Adaptive vasodilatory response after octreotide treatment

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Yang, Ying-Ying, Han-Chieh Lin, Yi-Tsau Huang, Tzung-Yan Lee, Wui-Chiang Lee, Ming-Chih Hou, Fa-Yauh Lee, Full-Young Chang, and Shou-Dong Lee. Adaptive vasodilatory response after octreotide treatment. Am J Physiol Gastrointest Liver Physiol 281: G117–G123, 2001.—Despite the suppression of glucagon release, an adaptive response aimed at maintaining vasodilatation after octreotide treatment may exist in portal hypertension. The present study was undertaken to evaluate the possible interaction between endothelium and non-endothelium-derived vasodilators after 1-wk octreotide administration in cirrhotic rats. Rats were allocated to receive either vehicle or octreotide (30 or 100 μg/kg every 12 h subcutaneously). Hemodynamic values, plasma glucagon levels, endothelium-related vasodilatory activities, and aortic endothelial nitric oxide synthase (eNOS) expression were determined after treatment. Octreotide administration decreased plasma glucagon and increased serum 6-keto-PGF1α and NOx levels without affecting the hemodynamic values. In cirrhotic rats receiving octreotide, there was a blunt response to either L-NAME or indomethacin administration alone, but this blunt pressor response disappeared after simultaneous administration of the two drugs. Additionally, an increased aortic eNOS expression was observed in cirrhotic rats receiving 1-wk octreotide. It is concluded that 1-wk octreotide treatment did not correct the hemodynamic derangement in cirrhotic rats. The enhanced endothelium-related vasodilatory activity was noted after octreotide treatment that overcame the octreotide-induced hemodynamic effects in portal hypertension.

It has been shown that peripheral arterial vasodilatation is an initial phenomenon of the hemodynamic derangements after the development of portal hypertension (7, 30, 35). The increased endothelium- (both nitric oxide and prostacyclin) and non-endothelium- (glucagon, etc.) derived vasodilators are responsible for the pathogenesis of peripheral arterial vasodilatation in portal hypertension (4, 13, 29, 34). For many years, the present pharmacological treatment can only partially correct the above hemodynamic derangement of portal hypertension. Recently, it had been reported that inhibition of both nitric oxide and prostacyclin by long-term anti-tumor necrosis factor (TNF)-α administration in portal vein stenosed (PVL) rats was accompanied by a compensatory release of glucagon (25). Similarly, chronic inhibition of cyclooxygenase by indomethacin led to an enhanced nitric oxide synthase activity and consequently to sustained hyperemia in both systemic and splanchnic circulation (8). Taken together, it is possible that an adaptive response aimed at maintaining vasodilatation after pharmacological treatment may exist in portal hypertension (8, 25). Octreotide is a synthetic octopeptide analog of somatostatin that had a much longer biological half-life (3). In cirrhotic patients, short-term administration of octreotide decreased hepatic and azygous blood flow with minimal portal hypertensive effect (17, 22). In addition, a number of studies in patients with cirrhosis and portal hypertension showed minimal or transient systemic hemodynamic effects after octreotide treatment (17, 21, 22). In PVL rats, both acute and chronic administration of octreotide effectively decreased portal pressure, but its influence on systemic hemodynamics was inconsistent (1, 2, 5, 19). Moreover, the effects of octreotide on hemodynamics of cirrhotic rats were controversial (6, 9). Previous studies have demonstrated that chronic octreotide administration exhibited its hemodynamic effects by reducing plasma glucagon levels and increasing vascular reactivity in portal hypertensive animals (11, 19, 31). However, the influence of octreotide administration on endothelium-derived vasodilatory system (both nitric oxide and prostacyclin) has not yet been established. The present study is undertaken to evaluate the hemodynamic effects of 1-wk octreotide treatment in cirrhotic rats produced by chronic bile duct ligation. To evaluate the interaction between 1-wk octreotide treatment and the endothelium-derived vasodilatory activity, the vascular re-
MATERIALS AND METHODS

Animals. Adult male Sprague-Dawley rats weighing between 250 and 350 g were used in all experiments. Cirrhosis with portal hypertension was produced by common bile duct ligation (CBL), as previously described (15). In brief, under ether anesthesia, the common bile duct was ligated with 3-0 silk and sectioned between the ligatures. The midline abdominal incision was closed with catgut. Sham-operated rats had their bile duct exposed but not ligated or sectioned. All rats were caged at 24°C with a 12:12-h light-dark cycle and were allowed free access to food and water. Animal studies were approved by the Animal Experiment Committee of the National Yang-Ming University and were conducted humanely.

