β-Site amyloid precursor protein-cleaving enzyme 1 (BACE1) is a membrane-bound aspartic protease that cleaves amyloid precursor protein to produce a neurotoxic peptide, Aβ, and is implicated in triggering the pathogenesis of Alzheimer disease. We previously reported that BACE1 cleaved rat β-galactoside α2,6-sialyltransferase (ST6Gal I) that was overexpressed in COS cells and that the NH₂ terminus of ST6Gal I secreted from the cells (E41 form) was Glu⁴¹. Here we report that BACE1 gene knock-out mice have one third as much plasma ST6Gal I as control mice, indicating that BACE1 is a major protease which is responsible for cleaving ST6Gal I in vivo. We also found that BACE1-transgenic mice have increased level of ST6Gal I in plasma. Secretion of ST6Gal I from the liver into the plasma is known to be up-regulated during the acute-phase response. To investigate the role of BACE1 in ST6Gal I secretion in vivo, we analyzed the levels of BACE1 mRNA in the liver, as well as the plasma levels of ST6Gal I, in a hepatopathological model, i.e. long-Evans Cinnamon (LEC) rats. This rat is a mutant that spontaneously accumulates copper in the liver and incurs hepatic damage. LEC rats exhibited simultaneous increases in BACE1 mRNA in the liver and in the E41 form of the ST6Gal I protein, the BACE1 product, in plasma as early as 6 weeks of age, again suggesting that BACE1 cleaves ST6Gal I in vivo and controls the secretion of the E41 form.

A characteristic feature of Alzheimer disease (AD) is deposition of amyloid β-peptide (Aβ) in the brain, which is implicated in the pathogenesis of AD (1). Aβ, a 39–43-residue peptide, is generated from the amyloid precursor protein (APP) by the action of β- and γ-secretases. APP is a type I transmembrane glycoprotein which is present in the trans-Golgi network and endosomes. Cleavage of APP by β-secretase (BACE1 (β-site APP-cleaving enzyme 1)) initially produces a soluble NH₂-terminal fragment (APPβ) and a 12-kDa COOH-terminal fragment (C99) that remains membrane-bound. Subsequently, C99 is cleaved by γ-secretase in its transmembrane region, resulting in production of the pathogenic Aβ peptide (2, 3). Alternative cleavage of APP by α-secretase within the Aβ sequence produces a soluble NH₂-terminal fragment (APPα) and a 10-kDa membrane-bound COOH-terminal fragment (C83) (4, 5). C83 is also cleaved by γ-secretase to produce the nonpathogenic p3 peptide.

BACE1, a pepsin-like membrane-bound aspartic protease, was recently identified as β-secretase (6–10). A close homologue of BACE1, designated BACE2, was found to share 60% similarity in amino acid sequence with BACE1 (10–13). BACE1 knock-out mice completely lack Aβ production in the brain (14, 15), indicating that BACE1 carries majority of β-secretase activity in the brain. BACE2 may be important in Down syndrome pathology, because the enzyme is encoded by chromosome 21 (12) and its expression is elevated in trisomic brains (16).

A series of extensive studies showed that γ-secretase activity is performed by a protein complex that includes presenilins (PS1 or PS2) (17). γ-Secretase is essential, not only for Aβ production, but also for neuronal development, due to its cleavage of a Notch receptor (3, 18). Nevertheless, development of inhibitors to γ-secretase is a promising approach for treating Alzheimer disease, as is also true for β-secretase inhibitors (19).

ST6Gal I (β-galactoside α2,6-sialyltransferase) is a type II membrane protein that is localized in the trans-Golgi network. It catalyzes α2,6-sialylation of Galβ1,4-GlcNAc structures on N-glycans. ST6Gal I is highly expressed in the liver and is expressed in most other tissues to some extent (20). The majority of serum ST6Gal I is secreted from the liver (21, 22), and secretion is enhanced during acute-phase hepatic reactions (23, 24). We previously found that BACE1 is involved in the cleavage and secretion of ST6Gal I, at least in cultured cells (25, 26), leading to an assumption that BACE1 cleaves ST6Gal I in the liver and triggers its secretion into plasma.

