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DIFFERENTIAL EFFECTS OF HUMAN RECOMBINANT INTERLEUKIN-1β AND DEXAMETHASONE ON HEPATIC DRUG-METABOLIZING ENZYMES IN MALE AND FEMALE RATS

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Abstract—Interleukin-1β (IL-1) is one of the major inflammation mediators, commonly reported to be an inhibitor of hepatic drug metabolism. We studied the effect of IL-1 treatment on various drug-metabolizing enzymes in male and female rats. IL-1 induced both cytochrome P450 (P450) 3A1 activity and protein in females, but in males, IL-1 repressed P450 3A2 activity, without decreasing the protein. P450 1A1 was impaired in males, but was retained after dexamethasone pretreatment. IL-1 did not change P450 2B1/2 activity and protein, but counteracted their induction by dexamethasone. Uridine diphospho-glucuronosyltransferase (UGT) 1A2 (bilirubin) activity and its induction by dexamethasone were not affected by IL-1 treatment. Both P450 2C11 and epoxide hydrolase activities were repressed by IL-1 treatment, and both activities were impaired after dexamethasone treatment. These results clearly demonstrate that IL-1 acts at different steps of protein synthesis and gene expression. The effect of IL-1 on P450 was isoform-dependent, indicating that IL-1 can act on pretranscriptional events. The discrepancy between the variations of the activities and the protein of P450 3A2 suggests a post-translational regulation. For P450 2C11, 3A1, and for microsomal epoxide hydrolase, but not for P450 1A1 and 2B1/2, IL-1 mimics the glucocorticoid effects. These differential effects can affect the kinetics and the bioavailability of drugs used in pathologies in which IL-1 is increased.

Interleukin-1β (IL-1†) is one of the first inflammation mediators. This cytokine is an initiator for many events in the inflammation process and in the immune response. This protein induces the acute phase proteins, glucocorticoids, and is commonly reported as a cytochrome P450 (P450)-dependent activity inhibitor [1].

P450 is the generic name for a gene superfamily coding for drug-metabolizing enzymes of the monooxygenase system [2]. Since the last decade, several authors have studied the effect of cytokines on various P450s. Among those studied were P450 1A1 [3], the major 2,4,7,8-tetrachloro-dibenzo-dioxin (TCDD) inducible P450 [4], 2C11 and 2C12 [5], two constitutive sex-dependent isoforms in rats [4], and 3A2 [6], the steroid-inducible family member constitutive in male rats [4]. Their activities were impaired by cytokines [3, 5–7]. IL-1 also decreases total P450 [7]. In the case of P450 2C12, IL-1 impairs the gene transcription [5]. Recently, it was demonstrated that interferon (IFN) effectively decreased P450 3A2, but not P450 3A1 [6], the female specific isoform in rats [4]. More recently, Stanley *et al.* [8] demonstrated that IFN differentially regulates *CYP1A1* and *CYP2B1/2* expression. Endotoxin in mice also presented a differential effect regarding specific isoforms of P450 [9]. Endotoxin, as well as IFN, is an inducer of IL-1 [1]. It was therefore of great interest to study if IL-1 also presented a differential effect on the drug-metabolizing isoenzymes studied.

Drug-metabolizing enzymes refer to a large number of proteins metabolizing exogenous compounds such as therapeutic drugs or toxic compounds. Many of these enzymes have a physiological role in the metabolism of endogenous compounds, such as steroids or bile acids. In addition to the major phase I enzymes, exist several phase II enzymes, including uridine diphospho-glucuronosyltransferases (UGT) and epoxide hydrolases (EH).

UGT refers to a superfamily of enzymes involved in the glucuronidation of endogenous compounds such as bilirubin and bile acids, or exogenous compounds such as carcinogens, drugs and other xenobiotics [10, 11]. EH catalyses the conversion of epoxides to 1,2 diols. Substrates can be endogenous such as leukotrienes, but also exogenous, including metabolites of exogenous compounds issued from the monooxygenase oxidation pathway. This mechanism represents generally a detoxification pathway [12].

In previous *in vivo* studies, we demonstrated that various cytokines (e.g. tumor necrosis factor, IL-1 and interleukin-6) could impair drug-metabolizing enzyme activities differentially [13]. We also demonstrated *in vitro* that the effect of IL-1 on cultured fetal rat hepatocytes was P450 isoform-dependent [14]. As several of the studied enzymes present a gender specificity in rats, we studied the effects of IL-1 in the present work in both males

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† Abbreviations: IL-1, interleukin-1β; P450, cytochrome P450; UGT, uridine diphospho-glucuronosyltransferase; EH, epoxide hydrolase; DXM, dexamethasone; IFN, interferon; and TCDD, 2,4,7,8-tetrachloro-dibenzo-dioxin.

and females. Dexamethasone (DXM) and IL-1 presented opposite effects [15]. DXM has been proposed as a protector for drug-metabolizing enzymes [14, 16], and therefore we treated male and female rats with different doses of IL-1, with or without DXM. We explored various enzymes, e.g. P450 1A1, 2B1/2, 2A1/2, 2C11, 3A1/2, UGT 1A1, 1A2, 2B3/6, and microsomal EH.

