Carbonyl Reductases: The Complex Relationships of Mammalian Carbonyl- and Quinone-Reducing Enzymes and Their Role in Physiology

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Key Words

carbonyl reduction, oxidative stress, detoxification, Phase I metabolism, quinone reductase

Abstract

Carbonyl groups are frequently found in endogenous or xenobiotic compounds. Reactive carbonyls, formed during lipid peroxidation or food processing, and xenobiotic quinones are able to covalently modify DNA or amino acids. They can also promote oxidative stress, the products of which are thought to be an important initiating factor in degenerative diseases or cancer. Carbonyl groups are reduced by an array of distinct NADPH-dependent enzymes, belonging to several oxidoreductase families. These reductases often show broad and overlapping substrate specificities and some well-characterized members, e.g., carbonyl reductase (CBR1) or NADPH-quinone reductase (NQO1) have protective roles toward xenobiotic carbonyls and quinones because metabolic reduction leads to less toxic products, which can be further metabolized and excreted. This review summarizes the current knowledge on structure and function relationships of the major human and mammalian carbonyl reductases identified.

INTRODUCTION

ALDH: aldehyde dehydrogenase

QR: quinone reductase

The chemical carbonyl function (aldehydes or ketone group) occurs frequently in endogenous compounds such as hormones (e.g., steroids), mediators (e.g., eicosanoids), cofactors (e.g., biopterins), neurotransmitter precursors (e.g., gamma-aminobutyraldehyde), and lipid aldehydes derived from oxidative stress (e.g., 4-hydroxy-2-nonenal) and their metabolites, and, furthermore, is widely found in xenobiotics such as food ingredients, drugs, or environmental pollutants. The carbonyl moiety often is a determining factor for the biological activity of a molecule, for example, a 3-keto group in steroid hormones is essential for binding to their specific receptor. Consequently, metabolic conversion of a carbonyl group can be an essential metabolic route to regulate and control endogenous processes of endogenous and xenobiotic ligands (1, 2). This concept has resulted in the development of inhibitors against critical enzymes activating endogenous ligands, such as glucocorticoids, androgens, estrogens, or eicosanoids (3–7). Additionally, many aldehyde compounds are toxic owing to the chemical reactivity of this group (8–14). Of further toxicological importance are conjugated ketones, such as quinones, α/β unsaturated aldehydes, or α/β dicarbonyls, owing to their intrinsic potential of reactivity or toxicity toward cellular macromolecules.

This review discusses the whole array of different NADPH-dependent enzymes belonging to different protein families that participate in the metabolism of carbonyl compounds. This metabolism, to a large extent, depends on tissue-specific expression of metabolizing enzymes, their cofactor dependence and regulation, and substrate specificities. Despite different underlying reaction mechanisms, carbonyl-reducing enzymes display a high degree of plasticity, and as a unifying feature, they show broad and partially overlapping substrate specificities (**Table 1**) (9, 13, 15–17). Moreover, in vitro studies have shown that a number of enzymes, such as several hydroxysteroid dehydrogenases (HSDs, e.g., 3α-HSDs or 11β-HSD type 1), with a previously well-defined role in endogenous metabolism are capable of reducing xenobiotic carbonyl compounds (13, 15).

In general (as shown in **Figure 1**), molecules containing ketone groups are reduced to their hydroxy metabolites, whereas aldehydes can be oxidized to the carboxylic acid by aldehyde dehydrogenases (ALDHs) or undergo reduction to the primary alcohol product. Depending on the individual pharmacodynamic properties of carbonyl compounds, carbonyl reduction can constitute an activation or an inactivation step, thus establishing carbonyl reduction as a typical Phase I reaction. An incomplete list of examples of widely encountered xenobiotic carbonyl compounds undergoing carbonyl reduction, as well as the enzymes involved in this metabolic route, is given in **Table 1**. Importantly, many of the products of carbonyl reductions can be readily conjugated with glucuronyl or sulfonyl groups by various transferases (UDP glucuronyl transferases and sulfonyl transferases, respectively), thus making the compounds more hydrophilic and excretable. Quinones are transformed to semiquinone radicals in one-electron reductions or reduced to hydroquinones by two-electron reductions. The latter reaction is carried out by several carbonyl reductases and quinone reductases (QRs). Hydroquinones can be further conjugated by Phase II enzymes (e.g.,

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Table 1 Human major xenobiotic NADPH-dependent carbonyl and quinone reducing enzymes

Human enzyme	Enzyme family	Subcellular localization	Endogenous substrates	Xenobiotic substrate	Structure (PDB ID)	Rodent ortholog	Key Reference
CBR1	SDR	Cytosol	Prostaglandins, steroids, lipid aldehydes	Aromatic aldehydes and ketones, quinones, NNK	1 WMA (human); 1N5D (porcine), 1SNY (*Drosophila*)	Yes	(18, 47, 50)
CBR3	SDR	Unknown/probably cytosol	Unknown	Quinones	-	Yes	(13)
11β-HSD1	SDR	ER	Cortisone, oxysterols	NNK, ketoprofen, metyrapone, oracin	2BEL (human)	Yes	(13, 68)
DHRS2	SDR	Cytosol, nucleus	α-dicarbonyls	α-dicarbonyls	-	Yes	(72)
DHRS4	SDR	Peroxisomes	Retinoids	Alkylphenyl ketones	-	Yes	(13)
DCXR	SDR	Mitochondria	L-xylulose, α-dicarbonyls	α-dicarbonyls, quinones, aromatic aldehydes and ketones	1WNT (human)	Yes	(71)
Not found in humans	SDR	Mitochondria	Lipid aldehydes (steroids)	Aliphatic, alicyclic, and aromatic carbonyls	1CYD (mouse)	CBR2 (mouse)	(61)
AKR1A1	AKR	Cytosol	Lipid aldehydes, aliphatic and aromatic aldehydes, D-glucuronic acid	Haloperidol, metyrapone, daunorubicin, acetoheximide	1ADS (human), 1MAR (human)	Yes	(124)
AKR1B1	AKR	Cytosol	Lipid aldehydes, methyl glyoxal, aliphatic and aromatic aldehydes, glucose	Daunorubicin, aliphatic and aromatic aldehydes	2AO0 (human)	Yes	(125)
AKR1B10	AKR	Cytosol	Unknown	Dolasetron, oracin, daunorubicin, NNK	Unpublished	Yes	(88)

(*Continued*)

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Table 1 (*Continued*)

Human enzyme	Enzyme family	Subcellular localization	Endogenous substrates	Xenobiotic substrate	Structure (PDB ID)	Rodent ortholog	Key Reference
AKR1C1	AKR	Cytosol	3- and 20-ketosteroids	Aromatic aldehydes and ketones, quinones, NNK, *trans* dihydrodiols of PAH, alicyclic alcohols, dicarbonyls	1MRQ (human)	Yes	(39)
AKR1C2	AKR	Cytosol	3-ketosteroids	Aromatic aldehydes and ketones, quinones, NNK, *trans* dihydrodiols of PAH, alicyclic alcohols, dicarbonyls	1J96 (human)	Yes	(39)
AKR1C3	AKR	Cytosol	3-, 17-, and 20-ketosteroids, prostaglandins	9,10-phenanthrene quinone, *trans* dihydrodiols of PAH, alicyclic alcohols	1S1R (human)	Yes	(39, 89)
AKR1C4	AKR	Cytosol	3-ketosteroids	Aromatic aldehydes and ketones, quinones, NNK, *trans* dihydrodiols of PAH, alicyclic alcohols, dicarbonyls	2FVL (human)	Yes	(39)
AKR7A2	AKR	Golgi	Succinic semialdehyde	Aflatoxin B1 dialdehyde, dicarbonyl compounds, aromatic aldehydes	2BP1 (human)	Yes	(93–95, 98, 99)

(*Continued*)

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Table 1 (*Continued*)

Human enzyme	Enzyme family	Subcellular localization	Endogenous substrates	Xenobiotic substrate	Structure (PDB ID)	Rodent ortholog	Key Reference
AKR7A3	AKR	Cytosol	Unknown	Aflatoxin B1 dialdehyde, quinones	2CLP (human)	Yes	(93–95, 98, 99)
NQO1		Cytosol		Quinones, nitroaromatic and azo compounds	1D4A	Yes	(126)
NQO2		Cytosol		Quinones, nitroaromatic and azo compounds with nicotinamide riboside as cofactor	1QR2	Yes	(126)
TxnRD		Cytosol, mitochondria	Thioredoxin, peroxiredoxins	Quinones	2CFY	Yes	(26)
CRYZ	MDR	Cytosol	Endogenous quinones	Quinones	1YB5	Yes	(116)
TP53I3, PIG3	MDR	Cytosol	Endogenous quinones	Quinones	-	Yes	-
LTB4DH	MDR	Cytosol	Eicosanoids, lipid aldehydes (reduction of double bond)	α/β unsaturated aldehydes and ketones	1ZSV	Yes	(36, 122)

glutathione transferase) and excreted. Importantly, most quinones undergo redox cycling with molecular oxygen, and thus can initiate and sustain the production of reactive oxygen species (ROS), leading to lipid peroxidation, protein adducts, and DNA modifications, followed by a cascade of altered cellular responses and defense mechanisms.

The multiplicity of enzymes involved in the reduction of aldehydes and ketones has been noted already (9, 15, 18, 19), and the main mammalian enzymes involved in this metabolic conversion have been cloned and characterized in considerable detail. Consequently, the high diversity of enzymes capable of mediating carbonyl reduction necessitates a discussion of the particular enzymes involved, which is the object of this review. At present, the main enzymes acting as carbonyl reductase (discussed further below) are monomeric, NADPH-dependent carbonyl reductase forms (EC. 1.1.1.181, CBR1 and CBR3); several members of the aldo-keto reductase family, such as the NADPH-dependent aldose reductase (AKR1B1) and aldehyde reductase

ROS: reactive oxygen species

CBR1: type 1 carbonyl reductase

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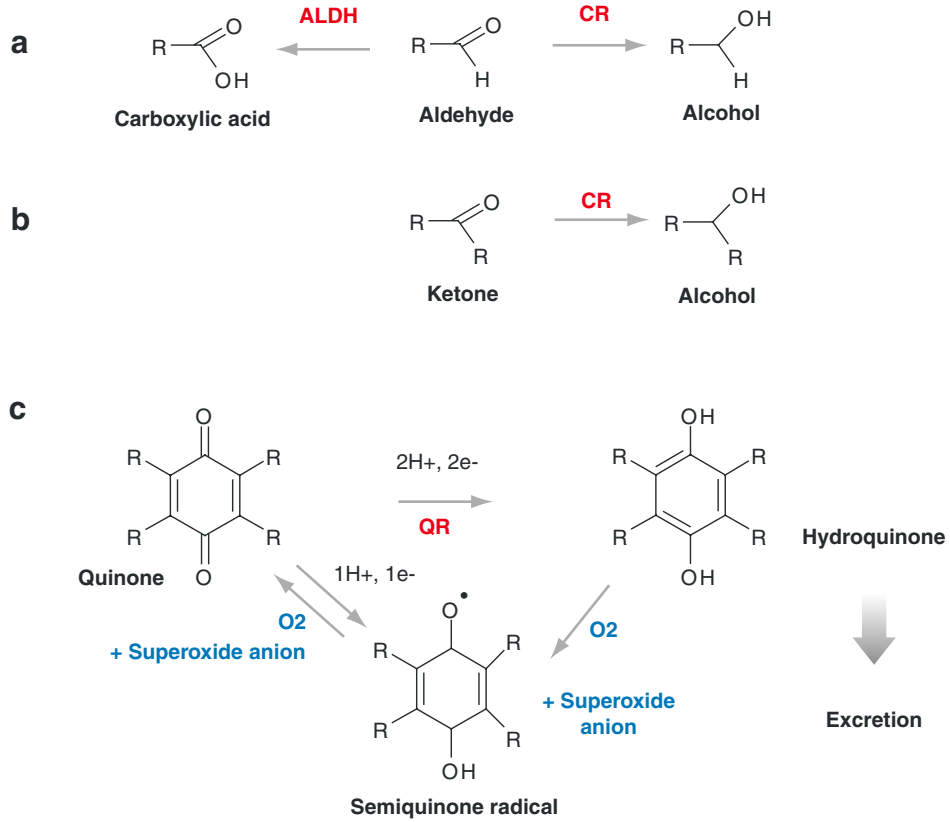

Figure 1

Metabolic conversion of carbonyl compounds. (*a*) Aldehydes can be converted by aldehyde dehydrogenases (ALDH) to carboxylic acids or by carbonyl reducing enzymes (CR) to the primary alcohol. (*b*) Ketones are reduced to the corresponding alcohol by CR. (*c*) Quinone reduction and redox cycling. Quinone reduction by one-electron transfer yields the semiquinone radical. Two–electron reduction of quinones by quinone reducing enzymes (QR) yields the hydroquinone, which can be excreted or be oxidized to the semiquinone radical. Both the hydroquinone and semiquinone states can be oxidized in the presence of molecular oxygen (O_2), yielding superoxide anion, thereby sustaining oxidative stress.

