The mRNA (mRNA14) coding for the rat liver S14 protein (Mr = 17,000, pI 4.9) is subject to tissue-specific, developmental, hormonal, and nutritional regulation (1-9). The overall pattern of regulation of this sequence shares many characteristics in common with the regulation of hepatic lipogenic enzymes and their mRNAs (9, 10). Although the function of the S14 protein is unknown, these similarities suggest that the S14 protein plays some role in lipid metabolism (2, 7, 9).

We have focused on defining the molecular basis of the multifactorial regulation of S14 gene expression by analysis of S14 gene transcription and chromatin structure. Previous studies suggest that specific loci located upstream from the 5'-end of the S14 gene harbor key cis-acting elements affecting gene transcription (3, 6, 7, 11). For example, the T3 induction of S14 gene transcription in hypothyroid rats is preceded by induction of a single DNase I-hypersensitive site located nearly 3 kb upstream from the S14 cap site. Based on studies of steroid-responsive genes (12-15), we suggested the T3-regulated DNase I-hypersensitive site marks the location of a thyroid hormone response element (TRE) controlling S14 gene transcription (6).

Changes in nutritional status have major effects on S14 gene expression in the adult rat. Starvation reduces hepatic mRNA14 levels, while feeding animals a high carbohydrate-fat-free diet or administering sucrose induces hepatic mRNA14 (1, 4, 5, 7, 8). In contrast to euthyroid animals, mRNA14 was only marginally induced following sucrose gavage of starved hypothyroid rats implicating a role for T3 in the carbohydrate-mediated regulation of this gene. Although Mariash et al. (4) previously reported that T3 and carbohydrate interact synergistically to regulate hepatic levels of mRNA14, the mechanism for this interaction is unknown.

This report examines the mechanism of nutritional regulation of S14 gene expression. Activation of S14 gene transcription was established as the principal mechanism accounting for the induction of mRNA14 following sucrose administration to starved euthyroid rats. Although both sucrose and T3 regulate S14 gene transcription in the starved hypothyroid rat, neither stimulus alone was sufficient to induce S14 gene transcription to euthyroid-fed levels. Induction of S14 gene transcription to euthyroid-fed levels required both stimuli. Analysis of S14 chromatin structure showed that both T3 and dietary carbohydrate induce major changes in the structure of specific DNase I-hypersensitive sites flanking the S14 gene. Our findings suggest that each stimulus regulates S14 gene transcription, at least in part, through local modification of chromatin structure.

MATERIALS AND METHODS

Animals—Euthyroid Sprague-Dawley male rats were obtained from Charles River Breeding Laboratories. Rats were made hypothyroid by maintenance on methimazole (0.025% in drinking water) for 4 weeks. Euthyroid animals were made hyperthyroid by injection of T3 (15 μg/100 g body weight) for 5 days (6). All animals used in this study were obtained from Charles River Breeding Laboratories. Rats were made hypothyroid by maintenance on methimazole (0.025% in drinking water) for 4 weeks. Euthyroid animals were made hyperthyroid by injection of T3 (15 μg/100 g body weight) for 5 days (6). All animals used in this study were obtained from Charles River Breeding Laboratories.
study ranged from 3 to 4 months of age and were killed between 0800 and 1200 h by ether anesthesia and exsanguination.

DNA Probes—All DNA probes, with the exception of pEMBLS14-0.7P, were described previously (3, 6). The pEMBLS14-0.7P plasmid was subcloned from a genomic clone (pEMBLS14-13E). The genomic clone was obtained from a size-selected (EcoRI) rat liver genomic library screened with a S14 5'-exon probe. The sequences in pEMBLS14-0.7P extend from −3350 to −4010 bp relative to the 5'-end of the S14 gene. The cDNA and genomic probes were labeled with [35S]dATP using either nicked translation or primed synthesis (6).

Measurement of Hepatic mRNAs14—Total hepatic RNA was extracted from livers as described by Chirgwin et al. (16), and hepatic mRNAs14 expression was measured by dot-blot hybridization and quantified (6). Results are expressed as units of mRNAs14 (1 unit = 4.8 × 10^10 copies of mRNAs14/μg of total RNA).

