# Aldo-Keto Reductases and Bioactivation/Detoxication

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## Key Words

hormone replacement therapeutics, cancer chemotherapeutics, CNS-acting drugs, polycyclic aromatic hydrocarbons, reactive aldehydes, gene regulation

## Abstract

Aldo-keto reductases (AKRs) are soluble NAD(P)(H) oxidoreductases that primarily reduce aldehydes and ketones to primary and secondary alcohols, respectively. The ten known human AKR enzymes can turnover a vast range of substrates, including drugs, carcinogens, and reactive aldehydes. They play central roles in the metabolism of these agents, and this can lead to either their bioactivation or detoxication. AKRs are Phase I drug metabolizing enzymes for a variety of carbonyl-containing drugs and are implicated in cancer chemotherapeutic drug resistance. They are involved in tobacco-carcinogenesis because they activate polycyclic aromatic *trans*-dihydrodiols to yield reactive and redox active *o*-quinones, but they also catalyze the detoxication of nicotine derived nitrosamino ketones. They also detoxify reactive aldehydes formed from exogenous toxicants, e.g., aflatoxin, endogenous toxicants, and those formed from the breakdown of lipid peroxides. AKRs are stress-regulated genes and play a central role in the cellular response to osmotic, electrophilic, and oxidative stress.

## INTRODUCTION

Aldo-keto reductases (AKRs)* are an emerging protein superfamily that is evolutionarily conserved from bacteria to humans (1, 2). AKRs are soluble NAD(P)(H) oxidoreductases whose primary purpose is to reduce aldehydes and ketones to yield primary and secondary alcohols, respectively (3, 4). Because this reaction leads to functionalization to permit subsequent conjugation reactions to occur (e.g., sulfation and glucuronidation), AKRs can be referred to as Phase I drug-metabolizing enzymes. The human AKRs can turnover a vast range of substrates, including drugs, carcinogens, and reactive aldehydes. They play a central role in the metabolism of these agents, and this can lead to either their bioactivation or detoxication. This article reviews the human AKRs; their involvement in drug, carcinogen, and reactive aldehyde metabolism; their tissue distribution; gene regulation; inhibition; and the impact of single nucleotide polymorphisms (SNPs).

**Aldo-keto reductases (AKRs):** generally soluble monomeric 37 kDa NAD(P)(H)-dependent oxidoreductases

**Phase I enzymes:** a group of enzymes (cytochrome P450, prostaglandin H synthase, oxidoreductases) that functionalize hydrophobic substrates for conjugation and elimination

**Single nucleotide polymorphism (SNP):** a variant DNA sequence in which the base of a single nucleotide has been replaced by another base

**Hydroxysteroid dehydrogenases (HSDs):** NAD(P)(H)-dependent oxidoreductases that interconvert ketosteroids to the corresponding secondary alcohols with preferred positional and stereospecificity

## ALDO-KETO REDUCTASE SUPERFAMILY

### Superfamily Structure and Human Members

There are currently more than 140 members in the AKR superfamily, which is divided into 15 families (as of March 2006) (1, 4, 5). Members of individual families have less than 40% sequence identity to members of other families. Proteins with greater than 60% sequence identity are further grouped into a subfamily. The nomenclature system includes the AKR root to indicate the protein as an aldo-keto reductase, a number to identify the family (AKR1), a letter to designate the subfamily (AKR1A), and a second number to assign the unique protein (AKR1A1) (e.g., human aldehyde reductase). Mammalian AKRs are found in the AKR1, AKR6, and AKR7 families, with AKR1 being the largest of the 15 families. A complete list of AKR members can be found at **http://www.med.upenn.edu/akr**.

The human genome project (HUGO) has identified 13 human AKRs, which are listed in **Table 1**. Eight of the human AKRs belong to the AKR1 family, which includes the human homologs of aldehyde reductase (AKR1A1), aldose reductases (AKR1B1 and AKR1B10), hydroxysteroid dehydrogenases (HSDs) (AKR1C1–AKR1C4), and steroid 5β-reductase (AKR1D1). Other human AKRs include the human homologs of aflatoxin aldehyde reductases (AKR7A2 and AKR7A3). The human β-subunits of the voltage-dependent potassium channel of the AKR6 family are excluded from the review because they are not involved in xenobiotic metabolism. AKRs catalyze

*Abbreviations used in the text: AFB1, aflatoxin $B_1$; AKR, aldo-keto reductase; AKR1A1, aldehyde reductase; AKR1B1, aldose reductase; AKR1C1-AKR1C4, hydroxysteroid dehydrogenases, HSDs; AKR7A2 and AKR7A3, aflatoxin aldehyde reductase, AFAR; AhR, aryl hydrocarbon receptor; ARE, antioxidant response element; ArnT, aryl hydrocarbon nuclear translocator; BP, benzo[*a*]pyrene; CR, carbonyl reductase; GABA, γ-amminobutyric acid; 4-HNE, 4-hydroxy-2-nonenal; MSRE, multiple stress response element; MAPK, mitogen-activated protein kinase; NNAL, nicotine derived nitroamino-alcohol; NNK, nicotine derived nitrosamino-ketone; NSCLC, nonsmall cell lung carcinoma; 4-ONE, 4-oxo-2-nonenal; ORE, osmotic response element; PKC, protein kinase C; ROS, reactive oxygen species; SNP, single nucleotide polymorphism; *t*-BHQ, *tert*-butylhydroquinone, TonE, tonicity response element; XRE, xenobiotic response element.

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**Table 1 Human AKR members identified by HUGO**

| Gene | Protein | Chromosomal localization | Putative natural substrates and physiological role |
|---|---|---|---|
| AKR1A1 | Aldehyde reductase L-hexonate dehydrogenase | 1p33-p32 | Reduction of aldehyde to alcohol (e.g., glyceraldehyde to glycerol) |
| AKR1B1 | Aldose reductase | 7q35 | Reduction of aldehyde to alcohol (e.g., glucose to sorbitol in the polyol pathway) |
| AKR1B10 | (Small intestine) aldose reductase | 7q33 | Reduction of aldehyde to alcohol (e.g., retinal to retinol) |
| AKR1C1 | 20α-HSD, DD1 | 10p15-10p14 | Reduction of 20-ketosteroid to 20α-hydroxysteroid (e.g., elimination of progesterone) |
| AKR1C2 | Type 3 3α-HSD, DD2, bile acid binding protein | 10p15-10p14 | Reduction of 3-ketosteroid to 3α-hydroxysteroid (e.g., elimination of 5α-dihydrotestosterone) |
| AKR1C3 | Type 2 3α-HSD, type 5 17β-HSD, prostaglandin F synthase, DDx | 10p15-10p14 | Reduction of 17-ketosteroid to 17β-hydroxysteroid (e.g., formation of testosterone and 17β-estradiol) Prostaglandin F synthesis (e.g., reduction of $PGH_2$ to $PGF_{2\alpha}$) |
| AKR1C4 | Type 1 3α-HSD, DD4, chlordecone reductase | 10p15-10p14 | Reduction of 3-ketosteroid to 3α-hydroxysteroid, hepatic clearance of steroids, bile acid synthesis |
| AKR1D1 | 5β-reductase | 7q32-q33 | Reduction of $\Delta^4$–3-ketosteroids to 5β-dihydrosteroids, bile acid synthesis |
| AKR6A3 | Potassium voltage gated channel, β-subunit-1 | 3q26.1 | Redox-regulation of *Shaker* potassium channel inactivation |
| AKR6A5 | Potassium voltage gated channel, β-subunit-1 | 1p36.3 | Redox-regulation of *Shaker* potassium channel inactivation |
| AKR6A9 | Potassium voltage gated channel, β-subunit-1 | 17p13.1 | Redox-regulation of *Shaker* potassium channel inactivation |
| AKR7A2 | Aflatoxin aldehyde reductase | 1p35.1-p36.23 | Reduction of aldehyde to alcohol (e.g., succinic semialdehyde) |
| AKR7A3 | Aflatoxin aldehyde reductase | 1p35.1-p36.23 | Reduction of aldehyde to alcohol |

HSD, hydroxysteroid dehydrogenase; DD, dihydrodiol dehydrogenase.

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reactions on a broad and overlapping spectrum of substrates. It is often difficult to assign natural substrates and physiological function to these enzymes. Endogenous substrates for the human enzymes include, but are not limited to, sugar aldehydes, retinals, steroid hormones, prostaglandins, lipid derived aldehydes, and bile acid precursors (**Table 1**).

