Cytochrome P-450 3A4 (Nifedipine Oxidase) Is Responsible for the C-oxidative Metabolism of 1-Nitropyrene in Human Liver Microsomal Samples

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ABSTRACT

The nitrated polycyclic aromatic hydrocarbon 1-nitropyrene is a ubiquitous environmental pollutant. The role of cytochromes P-450 in the human metabolism of [3H]-1-nitropyrene was investigated using human liver microsomes. The range of microsomal metabolism from 16 individual liver specimens was 0.13 to 0.99 nmol/min/mg protein. Using 3 microsomal samples exhibiting different maximal velocities, the Km of 1-nitropyrene metabolism was 3.3 ± 0.5 μM, indicating that a single or similar cytochromes P-450 was involved in the metabolism of 1-nitropyrene in these samples. The P-450 3A inhibitor triacetyloleanol-1-aminopyrene inhibited 85 ± 8% of the microsomal metabolism of 1-nitropyrene. Further evidence for the role of P-450 3A in human microsomal metabolism of 1-nitropyrene was gained using inhibitory anti-P-450 3A antibodies. Using 3 separate microsomal samples, antibody conditions that inhibited approximately 90% of the metabolism of the P-450 3A-specific substrate nifedipine inhibited approximately 60-70% of the metabolism of 1-nitropyrene. Human liver microsomes demonstrated a preference for 1-nitropyren-3-ol formation over 1-nitropyren-6-ol or 1-nitropyren-8-ol, which is in contrast to that noted in rodents where the 6-ol and 8-ol are preferentially formed over the 3-ol, yet in agreement with earlier studies on the metabolism of 1-nitropyrene using Vaccinia-expressed human cytochromes P-450. These results indicate that the human hepatic metabolism of 1-nitropyrene is carried out by at least two or more P-450s including those in the P-450 3A subfamily. These studies also suggest that the metabolism of this compound by humans may differ from that in rodents in both the cytochromes that are involved and the specific metabolites that are formed.

INTRODUCTION

The nitro-PAH are ubiquitous environmental pollutants found in diesel engine exhaust, gasoline engine exhaust, coal-fired power plant exhaust, Yakitori chicken, kerosene home heater exhaust, urban atmospheres, liquified propane burner exhaust, and wood smoke (reviewed in Refs. 1-4). Among the most abundant of the nitro-PAH in diesel exhaust is 1-nitropyrene. The nitro-PAH are mutagenic in many prokaryotic and eukaryotic mutagenicity tests and have been shown to induce tumors in several animal species (3-7).

It is not yet established which metabolites of 1-nitropyrene are responsible for the tumorigenicity of this compound in rodents. Initial reports focused on the C8-guanyl adduct [N-(2'-deoxyguanosin-8-yl)-1-aminopyrene] formed by N-hydroxy-1-aminopyrene (8) as the ultimate mutagenic metabolite of 1-nitropyrene. It is not yet established which metabolites of 1-nitropyrene are responsible for the tumorigenicity of this compound in rodents. Initial reports focused on the C8-guanyl adduct [N-(2'-deoxyguanosin-8-yl)-1-aminopyrene] formed by N-hydroxy-1-aminopyrene (8) as the ultimate mutagenic metabolite of 1-nitropyrene.

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1 To whom requests for reprints should be addressed.

2 The abbreviations used are: nitro-PAH, nitrated polycyclic aromatic hydrocarbons; TAO, triacetyloleanol-1-aminopyrene; MI complex, metabolite intermediate complex; HPLC, high performance liquid chromatography.

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6237
HUMAN LIVER MICROSOMAL METABOLISM OF 1-NITROPYRENE

Fig. 1. The metabolites of [3H]-1-nitropyrene were separated on a Waters Bondapak (0.78- x 30-cm) HPLC column with a water/ethanol gradient as described in the text. Metabolites were detected using a flow-through scintillation counter and had the following retention times: 1-nitropyrene-9,10-dihydrodiol, 5 min; 1-nitropyrene-4,5-dihydrodiol, 10.5 min; mixture of 1-nitropyrene K-region epoxides, 27.5 min; 1-nitropyrene-6-ol and 1-nitropyrene-8-ol, 36 min; 1-nitropyrene-3-ol, 43 min; 1-nitropyrene, 49 min. The material eluting at 57 min is a decomposition product of [4,5,9,10'-H]-1-nitropyrene.

