Effects of 3-Methylcholanthrene, β-Naphthoflavone, and Phenobarbital on the 3-Methylcholanthrene-inducible Isozyme of Cytochrome P-450 within Centrilobular, Midzonal, and Periportal Hepatocytes*

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Rabbit antiserum produced against cytochrome P-450 MC-B, the major isozyme of cytochrome P-450 isolated from hepatic microsomes of 3-methylcholanthrene-pretreated rats, was utilized in unlabeled antibody peroxidase-antiperoxidase and indirect fluorescent antibody staining techniques to investigate the effects of 3-methylcholanthrene, β-naphthoflavone, and phenobarbital on the hemeprotein within centrilobular, midzonal, and periportal hepatocytes in livers of male rats. In livers of untreated and vehicle-pretreated rats, midzonal and periportal hepatocytes were found to bind the anti-cytochrome P-450 MC-B to equal extents while centrilobular hepatocytes bound approximately 25% more antibody. Pretreatment of rats with phenobarbital did not result in alterations in either the intensity or pattern of immunohistochemical staining for cytochrome P-450 MC-B within the liver lobule. In livers of rats which had been pretreated with 3-methylcholanthrene, microfluorometric analyses revealed that the extent of anti-cytochrome P-450 MC-B binding increased by approximately 215% within both the midzonal and periportal regions of the lobule and by approximately 150% within centrilobular regions. Pretreatment of rats with β-naphthoflavone resulted in alterations in the hemeprotein which were similar to those produced by 3-methylcholanthrene. Thus, after rats had been pretreated with either 3-methylcholanthrene or β-naphthoflavone, the pattern of intralobular distribution of cytochrome P-450 MC-B was altered so that the antibody bound to approximately equal extents to hepatocytes within the three regions of the lobule. These results demonstrate that 3-methylcholanthrene and β-naphthoflavone exert similar inductive effects on cytochrome P-450 MC-B within the liver lobule, with the least degree of induction of the hemeprotein being produced within centrilobular hepatocytes.

Extensive evidence has been presented for the presence of several isozymes of cytochrome P-450 within hepatocytes (1–5). The different forms of the hemeprotein are associated with microsomal, nuclear, and mitochondrial membranes where they mediate the oxidative metabolism of a multitude of endogenous and exogenous substrates (1–14). The contents and enzymatic activities of the different hepatic microsomal and nuclear cytochromes P-450 can be selectively induced by numerous chemicals, including drugs such as phenobarbital and polycyclic aromatic hydrocarbons such as 3-methylcholanthrene and β-naphthoflavone (5,6-benzoflavone) (2–11, 15–19). However, while the inductions of hepatic cytochromes P-450 have been intensively investigated during the past three decades, little knowledge is available regarding the effects of xenobiotics on the various isozymes of the hemeprotein within centrilobular, midzonal, and periportal hepatocytes. Since hepatic microsomal and nuclear cytochromes P-450 play important roles in both the detoxification and activation of chemicals (3–5, 8, 10, 11, 16–23), differential inductions of the several cytochrome P-450 isoforms within the liver lobule could profoundly modify the locations and severities of certain chemically induced toxicities.

In earlier studies (24–26), we employed qualitative and semiquantitative immunohistochemical techniques to demonstrate that two different forms of hepatic cytochrome P-450, the major isozymes induced by phenobarbital and 3-methylcholanthrene, exhibit different nonuniform patterns of intralobular distribution in livers of untreated rats. In the present study, these techniques were used to investigate the effects of 3-methylcholanthrene, β-naphthoflavone, and phenobarbital on cytochrome P-450 MC-B, the major cytochrome P-450 isozyme isolated from livers of 3-methylcholanthrene-pretreated rats, within hepatocytes in the three regions of the liver lobule.

EXPERIMENTAL PROCEDURES

Male albino Holtzman rats weighing 180–210 g were used in this study and were fasted for 24 h prior to killing. Groups of rats were pretreated either for 3 days with 3-methylcholanthrene (25 mg/kg/day, intraperitoneally, in corn oil) or β-naphthoflavone (40 mg/kg/day, intraperitoneally, in corn oil) or for 4 days with ph. noharbital (40 mg/kg/day, intraperitoneally, in 0.9% NaCl solution). Control rats were either untreated or administered appropriate volumes of vehicle. Rats were killed by decapitation 24 h after the last treatment, and the median lobe from each liver was removed and fixed by immersion in parabenzoxirone (26).

