LIVER regeneration following partial hepatectomy provides one of the few systems for analysis of mitogenesis in the fully developed, intact animal. Immediate-early growth response genes, induced in the absence of prior protein synthesis, play an important regulatory role in the regenerative process. During screening of a subtracted cDNA library of immediately-early genes induced during liver regeneration, a novel member of the thyroid/steroid receptor superfamily, RNR-1 (regenerating liver nuclear receptor), was identified. This gene is not expressed in quiescent liver but is rapidly induced following partial hepatectomy and is specific to hepatic growth as it is not induced in other mitogen-treated cells. RNR-1 is also expressed in brain. A full-length cDNA clone of RNR-1 encodes a 66-kDa, 597-amino acid protein as verified by in vitro translation in reticulocyte lysate. RNR-1 is highly homologous to r-NGFI-B/m-Nur77 particularly in the DNA binding (94%) and putative ligand binding (59%) domains. Using a mobility shift assay, we have shown that RNR-1 specifically binds to the NGFI-B DNA half-site and forms a complex very similar in size to the Nur77 complex, suggesting that RNR-1 also may bind as a monomer. Consistent with this finding, the A-box region important in mediating half-site binding is 100% conserved between r-NGFI-B/m-Nur77. Both RNR-1 and Nur77 strongly transactivate a reporter driven by a consensus r-NGFI-B/Nur77 binding site, and their effect together is additive. As both the RNR-1 and r-NGFI/m-nur77 genes are induced during liver regeneration, it is very possible that RNR-1 acts concomitantly with r-NGFI/m-Nur77 in regulating the expression of delayed-early genes during liver regeneration.

The liver is one of the few tissues in an adult mammal which, although normally quiescent, retains the capacity to regenerate under the appropriate stimulus. Therefore, regenerating liver provides the opportunity to study the mitogenic response in a unique, physiologically normal, multicellular system. In the rat, following a 70% hepatectomy but is rapidly reenter the cell cycle, and the liver regains its original mass in about 10 days (1, 2). Although it is known that circulating hormones, growth factors, and nervous input participate in the regulation of this response, the actual mechanism is incompletely understood.

Immediately-early growth response genes, which are induced in the transition from quiescence into the G1 phase of the cell cycle, have been identified in various mitogen-stimulated cell systems (3-10). Characterized by their transcriptional activation immediately following mitogenic stimulation and superinduction by cycloheximide-induced protein synthesis blockade, proteins encoded by immediate-early genes are likely to play an important role in the regenerative process. Immediate-early genes encode several different functional classes (for reviews see Refs. 9 and 10): transcription factors, secreted proteins, structural proteins, and others. Similar to other mitogenically stimulated cells, several types of immediate-early transcription factors are induced in regenerating liver including leucine zipper containing proteins like Jun, Fos, and LRF-1 (11), zinc finger proteins like egr-1 (12), and nuclear receptors such as r-NGFI-B/m-Nur77 (13, 14).

Previously, using subtraction and differential screening analyses of cDNA libraries derived from regenerating rat liver, this laboratory isolated several novel immediate-early genes (8). One of these novel genes, SL-322, was particularly interesting because unlike most immediate-early genes, it showed liver-specific induction. On sequence analysis, we found that SL-322 is a member of the steroid/thyroid receptor superfamily (for reviews see Refs. 15-20), and it was renamed RNR-1 (regenerating liver nuclear receptor). RNR-1 is most similar to rat NGFI-B (22) and its mouse homolog, Nur77 among known nuclear receptors (10, 13, 21). m-nur77/NGFI-B expression is rapidly induced by nerve growth factor (NGF) in rat pheochromocytoma cells (PC12) (22) and is differentially modified by membrane depolarization and growth factor treatment (23). m-nur77 mRNA is induced in serum-stimulated fibroblasts (13) and regenerating liver within 1 h of partial hepatectomy (14). A DNA binding site has been identified for NGFI-B (24), and the amino acid residues that participate in the binding to that site have been identified (25).

Here we describe the isolation and characterization of the RNR-1 cDNA and protein. As RNR-1 mRNA is rapidly induced in regenerating liver, RNR-1 is likely to have a role...
in regulating progression through the G_1 phase of the hepatic growth response.

