liver (Short et al., 2006), but its capabilities to metabolize lipid peroxidation or glycoxidation products have yet to be examined. One member of the MDR family is known to reduce the carbon–carbon double bond of alpha, beta-unsaturated aldehydes and ketones. This enzyme was originally characterized as a leukotriene B4 12-hydroxydehydrogenase/15-oxo-prostaglandin 13-reductase, but has been shown to reduce HNE and acrolein and may therefore contribute to the detoxication of these compounds. This has been demonstrated by overexpression of the enzyme in cell lines, revealing significant protection against HNE (Dick et al., 2001).

3.2.2. Short chain dehydrogenase reductases

The SDR family has 6 members that have been characterized in human. These are CBR1, CBR3, 11-β-hydroxysteroid dehydrogenase (11-β-HSD), short chain retinol dehydrogenase (DHRS4), DHRS2, and L-xylulose reductase (DCXR) (Oppermann, 2007). Of these, only CBR1 has been shown to metabolize lipid peroxidation products, for example 4-oxo-non-2-enal (Doorn et al., 2004; Oppermann, 2007). In the fruit fly *D. melanogaster*, a mutation in the gene encoding a homologue of CBR1 caused oxidative stress-induced neurodegeneration, and overexpression of CBR1 is important for protection against oxidants (Botella et al., 2004). Overexpression of the human CBR1 in NIH3T3 cells similarly protects against ROS induced by the redox-cycler paraquat (Kelner et al., 1997). These results indicate the potential importance of CBR1 in neuroprotection particularly against ROS-dependent disease (Maser, 2006).

3.2.3. Aldo-keto reductases

AKR are a large family of NADPH-dependent enzymes that are known to play a significant role in the reduction of aldehydes to alcohols (Jin & Penning, 2007). The superfamily contains over 100 members, with 10 enzymes characterized from human falling in the AKR1A, AKR1B, AKR1C, AKR1D, and AKR7A subfamilies (Hyndman et al., 2003). They are expressed in a range of tissues, including liver, brain, and kidney (O'Connor et al., 1999). AKR are known to play roles in the metabolism of sugars, steroids, prostaglandins, and other metabolites, and several have been shown to metabolize aldehydes that are produced as a consequence of oxidative stress.

The aldehyde reductase subfamily (AKR1A) catalyzes the reduction of a range of aldehydes (Flynn, 1982) but members have been shown to be capable of reducing several lipid peroxidation and glycoxidation products, including methylglyoxal, 3-deoxyglucosone, acrolein, and HNE (Kanazu et al., 1991; Suzuki et al., 1998; O'Connor et al., 1999).

Aldose reductase (AKR1B) was originally thought to play a role in sugar metabolism, specifically the reduction of glucose to sorbitol as part of the polyol pathway. However, it can also reduce MG and other trioses (Vander Jagt et al., 1992). In addition, AKR1B has been shown to reduce medium to long chain (C6–C18) aldehyde, including HNE (Srivastava et al., 1995; Vander Jagt et al., 1995) and was identified as the major enzyme involved in the reduction of HNE and its GSH conjugate in the heart (Srivastava et al., 1998).

The AKR1C enzymes were identified in human as hydroxysteroid dehydrogenases that can also oxidize polycyclic aromatic hydrocarbon *trans*-dihydrodiol proximate carcinogens but are also capable of reducing toxic aldehydes (O'Connor et al., 1999; Burczynski et al., 2001). They are not particularly efficient at reducing methylglyoxal. However, AKR1C1 and

AKR1C4 can reduce acrolein and to a lesser extent HNE (O'Connor et al., 1999; Burczynski et al., 2001).

The AKR7A enzymes have a particularly wide substrate specificity and are thought to play a major role in aldehyde detoxication (Hinshelwood et al., 2002). Human AKR7A2 can reduce HNE, acrolein, and MG, although not as efficiently as AKR1A1 (O'Connor et al., 1999). Other AKR7A enzymes can reduce MG and a range of reactive carbonyls including acrolein and crotonaldehyde (Ellis & Hayes, 1995; Hinshelwood et al., 2003).

Overexpression of AKR in cell lines has established their roles in detoxication. For example, overexpression of aldehyde reductase AKR1A protects PC12 neuronal cells against MG toxicity (Suzuki et al., 1998), and overexpression of AKR7A enzymes protects V79 cells from HNE induced apoptosis and toxicity (Li et al., 2006a).

3.3. Glutathione S-transferases

Conjugation with GSH is a major detoxication pathway for several aldehydes that are produced as a result of oxidative stress (Esterbauer et al., 1975). The GST enzymes have been placed into families: Alpha (GSTA1 to GSTA5), Mu (GSTM1 to GSTM5), Pi, (GSTP), Theta (GSTT1 and GSTT2), Zeta (GSTZ), and Omega (GSTO1-GSTO2). In addition to their cytosolic location, several GST have been reported as being associated with the mitochondria or with microsomes (reviewed in Hayes et al., 2005). GST are dimeric proteins, generally acting as heterodimers to conjugate GSH. This conjugation is compromised when GSH concentrations are depleted, such as may occur as a consequence of increased oxidant levels. Despite this limitation, many GST have been shown to contribute to reactive aldehyde detoxication. For example, GSTP1-1 can catalyze the conjugation of GSH to short chain α,β-unsaturated aldehydes, such as acrolein and crotonaldehyde. GSTP1-1 has the highest activity towards acrolein, and GSTA4-4 has high activity toward HNE (Hubatsch et al., 1998). GSTM1-1 and GSTA1-1 are better at conjugating longer chain 4-hydroxy-α,β, unsaturated aldehydes (Goon et al., 1993). An Alpha class microsomal GST has been shown to conjugate HNE (Prabhu et al., 2004), and the activity of Alpha and Pi class mitochondrial GST towards HNE is higher in mitochondria than in the cytosol (Gallagher et al., 2006). Several GST have been identified in tissues that are susceptible to oxidative damage. For example, Alpha, Pi, and Mu class GST have been detected in the aorta, heart, and brain (Hayes & Pulford, 1995).

Evidence that alpha class GST are involved in the detoxication of aldehydes is derived from experiments in which GST are overexpressed in tissue culture cells. Expression of mouse GSTA4-4 and rat GSTA5-5 protects cells against acrolein, HNE, and other aldehydes (Cheng et al., 2001; Kazi & Ellis, 2002; Yang et al., 2004).

3.4. Glyoxalase 1/II

One of the main enzyme systems known to be involved in the metabolism of MG and other α-oxoaldehydes is through a specific 2-step pathway involving glyoxalase I and II. These catalyze the formation of α-hydroxy acids from oxoaldehydes. However, this system is GSH-dependent and as a consequence is not efficient when GSH levels are depleted, such as may occur when oxidant or reactive carbonyl levels are high. Its activity also decreases upon aging and oxidative stress (Thornalley, 2003). The glyoxalase system is not known to be involved in the metabolism of other classes of aldehydes, for which other enzyme pathways are likely to be responsible.

4. Therapeutic interventions for removing carbonyl stress

4.1. Aldehyde scavengers

Although direct oxidative damage is often considered the most serious consequence of increased levels of oxidants within the cell, as described above, the increased presence of toxic aldehydes leads to carbonyl stress and has been shown to cause a significant amount of macromolecular damage. In order to counter this problem, specific carbonyl scavengers have been used to reduce the "aldehyde load" (Aldini et al., in press). Hydroxylamine scavengers such as *N*-benzylhydroxylamine, cyclohexylhydroxylamine, and *t*-butylhydroxylamine have been shown to protect against 3-aminopropenal neurotoxicity in vitro (Wood et al., 2006). Similarly, aminoguanidine and tenilsetam were able to protect SH-SY5Y neuroblastoma cells against methylglyoxal toxicity (Webster et al., 2005; de Arriba et al., 2006), and tenilsetam has been used to improve cognitive function in senile dementia and AD patients (Saletu et al., 1989). Hydralazine, aminoguanidine, carnosine, and methoxyamine were all able to prevent acrolein-induced protein carbonylation and protected mouse hepatocytes in vitro (Burcham et al., 2000). These studies show that the removal of reactive aldehydes is a valid approach in the treatment of oxidant damage-dependent disease.