## Structure-Function Properties

Crystal structures of 25 AKR members have now been determined and share common features (2). The majority of AKRs are monomeric proteins of 34–37 kDa, whereas multimeric proteins are found in families AKR2, AKR6, and AKR7. The characteristic fold of the AKR superfamily is an $(\alpha/\beta)_8$-TIM barrel structure with three large

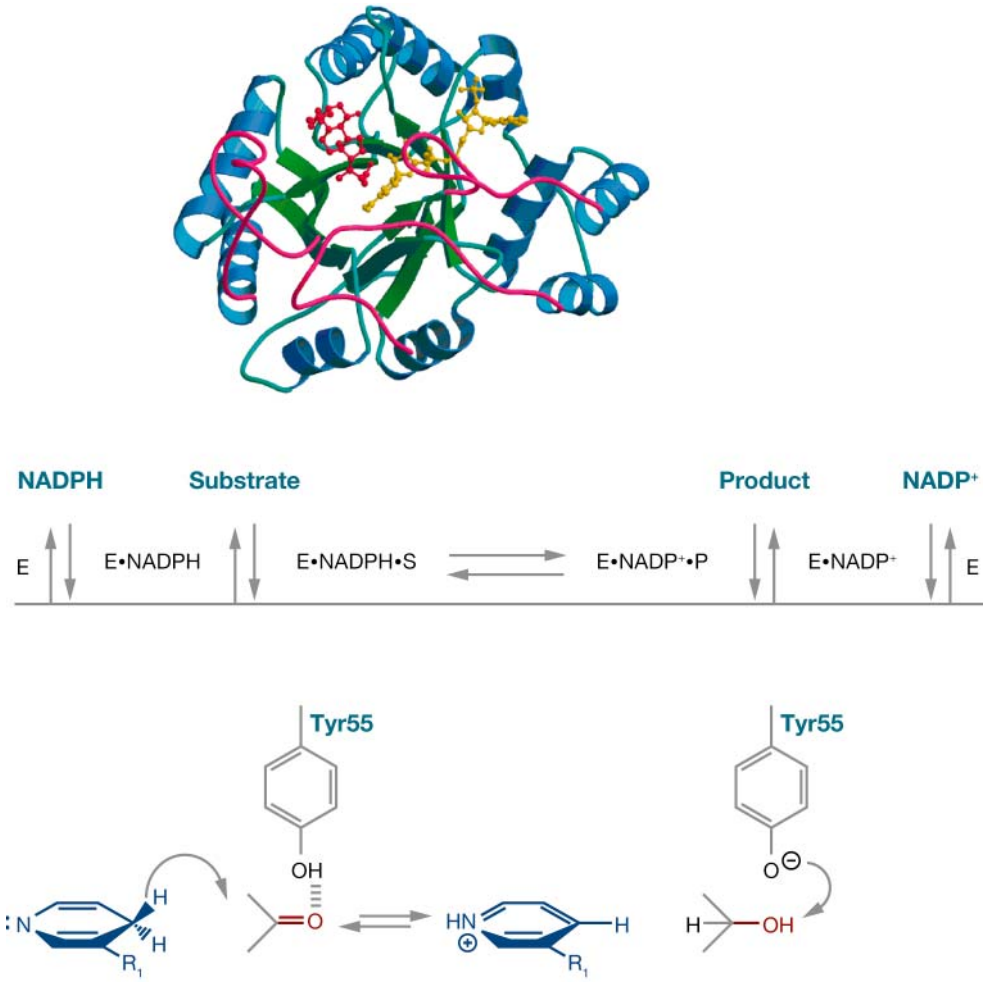


**Figure 1**

Structure motif of AKR enzymes and the kinetic and chemical mechanism of the carbonyl reduction catalyzed by AKRs. The structure of the ternary complex AKR1C2 • $NADP^+$ • ursodeoxycholate is shown with the cofactor in yellow and the bile acid in red (*top*). AKRs catalyze an ordered bi-bi reaction (*middle*). The hydride transfer from NADPH to the carbonyl group is stereospecific, and a conserved Tyr serves as the general acid-base for the reaction (*bottom*).

associated loops (**Figure 1**). In the ternary complexes of AKR enzymes, the cofactor and the substrate/inhibitor bind in two different regions of the protein and converge at the active site. The cofactor binding site and the active site are highly conserved across the superfamily. The active site contains a conserved catalytic tetrad (Tyr, Asp, Lys, and His), which forms an oxyanion binding site with the nicotinamide ring of the cofactor via a hydrogen bonding network. In contrast, strong variation exists in



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the structure of the substrate binding cavity, which is largely defined by the residues from the loops.

The AKR kinetic mechanism reaction is strictly ordered, where the cofactor binds first and leaves last (6–8). Hydride transfer is 4-pro-*R* specific and the acceptor group (carbonyl or α,β-unsaturated ketone) is polarized by the Tyr in the tetrad, which acts as the general acid-base for the reaction (9–11). Transient kinetic studies show that significant conformational changes occur upon cofactor binding to form the tight binary complexes. Conformational changes during the release of cofactor product partially or completely govern the overall turnover rate (12, 13). The rate of chemical conversion and the rate of the release of steroid product also contribute to the rate determination for the AKR1C ketosteroid reductases (14).

## Phenotyping Reactions

Assigning a specific human AKR to a xenobiotic transformation can be difficult, and it is complicated by the fact that carbonyl reductase (CR) of the short-chain dehydrogenase/reductase protein family may catalyze the same reaction. Traditional approaches to assigning cytochrome P450 isoforms to particular reactions include assignment of the reaction to a single recombinant isoform, expression profiling, the use of immunoprecipitation or immunodepletion assays, the use of isoform-specific inhibitors, and the use of iRNA technology. Each of these approaches can be applied to assign AKR isoforms to specific reactions and a combination of approaches may be needed.

Each of the human AKRs has been expressed recombinantly in *Escherichia coli* and purified to homogeneity and are available for in vitro reactions (5, 15–22). The one exception is 5β-reductase (AKR1D1), which has been cloned but studied only in mammalian transfection studies (23). Expression profiling requires validated molecular probes that are isoform specific [e.g., real-time PCR primers and antibodies to detect mRNA and protein expression, respectively]. This is a challenge because some of the human isoforms, e.g., AKR1C1-AKR1C4, share >86% sequence identity but catalyze vastly different reactions. Isoform-specific RT-PCR and real-time PCR protocols have been described for AKR1C1–AKR1C4 (24, 25). Validated peptide-derived polyclonal antibodies have been developed for AKR1C1/2 and AKR1C3 and a monoclonal antibody for AKR1C3 has also been described (26–28). So far there have been no reports on the use of the available antibodies for immunoprecipitation or immunodepletion assays. However, early work with the AKR1C9 antibody shows the feasibility of this approach (29).

AKR1A1 and AKR1B1 are potently inhibited by the aldose reductase inhibitors (ponalrestat, tolrestat, and alrestatin) (30–32). Similarly, AKR1C1–AKR1C4 are potently inhibited by the nonsteroidal antiinflammatory drug (NSAID) flufenamic acid (33, 34). AKR1C involvement can be further deconvoluted by using isoform selective inhibitors, e.g., ursodeoxycholate (for AKR1C2), indomethacin (for AKR1C3), and phenolphthalein (for AKR1C4) (19, 35, 36).

iRNA technology has been used to knockdown endogenous expression of AKR1C1/AKR1C2 (27). However, this strategy still requires development to phenotype reactions.

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## AKRS AND DRUG METABOLISM

A large variety of drugs or their metabolites contain carbonyl groups that undergo carbonyl reduction (36). Human AKRs have been implicated in the metabolism of synthetic hormones, cancer chemotherapeutics, and CNS-acting drugs.

### Activation of Synthetic Steroid Hormones-Tibolone by AKRs

Tibolone [(7α, 17α)-17β-hydroxy-7′-methyl-19-norpregn-5(10)-en-20-yn-3-one, also known as 7α-methyl-norethynodrel] is a synthetic hormone used to treat menopausal symptoms and to prevent osteoporosis. It is a prodrug and requires metabolic activation to estrogenic metabolites (3α- and 3β-hydroxytibolone) (**Figure 2**) and a progestagenic metabolite ($\Delta^4$-isomer) in a tissue-specific manner. As a consequence the active metabolites stimulate the bone but not the breast and endometrium. In vitro studies showed that AKR1C1 and AKR1C2 catalyze exclusively the formation of 3β-hydroxytibolone, whereas AKR1C3 shows weak 3β/3α-HSD activity and the liver-specific AKR1C4 catalyzes the formation of 3α-hydroxytibolone (37). This led to the concept that AKR1C1 and AKR1C2 may account for the appearance of 3β-hydroxytibolone, the major metabolite in target tissues, and that AKR1C4 may be responsible for the formation of 3α-hydroxytibolone, the major metabolite in the circulation.