**EXPERIMENTAL PROCEDURES**

**Cell Culture**—H-35 cells were grown in Dulbecco's modified Eagle's medium (DMEM, Gibco), low glucose, supplemented with 5% fetal bovine serum (Gibco), 5% calf serum (Gibco), 2 mM l-glutamine (Glu, Flow Laboratories), and 100 units of penicillin and 50 units of streptomycin/ml (p/s, Flow Laboratories) as reported previously (26).

To produce quiescence, the medium was changed to serum-free DMEM for 72 h at which time the cells were in between 50 and 80% confluent. Following serum deprivation, cells were treated for the indicated time periods with various agents; insulin (10^-8 M, Sigma), serum (20% fetal bovine serum), and cycloheximide (10 µg/ml, Sigma). Balb/c 3T3 cells were grown in DMEM supplemented with 10% fetal bovine serum, Glu and p/s (6). Medium was changed to DMEM plus 0.5% fetal bovine serum, Glu and p/s for 48 h to produce quiescence and, thereafter, cells were treated as described above and in the figure legends. Cells were harvested by scraping in 4 µm gaudine thiocyanate buffer and stored at −70°C (27). Samples were homogenized (Polytron, Brinkmann) prior to RNA preparation as described above.

**Rat Tissue Preparation**—For regenerating liver, female Fischer rats (160-200 g, Bantin-Kingman) were ether anesthetized and subjected to midventral laparotomy with minimal trauma to the liver. Animals were allowed to recover for the times indicated in the figure legends prior to decapitation and isolation of the remaining liver lobes. Tissue was immediately homogenized in 4 µm gaudine thiocyanate buffer (27) at −70°C.

**RNA and Blot Preparation**—Frozen homogenates were thawed, layered over a 5.6 M CsCl, 25 mM sodium acetate cushion, and centrifuged at 175,000 × g for 18 h (27). RNA was resuspended in H2O, phenol/CHC13 extracted, ethanol precipitated, resuspended in H2O, and quantified according to An. For Northern blots, 10 µg of heat-denatured total RNA/lane was separated by electrophoresis in 1% agarose, 0.6% formaldehyde, MOPS denaturing gel and transferred to nitrocellulose (Schleicher & Schuell)-supported nitrocellulose.

Genomic DNA was extracted from normal rat liver, H-35 cells and human IM9 lymphocytes and HeLa cells, as described (27), and Southern transfers were performed.

**Probes and Hybridization**—Recombinant RNR-1 plasmids or isolated cDNA inserts were labeled through the incorporation of [32P]dCTP (Du Pont-New England Nuclear) by nick translation (Bethesda Research Laboratories nick translation reagent kit). Hybridization buffer consisted of 10% dextran sulfate, 40% formamide, 0.6 M NaCl, 0.06 M sodium citrate, 7 mM Tris (pH 7.6), 0.8 × Denhardt's solution, and 0.002% heat-denatured, sonicated salmon sperm DNA for nick-translated probes and 50% formamide, 0.75 M NaCl, 0.075 M sodium citrate, 0.5% SDS, and 5 × Denhardt’s solution for cDNA probes. Blots were hybridized at 42°C for 10 h and washed 2 × 30 min at 60°C or indicated temperatures in 0.15 M NaCl, 0.0015 M sodium citrate, 0.1% SDS prior to exposure to film (28).

**CDNA Library Screening**—The regenerating liver and rat brain CDNA libraries were screened as described (8). Full-length RNR-1 clones were obtained and sequenced in both directions using the dideoxy sequencing method (29). The sequence was compared with other reported sequences using the Intelligenetics and GCG software databases.

**In Vitro Transcription and Translation**—In vitro transcription was accomplished with the Bethesda Research Laboratories capping kit with the addition of RNasin (Promega Biotech). RNR-1 was transcribed in the presence of [α-32P]UTP with T3 RNA polymerase from pBluescript recombinant plasmid linearized with XhoI. nur77 was transcribed with T7 RNA polymerase from pGEM-2 recombinant plasmid (13) linearized with XhoI. This transcript was used to program rabbit reticulocyte lysate (Promega Biotech) as described by the manufacturer. The translation was carried out in the presence of [35S]methionine and run on a 12.5% denaturing sodium dodecyl sulfate (SDS) polyacrylamide gel or 20 µm cold methionine for use in the mobility shift assay.

