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Oxidative and reductive metabolism of lipid-peroxidation derived carbonyls

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Abstract

Extensive research has shown that increased production of reactive oxygen species (ROS) results in tissue injury under a variety of pathological conditions and chronic degenerative diseases. While ROS are highly reactive and can incite significant injury, polyunsaturated lipids in membranes and lipoproteins are their main targets. ROS-triggered lipid peroxidation reactions generate a range of reactive carbonyl species (RCS), and these RCS spread and amplify ROS-related injury. Several RCS generated in oxidizing lipids, such as 4-hydroxy *trans*-2-nonenal (HNE), 4-oxo-2-(E)-nonenal (ONE), acrolein, malondialdehyde (MDA) and phospholipid aldehydes have been shown to be produced under conditions of oxidative stress and contribute to tissue injury and dysfunction by depleting glutathione and other reductants leading to the modification of proteins, lipids, and DNA. To prevent tissue injury, these RCS are metabolized by several oxidoreductases, including members of the aldo-keto reductase (AKR) superfamily, aldehyde dehydrogenases (ALDHs), and alcohol dehydrogenases (ADHs). Metabolism via these enzymes results in RCS inactivation and detoxification, although under some conditions, it can also lead to the generation of signaling molecules that trigger adaptive responses. Metabolic transformation and detoxification of RCS by oxidoreductases prevent indiscriminate ROS toxicity, while at the same time, preserving ROS signaling. A better understanding of RCS metabolism by oxidoreductases could lead to the development of novel therapeutic interventions to decrease oxidative injury in several disease states and to enhance resistance to ROS-induced toxicity.

Keywords

Aldo-keto reductases; Aldose reductase; Lipid peroxidation; Metabolism; Reactive carbonyl species; Signaling; Toxicity

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Conflict of interest

The authors declare that there are no conflicts of interest.

1. Introduction

Pathological events such as tissue injury, ischemia, or metabolic stress lead to an increase in the production of reactive oxygen species (ROS) that can cause additional tissue damage. While low levels of ROS are readily detoxified by both enzymatic and non-enzymatic processes, excessive ROS production can overwhelm the intrinsic antioxidant capacity of the tissue and induce injury and dysfunction. Such ROS-mediated injury is a significant feature of several disease states such as diabetes, cardiovascular diseases, hypertension [1] and Alzheimer's disease [2]. Due to their high reactivity, ROS are relatively unspecific and react with nucleophilic centers in most biological molecules, however, polyunsaturated lipids that are constituents of lipoproteins and cell membranes are their most vulnerable targets. Polyunsaturated lipids have a high propensity for stabilizing free radicals and therefore, once attacked by free radicals, they undergo a series of autocatalytic reactions that produce a wide range of intermediates and other end products. Some of the most reactive and abundant of these are metastable carbonyl species that can further perpetuate the injury triggered by ROS production by reacting with nucleophilic cell constituents such as sulfhydryl side chain of polypeptides and amine groups in proteins, DNA and lipids [3–5].

In biological tissues, the major source of reactive carbonyl species (RCS) is the autoxidation of polyunsaturated fatty acids (PUFA) such as linoleic acid, linolenic acid, arachidonic acid, and ω -3 fatty acids. The basic mechanism of autoxidation has been extensively reviewed in the literature [6, 7]. Like ROS, RCS can react with multiple cell components by forming covalent adducts and thereby alter their structure and function or both. However, at low concentrations, RCS also trigger adaptive signaling and transcriptional changes in gene expression. The signaling role and the toxicological effects of RCS are regulated by several metabolic pathways that convert reactive carbonyls to less reactive metabolites. Nevertheless, excessive production and accumulation of RCS are characteristic features of ROS production. In this review, we highlight the role of RCS, the downstream products of ROS, as critical cell-damaging agents generated during normal metabolism and under various pathological conditions. In particular, we discuss the role of oxidoreductases and related enzymes in mediating RCS metabolism and in regulating ROS-related toxicity.

2. Major carbonyl compounds

The oxidation of biological lipids generates a large number of carbonyl compounds that includes unsaturated and saturated carbonyls and phospholipid carbonyls of variable structures. The specific carbonyls generated depend upon the nature of PUFA oxidized, the site of free radical attack and whether or not the PUFA was free or esterified. While the reactivity, signaling and metabolism of each of these carbonyls are of high mechanistic interest, the following carbonyls have been studied most extensively as general markers of oxidative stress and as model compounds for investigating the biological effects of RCS. Chemical structures of these major carbonyl species are shown in Fig. 1.

2.1. HNE

First discovered in 1960 [8], HNE (4-hydroxy *trans*-2-nonenal, Fig. 1A) is a major aldehydic byproduct of ω -6-PUFA peroxidation (arachidonic and linoleic acid are

precursors) during oxidative stress. The abundance of HNE within tissues is dependent not only on the rate of formation during lipid-peroxidation but also its metabolism, which is regulated by enzymes such as aldose reductase (AR), glutathione-S-transferases (GSTs), aldehyde dehydrogenases (ALDHs), and alcohol dehydrogenases (ADHs). Depending on its relative concentration, HNE can induce a range of hormetic effects in variety of cell types such as vascular endothelial cells (VECs) and smooth muscle cells (SMCs) through activation of signaling cascades and by the induction of phase II enzymes. In high doses, HNE exerts overt toxicity leading ultimately to cell necrosis or apoptosis. Free HNE concentrations in the plasma of healthy individuals are between 0.3 and 0.7 μM [9], but can increase significantly during aging [10] and in diseases associated with oxidative stress [11], when HNE levels can range from 1–20 μM . Because HNE is produced by the oxidation of unsaturated lipids by ROS and forms relatively stable covalent adducts with proteins and DNA, levels of HNE, HNE metabolites and adducts are frequently measured as indices of oxidative stress and increased ROS production. In response to increased ROS production, HNE is generated both by free and esterified PUFAs. *In vitro* incubation of vascular cells with PUFAs such as linoleic and arachidonic acid directly increases HNE formation [12]. HNE can also be generated from phospholipids associated with lipoproteins and cholesterol consumption thereby leading to a further increase in its production [13]. Once formed, HNE undergoes a series of reactions that can result in the formation of covalent adducts with lysine residues of lipoproteins [3, 4]. Because the formation of such adducts alters the charge distribution in the lipoprotein, the modified protein is recognized and engulfed by macrophages [14]. Such HNE-modified proteins have been demonstrated in atherosclerotic plaques [15] and the modification of lipoproteins by HNE and related RCS have been suggested to be the key initiating event in atherosclerotic lesion formation [16].