MATERIALS AND METHODS

Chemicals. Recombinant human IL-1 was a gift from Dr B. Terlain (Rhône-Poulenc Rorer, Vitry/Seine, France); DXM phosphate, testosterone, 1-dehydrotestosterone, and bovine serum albumin were purchased from the Sigma Chemical Co. (Saint Quentin Fallavier, France), tetrahydrofuran was from Merck (Nogent sur Marne, France), RPMI 1640 without L-glutamine medium was from Gibco (Cergy-Pontoise, France) and human serum albumin from Mérieux (Lyon, France). Testosterone hydroxylated standards were provided by Steraloids (Wilton, NH, U.S.A.).

Animals and treatments. Mature male (220–300 g) and mature female (140–180 g) Wistar Furth rats obtained from IFFA CREDO (L'Arbresle, France) were separated immediately into groups of five in solid bottomed plastic cages. They were housed in an animal room with a light/dark cycle (12/12 hr) at a regulated temperature of 23° and allowed free access to water and standard laboratory chow (UAR, Villemoisson/Orge, France). A recent pharmacokinetic study for IL-1 in rats indicated that s.c. injection could be more efficient than i.p. injection [17]. Animals received DXM (100 mg/kg, phosphate salt) i.p. in saline and IL-1 s.c. (0.1, 1.0 and 10.0 μg/kg) in RPMI 1640 medium with 2.5% human serum albumin for 3 days, or only vehicles. They were fasted 12 hr before being killed.

Microsomal fractions. Animals were killed by decapitation, the liver was quickly removed and microsomes were prepared as described previously [18]. Microsomes were stored as aliquots at −80° until use.

Enzymatic activities. Protein concentration determination was performed by the method of Lowry *et al.* [19] using bovine serum albumin as standard. Total P450 was determined as described by Matsubara *et al.* [20]. NADPH P450 reductase activity was determined as described by Strobel and Dignam [21]. Testosterone hydroxylation was determined after 5 min incubation (microsomes 0.5 mg, testosterone 2 mM, glucose-6-phosphate 50 mM, glucose-6-phosphate dehydrogenase 1 U/mL, NADP 0.5 mM in 50 mM Hepes buffer at pH 7.6; final volume was 2 mL). The incubation mixture was then filtered using a Sep-Pak C18 cartridge (Waters, Milford, MA, U.S.A.) to remove proteins and water. Testosterone and its metabolites were eluted with methanol, which was evaporated under nitrogen gas flow. The steroids were recovered in a methanol solution containing 1-dehydrotestosterone (0.01 μg/mL) as internal standard, and then separated by HPLC on a Superspher C18 column (250 × 5 mm, 4 μ, Merck) according to Narimatsu *et al.* [22], using an eluant of tetrahydrofuran:water (30:70, v/v), with a flow rate of 0.6 mL/min. Metabolites were identified

