View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

Hepatology Snapshot

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Histamine regulation of biliary proliferation

Heather Francis, Fanyin Meng, Eugenio Gaudio, Gianfranco Alpini*

Central Texas Veterans Health Care System, Scott & White Digestive Disease Research Center, Scott & White and Texas A&M Health Science Center, College of Medicine, TX, USA; Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, "La Sapienza", Rome, Italy

Cholangiocytes, which line the biliary epithelium, are hormone-responsive and responsible for the modification of canalicular bile before reaching the duodenum. Cholangiocytes are the target cells in cholangiopathies such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) that are characterized by cholangiocyte proliferation/loss [1]. The biliary epithelium is morphologically and functionally heterogeneous and is lined by small (<15 μm in diameter) and large (>15 μm in diameter) cholangiocytes lining small and large bile ducts, respectively [2]. Cholangiocyte responses are regulated by both Ca^{2+}- and cAMP-dependent signaling [2–5].

Histamine is a biogenic amine that is mostly recognized for its role in allergy-related diseases. After histamine is formed from the decarboxylation of the amino acid histidine, by histidine decarboxylase (HDC), it is rapidly stored or degraded. Histamine exerts its effects through four G-protein coupled receptors (GPCRs), H1–H4 histamine receptors (HRs) [6]. Activation/inhibition of HRs triggers downstream signaling pathways to elicit cellular responses such as proliferation, apoptosis, and differentiation.

It has been shown that histamine plays a critical role in liver repair and regeneration. The H1 histamine receptor affects gamma-glutamyltransferase (γ-GT) levels during liver regeneration after partial hepatectomy in rats [7]. Blocking H1HR increased serum γ-GT activity, whereas inhibition of H2HR did not have a significant effect in this model [7]. Histamine, via the H4HR, protects against ischemia/reperfusion liver injury by decreasing cytokine release [8]. These studies demonstrate the varying role of histamine in liver injury and the potential benefits of histamine during the progression of liver damage.

Our group has demonstrated that histamine, via the four histamine receptors, H1–H4HRs, induces a differential response in cholangiocyte proliferation via diverse signaling pathways as shown in Fig. 1 [4,5,9,10]. We have found that all HRs are present on cholangiocytes and that these receptors are both inhibitory (H3–H4HRs) and stimulatory (H1–H2HRs) during cholangiocyte proliferation [4,5,9,10].

In a rodent model of cholangiocyte proliferation induced by bile duct ligation (BDL), we have demonstrated that stimulation of the inhibitory H3HR by an H3HR agonist decreases BDL-induced cholangiocyte hyperplasia [4]. Activation of H3HR (that couples to Gαi) inhibits cAMP signaling with a subsequent decrease in the phosphorylation of ERK1/2 and the transcription factor, Elk1 [4]. Inhibition of cholangiocyte proliferation may be a useful therapy for treatment of cholangiopathies characterized by increased biliary hyperplasia (Fig. 1, top panel).

We also found that histamine, via H1HR (coupled to Gαq) regulates small cholangiocyte proliferation without inducing any effects in large cholangiocytes [5]. Using cultured mouse cholangiocytes, we found that stimulation of H1HR increases the proliferation of small (but not large) cholangiocytes via activation of IP_3/Ca^{2+}/PKC/CaMKI/CREB-dependent pathway as shown in Fig. 1, top panel [5].

The H3HR signals either via Gαi (inhibition of cAMP) or Gαo (activation of Ca^{2+}). Using a specific agonist for the H3HR, we evaluated the effects of this agonist on cholangiocarcinoma growth [9]. We demonstrated that activation of H3HR decreases cholangiocarcinoma growth both *in vitro* and *in vivo* [9]. Surprisingly, the effects by RAMH were mediated not by inhibition of cAMP signaling, but by activation of the IP_3/Ca^{2+}/PKCα [9]. We demonstrated that activation of PKCα led to decrease ERK1/2 phosphorylation and subsequent decreased biliary proliferation as shown in Fig. 1, bottom panel.