Details of the procedures for the immunohistochemical localization of cytochrome P-450 MC-B in liver sections using the unlabeled antibody peroxidase-antiperoxidase and the indirect fluorescent antibody staining techniques have been presented elsewhere (24, 26). Sections stained using the unlabeled antibody peroxidase-antiperoxidase method were examined by transmitted light microscopy and were photographed using Kodak Tri-X pan film (ASA 400) at an ASA setting of 32. Sections stained using the indirect fluorescent antibody technique were examined by incident-light fluorescence microscopy as described previously (26) and were photographed using Kodak Tri-X pan film (ASA 400) at an ASA setting of 6400.

Measurements of the intensity of fluorescence emitted at 525 nm
were obtained as described previously (26) following indirect fluorescent antibody staining from circular areas (diameter = 6 μm) on serial tissue sections exposed to rabbit antiserum to rat hepatic microsomal cytochrome P-450 MC-B, normal (nonimmune) rabbit serum, and rabbit anti-cytochrome P-450 MC-B serum which had been adsorbed with cytochrome P-450 MC-B. For the microfluorometric analyses, at least 4 sections from each liver were exposed to each serum, and 10 microfluorometric measurements were taken from within centrilobular, midzonal, and periportal regions in each section. The extents of anti-cytochrome P-450 MC-B binding to centrilobular, midzonal, and periportal hepatocytes were determined by subtracting the mean fluorescence intensity emitted from regions in sections exposed to normal rabbit serum from each individual microfluorometric measurement obtained from corresponding regions in serial sections exposed to rabbit antiserum to cytochrome P-450 MC-B. Means ± S.E. of antibody binding values reported for each pretreatment group were

Fig. 1. Immunohistochemical localization of cytochrome P-450 MC-B within livers of untreated and 3-methylcholanthrene-, β-naphthoflavone-, and phenobarbital-pretreated rats. The photomicrographs in A-D show areas in 7-μm thick sections of livers from an untreated rat (A) and from rats pretreated with 3-methylcholanthrene (B), β-naphthoflavone (C), and phenobarbital (D) which had been exposed to rabbit antiserum to rat hepatic microsomal cytochrome P-450 MC-B in the unlabeled antibody peroxidase-antiperoxidase staining protocol. E-P show higher magnification photomicrographs of centrilobular (E-H), midzonal (I-L), and periportal (M-P) regions in the sections shown in A-D. E, I, and M, regions in the section from the liver of an untreated rat. F, J, and N, regions in the section from the liver of a 3-methylcholanthrene-pre treated rat. G, K, and O, regions in the section from the liver of a β-naphthoflavone-pretreated rat. H, L, and P, regions in the section from the liver of a phenobarbital-pretreated rat. Two central veins (V) and a portal triad (P) are indicated in A.
When fixed paraffin-embedded sections prepared from livers of untreated male rats were exposed to rabbit antiserum raised against rat hepatic microsomal cytochrome P-450 MC-B in both the unlabelled antibody peroxidase-antiperoxidase and the indirect fluorescent antibody staining procedures, hepatocytes throughout the liver were found to be stained for this cytochrome P-450 MC-B isozyme (Figs. 1A and 2A). Immunohistochemical staining for cytochrome P-450 MC-B was not apparent within either cells associated with the hepatic vasculature, Kupffer cells, or sinusoidal cells. Although antibodies produced against hepatic microsomal cytochrome P-450 MC-B cross-react with hepatic nuclear cytochrome P-450 (8), hepatocyte nuclei did not appear to be appreciably stained for this isozyme of the heme protein. However, as reported in a previous communication (26), hepatocyte nuclei were frequently observed to be surrounded by rings of stain after unlabelled antibody peroxidase-antiperoxidase staining (Fig. 1, E, I, and M). In addition, intracellular staining for cytochrome P-450 MC-B was frequently observed to occur as large granular deposits scattered throughout the cytoplasm of hepatocytes, especially those within the midzonal and periportal regions of the lobule (Fig. 1, I and M). Although the data are not presented, identical observations were made after rats had been pretreated with the two vehicles used in this study, corn oil and saline.