Experiment 1: Hemodynamic studies. Three weeks after CBL, three groups of bile duct-ligated rats (nine rats in each group) received vehicle, or 30 μg/kg or 100 μg/kg of octreotide every 12 h subcutaneously (Novartis Pharmaceutical, Basel, Switzerland) for 7 consecutive days. Another group of 4-wk sham-operated rats was included for comparison. Hemodynamic studies were performed at the eighth day after drug administration. The two doses of octreotide chosen in the present study were followed as in our previous studies (10–12, 18, 19).

All rats were fasted 18 h before the hemodynamic studies and had free access to water. Under ketamine anesthesia (100 mg/kg im), a tracheostomy was performed to keep the airway patent. A catheter was inserted into the left ventricle through the right carotid artery for radioactive microsphere injection. Correct positioning of the catheter was confirmed by blood pressure tracing. A femoral artery catheter was also inserted to monitor the arterial pressure and heart rate and to withdraw the reference blood sample. The abdomen was then opened by a midline incision, and the portal vein was cannulated via a small ileal vein for measurement of portal pressure. The tip of the catheter was placed in the distal part of the superior mesenteric vein. The rectal temperature was maintained at 37°C by use of a heating lamp. All pressures were measured and recorded with a multichannel recorder (model RS 3400, Gould, Cupertino, CA). After the hemodynamic values had stabilized, cardiac output and regional organ blood flows were measured by the radioactive microsphere technique with the reference sample method as previously described (19). In brief, the reference sample was withdrawn from the femoral artery into a syringe for 75 s at a rate of 0.8 ml/min, by use of a Harvard pump (Harvard Apparatus, Millis, MA). Ten seconds after the withdrawal of the reference sample, ~60,000 57Co-labeled microspheres of 15-μm diameter (New England Nuclear, Boston, MA) were injected and flushed with 0.4 ml saline into the left ventricle through the right carotid artery catheter over a period of 20 s. After hemodynamic measurement, the animals were killed with a bolus of saturated KCl, and the individual organs were dissected. The radioactivity of each organ and the reference blood sample was counted in a γ-scintillation counter (Auto Gamma 5000, Packard, Downers Grove, IL). Adequate mixing of microspheres was assumed when the difference of radioactivity between the left and right kidney was below 10%.

Cardiac output (CO) (ml/min) was calculated as

\[
\text{[radioactivity injected (cpm)/reference sample radioactivity (cpm)]} \times 0.8 \text{ (ml/min)}
\]

Cardiac index (CI) was derived from the formula

\[
\text{CI (ml/min}^{-1} \cdot 100 \text{ g body wt}^{-1}) = \frac{CO}{100 \text{ g body wt}}
\]

Regional organ blood flows were calculated according to the following formula

\[
\text{organ blood flow (ml} \cdot \text{min}^{-1} \cdot 100 \text{ g body wt}^{-1}) = \left[ \frac{\text{organ radioactivity (cpm)}}{\text{radioactivity injected (cpm)}} \times \text{CI} \right]
\]

Portal territory blood flow (PTBF, expressed in ml·min⁻¹·100 g body wt⁻¹) was taken as the sum of spleen, stomach, small bowel, colon, and mesentery with pancreas blood flows. Systemic vascular resistance (SVR) was calculated according to the following formula

\[
\text{SVR} = \frac{\text{MAP (mmHg) \times 80/CI}}{10^4/100 \text{ g body wt}}
\]

Vascular resistances were expressed as dyn·s·cm⁻⁵·10⁴/100 g body wt.

Experiment 2: Plasma glucagon, NOx, and 6-keto-PGF₁α determinations. To avoid the confounding factors induced by saline injection during hemodynamic measurement or anesthesia, another set of octreotide and vehicle-treated CBL rats and a group of sham-operated rats as described in experiment 1 were used for measuring plasma NOx, 6-keto-PGF₁α, and glucagon concentrations. The study protocol was exactly the same as in previous experiments. All rats were fasted 18 h before measurement. Thereafter, blood samples were obtained by decapitation and collected in prechilled tubes containing EDTA. The samples were centrifuged for 15 min at 4°C and stored at −70°C until assays. Plasma glucagon levels were determined by RIA (Daichi Radioisotope Laboratories, Tokyo, Japan) with cross-reactivity 100% to glucagon, <0.1% to oxytostatinulin, 0% to human insulin, human proinsulin, human C-peptide, somatostatin, and pancreatic polypeptide. Serum levels of NOx, an index of nitric oxide generation (13), were measured by a colorimetric method based on the Griess reaction (Cayman Chemical, Ann Arbor, MI). Levels of 6-keto-PGF₁α, the stable metabolite of prostacyclin, were also determined by means of ELISA (Cayman Chemical, Ann Arbor, MI) with intra- and interassay coefficient of variation ≤10%.

