TRANSIENT TRANSCRIPTIONAL REGULATION OF RAT HEPATIC ARYL SULFOTRANSFERASE (SULT1A1) GENE EXPRESSION BY GLUCOCORTICOIDS

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ABSTRACT:
The 5'-flanking region [1892 base pairs (bp)] of the rat aryl sulfotransferase (SULT1A1) gene was cloned and the cis-acting sequences involved in glucocorticoid-inducible SULT1A1 gene transcription were characterized. SULT1A1 promoter and 5'-flanking sequences lacked a TATA box and a consensus glucocorticoid response element. Using a 5'-rapid amplification of cDNA ends approach, four SULT1A1 transcription start sites were identified. Transient transfection studies with SULT1A1-5'-luciferase reporter constructs in primary cultured rat hepatocytes revealed that treatment with the potent glucocorticoid dexamethasone (10^-10^-5 M) produced concentration-dependent increases in luciferase activity in constructs containing from 1892 to 119 bp of the SULT1A1 5'-flanking region. Relative to the most upstream SULT1A1 transcription start site, the minimal cis-acting sequences that were required for dexamethasone-inducible SULT1A1 expression were located between 84 and 69 bp. Treatment of transfectants with a panel of steroids, including dexamethasone, triamcinolone acetonide, hydrocortisone, dihydrotestosterone, 17β-estradiol, and pregnenolone-16α-carbonitile, revealed that steroid-inducible SULT1A1 gene expression was specific for glucocorticoid-class steroids. Concentration-response studies, coupled with a robust inhibition of glucocorticoid-inducible SULT1A1-5'-luciferase reporter activity by antiglucocorticoid/antiprogestin RU-486, recapitulated earlier findings on endogenous SULT1A1 gene expression and implicated a major role for the glucocorticoid receptor transcription factor in the regulation of glucocorticoid-inducible SULT1A1 gene expression.

The aryl sulfotransferase (SULT)1 enzyme family plays a major role in xenobiotic metabolism. Sulfate conjugation generally results in the formation of a polar end product that is amenable to excretion and elimination from the body (detoxication). In rat liver, the presence of four classes of distinct SULT1 isoforms, including aryl/minoxidil sulfotransferase (SULT1A1) (Falany and Kerl, 1990; Hirshey et al., 1992), a thyroid hormone/dopa-tyrosine sulfotransferase (SULT1B1) (Yamazoe et al., 1994; Sakakibara et al., 1995; Araki et al., 1997), two estrogen sulfotransferases (SULT1E) (Demyan et al., 1992; Falany et al., 1995; Rikke and Roy, 1996), and a SULT1 enzyme that catalyzes the bioactivation of N-hydroxy-2-acetylamino fluorene carcinogen (SULT1C1) (Nagata et al., 1993; Yamazoe et al., 1994), underscores the broad range of substrate specificities that stamp this important subfamily of conjugating enzymes.

SULT1A1 readily catalyzes the sulfation of simple phenols such as 1-naphthol and p-nitrophenol and also sulfates estrogens at micromolar concentrations (Falany et al., 1994). Of all the SULT1 enzymes, SULT1A1 is particularly active in drug metabolism. SULT1A1 is widely expressed in both hepatic and in metabolically active extrahepatic tissues (Dunn and Klaassen, 1998; Dooley et al., 2000) and catalyzes the sulfation of a number of common pharmacies such as acetaminophen and minoxidil (Nagata et al., 1993; Yamazoe et al., 1994). In most cases, sulfation by SULT1A1 is a detoxication reaction for labile reactive intermediates (Larrey et al., 1986). However, the sulfation of minoxidil by SULT1A1 is required for prodrug activation, and represents an essential step in the conversion of minoxidil to its physiologically active form (McCall et al., 1983; Meisher et al., 1993). Because alterations in SULT1A1 expression may have important implications for drug metabolism and for hepatocellular toxicity during drug therapy, it is critical to gain a clear understanding of the molecular regulation of the SULT1A1 gene.