The role of AKRs in the hepatic metabolism of tibolone was investigated further using liver autopsy samples (which express AKR1C1–AKR1C4), HepG2 cells (which express AKR1C1–AKR1C3, but not AKR1C4), and primary hepatocytes (which express AKR1C1–AKR1C4) (38). In all cases, formation of 3β-hydroxytibolone was observed and could be blocked by AKR1C1–AKR1C3-selective inhibitors. In liver autopsy samples and primary hepatocytes, where AKR1C4 is also expressed, 3α- and 3β-hydroxytibolones were formed in a 1:4 ratio. The formation of 3α-hydroxytibolone was exclusively inhibited by the AKR1C4-selective inhibitor phenolphthalein. However, the low formation of 3α-hydroxytibolone by AKR1C4 cannot account for 3α-hydroxytibolone being the major circulating metabolite, suggesting that the primary source of this metabolite may be intestinal or enterobacterial 3α-HSDs. It is likely that AKR1Cs are involved in the metabolism of other 19-nor contraceptive steroids that contain a 17α-ethinyl group, e.g., norethynodrel.

### AKRs and Cancer Chemotherapeutics

Anthracycline antibiotics such as daunorubicin and doxorubilcin are a major class of anticancer agents (39). Anthracyclines inhibit DNA and RNA synthesis by intercalating with DNA. Carbonyl reduction is often a major but undesired metabolic pathway for these drugs (**Figure 2**). The resulting secondary alcohols are responsible for the life-threatening cardiac toxicity that limits the clinical use of the parent drugs. Daunorubicin is efficiently reduced by AKR1A1, AKR1C2, and CR in vitro, with CR being the most efficient enzyme (40). The role of AKRs in doxorubicin metabolism is supported by the reduced formation of the alcohol metabolite in rat heart and liver

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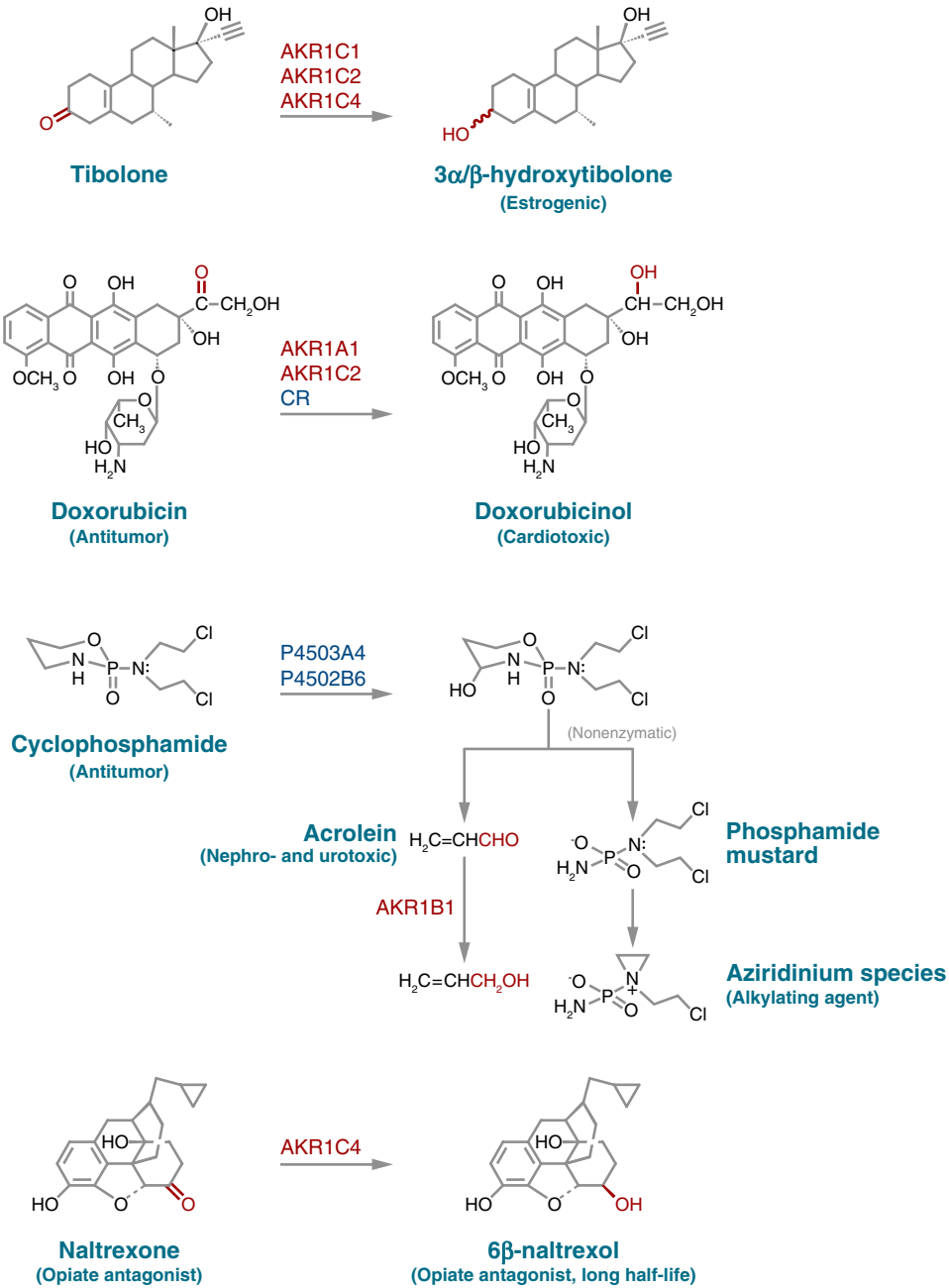


**Figure 2**

Examples of drug metabolism involving AKRs.

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cytosols in the presence of the AKR inhibitor phenobarbital (41). In addition to their cardiotoxicity, anthracycline alcohol metabolites may not have antitumor activity and may increase the resistance of cancer cells to the parent drug. Thus anthracycline analogues that are resistant to carbonyl reduction and/or form less cardiotoxic metabolites are desired, e.g., epirubicin (42).

The resistance of human stomach carcinoma cells to daunorubicin has been linked to the induction of carbonyl-reducing enzymes (43). Increased mRNA expression of AKR1B1, AKR1C2, and CR were observed in drug-resistant tumor cells. AKR1B1 was also linked to doxorubicin and *cis*-platin resistance in HeLa cervical carcinoma cells because an AKR1B1 inhibitor enhanced the cytotoxic effects of these anticancer agents (44).

Cyclophosphamide is a cytotoxic anticancer drug that undergoes metabolic activation by cytochrome P450 (CYP3A4 and CYP2B6)-mediated hydroxylation (**Figure 2**). The activated intermediate cleaves spontaneously to generate a phosphamide mustard and acrolein. The former is responsible for antitumor activity because it forms the alkylating aziridinium species, whereas acrolein is responsible for the dose-limiting side effect of cyclophosphamide treatment hemorrhagic cystitis. AKR1B1 was shown to catalyze the efficient reduction of acrolein with the catalytic efficiency 1000 times greater than that for glucose, the putative natural substrate of AKR1B1 (45). AKR1B1 is thus involved in acrolein detoxication and permits tolerance to the drug.

An emerging theme is the role of AKRs in cancer chemotherapeutic drug resistance (46, 47). Although induction of carbonyl metabolizing enzymes, e.g., AKR1B1 and AKR1C2, can account for drug resistance to daunorubicin, it is less clear why induction of AKR1C1 is linked to *cis*-platin drug resistance. Growth of ovarian cancer cells in the presence of *cis*-platin induced *cis*-platin resistance that was characterized by overexpression of AKR1C1. Transfection of naïve cells with AKR1C1 produced the chemotherapeutic drug-resistance phenotype, even though a link between AKR1C1 and *cis*-platin metabolism is not apparent (46, 47).

## AKRs and the Metabolism of CNS-Active Drugs

Naltrexone is an opioid receptor antagonist used for the prevention of relapse in opiate and alcohol dependence. Carbonyl reduction results in the formation of 6β-naltrexol, which retains the pharmacological activity of the parent drug but has a longer half-life, and an ensuing long duration of action (**Figure 2**). Naltrexone is reduced exclusively in the cytosolic fractions of the liver, and although there is some disagreement in kinetic parameters, all studies implicate AKR1Cs as the enzymes responsible for the formation of 6β-naltrexol (40, 48, 49). Of these isoforms, AKR1C4 appears to play the dominant role (49).

AKRs also catalyze the carbonyl reduction of the antidepressant nortriptyline (50). AKR1C1 and AKR1C2 catalyze stereospecific reduction of both *E*- and *Z*-oxonortriptyline, whereas no activity was observed with CR. In contrast, AKRs have 10- or 100-fold lower catalytic efficiency than CR for the reduction of haloperidol.