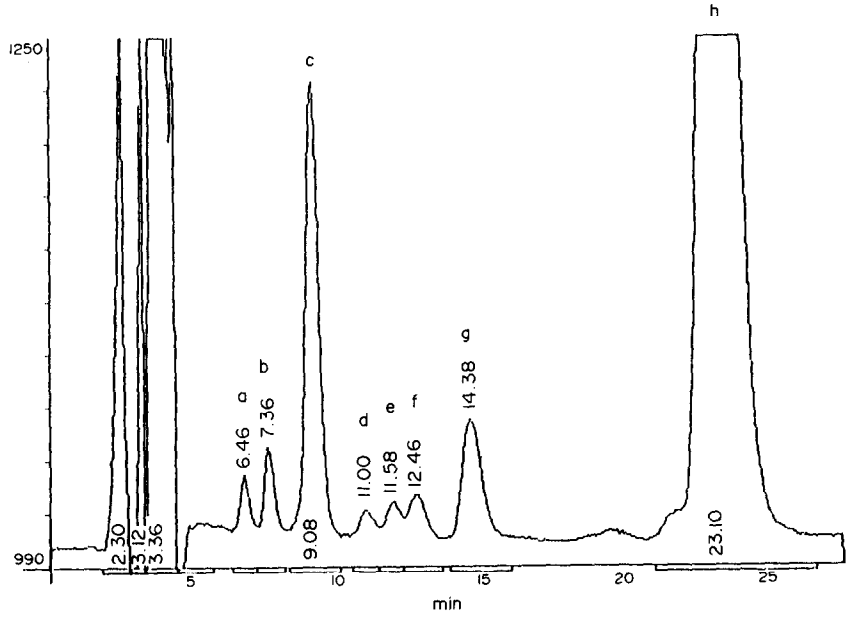

Fig. 1. Elution profile of testosterone metabolites. Experimental conditions are as described in Materials and Methods. Specific metabolites corresponding peaks are: (a) 7α-hydroxytestosterone; (b) 16α-hydrotestosterone; (c) 6β-hydroxytesterone; (d) 16β-hydrotestosterone; (e) 2α-hydroxytestosterone; (f) 2β-hydroxytestosterone; (g) 1-dehydrotestosterone (internal standard); (h) testosterone.

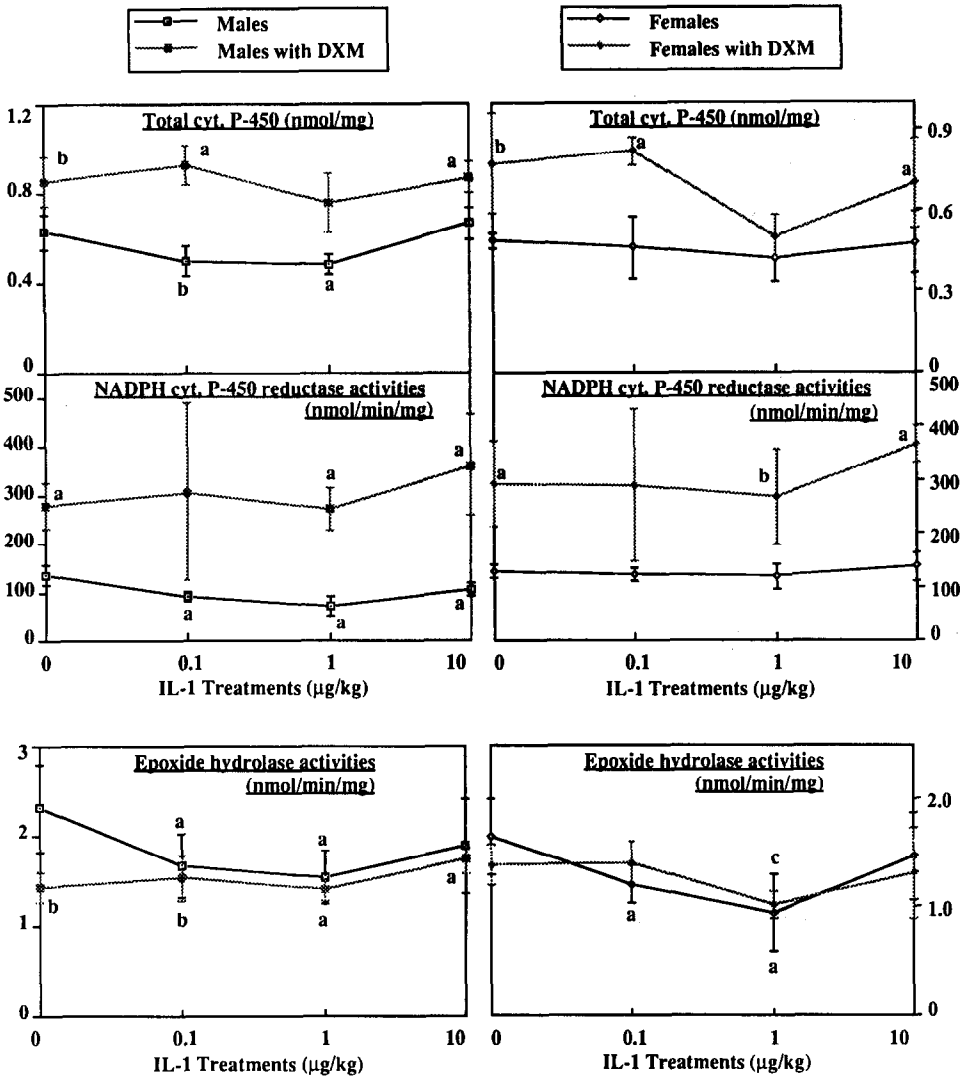

Fig. 2. Effects of IL-1 and DXM on total P450, NADPH P450 reductase, and microsomal EH activity. Experimental procedures as described in Materials and Methods. EH activity is benzopyrene transdiol formation. (a) Different from control (IL-1 0.0 μg/kg, and −DXM) with P ≤ 5%. (b) Different from control (IL-1 0.0 μg/kg, and −DXM) with P ≤ 1%. (c) Different from animal treated with DXM with P ≤ 5%. (d) Different from animal treated with DXM with P ≤ 1%.

by comparison with the available standards. Alkoxyresorufin-*O*-dealkylases [23], EH [12] and UGT [24] activities were determined as described previously.