**Mobility Shift Assay**—The conditions for the mobility shift assay were adapted from Ref. 30. Synthetic HPLC-purified single-stranded oligonucleotides were annealed, and double-stranded oligonucleotides were further purified by HPLC. The binding reactions were preformed in 10 mM HEPEs (pH 7.9), 1 mM dithiothreitol, 5% glycerol, 180 ng of denatured salmon sperm DNA and various cold double-stranded oligonucleotides as indicated as well as 5 µl of rabbit reticulocyte lysate (Promega Biotech) programmed either with RNA transcribed in vitro (Bethesda Research Laboratories) or water. These reactions were incubated for 5 min at room temperature after which preannealed, HPLC-purified, double-stranded, radiolabeled B1a oligonucleotide was added to the reaction. The incubations were continued for 20 min at room temperature. The reactions were brought to 15% glycerol and loaded on 4% acrylamide gels in 0.25 × TBE (22 mM Tris, 22 mM borate, 0.5 mM EDTA) buffer and run at 200 V for 2 h. The gels were dried and autoradiographed.

**Transfection Analyses**—The reporter plasmid was made by cloning a double-stranded oligonucleotide, Nur77-RE (TCCAGAAGAGTCGAGCTGAACTCCTCGAAAGAAGCTGAACTGCCAGGACTTCGAGGACTCGCCAGCACAGTCTT). NIH 3T3 cells growing in DMEM (high glucose)/10% fetal calf serum were transfected using the calcium phosphate protocol (11) with 5 µg of reporter plasmid and pCMV-nur77 or pCMV-RNR-1 and control β-galactosidase reporter making the amounts of plasmid equal using pCMV without insert. 16 h after transfection, the cells were serum deprived (0.5% fetal calf serum), and 24 h later the cells were harvested and luciferase activities determined as per the Promega protocol. β-Galactosidase activity was determined as described (34).

**RESULTS**

Although many of the immediate-early genes previously identified are induced in other mitogen-treated cells, RNR-1 is among a few that are specifically induced in regenerating liver (8). RNR-1 shows no expression in normal liver but is strongly induced in liver 3 h posthepatectomy in the presence of cycloheximide, indicating that it is an immediate-early gene (Fig. 1A). In Reuber H-35 rat hepatoma cells, which become quiescent under serum-starved conditions and show induction of most immediate-early genes in response to insulin (7, 8, 26), there appears to be low level RNR-1 mRNA expression in serum-starved cells. This expression is not increased by insulin stimulation in the presence of cycloheximide. Unlike most immediate-early genes, RNR-1 shows no expression in Balb/c3T3 fibroblasts, either in serum-deprived cells or following serum stimulation in the presence of cycloheximide. Following partial hepatectomy in the absence of cycloheximide, RNR-1 mRNA peaks at 30 min followed by a gradual decline in message which is no longer detectable 6 h posthepatectomy (Fig. 1B). There was also no induction of the gene in sham surgery control animals (not shown). Survey of expression in normal tissues indicates that brain is the only other tissue that shows significant RNR-1 gene expression, although there is marginal expression in lung, spleen, and stomach (Fig. 1C).

Sequence analysis of an RNR-1 CDNA clone obtained from the subtracted regenerating liver library indicated that this gene encodes a member of the thyroid/steroid receptor superfamily with strongest similarity to the rat nuclear receptor, NGF1-B, and its mouse homolog, Nur77. Nearly full-length clones that contain the whole open reading frame were ob-
tained from a rat brain cDNA library. Bidirectional sequence analysis of several overlapping cDNA clones identified an open reading frame of 597 amino acids with a predicted molecular mass of 66,475 daltons (Figs. 2A and 3A). The predicted size of RNR-1 was confirmed following SDS-polyacrylamide gel electrophoresis of in uitro translation of mRNA, which is shown (Fig. 3A). Within the DNA binding domain, 81 of 263-347 of RNR-1; amino acids 270-354/232-316 of m-Nur77/r-NGFI-B. The carboxyl terminus of the protein also shows considerable similarity to Nur77/NGFI-B, with identity among 59% or 148 of 249 residues. The amino terminus among 591 or 148 of 249 residues. The amino terminus shows the least homology, with 85 of 262 amino acids (32%) identical. In Fig. 3B the DNA binding regions are compared among seven steroid/thyroid receptors. In the P box region, which is important in DNA sequence recognition (25), RNR-1 shows homology to the thyroid and estrogen rather than the glucocorticoid and progesterone receptors. On the other hand, in the D box region, which is important in the orientation of
dimeric receptors, there is no notable homology to either the glucocorticoid, progesterone, estrogen, or thyroid receptors, 60% homology to H-2RIIBP (RXR-β), and 80% homology to r-NGFI-B/m-Nur77. In the A box region, which is important in the recognition of adenine residues adjacent to the thyroid response element (TRE) half-site by NGFI-B/Nur77 (25), there is 100% homology between RNR-1 and r-NGFI-B/m-Nur77, and some similarity to an RGRGR motif in the estrogen receptor.

