## Gonadotropin-releasing hormone induces biliary proliferation by both paracrine and autocrine mechanisms

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During cholestatic liver disease, there is dysregulation in the balance between biliary growth and loss. In bile duct-ligated (BDL) rats, this balance is modulated by neuroendocrine peptides via autocrine/paracrine pathways (1). Gonadotropinreleasing hormone (GnRH) is a trophic peptide hormone that modulates reproductive function and proliferation in many cell types (2). We evaluated the autocrine role of GnRH in the regulation of cholangiocyte growth. The expression of GnRH receptors was evaluated in a normal mouse cholangiocyte cell line (NMC), sham and BDL rats. The effect of GnRH administration was evaluated in normal rats and in NMC. GnRH-induced biliary proliferation was evaluated by changes in intrahepatic bile duct mass (IBDM) by CK19 specific staining, the expression of proliferation and function markers. The expression and secretion of GnRH in NMC and isolated cholangiocytes was assessed. GnRH receptor subtypes GnRHR1 and GnRHR2 were expressed in biliary epithelium. Treatment with GnRH increased IBDM as well as proliferation and function markers in cholangiocytes. Transient knockdown and pharmacologic inhibition of GnRHR1 in NMC decreased proliferation. BDL cholangiocytes had increased expression of GnRH compared with normal rats, accompanied by increased GnRH secretion. In vivo and in vitro knockdown of GnRH decreased intrahepatic bile duct mass/cholangiocyte proliferation and fibrosis. GnRH secreted by cholangiocytes promotes biliary proliferation via an autocrine pathway. Disruption of GnRH/ GnRHR signaling may be important for the management of cholestatic liver diseases.

## References

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## Keywords

Biliary epithelium; GnRH; neuroendocrine peptides; cholestatic diseases.