Transcriptional and Posttranscriptional Effects of Dexamethasone on Albumin and Procollagen Messenger RNAs in Murine Schistosomiasis†

Francis R. Weiner, Mark J. Czaja, Marie-Adele Giambrone, Shizuko Takahashi, Luis Biempica, and Mark A. Zern*

Marion Bessin Liver Research Center and Departments of Medicine, Biochemistry, and Pathology, Albert Einstein College of Medicine, Bronx, New York 10461

Received September 4, 1986; Revised Manuscript Received November 21, 1986

ABSTRACT: We have previously shown that dexamethasone increases albumin mRNA and decreases procollagen steady-state mRNA levels in rat hepatocyte cultures. These studies were extended by evaluating an in vivo model of fibrogenesis (murine schistosomiasis) and by determining a more precise level of gene expression responsible for these changes. Control mice and litter mates infected with *Schistosomiasis mansoni* were evaluated at 8 weeks postinfection when the livers of the infected mice had become fibrotic and their serum albumin levels significantly decreased. The addition of 4 μg/mL dexamethasone to the drinking water of half of the infected mice led to a 75% decrease in the liver collagen content as determined by high-performance liquid chromatography. RNA was extracted from the livers of mice under three conditions: control and infected ± dexamethasone. This RNA was then hybridized with cDNA probes to determine steady-state levels of specific mRNAs. In the infected mice, albumin mRNA levels were decreased compared to control; however, infected mice treated with dexamethasone increased their albumin mRNA content by 3-fold at 8 weeks. Types I and IV procollagen steady-state mRNA levels in infected mice were increased compared to control while dexamethasone suppressed the mRNA level of collagen in infected mice by 50%. The level of gene expression responsible for these steady-state changes was evaluated by nuclear run-on analysis. While the effect of schistosomiasis on these genes was primarily at a transcriptional level, dexamethasone exerted its effect on different genes in the injured liver by diverse mechanisms, i.e., decreasing collagen synthesis at a transcriptional level and increasing albumin by posttranscriptional mechanisms. Corticosteroid-induced changes appear to lead to a stabilization of liver function and inhibition of fibrogenesis. This may explain why corticosteroids are beneficial in some forms of chronic liver disease in man.

Hepatic schistosomiasis is probably the world's most prevalent chronic liver disease (Dunn & Kanel, 1981). The eggs of *Schistosomiasis mansoni* cause an inflammatory response when trapped in liver sinusoids, leading to granuloma formation and ultimately to hepatic fibrosis. This fibrosis involves the excessive deposition of newly synthesized connective tissue matrix, with collagen being the major component. The deposited collagen causes interference with normal architecture and circulation, and in some cases, hypoalbuminemia occurs after long-term hepatic fibrosis (Cook et al., 1974). When mice are infected with *S. mansoni*, they consistently develop hypoalbuminemia (Knauft & Warren, 1969) and a massive increase in liver collagen (Dunn et al., 1977). Therefore, murine schistosomiasis is an excellent model to study gene regulation of collagen, albumin, and other hepatic proteins in the presence of this fibrogenic stimulus. In human (Dunn et al., 1979) and murine schistosomiasis (Takahashi et al., 1980), this increased collagen content has been associated with increased collagen synthesis. Previous studies have focused on pathophysiological explanations for the hypoalbuminemia (Soliman et al., 1973; Page et al., 1972; Saif et al., 1977), while our work evaluated the molecular mechanisms responsible for the hypoalbuminemia and fibrosis (Zern et al., 1983a). We demonstrated that mice infected with *S. mansoni* had a reduction in hepatic albumin mRNA steady-state levels, and that type I procollagen mRNA content was increased in infected livers (Zern et al., 1983a). A more precise delineation of the level of gene regulation responsible for these changes in albumin and procollagen mRNA requires transcriptional analysis. Such analysis was one of the major objectives of this study.