Many chemical carbonyl scavengers show a relative lack of specificity and may interfere with the metabolism of endogenous aldehydes. An alternative strategy presented below would be to lower the aldehyde load by enhancing their metabolism.

4.2. Enhancing carbonyl metabolism via enzyme induction

Increased carbonyl detoxication can also be achieved through increased activity of carbonyl metabolizing enzymes. This can arise through the activation of enzymes or by increased levels of the enzymes themselves, dependent on increased transcription, stabilization of mRNA, or increased translation. Previous work, mainly in the area of cancer research, has uncovered a range of natural and synthetic compounds that can lead to increased expression of carbonyl metabolizing enzymes in different tissues (Hayes & McMahon, 2001). Compounds that have been successfully used for induction studies include natural compounds such as sulphoraphane, benzyl isothiocyanate, phenethyl isothiocyanate, resveratrol, and other chemicals, such as butylated hydroxyanisole, 3-methylcholanthrene, dithiolethiones, and certain drugs (Table 2). Many of the former compounds are phytochemicals that are present in food and beverages, such as tea or wine, and some have been used as antioxidants.

Table 2
Chemoprotective compounds capable of elevating carbonyl-metabolizing enzymes

Compound	Source	Enzyme/gene elevated	Mechanism	Reference
3-Methyl cholanthrene	Polycyclic aromatic hydrocarbons	ALDH3A	XRE/AhR and ARE/Nrf2	Sladek, 2003
D3T	Cruciferous vegetables	AKR1B, AKR1A, CBR1, GSTM1, GSTM2, GSTM3, GSTA4, GSTA2, GSTT2	ARE/Nrf2	Kwak et al., 2003; Li et al., 2005
Sulphorophane	Cruciferous vegetables	AKR1C1, GSTA2, GSTA4, GSTM1, GSTM2, GSTM3, ALDH2, AKR7A5, AKR1C13, CBR1	ARE/Nrf2	Bonnesen et al., 2001; Thimmulappa et al., 2002; Hu et al., 2006a
Benzyl isothiocyanate	Cruciferous vegetables	AKR1C1	ARE/Nrf2	Bonnesen et al., 2001
Phenethyl isothiocyanate	Cruciferous vegetables	AKR1C1, GSTA2, GSTM1, GSTM3, GSTT1, CBR1	ARE/Nrf2	Bonnesen et al., 2001; Hu et al., 2006b
Butylated hydroxyanisole	Synthetic antioxidant	ALDH1A3, ALDH2, GSTM1, GSTM3	ARE/Nrf2	Nair et al., 2006
Bezafibrate	Lipid lowering drug	ALDH3A2	PPAR	Gloerich et al., 2006
β-Naphthoflavone	Synthetic flavone	AKR1B3	ARE/Nrf2	Nishinaka & Yabe-Nishimura, 2005

These inducers appear to convey their beneficial effects through 2 mechanisms that depend on regulatory elements in the promoters of genes that are induced: (1) the xenobiotic response element (XRE) that is bound by the AH receptor (AhR) transcription factor (Sogawa & Fujii-Kuriyama, 1997) and (2) the antioxidant/electrophile response element (ARE/EpRE) that is bound by the nuclear factor-erythroid 2-related factor 2 (Nrf2) transcription factor (Rushmore et al., 1991; Motohashi & Yamamoto, 2004; Kensler et al., 2007). Nrf2 appears to be the endpoint of a major pathway for controlling the levels a range of antioxidant and protective enzymes, and its nuclear availability is dependent on a redox-sensitive regulatory protein Keap1 (Motohashi & Yamamoto, 2004; McMahon et al., 2006). Nrf2 is also a downstream target of the Ah receptor, indicating that these 2 pathways overlap to some extent (Miao et al., 2005; Kohle & Bock, 2006). The Nrf2/ARE pathway is though to represent an adaptive response to oxidative stress, as the enzymes that are induced are considered to be protective and/or antioxidant enzymes (Fig. 2). These enzymes include many of those that are involved in carbonyl metabolism (Table 2).

There is already considerable information about the mechanism of action of these chemoprotective compounds, and this makes them attractive as potential therapeutic agents not only in cancer but also in a range of oxidative stress-dependent disease, such as neurodegeneration (van Muiswinkel & Kuiperij, 2005), inflammation (Chen & Kunsch, 2004), lung disease (Cho et al., 2006), and asthma (Li & Nel, 2006; Mandlekar et al., 2006). As many of the agents are natural compounds that occur in the diet, many of the potential benefits could be achieved through changes or supplements to the diet. Finally, the doses required to cause induction of protective enzymes are generally non-toxic and are likely to have few side effects.

4.2.1. Induction of aldehyde dehydrogenases

Increased ALDH3A levels in cultured human breast carcinoma cell lines can be achieved by treatment of cells with 3-methylcholanthrene, and this has been shown to occur via transactivation of XRE present in the 5′-upstream regions of the gene (Sladek, 2003). ALDH3A enzymes are particularly good at protecting against HNE (Townsend et al., 2001). Another ALDH3 enzyme, ALDH3A2 (fatty ALDH) was found to be inducible by bezafibrate via a peroxisome proliferator-activated receptor alpha-dependent mechanism (Gloerich et al., 2006). This additional mechanism suggests alternative types of inducing compound can be used (Fig. 2).

Mitochondrial ALDH2, which is thought to play a role in the prevention of AD, hypertension, and myocardial infarction, is induced by sulphorophane (Hu et al., 2006a). In addition, ALDH1A3 and mitochondrial ALDH2 have been shown to be induced by butylated hydroxyanisole (Nair et al., 2006), and this is likely to involve an ARE/Nrf2 dependent mechanism.

4.2.2. Induction of aldo-keto reductases

Aldose reductase (AKR1B) has been known for some time to be regulated by osmotic stress in the kidney (Burg et al., 1996). However, more recent work has shown that it is responsive to a range of stresses, including oxidative stress in rat vascular

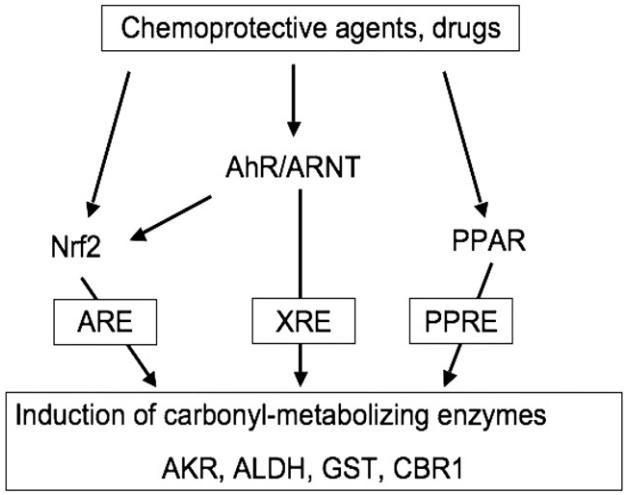


Fig. 2. Induction of carbonyl-metabolizing enzymes by chemoprotective agents and drugs. Exposure to chemoprotective agents and some drugs leads to the induction of carbonyl-metabolixing enzymes via the activation of the Nrf2/ARE pathway, the AhR/XRE pathway, or the PPAR/PPRE pathway.

smooth muscle cells (Spycher et al., 1997). In addition, AKR1B appears to be inducible by some of its proposed substrates, MG, and HNE via an oxidative stress-linked mechanism (Spycher et al., 1996; Chang et al., 2002). Although such a mechanism may be important for understanding ischaemic preconditioning, in both the heart and the brain, the significance of this inducibility is that it opens a route for finding drugs and other compounds that can mimic such an adaptive response without any of the potential hazards of using highly reactive reagents. For example, in cardiomyocytes, aldose reductase has been shown to be inducible by 3H-1,2-dithiole-3-thione (D3T; Li et al., 2005), a compound which is known to act via ARE/Nrf2 (Table 2). This is supported by evidence from the mouse in which AKR1B3 was shown to be inducible in response to D3T in a Nrf2-dependent manner (Nishinaka & Yabe-Nishimura, 2005).