SULT1A1 is one of the “male dominant” SULT1 enzymes that undergoes age-related changes in gene expression and is more abundantly expressed in male relative to female rat liver (Liu and Klaassen, 1996a). The basis for age- and gender-dependent changes in rat hepatic SULT1A1 gene expression is not yet known, but may involve pituitary factors other than growth hormone (Liu and Klaassen, 1996a). Other conditions that, like hypophysectomy, have pleiotropic effects on gene expression, also affect rat hepatic SULT1A1 gene expression. For example, the administration of CYP2B-inducing doses of phenobarbital to rats significantly suppressed rat hepatic SULT1A1 mRNA expression (Runge-Morris et al., 1998). Similarly, treatment of primary cultured rat hepatocytes with CYP1A1-inducing
concentrations of the “environmental hormone” 2,3,7,8-tetrachlorodibenzo-p-dioxin produced substantial decreases in SULT1A1 expression (Runge-Morris, 1998).

Glucocorticoids have been strongly implicated in the transcriptional regulation of SULT1A1 gene expression, both in hepatic and extrahepatic tissues. For example, the treatment of cultured bovine tracheobronchial epithelial cells with hydrocortisone produced concentration-dependent increases in SULT1A1 enzyme activity (Beckmann et al., 1994) and mRNA levels (Schauss et al., 1995). Similarly, the administration of pharmacological doses of the potent glucocorticoid DEX to rats increased SULT1A1 mRNA levels in both male and female rat liver (Liu and Klaassen, 1996b). Additional studies, which demonstrated glucocorticoid-mediated induction of SULT1A1 expression in primary cultured rat hepatocytes, provided sound evidence that glucocorticoids regulate SULT1A1 gene expression directly at the level of the hepatocyte and suggested a proximal role for the glucocorticoid receptor transcription factor in the transcriptional control of SULT1A1 (Runge-Morris et al., 1996). The purpose of the present analysis was to probe the molecular mechanisms that control glucocorticoid-inducible SULT1A1 gene transcription. For these studies, the 5′-flanking region of the rat SULT1A1 gene was cloned and cis-acting genomic sequences that mediate glucocorticoid-sensitive SULT1A1 gene expression were evaluated in transient transfection studies conducted in primary cultured rat hepatocytes.

### Experimental Procedures

#### Materials.
Steroids (DEX, triamcinolone acetonide, hydrocortisone, dibydrotestosterone, β-estradiol, and progrenenolone 16a-carbonitrile) were purchased from Sigma Chemical Co. (St. Louis, MO). Custom-synthesized oligonucleotides were purchased from Integrated DNA Technologies, Inc. (Coralville, IA). The Rat GenomeWalker kit was obtained from CLONTECH (Palo Alto, CA). The FirstChoice RLM-RACE kit was obtained from Ambion (Austin, TX). All other supplies and reagents were obtained from the sources previously described (Runge-Morris et al., 1996; Kocarek et al., 1998).

#### Cloning of 5′-Flanking Region of SULT1A1 Gene.
An ~1.9-kb fragment of the 5′-flanking region of the rat SULT1A1 gene was isolated using the PCR-based gene walking method (Rat GenomeWalker kit). In a PerkinElmer Gene Amp PCR system 9700, two nested PCR reactions were performed according to the manufacturer’s instructions with minor modifications. Five genomic GenomeWalker libraries were used as templates, and two primers API and AP2, corresponding to the adapter sequences, were provided in the kit. Two gene-specific primers (GSP1 and GSP2) were selected based on the published rat aryl sulfotransferase IV (SULT1A1) structural gene sequence (Khan et al., 1993; GenBank accession no. L16241). GSP1 (5′-CACCTGATC-CTGGGCTCCTGTA-3′, +63 to +83) was paired with API and used for primary PCR, while GSP2 (5′-CTTCCCAGGTGCTAGTGATA-3′, +37 to +56) and AP2 were used for secondary PCR. The annealing temperature was 70°C for primary PCR and 72°C for secondary PCR. An ~1.9-kb PCR product was obtained using the DraI library, cloned into the pGEM-T Easy vector (Promega, Madison, WI) and sequenced completely. The insert was then transferred into pBluescript SK+ (Stratagene, La Jolla, CA) at the XhoI site, and finally ligated into the firefly luciferase reporter plasmid pGL3-Basic (Promega) at the SacI and XhoI sites.