A second objective was to evaluate the effects of glucocorticoids on hepatic gene expression in an in vivo system. Steroids, in addition to their generalized antiinflammatory effects, have been found to decrease collagen synthesis and the levels of posttranslational enzymes associated with collagen synthesis (James et al., 1983; Newman & Cutroneo, 1977; Risteli, 1977). Previous studies of the molecular effects of dexamethasone on collagen synthesis have been done in cell culture systems. Dexamethasone has been shown to decrease type I procollagen mRNA content in cultured hepatocytes (Jefferson et al., 1985) and in chicken skin fibroblasts (Sterling et al., 1983). In addition, dexamethasone appears to be beneficial in augmenting tissue-specific functions in primary hepatocyte cultures (Guguen-Guillouzo & Guillouzo, 1983). We have shown that hepatocytes maintained in serum-supplemented media with dexamethasone have increased albumin mRNA content when compared to cells without dexamethasone (Jefferson et al., 1985). Such results may explain the beneficial effect of steroids in the treatment of chronic liver disease, but in vivo analysis seems desirable.

† This investigation was supported in part by National Institutes of Health Grants AA06386 and AI-15631 and a Sinsheimer Foundation Award (M.A.Z.). M.J.C. is a recipient of the American Liver Foundation Fellowship Award, and F.R.W. was funded by National Research Service Award 1F32AA05224-01 and by an American Liver Foundation Fellowship Award. This study was presented in part at the Meeting of the American Society for the Study of Liver Disease and has been published in abstract form (Weiner et al., 1985).

* Address correspondence to this author at the Marion Bessin Liver Research Center, Albert Einstein College of Medicine.

0006-2960/87/0426-1557$01.50/0

In the present study, we have attempted to define the level of gene expression responsible for the observed decrease in serum albumin as well as the increase in collagen content in murine schistosomiasis. In addition, we have examined the effects of dexamethasone on collagen and albumin gene regulation in this in vivo model of liver fibrosis.

Materials and Methods

Animals. CF1 female mice were infected subcutaneously with 50 cercariae, the larval stage of *S. mansoni*, Puerto Rican strain (received from the Department of Geographic Medicine, Case Western Reserve Medical School, Cleveland, OH), and litter mate controls were provided by the same source. Dexamethasone at a concentration of 4 μg/mL was added to the drinking water of half the infected mice starting at 4 weeks postinfection. Animals were killed by cervical dislocation at 8 weeks postinfection. Blood was taken for evaluation of serum albumin by the Technicon Bromocresol Green procedure. Histological sections of liver from the sacrificed animals were evaluated by Trichrome stain.

Determination of Collagen Content. The collagen content of mouse liver was measured and expressed as micromoles of protein-bound hydroxyproline per milligram of DNA as described previously (Takahashi & Biempica, 1985) with a slight modification. Aliquots of tissue (10–15 mg of wet tissue) containing aminobutyric acid and/or norleucine as recovery standards were hydrolyzed with 6 N HCl for 24 h at 110 °C. The hydrolysate was neutralized and derivatized with dansyl chloride. The dansylhydroxyproline formed was separated on a reverse-phase octadecyl C-18 column using high-performance liquid chromatography (HPLC) with a buffer system based on that of Kaneda et al. (1982).

RNA Isolation and "Dot" Blot Hybridization Analysis. Ribonucleic acid was isolated by using minor modifications of the procedure of Chirgwin et al. (1979) as we previously described (Zern et al., 1985). The livers from two animals were homogenized in 3.5 mL of 4 M guanidine thiocyanate solution. The homogenate was then cleared of cellular debris by low-speed centrifugation, and the RNA was pelleted through a cesium chloride gradient. The resultant RNA was redissolved, precipitated with 0.2 M sodium acetate and 2.5 volumes of ethanol, quantitated by A_{260} spectrophotometry, and used for molecular hybridization. The quantity of RNA isolated was correlated with the protein and DNA contents of the homogenized samples.