Microarray experiments in mouse have revealed that levels of another AKR, aldehyde reductase (AKR1A4), are up-regulated by D3T (Kwak et al., 2003) as part of a chemoprotective response.

AKR7A1 in the rat was the one of the first AKR that was shown to be particularly responsive to chemical inducers (Ellis et al., 1993). These include dietary chemoprotectors and some drugs. Analysis of the promoter of the AKR7A1 gene revealed the presence of several ARE-type elements, and it is extremely likely that this is regulated via an Nrf2-dependent mechanism (Ellis et al., 2003). Despite this wealth of evidence for the inducibility of this enzyme in rat, there is very little known about the induction of human AKR7A enzymes. AKR7A2 is elevated in AD, indicating that it might be inducible by oxidative stress (Picklo et al., 2001). In mouse, a microarray study has shown that AKR7A5 is inducible by sulphorophane in an Nrf2-dependent manner (Thimmulappa et al., 2002), suggesting the potential for enhancing the metabolism of reactive aldehydes through induction of this family of enzymes.

Several of the AKR1C enzymes have been shown to be induced by chemopreventive agents. For example, AKR1C2 levels are elevated by phase II inducers (Lou et al., 2006), and AKR1C1 is induced by polycyclic hydrocarbons, electrophiles and oxidative stress (Burczynski et al., 1999). Nontoxic doses of sulforaphane, benzyl isothiocyanate and phenethyl isothiocyanate caused an increase of between 11-fold and 17-fold in the protein levels of AKR1C1 in human colon cell lines, and this correlated with protection against chemical stress (Bonnesen et al., 2001). From microarray experiments, mouse AKR1C13 appears to be regulated by sulphorophane (Thimmulappa et al., 2002; Hu et al., 2006a). However, AKR1C enzymes are not particularly efficient at removal of aldehydes such as HNE or MG, so the physiological relevance of their induction to reactive aldehyde load is not clear.

4.2.3. Induction of carbonyl reductases

Until recently, little work had studied the upregulated of carbonyl reductase (CBR1) by chemoprotective agents. The advent of microarray studies has lead to the identification of this enzyme as one that is responsive to a range of inducers, including phenethyl isothiocyanate in mouse liver (Hu et al., 2006b), D3T in mouse (Kwak et al., 2003), and sulphorophane in mouse (Thimmulappa et al., 2002). CBR1 expression appears to be dependent on the transcription factor Nrf2. Given that this enzyme is present in a range of tissues, including brain, its induction may represent a useful defensive strategy against reactive aldehydes (Maser, 2006).

4.2.4. Induction of glutathione S-transferases

GST were some of the first ARE-dependent enzymes to be studied (Rushmore et al., 1991). More recent work in mouse has shown that several GST genes (GSTA1, GSTA2, GSTM1, GSTM2, GSTM3 and GSTM4) are induced by chemopreventive agents, such as butylated hydroxyanisole, ethoxyquin, and oltipraz, as well as phytochemicals such as indole-3-carbinol, sulforaphane, and coumarin (McMahon et al., 2001; Chanas et al., 2002). By using Nrf2 knockout mice, the basal and inducible expression was shown to be Nrf2-dependent (McMahon et al., 2001; Chanas et al., 2002). A range of inducible GST have also been identified by microarray experiments. Several GST including GSTA2, GSTM1, GSTM3, and GSTT1 are inducible by phenethylisothiocyanate (PEITC) in mouse liver (Hu et al., 2006b) via an Nrf2-dependent mechanism, and GSTA2, GSTA4, GSTM1, GSTM2, GSTM3 subunits are induced by sulphorophane treatment (Hu et al., 2006a). GSTM1 and GSTM3 are induced by BHA (Nair et al., 2006) and GSTM1, GSTM2, GSTM3, GSTA4, GSTA2, and GSTT2 all appear to be regulated by D3T in mouse (Kwak et al., 2003). The most significant of these in terms of aldehyde detoxication are GSTA4, GSTM1, and GSTP1 which have been shown to conjugate short and long chain a,β-unsaturated aldehydes (Goon et al., 1993). Induction of cellular GSH levels and GST by D3T in rat aortic smooth muscle cells has also been observed, and this has been correlated with protection against acrolein- and HNE-induced toxicity (Cao et al., 2003a,2003b).

5. Potential therapeutic areas

The potential for using chemopreventive compounds to counter some of the consequences of carbonyl stress has been tested recently in several disease models. For example, in models of cardiovascular disease, D3T has been used to treat aortic smooth muscle cells, and leads to an increase in GST levels which give increased protection against HNE-induced damage (Cao et al., 2003a). Resveratrol, present in red wine, has been shown to protect cultured aortic smooth muscle cells against HNE, and has the potential to protect against vascular injury (Li et al., 2006b). Treatment of human adult retinal pigment epithelial cells (ARPE-19) with sulphorophane leads to increased protection against HNE and is associated with an increase in detoxication enzymes (Gao et al., 2001).

Chemoprotective strategies are being adopted in other model systems, although the involvement of aldehyde-metabolizing enzymes has yet to be established. For example, in a model of AD, diallyl disulfide, a garlic-derived compound, was able to protect PC12 neuronal cells against oxidative stress (Koh et al., 2005). A chemoprotective approach has also been adopted in a model of ischaemia-reperfusion injury, where treatment of cardiomyocytes with D3T has been shown to protect cells

against oxidative stress (Cao et al., 2006). There is also potential to test whether treatment with any of the known inducers of aldehyde-metabolizing enzymes can protect against the aldehyde-dependent toxicity that is prevalent in diabetes and atherosclerosis. To date there have been no in vivo studies that have tested whether chemopreventive compounds can protect against aldehyde toxicity and aldehyde-dependent disease progression. These studies are urgently needed to translate the cell-based models into valid therapeutic strategies.

6. Concluding remarks

There is substantial evidence that carbonyl stress is contributory to the progression of several oxidant stress-dependent diseases. Enhancing carbonyl metabolism through the manipulation of enzyme levels is a potential avenue for developing new therapeutics. These may be derived from natural compounds that act through known mechanisms or may be chemically synthesized analogues that convey similar properties. In many cases, in addition to their protective effects against carbonyl stress, many of these compounds are likely to provide protection against the oxidative stress that initiated the production of carbonyls. This represent a 2-pronged approach, as both the damaging agent and its route of production have the potential to be halted.

References

Abordo, E. A., Minhas, H. S., & Thornalley, P. J. (1999). Accumulation of alpha-oxoaldehydes during oxidative stress: a role in cytotoxicity. *Biochem Pharmacol 58*(4), 641−648.

Ahmed, N., Ahmed, U., Thornalley, P. J., Hager, K., Fleischer, G., & Munch, G. (2005). Protein glycation, oxidation and nitration adduct residues and free adducts of cerebrospinal fluid in Alzheimer's disease and link to cognitive impairment. *J Neurochem 92*(2), 255−263.

Akhand, A. A., Hossain, K., Mitsui, H., Kato, M., Miyata, T., Inagi, R., et al. (2001). Glyoxal and methylglyoxal trigger distinct signals for map family kinases and caspase activation in human endothelial cells. *Free Radic Biol Med 31*(1), 20−30.

