Regulation of Cytochrome P450 2C11 (CYP2C11) Gene Expression by Interleukin-1, Sphingomyelin Hydrolysis, and Ceramides in Rat Hepatocytes

(Received for publication, July 23, 1995, and in revised form, August 18, 1995)

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Interleukin-1 triggers the down-regulation of several hepatic cytochrome P450 gene products, but the cellular signaling pathways involved are not known. We have examined the role of sphingomyelin hydrolysis to ceramide in the suppression of CYP2C11, a major constitutive form of cytochrome P450, by interleukin-1. Treatment of rat hepatocytes cultured on matrigel with interleukin-1β caused a rapid turnover of sphingomyelin and an increase in cellular ceramide, with no change in cellular phosphatidylcholine. The ceramide was composed mainly of a D-erythro-sphingosine backbone, suggesting that it was derived from sphingolipid hydrolysis rather than from increased de novo synthesis. Treatment of the cells with either N-acetyl-D-erythro-sphingosine (C2-ceramide) or bacterial sphingomyelinase suppressed the expression of CYP2C11 and induced the expression of the interleukin-1-responsive α1-acid glycoprotein mRNA. In contrast, the acute-phase gene β-fibrinogen, which is induced by interleukin-6 but not by interleukin-1, did not respond to C2-ceramide. N-Acetyl-D-erythro-sphinganine mimicked the effect of C2-ceramide on CYP2C11, but not on α1-acid glycoprotein expression. These results are consistent with a role for ceramide or a related sphingolipid in mediating the down-regulation of CYP2C11, the induction of α1-acid glycoprotein, and perhaps other cellular effects of interleukin-1 in hepatocytes.

Stimulation of the immune system during an infection or inflammation results in an impairment of hepatic drug metabolism and a decrease in the hepatic content of cytochrome P450, the family of enzymes that are responsible for the metabolism of many drugs and chemical toxins (2–4). The decrease in drug clearance can result in adverse reactions to normal doses of clinically important drugs, such as theophylline (5), that have low therapeutic indices.

At least part of the decrease in P4501-catalyzed metabolism in response to inflammatory stimuli such as bacterial endotoxin is due to the down-regulation of multiple P450 gene products (6, 7), which appear to be manifested mainly at the transcriptional level (8). The down-regulation of P450 genes is accompanied by a well-characterized induction of hepatic plasma proteins (such as fibrinogen and α1-acid glycoprotein (9), which are called the “positive acute-phase proteins”) and a decreased synthesis of “negative acute-phase proteins” (such as albumin (9)).

Cytokines, together with glucocorticoids, are the major humoral mediators of the acute phase of host defense after injury and infection (9). Numerous in vivo and in vitro studies have shown that IL-1β plays a key role in inducing many of the acute-phase proteins at both transcriptional and post-transcriptional levels (9), whereas others are induced mainly by the action of interleukin-6 (9). A role for IL-1β in the down-regulation of P450 genes has been inferred from several studies in which injection of IL-1β in vivo reduced the expression of various P450 gene products (10–13). However, until now, studies on the mechanism of the IL-1β suppression of P450 gene expression have been impeded by the lack of a culture system in which hepatocyte P450s are expressed stably and constitutively at levels approaching those in vivo and a relative paucity of knowledge of the intracellular signaling pathways utilized by the IL-1β receptor to regulate gene expression.

Significant developments have occurred recently in both of these areas. (a) Hepatocytes cultured on matrigel with insulin as the only hormone present were shown to express CYP2C11, a major constitutively expressed P450 in male adult rats (6), stably and at levels approaching those seen in vivo in the absence of growth hormone (14). We have shown that CYP2C11 expression in this system is pretranscriptionally suppressed by interleukin-1β (15). (b) IL-1β has been found to induce the hydrolysis of sphingomyelin and accumulation of ceramide in a number of nonhepatic cell types (16–18). Ceramide appears to play a role as a second messenger since cell-permeable ceramide analogs and addition of exogenous sphingomyelinase to release endogenous ceramide can bypass receptor activation and mimic the effect of TNF-α (19) and IL-1β, e.g. IL-1-mediated induction of cyclooxygenase mRNA (20) in fibroblasts and activation of IL-2 production in thymoma cells (21). This novel signaling pathway, referred to as the “sphingomyelin pathway,” was originally described in HL-60 cells upon stimulation with 1α,25-dihydroxyvitamin D3, γ-interferon, or TNF-α (16, 17, 22). Ceramide has been implicated as a modulator of a variety of downstream events, such as activation of specific protein phosphatases and protein activation and induces transcription of the IL-1-responsive α1-acid glycoprotein gene (23).

