Effects of somatostatin analog on splanchnic hemodynamics and plasma glucagon level in portal hypertensive rats

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AIM: To investigate the effects of somatostatin analog on splanchnic hemodynamics and plasma glucagon level in portal hypertensive rats.

METHODS: Twenty-eight male Sprague-Dawley rats were equally divided into a intrahepatic portal hypertension (IHPH) model group (n = 14, established by injection of CCl4) and a prehepatic portal hypertension (PHPH) model group (n = 14, established by stenosis of the portal vein). Animals in each group were subdivided into an octreotide treatment (injection) group and a control (normal saline injection) group. Seven age-matched unmodeled/untreated rats served as normal controls. The mean systemic arterial pressure (MSAP) and free portal venous pressure (FPP) were measured. The splanchnic blood flow was detected by injection of toad blood red cell labelled with 51Cr and 125I-Ti. The concentration of plasma glucagon was determined by radioimmunoassay.

RESULTS: All rats with portal hypertension showed significantly decreased splanchnic blood flow and FPP in response to octreotide treatment, as well as markedly increased splanchnic vascular and portal venous resistance. The octreotide treatment did not appear to significantly lower the plasma glucagon levels in either the peripheral or the portal veins.

CONCLUSION: Octreotide induces a decrease in splanchnic blood flow in rats with portal hypertension, and this effect results primarily from direct vasoconstriction and to a lesser extent from decreased plasma glucagon level.

Key words: Portal hypertension; Octreotide; Glucagon; Splanchnic hemodynamics; Somatostatin analog

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INTRODUCTION
Somatostatin has been widely used as treatment for variceal bleeding in patients with portal hypertension. However, the collective research on the mechanisms of somatostatin therapeutic action have not definitely determined whether the decreased splanchnic blood flow and free portal venous pressure (FPP) result from splanchnic vasoconstriction or decreased concentration of plasma glucagon or both[1]. The present study was designed to observe the effects of a commonly used somatostatin analog, octreotide, on splanchnic hemodynamics and concentration of plasma glucagon using rat model systems of both intrahepatic portal hypertension (IHPH) and prehepatic portal hypertension (PHPH) in order to investigate the underlying mechanism.

MATERIALS AND METHODS
Thirty-five male Sprague-Dawley rats, weighing 31.7 ± 15.8 g, were used in the study. All animals were housed in an environmentally controlled vivarium and allowed free access to a standard pellet diet and water.

IHPH modeling
Rats were given a subcutaneous injection of CCl4 (60% vol/vol in mineral oil, at a dose of 0.3 mL/100 g body weight) every 4 days for a total of 20 times. During the full modeling course, the rats were allowed to drink 10% alcohol.

PHPH modeling
Rats were put under ether anesthesia and after surgically isolating the portal vein a 7-gauge needle was placed alongside it. A ligature was then tied snugly to the needle and the vein at a location between the portal hepatic vein and the coronary vein. The needle was then removed to yield a calibrated stenosis of the portal vein.

Experimental and control treatment groups
Fourteen of the rats used in the IHPH and PHPH modeling (n = 7 each) were divided into two groups: octreotide (injection) treatment and untreated (normal saline injection) control. In addition, 7 age-matched unmodeled/untreated rats served as normal controls.

Hemodynamics study
According to the method described by Zang et al[2], toad red...
**Table 1**  Effects of octreotide on splanchic hemodynamics