In a separate study, we have evaluated the specific role of the H4HR agonist, clobenpropit, on cholangiocarcinoma growth and metastatic potential [10]. We demonstrated that by activation of H4HR cholangiocarcinoma growth decreases (both *in vitro* and in a xenograft tumor model) and epithelial–mesenchymal transition is also inhibited. Our findings suggest that the activation of H4HR decreases the expression of extracellular matrix degrading enzymes, matrix metalloproteinases preserving the extracellular matrix and making tumor spreading more difficult [10]. Further, we found that H4HR allows cholangiocarcinoma cells to maintain more of an epithelial cell-type phenotype by preserving the expression of numerous hepatobiliary markers including the cytokeratins, CK-7, -8, and -19. The actions of H4HR were mediated by activation of a Ca^{2+}/PKC-dependent pathway similar to what we found using an agonist for H3HR as depicted in Fig. 1, bottom panel [10].

Studies have shown that cholangiocytes (that are normally) dormant, proliferate after BDL, a model that mimics human

Keywords: Cholangiocytes; Biogenic amines; cAMP; Ca^{2+}; Proliferation; Receptor; Cholestasis; Cholangiocarcinoma.
Received 30 June 2011; received in revised form 13 August 2011; accepted 4 September 2011

* Corresponding author. Address: Central Texas Veterans Health Care System and Texas A&M HSC COM, 702 SW HK Dodgen Loop, 76504, Temple, TX, USA.
E-mail address: galpini@tamu.edu (G. Alpini).

Open access under CC BY-NC-ND license.