The abbreviations used are: P450, cytochrome P450; IL, interleukin; TNF, tumor necrosis factor; SM, sphingomyelin; AGP, α1-acid glycoprotein; C2-ceramide, N-acetyl-D-erythro-sphingosine; C2-dihydroceramide, N-acetyl-D-erythro-sphinganine; HPLC, high pressure liquid chromatography.
protein kinases, down-regulation of the c-myc proto-oncogene, apoptosis, and activation of nuclear factor NF-κB (16, 17, 18).

The findings prompted us to investigate whether sphingolipids are involved in the regulation of P450 and acute-phase genes during inflammation. In this study, we report that IL-1β initiates SM turnover in hepatocytes and that exogenous and endogenous ceramides mimic the effects of IL-1β on the expression of the CYP2C11 and AGP genes. These results suggest that sphingolipids are involved in the response of hepatocytes to this cytokine.

EXPERIMENTAL PROCEDURES

Materials—Cell culture media and murine recombinant IL-1β were purchased from Life Technologies, Inc. [methyl-3H]Choline chloride (55 mCi/mmol) was from Amersham Corp. Sphingomyelinase (Staphylococcus aureus), standard sphingomyelin (bovine brain), and ceramide (bovine brain, type II) were from Sigma. N-Acetyl-o-erythro-sphingosine (C2-er-Ceramide), N-acetyl-o-erythro-sphingosine (C2-dh-Ceramide), and N-acetyl-C20-sphinganine were synthesized as described previously (23). The β-fibrinogen cDNA was kindly supplied by Dr. Gerald Fuller (University of Alabama at Birmingham). Recombinant IL-1 receptor antagonist protein was generously provided by Dr. Daniel Tracey (The Upjohn Co.).

Cell Culture—Matrigel was prepared as described by Schuetz et al. (24) and stored at −20 °C. 400 μl of matrigel (diluted to 6.3 mg/ml with Waymouth’s medium) was applied to 0.6-mm plastic culture dishes and allowed to gel at 37 °C for 1–2 h, after which 3 ml of Waymouth’s medium was added to each dish.

Hepatocytes were isolated from ether-anesthetized, male Sprague-Dawley rats by in situ collagenase perfusion (14). Cells (3.5 × 106/plate; viability > 80%) were plated in 3 ml of Waymouth’s medium containing insulin (0.15 μg/ml) as the only hormone. Cultures were maintained for 5 days at 37 °C in 5% CO2 atmosphere. The medium was replaced every 48 h, commencing 3 h after plating. In some cases, the hepatocytes were labeled with 1H]choline chloride (0.4 μCi/dish). To obtain greater labeling of SM, these cells were cultured in Waymouth’s MD 7051 medium ( post-choline chloride) which lacks choline chloride.

Treatments—Cells were cultured for 5 days before beginning treatment to allow recovery of stable expression of CYP2C11 (14). The cells were treated on day 5 by changing to medium containing 5 ng/ml IL-1b, 30 μg/ml C2-Ceramide, 0.1 unit/ml sphingomyelinase, or vehicles for the time course experiments, or indicated concentrations for dose-response studies.

Lipid Analysis—Hepatocytes were harvested at appropriate times with 2 ml of phosphate-buffered saline. Aliquots were taken for protein determination, and the lipids were extracted by the method of Bligh and Dyer (25), modified as described previously (26). Lipids from each dish were analyzed by thin-layer chromatography on Silica Gel H plates with chloroform, methanol, triethylamine, 2-propanol, 0.25% potassium chloride (30:9:25:18:6, by volume) as the developing solvent. The lipids were visualized with I2 or 50% H2SO4. Those spots migrating with standard SM were scraped and quantitated by a phophate assay. In the case of labeled cells, the assay mixtures were neutralized after phosphate assay and counted with a scintillation counter.