#### Determination of SULT1A1 Transcription Start Site.
The transcription start site of the SULT1A1 gene was identified using the 5′-RACE method and the First Choice RLM-RACE kit (Ambion), according to the manufacturer’s instructions. Brieﬂy, following treatment of total RNA from mature (~55 days) male Sprague-Dawley rat liver with calf intestinal alkaline phosphatase and tobacco acid pyrophosphatase, an RNA adapter was ligated to the 5′ ends of the decapped mRNAs. The complementary DNA strands were then generated by reverse transcription of the adapter-containing RNAs, and fragments containing the 5′ end of SULT1A1 mRNA were amplified by two consecutive PCR reactions. The first amplification was performed using the outer RNA adaptor primer provided with the kit and an inner SULT1A1 gene-specific primer (5′-GGAACCCCGTGAATTTGAACTCA-3′). The inner RNA adapter primer was ligated with the inner SULT1A1 gene-specific primer (5′-CGGGGCACACCTTCTGACTGACCACCTGAT-3′) used for secondary PCR. The annealing temperature for both PCR reactions was 60°C. The PCR products were subcloned into the pGEM-T Easy vector, and the inserts contained in seven independent clones were sequenced.

#### Preparation of SULT1A1-5′-Luciferase Reporter Constructs.
A fragment of the SULT1A1 5′-flanking region from −1892 to +56 was inserted into the promoter-less luciferase reporter plasmid pGL3-Basic as described above. Reporter plasmids containing nested deletions of the SULT1A1 5′-flanking region were generated either by unique restriction enzyme digestions or by PCR reactions. Specifically, constructs −745 and −449 were generated by restriction enzyme digestion with KpnI and XhoI, respectively, followed by religation with T4 DNA ligase. Constructs −334, −230, −119, −84, and −69 were generated by PCR. Using a −1892- to +56-bp fragment of the SULT1A1 gene as template, a set of 5′ primers were designed to incorporate a SacI site for subcloning (5′-GAGCTCAAGGTGTTAATGCTGTC-3′ for construct −320, 5′-GAGCTCTAACAACTCCGGCCACACT-3′ for construct −119, 5′-GAGCTCTGTTTCTTGAGGACACAGCCA-3′ for construct −84, 5′-GAGCTCGGCCAGTCTACACTGTTT-3′ for construct −69). The 3′ primers were designed with a XhoI site that was identical for all of the constructs (5′-CTCAGTCTCCGGTGTCAGTATA-3′). These amplified fragments were initially ligated into the pGEM-T Easy vector and then cloned into the SacI and XhoI sites of pGL3-Basic. The sequences of all constructs were verified by sequence analysis (Center for Molecular Medicine and Genetics DNA Sequencing Facility, Wayne State University, Detroit, MI).

#### Transient Transfections and Luciferase Assays.
The procedures for the isolation, culture, and transient transfection of rat hepatocytes have been described previously (Kocarek and Reddy, 1996; Runge-Morris et al., 1999). Briefly, hepatocytes isolated from mature male Sprague-Dawley rats (220–300 g; Harlan, Indianapolis, IN) were plated onto 12-well Nitrogen-coated plates (3 × 10⁵ hepatocytes/well) in Williams’ medium E supplemented with 0.25 U/ml insulin, 100 U/ml penicillin, 100 μg/ml streptomycin, and 10⁻⁷ M triamcinolone acetonide. After ~21 h, the hepatocytes in each well were transfected with 0.8 μg of reporter plasmid and cotransfected with 0.08 μg of the pRL-TK plasmid (Promega) in 0.6 ml of Opti-MEM containing 5.5 μg of Lipofectin reagent (Life Technologies, Inc., Grand Island, NY). The pRL-TK plasmid, which expresses Renilla luciferase, was used to normalize for variations in transfection efficiency among samples. After 5 h of incubation, culture medium was replaced with standard Williams medium E without triamcinolone acetonide, and hepatocytes were overlaid with 100 μg/ml of Matrigel (Collaborative Research Products, Bedford, MA) pipetted into the medium. At 48 h after plating, hepatocytes were treated with either steroid or 0.1% DMSO and lysed for luciferase activity measurement. The Dual Luciferase Reporter Assay system (Promega) and a Dynex model MLX luminometer were used for luciferase assays. Experimental data were analyzed by the Student’s t-test using a two-tailed distribution and two-sample equal variance (GraphPad Software, San Diego, CA).

