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Treatment of a Mouse Model of Cholestasis with a Thyromimetic Improves Biliary Injury But Exacerbates Hepatocyte Injury

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Chronic cholestasis results from bile secretory defects or impairment of bile flow, and there are few effective medical therapies available. Thyroid hormone T3 and synthetic thyroid hormone receptor agonists are known to cause induction of hepatocyte proliferation during liver regeneration through activation of b-catenin. However, whether these drugs have therapeutic benefits in cholestatic liver disease is unknown. In this study, we administered GC-1, a thyromimetic that preferentially acts through the TRb receptor found predominantly in liver, to Mdr2 knockout (KO) mice, which is a commonly used model of sclerosing cholangitis characterized by bile acid (BA) regurgitation, periductular inflammation, and fibrosis. We determined Mdr2 KO mice fed 5mg/kg GC-1 diet had decreased bilirubin, liver to body weight ratios, serum alkaline phosphatase, but increased serum alanine aminotransferase and aspartate aminotransferase compared to KO mice fed normal diet as early as 1 week on diet. Histologically, KO mice on GC-1 diet had decreased ductular response, less bridging fibrosis, and fewer SOX9 positive hepatocytes compared to KO on normal diet. Although total liver BA were higher in KO mice fed GC-1 diet for 2 weeks compared to normal diet, they normalized to KO levels at 4 weeks of diet. To elucidate the mechanism of increased BA accumulation and liver injury, we examined expression of BA transporters and detoxification enzymes. KO mice on GC-1 diet had decreased bilirubin transport and detoxification genes, such as Mrp2, Mrp3, Cyp2b10, and Oatp4, compared to KO mice on normal diet, with the net result being retention of BA in the hepatocyte. Interestingly, KO mice on GC-1 diet had decreased total and phosphorylated, active b-catenin compared to KO mice on normal diet, suggesting an alternate mechanism for GC-1 activation in this model. Thus, GC-1 reduces cholangiocyte injury during cholestasis by inducing retention of BA in hepatocytes, causing injury to the hepatocytes; this occurs through as-yet unknown mechanisms that are upstream of BA transporters and biosynthesis enzymes and appears to be b-catenin independent.

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