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Negative Regulation of Angiotensinogen Gene Expression by Glucocorticoids in Fetal Sheep Liver

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ABSTRACT. The effect of glucocorticoids in regulating liver angiotensinogen gene expression was studied in chronically instrumented fetal sheep during the last trimester of gestation and was compared with the expression of other hepatic genes (prothrombin, factor IX, and albumin). Four sets of twins were studied at 118 d of gestation, and three sets were studied at 138 d of gestation (term, 145 d). One of each set of twins was infused intraperitoneally with cortisol (5 $\mu mol \cdot mL^{-1} \cdot h^{-1}$) for 48 h, whereas the other twin received the same volume (1 mL/h) of normal saline. Plasma cortisol concentration increased from 0.32 ± 0.12 and 2.7 ± 0.12 nmol/100 mL to 44.2 ± 20.0 and 37.7 ± 8.2 nmol/100 mL in 118- and 138-d fetuses, respectively, during the cortisol infusion; no changes were observed in fetuses infused with saline alone. At the end of the infusion period, the animals were anesthetized, the fetal liver was removed, and total cellular RNA was isolated and probed for angiotensinogen, prothrombin, factor IX, and albumin. The results demonstrated that cortisol infusion decreased angiotensinogen mRNA by 61% in 138-d fetuses and albumin mRNA expression by 2.4-fold in 118-d fetuses and by 3.4-fold in 138-d fetuses. On the other hand, cortisol had no effect on fetal factor IX gene expression but increased prothrombin mRNA levels by 65% in 118-d fetuses and 62% in 138-d fetuses. Taken together, our results suggest that, during fetal life, angiotensinogen gene expression is negatively regulated by glucocorticoids. This effect is not universal because cortisol increases fetal prothrombin gene expression. (*Pediatr Res* 30: 256–260, 1991)

Abbreviations

SSPE, sodium chloride, sodium phosphate, EDTA

Angiotensinogen, the precursor of angiotensin II is primarily synthesized and secreted by the liver in the adult (1). It has also been shown that all of the components of the renin-angiotensin system, including renin, angiotensinogen, and angiotensin I and II, are present in the circulation of fetal animals (2, 3). Recently, angiotensinogen mRNA has been detected in fetal rats (1, 4) and in fetal sheep (5). Liver angiotensinogen gene expression increases during the last trimester of gestation but has been shown to decrease in the 1st wk after birth (5).

Studies in mature rats have demonstrated that multiple factors, including glucocorticoids, can modulate liver angiotensinogen gene expression (6–9). Less is known about regulation of angiotensinogen mRNA levels in the fetus, but it has been suggested that glucocorticoid hormones play an important role in organ maturation and enzyme induction during fetal life (10, 11). *In vitro* studies with cultured rat fetal hepatocytes (12) have shown that addition of dexamethasone to culture media causes fetal hepatocytes to express adult levels of mRNA for albumin, tyrosine aminotransferase, and transferrin while decreasing the level of α-fetoprotein mRNA. Information about glucocorticoid effects on gene expression in fetal liver *in vivo* is more limited and differs from results obtained *in vitro*. Johnson *et al.* (13) have shown that tyrosine aminotransferase mRNA is not affected by glucocorticoids in near-term fetal rats but that hormone responsiveness develops postnatally.

In an effort to determine if glucocorticoids play a role in the expression of liver angiotensinogen gene during fetal life, we studied the effect of cortisol on the hepatic expression of angiotensinogen gene in chronically instrumented fetal sheep. We also compared the effect of cortisol on angiotensinogen gene expression with its effect on the expression of other genes (prothrombin, factor IX, and albumin) that are only expressed in mature hepatocytes. Finally, we tested the hypothesis that the regulation of gene expression by cortisol in fetal liver is selective and varies at different stages of development.

MATERIALS AND METHODS

Animals and surgical preparation. Seven pregnant mixed-breed sheep carrying twin fetuses were obtained from a local supplier. The gestational ages of the fetuses were known on the basis of induced ovulation (14). Anesthesia and surgical procedures used were performed as previously described (15). Catheters were placed in the femoral veins and in the peritoneal cavity of each twin. The animals were allowed 5 d to recover from the surgery.

