Aliskiren reduces portal pressure and intrahepatic resistance in biliary cirrhotic rats

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Received February 3, 2012; accepted May 21, 2012

Abstract

Background: It is a well-accepted fact that angiotensin II (Ang II) contributes to increased vascular tone in cirrhotic livers. However, aliskiren attenuates the effect of Ang II through direct renin inhibition. Our study aimed to evaluate the effects of aliskiren on portal pressure and intrahepatic resistance in bile duct ligated (BDL) rats.

Methods: The effects of acute intravenous infusion (1 mg or 3 mg) or a course of 2-day oral administration of aliskiren (20 mg/kg/day) on blood pressure and portal pressure were evaluated in BDL and sham rats. Intrahepatic resistance was evaluated by a liver perfusion study isolated in situ. Ang II efflux was measured by Enzyme-linked immunosorbent assay (ELISA). The hepatic gene expression of angiotensinogen, renin, angiotensin-converting enzyme (ACE), Ang II type 1 receptor (AT1R) was analyzed with quantitative reverse transcription polymerase chain reaction.

Results: Aliskiren infusion intravenously reduced portal pressure with a minimal effect on blood pressure in BDL rats. Direct infusion of aliskiren in an isolated cirrhotic liver caused greater vasorelaxation and decreased hepatic production of Ang II. Two days of aliskiren treatment reduced portal pressure and hepatic ACE mRNA; in addition, it improved the vasodilator response to acetylcholine in the cirrhotic livers and decreased Ang II efflux.

Conclusion: Aliskiren reduced portal pressure in cirrhotic rats. The portal hypotensive effect of aliskiren was related to the amelioration of the Ang II induced intrahepatic vasoconstriction.

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Keywords: angiotensin II; direct renin inhibitor; intrahepatic resistance; portal hypertension

1. Introduction

Increased hepatic resistance to portal blood inflow is the initial hemodynamic derangement that contributes to portal hypertension in cirrhosis. Thereafter, an increased portal blood inflow maintains and worsens portal hypertension.1 Increased intrahepatic resistance (IHR) is mainly caused by the disruption of the vascular architecture due to an irreversible structural change in cirrhotic livers. Additionally, an enhancement in intrahepatic vascular tone also contributes to the increased IHR.2 As IHR increases, the increased portal resistance results in dilatation of the mesenteric and systemic vasculature and decreases the effective blood volume. A compensatory change that restores the effective blood volume is the activation of the renin-angiotensin-aldosterone system (RAS).

The RAS plays an important role in the regulation of local hemodynamics in a cirrhotic liver.3 The primary effector
peptide of the system is angiotensin II (Ang II).3 In cirrhotic rats, the hepatic expression of angiotensin type I receptor (AT1R) and plasma Ang II concentration has been shown to increase significantly when compared with those in healthy rat livers.4,5 Administration of Ang II also increases intrahepatic vascular resistance in cirrhosis,6,7 while treatment with Ang II receptor blockers has the opposite effect.7,8 Therefore, as the action of Ang II in the cirrhotic liver contributes to the increase of IHR,9 inhibition of Ang II production is a rational way to decrease IHR.

Renin, which cleaves liver-produced angiotensinogen to angiotensin I (Ang I), is the first rate-limiting enzyme in the synthesis of Ang II.10 Inhibition of renin activity has been a potential way to down-regulate the RAS. Recently, a direct renin inhibitor, aliskiren, had been approved for treatment of hypertension.10 Aliskiren occupies the active site of renin11 to block the enzyme activity of renin. This effect leads to lower plasma renin activity, plasma Ang I, and Ang II.12,13 We hypothesized that aliskiren may lower the production of Ang II in cirrhotic rat livers and subsequently reduce IHR. To date, there has been no data published regarding the effects of aliskiren on IHR in cirrhosis. The aim of this study is to investigate the possible effects of aliskiren on portal pressure and IHR in a bile duct ligated cirrhotic rat model.

