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Secretin

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Gene Symbol: Sct

Abstract

Secretin is one of the “classical” gastrointestinal hormones and in fact was the first peptide hormone identified. The mature hormone is a 27 amino acid peptide produced and secreted by a specific type of enteroendocrine cell, the S cell which is of the open type with its apical surface exposed to luminal content. Secretin is packaged into granules and released across the basolateral membrane into the blood in response to acid in the duodenum when the pH falls below 4.5; it is also released in response to fatty acids but without a response to glucose or amino acids. Basal and stimulated concentrations are low normally in the 1-10 pM range. The principal action of secretin is to stimulate bicarbonate secretion by pancreatic and biliary ducts and duodenal Brunner’s glands into the lumen such that acid in the duodenum will be neutralized. Secretin also acts to potentiate CCK action on acinar cells, to inhibit gastric acid secretion and to inhibit gastric emptying. Secretin also has actions in the brain. At the cellular level the action of secretin is primarily mediated by cAMP which is increased in response to activation of secretin receptors.

1. General

Secretin has the distinction of being the first peptide hormone identified. Bayliss and Starling in 1902 showed that an acid extract of the proximal small intestine mucosa, when injected intravenously into dogs, brought about pancreatic secretion similar to that induced by acid perfusion of the duodenum (4). They named the messenger, “Secretin” and a few years latter Starling coined the word “hormone” for a substance released into the blood which acts on targets at a distance. Thus was born the field of Endocrinology. For a personal view of more recent secretin research from a leading investigator see (15).

After multiple attempts and improvements, secretin was isolated in purified form through the work of Jorpes and Mutt (50) and later its amino acid sequence was determined (11,77). It is a linear peptide of 27 amino acids and is structurally similar to glucagon and VIP (111). Its cDNA (56) and gene sequences (57,116) have been determined and the gene consists of four exons with the mature peptide in a single exon. A precursor for secretin was isolated from porcine and rat intestine which has additional N-terminal and C- terminal peptides that are cleaved to result in the mature peptide which is then amidated at

the C-terminal (36,56). The domain structure of the precursor and the amino acid sequence of secretin is shown in **Fig. 1**. It's amino acid sequence is highly conserved except for the three amino acids in the middle of the molecule. At present there are no known functions for the N or C-terminal peptides. Secretin gene expression is regulated by a 5' flanking sequence (115). The entire 27 amino acid sequence is required for maximal potency but the 5-27 amino acid C-terminal fragment has partial activity (71).

150-250 nm located in the basal pole of the cell which have been identified as containing secretin by immunogold staining (106,107). The cell type is termed S-cells, originally for small granules but "S" can also stand for secretin. Their differentiation as part of the secretory lineage and the importance of the transcription factors NeuroD in the endocrine lineage has been reviewed (93). The distribution of secretin in the GI tract has also been studied by radioimmunoassay (RIA) and by identification of mRNA. These studies have shown decreasing concentration of secretin from the duodenum to ileum (76,101). One early report identified immunoreactive secretin mRNA in the brain (82) and this has subsequently been confirmed and studied in detail by quantitative PCR and in-situ hybridization. Both secretin and its receptor have been found in the cerebellum, amygdala, hippocampus and other areas (66,104). Thus secretin clearly belongs to the general family of brain – gut peptides.

Secretin producing cells have been identified as a specific type of enteroendocrine cell by immunohistochemistry and are located in the duodenal and jejunal mucosa (18,63,83,86). Chey et al also reported the presence of secretin containing cells in the gastric antral mucosa but this has not been confirmed (17). These cells are of the open type with apical surface exposed to the intestinal luminal contents. Ultrastructurally, they possess small dense granules of diameter

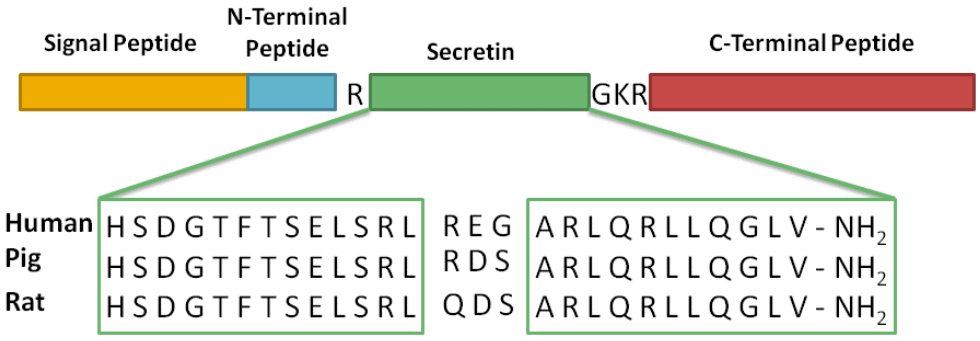

Figure 1. The domain structure and amino acid sequence of secretin. Individual amino acids serving to localize processing sites are shown in the domain structure.

