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Detoxication of carcinogenic fjord-region diol epoxides of polycyclic aromatic hydrocarbons by glutathione transferase P1-1 variants and glutathione

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Abstract Epidemiological studies suggest that individuals differing in the expression of allelic variants of the human glutathione transferase (GST) Pi gene differ in susceptibility to chemical carcinogens such as polycyclic aromatic hydrocarbons (PAH). This study reports the catalytic efficiencies (k_{cat}/K_m) of two naturally occurring variants, GSTP1-1/I-105 and GSTP1-1/V-105, towards a series of fjord-region diol epoxides representing potent biologically active PAH metabolites, and two GSTP1-1 mutants with Ala^{105} and Trp^{105} in the active site. The results indicate that individuals who are homozygous for the allele encoding GSTP1-1/V-105 might be more susceptible to PAH carcinogenesis due to other reasons than a reduced capacity for detoxifying diol epoxides.

Key words: Polycyclic aromatic hydrocarbon; Fjord region; Diol epoxide; Human glutathione transferase P1-1; Glutathione conjugation; Carcinogenesis

1. Introduction

Polycyclic aromatic hydrocarbons (PAH) are environmental pollutants and highly suspected as carcinogens in humans [1,2]. Following their metabolic activation to diastereomeric bay- and fjord-region diol epoxides, the mutagenic and carcinogenic activities appear to be linked to the covalent binding of these reactive intermediates to the exocyclic amino group of deoxyguanosine (dG) and deoxyadenosine (dA) in DNA [3–5].

Available information indicates that fjord-region diol epoxides in general are more biologically potent than bay-region diol epoxides [6]. The former intermediates demonstrate a higher preference for adduct formation with dA than bay-region diol epoxides [7,8], which in part may explain the increased potency. Furthermore, whereas the (+)-*anti*-enantiomers of the bay-region diol epoxides with *R*,*S*,*S*,*R*-absolute configuration seem to be the principal tumor initiators among the four possible stereoisomers, both the *anti*- and *syn*-stereoisomers of the fjord-region diol epoxides demonstrate high mutagenic and/or tumorigenic activity [9,10]. The diequatorial orientation of the hydroxyl groups in all fjord-region diol epoxides due to the non-planarity and the steric hindrance in the molecule are likely part of the explanation [9,10].

The most important intracellular system preventing the formation of diol epoxide-DNA adducts is glutathione transferase (GST)-catalyzed conjugation of the intermediates with glutathione (GSH) [11]. In this context the Pi class of GSTs seems to be of particular importance [12,13] and recently it was demonstrated that GSTPi gene deleted mice exhibit an increased susceptibility to PAH-induced tumors [14]. In humans, an allelic variant with Val^{105} (GSTP1-1/V-105) rather than Ile^{105} (GSTP1-1/I-105) has been associated with higher tumor susceptibility in organs exposed to PAH [15]. In another study Matthias et al. [16] showed that the frequency of *GSTP1*A* (encoding GSTP1-1/V-105) in individuals with squamous carcinomas of the upper aerodigestive tract was lower than in control individuals. Harris et al. [17] recently examined individuals with colorectal or lung cancer but found no significant associations between a particular GSTP1-1 variant and either form of tumor. Thus, the results to date on GSTP1-1 polymorphism and cancer susceptibility are variable and further evaluation in larger populations seems to be needed.

Previous studies have shown that the GSTP1-1/I-105 and GSTP1-1/V-105 exhibit different catalytic efficiencies towards bay-region diol epoxides. With most compounds examined GSTP1-1/V-105 was more efficient than GSTP1-1/I-105 [18,19]. In organs in which tumor formation is initiated by DNA adducts derived from bay-region diol epoxides this difference may be a significant factor in tumor susceptibility. Fjord-region diol epoxides are considerably more carcinogenic in experimental animals and may pose a higher risk as tumor initiators in humans. Therefore, it is important to evaluate the role of their GST-catalyzed detoxication. In this study the catalytic efficiencies of the two naturally occurring GSTP1-1 allelic variants, GSTP1-1/I-105 and GSTP1-1/V-105, towards several of these compounds have been determined. The metabolically most relevant (−)-*anti*- and (+)-*syn*-diol epoxide stereoisomers from benzo[*c*]phenanthrene (B[*c*]Ph), benzo[*c*]chrysene (B[*c*]C), benzo[*g*]chrysene (B[*g*]C) and dibenzo[*a,l*]pyrene (DB[*a,l*]P), the most carcinogenic PAH yet identified [20,21], have been investigated.

