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Review

Secretin, 100 years later

William Y. Chey and Ta-Min Chang

Rochester Institute for Digestive Diseases and Sciences, 222 Alexander Street, Suite 3100, Rochester, NY 14607, USA

One hundred years have elapsed since the discovery of secretin by Bayliss and Starling in 1902. In the past century, the research of secretin has gone by many milestones including isolation, purification and structural determination, chemical synthesis, establishment of its hormonal status by radioimmunoassay and immunoneutralization, identification of the specific receptor, cloning of secretin and its receptor, and identification of a secretin-releasing peptide. It has become clear that secretin is a hormone-regulating pancreatic exocrine secretion of fluid and bicarbonate, gastric acid secretion, and gastric motility. The release and actions of secretin is regulated by hormone–hormonal and neurohormonal interactions. The vagus nerve, particularly its afferent pathway, plays an essential role in the physiological actions of secretin. Substantial information about the property of the secretin receptor has been accumulated, but a potent secretin receptor-specific antagonist remains to be formulated. The neural regulatory mechanisms of the release and action of secretin await further elucidation. The physiological role of secretin in intestinal secretions and motility and extragastrointestinal organs remains to be defined. The presence of secretin and its receptor in the central nervous system is well documented, but its function as a neuropeptide has been recognized gradually and requires extensive study in the future.

Key words: secretin, discovery, first gut hormone, secretin-releasing peptides

At the end of the nineteenth century, Pavlov observed in the dog that pancreatic exocrine secretion is controlled by a dual mechanism, one part by the vagus nerve and the other by a stimulus originating from the contact of the duodenal mucosa with the acidic material emptied from the stomach.[1] However, Pavlov's school strongly believed that the stimulus elicited by acid in the duodenum involved a peripheral nervous reflex mechanism between the duodenal mucosa and the pancreas. In January 1902, Bayliss and Starling[2] reported the historical observation that infusion of 0.4% HCl into a denervated jejunal loop, but not intravenous infusion of the acid, resulted in continuous secretion from the pancreas for some minutes. They believed that the active agent must be originated from the intestinal mucosa and proceeded to demonstrate that intravenous injection of an acid extract from the mucosa of the denervated jejunal loop stimulated pancreatic secretion. They named the active agent from the intestinal mucosa "secretin" and subsequently coined the term "hormone" to describe an active chemical messenger-like secretin that is produced in one organ and carried through the circulation to another organ to exert its effect. Their observation thus had introduced a new epoch of an exciting "Hormone Concept" on the regulatory mechanism of digestive system and modern physiology. More than 100 years have elapsed since the discovery of secretin. In this article, we review some of the major events and important findings in secretin research, particularly those accomplished in our laboratory in the past.

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Reprint requests to: W.Y. Chey

Milestones of secretin research

The research on secretin has gone through many major events of isolation, purification, structural determination and verification, establishment of its hormonal status, molecular cloning of secretin and its receptor, and mechanism of its release and action that can be considered as milestones for secretin research (Fig. 1).

It took more than 60 years after its discovery before porcine secretin was purified by Jorpes and Mutt[3] and its amino acid sequence was determined.[4] Soon after the

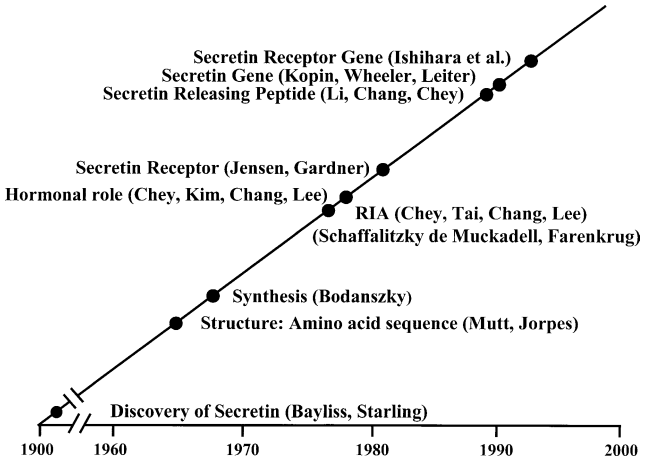

Fig. 1. Milestones of secretin research

sequence of porcine secretin was determined, it was chemically synthesized and its bioactivity confirmed by Bodanszky and coworkers.[5,6] The next major obstacle for secretin research was to establish its hormonal status in late 1970s. Using Bodanszky's synthetic secretin, we had successfully raised a high-titer and specific rabbit antisecretin serum to develop a specific high sensitivity radioimmunoassay method for secretin, and we used it to demonstrate that plasma secretin level is elevated in the dog and human upon duodenal administration of diluted acid and, more importantly, after ingestion of a meal.[7,8] Schaffalitzky de Muckadell and Fahrenkrug[9] reported similar results at the same time.[9] Subsequently, immunoneutralization studies in dogs[10] decisively proved that secretin is a hormone that drives pancreatic secretion of fluid and bicarbonate. In that study, we showed that antisecretin serum nearly abolished the postprandial pancreatic secretion (Fig. 2). The next major event was the demonstration of secretin receptor in the pancreas by Gardner and Jensen[11] that appeared to a prerequisite for its action in the pancreas. In the early 1990s, three major accomplishments were made, namely, the discovery of secretin-releasing peptide,[12] cloning of the secretin gene,[13] and cloning of the secretin receptor.[14] Today, the research in secretin has become ever more diversified, particularly with questions regarding its physiological roles in other organs, neurohormonal regulation of its release and action, and its function as a neuropeptide, which remain to be elucidated.

