THE VARIABLE EFFECTS OF PREGNANCY ON IN VITRO DRUG METABOLISM BY RAT LIVER PREPARATIONS

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A variety of factors such as age, sex and pregnancy are known to alter drug metabolism in man and animals. Generally, pregnancy causes a significant decrease in the activity of most drug metabolising enzymes, so that reactions such as hydroxylations and glucuronide conjugations are decreased in rats, particularly near term (Creaven and Parke 1965; Cessi 1952).

The alkaloid, nicotine, present in tobacco smoke and 7,12-dimethylbenz(a)anthracene (DMBA), a hydrocarbon related to aromatic polycyclic hydrocarbons also present in tobacco smoke, were metabolised in vitro by liver preparations obtained from Wistar rats approximately 18 days pregnant. Virgin sisters were used as controls to keep other factors affecting metabolism to a minimum. The major metabolites of nicotine, nicotine-1'-N-oxide and cotinine were estimated by gas liquid chromatography after extraction from incubation mixtures. ^{3}H-DMBA and its metabolites were extracted from incubation mixtures, separated by thin layer chromatography and the radioactivity associated with the 8,9-dihydrodiol derivative estimated by liquid scintillation counting.

The results, using nicotine as substrate show that pregnancy, as expected causes a decrease in total metabolism. However, the two metabolites are affected to different extents so that the cotinine/N-oxide ratio (C/N) is increased. This is of interest because the C/N ratio in the urine of smokers known to have bladder cancer is significantly higher than in control smokers (Gorrod et al 1974). Furthermore the metabolism of nicotine in women smokers shows an increase in the C/N ratio between the 29th and 32nd week of gestation (Klein and Gorrod 1978).

Substrate	The metabolism in pregnant rats is expressed as a percentage of the amount of metabolism in control virgin rats ± SE
1. Nicotine	
a) Nicotine-1'-N-oxide	47 ± 5
b) Cotinine	79 ± 7
c) Total metabolism (a + b)	55 ± 5
d) C/N Ratio (b/a)	183 ± 12
2. DMBA	
a) 8,9-dihydrodiol	237 ± 52

When DMBA was used as a substrate, the formation of the 8,9-dihydrodiol was increased using liver preparations from pregnant rats. A related carcinogenic hydrocarbon, benzo(a)pyrene, found in tobacco smoke, is also metabolised into a similar non-K-region dihydrodiol. This dihydrodiol, which shows greater mutogenic activity than the parent hydrocarbon, can be metabolised further into a vicinal dihydrodiol-epoxide that alkylates DNA in vivo (Sims et al 1974).

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