(AKR1A1); AKR-type hydroxysteroid dehydrogenases of the AKR1C family; microsomal NADPH-dependent carbonyl reductases, such as 11β-hydroxysteroid dehydrogenase (11β-HSD); other SDR-type carbonyl reductases, such as DHRS2 and DHRS4; and NADPH-dependent quinone reductases, such as type 1 and 2 quinone reductases (DT-Diaphorase, NQO1, NQO2).

OXIDATIVE STRESS AND CARBONYL METABOLISM

CR: carbonyl reductase

A substantial amount of research has provided evidence that links oxidative stress as a source of cellular damage to age-related processes such as cancer, neurodegeneration,

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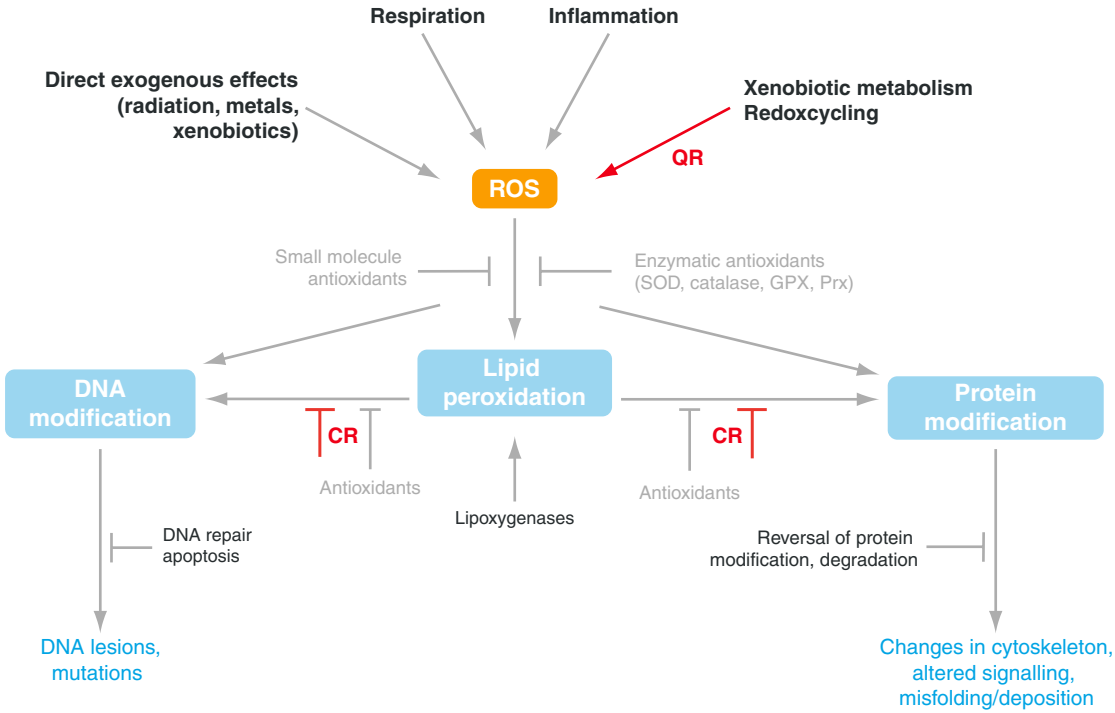

Figure 2

Schematic overview on the involvement of quinone (QR) and carbonyl reductases (CR) in oxidative stress. ROS are produced through different initiating events, such as direct exogenous effects, aerobic metabolism, inflammation, and redox cycling of quinones. The ROS generated cause DNA lesions and mutations (eventually leading to neoplastic transformation) or protein modifications with altered cytoskeleton, protein degradation, misfolding and deposition, or signaling (eventually leading to degenerative diseases). ROS can also initiate lipid peroxidation if not inactivated by primary antioxidants, such as α-tocopherol, glutathione, or ascorbic acid. Inactivation of ROS is also achieved through enzymatic inactivation by superoxide dismutase (SOD), catalase, glutathione peroxidase (GPX), or peroxiredoxins (Prx). Lipid peroxidation products comprise highly reactive lipid aldehydes, such as 4-oxonon-2-enal, 4-hydroxynon-2-enal, and acrolein, which are able to modify proteins and DNA. The reactive lipid metabolites can be inactivated by a variety of CR, as discussed in the text.

and cardiovascular disease (20–24, and references therein). Importantly, oxidative stress can be initiated through redox cycling involving several of the above-mentioned oxidoreductases (25), and also, several carbonyl reductases are involved in the reductive metabolism of secondary products, such as reactive lipid aldehydes produced during oxidative stress (**Figure 2**, **Table 2**). Oxidative stress is defined as an imbalance between prooxidative and antioxidative states, leading to an overall increase in cellular levels of ROS, and it is accompanied with an altered gene transcription profile, carried out by redox-sensitive transcription factors, e.g., NFkB, AP1, or MAP kinases (22).

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Table 2 Reactive oxygen species: Examples of lipid peroxidation products and defense mechanisms

	Sources	Inactivation	Products/reaction
Primary ROS molecule			
Superoxide anion (O_2^-)	Mitochondrial electron chain Inflammation (phagocytes, NADPH oxidase) Flavin-dependent enzymes Oxidation of xenobiotic quinones	Superoxide dismutase Ascorbic acid	$H_2O_2 + O_2$
Hydrogen peroxide (H_2O_2)	Product of the SOD reaction Xanthine oxidase	Glutathione peroxidases (GPX) Catalase Peroxiredoxins (Prx) Ascorbic acid	$H_2O + GGSG$ $H_2O + O_2$ H_2O
Hydroxyl radical	Fenton reaction (transition metals and $O_2^- + H_2O_2$		
Lipid peroxidation products			
Lipid peroxides	Lipoxygenase, ROS	Glutathione peroxidase (GPX4)	Lipid alcohol + GSSG
Lipid radical	ROS	Radical scavenger (e.g., tocopherol or GSH)	Alkyl, stable scavenger radical, or GSSG
Substituted α/β-unsaturated lipid aldehydes (e.g., 4-hydroxy-2-nonenal, 4-oxo-2-ononenal)	Nonenzymatic cleavage of lipid peroxides	AKR1B1 LTB4DH, CBR1 CBR1, AKR1B1 CBR1	Reduction of aldehyde to lipid alcohol Reduction of double bond Reduction of keto group
Cyclopentenone eicosanoids (isoprostanes)	ROS-mediated peroxidation and nonenzymatic rearrangement of arachidonic acid	Unknown	

The relationship between ROS formation, cellular damage, and protective mechanisms are schematically depicted in **Figure 2**, and several of the mechanisms identified are listed in **Table 2**. Major sources for ROS production include respiration, inflammatory mechanisms, endogenous metabolism (e.g., through peroxisomal or flavin-containing enzymes), metabolic activation of xenobiotics, or through direct prooxidative effects of environmental agents (e.g., metals, radiation, chlorinated compounds). Oxidative stress is an inevitable cellular process in an aerobic environment, and it is estimated that 4%–5% of molecular oxygen during respiration is converted to ROS, primarily superoxide (O_2^-). Besides O_2^-, major ROS molecules include hydrogen peroxide (H_2O_2) and the hydroxyl radical ($^{\cdot}OH$); other reactive species related to ROS are nitric oxide (NO) and hypochlorous acid (HOCl) (26). The stepwise reduction of O_2 to water during respiration in mitochondria leads to superoxide, which is converted by superoxide dismutase to hydrogen peroxide. In mammals, H_2O_2 can be inactivated by several antioxidant enzymes, such as catalase, peroxiredoxins, and glutathione peroxidases, to O_2 and water. Importantly, the presence of transition metals such as Fe^{2+} or Cu^{2+} can lead to the decomposition of H_2O_2 to the hydroxyl radical

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·OH and to OH^- (the Fenton reaction). The short-lived hydroxylradical is able to react with nucleic acids, proteins, or lipids in its immediate vicinity, leading to altered macromolecules.

CR: carbonyl reducing enzymes

Within this context, the metabolic activation of xenobiotics with the concomitant production of ROS is performed through redox cycling of, for example, quinones by several oxidoreductases in the presence of O_2, or through one-electron reductions of peroxidases or through futile cycling of cytochrome P450 (e.g., P450 2E1 and ethanol metabolism) (23, 27) (**Figure 1**).

Besides the antioxidative defense enzymes listed above and the thioredoxin and glutaredoxin systems (26), which play an essential role in providing an antioxidant protection mechanism, the cell contains multiple low-molecular-weight antioxidant compounds. These comprise glutathione, lipoic acid, ascorbic acid, tocopherol, ubiquinone, and bilirubin (23, 26), all of which can quench ROS. The sources and metabolic defense mechanisms for these molecules are summarized in **Table 2** (23, 26). Production of ROS leads to a shift in the cellular redox state, which is accompanied by an altered transcriptional profile of antioxidant enzymes and cellular responses (28) and leads to significant modifications of nucleic acid, proteins, and lipids, a process that appears to be central to, for example, neurodegenerative diseases, cancer, and atherosclerosis (22, 23, 29–33).

Lipid peroxidation by ROS plays a central role in the pathogenesis of oxidative stress because lipid peroxidation products are highly reactive and can modify nucleic acids and proteins (**Figure 2**). The acyl chain of polyunsaturated fatty acids (PUFAs) such as linoleic or arachidonic acid, found in cell membranes and lipoproteins, is particularly susceptible to free radical–mediated oxidation and leads to the release of reactive aldehydes, such as malondialdehyde, acrolein, glyoxal, and 4-hydroxy-2-nonenal (HNE) or 4-oxo-2-nonenal (ONE) (14, 30, 34). Other, less-investigated metabolites include electrophilic cyclopentenone eicosanoids able to form Michael adducts with cellular thiols (21, 35). Alpha, beta unsaturated aldehydes such as HNE and ONE exert a wide array of biological activities, such as modification of the proteasome, alteration of the cytoskeleton, change in transcriptional activity, as well as diffuse cytotoxic effects (30, 33). HNE and ONE react primarily through Michael addition to nucleophiles, such as Cys thiol groups or His and Lys side chains, although Schiff base formation with Lys residues is also observed. Detoxification of these electrophilic aldehydes occurs through reaction with glutathione or, as recently demonstrated, through reductive metabolism of the carbonyl moieties or reduction of the double bond, leading to lipid products that are less reactive and can be further metabolized or excreted (**Table 2**) (30, 36, 37).