To confirm in vivo cleavage of ST6Gal I by BACE1, in the protein ligand-1; GDPAH, glyceraldehyde-3-phosphate dehydrogenase; MES, 4-morpholineethanesulfonic acid; LMW, lower molecular weight.
present study we analyzed plasma ST6Gal I levels in BACE1-deficient and BACE1-transgenic mice. We also used a mutant animal strain, the Long-Evans Cinnamon (LEC) rat, to analyze the mechanisms of ST6Gal I secretion in hepatopathological conditions. The LEC rat, a model of Wilson disease, has a deletion in the gene for the copper-transporting ATPase gene (ATP7B) (27–29). Golgi-localized ATP7B is involved in copper secretion into the plasma, which is coupled with ceruloplasmin synthesis and biliary copper excretion (30). Like patients with Wilson disease, LEC rats suffer from toxic accumulation of copper in the liver and eventually develop hepatitis and then hepatocellular carcinoma (31). This rat strain is often utilized for studying the pathogenesis of hepatitis and hepatoma.

On the assumption that ST6Gal I secretion is stimulated in the hepatopathological model of LEC rats and that such stimulation is related to the level of BACE1 activity, we analyzed the expression profiles of mRNAs of ST6Gal I and BACE1 in the liver of LEC rats and also the secretion of ST6Gal I into plasma.

**EXPERIMENTAL PROCEDURES**

**Materials**—Male LEC and Wistar rats, maintained in specific-pathogen-free conditions, were purchased from Charles River Japan Inc. (Yokohama, Japan) and the Shizuoka Agricultural Cooperative Association for Laboratory Animals (Shizuoka, Japan), respectively. Samples of LEA (Long-Evans Agouti) rats were kindly provided by Dr. Noriyuki Kaisi, Tohoku University. BACE1 knock-out mice and their control mice from Angen were maintained in the Charles River Laboratories, Inc. (Wilmington, MA). BACE1-transgenic mice were prepared by an overexpression cassette, in which the chicken β-actin promoter drove the expression of human BACE1 (32). The sources of materials used in this work were as follows: tissue culture media and reagents, including Dulbecco’s modified Eagle’s medium and William’s E medium, were from Invitrogen; ExpreS3/S3 protein labeling mix was from Fermentas (Hannover, Germany); recombinant human ST6Gal I purified from Diagnostics, CMP-14NεAuc and protein A-Sepharose Fast Flow were from Amersham Biosciences; affinity Gel-CDP from Merck/EMD Bioscience (San Diego, CA); protein molecular weight standards were from Bio-Rad; and all other chemicals from Sigma or Wako Chemicals (Osaka, Japan). Protein concentration was determined with Pierce BCA protein assay reagents. Anti-BACE1 antibody was purchased from MoBiTec Co. (Göttingen, Germany). We used anti-ST6Gal I or E41 polyclonal antibodies. Immunoprecipitated proteins were detected in wild-type mice, and a 3.5-kb fragment was detected in the livers of BACE1-deficient and BACE1-transgenic mice by Western blot analysis. Mouse livers were homogenized with buffer H (50 mM MES, pH 6.0, 1 mM EDTA, 0.15 mM NaCl). Micosome fraction (50 or 100 μg) that was solubilized with buffer S (50 mM Tris-HCl, pH 8.0, 10 μM NaCl, 1% Triton X-100) was treated with Laemmli sample buffer (36), subjected to SDS-polyacrylamide gel electrophoresis (5–20% gradient), and then transferred to a nitrocellulose membrane. The membrane was incubated with anti-BACE1 (1:1,000), horseradish peroxidase-antianti-tubulin IgG (Cappel, 1:1,000) was used as the secondary antibody, and chemiluminescent substrate (Pierce) was used for detection (25).

