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New Phenomenon

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Octreotide protects against hepatic ischemia/reperfusion injury via HO-1-mediated autophagy

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Octreotide is a synthetic octapeptide. Since octreotide resembles somatostatin in physiological activities, it can reduce portal hypertension, impede gastrointestinal tumor growth, and inhibit the release of growth hormone [1]. *In vivo*, octreotide appears to exert

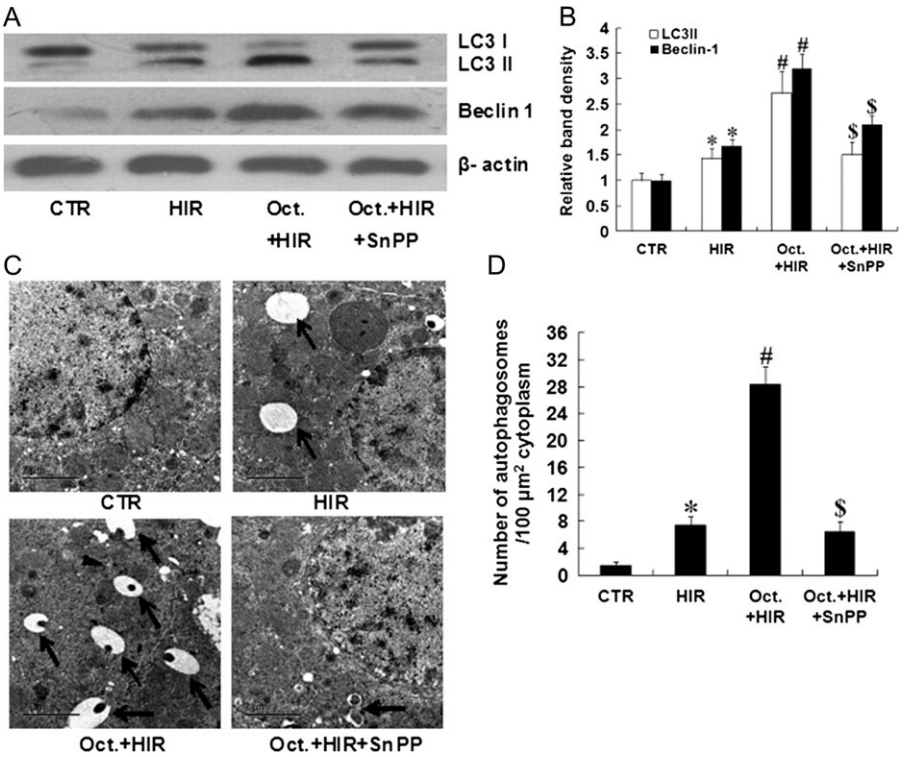

Figure 1. Effects of octreotide on hepatocyte autophagy after hepatic I/R Rats were pretreated with or without SnPP (50 mg/kg, IP) 0.5 h prior to octreotide treatment (20 μg/kg, IP and 30 μg/kg, IC) and sacrificed after 60 min of liver ischemia and 24 h of reperfusion. (A,B) Representative western blots and quantitative evaluation of LC3-II and Beclin 1 expressions in liver tissues. (C) Representative transmission electron microscopy images for autophagy ultrastructures. Scale bar = 2 μm. (D) Statistical analysis of the number of autophagosomes per 100 μm^2. Data are presented as the mean ± SD. $n = 8$ per group. $^*P < 0.05$ *vs* CTR group, $^{\#}P < 0.05$ *vs* HIR group, and $^{\$}P < 0.05$ *vs* Oct.+ HIR group.

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organ protective effects. We previously demonstrated that octreotide plays a protective role in a rabbit model of hepatic ischemia-reperfusion (I/R) [2]. However, the exact mechanism remains to be elucidated. Autophagy is an evolutionarily conserved process involved in the degradation of long-lived or damaged proteins and organelles [3]. During hepatic I/R, hepatocyte autophagy is increased. Inhibition of autophagy after hepatic I/R can lead to increased hepatocyte death [4]. Conversely, induction of autophagy can protect animals from hepatic I/R injury [5]. Thus, a restoration or enhancement of autophagy might be a novel therapeutic modality to ameliorate liver function after I/R in livers. Therefore, in this study we evaluated whether autophagy is an essential mediator in octreotide-mediated hepatoprotective effects during I/R.

