Angiotensin II Regulates Liver Regeneration via Type 1 Receptor Following Partial Hepatectomy in Mice

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Angiotensin II (Ang II) is an important mediator stimulating liver fibrosis after liver injury. However, it is not known whether Ang II plays a role in liver regeneration. Here, we investigate the effects of Ang II type 1 (AT1) receptor blocker (ARB), angiotensin-converting enzyme inhibitor (ACEI), systemic infusion of Ang II, and genetic deficiency of the AT1a receptor (AT1a-KO) on the hepatic regenerative response to partial hepatectomy (PH) in mice. Administration of ARB (candesartan cilexetil and losartan) or ACEI (enalapril and lisinopril) enhanced 5-bromo-2′-deoxyuridine (BrdU) incorporation into hepatocyte nuclei in remnant liver as well as the restoration of liver weight after PH. Systemic infusion of Ang II (100 ng/kg/min) suppressed the PH-induced BrdU incorporation and the restoration of liver weight. In contrast to Ang II infusion, these hepatic responses to PH were significantly greater in AT1a-KO mice than in wild-type mice. The PH-induced increases in hepatic levels of hepatocyte growth factor (HGF) mRNA and plasma HGF concentrations were greater in candesartan- and enalapril-treated mice or in AT1a-KO mice than in vehicle-treated mice or wild-type mice, respectively, whereas they were less in Ang II-infused mice than in vehicle-infused mice. In contrast to HGF, blockades of the renin-angiotensin system or Ang II infusion produced opposite effects on the PH-induce increases in hepatic transforming growth factor (TGF)-beta 1 mRNA and plasma TGF-beta 1 levels. These studies suggest that Ang II plays a role in the liver regeneration as a suppressor of hepatocyte proliferation via the AT1 receptor-mediated control of growth factor production.

Key words liver regeneration; angiotensin II; angiotensin receptor blocker

After acute liver injury such as viral hepatitis, toxic damage, and surgical resection, liver parenchymal cells regenerate and replace the necrotic or apoptotic cells. However, if the hepatic injury persists then, eventually, liver regeneration fails and hepatocytes are substituted with the deposition of extracellular matrix proteins, resulting in hepatic fibrosis.1) Recent evidence indicates that angiotensin II (Ang II) is an important mediator of liver fibrosis: systemic Ang II is frequently elevated in patients with cirrhosis2) and the hepatic renin-angiotensin system is up-regulated in human and rat livers undergoing active fibrogenesis.3,4) Blockade of the renin-angiotensin system by angiotensin-converting enzyme inhibitors (ACEIs) or AT1 receptor blockers (ARBs) attenuates inflammation and extracellular matrix accumulation in chronic liver injury in rats or in patients with chronic hepatitis C.5—8) Thus, the inhibition of the renin-angiotensin system is thought to be one of the important therapeutic approaches to the treatment of liver fibrosis.1,9)

Whereas much evidence has accumulated on the important role of the renin-angiotensin system in liver fibrosis, little information has been available on the role of Ang II in the regenerative response of hepatic parenchymal cells to liver injury. To our knowledge, only two studies including our own genetic deficiency of AT1a receptor on the PH-induced hepatic regenerative response to 70% PH in mice. We also examined effects of the exogenous Ang II and genetic deficiency of AT1a receptor on the PH-induced hepatic regenerative response in mice.

MATERIALS AND METHODS

Animal Experiments All animal manipulations were performed in accordance with the guidelines of the Kobe Gakuin University Experimental Animal Care and Use Committee. Male ddY mice (7-week-old) were obtained from Japan SLC (Hamamatsu, Japan). The AT1a-receptor-deficient homozygous (male, 7-week-old) (AT1a-KO) and wild-type (C57/BL/6; male, 7-week-old) (WT) mice were also used.11) During this study, the mice were allowed free access to food and water and were housed at a constant temperature with a 12-h light/dark cycle. The animals were maintained under rest conditions for at least one week prior to any experiment. They were anesthetized with an injection of sodium pentobarbital (40 mg/kg i.p.). A 70% hepatectomy was performed by the excision of the median and left lateral lobes of the liver, as described previously.12) Control mice received a sham operation in which the abdominal cavity was opened and the liver was gently manipulated but not resected.