2.2. ONE

In addition to HNE, the 4-oxo-2-(E)-nonenal (ONE) is also an abundant product of lipid-peroxidation. ONE (Fig. 1B) is similar in structure to 4-HNE (Fig. 1A); however, it differs in reactivity as it can form stable ketoamide adducts [17–19]. Like HNE, it reacts with nucleophilic side chain of proteins and generates products in higher yields than HNE [20]. Interestingly, the lysine–histidine imidazolyl pyrrole cross-links appear to form with an unusual degree of efficiency, and may be responsible for the significant intermolecular cross-linking of proteins induced by ONE. In addition, ONE forms simple 4-ketoaldehyde Michael adducts that can exist as such or undergo Paal Knorr condensation [21]. The cross-link products are quite stable and have been detected in proteins [22, 23]. In the absence of an available residues such as lysine, the ONE-derived 4-ketoaldehydes can cyclize to give furans [24]. In fact, products that are formed by ONE by reacting with proteins can be found long after the modification is complete, without any further need for reductive stabilization. It was noticed that lysine-derived pyrrolinone, the Lys-derived 4-ketoamide, and the histidine–lysine imidazolylpyrrole cross-link are all important long-lived markers of protein modification by ONE. The most prevalent ‘early’ reaction of ONE with lysine residues is reversible formation of a Schiff base [25]. ONE-derived 4-ketoamide adducts have been observed in atherosclerotic lesions, suggesting a role in inflammation-related disease pathogenesis [26]. As a direct product of lipid-oxidation [27, 28] it arises independently from the same hydroperoxide precursor. Further, it seems that ONE is a more protein

reactive and cytotoxic agent than HNE and more reactive as a protein cross linking reagent than HNE [25]. Like HNE, ONE readily modifies DNA bases [29, 30].

2.3. Acrolein

Acrolein (Fig. 1C) is a reactive α , β -unsaturated aldehyde. It is generated in high quantities in cigarette smoke, cotton, wood, and coal smoke. Gasoline and diesel exhaust contain relatively higher acrolein levels [31]. Acrolein is also present in beverages and foods including coffee, alcohol, cheese, and donuts; and it has been shown that heating and cooking of fats, oils and sugars increases their acrolein content [31]. In addition, acrolein is generated endogenously by the degradation of polyamines or by myeloperoxidase [32] present in neutrophils. It is also generated by the oxidation of unsaturated lipids [33]. As a result, high levels of protein-acrolein adducts accumulate at sites of ROS production as well as during inflammation [31]. Like HNE, acrolein also readily forms covalent adducts with nucleophilic sites in proteins, lipids and DNA and acrolein-modified proteins have been detected in oxidized LDL [34] and human atherosclerotic lesions [35]. Indeed, the uptake of acrolein-modified LDL by the SR-A1 receptors (scavenger receptor class A type 1) has been implicated in the formation of foam cells, which constitute the characteristics fatty streaks of early atherosclerotic lesions in the affected arteries [36].

2.4. MDA

Malondialdehyde (MDA, Fig. 1D) is one of the most abundant byproducts of lipid-peroxidation and is generated via radical-initiated oxidative decomposition of PUFAs but it is much less reactive than HNE, ONE or acrolein. It is a frequently used biomarker for oxidative stress. Protein adducts of MDA have been detected in a variety of diseased tissues. The tissue antigens can serve as potential key candidates for use in characterizing immune responses relevant to atherogenesis [37, 38]. It has been recently reported that the levels of MDA-LDL in circulating immune complexes can predict the occurrence of myocardial infarction (MI) and acute cardiovascular events in patients with type 2 diabetes [39]. During lipid-peroxidation, unstable hydroperoxides resulting from peroxy radical-dependent chain reactions involving unsaturated fatty acyl moieties break down to smaller and more stable products like MDA or thiobarbituric acid-reactive substances. Hence, these products are considered as important oxidative stress markers. MDA-modified LDL has been shown to accumulate in atherosclerotic lesions, and a growing body of evidence indicates that oxidized LDL is involved in the pathogenesis of coronary artery disease (CAD), acute coronary syndrome (ACS), and vulnerable plaques [40].

2.5. Oxidized phospholipids

In addition to free aldehydes, peroxidation of phospholipids also generates carbonyls that remain esterified to the phospholipid backbone. The most commonly studied oxidized phospholipids are 1-palmitoyl-2-oxo-valeroyl-sn-glycero-phosphocholine (POVPC, Fig. 1E), and 1-palmitoyl-2-glutaroyl-sn-glycero-phosphocholine (PGPC) and 1-palmitoyl-2-(5,6-epoxyisopropane E2)-sn-glycero-phosphocholine (PEIPC) [41]. These phospholipids are derived from the oxidation of 1-palmitoyl-2-arachidonoyl-glycerol-3-phosphocholine (PAPC), one of the most abundant phospholipids in LDL and are recognized by scavenger receptors. They also form covalent adducts with amine side chains of proteins and trigger a

number of signaling pathways leading to inflammation and increased cell adhesion. Previous studies have shown that aortae obtained from rabbits fed an atherogenic diet contained higher levels of POVPC, PGPC and PEIPC than those from rabbits fed with the control diet [42]. The levels of oxidized phospholipids bound to lipoproteins correlated with the extent of angiographically-documented atherosclerotic disease [43] indicating that oxidized phospholipids may be involved in the formation of atherosclerotic lesions [44].

3. Metabolism of carbonyls

Several enzymatic and non-enzymatic processes detoxify RCS generated in tissues. These biological processes protect cells and tissues from the harmful effects of RCS and thereby minimize the secondary effects of ROS generation. Increasing RCS concentrations lead to an imbalance between oxidants and antioxidants, and exceeding a certain threshold, can potentially damage a host of biomolecules leading to disturbances in cellular homeostasis (Fig. 2). Of the several processes involved in RCS metabolism oxidoreductases play an important role in RCS detoxification. These oxidoreductases act in concert with other enzymatic pathways such as those catalyzed by glutathione S-transferases (GSTs) and cytochrome P450 enzymes. Collectively, these metabolic pathways prevent tissue accumulation of RCS or RCS-modified proteins. Major oxidoreductases involved in RCS metabolism are discussed individually below:

3.1. Aldo-keto reductases

The aldo-keto reductases (AKRs) superfamily is comprised of several structurally related oxidoreductases. These enzymes are involved in the synthesis of endogenous compounds as well as xenobiotic detoxification. The active site of AKRs is located at the C-terminus of the protein and is optimized for high-affinity interaction with pyridine nucleotides in the absence of a canonical Rossmann fold. The AKRs adopt a (α/β)8-barrel or triphosphate isomerase (TIM) barrel motif, which provides sturdy scaffolding required for the binding of a wide range of structurally-diverse carbonyl substrates. AKRs are an integral part of eubacteria, fungi, plants, and vertebrates [45]. Using pyridine nucleotides as cofactors, they catalyze a wide range of reactions involved in the metabolism of carbohydrates, steroids, glycosylation end products, and other metabolites and xenobiotics. The substrate specificity is dependent on three flexible loops (A, B, and C) [46]. Three families of the AKR superfamily are comprised of mammalian proteins (AKR1, AKR6 and AKR7) [45] and are discussed individually in the following sub-sections.

