Chronic administration of octreotide ameliorates portal hypertension and portal hypertensive gastropathy in rats with cirrhosis

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INTRODUCTION

Portal hypertensive gastropathy is frequently observed in cirrhotic patients and has been documented as a potential source of gastrointestinal bleeding [1, 2]. Histological studies of portal hypertensive gastropathy have demonstrated an increased number of vessels, vascular congestion and vascular ectasia in both mucosa and submucosa layers [3, 4]. In experimental models of chronic portal hypertension, both dilatation of gastric mucosal vessels and increased gastric mucosal blood flow have been observed [5–7]. Although the pathogenesis of portal hypertensive gastropathy is unknown, it may be related to the presence of portal hypertension (passive congestion) [4, 8] or the increased splanchnic blood flow due to hyperdynamic circulation (hyperdynamic congestion) [6, 9–11].

It has been suggested that the correction of hyperdynamic circulation alone may be inadequate to prevent the development of portal hypertensive gastropathy and its treatment should be focused on reducing portal pressure [12]. Octreotide is a long-acting synthetic analogue of somatostatin that inhibits the release of several vasoactive peptides of the gastropancreatic endocrine system [13]. Chronic administration of octreotide has been demonstrated to reduce portal pressure and ameliorate peripheral vasodilatation in both partially portal vein-ligated and cirrhotic rats [14–17]. However, the effects of octreotide on the development of portal hypertensive gastropathy in cirrhotic rats is unknown.

The aim of our study was to investigate the effects of chronic octreotide treatment on systemic and portal haemodynamics and the development of portal hypertensive gastropathy in cirrhotic rats.

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats weighing 100–120 g were used for this study. Cirrhosis was induced by carbon tetrachloride as described previously [16, 18, 19]. After induction with phenobarbital (0.33 mg/ml) in the drinking water for 10 days, carbon tetrachloro-
ide was administered once a week by intragastric gavage for 12 consecutive weeks and phenobarbital was given continuously in the drinking water. Both treatments were discontinued 1 week before the experiments. Haemodynamic study and gastric morphometric analysis were performed under ether anaesthesia followed by ketamine hydrochloride (100 mg/kg body weight, intramuscularly). All rats were in cages at 24°C with a 12 h light/dark cycle and were allowed free access to food and water. The experiments reported here were conducted according to the American Physiological Society guiding principles for the care and use of laboratory animals.

After 12 weeks of carbon tetrachloride administration, rats were randomly assigned to receive a 10-day course of either octreotide (65 μg/kg in 5% dextrose in water; Sandoz Pharmaceutical Co., Basel, Switzerland) or an equivalent volume of placebo (5% dextrose in water) subcutaneously twice daily. Haemodynamic measurements and gastric morphometric analyses were then conducted. To avoid possible confounding effects caused by haemodynamic measurements, a different set of rats was used for gastric morphometric analyses. All rats were fasted for 18 h before the experiments and had free access to water.

Systemic and portal haemodynamics

The right femoral artery was cannulated with a PE-50 catheter connected to a Spectramed DTX transducer (Spectramed Inc., CA, U.S.A.), and continuous recordings of mean arterial pressure were made on a multi-channel recorder (model RS 3400, Gould Inc., Cupertino, CA, U.S.A.). The external zero reference limit was placed at the mid portion of the rat. Heart rate was determined from the recording. Right atrial pressure was obtained by placing a PE-50 catheter in the right atrium. The abdomen was then opened with a midline incision, and a mesenteric vein was cannulated with a PE-50 catheter connected to a Spectramed DTX transducer. The abdominal cavity was closed and the portal pressure was recorded on a Gould model RS 3400 recorder.

Cardiac output was measured by thermodilution as described previously [20]. Briefly, a thermistor was placed in the aortic arch just distal to the aortic valve and the thermal indicator (100 μl of normal saline) was injected into the right atrium through a PE-50 catheter. The aortic thermistor was connected to a Columbus Instruments Cardotherm 500-AC-R (Columbus Instruments International Co., OH, U.S.A.). Five thermodilution curves were obtained for each cardiac output measurement. The final cardiac output value was obtained from the arithmetic mean of the computer results. Cardiac index (ml·min⁻¹·100 g⁻¹) was calculated as cardiac output per 100 g body weight. Systemic vascular resistance (mmHg/ml·min⁻¹·100 g⁻¹) was calculated by dividing mean arterial pressure by cardiac index.