Structure of secretin

Secretin has been isolated in several animal species including humans, pigs, dogs, rats, mouse, goats, rabbits, guinea pigs, and chickens. Aside from avian secretin,

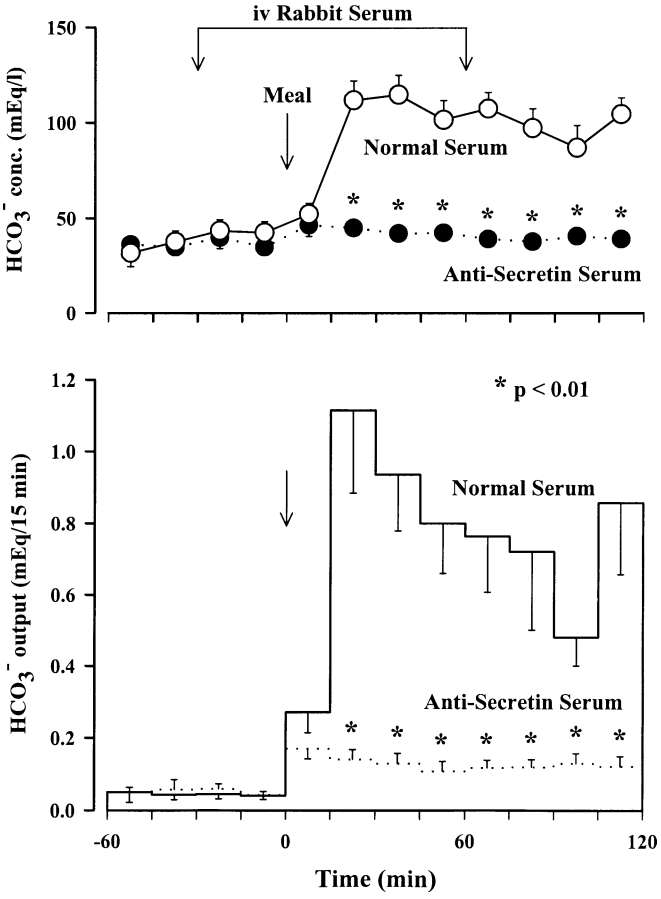

Fig. 2. Effect of a rabbit antisecretin serum on postprandial pancreatic bicarbonate secretion in dogs. (From Chey et al.,[10] with permission)

	1				5				10				15				20				25			
Pig, Cow, sheep	H	S	D	G	T	F	T	S	E	L	S	R	L	R	D	S	A	R	L	Q	R	L	L	Q	G	L	V*
Dog	H	S	D	G	T	F	T	S	E	L	S	R	L	R	**E**	S	A	R	L	Q	R	L	L	Q	G	L	V*
Rat	H	S	D	G	T	F	T	S	E	L	S	R	L	**Q**	D	S	A	R	L	Q	R	L	L	Q	G	L	V*
Human	H	S	D	G	T	F	T	S	E	L	S	R	L	R	**E**	**G**	A	R	L	Q	R	L	L	Q	G	L	V*
Mouse	H	S	D	G	**M**	F	T	S	E	L	S	R	L	R	D	S	A	R	L	Q	R	L	L	Q	G	L	V*
Rabbit	H	S	D	G	T	**L**	T	S	E	L	S	R	L	R	D	**R**	A	R	L	Q	R	L	L	Q	G	L	**L***
Guinea pig	H	S	D	G	T	F	T	S	E	**K**	S	R	L	R	D	S	A	R	L	Q	R	L	L	Q	G	L	V*
Chicken	H	S	D	G	**L**	F	T	S	E	**Y**	S	**K**	**M**	R	**G**	N	A	**Q**	V	Q	**K**	**F**	***I***	Q	N	L	**M***

Fig. 3. Structure of secretins from various animal species. The *boldface characters* denote amino acid residues different from those of porcine, bovine, and ovine secretins, which are identical. *, $-CONH_2$

mammalian secretins (Fig. 3) are highly homologous, with 1–3 amino acid residues differing from the sequence of porcine/ovine/bovine secretin (which are identical). The structure of secretin also has sequence homology with other subsequently isolated regulatory peptides forming a secretin/glucagons/vasoactive intes-

tinal polypeptide (VIP) superfamily of more than 10 peptides (Table 1). In addition, Mutt and coworkers have isolated several forms of prosecretins with either C- or N-terminal extensions that exhibited various extents of bioactivity. The structures of porcine prosecretins agree well with those deduced from the nucleotide sequence of secretin cDNA cloned by Kopin et al.[13] To date, secretin cDNAs have been cloned from the rat, mouse, pig, and human.[14]

Distribution of secretin

Secretin-containing cells are distributed mainly in the upper small intestine (duodenum and jejunum).[15] However, secretin has also been shown, either through immunochemical or molecular biological methods, to exist in other organs including heart, lung, kidney, ileum, colon, stomach, and brain of various species. For example, secretin cells that are found in the antral and oxyntic mucosae of rat stomach are distinguished from gastrin and somatostatin cells, respectively.[16] Moreover, secretin mRNA in the same molecular size as that found in the duodenum is found in both gastric mucosae either by reverse transcriptase-polymerase chain reaction (RT-PCR) or Southern blot after RT-PCR.