For dot blots, the RNA was serially diluted, incubated for 5 min at 65 °C in 3% formaldehyde, spotted on the Gene Screen matrix (New England Nuclear, Boston, MA), and baked for 2 h at 80 °C in a vacuum oven before prehybridization and hybridization with ^{32}P-labeled probes (Zern et al., 1985). The blots were then washed by using stringent conditions and exposed to film, and densitometry was performed as previously described (Zern et al., 1985). The cDNA clones complementary to specific mRNA were radioactively labeled by primer extension as described by Summers and Mason (1982). [^{32}P]dCTP (specific activity 3000 Ci/mmol) was included in the reaction to obtain a specific activity of (2–6) × 10^8 cpm/μg of DNA. Recombinant cDNA plasmids used as probes in these experiments included rat albumin (Zern et al., 1983b), chicken β-actin (Cleveland et al., 1980), rat proα2(I) collagen (Genovese et al., 1984), and mouse type IV collagen (Wang & Gudas, 1983).

Nuclear Transcription Rate Analysis. Whole liver nuclei were isolated by a method previously described (Clayton & Darnell, 1983). Nuclei were prepared from two mice by sucrose gradient centrifugation at 20 000 rpm in an SW-41 rotor for 1 h. Nuclei were then suspended at 30 °C in a reaction buffer containing 10 mM tris(hydroxymethyl)-aminomethane (Tris) (pH 7.9), 20% glycerol, 140 mM KCl, 5 mM $MgCl_2$, 1 mM $MnCl_2$, 14 mM 2-mercaptoethanol, 1 mM each of ATP, CTP, and GTP, 10 mM phosphocreatine, 100 μg of creatine phosphokinase, and 0.5–1 mCi of high specific activity [^{32}P]UTP (Amersham Corp.) per milliliter. A typical reaction consisted of 0.3 mL of reaction buffer added to a 0.1–0.2-mL nuclear pellet. The nuclear transcription was allowed to continue for 15 min at 30 °C (with occasional tapping), and then the nuclei were lysed with a hypotonic solution followed by proteinase K digestion at 37 °C for 30 min. Labeled nuclear RNA was then extracted with a phenol/chloroform/isoamyl alcohol mixture followed by RNA precipitations with 2.5 volumes of ethanol, 0.2 M sodium acetate, and yeast tRNA carrier. Five micrograms of each plasmid cDNA was dotted on sheets of nitrocellulose (Schleicher & Schuell) with a 96-well dot blot manifold. The sheets were then prehybridized in a solution containing 5× SSC, 50 mM sodium phosphate, 4× Denhardt's, 50% formamide, 0.1% sodium dodecyl sulfate (SDS), and 500 μg/mL yeast tRNA for 12–24 h at 37 °C. Hybridization was performed by using a similar solution except that the Denhardt's solution was decreased from 4× to 1×. The precipitated RNA was suspended in 3 mL of hybridization solution for 48 h at 37 °C. Equal amounts of labeled RNA were hybridized for each condition. Filters were washed several times with 2× SSC at 65 °C and then digested at 37 °C with 10 μg/mL RNase A (Worthington) for 30 min followed by a wash in 2× SSC at 37 °C for 60 min. Filters were exposed to Kodak XAR-5 film with intensifying screens at −70 °C for autoradiographic detection. Densitometric scanning and correlation of the densitometry with an arginine transfer RNA control were undertaken with a Quantimet 920 analyzer (Cambridge Instruments).

Results

Most of the mice infected with schistosomiasis continued to gain weight at approximately the same rate as control mice or infected mice treated with dexamethasone. We used the animals with normal growth rates to eliminate the deleterious effects of protein–calorie malnutrition on protein synthesis or albumin mRNA content (Yap et al., 1978; Pain et al., 1978). Although there were no differences in the weights of the three groups of mice, there was a difference in their serum albumin levels. Infected mice were hypoalbuminemic at 8 weeks with their serum albumin levels averaging 2.50 g/dL which was 85% of normal. Dexamethasone improved the serum albumin levels of the infected mice to 3.29 g/dL or 131% of the value for infected mice without dexamethasone.