Experimental protocol. After recovering from the surgery, one of each set of twins was infused intraperitoneally with 5 μmol/mL of cortisol (mol wt, 404) for exactly 48 h at a rate of 5 μmol/h as previously described (16). The other twin (control) was infused with the same volume of normal saline. The infusions were carried out with constant infusion pumps (Cormed, Inc., Middleport, NY) secured on the back of the ewe in pockets of a specially designed jacket that allowed the animals to move freely during the infusion.

At the end of the infusion period, ewes were anesthetized with a mixture of 1.0% halothane, 33% oxygen, and 66% nitrous oxide administered by endotracheal tube. The uterus was exter-

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iorized to gain access to the fetuses. The entire fetal liver was removed and snap-frozen in liquid nitrogen, homogenized in liquid nitrogen, and stored at −70°C. All procedures were approved by the University of Iowa Committee for the Care and Use of Animals.

Isolation of RNA and preparation of probes. Total cellular RNA was isolated by a modified isothiocyanate-CsCl method as previously described (5). RNA was quantitated spectrophotometrically by absorbance at 260 nm, and purity was monitored by A260/A280 ratios as well as by agarose gel electrophoresis. RNA samples were stored as an ethanol precipitate at −70°C until further analysis.

All experiments were performed with RNA probes complementary to the sequences of interest. A clone containing full-length rat angiotensinogen cDNA (pRANG 6) (17) was obtained from K. R. Lynch (University of Virginia, Charlottesville, VA). This cDNA yields the antisense RNA when transcribed from the T7 promoter after linearizing with *Eco*RI.

A full-length human serum albumin cDNA was obtained from J. Murray (University of Iowa, Iowa City, IA). This cDNA, which was subcloned into pBluescript II SK- (Stratagene, La Jolla, CA), yields the antisense RNA when transcribed from the T7 promoter after linearizing with *Bam*HI.

A human prothrombin cDNA was obtained from S. J. Friezner-Degen *et al.* (18). This cDNA was subcloned into pSP18 (Promega Biotec, Madison, WI) as described by Kisker *et al.* (19). Transcription of this plasmid from the SP6 promoter yields antisense RNA after linearizing with *Eco*RI.

A full-length human factor IX was obtained from S. P. Bajaj (20). The factor IX fragment was removed by digestion with *Pst*I and subcloned into pIB130 (International Biotechnologies, Inc., New Haven, CT) at the *Pst*I site. After linearization with *Hin*dIII, transcription from the T7 promoter yields the antisense RNA.

Radiolabeled probes were generated by the method of Melton *et al.* (21) by using [α-^{32}P]uridine triphosphate (Amersham Corp., Arlington Heights, IL).

Northern blot hybridization. Aliquots of 5 μg of RNA as measured by absorbance at 260 nm were fractionated by 1% agarose-formaldehyde gel electrophoresis (22). After electrophoresis, RNA was transferred to Nytran filters (0.45 μm) (Schleicher and Schuell, Inc., Keene, NH). The filters were prehybridized for 1 h at 60°C in a solution of 50% deionized formamide, 5× SSPE, 5× Denhardt's reagent, 1.0% SDS, and 200 μg/mL of denatured fractionated salmon sperm DNA. Hybridization of filters was carried out with fresh prehybridization buffer solution containing 2×10^6 cpm/mL of the appropriate radiolabeled probe. The hybridization reaction was carried out at 60°C for 12–18 h.

Filters were washed according to the manufacturer's specifications. Briefly, this included three low-stringency washes (1× SSPE, 1.0% SDS) at 65°C, a high-stringency wash (0.1× SSPE, 1.0% SDS) at 60°C followed by treatment with RNAse A (10 μg/mL in 2× SSPE) at 37°C for 15 min. The washed filters were exposed to Kodak XAR film at −70°C.

Slot blot hybridization. Aliquots of 5 μg of RNA as measured by absorbance at 260 nm were applied to Nytran filters (Schleicher and Schuell, Inc.) by using a Bio-Dot SF microfiltration apparatus (Bio-Rad Laboratories, Richmond, CA). Before application to filters, the RNA was suspended in 7.5× sodium chloride-sodium citrate and 13.8% formaldehyde solution and heated at 65°C for 15 min. After application, the filter was baked *in vacuo* at 80°C for 1 h. Prehybridization and hybridization of filters and autoradiography were carried out as described above. The autoradiographs were quantitated by using a Soft Laser scanning densitometer (model SL4-2010; Biomed Instruments, Inc., Fullerton, CA).

