Biochemical Pharmacology, Vol. 24. pp. 1445–1448. Pergamon Press, 1975. Printed in Great Britain.

EPOXIDATION OF XENOBIOTICS IN THE HUMAN FETUS AND PLACENTA: A POSSIBLE MECHANISM OF TRANSPLACENTAL DRUG-INDUCED INJURIES

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(Received 26 April 1975; accepted 20 May 1975)

Studies during recent years have shown that many compounds implicated as carcinogens and other toxicants, are not harmful per se, but are transformed to active metabolites in the body through the action of the microsomal drug-oxidizing enzyme system of the liver, lung, skin and other tissues (1-4). Human fetal tissues are able to oxidize foreign compounds and this ability can be linked with the existence of the microsomal cytochrome P-450-linked drug-oxidizing system in the fetal liver and adrenal gland (5-7). This finding gives reason to suspect that reactive intermediary metabolites are formed in the human fetus, with possible harmful consequences. In the present study we have investigated the fetal and placental metabolism of two compounds whose intermediary metabolites have been shown to be epoxides, namely aldrin (8) and benzo(α)pyrene (9).

60 nmole of aldrin (with 0.5 to 1×10^5 cpm of ^{14}C-aldrin, Radiochemical Centre, Amersham, Bucks, England) or 100 nmole of benzo(α)pyrene (with 0.8 to 1.5×10^6 cpm of ^{3}H-benzo(α)pyrene, Radiochemical Centre) were incubated for 10 min in the presence of NADPH-regenerating system (NADP, 0.2 mM; glucose-6-phosphate, 6 mM; and glucose-6-phosphate dehydrogenase, 10 units); KCl, 50 mM; $MgCl_2$, 10 mM; sodium-potassium phosphate buffer, pH 7.4, 200 mM; and an enzyme preparation (homogenate from the human fetal liver, adrenal gland or placenta). Dieldrin formed during the incubation was isolated and quantitated by the method of Chang and Hodgson (10). The general procedure for the separation and quantitation of benzo(α)pyrene metabolites is described by Sims (11) and Borgen et al. (12).

Fig. 1 shows TLC radioactivity profiles of extracted incubates of both aldrin and benzo(α)pyrene with human fetal liver homogenate. Radioactive peaks are clearly related to marker compounds, aldrin and dieldrin in A and to 9,10-, 7,8-, 4,5-diols and hydroxymetabolites of benzo(α)pyrene in B. The identification of metabolites of benzo(α)pyrene is only tentative because other metabolites than the reference compounds we had available may also have same mobilities in TLC (13, 14). Table 1 shows the formation of diols and hydroxymetabolites of benzo(α)pyrene and the formation of dieldrin from aldrin by human fetal liver, adrenal gland and placenta. The benzo(α)pyrene metabolizing activity of fetal liver and adrenal gland is rather low, being only a few per