3.1.1. AKR1A1—The enzyme aldehyde reductase is encoded by the AKR1A1 gene [47, 48]. It is involved in the reduction of biogenic and xenobiotic aldehydes and is present in most tissues [49, 50]. Multiple alternatively spliced transcript variants of this gene exist, all encoding the same protein. AKR1A1 is also known as mevaldate reductase and it reduces DL-glyceraldehyde to glycerol [51, 52]. Further, it has been shown to play an important role in ascorbic acid biosynthesis in mammalian species. The enzyme catalyzes the reduction of D-glucuronic acid and D-glucurono- γ -lactone during ascorbic acid biosynthesis and genetic deletion of this enzyme in mice results in severe osteopenia and spontaneous fractures due to ascorbic acid deficiency [53, 54]. Humans do not synthesize ascorbic acid,

however, recent evidence suggests that AKR1A1 may be involved in RCS detoxification. In support of this role it was shown that overexpression of AKR1A1 in mouse embryonic fibroblasts (MEFs) increased their resistance to acrolein-induced cell death. In addition, acrolein-induced protein modification and ER stress were also attenuated in AKR1A1 transgenic MEFs [55]. Conversely, it has also been reported that knock-down of AKR1A1 in 1321N1 cells increased their sensitivity to H₂O₂ and HNE-induced cytotoxicity [56]. Despite this evidence, it remains unclear whether AKR1A1 mediated protection is due to direct RCS reduction or via some other indirect mechanism(s). The K_m of the enzyme for acrolein is rather high (2.4 mM) suggesting that the enzyme may not be as efficient in reducing acrolein as other enzymes (Table 1). Moreover, knockdown of AKR1A1 also increased ROS levels [55], suggesting that the enzyme may be involved in other redox-regulated activities and that it protects cells against oxidative stress by mechanism(s) other than direct RCS reduction.

3.1.2. AKR1B1—AKR1B1 or human aldose reductase (AR) is one of the most extensively studied members of the AKR superfamily [47, 57]. AKR1B1 has closely related relatives, AKR1B3; mouse aldose reductase and AKR1B5; bovine aldose reductase. Aldose reductases use nicotinamide coenzymes NADP(H) in the oxidation and reduction of endogenous metabolites such as aldehydes, ketones, monosaccharides, steroids, prostaglandins, bile acids and xenobiotic substrates. Like other members of the AKR superfamily, AR has a (α/β) 8-barrel motif that forms a unique AKR domain for binding pyridine nucleotides with high affinity. The substrate binding pocket of AR has a rather open conformation that can accommodate relatively a large range of carbonyl compounds [58–62]. AR has been shown to catalyse the reduction of HNE and related aldehydes as well as their glutathionyl conjugates [63, 64]. In addition to the reduction of free aldehydes such as HNE and acrolein (Table 1), AR is also an efficient catalyst for the reduction of POVPC [65] and related phospholipid aldehydes that are generated from the oxidation of phosphatidylcholine, phosphatidylethanolamines and phosphatidylserine [66]. The role of AR in the metabolism and removal of RCS is supported by several lines of evidence confirming that AR is induced during oxidative stress and that pharmacological inhibition or genetic deletion of the enzyme increases RCS accumulation and the abundance of RCS-modified proteins in diseased tissues. For instance, inhibition of AR by Sorbinil or Zopolrestat, led to an increase in the accumulation of lipid-peroxidation products in mice grafted with inflamed temporal arteries. Similarly, in a mouse model of giant cell arteritis, AR was upregulated in arteritic lesions, which were confined to areas of tissue destruction. Mice treated with AR inhibitors had a threefold increase in apoptotic cells in the arterial wall along with simultaneous increase in the HNE-adducts [67]. In agreement with an important role of AR in RCS metabolism and detoxification, it has been shown that exposure to RCS such as HNE results in rapid induction of AR synthesis in monocytes [67]. These observations suggest that AR is induced upon oxidative stress and that inhibition of AR increases RCS accumulation. The expression of AR is also increased upon tissue injury induced by balloon angioplasty [68] as well as in atherosclerotic lesions. That pharmacological inhibition or genetic deletion of AR increases atherosclerotic lesion formation and the accumulation of protein-HNE adducts in the lesions suggests that detoxification of HNE via AR may be an important step that protects against atherosclerotic

lesion formation [16]. These observations are also consistent with the idea that RCS such as HNE and POVPC contribute to the formation of atherosclerotic lesions as an increase in the metabolism via AR delayed atherogenesis. A similar role of RCS could be postulated in the formation of neointimal lesions as treatment with AR inhibitors has been shown to prevent neointimal lesions in balloon-injured arteries [69].

Interestingly, treatment with AR inhibitors also attenuates the activation of the inflammatory transcription factor NF- κ B in the restenotic lesions, suggesting that AR and potentially the metabolism of RCS via AR may be an important regulator of inflammation in response to injury. Developing on these observations, it has been shown that when transported into cells as esters both glutathione-4-hydroxynonenal (GS-HNE) and glutathionyl-1,4 dihydroxynonene (GS-DHN) activate NF- κ B, while treatment with AR inhibitors prevented GS-HNE induced NF- κ B activation. However, the effect of GS-DHN was not prevented by AR inhibitors [70] suggesting that reduction of GS-HNE to GS-DHN by AR is essential for NF- κ B activation. Importantly, these observations raise the possibility that metabolism of lipid- peroxidation products such as HNE via AR could lead to the development of metabolic products that might be important danger signal(s) or signaling molecule(s) which can potentially regulate inflammatory responses (Fig. 2).