Drug Administration With the exception of candesartan, the following drugs were dissolved in saline. All the drugs were administered to male ddY mice (8-week-old) once a day from 3 d before surgery until sacrifice: enalapril
(1 mg/kg i.p.; Sigma Aldrich, St. Louis, MO, U.S.A.), lisinopril (1 mg/kg i.p.; kindly supplied by Shionogi & Co., Ltd., Osaka, Japan), candesartan cilexetil (candesartan; 1 mg/kg p.o., as a suspension in 10% gum arabic; kindly supplied by Takeda Pharmaceutical Co., Ltd., Osaka, Japan), losartan (1 mg/kg i.p.; LKT Laboratories, St. Paul, MN, U.S.A.), PD123319 (1 mg/kg i.p.; Sigma Aldrich) and icatibant (1 mg/kg s.c.; Peptide Institute, Inc., Osaka, Japan). The control animals received i.p. injection of saline. The animals were sacrificed 24 h after the last administration of drug or vehicle.

Ang II Infusion Mice (male ddY mice, 8-week-old) were infused with either vehicle (10 mM HCl) or Ang II (100 ng/kg/min, dissolved in 10 mM HCl; Peptide Institute) through s.c. osmotic mini-pumps (Alzet model 1007D for 7 d delivery; Muromachi-kikai, Tokyo, Japan) from 1 d before surgery until sacrifice.

- **5-Bromo-2′-deoxyuridine (BrdU) Labeling** In order to measure the proliferation of hepatocytes in remnant liver after PH, the mice were i.v. injected with 200 mg/kg of BrdU (Roche Diagnostics, Tokyo, Japan) into the tail vein. One hour after the BrdU injection, the animals were anesthetized with sodium pentobarbital (40 mg/kg i.p.), and the remnant liver was perfused with saline to remove blood. A piece of liver (ca. 100 mg) was excised in order to extract total RNA and the remnant liver was perfused with 10 ml of 20% neutral-buffered formalin. The liver was resected, weighed, and fixed in 20% neutral-buffered formalin for 1 h. The fixed liver pieces were paraffin embedded, sectioned (6 mm), then stained with hematoxylin and eosin. For the immunohistochemical assessment of hepatocellular BrdU incorporation, the sections were stained using the BrdU Labeling and Detection Kit II (Roche Diagnostics, Tokyo, Japan). A BrdU-labeling index was determined by counting the number of BrdU-positive nuclei in at least three different random ×200 fields (>300 cells) in the liver sections and was expressed as a percentage of the number of labeled nuclei divided by the total number of nuclei.

**Northern Blots of Hepatocyte Growth Factor (HGF) and Transforming Growth Factor Beta-1 (TGF-beta 1) mRNA** The expression of HGF and TGF-beta 1 mRNAs in the liver was analyzed by northern blotting using specific cDNA probes for mouse HGF and TGF-beta 1 mRNA, respectively. The probes were 658-bp and 595-bp fragments of mouse HGF and TGF-beta 1 cDNA, respectively, obtained by polymerase chain reaction amplification using RNA from mouse liver as a template following TA cloning. The probes were radiolabeled with [alpha-32P]dCTP by random priming. Total RNA was extracted from liver samples using acid guanidium thiocyanate–phenol–chloroform. Aliquots (10 μg) of the total RNA were resolved by electrophoresis on a 1.2% agarose gel containing 20 mM 3-(N-morpholino)propane-sulfonic acid, 1 mM EDTA, 8 mM sodium acetate (pH 4.0), and 2.2 mM formaldehyde, then transferred to nylon membrane (Hybond N+; Amersham, Little Chalfont, U.K.). The membranes were irradiated with UV and prehybridized at 65 °C for 30 min in hybridization buffer containing 1% bovine serum albumin, 1 mM EDTA, 7% sodium dodecyl sulfate (SDS), and 5% formamide in 0.5 M sodium phosphate, pH 7.2. The membranes were then hybridized in hybridization buffer at 65 °C with 32P-labeled cDNA for 16–18 h, and then rinsed in 40 mM sodium phosphate, pH 7.2, containing 1 mM EDTA and 0.1% SDS. The blots were autoradiographed and quantified using a Fuji Film Bio Imaging Analyzer BAS1000 (Fuji Photo Co., Tokyo, Japan). The membranes were reprobed with a 32P-labeled oligonucleotide (41-mer) that hybridized with 18S rRNA as a control for loading. The HGF and TGF-beta 1 mRNA/18S rRNA ratios were determined in order to estimate the hepatic concentrations of HGF and TGF-beta 1 mRNAs.

