MINIREVIEW

Biogenic Amine Actions on Cholangiocyte Function

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Biogenic amines, such as serotonin, histamine, dopamine, and the catecholamines epinephrine and norepinephrine, regulate a multitude of cellular responses. A great deal of effort has been invested into understanding the effects of these molecules and their corresponding receptor systems on cholangiocyte secretion, apoptosis, and growth. This review summarizes the results of these efforts and highlights the importance of these regulatory molecules on the physiology and pathophysiology of cholangiocytes. Exp Biol Med 232:1005–1013, 2007

Key words: histamine; serotonin; dopamine; adrenergic receptors; cell growth; bile duct epithelia

Background on Cholangiocytes

Cholangiocytes are the epithelial cells that line the intrahepatic and extrahepatic biliary tree (1). These cells are normally mitotically dormant (2), but they proliferate in response to certain pathologic stimuli, including bile duct ligation (BDL), partial hepatectomy, and bile acid feeding (1–3). The intrahepatic biliary tree is the target of several human diseases defined as *cholangiopathies* (1), which are characterized by chronic cholestasis leading to liver failure (1, 4). Studies have shown that such disorders are responsible for more than 20% of liver transplantations among adults and 50% of liver transplantation among pediatric patients in the United States (5). The pathophysiology of cholangiopathies commonly consists of an impaired balance between proliferation and death of cholangiocytes (1). What regulates cholangiocyte proliferation and death and how these mechanisms fail is still undefined (1, 6).

General Background on Biogenic Amines

Serotonin, norepinephrine, epinephrine, dopamine, and histamine are often collectively referred to as *biogenic amines* (7–9). These agents play key roles in neurotransmission and other signaling functions (7–9). They are relatively small in size and contain a protonated amino group or a permanently charged ammonium moiety. Biogenic amines can act as neurotransmitters to elicit various physiologic responses, and they all have various other sites of action throughout the body (7–9). Generally, they can be synthesized at various sites throughout the body and are released from intracellular vesicles into the surrounding tissue, where they can then bind to cell membrane–located receptors on the neighboring cells to elicit their responses (10). These molecules are capable of affecting mental functions, such as mood and appetite, and regulating blood pressure, body temperature, and other bodily processes (10).

Serotonin

General Background. Serotonin, or 5-hydroxytryptamine (5-HT), is a neuromodulator with both neuro-

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endocrine and neurotransmitter functions that is synthesized in serotonergic neurons in the central nervous system (11) and in enterochromaffin cells throughout the gastrointestinal tract (12). It is synthesized by the systematic hydroxylation and decarboxylation of the amino acid tryptophan by the enzymes tryptophan hydroxylase and amino acid decarboxylase, respectively (11). There are 16 serotonin receptors through which serotonin exerts its multiple effects. With the exception of the 5-HT3 receptor, a ligand-gated ion channel, all other 5-HT receptors are G protein coupled, seven-transmembrane receptors that activate intracellular second messenger systems (13).

Serotonin Functions in Other Cells. Serotonin regulates a wide variety of mood disorders, including depression, schizophrenia, and bipolar disorders (14). In addition, the local release of this hormone leads to changes in the functions of gastrointestinal epithelial cells. For example, the application of serotoninergic agents enhances fluid and ion secretion of the intestinal mucosa (15, 16), whereas the paracrine release of serotonin by enterochromaffin cells mediates the pancreatic secretion induced by intestinal lumenal factors (17, 18). In addition, serotonin modulates cell proliferation of vascular smooth muscle cells (19), kidney epithelial cells (19), and hepatocytes (20).

Serotonin and the Liver. In the liver, inhibition of the 5-HT2 receptors by ketanserin arrested liver regeneration only when administered late (16 hrs) after partial hepatectomy, and it was suggested that through 5-HT2 receptors, serotonin may have a role in the G_1/S transition checkpoint (21). Studies have shown (21, 22) that liver regeneration after partial hepatectomy was completely dependent upon platelet-derived serotonin, as a mouse model of thrombocytopenia inhibited normal liver regeneration in a 5-HT2 receptor–dependent manner (22). In addition, key regulatory components of the serotonin system are expressed in hepatic stellate cells, which appear to be integral in the storage and release of serotonin and the subsequent response to the neuromodulator in a profibrogenic manner (23). Indeed, antagonists for particular 5-HT receptors may prove beneficial as therapy against liver fibrosis (23).