The livers of mice infected with *S. mansoni* were larger than those of control animals or the livers of infected mice treated with dexamethasone. This difference was caused by the presence of granulomas and fibrosis. Histologic examination of liver sections from mice infected with schistosomiasis showed numerous granulomas and marked collagen deposition (Figure 1). However, sections obtained from mice infected with *S. mansoni* and treated with dexamethasone revealed fewer and smaller granulomas and less fibrosis (Figure 1). This is reflected in the collagen content data (Table I). Infection led to a 7-fold increase in collagen content at week 8, the period of maximal collagen synthesis (Takahashi et al., 1980). Treatment of the infected mice with dexamethasone led to a 67% decrease in collagen content.

To evaluate the molecular effects of schistosomiasis and dexamethasone administration, we isolated total liver RNA

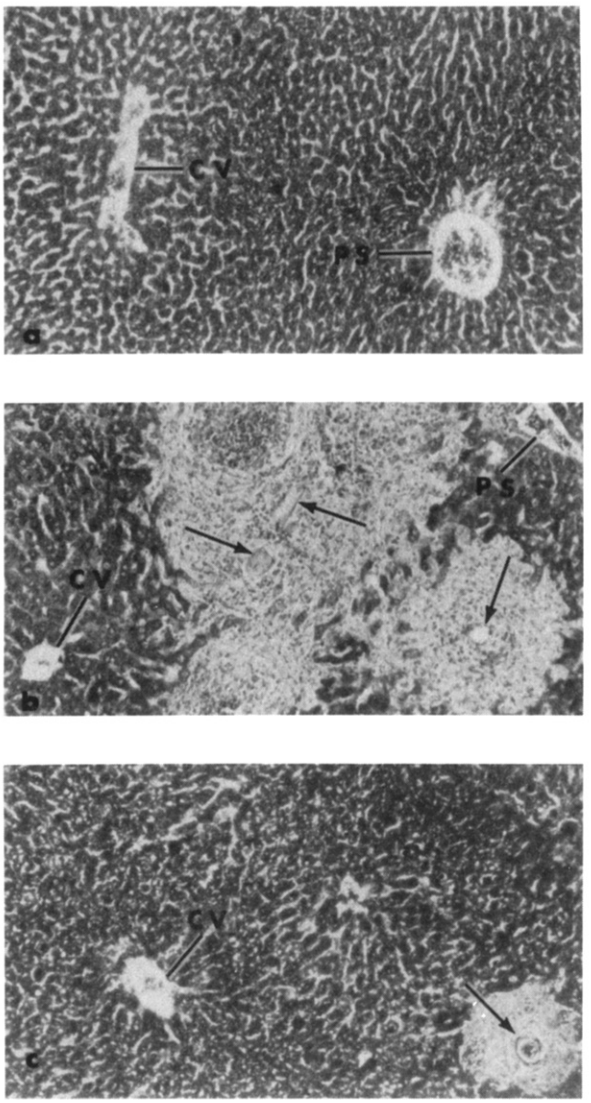

FIGURE 1: Hepatic morphology of control mice, mice infected with *Schistosoma mansoni*, and infected mice treated with dexamethasone. (a) Control mouse liver. (b) Mouse liver, 8 weeks after infection. Large areas of the parenchyma are occupied by numerous granulomas. They show a tendency to coalesce, leaving many hepatocytes trapped. Most granulomas show marked collagen deposits. The cellular infiltrates are made up of lymphocytes, eosinophils, macrophages, occasional polymorphonuclear cells, and numerous fibroblasts. Parasite eggs in various stages of preservation are seen, usually in the center of granulomas. (c) Mouse liver, 8 weeks after infection, treated with dexamethasone. Granulomas are scanty, isolated, and small. The amount of collagen is moderate. All pictures 72× magnification. Gomori's Trichrome stain. CV, central vein; PS, portal space. Arrows point to schistosoma egg.