Blots. SDS–PAGE blots were performed according to Laemmli [25] and immunoblots according to Burnette [26]. P450 3A1/2 were detected using a monoclonal antibody KO3 [27], and P450 1A1 and 2B1/2 using polyclonal antibodies prepared in the rabbit with purified proteins from induced rats as described previously [18]. Simultaneous migration of microsomes from rats induced with DXM, 3-methylcholanthrene and phenobarbital respectively, were performed to ensure a correct identification of the protein (not shown).

Statistics. All statistical analyses were made using a non parametric Mann–Whitney test.

RESULTS

In a preliminary experiment 50 mg/kg of DXM increased the 6β-hydroxylation of testosterone 2-fold (not shown). In this experiment DXM was 100 mg/kg to obtain a sufficient induction of the P450 3A activity. Since we expected a dose-dependent effect of IL-1, we treated rats with doses ranging from 0.1 to 10.0 μg/kg. The use of a Superspher 4 μ (Merck) solid phase allowed us to separate several testosterone hydroxylated metabolites, including 2αT, 7αT and 6βT (Fig. 1).

Total P450 and NADPH P450 reductase (Fig. 2) were slightly inhibited by IL-1 treatment in male rats. However, in females neither was affected. Both total P450 and reductase were increased by DXM, co-administration of IL-1 being devoid of effect.