Table 1. Peptides of secretin/glucagons/vasoactive intestinal polypeptide superfamily

Peptide	Discovered or isolated by
Secretin	Bayliss and Starling 1902
Glucagon	Kimball and Murlin 1923
GIP	Brown et al. 1970
VIP	Said and Mutt 1974
Glycentin (proglucagon)	Moody et al. 1976
Oxytomodulin (glucagons-37)	Bataille et al. 1981
PHI (PHM)	Tatemoto and Mutt 1981 (Itoh et al. 1983)
GLP-1, GLP-2	Lund et al. 1982
GRF	Guillemin et al. 1982
PACAP	Miyata et al. 1989
Hypocretins (orexins)	De Lecea et al. 1998 (Sakurai et al. 1998)
Helodermin	Hoshino et al. 1984
Helospetins	Parker et al. 1984
Exendin-3, -4	Eng et al. 1990, 1992

VIP, vasoactive intestinal polypeptide; PACAP, pituitary adenylate cyclase-activating polypeptide; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; GIP, gastric inhibitory peptide or glucose-dependent insulinotropic peptide; GRF, growth hormone-releasing factor; PHI, peptide histidine isoleucinamide; PHM, peptide histidine methioninamide (human analogue of PHI)
Helodermin, helospectins, and exendins were isolated from the Gila monster (*Heloderma suspectum*); PHI (PHM) and GLPs are VIP and glucagon gene-associated peptides, respectively

The mechanism of secretin release

Secretin is released mainly by gastric acid delivered into the duodenal lumen. In addition, secretin is also released by digested products of fat and protein, bile acid, and herbal extracts.[17] The stimulants of secretin release are listed in Table 2. The importance of gastric acid for postprandial release of secretin is demonstrated by the observation that suppression of gastric acid secretion with a histamine H_2 blocker, cimetidine, resulted in a complete suppression of secretin release after ingestion of a meal in dogs (Fig. 4).[8] Like cholecystokinin, the release of secretin along with pancreatic exocrine secretion is controlled through a feedback regulatory mechanism, as first proposed by Green and Lyman,[18] that is mediated by pancreatic proteases. Thus, diversion of pancreatic juice from the duodenum in dogs augmented postprandial pancreatic secretion and the release of secretin that was suppressed by duodenal infusion of pancreatic juice or trypsin but not by infusion of bicarbonate.[19] This feedback effect was shown to involve suppression of secretin release in both fasting and postprandial states in both humans and rats.[20] In anesthetized rats, diversion of pancreatic juice from the duodenum results in a time-dependent increase in secretin release and pancreatic secretion. The increased secretin release and pancreatic exocrine secretion was suppressed by duodenal infusion of either freshly collected or precollected pancreatic juice.[21] At present, the effect of proteases or pancreatic juice is believed to result from degradation of a luminal secretin-releasing peptide (SRP).

Table 2. Stimulants of secretin release

Exocrine secretions	Digested food	Herbal extracts	Chemicals
Gastric acid	Long-chain fatty acids	Licorice extract	Camostat
Bile salts	Sodium oleate	1-Phenylpentanol	Terprenone[a]
Pancreatic juice (SRP)[b]	Peptone		Plaunotol[a]
Intestinal secretion (SRP)[b]	Oligopeptides		MCI-727[a]

[a] Terprenone (geranyl geranyl acetone), plaunotol, and MCI-727 are antiulcer agents used in Japan
[b] Both pancreatic juice and intestinal secretion contain a secretin-releasing peptide (SRP) to stimulate secretin release

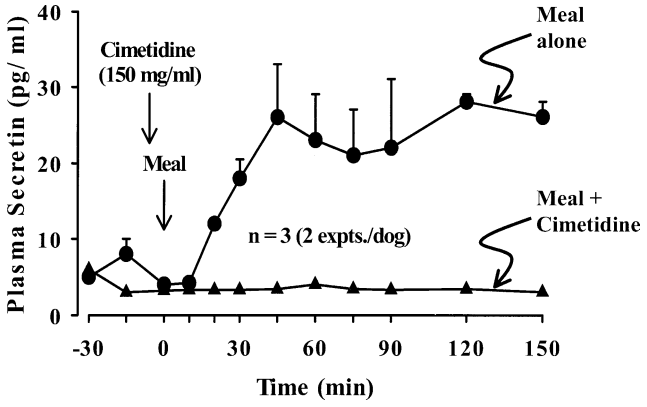

Fig. 4. Effect of cimetidine on postprandial plasma secretin concentration in dogs. Suppression of gastric acid secretion with a histamine H_2 blocker, cimetidine, abolished meal-stimulated secretin release. (From Kim et al.,[8] with permission)

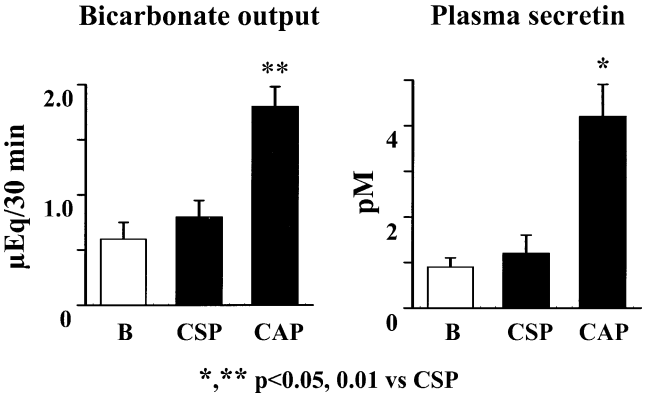

Fig. 5. Stimulation of pancreatic bicarbonate secretion (*left panel*) and elevation of plasma secretin concentration (*right panel*) by a concentrate of acid perfusate (*CAP*) from upper small intestine in recipient rats. CAP stimulated pancreatic bicarbonate secretion and secretin release whereas a concentrate of saline perfusate (*CSP*) did not. (From Li et al.,[22] with permission.) *, **$P < 0.05$, 0.01 vs CSP

