Review Article

The physiological roles of secretin and its receptor

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Abstract: Secretin is secreted by S cells in the small intestine and affects the function of a number of organ systems. Secretin receptors (SR) are expressed in the basolateral domain of several cell types. In addition to regulating the secretion of a number of epithelia (e.g., in the pancreas and biliary epithelium in the liver), secretin exerts trophic effects in several cell types. In this article, we will provide a comprehensive review on the multiple roles of secretin and SR signaling in the regulation of epithelial functions in various organ systems with particular emphasis in the liver. We will discuss the role of secretin and its receptor in health and biliary disease pathogenesis. Finally, we propose future areas of research for the further evaluation of the secretin/secretin receptor axis in liver pathophysiology.

Keywords: Secretin; Secretin receptors

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General background

The gastrointestinal peptide hormone, secretin, was originally identified by Bayliss and Starling in 1902 (1). Secretin is a member of the secretin-glucagon family and is secreted by S cells of the duodenum in the crypts of Lieberkühn (2). Secretin affects the function of a number of organ systems and cell types (1-7). Secretin exerts its biological effects through G-protein coupled secretin receptors (SR), which are expressed in the basolateral domain of several cells (3,5,8-11). In addition to regulating the pH of the duodenal content by the control of gastric acid secretion (12), secretin regulates the secretion of bicarbonate ions into the duodenum from the epithelia lining the pancreatic and biliary ducts (3,6,7,13). In addition to regulating water homeostasis (4), secretin has been considered as a neuropeptide hormone since it is also expressed in the central nervous system (CNS) (14-16). Recent evidence has indicated that secretin has pleiotropic effects in several organ systems (including the biliary epithelium) (17) and has been termed a neuroendocrine hormone (18).

The neuroendocrine hormone secretin

Structure of secretin

The peptide sequence of secretin was first determined with porcine secretin in 1970 (19). The human secretin gene is 514 bp, which is longer than that of mouse or rat, 507 bp and 405 bp, respectively (20,21), NCBI Reference Sequence: NM_022670.2. The human secretin gene shows 42.7% homology to the mouse secretin gene, and 46.8% homology to the rat secretin gene. Homology was analyzed using SCAN2 software from Softberry, http://linux1.softberry.com/berry.phtml?topic=scan2&group=programs&subgroup=scanh subsequently, % homology was calculated independently. Secretin is a 27-amino acid

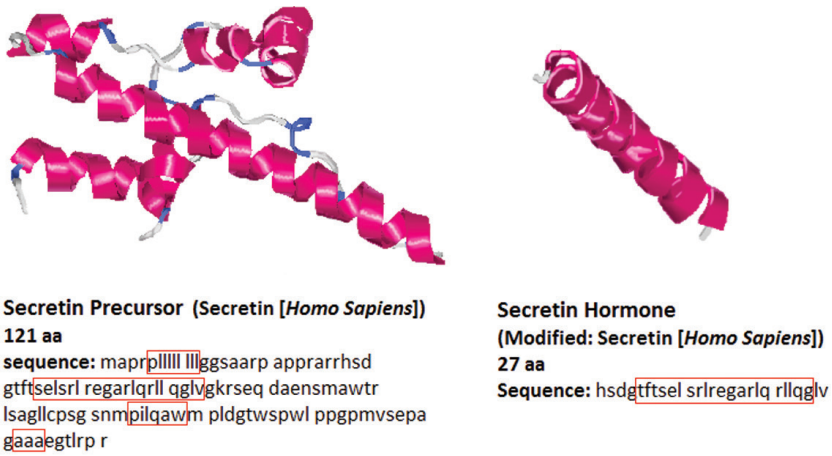

Figure 1 Ribbon structures for secretin precursor and secretin hormone. The peptide sequence for full-length secretin is 121 aa, and contains multiple stretches capable of hydrogen bonding (red boxes) to support α-helical arrangement. The secretin hormone is 27 aa, and contains one long sequence that supports α-helical formation. 3D structures were predicted with the help of I-tasser software (27,28).

peptide and is the active form of pro-secretin, which is known as a preprohormone and is synthesized as a larger precursor like other regulatory peptides (22,23). Secretin is initially synthesized as a 120 amino acid precursor protein. This precursor contains an N-terminal signal peptide, spacer, secretin itself (residues 28-54), and a 72-amino acid C-terminal peptide (24). This peptide is proteolytically processed to yield a single linear 27-amino acid peptide hormone with a molecular weight of 3,055 kD by removal of the signal peptide, plus amino and carboxy-terminal extensions (25). The sequence of the mature peptide has homology to that of other peptides isolated from the gastrointestinal tract including glucagon, vasoactive intestinal peptide (VIP) and gastric inhibitory peptide (PHI-27), which are the members of the secretin family (25,26). The gene and amino acid sequence of the human secretin is depicted in *Figure 1*.