Table I: Collagen Content of Mouse Livers As Determined by HPLC

nature of treatment[a]	collagen content (μmol of Hypro/mg of liver DNA)[b]
CON	0.34
SCH	2.40
SCH + DEX	0.79

[a] Control (CON), schistosoma infected (SCH), or schistosoma infected + dexamethasone treatment (SCH + DEX). [b] Mean of two experiments.

from animals at 8 weeks postinfection and analyzed the mRNA content of four proteins by "dot" blot hybridization. Figure 2 shows the results obtained by dotting onto a Gene Screen filter decreasing amounts of RNA from control and

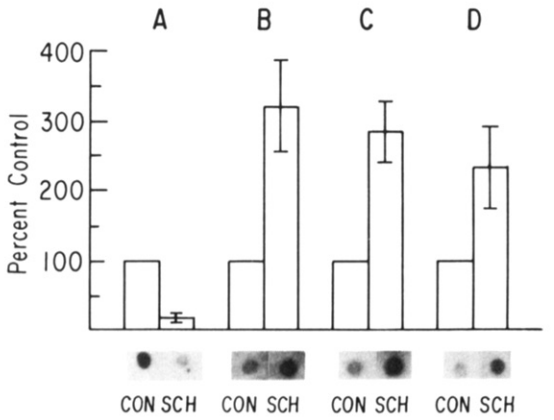

FIGURE 2: Autoradiographs of dot blot hybridization of mouse liver mRNAs with specific cDNA probes and results of densitometry tracings. Total RNA was extracted from livers of control (CON) and schistosoma-infected mice (SCH) at 8 weeks, diluted in formaldehyde, spotted on Gene Screen matrix, hybridized to ^{32}P-labeled cDNA probes, autoradiographed, and scanned by densitometry as described under Materials and Methods. The mRNAs were probed with the following specific cDNAs: (A) albumin; (B) type I procollagen; (C) type IV procollagen; and (D) β-actin. Above the dot blot hybridization figures is the graphic presentation of the densitometry tracing of three experiments. The RNA from infected mice is represented as a percentage of control ± SEM for each of the four specific genes.

Table II: Densitometry Readings of Autoradiographs from Nuclear Run-On Experiments Comparing RNA Transcripts of Mice Infected with Schistosomiasis and Their Litter Mate Controls

specific mRNA	infected liver as % of control[a]
albumin	45.0 ± 6
type I procollagen	264 ± 31
type IV procollagen	344 ± 84
β-actin	342 ± 105

[a] Mean ± SEM for three experiments.

infected mouse liver at week 8, hybridization of the RNA with specific ^{32}P-labeled cDNA probes, and scanning the resultant autoradiographs from three such experiments. Infection with *S. mansoni* for 8 weeks led to an increase in the hybridization signals of type I and type IV procollagen and the constitutive protein β-actin. In contrast, as expected in these mice with hypoalbuminemia, there was a marked decrease in the steady-state level of albumin mRNA. Densitometry scanning of dot blots from three sets of experiments revealed that the increase in steady-state levels ranged from 236% of control for β-actin to 319% of control for type I collagen. The albumin mRNA content was only 24% of control levels.

To determine the level of gene expression responsible for these steady-state changes, we isolated nuclei from the same mouse livers, labeled the RNA transcripts with [^{32}P]UTP, and hybridized these transcripts with specific cDNAs bound to nitrocellulose filters. The results of the transcription assay for control mice and mice infected for 8 weeks are shown in Figure 3 and Table II. These data indicate that the increase in steady-state levels of types I and IV procollagen and β-actin was associated with an increased transcription of the genes. The decrease in albumin mRNA was associated with a decrease in albumin transcription.

In order to delineate the molecular mechanisms responsible for the effects of corticosteroids on hepatic liver injury, we evaluated steady-state mRNA levels by dot blots and transcriptional rates by nuclear run-on experiments in infected animals treated with dexamethasone. Dexamethasone administration resulted in an increased hybridization signal for

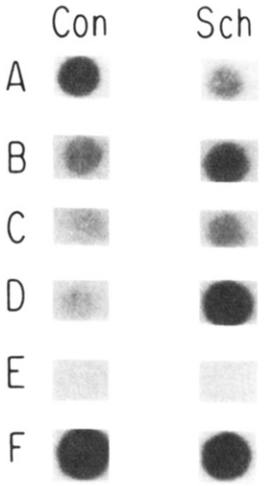

FIGURE 3: Autoradiographs of specific gene transcriptional rate analysis in mouse liver. Nascent labeled nuclear RNA transcripts [(1–1.4) × 10^7 cpm] from whole liver of control (CON) and infected mice (SCH) were isolated, hybridized with 5 μg of specific cDNAs on nitrocellulose, and autoradiographed as described under Materials and Methods. Analysis of transcription of the following genes was performed: (A) albumin; (B) type I procollagen; (C) type IV procollagen; (D) β-actin. *Escherichia coli* plasmid PBR322 DNA (E) was used to determine background activity and rat t-arginine (F) was used to determine that total transcription between conditions was equal.

