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

Paolo Onori¹, Romina Mancinelli¹, Shannon Glaser³, Antonio Franchitto¹, Luigi Pannarale¹, Roberta Sferra², Antonella Vetuschi², Gianfranco Alpini³, Eugenio Gaudio¹

¹ Department of Human Anatomy, “Sapienza”, University of Rome, Italy
² Department of Experimental Medicine, University of L’Aquila, Italy
³ Department of Medicine, Scott & White, College of Medicine, Temple, TX, USA

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. Taurocholic 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

Key words Liver, cholangiocyte, taurocholic acid, VEGF