Serotonin is involved in the pathogenesis of certain clinical features of cholangiopathies, pruritus, and fatigue in particular (24, 25). In animal models of chronic cholestasis, this may be due to an enhanced release of serotonin in the central nervous system and its interactions with subtype 1 serotonin receptors (25).

Recently, we demonstrated that cholangiocytes have the capacity to synthesize and secrete serotonin, both of which are increased in proliferating rat cholangiocytes after BDL (26). We postulate that this autocrine loop is integral in limiting the growth of the biliary tree as a result of chronic cholestasis. Our hypothesis is based on the observation that chronic treatment of rats with the 5-HT 1A and 1B receptor agonists inhibited cholangiocyte proliferation in BDL rats (26). Furthermore, we demonstrated that this effect is more than likely due to a direct effect of the receptor agonists on cholangiocytes, as the treatment of cholangiocytes with serotonin had a similar inhibitory effect. By using an antiserotonin antibody to immunoneutralize the endogenous serotonin secreted from cholangiocytes as a result of BDL, we were able to enhance the growth of the biliary tree in the course of chronic cholestasis, suggesting that the autocrine secretion of serotonin does, indeed, play an important role in the control of cholangiocyte growth (26).

Certain physiologic aspects of cholangiocyte functions were also inhibited by 5HT 1A and 1B receptor agonists in proliferating cholangiocytes after BDL, but not in mitotically dormant cholangiocytes (26). Both secretin-stimulated bile and bicarbonate secretion was inhibited by chronic *in vivo* administration of the serotonin receptor agonists (26). In freshly isolated cultures of cholangiocytes, serotonin receptor agonists inhibited both the secretin-stimulated cAMP synthesis and protein kinase A (PKA) activity (26). This suggests that activation of both 5-HT 1A and 1B receptors can modulate not only cholangiocyte proliferation and survival but also physiologic functions of cholangiocytes as well.

We dissected the intracellular signaling pathways that may be responsible for the antiproliferative effects of serotonin and observed that the serotonergic effects on cholangiocyte proliferation were associated with enhanced IP_3 levels and increased Ca^{2+}-dependent PKC activity and reduced cAMP/PKA pathway (26). Downstream of these events was a reduced activation of the Src/ERK1/2 (extracellular signal-regulated kinase 1/2) cascade, which directly effects cholangiocyte proliferation (26). A schematic representation of this pathway can be seen in Figure 1.

Histamine

General Background. The aminergic peptide histamine is responsible for many functions in the body, such as neurogenic functions, inflammatory responses, allergic responses, and gastric secretion (27–29). Four G protein–coupled histamine receptors (H1R, H2R, H3R, and H4R) exist (30, 31). Whereas H1R acts via $G\alpha_q$-mobilizing $[Ca^{2+}]_i$ (32), the activation of H2R is modulated by $G\alpha_s$ proteins coupled to adenylyl cyclase (33). Cloning and functional characterization of the human and rat H3R cDNA show that this receptor belongs to the family of G protein–coupled receptors (34, 35). Recently, H4R was cloned (36). This receptor is over 35% homologous to the H3R and appears to have similar functions, such as its ability to inhibit forskolin-stimulated cAMP levels (although not as potently as the H3R) in bone marrow cells (36). Histamine is synthesized by the decarboxylation of the amino acid histidine by L-histadine decarboxylase and is degraded in the target cells by monoamine oxidase B (37).

