

Histamine induces small and large cholangiocytes growth by activation of IP₃/Ca²⁺ and cAMP-dependent signalling mechanisms

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The intrahepatic biliary epithelium is formed by different-sized cells called large and small cholangiocytes (Alpini et al., 1996). Large cholangiocytes exert their functions by activation of cAMP, while Ca²⁺-dependent signalling regulates the function of small cholangiocytes (Francis et al., 2007). Histamine interacts with four receptors, H1–H4HRs (Onori et al 2010). H1HR acts by IP₃/Ca²⁺-dependent mechanism, whereas H2HR stimulates cAMP signalling pathway. We hypothesize that histamine increases biliary growth by activating H1HR on small and H2HR on large cholangiocytes. The expression of H1–H4HRs was evaluated in liver sections and in isolated and cultured cholangiocytes (normal rat intrahepatic cholangiocyte culture, NRIC). Normal rats were treated with H1-H4HRs agonists for 1 week. Small and large cholangiocytes express H1-H4HR. . Histamine and the H1HR agonist increased small Bile Duct Mass (BDM), whereas histamine and the H2HR agonist increased large BDM. H1HR agonists stimulated IP(3) levels and PKC α phosphorylation, whereas H2HR agonist increased cAMP levels and PKA phosphorylation. The activation of differential signaling mechanisms targeting small and large cholangiocytes may be important for biliary regeneration during pathologies affecting different-sized bile ducts.

References

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