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Relaxin Reduces Fibrosis in Models of Progressive and Established Hepatic Fibrosis

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Abstract

The effect of relaxin administration before (prevention) or after (treatment) the establishment of hepatic fibrosis in a mouse model was examined. In the prevention study, relaxin reduced collagen and smooth muscle actin (SMA) content, and significantly reduced serum levels of the liver enzymes ALT and AST. In the treatment study, relaxin for 1 week reduced collagen and SMA, but not liver enzyme levels. Relaxin for 2 weeks had no significant effect. In conclusion, the data suggest that relaxin treatment before fibrosis can reduce collagen and improve liver function, but that there is little effect of short-term relaxin treatment after fibrosis is established.

Keywords

Hepatic fibrosis; liver; collagen; relaxin

Introduction

Relaxin inhibits the myofibroblastic phenotype of the hepatic stellate cells (HSC) that produce most of the fibrillar collagen in hepatic fibrosis and cirrhosis 1⁻3. Relaxin, when administered before fibrosis is established, can reduce the severity of carbon tetrachloride-induced hepatic fibrosis 1. In this study, the effect of relaxin before the induction of hepatic fibrosis was compared with the effect of relaxin treatment after first establishing fibrosis.

Results

In the prevention model, mice were treated with porcine relaxin via subcutaneous osmotic pumps to deliver 0.5mg/kg/day. At the same time, carbon tetrachloride (CCl4) was injected intraperitoneally twice weekly, with a total relaxin and CCl_4 treatment duration of 4 weeks. Relaxin significantly reduced liver collagen as measured by hydroxyproline content. Relaxin also reduced the amount of smooth muscle actin (SMA), suggesting inhibition of activation of the HSC. There was no effect on liver weight. Relaxin significantly reduced the levels of the liver enzymes ALT and AST, indicative of improved liver function.

In the treatment model, mice were first treated with CCl_4 for 4 weeks to establish fibrosis, after which relaxin was administered via osmotic pumps, and the relaxin and CCl_4 treatment was continued to 1 or 2 weeks further. After 1 week, relaxin significantly reduced liver collagen content and reduced the amount of activated HSC cells in the parenchyma. Relaxin also induced modest decreases liver weight, and ALT and AST levels, that were not

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statistically significant. After 2 week treatment, the liver SMA content was reduced, but there was no significant effect on any other parameter.

Discussion

The ability of relaxin to reduce liver injury in a preventive manner, shown previously in rats 1, was confirmed in a mouse model. Relaxin was also effective when administered after fibrosis was established, but only after 1 week of relaxin treatment. Longer (2-week) relaxin treatment reduced hepatic stellate cell activation, but this was not accompanied by a decrease in collagen. It is possible that the perisitent presence of the injurious stimulus (CCl_4) was too toxic for a sustained response. Studies are underway to examine if relaxin would be effective in a model with less extensive fibrosis, or in the recovery from fibrosis after CCl_4 withdrawal.

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References

1. Williams EJ, et al. Relaxin inhibits effective collagen deposition by cultured hepatic stellate cells and decreases rat liver fibrosis in vivo. Gut. 2001; 49:577–583. [PubMed: 11559657]
2. Bennett RG, Kharbanda KK, Tuma DJ. Inhibition of markers of hepatic stellate cell activation by the hormone relaxin. Biochem Pharmacol. 2003; 66:867–874. [PubMed: 12948868]
3. Bennett RG, et al. Relaxin receptors in hepatic stellate cells and cirrhotic liver. Biochem Pharmacol. 2007; 73:1033–1040. [PubMed: 17214975]