Discovery of secretin-releasing peptide

Li et al.[12] reported that the acid-stimulated release of secretin is mediated by an SRP. SRP was discovered in the intestinal acid perfusate collected from donor rats. The rat was anesthetized, a duodenal cannula was inserted through the stomach, and the pylorus was ligated. Diluted HCl or saline was then infused and the intestinal perfusate was collected from a distal cannula placed in the jejunum. After neutralization, the concentrated acid perfusate (CAP) and saline perusate (CSP) were prepared and administered intraduodenally to recipient rats and their effect on pancreatic secretion and secretin release were compared. As shown in Fig. 5,[22] CAP caused an increase in pancreatic bicarbonate output whereas CSP did not. Plasma secretin level increased to 6.5 pM after infusion of CAP, whereas no increase was found with CSP, indicating the presence of an SRP in CAP. The bioactivity in CAP was inactivated by trypsin but withstood boiling, indicating that it is a heat-stable peptide. The result of an ultrafiltration study indicated that SRP in CAP had an apparent MW less than 10000. It was therefore concluded that an SRP mediates the release of secretin and that the activity of SRP was subject to feedback regulation by pancreatic proteases.[12]

Canine pancreatic juice also contains a secretin-releasing factor because the concentrate of pancreatic juice stimulated secretin release and pancreatic bicarbonate secretion when it was infused into the duodenum of both dogs and rats.[23,24] An active fraction of canine pancreatic juice with an apparent MW < 4000 (Fr. 3) was found to stimulate pancreatic juice volume and bicarbonate outputs as well as elevation of plasma secretin concentration in recipient rats. These effects of the fraction were abolished by i.v. infusion of a specific antisecretin serum.[24] Thus, a factor in pancreatic juice that mediates a positive feedback regulation for secretin release and pancreatic secretion was found. Subsequently, two SRPs of 14 kDa, SRF-1 and SRF-2, were purified from canine pancreatic juice.[25] The N-terminal sequence (31 residues) of SRF-1 was identical to canine pancreatic phospholipase A (PLA_2), whereas SRF-2 had 71% homology with the enzyme. Both canine SRFs[25] and procine pancreatic PLA_2 stimulated secretin release from secretin-producing cells in vitro through activation of calcium influx and protein kinase C.[26] In addition, acid in the duodenum released pancreatic PLA_2-like immunoreactivity. Moreover, pretreatment of CAP with a specific anti-PLA_2 serum abolished its stimulatory effects on secretin release and pancreatic exocrine secretion (the SRP activity) in recipient rats (Fig. 6).[27] These observations suggested that PLA_2 acts as an SRP. It should be noted, however, that intraduodenal infusion of purified porcine pancreatic PLA_2 is unable to elicit secretin release in rats, suggesting that an additional factor is required for its action. The unidentified factor may either function as a costimulating factor for S-cells or provide transport of PLA_2 through the mucus layer.

Physiological actions of secretin

Physiologic actions of secretin include stimulation of pancreatic exocrine secretion of water and bicarbonate and inhibition of gastric acid secretion and emptying. As shown in Fig. 7, i.v. administration of an antisecretin serum augmented postprandial gastrin release and acid output in dogs,[28] suggesting that secretin is an entero-

gastrone that functions as a feedback inhibitor of gastrin release and gastric acid secretion. Also in dogs, gastric acid secretion in response to a liquid amino acid (AA) meal was inhibited dose-dependently by secretin in physiological doses, whereas i.v. antisecretin serum augmented AA meal-stimulated acid output, thereby confirming the physiological role of secretin to inhibit gastric acid secretion.[29] Moreover, secretin also dose-dependently inhibited gastric emptying of the AA meal, whereas antisecretin serum accelerated gastric emptying, indicating that secretin is also a regulator of gastric motility.[29] The physiological roles of secretin in intestinal secretion and motility as well as in the functions of other organs remain to be elucidated.

The regulatory mechanism of release and actions of secretin

The physiological actions of secretin are subject to hormone–hormonal and neuro-hormonal interactions.

