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Poster presentation

Antifibrotic effects of an sGC activator in rat models of liver fibrosis

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Background

Liver fibrosis and cirrhosis are late complications common to liver diseases of different etiology such as viral hepatitis and alcoholic liver disease. Irrespective of the initial cause of liver disease, activation of hepatic stellate cells is a crucial step in the fibrotic pathomechanism. Activated hepatic stellate cells produce excess collagen as well as profibrotic cytokines and change to a contractile phenotype which reduces the diameter of the hepatic sinusoids. Activation of hepatic stellate cells is reduced by an increase in intracellular cyclic guanosine monophoshate (cGMP). Stable cGMP analogues also reduce the contractile response of hepatic stellate cells. However, cGMP production is downregulated in the cirrhotic liver due to reduced activity of the endothelial NO synthase. The recently discovered activators of soluble guanylate cyclase (sGC) increase cGMP production independently of NO. We therefore investigated the effects of an sGC activator in two classical rat models of liver fibrosis, the pig serum model and the carbon tetrachloride model.

Material and Methods

Liver fibrosis was induced by i. p. administration of sterile pig serum (twice weekly) or oral administration of carbontetrachloride (every fifth day), respectively in female Sprague Dawley rats. Ths sGC activator was administered at doses of 0.1 and 0.3 mg/kg p.o. daily concomitantly to the fibrotic stimulus. After 7 weeks the rat were sacrificed and liver fibrosis was assessed both morphometrically by Sirius Red staining of fibrous collagen and by hydroxyproline determination.

Results

Both fibrotic stimuli resulted in a massive increase in hepatic collagen compared to healthy controls. In the serum model concomitant treatment with 0.1 mg/kg p.o. of the sGC activator was sufficient to reduce this increase by about 75%. A reduction of hepatic fibrosis by about 60% was achieved with 0.3 mg/kg p.o. in the carbon tetrachloride model.

Conclusion

Activation of soluble guanylate cyclase prevented hepatic collagen accumulation both in inflammatory and non-inflammatory models of liver fibrosis. sGC activators might thus provide a new antifibrotic principle for liver diseases of different etiology.