|          | Normal Cont | IHPH Cont | IHPH Thera | PHPH Cont | PHPH Thera |
|----------|-------------|-----------|------------|-----------|------------|
| THBF, mL/min/100 g BW | 8.30 ± 0.3 | 5.86 ± 0.9 | 4.53 ± 0.9 | 7.86 ± 0.4 | 2.12 ± 0.4 |
| THBF, mL/min/g LW | 2.50 ± 0.3 | 1.61 ± 0.3 | 1.37 ± 0.3 | 1.17 ± 0.2 | 0.09 ± 0.2 |
| PVI, mL/min/100 g BW | 4.85 ± 0.4 | 7.03 ± 0.7 | 5.85 ± 0.6 | 7.36 ± 0.4 | 5.38 ± 0.6 |
| SVR, mmHg·min/ml·100 g BW | 26.68 ± 2.1 | 37.6 ± 2.3 | 20.64 ± 2.8 | 12.84 ± 1.0 | 19.88 ± 2.4 |
| PVR, mmHg·min/ml·100 g BW | 1.72 ± 0.2 | 2.01 ± 0.3 | 1.95 ± 0.2 | 1.76 ± 0.1 | 2.38 ± 0.3 |
| PSS, % | 1.46 ± 0.3 | 34.29 ± 11.7 | 38.77 ± 11.2 | 94.4 ± 13.7 | 87.7 ± 4.5 |

*P < 0.05 vs unmodeled/untreated normal controls; *P < 0.05 vs the IHPH control group.

Cont: Control; Thera: Therapy; THBF: Total hepatic blood flow; PVI: Portal venous inflow; SVR: Splanchnic vascular resistance; PVR: Portal venous resistance; PSS: Portosystemic shunt.

**RESULTS AND DISCUSSION**

**Effects of octreotide on MSAP and FPP**

The initial MSAP in PHPH and IHPH rats was lower than that in the unmodeled/untreated normal control rats (111.1 ± 2.6 mmHg and 126.9 ± 6.6 mmHg vs 137.3 ± 9.8 mmHg). In addition, the initial MSAP of the PHPH rats was significantly lower than that of the IHPH rats (P < 0.05). Octreotide treatment had no effects on MSAP. FPP in IHPH and PHPH rats was higher than that in the unmodeled/untreated normal control rats (14.01 ± 0.56 mmHg and 13.79 ± 0.31 mmHg vs 8.37 ± 0.10 mmHg). Octreotide treatment decreased FPP in both the IHPH rats (11.29 ± 0.64 mmHg) and PHPH rats (11.70 ± 0.36 mmHg).

**Effects of octreotide on splanchic hemodynamics**

Table 1 presents the effects of octreotide on splanchic hemodynamics. Portal venous inflow (PVI) of the PHPH and IHPH rats was significantly increased as compared with that of the unmodeled/untreated normal rats, indicating hyperhemodynamics in portal hypertension. Octreotide markedly reduced PVI in both the IHPH and PHPH rats (P < 0.05). Splanchnic vascular resistance (SVR) in the IHPH and PHPH rats was much lower than that in the unmodeled/untreated normal rats (P < 0.05), and octreotide increased SVR in both; however, the changes in SVR in the PHPH rats were not significantly different from the SVR in the unmodeled/untreated normal rats while the SVR in the PHPH rats was still lower than that of unmodeled/untreated normal ones. Portal venous resistance (PVR) was significantly increased in the IHPH rats (P < 0.05) but showed no change in the PHPH rats, fitting with the observation of the magnitude of portosystemic shunt (PSS) being much higher in the PHPH rats than in the IHPH rats. However, FPP of the PHPH rats was still higher than that of the unmodeled/untreated normal rats, possibly related to both the increased PVI and collateral resistance observed in the PHPH rats. The octreotide treatment led to significantly increased PVR in the PHPH rats (P < 0.05). PSS was 34.29% ± 11.72% and 94.4% ± 1.3% in the IHPH and PHPH rats, respectively. The magnitude of PSS was much greater in the PHPH rats than in the IHPH rats. However, the octreotide treatment produced no effects on PSS in either the IHPH or the PHPH rats.