3.1.3. AKR1B7—AKR1B7, also known as the mouse vas deferens protein, is expressed in the vas deferens [71], adrenal cortex [72, 73], and the ovarian theca cells [74]. It is also expressed in the intestine, eye, kidney and liver in lesser quantities [75]. AKR1B7 is regulated by the androgen receptor, adrenocorticotrophic hormone and human chorionic gonadotropin, respectively. Two major substrates of the enzyme have been identified: isocaproaldehyde and HNE (Table 1) [76]. Isocaproaldehyde is formed in the adrenal cortex and the ovarian theca cells as a by-product of steroidogenesis and is hypothesized to be the primary function of AKR1B7 in steroid-synthesizing tissues. The vas deferens, however, is not a known site of steroidogenesis. The role of AKR1B7 in the vas deferens has been investigated by several investigators and current literature suggests that AKR1B7 detoxifies and removes acrolein (Table 1), derived primarily from the catabolism of the polyamines, spermine and spermidine, but not lipid-peroxidation [75]. Interestingly, AKR1B7 is also present in white adipose tissue [77] and is associated with a higher ratio of pre-adipocytes vs adipocytes, where it might be linked to an inhibition of adipogenesis. AKR1B7 has an ortholog in rats; AKR1B14, and shares up to 87% sequence identity. Like AKR1B7, AKR1B14 is abundant in the adrenal gland, however unlike AKR1B7; AKR1B14 is also expressed in the female rat liver. The expression of AKR1B14 is sexually differentiated, and is regulated by growth hormone. The kinetic constants for AKR1B14 for substrates such as HNE closely mimic those for AKR1B7. In addition, AKR1B14 metabolizes furfural and 5-hydroxyfurfural while being unable to reduce D-glucose and D-xylose. ONE has been identified as a major substrate for AKR1B14 [78, 79], which is a particularly toxic byproduct of lipid-peroxidation (vide supra).

3.1.4. AKR1B8—Previously named as murine fibroblast growth factor related protein (FR-1), AKR1B8 is an AR-like enzyme that is structurally related to other members of the ARK1B family members. It was detected in testis, heart, adrenal glands, intestine and liver

[80] and was subsequently shown to be capable of reducing several different substrates [81]. Mouse AKR1B8 associates with murine acetyl-CoA carboxylase- α and mediates fatty acid synthesis in colon cancer cells [82]. *In vitro*, the purified enzyme is capable of catalyzing the reduction of both free and phospholipid bound aldehydes [66], therefore AKR1B8 could act as a physiological scavenger of toxic RCS (Table 1) derived from lipid-peroxidation in several tissues where it is expressed [80]. Because its expression is induced by growth factors, the enzyme may be one potential mechanism, by which growth factors enhance resistance to oxidative injury and cell death.

3.1.5. AKR1B10—Human AKR1B1 and AKR1B10 are similar in their amino acid sequences, stereo structures, and substrate specificity, but they exhibit distinct tissue distributions. AKR1B10 is primarily expressed in the gastrointestinal tract and adrenal gland, whereas AKR1B1 is ubiquitously present in all tissues/organs, suggesting differences in their biological functions. A comparison of the kinetic activities of AKR1B1 and AKR1B10 with α , β -unsaturated carbonyl compounds including acrolein, crotonaldehyde, HNE, *trans*-2-hexenal, and *trans*-2,4-hexadienal showed that AKR1B10 had much better enzyme activity and turnover rates than AKR1B1 (Table 1). Moreover, both enzymes showed significant catalytic activity with glutathione-conjugated carbonyl compounds, although AKR1B1 appeared to be more active. These results suggest that AKR1B10 is more effective in eliminating RCS, but AKR1B1 seems more important for the detoxification of glutathione-conjugated carbonyl compounds [83]. However, the best substrates for AKR1B10 are retinals [58] but the enzyme may also be involved in the metabolism of biogenic aldehydes [84] as well as the removal of toxic aldehydes, in general.

3.1.6. AKR1C1—AKR1C1 regulates progesterone action by converting the hormone into its inactive metabolite 20- α -hydroxyprogesterone and has been shown to activate polycyclic aromatic hydrocarbon trans-dihydrodiols to redox-cycling o-quinones. AKR1C1 and AKR1C2 (bile acid-binding protein), a near identical enzyme, with only a single conservative amino acid substitution in its active site, can reduce HNE and other α , β -unsaturated aldehydes that are produced during lipid-peroxidation with high catalytic efficiency. Kinetic studies showed that AKR1C1 reduced HNE with K_{cat}/K_m values similar to that for 20- α -hydroxysteroids (Table 1). AKR1C1 is induced by oxidative stress and by agents that deplete glutathione. Several hydroxysteroid dehydrogenases of the AKR1C subfamily have been shown to catalyze the reduction of HNE with higher activity than aldehyde reductase (AKR1A1). Isoform-specific RT-PCR revealed that exposure of HepG2 cells to HNE resulted in elevated levels of AKR1C1 mRNA implying that HNE induces its own metabolism to counter oxidative stress [85].

3.1.7. AKR1C3—AKR1C3 is a key steroidogenic enzyme [86, 87] that catalyzes the reduction of prostaglandin (PG) D₂, PGH₂ and phenanthrenequinone (PQ), and the oxidation of 9- α , 11- β -PGF₂ to PGD₂. It also plays an important role in the pathogenesis of allergic diseases such as asthma, and has a role in controlling cell growth and/or differentiation. Notably, AKR1C3 gene shares high sequence identity with other gene members encoding various isoforms. AKR1C3 is overexpressed in prostate cancer and is associated with the development of castration-resistant prostate cancer. Therefore, its

overexpression may serve as a potential biomarker for prostate cancer progression [88]. In a recent study using gene-specific RNA interference (RNAi) in neuroblastoma SH-SY5Y cells, it was observed that AKR1C3 contributed to HNE reduction and its knockdown lowered the IC₅₀ of HNE from 1.2 to 0.5 μ M. In addition, it was shown that pretreatment of cells with sub-lethal concentrations of HNE or methylglyoxal led to a significant increase in IC₅₀ when cells were later exposed to higher concentrations of toxic aldehydes. The IC₅₀ for methylglyoxal increased from 410 μ M to 1.9 mM, and the IC₅₀ for HNE increased from 120 to 690 nM respectively. It was also shown that AKR1C3 could be induced 8-fold in SH-SY5Y cells by treatment with sub-lethal concentrations of methylglyoxal, and 5-fold by HNE treatment. Furthermore, it was found that this adaptive response could also be induced using the chemoprotective agent tert-butyl hydroquinone (t-BHQ), and that this also evoked an increase in the expression and activity of AKR1C3. Based on these results, it was proposed that the reduction of aldehydes to alcohols by AKRs may represent an important detoxification route within neuronal cells further highlighting the potential for the interventional upregulation of AKRs via non-toxic derivatives or natural compounds representing a novel therapeutic approach towards the detoxification of aldehydes with the aim of halting the progression of aldehyde-dependent neurodegenerative diseases [89].