A Southern analysis of genomic DNA isolated from rat and
human cells indicates that the RNR-1 gene is conserved (Fig. 4). Rat DNA digested with HindIII or BamHI shows hybridization of the RNR-1 probe to several bands. Under low stringency conditions, there are three bands using each enzyme which hybridize with the RNR-1 probe. However, after these same blots were washed at a higher temperature (50 or 55°C), only two of the bands remained. These bands are distinct from the nur77 genomic fragments (indicated) which correspond to previously published sizes (35). In addition to

strongly hybridizing fragments derived from the RNR-1 gene (in part confirmed by genomic cloning), the more weakly hybridizing fragment could correspond to a related gene, a pseudogene, or an RNR-1 gene fragment that only partially overlaps with the cDNA probe.

Given the high degree of homology of RNR-1 and r-NFIB/m-Nur77 in the DNA binding domain, we wondered if RNR-1 would bind to similar promoter sequences. In vitro translated RNR-1 and Nur77 proteins (Fig. 2B) were used in
a mobility shift assay to test the binding of the peptide to B1a, an oligonucleotide that has been identified as an r-NGFI-B/m-Nur77 response element (NBRE) (24). Reticulocyte lysate has endogenous binding activity to the B1a oligonucleotide. However, conditions were found which allowed the binding activity specific to RNR-1 to be separated from the endogenous activity (Fig. 5A). RNR-1 binding appears significantly greater than Nur77 binding. However, this is probably because of the low abundance of Nur77 in the heterogeneous complex. However, as the RNR-1 and Nur77 complexes are very similar in mobility, heterodimers might be difficult to detect. Additionally, evidence thus far indicates that unlike most nuclear receptors, NGFI-B/Nur77 binds DNA as a monomer (25).

The binding of RNR-1 to the endogenous activity of the B1a probe remains relatively high (lane 4). This might indicate that Nur77 mRNA is affecting the translation of RNR-1 mRNA. The cotranslation or mixing experiments give no indication of the formation of an RNR-1/Nur77 heterodimeric complex. However, as the RNR-1 and Nur77 complexes are very similar in mobility, heterodimers might be difficult to detect. Additionally, evidence thus far indicates that unlike most nuclear receptors, NGFI-B/Nur77 binds DNA as a monomer (25).

As both the nur77 and RNR-1 genes are induced during liver regeneration, we were interested in measuring their relative ability to transactivate a reporter containing a consensus NGFI-B/Nur77 binding site, (Nur77-RE) placed upstream of a β-globin promoter (Fig. 6). We first tested the ability of RNR-1 to interact with an oligonucleotide containing this sequence (Fig. 6A). As can be seen, Nur77-RE effectively inhibits the binding of RNR-1 to [32P]-B1a. In transfection studies in NIH 3T3 cells, both RNR-1 and nur77 expression plasmids strongly transactivated the Nur77-RE reporter (at least 40-fold over background) (Fig. 6B). In three separate determinations, the effect of RNR-1 and nur77 together was additive, not synergistic.

**DISCUSSION**

We have identified RNR-1, a novel member of the thyroid/steroid receptor family which is induced during liver regeneration. The RNR-1 gene is most similar to the m-nur77/r-NGFI-B gene, which is also induced during liver regeneration. Southern blot analysis of rat DNA digested with two different restriction digests indicates that there is only a single strongly homologous genomic fragment other than the RNR-1 gene itself. This indicates that there may be at most one other family member and that this nuclear receptor family is likely to be limited to relatively few members.