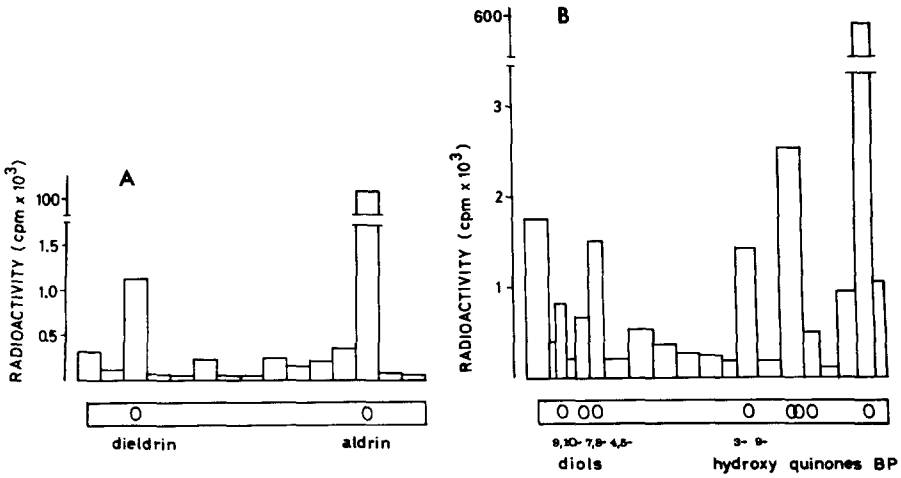

Fig. 1. Metabolism of ^{14}C-aldrin (A) and ^{3}H-benzo(α)pyrene (B) by human fetal liver homogenate from a 14-week old fetus. Unlabelled reference compounds were co-chromatographed with extracts of incubation mixtures, located by fluorescence under UV light and the profile of radioactivity determined by liquid scintillation counting.

cent of rat-liver activity. In term placenta the diol formation may be considerable, as demonstrated by two placentas from smoking mothers. In the formation of diols of benzo(α)pyrene, epoxides are thought to be obligatory intermediates (4, 9) and the

Table 1. The formation of monohydroxy- and dihydrodihydroxy-metabolites of benzo(α)pyrene and the formation of dieldrin from aldrin by human fetal liver, adrenal gland and placental homogenates and by rat liver homogenate.

Tissue[1)]	Formation of benzo(α)pyrene metabolites (pmole/g of tissue/min)				Aldrin epoxidase activity
	diol I[2)]	diol II	diol III	OH-	dieldrin
Liver	29.2	14.6	21.9	37.0	752
% of rat liver	4.4	6.5	12.0	1.9	36.7
Adrenal gland	37.8	20.1	6.1	50.3	329
Immature placenta	0	0	0	0	0
Term placenta					
mother A.K.	319	291	97	567	0
mother T.S.	247	187	52	361	0
nonsmokers	0	0	0	0	0
Rat liver	665	225	183	1926	2047

[1)] Liver and immature placental homogenates were from five fetuses of 10 to 15 weeks of fetal age. Adrenal gland homogenates were from two largest fetuses (14 and 15 weeks of age). Mothers A.K. and T.S. smoked about 20 cigarettes per day. Values for rat liver are based on triplicate determinations of pooled homogenates from five untreated animals.

[2)] Different diols refer to reference compounds of the following structures: 9,10-diol (I), 7,8-diol (II), and 4,5-diol (III) of benzo(α)pyrene.

formation of three epoxides (tentatively 9,10-, 7,8-, and 4,5-oxides) by human fetal liver, adrenal gland and placenta from smoking mothers is apparent. The fetal hepatic aldrin epoxidase activity was almost 40 per cent of rat liver activity. If we also consider that in relation to the body weight the fetal liver is twice the size of adult liver, the ability of the human fetal liver to epoxidate aldrin per unit body weight may be very significant. Studies on cofactor requirements and on inhibition by CO and N_2 suggested the participation of a typical microsomal drug-oxidizing system. Experiments with two adrenal glands indicate epoxidase activity, but immature or term placentas do not epoxidate aldrin to a measurable extent.

In this study we have shown that epoxides of aldrin (epoxide directly shown) and benzo(α)pyrene (several epoxides implicated) are formed in in vitro incubations with tissues from human fetus and placenta, although different tissues differed with respect to substrate specificity and activity. Results on benzo(α)pyrene metabolism also suggest the presence of active epoxide hydrase in fetal liver, adrenal gland and term placenta. This has also been shown by Juchau and Namkung (15) with naphthalene 1,2-oxide as a substrate. The role of active metabolites in tissue lesions, malignant transformation, carcinogenesis and mutagenesis (1-4) raises important questions concerning the possible carcinogenic, teratogenic and toxicological hazards in the human fetus. In the majority of cases of human fetal injuries the specific cause remains unidentified (16). We suggest that the possibility of reactive metabolites of fetal origin, as a cause of fetal injuries is worth of further investigations.

Acknowledgements. The skillful technical assistance of Miss Vuokko Väisänen is gratefully acknowledged. We also thank Dr. P. Jouppila for help in obtaining fetal material and Drs. H. V. Gelboin and P. Sims for authentic metabolites of benzo(α)pyrene. This study was supported by the grant from the Academy of Finland.

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