Anatomical sites of secretin synthesis and secretion

The predominant anatomical site of secretin synthesis is in the cytoplasmic secretory granules of S-cells that are located in the mucosa of the small intestine in the crypts of Lieberkühn (2). Secretin is also secreted by specific endocrine cells in the mucosa of the proximal small intestine and expressed in smaller numbers in the jejunum of duodenum (2,29). In addition to being localized in the duodenum (2,24), secretin is also expressed in the CNS (30,31). Indeed, a study has demonstrated that secretin is expressed in both the pituitary and pineal glands and at lower levels in the hypothalamus, thalamus, and olfactory lobe (32-34). The mRNA encoding secretin is also expressed in the Purkinje cells of the rat cerebellar cortex (35). The fact that secretin precursor mRNA in the brain has the same coding sequence as that of the duodenum suggests the secretin precursor protein in the small intestine is perhaps the same as the one synthesized in the brain. Conversely, another study has shown low secretin immunoreactivity in the brain (24). Further studies are warranted to clarify this discrepancy. The secretin precursor gene is also expressed in the heart, lung, kidney, testis, and brain as well as the gastrointestinal tract including the biliary epithelium (36,37). The mRNA for secretin and its receptor have been also demonstrated in the intestine, heart, and pancreas (24,38,39). Preliminary data from our laboratory have also shown that: (I) cholangiocytes express the mRNA for secretin and synthesize secretin; and (II) knockout of the gene for secretin reduces biliary growth in cholestatic mice likely by an autocrine mechanism (37).

Brief general background on secretin biological effects

Secretin exerts pharmacological effects in a number of organs including the heart, kidney, lung, and brain (40-43). Secretin has been show to stimulate bile and bicarbonate secretion in the duodenum (44), pancreatic (45) and biliary (3,7,46) ducts as well gastric pepsin secretion (47). Also, secretin inhibits gastric acid secretin and food-stimulated gastrin release (48) as well as upper small intestinal

motility and lower esophageal sphincter pressure (49). Secretin induces the release of insulin from the pancreas following ingestion of glucose and may be important for the management of blood sugar levels (50).

The G-protein coupled secretin receptor

Expression of secretin in various tissues and cell types

Human secretin receptor was originally isolated from lung cells (51) and found on the basolateral domain of the epithelia within the tertiary bronchus (52). The expression of the secretin receptor has been demonstrated in a number of organs including the brain (cerebellum, hippocampus and central amygdala) of humans and rodents (33,53,54), pancreas (14), stomach (14,55), kidney (14,41) as well the biliary epithelium in the liver (3,8,56-58). Immunoreactivity for secretin receptors is present in the renal medulla, proximal tubules, and ascending thick segment of the loop of Henle in the kidney (53).

A number of studies have also shown that secretin receptors are only expressed in cholangiocytes in the liver (3,8,38,57,59,60). An *in vivo* autoradiography study in rat liver has shown specific binding of ^{125}I-labeled secretin to bile duct areas of normal and BDL rats, binding that increased following BDL (59). *In vitro* studies have shown that secretin stimulates exocytosis in normal cholangiocytes by increasing intracellular adenosine 3',5'-cyclic monophosphate (cAMP) levels by interaction with secretin receptors (61). Conclusive evidence came from our recent studies showing that: (I) large (but not small) cholangiocytes in rodent liver express secretin receptors (3,57); and (II) the expression of this receptor increases in models of intra- and extra-hepatic cholestasis such α-naphthylisothiocyanate feeding (62) and BDL (8,56) and decrease in models of biliary damage loss (e.g., after CCl_4 administration) (63,64). Small cholangiocytes (which normally do not express secretin receptor) (63,64) acquire *de novo* this receptor only during damage of large cAMP-responsive cholangiocytes (63-65). The secretin receptor is also expressed and up-regulated in kidney and cholangiocytes in rodent models of polycystic kidney and liver disease such as in Pkd2(-/WS25) mice (66). A study (analyzing the expression of secretin receptor in human samples) has demonstrated the presence of these receptors in normal bile ducts and ductules but not in hepatocytes (67). The expression of this receptor was higher in ductules during liver cirrhosis and cholangiocarcinoma, whereas no immunohistochemical reaction was observed in hepatocellular carcinomas (67). Conclusive evidence for the presence of secretin receptor in cholangiocytes came from a recent study showing that knockout of secretin receptor reduces large cholangiocyte hyperplasia in cholestatic BDL mice (17). Thus, changes in the expression of this receptor may be a unique tool for managing the balance between biliary growth/damage in chronic cholestatic liver diseases (17,62-65).