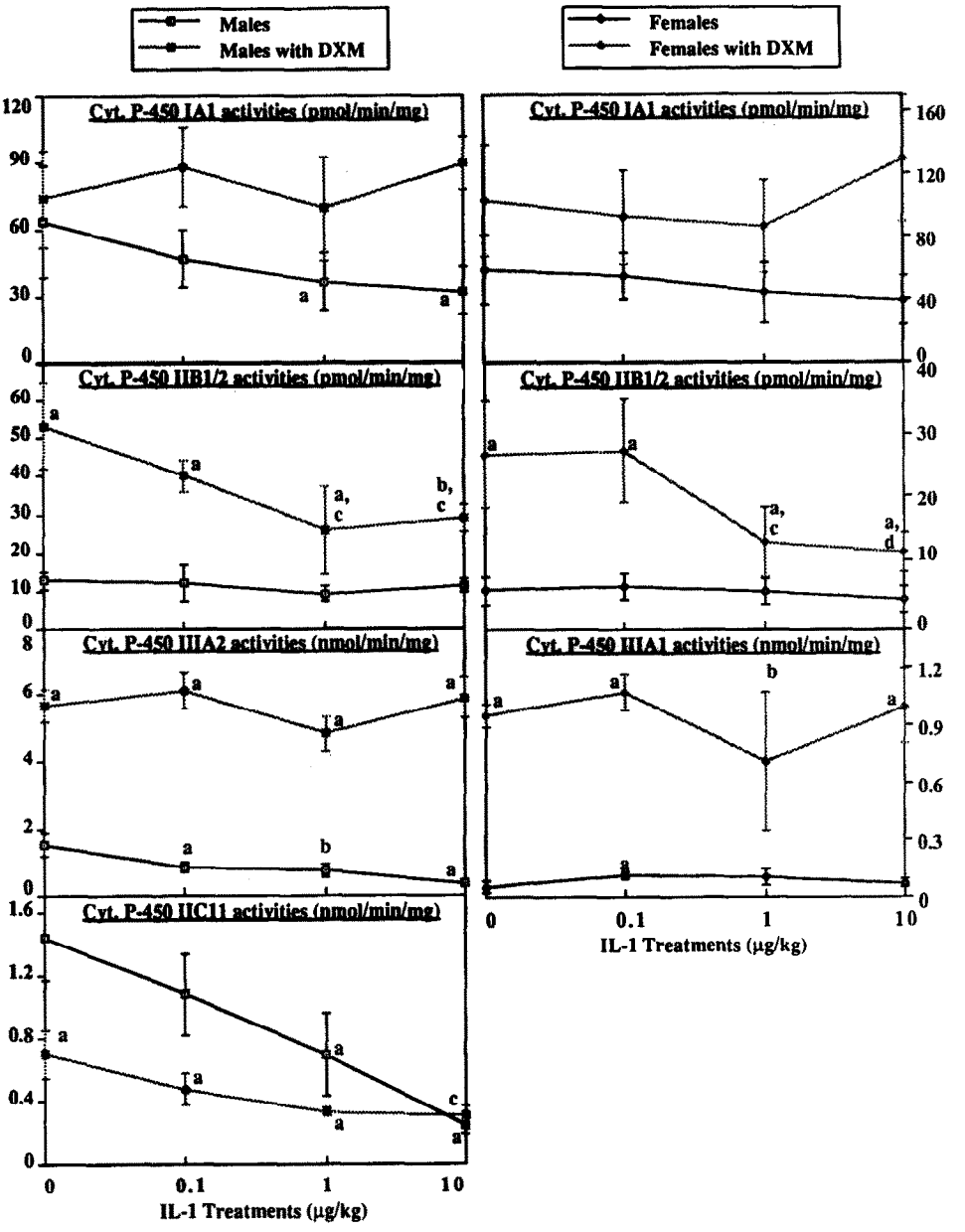

Fig. 3. Effects of IL-1 and DXM on alkoxyresorufin-*O*-dealkylase, testosterone 6β hydroxylation, and testosterone 2α-hydroxylation. P450 1A1 activity is ethoxyresorufin-*O*-dealkylase, P450 2B1/2 activity is pentoxyresorufin-*O*-dealkylase, P450 3A1 and 3A2 activity is testosterone 6β-hydroxylase, P450 2C11 activity is testosterone 2α hydroxylase. Experimental procedures as described in Materials and Methods. (a) Different from control (IL-1 0.0 μg/kg, and −DXM) with $P \leq 5\%$. (b) Different from control (IL-1 0.0 μg/kg, and −DXM) with $P \leq 1\%$. (c) Different from animal treated with DXM with $P \leq 5\%$. (d) Different from animal treated with DXM with $P \leq 1\%$.

Microsomal EH activity (Fig. 2) was slightly decreased by the 1.0 μg/kg treatment. DXM decreased the activity in both genders. Co-administration of IL-1 had no effect in male, and impaired the activity in female rats at the dose of 1.0 μg/kg. Ethoxyresorufin-*O*-deethylase (EROD) activity (Fig. 3), corresponding to P450 1A1, was impaired by IL-1 treatment in males, but not in females. DXM protected this activity in males. As shown in Fig. 4, IL-1 had no effect on the protein, and DXM slightly increased it. IL-1 had no effect on pentoxyresorufin-*O*-deethylase (PROD) activity, corresponding to P450 2B1/2, in either males and females (Fig. 3). However DXM induction was counteracted by IL-1. Corresponding western blots are shown in Fig. 5. IL-1 alone had no effect on the