Alary, J., Gueraud, F., & Cravedi, J. P. (2003). *Fate of 4-hydroxynonenal in vivo: disposition and metabolic pathways Vol. 24 (4-5)* (pp. 177−187).

Aldini, G., Dalle-Donne, I., Facino, R. M., Milzani, A., & Carini, M. (in press). Intervention strategies to inhibit protein carbonylation by lipoxidation-derived reactive carbonyls. *Med Res Rev.* doi:10.1002/med.20073

Amunom, I., Stephens, L. J., Conklin, D. J., Srivastava, S., Bhatnagar, A., & Prough, R. A. (2005). In H. Weiner (Ed.), *Enzymology and Molecular Biology of Carbonyl Metabolism vol. 12* (pp. 118−123). Purdue: Purdue University Press.

Asselin, C., Bouchard, B., Tardif, J. C., & Des Rosiers, C. (2006). Circulating 4-hydroxynonenal-protein thioether adducts assessed by gas chromatography-mass spectrometry are increased with disease progression and aging in spontaneously hypertensive rats. *Free Radic Biol Med 41*(1), 97−105.

Barros, A. R., Sierra, L. M., & Comendador, M. A. (1994). Acrolein genotoxicity in *Drosophila melanogaster*: III. Effects of metabolism modification. *Mutat Res 321*(3), 119−126.

Beisswenger, P. J., Howell, S. K., O'Dell, R. M., Wood, M. E., Touchette, A. D., & Szwergold, B. S. (2001). alpha-Dicarbonyls increase in the postprandial period and reflect the degree of hyperglycemia. *Diabetes Care 24*(4), 726−732.

Benedetti, A., Comporti, M., & Esterbauer, H. (1980). Identification of 4-hydroxynonenal as a cytotoxic product originating from the peroxidation of liver microsomal lipids. *Biochim Biophys Acta 620*(2), 281−296.

Bonnesen, C., Eggleston, I. M., & Hayes, J. D. (2001). *Dietary indoles and isothiocyanates that are generated from cruciferous vegetables can both stimulate apoptosis and confer protection against DNA damage in human colon cell lines Vol. 61 (16).* (pp. 6120−6130).

Botella, J. A., Ulschmid, J. K., Gruenewald, C., Moehle, C., Kretzschmar, D., Becker, K., et al. (2004). The *Drosophila carbonyl* reductase sniffer prevents oxidative stress-induced neurodegeneration. *Curr Biol 14*(9), 782−786.

Bourajjaj, M., Stehouwer, C. D., van Hinsbergh, V. W., & Schalkwijk, C. G. (2003). Role of methylglyoxal adducts in the development of vascular complications in diabetes mellitus. *Biochem Soc Trans 31*(Pt 6), 1400−1402.

Brambilla, G., Sciaba, L., Faggin, P., Maura, A., Marinari, U. M., Ferro, M., et al. (1986). Cytotoxicity, DNA fragmentation and sister-chromatid exchange in Chinese hamster ovary cells exposed to the lipid peroxidation product 4-hydroxynonenal and homologous aldehydes. *Mutat Res 171*, 169−176.

Burcham, P. C., Kerr, P. G., & Fontaine, F. (2000). The antihypertensive hydralazine is an efficient scavenger of acrolein. *Redox Rep 5*(1), 47−49.

Burczynski, M. E., Lin, H. K., & Penning, T. M. (1999). Isoform-specific induction of a human aldo-keto reductase by polycyclic aromatic hydrocarbons (PAHs), electrophiles, and oxidative stress: implications for the alternative pathway of PAH activation catalyzed by human dihydrodiol dehydrogenase. *Cancer Res 59*(3), 607−614.

Burczynski, M. E., Sridhar, G. R., Palackal, N. T., & Penning, T. M. (2001). The reactive oxygen species- and Michael acceptor inducible human aldo-keto reductase AKR1C1 reduces the alpha-beta unsaturated aldehyde 4-hydroxy-2-nonenal to 1,4-dihydroxy-2-nonene. *J Biol Chem 276*(4), 2890−2897.

Burg, M. B., Kwon, E. D., & Kultz, D. (1996). Osmotic regulation of gene expression. *FASEB J 10*(14), 1598−1606.

Calingasan, N. Y., Uchida, K., & Gibson, G. E. (1999). Protein-bound acrolein: a novel marker of oxidative stress in Alzheimer's disease. *J Neurochem 72*(2), 751−756.

Cao, Z., Hardej, D., Trombetta, L. D., & Li, Y. (2003). The role of chemically induced glutathione and glutathione *S*-transferase in protecting against 4-hydroxy-2-nonenal-mediated cytotoxicity in vascular smooth muscle cells. *Cardiovasc Toxicol 3*(2), 165−177.

Cao, Z., Hardej, D., Trombetta, L. D., Trush, M. A., & Li, Y. (2003). Induction of cellular glutathione and glutathione *S*-transferase by 3H-1,2-dithiole-3-thione in rat aortic smooth muscle A10 cells: protection against acrolein-induced toxicity. *Atherosclerosis 166*(2), 291−301.

Cao, Z., Zhu, H., Zhang, L., Zhao, X., Zweier, J. L., & Li, Y. (2006). Antioxidants and phase 2 enzymes in cardiomyocytes: chemical inducibility and chemoprotection against oxidant and simulated ischemia–reperfusion injury. *Exp Biol Med (Maywood) 231*(8), 1353−1364.

Ceriello, A., & Motz, E. (2004). Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol 24*(5), 816−823.

Chanas, S. A., Jiang, Q., McMahon, M., McWalter, G. K., McLellan, L. I., Elcombe, C. R., et al. (2002). Loss of the Nrf2 transcription factor causes a marked reduction in constitutive and inducible expression of the glutathione *S*-transferase Gsta1, Gsta2, Gstm1, Gstm2, Gstm3 and Gstm4 genes in the livers of male and female mice. *Biochem J 365*(Pt 2), 405−416.

Chang, K. C., Paek, K. S., Kim, H. J., Lee, Y. S., Yabe-Nishimura, C., & Seo, H. G. (2002). Substrate-induced up-regulation of aldose reductase by methylglyoxal, a reactive oxoaldehyde elevated in diabetes. *Mol Pharmacol 61*(5), 1184−1191.

Chen, X. L., & Kunsch, C. (2004). Induction of cytoprotective genes through Nrf2/antioxidant response element pathway: a new therapeutic approach for the treatment of inflammatory diseases. *Curr Pharm Des 10*(8), 879−891.

Cheng, J. Z., Singhal, S. S., Sharma, A., Saini, M., Yang, Y., Awasthi, S., et al. (2001). Transfection of mGSTA4 in HL-60 cells protects against 4-hydroxynonenal-induced apoptosis by inhibiting JNK-mediated signaling. *Arch Biochem Biophys 392*(2), 197−207.

Chiarpotto, E., Domenicotti, C., Paola, D., Vitali, A., Nitti, M., Pronzato, M. A., et al. (1999). Regulation of rat hepatocyte protein kinase C beta isoenzymes by the lipid peroxidation product 4-hydroxy-2,3-nonenal: a signaling pathway to modulate vesicular transport of glycoproteins. *Hepatology 29*(5), 1565−1572.

Cho, H. Y., Reddy, S. P., & Kleeberger, S. R. (2006). Nrf2 defends the lung from oxidative stress. *Antioxid Redox Signal 8*(1-2), 76−87.

Cooper, K. O., Witz, G., & Witmer, C. M. (1987). Mutagenicity and toxicity studies of several alpha,beta-unsaturated aldehydes in the *Salmonella typhimurium* mutagenicity assay. *Environ Mutagen 9*(3), 289–295.

de Arriba, S. G., Krugel, U., Regenthal, R., Vissiennon, Z., Verdaguer, E., Lewerenz, A., et al. (2006). Carbonyl stress and NMDA receptor activation contribute to methylglyoxal neurotoxicity. *Free Radic Biol Med 40*(5), 779–790.