Signaling mechanisms

The effects of secretin on the gastrointestinal tract and other organ systems are mediated by interaction with basolateral SR (15). The secretin receptor has seven membrane-spanning domains and it is a typical G protein-coupled receptor (GPCR) under the class B GPCR subfamily (5). The messenger system, cAMP, is classical signaling that is activated by secretin in a number of systems such as the pancreas, brain, kidney as well as the biliary epithelium. For example, in bile ducts the activation of cAMP signaling by secretin induces phosphorylation of protein kinase A (PKA) that causes activation of cystic fibrosis transmembrane conductance regulator (CFTR), which in turn induces activation of the Cl^-/HCO_3^- anion exchanger 2 (AE2) (3,7,57,68). Also, impaired pancreatic ductal bicarbonate secretion has been observed in cystic fibrosis (6,69). The cAMP signaling system plays a key role in the modulation of large biliary secretion and proliferation since it is activated by secretin (stimulating bicarbonate secretion) (3,57,68) and also stimulates large cholangiocyte proliferation (17,56). Down- or up-regulation of cAMP signaling (for example by somatostatin, gastrin, endothelin-1, the α_2-adrenergic receptor agonist, UK14, 304, or the α1-adrenergic agonist, phenylephrine) (70-74) has also been associated with decreases/increases of secretin-stimulated ductal secretion. While some of the inhibitory effects on secretin-induced choleresis are mediated by direct downregulation of cAMP signaling, others depend on the activation of Ca^{2+}-dependent PKC isoforms that subsequently induce (by Ca^{2+}→cAMP cross-talk) changes in cAMP levels and secretin-stimulated ductal secretion (70-74). The cAMP second messenger system (that is not constitutively active in small cholangiocytes) (63,64) is *de novo* activated in these cells during the damage of large, cAMP-responsive bile ducts.

In the pancreas, secretin receptors are key for the maintenance of healthy ductal epithelial cells, but they are functionally altered in ductal pancreatic adenocarcinomas.

Recently, silencing of secretin receptor function by dimerization with a misspliced variant secretin receptor has been shown in ductal pancreatic adenocarcinoma (75). Although wild-type secretin receptor mRNAs were detected in the primary tumors in these studies, the lack of biological response to secretin is likely due to the co-expression of a second and predominant transcript in these tumor lines (75). This represented a variant of the secretin receptor in which the third exon is spliced out to eliminate residues 44-79 from the NH[2]-terminal tail (75). The study suggested that suppression of SR activity in pancreatic carcinoma might facilitate tumor growth and progression of this neoplasm. Wild-type and splice-variant secretin receptors have been shown in tumor and non-tumor lung pathology as well (76). Dominant negative action of an abnormal SR arising from mRNA missplicing has been detected in gastrinoma (77). Reduced secretin binding has also been shown in pancreatic ductal tumors and likely relate to (alternatively spliced) secretin receptor isoforms (78). Targeting secretin receptors may be important in the management of pancreatic tumors.

Regulation of gastric acid secretion by secretin

A number of studies and review articles exist regarding the role of secretin in the regulation of acid secretion from oxyntic cells (12,79-82). For example, secretin inhibits gastric acid secretion and motility via a vagal afferent pathway in rats (79). These results indicate that inhibition of pentagastrin-stimulated acid secretion by secretin is mediated by a capsaicin-sensitive vagal afferent pathway (79). Other studies in rats have demonstrated that the inhibitory action of secretin on pentagastrin-stimulated gastric acid secretion is regulated by both somatostatin and prostaglandins (80,81). This topic is beyond the purpose of this review and we refer to other studies for further detial (12,79-82).

