



PRAXIS
PEPTIDE INSTITUTE

SECRETIN

ADVANCED MECHANISM AND EVIDENCE GUIDE

DUODENAL ACID-SENSING HORMONE AND BICARBONATE-COORDINATION SIGNAL

27 amino acids • S cells • SCTR • cAMP / PKA • pancreatic ducts • bicarbonate • bile • duodenal defense • functional testing

MEMORY KEY: SECRETIN IS THE DUODENUM'S ACID ALARM: ACID ARRIVES, S CELLS SIGNAL, AND BICARBONATE-RICH FLUID RESTORES THE ENVIRONMENT.

Educational monograph • Foundational endocrine physiology • Strong pancreatic and diagnostic evidence • Application-specific therapeutic limits

HOW TO USE THIS GUIDE

This guide converts a long-form research narrative into a repeatable learning system. Every future PPI molecule guide can use the same architecture, visual language, evidence labels, and memory devices.

01	IDENTITY What it is - and what it is not
02	PHYSIOLOGY The normal system before the compound
03	MECHANISM Target, pathway, and downstream logic
04	EVIDENCE Cell, animal, and human evidence separated
05	RISK Known concerns, unknowns, and translation limits
06	MONITORING What a legitimate research framework would measure
07	PATIENT CONTEXT Which phenotype might fit the biology
08	RECALL Memory hooks, seven questions, and bottom line

EVIDENCE CODE	CELL = mechanistic ANIMAL = organism-level preclinical HUMAN = clinical translation	CORE DISCIPLINE Mechanism does not equal outcome. Unknown does not equal failed - and unknown does not equal proven.
------------------	---	---

RAPID RECALL

Read this page first. These anchors provide the complete high-level story of Secretin; the remaining pages add mechanism, evidence, context, and nuance.

01	IDENTITY A 27-amino-acid hormone released mainly by duodenal S cells when acidic gastric contents enter the small intestine.
02	TARGET Secretin activates SCTR, a class B GPCR, increasing cAMP/PKA-related signaling in responsive tissues.
03	PANCREAS Its defining action is bicarbonate-rich fluid secretion from pancreatic duct cells, creating the pH needed for enzymes to work.
04	COORDINATION Biliary epithelium and Brunner glands add alkaline fluid while gastric acid delivery and motility may be restrained.
05	PARTNER Secretin supplies bicarbonate-rich fluid; CCK supplies enzyme-rich secretion. Digestion needs both environment and tools.
06	PROBE Secretin can test pancreatic ductal function, enhance MRCP, and provoke a paradoxical gastrin response in gastrinoma evaluation.
07	LIMIT Pathway presence does not establish a treatment; controlled trials did not support secretin as an autism therapy.
08	PRAXIS QUESTION Is the failure the secretin signal, the receptor-effector response, anatomy, or another part of acid-base digestion?

ONE-SENTENCE MEMORY
SECRETIN IS THE DUODENUM'S ACID ALARM: ACID ARRIVES, S CELLS SIGNAL, AND BICARBONATE-RICH FLUID RESTORES THE ENVIRONMENT.

UNDERSTAND THE PEPTIDE

Secretin is a 27-amino-acid gastrointestinal peptide hormone released primarily from S cells in the proximal small intestine when acidic gastric contents enter the duodenum.

Its central job is remarkably logical:

THE STOMACH PRODUCES ACID.

That acid enters:

THE DUODENUM.

The small intestine now needs protection.



Secretin is released.



The pancreas and biliary system deliver:

BICARBONATE-RICH FLUID.



Acid is neutralized.



The intestinal environment becomes more appropriate for:

DIGESTIVE ENZYMES + MUCOSAL PROTECTION.

Secretin therefore participates in:

- pancreatic bicarbonate secretion
- biliary bicarbonate secretion
- duodenal pH regulation
- gastric motility
- bicarbonate homeostasis
- pancreatic duct physiology
- Brunner-gland secretion
- gastric acid feedback
- pancreatic diagnostic testing

Modern physiology reviews increasingly frame Secretin as a hormone of HCO_3^- homeostasis, extending its role beyond the pancreas to biliary, intestinal, and even renal bicarbonate handling.

The most useful way to understand Secretin is not:

“A PANCREATIC HORMONE.”

That is too narrow.

A better description is:

AN ACID-RESPONSE PEPTIDE THAT COORDINATES BICARBONATE DELIVERY AND DIGESTIVE PHYSIOLOGY WHEN ACIDIC GASTRIC CONTENT ENTERS THE SMALL INTESTINE.

That is the core biology.