#### Results

Cloning and Sequence Analysis of 5′-Flanking Region of SULT1A1 Gene. Although the coding sequence of the rat SULT1A1 gene (trivial name aryl sulfotransferase IV) was previously reported (Khan et al., 1993), the sequence of the SULT1A1 5′-flanking region and the location of the transcription start site of this gene have not been established. To explore the molecular mechanism of glucocorticoid-inducible SULT1A1 gene expression, an ~1.9-kb fragment of the rat SULT1A1 gene was amplified by anchored PCR using oligonucleotides corresponding to sequences located near the 5′ end of the published SULT1A1 structural gene sequence as gene-specific primers (Fig. 1). The fragment was subcloned into the pGEM-T Easy vector, and sequence analysis confirmed that 27 bp of the 3′ end of the PCR fragment were identical to the published 5′ end of the SULT1A1 structural gene (Khan et al., 1993). A computer-based search of the cloned SULT1A1 gene 5′-flanking region (TRANSFAC (http://transfac.gbf.de/TRANSFAC/index.html), Downloaded from dmd.aspetjournals.org at ASPET Journals on June 22, 2017
MatInspector V2.2, and PatSearch V1.1 (Wingender et al., 2000) failed to identify a consensus binding site for the glucocorticoid receptor (i.e., GRE). The consensus GRE (GGTACA NNN TGT(T/C)CT, TRANSFAC matrix table) is a variation of the palindromic repeat of AGAACA, in which the two halves are separated by 3 bp (i.e., AGAACA NNN TGTTCT). This motif is also known as an IR3 for inverted repeat separated by 3 bp. We noted that, located slightly upstream of the SULT1A1 transcription start site, at bp 275 to 270 (see below for an explanation of this numbering scheme), the perfect AGAACA hexanucleotide sequence was present (Fig. 1). Beginning 4-bp downstream from this half-site was a sequence (AGTCCT) that differed from the GRE TGT(T/C)CT consensus sequence by only one base (underlined), suggesting the possible existence of an IR3 steroid receptor motif (Fig. 1). In addition, the sequence TGTTTC, which also resembled a GRE half-site, was located just upstream of the AGAACA half-site, suggesting the possible presence of an ER3 (everted repeat) motif (Fig. 1). We also noted that, as has been frequently reported for sulfotransferase genes (Her et al., 1995, 1998), the SULT1A1 gene did not contain a TATA box.

**Determination of SULT1A1 Transcription Start Site.** The transcription start site of the rat SULT1A1 gene was determined using a 5′-RACE approach. Seven independent clones were sequenced and aligned to the SULT1A1 gene sequence. The results suggested the existence of multiple transcription start sites within a 30-bp region (Fig. 1A). We have assigned the 5′-most site (30 bp upstream from the published 5′ end of the rat structural gene) as bp 111 and all positions in the 5′-flanking region have been indexed relative to this reference transcription start site.

**Functional Characterization of 5′-Flanking Region of SULT1A1 Gene.** To locate the region of the SULT1A1 gene that is essential for conferring glucocorticoid-inducible promoter activity, a series of deletion constructs of the 5′-flanking region were prepared and subcloned into a promoter-less luciferase reporter plasmid (Fig. 1B). Primary cultured rat hepatocytes were transiently transfected with each of these luciferase reporter constructs and then treated for 24 h with the potent glucocorticoid DEX (10^{-7} M). As shown in Fig. 2, luciferase activity was markedly increased in hepatocyte cultures that were transfected with each of the SULT1A1 constructs containing from 119 to 1892 bp of 5′-flanking sequence. Relative to the benchmark −1892 construct, the basal expression and magnitude of glucocorticoid-inducible luciferase activity were diminished in transfec-tants containing some of the more truncated constructs, such as −119 and −69 (Fig. 2). These results suggest that there may be cis-acting regulatory elements located between −1892 and −119 that are nec-

![Fig. 1. Cloning of the 5′-flanking region of the SULT1A1 gene.](image)

A, nucleotide sequence of the 5′-flanking region of the rat SULT1A1 gene. * indicates the transcription start sites determined by 5′-RACE analysis. The 5′-most transcription start site is designated +1. The first base of the published gene sequence is denoted by an asterisk. Sequences comprising the imperfect inverted and everted repeats are underlined. B, schematic diagram of SULT1A1 5′-luciferase deletion constructs that were used in transient transfections. In each construct, the arrow indicates the location of the transcription start site.