Analysis of S14 Gene Activity and Chromatin Structure—Nuclei were isolated and used for gene transcription and chromatin studies (6).

DNA Sequence Analysis of the DNA Flanking the 5'-End of the S14 Gene—The pS14-6.8 genomic plasmid contains S14 genomic DNA extending from +1.7 kb to −5.2 kb relative to the 5'-end of the S14 gene. Portions of this plasmid were restricted and subcloned into pGEM-1 or pGem-blue vectors (Promega). A series of additional subclones were generated by deletion from either end and unidirectional digestion with exonuclease III (17). DNA sequencing was performed by the dideoxy chain termination method of Sanger (18) using [32P]dATP and T4 DNA polymerase (Sequenase; U.S. Biochemicals). All portions of the sequence were determined independently in both directions from overlapping clones. Sequence data were mailed and analyzed using computer programs developed by Deveroux et al. (19).

RESULTS

Nutritional Status Regulates Hepatic S14 Gene Transcription—When compared to levels of S14 expression in euthyroid-fed animals, starvation of euthyroid rats for 48 h repressed both hepatic mRNAs14 and in vitro transcriptional activity by ≥90% (Fig. 1). Following sucrose administration, a 1-h lag period precedes the 35- and 22-fold induction of hepatic mRNAs14 and S14 run-on activity, respectively, that is observed at 4 h. S14 gene expression was restored to ≥80% of euthyroid-fed values within 4 h. During this short term experiment, we found that activation of S14 gene transcription accounted for nearly the full induction of mRNAs14.

Fig. 1. Dietary carbohydrate regulates hepatic S14 gene transcription and mRNAs14 abundance. Male chow-fed euthyroid animals were maintained on rat chow and water ad libitum. Euthyroid animals were starved for 48 h, but were provided water ad libitum. Starved rats were administered sucrose (1 ml/100 g body weight) intravenously (sucrose via gavage) or 50 mM NaOH, intravenously (T3 vehicle). All animals were killed 4 h after treatment. Livers were removed for RNA extraction and isolation of nuclei. Measurement of the tissue abundance of mRNAs14 and S14 transcriptional run-on activity was described under "Materials and Methods" and in Fig. 1. Results are expressed as mean ± S.E. and n = 6. The chart below the figure describes the treatments.

indicating that post-transcriptional processes do not contribute significantly to the induction of mRNAs14.

In order to establish that sucrose induced rapid effects on hepatic gene expression, we examined phosphoenolpyruvate carboxykinase (PEPCK) gene expression. PEPCK gene transcription and mRNAPEPCK was induced 5-fold by starvation, while sucrose gavage attenuated PEPCK gene transcription and mRNAPEPCK levels by >80% within 1 h and >95% within 4 h. The sucrose-induced effect on hepatic gene expression was similar to reports by others (20). The rapid inhibition of PEPCK gene transcription indicates that the 1-h lag period preceding induction of S14 gene transcription was not due to a delay in carbohydrate-mediated changes in hepatic gene expression.

T3 and Dietary Carbohydrate Interact to Regulate S14 Gene Transcription—Marshall et al. (4) reported that dietary carbohydrate and T3 interact synergistically to regulate hepatic mRNAs14 abundance. We examined the mechanism for this interaction by administering sucrose, T3, or a combination of both treatments to starved hypothyroid rats. When compared to euthyroid animals, S14 gene transcription and mRNAs14 levels in fed hypothyroid rats were reduced to 15 and 25%, respectively (Fig. 2). However, starvation of hypothyroid rats further reduced both mRNAs14 abundance and S14 run-on activity to ≤2% of fed euthyroid animals.

Examination of the effect of T3 and sucrose on S14 gene expression in hypothyroid rats involved treatment of rats with either sucrose or a physiological dose of T3 (400 ng/100 g body weight; intravenously) and killing 4 h later (Fig. 2). Each treatment induced a significant (12-fold to 14-fold) increase in S14 run-on activity and mRNAs14 abundance. However, neither treatment exceeded 30% of S14 gene expression in euthyroid-fed animals. Administration of T3 at a supraphysiological dose (200 μg/100 g body weight) also did not induce S14 gene transcription or mRNAPEPCK levels of T3 above that found for the physiological replacement dose of T3. In contrast, 4 h after treatment with both T3 and sucrose, hepatic mRNAPEPCK and S14 gene transcription were induced 103-fold and 68-fold, respectively. These values exceeded the level of S14 gene expression in euthyroid-fed animals and indicated

D. B. Jump and A. Bell, unpublished observations.
that T₃ and dietary carbohydrate act rapidly and synergistically to regulate hepatic mRNAs; abundance at the transcriptional level.