To quantitate the mass of ceramide, 600 pmol of N-acetyl-C20-sphinganine sample (27) was added to the regions where ceramide migrated (as an internal standard). These spots were scraped, and 2 ml of chloroform/methanol (1:2, by volume) was added to each sample. After mixing for 1–2 min, the silica was sedimented by centrifugation for 10 min in a tabletop centrifuge. This procedure was repeated three times, and pooled supernatants were evaporated under reduced pressure. Ceramide mass was quantitated by analyzing the long-chain bases released after acid hydrolysis using a reverse-phase HPLC method, and the values were corrected for recovery of the internal standard.

Isolation of Total RNA and Slot-blot Assays—Total hepatocyte RNA was prepared by the acid-phenol extraction method (28). The relative abundances of CYP2C11, AGP, and β-fibrinogen mRNAs in total RNA were measured by slot-blot hybridization assay as described previously (6) using a full-length cDNA for CYP2C11 (6) and fibrogen and an oligonucleotide complementary to nucleotides 655–684 of AGP mRNA (29). These probes hybridized to single mRNA bands of appropriate size in Northern blots of RNA from 6-day hepatocyte cultures. Bound probe was assayed by autoradiography and densitometric scanning. All results were normalized to the content of poly(A)+ RNA, measured by probing slot blots with an oligo(dT)18 probe (30). The amounts of total RNA were previously determined to be in the range giving a linear response.

Microsomal Protein Isolation and Western Blot for CYP2C11—Microsomal proteins were isolated from hepatocytes by differential centrifugation (14) using a Beckman TLK tabletop ultracentrifuge, and Western blotting for CYP2C11 protein was performed with anti-CYP2C11 polyclonal antibody as described by Morgan (6). Cellular protein was determined by the procedure of Lowry et al. (30) using bovine serum albumin as a standard.

Statistical Analyses—Data from Western blot assays and slot-blot assays were expressed as the percentage of the mean of the control group in each experiment. One-way analysis of variance and the Newman-Keuls test or Dunnett’s test (where appropriate) were used to determine differences among treatment groups.

RESULTS

Effects of IL-1β on SM Turnover—To determine whether IL-1β induces SM turnover in hepatocytes, cells were cultured for 5 days on matrigel and labeled with [3H]choline chloride for the last 48–72 h; then 5 ng/ml IL-1β was added, and the amount of label remaining in SM was measured. Loss of label from SM was significant within 15 min after adding IL-1β and appeared to be complete by 45 min (Fig. 1). There was also a decrease in SM mass, as shown in Table I. After 45 min of treatment with 5 ng/ml IL-1β, the mass of SM was reduced by about half and after 120 min had clearly begun to return to the initial level. In some experiments (data not shown), the amount of [3H]choline in SM also increased at 120 min. This increase may be variable because the SM headgroup is derived from phosphatidylcholine, which, in hepatocytes, is also synthesized de novo both from choline and by methylation of phosphatidylethanolamine. The amount of radioactivity and mass in phosphatidylcholine were also examined; however, no changes were seen in this other choline-containing lipid (data not shown).

The IL-1β dose dependences for the loss of radiolabel and mass from SM are shown in Fig. 2. SM turnover was evident at 1 ng/ml IL-1β and only increased slightly at higher concentrations. Suppression of CYP2C11 by IL-1β in rat hepatocytes begins to be significant at concentrations as low as 0.5 ng/ml and reaches a plateau at 2 ng/ml (15). Therefore, the levels of IL-1β that cause suppression of CYP2C11 also induce SM hydrolysis.