2. Methods

2.1. Animals

Adult male Sprague Dawley rats (BioLasco Taiwan Co., Ltd, Taipei, Taiwan) were used in all experiments. Cirrhotic rats were created by bile duct ligation (BDL) as previously described.14 The rats underwent median laparotomy with the common bile duct exposed, but without ligation and served as the control (sham rats). According to the previous findings, the expression of AT1R in liver and Ang II levels in plasma increased dramatically in the BDL rats 4 weeks after ligation of the common bile duct.4 The BDL rats after 4 weeks were thereafter used for the experiment. This study was approved by the Animal Experiment Committee of Taipei Veterans General Hospital and performed according to the Guide for the Care and Use of Laboratory Animals prepared by the U.S. National Academy of Sciences.

2.2. Experimental protocol

2.2.1. Experiment I: Evaluation of the effects of acute intravenous administration of aliskiren on arterial pressure and portal pressure

In a previous study, it was found that aliskiren dose-dependently decreased blood pressure in spontaneously hypertensive rats.15 In this pharmacokinetic study, the rats receiving 30 mg/kg aliskiren orally or 3 mg/kg aliskiren intravenously showed similar plasma concentration-time profiles.15 When the experiments began, we administered aliskiren (Novartis Pharmaceuticals, East Hanover, NJ, USA) 10 mg/kg intravenously to the BDL rats; however, dramatic hypotension was noted. Therefore, in the subsequent study, the rats (n = 5 in each sham group, n = 7 in each BDL group) were given smaller doses of aliskiren (1 or 3 mg/kg, intravenously), which had a more moderate effect on systemic blood pressure.

The hemodynamic studies were performed by catheterization method. With the rats sedated by pentobarbital (50 mg/kg, intraperitoneally), the femoral artery and vein were cannulated with PE-50 (ADInstruments, Inc, Colorado, USA) tubing to monitor blood pressure and infuse drugs. The portal vein was cannulated via an ileal vein for the measurement of portal venous pressure (PVP). The rectal temperature was maintained at 37°C using a heating pad. All pressures were recorded using a multichannel recorder (BIOPAC Systems, Inc, CA, USA). After an initial stable period, the basal values were obtained. One mg/kg or 3 mg/kg aliskiren in 1 ml 5% dextrose water (D5W) was then injected for 10 minutes via the femoral vein through an automatic pump. Blood pressure and PVP were concomitantly monitored and recorded for 60 minutes.

2.2.2. Experiment II: Evaluation of the effects of direct infusion of aliskiren on intrahepatic resistance in an in situ liver perfusion system

The second set of BDL rats and sham rats (n = 4 in each group) were used in this experiment. The in situ liver perfusion was performed in a recirculating system as previously described.14 The flow rate of the perfusate was 25 ml/minute. The viability of each liver was assessed by gross appearance of the liver, bile production, and curve pattern of portal perfusion pressure (PPP). The livers were allowed to stabilize for 30 minutes before basal PPP was measured.

After basal measurements of PPP, 10e4 M methoxamine (MTX) was added to the perfusate for preconstriction 5 minutes before the challenge of sequential doses of aliskiren (10e9 to 10e4 M) or D5W. Then, the concentration-responed curve of PPP to aliskiren or vehicle was measured. Before the MTX administration, and after aliskiren or vehicle administration, each 3 ml of effluent was collected for further measurement of Ang II. All livers were weighed after the experiment. The absolute increase of Ang II levels in liver perfusates after drugs administration was expressed in pg/ml/gm of liver weight. The response to aliskiren or vehicle was calculated as the percentage change of PPP from baseline.

2.2.3. Experiment III: Evaluation of the effects of oral administration of aliskiren on blood pressure, PVP, and IHR

Because the effect of aliskiren was most apparent at 24 and 48 hours. After drug intake,13,16 we performed another hemodynamic study 2 days after administration of aliskiren. Thus, the third set of BDL rats were treated orally with aliskiren (20 mg/kg/day, BDL-Alil n = 8) or vehicle (BDL-V; n = 8). The sham rats receiving aliskiren (sham-Alil; n = 5) or vehicle (sham-V; n = 5) were used for comparison. After measurement of arterial blood pressure and PVP, the rats received the in situ liver perfusion study, which ran in a recirculating system at a constant flow (25 ml/minute). Each
3 ml of effluent was harvested at 0 minutes and at 30 minutes after stabilization to estimate the basal production of Ang II. The basal production rate of Ang II in liver perfusates was expressed in pg/ml/minute/g of liver weight. Afterward, the responses of PPP to MTX (10^{-4} M) were measured, both before and subsequent to the cumulative doses of acetylcysteine (Ach; 10^{-7} – 10^{-4} M). The relaxation response to Ach was calculated as the percentage change of PPP from baseline.