Experiment 3: Dose response of indomethacin or 1-NAME on systemic hemodynamics. Two sets of octreotide or vehicle-treated CBL rats and sham-operated rats as described in experiment 1 were used in this experiment for evaluation of the dose response of indomethacin or L-NAME on systemic hemodynamics. The study protocol was exactly the same as in previous experiments. Under ketamine anesthesia, the right femoral artery and the right femoral vein were cannulated with PE-50 tubing to monitor MAP and to infuse drugs. CO was measured by thermodilution, as previously described (6). Briefly, a theremistor was placed in the aortic arch just distal to the aortic valve, and the thermal indicator (100 μl of 5% normal saline) was injected into the right atrium through a PE-50 catheter. The aortic thermistor was connected to a cardiac output computer (cardiotherm-500-AC-R, Columbus Instruments International, OH). Five thermodilution curves were obtained for each CO measurement. The final cardiac output value was obtained...
from the arithmetic mean of the computer results. CI and SVR were calculated as described above.

After an initial stable period of 30 min, the basal values were obtained. Then the sequential doses of indomethacin (5, 10, and 20 mg/kg, Sigma Chemical, St. Louis, MO) or L-NAME (3, 6, 12, and 24 mg/kg, Sigma Chemical) were administered intravenously in each set of cirrhotic and sham-operated rats, respectively. All the hemodynamic parameters were recorded continuously. CO was measured at the point of maximal change of MAP after the injection of each dose of indomethacin or L-NAME in each animal. CI and SVR were calculated as described above. Above doses of indomethacin or L-NAME were chosen by previous report and preliminary calculated as described above. Above doses of indomethacin were infused in cirrhotic rats receiving vehicle and those receiving 1-wk octreotide or vehicle-treated rats. Aortic eNOS protein expressions were examined by western blotting. Aortic eNOS protein expressions were examined by western blotting. Aortic eNOS protein expressions were examined by western blotting.

We therefore chose the combined administration of L-NAME (6 mg/kg) and indomethacin (5 mg/kg) to assess the vascular response in octreotide or vehicle-treated CBL and sham-operated rats. The procedure was similar to experiment 3; after basal values were obtained, the combined doses of 6 mg/kg of L-NAME and 5 mg/kg of indomethacin were infused through bilateral femoral veins in each set of cirrhotic and sham-operated rats. The total duration of the experiment was up to 40 min.

**Experiment 4: Influence of the combination of indomethacin and L-NAME on systemic hemodynamics.** Another set of octreotide or vehicle-treated CBL and sham-operated rats as described in experiment 1 was used in this experiment to assess of the effects of the combination of indomethacin and L-NAME on systemic hemodynamics. The study protocol was exactly the same as in previous experiments. In a preliminary study, the CBL rats could not tolerate the combined administration of higher doses of indomethacin and L-NAME. We therefore chose the combined administration of L-NAME (6 mg/kg) and indomethacin (5 mg/kg) to assess the vascular response octreotide or vehicle-treated CBL and sham-operated rats. The procedure was similar to experiment 3; after basal values were obtained, the combined doses of 6 mg/kg of L-NAME and 5 mg/kg of indomethacin were infused through bilateral femoral veins in each set of cirrhotic and sham-operated rats. The total duration of the experiment was up to 40 min.

**Results**

**Experiment 1: Systemic and splanchnic hemodynamics.** Four weeks after bile duct ligation, CBL rats receiving vehicle had significantly lower MAP and SVR associated with higher CI than sham-operated rats (P < 0.01). After 1-wk octreotide administration, lower CI and higher SVR (P < 0.05) were noted in CBL rats treated with 30 µg/kg octreotide per 12 h than in vehicle-treated CBL rats. The values of systemic hemodynamics in CBL rats treated with 100 µg/kg octreotide per 12 h were not significantly different from those in vehicle-treated CBL rats (Table 1). Similar changes of CI and SVR were also observed in experiments 3 and 4. The portal pressure, portal territory resistance, and systemic vascular resistance were determined by hatched regression.