Effect of IL-1β on Ceramide and Dihydroceramide Levels—Incubation of hepatocytes with 5 ng/ml IL-1β also resulted in increases in ceramide (Table I). After 45 min, the increase in ceramide (0.37 nmol/mg of protein) was about two-thirds of the change in SM (0.64 nmol/mg of protein). The ceramide mass returned to the initial levels at 120 min (Table I). The IL-1β concentration dependences for SM turnover versus the increase in ceramide differed, however (cf. Figs. 2 and 3). The explanation for this difference is not clear; it might indicate that IL-1β...
TABLE I

Changes in the level of SM and ceramides during treatment of hepatocytes with IL-1β

| Time of incubation | 0 min | 45 min | 120 min |
|--------------------|-------|--------|---------|
| nmol sphingolipid/mg protein |       |        |         |
| SM                 | 1.050 ± 0.190 | 0.410 ± 0.100 | 0.815 ± 0.005 |
| Cer<sup>a</sup>     | 1.111 ± 0.008 | 1.482 ± 0.068 | 1.115 ± 0.245 |
| DHCer              | 0.026 ± 0.008 | 0.023 ± 0.002 | 0.017 ± 0.004 |

<sup>a</sup>Cer, ceramide; DHCer, dihydroceramide.

FIG. 2. Effect of IL-1β on degradation of sphingomyelin. Hepatocytes were cultured in modified Waymouth's medium and prelabeled with [14C]choline chloride for 48 h as described for Fig. 1 (upper panel) or in Waymouth's medium only (lower panel) and then treated with different concentrations of IL-1β for 45 min. The upper panel shows the disappearance of radiolabeled SM, while the lower panel presents changes in its mass, as determined by phosphate assay. Values are means ± S.E. (n = 3).

FIG. 3. Effect of IL-1β on hepatocyte ceramide level. Hepatocytes were cultured in Waymouth's medium for 5 days and treated with the indicated amounts of IL-1β for 45 min. The ceramide mass was measured by HPLC of o-phthalaldehyde derivatives of sphingosine, which is formed after acid hydrolysis of ceramide. Values are means ± S.E. (n = 3).

on the outer leaflet of the membrane; however, as a highly nonpolar lipid, the ceramide released is able to traverse the membrane. Treatment with either C<sub>2</sub>-ceramide or sphingomyelinase reduced CYP2C11 mRNA (Fig. 4). The effects on CYP2C11 mRNA were statistically significant by 12 h of incubation (34% of the corresponding control group) and were still evident at 24 h. Although in Fig. 4 it appears that the mean CYP2C11 mRNA levels are reduced at earlier time points, the difference was not statistically significant. In several other experiments (data not shown), we found no consistent effect of ceramide on CYP2C11 mRNA at time points earlier than 12 h. These findings are in good agreement with the time course of IL-1β suppression of CYP2C11 mRNA. CYP2C11 mRNA levels are also variable in the first 8 h after IL-1 treatment and become significantly suppressed after 12 h (15). The treatment with sphingomyelinase (0.1 unit/ml) resulted in a 30% reduction in the SM content of the hepatocytes with a similar increase in the amount of ceramide at 1 h of incubation (data not shown).

The decreases in CYP2C11 mRNA evoked by sphingomyelinase and C<sub>2</sub>-ceramide were followed by suppression of its protein product at 48 and 72 h of incubation (Fig. 5), with a maximal reduction of ~65% (CYP2C11 protein levels remained relatively constant in untreated cultures). Smaller effects on CYP2C11 apoprotein were observed after 24 h (data not shown). The effects of sphingomyelinase and C<sub>2</sub>-ceramide on CYP2C11 protein were similar in time dependence and magnitude to those of IL-1 (Fig. 5).

Effect of C<sub>2</sub>-ceramide on the Acute-phase Proteins—To investigate the concentration dependence and specificity of ceramide action in hepatocytes, we tested the expression of CYP2C11 and two other genes: AGP, a type I positive acute-phase protein that is responsive to IL-1β, and β-fibrinogen, a type II acute-phase protein that is regulated by interleukin-6 (9). Significant suppression of CYP2C11 was observed at 3 μM C<sub>2</sub>-ceramide and was near-maximal at 10 μM (Fig. 6, upper panel). C<sub>2</sub>-ceramide strongly induced AGP mRNA in a concentration-dependent manner, with a >3-fold stimulation at the highest dose, while it had no effect on fibrinogen mRNA (Fig. 6, lower panel). It was notable that C<sub>2</sub>-ceramide affected both CYP2C11 and AGP, but the concentration of C<sub>2</sub>-ceramide that gave the half-maximal change was much lower for CYP2C11 (~3 μM) than for AGP (~15 μM).