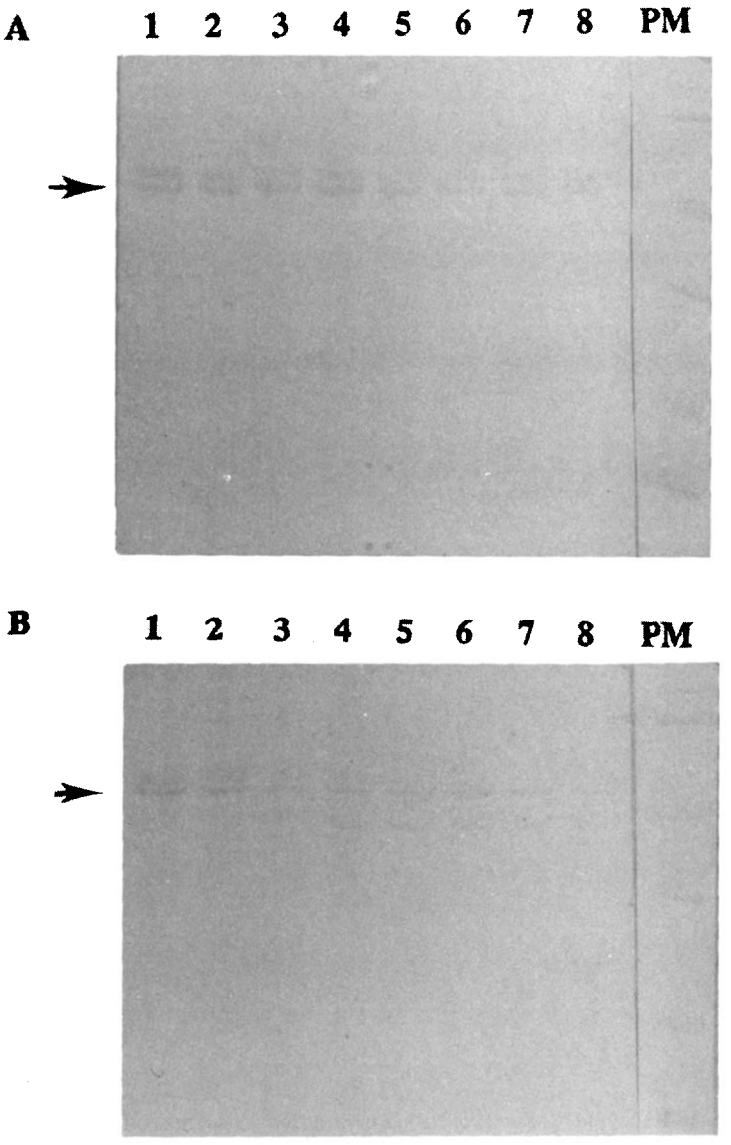

Fig. 4. Effects of IL-1 and DXM on P450 1A1 in male and female rats. (A) Males. (B) Females. The bands corresponding to P450 1A1 are indicated by the arrows. Lane 1: control, lane 2: treatment with IL-1 0.1 μg/kg, lane 3: treatment with IL-1 1.0 μg/kg, lane 4: treatment with IL-1 10 μg/kg, lane 5: treatment with DXM 100 mg/kg, lane 6: treatment with DXM 100 mg/kg plus IL-1 0.1 μg/kg, lane 7: treatment with DXM 100 mg/kg plus IL-1 1.0 μg/kg, lane 8: treatment with DXM 100 mg/kg plus IL-1 10 μg/kg.

protein, and DXM induction was not counteracted by IL-1.

In females testosterone 6β-hydroxylase activity (Fig. 3), corresponding to P450 3A1/2, was increased 2-fold by 0.1 and 1.0 μg/kg IL-1 treatment and not significantly affected by the highest dose. In males, IL-1 decreased in a dose-dependent manner this activity. Corresponding western blots, presented in Fig. 6 showed that the protein variations were similar to those of the activities in females, but not in males, where we noticed no changes in the protein after IL-1 treatment. DXM increased testosterone 6β-hydroxylation. After DXM treatment (Fig. 3), IL-1 had no effect on either the activity, or the protein in both genders (Fig. 6). The effect of IL-1 on testosterone 2α-hydroxylase (Fig. 3), corresponding to P450 2C11, was a dose-dependent decrease. In males DXM decreased the activity. IL-1 impaired the 2α-hydroxylation activity even in the presence of DXM, but less markedly.