As part of the active site of GSTP1-1 the side-chain of the amino acid residue in position 105 appears to influence catalytic efficiency. To gain insight into the steric requirements for

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Abbreviations: PAH, polycyclic aromatic hydrocarbons; DB[*a,l*]P, dibenzo[*a,l*]pyrene (IUPAC systematic name: dibenzo[*def,p*]chrysene); B[*c*]C, benzo[*c*]chrysene; B[*g*]C, benzo[*g*]chrysene; B[*c*]Ph, benzo[*c*]-phenanthrene; *syn*- and *anti*-DB[*a,l*]PDE, *syn*- and *anti*-dibenzo[*a,l*]-pyrene-11,12-diol 13,14-epoxide; *syn*- and *anti*-B[*c*]CDE, *syn*- and *anti*-benzo[*c*]chrysene-9,10-diol 11,12-epoxide; *syn*- and *anti*-B[*g*]CDE, *syn*- and *anti*-benzo[*g*]chrysene-11,12-diol 13,14-epoxide; *syn*- and *anti*-B[*c*]PhDE, *syn*- and *anti*-benzo[*c*]phenanthrene-3,4-diol 1,2-epoxide; CDNB, 1-chloro-2,4-dinitrobenzene

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efficient catalysis of fjord-region diol epoxides conjugation, mutants with Ala[105] (GSTP1/A-105) or Trp[105] (GSTP1-1/W-105) at this position have also been studied.

2. Materials and methods

2.1. Chemicals

Synthesis of the optically active *syn*-and *anti*-diol epoxides of B[*c*]Ph [(−)-*anti*- and (+)-*syn*-B[*c*]PhDE], B[*c*]C [(−)-*anti*- and (+)-*syn*-B[*c*]CDE], B[*g*]C [(−)-*anti*- and (+)-*syn*-B[*g*]CDE] and DB[*a,l*]P [(−)-*anti*- and (+)-*syn*-DB[*a,l*]PDE] was performed as previously described [22–24]. Chromatographic standards of derivatives of B[*c*]PhDE, B[*c*]CDE and B[*g*]CDE were obtained as previously described [22,25]. A similar procedure was used to obtain standard derivatives of DB[*a,l*]PDE. In brief, GSH conjugates were prepared by incubating each diol epoxide isomer with a 10 000-fold excess of GSH in Na_2CO_3-saturated water (pH = 8.5) and N_2 followed by removal of unreacted diol epoxide and hydrolysis products by ethyl acetate extraction. Tetraols were obtained by hydrolysis of the diol epoxides in diluted HCl and conjugates with 2-mercaptoethanol by reacting the diol epoxides with a 5000-fold excess of 2-mercaptoethanol in aqueous NaOH. All incubations were carried out at ambient temperature and for at least 12 h. The derivatives of DB[*a,l*]PDE were subsequently purified by HPLC using the conditions described below.

2.2. Glutathione transferases

The GSTP1-1 variants were produced and treated prior to the experiments as recently described [19]. The specific activities of 98, 59, 37 and 56 μmol CDNB/mg/min were used to calculate the amount of active protein of GSTP1-1 variants I-105, V-105, A-105, and W-105, respectively.

