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Cytoplasmic Aldo-Keto Reductases: A Class of Drug Metabolizing Enzymes

Abstract. *Aldehyde and ketone xenobiotic substances are preferentially reduced to alcohols by cytoplasmic enzymes in mammals. These enzymes are widely distributed in the tissues, have broad substrate specificities, have similar physical-chemical characteristics, and require reduced nicotinamide adenine dinucleotide as cofactor for the reductions. These reductases define a system of detoxification for aldehyde and ketone groups.*

Xenobiotic aldehydes and ketones are metabolized in mammals through both oxidative and reductive pathways (*1, 2*). However, many aliphatic and aromatic ketones and aldehydes yield corresponding alcohol metabolites as prominent excretory products in vivo, and reduction appears to be the favored pathway for these carbonyl group biotransformations (*3–5*). From studies designed to characterize the enzymes catalyzing carbonyl reduction, the aldo-keto reductases are localized to the cellular cytoplasm. These cytoplasmic enzymes show similarities in substrate specificity, tissue distribution, cofactor requirement, *p*H optimum, molecular weight, sulfhydryl sensitivity, noninducibility, and reaction equilibrium. They appear to compose a class.

The enzymatic reduction of several drugs and xenobiotic substances containing the carbonyl group have been studied and described (Table 1). Aromatic aldehydes (such as benzaldehyde) (*6, 7*), aromatic ketones (such as acetophenone) (*8, 9*), aliphatic ketones (such as oxisuran and naloxone) (*10–12*); methyl ketones (such as daunorubicin and warfarin) (*13–15*), a tetralone (such as bunolol) (*16*), and unsaturated ketones (*17*) are substrates of proven cytoplasmic enzyme activities that generate alcohol products.

One characteristic of the few reductases that have been purified and studied is a broad substrate specificity (*6, 7, 9, 14, 20, 21*). The enzymes reduce xenobiotic carbonyls as well as naturally occurring substrates. For example, a purified rat liver aldehyde reductase that reduces several aromatic aldehydes very effectively reduces the methyl ketone daunorubicin and the natural substrate glucuronic acid (*7*). However, absolute substrate specificity is difficult to assess because crude cytoplasmic extracts may contain several reductases. During the purification of rat liver aldehyde reductase, clear separation of the aldehyde reductase and other reductases occurs (*7*), an indication that several enzymes with aldo-keto reducing activity are present in rat liver cytoplasm. In rabbit liver, different cytoplasmic enzymes reduce acetone and acetophenone (*8*) or warfarin, oxisuran, and daunorubicin (*20*). For these reasons, purifications of the cytoplasmic aldo-keto reductases are necessary to resolve the substrate specificity enigma.

The aldo-keto reductases are widely distributed among tissues (Table 1). Although many investigations are limited to liver cytosol reductases, reductase activities occur in several other organ locations (*8, 10, 11, 18*). In fact, the cytosol of every mammalian tissue examined reduces daunorubicin (*13, 14, 19*). Even erythrocytes contain aldo-keto reductases (*8, 13, 17–19*). The wide tissue distribution indicates the large reservoir of catalytic activity that is available.

All the aldo-keto reductases preferentially utilize reduced nicotinamide adenine dinucleotide phosphate (NADPH) as cofactor (Table 1). Purified preparation of rabbit liver oxisuran reductase (*20*), rat liver aldehyde reductase (*14*), and hog kidney aldehyde reductase (*6*), as well as the other unpurified enzymes, require NADPH as cofactor. Only the aliphatic keto reductase activity of crude rat liver cytosol utilizes NADPH and NADH equally (*8*). No other cofactors or prosthetic groups have been identified in these enzymes (*20*).

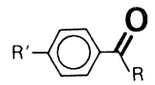
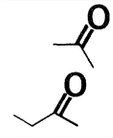
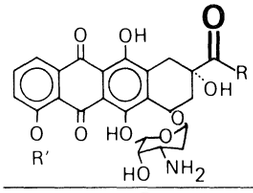
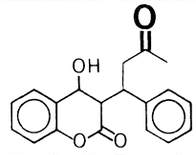
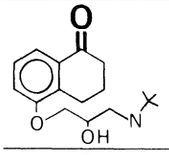
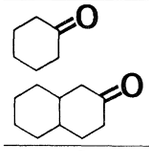
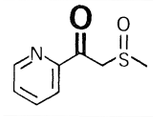
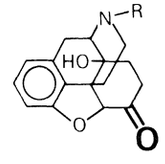
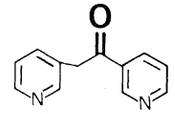
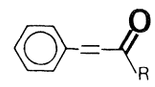
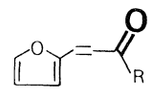
The *p*H optima of enzymatic carbonyl reductions range between *p*H 6 and *p*H 8 for those enzymes that have been assessed (*6, 7, 9, 14, 16*). As a result, near-maximal enzymatic activities are expressed at the physiological intracellular *p*H range. However, substrate classes with dual *p*H optima have been established for the aldehyde rat liver reductase (*7*).

