Effect of Enzyme Induction on the Metabolism of Benzo(a)pyrene and 3'-Methyl-4-monomethylaminoazobenzene in the Pregnant and Fetal Rat

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SUMMARY

Administration of benzo(a)pyrene (BP) or certain other polycyclic aromatic hydrocarbons to pregnant rats increased the in vitro hydroxylation of BP and the N-demethylation of 3'-methyl-4-monomethylaminoazobenzene by fetal liver. Treatment of pregnant rats with as little as 0.5 mg of BP per kg p.o. for 3 days stimulated the metabolism of the hydrocarbon by maternal liver and placenta, while a 20-fold higher dose of this hydrocarbon was necessary for stimulation of BP hydroxylation in fetal liver. BP metabolism was increased in fetal and maternal liver microsomes after treatment of pregnant rats with 3-methylcholanthrene, and this increase in enzyme activity was paralleled by an increase in microsomal hemoprotein concentration, as measured by the change in absorbance at 450 or 455 nm when CO or ethyl isocyanide, respectively, was added as the ligand to reduced liver microsomes. Administration of 3-methylcholanthrene also increased the ratio of the peak at 455 nm to the peak at 430 nm in the ethyl isocyanide difference spectra and shifted by 2 nm the maximum absorption of the 450 nm peak to a shorter wavelength in the CO-induced difference spectra of maternal and fetal liver microsomes, thus indicating a qualitative alteration of the microsomal hemoprotein(s). Treatment of pregnant rats with phenobarbital increased the hydroxylation of BP and increased the hemoprotein concentration in maternal liver microsomes, but no effect was observed on these same parameters in fetal liver microsomes. The in vivo metabolism of BP-3H was increased in pregnant rats pretreated for 3 days with nonradioactive BP. Although the total radioactivity found in fetuses of pregnant rats pretreated with nonradioactive BP prior to administration of BP-3H was only slightly decreased, the concentration of BP-3H in the fetus was markedly decreased, and the ratio of BP-3H metabolites to BP was increased 84-fold. The ratio of BP-3H metabolites to BP-3H was also markedly increased in maternal lung and placenta.

INTRODUCTION

Enzymes in liver microsomes required for the oxidation of drugs and other foreign compounds are deficient in the fetus and neonate (4, 9, 13). The absence of this important group of enzymes in the fetus may be toxicologically significant when the pregnant animal is exposed to potentially harmful substances. Carcinogens present in cigarette smoke, such as polycyclic hydrocarbons, apparently reach the human placenta and perhaps the fetus, since an increase in the activity of enzymes that metabolize BP and 3-methyl-MAB has been observed in placentas from individuals who smoke cigarettes (14, 20, 26, 27). Increased activity of mixed-function oxidases in liver microsomes of newborn animals has been observed when pregnant animals were treated with drugs or polycyclic hydrocarbons (4, 7, 8, 10, 19, 21). The results of the present investigation demonstrate a stimulatory effect of polycyclic hydrocarbons on the metabolism of BP and 3-methyl-MAB in maternal and fetal liver. Studies are also presented that indicate a marked effect of enzyme induction on the in vivo metabolism of BP in the pregnant rat.

MATERIALS AND METHODS

Animals. Sprague-Dawley rats, pregnant for 14 to 19 days and weighing 250 to 300 g, were obtained from Blue Spruce Farms, Altamont, N. Y. Rats were fed Rockland rat diet and water ad libitum. Polycyclic aromatic hydrocarbons were dissolved in dimethyl sulfoxide, and sodium phenobarbital was dissolved in water prior to the p.o. administration of these compounds in 0.5 ml of vehicle. Control animals received only an equivalent amount of vehicle.

Radiochemicals. Randomly labeled BP-3H with a specific activity of 8 Ci/m mole was obtained from Amersham/Searle Corporation, Arlington Heights, Ill. The radiopurity of the BP-3H was verified at 99% by thin-layer chromatography on Gelman ITLC type SA paper in a solvent system of hexane:benzene (3:1).