**Table 1. Systemic and splanchnic hemodynamic values in sham-operated rats and in cirrhotic rats receiving vehicle and octreotide**

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>CBL-Vehicle</th>
<th>CBL-30</th>
<th>CBL-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index, ml·min⁻¹·100 g⁻¹</td>
<td>27.3 ± 1.9*</td>
<td>47.1 ± 2.4</td>
<td>36.9 ± 1.4†</td>
<td>40.5 ± 2.4</td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
<td>121 ± 4*</td>
<td>92 ± 4</td>
<td>99 ± 4</td>
<td>96 ± 2</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn·s·cm⁻⁵·10³·100 g⁻¹</td>
<td>368 ± 32*</td>
<td>159 ± 12</td>
<td>217 ± 12†</td>
<td>184 ± 8</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>330 ± 4*</td>
<td>315 ± 13</td>
<td>337 ± 9</td>
<td>318 ± 5</td>
</tr>
<tr>
<td>Portal pressure, mmHg</td>
<td>6.2 ± 0.2*</td>
<td>16.6 ± 0.3</td>
<td>16.0 ± 0.3</td>
<td>17.6 ± 0.4</td>
</tr>
<tr>
<td>Portal territory blood flow, ml·min⁻¹·100 g⁻¹</td>
<td>2.8 ± 3*</td>
<td>4.6 ± 0.4</td>
<td>3.7 ± 0.2</td>
<td>4.3 ± 0.2</td>
</tr>
<tr>
<td>Portal territory vascular resistance, dyn·s·cm⁻⁵·10⁵·100 g⁻¹</td>
<td>3,434 ± 354*</td>
<td>1,401 ± 151</td>
<td>1,810 ± 145</td>
<td>1,460 ± 70</td>
</tr>
<tr>
<td>Hepatic artery blood flow, ml·min⁻¹·100 g⁻¹</td>
<td>0.6 ± 0.1*</td>
<td>1.6 ± 0.4</td>
<td>1.6 ± 0.1</td>
<td>1.5 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE; 9 rats in each group. Sham, sham-operated rat; *P < 0.01 vs. common bile duct-ligated (CBL) rats receiving vehicle (CBL-vehicle), octreotide 30 µg·kg⁻¹·12 h⁻¹ (CBL-30), and octreotide 100 µg·kg⁻¹·12 h⁻¹ (CBL-100), respectively; †P < 0.05 vs. CBL-vehicle rats.
blood flow, and portal territory vascular resistance were the same among the three groups of cirrhotic rats.

Experiment 2: Plasma glucagon, 6-keto-PGF1α, and NOx after octreotide treatment. Higher plasma glucagon, 6-keto-PGF1α, and NOx levels were noted in all CBL rats than in sham-operated rats. In CBL rats receiving two different doses of octreotide, plasma glucagon level was remarkably decreased in a dose-dependent manner (P < 0.01) in all CBL rats (Fig. 1A). Conversely, serum levels of 6-keto-PGF1α and NOx were dose-dependently increased (P < 0.01) after treatment (Fig. 1B and C). In CBL rats, plasma glucagon levels were negatively correlated to both 6-keto-PGF1α (r = -0.86, P < 0.05) and NOx (r = -0.78, P < 0.05) (Fig. 2, A and B).

Experiment 3: Dose response changes of SVR to indomethacin or L-NAME infusion. At each dose of indomethacin administration, the percent change of SVR from baseline values was significantly elevated in all experimental groups, but dose-dependent elevation was noted only in CBL rats receiving vehicle and 30 μg/kg per 12 h octreotide (Fig. 3A). Similar to indomethacin administration, the dose-dependent increment of the percent change of SVR from baseline by incremental doses of L-NAME was also noted in CBL rats treated with vehicle and with 30 μg/kg octreotide per 12 h (Fig. 3B). Moreover, a blunt response to L-NAME administration expressed as smaller percent change of SVR from baseline was noted in CBL rats treated with 100 μg/kg octreotide per 12 h by incremental doses of L-NAME infusion (Fig. 3B). Basically, the percent change of SVR from baseline after L-NAME or indomethacin administration in cirrhotic rats receiving octreotide was lower than in those receiving vehicle (Fig. 3, A and B).

Experiment 4: Influence of the combination of indomethacin and L-NAME on systemic hemodynamics. After the combination of indomethacin and L-NAME administration, the percent change of SVR from baseline in cirrhotic rats receiving octreotide was higher than in those receiving vehicle (Fig. 4). But the percent change in SVR was not different between cirrhotic rats receiving 30 and 100 μg/kg per 12 h octreotide.