Demozay, D., Rocchi, S., Mas, J. C., Grillo, S., Pirola, L., Chavey, C., et al. (2004). Fatty aldehyde dehydrogenase: potential role in oxidative stress protection and regulation of its gene expression by insulin. *J Biol Chem 279*(8), 6261–6270.

Dick, R. A., Kwak, M. K., Sutter, T. R., & Kensler, T. W. (2001). Antioxidative function and substrate specificity of NAD(P)H-dependent alkenal/one oxidoreductase. A new role for leukotriene B4 12-hydroxydehydrogenase/15-oxoprostaglandin 13-reductase. *J Biol Chem 276*(44), 40803–40810.

Doorn, J. A., Maser, E., Blum, A., Claffey, D. J., & Petersen, D. R. (2004). Human carbonyl reductase catalyzes reduction of 4-oxonon-2-enal. *Biochemistry 43*(41), 13106–13114.

Echtay, K., Esteves, T., Pakay, J., Jekabsons, M., Lambert, A., Portero-Otin, M., et al. (2003). A signalling role for 4-hydroxy-2-nonenal in regulation of mitochondrial uncoupling. *EMBO J 22*, 4103–4410.

Eckl, P. M., Ortner, A., & Esterbauer, H. (1993). Genotoxic properties of 4-hydroxyalkenals and analogous aldehydes. *Mutat Res 290*(2), 183–192.

Ehrig, T., Bosron, W. F., & Li, T. K. (1990). Alcohol and aldehyde dehydrogenase. *Alcohol Alcohol 25*(2-3), 105–116.

Ellis, E. M., & Hayes, J. D. (1995). Substrate-specificity of an aflatoxin-metabolizing aldehyde reductase. *Biochem J 312*(Pt2), 535–541.

Ellis, E. M., Judah, D. J., Neal, G. E., & J.D, H. (1993). An ethoxyquin-inducible aldehyde reductase from rat liver that metabolises aflatoxin B1 defines a subfammily of aldo-keto reductases. *Proc Natl Acad Sci U S A 90*, 10350–10354.

Ellis, E. M., Slattery, C. M., & Hayes, J. D. (2003). Characterization of the rat aflatoxin B(1) aldehyde reductase gene, AKR7A1. Structure and chromosomal localization of AKR7A1 as well as identification of antioxidant response elements in the gene promoter. *Carcinogenesis 24*(4), 727–737.

Esterbauer, H., Zollner, H., & Scholz, N. (1975). Reaction of glutathione with conjugated carbonyls. *Z Naturforsch C 30*(4), 466–473.

Esterbauer, H., Cheeseman, K. H., Dianzani, M. U., Poli, G., & Slater, T. F. (1982). Separation and characterization of the aldehydic products of lipid peroxidation stimulated by ADP-Fe^{2+} in rat liver microsomes. *Biochem J 208*(1), 129–140.

Esterbauer, H., Schaur, R. J., & Zollner, H. (1991). Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. *Free Radic Biol Med 11*(1), 81–128.

Estey, T., Piatigorsky, J., Lassen, N., & Vasiliou, V. (2007). ALDH3A1: a corneal crystallin with diverse functions. *Exp Eye Res 84*(1), 3–12.

Flynn, T. G. (1982). Aldehyde reductases: monomeric NADPH-dependent oxidoreductases with multifunctional potential. *Biochem Pharmacol 31*(17), 2705–2712.

Gallagher, E. P., Gardner, J. L., & Barber, D. S. (2006). Several glutathione *S*-transferase isozymes that protect against oxidative injury are expressed in human liver mitochondria. *Biochem Pharmacol 71*(11), 1619–1628.

Gao, X., Dinkova-Kostova, A. T., & Talalay, P. (2001). Powerful and prolonged protection of human retinal pigment epithelial cells, keratinocytes, and mouse leukemia cells against oxidative damage: the indirect antioxidant effects of sulforaphane. *Proc Natl Acad Sci U S A 98*(26), 15221–15226.

Gloerich, J., Ijlst, L., Wanders, R. J., & Ferdinandusse, S. (2006). Bezafibrate induces FALDH in human fibroblasts; implications for Sjogren-Larsson syndrome. *Mol Genet Metab 89*(1-2), 111–115.

Goon, D., Saxena, M., Awasthi, Y. C., & Ross, D. (1993). Activity of mouse liver glutathione *S*-transferases toward *trans*,*trans*-muconaldehyde and *trans*-4-hydroxy-2-nonenal. *Toxicol Appl Pharmacol 119*(2), 175–180.

Guengerich, F. P. (2001). Common and uncommon cytochrome P450 reactions related to metabolism and chemical toxicity. *Chem Res Toxicol 14*(6), 611–650.

Gueraud, F., Alary, J., Costet, P., Debrauwer, L., Dolo, L., Pineau, T., et al. (1999). In vivo involvement of cytochrome P450 4A family in the oxidative metabolism of the lipid peroxidation product trans-4-hydroxy-2-nonenal, using PPARalpha-deficient mice. *J Lipid Res 40*(1), 152–159.

Halliwell, B. (2001). Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. *Drugs Aging 18*(9), 685–716.

Hartley, D. P., Ruth, J. A., & Petersen, D. R. (1995). The hepatocellular metabolism of 4-hydroxynonenal by alcohol dehydrogenase, aldehyde dehydrogenase, and glutathione *S*-transferase. *Arch Biochem Biophys 316*(1), 197–205.

Hayes, J. D., & McMahon, M. (2001). Molecular basis for the contribution of the antioxidant responsive element to cancer chemoprevention. *Cancer Lett 174*(2), 103–113.

Hayes, J. D., & Pulford, D. J. (1995). The glutathione *S*-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. *Crit Rev Biochem Mol Biol 30*(6), 445–600.

Hayes, J. D., Flanagan, J. U., & Jowsey, I. R. (2005). Glutathione transferases. *Annu Rev Pharmacol Toxicol 45*, 51–88.

Hinshelwood, A., McGarvie, G., & Ellis, E. (2002). Characterisation of a novel mouse liver aldo-keto reductase AKR7A5. *FEBS Lett 523*, 213–218.

Hinshelwood, A., McGarvie, G., & Ellis, E. M. (2003). Substrate specificity of mouse aldo-keto reductase AKR7A5. *Chem Biol Interact 143-144*, 263–269.

Holvoet, P., & Collen, D. (1998). Oxidation of low density lipoproteins in the pathogenesis of atherosclerosis. *Atherosclerosis 137*, S33–S38 (Suppl).

Hu, R., Xu, C., Shen, G., Jain, M. R., Khor, T. O., Gopalkrishnan, A., et al. (2006). Gene expression profiles induced by cancer chemopreventive isothiocyanate sulforaphane in the liver of C57BL/6J mice and C57BL/6J/Nrf2 (−/−) mice. *Cancer Lett 243*, 170–192.

Hu, R., Xu, C., Shen, G., Jain, M. R., Khor, T. O., Gopalkrishnan, A., et al. (2006). Identification of Nrf2-regulated genes induced by chemopreventive isothiocyanate PEITC by oligonucleotide microarray. *Life Sci 79*(20), 1944–1955.

Hubatsch, I., Ridderstrom, M., & Mannervik, B. (1998). Human glutathione transferase A4-4: an alpha class enzyme with high catalytic efficiency in the conjugation of 4-hydroxynonenal and other genotoxic products of lipid peroxidation. *Biochem J 330*(Pt 1), 175–179.

Hyndman, D., Bauman, D. R., Heredia, V. V., & Penning, T. M. (2003). The aldo-keto reductase superfamily homepage. *Chem-Biol Interact 143-144*, 621–631.