Structural Specificity of Ceramide Action—Hannun (16) and Mathias et al. (32) have shown that ceramide treatment of various cells results in activation of a protein phosphatase (ceramide-activated protein phosphatase) that is thought to affect more than one aspect of sphingolipid metabolism, such as the formation of sphingosine, for example. We quantitated a role in mediating the effects of IL-1β on CYP2C11 gene expression in hepatocytes, cells were incubated with C<sub>2</sub>-ceramide or with a bacterial sphingomyelinase to increase cellular ceramides. C<sub>2</sub>-ceramide is used because it is more resistant to ceramidase and more soluble in aqueous solution than is natural ceramide. Sphingomyelinase presumably hydrolyzes SM...
mediate some of the cellular actions of ceramide. Activation of this protein phosphatase by ceramide is selective for the D-erythro-stereoisomer and also requires the presence of the 4,5-trans-double bond on the alkyl chain (16). In contrast, Kolesnick and co-workers found that ceramide activates a protein kinase activity (17), and this activation has less structural specificity (33). Therefore, we tested whether D-erythro-C2-dihydroceramide (lacking the double bond) could suppress CYP2C11 and induce AGP expression. C2-ceramide and C2-dihydroceramide had similar potencies in suppression of CYP2C11, although the maximum effect produced by C2-dihydroceramide appears to be slightly less than that of C2-ceramide (Fig. 7, upper panel). In contrast, C2-dihydroceramide failed to induce AGP mRNA in this experiment. In some experiments (data not shown), a small effect of C2-dihydroceramide on AGP was seen, but not of the magnitude of the C2-ceramide effect. Therefore, it is possible that these two genes are regulated by ceramide via different pathways. It is also possible, however, that short-chain analogs of ceramide affect the levels of endogenous ceramides. Analyses of the amounts of endogenous ceramides in the hepatocytes revealed that 30 μM C2-dihydroceramide increased the endogenous ceramides by 2.1 ± 0.1-fold after 4 h of incubation. Therefore, the suppression of CYP2C11 by C2-dihydroceramide may be indirect.

Ceramide Acts after the IL-1 Receptor—The above data are consistent with the hypothesis that ceramide or a related sphingoid molecule may mediate specifically the action of IL-1 on rat hepatocytes. The site of action is not known; however, it appears to be distal to IL-1 receptor activation because an IL-1 receptor antagonist protein that blocks the effects of IL-1 on CYP2C11 in hepatocytes (15) did not prevent C2-ceramide from suppressing CYP2C11 (i.e. the suppression by ceramide was 59.1 ± 5.5 versus 59.8 ± 7.6% with and without the antagonist, respectively).

**DISCUSSION**

This study provides the first evidence that sphingolipids may be involved in the regulation of hepatic P450 mRNA by cytokines and also suggests a role for sphingolipids in the induction of acute-phase protein gene expression. The induction of SM turnover and ceramide accumulation by IL-1β implies that ceramides mediate the action of this cytokine (as has been seen in other systems), and this was supported by the ability of C2-ceramide to effect the inflammatory response of two genes known to be regulated by IL-1, CYP2C11 and AGP, but not the expression of another acute-phase gene, fibrinogen, which is specifically regulated by interleukin-6. Furthermore, an exog-
enously added sphingomyelinase also mimicked the action of IL-1β in suppression of CYP2C11 expression.

The finding that ceramide can mimic these effects of IL-1β will allow experiments to determine if the protein kinase(s) and phosphoprotein phosphatase(s) that have been proposed as the target of ceramides in other systems are involved in signal transduction from IL-1β and related cytokines in hepatocytes. IL-1 regulation of acute-phase genes, including AGP, involves the participation of at least two types of cis-acting elements on responsive genes that bind transcription factors of the NF-κB and cAMP response element-binding protein (C/EBP) families. Ceramide has been reported to mediate the activation of NF-κB by TNF-α in HL-60 cells and to activate proteolytic degradation of IκB in lysates of monocytic cells. However, other workers have found no activation of NF-κB in HL-60 cells or Jurkat T cells. It remains to be seen whether the ceramide pathway is coupled to CYP2C11 and/or AGP gene regulation via NF-κB in our system. However, three observations indicate that the signaling pathways for regulation of the P450 and type I acute-phase genes may diverge at a point after ceramide formation. (i) The genes are affected in an inverse manner by cytokines and ceramide; (ii) ceramide is more potent in CYP2C11 down-regulation than in AGP induction; and (iii) C2-dihydroceramide suppresses CYP2C11 expression similarly to C2-ceramide, but C2-ceramide is more effective in AGP induction than is dihydroceramide.