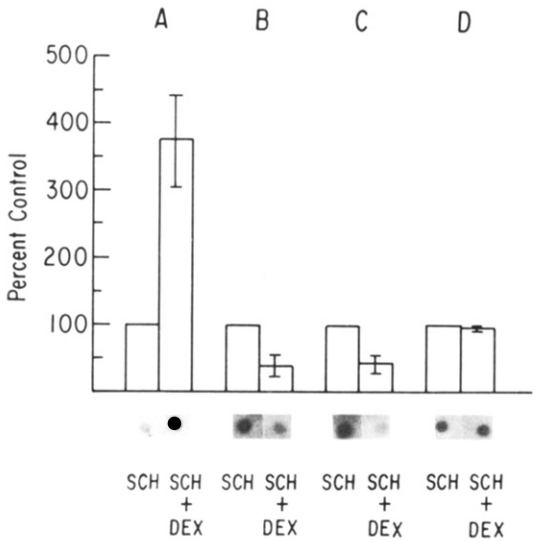

FIGURE 4: Dot blot assay and densitometry tracings of steady-state levels of RNA from liver of infected mice (SCH) and infected mice treated with dexamethasone (SCH + DEX). Total RNA was extracted from the livers at 8 weeks, dotted on Gene Screen filters, and hybridized with specific cDNA clones, and autoradiography was performed as described under Materials and Methods. The specific mRNAs evaluated were (A) albumin, (B) type I procollagen, (C) type IV procollagen, and (D) β-actin. Above the dots are the densitometry scanning results from three experiments. The densitometry results from infected mice are presented as percentage of control ● SEM for each of the four specific genes.

albumin, decreased amounts of type I and IV procollagen mRNA, and no change in β-actin levels at 8 weeks as shown in a representative dot blot (Figure 4). Densitometry scanning of a series of experiments confirmed these findings (Figure 4). This increase in albumin mRNA levels was consistent with the reversal of the hypoalbuminemia caused by the dexamethasone. The decrease in the procollagen mRNAs was associated with diminished collagen content in the mice treated with dexamethasone (Table I). Dexamethasone caused a decrease in the transcription of the procollagen mRNAs which correlated with their diminished steady-state levels, but no

Table III: Densitometry Readings of Autoradiographs from Nuclear Run-On Experiments Comparing RNA Transcripts of Mice Infected with Schistosomiasis and Treated with Dexamethasone (DEX) to Infected Mice without DEX

specific RNA	infected liver + DEX as % of infected − DEX[a]
albumin	112 ± 13
type I procollagen	51 ± 7
type IV procollagen	57 ● 8
β-actin	95 ● 45

[a] Mean ● SEM for three experiments.

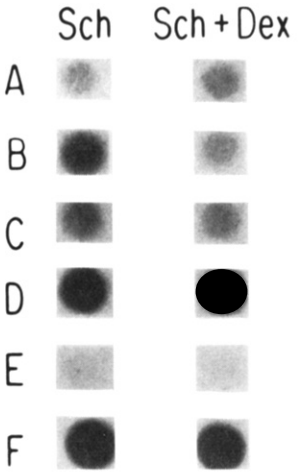

FIGURE 5: Transcriptional analysis of a series of genes from mouse liver nuclei. Nascent labeled nuclear RNA transcripts from liver of infected mice (SCH) and infected mice treated with dexamethasone (SCH + DEX) were hybridized with 5 μg of specific cDNAs bound to nitrocellulose. Analysis of hepatic gene transcription was performed for (A) albumin, (B) type I procollagen, (C) type IV procollagen, (D) β-actin, and (F) t-arginine. PBR322 (E) served as a control for background activity.