Microfluorometric measurements of the intensity of fluorescence emitted from 28.3-μm² circular areas within the three regions of the liver lobule in sections after indirect fluorescent antibody staining revealed that, while the anti-cytochrome P-450 MC-B bound to the same extent to hepatocytes within the midzonal and periportal regions, between 20 and 25% more antibody bound to centrilobular hepatocytes in livers of untreated and vehicle-pretreated rats (Table I and Fig. 3). The data presented in Table I also demonstrate that binding of the anti-cytochrome P-450 MC-B to hepatocytes throughout the liver was abolished after the antibody had been removed from the antiserum by adsorption with the purified rat hepatic microsomal heme protein.

RESULTS

Localization and Distribution of Cytochrome P-450 MC-B within Livers of Untreated and Vehicle-pretreated Rats—When fixed paraffin-embedded sections prepared from livers of untreated male rats were exposed to rabbit antiserum raised against rat hepatic microsomal cytochrome P-450 MC-B in both the unlabelled antibody peroxidase-antiperoxidase and the indirect fluorescent antibody staining procedures, hepatocytes throughout the liver were found to be stained for this cytochrome P-450 MC-B isozyme (Figs. 1A and 2A). Immunohistochemical staining for cytochrome P-450 MC-B was not apparent within either cells associated with the hepatic vasculature, Kupffer cells, or sinusoidal cells. Although antibodies produced against hepatic microsomal cytochrome P-450 MC-B cross-react with hepatic nuclear cytochrome P-450 (8), hepatocyte nuclei did not appear to be appreciably stained for this isozyme of the heme protein. However, as reported in a previous communication (26), hepatocyte nuclei were frequently observed to be surrounded by rings of stain after unlabelled antibody peroxidase-antiperoxidase staining (Fig. 1, E, I, and M). In addition, intracellular staining for cytochrome P-450 MC-B was frequently observed to occur as large granular deposits scattered throughout the cytoplasm of hepatocytes, especially those within the midzonal and periportal regions of the lobule (Fig. 1, I and M). Although the data are not presented, identical observations were made after rats had been pretreated with the two vehicles used in this study, corn oil and saline.

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Effects of 3-Methylcholanthrene, β-Naphthoflavone, and Phenobarbital on Cytochrome P-450 MC-B within the Liver Lobule—After rats had been pretreated with 3-methylcholanthrene, immunohistochemical staining for cytochrome P-450 MC-B was markedly enhanced within all regions of the liver lobule (Fig. 1, B, F, J, and N, and Fig. 2B). Although the intensity of staining for the heme protein was dramatically increased within the cytoplasm and around nuclei, the administration of the polycyclic aromatic hydrocarbon did not appear to result in an appreciable degree of staining of hepatocyte nuclei for cytochrome P-450 MC-B. Visually, both unlabelled antibody peroxidase-antiperoxidase (Fig. 1B) and indirect fluorescent antibody (Fig. 2B) staining for cytochrome P-450 MC-B appeared to be uniform throughout the lobule in livers of 3-methylcholanthrene-pretreated rats. This observation was verified by microfluorometric analyses of liver sections after indirect fluorescent antibody staining (Figs. 3 and 4). The data presented in Fig. 4 show that while 3-methylcholanthrene pretreatment resulted in an increase of approximately 150% in the extent of anti-cytochrome P-450 MC-B binding to centrilobular hepatocytes, antibody binding to midzonal and periportal hepatocytes increased between 210 and 225%. Thus, after pretreatment of rats with 3-methylcholanthrene, the intralobular pattern of distribution of cytochrome P-450 MC-B is altered so that hepatocytes within the midzonal and periportal regions of the liver lobule bind the anti-cytochrome P-450 MC-B to similar extents (Fig. 3).

