Targeted delivery of losartan reduces liver inflammation and scarring

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A recent study found that rats with advanced fibrosis that were administered a short-term dose of losartan-M6PHSA had reduced liver inflammation and fibrosis. Those animals treated with oral losartan alone did not experience a similar reduction in disease activity. Results of this study appear in the March issue of *Hepatology*, a journal published by Wiley-Blackwell on behalf of the American Association for the Study of Liver Diseases.

Liver fibrosis a consequence of liver disease was thought to be irreversible and only transplantation of the liver would offer survival to the patient. Doctors now believe that early detection of fibrosis offers potential for therapies that prevent further liver scarring and the imminent need for transplantation.

In the current study, a Spanish research team led Ramón Bataller, M.D., from the Hospital Clínic in Barcelona investigated such a treatment, losartan-M6PHSA, in rat models. Losartan is an angiotensin (AT1) receptor blocker that was linked to mannose-6-phosphate modified human serum albumin (M6PHSA), a selective drug carrier targeting hepatic stellate cells (HSC). An average of 7 losartan molecules were coupled to M6PHSA. The study verified that losartan-M6PHSA accumulates in the fibrotic liver only, and other organs such as the lungs, heart, spleen and kidneys did not display the conjugate.

Researchers induced liver fibrosis in male rats by bile duct ligation to study short-term treatment outcomes. In both models, rats were given

daily injections of saline, losartan-M6PHSA (3.3 mg/kg/day, to 125 µg losartan/kg), M6PHSA alone (3.3 mg/kg/day), or oral losartan (5 mg/kg/day). Bile duct-ligated rates treated with saline of M6PHSA alone showed severe fibrosis. "Animals treated with losartan-M6PHSA displayed less collagen deposition with less frequent formation of bridging fibrosis," said Dr. Bataller. "Short-term oral treatment with losartan alone did not reduce fibrosis or the amount of collagen."

In the long-term results, advanced liver fibrosis was established in male rats by chronic treatment of carbon tetrachloride (CCl_4). Treatment by saline, losartan-M6PHSA or M6PHSA alone was administered twice a week for three weeks. "While losartan-M6PHSA was able to reduce collagen synthesis, the degree of fibrosis reduction was not significant. Further studies identifying the ideal route and drug dosage for long-term treatment are clearly required," concluded Dr. Bataller.

More information: "Reduction of Advanced Liver Fibrosis by Short-term Targeted Delivery of an Angiotensin Receptor Blocker to Hepatic Stellate Cells in Rats." Montserrat Moreno, Teresa Gonzalo, Robbert J. Kok, Pau Sancho-Bru, Marike van Beuge, Josine Swart, Jai Prakash, Kai Temming, Constantino Fondevila, Leonie Beljaars, Marie Lacombe, Paul Vd Hoeven, Vicente Arroyo, Klaas Poelstra, David A. Brenner, Pere Ginčs and Ramón Bataller. *Hepatology*; Published Online: March 1, 2010 (DOI: 10.1002/hep.23419); Print Issue Date: March 2010.

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