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## CARCINOGEN METABOLISM

### AKRs and the Activation of Polycyclic Aromatic Hydrocarbons

Human AKRs (AKR1A1, AKR1C1) are implicated in the metabolic activation of polycyclic aromatic hydrocarbons (PAHs). PAHs are ubiquitous environmental pollutants produced as products of fossil fuel combustion and are present in car exhaust, tobacco smoke, and barbecued food. They are suspected human carcinogens and implicated in the causation of lung cancer. PAHs require metabolic activation to exert their deleterious effects.

**Pathways of PAH activation.** Three pathways of PAH activation have been described: the formation of radical cations (P450-peroxidase derived) (51), the formation of diol-epoxides (P450 derived) (52), and the formation of reactive and redox active *o*-quinones (AKR derived) (53) (**Figure 3**).

The discrete steps in PAH *o*-quinone formation were first described using rat liver dihydrodiol dehydrogenase or AKR1C9, but the same sequence operates for human AKR1A1 and AKR1C1–AKR1C4 (52, 54–58). These enzymes catalyze the $NAD(P)^+$-dependent oxidation of BP-7,8-diol to form a ketol (dihydrodiol dehydrogenase reaction). Subsequent tautomerization of the ketol yields the catechol, 7,8-dihydroxybenzo[*a*]pyrene. Although, AKRs prefer to catalyze reduction reactions, this oxidation event is thermodynamically favored owing to the formation of an aromatic ring. The catechol product is extraordinarily air sensitive and undergoes two sequential 1-electron autooxidation events to produce the *o*-semiquinone anion radical followed by the formation of the *o*-quinone, BP-7,8-dione. Each of the autooxidation steps produces reactive oxygen species (ROS) (56).

**Properties of PAH *o*-quinones produced by AKRs.** The PAH *o*-quinones produced by AKRs are reactive and redox active. They are free to react with DNA, RNA, protein, or GSH (59–62). Alternatively, in the presence of cellular reducing equivalent (NADPH), the *o*-quinone can be readily oxidized back to the catechol. The catechol can then be autooxidized a second time to generate ROS once more. These events establish a futile redox-cycle in which trace amounts of the *o*-quinone are not consumed but instead are redox-cycling until cellular reducing equivalents are depleted and as a consequence ROS amplification is achieved. By entering futile redox-cycles, they can also produce a prooxidant state and cause oxidative lesions within DNA (63). The electrophilic and prooxidant signals produced can lead to induction of genes regulated by the antioxidant response element (ARE) (64, 65) and to the activation of downstream targets of PKC and activated Ras (66–68). Thus, formation of PAH *o*-quinones by the AKRs may impact both the initiation and promotion stages of PAH carcinogenesis and contribute to the complete carcinogenic potential of the parent hydrocarbon.

BP-7,8-dione was found to be a potent inducer of the aryl hydrocarbon receptor (AhR) in HepG2 and H358 cells (69, 70). In HepG2 cells it was equipotent with BP as an inducer of -CYP1A1 mRNA. This affect was lost in AhR or ARNT-negative cells. BP-7,8-dione also *trans*-activated a stably integrated xenobiotic response

**Polycyclic aromatic hydrocarbons (PAHs):** products of fossil fuel combustion that typically contain two or more fused aromatic rings, represented by benzo[*a*]pyrene

**Antioxidant response element (ARE):** consensus sequence (5′-GTGAC/GNNN-GC-3′) that binds the heterodimeric pair Nrf2 and small Maf in genes that are responsive to monofunctional inducers

**Aryl hydrocarbon receptor (AhR):** a basic helix-loop-helix-PAS (Per-Arnt-Sim domain) transcription factor that binds to the xenobiotic response element when occupied with ligand, e.g., TCDD [2,3,7,8-tetrachlorodibenzo-p-dioxin]. It forms a heterodimeric partner with ArnT

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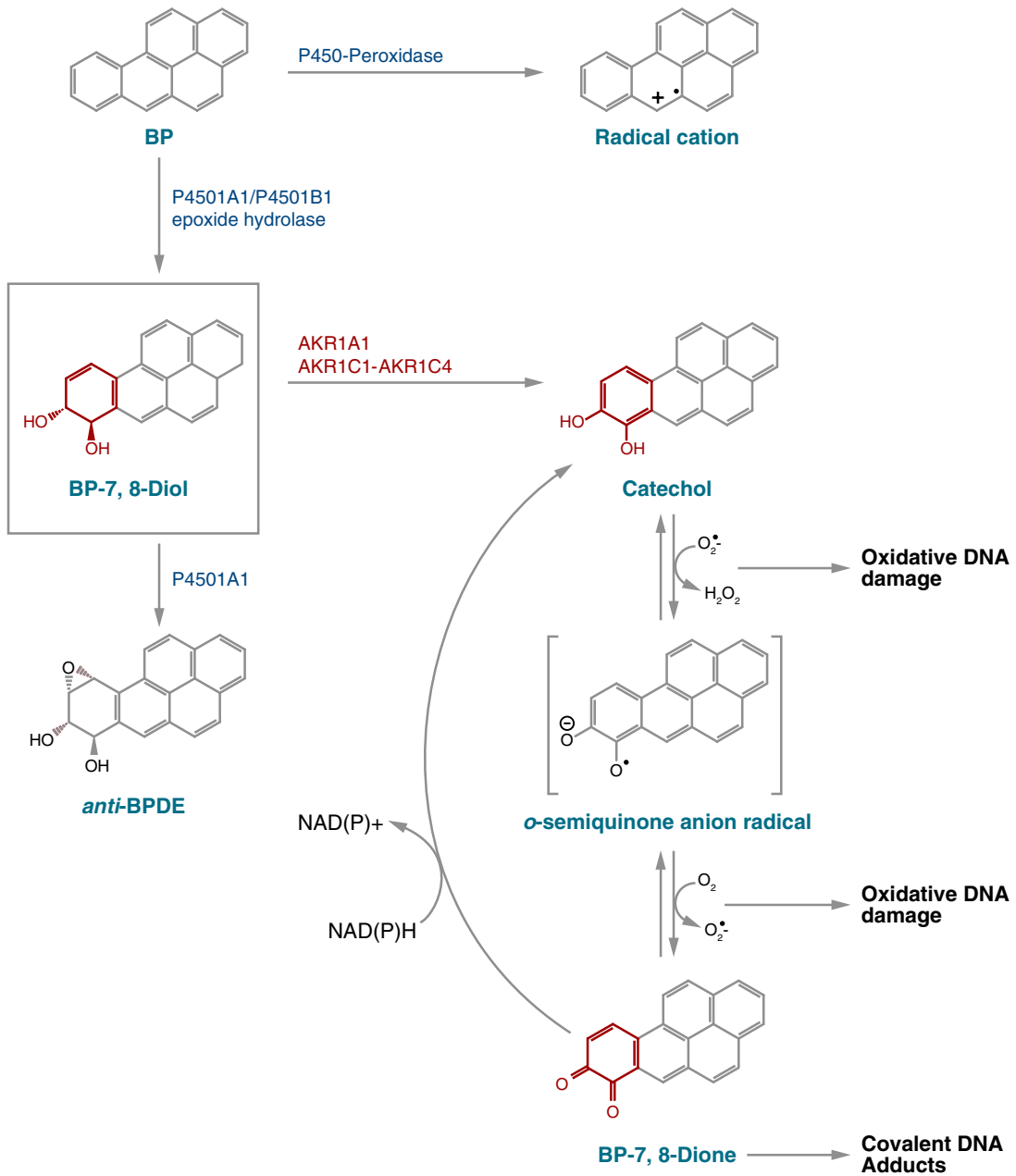


**Figure 3**

Metabolic pathways of PAH activation. Benzo[*a*]pyrene (BP) is used as a representative PAH. Adapted from Reference 53.



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element (XRE)-luciferase construct in HepG2 cells and caused translocation of the AhR to the HepG2 cell nucleus, as determined by electrophoretic mobility shift assays and by immunocytochemistry (69). A functional consequence of this induction was observed in H358 cells that stably express AKR1A1. Treatment of these cells with BP-7,8-diol (AKR substrate) resulted in *anti*-BPDE formation (measured as tetrols) even though the cells are P4501B1 null. Formation of the tetrols was blocked with an AhR antagonist, a P450 inhibitor, and an AKR1A1 inhibitor, showing its dependence on the AKR1A1-mediated reaction (70). BP-7,8-dione also induces AKR1C1 expression owing to its electrophilicity and redox activity (65). AKR1C1 is induced by monofunctional inducers (hydrogen peroxide, ethacrynic acid, ethoxyquin, and *tert*-buytl-hydroquinone) consistent with an ARE-dependent mechanism implicating the Nrf2-Keap1 pathway (65, 71, 72). Thus BP-7,8-dione appears to be a typical bifunctional inducer produced by AKRs (Phase I enzymes) in that it can activate both an XRE and an ARE.