![Fig. 2. Fluorescent immunohistochemical localization of cytochrome P-450 MC-B within livers of untreated (A) and 3-methylcholanthrene (B), β-naphthoflavone (C), and phenobarbital (D) pretreated rats. The photomicrographs show areas in 7-μm thick sections which had been exposed to rabbit antiserum to rat hepatic microsomal cytochrome P-450 MC-B in the indirect fluorescent antibody staining protocol. V, central vein; P, portal triad.](http://www.jbc.org/)
within the three lobular regions were determined as described under "Experimental Procedures."

The values of relative fluorescence units given represent the mean ± S.E. of at least 40 measurements taken within the specified region. The extents of anti-cytochrome P-450 MC-B binding to hepatocytes within the three lobular regions were determined from the data presented in Fig. 3 for the binding of anti-cytochrome P-450 MC-B within regions in livers of xenobiotic and vehicle-pretreated rats.

![Fig. 3. Binding of antibody to cytochrome P-450 MC-B within centrilobular, midzonal, and periportal regions in livers of untreated and 3-methylcholanthrene (MC), β-naphthoflavone (BNF), phenobarbital (PB), and vehicle pretreated rats. Each bar represents the mean ± S.E. extent of anti-cytochrome P-450 MC-B binding within the specified region.](http://www.jbc.org/)

The administration of β-naphthoflavone to male rats resulted in alterations in cytochrome P-450 MC-B which were indistinguishable from those seen after rats had been pretreated with 3-methylcholanthrene. Thus, unlabeled antibody peroxidase-antiperoxidase (Fig. 1, C, G, K, and O) and indirect fluorescent antibody staining (Fig. 1, D, H, L, and P) or indirect fluorescent antibody staining (Fig. 2D) for cytochrome P-450 MC-B within rat liver. These visual findings were confirmed when the extents of binding of the anti-cytochrome P-450 MC-B to hepatocytes within the three regions of the lobule were determined in sections prepared from livers of phenobarbital- and saline-pretreated rats (Figs. 3 and 4).

**DISCUSSION**

Antiserum produced against cytochrome P-450 MC-B, the major isozyme of cytochrome P-450 isolated from livers of rats pretreated with 3-methylcholanthrene, has been utilized in unlabeled antibody peroxidase-antiperoxidase and indirect fluorescent antibody staining techniques to demonstrate that the hemoprotein is present within hepatocytes throughout the livers of untreated and xenobiotic-pretreated rats. Consistent with earlier observations (24–26), cytochrome P-450 MC-B was shown to be distributed nonuniformly within the lobule in livers of untreated and vehicle-pretreated rats; while hepatocytes within the midzonal and periportal regions of the lobule contain equal amounts of the hemoprotein, centrilobular hepatocytes contain significantly more (approximately 25% more) enzyme. This finding is also consonant with reports that centrilobular hepatocytes in livers of untreated rats possess the greatest content of total cytochrome P-450 (27), the greatest amount of smooth endoplasmic reticulum (28), and the greatest ary hydrocarbon hydroxylase (29) and 7-ethoxycoumarin O-de-ethylase (30) activities. In addition, this observation may aid in explaining the centrilobular location of hepatocellular carcinomas induced by many xenobiotics which are oxidatively metabolized by the hepatic monooxygenase enzyme systems to highly reactive and toxic electrophiles (31–34).

The results of the present study also demonstrate that cytochrome P-450 MC-B is induced within hepatocytes throughout the liver following the pretreatment of rats with 3-methylcholanthrene and β-naphthoflavone. Moreover, the two polycyclic aromatic hydrocarbons were found to exert similar, if not identical, inductive effects on the hemoprotein.

This observation is in agreement with reports (4, 5, 35, 36) that the major isozyme of hepatic cytochrome P-450 induced by 3-methylcholanthrene is also induced by β-naphthoflavone. However, while both 3-methylcholanthrene and β-naphthoflavone induce cytochrome P-450 MC-B within all hepatocytes, the induction does not occur uniformly through-

**Table I**

| Region          | Serum¹   | Emitted fluorescence | Antibody binding |
|-----------------|----------|----------------------|------------------|
| Centrilobular   | NRS      | 26.1 ± 1.6           |                  |
|                 | RAMC-B   | 62.2 ± 2.3*          | 36.1 ± 2.1*      |
| Midzonal        | NRS      | 22.9 ± 1.5           |                  |
|                 | RAMC-B   | 52.1 ± 1.8*          | 29.2 ± 1.8*      |
| Periportal      | NRS      | 23.3 ± 1.4           |                  |
|                 | RAMC-B   | 52.9 ± 1.6*          | 29.6 ± 1.6*      |

¹ NRS, normal rabbit serum; RAMC-B, rabbit anti-cytochrome P-450 MC-B serum; A-RAMC-B, adsorbed rabbit anti-cytochrome P-450 MC-B serum.