Experiment 5: Western blotting for aortic eNOS protein expression in cirrhotic rats. Western blot analysis for the aortic eNOS protein expressions in CBL rats after 1-day or 1-wk octreotide and vehicle administration was shown in Fig. 5. The expression of eNOS protein was significantly higher in CBL rats receiving 1-wk octreotide than in those treated with vehicle.
Meanwhile, the expression of eNOS protein was not different between CBL rats receiving vehicle and those receiving 1-day octreotide.

**DISCUSSION**

In the present study, we found a modest increase in SVR and decrease in CI of cirrhotic rats receiving 30 μg/kg per 12 h octreotide. In contrast, all the systemic effects in cirrhotic rats receiving 100 μg/kg per 12 h octreotide were not different from cirrhotic rats receiving vehicle. Our results suggested the absence of the dose-dependent effects of octreotide on systemic hemodynamics in cirrhotic rats with portal hypertension. Please note that the hemodynamics in this study was measured under ketamine anesthesia. Sikuler et al. (33) have demonstrated that hemodynamics studies in portal hypertensive animals were preferably performed under ketamine anesthesia. It is conceivable that the influence of anesthesia in this study should have been minimized to the least extent. However, in this study, we found that plasma glucagon levels were significantly higher in cirrhotic than in sham-operated rats. This is in line with previous observations showing the presence of hyperglucagonemia in portal hyperten-

Fig. 3. A: percent changes in systemic vascular resistance (SVR) in CBL rats treated with 30 (hatched bars) or 100 μg/kg (cross-hatched bars) octreotide per 12 h or with vehicle (solid bars) and in sham-operated rats (open bars); SVR was increased by incremental dose of indomethacin (5, 10, and 20 mg/kg). Dose-dependent increment of SVR was noted only in vehicle- (**P < 0.01) and 30 μg/kg per 12 h (***P < 0.05) octreotide-treated CBL rats. B: percent changes in SVR by infusion of Nω-nitro-L-arginine methyl ester (L-NAME) in another 4 experimental groups; significant elevations (**P < 0.01; *P < 0.05) of SVR from baseline values in different groups with incremental doses of L-NAME (3, 6, 12, and 24 mg/kg) were similar to indomethacin administration.

Fig. 4. Percent changes in SVR in CBL rats treated with 30 (hatched bars) or 100 μg/kg octreotide per 12 h or with vehicle (solid bars) and in sham-operated rats (open bars). Percent change in SVR from baseline by combination of indomethacin (5 mg/kg) and L-NAME (6 mg/kg) was significantly (**P < 0.05) higher in CBL rats treated with 30 and 100 μg/kg octreotide per 12 h than in vehicle-treated CBL rats. The percent changes were not different between CBL rats treated with 30 or with 100 μg/kg octreotide per 12 h.

Fig. 5. Western blot analysis of endothelial nitric oxide synthase (eNOS) protein (molecular mass 140 kDa) expression from thoracic aorta in cirrhotic rats receiving vehicle, 1-wk octreotide, and 1-day octreotide; 20 μg of protein was loaded per lane. A: CBL rats receiving octreotide 30 μg/kg per 12 h for 7 days. B: CBL rats treated with vehicle. C: CBL rats receiving octreotide 100 μg/kg per 12 h for 7 days. D: CBL rats treated with 1 day octreotide 30 μg/kg per 12 h. E: CBL rats treated with 1 day octreotide 100 μg/kg per 12 h. BSA, bovine serum albumin (molecular mass 96 kDa). An upregulation of eNOS protein expression was noted after 1 wk of octreotide administration especially in rats receiving 100 μg/kg per 12 h compared with those receiving vehicle. In contrast, eNOS protein expression was similar between cirrhotic rats receiving 1 day of octreotide and those receiving vehicle.
vascular responses to L-NAME or indomethacin. This finding was in contrast to the expected enhanced response between vasodilators aimed at maintaining vasodilatation in portal hypertension (28). Glucagon is a potent vasodilator and is involved in the vasodilatation in portal hypertension (4). In addition to nitric oxide (16), hyperglucagonism also contributes, in part, to the pathogenesis of decreased vascular reactivity in portal hypertension (23, 27). Moreover, chronic octreotide treatment increased vascular reactivity in portal hypertensive animals (11, 31). Increased circulating vasodilators (i.e., glucagon, etc.), decreased vascular responsiveness to vasoconstrictors and increased activity of nitric oxide and prostacyclin are the major factors involved in the pathogenesis of vasodilatation in portal hypertension (4, 14, 16, 26, 29, 34). However, most of the studies in cirrhotic patients have demonstrated a minimal or transient systemic effect after octreotide treatment whereas the systemic hemodynamics could only be partially corrected in portal hypertensive animals receiving octreotide (1, 2, 5, 17, 19, 21, 22). Taken together, it would be of interest to know whether there is an interaction between chronic octreotide administration and the activity of nitric oxide and prostacyclin.