Results

It was previously shown that among 12 human cytochromes P-450, only P-450 3A3 and 3A4 demonstrated catalytic activity toward 1-nitropyrene. The inclusion in the preincubation of a 2.5:1 ratio (w:w protein) of anti-P-450 3A antibodies to lysates from HepG2 cells expressing the cytochrome P-450 3A is via the Vaccinia system resulted in the loss of 95.9 ± 0.2% of 1-nitropyrene metabolism. This verified the ability of the anti-P-450 3A antibodies to inhibit the P-450 3A4 activity in our preincubation system. Additionally, since nifedipine is a specific substrate for human P-450 3A4, the inclusion of this dihydropyridine should also inhibit the Vaccinia-expressed P-450 3A4 (Fig. 2). Indeed, inclusion of nifedipine as low as 10 μM inhibited approximately 75% of the metabolism of 10 μM 1-nitropyrene, and concentrations of 50 μM nifedipine inhibited approximately 90% of 1-nitropyrene metabolism catalyzed by Vaccinia-expressed human P-450 3A4. These results also suggest that human P-450 3A4 has a higher affinity for nifedipine than 1-nitropyrene. Thus nifedipine can be used as an effective inhibitor for 1-nitropyrene metabolism.

Fig. 2. Effect of the presence of nifedipine on 10 μM [3H]-1-nitropyrene metabolism by Vaccinia-expressed human cytochrome P-450 3A4 in HepG2 cell lysates. The incubations were conducted as described in the text, and analysis of the metabolites was done by HPLC techniques. The results are from triplicate determinations.
that were produced. The data are from one of the incubations, and the rate of [3H]-l-nitropyrene metabolism is calculated from the total metabolites that were produced.

The $K_m$ of 1-nitropyrene metabolism was determined using several preparations of human liver microsomes with varying maximal velocities. The results from a representative experiment are shown in Fig. 3, where the data were analyzed by nonlinear regression analysis (Enzfitter; Elsevier Biosoft) for best fit of the velocity versus substrate curve. For the 3 microsomal samples where the $V_{max}$ differed by almost 10-fold, the $K_m$ for the three samples averaged 3.3 ± 0.5 μM. The solubility limit for 1-nitropyrene in aqueous systems has been reported to be between 20 and 25 μM (25); therefore, the use of [3H]-1-nitropyrene at 10 μM allowed us to use a 1-nitropyrene concentration that was at least 3 times the $K_m$ yet was below the solubility limit.

Since previous studies with Vaccinia-expressed human cytochromes had indicated that the cytochromes P-450 3A family was involved in the metabolism of 1-nitropyrene, we determined the human liver microsomal metabolism of 1-nitropyrene in the presence of either nifedipine or TAO (Fig. 4). With the human microsomes, concentrations of nifedipine up to 50 μM were able to inhibit approximately 60% of the microsomal metabolism of 1-nitropyrene. TAO, on the other hand, was able to inhibit approximately 80% of the metabolism of 1-nitropyrene with these microsomes. In view of the fact that TAO is a P-450 3A mechanism-based inhibitor and that nifedipine is a substrate for P-450 3A4, we used TAO for the inhibition studies on 1-nitropyrene microsomal metabolism.

Sixteen human liver microsomal samples were screened for their C-oxidative metabolism of [3H]-1-nitropyrene. The total activities of the human liver microsomes for [3H]-1-nitropyrene C-oxidation are indicated by the total height of the bars in Fig. 5 and ranged from 0.13 nmol/min/mg protein with microsome sample 22 to 0.99 nmol/min/mg protein with microsome sample 8. The mean activity of [3H]-1-nitropyrene C-oxidation was 0.4 ± 0.3 nmol/min/mg protein. The effect of the inclusion of TAO, a specific inhibitor of P-450 3A, on 1-nitropyrene C-oxidation by the microsomes is shown by the open (lower) bars in Fig. 5. The average inhibition by TAO of [3H]-1-nitropyrene C-oxidation was 86 ± 8%, although the samples ranged from approximately 60% inhibition (microsome sample 18) to approximately 90% of the nifedipine metabolism with microsome sample 22. In Fig. 6A, preincubation of microsomes with an antibodies:microsomal protein ratio of 5:1 or 10:1 inhibited 92–98% of the nifedipine metabolism, yet inhibited only approximately 70% of the [3H]-1-nitropyrene metabolism, at which time a reduced carbonyl spectra could be generated with CO and dithionite. Therefore, we can conclude that under conditions that allowed for the formation of a reversible MI complex of TAO with human P-450 3A, we likewise lost approximately 86% of the microsomal metabolism of [3H]-1-nitropyrene, presumably through the loss of P-450 3A activity.