WHAT IS SECRETIN?

Secretin is a:

27-AMINO-ACID PEPTIDE.

It belongs to the broader:

SECRETIN / GLUCAGON / VIP FAMILY

of peptide hormones.

Its major endogenous source is:

S CELLS

located predominantly in the:

- duodenum
- proximal small intestine

Secretin is particularly important because it occupies a foundational place in endocrinology.

The discovery of Secretin helped establish the idea that:

ONE ORGAN CAN RELEASE A CHEMICAL SIGNAL INTO THE BLOOD THAT CHANGES THE FUNCTION OF ANOTHER ORGAN.

In other words:

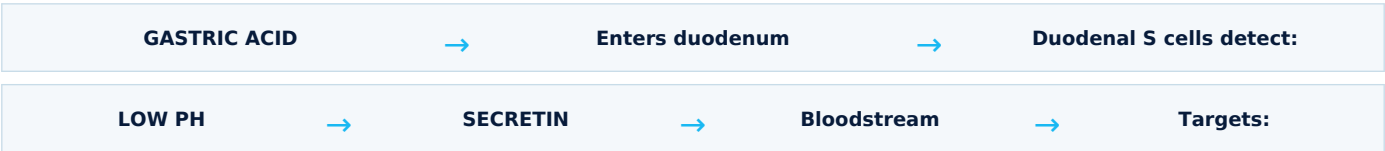
HORMONAL SIGNALING.

So Secretin is not merely another GI peptide.

It helped define:

ENDOCRINOLOGY ITSELF.

THE IDENTITY MODEL



PANCREATIC DUCT CELLS

BILIARY EPITHELIUM

BRUNNER GLANDS



MUCOSAL PROTECTION

OPTIMAL ENZYME FUNCTION

DIGESTION

The core concept is:

SECRETIN HELPS THE INTESTINE DEFEND ITSELF AGAINST THE STOMACH.

WHY THE DUODENUM NEEDS SECRETIN

The stomach is designed for:

ACID.

The duodenum is not.

Gastric hydrochloric acid helps:

- denature protein
- activate pepsin
- reduce microbial burden
- facilitate digestion

But pancreatic enzymes work best in a:

LESS ACIDIC ENVIRONMENT.

And the duodenal mucosa needs protection from:

EXTREME ACID EXPOSURE.

So when gastric contents enter the duodenum:

the digestive system must rapidly shift from:

ACID GENERATION

to:

ACID NEUTRALIZATION.

Secretin is one of the central signals controlling:

THAT TRANSITION.

THE ACID-NEUTRALIZATION MODEL

Stomach → **HCl** → **Duodenum** → **pH falls** → **SECRETIN** ↑ → **Pancreatic bicarbonate** ↑ → **Biliary bicarbonate** ↑ → **Duodenal pH rises**

- Pancreatic digestive enzymes can function more effectively

This is:

FEEDBACK PHYSIOLOGY.

THE SECRETIN RECEPTOR

Secretin acts through:

SCTR - SECRETIN RECEPTOR.

SCTR belongs to the:

CLASS B / SECRETIN-FAMILY G-PROTEIN-COUPLED RECEPTORS.

It has:

- seven transmembrane domains
- a relatively large extracellular amino-terminal domain
- intracellular signaling domains

Its classical pathway is:

SECRETIN

SCTR



primarily:

Gs



ADENYLYL CYCLASE



cAMP ↑



**PKA-RELATED
SIGNALING**



**Cell-specific
response**

The Secretin receptor is well characterized and remains the single principal receptor through which Secretin's known physiological actions are organized.

THE RECEPTOR MODEL

SECRETIN



SCTR



Gs



Adenylyl cyclase



cAMP



**In pancreatic
duct cells:**

BICARBONATE SECRETION ↑

In other tissues:

- different downstream effects

Again:

SAME RECEPTOR.

Different tissue.

Different:

PHYSIOLOGICAL OUTPUT.

PANCREATIC BICARBONATE - SECRETIN'S DEFINING ROLE

The exocrine pancreas has two major functional compartments.

ACINAR CELLS

Primarily produce:

DIGESTIVE ENZYMES.

DUCTAL CELLS

Primarily contribute:

BICARBONATE-RICH FLUID.

Secretin is especially important for:

THE DUCTAL COMPONENT.

This distinction matters.

Secretin is not simply telling the pancreas:

“DIGEST MORE.”

It is telling the pancreatic ducts:

“DELIVER THE ALKALINE FLUID NEEDED TO MAKE DIGESTION POSSIBLE.”