3.1.8. AKR6—In mammals, AKR6 family is comprised of three different genes Kv β 1–3 encoding proteins that serve as β -subunits of the potassium gated voltage channels. These subunits regulate the gating properties of the channel and assist in channel trafficking and membrane localization [90]. They contain the conserved NADP(H) binding domain and exist as tetramers [91]. As a result of the isomerization steps involved in cofactor binding a large number of NADP(H)-occupancy states can exist in the tetramers of AKR6A3, AKR6A5, and AKR6A9 which may fine tune channel opening. NADP(H) binding appears to be essential for the optimal interaction between Kv α and β subunits and for Kv β -induced inactivation of Kv currents [92] and for the differential regulation of Kv currents by oxidized and reduced cofactor [93]. These findings suggest that channel opening may be redox-regulated. In contrast to the splice variants described for the AKR1 family, three splice variants of AKR6A3 (AKR6A3-001, AKR6A3-002, and AKR6A3-004) have been detected as expressed proteins of 401 amino acids in length AKR6A3.1; 408 amino acids in length AKR6A3.2; and 419 amino acids in length AKR6A.3. In addition, seven splice variants have been detected for AKR6A5 which give rise to two different proteins AKR6A5.1 and AKR6A5.2 of 367 amino acids and 353 amino acids in length, respectively.

It has been recently shown that Kv β 2 catalyzes the reduction of a broad range of compounds such as aromatic carbonyls, electrophilic aldehydes and prostaglandins [94]. Kinetic studies with rat Kv β -2 revealed that the chemical step is largely responsible for the rate-limitation but nucleotide exchange could also contribute to the overall rate. Kv β 2 is the only known AKR that binds to an ion channel; the Kv channel, possibly allowing a role for Kv β 2 as a sensor of oxidative changes. This is further supported by evidence showing that nucleotide exchange occurs on a seconds-to-minutes time scale thus setting the upper limit for the maximal possible rate of catalysis by Kv β -2. Slow cofactor exchange is consistent with the role of the β -subunit as a metabolic sensor implicated in the tonic regulation of potassium currents. Further work using electrospray ionization mass spectrometric analysis showed

that Kv β 2 catalyzed the NADP(H)-dependent reduction of several products of 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine (PAPC), including 1-palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphorylcholine (POVPC), 1-palmitoyl-2-(epoxycyclopentenone)-sn-glycero-3-phosphorylcholine (PECPC), 1-palmitoyl-2-(5,6)-epoxyisoprostane E2-sn-glycero-3-phosphocholine (PEIPC). Time course analysis revealed that the reduced products reached significant levels for ions at m/z 594/596 (POVPC/PHVPC), 810/812 (PECPC/2H-PECPC) and 828/830 (PEI-PC/2H-PEIPC) in the oxPA-PC +Kv β 2 mixture. These results suggested that Kv β could serve as a sensor of lipid-oxidation via its catalytic activity and thereby alter Kv currents under conditions of oxidative stress [95, 96].

3.1.9. AKR7A1—It is also known as rat aflatoxin aldehyde reductase and is considered to be the founder member of the AKR7A subfamily [97]. Several mammalian enzymes related to AKR7A1 have also been identified and include human AKR7A2 and AKR7A3, and mouse AKR7A5 [98–102]. Initial studies conducted demonstrated that AKR7A1 can reduce a variety of carbonyl compounds however it does not participate in sugar metabolism [103]. Furthermore, it was demonstrated that AKR7A1 is capable of detoxifying aflatoxin B1 (AFB1), a hepatocarcinogen [104, 105]. Analogous to several aldo-keto reductases, AKR7A1 enzyme has also been shown to catalyze the reaction between reactive aldehydes including α -unsaturated carbonyl compounds to alcohols [103]. Specifically, the role of AKR7A1 in the cytoprotection against acrolein has been studied in animal models and along with cell viability and mutagenicity studies showed an increase in protection of cells producing AKR7A1 [106].

3.1.10. AKR7A2—It was identified as a human brain succinic semialdehyde reductase and is responsible for the reduction of succinic semialdehyde to gamma-hydroxybutyrate [107]. AKR7A2 is present in several tissues including brain, liver, and kidney [108]. Accumulation of AKR7A2 in specific regions of the brain in Alzheimer's disease has been shown [109]. The enzyme has been linked in the metabolism of lipid-peroxidation-derived carbonyls. In an order to assess endogenous cellular protection against oxidants and aldehydes in neurodegenerative diseases, the role of AKR7A2 in protecting human astrocytoma 1321N1 cells against oxidant and aldehyde toxicity was investigated using siRNA gene silencing technology. Results showed that the enzyme was responsible for part of the intrinsic protection against aldehydes and oxidants [110]. Treating cells with sub-lethal concentrations of an oxidant or placing cells under aldehyde stress or with the natural coumarone 7-hydroxycoumarin (umbelliferone) revealed that endogenous resistance to aldehydes and oxidants can be induced significantly. The basis of the inducible protection by 7-hydroxycoumarin was shown to be associated with induction of AKR7A2 [110]. AKR7A2 enzyme is catalytically active towards aldehydes arising from lipid-peroxidation. Based on above properties of the enzyme, a transgenic mammalian cell model was developed in which AKR7A2 was overexpressed in V79-4 cells and was used to evaluate the ability of AKR7A2 in providing resistance against toxic aldehydes. Findings showed that AKR7A2 offered increased resistance to the cytotoxicity of HNE and modest resistance to the cytotoxicity of *trans*, *trans*-muconaldehyde (MUC) and methylglyoxal but provided no protection against crotonaldehyde and acrolein. Cells expressing AKR7A2 were also found

to be less susceptible to DNA damage, showing a decrease in mutation rate caused by HNE compared to control cells [111]. Together, it appears that AKR7A2 is involved in cellular detoxification pathways and may play a defensive role against oxidative stress [111]. However, the efficacy of the enzyme in protecting against RCS toxicity *in vivo* has not been proven so far.

3.1.11. AKR7A5—It is a mouse aldo-keto reductase which is 78% identical to rat AKR7A1 and 89% identical to human AKR7A2. AKR7A5 has a wide substrate specificity including several aldehydes and diketones. Although AKR7A5 displays low activity against α/β -unsaturated carbonyls, a detoxifying effect has been described [97]. Li et al used V79-4 Chinese hamster lung fibroblasts, transfected with mouse AKR7A5 to demonstrate the protective capacity of AKR7A5 against HNE. When treated with sub-lethal doses of HNE, control cells showed an increase in the frequency of mutations by 1.5 times whereas the V79-AKR7A5 cells showed no increase in mutations. It was also demonstrated that the number of spontaneous mutations in AKR7A5 was lower than control cells even without treatment with HNE suggesting decreased sensitivity to endogenous mutations [112]. In a follow up study by Ellis *et al.*, a direct protective effect of AKR7A5 against oxidative stress induced using H₂O₂ and menadione was observed [113].