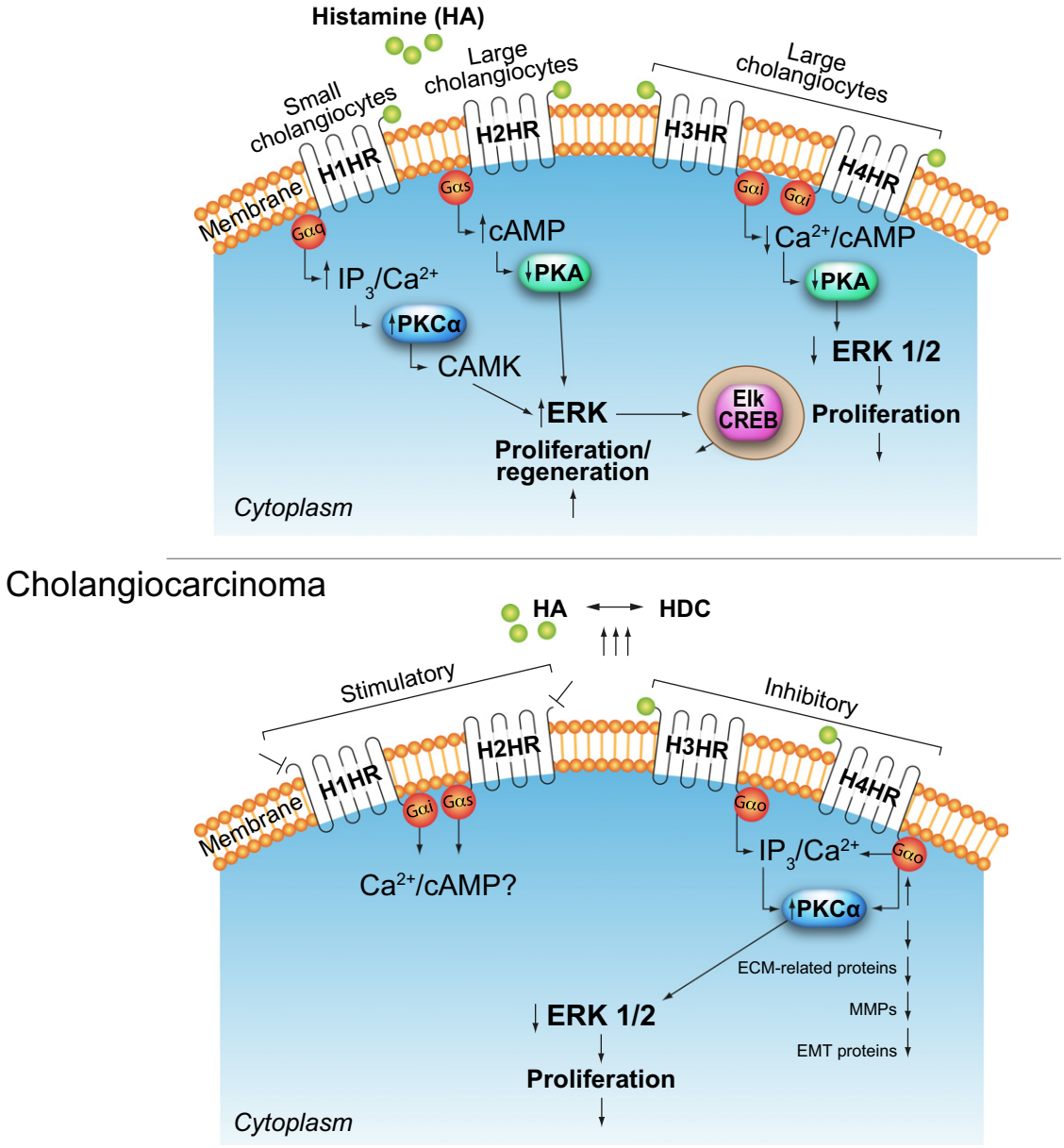

Fig. 1. Top panel: In normal and during cholestatic injury, histamine receptors are found in small and large cholangiocyte populations. Expression levels of HRs have not been found to have a significant impact on cholangiocyte response, however, activation of specific histamine receptors results in differential downstream signaling. H1HR couples mainly to Gαq that mobilizes the IP_3/Ca^{2+}/PKC-dependent pathway with subsequent increased cholangiocyte proliferation. Our data suggests that the effects of H1HR are predominantly found in small cholangiocytes, as this population is known to signal via Ca^{2+}-dependent pathways. H2HR activates cAMP-dependent mechanisms that increase cholangiocyte proliferation. Large cholangiocyte proliferation is regulated primarily by cAMP activation and our data has supported this concept. The H3 and H4HRs are predominantly inhibitory receptors that are able to either inhibit cAMP synthesis or activate Ca^{2+}/PLC-dependent pathways. The result of H3 or H4 activation is decreased cholangiocyte proliferation that we believe occurs mostly in large cholangiocytes. **Bottom panel: During cholangiocarcinoma, histamine and the enzyme responsible for histamine synthesis, histidine decarboxylase (HDC), are upregulated thus activating specific histamine receptors**. We have found that after activation of the inhibitory receptors, H3 and H4, cholangiocarcinoma growth decreases. H3HR activates Ca^{2+}/PKCα-dependent signaling that decreases cholangiocarcinoma growth, whereas H4HR signals via Ca^{2+}-dependent mechanisms to decrease EMT, ECM degradation and tumor spreading. We suggest that inhibition of the stimulatory H1 or H2 HR will result in decreased cholangiocarcinoma growth presumably by inhibition of Ca^{2+}-dependent or cAMP-dependent pathways. ECM, extracellular matrix; EMT, epithelial mesenchymal transition; HA, histamine; HDC, histidine decarboxylase; HR, histamine receptors; MMPs, matrix metalloproteins.

cholestatic liver disease [3,4]. While these studies above document the role of histamine and HRs during diseased states, preliminary data show that normal cholangiocytes can be activated to proliferate via histamine and two stimulatory histamine receptors, H1HR and H2HR. We demonstrated that histamine increases normal cholangiocyte proliferation via activation of both Ca^{2+}- and cAMP-dependent pathways. When elucidating the specific histamine receptors, we discovered that