Both T₃ and Dietary Carbohydrate Regulate S14 Chromatin Structure—In an effort to gain additional insight into the T₃ and dietary carbohydrate regulation of S14 gene transcription, we examined the chromatin organization of the S14 gene. Previous studies from our laboratory showed that changes in S14 chromatin structure accompanied activation of S14 gene transcription induced by T₃ or during postnatal development (3, 6, 7). A genomic probe (pEMBLS14-0.7P) was used to examine S14 chromatin structure. We mapped the location of the T₃-inducible DNase I-hypersensitive site and determined whether nutritional manipulation induced changes in S14 chromatin structure.

Fig. 3 shows the location of three DNase I hypersensitive sites flanking the 5'-end of the S14 gene: Hss-1 (-65 to -265 bp), Hss-2 (-1.2 kb), and Hss-3 (-2.67 kb). Hss-3' is a minor site at -1.8 kb. As previously reported, the DNase I sensitivity of the Hss-3 site is the only site significantly affected by a change in thyroid status and a 10-fold change in S14 gene transcription (6). The Hss-3 site is located 2.7 kb from the S14 gene cap site. This location is closer to the S14 gene than previously reported (6), and we attribute this discrepancy to the inaccuracy of determining the size of large restriction fragments.

Since steroid-inducible DNase I-hypersensitive sites are located at or near hormone response elements (12-15), the DNA sequence in the vicinity of the Hss-3 site was examined for homology to the rat growth hormone TRE (Fig. 4A). The region extending from -160 to -200 bp relative to the growth hormone gene (Fig. 4B) has been reported to harbor TRE(s) and to bind salt-extracted T₃ receptors (21-24). Comparison of these sequences shows the presence of an element with significant homology (77%) to the growth hormone TRE within the boundaries of the Hss-3 site (Fig. 4B). The region of highest homology corresponds to where Glass et al. (22, 23) reported binding of salt-extracted T₃ receptors to the growth hormone promoter. These findings suggest that T₃ receptors may bind to the putative TRE within the Hss-3 site.

Does sucrose regulate the structure of the T₃-inducible site or other DNase I-hypersensitive sites flanking the S14 gene? Starvation of euthyroid (7) and hypothyroid rats (Fig. 5) inhibits the formation of the Hss-1, Hss-2, and Hss-3 sites. Two DNase I-hypersensitive sites located at -5.3 kb (Hss-4) and -6.2 kb (Hss-5) were only marginally affected by changes in nutritional status. Thus, starvation effects on S14 chromatin structure appear to be restricted to a region within 3 kb of the S14 gene. Loss of the DNase I-hypersensitive sites in this 3-kb region correlated with nearly full inhibition of S14 gene transcription.

Administration of sucrose to starved hypothyroid rats consistently induced the DNase I sensitivity of the Hss-1 and Hss-2 sites to levels equal to or greater than that seen in

Fig. 4. Location of a putative thyroid hormone response element (TRE) upstream from the S14 gene. A, DNA sequence analysis of the Hss-3 region. DNA sequence analysis was performed as described under "Materials and Methods." A computer-assisted homology search of the 4314 bp of DNA flanking the 5'-end of the S14 gene revealed a single sequence resembling the growth hormone TRE. This sequence was found within the Hss-3 gene revealed a single sequence resembling the growth hormone TRE. This sequence was found within the Hss-3 region extending from -160 to -200 bp relative to the growth hormone gene (Fig. 4B) has been reported to harbor TRE(s) and to bind salt-extracted T₃ receptors (21-24). Comparison of these sequences shows the presence of an element with significant homology (77%) to the growth hormone TRE within the boundaries of the Hss-3 site (Fig. 4B). The region of highest homology corresponds to where Glass et al. (22, 23) reported binding of salt-extracted T₃ receptors to the growth hormone promoter. These findings suggest that T₃ receptors may bind to the putative TRE within the Hss-3 site.