**Assays of HGF and TGF-beta 1 in Plasma** The plasma concentrations of HGF were assayed by the enzyme-linked immunosorbent assay (ELISA) using HGF Assay Kit (Institute of Immunology, Tokyo, Japan). The plasma concentrations of TGF-beta 1 were assayed by ELISA using the TGF-beta 1 Immuno Assay System (R & D Systems, Minneapolis, MN, U.S.A.). In order to convert the inactive form of TGF-beta 1 to the active form prior to assay, diluted plasma was acidified by the addition of 1 M HCL, incubated for 15 min at room temperature, and then neutralized by 1 M NaOH.

**Statistical Analysis** The data are expressed as the mean±S.E.M. Statistical comparisons were performed using a one-way analysis of variance with pairwise comparison by the Bonferroni–Dunnett method. Differences were considered significant at the p<0.05 level.

**RESULTS**

**Effects of ARBs and ACEIs on Liver Regeneration in Mice** The BrdU incorporation into hepatocyte nuclei was used to evaluate cell proliferation in vivo in the regenerating liver after PH. In control animals, the BrdU incorporation significantly increased from 12 h after PH, peaked at 48 h, and decreased thereafter; ca. 10% of the hepatic nuclei were in the S phase at 48 h after PH, whereas the sham operation did not influence the BrdU-labeling index (Fig. 1). A similar time-course profile to a greater extent of BrdU-labeling indices was observed in mice treated with losartan: the BrdU-labeling indices were ca. 3-fold greater in losartan-treated animals between 24 and 72 h and peaked at 48 h after PH (Fig. 1). Losartan administration into sham-operated animals did not affect on the BrdU-labeling indices (data not shown). Therefore, pharmacological blockade of the renin-angiotensin system by other drugs on liver regeneration was evaluated by measuring BrdU-labeling index 48 h after PH.

As shown in Fig. 2, the BrdU-labeling indices were ca. 2-fold greater in the mice treated with candesartan, enalapril, or lisinopril than in the vehicle-treated mice at 48 h after PH (Figs. 2A, B). The administration of PD123319, an Ang II type 2 (AT2) receptor antagonist, or icatibant, a bradykinin B2 receptor antagonist, did not affect the PH-induced increase in the BrdU-labeling index (Fig. 2B). The administration of icatibant in combination with candesartan or enalapril did not influence the candesartan- or enalapril-induced enhancement of BrdU-labeling indices after PH, respectively (Fig. 2B).

The surgical resection of 70% of the liver led to an increase in the weight of the remnant hepatic lobes: the liver/body weight ratio was restored by ca. 49%, 62%, and 74% of the preoperative weight ratio at 48, 96, and 120 h after PH, respectively (Fig. 3). The restoration of liver weight was significantly enhanced by the treatments with candesar-
Fig. 1. Increase in the BrdU Incorporation into Hepatocytes Following PH in Mice Treated with or without Losartan

Mice were injected with losartan (1 mg/kg, i.p) or vehicle (saline) once a day from 3 d before the sham operation or PH to 1 d before sacrifice. At various times after a sham operation and PH, mice received 200 mg/kg of BrdU in the tail vein 1 h before sacrifice. A BrdU-labeling index was determined by counting the number of BrdU-positive nuclei in at least three different random fields (300 cells) in the liver sections and was expressed as a percentage of the number of labeled nuclei divided by the total number of nuclei. Each bar represents the mean ± S.E.M. (n=5). *p<0.001 versus the sham-operated mice; †p<0.001 versus the PH-operated mice treated with saline.

Fig. 2. Effects of ARBs and ACEIs on the PH-Induced Increase in BrdU Incorporation into Hepatocytes

Drugs were administered once a day from 3 d before the sham operation or PH to 1 d after surgery: enalapril (Ena; 1 mg/kg, i.p), lisinopril (Lis; 1 mg/kg, i.p.), candesartan (Cand; 1 mg/kg, orally as a suspension in 10% gum arabic), losartan (Los; 1 mg/kg, i.p), PD123319 (PD; 1 mg/kg, i.p), and icatibant (Ica; 1 mg/kg, s.c.). Sham- and PH-operated mice without drug treatment were i.p. injected with saline. Animals were sacrificed 48 h after the sham operation or PH. BrdU was i.v. injected 1 h before sacrifice. (A) Representative photomicrographs (>200x) of liver sections stained for immunohistochemical assessment of BrdU incorporation, which were harvested from sham- or PH-operated mice, and PH-operated mice treated with lisinopril (PH+Lis) or candesartan (PH+Cand). BrdU-positive cells are identified by the dark brown (3,3'- diaminobenzidine-stained) nuclei in the photomicrographs. (B) Data represent the average percentage of BrdU-positive nuclei (±S.E.M.) in liver tissues of five mice from each group treated with drugs or their combination. *p<0.001 versus the sham-operated mice; †p<0.001 versus the PH-operated mice treated with saline. ¶p<0.1 and §p<0.01 indicate no significant difference from the PH-operated mice treated with candesartan and enalapril, respectively.