**Detection of ST6Gal I Protein**—Plasma from mice (50 μl) were diluted with 10 volumes of buffer A (20 mM Tris-HCl, pH 8.0) and then loaded onto a HiTrap Q-Sepharose column (1 ml of gel volume, Amersham Biosciences) using Trizol reagent (Invitrogen), and 5–10 μg of RNA was reverse-transcribed with random hexamers by using a Super Script II RT kit (Invitrogen) according to the manufacturer’s protocol. The cDNA was then amplified with 900 nm forward primer, 900 nm reverse primer, 250 nm fluorescent probe, and 25 μl of Universal PCR Master Mix (Applied Biosystems) in a total volume of 20 μl, using an ABI PRISM 7900HT sequence detection system (Applied Biosystems). The PCR conditions were 1 cycle at 50 °C for 2 min, 1 cycle at 95 °C for 10 min, and 40 cycles at 95 °C for 15 s and 50 °C for 1 min. All primers and probes were purchased from Applied Biosystems. The sequences of primers and probes were as follows: ST6Gal I, 5′-CAGCAAGAAGACTGACTTCTCTT-3′ (forward primer) and 5′-CTGAAGAAGAAGCTCTGTTT-3′ (reverse primer), 5′-CAACATCTCATTTCTACAGGAGGTACAGC-3′ (probe); BACE2, 5′-GAAGAGCCCGCTGGGCTCTTTT-3′ (forward primer), 5′-ATTTAAAGGCCACAGTTATCTAGT-3′ (reverse primer), 5′-CCATCATGCAAGCTCTTACATCAGC-3′ (probe). For BACE1 and GAPDH primers and probes, we used Assays-on-Demand Gene Expression Products, and cDNAs were added to the TaqMan Universal PCR Master Mix (Applied Biosystems), which contained all reagents for PCR. The probes for ST6Gal I, BACE1, and BACE2 were labeled with the reporter fluorescent dye FAM. The probes for GAPDH were labeled with VIC at the 5′ ends and at the 3′ ends were labeled with the quencher dye TAMRA. The expression levels of target genes were measured in duplicate and were normalized to the GAPDH expression level.

**Characterization of BACE1-deficient and BACE1-transgenic Mice**—Genotypes of BACE1-deficient and control mice were confirmed by PCR analysis using genomic DNA prepared from livers and primers (primer 1, 5′-TGGA TGT ACC ATT TCT TCT GAC GA-3′ and primer 2, 5′-AGG CAA TAA CCA GTA CCC TGT CTA-3′). A 770-bp fragment was detected in wild-type mice, and a 3.5-kb fragment was detected in the BACE1-deficient mice. We also examined the levels of ST6Gal I protein in the livers of BACE1-deficient and BACE1-transgenic mice by Western blot analysis. Liver samples were homogenized with buffer H (50 mM MES, pH 6.0, 1 mM EDTA, 0.15 mM NaCl). Micosome fraction (50 or 100 μg) that was solubilized with buffer S (50 mM Tris-HCl, pH 8.0, 0.15 mM NaCl, 1% Triton X-100) was treated with Laemmli sample buffer (36), subjected to SDS-polyacrylamide gel electrophoresis (5–20% gradient), and then transferred to a nitrocellulose membrane. The membrane was incubated with anti-BACE1 (1:1,000), horseradish peroxidase-antianti-tubulin IgG (Cappel, 1:1,000) was used as the secondary antibody, and chemiluminescent substrate (Pierce) was used for detection (25).
RESULTS

Plasma ST6Gal I Levels Were Decreased in BACE1-deficient Mice—ST6Gal I is highly expressed in the liver (20), and a membrane-bound form of ST6Gal I is proteolytically cleaved in the trans-Golgi network and then secreted into the plasma (22, 33). We previously reported that secretion of ST6Gal I was markedly increased by overexpression of BACE1 in COS cells (25), indicating that BACE1 cleaves ST6Gal I at least in the cultured cells. To demonstrate cleavage of ST6Gal I by BACE1 also in vivo, we utilized BACE1-deficient mice for analyzing plasma ST6Gal I levels, expecting ST6Gal I cleavage and secretion to be lacking or diminished. At first we examined genotypes of BACE1-deficient and control mice by PCR (Fig. 1A), and then confirmed the absence or presence of BACE1 protein in the microsome fraction prepared from the liver (Fig. 1B).

From mouse plasma, ST6Gal I was partially puriﬁed or enriched by HiTrap Q anionic exchange chromatography. Western blot analysis of ST6Gal I-enriched fraction revealed that ST6Gal I levels in BACE1-deficient mice were decreased to ~30% that of control mice (Fig. 1C), suggesting that BACE1 is a major protease that cleaves ST6Gal I to induce its secretion in vivo and that the remaining plasma ST6Gal I in BACE1-deficient mice may be cleaved by some other protease(s). We next studied whether the elevated level of BACE1 could cause the elevation of the plasma ST6Gal I in vivo. To do so, we have generated the two lines of BACE1-transgenic mice that express human BACE1 under the control of actin promoter for ubiquitous expression. We detected high BACE1 expression in the liver of both of two lines (Fig. 2, upper panel). Both of BACE1-transgenic mice had elevated levels of plasma ST6Gal I as compared with the control mice (Fig. 2, lower panel).