CARBONYL REDUCING ENZYMES

As outlined above, reduction of carbonyl compounds is achieved by a diverse set of ubiquitously occurring carbonyl reducing enzymes (CR). These enzymes have been described in plants, bacteria, yeast, teleosts, and insects (9); however, the most investigated enzymes are the human and rodent members. These are described in detail below and belong to two fundamentally distinct enzyme families, namely the

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short-chain dehydrogenase/reductase (SDR) and the aldo-keto reductase (AKR) superfamilies. These are evolutionarily conserved protein families and differ in their general architecture and nucleotide/hydride transfer stereospecificity but share a similar, Tyr-based acid-base mechanism (16, 38–40).

Carbonyl Reducing Enzymes of the SDR Family

Several members of the SDR family have been shown to reduce in vitro endogenous and xenobiotic carbonyl compounds. The best-studied member is CBR1; however, a number of other reductases, such as the microsomal 11β-HSD1, dicarbonyl/xylulose reductase (DCXR), and DHRS2 and DHRS4, have demonstrated in vitro xenobiotic reductase activity. However, with the exception of CBR1, no in vivo data or animal model data are available at this point on the role of these enzymes in xenobiotic metabolism. The relationship between these SDR-type carbonyl reductases is illustrated by a multiple sequence alignment in **Figure 3**. In general, SDRs display a similar architecture consisting of a central 7–8-stranded β-sheet with flanking α-helices on each side, characteristic of a Rossmann-fold necessary to bind the dinucleotide cofactor (**Figure 3**). A highly variable C-terminal part of the protein constitutes the substrate binding site close to the active site with a tetrad of largely conserved Asn-Ser-Tyr-Lys residues. The sequence identities between different SDR members are most often only between 15%–25% and are restricted to the conserved cofactor binding and active site tetrad sequence motifs (38, 41). Despite the low sequence identities, the structures show a superimposable folding pattern. Mammalian CBR1 orthologs are monomeric enzymes, a feature that is achieved by additional inserted helices found at the main oligomerization site. Active sites and substrate specificities between carbonyl reductases of the SDR family differ considerably owing to their variable C-terminal sequences (**Figure 3**).

Carbonyl reductases (CBR1, CBR2, CBR3). A human cytosolic enzyme, able to catalyze the NADPH-dependent reduction of a variety of xenobiotic ketones and quinones was first described by Ris & von Wartburg (42) and later cloned and purified from human brain by the Wermuth group (18, 43, 44). The human enzyme is a monomer of 277 amino acid residues and was named carbonyl reductase (gene name CBR1) owing to its properties to reduce efficiently various endogenous and xenobiotic carbonyl compounds. Human CBR1 is expressed in a large variety of tissues, with high levels found in liver, placenta, and the CNS (45), consistent with a possible protective role against toxic carbonyls. However, species-specific differences in its expression pattern are noted. The human gene is located on chromosome 21 at 21q22.12 (46), in the vicinity of the SOD1 gene at 21q22.11, and close to the related gene CBR3 (21q22.2), which codes for a homolog with presumably similar catalytic properties (13). Subsequent description of tetrameric carbonyl reductase (CBR2), a form not present in the human genome but found in several rodents, and the discovery of the CBR3 gene has led to the current nomenclature system of CBRs (13). The assignment of a human carbonic reductase (CBR4) gene is at present without any proof of function in carbonyl metabolism, and hence is not further discussed in this article.

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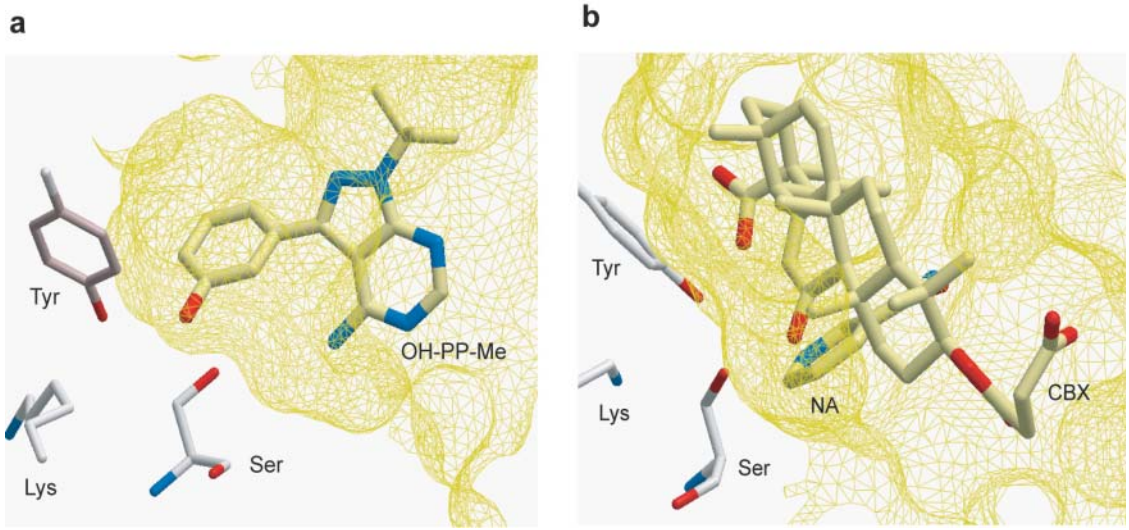

Figure 3

Structural features and comparison of SDR-type carbonyl reducing enzymes. Panels *a* and *b* show structural differences in ligand pockets. (*a*) Ligand environment for human CBR1, showing a compact shape with a wide opening, able to accommodate the specific inhibitor hydroxy-PP-Me (OH-PP-Me). The catalytic residues Tyr, Ser, and Lys are shown. The cofactor nicotinamide was omitted for clarity. (*b*) The ligand pocket for human microsomal carbonyl reductase (11β-HSD1) in complex with carbenoxolone (CBX). The pocket appears more elongated as compared with CBR1. The nicotinamide ring (NA) of the NADP cofactor is displayed. (*c*) Structure-based sequence alignment CBR1 forms (human, porcine, and *Drosophila*), human microsomal carbonyl reductase (HSD11B1), mouse lung carbonyl reductase (CBR2), human dicarbonyl reductase/xylulose reductase (DCXR). Secondary structure elements are depicted below the alignment for CBR1 and HSD11B1, and the catalytic residues forming a tetrad are marked by asterisks. The conserved sequence motifs characteristic of the SDR family (*highlighted in green*) (41) are restricted to N-terminal cofactor binding sites or contribute to the active site architecture. (*d*) Ribbon model overlay of SDR-type carbonyl reductases whose structures are determined, showing an essentially identical folding pattern. Position of the NADP cofactor is shown as a stick representation. The inserted helices, specific to mammalian monomeric CBRs, stabilizing the fold are shown in yellow. In oligomeric SDRs symmetry related helices pack against this surface. (*e*) Ligand variability of CBR1. Carbonyl substrates identified are o-quinones (9,10 phenanthrenequinone), lipid aldehydes (4-oxo-2-nonenal), and prostaglandin E2. A selective CBR inhibitor 3-(7-isopropyl-4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenol (OH-PP-Me) has been identified and a ternary complex structure has been determined (1WMA) (51).

The role of CBRs in mammalian physiology is still incompletely understood; however, recent cellular and animal model studies suggest an important function of CBR1 in the protection against ROS and the mediation of apoptosis, as discussed below.

CBR1 metabolism of xenobiotic carbonyls and quinones. The xenobiotic substrates shown to be metabolized by CBR1 include o-quinones derived from polycyclic

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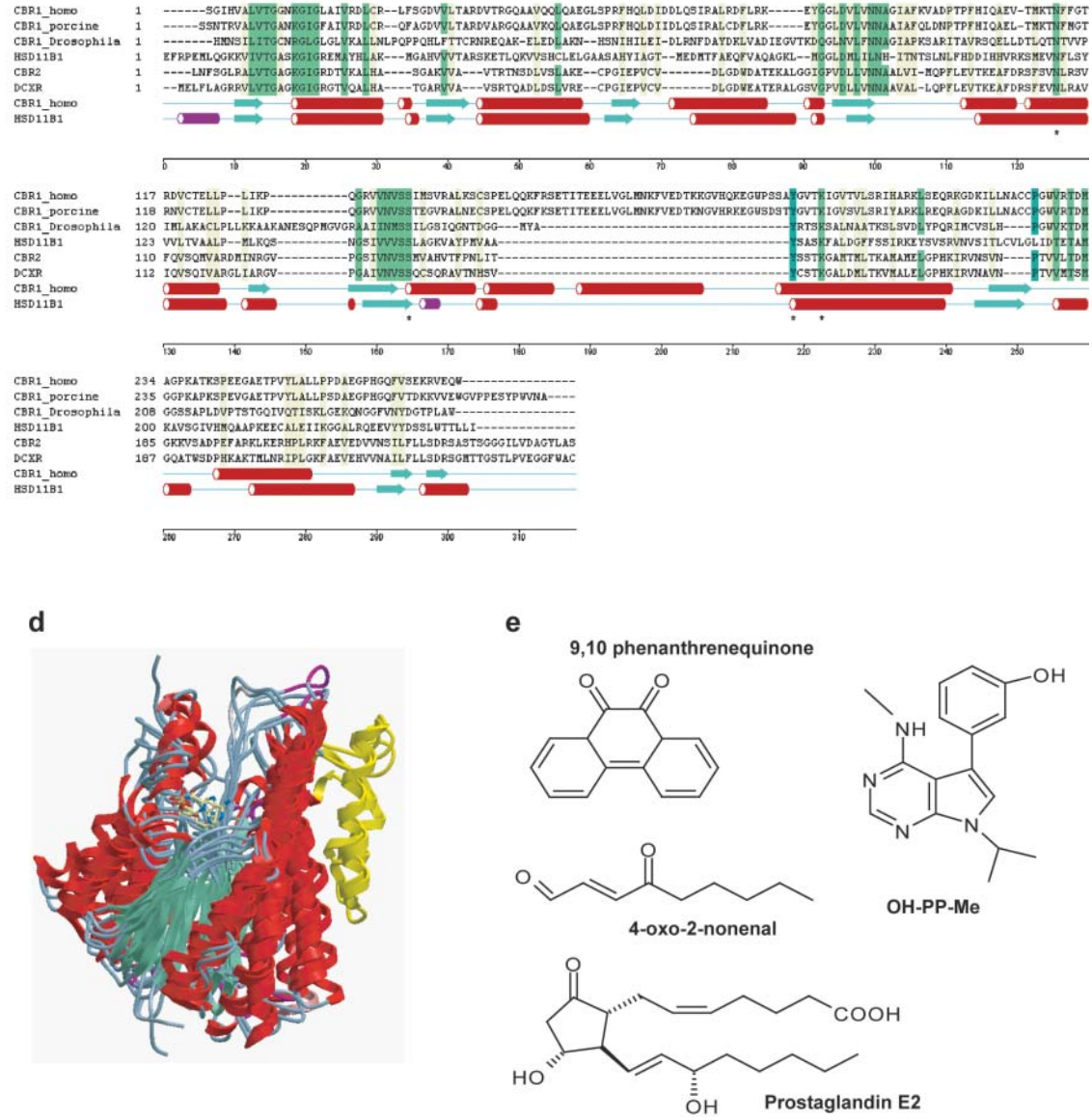