2.2.4. Experiment IV: Evaluation the effect of aliskiren on blood and liver biochemistry

The fourth set of BDL/sham rats was treated orally with aliskiren (20 mg/kg/day) or vehicle (n = 5 in each group). After this step was completed, the rats were sacrificed. Blood samples were collected on ice with tubes containing 0.1 M sodium citrate. Plasma was separated by refrigerated centrifugation and processed immediately or stored at −80°C until assay. The liver was rapidly excised and weighted after ice-cold phosphate buffered saline (PBS) perfusion. Aliquots of liver were snap frozen in liquid nitrogen and kept at −80°C until analysis.

The plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALK-P) total bilirubin (TB), blood urea nitrogen (BUN), creatinine (Cr), sodium (Na), and potassium (K) were measured using standard auto-SMAC analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

2.3. Measurements of Ang II in liver perfusates

The perfusates collected from the in situ liver perfusion study were measured for the content of Ang II. The Ang II levels were determined by the AssayMax Angiotensin II Enzyme-linked immunosorbent assay (ELISA) kit (AssayPro Co., St. Charles, MO, USA). This assay has an intra-assay coefficient of variation of 5.0% and an interassay coefficient of variation of 7.1%.

2.4. Real-time quantitative reverse transcriptase—polymerase chain reaction

Complementary DNAs were synthesized by reverse transcription of 1 μg of total RNA according to the MMLV reverse transcriptase first-strand cDNA Synthesis Kit (Epicentre Technologies Corp., Madison, WI, USA). The primers used are listed in Table 1. Quantitative gene expression was performed on the ABI PRISM 7900HT Sequence detection system (Applied Biosystems Inc., Foster City, CA, USA) using SYBR green (Roche Diagnostics GmbH, Mannheim, Germany) technology. The expression of target genes was calculated by the 2^{-\Delta \Delta Ct} method. The results were expressed as fold change relative to the control group.

2.5. Statistical analysis

Data were analyzed by GraphPad Prism 4 (GraphPad Software, San Diego, CA, USA) and expressed as means ± standard deviation. Kruskal-Wallis test followed by Dunn’s test or Mann-Whitney U-test was used for comparison between groups. Concentration-response curves of PPP were analyzed by repeated-measure analysis of variance. Significance was determined at a p value less than 0.05.

3. Results

3.1. Aliskiren infusion reduces portal pressure with modest effect on arterial blood pressure

In sham groups, the rats receiving aliskiren of 1 mg or 3 mg exhibited no significant changes of MAP and PVP during the observation period (Fig. 1A and B). In the BDL groups, both 1 mg and 3 mg doses of aliskiren caused a transient drop in MAP during the period of aliskiren infusion (−7.44 ± 2.01 mmHg, −9.69 ± 1.54 mmHg respectively; Fig. 1C). However, although the MAP returned to baseline later and remained stable in the following period (Fig. 1C), the PVP decreased significantly 50 minutes after the intravenous administration of 1 mg aliskiren in the BDL rats. In BDL rats receiving 3 mg aliskiren, the PVP decreased significantly from 20 minutes after drug infusion (Fig. 1D). The 3 mg dosage also had a stronger effect on PVP in BDL rats compared with the 1 mg dose (p = 0.0096 by repeated-measure analysis of variance; Fig. 1D).

3.2. Direct effect of aliskiren on intrahepatic resistance

Based on the data from Experiment I, we assumed that the reduction in PVP may have resulted from a direct influence of aliskiren on IHR. This prompted us to measure the responses of liver to the cumulative doses of aliskiren or D5W in the rats (Fig. 2A). The result was that there was significantly less vasorelaxation (a smaller percentage reduction of PPP) in both groups of cirrhotic livers when compared with the sham livers (p < 0.01). The BDL rat livers receiving sequential doses of aliskiren had significantly greater vasorelaxation than the BDL rat livers receiving D5W (p = 0.002). However, the degree of vasorelaxation was not significantly different between sham rat livers receiving aliskiren or D5W. In addition, the absolute increase in Ang II in BDL rat liver perfusion effluent after
aliskiren administration was significantly lower than that in BDL rat livers receiving D5W (p = 0.035) (Fig. 2B). Nevertheless, the absolute increases in Ang II in liver perfusion effluents after aliskiren or D5W administration were not different in the sham rats (p = 0.26; Fig. 2B).