Effects of Ang II Infusion and AT₁-Receptor-Deficiency on Liver Regeneration in Mice

In order to determine the effect of exogenous Ang II on the PH-induced liver regeneration, Ang II (100 ng/kg/min) was infused into mice for 72 h through s.c. osmotic pumps from 24 h before PH. The BrdU incorporation 48 h after PH was reduced to ca. 76% in mice receiving Ang II as compared with the vehicle-infused mice (Fig. 4), whereas Ang II infusion did not affect the BrdU-labeling indices of the sham-operated animals (data not shown). In contrast, the BrdU incorporation 48 h after PH was ca. 2-fold greater in AT1a-KO mice than in the WT mice (Fig. 4).

The restoration of liver weight after PH was significantly suppressed in Ang II-infused mice as compared with the vehicle-infused mice at 48, 96, and 120 h after PH, while it was significantly greater in AT1a-KO mice than in WT mice at 96 and 120 h after PH (Fig. 5). Body weight changes after PH were not significantly different between groups of animals treated with vehicle, candesartan and enalapril (data not shown).

Effects of Candesartan, Enalapril, Ang II, and AT₁a-Receptor-Deficiency on Hepatic Expression of HGF mRNA and TGF-beta 1 mRNA after PH

We analyzed the hepatic expression of HGF mRNA and TGF-beta 1 mRNA by northern blotting after PH. Both the HGF and TGF-beta 1 mRNA levels increased in the remnant livers of mice and reached peaks at 48 and 24 h after PH, respectively (data not shown). Therefore, we studied the effects of candesartan, enalapril, and Ang II-infusion on the HGF mRNA or TGF-beta 1 mRNA in remnant liver 48 or 24 h after PH, respectively. As shown in Fig. 6, PH alone resulted in a ca. 140% increase in HGF mRNA levels, and the treatment with either candesartan or enalapril further increased hepatic levels of HGF mRNA by ca. 45% as compared with the vehicle-treated mice after PH. In contrast, the PH-induced elevation of TGF-beta 1 mRNA was significantly suppressed by treatments with candesartan and enalapril (Fig. 6). Neither candesartan nor enalapril affected the hepatic levels of either HGF or TGF-beta 1 mRNAs in the sham-operated mice (data not shown).

The systemic infusion of Ang II significantly suppressed the hepatic levels of HGF mRNA, whereas it enhanced the expression of TGF-beta 1 mRNA after PH (Fig. 6). Neither of the mRNA levels was affected by Ang II infusion in the...
sham-operated mice (data not shown). In the AT1a-KO mice, basal hepatic levels of both HGF and TGF-beta 1 mRNAs were not significantly different from those in the WT mice (Fig. 6). However, the PH-induced expression of HGF mRNA in AT1a-KO mice was ca. 44% greater than in the WT mice, while that of TGF-beta 1 mRNA was significantly less than in WT mice (Fig. 6).

Effects of Candesartan, Enalapril, Ang II, and AT1a-Receptor-Deficiency on Plasma Concentrations of HGF and TGF-beta 1 after PH

The PH resulted in the elevation of the plasma concentration of HGF with a peak at 48 h, while that of TGF-beta 1 peaked at 24 h (data not shown). Therefore, we examined the effects of candesartan, enalapril, and Ang II-infusion on the plasma levels of HGF or TGF-

Fig. 3. Effects of Candesartan (Cand) and Enalapril (Ena) on the Restoration of Liver Weights after PH

Drugs were administered as described in the legend to Fig. 2. The ratios of liver weight (wet) to body weight were measured at the indicated times after PH. Each bar represents the mean±S.E.M. (n=5); *p<0.01 and $p<0.05$ versus the saline-injected mice.