3.2. Aldehyde dehydrogenases

The aldehyde dehydrogenase (ALDH) family of enzymes metabolizes a wide variety of aldehydes into their carboxylic acids. ALDH are NAD(P)-dependent enzymes grouped on the basis of their evolutionary divergence. Members belonging to the same family share >40% amino acids as well as those belonging to the same subfamily share >60% amino acid homology [114–117]. These enzymes are highly conserved from bacteria to humans. Twenty one gene families have been identified in eukaryotes [115] and at least 17 genes encoding members of these enzymes have been found in humans. The human gene families have been arranged into 10 families and 13 sub-families [118]. The ALDH superfamily is polymorphic in its role, extending from increased levels in cancer of breast, to the cancers of lung and ovaries [119–122].

3.2.1. ALDH1—Both ALDH1 and ALDH2 are 54 kDa tetrameric proteins while ALDH3 is a 54 kDa dimeric protein. ALDH1 is encoded by the chromosome 9q21 and is best known for its conversion of retinal to retinoic acid. ALDH1A1 expression in human tissues can be classified into 3 groups; tissues with absent/limited expression of ALDH1A1 (breast and lung) tissues with weak ALDH1A1 expression (colon or gastric epithelium) and finally tissues with extensive ALDH1A1 expression (liver and pancreas) [121]. In the epithelium of the human lens there is a high level of ALDH1A1 and a low level of ALDH3A1, thus a functional role of ALDH1A1 in the detoxification of aldehydes generated through the action of UV light has been described [123]. The correlation between ALDH1A1 and ALDH3A1 in the prevention of oxidative stress induced cataractogenesis has also been investigated in human lens epithelial cells showing an increase in oxidation induced opacification in the presence of ALDH inhibitors. Furthermore, ablation of ALDH1A1 led to a decrease in the ability of human lens epithelial cells to oxidize HNE, as measured by cell viability and apoptosis assays [124]. In human lens epithelial cells, kinetic values for ALDH1A1 were

demonstrated to be 4.8 μM and 3.5 μM for HNE and MDA respectively [125]. Numerous studies have detected a correlation between ALDH1 and carcinomas [120, 126–130]. ALDH1 activity has been studied in transgenic mice in an order to use it as a marker for cancer detection. Interestingly, a higher ALDH activity is detected in stem cells and progenitor cells and it has been hypothesized that such activity can also be detected in cancer stem cells [121]. In lung cancers and leukemia cells an overexpression of ALDH1A1 was described [131] whereas in cyclophosphamide treated breast cancer patients, a high ALDH1A1 was revealed in metastatic tumor cells that survived [132] thereby suggesting a potential role of ALDH1A1 in the resistance of cells to chemotherapy. Overexpression of ALDH1A1 in lung cancer cells and leukemia cells led to an increased proliferation and drug resistance [131]. Whereas breast cancer patients treated with cyclophosphamide revealed high levels of ALDH1A1 in metastatic tumor cells that survived exposure to cyclophosphamide and in metastatic tumors that did not respond to cyclophosphamide treatment [132], demonstrating further a causal role of ALDH1A1 in developing chemo resistance.

3.2.2. ALDH2—ALDH2 is located in the mitochondrial matrix and has been extensively studied within the context of several important human pathologies such as cardiovascular diseases, diabetes, neurodegenerative diseases, stroke, and cancer [133]. Recent studies suggested that ALDH2 dysfunction is associated with Fanconi anemia, pain, osteoporosis, and aging [134]. Furthermore, an ALDH2 inactivating mutation (ALDH2*2) was found to be the most common single point mutation in humans responsible to alcohol intolerance, and epidemiological evidence suggests a strong correlation between this inactivating mutation and increased propensity for common human pathologies [135]. In affected individuals, a lysine residue replaces a glutamate (E487K) of ALDH2 [136]. Homozygous individuals with the mutant allele have almost no ALDH2 activity, and those heterozygous for the same mutation have reduced activity. The mutation related deficiency is manifested by slow acetaldehyde removal with low alcohol tolerance [137, 138]. In animal models of myocardial or cerebral ischemia/reperfusion (I/R) injury, the accumulation of toxic aldehydes, such as HNE and MDA, is prevented by ALDH2; consequently ALD2 is believed to play a major role in the clearance of toxic aldehydes. Interestingly, a newly identified ALDH2 activator, Alda-1 (Alda-1 is an agonist and a chemical chaperone for the common human aldehyde dehydrogenase 2 variant) demonstrated beneficial effects on heart and brain I/R injuries [139]. Thus, ALDH2 might be a potential drug target for protection of the heart or brain from I/R injuries. In addition to causing general cell toxicity, aldehydes such as HNE have also been shown to cause pain and therefore their metabolism via ALDH2 and other oxidoreductases could regulate nociception. In support of this concept, it has been recently shown that knock-in of ALDH2*2 in mice heighten nociception, which could be attenuated upon treatment with Alda-1, suggesting that treatment with Alda-1 could increase pain tolerance in individuals carrying the ALDH2 point mutation [140].

3.2.3. ALDH3—The subfamily of ALDH3 enzymes such as ALDH3A1 are encoded by the chromosome 17p11.2 [141] and have been reported to have multiple functions including the maintenance of hematopoietic stem cells, protection of the eye from UV radiation [142], regulating cell proliferation and lipid-peroxidation mediated growth inhibition [143], in

attenuating ROS induced protein modification [144], preventing DNA damage and apoptosis [145] and providing resistance against chemotherapeutic drugs [143, 146–152]. Since ALDH3A1 is expressed abundantly in corneal epithelium [153] it is considered to play a role in maintaining the corneal function of light transparency and refraction [154]. In previous studies, ALDH3A1 expression has been studied in V79 cells, where an increase in the expression of ALDH3A1 led to a dramatic decrease in HNE adducts formation and apoptosis [155, 156]. The kinetic parameters for ALDH3A1 with respect to HNE metabolism were found to be in the range of $45 \pm 18 \mu\text{M}$ [153]. Furthermore, in comparative studies, it was discovered that medium chain aldehydes were good substrates for ALDH3A1 but were surprisingly poor substrates for ALDH1A1. In the same study, MDA was identified to be a poor substrate for both enzymes [156]. In agreement with its role in RCS detoxification, it has been demonstrated that hepatoma cells are protected from lipid-peroxidation due to an abundance of ALDH3 activity, thus these cells are more likely to be resistant to drugs exerting their anticancer effect through the induction of lipid-peroxidation [143]. Particularly relevant to their detoxifying role is the protection conferred by ALDH3A1 to airway epithelial cells against cigarette smoke as an increase in the ALDH3A1 gene expression, protein content and enzyme activity has been found to be increased in smokers compared with non-smokers [143, 157–159]. Similarly, ALDH enzymes are upregulated in human bronchial epithelial cells exposed to cigarette smoke extract. Multiple isoforms were studied and it was found that the ALDH3A1 enzyme displays the most drastic upregulation, though ALDH1A3, ALDH2, ALDH3A2, ALDH3B1, ALDH5A1, ALDH19A1, ALDH16A1 and ALDH18A1 were also upregulated [152]. Besides its role in lipid-peroxidation, an increase in ALDH3A1 has been shown to be associated with prostate carcinoma where increased level of ALDH3A1 correlated with an increased severity of prostate cancer [160].

