THE IN VITRO METABOLISM OF SOME AROMATIC POLYCYCLIC HYDROCARBON 'K-REGION' EPOXIDES AND DIHYDRODIOL EPOXIDE DERIVATIVES BY RAT LIVER PREPARATIONS

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Many carcinogenic polycyclic hydrocarbons, including benz(a)anthracene (BA), 7-methylbenz(a)anthracene (7-MBA) and 7,12-dimethylbenz(a)anthracene (DMBA) can be metabolised to form K-region and non-K-region dihydrodiols (Sims 1970). The 'K-region' dihydrodiols of these hydrocarbons are formed from intermediate epoxides (Keysell et al 1973) which are active alkylating agents that can alkylate DNA, RNA and protein in vivo and in vitro. The non-K-region dihydrodiols can be metabolised further into diol epoxides (Booth and Sims 1974) which are less active as alkylating agents than K-region epoxides. Studies on the mutogenicity and carcinogenicity of the dihydrodiols and diol-epoxides derived from 7-MBA and BA, suggest that the biological activities shown by polycyclic hydrocarbons, as a class of chemical carcinogens, are mediated by diol-epoxides formed by the further metabolism of non-K-region dihydrodiols (Hemminki et al 1980). 'K-region' epoxides and diol-epoxides can be inactivated by metabolism either by epoxide hydrase into dihydrodiols and tetrahydrotetrols respectively, or by glutathione transferase enzymes into glutathione conjugates.

In these experiments the ^{3}H-K-region epoxides and ^{3}H-8,9-diol 9,10-epoxides of BA, 7-MBA and DMBA were incubated with rat-liver preparation containing either a) the membrane-bound epoxide hydrase and no cofactors, or b) the soluble glutathione S-transferases and the cofactor, glutathione. The incubation mixtures were extracted with ethyl acetate, the metabolites purified by thin layer chromatography and the radioactivity estimated by liquid scintillation counting. The results below demonstrate that the K-region epoxides of BA, 7-MBA and DMBA are hydrated or conjugated much more quickly than the 8,9-dihydrodiol 9,10-epoxide derivatives.

Incubations	Substrate	Tetrahydrotetrol or glutathione conjugate formed nmoles/g liver/10 min from the substrates	
		K-region epoxide	diol epoxide
a) Epoxide hydrase	BA	10.6	0.21
	7-MBA	11	0.22
	DMBA	2.8	0.13
b) Glutathione S-transferases glutathione	BA	6.4	0.2
	7-MBA	7.4	0.22
	DMBA	5.6	0.15

K-region epoxides can also be inactivated by an epoxide reductase (Booth et al 1975) and it appears that diol-epoxides will not be reduced by this enzyme. This observation and the results obtained above may explain why the more reactive K-region epoxides are not the metabolites that bind to DNA in vivo, since they would be inactivated by metabolism into non-alkylating products more quickly than the diol-epoxides.

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