Gastric morphometric analysis

The morphometric study was performed as reported previously [12, 21]. In brief, a transverse section of the corpus stomach was embedded in paraffin, stained with Haematoxylin and Eosin, and examined under code. The technician performing the morphometric analysis was blinded to the actual treatment received. From each coded mucosal specimen, five microphotographs of five adjacent fields of the mucosa were taken with an Olympus AH-2 light microscope (Olympus Optical Co. Ltd, Tokyo, Japan) at a final magnification of ×400. A graph-sheet device (Summagraphic model MMII1201, Seymour, CT, U.S.A.) and a computer software AutoCAD were used to delineate the outlines of mucosal microvessels in each microphotograph. The size of gastric vessels was expressed as the mean cross-sectional area, calculated by dividing the total vascular area by the number of vessels. To ensure accurate determination of the cross-sectional area at a final magnification of ×400, vessels with a cross-sectional area smaller than 400 μm² were not included in the analysis.

Statistical analysis

All results are expressed as mean± S.E.M. Statistical analyses were performed using the unpaired Student’s t-test or χ²-test as appropriate. Results were considered statistically significant at P<0.05.

RESULTS

Systemic and portal haemodynamics (Figure 1)

After a 10-day treatment, there was no significant difference in the body weight of octreotide- and placebo-treated cirrhotic rats [376±17 g (n=10) versus 402±29 g (n=8), P>0.05]. Chronic octreotide administration significantly decreased portal pressure (12.5±1.2 versus 9.9±0.5 mmHg, P<0.05) and increased systemic vascular resistance (2.7±0.2 versus 3.4±0.2 mmHg/ml·min⁻¹·100 g⁻¹, P<0.05). No significant difference was observed in mean arterial pressure (123±5 versus 122±7 mmHg respectively, P>0.05) and heart rate (388±11 versus 408±12 beats/min respectively, P>0.05) of octreotide- and placebo-treated rats.

Gastric morphometric analysis (Figures 2 and 3)

The body weights were similar between octreotide- and placebo-treated rats after treatment
Octreotide ameliorates portal hypertensive gastropathy

Mean Arterial Pressure

Cardiac Index

Systemic Vascular Resistance

Portal Pressure

Cross-sectional Area

Fig. 1. Effects of chronic octreotide treatment on systemic and portal haemodynamics in carbon tetrachloride-induced cirrhotic rats (octreotide, \( n = 10 \); placebo, \( n = 8 \))

Fig. 2. Effects of chronic octreotide treatment on the cross-sectional area of gastric mucosal vessels in carbon tetrachloride-induced cirrhotic rats (octreotide, \( n = 9 \); placebo, \( n = 7 \))

Fig. 3. Frequency distribution of the cross-sectional area of gastric mucosal vessels in placebo- and octreotide-treated cirrhotic rats. Cirrhotic rats treated with octreotide had a significantly greater proportion of gastric mucosal vessels with smaller cross-sectional area compared with placebo-treated rats (\( P < 0.05 \)).
[424 ± 18 g (n = 9) versus 393 ± 14 g (n = 7), P > 0.05]. Octreotide treatment significantly reduced the mean cross-sectional area of gastric mucosal vessels (1810 ± 101 versus 2290 ± 145 μm², P < 0.05, Figure 2) and increased the proportion of vessels with smaller cross-sectional area in cirrhotic rats (P < 0.05, Figure 3).

DISCUSSION

In the present study, chronic octreotide treatment in cirrhotic rats significantly reduced portal pressure and cardiac index and increased systemic vascular resistance, similar to the previous studies in experimental portal hypertension [14–17]. In addition, the mean cross-sectional area of gastric mucosal vessels was significantly reduced after octreotide treatment. As the body weights were similar between octreotide- and placebo-treated groups, the difference in the mean cross-sectional area of gastric mucosal vessels is not due to a difference in body weight between the two groups. These results demonstrate that chronic administration of octreotide in cirrhotic rats ameliorates portal hypertension, hyperdynamic circulation and portal hypertensive gastropathy.