![Fig. 2. Deletion analysis of the SULT1A1 promoter activity.](image)

Each of the series of luciferase reporter constructs containing 1892, 745, 449, 320, 119, or 69 bp of the SULT1A1 5′ sequence was transiently transfected into primary cultured rat hepatocytes. The 3′ ends for these constructs are +46 (for constructs −1892, −745, and −449) or +54 (for the rest of the constructs). Transfected hepatocytes were treated for 24 h with 10^{-7} M DEX in DMSO or 0.1% DMSO alone as control. Promoter activity is expressed as normalized luciferase activity (mean ± S.D., n = 3/treatment group). This figure is a composite from three experiments. Similar results were obtained in two to three independent experiments. * significant differences in luciferase activities of DEX-treated group relative to DMSO-treated group (p < 0.05).
Primary cultured rat hepatocytes, transfected with SULT1A1 construct −1892 or −119, were treated for 24 h with DEX at concentrations ranging from $10^{-8}$ to $10^{-6}$ M (concentrations are shown as log molar) and harvested for luciferase activity determination. Results are expressed as normalized luciferase activity (mean ± S.D., n = 3/treatment group). This figure depicts data from a representative study. Similar observations were obtained in two to three independent experiments. * indicates significant differences in luciferase activities of DEX treatment groups relative to DMSO control (p < 0.05).

In our previous studies, we indicated a role for the glucocorticoid receptor in SULT1A1 gene regulation by demonstrating that treatment of hepatocytes with the anti-glucocorticoid RU-486 inhibited DEX-stimulated induction of endogenous SULT1A1 mRNA expression (Runge-Morris et al., 1996). In the current study, we examined the effect of RU-486 on DEX-inducible luciferase activity in primary cultured rat hepatocytes that were transiently transfected with three different SULT1A1-5′:luciferase reporter constructs (−1892, −320, or −119). As shown in Fig. 5, cotreatment of transfecants with $10^{-6}$

**Fig. 3.** Concentration-dependent effects of dexamethasone treatment on luciferase activity in primary cultured rat hepatocytes transiently transfected with SULT1A1-5′:luciferase reporter constructs.

**Fig. 4.** Effects of steroid treatments on luciferase activity in primary cultured rat hepatocytes transiently transfected with SULT1A1-5′:luciferase reporter constructs.

Primary rat hepatocyte cultures, transfected with SULT1A1 construct −1892 or −119, were treated for 24 h with 0.1% DMSO (control) or with one of the following steroids: 1) DEX ($10^{-6}$ M), 2) triamcinolone acetonide (TA,$10^{-6}$ M), 3) hydrocortisone (HC, $10^{-3}$ M), 4) dihydrotestosterone (DHT, $10^{-6}$ M), 5) β-estradiol ($E_2$, $10^{-6}$ M), and 6) pregnenolone 16α-carbonitrile (PCN, $10^{-6}$ M). Following treatment, hepatocytes were harvested for luciferase activity determination. Results are expressed as normalized luciferase activity (mean ± S.D., n = 3/treatment group). This figure depicts data from a representative study. Similar observations were obtained in two independent experiments. * indicates significant differences in luciferase activities of steroid treatment groups relative to DMSO control (p < 0.05).
M RU-486 effectively inhibited DEX (10^{-7} M)-mediated increases in luciferase activity.

Because our results suggested that DEX-inducible SULT1A1 expression was mediated through a classical glucocorticoid receptor-dependent mechanism, and that the cis-acting elements supporting this response was contained within the first 119 bp upstream of the SULT1A1 transcription start site, we performed transfection analysis with an additional SULT1A1 5'-deletion construct to investigate the possibility that the previously noted AGAACA-containing motif might function as a GRE. Our results indicated that a −84 SULT1A1 reporter construct (containing the putative IR3 and ER3 motifs) retained glucocorticoid responsiveness, while the −69 construct (lacking the motifs) was devoid of glucocorticoid-inducible luciferase activity (Fig. 6).

Discussion

The genomic structure of the rat SULT1A1 gene coding region was previously published and found to contain eight exons and seven intervening introns (Khan et al., 1993). In the present study, we found that the promoter region of the rat SULT1A1 does not contain a TATA box. This is consistent with previous observations on sulfotransferase gene structure. A canonical TATA box has been described for relatively few of the cloned sulfotransferase genes (Her et al., 1995, 1998). Our results, which indicate several alternative transcription start sites in SULT1A1 promoter region, are also typical of other genes with TATA-less promoters (Smale, 1997). They also reconcile with GenBank information, which indicated that the 5'-untranslated region of the mouse mSTp1 aryl sulfotransferase (SULT1A1) cDNA (GenBank accession no. L02331) (Kong et al., 1993) extended farther upstream than did the corresponding region of the rat SULT1A1 gene.