Regulation of pancreatic bicarbonate secretion

Secretin stimulates the secretion of a bicarbonate-rich pancreatic fluid (45). Secretin enters the blood stream or intestinal lumen and stimulates bicarbonate secretion (by interacting with pancreatic ductal cells), which neutralizes the pH of the gastric chyme upon entering the small intestine (83,84). cAMP signaling plays a key role for the secretion of bicarbonate ions from the pancreatic ducts. Secretin-induced bicarbonate secretion depends on the activation of the cAMP-dependent anion channel, CFTR, which is localized in the apical membrane of various epithelia including pancreas and bile ducts (6). In fact, pancreatic ducts from CFTR-null mice secrete water and bicarbonate at lower levels compared to wild-type animals (85).

Role of secretin in water homeostasis

Body water homeostasis is a critical phenomenon for the survival of cells since it maintains the balance between water intake and excretion in the body. Kidney are essential parts of the urinary system and serve homeostatic functions by regulating acid-base balance as well as blood-pressure via maintaining salt and water balance (86). Several hormones have direct influence on the regulation of renal handling of water and electrolytes by anti-diuretic or diuretic effects. As an anti-diuretic hormone, vasopressin regulates the osmolarity of extracellular fluids by modulating the amount of free water excreted by the kidney. Vasopressin has an effect on the collecting ducts, where it induces the insertion of aquaporin 2 (AQP2) water channels on the apical membranes of these cells (87,88). Regarding secretin, a study suggested that this gastrointestinal hormone has diuretic effects in a number of species including humans and dogs (89). Secretin has been shown to induce an increase in urinary volume and bicarbonate excretion in normal human subjects (89,90). A study by Waldum *et al*. has shown that secretin induced an increase in renal plasma flow that may be due to enhanced renal vasodilation or cardiac output, or a combination of both that impairs tubular sodium reabsorption (91). Another study has demonstrated the diuretic effect of secretin in dogs, which resulted in diuresis and significant increases in sodium and potassium output (92).

Role of secretin in the central nervous system

A number of studies suggest that secretin is expressed in the brain and regulates the function of the central nervous system (CNS) (24,35,36). For example, impaired hippocampal synaptic function has been demonstrated in secretin-deficient mice (16). Impaired synaptic plasticity and social behavior has been shown in secretin receptor-deficient mice (14). The studies demonstrate that the secretin/secretin receptor axis may be important in the regulation of the function of the CNS (14,16). Other studies have shown that the secretin gene is expressed in serotoninergic mesencephalic neurons during development (93). It was shown that secretin has trophic effects on these neurons, effects that are lost in neurodegenerative disorders (93). Additional evidence

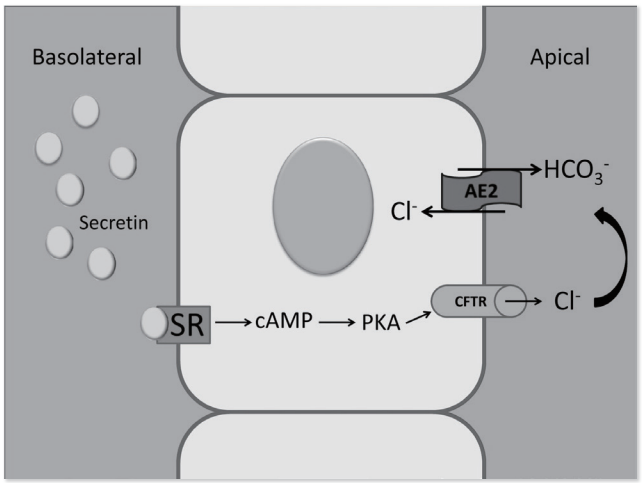

Figure 2 The diagram illustrates that secretin stimulates the secretion of bicarbonate ions by cholangiocytes into the duct lumen by activating cAMP synthesis that induces phosphorylation of PKA, opening of CFTR and activation of the apically located Cl^-/HCO_3^- exchanger AE2.

suggests that secretin can act as a neuropeptide within the CNS (94).