Histamine Functions in Other Cells. The major function of histamine is in the inflammation and the innate immune response (38). Most tissue histamine is found in

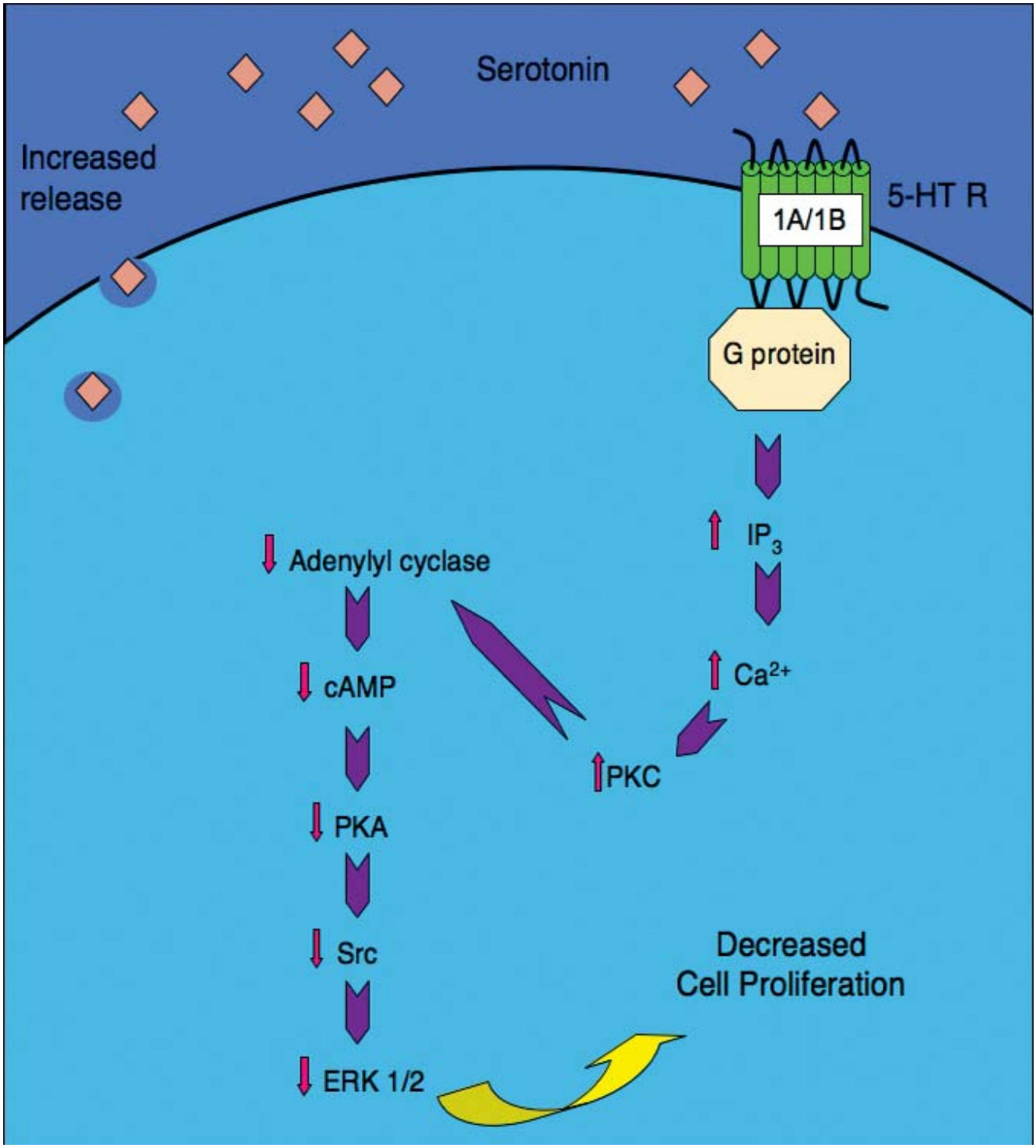

Figure 1. Schematic representation of the mechanism of the serotonin-induced decrease in cholangiocyte proliferation. Activation of 5-HT 1A/1B receptors results in an increase in IP_3/Ca^{2+}/PKC pathway, which in turn decreases the adenylyl cyclase/cAMP/PKA/ERK1/2 pathway. This ultimately leads to a decrease in cholangiocyte proliferation (This figure was adapted from Marzioni *et al.* (26) and reproduced with permission from the American Gastroenterological Society).

granules in mast cells or basophils (38). Non–mast cell histamine is found in several tissues, including the brain, where it functions as a neurotransmitter (39). Another important site of histamine storage and release is the enterochromaffin-like cell of the stomach (40).