**Xenobiotic response element (XRE):** consensus sequence (5′-TNGCGTG-3′) that binds the aryl hydrocarbon receptor in genes that are responsive to TCDD and bifunctional inducers

**Role of human AKRs in PAH activation.** Five human AKRs are implicated in the metabolic activation of PAH *trans*-dihydrodiols. Of these isoforms, AKR1A1 (aldehyde reductase) has the highest catalytic efficiency for the oxidation of (±)-BP-7,8-diol. It is stereoselective and oxidizes only the metabolically relevant isomer (−)-BP-7,8-diol. The product of the reaction was trapped as the thiol-ether conjugate of BP-7,8-dione and identified by LC/MS. AKR1A1 is ubiquitously and constitutively expressed in human tissues and is coexpressed with P4501A1, P4501B1, and epoxide hydrolase. Thus it resides in the same sites that would produce its substrate (−)-BP-7,8-diol (57) .

By contrast, AKR1C1–AKR1C4 have broad substrate specificity against a panel of PAH *trans*-dihydrodiols and display higher catalytic efficiencies toward bay-region methylated dihydrodiols. Bay-region methylation often increases the carcinogenicity of the parent hydrocarbon which suggests that these enzymes play a role in their bioactivation. Unlike AKR1A1, AKR1C1–AKR1C4 are not stereoselective and oxidize both stereoisomers of the racemic dihydrodiol substrates tested (58). Two independent studies using either differential display or Affymetrix microarray technology have identified AKR1C1 as being overexpressed in nonsmall-cell lung carcinoma (NSCLC) (73, 74). These observations were validated by RT-PCR, Northern blot analysis, and functional assays in A549 human lung adenocarcinoma cells. Lysates of these cells catalyzed the $NADP^+$-dependent oxidation of DMBA-3,4-diol (a methylated bay-region *trans*-dihydrodiol) to DMBA-3,4-dione, which was trapped as a mixture of mono- and bis-thioether conjugates (52, 57).

Human bronchoalveolar (H358) cell models were created to examine the competing roles of P450 and AKRs in the metabolic activation of BP-7,8-diol (70, 75). Lysates from P4501B1- or AKR1A1-expressing cells produced either *anti*-BPDE (detected as tetrols) or BP-7,8-dione, respectively, as expected (75). In contrast, cell lysates expressing both enzyme systems produced both metabolites. Estimates of P4501B1 and AKR1A1 expression achieved in these cells indicated that the latter was expressed at a level that was 100 times higher than P4501B1. The higher expression of AKR1A1 may be physiological because it is a general metabolic enzyme that is constitutively

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expressed (57). The tetrol:BP-7,8-dione ratio was altered by changing the redox state (NADPH:$NAD^+$ ratio) in the cell lysate. When a NADPH-generating system was used, tetrol formation was favored, and when $NAD^+$ was used, BP-7,8-dione formation was favored. The effects of redox state on the metabolic profiling of BP-7,8-diol has not been previously considered and is an important aspect because the futile redox cycles generated by the AKRs would deplete reducing equivalent and favor the AKR-catalyzed reaction.

## AKRs and the Detoxication of Nicotine-Derived Carcinogens

Nicotine in tobacco smoke gives rise to a nicotine-derived nitrosamino-ketone (NNK), which is highly carcinogenic and tumorigenic in the A/J mouse lung model for carcinogenesis (76). NNK is metabolically activated by P4502A6/3A4 by α-methylene hydroxylation to yield a methyldiazonium ion which results in $O^6$-methylguanine formation or it can undergo α-methyl hydroxylation to yield pyridyloxobutylated DNA adducts (76) (**Figure 4**). A major route of detoxication of NNK involves carbonyl reduction to yield *R*- and *S*-nicotine-derived nitrosamino-alcohols (NNAL). Although these alcohols can still be metabolically activated by the P450 isoforms, the presence of the alcohol allows NNALs to be conjugated with glucuronide and hence excreted. Enzymes assigned to this carbonyl reduction include the hepatic 11β-HSD type 2 (a short-chain dehydrogenase/reductase) as well as AKR1C1, AKR1C2, and AKR1C4 (77).

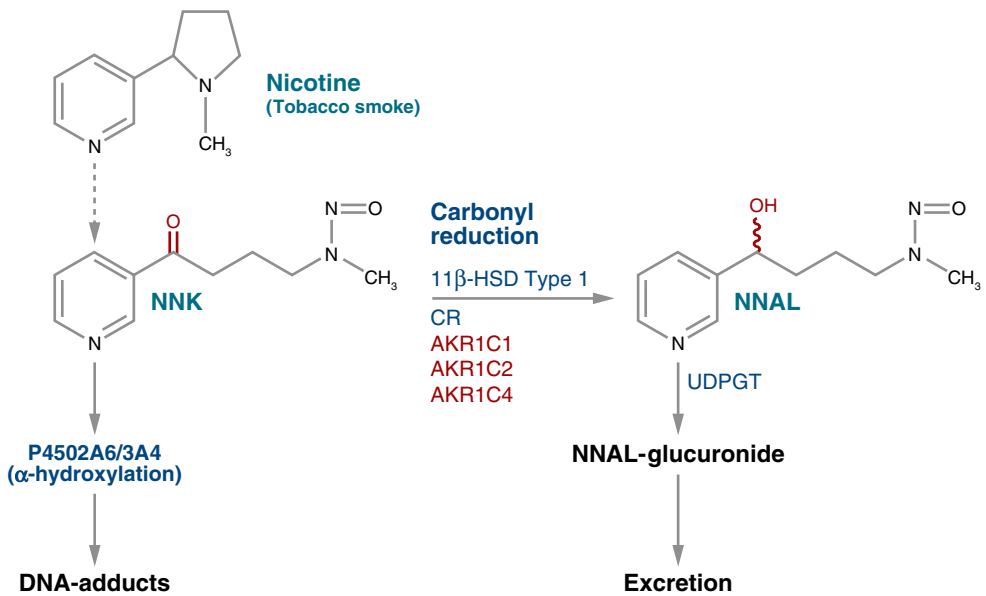


**Figure 4**

Metabolic pathways of the tobacco-derived carcinogen NNK. Adapted from Reference 4.

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## AKRs and the Detoxication of Aflatoxin

Aflatoxin B1 is a rodent and human hepatocarcinogen found on cereals and nuts contaminated with the fungus *Aspergillus flavus*. It is metabolically activated by P450 3A4 to yield the aflatoxin B1-8,9-epoxide, which is its ultimate carcinogen form (78). The epoxide can hydrolyze to form the aflatoxin B1-dihydrodiol, which upon ring opening can yield the aflatoxin B1-dialdehyde, which is cytotoxic in its own right by forming lysine and protein conjugates (79) (**Figure 5**). AKR7A family members [aflatoxin aldehyde reductases (AFAR)] reduce the dialdehyde sequentially to form the monoaldehyde and the dialcohol, thus preventing protein adduct formation. The first AKR demonstrated to perform this reaction was the rat ethoxyquin-inducible aflatoxin aldehyde reductase (AKR7A1) (80). AKR7A1 is dimeric in structure and can form heterodimers with AKR7A4 to form AKR7A1-1, AKR7A1-4, and AKR7A4-4 (81). In humans, two AFARs exist, AKR7A2 and AKR7A3, and the latter has the