Role of secretin in the heart and cardiovascular system

Sympathetic and parasympathetic nerve fibers have been shown to regulate cardiovascular function through an autonomic system (95). Indeed, several neuropeptides are secreted in the heart (95-97) and may play an important role in the autonomic regulation of cardiac function as neurotransmitters or neuromodulators (95). In this review, we discuss the role of secretin in the regulation of heart function, which acts not only a hormone, but also as a neurotransmitter or neuromodulators (98). Generally speaking, secretin effects are mediated by activation of cAMP synthesis that is decreased during cardiac pathologies. For example, reduced responsiveness of cardiac secretin-stimulated adenylate cyclase was observed in the spontaneous hypertensive rat heart model (99,100). Similarly, in the hypertrophic rat heart model there was reduced secretin stimulated adenylate cyclase that was likely due to a decrease in the number of secretin receptors in cardiac myocytes (101). In cats and dogs, secretin has been shown to increase cardiac output and heart rate, whereas it decreases systemic arteriolar resistance and left ventricular end-diastolic pressure, with no significant change in stroke volume (102,103).

Role of secretin in cholangiocytes

Secretin-induced choleresis

A number of studies have shown that secretin stimulates the secretion of water and electrolytes in cholangiocytes by activating cAMP synthesis that induces phosphorylation of PKA, opening of CFTR and activation of the apically located Cl^-/HCO_3^- exchanger AE2 (3,7,56,57,61,68,70,72,104) (*Figure 2*). Consistent with these data regarding the role of cAMP in the modulation of secretin-induced choleresis, a study has shown that chronic administration of cAMP agonists (i.e., forskolin) enhances secretin-stimulated bile and bile secretion (105). Other studies have shown that maintenance of the bile acid pool is important for bile secretion, an effect that is mediated by the function of the chloride-bicarbonate exchange AE2 (106). Further mechanistic studies have also shown that secretin-stimulated bile secretion is mediated by the microtubule-dependent insertion of aquaporin-1 water channels (AQP1) into the apical membrane of rodent cholangiocytes.

Recent studies have demonstrated that large but not small cholangiocytes (lining small and large bile ducts, respectively) (3,57,107) are the anatomical sites of secretin-stimulated water and bicarbonate secretion (3,56,57) (*Figure 3*). In fact, these cells are the only epithelia in the liver to express SR, CFTR and Cl^-/HCO_3^- exchanger AE2 and to respond to secretin with enhanced cAMP levels, Cl^- efflux and chloride bicarbonate exchanger (3,56,57). Large (but not small) bile ducts have also been shown to express SSTR2 receptors and to respond to somatostatin with inhibition of cAMP levels, exocytosis and ductal bile secretion (56,70).

Small cholangiocytes (which do not express CFTR) (3,58) secrete water and electrolytes by activation of Ca^{2+}-dependent pathways (*Figure 3*). For example, adenosine triphosphate release and purinergic (P2) receptor-mediated secretion has been demonstrated in small mouse cholangiocytes (108). The identification of TMEM16A channels and Ca^{2+}-activated Cl^- efflux in small cholangiocytes in response to extracellular nucleotides supports the concept of an alternate, non-cystic fibrosis transmembrane conductance regulator, Cl^- channel in cholangiocytes that may be an important compensatory

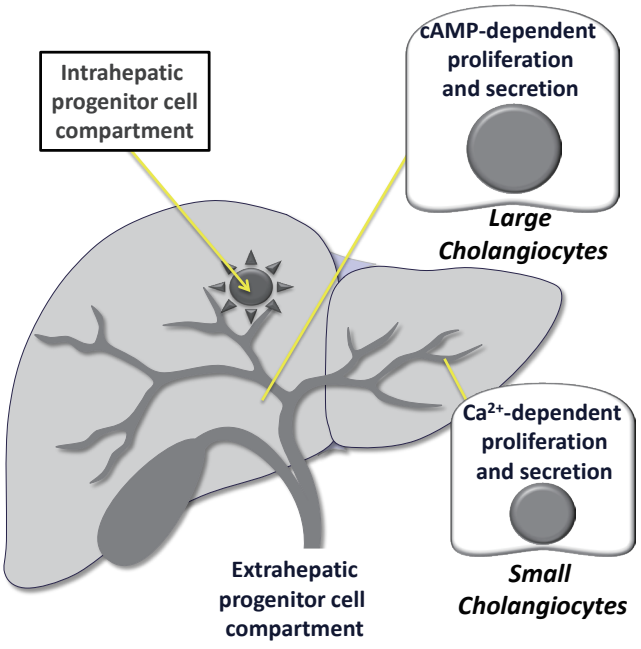

Figure 3 Diagram depicting the functional heterogeneity of small and large cholangiocytes, lining small and large bile ducts, respectively. Large but not small cholangiocytes are the anatomical sites of secretin-stimulated, cAMP-dependent bicarbonate secretion. Small cholangiocytes secrete water and electrolytes by activation of Ca^{2+}-dependent pathways. The cartoon indicates also the possible presence of intra- and extra-hepatic cell compartments in the biliary epithelium.

secretory mechanism during damage of larger, cAMP-responsive bile ducts (109). Also, small, mitotically dormant cholangiocytes *de novo* proliferate and secrete (by amplification of Ca^{2+}-dependent signaling) and acquire markers of large cholangiocytes following damage of these cells for example after treatment with CCl_4 or GABA (63-65).