Through its receptors histamine has been shown to regulate proliferation and migration in a number of cell types, including human embryonal kidney cells (41), various cancer cell lines (42–44), gastrointestinal epithelial cells (45), and in rat oxyntic mucosa (46).

Histamine and the Liver. Histamine modulates inflammatory processes within the liver, modulates certain aspects of the fibrogenic process, and protects against ischemia/reperfusion liver injury (47, 48). It has also been shown that plasma histamine levels are increased in chronic cholestatic liver diseases, such as primary biliary cirrhosis and sclerosing cholangitis (49), and that histamine may regulate some of the symptomatic processes associated with these diseases, such as pruritus (49). In addition, histamine, via H1R, causes the contraction of the sphincter of Oddi and the bile duct (50) and increases the rate of bile flow (51, 52).

Our studies into the effects of histamine on cholangiocyte growth and function have predominantly focused of the antiproliferative actions of H3R activation (53) and, to a lesser extent to date, the growth stimulatory effects of H1R and H2R receptor activation (54). Under normal conditions when cholangiocytes are predominantly mitotically dormant, H1R and H2R are the most prevalent subtype of histamine receptors expressed on cholangiocytes. However, in proliferating cholangiocytes as a result of BDL, the expression of H3R and H4R increases and that of H1R and H2R decreases. This differential expression of histamine receptors is consistent with the differential effects on cholangiocyte growth.

The expression of H3R is significantly increased in proliferating cholangiocytes observed after BDL (53). Activation of this receptor by chronically administering the H3R agonist (R)-(α)-(–)-methylhistamine dihydrobromide (RAMH) to rats for 7 days after BDL surgery resulted in a decrease in the growth of the biliary tree with no observable difference in the incidence of apoptosis, suggesting that H3R activation may slow the rate of cell cycle progression and proliferation rather than reduce the number of cholangiocytes by a cell death mechanism (53). Furthermore, administration of histamine to this animal model of cholestasis also resulted in a decrease in cholangiocyte proliferation, and blocking H3R activation by histamine using the selective H3R antagonist thioperamide maleate resulted in a partial reversal of this effect (53). Associated with the antiproliferative effects of H3R activation was the decrease in intracellular cAMP levels, which in turn decreased PKA activation and subsequent ERK 1/2 and Elk-1 activation in a manner similar to that observed with serotonin (53). A schematic representation of this can be seen in Figure 2.

In parallel experiments, treatment of mitotically dormant cholangiocytes *in vivo* with both the H1R and H2R agonists results in biliary tree outgrowth, proliferation of cholangiocytes, and a concomitant increase in intracellular cAMP levels (54). The intracellular mechanisms by which the activation of these two receptors results in cholangiocyte proliferation are through two distinct pathways, although a certain degree of cross-talk between the two exists (54). Administration of the selective H1R agonists to cholangiocytes in culture results in increased Ca^{2+} release and intracellular IP_3 levels with no observable difference on cAMP, as well as subsequent activation and translocation of PKC from the membrane to the cytoplasm (54). In contrast, activation of the H2R on cholangiocytes in culture increased cAMP levels and PKA activation. One of the downstream targets of both PKC and PKA is Src, which is activated by both H1R and H2R receptor agonists and results in the activation of Raf/B-Raf and ERK 1/2 (Fig. 2; Ref. 54).

Taken together, our data lend themselves to the hypothesis that there is a molecular switch that toggles between the expression of the cholangiocyte growth-promoting histamine receptor (H1R and H2R) and the growth-suppressive histamine receptors (H3R and H4R) under the appropriate conditions that require the diametric effects of histamine (normal conditions and BDL, respectively). Specifically, when cholangiocytes are mitotically dormant, H1R and H2R are the predominant receptors expressed and, hence, histamine would supposedly exert a net growth-promoting effect through activation of these two receptor subtypes. When cholangiocytes are induced to proliferate (for example, in response to BDL), the expression of H3R and H4R is upregulated and, as such, histamine would exert a net growth-suppressive effect on cholangiocyte proliferation. Presumably, these events are important in limiting the biliary outgrowth that results from chronic cholestasis in a manner similar to serotonin.