Tissue Preparation. Rats were killed by decapitation. Maternal liver, placenta, and fetal livers were homogenized at 4° in a tightly fitting ground-glass homogenizer with 0.25 M

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sucrose to make a 10, 10, and 20% homogenate, respectively. Enzyme determinations were made on all the pooled placentas or fetal livers from the same rat. Liver homogenates were centrifuged at 9,000 X g for 20 min. Microsomes were prepared by centrifugation of the 9,000 X g supematant at 105,000 X g for 60 min. The pellet was washed with 1.15% KCl and resedimented at 105,000 X g for 60 min.

**CO and Ethyl Isocyanide Difference Spectra.** The CO and ethyl isocyanide difference spectra of the various microsomal preparations were determined with a recording Amino-Change dual-beam spectrophotometer. Each cuvet contained a 3-ml suspension of microsomes equivalent to 100 mg of maternal liver per ml of 200 mg of fetal liver per ml in 1.0 M phosphate buffer (pH 7.5), and excess dithionite was added to reduce the hemoprotein in each cuvet. Carbon monoxide was bubbled through the sample cuvet for 30 sec. The difference in absorption at 450 to 500 nm was used for the determination of cytochrome P-450 in maternal liver microsomes. The absorption maximum of the CO-binding hemoprotein(s) from fetal liver microsomes of control and phenobarbital-treated rats consistently appeared at 453 nm and was probably due to the presence of a small amount of absorbed hemoglobin that could not be removed by 2 washings with 1.15% KCl. The ethyl isocyanide-induced difference spectra were determined by substitution of ethyl isocyanide for carbon monoxide, and the final concentration of this substance was 4.5 mM. The difference in absorption between 455, 430, and 500 nm was used as an estimate of the ratio of the peak at 455 nm to the peak at 430 nm that occurred when the ethyl isocyanide-induced difference spectra were recorded.

**Enzyme Activity.** The metabolism of BP was studied by addition of 50 µg of BP dissolved in 0.1 ml of acetone to 3.5 ml of incubation media containing an NADPH-generating system, fetal liver microsomes equivalent to 20 mg of liver, or maternal liver microsomes equivalent to 10 mg of liver. In some experiments, whole homogenate equivalent to 10 mg of maternal liver, 20 mg of fetal liver, or 100 mg of placenta was used. Placenta and liver were incubated 15 and 10 min, respectively, at 37°. Bovine serum albumin (0.6 mg) was added to the incubation mixture containing liver microsomes to assure linearity of the enzyme reaction with time (1). The cofactors added to the incubation mixture and the assay for hydroxylated metabolites of BP were similar to those previously described (16). For measurement of the N-demethylation of 3-methyl-MAB, 150 µg of 3-methyl-MAB were dissolved in 0.1 ml of acetone and incubated with homogenate equivalent to 50 mg of maternal liver for 12 min, with 100 mg of fetal liver for 60 min, or as indicated in the tables. Incubations were carried out aerobically, with shaking, at 37° and in the presence of a cofactor mixture identical with that used for the metabolism of BP. Analysis of the N-demethylated product was as previously described (5).