To further verify the role of the P-450 3A subfamily in the human liver microsomal metabolism of 1-nitropyrene, we preincubated human liver microsomes with anti-P-450 3A antibodies, and using the same preincubation we determined both the rate of cytochrome P-450-mediated nifedipine oxidation and cytochrome P-450-mediated [3H]-1-nitropyrene C-oxidation. These results are shown in Fig. 6. In the microsomes represented in Fig. 6A, the anti-P-450 3A antibodies at a 5:1 ratio of antibody to microsomal protein inhibited 40–50% of both 1-nitropyrene and nifedipine metabolism, while at an antibody to microsomal protein ratio of 10:1 the anti-P-450 3A antibodies inhibited 62% of the [3H]-1-nitropyrene C-oxidation and all of the nifedipine metabolism. This would then indicate that the 1-nitropyrene metabolism was inhibited to approximately the same extent as the nifedipine metabolism by the anti-P-450 3A antibodies with microsome sample 6. In Fig. 6B, the anti-P-450 3A antibodies at a 5:1 and a 10:1 ratio inhibited approximately 60% of the [3H]-1-nitropyrene metabolism, while inhibiting approximately 90% of the nifedipine metabolism with microsomes sample 22. In Fig. 6C, preincubation of microsomes with an antibodies:microsomal protein ratio of 5:1 or 10:1 inhibited 92–98% of the nifedipine metabolism, yet inhibited only approximately 70% of the [3H]-1-nitropyrene metabolism.
HUMAN LIVER MICROSOMAL METABOLISM OF 1-NITROPYRENE

Fig. 6. Effect of anti-P-450 3A antibodies on the human liver microsomal metabolism of nifedipine and [3H]-1-nitropyrene. Human liver microsome samples (A: 6; B: 22; C: 23) were preincubated with various amounts of the anti-P-450 3A antibodies, and the microsomes were quantified for both nifedipine oxidation (formation of dehydronifedipine diester; •) and [3H]-1-nitropyrene C-oxidation (formation of all phenolic and diol metabolites; □) by HPLC techniques as described in the text.

C-oxidation. Together the results shown in Fig. 6 indicate that under conditions where the anti-P-450 3A antibodies almost completely inhibited nifedipine metabolism, [3H]-1-nitropyrene C-oxidation was inhibited by approximately 60–70%. Together, the data of Figs. 5 and 6 suggest that the majority of [3H]-1-nitropyrene C-oxidation in human liver microsomes is mediated through P-450 3A and that another class(es) of cytochrome P-450 is (are) responsible for a minor component of 1-nitropyrene metabolism.

In Fig. 7, we contrast the rates of total microsomal metabolism of 1-nitropyrene (Fig. 7A) by the sex of the donor. The metabolism of 1-nitropyrene by the male liver-derived microsomes demonstrated bimodal distribution with mean ± SD of 0.59 ± 0.06 (n = 4) and 0.21 ± 0.05 (n = 4) nmol/min/mg protein. The microsomes derived from female liver donors had a unimodal distribution at 0.32 ± 0.09 (n = 5) nmol/min/mg protein, with one outlier at 0.99 nmol/min/mg protein. However, since the P-450 3A subfamily of proteins are highly inducible with many xenobiotics, we needed to take into consideration the treatment of the donors prior to obtaining the livers. In Fig. 7A we have denoted with closed circles the samples that came from donors the pretreatment of whom might have induced the P-450 3A subfamily of proteins. As shown in Fig. 7A, the highest activities in both the males and females are from these potentially induced samples. Additionally, elimination of these potentially induced activities results in unimodal distribution of 1-nitropyrene metabolism with mean ± SD of 0.27 ± 0.14 (n = 5) and 0.30 ± 0.09 (n = 4) nmol/min/mg protein for the males and females, respectively. Additional attempts to correlate the metabolism of 1-nitropyrene by age, alcohol consumption, or tobacco consumption did not yield any significant correlations. In Fig. 7B we show the correlations of the TAO-inhibited microsomal 1-nitropyrene metabolism as a function of the pretreatment of the donor, where essentially the same conclusions can be reached as with the data presented in Fig. 7A. The microsomes from donors that were pretreated with potential P-450 3A inducers have an activity of 0.53 ± 0.20 (n = 5) nmol/min/mg protein while the microsomes from the other donors without such pretreatment had activities of 0.29 ± 0.15 (n = 4) nmol/min/mg protein. More human liver samples would be needed to substantiate the correlation suggested by these data.