Dopamine

Background. Dopamine is synthesized mainly by nervous tissue and adrenal glands, first by the enzymatic conversion of tyrosine to DOPA (3,4-dihydroxyphenilalanine) by tyrosine hydroxylase and then by the decarboxylation of DOPA by aromatic-L-amino acid decarboxylase. As a member of the catecholamine family, dopamine is also a precursor to epinephrine and norepinephrine. The dopamine receptors are a class of metabotropic G protein–coupled receptors, and to date there are five types, D1–D5 (55). Activation of these receptors has differing effects on signal transduction pathways. For example, the D1 receptor interacts with the G_s complex to activate adenylyl cyclase, whereas the D2 interacts with G_i to inhibit cAMP production (55).

Dopamine in Other Cell Systems. In the brain dopamine acts as a neurotransmitter, activating dopamine receptors, but it can also act as a neurohormone released by the hypothalamus and exerting various effects on the pituitary (56). Dopamine has been implicated in the etiology of Parkinson's disease (57) and schizophrenia (58) and plays a major role in the reward system of behavior (59).

Dopamine in the Liver. Our studies into the effects of dopaminergic innervation on cholangiocytes have focused on the D2 dopamine receptor (60). Expression of the other dopamine receptors was absent from cholangiocytes under all conditions studied (mitotically dormant and proliferating cholangiocytes), whereas the D2 dopamine receptor was expressed in normal cholangiocytes and