Analytical procedures. Cortisol levels were measured by RIA (Diagnostic Products Corp., Los Angeles, CA). The level of detection of plasma cortisol by this method is 0.1 μg/dL; therefore, this value was assigned to all samples that had undetectable concentrations of plasma cortisol.

Data analysis. For quantitation of mRNA abundance, all samples were analyzed together on a single slot blot to control for day-to-day variation in hybridization efficiency. Slot blots were done in duplicate. Abundance of the specific mRNA was expressed as densitometry units. Average values for each animal and then for sets of animals in each group were calculated. Messenger RNA levels were compared between treatment groups at each age by using a two sample *t* test (23).

RESULTS

Fetal sheep were studied at two ages during the last trimester of gestation. Four sets of twins were studied at 118 d, which is near the beginning of the 3rd trimester (term, 145 d), and three sets were studied at 138 d of gestation, before the surge in plasma cortisol levels that occurs just before birth (24, 25). Sets of twin fetuses were studied so that a paired control was included in each experiment. The experimental period lasted for 48 h and was begun 5 d after the catheters had been placed in the fetuses. Blood samples were obtained immediately before and after the cortisol infusion period.

At the beginning of the infusion period, plasma cortisol levels were similar for all sets of twins at both ages (Table 1). Cortisol infusion substantially increased plasma cortisol levels in the experimental twin, whereas plasma cortisol in the control twin remained unchanged. Plasma cortisol levels reached in the test twin were similar to cortisol concentrations found in newborn lambs at birth (25).

As shown by Northern blot analysis (Fig. 1*A*), angiotensinogen mRNA was only slightly affected by cortisol treatment. Slot blot analysis (Fig. 1*B*) demonstrated a slight but not statistically significant decrease in angiotensinogen mRNA in cortisol-treated fetuses at 118 d of gestation. On the other hand, angiotensinogen mRNA decreased by 61% ($p < 0.05$) in cortisol-treated twins at 138 d of gestation.

These results were compared with similar analyses performed on other proteins (albumin, prothrombin, and factor IX) produced by differentiated hepatic cells. The effects of cortisol treatment on albumin mRNA were more pronounced than for angiotensinogen mRNA (Fig. 2). Cortisol infusion decreased albumin mRNA expression 2.4-fold at 118 d ($p < 0.05$). At 138 d of gestation, albumin mRNA was decreased 3.4-fold ($p < 0.01$).

In marked contrast, levels of prothrombin mRNA were higher in cortisol-stimulated animals at both 118 and 138 d (Fig. 3). As quantified by slot blot analysis, prothrombin mRNA increased by 65% ($p < 0.025$) in cortisol-stimulated animals at 118 d and by 62% ($p < 0.05$) at 138 d (Fig. 3). To investigate if the increase in prothrombin mRNA in response to cortisol treatment represented a universal response of all vitamin K-dependent coagulation proteins, factor IX mRNA levels were also measured in control and cortisol-treated fetuses. Northern blot analysis for factor IX (Fig. 4) did not demonstrate an increase in factor IX mRNA in cortisol-treated fetuses. Quantitation by slot blot analysis confirmed these findings.

Table 1. *Effect of cortisol infusion on plasma cortisol concentration**

	Plasma cortisol (nmol/100 mL)			
	Cortisol-treated		Saline-treated	
Age	Before	After	Before	After
118 d	0.32 ± 0.12	44.2 ± 20.0†	0.25 ± 0	0.5 ± 0.5
138 d	2.75 ± 0.12	33.7 ± 8.2†	0.5 ± 0.1	2.0 ± 1.5

* Values are mean ± SD.

† Serum cortisol level was significantly higher after hydrocortisone infusion ($p < 0.001$) using one-tailed *t* test.