Here, we first investigated whether octreotide pretreatment could induce autophagy in livers after hepatic I/R. As shown in **Fig. 1A,B**, LC3 and Beclin-1 (the protein markers for autophagy) expressions in liver tissue were increased in the HIR group. In contrast, octreotide treatment significantly increased the expressions of LC3 and Beclin-1 in livers after hepatic I/R when compared with the HIR group. Furthermore, transmission electron microscopy was used to measure the quantity of autophagosomes per unit cytoplasmic area. As shown in **Fig. 1C,D**, an increased number of autophagosomes was detected in the liver after HIR. Compared with the HIR group, a greater number of autophagosomes was seen in the Oct. + HIR group. These results implied that octreotide induces autophagy in the liver after HIR.

Given that octreotide could reduce liver injury after hepatic I/R, we further investigated whether the hepatoprotective effect of octreotide is mediated via induction of autophagy. A pharmacological autophagy inhibitor 3-methyladenine (3-MA) was used. As shown in **Fig. 2A**, the serum levels of AST and ALT were significantly increased in 3-MA-treated rats when compared with the Oct. + HIR group. Consistently, severe histological abnormalities were present in liver tissues obtained from 3-MA-treated rats (**Fig. 2B,C**). These results appear to support that octreotide protects against hepatic I/R injury via induction of autophagy.

Heme oxygenase-1 (HO-1) is a stress-inducible enzyme that shows several biological activities including anti-inflammatory, anti-apoptotic, and anti-oxidant properties. During hepatic I/R, HO-1 has been shown to confer its protection by modulating oxidative stress and inflammation [6]. In addition to these actions, HO-1 can also attenuate hepatic I/R injury by induction of autophagy [7]. Interestingly, some previous studies have shown that octreotide have protective effects against 2,4,6 trinitrobenzene sulfonic acid (TNBS)-induced colonic damage, intestinal ischemia-reperfusion injury, and experimental ischemic stroke through the induction of HO-1 [8–10]. Thus, we speculate that HO-1 may play a role in octreotide-induced autophagy during hepatic I/R.

Given that HO-1 is essential for the regulation of autophagy, we then investigated whether octreotide-induced autophagy is dependent on HO-1 during hepatic I/R. We first examined the role of octreotide in HO-1 expression in livers after hepatic I/R by western