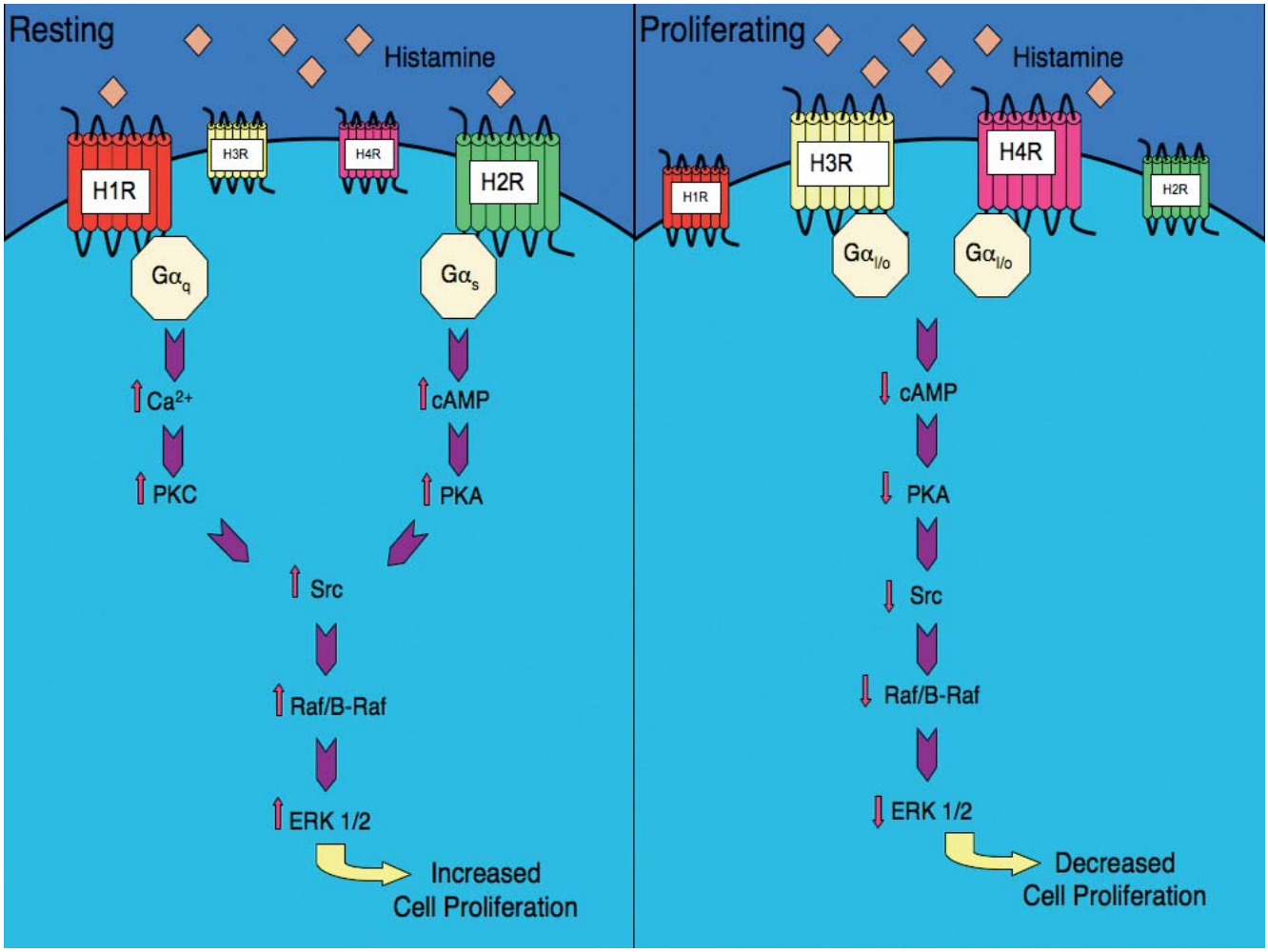

Figure 2. Working model for the opposing effects of histamine receptor activation on cholangiocyte growth. Under resting conditions, H1R and H2R predominate. Activation of these two receptors results in the activation of a signal transduction cascade that results in increased cholangiocyte proliferation. However, in proliferating cholangiocytes (e.g., after BDL) the expression of H1R and H2R is decreased and the expression of H3R and H4R is predominant. Activation of these receptors leads to antiproliferative effects on cholangiocyte growth.

markedly upregulated after BDL (60). In experiments similar to those described above for serotonin, the effects of D2 dopamine receptor activation on other aspects of cholangiocyte physiology have been determined (60). Infusion of quinelorane had no effect on basal bile flow and bicarbonate concentration and secretion. However, coinfusion of quinelorane with secretin resulted in a decrease in secretin-stimulated bile flow and bicarbonate secretion, an effect that could be abolished with the D2 receptor antagonist eticlopride (60). We have repeatedly demonstrated that agents that inhibit secretin-stimulated bile flow also exhibit growth-suppressive actions on cholangiocytes (26, 61–64). This further supports a tentative role for D2 dopamine receptor activation in the suppression of cholangiocyte proliferation after BDL.

The mechanism by which quinelorane inhibits secretin-induced ductal secretion and, by extension, cholangiocyte growth, is similar to that observed after serotonin receptor activation. That is, quinelorane activated the Ca^{2+}-dependent PKC-γ, but not any other PKC isoform and, once again, blocking PKC-γ activity effectively inhibited the effects of D2 dopamine receptor activation on ductal secretion (60).

The cross-talk between the Ca^{2+}- and cAMP-dependent signaling pathways has been shown repeatedly to be an integral signal transduction pathway in the control of cholangiocyte physiology and proliferation (65, 66). We have previously described this phenomenon for serotonin receptor activation (see above; Ref. 26) as well as for gastrin (61, 62). A similar pathway is responsible for the effects of quinelorane. D2 dopamine receptor activation by itself has no effect on intracellular cAMP levels (60). However, quinelorane treatment effectively blocks the increase in cAMP normally seen after secretin administration, which in turn blocks the cAMP-dependent activation of PKA (60).