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Administration of sucrose to starved hypothyroid rats consistently induced the DNase I sensitivity of the Hss-1 and Hss-2 sites to levels equal to or greater than that seen in
T₃ and Dietary Carbohydrate Regulate Hepatic S14 Gene Transcription

Fig. 5. T₃ and dietary carbohydrate interact to regulate S14 chromatin structure. Hepatic nuclei from euthyroid rats or from starved hypothyroid rats receiving vehicle, sucrose, T₃, or both T₃ and sucrose were digested with DNase I and processed as described in Fig. 3. The details of the physical manipulation of the starved hypothyroid rats are described in Fig. 2. Blots were exposed to x-ray film for 5 days. The figure is a composite photograph and is representative of five separate studies.

Euthyroid-fed animals, while the Hss-3 site was only marginally induced (Fig. 5). The induction of these sites correlated with the 15.5-fold induction of S14 gene transcription. Both the pattern of chromatin structure and the transcription rate in these animals is similar to that found in hypothyroid-fed rats (Figs. 2 and 3).

In fed hypothyroid rats, T₃ regulates the structure of one major DNase I-hypersensitive site and induces a 10-fold increase in S14 gene transcription (Fig. 3 and Ref. 6). In contrast, T₃ administration to starved hypothyroid rats consistently induced the DNase I sensitivity of the Hss-1, Hss-2, and Hss-3 sites to levels comparable to that found in euthyroid-fed rats (Fig. 5). While the formation of these sites correlated with a 14-fold induction of S14 gene transcription, this treatment did not restore S14 gene transcription to euthyroid-fed levels (Fig. 2). Both T₃ and sucrose were required to restore S14 gene transcription to euthyroid-fed levels; however, this treatment induced no further change in S14 chromatin structure over that observed with T₃ alone. Thus, regulation of chromatin structure alone is not the sole mechanism by which these stimuli regulate S14 gene transcription.

Discussion

While there are several examples of nutritional regulation of hepatic gene transcription, examples of nutritional effects on chromatin structure are rare (25–31). In this report, we provide evidence for site-specific changes in S14 chromatin structure induced by changes in nutritional status.

Sucrose administration to starved hypothyroid and euthyroid rats induces S14 gene transcription (Figs. 1 and 2). Within the 4-h interval examined, we find no evidence for the sucrose-mediated induction of mRNAs₁₄ through activation of a post-transcriptional process. Dozín et al. (29) reported that feeding rats a high carbohydrate-fat-free diet induced hepatic malic enzyme mRNA levels by augmenting RNA stabilization. We have found that feeding euthyroid rats a similar diet for 5 days increased hepatic mRNAs₁₄ levels 4-fold while not significantly increasing S14 gene transcription above the control euthyroid levels. These studies suggest that dietary carbohydrate induces a rapid effect on S14 gene transcription and a slow effect at the post-transcriptional level to regulate S14 gene expression.

The sucrose induction of S14 gene transcription in the starved euthyroid rat follows a pattern described for glucokinase and fatty acid synthase (25–28). Refeeding starved rats rapidly induced hepatic glucokinase and fatty acid synthase gene transcription through an apparent insulin-dependent mechanism. Although our preliminary studies show that insulin rapidly induces S14 gene transcription in the streptozotocin-induced diabetic rat, the precise role of insulin in the regulation of S14 and perhaps other carbohydrate-responsive genes is not clear. Volpe and Vagelos (32) reported that induction of fatty acid synthase was not a direct effect of insulin, since administration of fructose to diabetic rats induced full enzyme activity. Mariash and Oppenheimer (33) and Mariash and Schwartz (34), reported that specific intermediary metabolites induced mRNAs₁₄ and malic enzyme in hepatocyte cultures. Thus, insulin may regulate the cellular abundance of a specific mediator generated from intermediary metabolism rather than a primary carbohydrate-derived second messenger. The recent report by Kinlaw et al. (35) showing that administration of glucagon rapidly inhibits S14 gene expression implicates elevated hepatic cAMP as a suppressor of S14 gene transcription in the starved rat. From these studies, it appears that manipulation of nutritional status will set in motion a complex array of regulatory pathways affecting S14 gene transcription. The 1-h lag period preceding activation of S14 gene transcription may reflect the accumulation of specific protein(s) or non-protein mediator(s) or the decline in hepatic cAMP levels. Our studies do not allow us to distinguish between these various possibilities. Thus, additional studies will be required to establish the pathway for nutritional control of S14 gene transcription.