Figure 3

(*Continued*)

aromatic hydrocarbons (PAH) or p-quinones, such as menadione (47), as well as an extraordinarily wide spectrum of xenobiotic carbonyls, such as anthracyclines, metyrapone, or the carcinogen 4-methylnitrosamino-1-(3-pyridyl)-1-butanone (18, 48). Accordingly, the enzyme fulfills an important role in the Phase I metabolism of xenobiotics. Human CBR1A is the major hepatic reductase of PAH-derived quinones (47), suggesting a major role in detoxification of these compounds. This is in contrast to the metabolic preference in rat liver, where NADPH-dependent quinone reductase (NQO1) is the major quinone reductase. However, in the absence of superoxide dismutase (SOD), quinone reduction by CBR1 leads to redox cycling, with generation of superoxide anion and semiquinone radicals mediated through one-electron transfer from the reduced hydroquinones to molecular oxygen (see above, **Figure 1**) (25). Thus, CBR1 is an important determinant in the metabolism of PAH quinones; however, a possible protective role against quinone toxicity exerted by CBR1 depends on expression and activity of SOD and further metabolism, reactivity, and excretion of the hydroquinone formed. The CBR1-mediated metabolism of the anthracycline cytostatic agent, doxorubicin, to its alcohol metabolite constitutes an important determinant in the observed cardiotoxicity because mice heterozygous for a CBR1-null allele show decreased sensitivity toward the cardiotoxic effects of the anthracycline alcohol metabolite (49). Conversely, transgenic animals overexpressing the human CBR1 gene under the control of a heart-specific α-myosin-heavy chain promoter clearly confirm a role for CBR1 in heart muscle damage upon doxorubicin treatment (10, 50). Studies conducted in A549 cells with a selective CBR1 inhibitor revealed increased sensitivity toward anthracycline-induced apoptosis, possibly decreasing cardiotoxicity (by preventing formation of the cardiotoxic alcohol) and increasing cytostatic sensitivity (51). A recent study indicates that CBR1 supposedly is involved in tumor metastasis (52). Mouse lung adenocarcinomas showed distinct metastatic properties that were correlated with CBR1 expression levels. These effects were attributed to the prostaglandin-modulating activities of CBRs; however, further experimental proof is needed. Endogenous substrates for CBR1 comprise 5α-reduced steroids and prostaglandins (18), but the observed relatively low kinetic constants obtained in vitro for steroid and eicosanoid conversion argue against a physiological role in the metabolism of these lipid hormones and mediators in humans, although this issue remains controversial (53). The closely related human CBR3 protein has 71% amino acid sequence identity with human CBR1, and the recombinant human enzyme catalyzes menadione reduction. This suggests similar catalytic properties, further corroborated by studies with the hamster ortholog, which show high daunorubicin and isatin reductase activities (54). The expression pattern is similar but not identical to CBR1 and is accompanied by lower expression levels of CBR3 (13).

Role of CBR1 in oxidative stress and apoptosis. Several recent studies could provide essential clues as to the physiological role of CBR1. First, a screen of viable P-element insertions in the fruit fly *Drosophila melanogaster* resulted in the discovery of a novel hypomorphic mutant, *Sniffer*, which shows age-related severe neurological impairments and increased apoptosis in the CNS (55). The *Sniffer* gene represents the *Drosophila* ortholog of CBR1, and subsequent structure determination provided

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a model consistent with results on the mammalian structures (51, 56). Importantly, *Sniffer* is essential to the prevention of oxidative stress-induced neurodegeneration and cell death (55), and overexpression of the *Sniffer* gene results in neuronal protection against oxygen-induced apoptosis (55). These data are consistent with a role of *Sniffer*/CBR1 in the detoxification of a metabolite produced under conditions of oxidative stress. A possible experimental proof for this concept was provided by a study demonstrating in vitro that recombinant human CBR1 metabolizes and inactivates lipid aldehydes (37), such as the highly reactive and genotoxic 4-oxonon-2-enal product, formed during oxidative stress, to less reactive metabolites by reducing the carbonyl groups and the double bond, yielding 4-hydroxynon-2-enal, 1-hydroxy-2-en-4-one, and 4-oxononanal (37). These metabolites are thought to be less reactive than the parent compound (11, 30, 37, 57), and 4-keto reductase activity was also observed with the glutathione adduct. Additionally, results with murine NIH3T3 cells transfected with human CBR1 showed increased resistance against paraquat, a toxic herbicide known to generate ROS (53). These results, as well as other protective effects reported for CBR1 toward quinones, could be due to inactivation of reactive lipid aldehydes formed through oxidative stress. Combined, these data provide compelling support for a hypothesis that postulates a neuroprotective role of CBR1 during ageing and neurodegeneration (**Figure 2**) (55, 58). This model links the enzyme function by inactivation of toxic lipid peroxidation products to ROS-linked diseases, such as Alzheimer's or Parkinson's disease. Another important study, using recently identified selective CBR1 inhibitors or CBR1-directed RNAis, revealed that CBR1 plays an essential role in serum withdrawal–induced apoptosis in A549 cells (51). Treatment with the inhibitor 3-hydroxy-PP-Me [**Figure 3** (51)] resulted in a dose-dependent, nearly complete reversal of apoptosis induced by serum starvation, indicating a proapoptotic function of CBR1, which may be metabolizing a yet unidentified physiological substrate that is formed upon serum withdrawal. This pathway is apparently not directly linked to p53 function or interaction [as observed with another oxidoreductase, NQO1, see below (59, 60)] because no p53 increase or ubiquitination was observed (51). These results could further indicate that the observed nonviability of the CBR1 null mouse (49) is due to developmental deregulation related to lack of elimination of progenitor cells due to a missing proapoptotic function of CBR1. CBR1 is inducible by several xenobiotics, such as 2,(3)-t-butyl-4-hydroxyanisole, beta-naphtoflavone or Sudan 1 (46), indicating a xenobiotic responsive element in the promoter. However, no further studies have been conducted on the regulation of the CBR1 gene. Obviously, despite the clear indications for a neuroprotective role of CBR1 by the *Sniffer* model, further studies are necessary to clarify and correlate the roles of CBR1 in neurodegeneration and development with the observed proapoptotic function. Of particular interest are studies directed toward other less-characterized mediators, such as isoprostanes, which could have a functional role in neurodegeneration (21).

Tetrameric carbonyl reductase. A tetrameric carbonyl reductase (CBR2) with low sequence similarities to CBR1 or CBR3 (<30%) and highly expressed in mitochondria of lung epithelia was described for mouse, guinea pig, and pig; however, a homologous

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enzyme is not found in the human or rat genomes (13). CBR2 enzymes reduce a variety of aliphatic, alicyclic, and aromatic carbonyl compounds, and it is postulated that CBR2 might function in the detoxication of xenobiotic carbonyls and carbonyls derived from lipid peroxidation (13, 61).

Microsomal carbonyl reductase: 11β-hydroxysteroid dehydrogenase type 1. The purification and characterization of a microsomal enzyme mediating the reduction of the xenobiotic, metyrapone, was achieved by Maser & Netter (62). The enzyme was subsequently shown to be identical to type 1 11β-hydroxysteroid dehydrogenase (63, 64), which is located in the lumen of the endoplasmic reticulum (65) and is highly expressed in liver, adipose tissue, brain, and lung. This enzyme is a major determinant of glucocorticoid hormone action and has been recently identified as a promising target for the treatment of metabolic diseases (3, 5–7). As shown in different studies, the enzyme also mediates the reduction of different xenobiotics in addition to the endogenous activation of cortisone to cortisol (13, 63, 66, 67). The list of in vitro xenobiotic substrates includes the potent tobacco-derived 4-methylnitrosamino-1-(3-pyridyl)-1-butanone (NNK) or the anticancer compounds oracin and the antiinflammatory ketoprofen (13, 63, 67, 68). It was postulated that the activity of this enzyme might contribute to the increased risk for lung cancer in smoking individuals (69). This is supposedly due to the reduction of NNK and subsequent conjugation with UDP glucuronic acid at the ER site, a Phase II reaction that constitutes the major detoxification step of this potent carcinogen. However, at this point, no data from animal or cell culture models are available to prove this hypothesis. Moreover, several cytosolic and abundantly expressed enzymes, such as CBR1 or xenobiotic reductases of the AKR1C family, more efficiently mediate the reductive transformation of NNK (13, 48). Taken together, it is at present unknown to what extent exogenous substrates interfere with the physiological role in steroid metabolism.

Other SDR-type carbonyl reducing enzymes: DCXR, DHRS2, and DHRS4. The SDR enzymes dicarbonyl/xylulose reductase (DCXR), dehydrogenase/reductase 2 (DHRS2), and dehydrogenase/reductase 4 (DHRS4) constitute a cluster of sequence-related SDR enzymes whose physiological roles are insufficiently understood at present. All three belong to a cluster of evolutionarily conserved SDRs, with orthologs found in mammals, *Arabidopsis thaliana*, *Caenorhabditis elegans*, and *Drosophila* (70).

DCXR catalyzes the reduction of L-xylulose to xylitol and accordingly plays a role in the uronate cycle of glucose, although less certain, several possible endogenous substrates for human DHRS2 and DHRS4 have been described. Accordingly, human DHRS4 reduces all-trans retinal with low catalytic efficiency; however, species-specific differences for orthologous enzymes are known (13), pointing to a possible role in the metabolism of this nuclear receptor ligand in other mammalian species than humans. However, all three enzymes show activity toward certain carbonyl compounds. DHRS4 reduces alkyl phenyl ketones (13) and DCXR and DHRS2 efficiently reduce α-dicarbonyls with a partially overlapping specificity pattern (71, 72). These reactive dicarbonyls are generated through oxidative stress or are found as

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dietary constituents and can be cytotoxic (73–75) or further processed into advanced glycation endproducts (AGEs) (73, 76). These AGEs are thought to cause several complex underlying pathologies, including inflammation or sclerotic effects found in chronic diseases (76, 77). Accordingly, DCXR and DHRS4 could play an important role as scavenging enzymes of reactive α-dicarbonyls.

AKR-Type Carbonyl Reducing Enzymes

AKRs constitute a large family of monomeric or dimeric NADP(H)-dependent enzymes with diverse substrate specificities, including steroids, eicosanoids, polyols, and xenobiotics (39). A nomenclature system to group AKRs has been adopted (**http://www.med.upenn.edu/akr**), and currently 14 subfamilies have been identified. AKRs show a $(\alpha/\beta)_8$-folding pattern (triose isomerase or TIM barrel fold), where the central β-strands form the staves of a barrel, with large loops at the back that form the ligand binding site. At the base of the barrel, nucleotide cofactor and substrate bind in the vicinity of a seemingly conserved tetrad of catalytically important residues consisting of Tyr-Asp-His-Lys (39). The reaction mechanism for several members have been studied in detail, revealing an ordered bi-bi mechanism, with important differences in rate-limiting steps (78–80). This is extensively complemented by structural information using X-ray crystallography on all of the relevant AKR enzymes involved in xenobiotic carbonyl reduction. Four AKR subfamilies, namely 1A, 1B, 1C, and 7A, have documented roles in xenobiotic carbonyl metabolism and are briefly discussed in the following sections.