Information regarding the ability of cholangiocytes to synthesize and secrete dopamine is lacking, so it cannot be said that these dopamine-induced effects on cholangiocytes

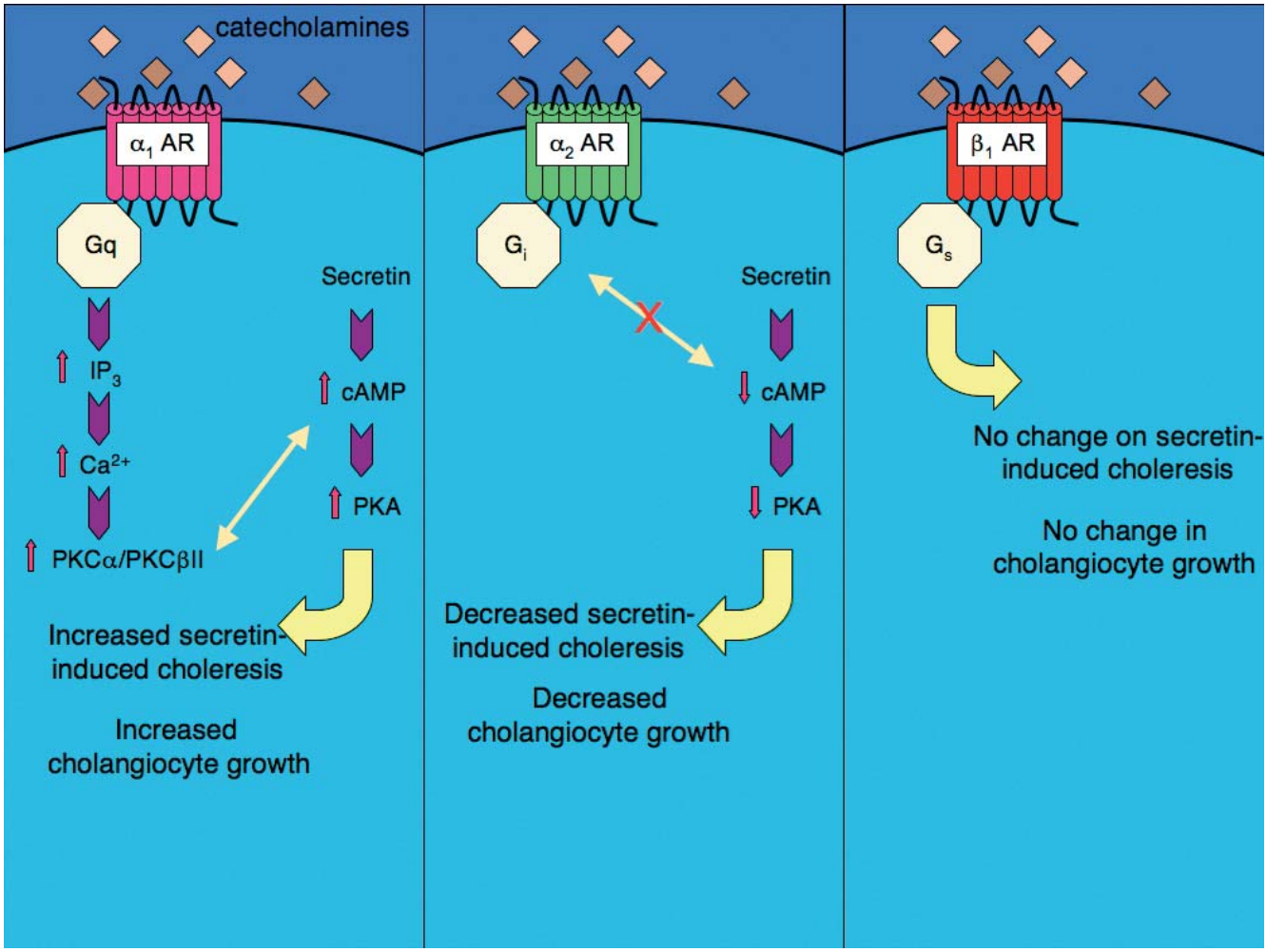

Figure 3. Activation of adrenic receptors gives a wide range of responses in cholangiocyte growth and secretion. Activation of α_1 AR increases the Ca^{2+}/IP_3/PKC pathway. This has a positive effect on secretin-induced cAMP and PKA activation. This increases secretin-induced choleresis and cholangiocyte growth. Conversely, activation of α_2 AR has a negative effect on secretin-induced cAMP and PKA activation, which decreases secretin-induced choleresis and cholangiocyte growth. Activation of the β_1 AR has no effect on cholangiocyte growth or secretion.

are through an autocrine mechanism and/or are a direct result of dopaminergic innervation of the liver.