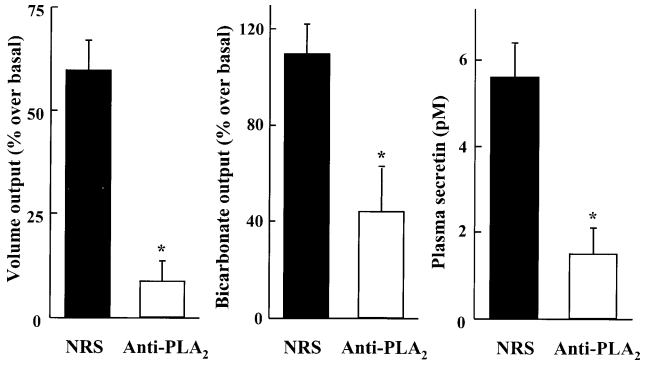

Fig. 6. Effect of pretreatment of CAP with an antiphospholipase A (*anti-PLA_2*) serum on CAP-stimulated pancreatic secretion and secretin release in recipient rats. Pretreatment of CAP with an anti-PLA_2 serum but not with a normal rabbit serum (*NRS*) resulted in substantial decrease in CAP-stimulated pancreatic secretion and secretin release, indicating that a PLA_2-like substance in CAP functions as an SRP. (From Li et al.,[27] with permission)

Pancreatic exocrine secretion after a meal is mainly stimulated by synergistic interaction between secretin and cholecystoking (CCK),[30,31] so that an adequate amount of pancreatic juice is produced for proper digestion. For example, pancreatic secretions of bicarbonate and protein in dogs stimulated by a combination of secretin and CCK-8 in physiological doses are abolished by the CCK anatagonist proglumide.[32] Secretin also potentiates with neurotensin to stimulated pancreatic enzyme secretion.[33] Another example of hormone–hormonal interaction is that insulin plays a permissive role on the action of secretin and CCK. When the circulating insulin was neutralized with a specific antiinsulin serum in rats, there was a profound inhibition of pancreatic secretion stimulated with secretin in combination with CCK (Fig. 8) or a meal.[34] In both isolated and perfused rat stomach[35] and the intact animals,[36] it has been clearly shown that inhibition of gastric acid secretion by secretin is mediated by somatostatin and prostaglandin.

Except in the rat, the action of secretin on exocrine pancreas in a physiological dose is highly sensitive to atropine, indicating an important mediation by cholinergic neurons. For example, pancreatic bicarbonate secretion in humans stimulated by secretin in graded doses (Fig. 9),[37] and its potentiation with CCK[38] was profoundly inhibited by administration of atropine.

The physiological action of secretin is highly dependent on the vagal afferent pathway. Thus, chemical ablation of vagal afferent fibers by perivagal application of capsaicin in rats resulted in a profound inhibition of the pancreatic secretion stimulated by a physiological, but not by a pharmacological, dose of secretin (Fig. 10).[22] The release and actions of SRP are also neurally mediated and depend on the vagal afferent pathway. Thus, CAP prepared from donor rats treated with tetrodotoxin, vagotomy, or perivagal capsaicin was unable to stimulate pancreatic exocrine secretion or release of secretin in recipient rats, indicating substantial reduction in SRP activity.[22] In addition, CAP prepared from untreated donor rats was also unable to stimulate secre-

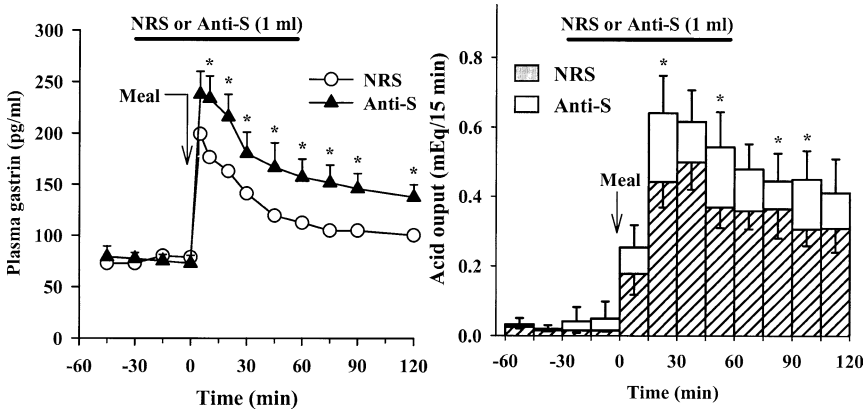

Fig. 7. Effect of an antisecretin serum on postprandial gastrin release (*left panel*) and gastric acid secretion (*right panel*) in dogs. (From Chey et al.,[28] with permission)

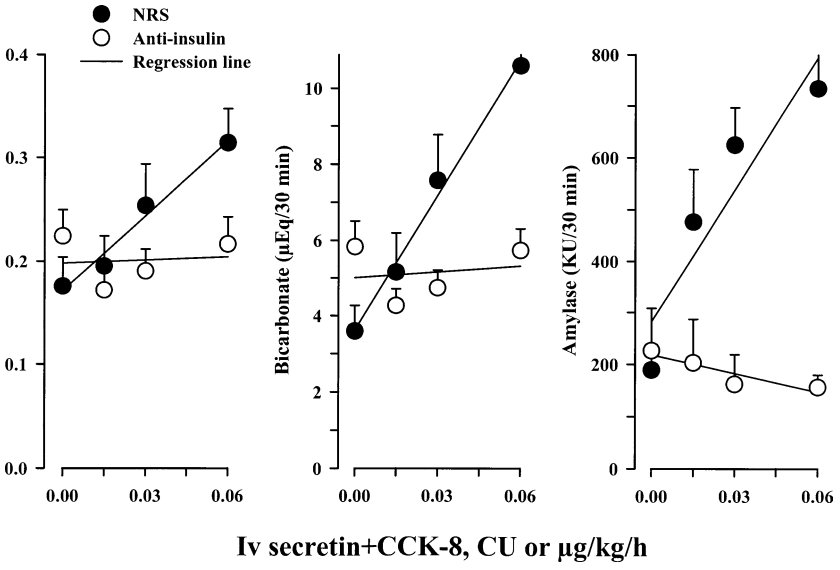

Fig. 8. Effect of an antiinsulin serum or normal rabbit serum (*NRS*) on pancreatic exocrine secretion stimulated by a combination of physiological doses of secretin and CCK-8 in rats. The antiinsulin serum abolished stimulation of pancreatic secretion by secretin and CCK-8. (From Lee et al.,[34] with permission)