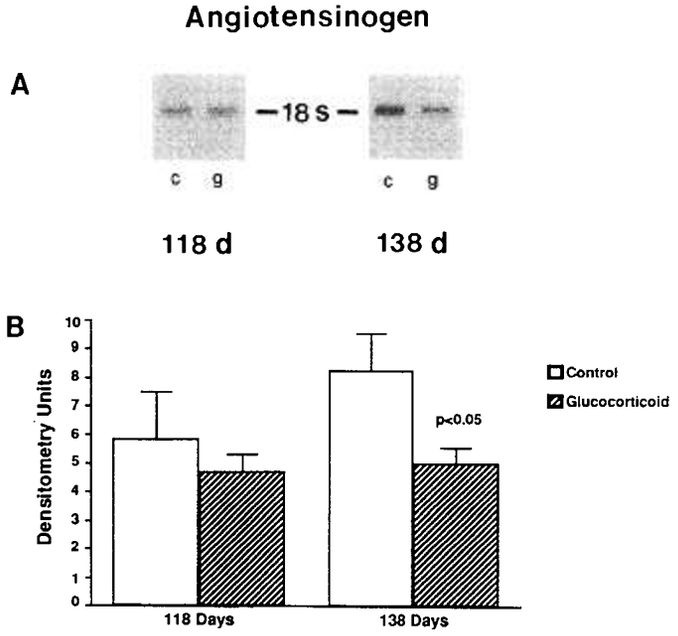

Fig. 1. Effect of glucocorticoids on angiotensinogen mRNA in livers of fetal sheep at 118 and 138 d gestational age. *A*, Representative Northern blot analysis of 5 μg of total cellular RNA from glucocorticoid-treated (*g*) and saline control (*c*) isolated from livers of 118- and 138-d gestational age lambs. *B*, Quantitation of angiotensinogen mRNA sequences in glucocorticoid-treated and control animals at 118 and 138 d gestational age. Slot blots containing 5 μg of total cellular RNA were hybridized with ^{32}P-labeled antisense angiotensinogen RNA. Autoradiographs were quantitated by densitometry. The effect of glucocorticoid treatment on mRNA abundance was determined by one-tailed *t* test. The data shown indicate the mean and SD for four sets of twins studied at 118 d and three sets studied at 138 d.

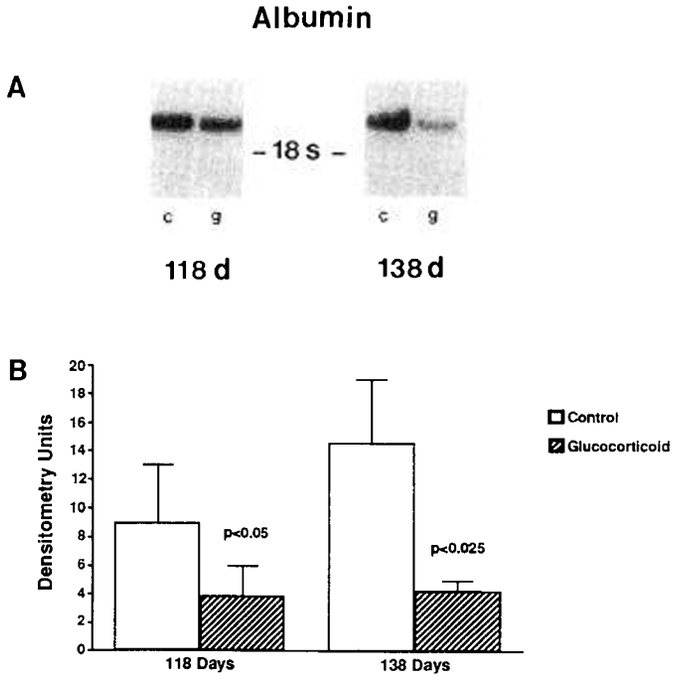

Fig. 2. Effect of glucocorticoids on albumin mRNA livers of fetal sheep at 118 and 138 d gestational age. *A*, Representative Northern blot analysis of 5 μg of total cellular RNA from glucocorticoid-treated (*g*) and saline control (*c*) isolated from livers of 118- and 138-d gestational age lambs. *B*, Quantitation of albumin mRNA sequences in glucocorticoid-treated and control animals at 118 and 138 d gestational age. Slot blots containing 5 μg of total cellular RNA were hybridized with ^{32}P-labeled antisense albumin RNA. Data were analyzed as described in the legend to Figure 1.