Since few of these enzymes have been purified, little is known of their physical-chemical characteristics. But for those that have been studied, molecular weights ranging from 30,000 to 40,000 are reported (*14, 20*). Another common feature of the enzymes is the dependence of reductase activity on sulfhydryl groups in the enzyme. *P*-Chloromercuribenzoate, *N*-ethylmaleimide, and other sulfhydryl reagents inhibit these enzymes (*6, 7, 19*).

Unlike microsomal drug metabolizing enzymes, the aldo-keto reductases are not induced or are only slightly affected by phenobarbital pretreatment (*8, 10, 15, 20*). Even prior treatment of rats for 3 days with carboxybenzaldehyde, the favored substrate for the rat liver aldehyde reductase, did not induce that enzyme (*20*).

Although these enzymes are theoretically oxidoreductases, their observed apparent equilibria favor reduction. This is observed in vivo in animals and humans and in vitro with enzyme systems. Reversibility for the oxidative reaction is attainable at low hydrogen ion concentrations (*14*), but some reactions could not be reversed (*11, 16*).

Table 1. Cytoplasmic aldo-keto reductions in vertebrates. Abbreviations for tissues are: B, brain; E, erythrocytes; H, heart; I, intestine; K, kidney; L, lung; LI, liver; M, muscle; P, platelets; W, leukocytes. Abbreviations for species are: BT, bovine; CF, dog; CP, guinea pig; EC, horse; GG, chicken; HS, human; MG, turkey; MM, mouse; OC, rabbit; RN, rat; SS, pig.

SUBSTRATE STRUCTURE	R	R′	NAME	TISSUE	SPECIES	COFACTOR	REF
	H	H	Benzaldehyde	K	SS	NADPH	6
	H	Cl	pCl "				
	H	NO_2	pNO_2 "	LI	RN	NADPH	7
	CH_3	H	Acetophenone	LI,K,H,L	OC	NADPH	8
	CH_3	Cl	pCl "				
	CH_3	NO_2	pNO_2 "	E	HS	NADPH	9
	CH_3CH_2	H	Propriophenone				
	—	—	Acetone	LI	OC	NADPH	8
	—	—	2 - Butanone			NADH	
	CH_3	CH_3	Daunorubicin	B,L,H, LI,K,M	OC,RN, MM,CF,		13
	CH_3	H	Carminomycin	I,E,W,P	HS	NADPH	
	CH_2OH	CH_3	Adriamycin				14
	—	—	Warfarin	LI,K	HS, RN	NADPH	15
	—	—	Bunolol	B,L,H, LI,K,E,	HS, RN	NADPH	18
	—	—	Cyclohexanone	K	OC	NADPH	6
	—	—	2-Decalone				
	—	—	Oxisuran	B,L,LI, K, I	OC	NADPH	10
	$CH_2CH{=}CH_2$	—	Naloxone	L,LI,K	OC,SS, BT,RN EC,MC GG,HS +mushroom	NADPH	11
	CH_2	—	Naltrexone				12
	CH_2	—	EN–1665				
	—	—	Metyrapone	LI	OC	NADPH	8
	CH_3	—	Benzylidine Acetone	LI,E	CF,HS	NADPH	17
		—	Benzylidine Acetophenone				
	CH_3	—	Furfurylidine Acetone	LI,E	CF,HS	NADPH	17
		—	Furfurylidine Acetophenone				

Aldo-keto reductases exist in all mammalian species analyzed and are found in submammalian species such as chickens, turkeys, and fungi (Table 1). Because of their wide distribution in tissue and their ability to metabolize normally occurring substrates (*7, 8, 14, 20, 21*), it is likely that aldo-keto reductases function in some ordinary capacity in cellular metabolism. These enzymes catalyze glucuronic acid reduction (*14*), crotonyl CoA reduction (*6*), aldose reduction (*21*), β-hydroxylated phenylethyl aldehyde reduction (*5*), and possibly other reactions. Since enzymes from different species display many similarities, comparative biochemical studies may substantiate the functional role of the catalysts.