2.3. Incubations

Enzyme corresponding to 10–500 μg active protein/ml was incubated at 37°C for 1 min with 40 and 80 μM diol epoxide (added in dimethylsulfoxide, final concentration 5%, v/v) and 5 mM GSH in 50 mM Tris-HCl buffer, pH 7.5 (final volume 100 μl) and the GSH conjugates by HPLC as described [22]. The HPLC analysis of GSH conjugates analyzed of DB[*a,l*]PDE was performed in principle as described [22]. In brief, an analytical column (Nova Pak 4μm C18, 3.9×150 mm, Waters Inc.) and a solvent system composed of 25 mM ammonium acetate/acetic acid, pH 3.5 (solvent A) in acetonitrile (solvent B) delivered at a flow rate of 1 ml/min. The following solvent composition was used: 20–30% B linear gradient for 10 min and 30–60% B linear gradient for 20 min. The effluent was monitored by UV absorbance at 290 nm. The identities of the peaks were determined by comparison with standard derivatives. The quantitation of GSH conjugates was performed by comparison with authentic standard conjugates and using the determined extinction coefficients for the conjugates of B[*c*]PhDE, B[*c*]CDE and B[*g*]CDE [22]. For the quantitation of GSH conjugates of DB[*a,l*]PDE the extinction coefficients of the parent *syn*- (ε_{294} = 34 000 cm^2/mmol) and *anti*-DB[*a,l*]PDE (ε_{295} = 36 500 cm^2/mmol) were used. As shown for other diol epoxides [22] the HPLC procedure employed for the analysis of DB[*a,l*]PDE derivatives permits separation of tetraols and 2-mercaptoethanol conjugates in addition to the separation of diastereomeric GSH conjugates, thus allowing calculation of total product recovery.

3. Results and discussion

Recent studies have identified a polymorphism in the human GSTP1-1 gene which results in three variant protein products. These are Ile or Val at position 105 and Ala at