DISCUSSION

We have demonstrated that, in contrast to previous findings in mature animals in which glucocorticoids increase angiotensinogen mRNA levels (6, 7), a physiologic increase in fetal plasma cortisol concentration decreases liver angiotensinogen mRNA accumulation in near-term fetal sheep. This negative effect of cortisol in the fetal liver is not universal, because cortisol positively regulates prothrombin gene expression without affecting expression of the factor IX gene.

The decrease in angiotensinogen mRNA in fetal sheep liver after cortisol stimulation differs from the results of a previous study in fetal rats (26). In that study (26), administration of pharmacologic doses of dexamethasone to pregnant rats for 5 consecutive d increased fetal hepatic angiotensinogen mRNA levels but had no effect on fetal heart, kidney, and brain angiotensinogen gene expression. Reasons for the differences between the present study and the study by Everett *et al.* (26) are not clear but may represent either a different species' response to the drugs, different responses to cortisol *versus* dexamethasone, or the use of physiologic *versus* pharmacologic dosages of steroid. In addition, dexamethasone binds to both mineralocorticoid and glucocorticoid receptors, whereas cortisol binds preferentially to glucocorticoid receptors (27).

The effect of glucocorticoid in regulating angiotensinogen mRNA levels may be dependent on the physiologic state of the cell. Thus, in growth-arrested cells, dexamethasone stimulates the accumulation of angiotensinogen mRNA, whereas this effect is completely inhibited in growth-stimulated cells (28). Therefore, one may speculate that the decrease in angiotensinogen mRNA response after cortisol infusion during fetal life may be secondary to stimulation of growth factors (28). It is interesting that liver

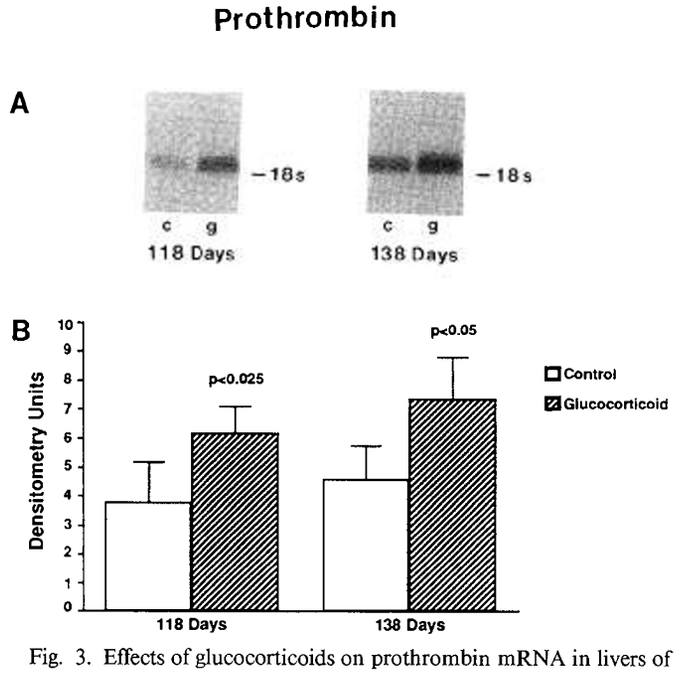

Fig. 3. Effects of glucocorticoids on prothrombin mRNA in livers of fetal sheep at 118 and 138 d gestational age. *A*, Representative Northern blot analysis of 5 μg of total cellular RNA from glucocorticoid-treated (*g*) and saline control (*c*) isolated from livers of 118- and 138-d gestational age lambs. *B*, Quantitation of prothrombin mRNA sequences in glucocorticoid-treated and control animals at 118 and 138 d gestational age. Slot blots containing 5 μg of total cellular RNA were hybridized with ^{32}P-labeled antisense prothrombin RNA. Data were analyzed as described in the legend to Figure 1.