**Determination of BP-3H in Tissues.** BP-3H (6 mg, 100 µCi) was dissolved in 0.5 ml of dimethyl sulfoxide and administered p.o. to rats by intubation. Rats were killed 2 hr later, and various tissues were homogenized in ice-cold water. The fetuses were homogenized with an equal weight of water in a Waring Blendor. Placentas and lungs were homogenized with 1 and 4 parts of water, respectively, in ground-glass homogenizers. Ten ml of fetuses homogenate, 5.0 ml of placenta homogenate, and 4.0 ml of lung homogenate were added to shaking bottles containing 10 ml of acetone and were mixed for 10 sec. After the addition of 30 ml of hexane, the bottles were shaken for 20 min and centrifuged. Twenty-five ml of the organic phase were transferred to 50-ml conical tubes and evaporated to dryness under nitrogen. The amount of BP-3H present in the residue was determined as follows. The residue was dissolved in 1 ml of acetone, and the total volume was streaked on Gelman ITLC type SA paper and chromatographed in a solvent system of hexane : benzene (3:1). The chromatogram was cut into 1-cm strips and placed in vials, and the radioactivity was quantified in a liquid scintillation spectrometer by use of a toluene scintillation mixture (0.5% PPO and 0.1% POPOP in toluene). Total radioactivity was determined by addition of 0.2 ml of homogenate to the dioxane scintillation mixture of Bray (3). Metabolites were quantified by subtracting chromatographically determined BP-3H from total radioactivity in the homogenate. Aliquots of the homogenates were lyophilized to determine the content of tritiated water in the tissue samples. In each case, less than 1% of the radioactivity could be accounted for as tritiated water. Appropriate corrections were made for quenching. Recovery of BP-3H from the various tissues ranged from 85 to 95%, and the values for BP-3H in the text were corrected for recoveries.

**RESULTS**

**Effect of 3-MC and Phenobarbital on BP Hydroxylase and Aminoozo Dye N-Demethylase in the Pregnant Rat.** Rats pregnant for 14 or 19 days were treated with a single p.o. dose of 3-MC, 60 mg/kg, and killed 24 hr later. The ability of fetal and maternal liver homogenate to N-demethylate 3-methyl-MAB and hydroxylate BP was measured. Table 1 indicates that 3-MC stimulated the hydroxylation of BP and enhanced the N-demethylation of 3-methyl-MAB by maternal and fetal liver. BP hydroxylase activity was not detected in fetal liver homogenate obtained from control animals, but treatment of pregnant rats with 3-MC increased enzyme activity in fetal liver to levels approximating those found in normal maternal liver. Similar enzyme changes were observed in fetal and maternal liver when 3-MC was administered to rats pregnant for 14 or 19 days. In contrast, treatment of rats pregnant for 16 days with phenobarbital, 50 mg/kg, daily for 3 days did not increase the metabolism of BP by fetal liver homogenate.

**Effect of 3-MC and Phenobarbital on the Concentration of Microsomal Hemoproteins in the Pregnant Rat.** Since induction of mixed-function oxidases in liver microsomes of animals is usually accompanied by an increase in microsomal hemoproteins, studies were initiated to determine the effect of 3-MC and phenobarbital on the concentration of hemoproteins in microsomes of maternal and fetal liver. Rats pregnant for 16 days were treated with 3-MC, 60 mg/kg, or phenobarbital, 50 mg/kg, p.o. for 3 days and killed 24 hr after the last dose. The
concentration of the CO and ethyl isocyanide-binding hemoprotein(s) and BP hydroxylase activity of maternal and fetal liver microsomes are shown in Table 2. The administration of 3-MC to pregnant rats increased the activity of BP hydroxylase in maternal liver more than 50-fold, and the activity of this enzyme in fetal liver increased from undetectable activity to levels greater than 7 times those found in normal maternal livers. Although phenobarbital treatment caused a 90% increase in BP hydroxylase activity in maternal liver, no increase was observed in fetal liver. Phenobarbital treatment increased the concentration of CO-binding pigment(s) with an absorption maximum at 450 nm and increased the ethyl isocyanide-binding pigment(s) with absorption maxima at 430 and 455 nm in maternal liver microsomes. However, no change in the ratio of the peak at 455 nm to the peak at 430 nm was observed in the ethyl isocyanide spectra. Phenobarbital treatment did not increase the concentration of hemoprotein(s) in fetal liver microsomes. Administration of 3-MC to pregnant rats caused a marked increase in CO-binding hemoprotein(s) of maternal and fetal liver microsomes that was significantly greater than that observed after treatment of pregnant rats with phenobarbital. In contrast to the CO-binding hemoprotein(s) in maternal liver microsomes from phenobarbital-treated rats, the CO-binding hemoprotein(s) in maternal liver microsomes from 3-MC-treated rats had an absorption maximum at 448 nm.