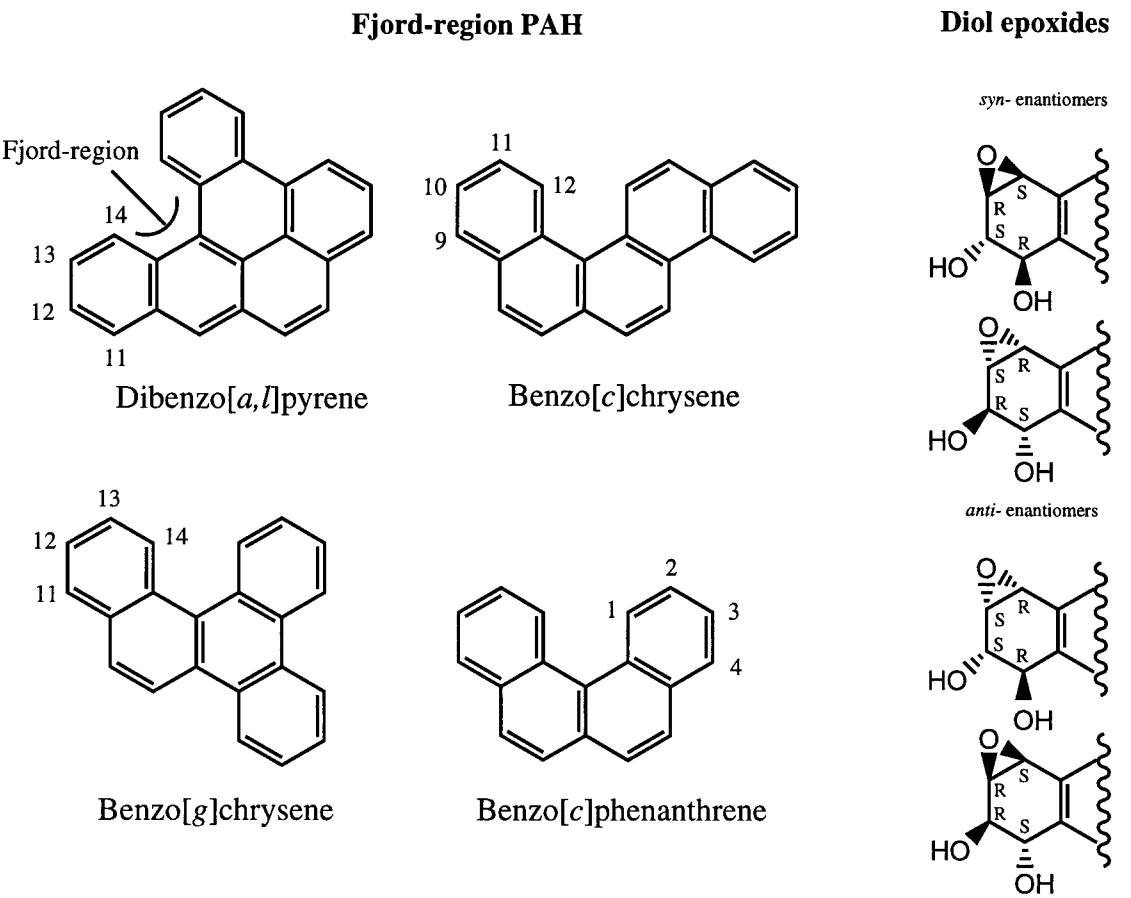

Fig. 1. Structure and numbering system of the fjord-region PAHs from which the diol epoxides used in this study are derived. The absolute stereochemistry of the *syn*- and *anti*-diol epoxides is shown to the right. The prefix *syn* indicates that the oxirane ring and the benzylic hydroxyl group are located on the same face of the molecule whereas *anti* indicates location of these groups on opposite faces.

position 114 (GSTP1-1/I-105 and GSTP1-1/V-105, respectively), and Val at both position 105 and 114 [26–29]. Position 105 is an integral part of the second substrate binding site (the H-site) of the enzyme whereas position 114 is not [30]. It has been shown previously that the allelic variants differ in their catalytic activity towards (+)-*anti*-BPDE, an ultimate carcinogenic metabolite of benzo[*a*]pyrene, and other carcinogenic bay-region diol epoxides [18,19,31]. GSTP1-1/V-105, which is the less common variant in the human population, demonstrates a higher catalytic efficiency than GSTP1-1/I-105 towards most of the diol epoxides studied up to now. As with GSTP1-1/I-105, the GSTP1-1/V-105 variant demonstrates an almost exclusive preference for the diol epoxide isomers with *R*-absolute configuration of the benzylic oxiranyl carbon [18,19]. Interestingly, in both the *syn*- and the *anti*-series these intermediates are more mutagenic and/or carcinogenic than the corresponding diol epoxide enantiomers with *S*-absolute configuration [10,33]. P1-1 is the dominating GST isoform in extrahepatic tissues such as the respiratory and digestive tract, skin and urinary bladder, all tumor-susceptible organs in which PAH may play a role in tumor initiation [34].

Recent epidemiological data indicate that individuals expressing the GSTP1-1/V-105 variant may be more susceptible to tumor formation in organs exposed to PAH [15–17,35,36]. As discussed recently [19] the elevated activity of GSTP1-1/V-105 relative to GSTP1-1/I-105 towards carcinogenic bay-region diol epoxides suggests that the correlation between the *GSTP1*B* allele and a higher risk for PAH-induced carcinogenesis is not due to a lower catalytic efficiency of the corresponding GST. This may have a number of alternative explanations. One possibility is that bay-region diol epoxides are not the most important tumor initiators in the organs believed to be susceptible to PAH exposure but rather the more potent fjord-region analogues. Thus in this study the catalytic efficiency (k_{cat}/K_m) of GSTP1-1/I-105 and GSTP1-1/V-105 towards the highly mutagenic and carcinogenic fjord-region *anti*- and *syn*-diol epoxides of B[*c*]Ph, DB[*a,l*]P, B[*c*]C and B[*g*]C (see Fig. 1 for structures) have been compared. The investigation was restricted to the stereoisomers with *R*-absolute configuration at the benzylic oxiranyl carbon because a high degree of stereoselectivity exists in the metabolic activation pathway favoring the formation of isomers with this stereochemistry and previous work with bay-region diol epoxides clearly demonstrated that GSTP1-1 exclusively catalyzes the reaction of these enantiomers with GSH [32]. Finally, the assumption was made that both allelic GSTP1-1 variants are identical in this latter respect.

Measuring conjugates of diol epoxides with GSH includes brief incubation of enzyme, GSH and the second substrate followed by addition of alkaline mercaptoethanol to trap unreacted diol epoxide. Reaction products were subsequently estimated by HPLC. Fig. 2A,B shows the results obtained with the (−)-*anti*- and (+)-*syn*-DB[*a,l*]PDE and GSTP1-1/A-105. As is evident from Fig. 2 the reaction products are chromatographically well resolved including the diastereomeric GSH conjugates ($R_t = 8$ and 12 min, respectively in A and B).