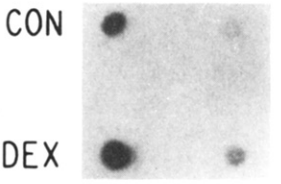

FIGURE 6: Dot blot assay of albumin mRNAs in total RNA from mouse liver. Total RNA was extracted from livers of control (CON) and uninfected mice treated with dexamethasone (DEX). RNA was serially diluted, spotted onto Gene Screen matrix (1.0 and 0.25 μg), and hybridized with the cDNA clone for albumin. Dexamethasone increased albumin mRNA levels in normal animals.

transcriptional change was shown for the large increase in the steady-state level of albumin mRNA induced at this time (Figure 5 and Table III).

To determine whether the effect of dexamethasone was merely an inhibition of the liver's inflammatory response, we evaluated its effect on uninfected mice with normal livers. After 4 weeks of dexamethasone administration, uninfected mice treated with dexamethasone had more albumin mRNA per microgram of total liver RNA than did uninfected mice not treated with dexamethasone (Figure 6). This indicated that the differences in the infected mice treated with dexamethasone were not merely a result of fewer inflammatory cells but also an effect of dexamethasone on hepatocyte gene expression.

Discussion

Murine schistosomiasis is an excellent model system for the evaluation of hepatic gene regulation because it produces both hypoalbuminemia and increased collagen synthesis. In pre-

vious studies, we demonstrated that the hypoalbuminemia was associated with a decreased albumin mRNA content and that increased collagen content was associated with an increase in type I procollagen mRNA content (Zern et al., 1983a). In the present study, we confirm these findings and also demonstrate that the steady-state levels of type IV procollagen mRNA and β-actin mRNA are increased in the infected fibrotic liver.

We have also extended our previous study by examining the mechanism of gene regulation responsible for the observed changes in steady-state levels of specific mRNAs. Current evidence suggests that transcription is the most common level of gene regulation in eukaryotic cells (Darnell, 1982; Powell et al., 1984). Our study of the effect of schistosomiasis shows that transcriptional rates correlated with the steady-state changes in albumin, collagen types I and IV, and β-actin. Thus, in this pathophysiological state, several genes with a variety of functions appear to be regulated primarily at the level of transcription. These results are also consistent with our findings in rats with carbon tetrachloride induced liver disease (Panduro et al., 1986). While we believe that these changes observed in types I and IV procollagen and albumin mRNA levels are due to a transcriptional effect of schistosomiasis on gene transcription, changes in the cell population probably also play a role in these observed mRNA alterations. That is, decreased albumin mRNA levels probably result from decreased transcription of the albumin gene in hepatocytes as well as from a decreased number of hepatocytes due to schistosomiasis. On the other hand, increased procollagen mRNA represents both increased transcription by preexisting cells and also increased numbers of fibroblasts. A major basis for our belief that transcriptional effects are occurring on a per cell line basis is our previous in situ hybridization studies (Saber et al., 1983). In those studies, we demonstrated that schistosomiasis decreased albumin mRNA content in individual hepatocytes as well as in tissue sections from infected livers. Moreover, type I procollagen mRNA content was increased in individual isolated hepatocytes and in tissue sections from infected livers.

The effects of dexamethasone on hepatic mRNAs are more complicated than the effects of schistosomiasis. We have previously shown that dexamethasone increased albumin mRNA content and decreased type I procollagen mRNA content in hepatocytes cultured in serum-supplemented media (Jefferson et al., 1985), and Sterling et al. (1983) have shown that dexamethasone decreased type I procollagen mRNA in cultured fibroblasts. In the present studies of an in vivo model, we demonstrated that at 8 weeks postinfection, dexamethasone increased albumin mRNA content, decreased types I and IV procollagen mRNA levels, and had no effect on β-actin. These mRNA steady-state changes were associated with an increase in serum albumin levels and a decrease in fibrosis.