Regulation of secretin secretion

The primary physiological stimulus for release of secretin is acidification of the duodenal lumen which brings about an increase in plasma secretion and thereby pancreatic bicarbonate secretion (7,32,52). In dogs, both a normal meal and infusion of acid into the duodenum brings about secretion with a duodenal pH threshold of about 4.5 (16,41,97). Increased gastric acid secretion or experimental infusion of acid brings about more secretin release both by being a stronger stimulus to individual S-cells and by extending acidification further down the small intestine thereby stimulating more S-cells (73). Inhibition of acid secretion as brought about by H2 blocker cimetidine inhibits the plasma secretin increase. The plasma half life is about 2-3 minutes (27). In humans, either feeding a normal meal or infusing acid into the duodenum increased plasma secretin with a similar pH threshold of 4.5 (20,32). No significant changes occurred after intraduodenal infusion of glucose,

amino acids, fat emulsion or ethanol (32). The secretin response was also reported similar in normal subjects, patients with duodenal ulcers and after vagotomy (113). The half life of secretin in human plasma was reported to be 4 minutes (55). Studies in other species include the showing that luminal acid stimulates secretin release in anesthetized pigs (88), in the perfused pig intestine (44) and in fasting rats (67). The mechanism by which acid brings about secretin release is not fully understood but probably involves acid sensing ion channels of the Trp family present in the brush border of S-cells. An alternative mechanism presented by Chey and colleagues based on studies in rats was for the existence of a intestinal derived secretin releasing peptide, analogous to the CCK releasing peptide concept, that was released in response to acid (67). A secretin releasing peptide was also reported in dog pancreatic juice (68). The existence of such a mechanism has not been further confirmed. What is currently needed is the development of a mechanism to sort and study S-cells similar to methods being used for CCK release from I-cells. For more detailed coverage of the older literature on secretin secretion see Walsh (111).

In addition to acid, there is a considerable amount of evidence that fatty acids can stimulate secretin release in dogs (31,79,114), humans (92) and rats (95) although the plasma secretin levels are usually lower than the response to acid. Oleic acid is the most common form of fat used and some studies show no response although this could be due to limits on the RIAs used. One report indicated that intraduodenal oligopeptides could also increase plasma secretin and stimulate pancreatic bicarbonate output in rats (94). Multiple studies have shown the lack of neural involvement in secretin release using both atropine administration and vagotomy in dogs, humans and rats (19,42,95,113).

Both basal and stimulated levels of plasma secretin are low (1 to 10 pM) and there are issues with preparing samples as well as the need for sensitivity that make it hard to perform in small animals. Description and validation of secretin RIAs used in studies reviewed here have been presented (10,12,89). Antibodies have usually been raised against the C- terminal of the secretin molecule. Studies have indicated that the kidney is the major organ metabolizing secretin (33).

Actions of Secretin

All known actions of secretin are mediated by the secretin receptor, a G-protein coupled, 7 transmembrane domain protein whose primary signal transduction mechanism is to activate adenylate cyclase and stimulate formation of cAMP (75). The receptor is structurally similar to receptors for VIP, glucagon, parathyroid hormone and other Class II G-protein linked receptors. Secretin receptors have been identified by ligand binding and recognition of its mRNA in pancreas, biliary system, stomach, brain and kidney (47,48,58,59). For more information see the Secretin Receptor Molecule Page.

The principle action of secretin is to stimulate bicarbonate secretion to neutralize gastric acid in the duodenum (37,62,111). Actions on the pancreas to stimulate duct cells to secrete bicarbonate is considered in the next section. Secretin also stimulates bicarbonate secretion by cholangiocytes, the cells lining the bile ducts with most studies having been carried out in dogs, humans and rats (39,43,51). The cellular mechanism appears identical to pancreatic secretion by pancreatic duct cells although the final concentration in bile is not as high. Secretin does not appear to affect canalicular bile formation where the driving force is secretion of bile salts (8). In addition to stimulating bicarbonate secretion from the pancreas and liver, secretin also stimulates Brunners glands in the duodenal submucosa to secrete bicarbonate rich fluid (53,70).