Position 105 in GSTP1-1 is part of the second substrate binding site (H-site) and recent results with bay-region *anti*-diol epoxides demonstrated a reciprocal correlation between the bulkiness (Trp > Ile > Val > Ala) of the amino acid residue at this position and the catalytic efficiency k_{cat}/K_m. With the bay-region *syn*-diol epoxides a gradual reduction in k_{cat}/K_m was observed with the Ala^{105}, Val^{105}, and Ile^{105} variants but not with the Trp^{105} variant. In fact, the introduction of Trp^{105} substantially increased the activity [19].

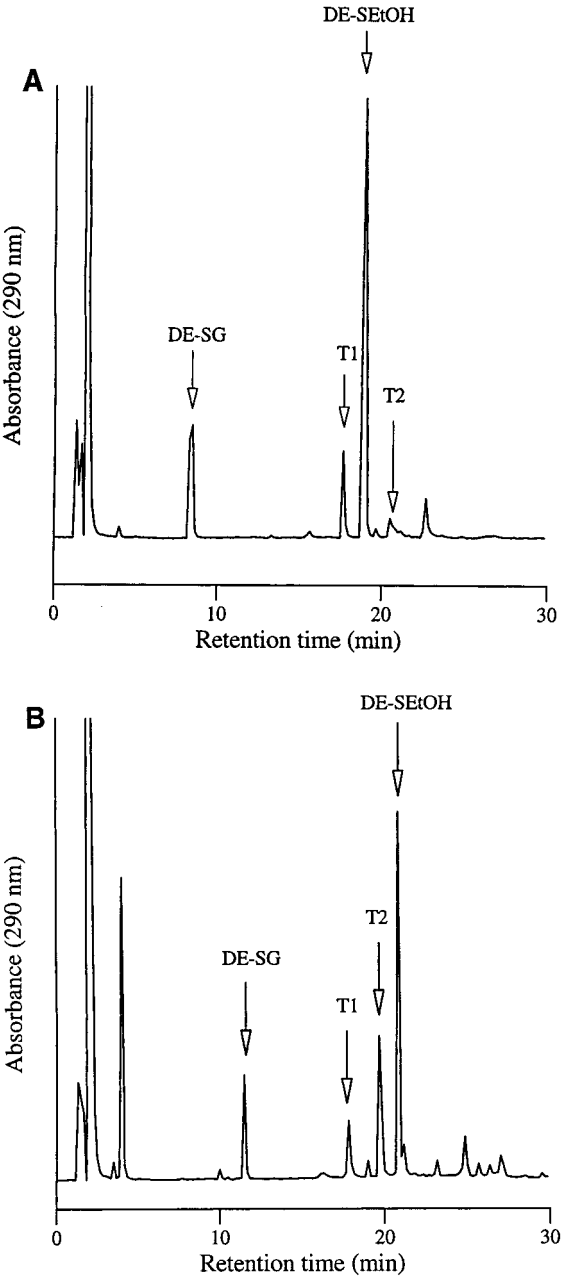

Fig. 2. HPLC elution profile of products derived from (−)-*anti*-DB[*a,l*]PDE (A) and (+)-*syn*- DB[*a,l*]PDE (B). DE-SG: glutathione conjugate of the corresponding diol epoxide. T1 and T2: the tetraols resulting from hydrolytic *trans* and *cis* opening of the epoxide. DE-SEtOH: 2-mercaptoethanol conjugate of the corresponding diol epoxide.

The k_{cat}/K_m values obtained with all fjord-region diol epoxides and GSTP1-1 variants employed are compiled in Table 1. From these and previous results [22,25,31] it can be concluded that fjord-region diol epoxides are inferior as substrates for GSTP1-1 relative to most of the bay-region diol epoxides studied. Focusing on the results obtained with GSTP1-1/V-105 and GSTP1-1/I-105 it can be concluded that both variants demonstrate a similar activity towards each *anti* enantiomer

Table 1
Catalytic efficiencies for human GSTP1-1 variants (GSTP1-1/I-105 and V-105) and two mutants (GSTP1-1/A-105 and W-105) with metabolically relevant fjord-region diol epoxide isomers of polycyclic aromatic hydrocarbons