Aldehyde reductase (AKR1A) and aldose reductase (AKR1B). Members of the AKR1 subfamily members AKR1A (aldehyde reductase) and AKR1B (aldose reductase) participate in the reduction of a wide range of carbonyl compounds. AKR1A efficiently reduces a broad spectrum of endogenous and xenobiotic carbonyls, including succinic semialdehyde, 4-carboxybenzaldehyde, 4-hydroxynonenal, haloperidol, metyrapone, loxoprofen, daunorubicin, acetoheximide phenylglyoxal, methylglyoxal 2,3 hexanedione, and D-glucuronic acid (81, 82). The enzyme is abundantly expressed in liver, CNS, intestine, and kidney (82). Numerous physiological aldehydes, including glucose, were identified as substrates for aldose reductase (leading to sorbitol), the first enzyme of the polyol/sorbitol pathway (83). Inhibitors against AKR1B have been developed to prevent diabetic neuropathies (84). AKR1B reduces many of the substrates identified for AKR1A, however, with lower efficiency (82), and AKR1A efficiently catalyzes the reduction of methylglyoxal, certain xenobiotics such as the anthracycline daunorubicin, or bioactive aldehydes derived from phospholipids or products from lipid peroxidation such as 4-hydroxynon-2-enal and its 4-keto derivative 4-oxo-non 2-enal (85). These data imply that AKR1B plays a significant role in the protection against reactive carbonyls derived from oxidative stress or hyperglycemic states. AKR1B is expressed at high levels in the CNS but at low or undetectable levels in liver; however, it appears to be highly upregulated in 3′-methyl-4-dimethylaminoazobenzene-induced hepatocarcinomas (86) or during daunorubicin resistance selection of a human stomach carcinoma cell line (87). A recent study reported the

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purification and characterization of an AKR1B-related human enzyme (AKR1B10) with reductase activity toward several relevant xenobiotic carbonyls, such as the 5-HT3 receptor antagonist dolasetron, the cytostatic agents oracin and daunorubicin, or the carcinogen NNK (88).

Hydroxysteroid dehydrogenases (AKR1C family). Human (AKR1C1–AKR1C4) as well as the rodent orthologs of this subfamily have dual roles in endogenous steroid or eicosanoid regulation and in xenobiotic metabolism. The four human isozymes act on androgens as 3α-hydroxysteroid dehydrogenases/3oxo reductases (13, 17). In addition, AKR1C1 has 20α-HSD activity toward neuroactive steroids such as 5α- or 5β-pregnane 3α-ol,20-one (13, 17). AKR1C3 has significant 17β-HSD activity toward 17-oxo androgens and also acts as prostaglandin F2 synthase activity (89, 90). The enzyme activities toward endogenous potent ligands involved in proliferation of, for example, prostate cancer, make these AKR1C enzymes potential targets in cancer therapy (4). Importantly, these enzymes also display two different types of xenobiotic activities, namely $NADP^+$-dependent *trans*-dihydrodiol dehydrogenase activity toward dihydrodiols derived from activated polyaromatic hydrocarbons (91) and NADPH-dependent xenobiotic carbonyl reductase activity toward a variety of pharmacologically and toxicologically relevant substances (13) (**Table 1**, compare below). In a study using the human isoforms AKR1C1–AKR1C4 (91) the *trans*-dihydrodiol dehydrogenase activity was selectively directed toward the non-K region *trans* dihydrodiols, without activity on K region dihydrodiols. It was shown in vitro that AKR1C isozymes produce the proximate carcinogen, dimethylbenzanthracen, 3,4 dione (DMBA, 3,4 dione) from its *trans* 3,4 diol precursor, which is a product of the concerted action of CYP1A1 and epoxide hydrolase on DMBA (91). Hence, AKR1C1–AKR1C3 might play an important role in the activation of potent PAHs to proximate carcinogens and hence have significance in the etiology of lung cancer on exposure to these environmental pollutants or tobacco smoke ingredients (13, 91). AKR1C4 is not expressed in lung tissue and appears restricted to liver. The resulting o-quinones from this activation step can undergo redox cycling (compare with above) and sustain oxidative damage or form covalent Michael adducts (91). However, despite these compelling in vitro data, further in vivo research is required to unequivocally clarify the role of this subfamily in PAH activation and also correlate the data with the observed activity on 4-hydroxynonenal reduction, which constitutes, in principle, a protective measure against the detrimental effects of ROS and lipid peroxidation. Furthermore, a recent comparison of xenobiotic carbonyl reductases (13) reveals that AKR1C1 and AKR1C2 efficiently reduce the tobacco-derived carcinogen NNK with a rank order in Vmax/Km of CBR1≫AKR1C1>AKR1C2>HSD11B1>AKR1C4. Furthermore, to different degrees they can reduce important drugs, such as ketotifen, dolasetron, naloxone, naltrexone, and oxycodone (13).

Aflatoxin reductases (AKR7A subfamily). Members of the AKR7A subfamily are involved in the metabolic inactivation pathways of aflatoxin B1. This highly toxic metabolite is produced under conditions of high heat and humidity by fungal molds of the genus *Aspergillus*. The carcinogenic effects of aflatoxin B1 are due to

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bioactivation to the reactive and carcinogenic epoxide (catalyzed by CYP1A2 and CYP3A4 enzymes) and ultimately form DNA adducts and lead to lesions (92). In humans, inactivating pathways include ring opening and reduction of an intermediate aflatoxin dialdehyde (which still forms protein adducts) to the dialcohol product. The reduction is catalyzed by the human AKRs AKR7A3 and AKR7A2 or, e.g., the rodent ortholog AKR7A1 (93–96). These orthologs share 80% sequence identities and show different kinetic properties toward model compounds, such as p-nitrobenzaldehyde, and the aflatoxin B1 dialdehyde or the endogenous substrate succinic semialdehyde. Enhancement of aflatoxin B1 dialdehyde reduction may lead to a decreased susceptibility of this potent carcinogen, putting these two human AKR members into focus as an important defense mechanism. Studies in several animal models have shown that variations in aflatoxin B1–activating and -detoxifying enzymes can have a dramatic effect on cancer incidence. In addition, members of the 7A subfamily have been shown to have the potential to protect against cytotoxicity of other reactive aldehydes, such as acrolein (97). Structure determination of rodent AKR7A members (98, 99) and recently of human AKR7A2 and AKR7A3 (J. Debreczni, K.L. Kavanagh, B. Marsden, U. Oppermann, unpublished) provide a basis to rationalize structure-activity relationships of this subfamily.

QUINONE REDUCTASES

As discussed above, redox cycling of quinones is initiated by different oxidoreductases of the SDR or AKR type. In addition to those enzymes, several other types of oxidoreductases have been discovered to catalyze NADPH-dependent quinone reduction. Besides the endogenous production of ROS through oxidoreductases in the respiratory chain (not discussed in this review), three distinct classes of oxidoreductases are summarized, including the classical NAD(P)(H)-dependent quinone reductase (NQO1, DT diaphorase), thioredoxin reductase, and a largely undefined class of quinone reductases belonging to the medium-chain dehydrogenase/reductase (MDR) family.

NAD(P)H-Dependent Quinone Reductases (NQO1, NQO2)

The dimeric, flavin-dependent enzyme NADPH-dependent quinone reductase (NQO1) is a well-characterized enzyme system of crucial importance in protection against oxidative stress (100, 101). This function can occur through at least three different mechanisms: (*a*) two-electron reduction of xenobiotic quinones [mainly para-quinones (100)] to their hydroquinones; (*b*) recycling of endogenous low-molecular-weight antioxidants, such as ubiquinone and α-tocopherol quinone, to their antioxidant hydroquinones; and (*c*) by direct interaction of NQO1 with the central regulator of DNA damage control and apoptosis, the p53 protein. The enzymatic mechanism of quinone reduction proceeds through a ping-pong mechanism, whereby NADPH binds to the enzyme, reduces the protein bound flavin to FADH2, and leaves the protein before the substrate binds and gets reduced (102). NQO1 displays a wide, species-specific substrate spectrum, including quinones and

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their glutathione metabolites, quinoneimines, and several azo- and nitroaromatic compounds. The four-electron reduction of nitroaromatic compounds to the hydroxylamine derivatives is likely achieved through a cooperative behavior of the two subunits. The enzymatic properties of NQO1 have been exploited in antitumor therapy using several prodrugs (e.g., mitomycin C, the diaziridinylbenzoquine RH1, or 5-[aziridin-1-yl] -2,4-dinitrobenzamide [CB1954]) that are converted to cytotoxic, DNA-alkylating metabolites (103). Although extremely effective in rodent models of tumorigenesis, human therapy is rather limited with mitomycin C or CB1954 owing to distinct differences in the active sites of rodent and human NQO1 (104, 105), whereas RH1 appears to be more effective (103). A conceptually different approach is used by targeting the related enzyme NQO2, a paralog found in the mammalian genome. NQO2 is structurally similar to NQO1 (106); but lacks a C-terminal stretch of residues. This structural feature makes it impossible to bind NADPH; instead, NQO2 can only reduce quinones or nitroaromatic compounds by utilizing a shortened nicotinamide derivative such as nicotinamide riboside, a cofactor that is not found in the cell (107). This property makes NQO2-mediated activity dependent on exogenous cofactor administration, and, when given in combination with CB1954, it is highly cytotoxic to tumor cells, thus constituting a unique prodrug-activating mechanism (107).

Animal models and cell culture studies substantiate the importance of NQO1 in protection against oxidative stress and toward carcinogenic properties of benzo(a)pyrene-mediated through quinone metabolism (100, 101, 108, 109). Its role as an antioxidant enzyme is highlighted by the fact that NQO1 expression is regulated through the antioxidant response element (110), conferring inducibility toward a variety of reagents, such as catechols, dithiolethiones, hydroperoxides, quinones, or α/β unsaturated carbonyls.

Thioredoxin Reductase

Thioredoxin reductases (TxnRDs) are essential components of cellular redox homeostasis and are involved in the regulation of many cellular functions, such as proliferation and apoptosis. They regulate central transcription factors (Jun, Fos, NFκB, Ref-1, and p53) and modulate the signaling of MAP kinases and their phosphatases (28). TxnRDs are flavin-containing selenoproteins with a penultimate C-terminal selenocystein residue that is required for activity. The best-studied function of TxnRDs is its mechanism in the NADPH-dependent reduction of the redox active disulfide of thioredoxins and low-molecular weight compounds, such as dithionitrobenzoic acid or lipoic acid (26). However, recent studies show a direct involvement of mammalian type 1 TxnRD in the reduction of quinones and nitroaromatic compounds. TxnRD catalyzes the compound-specific 1- or 2-electron reduction of ortho- (e.g., 9,10 phenanthrenequinone) and para-quinones (e.g., 1,4 benzoquinone; 5,8-dihydroxy-1,4 naphtoquinone). It also reduces nitroaromatic compounds such as p-dinitrobenzene (111, 112). The one-electron reductions lead to the production of semiquinones and superoxide, which produce caspase 3/7 activation and apoptosis in HeLa cells (111, 112).

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MDR-Type Quinone Reductases

Quinone reduction has been reported for the quinone reductase subgroup of the MDR superfamily (113–116). The MDR family, like SDRs, comprises a large variation of activities. Whereas the Zn-dependent alcohol dehydrogenases constitute a well-studied branch of the MDRs (117–120), few studies have addressed the quinone subfamily. Probably the best-studied members of this group are ζ-crystallin (CRYZ), p53-inducible gene 3 [PIG-3, TP53I (tumor protein 53 inducible)], and leukotriene B4 dehydrogenase (LTB4DH) (116, 117). The ζ-crystallin and PIG-3 enzymes show high catalytic activity toward several quinones; however, their precise role in human physiology and in ROS metabolism needs to be determined. Besides inactivation of eicosanoids, LTB4DH catalyzes the reduction of the double bond of unsaturated reactive lipid aldehydes, such as 4-hydroxy-2-nonenal, and thus constitutes an important detoxification mechanism because this reaction prevents Michael addition reactions by the lipid aldehyde (36, 121). Interestingly, structure determination of LTB4DH reveals that the enzyme has a protein interaction site able to interact with SH3 domains (122). The role of this MDR protein in antioxidant responses is further highlighted by the fact that gene regulation occurs through the Keap/Nrf2 pathway (123). Besides the three MDR members, at least four additional highly conserved genes with possible homologous functions are present in the human genome but they have not been characterized to date.