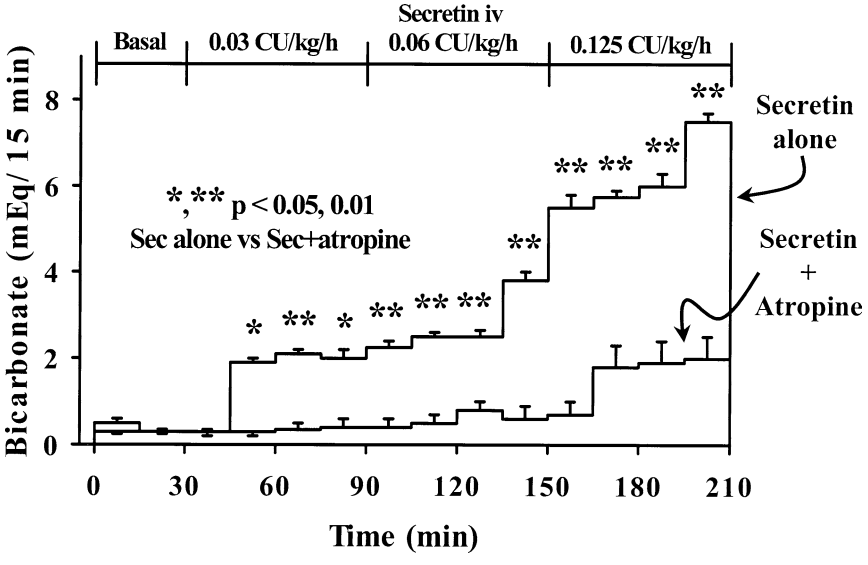

Fig. 9. Inhibition of secretin-stimulated pancreatic secretion by atropine in humans. Atropine profoundly inhibited pancreatic secretion stimulated by secretin at various doses. (From You et al.,[37] with permission.) *, **$P < 0.05, 0.01$: secretin alone vs secretin + atropine

tin release from the recipient rats pretreated with tetrodotoxin (TTX), vagotomy, or perivagal application of capsaicin (Fig. 11). Similarly, perivagal capsaicin treatment and vagotomy in conscious rats[39] blocked the inhibition of pentagastrin-stimulated gastric acid secretion by secretin. Lu and Owyang[40] also demonstrated that the vagal afferent pathway mediates inhibition of gastric motility by a physiological dose of secretin, confirming a previous observation made by Raybould and Holzer.[41] Electrical stimulation of medial amygdaloid in the rat augmented pancreatic bicarbonate and fluid secretion in response to duodenal acidification and a low dose of secretin.[42] This effect of medial amygdaloid stimulation was abolished by bilateral truncal vagotomy, suggesting that stimulation of medial amygdaloid elicited a stimulatory signal transmitted through the vagus nerve to potentiate the action of secretin. We have also observed in rats that vagotomy, vagal ligation, or perivagal colchicine, but not perivagal capsaicin treatment, decreased the number of high-affinity secretin-binding sites in rat forestomach and reduced secretin-elicited relaxation of rat forestomach muscle strips.[43] This observation suggested that the vagal efferent pathway also regulates secretin action through modulation of secretin receptor in the rat forestomach.

Some neuropeptides and neurotransmitters may modulate or mediate the release and action of secretin. Both Met-enkephalin (MEK) and somatostatin inhibit the release and action of secretin on the exocrine pancreas. Recently, we have observed that MEK also inhibited the release of SRP and its action on secretin release through the release of somatostatin.[44] Thus, as shown in

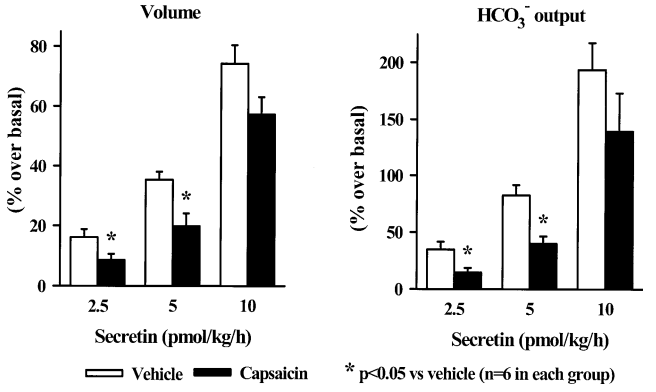

Fig. 10. Effect of perivagal treatment with capsaicin on secretin-stimulated pancreatic secretion in rats. Perivagal treatment with capsaicin significantly inhibited PES stimulated by secretin at physiological doses (2.5 and 5 pmol/kg/h) but not at a pharmacological dose (10 pmol/kg/h). (Li et al., unpublished results; confirming data shown in reference 22.) $*P < 0.05$ vs vehicle ($n = 6$ in each group)