Rat “phenol sulfotransferase” (SULT1A1) enzyme activity has long been observed to be positively regulated by glucocorticoids (Maus et al., 1982). In corroboration of this perception, in vivo studies in rats, using either SULT1A class-specific cDNA probes or SULT1A1 isoform-specific probes, confirm that treatment with DEX and other glucocorticoids induces SULT1A1 enzyme activity and mRNA expression in rat liver (Runge-Morris et al., 1996; Liu and Klaiassen, 1996b). Emerging evidence indicates that the induction of SULT1A1 gene expression by glucocorticoids is biologically relevant. We found that the administration of even moderate doses of triamcinolone acetonide to rats in conjunction with minoxidil treatment, induced hepatic SULT1A1 gene expression and significantly amplified the hypotensive effects of minoxidil (Duanmu et al., 2000), a drug that is dependent upon SULT1A1 activity for produg bioactivation (McCall et al., 1983; Meisher et al., 1993).

Foundation experiments in primary cultured rat hepatocytes have set the stage for demonstration of the glucocorticoid receptor transcription factor as a master regulator in the control of glucocorticoid-inducible SULT1A1 gene expression (Runge-Morris et al., 1996). Our previous work showed that incubation of primary cultured rat hepatocytes with concentrations of glucocorticoid that would be expected to bind to the glucocorticoid receptor substantially induced SULT1A1 mRNA expression (Runge-Morris et al., 1996). In addition, cotreatment with the antgliocorticoid/antiprogestin RU-486 inhibited DEX-inducible SULT1A1 expression in a manner that was consistent with glucocorticoid-inducible tyrosine amino transferase gene expression (Runge-Morris et al., 1996); a gene that is known to be regulated by the classical glucocorticoid receptor transcription factor (Shinomiya et al., 1984).

The results of the present series of transient transfection studies provide the first direct evidence for the transcriptional regulation of SULT1A1 by glucocorticoids and recapitulate our previous findings on endogenous SULT1A1 gene regulation (Runge-Morris et al., 1996). As illustrated in Fig. 2, luciferase activity in reporter constructs that contained fragments of SULT1A1 5'-flanking sequences indicated that a maximal induction of luciferase activity occurred with DEX concentrations (10^{-7}M) that would be expected to saturate the glucocorticoid receptor. Deletional analyses established that the SULT1A1 5'-flanking sequences located in proximity to the core promoter contain sufficient glucocorticoid-sensitive sequences to support the induction of gene transcription (Figs. 2 and 6). More distal
sequences appear to contain information that regulates the basal level of SULT1A1 gene transcription and influences the magnitude of DEX-inducible expression. In further support of prior studies on endogenous SULT1A1 gene regulation in rat hepatocytes (Runge-Morris et al., 1996), steroid induction of SULT1A1 transcriptional activity appeared to be specific to steroids of the glucocorticoid class. In addition, our results showed that DEX induction of luciferase activity in transfectants containing any of three of the glucocorticoid-sensitive SULT1A1-5’-flanking constructs tested (~1892, ~320, or ~119) was effectively inhibited by cotreatment with anti-glucoorticoid/anti-progesterin RU-486 (Fig. 5).

The transient transfection data presented in this study provide functional evidence in support of a classical glucocorticoid response element located within ~84 bp of the SULT1A1 5’-flanking sequence just proximal to the core promoter. As shown in Fig. 6, the deletion or disruption of either the IR3 or ER3 putative glucocorticoid response sequence located in this gene domain, effectively ablated glucocorticoid inducibility in SULT1A1 reporter constructs. Comparison of the two candidate glucocorticoid response elements in SULT1A1 against available profiles of consensus and variant glucocorticoid response elements indicated that the more proximal IR3 element (i.e., AGAACA GCC AGTCCT) had the structural features that are most consistent with a classical GRE. The present investigation in primary cultured rat hepatocytes provides convincing evidence in support of a primary role for the glucocorticoid receptor transcription factor in the regulation of glucocorticoid-inducible SULT1A1 gene expression. Future work will focus on characterizing the binding and functional interactions between the glucocorticoid transcription factor and the putative SULT1A1 glucocorticoid response element(s) that have been identified in this study.

References