DISCUSSION

The absence of dose-dependence for the impair-

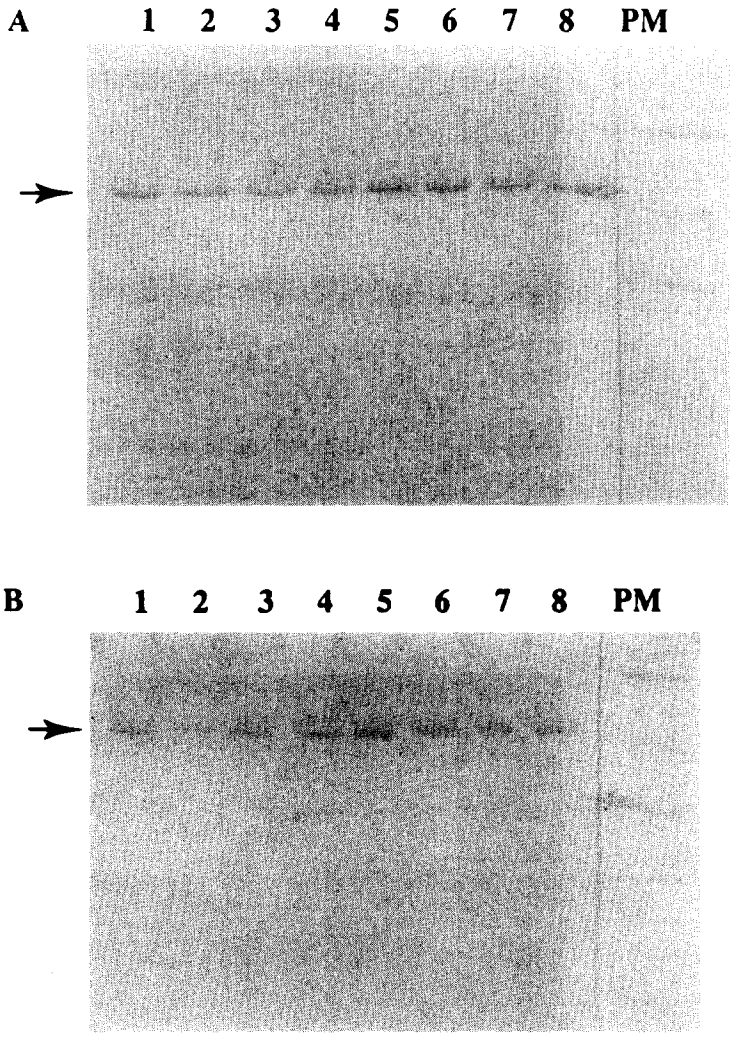

Fig. 5. Effects of IL-1 and DXM on P450 2B1/2 in male and female rats. (A) Males. (B) Females. The bands corresponding to P450 2B1/2 are indicated by the arrows. Lane 1: control, lane 2: treatment with IL-1 0.1 μg/kg, lane 3: treatment with IL-1 1.0 μg/kg, lane 4: treatment with IL-1 10 μg/kg, lane 5: treatment with DXM 100 mg/kg, lane 6: treatment with DXM 100 mg/kg plus IL-1 0.1 μg/kg, lane 7: treatment with DXM 100 mg/kg plus IL-1 1.0 μg/kg, lane 8: treatment with DXM 100 mg/kg plus IL-1 10.0 μg/kg.

ment of total P450 is in contradiction with the results of Poüs *et al.* [7]. However this group used a different strain of animals, their treatment was only for 24 hr, and their doses of IL-1 were lower than those used in this study. All these differences could explain the discrepancy between our results. In the case of P450 2C11, similar results have been reported by Wright and Morgan [5] after administration of IL-1α and determination of P450 2C12 mRNA and protein, the corresponding female-specific enzyme. IL-1 and IL-1α have similar, glucocorticoid-like effects on P450 2C11/12. This supports the hypothesis that the effects of IL-1 on some P450 could be mediated by the induction of glucocorticoids. Impairment of microsomal EH activity suggests that, as for P450 2C11, the effects of IL-1 on the enzyme could be mediated by glucocorticoids, which can repress microsomal EH expression [28]. This hypothesis is supported by the already described synergistic effects of cytokines and glucocorticoids on the regulation of acute phase proteins [29]. P450 2B1/2 activity (Fig. 3), presented similar results to those obtained in cultured hepatocytes after induction by phenobarbital and treatment with IL-6 [30]. The regulation of P450 gene *CYP2B1/2* expression involves several mechanisms including pre-transcriptional events, mRNA stabilization, or a post-translational mechanism [31]. Rao *et al.* demonstrated that DXM blocks