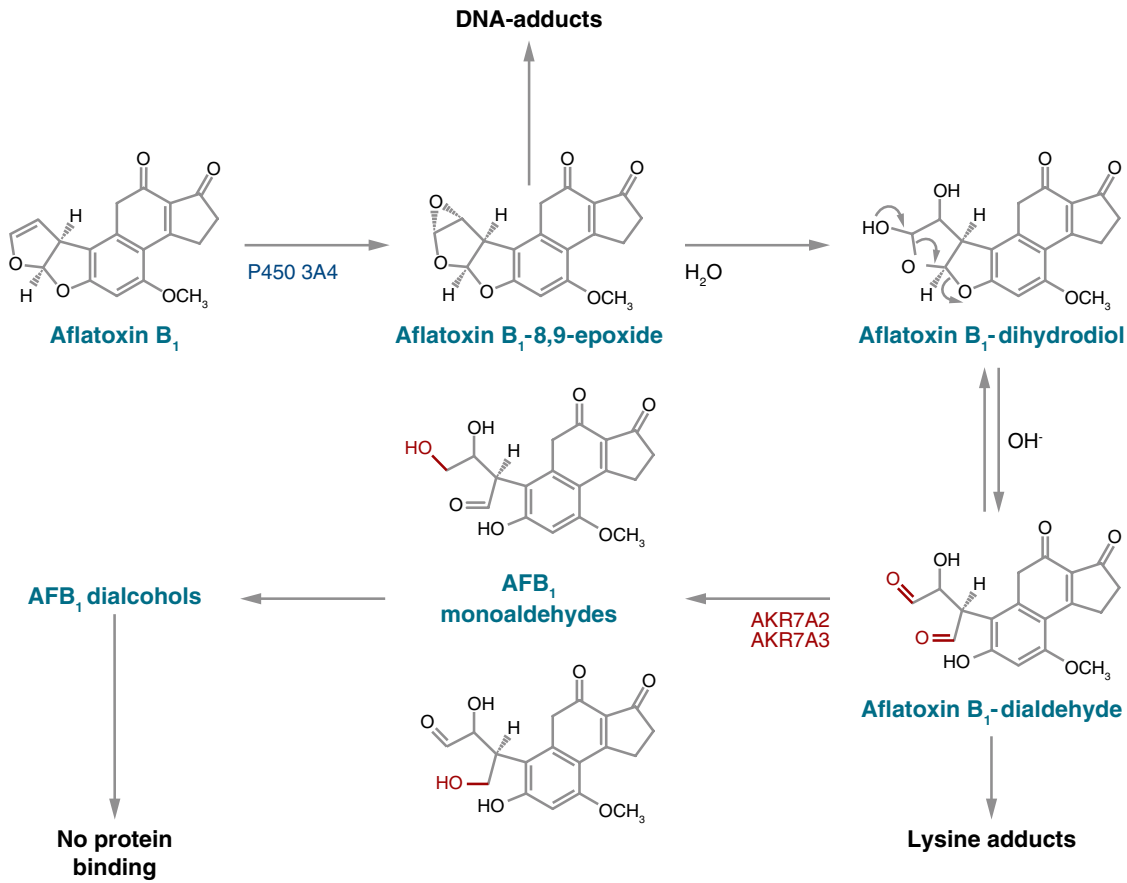


**Figure 5**

Metabolic pathways of aflatoxin B1. Adapted from Reference 4.

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higher catalytic efficiency for aflatoxin dialdehyde (21, 22). The catalytic efficiency of AKR7A3 for dialdehyde reduction equals or exceeds those reported for other enzymes known to metabolize AFB1 in vivo, for example, cytochrome P450s and glutathione S-transferases. These findings indicate that, depending on the extent of AFB1 dihydrodiol formation, AKR7A isoforms may contribute to the protection against AFB1-induced hepatotoxicity.

## AKRS AND THE DETOXICATION OF REACTIVE ALDEHYDES

Human AKRs protect cells from reactive aldehydes formed endogenously (e.g., glyoxal, methylglyoxal from sugar aldehydes, aldehydes from biogenic amines, and succinic semialdehyde from GABA), encountered in the diet (e.g., 2-hexenal in vegetables and diacetyl in butter and wine) and the environment (e.g., chloroacetaldehyde from vinyl chloride and *trans-trans*-muconaldehyde from benzene) and those that result from exposure to chemically induced oxidative stress (e.g., 4-hydroxy-2-nonenal).

### Xenobiotic Aldehydes

The role of human AKRs in the detoxication of xenobiotic aldehydes was elucidated by O'Connor, who compared the ability of AKR1A1, AKR1B1, AKR1C1, AKR1C4, and AKR7A2 to detoxify a range of reactive aldehydes and/or dicarbonyls (82). AKR1A1 and AKR7A2 gave the highest $k_{cat}/K_m$ values for the reduction of succinic semialdehyde, 1,2-naphthoquinone, and 16-ketoestrone. AKR7A2 was found to differ from the AKR1 isoforms because it was the only isoform that could catalyze the reduction of 2-carboxbenzaldehyde. Its narrow specificity for the reduction of succinic semialdehyde, 2-nitrobenzaldehyde, pyridine-2-aldehyde, isatin, and 1,2-naphthoquinone suggest a role for AKR7A2 in the detoxication of these metabolites. 1,2-Naphthoquinone is a reactive and redox-active metabolite of naphthalene, which is implicated in naphthalene cataractogenesis and carcinogenesis (83). AKR1A1 showed a preference over AKR7A2 for the detoxication of methyl- and phenylglyoxal. AKR1A1 and AKR1B1 shared many of the same substrates but AKR1B1 gave lower $k_{cat}/K_m$ values. In contrast, the AKR1C1 and AKR1C4 isoforms were poor catalysts of aromatic aldehydes, aldoses, or dicarbonyls, consistent with their preference for steroid hormones, prostaglandins, and PAH *trans*-dihydrodiols (82).

### Reactive Lipid Aldehydes

Oxidative stress that results in the formation of ROS (e.g., superoxide anion radical, hydroxyl radical, and hydrogen peroxide) can result from exposure to endogenous (catecholamines, estrogens, etc.) and exogenous (halogenated alkanes, e.g., CCl4, quinones, equine estrogens, heavy metals) stressors. One target of ROS are polyunsaturated fatty acids (e.g., linoleic acid and arachidonic acid) that form lipid hydroperoxides [13-HPODE (13-hydroperoxyoctadecanoic acid) and 15-HPETE (15-hydroperoxyeicosatetraenoic acid)], which decompose to form reactive lipid

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aldehydes, e.g., 4-hydroxy-2-nonenal (4-HNE) and 4-oxo-2-nonenal (4-ONE) (84). These lipid aldehydes are known as bifunctional electrophiles because they undergo Schiff's base formation with the ε-$NH_2$ group of reactive lysines and also undergo 1,4-Michael addition, which can result in protein cross-links. The formation of HNE adducts has been observed in Parkinson's disease (85), Alzhiemer's disease (86), and artherosclerotic plaques (87). Moreover, if 4-HNE and 4-ONE are not detoxified they react with bases in DNA to form a series of etheno- and heptano-etheno-DNA adducts, which can be highly mutagenic (88–90). Human AKRs are implicated as one group of enzymes involved in the detoxication of 4-HNE and 4-ONE (**Figure 6**).

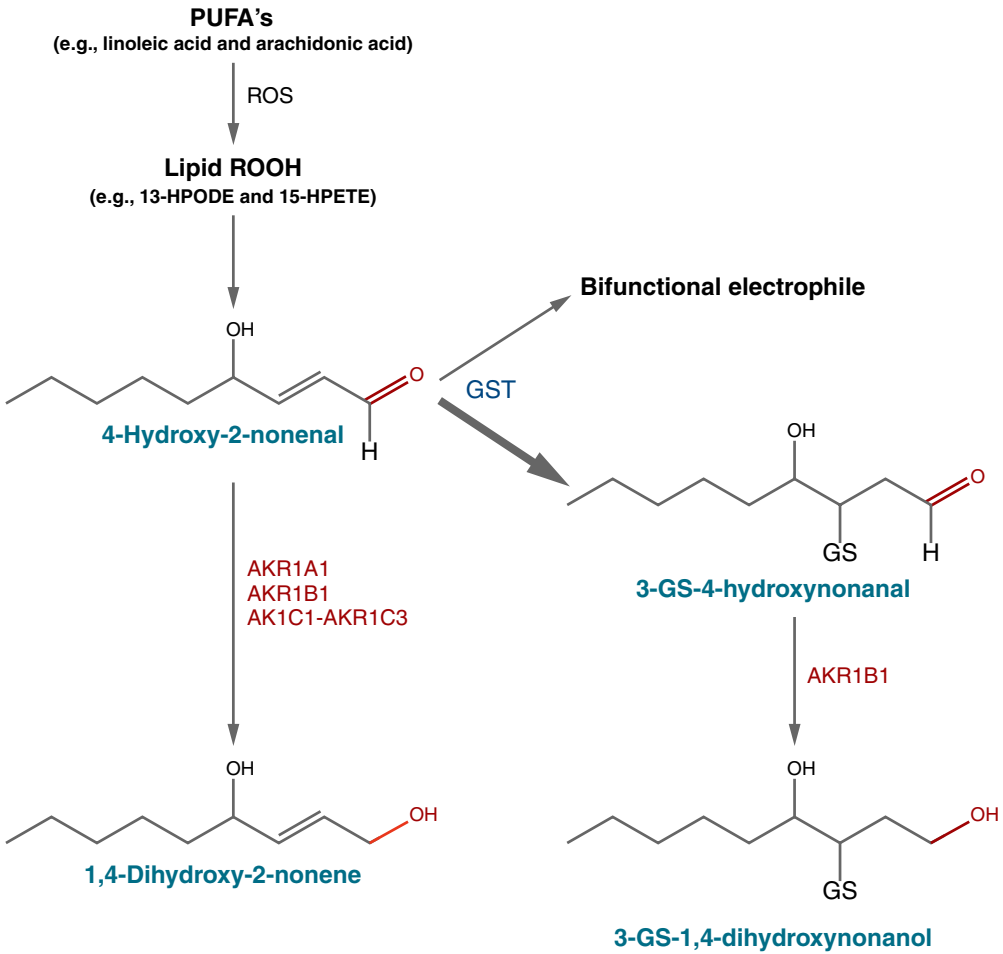


**Figure 6**

Role of AKRs in the detoxication of lipid aldehydes. Adapted from Reference 4.