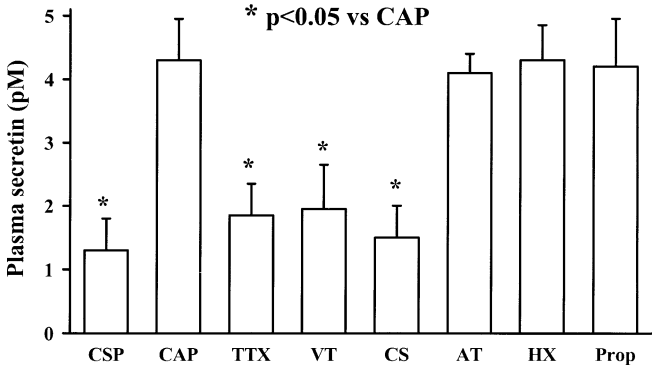

Fig. 11. Effect of various neural blockade, vagotomy, or perivagal capsaicin treatment in recipient rats on CAP-stimulated secretin release. *CSP*, concentrate of saline perfusate (from upper small intestine); *CAP*, concentrate of acid perfusate (from upper small intestine); *TTX*, tetrodotoxin; *VT*, bilateral vagotomy; *CS*; perivagal capsaicin; *AT*, atropine; *HX*, hexamethonium; *Prop*, propranolol. CAP-stimulated secretin-release was blocked by TTX, VT, and CP but not by AT, Hx, or Prop, suggesting that the action of SRP in CAP is mediated by a noncholinergic and nonadrenergic vagal afferent pathway. (From Li et al.,[22] with permission.) $*P < 0.05$ vs CAP

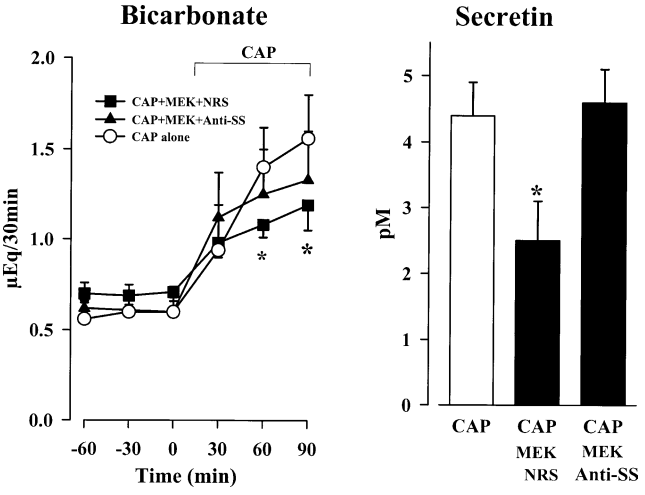

Fig. 12. Effect of Met-enkephalin (*MEK*) on CAP-stimulated pancreatic secretion and secretin release and its reversal by an antisomatostatin serum (*anti-SS*) in recipient rats. MEK significantly inhibited pancreatic eocrine secretion (PES) and secretin release elicited by CAP. The inhibition by MEK was reversed by cotreatment of the recipients with an anti-SS, indicating that the inhibition was mediated through the release of somatostatin. (From Li et al.,[44] with permission)

Fig. 12, CAP collected from donor rats pretreated with MEK had reduced SRP activity to stimulate pancreatic secretion and secretin release. The reduction in SRP activity was partially reversed by cotreatment of the donors with an antisomatostatin serum. Pituitary adenylate cyclase-activating polypeptide (PACAP) stimulated pancreatic exocrine secretion through the release of both secretin and CCK[45] in anesthetized rats, as demonstrated by the inhibition of PACAP-stimulated pancreatic exocrine secretion by i.v. infusion of an antisecretin serum and the CCK-A receptor antagonist, loxiglumide. PACAP also stimulated the release of secretin in vitro.[46] In conscious rats, secretin-stimulated pancreatic exocrine secretion was inhibited by a NO synthase inhibitor, *N*-nitro-L-arginine, and the inhibition was reversed by the substrate of the enzyme arginine, suggesting that NO mediates the action of secretin.[47] In anesthetized rats, both the serotonin (5-hydroxytryotamine, 5-HT_2) antagonist ketanserin and the 5-HT_3 antagonist ondansetron dose-dependently inhibited pancreatic volume and bicarbonate secretion and secretin release elicited by duodenal acidification.[48] Moreover, both 5-HT antagonists inhibited pancreatic secretion stimulated by physiological doses of secretin. These observations suggest that 5-HT mediates the release and action of secretin through the two 5-HT receptor subtypes. In isolated and perfused rat pancreas, electrical field stimulation enhanced stimulation of pancreatic secretion by secretin. The enhanced secretion was reduced by atropine[49] or a specific anti-GRP serum[50] and abolished by the combination of atropine and the antiserum,[50] suggesting that the enhancement of the effect of secretin was mediated by acetylcholine and GRP released from intrapancreatic neurons. The physiological stimulant of these intrapancreatic neurons is unknown at present. In isolated rat pancreatic ducts, secretin-stimulated fluid secretion was potentiated by acetylcholine,[51] an observation also suggesting a possible interaction between the two stimulants.