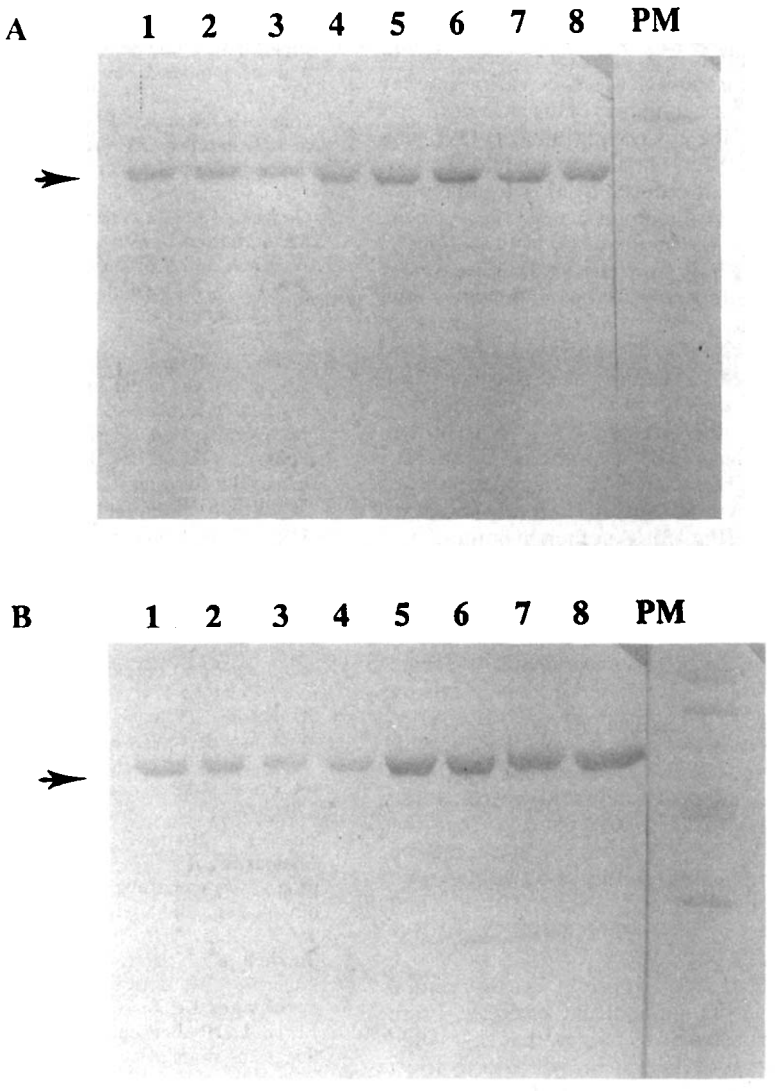

Fig. 6. Effects of IL-1 and DXM on P450 3A1/2 in male and female rats. (A) Males. (B) Females. The bands corresponding to P450 3A1/2 are indicated by the arrows. Lane 1: control, lane 2: treatment with IL-1 0.1 μg/kg, lane 3: treatment with IL-1 1.0 μg/kg, lane 4: treatment with IL-1 10 μg/kg, lane 5: treatment with DXM 100 mg/kg, lane 6: treatment with DXM 100 mg/kg plus IL-1 0.1 μg/kg, lane 7: treatment with DXM 100 mg/kg plus IL-1 1.0 μg/kg, lane 8: treatment with DXM 100 mg/kg plus IL-1 10.0 μg/kg.

the transcription, but simultaneously, stabilizes the mRNA, resulting in an increase of the protein [32]. IL-1 decreased the activity of P450 2B1/2 after DXM induction. So it is possible that IL-1 blocked or reversed the DXM mRNA-stabilization, or acted as a transcription inhibitor, as for P450 2C12 [33].The impairment of EROD activity by IL-1 treatment is in accordance with Ghezzi and co-workers [3, 34]. The apparent absence of change in the protein, on western blot (Fig. 4) suggests a post-translational regulation, as was proposed for P450 1A1 by Stanley *et al.* [9] after IFN treatment in mice. As we and others had suggested [14, 16], DXM had a protective effect on P450 1A1 related activities against impairment by IL-1 (Fig. 3). This result is in contradiction to that reported by Moreno *et al.* [35]. However these authors used a lower dose for their DXM treatment, and it is known that low doses of DXM decrease total P450 [36]. UGT 1A1 activity, which is also regulated by the Ah locus, was not protected by DXM (not shown). This suggests a different regulatory pathway for these two enzymes.

Both P450 3A1 and 3A2 can metabolize testosterone at the 6β position [37]. Thus, it is difficult to deduce from the activity which enzyme is present in the liver. *CYP3A2* is constitutively expressed in male, while the only expressed gene in mature female is *CYP3A1* [38]. Craig *et al.* suggested

that IFN decreased P450 3A2 but not P450 3A1 expression [6]. Our results suggest that the effect of IL-1 could be similar. The classical inducer for the 3A family in rats is DXM, but various other compounds, which are members of the glucocorticoid family, were described as potent inducers [39]. The increase of P450 3A1 in female rats could be related to the glucocorticoids induced by IL-1 treatment or inflammation. It was demonstrated that plasma adrenocorticotropic hormone (ACTH) was induced from 20 to 200 pg/mL by 10 μg/kg IL-1 treatment in rats [40]. This effect may not be important enough to obtain a large increase of 6β testosterone in females (2-fold only, Fig. 3). In the same way, P450 2A1 and UGT 1A2 activities, also glucocorticoid-inducible [4, 10] but poorly induced by our DXM treatment, were not affected by IL-1 treatment (results not shown). The hypothesis of an IL-1 induced anorexic effect on 3A1 in females [40] was ruled out while we did not observe any increased activity in males (Fig. 3). Another hypothesis was that the inhibition of growth hormone by IL-1 [1] could have changed the regulation of the gender-specific P450 (2C11/12 and 3A1/2) in females [42]. If this was the case, we should also have noticed in females a surge of 2α testosterone activity, specific for P450 2C11, which is repressed in female rats by growth hormone [42]. The increase of P450 3A1 in females was probably not related to the IL-1 growth hormone inhibition. Western blots for P450 3A in males showing that the protein did not decrease after IL-1 treatment (Fig. 6), indicate that the regulation of *CYP3A2* expression in male rats by IL-1 is more complicated. In this case, we suggest a post-translational regulation, as for P450 1A1, and as was postulated by others for the effects of IFN or IFN inducers [9, 33].

We demonstrated that IL-1 produces a differential effect on various drug metabolizing enzymes. From our results it seems logical to suggest that IL-1 could act at different steps of the protein synthesis to affect P450 gene expression. The argument for this will be reinforced after studying the mRNAs of these enzymes. This may include different factors and different receptors. Our results do not solve the problem of the exact effect of IL-1 on hepatic drug-metabolizing enzymes, but have clearly demonstrated that IL-1 regulates them by different mechanisms, even in the presence of DXM. The identification of the mechanisms involved are an interesting challenge.

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