

Vasopressin induces cholangiocyte proliferation in experimental cholestasis and in Polycystic Liver Disease

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The hormone vasopressin (hereafter AVP) is a neuropeptide mainly synthesized in the brain's hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei, works by three distinct receptor subtypes: V1a, V1b, and V2 [1]. In liver, AVP is involved in glycogenolysis and neoglucogenesis and regenerative processes [2]. Cholangiocytes are the cells that line the biliary ducts and they are the target in a number of animal models of cholestasis including bile duct ligation (BDL) and in several human pathologies such as polycystic liver disease (PLD) characterized by the presence of numerous cysts within the liver that arise from biliary epithelium [3]. Since no data exist about the presence and the role of AVP and receptors in biliary epithelium, we aimed to evaluate the effects of AVP in experimental model of cholestasis and in course of PLD. In vivo, normal and BDL liver fragments from rats, normal and PLD from human patients were collected to evaluate: (i) intrahepatic bile duct mass (IBDM) by immunohistochemistry for citokeratin-19 (CK-19); and (ii) expression of V1a, V1b and V2 by immunohistochemistry, immunofluorescence and real time PCR. In vitro, small and large mouse cholangiocytes, H69 (non-malignant human cholangiocytes) and LCDE (human cholangiocytes from cystic epithelium) were stimulated with AVP in the absence/presence of antagonists such as OPC-31260 and Tolvaptan, before assessing cellular growth by MTT proliferation assay, cAMP levels by a RIA kit and the expression of some angiogenic factors, such as platelet-derived growth factor (PDGF) and Angiopoietins (Ang-1 and Ang-2). Cholangiocytes express V2 receptor that was upregulated following BDL and in course of polycystic disease. Treatment with AVP of cholangiocyte cultures increased proliferation, cAMP levels and expression of PDGF, Ang-1, Ang-2 in small cholangiocytes and LCDE cells. These increments were blocked by pre-incubation with the AVP antagonists. Our results showed that AVP play an important role in growth of the biliary epithelium during cholestasis and in cystic epithelium in course of PLD acting on the cAMP signalling pathway and increasing angiogenic factors. Additional studies are necessary, but these first results may be considered important in the regulation of the biliary growth/loss in course of cholangiopathies.

References

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Keywords

Biliary epithelium; vasopressin; cholestasis; polycystic liver disease.