In a second protective action against duodenal acid, secretin acts as an enterogastrone and both reduces acid secretion and inhibits gastric

emptying thereby reducing entry of acid into the duodenum (23,54,108,122). Some of the antisecretory effects are mediated by release of somatostatin and involve inhibition of gastrin secretion (119). Somewhat paradoxically secretin stimulates pepsinogen release both in intact animals (6,99) and from isolated gastric chief cells (84,102).

Considerable recent interest has focused on a role for secretin in the brain (62) after the claim based on anectdotal evidence that secretin was an effective treatment for autism spectrum disorders (ASD) (45). Both secretin protein and secretin receptors are present in brain in various regions including the hippocampus, cerebellum and mortor cortex (60,66,80,82,104). Secretin administration intravenously affects the firing rate of hypothalamic neurons including oxytocin and vasopressin neurons (13,109). Secretin administration suppressed feeding in wild type but not secretin receptor KO mice through an action on the melanocortin Mc4 receptor (14). Using brain slices, secretin was shown to affect transmission from Purkinje neurons to basket cells (124). Both secretin and secretin receptor KO mice have been studied as to brain function and showed impaired hippocampal neurotransmission in brain slices (80,121) and some impaired social behavior (80). A mouse equivalent to ASD, however, has not been reported and systematic reviews of randomized trials have not confirmed an effect of secretin on children with ASD (61,118).

Other effects of secretin have been reported in the kidney and heart and are reviewed elsewhere (24,62). A recent report has shown effects on preadipocye differentiation and mature adipocyte function (74).

2. Effects of Secretin on the Pancreas

In vivo studies of secretin action

The primary action of secretin on the pancreas is to stimulate the flow of bicarbonate rich pancreatic juice from the duct cells. Proof of this required the advent of purified and then recombinant secretin to avoid possible effects of contaminants along with sensitive secretin RIAs. A number of studies have addressed the question of whether secretin in amounts released after a meal when duplicated by exogenous infusion can stimulate normal pancreatic bicarbonate. This has been especially difficult to establish in humans because the normal postprandial rise in secretin is only a doubling from a baseline of a few pM. In one complete study with multiple doses, Schaffalitzky de Muckadell et al (90) infused 0.25 and 0.5 pmol/kg which increased plasma secretin by 3 and 6 pM and stimulated normal amounts of bicarbonate secretion when collected by ERCP or intraduodenally. In another study the same group showed that the secretion of bicarbonate was linearly related to the rise in plasma secretin (91). Studies by others infusing 1-2.8 pmol/kg also showed pancreatic bicarbonate secretion but less than meal stimulated (5,38,123). Several of these studies also showed that adding physiological amounts of CCK or caerulein would potentiate the submaximal bicarbonate secretion. In all studies secretin infusion had no effect on trypsin secretion. Similar studies in dogs and pigs where plasma secretin levels are higher have led to the same conclusion, that infusion of secretin to reproduce physiological levels induces pancreatic bicarbonate secretion but to a submaximal amount which can be potentiated by CCK or by endogenous cholinergic tone (16,21,40,96). Secretin infusion could also stimulate bicarbonate secretion from the perfused pig pancreas confirming its ability to work in the absence of other stimulants (49). A different approach to evaluating the physiological role of a hormone is to block its action with a antagonist, antibody administration, or by gene knockout. In an important study in dogs, Chey and colleagues (22) showed that administration of secretin antibody sufficient to bind all plasma secretin

essentially blocked the bicarbonate response to a meal as well as the response to exogenous secretion thus showing that secretin plays an essential role. Interestingly, cervical vagotomy or administration of atropine also reduced bicarbonate secretion. At present there are no usable secretin antagonists and deletion of secretin or its receptor in mice has not been studied on pancreatic bicarbonate secretion. In total these studies indicate that secretin is the primary driver of pancreatic bicarbonate secretion but requires potentiation by CCK, cholinergic tone and possibly insulin (64) to exert its physiological action.