ST6Gal I Secretion in Rat Plasma—We previously reported that rat ST6Gal I secreted from COS cells has a sequence of Glu41-Phe42-Gln43 at its amino terminus (E41 form) (25, 35). Overexpression of BACE1 in COS cells markedly increased the secretion of the E41 form (25). We found that BACE1 first cleaved rat ST6Gal I between Leu27 and Gln30 to generate the sequence Gln44-Ala45-Lys46-Glu47-Phe48-Gln49 at the amino terminus, and then the three terminal amino acids, Gln-Ala-Lys, were trimmed by a luminal aminopeptidase(s) to produce the E41 form that is secreted from the cells (26).

For further clariﬁcation of the in vivo cleavage and secretion of ST6Gal I, we looked for E41 form in rat plasma. Western blot analysis using anti-ST6Gal I antibody revealed two isoforms of soluble ST6Gal I in the plasma of Wistar rats (Fig. 3). After N-glycosidase F treatment to remove N-glycans, the two isoforms were still detected as a pair of bands on an immuno-blot, but with slightly increased mobility, suggesting that the difference between the isoforms is not due to the presence of N-glycan structures but rather to the position of the cleavage sites. The two isoforms were separated by anion-exchange FPLC chromatography (Fig. 4A). These isoforms were subjected to immunostaining in which we used an E41-antibody that speciﬁcally recognizes the E41 form (25, 26). E41-antibody reacted only with the higher molecular weight isoform, suggesting that it is the E41 form, most likely produced by BACE1 (Fig. 4B). The lower molecular weight isoform (LMW form) has a distinct cleavage site, possibly produced by some other protease(s).

To characterize these isoforms further, we used CDP-hexanamine-agarose column chromatography, which is often used for purifying sialyltransferases (33, 37). The E41 form bound to the afﬁnity column and was eluted with CDP, whereas the LMW form did not bind to the column (Fig. 5A). The result suggests that the LMW form lacks afﬁnity for the donor substrate, CMP-sialic acid, and does not have catalytic activity. The E41 form and the LMW form, which were separated each other by the anion-exchange column chromatography...
were subjected to sialyltransferase assay. Indeed, the LMW fraction contained less than one-tenth the activity that the E41 fraction had (Fig. 5B). The activity in the former fraction is possibly due to the trace contamination of the E41 form. Alternatively, the LMW form may carry a little activity.

ST6Gal I Secretion in Rat Hepatocytes—Cao et al. (38) showed that ST6Gal I is expressed in hepatocytes but not in nonparenchymal cells such as biliary epithelial cells, Kupfer cells, and Ito cells in the liver, suggesting that the plasma isoforms originate from hepatocytes. Thus, we prepared primary cultured hepatocytes from the livers of Wistar rats and metabolically labeled them with [35S]methionine. ST6Gal I proteins were immunoprecipitated from the cell lysates or media with anti-ST6Gal I antibody. We detected two bands corresponding to soluble ST6Gal I in the culture media (Fig. 6A). The molecular weights of the two ST6Gal I isoforms in the media were similar to those of soluble ST6Gal I in plasma (Figs. 3 and 6A). The two isoforms secreted form the cells had higher molecular weight than the cellular form. This may be due to glycosylation difference as proposed for N-acetylglucosaminyltransferase I (39).

The higher molecular weight isoform was immunoprecipitated with anti-E41 antibody (data not shown), suggesting that the higher molecular weight form corresponds to the E41 form and the lower molecular weight form has a different cleavage site.

Next, we performed a pulse-chase experiment to see difference in the secretion of these isoforms. When hepatocytes were pulse labeled and chased for 6 h, the majority of the soluble ST6Gal I isoform was the lower molecular weight form (Fig. 6B). After 18-h chase, the lower molecular weight form was a minor component (Fig. 6B). Thus the lower molecular weight form appeared first, degraded rapidly, and then later higher molecular weight form was generated, suggesting that the lower molecular weight form is not a secondary product derived from the higher molecular weight form (E41 form).