Analysis of the metabolites of [3H]-1-nitropyrene produced by the microsomes has additionally suggested a role for cytochromes P-450 3A3 or 3A4 (Table 1). Little difference was noted between the males and females in the metabolites of [3H]-1-nitropyrene that were formed. However, when the data were segregated into two categories, “potentially induced” or “potentially noninduced,” the metabolites produced by the potentially induced microsomes had a higher percentage of 1-nitropyrene-4,5-dihydrodiol and 1-nitropyren-3-ol as metabolites. This is reflected in the lowered ratio of formation of 1-nitropyren-6-ol + 1-nitropyren-8-ol to 1-nitropyren-3-ol in the potentially induced microsomal samples.

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DISCUSSION

A critical step in understanding the tumorigenic potential of a carcinogen is delineating the enzymatic processes involved in its metabolic activation and detoxification pathways. While the present studies were not designed to address which are the predominant pathways for \textit{in vivo} bioactivation of 1-nitropyrene, as a first step toward an understanding of the disposition of 1-nitropyrene in humans, we chose to address which cytochromes P-450 were responsible for microsomal 1-nitropyrene metabolism.

Human metabolism of 1-nitropyrene has been described in only two previous papers. In the paper of Howard et al. (16), the metabolism of 1-nitropyrene using 12 human cytochromes P-450 expressed by the \textit{Vaccinia} system in HepG2 cells was described. Only P-450 3A3 and 3A4 demonstrated specificity for the C-oxidation of 1-nitropyrene, and these cytochromes P-450 preferentially formed the 1-nitropyrene-3-ol metabolite. The other paper, by Kataoka et al. (26), describes the formation of the K-region epoxides and dihydrodial metabolites of 1-nitropyrene, where the authors conclude that the metabolism of 1-nitropyrene K-region oxides in the human microsomal samples differs from that of rodent species. In humans, there was a preference for 4,5-dihydrodial formation over glutathione conjugation, while in most rodents, glutathione conjugation was preferred.

To date, the present study is the first attempt to determine the nature of the P-450s involved in the human liver microsomal metabolism of 1-nitropyrene. In these studies, the cytochrome P-450 3A3 subfamily inhibitor TAO is shown to inhibit 86% of the human liver microsomal metabolism of 1-nitropyrene, while antibodies for the P-450 3A3 subfamily also inhibit approximately 70% of 1-nitropyrene metabolism. Further evidence for the role of P-450 3A4 comes from the inhibition of 1-nitropyrene metabolism by nifedipine, a specific substrate for P-450 3A4. Nifedipine at concentrations of 50 \( \mu M \) is capable of inhibiting approximately 60% of the 1-nitropyrene metabolism in human microsomes (Fig. 4) and 90% of the 1-nitropyrene metabolism by \textit{Vaccinia}-expressed cytochrome P-450 3A4 (Fig. 2). Together, we believe that this comparable inhibition by nifedipine and TAO in the human liver microsomal samples, under conditions that would inhibit approximately 90% of the 1-nitropyrene metabolism with pure protein, strongly suggests the involvement of cytochrome P-450 3A4 as the major protein in human liver microsomal metabolism of 1-nitropyrene.