The secretin receptor

Biochemical studies on the secretin receptor were carried out in the 1980s by the laboratories of Gardner and Jensen,[11] Robberecht and Christophe,[52] and Rosselin.[53] These investigators found that secretin receptor is a glycoprotein receptor coupled to adenylate cyclase through an oligomeric G protein and is widely distributed in many organs. The rat secretin receptor was first cloned by Ishihara et al.[14] Subsequently, human[54–56] and rabbit[57] secretin receptors were also cloned. Human secretin receptor is a 7-transmembrane G protein-coupled receptor with a long N-terminal extracellular tail, three extracellular and three intracellular loops, and a short hydrophilic cytoplasmic C-terminal chain. The extensive studies carried out by L. Miller's and P. Robberecht's groups have indicated that the N-terminal extracellular tail of the receptor is involved in binding secretin. The putative N-glycosylation site at position 72N is also crucial for ligand binding,[58] whereas extracellular loops are also essential, probably for maintaining the active conformation of the receptor's extracellular binding domain. The cytoplasmic C-terminal tail is involved in desensitization of the receptor through phosphorylation[59] by G protein-coupled receptor kinase. Secretin receptor is expressed in the pancreas, stomach, liver, kidney, colon, heart, lung, ovary, and brain of various species. In the pancreas, secretin receptor is present in both the ductal and acinar cells.[60]

Secretin as a neuropeptide

Secretin and its mRNA are detected in the brain. Secretin receptor is also present in the brain as demonstrated by specific binding,[61] stimulation of cAMP production in brain slices,[62] and presence of the receptor transcript in the brain.[63] Recent studies have indicated that secretin indeed may function as a neuropeptide. For example, secretin specifically stimulated adenylate cyclase in hypothalamus and hippocampus.[62] ^{125}I-[Tyr^{10}]-Secretin was found to cross the blood–brain barrier and entered every brain region, with fastest uptake found in hypothalamus and hippocampus.[64] Intravenous infusion was found to stimulate activation of c-Fos expression in the central amygdala of rats.[65] In isolated rat superior cervical ganglia, secretin dose-dependently stimulated tyrosine hydroxylase activity, an effect potentiated by carbachol that was abolished by atropine but not by hexamethonium.[66] Moreover, secretin is known to inhibit the release of corticotropin (ACTH)[67] and stimulates the release of somatostatin from enriched rat enteric synaptosomes.[68] Intracerebroventricular injection of secretin stimulated pancreatic exocrine secretion in rats.[69] Secretin is also found in the brainstem, including a subpopulation of neurons in the primary sensory ganglia.[70] Secretin was reported to stimulate γ-aminobutyric acid (GABA) transmission from Purkinje cells in rat cerebellar slices.[63]

Clinical aspects of secretin

Diagnosis

Secretin has been widely used for pancreatic function test for diseases involving the pancreas, particularly chronic pancreatitis. In recent years, secretin has been used to collect pancreatic juice for analysis of molecular biological markers to diagnose pancreatic cancer. Secretin is also used to enhance noninvasive magnetic resonance cholangiopancreatography. A secretin provocation test[71] is useful for detecting gastrinomas in the pancreas or extrapancreatic region, whereas a selective arterial secretin injection was found to be useful for detecting gastrinoma in the duodenal submucosa.[72]

Pathophysiology of secretin

Hyposecretinemia is observed in two pathological states, namely, in patients with achlorhydria and adult celiac sprue. In achlorhydria patients, the content of secretin cells in the intestinal mucosa is normal and hyposecretinemia can be corrected by providing acidic drinks such as orange juice. In adult celiac sprue, mucosal atrophy in upper small intestine leads to loss of secretin cells, and hyposecretinemia can be corrected only after mucosal regeneration with a gluten-free diet. In a recent report,[73] secretin and gastric inhibitory polypeptide contents in the duodenal bulb were reduced and correlated well with malnutrition in patients with familial amyloidotic polyneuropathy. Hypersecretinemia is found in patients with Zollinger–Ellison syndrome, duodenal ulcer with hypersecretion of gastric acid, and renal failure,[17] and in a patient with a secretin-producing endocrine tumor in the pancreas causing hypersecretion of pancreatic juice and watery diarrhea.[74] Secretin-producing cells were also found in the tumor of a patient with esophageal small cell carcinoma.[75] It is possible that secretin-producing endocrine tumors may occur more frequently than one realizes but are overlooked unless causing hypersecretinemia and watery diarrhea.

Therapeutic use of secretin

Secretin has been reported to improve the behavior of an autistic child.[76] This effect of secretin has been refuted by several groups of investigators.[77] However, in view of the observations that secretin uptake[64] and its

stimulation of adenylate cyclase[62] are highest in hypothalamus and hippocampus and the action of i.v. secretin on central amygdala[65] where neural abnormality has been reported in autism,[78,79] the treatment of autism with secretin probably merits further investigation.

Summary and future prospects

More than 100 years have elapsed since the discovery of secretin by Bayliss and Starling. Substantial accomplishments in secretin research have been made with respect to purification, structure determination, establishment of hormonal status, cloning of secretin and its receptor, and neural and hormonal regulation of its release and action during the past 10 decades. Although not mentioned in this article, a considerable amount of knowledge pertaining to the cellular action mechanism of secretin has also been acquired. It is hoped that future studies will focus on identification of neural pathways through which the vagus nerve and pancreatic neurons participate in regulation of release and/or action of secretin, particularly with respect to the key neurotransmitter(s) and/or neuropeptide(s) involved and their point of action in the neural pathways. It is our hope that the extensive molecular studies in secretin receptor will lead to formulation of a potent and specific secretin receptor antagonist to facilitate future study. The physiological roles of secretin in enterocolonic motility and secretion and in the brain and other nongastrointestinal organs remain to be determined. It will be also interesting to determine the physiological roles of various forms of prosecretins.

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