Factors that modulate secretin-stimulated ductal bile secretion

Several studies have shown that secretin-stimulated choleresis is modulated by a number of factors including gastrointestinal hormones, peptides and nerve agonists (104). For example, somatostatin has been shown to inhibit secretin-stimulated ductal bile secretion both *in vivo* and *in vitro* by selectively interacting with SSTR2 receptors by downregulation of cAMP-dependent exocytosis (70). While a study has shown that bombesin enhances bile flow, stimulated by infusion of acid into the duodenum by increasing secretin secretion, somatostatin inhibits bile flow produced likely by decreasing the release of secretin from the duodenal mucosa (110). We have shown that gastrin inhibits secretin-induced ductal secretion by interaction with specific receptors (CCK-B) on rat cholangiocytes by down-regulation of SR expression and secretin-stimulated cAMP levels (72,111); gastrin effects were mediated by translocation of Ca^{2+}-dependent PKC isoforms (72,111). Similarly, another study has demonstrated that gamma-interferon decreases collagen content and intrahepatic ductal mass in cirrhotic mice, which was associated with inhibition of secretin-induced choleresis (112). An inhibitory effect on secretin-stimulated choleresis has been demonstrated for the vasoactive peptide, endothelin-1 (ET-1), by interaction with ET_A receptors by downregulation of cAMP levels (71). We have demonstrated that insulin receptors are expressed by cholangiocytes, and that insulin inhibits secretin-induced ductal secretion in BDL rats by activation of PKCα and inhibition of secretin-stimulated cAMP levels and PKA activity (113).

With regard to the role of the nervous system in the modulation of biliary secretion, we have shown that: (I) D2 (but not D1 and D3) dopaminergic receptors are expressed by cholangiocytes; and (II) the D2 dopaminergic agonist, quinelorane, decreases the choleretic effect of secretin on bile and bicarbonate secretion, inhibition that was mediated by increased expression of the Ca^{2+}-dependent, PKC gamma, and decreased PKA activity (114). The role of nerve fibers in the modulation of biliary secretion has been supported by additional studies as follows. For example, a recent study has shown that M3 ACh receptors are present in rat cholangiocytes and that acetylcholine potentiated secretin-stimulated ductal secretion by activation of the Cl^-/HCO_3^- exchanger AE2 by a Ca^{2+}-dependent, protein kinase C-insensitive pathway that potentiates the secretin stimulation of adenylyl cyclase (115). Interruption of the parasympathetic system (by total vagotomy in BDL rats) induces biliary apoptosis and functional damage of cholangiocytes with loss of cAMP signaling and secretin-stimulated choleresis (116), that was prevented by the administration of forskolin or feeding bile acids such as taurocholic acid (117) and both ursodeoxycholic and tauroursodeoxycholic acids (118). Also, adrenergic denervation (by the intraportal administration of 6-hydroxydopamine) induces the functional damage of bile ducts with loss of secretin-stimulated choleresis (119), effects that were prevented by the administration of forskolin (an adenylyl cyclase activator), β1- and β2-adrenergic receptor

agonists (clenbuterol or dobutamine, respectively) (119) or feeding the bile acid, taurocholic acid (120). A recent study by Francis *et al*. has shown that cholangiocytes express α_{2A}-, α_{2B}-, and α_{2C}-adrenergic receptors and that the α_2-adrenergic receptor agonist, UK14, 304, inhibits secretin-stimulated ductal secretion by downregulation of cAMP signaling in cholestatic rats (73). The α-1 adrenergic receptor agonist, phenylephrine, increases secretin-stimulated cAMP levels and ductal secretion of cholestatic rats by Ca^{2+}-dependent activation of PKCα and βII (74). Thus, coordinated regulation (by stimulatory and inhibitory factors) of secretin-stimulated choleresis may be key in maintaining the functional homeostasis/integrity of the biliary epithelium in pathological conditions associated excessive growth or biliary loss.

