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Effect of taurocholic acid on biliary injury in course of hepatic artery ligation in cholestatic rats

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Background The hepatic artery nourishes the intrahepatic biliary tree by the peribiliary plexus (PBP) [1]. Ischemic injury induced by hepatic artery ligation (HAL) during bile duct ligation (BDL) results in bile duct damage, which can be prevented by administration of VEGF-A. Ttaurocholic acid (TC) partially protects against caffeic acid phenethyl ester-induced increases in apoptosis and decreases in cholangiocyte proliferation acting on VEGFs protein expression [2]. We aim to assess if TC can prevent HAL-induced cholangiocyte damage via the alteration of VEGFR-2 and/or VEGF-A expression.

Methods *In vivo*, we used experimental rat models: BDL, BDL+TC, BDL+HAL, BDL+HAL+TC, and BDL+HAL+wortmannin (phosphatidylinositol 3-kinase inhibitor)+TC to evaluate: i) ductal mass, ii) cholangiocyte proliferation and apoptosis, and iii) cholangiocyte expression and secretion of VEGF-A by immunohistochemistry and RIA. *In vitro*, we studied the effects of TC on cholangiocyte secretion of VEGF-A and how TC-induced cholangiocyte growth can be related to the activity of VEGFR-2 in normal rat cholangiocyte cell line (NRC) by ELISA.

Results TC prevents HAL-induced i) loss of bile ducts and ii) reduction of VEGF-A expression, iii) decreased cholangiocyte secretion of VEGF-A. TC feeding to BDL+HAL rats increased basal and secretin-stimulated cAMP levels (marker of biliary growth) compared to control cholangiocytes, effects blocked by wortmannin. In vitro, TC stimulated an increase in VEGF-A secretion by NRC, which was partially blocked by wortmannin and stimulated cholangiocyte proliferation that was blocked by VEGFR-2 kinase inhibitor.

Conclusion TC is able to prevent HAL-induced biliary damage acting on VEGF-A expression by a PI3-K-dependent mechanism. Manipulation of cholangiocyte VEGF presence by bile acids may be important in preventing the impairment of cholangiocyte proliferation induced by ischemia injury.

References

[1] Gaudio E, Onori P et al. (1996) Gastroenterology. 111:1118-1124.
[2] Mancinelli R, Onori P, Gaudio E (2009) Exp Biol Med. 234:462-474.

Key words
Liver, cholangiocyte, taurocholic acid, VEGF