Ji, C., Amarnath, V., Pietenpol, J. A., & Marnett, L. J. (2001). 4-hydroxynonenal induces apoptosis via caspase-3 activation and cytochrome c release. *Chem Res Toxicol 14*(8), 1090–1096.

Jin, Y., & Penning, T. M. (2007). Aldo-keto reductases and bioactivation/detoxication. *Annu Rev Pharmacol Toxicol 47*, 263–292.

Kamino, K., Nagasaka, K., Imagawa, M., Yamamoto, H., Yoneda, H., Ueki, A., et al. (2000). Deficiency in mitochondrial aldehyde dehydrogenase increases the risk for late-onset Alzheimer's disease in the Japanese population. *Biochem Biophys Res Commun 273*(1), 192–196.

Kanazu, T., Shinoda, M., Nakayama, T., Deyashiki, Y., Hara, A., & Sawada, H. (1991). Aldehyde reductase is a major protein associated with 3-deoxyglucosone reductase activity in rat, pig and human livers. *Biochem J 279*(Pt 3), 903–906.

Kang, Y., Edwards, L. G., & Thornalley, P. J. (1996). Effect of methylglyoxal on human leukaemia 60 cell growth: modification of DNA G1 growth arrest and induction of apoptosis. *Leuk Res 20*(5), 397–405.

Karlhuber, G. M., Bauer, H. C., & Eckl, P. M. (1997). Cytotoxic and genotoxic effects of 4-hydroxynonenal in cerebral endothelial cells. *Mutat Res 381*(2), 209–216.

Kasai, H., Kumeno, K., Yamaizumi, Z., Nishimura, S., Nagao, M., Fujita, Y., et al. (1982). Mutagenicity of methylglyoxal in coffee. *Gann 73*, 681–683.

Kawaguchi-Niida, M., Shibata, N., Morikawa, S., Uchida, K., Yamamoto, T., Sawada, T., et al. (2006). Crotonaldehyde accumulates in glial cells of Alzheimer's disease brain. *Acta Neuropathol (Berl) 111*(5), 422–429.

Kazi, S., & Ellis, E. M. (2002). Expression of rat liver glutathione-*S*-transferase GSTA5 in cell lines provides increased resistance to alkylating agents and toxic aldehydes. *Chem Biol Interact 140*(2), 121–135.

Kelner, M. J., Estes, L., Rutherford, M., Uglik, S. F., & Peitzke, J. A. (1997). Heterologous expression of carbonyl reductase: demonstration of prostaglandin 9-ketoreductase activity and paraquat resistance. *Life Sci 61*(23), 2317–2322.

Kensler, T. W., Wakabayashi, N., & Biswal, S. (2007). Cell Survival Responses to Environmental Stresses Via the Keap1-Nrf2-ARE Pathway. *Annu Rev Pharmacol Toxicol 47*, 89−116.

King, H., Aubert, R. E., & Herman, W. H. (1998). Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care 21*(9), 1414−1431.

Koh, S. H., Kwon, H., Park, K. H., Ko, J. K., Kim, J. H., Hwang, M. S., et al. (2005). Protective effect of diallyl disulfide on oxidative stress-injured neuronally differentiated PC12 cells. *Brain Res Mol Brain Res 133*(2), 176−186.

Kohle, C., & Bock, K. W. (2006). Activation of coupled Ah receptor and Nrf2 gene batteries by dietary phytochemicals in relation to chemoprevention. *Biochem Pharmacol 72*(7), 795−805.

Kruman, I., Bruce-Keller, A. J., Bredesen, D., Waeg, G., & Mattson, M. P. (1997). Evidence that 4-hydroxynonenal mediates oxidative stress-induced neuronal apoptosis. *J Neurosci 17*(13), 5089−5100.

Kuhla, B., Luth, H. J., Haferburg, D., Boeck, K., Arendt, T., & Munch, G. (2005). Methylglyoxal, glyoxal, and their detoxification in Alzheimer's disease. *Ann N Y Acad Sci 1043*, 211−216.

Kwak, M. K., Wakabayashi, N., Itoh, K., Motohashi, H., Yamamoto, M., & Kensler, T. W. (2003). Modulation of gene expression by cancer chemopreventive dithiolethiones through the Keap1-Nrf2 pathway. Identification of novel gene clusters for cell survival. *J Biol Chem 278*(10), 8135−8145.

Leonarduzzi, G., Chiarpotto, E., Biasi, F., & Poli, G. (2005). 4-Hydroxynonenal and cholesterol oxidation products in atherosclerosis. *Mol Nutr Food Res 49*(11), 1044−1049.

Li, N., & Nel, A. E. (2006). Role of the Nrf2-mediated signaling pathway as a negative regulator of inflammation: implications for the impact of particulate pollutants on asthma. *Antioxid Redox Signal 8*(1-2), 88−98.

Li, L., Hamilton, R. F., Kirichenko, A., & Holian, A. (1996). 4-Hydroxynonenal-induced cell death in murine alveolar macrophages. *Toxicol Appl Pharmacol 139*(1), 135−143.

Li, L., Hamilton, R. F., Jr., Taylor, D. E., & Holian, A. (1997). Acrolein-induced cell death in human alveolar macrophages. *Toxicol Appl Pharmacol 145*(2), 331−339.

Li, Y., Cao, Z., Zhu, H., & Trush, M. A. (2005). Differential roles of 3H-1,2-dithiole-3-thione-induced glutathione, glutathione *S*-transferase and aldose reductase in protecting against 4-hydroxy-2-nonenal toxicity in cultured cardiomyocytes. *Arch Biochem Biophys 439*(1), 80−90.

Li, D., Hinshelwood, A., Gardner, R., McGarvie, G., & Ellis, E. M. (2006). Mouse aldo-keto reductase AKR7A5 protects V79 cells against 4-hydroxynonenal-induced apoptosis. *Toxicology 226*(2-3), 172−180.

Li, Y., Cao, Z., & Zhu, H. (2006). Upregulation of endogenous antioxidants and phase 2 enzymes by the red wine polyphenol, resveratrol in cultured aortic smooth muscle cells leads to cytoprotection against oxidative and electrophilic stress. *Pharmacol Res 53*(1), 6−15.

Lindahl, R. (1992). Aldehyde dehydrogenases and their role in carcinogenesis. *Crit Rev Biochem Mol Biol 27*, 283−335.

Lindahl, R., & Petersen, D. R. (1991). Lipid aldehyde oxidation as a physiological role for class 3 aldehyde dehydrogenases. *Biochem Pharmacol 41*(11), 1583−1587.

Lou, H., Du, S., Ji, Q., & Stolz, A. (2006). Induction of AKR1C2 by Phase II Inducers: Identification of a distal consensus antioxidant response element regulated by Nrf2. *Mol Pharmacol 69*, 1662−1672.

Lovell, M., Xie, C., & Markesbery, W. (2001). Acrolein is increased in Alzheimer's disease brain and is toxic to primary hippocampal cultures. *Neurobiol Aging 22*, 187−194.

MacNee, W. (2005). Pathogenesis of chronic obstructive pulmonary disease. *Proc Am Thorac Soc 2*(4), 258−266 (discussion 290-251).

Madamanchi, N. R., Vendrov, A., & Runge, M. S. (2005). Oxidative stress and vascular disease. *Arterioscler Thromb Vasc Biol 25*(1), 29−38.

Mandlekar, S., Hong, J. L., & Kong, A. N. (2006). Modulation of metabolic enzymes by dietary phytochemicals: a review of mechanisms underlying beneficial versus unfavorable effects. *Curr Drug Metab 7*(6), 661−675.

Markesbery, W. R. (1997). Oxidative stress hypothesis in Alzheimer's disease. *Free Radic Biol Med 23*(1), 134−147.

Marnett, L. J., Hurd, H. K., Hollstein, M. C., Levin, D. E., Esterbauer, H., & Ames, B. N. (1985). Naturally occurring carbonyl compounds are mutagens in Salmonella tester strain TA104. *Mutat Res 148*, 25−34.