ST6Gal I Cleavage and Secretion in LEC Rats—ST6Gal I activity in the plasma increases in various pathological conditions such as hepatitis (23) and cancer (40–42). To analyze ST6Gal I isoforms in hepatopathological conditions, we used LEC rats, which have a genetic mutation in the copper-translocating ATPase (ATP7B), resulting in toxic accumulation of copper in the liver. At first we measured α2,6-sialyltransferase activity of plasma of LEC and control Wistar rats. As shown in...
BACE1 plays a critical role in the generation of amyloid β-peptide, the deposition of which is an initial pathological change occurring in Alzheimer disease. Inhibiting BACE1 activity may therefore be a promising way to treat the disease. This therapeutic strategy is supported by the observation that ST6Gal I, a homologue of BACE1, was also analyzed. Real-time PCR analysis revealed that LEC rats exhibited significant elevation of BACE1 mRNA at the ages of 6 and 8 weeks, whereas control Wistar rats did not show such significant elevation (Fig. 8). The levels of BACE2 and ST6Gal I mRNAs were very stable in both rat strains. These results suggest that the high levels of E41 form in LEC plasma at the ages of 6 and 8 weeks can be attributed mainly to enhanced transcription of the BACE1 gene in the liver.

**DISCUSSION**

In Vivo Cleavage of Sialyltransferase by Alzheimer β-Secretase

**Fig. 6.** ST6Gal I isoforms in cell lysates (C) and culture media (M) from rat hepatocytes. A, Rat primary cultured hepatocytes were isolated. The cells were labeled with a Expre35S35S protein labeling mix (100 μCi/ml) in methionine- and cysteine-free Dulbecco’s modified Eagle’s medium for 18 h (35, 49). ST6Gal I proteins were immunoprecipitated from cell lysates and media with anti-ST6Gal I antibody and then separated by SDS-polyacrylamide gel electrophoresis. Radiolabeled proteins were detected with a radioimage analyzer. B, Rat primary hepatocytes were pulse-labeled with Expre35S35S protein labeling mix for 2 h and then chased for 6 or 18 h. ST6Gal I in culture media was immunoprecipitated with anti-ST6Gal I antibody and analyzed as described in the legend to Fig. 5A.

Fig. 7A, LEC rats showed higher sialyltransferase activity in plasma than Wistar rats. The activity was increased at 6 and 8 weeks of age, while that of Wistar rat was stable. The result suggests a high level of the E41 form in LEC and its increase during the hepatopathological conditions. We then analyzed plasma ST6Gal I isoforms of LEC rats by Western blot analysis using anti-ST6Gal I antibody. LEA rats were used as the wild-type controls. The ratio of the E41 form to total ST6Gal I (E41 + LMW form) in LEC rats was higher than that in Wistar rats at all ages analyzed. The E41 ratio in LEC rats increased at ages of 6 and 8 weeks, whereas that in LEA rats exhibited little change along with age (Fig. 7B). Wistar rats, another control strain, also exhibited very little change in the isoform pattern (data not shown).

To understand the molecular mechanism of the elevation of the plasma E41 form in LEC rats, we analyzed the levels of the mRNAs for BACE1 and ST6Gal I in the liver. The level of mRNA for BACE2, a homologue of BACE1, was also analyzed. Real-time PCR analysis revealed that LEC rats exhibited significant elevation of BACE1 mRNA at the ages of 6 and 8 weeks, whereas control Wistar rats did not show such significant elevation (Fig. 8). The levels of BACE2 and ST6Gal I mRNAs were very stable in both rat strains. These results suggest that the high levels of E41 form in LEC plasma at the ages of 6 and 8 weeks can be attributed mainly to enhanced transcription of the BACE1 gene in the liver.
into a catalytic pocket of BACE1 in an appropriate orientation. There is another example showing that a membrane-tethered protease can process both types of substrate proteins, i.e., TACE (tumor necrosis factor α-converting enzyme) can cleave EGF (epidermal growth factor) receptor (type I protein) and pro-TNFα (type II protein). As mentioned above, Lichtenthaler et al. (44) reported that BACE1 cleaves PSGL-1, which bears sialyl-LewisX glycans (Sia2,3Galβ1,4(Fucα1,3)GlcNAc-), and mediates leukocyte trafficking, suggesting a possible function of BACE1 in the immune system. Cleavage of PSGL-1 by BACE1 may be an important down-regulation mechanism for controlling leukocyte migration during acute inflammation. In vivo cleavage of physiological substrates by BACE1 in non-neuronal tissues are important issues that need to be addressed.