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-HNE is readily scavenged by GSH, both enzymatically and nonenzymatically. However, the thio-ether conjugate formed by a 1,4-Michael addition still retains the reactive aldehyde group. AKR1B1 (aldose reductase) can reduce both 4-HNE to yield 1,2-dihydroxynonene ($k_{cat}/K_m$ = 1174 $min^{-1}$ $M^{-1}$) and its glutathionyl conjugate [3-GS-4-hydroxynonanal (GS-4-HNE)] to yield 3-glutathionyl-1,4-dihydroxynonanol [GS-DHN $k_{cat}/K_m$ 3556 $min^{-1}$ $M^{-1}$] (91, 92). The preferred catalytic efficiency for the GSH-4-HNE conjugate suggests that this pathway likely dominates when there is sufficient GSH present, but GSH can be depleted by oxidative stress. The AKR1B1-dependent metabolism of both GS-4-HNE and 4-HNE is important in those tissues in which it is abundantly expressed: heart, skeletal muscle, kidney, and vascular smooth muscle cells. In these tissues, aldose-reductase inhibition could lead to 4-HNE toxicity, which may account for the side effects of aldose-reductase inhibitors. In contrast, the reduction of 4-HNE to 1,4-dihydroxy-2-nonene by AKR1A1 and AKR1C1-AKR1C4 occurs in the liver, where the AKR1C enzymes are abundantly expressed. In a side-by-side comparison of hepatic AKRs, AKR1C1 and AKR1C2 were the most catalytically efficient at reducing 4-HNE (65). In contrast to the glutathionyl conjugation of 4-HNE, which leaves a reactive aldehyde in the product, the reduction of unconjugated 4-HNE by AKRs destroys the bifunctional electrophile in a single step. The resultant alcohol retains neither the reactive carbonyl nor the Michael acceptor. It has been proposed that AKRs form an additional cytosolic barrier to 4-HNE once GSH has been depleted (65).

## TISSUE DISTRIBUTION AND GENE REGULATION OF HUMAN AKRs

The ability of AKRs to bioactivate and/or detoxify xenobiotics and reactive aldehydes is governed by their tissue distribution and gene regulation.

### Tissue Distribution of Human AKRs

The distribution of AKRs has so far been examined by individual groups using a variety of methods (Northern analysis, RT-PCR, real-time PCR, and immunoblot analysis). Although there is agreement about the distribution of individual human isoforms, a comparison of the tissue distribution of all isoforms in a single study has yet to be performed.

AKR1A1 is a general metabolic enzyme that is involved in the reduction of D-glyceraldehyde to glycerol and melvadate to mevalonic acid, and it plays a central role in triglyceride and cholesterol biosynthesis. It is ubiquitously and constitutively expressed. RNA microarray analysis showed the following rank order of expression: kidney > liver > salivary gland > trachea > stomach > duodenum > fetal lung > prostate > placenta > mammary gland > lung > A549 cells (57). This distribution was confirmed based on immunoblot analysis (82). AKR1A1 is also highly expressed in brain regions, which is consistent with its role in the metabolism of aldehydes derived from monoamine oxidase.

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AKR1B1 catalyzes the first step in the polyol pathway and is also broadly expressed. However, two studies confirm that it is constitutively expressed in the liver. High expression is observed in skeletal muscle, cardiac muscle, kidney, ovary, testis, prostate, and small intestine (82, 93). In contrast, AKR1B10 shows discrete tissue expression and is predominately expressed in small intestine and colon, and it was originally referred to as human small intestine aldose reductase. Although it is not constitutively expressed in the lung, it is highly expressed in NSCLC (74).

The distribution of AKR1C1–AKR1C4 (hydroxysteroid/dihydrodiol dehydrogenases) has been examined in nine human tissues using isoform-specific RT-PCR, immunoblot analysis with nonspecific antibodies (AKR1C1/1C2), and using monoclonal- and peptide-derived antibodies for AKR1C3 (24–28, 82). These studies are in agreement that all four isoforms are expressed in the liver, but AKR1C4 is uniquely liver specific. AKR1C1–AKR1C3 because of their roles in xenobiotic and steroid metabolism are also highly expressed in the small intestine, lung, mammary gland, and prostate. NSCLC patients and A549 cells display high expression of AKR1C1 expression where it is a poor prognostic indicator (58, 73). In mammary gland, AKR1C3 is one of the dominant forms, and the expression of AKR1C1–AKR1C3 in human prostate shows differential expression based on disease state and cell type (stromal versus epithelial cells), which is consistent with their roles in the biosynthesis and metabolism of steroid hormones (25, 94–96).

AKR1D1, also known as steroid 5β-reductase, so far appears to be liver specific based on its role in bile acid biosynthesis and steroid hormone clearance.

AKR7A2 is widely distributed in human tissues and appears to be equally abundant in some tissues, like AKR1A1, based on immunoblot analysis. High expression is notable in liver, small intestine, kidney, and the cerebrum (82). Its distribution in brain regions is consistent with its role in the metabolism of the GABA metabolite succinic semialdehyde (97). AKR7A3 is found in the liver but is primarily expressed in the colon, kidney, and pancreas, and is less widely expressed than AKR7A2.

## Regulation of Human AKR Genes

AKRs are regulated by primordial signals, e.g., osmotic shock, ROS, electrophiles, and other environmental cues (4). These signals inform the cell that it is necessary to mount an effective counterresponse if it is to survive an osmotic, ROS, or electrophilic insult, etc. Each of these signals regulates AKR genes via osmotic response elements (OREs), AP-1 sites, and/or antioxidant response elements (ARE), respectively. In some instances, these elements may coexist within the same promoter to form a multiple stress response element (MSRE) (98). The activation of these signal transduction pathways by environmental stressors predicts that the metabolism of drugs, carcinogens, and reactive aldehydes will be affected in the target tissue. Whether this results in a harmful or beneficial effect depends on the physiological/toxicological context. For example, induction of AKRs may increase their ability to detoxify reactive aldehydes but may also cause resistance to anticancer drugs, tolerance to medications, or the bioactivation of PAH. Because the regulatory elements

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may be common in some AKR gene promoters, AKR gene regulation is discussed in the context of stress signals and their response elements.

**Osmotic response element.** AKR1B1 (aldose reductase) is induced by osmotic stress. This response is intuitive because the enzyme converts glucose to the hyperosmotic sugar sorbitol, which will aid in water retention. AKR1B1 is implicated in the detoxication of acrolein (a metabolite of cyclophosphamide), 4-HNE and GS-4-HNE, and 1,2-naphthoquinone, and these events will occur faster in the presence of increased tonicity. The ORE or tonicity response element (TonE) lies within the 5′-flanking region of the gene (5′-TGGAAAATCA-CCGC-3′) at -1.1 kb and binds the TonE-binding protein (TonEBP), a *rel*-like transcription factor and a member of the nuclear factor of activated T cell (NFAT) family (99–101). The transcription factor NF-κB also recognizes the TonE and activates the promoter in response to TNFα. Between −1167 and −1047 bp of the AKR1B1 promoter resides an AP-1 site and two ARE sites. Although functional interplay between these sites remains to be demonstrated, such interplay does exist on the mouse aldose reductase gene promoter AKR1B3 (98).