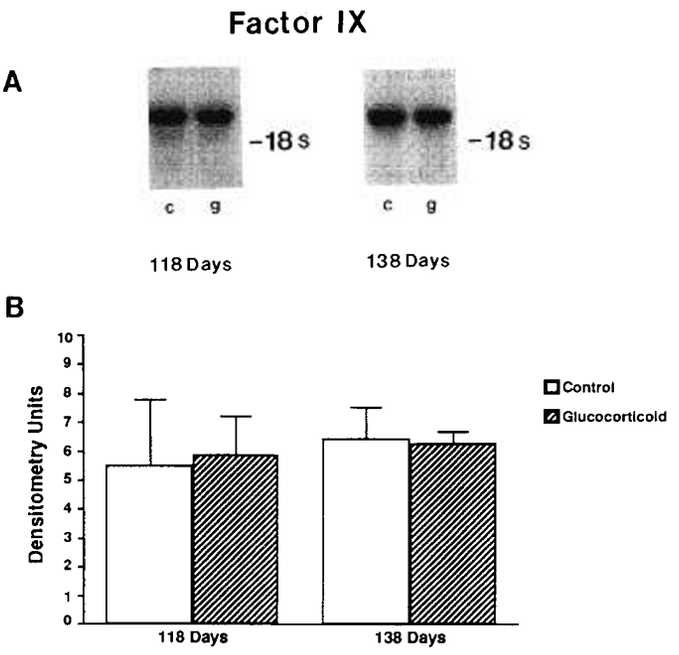

Fig. 4. Effect of glucocorticoids on factor IX mRNA in livers of fetal sheep at 118 and 138 d gestational age. *A*, Representative Northern blot analysis of 5 μg of total cellular RNA from glucocorticoid-treated (*g*) and saline control (*c*) isolated from livers of 118- and 138-d gestational age lambs. *B*, Quantitation of factor IX mRNA sequences in glucorticoid-treated and control animals at 118 and 138 d gestational age. Slot blots containing 5 μg of total cellular RNA were hybridized with ^{32}P-labeled antisense factor IX RNA. Data were analyzed as described in the legend to Figure 1.

angiotensinogen mRNA levels decrease after birth in sheep at a time when plasma cortisol levels are high (5).

The decrease in fetal albumin mRNA levels during cortisol infusion is similarly unexpected because dexamethasone stimulates albumin mRNA synthesis in adults (29, 30). Because the 5′ flanking region of both albumin and angiotensinogen gene contains sequences that are homologous to the glucocorticoid binding site (31), this negative regulation may occur by a common mechanism. Negative regulation of gene expression by cortisol is not unique, because glucocorticoids inhibit prolactin (32) and proopiomelanocortin synthesis (33, 34).

It is possible that the negative or positive glucocorticoid regulation of gene expression depends on factors interacting with specific DNA sequences on the glucocorticoid regulatory elements. For example, it has been suggested that oncogenes such as c-*jun* and c-*fos* may serve as selectors of hormone responsiveness (35). In mice, the presence of c-*jun* confers a positive glucocorticoid effect to the glucocorticoid regulatory element, whereas the combination of c-*jun* and c-*fos* tends to confer a negative effect to the same element (35). Additionally, because glucocorticoid receptors are themselves developmentally regulated (36, 37), changes in the physicochemical nature of receptors during organ maturation may affect the hormonal responsiveness of certain genes during fetal life (38).

Our observation that cortisol infusion modulated fetal prothrombin mRNA but did not affect angiotensinogen mRNA is provocative. Glucocorticoid hormone responsiveness of genes such as angiotensinogen most often occurs at the level of transcription (39). However, the action of glucorticoid hormones is not entirely restricted to transcriptional events. Paek and Axel (40) have shown that glucocorticoids act posttranscriptionally to modulate the level of hGH mRNA by increasing its stability. In view of this work, as well as the negative responsiveness of angiotensinogen and albumin to glucocorticoids, it will be important to determine the exact steps in the synthesis and processing of prothrombin mRNA that are affected by glucocorticoids in the fetus.

In summary, our study demonstrates that cortisol inhibits the expression of both angiotensinogen and albumin genes in liver of fetal sheep. This effect is not universal, however, because prothrombin gene expression increases after a rise in fetal plasma cortisol concentration. Mechanisms regulating these changes have not been investigated. However, one may speculate that developmental changes in glucocorticoid receptors and factors interacting with specific DNA sequences of the glucocorticoid regulatory element may also contribute to the negative regulation of angiotensinogen gene expression by cortisol during fetal life.

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