The basis for the beneficial effects of dexamethasone on schistosomiasis-induced fibrotic liver disease is undoubtedly complex, but it may include the following mechanisms: (1) Dexamethasone may help maintain liver-specific function in hepatocytes exposed to *S. mansoni* and therefore permits an adequate production of albumin. The ability of dexamethasone to augment tissue-specific function and specifically albumin expression in primary liver cultures has been previously reported (Guguen-Guillouzo & Guillouzo, 1983). (2) Dexamethasone may also have a direct effect on the collagen gene by inhibiting transcription in addition to other mechanisms by which it has been suggested to affect collagen synthesis (James et al., 1983; Newman & Cutroneo, 1977; Ristelli, 1977). Further support for a transcriptional effect of steroids on collagen gene expression is produced by studies of Cutraneo and co-workers, who showed decreased nuclear type I procollagen RNA levels in chicken fibroblast exposed to dexamethasone (Cockayne et al., 1986). Walsh and Sterling have also shown that dexamethasone decreased α1(I) and α2(I) procollagen gene transcription in neonatal rat liver and small intestine (Walsh et al., 1986). We have also recently shown that dexamethasone decreased type I proα2 collagen gene promoter activity in mouse fibroblast lines using the CAT transient expression system (Zern et al., 1986). Other levels of collagen synthesis may also be affected by steroids. Raghow et al. (1986) and Hamalainen et al. (1985) have shown that steroid treatment of skin fibroblasts leads to a decrease of the type I procollagen mRNA half-life. However, Cockayne et al. (1986) failed to show such alteration in collagen mRNA degradation. We did not perform measurements of procollagen mRNA half-life due to the difficulty in doing such studies in vivo and therefore cannot address the issue of a posttranscriptional effect of steroids in our system. Thus, this ability of glucocorticoids to augment liver-specific function and to limit collagen synthesis may explain the reported beneficial effects of steroid treatment of autoimmune chronic active liver disease (Davis et al., 1984; Wands et al., 1983).

The glucocorticoid effect on specific hepatic mRNA species appears to be variable. While the decrease in the procollagen mRNA content had a significant transcriptional component, this was not so for the increase in albumin mRNA, a hepatocyte-specific gene. The posttranscriptional level of regulation that we found is consistent with the studies of Jefferson et al. (1984). They demonstrated that mRNA stabilization, rather than increased gene transcription, was the primary level of gene regulation responsible for the observed changes in the steady-state levels of several tissue-specific mRNAs in cultured hepatocytes exposed to dexamethasone.

Some of the effects of dexamethasone on hepatic gene regulation may be explained by its antiinflammatory effect. Some of the decrease in procollagen mRNA could be secondary to a diminution of inflammatory infiltrate in the fibrotic liver and a subsequent loss of mesenchymal cell RNA. However, there are several reasons why we believe that this probably is not the predominant basis for the decrease in the procollagen mRNA induced by dexamethasone: (1) we have previously shown in schistosomiasis (Saber et al., 1983) and in cell culture (Jefferson et al., 1985) that hepatocytes also synthesize type I procollagen mRNA and in the latter study that dexamethasone inhibits type I procollagen mRNA content; (2) the source of type IV collagen is probably not the infiltrating fibroblasts but more likely the endothelial cells, Ito cells, or hepatocytes; (3) when normal livers were exposed to dexamethasone, it stimulated the albumin steady-state mRNA levels, indicating that at least these changes were not caused by alterations in the cell population; and (4) we have demonstrated that dexamethasone inhibits collagen synthesis by a direct effect on the collagen gene promoter using the CAT transient expression system (Zern et al., 1986). Therefore, we believe that steroids may exert a direct effect on collagen genes in the liver and that this involves transcriptional regulation.

The treatment of murine schistosomiasis with dexamethasone represents an excellent model system to study the pathogenesis of hepatic fibrosis and the effects of steroid therapy on chronic liver disease. Further analysis may not only provide a better understanding of the basic molecular mechanisms involved but also could conceivably be helpful in

determining which patients with chronic liver disease will benefit from steroid therapy.

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