A characteristic of the metabolism of 1-nitropyrene is the specificity of metabolism either proximal or distal to the nitro group, as indicated by the formation of 1-nitropyrene-3-ol or 1-nitropyrene-6-ol and 1-nitropyrene-8-ol, respectively. In this study, we show that all of the human microsomal samples demonstrated a preference for formation of 1-nitropyrene-3-ol over 1-nitropyrene-6-ol and 1-nitropyrene-8-ol (Table 1). This preference is consistent with our previous studies on 1-nitropyrene metabolism by \textit{Vaccinia}-expressed human cytochrome P-450 3A3 and 3A4 (16), where the 3-ol metabolite was formed at a rate at least 4-fold higher than 1-nitropyrene-6-ol and 1-nitropyrene-8-ol. This is in contrast to the metabolism of 1-nitropyrene in most rodent species. The ratio of 1-nitropyrene-6-ol and 1-nitropyrene-8-ol over 1-nitropyrene-3-ol produced by untreated male liver microsomes from several rodents has been reported to be between 1.1 and 5.4 for Sprague-Dawley rats (27, 28), CF1 mice (29), C57BL/6 \times C3H F, mice (28), Hartley guinea pigs (28), Syrian golden hamsters (28), and New Zealand White rabbits (20). When microsomes were obtained from livers of 3-methylcholanthrene- or Aroclor 1254 pre-treated rodents, the formation of 1-nitropyrene-6-ol and 1-nitropyrene-8-ol was greatly elevated thus increasing this ratio, while the pretreatment of rodents with phenobarbital greatly increased the formation of 1-nitropyrene-3-ol thus decreasing this ratio. Additionally, purified rabbit liver P-450s 1A1, 1A2, 2B1, 2C3, 2E1, and 3A2 all preferentially catalyzed the formation of 1-nitropyrene-6-ol and 1-nitropyrene-8-ol over 1-nitropyrene-3-ol by a ratio from 2 to 7.5 (20). In the present studies using 16 human liver microsomal samples, 1-nitropyrene-3-ol formation was approximately 3-fold higher than the formation of 1-nitropyrene-6-ol and 1-nitropyrene-8-ol (Table 1), and this ratio did not differ between males and females. Using \textit{Vaccinia}-expressed human cytochrome P-450 3A4 (16), the ratio of 1-nitropyrene-6-ol and 1-nitropyrene-8-ol to 1-nitropyrene-3-ol was likewise below 1. Therefore, it is safe to say that the metabolism of 1-nitropyrene in human liver microsomes differs based on regioselectivity from that of the rodents and that this specificity is consistent with cytochrome P-450 3A4 being the predominant cytochrome in human microsomal 1-nitropyrene metabolism.

P-450 3A3 and/or P-450 3A4 have been reported in almost all human liver samples tested to date. P-450 3A4 has been shown to be induced by rifampicin, barbiturates, macrolide antibiotics, and some steroids (30–35). The induction of this cytochrome has been suggested to be responsible for the rapid metabolism of ethynylestradiol in women under rifampicin or barbiturate therapy (36) as well as nephrotoxicity in patients receiving cyclosporin A and erythromycin (34, 37–38). Mainly P-450 3A4 and, to some extent, P-450 3A3 have recently been shown to participate in the metabolism of some steroids, benzodiazepines, macrolide antibiotics, immunosuppressants, 1,4-dihydropyridines, and other compounds such as tianeptine and lidocaine. Cytochromes P-450 3A have also been shown to be
involved in the metabolic activation of aflatoxin B₁, sterigmatocystin, and 6-aminochrysene. Shimada and Guengerich (39) have reported that cytochrome P-450 3A4 is responsible for the nitroreduction of 1,6- and 1,8-dinitropyrene. Thus, these P-450s are involved in both important drug oxidations and in metabolic activation of chemical carcinogens.

Kleinbloesem et al. (40) originally reported that the variability of nifedipine metabolism in humans is bimodal; however, in later reports, they indicated unimodal distribution in humans (41). Nifedipine is metabolized through P-450 3A4-catalyzed oxidation, while the subsequent metabolism by methyl hydroxylation and ester cleavage may not be strictly due to P-450 3A4. Therefore, there is not a clear picture of the P-450 3A4 polymorphism in humans. Because of the high amino acid sequence similarity (98%) between P-450 3A3 and P-450 3A4 (which are allelic variants (42)), specific antibodies have not been developed to discriminate between these two forms, and, therefore, their accurate form-specific quantitation in human tissues has not been forthcoming. However, several investigators have demonstrated that P-450 3A4 is a predominant cytochrome in human liver tissues based on immunochemical determination of protein (24, 43) and mRNA (44).

Our data on the metabolism of 1-nitropyrene with the human liver microsomes initially demonstrated bimodal distribution in tissues from males (Fig. 7). When we exclude the data from donors whose treatment could have resulted in the induction of cytochromes P-450 3A3 and P-450 3A4, the data suggest unimodal distribution. However, these data also suggest that the metabolism of 1-nitropyrene in humans might indeed be bimodal with the difference between individuals being prior exposure to cytochrome P-450 3A4 inducers.

Since P-450 3A4 is a predominant cytochrome in humans, it is inducible by synthetic steroid hormones and certain xenobiotics, and is responsible for the majority of 1-nitropyrene C-oxidation in human liver microsomal samples, it would seem apparent that the in vivo metabolic disposition of 1-nitropyrene in humans would be largely dependent on this cytochrome, the metabolism of 1-nitropyrene could be quite variable between individuals, and the question of 1-nitropyrene human carcinogenicity will still be debated. Our data, along with those of Kataoka et al. (26), indicate that a good animal model for the human metabolism and tumorigenicity of 1-nitropyrene does not exist.

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