Diol epoxide	GSTP1-1 [k_{cat}/K_m (mM^{-1} s^{-1})]			
	A-105	V-105	I-105	W-105
(−)-*anti*-DB[*a,l*]PDE	2.5 ± 0.3	1.1 ± 0.3	1.2 ± 0.2	1.1 ± 0.1
(+)-*syn*-DB[*a,l*]PDE	9.5 ± 0.5	2.1 ± 0.5	1.1 ± 0.3	12.6 ± 0.3
(−)-*anti*-B[*g*]CDE	2.5 ± 0.2	1.2 ± 0.5	1.3 ± 0.5	0.5 ± 0.2
(+)-*syn*-B[*g*]CDE	14.7 ± 1.7	1.5 ± 0.7	0.5 ± 0.2	4.6 ± 0.4
(−)-*anti*-B[*c*]CDE	2.5 ± 0.4	1.8 ± 0.3	1.9 ± 0.3	0.2 ± 0.06
(+)-*syn*-B[*c*]CDE	5.6 ± 0.3	0.87 ± 0.13	0.53 ± 0.09	6.0 ± 0.5
(+)-*anti*-B[*c*]PhDE	0.66 ± 0.05	0.54 ± 0.03	0.55 ± 0.1	nd
(−)-*syn*-B[*c*]PhDE	2.1 ± 0.2	0.46 ± 0.04	0.24 ± 0.03	2.9 ± 0.1

but differ towards the *syn* enantiomers. In this case GSTP1-1/V-105 is about 2–3-fold more active. As observed with the bay-region diol epoxides [19] the effect of gradually increasing the bulkiness of the amino residue at position 105 from Ala to Trp was dependent on the diol epoxide diastereomer studied. With the (−)-*anti* enantiomers, GSTP1-1/A-105 was generally the most active variant whereas GSTP1-1/W-105 showed the lowest activity. With the (+)-*syn* enantiomers, on the other hand, GSTP1-1/W-105 was in most cases equally active as or more active than GSTP1-1/A-105. Taking these and earlier results for bay-region diol epoxides together, the inhibiting effect of increasing the volume of the amino acid residue at position 105 on k_{cat}/K_m for the fjord-region analogues is probably due to disturbance of the hydrophobic/hydrophilic balance in the active site in conjunction with a more restricted binding site for the diol epoxide [18,19].

The reason for the high activity towards the *syn* enantiomers of both bay- and fjord-region diol epoxides in comparison with the *anti* enantiomers is still unclear. A factor expected to influence the activity is the preferred conformation of the hydroxyl groups of the diol epoxide. In the *syn* diastereomers of the bay-region diol epoxides a pseudo-axial orientation is preferred whereas a pseudo-equatorial orientation is preferred in the corresponding diastereomers of the more crowded fjord-region diol epoxides. Assuming that the spatial orientation of the hydroxyl groups remains the same when bound to the active site of the enzyme, the conformation of the *syn*-diol epoxides seems to play a minor role for the rate of GSTP1-1/W-105-catalyzed *S*-glutathionylation. However, the absolute configuration of the hydroxyl groups of the diol epoxides seems to be important. Since all GSTP1-1 variants demonstrate a high preference for *S*-glutathionylation at the benzylic oxiranyl carbon with *R*-absolute configuration the *R,S*-configuration of the hydroxyl groups in the *anti*-diol epoxides results in reduced activity with GSTP1-1/W-105 whereas the *S,R*-configuration in the *syn* forms leads to an enhanced activity.

In conclusion, the data obtained with the strongly carcinogenic fjord-region diol epoxides demonstrate an equal capacity of GSTP1-1/V-105 and GSTP1-1/I-105 to detoxify (−)-*anti* enantiomers and an increased activity of the Val^{105} variant to conjugate the (+)-*syn* enantiomers with GSH. These results together with those observed with the bay-region diol epoxides indicate that individuals who are homozygous for the allele encoding GSTP1-1/V-105 are more susceptible to carcinogenesis due to other reasons than a reduced capacity for detoxifying diol epoxides. Nevertheless, the data show that GSTP1-1-catalyzed conjugation is efficient and therefore an important inactivation mechanism of the highly carcinogenic fjord-region diol epoxides.

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