Fig. 4. Effects of Ang II Infusion (Ang II) and AT1a-Receptor Deficiency (AT1a-KO) on the PH-Induced Increase in BrdU Incorporation into Hepatocytes

Ang II (100 ng/kg/min) or vehicle was s.c. infused by an osmotic pump from 1 d before PH until sacrifice. The BrdU incorporation was measured at 48 h after PH. Each bar represents the mean±S.E.M. (n=5 for Sham, PH, and infusion experiments; n=6 for experiments using WT and AT1a-KO mice). *p<0.05 versus the vehicle-infused mice with PH; $p<0.001$ versus the sham-operated WT mice.

Fig. 5. Effects of Ang II Infusion (Ang II) and AT1a-Receptor Deficiency (AT1a-KO) on the Restoration of Liver Weights after PH

Ang II was infused as described in the legend to Fig. 4. The ratios of liver weight (wet) to body weight were measured at the indicated times after PH in vehicle-infused (vehicle) and Ang II-infused or in wild-type (WT) and AT1a-KO mice. Each bar represents the mean±S.E.M. (n=5 for infusion experiments, n=6 for experiments using WT and AT1a-KO mice); *p<0.001 versus the vehicle-infused mice; $p<0.01$ versus the WT mice.

Fig. 6. Effects of Candesartan (Cand), Enalapril (Ena), Ang II Infusion (Ang II), and AT1a-Receptor Deficiency (AT1a-KO) on the PH-Induced Increases in the Hepatic Levels of HGF and TGF-beta 1 mRNAs

Drugs were administered as described in the legend to Fig. 2. Ang II was infused as described in the legend to Fig. 3. HGF and TGF-beta 1 mRNAs were measured by northern blotting of the livers of mice 48 h after PH. (A) Representative northern blots of HGF and TGF-beta 1 mRNA. 18S rRNA was used as an internal control. (B) Densitometric data for HGF and TGF-beta 1 mRNA expressed as a ratio against 18S rRNA. Each bar represents mean±S.E.M. (n=5, with the exception of experiments using WT and AT1a-KO mice in which n=6). *p<0.001 versus the sham-operated mice; $p<0.001$ and $p<0.05$ versus the PH-operated mice; $p<0.05$ versus the PH-operated mice with vehicle infusion; †p<0.001 versus the sham-operated WT mice.
Liver regeneration occurs via a complex process that includes multiple signals mediated by many growth factors and sequences of events. These signals drive hepatocytes from the quiescent G0 state into the G1 phase of the cell cycle and then through the restriction points of G1 into the S phase, where commitment to division occurs. Of the several commitment points, the G1 phase is most easily controlled and can be regulated both positively and negatively.

Liver regeneration is initiated by cellular stress, which induces the expression of growth factors such as hepatocyte growth factor (HGF) and transforming growth factor beta (TGF-beta). These factors stimulate the proliferation and differentiation of hepatocytes and non-parenchymal cells, respectively.

**DISCUSSION**

The current study demonstrates that the pharmacological or genetic ablation of the renin-angiotensin system enhances, whereas the exogenous Ang II suppresses, the regenerative response of remnant liver to PH. The finding that an AT1 receptor antagonist had no effect on the PH-induced liver regeneration suggests that the suppression of liver regeneration by Ang II is mediated via the AT1 receptor. This was confirmed by the observation that the liver regeneration was enhanced in mice lacking the AT1 receptor as compared with the WT mice. Thus, we provide evidence that Ang II plays a role in the process of liver regeneration as a suppressor of cell proliferation via the AT1 receptor.

In a previous study, Ramalho et al. observed that the liver regeneration in rats was enhanced by ACEIs such as lisinopril, captopril, enalaprilat after PH. Based on the observation that the administration of bradykinin, but not losartan, enhanced liver regeneration after PH, these authors suggested that the augmentation of bradykinin action, rather than the attenuation of Ang II action, was responsible for the ACEI-induced enhancement of liver regeneration. This was confirmed in part by our previous study using rats that the lisinopril-induced enhancement of BrdU incorporation into hepatocyte nuclei after PH was partially blocked by treatment with bradykinin B2 receptor antagonist icatibant. Because the BrdU incorporation following PH was increased by the administration of ARBs (losartan and candesartan) as well as lisinopril, we concluded that the ACEI enhanced the hepatic regenerative response to PH in rats by two mechanisms: an activation of B2 receptor and inhibition of Ang II production. In contrast to these studies in rats, we found in the present study using mice that icatibant did not inhibit the enalapril-induced increase in the BrdU-labeling indices, suggesting that the ACEI-induced enhancement of liver regeneration in mice is not mediated by the activation of B2 receptor.