**AP-1 sites.** The AP-1 consensus sequence 5′-TGACTCA-3′ [also known as TPA (phorbol-ester response element)] is located in the promoter of AKR1B1 and AKR1C1 genes. In fact, four AP-1 sites exist in the AKR1C1 promoter between –2.0 kb and the transcription start site (H.K. Lin & T.M. Penning, unpublished). Activating-protein 1 (β-leucine-zipper) transcription factors c-jun and c-fos are recruited to this element as part of a stress-induced signal transduction pathway involving a mitogen-activated protein kinase (MAPK) cascade (102, 103). This pathway can be activated by extracellular ROS or PKC, and results in the activation of preexisting c-Jun (104, 105) and the activation of the c-Jun and c-fos promoters. In addition, both c-Jun and c-fos are redox regulated by intracellular ROS and must be kept fully reduced to maintain their DNA-binding ability (104). This is achieved by Ref-1 (an apurinic/apyrimdimic endonuclease), which is kept reduced by thioredoxin and thioredoxin reductase (106, 107). The functionality of the AP-1 sites in AKR1B1 and AKR1C genes needs to be formally demonstrated. However, because the AP-1 consensus sequence is embedded in the ARE consensus sequence, the possibility exists that ROS may mediate their effects via the AP-1 and electrophiles may mediate their effects via the ARE.

**Antioxidant response element.** AKR1C1–AKR1C3 belong to the battery of genes regulated by an ARE via the Nrf2-Keap-1 complex in humans (108, 109). Common inducers are bifunctional inducers, e.g., 3-methylcholanthrene, β-naphthoflavone, and benzo[*a*]pyrene, that must undergo metabolism to electrophiles to cause induction, and the monofunctional inducers that can prevent the ubiquintination and proteosome degradation of Nrf2 by targeting Keap-1 (e.g., ethoxyquin, t-BHQ, ethacrynic acid, and hydrogen peroxide) (110). Increased expression of AKR1C1–AKR1C3 will be beneficial for the elimination of 4-HNE, a product of oxidative stress, but could

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also be deleterious based on the pivotal roles of these enzymes in steroid hormone metabolism and the bioactivation of PAH *trans*-dihydrodiols.

AKR1C1 is upregulated in human colon cells induced to be cancer chemotherapeutic drug resistant with ethacrynic acid (111). AKR1C1 is also upregulated by a panel of monofunctional inducers, including ethoxyquin, t-BHQ, hydrogen peroxide, and bifunctional inducers β-naphthoflavone and benzo[*a*]pyrene in HepG2 cells (108). Induction by the bifunctional inducers showed a delayed response indicative of the requirement of metabolism to electrophiles to activate the Nrf2-Keap-1 complex. AKR1C1 was identified as the isoform induced by RNase protection assays, which also revealed that AKR1C3 was upregulated modestly. Isoform-specific induction was also supported by the demonstration that functional enzyme activity in HepG2 cell lysates could only be eliminated with high concentrations of ursodeoxycholate. Nanomolar concentrations of ursodeoxycholate, which are sufficient to inhibit AKR1C2 in vitro, were unable to inhibit the increase in functional activity in HepG2 cell lysates, indicating that AKR1C1 and not AKR1C2 was the induced gene (108). Recently, using real-time RT-PCR, both AKR1C1 and AKR1C2 transcripts were elevated in HepG2 cells following treatment with the bifunctional inducer β-naphthoflavone (109).

The AKR1C1–AKR1C4 genes have almost identical organization, containing 9 exons and introns with conserved boundaries and are localized to chromosome 10. The identification of the ARE (5′-GTGAC/GTCA-GC-3′) in the AKR1C1 promoter initially eluded identification. Dissection of –1.0 kb promoter identified a proximal ARE, which, when used in CAT reporter gene assays, was insufficient to account for the fold induction seen with the monofunctional inducers (112). Recently, characterization of the AKR1C2 promoter in HepG2 cells led to the localization of an ARE at –5.5 kb from the transcription start site. Transient transfection with Nrf2 increased the transcriptional activity from this ARE using an ARE-luciferase reporter gene construct comparable to that seen by Phase II inducers. Chromatin-immunoprecipitation analysis confirmed increased binding of Nrf2 to the ARE after induction by β-naphthoflavone (109). Comparison of −9.0 kb of the AKR1C1 and AKR1C2 promoters showed a remarkable degree of nucleotide sequence identity, >45%, and this led to the location of a similar functional ARE within the AKR1C1 promoter.

**Phase II enzymes:** a group of enzymes (glutathione-S-transferase, UDP-glucuronyl transferases, and sulfotransferases) that form soluble conjugates for elimination

## DRUG-DRUG INTERACTIONS

AKRs are inhibited by major classes of drugs, e.g., AKR1A1 and AKR1B1 are inhibited by AKR1B1 inhibitors developed for the prevention and treatment of diabetic complications (106, 107) and AKR1C isoforms are potently inhibited by NSAIDs in order of their anti-inflammatory drug potency (33, 113). This raises the specter of drug-drug interactions that may be beneficial or harmful.

Although AKR1B1 inhibitors successfully treat diabetic complications in animal models, outcomes of clinical trials have been disappointing. Studies with transgenic and AKR1B1 knockout mice demonstrate that the AKR1B1-mediated polyol pathway causes osmotic and oxidative stresses that lead to diabetic complications, such as

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cataract and neuronal dysfunction (114). However, AKR1B1 also detoxifies lipid aldehydes and regulates cell growth and inflammation (115), and in this context, AKR1B1 inhibition may be a disadvantage. Development of AKR1B1-specific/selective inhibitors (that do not inhibit AKR1A1) and possibly adjuvant therapy with antioxidants have been suggested to reduce the possible side effects of AKR1B1 inhibitors.

**Hormone replacement therapeutics:** drugs that replace ovarian estrogens and progestins, typically used to relieve climacteric complaints in postmenopausal women

Coadministration of AKR1A1 and AKR1C2 inhibitors with anthracycline anticancer drugs may be desirable because this would reduce the formation of the cardiotoxic alcohol metabolite and prevent drug resistance. However, coadministration of AKR1B1 inhibitors to patients on cyclophosphamide would be deleterious because this would block the removal of the nephro and urotoxic metabolite acrolein. Treatment with common NSAIDs may also affect the efficacy of hormone replacement therapeutics such as tibolone, which requires bioactivation by AKR1C enzymes. An attractive option is indomethacin because it selectively inhibits AKR1C3, which plays a minor role in tibolone bioactivation. Inhibition of AKR1Cs will be unwanted in the case of the opioid receptor antagonist naltrexone because the formation of the active metabolite 6β-naltrexol by AKR1C4 determines the duration of drug action.

## HUMAN AKR GENE POLYMORPHISMS

The role of AKRs in the bioactivation and detoxication of xenobiotics will also be affected by allelic variants. Most of the genetic variations occur in the noncoding region of the AKR genes. Only a small percent of the polymorphisms result in amino acid changes. Knowledge of the phenotypes associated with these polymorphisms is limited, and their impact on the metabolism of xenobiotics remains to be elucidated.

Genetic variants in *AKR1B1* have been implicated in the development of diabetic complications (116–120). The Z-2 allele of the $(CA)_n$ polymorphism and the C allele of the C106T SNP in the promoter region of *AKR1B1* have been associated with increased susceptibility for diabetic complications in both type 1 and type 2 diabetes of different ethnic groups. Increased expression of *AKR1B1* is linked to these variants, implicating the AKR1B1-mediated polyol pathway in the pathogenesis of diabetic complications.

In a recent study, the AKR1C3 Gln5His variant was associated with increased risk of PAH-induced lung cancer (121). Although the functional consequence of this SNP is yet to be determined, increased activity of AKR1C3 would increase the bioactivation of PAH *trans*-dihydrodiols.

The functional consequence of the AKR1C4 Leu311Val SNP has been described (122). The Leu311Val mutation resulted in a deficient enzyme with a three- to fivefold decrease in activity. In women using combined estrogen and progestin therapy, this genetic variant has been linked to a significantly greater increase in the percentage of mammographic density, or possibly a greater risk for breast cancer (123). This may be accounted for by decreased clearance of estrogens and progestins owing to lower AKR1C4 activity. The AKR1C4 Leu311Val polymorphism may also be responsible for the lack of positive outcomes in patients undergoing naltrexone treatment (48). Lower AKR1C4 activity would result in decreased levels of the circulating pharmacologically active 6β-naltrexol metabolite, thus affecting the efficacy of naltrexone.

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## SUMMARY POINTS

1. Human AKR enzymes are Phase I drug-metabolizing enzymes that convert carbonyl groups to primary or secondary alcohols.
2. Natural substrates for AKRs include sugar and lipid aldehydes, retinals, steroids, and prostaglandins.
3. AKRs bioactivate prodrugs, e.g., tibolone, and prolong drug action, e.g., naltrexone.
4. AKRs bioactivate chemical carcinogens, e.g., PAH *trans*-dihydrodiols.
5. AKRs mediate cancer chemotherapeutic drug resistance, e.g., daunorubicin and *cis*-platin.
6. AKRs detoxify reactive aldehydes, e.g., acrolein and 4-HNE.
7. AKRs show regulated expression by OREs, AP-1, and ARE.

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