**Effects of octreotide on splanchic blood flow**

Table 2 presents the effects of octreotide treatment on splanchic blood flow. Blood flow of the stomach, small and large intestines, mesentery and pancreas was markedly increased in both the IHPH and PHPH rats as compared with the unmodeled/untreated normal rats. Furthermore, the splanchic blood flow was increased to a greater extent in the PHPH rats than in the IHPH rats. Due to splanemegaly in the IHPH and PHPH rats, the blood flow/1 g spleen weight was not significantly different in the IHPH rats, the PHPH rats and the unmodeled/untreated normal rats, and the hepatic artery flow (HAF)/1 g liver weight in the IHPH rats was lower than that in the unmodeled/untreated normal rats (P < 0.05). In the PHPH rats, HAF was greater than that in the unmodeled/untreated normal rats because of the hepatopathy in the former. The ratio of liver weight to body weight in the PHPH rats was only decreased by 5.2% when compared with that of the unmodeled/untreated normal rats (2.40% ± 0.21% vs 2.53% ± 0.11%). However, the HAF/1 g liver weight was increased by 70.7% in PHPH rats when compared with that in the unmodeled/untreated normal rats (0.99...
Table 2  Effects of octreotide on splanchnic blood flow (mL•g•min)

|                  | Normal Cont | IHPH Cont | IHPH Thera | PHPH Cont | PHPH Thera |
|------------------|-------------|-----------|------------|-----------|------------|
| Stomach          | 0.59 ± 0.1  | 0.76 ± 0.2| 0.59 ± 0.1 | 0.31 ± 0.1| 0.53 ± 0.1 |
| Intestine and mesentery | 1.36 ± 0.1  | 1.65 ± 1.1*| 1.11 ± 1.1*| 1.83 ± 0.2 | 1.21 ± 0.1*|
| Pancreas         | 0.84 ± 0.1  | 0.97 ± 0.1*| 0.62 ± 0.1*| 1.27 ± 0.2 | 1.01 ± 0.2 |
| Spleen           | 0.98 ± 0.4  | 0.78 ± 0.2 | 0.46 ± 0.2*| 0.96 ± 0.2 | 0.72 ± 0.2 |
| Liver            | 0.58 ± 0.1  | 0.39 ± 0.1*| 0.28 ± 0.1*| 0.99 ± 0.1*| 0.62 ± 0.1*|

*P < 0.05 vs unmodeled/untreated normal controls; "P < 0.05 vs control group; "P < 0.05 vs the IHPH control group.

Table 3  Effects of octreotide on plasma glucagon levels (ng/L)

|                  | Peripheral Vein | Portal Vein |
|------------------|-----------------|-------------|
| Normal Cont      | 59.28 ± 1.5     | 44.23 ± 0.3 |
| IHPH Cont        | 49.37 ± 10.6e*  | 193.25 ± 31.2* |
| IHPH Thera       | 40.12 ± 14.6*   | 140.96 ± 41.9* |
| PHPH Cont        | 69.52 ± 17.2*   | 143.60 ± 25.6* |
| PHPH Thera       | 50.08 ± 7.6a*   | 106.33 ± 37.9* |

*P < 0.05 vs unmodeled/untreated normal controls.

Effects of octreotide on the concentration of plasma glucagon

Table 3 presents the effects of octreotide on the concentrations of plasma glucagon. The IHPH and PHPH rats showed significantly higher concentrations of plasma glucagon in both the peripheral and portal veins as compared with that in the unmodeled/untreated normal rats (P < 0.05), indicating hyperglucagonemia as part of the portal hypertension condition. However, the octreotide-induced decrease in plasma glucagon levels in the peripheral and portal veins did not reach statistical significance for either the IHPH rats or the PHPH rats.

In summary, the results of the present study demonstrate that octreotide significantly decreases PVI and HAF and increases SVR and PVR in rats with IHPH and PHPH. However, the octreotide-induced reduction in plasma glucagon concentrations in both the peripheral and portal veins did not reach statistical significance. These data suggest that the reduction of splanchnic blood flow produced by octreotide predominantly results from direct vasoconstriction, whereas the decrease in plasma glucagon levels is less important. However, the octreotide treatment was unable to produce a decrease in either PVI or FPP to normal levels in the portal hypertensive rat models, indicating that other factors in addition to glucagon may be responsible for the increased splanchnic blood flow in portal hypertension.

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