The last point is consistent with the participation of ceramide-activated protein phosphatase in AGP induction, but suggests that a different cellular target may be involved in the sphingolipid-mediated down-regulation of P450. One possibility is the previously described ceramide-sensitive kinase, which is generally more promiscuous than ceramide-activated protein phosphatase with respect to the sphingoid molecules that activate it. However, it should be noted that the lack of a differential response to exogenous C2-ceramides and C2-dihydroceramides in whole cells does not rule out the participation of ceramide-activated protein phosphatase in the signaling pathway because we have shown that addition of C2-dihydroceramide can increase cellular levels of endogenous free ceramides.

It is also intriguing that the concentration dependence of the increase in endogenous ceramide by IL-1β (Fig. 3) is similar to that for AGP induction, but less similar to that for CYP2C11 suppression (15), whereas SM turnover is induced by the low concentrations of IL-1β that suppress CYP2C11. These observations suggest that additional sphingolipid metabolites (and possibly other sources of ceramide) may be involved.

Hepatocytes may prove useful in biochemical studies of sphingolipid cycles. It is not yet known with certainty, for example, whether there are larger numbers of sphingolipid hydrolases that participate in signal transduction, if the enzymes are located in the plasma membrane and/or other cellular compartments, or how these systems are regulated. In Jurkat cells, activation of an acidic sphingomyelinase has been shown to be induced subsequent to TNF-α stimulation (43); in HL-60 cells, cytosol is considered to be the source of the cytochrome-mediated sphingomyelinase activity (44). However, in liver, the majority of the SM is in the plasma membranes, where a neutral sphingomyelinase activity has been identified and characterized (45, 46). It has been suggested that the sphingomyelinase is downstream from activation of phospholipase A2 (47). The relative ease with which highly purified plasma membranes may be isolated from liver (and even membrane subdomains) should provide a model to help clarify some of these questions.

The liver is a primary target for cytokines during the host defense reaction to injury and inflammation. Among the numerous systems affected is the P450 gene superfamily, which plays a critical role in the oxidative metabolism of drugs, toxins, and steroids. Decreases in multiple P450 enzymes during immunostimulatory conditions can have important clinical consequences. Similar to the induction of acute-phase protein synthesis and secretion, the induction of the homeostasis of inflammation may be important in the homeostasis of inflammation. Therefore, our discovery of a sphingolipid signaling pathway for IL-1 in rat liver may have implications not only for altered drug responses caused by the down-regulation of P450 under these conditions, but also for the development of the systemic response to infection and inflammation.

These findings may have broader implications because CYP2C11 expression is also down-regulated by glucocorticoids in vivo and by growth hormone both in vivo and in vitro. The possible involvement of sphingolipid mediators in these effects should be evaluated because deoxymethasone has been reported to stimulate SM hydrolysis in fibroblasts.

Acknowledgments—We thank Drs. David Menaldino and Dennis Diotta for preparing the C2-ceramide, o-erythro-sphingosine, and o-erythro-sphinganine, and Kirsten Tenney for expert technical assistance.

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While this manuscript was in preparation, Santana et al. (51) published data showing that the decrease in aromatase activity (catalyzed by P450 aromatase, CYP19) caused by treatment of rat granulosa cells with TNF is mediated by ceramide. Whether this reflects a change in CYP19 gene expression remains to be determined, but the study provides further support for the involvement of sphingolipid signaling in P450 regulation.
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J. Biol. Chem. 1995, 270:25233-25238.
doi: 10.1074/jbc.270.42.25233

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