We found two isoforms of soluble ST6Gal I in rat plasma: one is the E41 form having sialyltransferase activity and the other is the LMW form losing enzyme activity. Our results suggest that the LMW form is missing some important domain for catalytic activity, i.e., part of the catalytic and/or substrate-binding domain. We are currently unable to identify a protease(s) that is involved in formation of the LMW form. Purification of the LMW form and subsequent sequence analysis will provide information on the substrate specificity of the protease. Molecular cloning of the protease cDNA will be required for understanding the entire process of in vivo cleavage and secretion of ST6Gal I.

Two ST6Gal I isoforms showing different molecular weights were detected in rat plasma, whereas an apparent single band was observed in mouse plasma. The reason why we did not detect two bands in mouse plasma may be due to the amino acid difference at the position 41, i.e., Leu37-Gln38-Ala39-Lys40-Glu41-Phe42-Glu43 in the rat ST6Gal I and Leu37-Gln38-Ala39-Lys40-Val41-Phe42-Glu43 in the mouse ST6Gal I. Rat ST6Gal I was first cleaved by BACE1 between Leu37 and Gln38 to generate the sequence Gln38-Ala39-Lys40-Glu41-Phe42-Glu43 at the amino terminus, and then the three terminal amino acids, Gln38-Ala39-Lys40, were trimmed by a luminal aminopeptidase(s) to produce the E41 form (26). In the trimming process, the presence of Glu41 appeared to be a signal for preventing further trimming. Mouse ST6Gal I, which lacks the Glu residue, would be further trimmed by the aminopeptidase, and the trimmed product may overlap with the other ST6Gal I isoform on an immuno blot (Fig. 1C).

LEC rats were initially found as a natural mutant that spontaneously develops jaundice around the age of 16 weeks, then they turned out to be a good model of Wilson disease. Like patients with Wilson disease, LEC rats have a deletion in the gene for the copper-transporting ATPase (ATP7B), which transports copper to the lumen of the secretory compartment to supply it to various copper-dependent enzymes such as Cu,Zn-superoxide dismutase, ceruloplasmin, and cytochrome c oxidase. High copper and iron levels in the liver and low copper concentrations in the plasma of LEC rats appear to cause several biochemical abnormalities, including decreased levels of Cu,Zn-superoxide dismutase activity (SOD) (45), cytochrome P450 isoforms (46), and S-adenosylmethionine synthase (γ-GTP) (47), as well as induction of N-acetylglucosaminyltransferase III activity (48), even before hepatitis occurs (~16 weeks). We demonstrated that BACE1 mRNA transcription in the liver is significantly elevated in 6- and 8-week-old LEC rats, suggesting that elevation of BACE1 mRNA and plasma ST6Gal I can be used as early markers for hepatic stress prior to onset of hepatitis. Even though the level of BACE1 mRNA was higher at 8 weeks than 6 weeks of age, the ST6Gal I E41 form showed a maximum at 6 weeks. Although the expression level of BACE1 would be a major factor that controls the secretion of E41 form, other regulatory mechanisms may also affect the secretion, e.g., sorting of ST6Gal I to a particular subcellular compartment, in which the substrate ST6Gal I meet BACE1 protease. Such a mechanism other than BACE1 expression may also regulate the production of E41 form. Kaplan et al. (23) reported that serum ST6Gal I levels are enhanced during acute hepatitis, and the enhancement is attributed to elevation of ST6Gal I mRNA in the liver. Dalziel et al. (24) then reported that hepatic acute phase induction of ST6Gal I mRNA is controlled by a liver-specific promoter-regulatory region (P1) of ST6Gal I gene. Therefore, it will be necessary to examine the levels of ST6Gal I mRNA together with those of BACE1 mRNA in the liver during the hepatitis stage (after the age of 20 weeks) in LEC rats.

In conclusion, we showed that BACE1 is responsible for cleaving ST6Gal I in vivo and that increase of ST6Gal I secretion in the early hepatopathological condition of LEC rat is attributed mainly to up-regulation of BACE1 mRNA transcription in the liver.
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