Maser, E. (2006). Neuroprotective role for carbonyl reductase? *Biochem Biophys Res Commun 340*(4), 1019−1022.

McLellan, A. C., Phillips, S. A., & Thornalley, P. J. (1992). The assay of methylglyoxal in biological systems by derivatization with 1,2-diamino-4,5-dimethoxybenzene. *Anal Biochem 206*(1), 17−23.

McMahon, M., Itoh, K., Yamamoto, M., Chanas, S. A., Henderson, C. J., McLellan, L. I., et al. (2001). The Cap'n'Collar basic leucine zipper transcription factor Nrf2 (NF-E2 p45-related factor 2) controls both constitutive and inducible expression of intestinal detoxification and glutathione biosynthetic enzymes. *Cancer Res 61*(8), 3299−3307.

McMahon, M., Thomas, N., Itoh, K., Yamamoto, M., & Hayes, J. D. (2006). Dimerization of substrate adaptors can facilitate cullin-mediated ubiquitylation of proteins by a "tethering" mechanism: a two-site interaction model for the Nrf2-Keap1 complex. *J Biol Chem 281*(34), 24756−24768.

Miao, W., Hu, L., Scrivens, P. J., & Batist, G. (2005). Transcriptional regulation of NF-E2 p45-related factor (NRF2) expression by the aryl hydrocarbon receptor-xenobiotic response element signaling pathway: direct cross-talk between phase I and II drug-metabolizing enzymes. *J Biol Chem 280*(21), 20340−20348.

Misonou, Y., Takahashi, M., Park, Y. S., Asahi, M., Miyamoto, Y., Sakiyama, H., et al. (2005). Acrolein induces Hsp72 via both PKCdelta/JNK and calcium signaling pathways in human umbilical vein endothelial cells. *Free Radic Res 39*(5), 507−512.

Mitchell, D. Y., & Petersen, D. R. (1987). The oxidation of alpha-beta unsaturated aldehydic products of lipid peroxidation by rat liver aldehyde dehydrogenases. *Toxicol Appl Pharmacol 87*(3), 403−410.

Motohashi, H., & Yamamoto, M. (2004). Nrf2-Keap1 defines a physiologically important stress response mechanism. *Trends Mol Med 10*(11), 549−557.

Munch, G., Schinzel, R., Loske, C., Wong, A., Durany, N., Li, J. J., et al. (1998). Alzheimer's disease-synergistic effects of glucose deficit, oxidative stress and advanced glycation endproducts. *J Neural Transm 105*(4-5), 439−461.

Murphy, T. C., Amarnath, V., Gibson, K. M., & Picklo, M. J., Sr. (2003). Oxidation of 4-hydroxy-2-nonenal by succinic semialdehyde dehydrogenase (ALDH5A). *J Neurochem 86*(2), 298−305.

Nair, S., Xu, C., Shen, G., Hebbar, V., Gopalakrishnan, A., Hu, R., et al. (2006). Pharmacogenomics of Phenolic Antioxidant Butylated Hydroxyanisole (BHA) in the Small Intestine and Liver of Nrf2 Knockout and C57BL/6J Mice. *Pharm Res 23*(11), 2621−2637.

Nishinaka, T., & Yabe-Nishimura, C. (2005). Transcription factor Nrf2 regulates promoter activity of mouse aldose reductase (AKR1B3) gene. *J Pharmacol Sci 97*(1), 43−51.

O'Connor, T., Ireland, L. S., Harrison, D. J., & Hayes, J. D. (1999). Major differences exist in the function and tissue-specific expression of human aflatoxin B1 aldehyde reductase and the principal human aldo-keto reductase AKR1 family members. *Biochem J 343*(Pt 2), 487−504.

Ohsawa, I., Nishimaki, K., Yasuda, C., Kamino, K., & Ohta, S. (2003). Deficiency in a mitochondrial aldehyde dehydrogenase increases vulnerability to oxidative stress in PC12 cells. *J Neurochem 84*(5), 1110−1117.

Oppermann, U. (2007). Carbonyl reductases: the complex relationships of mammalian carbonyl- and quinone-reducing enzymes and their role in physiology. *Annu Rev Pharmacol Toxicol 47*, 293−322.

Pappa, A., Chen, C., Koutalos, Y., Townsend, A. J., & Vasiliou, V. (2003). Aldh3a1 protects human corneal epithelial cells from ultraviolet- and 4-hydroxy-2-nonenal-induced oxidative damage. *Free Radic Biol Med 34*(9), 1178−1189.

Parent, R. A., Paust, D. E., Schrimpf, M. K., Talaat, R. E., Doane, R. A., Caravello, H. E., et al. (1998). Metabolism and distribution of [2,3-14C] acrolein in Sprague-Dawley rats. II. Identification of urinary and fecal metabolites. *Toxicol Sci 43*(2), 110−120.

Picklo, M. J., Olson, S. J., Hayes, J. D., Markesbery, W. R., & Montine, T. J. (2001). Elevation of AKR7A2 (succinic semialdehyde reductase) in neurodegenerative disease. *Brain Res 916*, 229−238.

Picklo, M., Montine, T., Amarnath, V., & Neely, M. (2002). Carbonyl toxicology and Alzheimer's disease. *Toxicol Appl Pharmacol 184*, 187−197.

Prabhu, K. S., Reddy, P. V., Jones, E. C., Liken, A. D., & Reddy, C. C. (2004). Characterization of a class alpha glutathione-*S*-transferase with glutathione peroxidase activity in human liver microsomes. *Arch Biochem Biophys 424*(1), 72−80.

Rindgen, D., Nakajima, M., Wehrli, S., Xu, K., & Blair, I. A. (1999). Covalent modifications to 2'-deoxyguanosine by 4-oxo-2-nonenal, a novel product of lipid peroxidation. *Chem Res Toxicol 12*(12), 1195−1204.

Robertson, R. P. (2004). Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic islet beta cells in diabetes. *J Biol Chem 279*(41), 42351−42354.

Rushmore, T., Morton, M., & Pickett, C. (1991). The antioxidant response element. Activation by oxidative stress and identification of the DNA consensus sequence required for functional activity. *J Biol Chem 266*, 11632−11639.

Saletu, B., Semlitsch, H. V., Anderer, P., Resch, F., Presslich, O., & Schuster, P. (1989). Psychophysiological research in psychiatry and neuropsychopharmacology. II. The investigation of antihypoxidotic/nootropic drugs (tenilsetam and co-dergocrine-mesylate) in elderlies with the Viennese Psychophysiological Test-System (VPTS). *Methods Find Exp Clin Pharmacol 11*(1), 43−55.

Shamsi, F. A., Lin, K., Sady, C., & Nagaraj, R. H. (1998). Methylglyoxal-derived modifications in lens aging and cataract formation. *Invest Ophthalmol Vis Sci 39*(12), 2355−2364.

Short, D. M., Lyon, R., Watson, D. G., Barski, O. A., McGarvie, G., & Ellis, E. M. (2006). Metabolism of trans, trans-muconaldehyde, a cytotoxic metabolite of benzene, in mouse liver by alcohol dehydrogenase Adh1 and aldehyde reductase AKR1A4. *Toxicol Appl Pharmacol 210*, 163−170.

Siems, W., & Grune, T. (2003). Intracellular metabolism of 4-hydroxynonenal. *Mol Aspects Med 24*(4-5), 167−175.

Sies, H. (1997). Oxidative stress: oxidants and antioxidants. *Exp Physiol 82*(2), 291−295.

Sladek, N. E. (2003). Transient induction of increased aldehyde dehydrogenase 3A1 levels in cultured human breast (adeno)carcinoma cell lines via 5′-upstream xenobiotic, and electrophile, responsive elements is, respectively, estrogen receptor-dependent and -independent. *Chem Biol Interact 143–144*, 63−74.