3.3. Effects of oral aliskiren treatment for 48 hours on hemodynamics and blood chemistry

All cirrhotic rats had portal hypertension, ascites and splenomegaly. The blood chemistry, and weights of the body and liver are shown in Table 2. The plasma levels of BUN, Cr, Na, and K and body weight were not different for the experimental groups. The BDL rats receiving vehicle or aliskiren had a higher liver weight and higher plasma levels of ALT, AST, ALKP, and TB than the sham rats receiving vehicle. After treatment with aliskiren, these parameters remained unchanged.

The MAP was significantly lower in the BDL-V and BDL-Ali rats than that in the sham-V rats (p < 0.01; Fig. 3A). After aliskiren treatment, the MAP remained unchanged in both the BDL and sham rats. The PVP was significantly higher in the BDL-V rats than in the sham-V rats (p < 0.001; Fig. 3B). However, the BDL-Ali rats had a significantly lower PVP than the BDL-V rats (p < 0.01; Fig. 3B).

Fig. 2. (A) Dose-response curves to cumulative doses of aliskiren (Ali) or 5% dextrose water (D5W) in the liver from the sham or bile duct ligated (BDL) rats; (B) absolute increase of angiotensin II levels in liver perfusates after drug administration in four experimental groups. (Sham-D5W/Ali: sham rats receiving D5W or Ali; BDL-D5W/Ali: BDL rats receiving D5W or Ali; n = 4 in each group.) *p < 0.05 compared with BDL-D5W rats. **p < 0.01 compared with BDL-D5W rats. PPP = portal perfusion pressure; n.s. = not significant.
In the isolated in situ liver perfusion study, basal PPP was significantly higher in the BDL-V rats than in the sham-V rats ($p < 0.01$). A significant decrease in PPP was also observed in the BDL-Ali rats compared with the BDL-V rats ($p = 0.035$; Fig. 3C). Responses to accumulative doses of Ach in the four groups of rats are shown in Fig. 3D. There was significantly less vasorelaxation in both groups of cirrhotic livers compared with the sham livers ($p < 0.001$). The BDL-Ali rat livers had significantly more vasorelaxation than the BDL-V rat livers ($p = 0.0006$). Furthermore, the administration of aliskiren decreased the basal Ang II production in livers of BDL-Ali rats ($p < 0.01$; Fig. 3E).

### 3.4. Effects of aliskiren on classical RAS

The hepatic transcript expressions of angiotensinogen and renin were not different in all experimental groups (Fig. 4A and B). In the BDL-V rats, hepatic transcript expressions of ACE and renin were not different in all experimental groups (Fig. 4A and B). The administration of aliskiren decreased the basal Ang II production in livers of BDL-Ali rats ($p < 0.01$; Fig. 3E).