H1HR increases normal cholangiocyte growth via a Ca^{2+}/PKCα-dependent pathway, whereas H2HR activates cAMP synthesis to increase normal cholangiocyte proliferation. We have data demonstrating that H1HR-induced cholangiocyte proliferation occurs in small cholangiocytes (regulated by Ca^{2+}-dependent signaling) whereas H2HR-induced cholangiocyte proliferation exists in large cholangiocytes that signal via cAMP activation.

Overall, these findings are important in understanding the differential response induced by histamine that may regulate cholangiocyte proliferation during the progression of cholangiopathies or liver regeneration. Modulation of H1–H4HRs may be key for the management of the balance between biliary growth/loss in cholangiopathies.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Acknowledgments

We gratefully acknowledge Bryan Moss, Graphic Services Department S&W Hospital for his rendering of the artwork.

References

[1] Alpini G, Prall RT, LaRusso NF. The pathobiology of biliary epithelia. In: Arias IM, Boyer JL, Chisari FV, Fausto N, Jakoby W, Schachter D, Shafritz DA, editors. The liver: biology & pathobiology. Philadelphia, PA: Lippincott Williams & Wilkins; 2001. p. 421–435.

[2] Alpini G, Glaser S, Robertson W, Rodgers RE, Phinizy JL, Lasater J, et al. Large but not small intrahepatic bile ducts are involved in secretin-regulated ductal bile secretion. Am J Physiol Gastrointest Liver Physiol 1997;272:G1064–G1074.

[3] Mancinelli R, Franchitto A, Gaudio E, Onori P, Glaser S, Francis H, et al. After damage of large bile ducts by gamma-aminobutyric acid, small ducts replenish the biliary tree by amplification of calcium-dependent signaling and de novo acquisition of large cholangiocyte phenotypes. Am J Pathol 2010;176:1790–1800.

[4] Francis H, Franchitto A, Ueno Y, Glaser S, DeMorrow S, Venter J, et al. H3 histamine receptor agonist inhibits biliary growth of BDL rats by downregulation of the cAMP-dependent PKA/ERK1/2/ELK-1 pathway. Lab Invest 2007;87:473–487.

[5] Francis H, Glaser S, DeMorrow S, Gaudio E, Ueno Y, Venter J, et al. Small mouse cholangiocytes proliferate in response to H1 histamine receptor stimulation by activation of the IP_3/CAMK I/CREB pathway. Am J Physiol Cell Physiol 2008;295:C499–C513.

[6] Repka-Ramirez MS. New concepts of histamine receptors and actions. Curr Allergy Asthma Rep 2003;3:227–231.

[7] Kozlowski Jr VA, Mattos Filho TR. Effect of H1 and H2 receptor antagonists on the serum activity of gamma-glutamyltransferase during liver regeneration after partial hepatectomy in rats. Pharmacology 1995;51:134–136.

[8] Motoki A, Adachi N, Liu K, Takahashi HK, Nishibori M, Yorozuya T, et al. Suppression of ischaemia-induced cytokine release by dimaprit and amelioration of liver injury in rats. Basic Clin Pharmacol Toxicol 2008;102:394–398.

[9] Francis H, Onori P, Gaudio E, Franchitto A, DeMorrow S, Venter J, et al. H3 histamine receptor-mediated activation of protein kinase C alpha inhibits the growth of cholangiocarcinoma *in vitro* and *in vivo*. Mol Cancer Res 2009;7:1704–1713.

[10] Meng F, Han Y, Staloch D, Francis T, Stokes A, Francis H. The H4HR agonist, clobenpropit, suppresses human cholangiocarcinoma progression by disruption of EMT and tumor metastasis. Hepatology 2011, July 25 [Epub ahead of print]. doi:10.1002/hep.24573.