Despite these limitations, our studies show that changes in nutritional status, like changes in thyroidal status, induce rapid changes in chromatin structure at discrete loci upstream from the S14 gene. Starvation of hypothyroid rats promotes a loss of three major DNase I-hypersensitive sites flanking the S14 gene, and sucrose administration induces two of these sites within 4 h. The induction of these sites correlates with a 15-fold induction of S14 gene transcription. Since the kinetics of induction of these sites was not examined, we do not know whether the change in Hss-1 and Hss-2 structure is a pre- or co-transcriptional event. However, such a highly localized change in structure accompanying gene activation suggests the regulation of these structures may be of physiological importance to the carbohydrate-mediated regulation of S14 gene transcription. These carbohydrate-regulated sites may mark the location of carbohydrate-responsive cis-acting elements. Additional studies will be required to define how these elements function in the nutritional control of S14 gene transcription and how nuclear factors regulate the structure of these sites.

In hypothyroid-fed rats, T₃ regulates the structure of a single DNase I-hypersensitive site (Fig. 3 and Ref. 6). This site is located 2.67 ± 0.1 kb upstream from the 5'-end of the S14 gene (Fig. 3) and contains a sequence (CAGGCCCTTGACCφ) showing high homology to a T₃ receptor binding site and a distal
enhancer regulating S14 gene transcription requires functional analysis of the S14 gene regulatory elements.

Surprisingly, T3 induced three DNase I-hypersensitive sites in starved hypothyroid rats indicating that T3 effects on S14 chromatin structure may not be restricted to a single locus as previously reported (6). The effect of T3 on the Hss-1 and Hss-2 sites is apparent only in the starved animal, since changes in plasma T3 levels had no effect on these structures in hypothyroid-fed animals (Fig. 3 and Ref. 6). Dietary carbohydrate regulates these same structures. Thus, chow feeding apparently is sufficient to maintain the DNase I sensitivity of these structures in the hypothyroid-fed rat. It is not clear from our studies whether these structures are regulated by distinct T3, and carbohydrate mediated pathways. Although, we have not found high sequence homology to the growth hormone TRE in the vicinity of the Hss-1 and Hss-2 sites,2 we cannot exclude the possibility that T3 receptors interact with DNA at these sites. Alternatively, T3 may influence the structure of the Hss-1 and Hss-2 sites by regulating the abundance of specific trans-acting factors binding to cis-regulatory elements. Such hormone-regulated factors have been reported to bind to the Hss-1 site of the S14 gene (36) and several sites flanking the malar enzyme gene (37). Thus, some actions of T3 on gene transcription may not be restricted to T3 receptors bound to cis-linked hormone response elements.

Finally, we have established that the interaction between T3 and dietary carbohydrate to regulate hepatic mRNAPsk is directed at the transcriptional level. Although each factor induces changes in chromatin structure which accompany changes in S14 gene transcription, regulation of chromatin structure alone does not appear to be thesole mechanism by which these physiological stimuli affect S14 gene transcription. For example, T3 induced three major sites in the starved hypothyroid rat without fully activating S14 gene transcription. The combined treatment of T3 and sucrose induced S14 gene transcription to euthyroid-fed levels, but did not induce significant changes in S14 chromatin structure that had been induced by T3 alone (Figs. 2 and 5). These studies suggest T3 and dietary carbohydrate regulate the activity and/or abundance of ancillary factors ("transcription factors") which function in S14 gene transcription, but do not affect S14 chromatin structure. We speculate that the synergistic regulation of S14 gene transcription by T3 and dietary carbohydrate requires the regulation of the accessibility of putative cis-regulatory elements (chromatin structure effects) and the regulation of factors which interact with these elements (transcription factors). The nature of these factors is unknown.

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