3.3. Alcohol dehydrogenases

The family of alcohol dehydrogenases (ADHs) consists of up to 20 distinct isoenzymes and their distributions vary by tissue, such that the relative activities of different ADH classes vary from one tissue to another. ADHs have been shown to have multiple metabolic roles as members in this family metabolize a wide variety of substrates including ethanol, retinol, other aliphatic alcohols, hydroxysteroids, and lipid-peroxidation products [161]. ADHs function as dimers, which arise from association of eight distinct subunits into active dimeric molecules. Subunits hybridize within but not between classes. There are three types of subunit in class I – α , β , and γ . All known isoenzymes (homodimeric and heterodimeric) have been isolated and purified to homogeneity [162, 163]. Kinetic studies of the isoenzymes demonstrated marked differences in substrate and inhibitor specificities and catalytic activities [161, 164]. For example, the K_m values for NAD^+ and ethanol vary up to 1,000-fold across isoenzymes. A number of gene loci encoding for human ADHs have been characterized [165, 166]. Many classes of ADHs have been identified in humans primarily based upon their physical properties, structure, and tissue distributions. Human ADHs have different substrate specificity and tissue localization for each class, participating in different organs and tissues for distinct physiological functions.

In rats, class I and IV actively reduced HNE, 2-hexenal, and hexanal. However, class III showed poor activity with these aldehydes. Class IV exhibited the best kinetic values, which suggests a role for this enzyme in the elimination of the cytotoxic aldehydes in tissues that are susceptible to lipid-peroxidation, such as skin, cornea, and mucosa of the respiratory and digestive tracts, which is where the class IV is mainly localized. These classes are active with omega-hydroxy fatty acids, suggesting that most of them are involved in the physiological oxidation of these biomolecules in the rat tissues. Kinetic studies support the view that oxidation of omega-hydroxy fatty acids is a physiological function for class III, in addition to its role as formaldehyde dehydrogenase. Classes I and IV are active in retinol oxidation and retinal reduction. Class IV also plays a crucial role in the generation of retinoic acid in epithelia, where this metabolite is involved in development and cell differentiation [161].

Studies with a transgenic mouse model designed to examine the impact of enhanced acetaldehyde exposure on cardiac functions via cardiac-specific overexpression of ADH after 4% alcohol intake for 8 weeks revealed that ADH mice consuming ethanol exhibited elevated blood ethanol/acetaldehyde, cardiac acetaldehyde, and cardiac hypertrophy compared with non-ethanol-consuming mice [167]. Myocytes from ethanol-fed mice showed significantly depressed peak shortening, velocity of shortening/relengthening, rise of intracellular Ca^{2+} transients, and sarco(endo)plasmic reticulum Ca^{2+} load associated with similar duration of shortening/relengthening compared with myocytes from control mice. Interestingly, the ethanol-induced mechanical and intracellular Ca^{2+} defects were exacerbated in ADH myocytes compared with the control group except velocity of shortening. The lipid-peroxidation end products MDA and protein carbonyl formation were significantly elevated in both livers and hearts after chronic ethanol consumption, with the cardiac lipid and protein damage being exaggerated by ADH transgene. These results suggested that increased cardiac acetaldehyde exposure due to ADH transgene may play an important role in cardiac contractile dysfunctions associated with lipid and protein damage after alcohol intake [167].

Class I ADHs are widespread but show significant variability in activities across different tissues [168]. Under normal physiological conditions, class I alcohol dehydrogenases (ADH 2) mediate the majority of hepatic ethanol oxidation. ADH2 exhibits high activity for ethanol oxidation and plays a major role in oxidative ethanol degradation [169].

Polymorphic variants, including a common functional variant of class I ADHs have also been identified [170, 171]. These variants are known to exhibit distinct kinetic properties [172]. More often, a common variant results from a single nucleotide polymorphism [172] and the resultant variants may influence the risk and severity of alcoholism [173]. Class II ADHs have limited tissue distributions, whilst class III ADHs are abundant but show little variability in their activities [168]. Pancreatic tissue has the highest activity of all ADH isoenzymes tested and it was about 7 times higher than the activity of class I but the activities of II and IV were low. Furthermore, the relative activity of ADHs within a given tissue may vary by gender. For example, ADH isoenzyme activities have been measured in the livers of male and female patients and total ADH and class I and II activities were found to be significantly higher in males than in females [174, 175].

4. Metabolic regulation of the biological effects of RCS

Lipid-peroxidation is associated with multiple diseases via formation of toxic compounds from oxidized lipids. The toxicity of these oxidized lipids has been linked to the generation of secondary products of RCS rather than by ROS directly, because ROS are highly reactive and cause site-specific injury, whereas the RCS are more stable and can diffuse to places distant from their site of injury and thereby can amplify and prolong oxidative injury due to local ROS generation. Among the many products of lipid-peroxidation, RCS such as formaldehyde, acetaldehyde, acrolein, MDA, glyoxal, and methylglyoxal have received much attention as the potential oxidants that contribute to pathological changes under a variety of disease conditions [176, 177].