Bile acids have also been shown to prevent biliary damage (e.g., by caffeic acid and CCl_4) and loss of secretin-stimulated ductal secretion (121). For example, feeding the bile acid, taurocholic acid, to cholestatic rats prevents caffeic acid-induced biliary damage by enhanced cholangiocyte vascular endothelial growth factor (VEGF) expression (121). Also, taurocholic acid feeding prevents tumor necrosis factor-α-induced biliary damage and loss of secretin-induced bicarbonate-rich choleresis by a PI3K-mediated pathway (122).

Regarding the mechanisms of secretin-stimulated ductal secretion, a study has shown that the adenylyl cyclase isoform, AC8, is mostly expressed by large cholangiocytes (123) that are the only cell types expressing the secretin receptors and the target of secretin choleresis (57,124). Thus, this study suggests that AC8 may be a key player in the regulation secretin-induced choleresis in large bile ducts (123). In addition, inhibition of the biliary expression of arylalkylamine N-acetyltransferase (the enzyme key in melatonin synthesis) by administration of AANAT Vivo-Morpholinos increase the autocrine proliferative responses of cholangiocytes and the expression of cAMP/CFTR/Cl^-/HCO_3^- AE2 signaling and ductal secretion (125).

A number of sex hormones have been shown to modulate biliary functions. Following castration in cholestatic rats, testosterone serum levels decreased (prevented by the administration of testosterone), and were associated with reduced biliary proliferation and secretin-stimulated cAMP levels and bile and bicarbonate secretion (126). Also, follicle-stimulating hormone increases biliary proliferation and secretin-stimulated cAMP-dependent bile secretion (127). Some of the factors regulating secretin-stimulated choleresis are also summarized in *Table 1*.

Effect of secretin on biliary hyperplasia

A number of studies have suggested that the functional expression of SR may be an index of biliary growth since in models with enhanced biliary hyperplasia there is increased expression of SR and augmented response to secretin (7,8,17,56,62-65,105,127). Conversely, in models of biliary damage/apoptosis (e.g., after CCl_4 or GABA treatment) we have observed a reduction of SR expression and choleretic response to secretin (7,8,17,56,62-65,105,127). Recent findings have shown that secretin is a trophic factor for mouse cholangiocytes and that *in vivo* and *in vitro* ablation of SR reduces biliary hyperplasia in BDL mice (*Figure 4*) and in cholangiocyte lines (17). The study suggests the potential use of secretin as a therapy for ductopenic liver diseases (17). Further studies are needed to determine if secretin is an autocrine hormone secreted by cholangiocytes.

Role of secretin in human biliary diseases

There is growing information regarding the role of secretin and its receptor in the diagnosis and management of biliary disorders. For example, Prieto *et al*. have used positron emission tomography in humans for evaluating basal and secretin-stimulated biliary bicarbonate secretion as index of functionality of the biliary epithelium in normal and cholestatic (e.g., PBC) conditions (128). Consistent with the importance of secretin in biliary diseases, absence of choleretic response to secretin was observed in cholestatic and untreated PBC patients (128). Recently, secretin-mediated gene delivery has been developed to specifically target the intracellular pathways potentially important for the treatment of biliary and pancreatic disease in cystic fibrosis (9). Secretin stimulated magnetic resonance cholangiopancreatography has been used as diagnostic tool in diseases of the biliary and pancreatic ducts (129). The diagnostic role of secretin-enhanced cholangiopancreatography (MRCP) has been suggested in patients with unsuccessful endoscopic retrograde cholangiopancreatography (ERCP) (130).

Recent studies support the concept that biliary bicarbonate may be an important protective mechanism in cholangiopathies since a defective HCO_3^- umbrella has been observed in biliary disorders such as in PBC, and primary sclerosing cholangitis (131-134). In support of these findings, a recent study has shown that miR-506