In order to further determine the role of Ang II in the process of liver regeneration after PH, we performed two experiments using mice systemically infused with Ang II and those genetically lacking the AT1a receptors. The systemic infusion of Ang II through an osmotic pump significantly suppressed the PH-induced increase in the BrdU-labeling index of remnant liver. The effect of Ang II is unlikely to depend on an increase in arterial pressure because Ang II was infused at a subpressor dose in the mice. Therefore, it is conceivable that the increased levels of Ang II in circulation suppress the hepatic regenerative response to PH, probably via the stimulation of the AT1 receptors localized in the remnant liver. Although it is well known that in rodents the AT1 receptors are subdivided into two pharmacologically identical subtypes, designated AT1a and AT1b, tissue distribution studies have demonstrated that only the AT1a subtype is expressed in the liver. Thus, to determine the role of the hepatic AT1a receptor in liver regeneration, we compared the hepatic regenerative response to PH between the WT and AT1a-KO mice. We found that hepatic BrdU incorporation after PH was significantly greater in the AT1a-KO mice than in the WT mice, suggesting that in mice an endogenous Ang II inhibits the liver regeneration via the AT1a receptor.

Liver regeneration occurs via a complex process that includes multiple signals mediated by many growth factors and sequences of events. These signals drive hepatocytes from the quiescent G0 state into the G1 phase of the cell cycle and then through the restriction points of G1, into the S phase, where commitment to division occurs. Of the several growth factors regulating liver regeneration, HGF is the most potent mitogen, inducing DNA synthesis in hepatocytes with antifibrotic activity. HGF is produced by nonparenchymal cells in the liver, including the hepatic stellate cells, endothelial cells, and Kupffer cells, and rapidly appears in the blood after PH. In contrast, TGF-beta 1, which is also produced...
by nonparenchymal cells in the liver, appears to be a key mediator in fibrogenesis and to be involved in the termination response of liver regeneration.^{18,19} Recently, it has been demonstrated that Ang II is a potent negative regulator for HGF production in the myocardium, kidneys, and vessels^{20–23} as well as a positive regulator of TGF-beta 1 production in hepatic stellate cells.^{21,24} Therefore, it was hypothesized that Ang II suppressed the hepatocyte proliferation after liver injury by inhibiting HGF production and/or stimulating TGF-beta 1 production in the liver. In order to verify this hypothesis, we studied the expression levels of HGF and TGF-beta 1 mRNA in remnant liver, as well as the plasma levels of HGF and TGF-beta 1 after PH. The hepatic levels of both HGF and TGF-beta 1 mRNA, as well as the plasma levels of both proteins, were increased 24—48 h after PH. Blockade of the renin-angiotensin system before and after PH by the administration of enalapril and candesartan, augmented the PH-induced elevations of hepatic HGF mRNA and plasma HGF levels, whereas it suppressed the PH-induced elevations of hepatic TGF-beta 1 mRNA and plasma TGF-beta 1 levels. Similar observations were made in the AT1a-KO mice in which the PH-induced elevations of hepatic HGF mRNA and plasma HGF levels were greater than in the WT mice, and those of TGF-beta 1 mRNA and plasma TGF-beta 1 level were less than in the WT mice. In contrast, the systemic infusion of Ang II produced the opposite effects: inhibition of the PH-induced increases in HGF mRNA and plasma HGF levels, and the enhancement of the PH-induced increases in TGF-beta 1 mRNA and plasma TGF-beta 1 levels. These results suggest that Ang II regulates liver regeneration after PH, at least in part, by attenuating HGF production and by enhancing TGF-beta 1 production in the remnant liver. Thus, it seems likely that both ACEIs and ARBs enhance hepatocyte proliferation after PH by inhibiting the Ang II-dependent control of growth factor production including HGF and TGF-beta 1.

Overall, the present study demonstrated that the pharmacological and genetic ablation of the renin-angiotensin system enhanced liver regeneration in mice after PH, and that this was accompanied by an enhanced production of HGF and the attenuation of TGF-beta 1 production. Therefore, it is conceivable that Ang II may be one of the important factors regulating the process of liver regeneration. It should be noted that the pharmacological blockade of the renin-angiotensin system appears to be a strategy for therapies that accelerate the proliferation of parenchymal cells, as well as preventing fibrosis in chronic liver diseases.

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