Epinephrine and Norepinephrine

General Background. The catecholamines, epinephrine, and norepinephrine are synthesized from the hydroxylation of dopamine (norepinephrine) and subsequent methylation (epinephrine; Ref. 67). Catecholamines are synthesized predominantly in the sympathetic nervous system and activate adrenergic receptors found on the effector tissues (67, 68). Many cells possess these receptors, and binding of the agonists will usually cause the cell to respond in a "flight-or-flight" manner (69). Typical physiologic responses to epinephrine and norepinephrine include increased heart rate, mobilization of energy stores, and changes in blood flow away from other organs and towards the skeletal muscle (69). To date, there are many adrenergic receptors, which are categorized into five subclasses of receptors (α_1, α_2, β_1, β_2, and β_3) based on their relative affinity to various adrenergic compounds and the subsequent cellular responses given. For example, α_1 adrenergic receptors are G_q protein–coupled receptors that have a stronger affinity for norepinephrine than for either epinephrine or the synthetic catecholamine isoproterenol (a drug used to treat bronchial asthma; Ref. 70), whereas α_2 adrenergic receptors are G_i protein–coupled receptors that respond better to epinephrine than the other catecholamines (70). Finally, β_1 adrenergic receptors have a stronger affinity for isoproterenol than either of the endogenous chatecholamines and are coupled to the G_s subtype of G protein (70).

Adrenergic Receptor Activation in the Liver. In the liver, adrenergic nerve stimulation causes a decrease in bile flow in the isolated perfused rat liver through interactions with α_1 adrenergic receptors (71). Furthermore, in isolated perfused rat liver, adrenaline induces a complex response of bile secretion, including rapid, reversible stimulation, reversible inhibition, and prolonged stimulation *via* interaction with α_1 adrenergic receptors (72).

Similarly to our histamine data, it is evident that we have differential effects of specific adrenergic receptor subtypes on ductal secretion. The α_1 adrenergic receptor agonist phenylephrine had no effect on the basal rate of bile flow, bicarbonate secretion, and bicarbonate concentration in normal and BDL rats (66). However, after stimulation of choleresis by secretin, phenylephrine further increased ductal secretion of bile acids and bicarbonate (66). Interestingly, specific activation of the β_1 adrenergic receptors by dobutamine had no effect on secretin-induced choleresis or growth (66). We then further dissected the signaling pathway responsible for the effect of phenylephrine on bile flow. First, phenylephrine administration leads to an increase in intracellular Ca^{2+} and IP_3 levels (66). Sequestration of Ca^{2+} by BAPTA-AM effectively blocked the effects of phenylephrine (66). Associated with these events was an increased activation and membrane translocation of PKCα and PKCβII, which in turn effectively enhanced the effects of secretin on cAMP levels and PKA activity (Fig. 3; Ref. 66).

In contrast, activation of α_2 adrenergic receptors by the specific agonist UK14,304 effectively abrogated secretin-induced choleresis in BDL rats as well as secretin-induced increases in cAMP levels and PKA activity (Francis et al. submitted manuscript). Details as to the precise intracellular mechanism that leads to the suppression of secretin-induced cAMP levels are missing and are a topic of ongoing research within our laboratory; however, because α_2 adrenergic receptors are normally coupled to the G_i protein, presumably the intracellular mechanism is similar to that seen for H3 histamine receptors (Fig. 3).

Conclusions and Future Directions. Biogenic amines regulate a plethora of biologic responses. We have strived to dissect the precise effects of these important biologic molecules on cholangiocyte growth and physiology. Our efforts have highlighted the potential importance of these molecules and their receptors in the pathologic processes associated with chronic cholestatic liver diseases. Further research into the molecular events associated with the actions of the various biogenic amines on cholangiocyte proliferation is ongoing in our laboratory. Regulation of cholangiocyte growth and cell death by therapeutic agents aimed to activate or block these receptor systems may prove beneficial in the treatment of various cholangiopathies, such as primary biliary cirrhosis and sclerosing cholangitis.

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