The aldo-keto reductases function in detoxification to eliminate the chemically reactive carbonyl groups. Carbonyl reduction is a rapid, one-step pathway that simultaneously eliminates these reactive groups, modifies molecular polarity, and prepares the drug molecule for conjugation.

The alcohol metabolites resulting from carbonyl reduction of drugs usually retain pharmacologic activity (*12, 19, 20*). But an important modulating factor to activity is the stereochemical configuration of the alcohol product. Stereochemical configuration is determined by enzyme specificity and should be a prime consideration in drug design. The presence of a carbonyl group in a drug increases the variability in activity and possibly the toxicity through this biotransformation potential.

Certainly the similarities of the aldo-keto reductases from mammalian tissues are unlikely to be a matter of chance. From the cited collected studies it appears there is a system of related cytoplasmic aldo-keto reductases similar in several characteristics. These enzymes may be related genetically and through evolution, but these points remain for study.

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Differential Resource Utilization by the Sexes of Dioecious Plants

Abstract. *The distribution of male and female plants was examined in five dioecious, wind-pollinated species representing five plant families and two classes (gymnosperms and angiosperms). The arid to semiarid habitats occupied by these species in northern Utah were stratified for sampling into two categories: chronically xeric and seasonally moist. The results show that for all species, males are more abundant on xeric microsites, while females are overrepresented on the moister parts of each local environment. Differential distribution of the sexes along a soil moisture gradient is a strategy that maximizes seed set of females and pollen dispersal of males; it also tends to minimize intraspecific competition between the sexes.*

The importance of sexual dimorphism in animals as a means of reducing intraspecific competition for resources has received considerable attention (*1, 2*). Selander (*1*) found sexual dimorphism to be common among birds. Brown and Lasiewski (*2*) concluded that the phenomenon is an important attribute of elongate carnivores (such as weasels).

In contrast, the question of differential resource utilization by male and female plants has apparently been little investigated, although Putwain and Harper (*3*) described temporal differences in growth patterns of male and female individuals of two dioecious (*4*) species of *Rumex*. Sex ratios within populations of dioecious plants have received more notice (*3*), but little attention has been directed toward determining the selective forces responsible for unbalanced ratios. We have observed the relative abundance of male and female individuals of five wind-pollinated species along a strong environmental gradient. Our objective has been to determine whether environment exerts a significant influence on the proportion of males and females

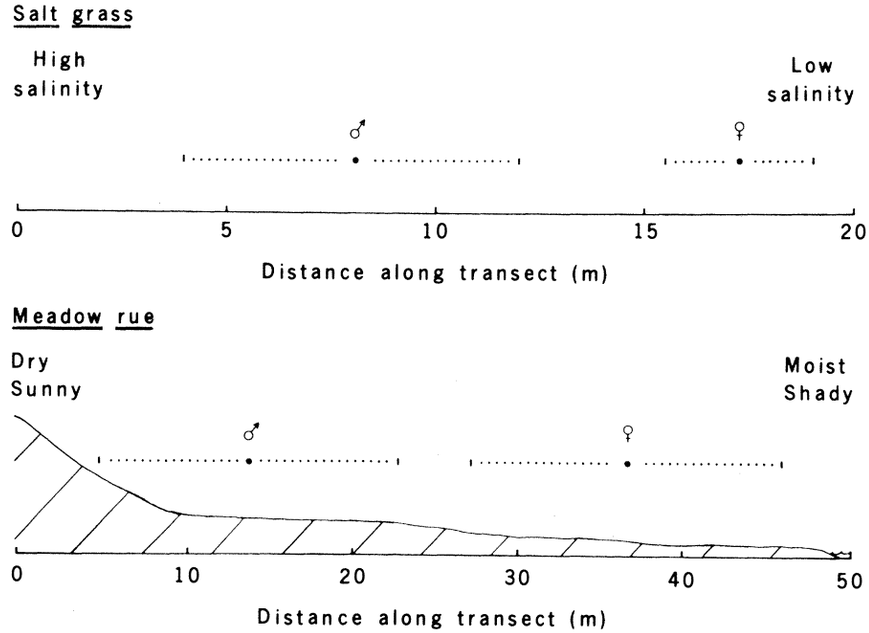

Fig. 1. Averages and standard deviations of distances of male (♂) and female (♀) individuals of salt grass and meadow rue along transects running from areas of moisture stress to moisture abundance. Distances are measured from the left in both cases.