SUMMARY POINTS

1. Carbonyl groups (ketones, aldehydes) are formed during endogenous metabolism or are found in xenobiotics. Reduction of xenobiotic carbonyls is a significant metabolic route to produce more soluble and often less toxic compounds, which can be conjugated and excreted. Carbonyl reductases belong to two main protein families, short-chain dehydrogenases (SDRs) and aldo-keto reductases (AKRs). The major xenobiotic metabolizing enzymes are carbonyl reductase (CBR1) and several members of the AKR1C and AKR7A subfamilies. These carbonyl reductases often show overlapping substrate specificities and frequently have defined physiological functions, e.g., in endogenous steroid or eicosanoid metabolism. Several of the carbonyl reductases participate in the detoxification of reactive lipid aldehydes, formed during oxidative stress and lipid peroxidation, and a protective role of CBR1 in neurodegeneration is likely.
2. Two-electron reduction of endogenous and toxic xenobiotic quinones yields the hydroquinone derivatives, which often are autoxidized and redox cycled by molecular oxygen, producing superoxide anion and the semiquinone radical, thus initiating oxidative stress. Besides the classical NADPH-dependent quinone reductase NQO1 and its paralog NQO2, quinones are efficiently metabolized by thioredoxin reductase and several poorly characterized

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members of the MDR family, as well as several of the carbonyl reductases of the SDR and AKR families.

UNRESOLVED ISSUES/FUTURE DIRECTIONS

1. Whereas the major carbonyl and quinone reductases appear to be identified in mammalian genomes, a surprising lack of in vivo data is apparent. This is further complicated by an obviously broad substrate specificity, species differences in substrate specificities, and, in certain cases, a lack of clear orthologs, which makes an extrapolation to human metabolism difficult. Animal or close to animal in vitro cell culture systems will be instrumental for human risk assessment studies. In particular, different CBR or AKR animal models need to be created or reevaluated for their potential role in protection against reactive or toxic carbonyls.
2. Progress on obtaining high-resolution X-ray crystal structures for human and rodent carbonyl and quinone reductases has been substantial over the past few years, but the work needs to be continued. Structural studies need to be more systematically directed toward obtaining ligand or substrate complexes to fully investigate chemical space and binding behavior. Despite the apparent large number of substrate specificity studies conducted thus far, more information on possible endogenous substrates, as well as further chemical scaffolds, is necessary for the majority of the carbonyl reductases described, and information on structure-activity relationships needs to be correlated to animal data.
3. Reductive xenobiotic carbonyl metabolism is now a well-established Phase I pathway. However, it needs to be further translated into preclinical pharmaceutical and toxicological research.
4. Few well-established genetic studies exist (e.g., on NQO1 or NQO2), making further pharmacogenomic and toxicogenomic investigations mandatory for carbonyl and quinone reductases.

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LITERATURE CITED

1. Bauman DR, Steckelbroeck S, Penning TM. 2004. The roles of aldo-keto reductases in steroid hormone action. *Drug News Perspect.* 17:563–78
2. Nobel S, Abrahmsen L, Oppermann U. 2001. Metabolic conversion as a prereceptor control mechanism for lipophilic hormones. *Eur. J. Biochem.* 268:4113–25
3. Oppermann U. 2006. Type 1 11β-hydroxysteroid dehydrogenase as universal target in metabolic diseases? *Drug Targets: Immune Endocr. Metabol. Disord.* 6:259–69
4. Penning TM, Steckelbroeck S, Bauman DR, Miller MW, Jin Y, et al. 2006. Aldo-keto reductase (AKR) 1C3: role in prostate disease and the development of specific inhibitors. *Mol. Cell Endocrinol.* 248:182–91
5. Draper N, Stewart PM. 2005. 11beta-hydroxysteroid dehydrogenase and the prereceptor regulation of corticosteroid hormone action. *J. Endocrinol.* 186:251–71
6. Seckl JR, Walker BR. 2004. 11beta-hydroxysteroid dehydrogenase type 1 as a modulator of glucocorticoid action: from metabolism to memory. *Trends Endocrinol. Metab.* 15:418–24
7. Thieringer R, Hermanowski-Vosatka A. 2005. Inhibition of 11beta-HSD1 as a novel treatment for the metabolic syndrome: do glucocorticoids play a role? *Expert. Rev. Cardiovasc. Ther.* 3:911–24
8. Doorn JA, Petersen DR. 2002. Covalent modification of amino acid nucleophiles by the lipid peroxidation products 4-hydroxy-2-nonenal and 4-oxo-2-nonenal. *Chem. Res. Toxicol.* 15:1445–50
9. **Felsted RL, Bachur NR. 1980. Mammalian carbonyl reductases. *Drug Metab. Rev.* 11:1–60**
10. Forrest GL, Gonzalez B, Tseng W, Li X, Mann J. 2000. Human carbonyl reductase overexpression in the heart advances the development of doxorubicin-induced cardiotoxicity in transgenic mice. *Cancer Res.* 60:5158–64
11. Lin D, Lee HG, Liu Q, Perry G, Smith MA, Sayre LM. 2005. 4-Oxo-2-nonenal is both more neurotoxic and more protein reactive than 4-hydroxy-2-nonenal. *Chem. Res. Toxicol.* 18:1219–31
12. Liu Q, Raina AK, Smith MA, Sayre LM, Perry G. 2003. Hydroxynonenal, toxic carbonyls, and Alzheimer disease. *Mol. Aspects Med.* 24:305–13
13. **Matsunaga T, Shintani S, Hara A. 2006. Multiplicity of mammalian reductases for xenobiotic carbonyl compounds. *Drug Metab. Pharmacokinet.* 21:1–18**
14. O'Brien PJ, Siraki AG, Shangari N. 2005. Aldehyde sources, metabolism, molecular toxicity mechanisms, and possible effects on human health. *Crit. Rev. Toxicol.* 35:609–62
15. **Maser E. 1995. Xenobiotic carbonyl reduction and physiological steroid oxidoreduction. The pluripotency of several hydroxysteroid dehydrogenases. *Biochem. Pharmacol.* 49:421–40**
16. Oppermann UC, Maser E. 2000. Molecular and structural aspects of xenobiotic carbonyl metabolizing enzymes. Role of reductases and dehydrogenases in xenobiotic phase I reactions. *Toxicology* 144:71–81

References 9 and 15 provide insights into relationships between xenobiotic carbonyl reductases and endogenous pathways and provide a good resource for nonmammalian carbonyl reductases.

Provides an excellent summary on the majority of mammalian xenobiotic carbonyl reductases.

Annu. Rev. Pharmacol. Toxicol. 2007.47:293-322.

17. Penning TM, Burczynski ME, Jez JM, Hung CF, Lin HK, et al. 2000. Human 3alpha-hydroxysteroid dehydrogenase isoforms (AKR1C1-AKR1C4) of the aldo-keto reductase superfamily: functional plasticity and tissue distribution reveals roles in the inactivation and formation of male and female sex hormones. *Biochem. J.* 351:67–77
18. Wermuth B. 1981. Purification and properties of an NADPH-dependent carbonyl reductase from human brain. Relationship to prostaglandin 9-ketoreductase and xenobiotic ketone reductase. *J. Biol. Chem*. 256:1206–13
19. Vander Jagt DL, Hunsaker LA, Robinson B, Stangebye LA, Deck LM. 1990. Aldehyde and aldose reductases from human placenta. Heterogeneous expression of multiple enzyme forms. *J. Biol. Chem*. 265:10912–18
20. Klaunig JE, Kamendulis LM. 2004. The role of oxidative stress in carcinogenesis. *Annu. Rev. Pharmacol. Toxicol*. 44:239–67
21. Musiek ES, Breeding RS, Milne GL, Zanoni G, Morrow JD, McLaughlin B. 2006. Cyclopentenone isoprostanes are novel bioactive products of lipid oxidation which enhance neurodegeneration. *J. Neurochem*. 97(5):1301–13
22. Storz P. 2006. Reactive oxygen species-mediated mitochondria-to-nucleus signaling: a key to aging and radical-caused diseases. *Sci. STKE* 2006:re3
23. Stocker R, Keaney JFJ. 2004. Role of oxidative modifications in atherosclerosis. *Physiol. Rev*. 84:1381–78
24. Beal MF. 2005. Mitochondria take center stage in aging and neurodegeneration. *Ann. Neurol.* 58:495–505
25. Jarabak J, Harvey RG. 1993. Studies on three reductases which have polycyclic aromatic hydrocarbon quinones as substrates. *Arch. Biochem. Biophys*. 303:394–401
26. Nordberg J, Arner ES. 2001. Reactive oxygen species, antioxidants, and the mammalian thioredoxin system. *Free Radic. Biol. Med*. 31:1287–312
27. Kovacic P, Jacintho JD. 2001. Mechanisms of carcinogenesis: focus on oxidative stress and electron transfer. *Curr. Med. Chem*. 8:773–96
28. Liu H, Colavitti R, Rovira II, Finkel T. 2005. Redox-dependent transcriptional regulation. *Circ. Res*. 97:967–74
29. Loft S, Poulsen HE. 1996. Cancer risk and oxidative DNA damage in man. *J. Mol. Med*. 74:297–312
30. Petersen DR, Doorn JA. 2004. Reactions of 4-hydroxynonenal with proteins and cellular targets. *Free Radic. Biol. Med*. 37:937–45
31. Soreghan BA, Yang F, Thomas SN, Hsu J, Yang AJ. 2003. High-throughput proteomic-based identification of oxidatively induced protein carbonylation in mouse brain. *Pharm. Res*. 20:1713–20
32. Perry G, Nunomura A, Hirai K, Zhu X, Perez M, et al. 2002. Is oxidative damage the fundamental pathogenic mechanism of Alzheimer's and other neurodegenerative diseases? *Free Radic. Biol. Med.* 33:1475–79
33. Sayre LM, Smith MA, Perry G. 2001. Chemistry and biochemistry of oxidative stress in neurodegenerative disease. *Curr. Med. Chem*. 8:721–38
34. Esterbauer H, Schaur RJ, Zollner H. 1991. Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. *Free Radic. Biol. Med*. 11:81–128

Annu. Rev. Pharmacol. Toxicol. 2007.47:293-322.