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Sham-V</th>
<th>Sham-Ali</th>
<th>BDL-V</th>
<th>BDL-Ali</th>
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<tr>
<td>Body weight (g)</td>
<td>293.8 ± 65.44</td>
<td>292.8 ± 38.50</td>
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<td>Liver weight (g)</td>
<td>11.48 ± 2.19</td>
<td>11.20 ± 2.06</td>
<td>20.59 ± 4.21*</td>
<td>21.98 ± 2.69*</td>
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<tr>
<td>ALT (U/L)</td>
<td>52.40 ± 6.19</td>
<td>42.80 ± 0.84</td>
<td>126.3 ± 16.62*</td>
<td>119.8 ± 33.93*</td>
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<tr>
<td>AST (U/L)</td>
<td>108.6 ± 27.34</td>
<td>82.00 ± 11.81</td>
<td>701.7 ± 329.8*</td>
<td>669.0 ± 186.8*</td>
</tr>
<tr>
<td>ALKP (U/L)</td>
<td>163.2 ± 20.60</td>
<td>139.8 ± 33.09</td>
<td>295.0 ± 18.35*</td>
<td>322.0 ± 45.36*</td>
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<tr>
<td>TB (mg/dL)</td>
<td>0.0400 ± 0.0187</td>
<td>0.0340 ± 0.0313</td>
<td>6.110 ± 0.2435*</td>
<td>6.398 ± 1.025*</td>
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<tr>
<td>BUN (U/L)</td>
<td>15.00 ± 1.87</td>
<td>15.60 ± 1.67</td>
<td>13.67 ± 1.03</td>
<td>13.60 ± 3.36</td>
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<tr>
<td>Cr (mg/dL)</td>
<td>0.2920 ± 0.054</td>
<td>0.2620 ± 0.079</td>
<td>0.1900 ± 0.054</td>
<td>0.1900 ± 0.077</td>
</tr>
<tr>
<td>Na (mg/dL)</td>
<td>162.2 ± 4.92</td>
<td>162.6 ± 3.51</td>
<td>154.4 ± 4.10</td>
<td>160.6 ± 6.19</td>
</tr>
<tr>
<td>K (meq/L)</td>
<td>4.920 ± 0.35</td>
<td>5.000 ± 0.76</td>
<td>5.133 ± 0.05</td>
<td>5.160 ± 0.82</td>
</tr>
</tbody>
</table>

All data are expressed as the mean ± SD. Ali = aliskiren; ALKP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BDL-Ali = bile duct ligated rats receiving aliskiren administration; BDL-V = bile duct ligated rats receiving vehicle; BUN = blood urea nitrogen; Cr = creatinine; K = potassium; Na = sodium; Sham-Ali = sham rats receiving aliskiren administration; Sham-V = sham rats receiving vehicle; TB = total bilirubin.

*p < 0.01 vs. sham-V.

Fig. 3. Effects of oral aliskiren (Ali) treatment for 48 hours on portal pressure and intrahepatic resistance. (A) Mean arterial pressure; (B) portal venous pressure; and (C) portal perfusion pressure in four experimental groups; (D) dose-response curves to cumulative doses of acetylcholine in livers from rats in all experimental groups; (E) basal production rate of angiotensin II in liver perfusates from BDL-V/Ali rats. (Sham-V/Ali: sham rats receiving vehicle or Ali; BDL-V/Ali: BDL rats receiving vehicle or Ali; n = 5 in each sham group, n = 8 in each BDL group.) **p < 0.05 vs. sham-V. ***p < 0.01 vs. sham-V. †p < 0.05 vs. BDL-V. ‡p < 0.01 vs. BDL-V. BDL = bile duct ligated.
AT1R were significantly increased when compared with those in the sham-V rats (p = 0.008 and p = 0.0002, respectively; Fig. 4C and D). After aliskiren treatment, although the hepatic expression of ACE decreased significantly (p = 0.03; Fig. 4C), hepatic AT1R mRNA was not altered (p = 0.07; Fig. 4D).

4. Discussion

Currently, there are three drug classes that can inhibit the effects of Ang II in the RAS. Both the ACE inhibitors and angiotensin II receptor blockers (ARBs) have been found effective for reducing portal pressure in several animal and human studies. However, the use of ACE inhibitors or ARB in cirrhotic patients remains controversial, because some clinical studies have shown that these drugs produce only a modest reduction in portal pressure with significant arterial hypotension. Aliskiren is the third and new class of drug that inhibits the RAS. In this study, we observed that the short-term administration of low-dose aliskiren reduced portal pressure and intrahepatic resistance associated with a decreased hepatic production of Ang II in BDL rats. Importantly, blood pressure was not significantly decreased.