Table 1 Eulators of secretin-stimulated ductal bile secretion

Regulators	Effect on secretin-stimulated bile secretion	Signaling pathway	References
Somatostatin	↓	Inhibition of cAMP levels and exocytosis by interaction with SSTR2	(56,70)
Gastrin	↓	Inhibition of SR expression and cAMP levels by interaction with CCK-B receptors by activation of PKCα	(72,111)
Endothelin-1	↓	Inhibition of cAMP levels by interaction with ET_A receptors	(71)
Insulin	↓	Inhibition of cAMP levels by activation of PKCα and inhibition of PKA	(113)
D2 dopamine agonists	↓	Inhibition of cAMP levels by interaction with D2 receptors by activation of PKCγ and inhibition of PKA	(114)
Acetylcholine	↑	Activation of the Cl^-/HCO_3^- exchanger AE2	(115)
Interruption of the parasympathetic system by vagotomy	↓	Downregulation of cAMP signaling that was prevented by taurocholic acid, ursodeoxycholic and tauroursodeoxycholic acids	(116-118)
Interruption of the sympathetic system by the intraportal administration of 6-hydroxydopamine	↓	Downregulation of cAMP signaling that was prevented by β1- and β2-adrenergic receptor agonists and taurocholic acid	(119,120)
α_2-adrenergic receptor agonist, UK14, 304	↓	Downregulation of cAMP signaling by interaction with α_{2A}-, α_{2B}-, and α_{2C}-adrenergic receptors	(73)
α-1 adrenergic receptor agonists	↑	Stimulation of cAMP levels by activation of PKCα and βII	(74)

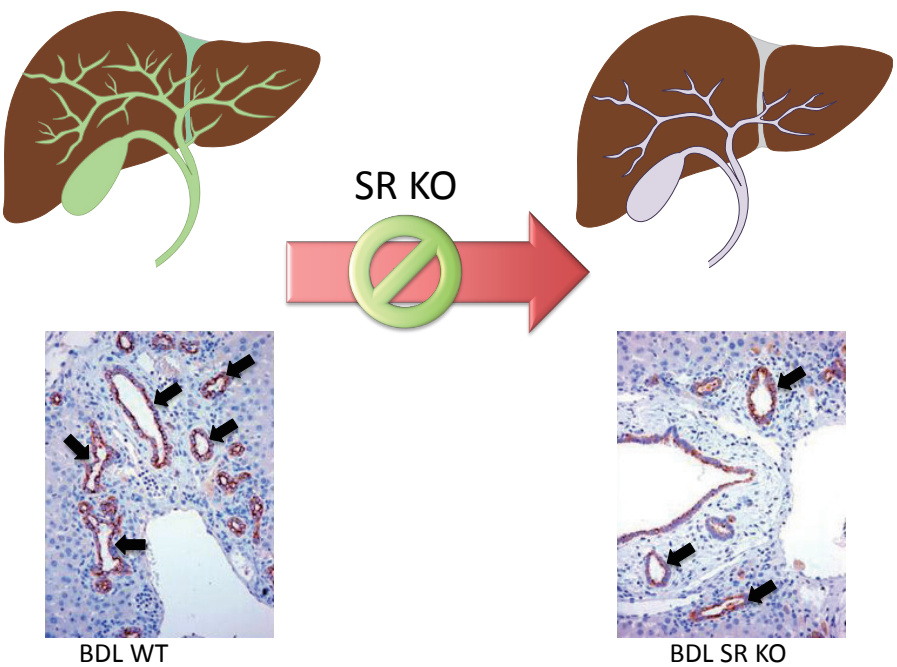

Figure 4 Ablation of the SR gene (expressed only in cholangiocytes) in 2-wk BDL mice reduces large biliary hyperplasia typical of cholestatic animals. Orig. magn., ×40.

is up-regulated in cholangiocytes from PBC, binds the 3'UTR region of AE2 mRNA, prevents protein translation thus causing diminished AE2 activity and impaired ductal secretion (135). The study suggests that miR-506 may constitute a potential therapeutic target for the management of PBC (135).

Conclusions/future perspectives

We have discussed that secretin and its receptors regulate the secretory activity of a number of organ tissues including the stomach, intestine, pancreas, heart and the biliary epithelium in the liver. Regarding the biliary epithelium, we have shown that secretin and its receptor (only expressed by cholangiocytes in the liver) play key role in the secretory and proliferative activity of large cholangiocytes, the only cell types that express SR and respond to secretin. Small cholangiocytes (which constitutively do not express SR) acquire large cholangiocyte phenotypes in pathological conditions associated with damage of large cholangiocytes and amplify their Ca^{2+}-dependent signaling to compensate for loss of large biliary functions and to maintain the homeostasis of the liver. We have also shown that secretin may be an important trophic autocrine factor that may sustain biliary proliferation during ductopenic states. It has also suggested the diagnostic role of secretin in biliary diseases such as PBC and biliary atresia. Further studies are necessary to determine the prognostic role of secretin in the diagnosis of ductopenic biliary diseases.

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