<table>
<thead>
<tr>
<th>Days pregnant</th>
<th>Treatment</th>
<th>Liver</th>
<th>Benzo(a)pyrene hydroxylase activity</th>
<th>3-Methyl-MAB N-demethylase activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Control</td>
<td>Maternal</td>
<td>50 ± 3</td>
<td>823 ± 21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fetal</td>
<td>&lt;0.2c</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>3-MC</td>
<td>Control</td>
<td>Maternal</td>
<td>783 ± 45</td>
<td>1480 ± 26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fetal</td>
<td>64 ± 8</td>
<td>50 ± 8</td>
</tr>
<tr>
<td>19</td>
<td>Control</td>
<td>Maternal</td>
<td>47 ± 5</td>
<td>568 ± 32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fetal</td>
<td>&lt;0.2c</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>3-MC</td>
<td>Control</td>
<td>Maternal</td>
<td>64 ± 17</td>
<td>1319 ± 48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fetal</td>
<td>62 ± 8</td>
<td>53 ± 4</td>
</tr>
</tbody>
</table>

a Homogenate equivalent to 10 mg, wet weight, maternal liver or 20 mg, wet weight, fetal liver was incubated with BP and an NADPH-generating system for 10 min as described under “Materials and Methods.” The results are expressed as hydroxybenzo(a)pyrene formed (µg/g/hr).

b Homogenate equivalent to 50 mg, wet weight, maternal liver or 200 mg of fetal liver was incubated with 3-methyl-MAB for 7 or 30 min, respectively, in the presence of an NADPH-generating system as described under “Materials and Methods.” The results are expressed as 3-methyl-MAB formed (µg/g/hr).

c Fluorescence was less than twice that obtained from the zero-time sample.

<table>
<thead>
<tr>
<th>Carbon monoxide</th>
<th>Ethyl isocyanide</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ΔA 450, 453, or 448–500 nm)</td>
<td>(ΔA 430–500 nm)</td>
</tr>
<tr>
<td>Protein x 10^3</td>
<td>Protein x 10^3</td>
</tr>
<tr>
<td>Ratio of peak at 455 nm to peak at 430 nm</td>
<td></td>
</tr>
</tbody>
</table>

a µg of hydroxybenzo(a)pyrene formed/mg protein/hr.
b CO-binding hemoprotein(s) were measured as the difference in absorbance between 500 nm and 450 nm, 453 nm, or 448 nm in control, fetal, or 3-MC microsomes, respectively.
c Significantly different from control group (p < 0.02).
d Significantly different from the phenobarbital and control group (p < 0.02).
Treatment with 3-MC also increased markedly the CO-binding hemoprotein(s) in fetal liver microsomes, and the absorption maximum was shifted from 453 to 451 nm. The ethyl isocyanide-binding hemoprotein(s) of maternal liver microsomes, with absorption maxima at 430 and 455 nm, were also increased after 3-MC treatment, and the ratio of the peak at 455 nm to the peak at 430 nm increased from 1.12 to 1.49. Administration of 3-MC to pregnant rats increased the absorption of the ethyl isocyanide-binding pigment of fetal liver microsomes at 455 nm but did not increase the peak at 430 nm. Thus, the ratio of the peak at 455 nm to the peak at 430 nm in fetal liver microsomes was greatly increased by 3-MC treatment. There was a small amount of hemoglobin present in fetal liver microsomes, but this amount of hemoglobin was constant among the groups and did not obscure the marked effect of 3-MC on the ratio of the peak at 455 nm to the peak at 430 nm in fetal liver microsomes.

Effect of Environmental Polycyclic Hydrocarbons on BP Hydroxylase and Aminoazo Dye N-Demethylase in the Pregnant Rat. The ability of several polycyclic hydrocarbons found in the environment and in cigarette smoke to increase the metabolism of BP and 3-methyl-MAB by fetal liver was measured, and the results are shown in Table 3. Dibenzo(a,h)anthracene and BP were the most potent enzyme stimulators tested, but benz(a)anthracene and chrysene also induced appreciable activity. Anthracene had little or no effect as an inducer of BP hydroxylase or aminoazo dye N-demethylase. Administration of as little as 0.5 to 1.0 mg of BP per kg once daily for 3 days increased BP hydroxylase activity in placenta and maternal liver (Table 4), but detectable hydroxylase activity in fetal liver was observed only when the dose of BP was increased to 10 mg/kg.