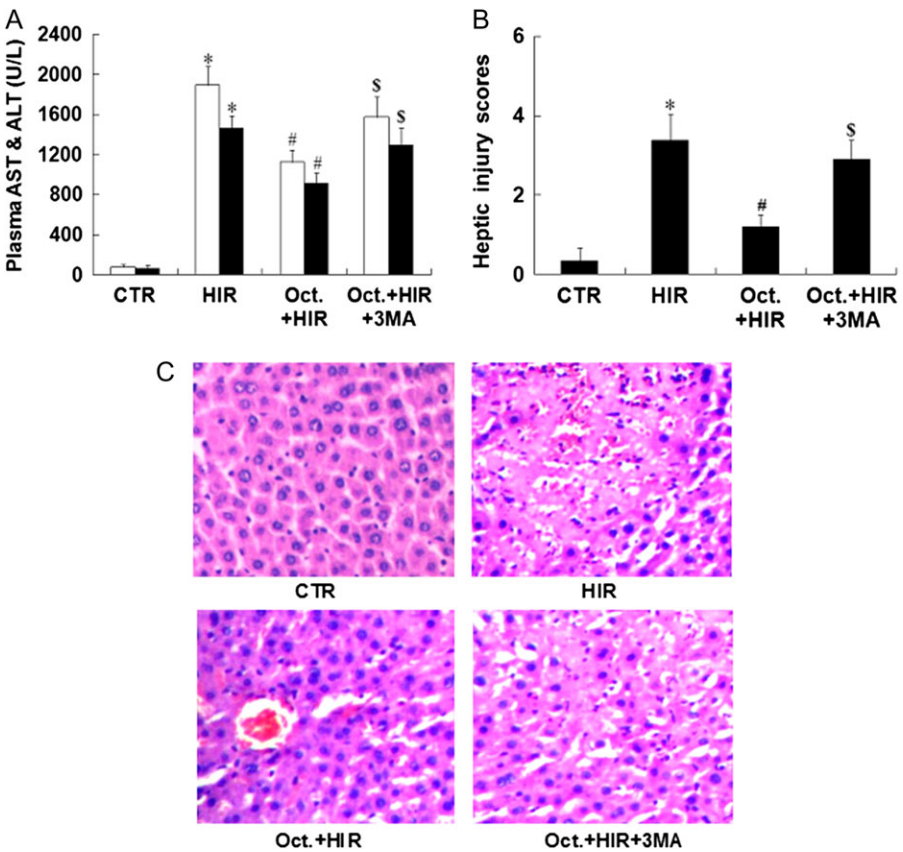

Figure 2. Degree of acute liver injury after hepatic I/R Rats were pretreated with or without 3MA (30 mg/kg, IP) 0.5 h prior to octreotide treatment (20 μg/kg IP and 30 μg/kg, IC) and sacrificed after 60 min of liver ischemia and 24 h of reperfusion. (A) Quantification of serum ALT and AST levels. (B) Quantification of histological damage. (C) Representative hematoxylin and eosin-stained photomicrographs of liver I/R injury (200× magnification). Data are presented as the mean ± SD. $n = 8$ per group. $^{*}P < 0.05$ *vs* CTR group, $^{\#}P < 0.05$ *vs* HIR group, and $^{\$}P < 0.05$ *vs* Oct.+HIR group.

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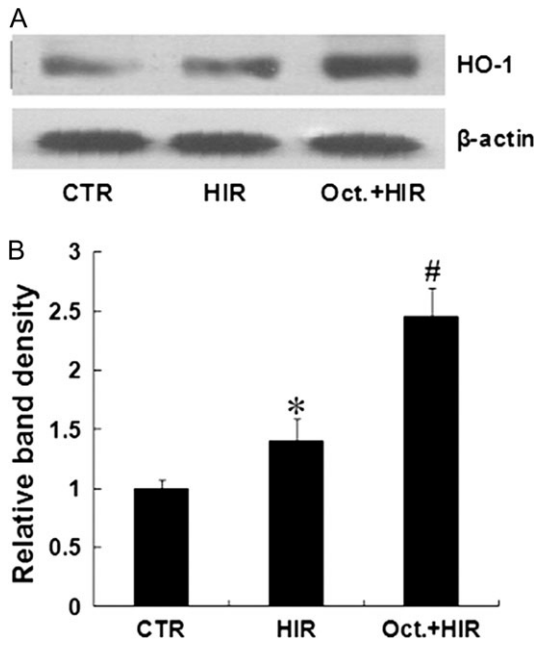

Figure 3. Effects of octreotide on HO-1 expression after hepatic I/R Rats were pretreated with or without octreotide (20 μg/kg, IP and 30 μg/kg IC) 0.5 h and then sacrificed after 60 min of liver ischemia and 24 h of reperfusion. (A) Representative western blot and (B) quantitative evaluation of HO-1 expression in liver tissues. Data are presented as the mean ± SD. $n = 8$ per group. $^{*}P < 0.05$ vs CTR group, and $^{\#}P < 0.05$ vs HIR group.

blot analysis. As shown in **Fig. 3A**, HO-1 was increased in livers subjected to hepatic I/R injury. In contrast, octreotide treatment significantly increased the expression of HO-1 in livers after hepatic I/R when compared with the HIR group. To further confirm that enhancement of HO-1 is responsible for octreotide-induced autophagy, specific HO-1 antagonist protoporphyrin IX (SnPP) was used. As shown in **Fig. 1A,B**, SnPP abrogated the auxo-action of octreotide on LC3 and Beclin-1 expressions in livers after hepatic I/R. Moreover, a decreased number of autophagosomes was seen in the Oct. + HIR + SnPP group when compared with the Oct. + HIR group. These results imply that octreotide-induced autophagy is dependent on HO-1 during hepatic I/R.

This preliminary study was conducted in only one animal model and extrapolation from rats to humans is always difficult. Additionally, only one dose of octreotide was tested and it is unclear if there would be an enhanced effect with a larger dose. Nevertheless, our study demonstrated that octreotide could ameliorate liver I/R injury possibly via the induction of HO-1-mediated autophagy, which may define a novel mechanism of octreotide in the control of acute liver injury and support the potential utility of octreotide to prevent and treat liver dysfunction after I/R.

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