Recently, our colleagues found that aliskiren decreased portal venous pressure in PVL rats. In PVL rats, both MAP and PVP were not reduced after subcutaneous aliskiren treatment at a dose of 10 or 30 mg/kg/day. But MAP and PVP decreased significantly after treatment at a dose of 50 mg/kg/day. In our current study, the BDL-Ali rats had a significant decrease in PVP but no reduction of MAP after 2-day oral administration of aliskiren at a dose of 20 mg/kg/day. Different routes of drug administration and models may explain the discrepancy. The oral route used in this study may facilitate getting aliskiren to the liver more efficiently than the subcutaneous route. Moreover, by contrast to the PVL rats that manifest with presinusoidal portal hypertension and normal IHR, the BDL rats are characterized by sinusoidal cirrhosis and high IHR. In our study, the BDL rats receiving a low-dose oral aliskiren had no significant reduction in MAP. Additionally, the BDL rats receiving acute intravenous administration of aliskiren exhibited only an initial transient drop in MAP, and there was a prolonged gradual decrease in PVP after return of MAP. Thus, the portal hypotensive effect of low-dose aliskiren in the BDL rats may be derived from its beneficial effect on IHR. This indicates that low-dose oral aliskiren through amelioration of intrahepatic resistance is effective and safe for the management of portal hypertension from sinusoidal cirrhosis.

Increased resistance to portal blood inflow in the cirrhotic liver is partially due to a reversible and dynamically enhanced intrahepatic vascular tone. Research has shown that Ang II is one of the vasoactive agents contributing to the increased vascular tone in cirrhotic livers. Ballet et al. demonstrated that the intrahepatic vascular resistance was dose-dependently increased in response to sequential doses of Ang II in isolated perfused livers of both cirrhotic and normal rats. More recently, Herath et al. also found that cirrhotic rat livers displayed a marked vasoconstriction response to Ang II. In the present study, the livers of BDL rats receiving 2-day aliskiren exhibited less basal production of Ang II and lower PPP when...
compared with the BDL-V rat livers. Moreover, the vasodilatation response to Ach was improved in cirrhotic livers of BDL-Ali rats. These results suggest that aliskiren attenuated IHR and subsequently decreased PVP through reduction of the hepatic production of Ang II.

In the current study, the hepatic gene expression of angiotensinogen and renin between the BDL-V and sham-V rats was not different. However, the hepatic ACE and AT1R gene expression were significantly higher in the BDL-V rats than in the sham-V rats. These results were in accord with previous research. After aliskiren treatment, the gene expression of angiotensinogen, renin and AT1R remained unchanged, whereas the ACE mRNA was significantly reduced in the cirrhotic livers. To our knowledge, there is no evidence that aliskiren directly lowers the gene expression of renin, ACE, or angiotensinogen. However, it has been shown that aliskiren increased renin expression in human plasma or mouse kidneys. In our current study, the dose of aliskiren was small and the duration of administration was short. Therefore, different species, tissues and dosages used may explain why the liver renin expression was not altered after aliskiren was administered. Moreover, it has been reported that in a human kidney tubular epithelial cell line, Ang II induces ACE gene and protein expressions in a time and dose-dependent manner. Similarly, in our study, the change of ACE expression in BDL-V and BDL-Ali rat livers paralleled the change of hepatic production of Ang II. This suggests that the decreased ACE expression in BDL-Ali rat livers may result from the reduction of local Ang II. However, hepatic ACE may be produced by inflammatory cells, activated stellate cells, hepatocytes, and proliferating bile duct epithelial cells. It is possible that aliskiren may have a direct inhibitory effect on ACE gene expression in these cells. Elucidation of the exact mechanism of how aliskiren influences the hepatic RAS requires further investigation.

It is generally believed that the conversion of locally generated angiotensinogen to Ang I in the liver may occur via renal renin from the circulation because the level of renin in normal or cirrhotic livers has been perceived to be low. We found that in the liver perfusion study, sequential dosages of aliskiren treatment induced more vasorelaxation and less hepatic production of Ang II in the cirrhotic livers. Our data imply that aliskiren might block the conversion of angiotensinogen by occupying the active site of local renin in the cirrhotic livers, leading to the reduction of local Ang II.

In conclusion, our findings demonstrate that there is a beneficial effect of aliskiren on portal pressure and intrahepatic resistance through reduction of Ang II production in the cirrhotic liver. Direct renin inhibition may serve as a potential and effective therapeutic strategy for the management of portal hypertension.

Acknowledgments

The authors gratefully acknowledge Miss Chia-Li Chen and Judy Huang for their excellent technical assistance. This work was supported by grant No. NSC 100-2314-B-075-018 from the National Science Council of Taiwan, and grant No. V100B-021, and V100C-037 from the Taipei Veterans General Hospital, Taipei, Taiwan.