35. Musiek ES, Milne GL, McLaughlin B, Morrow JD. 2005. Cyclopentenone eicosanoids as mediators of neurodegeneration: a pathogenic mechanism of oxidative stress-mediated and cyclooxygenase-mediated neurotoxicity. *Brain Pathol*. 15:149–58
36. Dick RA, Kwak MK, Sutter TR, Kensler TW. 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*. 276:40803–10
37. **Doorn JA, Maser E, Blum A, Claffey DJ, Petersen DR. 2004. Human carbonyl reductase catalyzes reduction of 4-oxonon-2-enal. *Biochemistry* 43:13106–14**
38. Oppermann U, Filling C, Hult M, Shafqat N, Wu X, et al. 2003. Short-chain dehydrogenases/reductases (SDR): the 2002 update. *Chem. Biol. Interact.* 143–144:247–53
39. Jez JM, Bennett MJ, Schlegel BP, Lewis M, Penning TM. 1997. Comparative anatomy of the aldo-keto reductase superfamily. *Biochem. J.* 326(Pt. 3):625–36
40. Penning TM. 1997. Molecular endocrinology of hydroxysteroid dehydrogenases. *Endocr. Rev*. 18:281–305
41. Filling C, Berndt KD, Benach J, Knapp S, Prozorovski T, et al. 2002. Critical residues for structure and catalysis in short-chain dehydrogenases/reductases. *J. Biol. Chem*. 277:25677–84
42. Ris MM, von Wartburg JP. 1973. Heterogeneity of NADPH-dependent aldehyde reductase from human and rat brain. *Eur. J. Biochem*. 37:69–77
43. Wermuth B, Bohren KM, Heinemann G, von Wartburg JP, Gabbay KH. 1988. Human carbonyl reductase. Nucleotide sequence analysis of a cDNA and amino acid sequence of the encoded protein. *J. Biol. Chem*. 263:16185–88
44. Wermuth B, Burgisser H, Bohren K, von Wartburg JP. 1982. Purification and characterization of human-brain aldose reductase. *Eur. J. Biochem*. 127:279–84
45. Wirth H, Wermuth B. 1992. Immunohistochemical localization of carbonyl reductase in human tissues. *J. Histochem. Cytochem*. 40:1857–63
46. Forrest GL, Akman S, Krutzik S, Paxton RJ, Sparkes RS, et al. 1990. Induction of a human carbonyl reductase gene located on chromosome 21. *Biochim. Biophys. Acta* 1048:149–55
47. Wermuth B, Platts KL, Seidel A, Oesch F. 1986. Carbonyl reductase provides the enzymatic basis of quinone detoxication in man. *Biochem. Pharmacol*. 35:1277–82
48. Atalla A, Breyer-Pfaff U, Maser E. 2000. Purification and characterization of oxidoreductases-catalyzing carbonyl reduction of the tobacco-specific nitrosamine 4-methylnitrosamino-1-(3-pyridyl)-1-butanone (NNK) in human liver cytosol. *Xenobiotica* 30:755–69
49. Olson LE, Bedja D, Alvey SJ, Cardounel AJ, Gabrielson KL, Reeves RH. 2003. Protection from doxorubicin-induced cardiac toxicity in mice with a null allele of carbonyl reductase 1. *Cancer Res*. 63:6602–6
50. Forrest GL, Gonzalez B. 2000. Carbonyl reductase. *Chem. Biol. Interact*. 129:21–40

Provides experimental evidence for the involvement of CBR1 in the detoxification of reactive lipid.

Annu. Rev. Pharmacol. Toxicol. 2007.47:293-322.

51. Tanaka M, Bateman R, Rauh D, Vaisberg E, Ramachandani S, et al. 2005. An unbiased cell morphology-based screen for new, biologically active small molecules. *PLoS Biol.* 3:e128

52. Ismail E, Al-Mulla F, Tsuchida S, Suto K, Motley P, et al. 2000. Carbonyl reductase: a novel metastasis-modulating function. *Cancer Res.* 60:1173–76

53. Kelner MJ, Estes L, Rutherford M, Uglik SF, Peitzke JA. 1997. Heterologous expression of carbonyl reductase: demonstration of prostaglandin 9-ketoreductase activity and paraquat resistance. *Life Sci*. 61:2317–22

54. Terada T, Sugihara Y, Nakamura K, Mizobuchi H, Maeda M. 2003. Further characterization of Chinese hamster carbonyl reductases (CHCRs). *Chem. Biol. Interact.* 143–144:373–81

55. Botella JA, Ulschmid JK, Gruenewald C, Moehle C, Kretzschmar D, et al. 2004. The *Drosophila* carbonyl reductase sniffer prevents oxidative stress-induced neurodegeneration. *Curr. Biol.* 14:782–86

56. Sgraja T, Ulschmid J, Becker K, Schneuwly S, Klebe G, et al. 2004. Structural insights into the neuroprotective-acting carbonyl reductase Sniffer of *Drosophila melanogaster*. *J. Mol. Biol.* 342:1613–24

57. Doorn JA, Petersen DR. 2003. Covalent adduction of nucleophilic amino acids by 4-hydroxynonenal and 4-oxononenal. *Chem. Biol. Interact.* 143–144:93–100

58. Maser E. 2006. Neuroprotective role for carbonyl reductase? *Biochem. Biophys. Res. Commun*. 340:1019–22

59. Anwar A, Dehn D, Siegel D, Kepa JK, Tang LJ, et al. 2003. Interaction of human NAD(P)H:quinone oxidoreductase 1 (NQO1) with the tumor suppressor protein p53 in cells and cell-free systems. *J. Biol. Chem.* 278:10368–73

60. Asher G, Lotem J, Tsvetkov P, Reiss V, Sachs L, Shaul Y. 2003. P53 hotspot mutants are resistant to ubiquitin-independent degradation by increased binding to NAD(P)H:quinone oxidoreductase 1. *Proc. Natl. Acad. Sci. USA* 100:15065–70

61. Nakayama T, Yashiro K, Inoue Y, Matsuura K, Ichikawa H, et al. 1986. Characterization of pulmonary carbonyl reductase of mouse and guinea pig. *Biochim. Biophys. Acta* 882:220–27

62. Maser E, Netter KJ. 1991. Reductive metabolism of metyrapone by a quercitrin-sensitive ketone reductase in mouse liver cytosol. *Biochem. Pharmacol*. 41:1595–99

63. Maser E, Bannenberg G. 1994. 11 beta-hydroxysteroid dehydrogenase mediates reductive metabolism of xenobiotic carbonyl compounds. *Biochem. Pharmacol.* 47:1805–12

64. Oppermann UC, Netter KJ, Maser E. 1995. Cloning and primary structure of murine 11 beta-hydroxysteroid dehydrogenase/microsomal carbonyl reductase. *Eur. J. Biochem*. 227:202–8

65. Odermatt A, Arnold P, Stauffer A, Frey BM, Frey FJ. 1999. The N-terminal anchor sequences of 11beta-hydroxysteroid dehydrogenases determine their orientation in the endoplasmic reticulum membrane. *J. Biol. Chem*. 274:28762–70

Describes a cell morphology–based screen for inhibitors, resulting in the characterization of CBR1-specific inhibitors, structure determination of a CBR1-ligand complex, and the determination of a critical role of human CBR1 in serum-induced apoptosis.

Reports on the essential role of *sniffer*, the *Drosophila* ortholog of mammalian CBR1, in the protection of oxygen-induced neurodegeneration, suggesting similar function in higher vertebrates.

Annu. Rev. Pharmacol. Toxicol. 2007.47:293-322.

66. Maser E. 1998. 11Beta-hydroxysteroid dehydrogenase responsible for carbonyl reduction of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in mouse lung microsomes. *Cancer Res.* 58:2996–3003
67. Wsol V, Szotakova B, Skalova L, Maser E. 2003. Stereochemical aspects of carbonyl reduction of the original anticancer drug oracin by mouse liver microsomes and purified 11beta-hydroxysteroid dehydrogenase type 1. *Chem. Biol. Interact.* 143–144:459–68
68. Maser E, Oppermann UC. 1997. Role of type-1 11beta-hydroxysteroid dehydrogenase in detoxification processes. *Eur. J. Biochem.* 249:365–69
69. Maser E. 1997. Stress, hormonal changes, alcohol, food constituents and drugs: factors that advance the incidence of tobacco smoke-related cancer? *Trends Pharmacol. Sci.* 18:270–75
70. Kallberg Y, Oppermann U, Jornvall H, Persson B. 2002. Short-chain dehydrogenase/reductase (SDR) relationships: a large family with eight clusters common to human, animal, and plant genomes. *Protein. Sci.* 11:636–41
71. Nakagawa J, Ishikura S, Asami J, Isaji T, Usami N, et al. 2002. Molecular characterization of mammalian dicarbonyl/L-xylulose reductase and its localization in kidney. *J. Biol. Chem.* 277:17883–91
72. Shafqat N, Shafqat J, Eissner G, Marschall H, Tryggvason K, et al. 2006. Hep27, a member of the short-chain dehydrogenase/reductase family, is an NADPH dependent dicarbonyl reductase expressed in endothelial tissue. *Cell Mol. Life Sci.* 63(10):1205–13
73. Monnier VM, Nagaraj RH, Portero-Otin M, Glomb M, Elgawish AH, et al. 1996. Structure of advanced Maillard reaction products and their pathological role. *Nephrol. Dial. Transplant.* 11(Suppl. 5):20–26
74. Monnier VM, Sell DR, Nagaraj RH, Miyata S, Grandhee S, et al. 1992. Maillard reaction-mediated molecular damage to extracellular matrix and other tissue proteins in diabetes, aging, and uremia. *Diabetes* 41(Suppl. 2):36–41
75. Zimmermann FK, Mohr A. 1992. Formaldehyde, glyoxal, urethane, methyl carbamate, 2,3-butanedione, 2,3-hexanedione, ethyl acrylate, dibromoacetonitrile and 2-hydroxypropionitrile induce chromosome loss in *Saccharomyces cerevisiae*. *Mutat. Res.* 270:151–66
76. Lyons TJ. 2002. Glycation, carbonyl stress, EAGLEs, and the vascular complications of diabetes. *Semin. Vasc. Med.* 2:175–89
77. Kalousova M, Zima T, Tesar V, Dusilova-Sulkova S, Skrha J. 2005. Advanced glycoxidation end products in chronic diseases-clinical chemistry and genetic background. *Mutat. Res.* 579:37–46
78. Askonas LJ, Ricigliano JW, Penning TM. 1991. The kinetic mechanism catalysed by homogeneous rat liver 3 alpha-hydroxysteroid dehydrogenase. Evidence for binary and ternary dead-end complexes containing nonsteroidal anti-inflammatory drugs. *Biochem. J.* 278(Pt. 3):835–41
79. Grimshaw CE, Bohren KM, Lai CJ, Gabbay KH. 1995. Human aldose reductase: rate constants for a mechanism including interconversion of ternary complexes by recombinant wild-type enzyme. *Biochemistry* 34:14356–65

Annu. Rev. Pharmacol. Toxicol. 2007.47:293-322.