Effect of Enzyme Induction on the in Vivo Metabolism of BP-3H in the Pregnant Rat. Studies were initiated to determine whether enzyme induction enhanced the in vivo metabolism of BP. Rats pregnant for 16 days were given p.o. injections for 3 days with 20 mg of nonradioactive BP per kg. Twenty-four hr after the last dose, the rats were given 20 mg of BP-3H per kg p.o. and killed 2 hr later. The tissue concentrations of BP-3H and its metabolites were quantified as described under "Materials and Methods." As shown in Table 5, when the dose of BP was increased to 10 mg/kg, the concentration of BP-3H in the fetus, placenta, and maternal lung was markedly lower and the concentration of metabolites of BP-3H was higher when pregnant animals were pretreated with BP as an enzyme inducer. Indeed, enzyme induction increased the ratio of BP-3H metabolites to BP-3H by 84- and 185-fold in the fetus, placenta, and maternal lung, respectively (Table 5).

DISCUSSION

The present study demonstrates that the administration of 3-MC, BP, chrysene, benz(a)anthracene, or dibenz(a,h)anthracene to pregnant rats stimulates the hydroxylation of BP and the N-demethylation of 3-methyl-MAB by enzymes in fetal liver. The p.o. administration of as little as 0.5 mg of BP per kg daily for 3 days to rats pregnant for 17 days increased the in vitro metabolism of BP by maternal liver and placenta. However, the enzyme activity in fetal liver was not detectable until the daily dose of BP was increased to 10 mg/kg, thus suggesting that the fetus responds to a high dose of BP but is protected...
from the action of low doses of BP that exert an effect on maternal tissues. Low levels of aminooz dye \( N \)-demethylase were present in livers from rat fetuses at 1 and 6 days before term, and the activity of this enzyme could be significantly increased by treatment of the pregnant rat with 3-MC 24 hr before sacrifice. These results differ from those of Bresnick and Stevenson (4), since the latter investigators were unable to demonstrate increased activity of aminooz dye \( N \)-demethylase in fetal liver by treatment of pregnant rats with 3-MC or by injecting the hydrocarbon into the amniotic sac. The reason for this discrepancy is unknown.

The increased levels of BP hydroxylase and aminooz dye \( N \)-demethylase in fetal liver obtained from pregnant rats treated with polycyclic hydrocarbons were paralleled by an increased concentration of hemoprotein(s). Administration of 3-MC to pregnant rats increased the concentration of CO-binding pigment(s) in fetal liver microsomes and caused a 2-nm shift to a shorter wavelength in the maximum absorption of the CO-hemoprotein complex. In addition, 3-MC administration increased the ratio of the peak at 455 nm to the peak at 430 nm in both maternal and fetal liver microsomes when ethyl isocyanide was used as the ligand. However, in contrast to the results obtained with maternal liver microsomes, 3-MC did not increase the 430 nm peak in fetal liver microsomes or cause a marked increase in the 455 nm peak. The parallel increase of the 455 nm peak and the increased ability of fetal liver microsomes to metabolize BP suggest a relationship between these 2 parameters and are in agreement with the interpretation that polycyclic hydrocarbon induction of mixed-function oxidases in liver microsomes is related to increases in the 455 nm peak (24). The observations with the CO and ethyl isocyanide complexes of reduced microsomal hemoprotein suggest that the administration of 3-MC to pregnant rats changes the composition of hemoprotein(s) in fetal liver microsomes in a manner similar to that reported previously for liver microsomes from adult animals (2, 15, 24).