Fernández et al. (8) have reported that, in portal hypertensive rats, long-term inhibition of cyclooxygenase activity by indomethacin led to an enhanced activity of nitric oxide synthase that maintained splanchic hyperemia. Munoz et al. (25) have shown that suppression of nitric oxide and prostacyclin release by anti-TNF-α administration did not correct splanchic vasodilatation in portal vein-stenosed rats. This effect may have resulted from a compensatory release of glucagon after long-term anti-TNF-α administration (25). Together, these results indicated the presence of an adaptive response between vasodilators aimed at maintaining vasodilatation in portal hypertension. In the present studies, the serum levels of NOx and 6-keto-PGF₁α were dose-dependently increased in cirrhotic rats receiving octreotide compared with those receiving vehicle, and the changes in plasma levels of the NOx and 6-Keto-PGF₁α were negatively correlated with plasma glucagon levels. We also observed that the magnitude of changes in systemic hemodynamics to 1-NAME or indomethacin was lower in cirrhotic rats receiving octreotide than in those receiving vehicle. This finding was in contrast to the expected enhanced vascular responses to 1-NAME or indomethacin infusion in the presence of increased nitric oxide or prostacyclin release. Because the serum levels of NOx and 6-keto-PGF₁α were “simultaneously” elevated in rats receiving octreotide, the expected increased in vascular response to 1-NAME may be masked by the overproduction of prostacyclin. A similar condition also existed when the cyclooxygenase activity was inhibited by indomethacin. In contrast, in cirrhotic rats receiving octreotide, the blunt vascular response after administration of either indomethacin or 1-NAME alone can be totally corrected by the combined administration of indomethacin and 1-NAME. Taken together, the present study suggested that, after the suppression of glucagon release by octreotide, an enhanced endothelial related vasodilatory effect might exist in cirrhotic rats. Our hypothesis is further confirmed by the Western blot analysis of aortic eNOS protein expressions. We found that the aortic eNOS protein expression was enhanced in cirrhotic rats receiving 1-wk octreotide compared with those receiving vehicle. By contrast, the aortic eNOS protein expression was similar between rats receiving 1 day of octreotide and those receiving vehicle. Therefore, the enhancement in endothelial related vasodilatory activity was mainly attributed to the chronic octreotide treatment rather than to the acute effect of the drug.

In this study, we found that portal pressure and splanchic hyperemia were not decreased in cirrhotic rats receiving both lower and higher doses of octreotide. This finding is different from a number of previous studies in portal vein-stenosed rats (a model of portal hypertension without the presence of cirrhosis), showing that chronic octreotide administration decreased portal pressure and corrected in part the splanchic hyperemia (12, 19, 31). However, the present results are in line with the study reported by Fort et al. (9) showing that in cirrhotic rats produced by bile duct ligation, portal pressure and mean arterial pressure remained unchanged after chronic octreotide treatment. The discrepant findings regarding the effects of octreotide between the two different models cannot be explained by our present study. However, in addition to the possible interaction between plasma glucagon, nitric oxide, and prostacyclin that contributes to maintaining splanchic hyperemia, different models of portal hypertension may also play a role for the different pharmacological responses observed between cirrhotic and portal vein stenosed rats (20). Although Cerini et al. (5) reported a reduction of portal pressure after acute intravenous infusion of octreotide in cirrhotic rats, the different route of administration (intravenous vs. subcutaneous) may probably be one reason for the discrepant responses between acute and chronic octreotide administration in cirrhotic rats.

In conclusion, the present study showed that, despite the suppression of plasma glucagon levels, 1-wk octreotide treatment did not correct the systemic hemodynamics and splanchic hyperemia in cirrhotic rats produced by chronic bile duct ligation. Increased nitric oxide and prostacyclin biosynthesis were noted after long-term octreotide treatment, indicating an enhancement of the endothelium-related vasodilatory activities.
that may probably overcome the octreotide-induced hemodynamic effects in portal hypertension.

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