² Significantly greater than values obtained using normal rabbit serum and adsorbed rabbit anti-cytochrome P-450 MC-B serum, p < 0.01.

³ Not significantly different from value obtained using normal rabbit serum, p > 0.05.

⁴ Significantly greater than values obtained from the midzonal and periportal regions, p < 0.01.

⁵ Values are not significantly different from each other, p > 0.05.

![Fig. 4. Effects of 3-methylcholanthrene (MC), β-naphthoflavone (BNF), and phenobarbital (PB) pretreatments on cytochrome P-450 MC-B within centrilobular, midzonal, and periportal regions of the liver lobule. Each bar represents the mean ± S.E. percentage of control antibody cytochrome P-450 MC-B binding within the specified region. Percentage of control antibody binding was determined from the data presented in Fig. 3 for the binding of anti-cytochrome P-450 MC-B within regions in livers of xenobiotic and vehicle-pretreated rats.](http://www.jbc.org/)
out the liver lobule; although the enzyme is induced by similar extents within midzonal and periportal hepatocytes, significantly less induction of this isozyme of cytochrome P-450 is seen within centrilobular hepatocytes. Furthermore, after rats have been pretreated with either 3-methylcholanthrene or β-naphthoflavone, the intralobular pattern of distribution of the hemeprotein is altered so that it is now distributed uniformly within the lobule.

Although 3-methylcholanthrene and β-naphthoflavone both markedly affected cytochrome P-450 MC-B within hepatocytes throughout the lobule, the administration of phenobarbital to rats did not produce alterations in either the intensity or pattern of immunohistochemical staining for this hemeprotein within the liver lobule. This finding is in accord with previous observations (1–5, 8, 10, 11, 15–18, 35–37) which have demonstrated that the isozyme of hepatic cytochrome P-450 induced by polycyclic aromatic hydrocarbons differs both biochemically and immunologically from that induced by phenobarbital.

The observation that cytochrome P-450 MC-B is induced to the least extent within centrilobular hepatocytes following the administration of 3-methylcholanthrene to rats appears to be at variance with the histochemical observations of Wattenberg and Leong (29) who reported that aryl hydrocarbon hydroxylase activity was enhanced by 3-methylcholanthrene to the greatest degree within the centrilobular regions of rat liver. Although cytochrome P-450 MC-B appears to be the most active toward benzo(a)pyrene (18, 35), and although anticytochrome P-450 MC-B preparations are capable of inhibiting more than 90% of the aryl hydrocarbon hydroxylase activity catalyzed by hepatic microsomes of 3-methylcholanthrene-pretreated rats (38), the reasons for this discrepancy are unknown at the present time. However, our immunohistochemical finding that the polycyclic aromatic hydrocarbon induces cytochrome P-450 MC-B to significantly greater extents within the midzonal and perportal regions of the liver lobule may aid, at least in part, in explaining why 3-methylcholanthrene affords protection against the centrilobular hepatotoxicities produced by certain xenobiotics (32–34, 39–41).

The findings that cytochrome P-450 MC-B is not induced uniformly throughout the liver lobule and that its pattern of intralobular distribution is altered as a consequence of the administration of certain xenobiotics are similar to those reported previously by this laboratory (42) for the induction of hepatic NADPH-cytochrome c (P-450) reductase by the steroid pregnenolone-16α-carbonitrile. Moreover, similar observations have also been made for the induction of epoxide hydrolase within hepatocytes following the pretreatment of rats with either phenobarbital or trans-stilbene oxide. Thus, not only can significant enzymatic differences exist among centrilobular, midzonal, and perportal hepatocytes, but there may also be significant differences in the inductions of enzymes such as cytochrome P-450 isozymes within hepatocytes in the different regions of the liver lobule.

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