Portal hypertension (passive congestion [4, 8]) and hyperdynamic circulation (hyperdynamic congestion [6, 9–11]) have been suggested to play a role in the pathogenesis of portal hypertensive gastropathy. The hyperdynamic circulation in portal hypertensive states is characterized by high cardiac output, decreased systemic vascular resistance and increased systemic and regional blood flows [6]. In addition, generalized vasodilatation has been recognized as an initiating event of hyperdynamic circulation [20, 22], and consequently results in augmented splanchnic inflow and bowel hyperaemia [23]. Therefore, it is conceivable that hyperdynamic circulation may be involved in the development of portal hypertensive gastropathy. However, chronic administration of aminoguanidine, a preferential inducible nitric oxide synthase inhibitor, to portal vein-ligated rats corrected hyperdynamic circulation without changes in portal pressure and portal hypertensive gastropathy [12]. In contrast, Panés et al. [24] have demonstrated that chronic oestrogen–progestagen treatment in portal vein-ligated rats significantly reduced portal pressure, gastric mucosal blood flow, number of blood vessels and relative area of vessels without modulation of hyperdynamic circulation. In the current study, we found that chronic octreotide treatment in cirrhotic rats not only alleviated hyperdynamic circulation but also ameliorated portal pressure and portal hypertensive gastropathy. All these observations suggest that, instead of correcting hyperdynamic circulation, treatment of portal hypertensive gastropathy should be aimed at reducing portal pressure.

Different possibilities may theoretically account for the action of octreotide in increasing systemic vascular resistance of cirrhotic rats. Octreotide inhibits the release of glucagon [17] and several peptide vasodilators such as vasoactive intestinal peptide, substance P and calcitonin gene-related peptide [25, which are increased in portal hypertension [14, 15, 17, 26, 27]. Glucagon mediates vasodilatation through a direct vasodilatory effect or the attenuation of vascular reactivity to vasoconstrictors in experimental portal hypertension [28, 29]. In addition, the vasodilatory effect of substance P or calcitonin gene-related peptide may act through an increased release of nitric oxide [30–32], an important mediator in the pathogenesis of hyperdynamic circulation in portal hypertension [33, 34]. Therefore, chronic administration of octreotide in cirrhotic rats may inhibit the activity of certain endogenous vasodilators and consequently increase systemic vascular resistance and decrease cardiac index. The amelioration of hyperdynamic circulation by octreotide may further decrease nitric oxide formation and increase systemic vascular resistance, because both flow [35] and shear stress [36] are potent stimuli for nitric oxide biosynthesis. Although octreotide may inhibit the secretion of tumour necrosis factor α [37], which has been shown to play a major role in the development of hyperdynamic circulation in rats with prehepatic portal hypertension or cirrhosis [38–40], it remains to be elucidated whether the effect of octreotide also occurs through this mechanism.

Portal hypertensive gastropathy is characterized by dilatation of mucosal vessels, increased number of vessels and increased mucosal blood flow [3–7]. The increased blood flow and dilatation of parent vessels are two important steps in the angiogenic process of neovascularization before the emergence of new capillary sprouts [41, 42]. Nitric oxide may function as a regulator in microvascular neovascularization and mediates angiogenesis [43, 44]. The inhibition of nitric oxide synthesis has been shown to abolish the capillary endothelial cell proliferation and migration produced by substance P [45]. In addition, there is evidence from studies that octreotide may inhibit neovascularization [46, 47]. Although small vessels could be recognized by immunohistochemistry staining with Von Willebrand factor [48, 49], in the present study we could not determine the actual number of vessels because those with a cross-sectional area smaller than 400 μm² were excluded to ensure accurate determination of cross-sectional area. As octreotide can inhibit the release of endogenous vasodilators such as substance P [25], it remains to be elucidated whether its effects on the development of portal hypertensive gastropathy may be partly mediated by inhibition of neovascularization.

In summary, chronic octreotide administration in cirrhotic rats ameliorates portal pressure, hyperdynamic circulation and the development of portal hypertensive gastropathy. This suggests that octreotide may be useful in the management of portal hypertensive gastropathy.
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