Other *in vivo* actions of secretin on the exocrine pancreas have been described but have not yet been convincingly been shown to be physiological actions. Pancreatic acinar cells have secretin/VIP responding receptors and *in vitro*, secretin has actions on pancreatic acini to increase cAMP and potentiate amylase secretion (117). However, *in vivo*, studies designed to evaluate the interaction of secretin and CCK have not shown an effect of physiological levels of secretin to potentiate digestive enzyme secretion (21,123). A potentiating action of secretin on pancreatic growth in response to CCK has also been proposed based on studies in rats where caerulein, secretin or both were injected multiple times daily (78,98). Secretin also increased the content of polyamines in the pancreas which accompanies and is required for growth (28). However, studies in mice with genetically deleted secretin or secretin receptor showed a normal sized pancreas which grew normally in response to elevated endogenous CCK (87). Another proposed action of secretin not fully evaluated is to stimulate the synthesis of pancreatic lipase. Infusion of secretin in supraphysiological doses for up to 24 hours in rats was shown to increase the synthesis of lipase and proelastase 2 (85). It was suggested that secretin might mediate the effect of high fat diets to increase pancreatic lipase. Pancreatic lipase, however, is normally present in mice lacking secretin receptors (Williams, JA, unpublished data).

In vitro studies of secretin action on pancreatic ducts

The *in vitro* studies of secretin action have primarily involved the use of microdisected duct fragments from rat, mouse and guinea pig pancreas. The secretin receptor (linked) is known to couple through $G\alpha_s$ (linked) to adenylyl cyclase and secretin increases cyclic AMP accumulation in isolated ducts (2,29,35). The first successful isolated ducts were dissected from rat pancreas in which acini were caused to atrophy on a copper deficient diet (2). Latter studies isolated ducts by microdissection from pancreas of rats, guinea pigs, and mice partially digested with collagenase. Secretin has been shown to stimulate bicarbonate fluid in the isolated duct fragments by microperfusion and by letting the ends of the ducts seal in culture after which the volume increase can be monitored by video microscopy and the ion content sampled by micropuncture (3,34,46). Guinea pig ducts have been especially useful because they secrete a high concentration of bicarbonate similar to humans while rats and mice secrete lower amounts (100). Using such preparations, secretin and other hormones that increase cyclic AMP have been shown to stimulate a cellular mechanism involving bicarbonate influx across the basolateral membrane primarily by a Na^+-HCO_3^- symporter and efflux of bicarbonate across the apical membrane through the anion channel, CFTR, and a Slc26a6 anion exchanger that is reviewed elsewhere (1,65). Cyclic AMP appears to act through protein kinase A (PKA) and a key step involves phosphorylation of CFTR. In the pig an alternate mechanism involves secretin stimulation of insertion of vesicles containing vacuolar type H^+-ATPase into the basolateral membrane of duct cells leading to export of H^+ which thereby increases the intracellular HCO_3^- (9,110).

Secretin action has also been studied in monolayer cultures of canine and bovine pancreatic ducts (26,125) and in Capan-1 cells

which are derived from a human tumor but which form a tight monolayer and possess secretin receptors (103,112). Only basic studies have been carried out to date but secretin will increase cAMP and ion transport in these monolayers.

3. Tools for the Study of Secretin

a. Peptide

Secretin was originally purified from pig or other large animal intestine and standardized in biological units termed clinical units (C.U.) based on pancreatic secretion in dogs or other animals. Today a number of chemical companies sell synthetic, HPLC purified (>98% pure) most commonly human and it is measured by weight.

b. Antibodies

Antibodies to secretin are available from a number of commercial sources. See Linscott's Directory or other directories

c. Assay

A number of RIA's capable of measuring secretin in human or canine plasma have been described in the past but are not routinely available today. Phoenix Pharmaceutical sells both ELISA and RIA kits and Antibodies.online.com and Elabscience sell similar ELISA kits said to have a sensitivity as low as 10pg/ml. Whether this will measure fasting levels is unclear but it would probably work if several ml of plasma could be absorbed onto resin and eluted. Measurement in mice and rats may be problematic.

d. Mouse Models

Mice with genetic deletion of secretin and secretin receptor have been described (25,80,121).

e. Clinical Testing

Synthetic human secretin in sterile single use vials can be obtained from ChiRhoStim. As a pancreatic function test it is usually given intravenously at 0.2 ug/kg over 1 min after injecting a test dose of 0.2 ug to check for an allergic reaction with collection of duodenal fluid (69,120). It is also given iv to test for gastrinoma (Zollinger-Ellison syndrome) by measurement of plasma gastrin. In control subjects secretin reduces or has no effect on plasma gastrin but stimulates gastrin release from gastrinomas (30,72). Secretin is also given to enhance contrast in some pancreatic imaging techniques (81,105)

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