Recent work shows that ROS generation at a moderate level is a physiological response as it triggers adaptive responses that minimize subsequent tissue injuries while high concentrations are harmful and damaging. In any cell, as the concentration of ROS increases, the transition from physiological effects to pathological injuries is demarcated by an increase in lipid oxidation. Therefore, the appearance of oxidized lipids reflects the emergence of injuries as the antioxidant capacity of the cell is overwhelmed. Once lipid-peroxidation starts, it becomes an autocatalytic process that amplifies and propagates the injurious effects of ROS in part because of the generation of highly toxic byproducts [6, 7]. Thus, inhibiting lipid-peroxidation or preventing the accumulation of lipid peroxidation derived products may be one way of preventing the toxic effects of ROS without interfering with their roles in signal transduction (Fig. 2). Because lipid-oxidation is a ROS-dependent process, it cannot be directly inhibited (e.g., by antioxidants) without inhibiting other effects of ROS, as well. Nevertheless, the accumulation of lipid-peroxidation products could be prevented by enhancing their metabolic detoxifications. Of the many reactive species generated by lipid-peroxidation, HNE and ONE are the most reactive ones [3, 25]. At concentrations comparable to their *in vivo* levels, RCS impair a variety of cellular processes [7] such as energy production [178], calcium homeostasis and ion channel activity [179]. In addition, RCS could also regulate cell signaling, proliferation, and adaptation to stress. Recent work has also shown that damage caused by alkylation may be selective, where certain functional protein networks (such as the cytoskeleton) are more sensitive than other networks such as those involved in protein synthesis and turnover [180]. Thus metabolism of RCS via multiple enzymatic pathways leading to the generation of different products could modify cellular responses and affect a wide range of biological processes both under physiological and pathological conditions and selectively affect the functioning of specific protein networks. Importantly, the processes involved in RCS metabolism could preserve ROS signaling, while preventing their indiscriminate toxicity. However, additional research is required to fully assess the importance of RCS metabolism in different disease states and to identify tissue-specific pathways that can modify and regulate redox chemistry *in vivo*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACS	acute coronary syndrome
AFB1	aflatoxin B1
AhR	aryl hydrocarbon receptor
AKRs	aldo-keto reductases
ADHs	alcohol dehydrogenases
ALDHs	aldehyde dehydrogenases
AR	aldose reductase
CAD	coronary artery disease
FR-1	fibroblast growth factor related protein
GS-DHN	glutathionyl-1,4 dihydroxynonene
GSH	reduced form of glutathione
GS-HNE	glutathione-4-hydroxynonenal
GSTs	glutathione-S-transferases
HNE	4-hydroxy-2-nonenal
I/R	ischemia/reperfusion
KO	knockout
LDL	low density lipoprotein
MDA	malondialdehyde
MEFs	mouse embryonic fibroblasts
MUC	muconaldehyde
MI	myocardial infarction
NADP(H)	nicotinamide adenine dinucleotide phosphate
ONE	4-oxo-2-(E)-nonenal
PAPC	1-palmitoyl-2-arachidonyl-glycerol-3-phosphocholine
PEIPC	1-palmitoyl-2-(5,6-epoxyisoprostane E2)-sn-glycero-phosphocholine
PG	prostaglandin
PGPC	1-palmitoyl-2-glutaroyl-sn-glycero-phosphocholine
PQ	phenanthrenequinone

POVPC	1-palmitoyl-2-(5'-oxo-valeroyl)- <i>sn</i> -glycero-3-phosphocholine
PUFAs	polyunsaturated fatty acids
RCS	reactive carbonyl species
RNAi	RNA interference
ROS	reactive oxygen species
SMCs	smooth muscle cells
t-BHQ	tert-butyl hydroquinone
TIM	triosphosphate isomerase
VECs	vascular endothelial cells

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- Overview of major RCS produced during lipid peroxidation and their salient features
- RCS amplify ROS related injury in many diseases during excessive oxidative stress
- Oxidoreductases including AKRs, ALDHs and ADHs are crucial in RCS metabolism
- RCS detoxification can prevent tissue injury while preserving their signaling role

(A) 4-hydroxy-2-nonenal

(B) 4-oxo-2-nonenal

(C) Acrolein

(D) Malondialdehyde

(E) 1-Palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphorylcholine

Fig.1.

Chemical structures of major carbonyl compounds generated during the process of lipid-peroxidation: (A) 4-hydroxy-*trans*-2-nonenal (HNE), (B) 4-oxo-2-(*E*)-nonenal (ONE), (C) Acrolein, (D) Malondialdehyde (MDA), and (E) 1-(Palmitoyl)-2-(5-oxovaleroyl)-phosphatidylcholine (POVPC).

Fig.2.

Hypothetical ROS concentration-response relationships. (A) At low concentrations ROS participate in cell signaling (green), whereas high concentrations ROS are toxic (red). The transition from signaling to injury is associated with the induction of lipid-peroxidation (arrow). (B) Antioxidant interventions diminish both ROS signaling and injury; whereas, (C) removal of lipid-peroxidation products prevents ROS toxicity, while preserving the ROS signaling arm.

Table 1

Salient features of aldo-keto reductases involved in RCS metabolism

Enzyme	Features	RCS	K _m (μ M)	K _{cat} (min ⁻¹)	kcat/K _m (min ⁻¹ · μ M ⁻¹)	References
AKR1A1	Induced by electrophilic Michael acceptors and ROS. AKR1A1 knock-out cells are sensitive to oxidative damage from H ₂ O ₂ and HNE induced cytotoxicity.	Acrolein	2.4 (mM)	0.70	290	[85, 181]
AKR1B1	Aldose reductases use the coenzyme NADP(H) in the first step of the polyol pathway, catalyzing the reduction of glucose to sorbitol.	Acrolein	880	43.7	50	[182]
AKR1B7	Known as mouse vas deferens protein, AKR1B7, has been shown to metabolize isocaproaldehyde and HNE. The role of AKR1B7 has been hypothesized to being the detoxification and of acrolein in the vas deferens.	Acrolein HNE	880 6.67	43.7 2.21	N/A* N/A*	[75]
AKR1B8	A murine aldo-keto reductase expressed in testis, heart, adrenal glands, intestine, and liver. It is considered an ortholog of human AKR1B10 based on its similarity in the amino acid sequence, computer modeled structure, substrate spectra and specificity.	HNE POVPC	230 14.8±4.6	3.18 18.4±1.0	N/A* 1.24	[66, 72, 81, 82, 85]
AKR1B10	AKR1B10 is similar to AKR1B1 in terms of its amino acid sequence, stereo structure, and substrate specificity however its biological function differs due to its distinct distribution as it is primarily limited to the gastrointestinal tract and adrenal gland. It has higher enzyme activity and turnover rates toward acrolein and HNE than AKR1B1.	Acrolein HNE POVPC	110±12 31±7 9.9±2.8	116 119 11.9±1.0	1070 3839 1.2	[66, 83, 84]
AKR1C1	The physiological role of this enzyme is to regulate progesterone action by converting the hormone into its inactive metabolite 20 α -hydroxyprogesterone but it also reduces HNE and other lipid-peroxidation products with high catalytic efficiency meaning that AKR1C1 has an antioxidant role.	HNE	34	8.8	0.27*10 ⁻⁶	[85]

* N/A – not available