Smith, M. A., Rudnicka-Nawrot, M., Richey, P. L., Praprotnik, D., Mulvihill, P., Miller, C. A., et al. (1995). Carbonyl-related posttranslational modification of neurofilament protein in the neurofibrillary pathology of Alzheimer's disease. *J Neurochem 64*(6), 2660−2666.

Sogawa, K., & Fujii-Kuriyama, Y. (1997). Ah receptor, a novel ligand-activated transcription factor. *J Biochem (Tokyo) 122*(6), 1075−1079.

Spycher, S., Tabataba-Vakili, S., O'Donnell, V. B., Palomba, L., & Azzi, A. (1996). 4-hydroxy-2,3-trans-nonenal induces transcription and expression of aldose reductase. *Biochem Biophys Res Commun 226*(2), 512−516.

Spycher, S. E., Tabataba-Vakili, S., O'Donnell, V. B., Palomba, L., & Azzi, A. (1997). Aldose reductase induction: a novel response to oxidative stress of smooth muscle cells. *FASEB J 11*(2), 181−188.

Srivastava, S., Chandra, A., Bhatnagar, A., Srivastava, S. K., & Ansari, N. H. (1995). Lipid peroxidation product, 4-hydroxynonenal and its conjugate with GSH are excellent substrates of bovine lens aldose reductase. *Biochem Biophys Res Commun 217*(3), 741−746.

Srivastava, S., Chandra, A., Ansari, N. H., Srivastava, S. K., & Bhatnagar, A. (1998). Identification of cardiac oxidoreductase(s) involved in the metabolism of the lipid peroxidation-derived aldehyde-4-hydroxynonenal. *Biochem J 329*(Pt3), 469−475.

Suzuki, K., Koh, Y. H., Mizuno, H., Hamaoka, R., & Taniguchi, N. (1998). Overexpression of aldehyde reductase protects PC12 cells from the cytotoxicity of methylglyoxal or 3-deoxyglucosone. *J Biochem 123*(2), 353−357.

Takagi, S., Baba, S., Iwai, N., Fukuda, M., Katsuya, T., Higaki, J., et al. (2001). The aldehyde dehydrogenase 2 gene is a risk factor for hypertension in Japanese but does not alter the sensitivity to pressor effects of alcohol: the Suita study. *Hypertens Res 24*(4), 365−370.

Takagi, S., Iwai, N., Yamauchi, R., Kojima, S., Yasuno, S., Baba, T., et al. (2002). Aldehyde dehydrogenase 2 gene is a risk factor for myocardial infarction in Japanese men. *Hypertens Res 25*(5), 677−681.

Thimmulappa, R. K., Mai, K. H., Srisuma, S., Kensler, T. W., Yamamoto, M., & Biswal, S. (2002). Identification of Nrf2-regulated genes induced by the chemopreventive agent sulforaphane by oligonucleotide microarray. *Cancer Res 62*(18), 5196−5203.

Thornalley, P. J. (1996). Pharmacology of methylglyoxal: formation, modification of proteins and nucleic acids, and enzymatic detoxification-a role in pathogenesis and antiproliferative chemotherapy. *Gen Pharmacol 27*(4), 565−573.

Thornalley, P. J. (2003). Glyoxalase I-structure, function and a critical role in the enzymatic defence against glycation. *Biochem Soc Trans 31*(Pt 6), 1343−1348.

Thornalley, P. J. (2005). Dicarbonyl intermediates in the maillard reaction. *Ann N Y Acad Sci 1043*, 111−117.

Thornalley, P. J., Langborg, A., & Minhas, H. S. (1999). Formation of glyoxal, methylglyoxal and 3-deoxyglucosone in the glycation of proteins by glucose. *Biochem J 344*(Pt 1), 109−116.

Touyz, R. M. (2004). Reactive oxygen species, vascular oxidative stress, and redox signaling in hypertension: what is the clinical significance? *Hypertension 44*(3), 248−252.

Townsend, A. J., Leone-Kabler, S., Haynes, R. L., Wu, Y., Szweda, L., & Bunting, K. D. (2001). Selective protection by stably transfected human ALDH3A1 (but not human ALDH1A1) against toxicity of aliphatic aldehydes in V79 cells. *Chem Biol Interact 130-132*(1-3), 261−273.

Toyokuni, S., Yamada, S., Kashima, M., Ihara, Y., Yamada, Y., Tanaka, T., et al. (2000). Serum 4-hydroxy-2-nonenal-modified albumin is elevated in patients with type 2 diabetes mellitus. *Antioxid Redox Signal 2*(4), 681−685.

Uchida, K., Kanematsu, M., Morimitsu, Y., Osawa, T., Noguchi, N., & Niki, E. (1998). Acrolein is a product of lipid peroxidation reaction. Formation of free acrolein and its conjugate with lysine residues in oxidized low density lipoproteins. *J Biol Chem 273*(26), 16058−16066.

van Muiswinkel, F. L., & Kuiperij, H. B. (2005). The Nrf2-ARE Signalling pathway: promising drug target to combat oxidative stress in neurodegenerative disorders. *Curr Drug Targets CNS Neurol Disord 4*(3), 267−281.

Vander Jagt, D., Robinson, B., & Taylor KK, H. L. (1992). Reduction of trioses by NADPH-dependent aldo-keto reductases. Aldose reductase, methylglyoxal, and diabetic complications. *J Biol Chem 267*(7), 4364−4369.

Vander Jagt, D. L., Kolb, N. S., Vander Jagt, T. J., Chino, J., Martinez, F. J., Hunsaker, L. A., et al. (1995). Substrate specificity of human aldose reductase: identification of 4-hydroxynonenal as an endogenous substrate. *Biochim Biophys Acta 1249*(2), 117−126.

Vasiliou, V., Pappa, A., & Estey, T. (2004). Role of human aldehyde dehydrogenases in endobiotic and xenobiotic metabolism. *Drug Metab Rev 36*(2), 279−299.

Warner, D. S., Sheng, H., & Batinic-Haberle, I. (2004). Oxidants, antioxidants and the ischemic brain. *J Exp Biol 207*(Pt 18), 3221−3231.

Webster, J., Urban, C., Berbaum, K., Loske, C., Alpar, A., Gartner, U., et al. (2005). The carbonyl scavengers aminoguanidine and tenilsetam protect against the neurotoxic effects of methylglyoxal. *Neurotox Res 7*(1-2), 95−101.

White, J. S., & Rees, K. R. (1984). The mechanism of action of 4-hydroxynonenal in cell injury. *Chem Biol Interact 52*(2), 233−241.

Williams, T. I., Lynn, B. C., Markesbery, W. R., & Lovell, M. A. (2006). Increased levels of 4-hydroxynonenal and acrolein, neurotoxic markers of lipid peroxidation, in the brain in Mild Cognitive Impairment and early Alzheimer's disease. *Neurobiol Aging 27*(8), 1094−1099.

Witz, G. (1989). Biological interactions of alpha,beta-unsaturated aldehydes. *Free Radic Biol Med 7*(3), 333−349.

Wood, P. L., Khan, M. A., Kulow, S. R., Mahmood, S. A., & Moskal, J. R. (2006). Neurotoxicity of reactive aldehydes: the concept of "aldehyde load" as demonstrated by neuroprotection with hydroxylamines. *Brain Res 1095*(1), 190−199.

Wu, L. (2006). Is methylglyoxal a causative factor for hypertension development? *Can J Physiol Pharmacol 84*(1), 129−139.

Yang, Y., Yang, Y., Trent, M. B., He, N., Lick, S. D., Zimniak, P., et al. (2004). Glutathione-*S*-transferase A4-4 modulates oxidative stress in endothelium: possible role in human atherosclerosis. *Atherosclerosis 173*(2), 211−221.