RNR-1 and r-NGFI/m-Nur77 are particularly similar in the DNA binding domains. This includes 100% homology in the A box region, which has recently been identified as essential for r-NGFI-B/m-Nur77 binding to the adenine residues 5' to the TRE half-site in the NBRE. The high degree of homology in the DNA binding domain allowed us to predict that RNR-1 would bind to the NBRE as confirmed by the mobility shift assay. The requirement of the 5' adenine residues for RNR-1 binding was established by the lack of competition of the TRE with the NBRE and the fact that when we changed the residues at the 5' end of the site to adenosines (TRE-AAA), the competition was very effective. Like NGFI-B/Nur77, RNR-1 binds almost equally strongly to the consensus sequence AAAGGTCAC with only 2 adenes upstream of the half-site (25), and thus, our findings suggest that the 3rd upstream adenine is not essential for optimal binding. Interestingly, although chicken ovalbumin upstream promoter has 2 upstream adenes, neither NGFI-B/Nur77 (24) nor RNR-1 (Fig. 5B) bound as well to this site, perhaps because the context of the site is different from Nur77-RE. It is noteworthy, however, that there are five amino acid differences in the DNA binding region of RNR-1 as compared with r-NGFI-B/m-Nur77, one of which occurs in the D box or “knuckle” region of the second zinc finger. These sequence differences may result in slight differences in response element binding affinities between the two proteins which have yet to be determined.

r-NGFI-B/m-Nur77 most likely binds to the NBRE half-site as a monomer (25). The fact that in the gel shift assay, the RNR-1-B1a complex migrates at nearly the same position as the Nur77-B1a complex indicates that RNR-1 may also bind as a monomer. In addition, given that there is almost 60% homology in the carboxyl terminus, the putative dimerization domain, one would expect these two proteins to behave similarly in this respect. However, because both proteins also contain another potential protein dimerization domain in the leucine repeat region, other types of protein-protein interactions cannot be ruled out.

Both RNR-1 and Nur77 strongly transactivate a Nur77-RE reporter, and the effect of the two proteins together is additive, suggesting that there is no cooperativity or inhibition mediated by either protein. However, although there are many
Fig. 5. RNR-1 binds specifically to the NGFI-B/Nur77 DNA-binding elements and is competed by related elements. Panel A, RNR-1 mRNA was translated in vitro with reticulocyte lysate and bound to the radiolabeled NBRE, Bla, and run on a 4% native acrylamide gel. Lane 1, probe alone; lane 2, reticulocyte lysate programmed with RNR-1 mRNA; lane 3, reticulocyte lysate programmed with RNR-1 mRNA mixed with an equal volume of reticulocyte lysate programmed with nur77 mRNA; lane 5, reticulocyte lysate programmed with equal volumes of RNR-1 and nur77 mRNA; lane 6, reticulocyte lysate programmed with nur77 mRNA. Panel B: lane 1, probe alone; lane 2, reticulocyte lysate programmed with H2O; lane 3, reticulocyte lysate programmed with RNR-1 mRNA; lanes 4–6, reticulocyte lysate as in lane 3 with 2, 10, or 100 × unlabeled Bla oligonucleotide; lanes 7–11, reticulocyte lysate as in lane 3 competed with 100 × cold oligonucleotide as indicated. Panel C, the sequences of the oligonucleotides used in panel B.

The similarities between m-Nur77/r-NGFI-B and RNR-1, the tissue-specific expression of the respective genes suggests that the encoded proteins may have different activities as well. NGFI-B mRNA is present in lung, brain, superior cervical ganglia and is high in adrenal tissue (22). In contrast, the RNR-1 gene is expressed at a very low level in lung, spleen, and stomach and a high level in brain. Further, the m-nur77 gene is expressed in serum-stimulated fibroblasts (13) whereas RNR-1 is not. In addition to the tissue-specific expression of the two genes, it is also notable that the amino terminus of the RNR-1, the putative transactivation domain, is only 32% homologous to the corresponding region in r-NGFI-B/m-Nur77. Because of the sequence divergence in this region, it is likely that these two proteins would exhibit important differences in whatever function is determined by this region. Although they both may be nearly equivalent in their ability to transactivate some promoters, there could be promoterspecific differences as well. The coordinate expression of both genes is consistent with a role in liver regeneration.
RNR-1 and NGFI-B/nur77 mRNAs in regenerating liver suggests that the RNR-1 and NGFI-B/Nur77 proteins may confer liver-specific regulation of delayed-early genes induced later in the G1 phase of regeneration.

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