Phenobarbital did not increase BP hydroxylase activity in fetal liver microsomes and did not increase the hemoprotein concentration, although phenobarbital did increase both of these parameters in maternal liver. Recently, Nebert and Gelboin (19) treated pregnant hamsters with phenobarbital or 3-MC and observed an increase in BP hydroxylase activity in fetal liver. Our inability to demonstrate a stimulatory effect of phenobarbital in the rat fetus suggests a difference between the rat and hamster in susceptibility to phenobarbital.

Pretreatment of rats with BP or other polycyclic hydrocarbons that induce BP hydroxylase activity stimulates the rate of disappearance of an i.v. dose of BP-\( ^3 \)H and decreases the concentration of BP-\( ^3 \)H in various tissues (23). This effect of enzyme inducers on the metabolism of BP-\( ^3 \)H is paralleled by an enhanced rate of biliary excretion of metabolites of BP-\( ^3 \)H (18, 22). The results of the present study suggest a marked stimulatory effect of BP pretreatment on the metabolism of a subsequent dose of BP-\( ^3 \)H in the pregnant rat. Although the average concentration of BP-\( ^3 \)H in fetuses from control rats was 657 ng of BP-\( ^3 \)H per g 2 hr after the p.o. administration of BP-\( ^3 \)H, 20 mg/kg, fetuses from rats pretreated with BP before the administration of BP-\( ^3 \)H showed only 11 ng of BP-\( ^3 \)H per g, and a decreased concentration of BP-\( ^3 \)H was also observed in the placenta and maternal lung. The ratio of BP-\( ^3 \)H metabolites to BP-\( ^3 \)H in maternal lung, placenta, and fetus was increased 185-, 19-, and 84-fold, respectively, by pretreatment of pregnant rats with BP for 3 days before the p.o. administration of BP-\( ^3 \)H. The marked increase in this ratio in the fetus occurred, although the concentration of total tritiated hydrocarbon (BP-\( ^3 \)H and its metabolites) in BP-pretreated rats was only 35% less than the concentration of total tritiated hydrocarbon in control rats that received BP-\( ^3 \)H. In addition, the ratio of concentration of BP-\( ^3 \)H in placenta to that in the fetus of control rats was 3:1; however, after pretreatment of pregnant rats with nonradioactive BP before administration of BP-\( ^3 \)H, this ratio increased to 23:1, thus suggesting that pretreatment with radioactive BP stimulated the metabolism of BP-\( ^3 \)H in the fetus.

Treatment of rats with 3-MC and other inducers of hepatic DMBA metabolism stimulates the metabolism of DMBA in vivo, resulting in a decreased concentration of tritiated hydrocarbon in the adrenal gland, mammary gland, and fat (17). This effect provides an explanation for the inhibitory

### Table 5

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Pretreatment</th>
<th>BP-( ^3 )H (ng/g)</th>
<th>BP-( ^3 )H metabolites (ng equivalents/g)</th>
<th>Ratio of BP-( ^3 )H metabolites to BP-( ^3 )H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus</td>
<td>Control</td>
<td>657 ± 115</td>
<td>525 ± 49</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>BP</td>
<td>11 ± 2</td>
<td>742 ± 113</td>
<td>67</td>
</tr>
<tr>
<td>Placenta</td>
<td>Control</td>
<td>1994 ± 266</td>
<td>364 ± 78</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>BP</td>
<td>253 ± 29</td>
<td>851 ± 138</td>
<td>3.4</td>
</tr>
<tr>
<td>Maternal lung</td>
<td>Control</td>
<td>4129 ± 652</td>
<td>93 ± 47</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>BP</td>
<td>353 ± 36</td>
<td>1315 ± 216</td>
<td>3.7</td>
</tr>
</tbody>
</table>
effect of 3-MC on the production of adrenal necrosis and mammary cancer by DMBA (11, 12, 28). The ability of enzyme inducers to enhance the in vivo metabolism of DMBA and BP suggests a need for additional studies of various factors that influence the in vivo metabolism of polycyclic hydrocarbons, since changes in the metabolism of these compounds may alter their carcinogenic activity.

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