80. Kratzer R, Kavanagh KL, Wilson DK, Nidetzky B. 2004. Studies of the enzymic mechanism of *Candida* tenuis xylose reductase (AKR 2B5): X-ray structure and catalytic reaction profile for the H113A mutant. *Biochemistry* 43:4944–54
81. Ohara H, Miyabe Y, Deyashiki Y, Matsuura K, Hara A. 1995. Reduction of drug ketones by dihydrodiol dehydrogenases, carbonyl reductase and aldehyde reductase of human liver. *Biochem. Pharmacol.* 50:221–27
82. O'Connor T, Ireland LS, Harrison DJ, Hayes JD. 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
83. Vander Jagt DL, Hassebrook RK, Hunsaker LA, Brown WM, Royer RE. 2001. Metabolism of the 2-oxoaldehyde methylglyoxal by aldose reductase and by glyoxalase-I: roles for glutathione in both enzymes and implications for diabetic complications. *Chem. Biol. Interact.* 130–132:549–62
84. Comer GM, Ciulla TA. 2005. Current and future pharmacological intervention for diabetic retinopathy. *Expert Opin. Emerg. Drugs* 10:441–55
85. Doorn JA, Srivastava SK, Petersen DR. 2003. Aldose reductase catalyzes reduction of the lipid peroxidation product 4-oxonon-2-enal. *Chem. Res. Toxicol.* 16:1418–23
86. Takahashi M, Fujii J, Miyoshi E, Hoshi A, Taniguchi N. 1995. Elevation of aldose reductase gene expression in rat primary hepatoma and hepatoma cell lines: implication in detoxification of cytotoxic aldehydes. *Int. J. Cancer* 62:749–54
87. Ax W, Soldan M, Koch L, Maser E. 2000. Development of daunorubicin resistance in tumor cells by induction of carbonyl reduction. *Biochem. Pharmacol.* 59:293–300
88. Martin HJ, Breyer-Pfaff U, Wsol V, Venz S, Block S, Maser E. 2006. Purification and characterization of akr1b10 from human liver: role in carbonyl reduction of xenobiotics. *Drug Metab. Dispos.* 34:464–70
89. Lovering AL, Ride JP, Bunce CM, Desmond JC, Cummings SM, White SA. 2004. Crystal structures of prostaglandin D(2) 11-ketoreductase (AKR1C3) in complex with the nonsteroidal anti-inflammatory drugs flufenamic acid and indomethacin. *Cancer Res.* 64:1802–10
90. Matsuura K, Shiraishi H, Hara A, Sato K, Deyashiki Y, et al. 1998. Identification of a principal mRNA species for human 3alpha-hydroxysteroid dehydrogenase isoform (AKR1C3) that exhibits high prostaglandin D2 11-ketoreductase activity. *J. Biochem.* 124:940–46
91. Palackal NT, Lee SH, Harvey RG, Blair IA, Penning TM. 2002. Activation of polycyclic aromatic hydrocarbon trans-dihydrodiol proximate carcinogens by human aldo-keto reductase (AKR1C) enzymes and their functional overexpression in human lung carcinoma (A549) cells. *J. Biol. Chem.* 277:24799–808
92. Eaton DL, Gallagher EP. 1994. Mechanisms of aflatoxin carcinogenesis. *Annu. Rev. Pharmacol. Toxicol.* 34:135–72
93. Ellis EM, Judah DJ, Neal GE, Hayes JD. 1993. An ethoxyquin-inducible aldehyde reductase from rat liver that metabolizes aflatoxin B1 defines a subfamily of aldo-keto reductases. *Proc. Natl. Acad. Sci. USA* 90:10350–54

Annu. Rev. Pharmacol. Toxicol. 2007.47:293-322.

94. Knight LP, Primiano T, Groopman JD, Kensler TW, Sutter TR. 1999. cDNA cloning, expression and activity of a second human aflatoxin B1-metabolizing member of the aldo-keto reductase superfamily, AKR7A3. *Carcinogenesis* 20:1215–23
95. Ireland LS, Harrison DJ, Neal GE, Hayes JD. 1998. Molecular cloning, expression and catalytic activity of a human AKR7 member of the aldo-keto reductase superfamily: evidence that the major 2-carboxybenzaldehyde reductase from human liver is a homologue of rat aflatoxin B1-aldehyde reductase. *Biochem. J.* 332(Pt. 1):21–34
96. Guengerich FP, Cai H, McMahon M, Hayes JD, Sutter TR, et al. 2001. Reduction of aflatoxin B1 dialdehyde by rat and human aldo-keto reductases. *Chem. Res. Toxicol.* 14:727–37
97. Gardner R, Kazi S, Ellis EM. 2004. Detoxication of the environmental pollutant acrolein by a rat liver aldo-keto reductase. *Toxicol Lett* 148:65–72
98. Kozma E, Brown E, Ellis EM, Lapthorn AJ. 2002. The crystal structure of rat liver AKR7A1. A dimeric member of the aldo-keto reductase superfamily. *J. Biol. Chem.* 277:16285–93
99. Zhu X, Lapthorn AJ, Ellis EM. 2006. Crystal structure of mouse succinic semialdehyde reductase AKR7A5: structural basis for substrate specificity. *Biochemistry* 45:1562–70
100. Dinkova-Kostova AT, Talalay P. 2000. Persuasive evidence that quinone reductase type 1 (DT diaphorase) protects cells against the toxicity of electrophiles and reactive forms of oxygen. *Free Radic. Biol. Med.* 29:231–40
101. Nioi P, Hayes JD. 2004. Contribution of NAD(P)H:quinone oxidoreductase 1 to protection against carcinogenesis, and regulation of its gene by the Nrf2 basic-region leucine zipper and the arylhydrocarbon receptor basic helix-loop-helix transcription factors. *Mutat. Res.* 555:149–71
102. Li R, Bianchet MA, Talalay P, Amzel LM. 1995. The three-dimensional structure of NAD(P)H:quinone reductase, a flavoprotein involved in cancer chemoprotection and chemotherapy: mechanism of the two-electron reduction. *Proc. Natl. Acad. Sci. USA* 92:8846–50
103. Danson S, Ward TH, Butler J, Ranson M. 2004. DT-diaphorase: a target for new anticancer drugs. *Cancer Treat. Rev.* 30:437–49
104. Faig M, Bianchet MA, Talalay P, Chen S, Winski S, et al. 2000. Structures of recombinant human and mouse NAD(P)H:quinone oxidoreductases: species comparison and structural changes with substrate binding and release. *Proc. Natl. Acad. Sci. USA* 97:3177–82
105. Knox RJ, Burke PJ, Chen S, Kerr DJ. 2003. CB 1954: from the Walker tumor to NQO2 and VDEPT. *Curr. Pharm. Des.* 9:2091–104
106. Foster CE, Bianchet MA, Talalay P, Faig M, Amzel LM. 2000. Structures of mammalian cytosolic quinone reductases. *Free Radic. Biol. Med.* 29:241–45
107. Knox RJ, Jenkins TC, Hobbs SM, Chen S, Melton RG, Burke PJ. 2000. Bioactivation of 5-(aziridin-1-yl)-2,4-dinitrobenzamide (CB 1954) by human NAD(P)H quinone oxidoreductase 2: a novel cosubstrate-mediated antitumor prodrug therapy. *Cancer Res.* 60:4179–86

Annu. Rev. Pharmacol. Toxicol. 2007.47:293-322.

108. Joseph P, Jaiswal AK. 1994. NAD(P)H:quinone oxidoreductase1 (DT diaphorase) specifically prevents the formation of benzo[a]pyrene quinone-DNA adducts generated by cytochrome P4501A1 and P450 reductase. *Proc. Natl. Acad. Sci. USA* 91:8413–17
109. Joseph P, Jaiswal AK. 1998. NAD(P)H:quinone oxidoreductase 1 reduces the mutagenicity of DNA caused by NADPH:P450 reductase-activated metabolites of benzo(a)pyrene quinones. *Br. J. Cancer* 77:709–19
110. Nioi P, McMahon M, Itoh K, Yamamoto M, Hayes JD. 2003. Identification of a novel Nrf2-regulated antioxidant response element (ARE) in the mouse NAD(P)H:quinone oxidoreductase 1 gene: reassessment of the ARE consensus sequence. *Biochem. J.* 374:337–48
111. Cenas N, Nivinskas H, Anusevicius Z, Sarlauskas J, Lederer F, Arner ES. 2004. Interactions of quinones with thioredoxin reductase: a challenge to the antioxidant role of the mammalian selenoprotein. *J. Biol. Chem.* 279:2583–92
112. Cenas N, Prast S, Nivinskas H, Sarlauskas J, Arner ES. 2006. Interactions of nitroaromatic compounds with the mammalian selenoprotein thioredoxin reductase and the relation to induction of apoptosis in human cancer cells. *J. Biol. Chem.* 281:5593–603
113. Duhaiman AS. 1996. Characterization of zeta-crystallin inhibition by juglone. *Biochem. Biophys. Res. Commun.* 218:648–52
114. Rao PV, Krishna CM, Zigler JSJ. 1992. Identification and characterization of the enzymatic activity of zeta-crystallin from guinea pig lens. A novel NADPH:quinone oxidoreductase. *J. Biol. Chem.* 267:96–102
115. Tumminia SJ, Rao PV, Zigler JSJ, Russell P. 1993. Xenobiotic induction of quinone oxidoreductase activity in lens epithelial cells. *Biochim. Biophys. Acta* 1203:251–59
116. Persson B, Zigler JSJ, Jornvall H. 1994. A superfamily of medium-chain dehydrogenases/reductases (MDR). Sub-lines including zeta-crystallin, alcohol and polyol dehydrogenases, quinone oxidoreductase enoyl reductases, VAT-1 and other proteins. *Eur. J. Biochem.* 226:15–22
117. Nordling E, Jornvall H, Persson B. 2002. Medium-chain dehydrogenases/reductases (MDR). Family characterizations including genome comparisons and active site modeling. *Eur. J. Biochem.* 269:4267–76
118. Plapp BV, Eklund H, Branden CI. 1978. Crystallography of liver alcohol dehydrogenase complexed with substrates. *J. Mol. Biol.* 122:23–32
119. Ramaswamy S, Eklund H, Plapp BV. 1994. Structures of horse liver alcohol dehydrogenase complexed with NAD+ and substituted benzyl alcohols. *Biochemistry* 33:5230–37
120. Hurley TD, Bosron WF, Stone CL, Amzel LM. 1994. Structures of three human beta alcohol dehydrogenase variants. Correlations with their functional differences. *J. Mol. Biol.* 239:415–29
121. Dick RA, Yu X, Kensler TW. 2004. NADPH alkenal/one oxidoreductase activity determines sensitivity of cancer cells to the chemotherapeutic alkylating agent irofulven. *Clin. Cancer Res.* 10:1492–99

Annu. Rev. Pharmacol. Toxicol. 2007.47:293-322.

122. Hori T, Yokomizo T, Ago H, Sugahara M, Ueno G, et al. 2004. Structural basis of leukotriene B4 12-hydroxydehydrogenase/15-Oxo-prostaglandin 13-reductase catalytic mechanism and a possible Src homology 3 domain binding loop. *J. Biol. Chem.* 279:22615–23
123. Primiano T, Li Y, Kensler TW, Trush MA, Sutter TR. 1998. Identification of dithiolethione-inducible gene-1 as a leukotriene B4 12-hydroxydehydrogenase: implications for chemoprevention. *Carcinogenesis* 19:999–1005
124. Wilson DK, Bohren KM, Gabbay KH, Quiocho FA. 1992. An unlikely sugar substrate site in the 1.65 A structure of the human aldose reductase holoenzyme implicated in diabetic complications. *Science* 257:81–84
125. El-Kabbani O, Carbone V, Darmanin C, Oka M, Mitschler A, et al. 2005. Structure of aldehyde reductase holoenzyme in complex with the potent aldose reductase inhibitor fidarestat: implications for inhibitor binding and selectivity. *J. Med. Chem.* 48:5536–42
126. Chen S, Knox R, Wu K, Deng PS, Zhou D, et al. 1997. Molecular basis of the catalytic differences among DT-diaphorase of human, rat, and mouse. *J. Biol. Chem.* 272:1437–39

RELATED REVIEWS

Sedlak TW, Snyder SH. 2004. Bilirubin benefits: cellular protection by a biliverdin reductase antioxidant cycle. *Pediatrics* 113:1776–82

Jin Y, Penning T. 2006. Aldo-keto reductases and bioactivation/detoxication. *Annu. Rev. Pharmacol. Toxicol.* 47:263–92

Kensler TW, Wakabayashi N, Biswal S. 2006. Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. *Annu. Rev. Pharmacol. Toxicol.* 47:89–116

Orrenius S, Gogvadze V, Zhivotovsky B. 2006. Mitochondiral oxidative stress: implications for cell death. *Annu. Rev. Pharmacol. Toxicol.* 47:143–83

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