THE PANCREATIC MODEL



- Acid neutralization

This is one of the cleanest:

STIMULUS → PEPTIDE → RECEPTOR → ORGAN → FUNCTION

models in GI endocrinology.

WHY BICARBONATE MATTERS FOR PANCREATIC ENZYMES

The pancreas secretes powerful enzymes including:

- lipase
- proteases
- amylase

But pancreatic enzymes require an appropriate:

LUMINAL PH.

If the duodenum remains excessively acidic:

enzyme function can become impaired.

So bicarbonate is not simply:

AN ANTACID.

It helps create:

THE CHEMICAL ENVIRONMENT REQUIRED FOR DIGESTION.

Secretin therefore links:

GASTRIC ACID

to:

PANCREATIC FUNCTION.

THE DIGESTION MODEL

Stomach acid → Secretin → Bicarbonate → Duodenal pH becomes appropriate → Pancreatic enzymes function → Macronutrient digestion → Nutrient absorption

Again:

Secretin is not directly:

DIGESTING FOOD.

It creates:

THE ENVIRONMENT IN WHICH DIGESTION WORKS.

SECRETIN AND CCK - A BEAUTIFUL PARTNERSHIP

Secretin and CCK work beautifully together.

SECRETIN

Primary pancreatic effect:

BICARBONATE-RICH FLUID.

CCK

Primary pancreatic effect:

DIGESTIVE ENZYME SECRETION.

So after a meal:

Secretin says:

NEUTRALIZE THE ACID.

CCK says:

DELIVER THE ENZYMES.

Together:

BICARBONATE + ENZYMES

Effective digestion.

This is a classic example of:

PEPTIDE COOPERATION.

And it is precisely why the next guide:

CCK

fits naturally after Secretin.

BILIARY PHYSIOLOGY

Secretin also stimulates:

BILIARY BICARBONATE AND FLUID SECRETION.

Cholangiocytes - the epithelial cells lining bile ducts - can respond to Secretin.

This helps create more:

ALKALINE BILE.

The resulting fluid contributes to:

- bile flow
- ductal environment
- bicarbonate delivery to the intestine

This again reinforces that Secretin is better thought of as:

A BICARBONATE-COORDINATION HORMONE

rather than:

A PANCREAS-ONLY HORMONE.

THE BILIARY MODEL

Secretin



SCTR on cholangiocyte-related pathways



cAMP ↑



Bicarbonate / fluid secretion ↑



Potential:

BILE FLOW ↑

DUCTAL ALKALINIZATION



Contribution to:

DUODENAL NEUTRALIZATION

Again:

the liver, pancreas, and intestine are acting as:

ONE DIGESTIVE SYSTEM.

BRUNNER GLANDS

Brunner glands are located primarily in:

THE DUODENUM.

They produce alkaline, mucus-rich secretions that help protect the proximal small intestine from:

GASTRIC ACID.

Secretin stimulates:

BICARBONATE-RICH BRUNNER-GLAND SECRETION.

A modern bicarbonate-homeostasis review identifies pancreatic ducts, bile ducts, and Brunner glands as major Secretin-responsive bicarbonate-secreting systems.

This creates multiple layers of defense:

PANCREAS

BILIARY SYSTEM

DUODENAL GLANDS



Protect:

THE DUODENUM.

SECRETIN AND GASTRIC ACID

Secretin does something especially elegant.

It does not only:

INCREASE BICARBONATE.

It also participates in feedback that can reduce:

GASTRIC ACID OUTPUT.

So the physiology becomes:

RESPONSE 1

Add more:

BASE.

RESPONSE 2

Reduce additional:

ACID LOAD.

That is much more efficient than relying on:

NEUTRALIZATION ALONE.

Secretin has long been recognized as participating in regulation of gastric acid secretion and gastric motility as part of its broader digestive role.

THE TWO-SIDED PH MODEL

Duodenal acid detected



Secretin



PANCREAS / BILE

BICARBONATE ↑

and:

STOMACH

Potential:

ACID DELIVERY ↓

- Duodenal pH restored

Again:

homeostasis often works by:

CHANGING BOTH SIDES OF THE EQUATION.

SECRETIN AND GASTRIC EMPTYING

Secretin can also influence:

GASTRIC MOTILITY.

Why would slowing gastric emptying make sense?

Because if the duodenum is already:

TOO ACIDIC,

dumping even more acidic gastric content into it immediately would worsen the problem.

So Secretin can participate in:

DUODENAL BRAKING.

The logic is:

Duodenal acid load ↑



Secretin



Potential:

GASTRIC DELIVERY SLOWS



Bicarbonate system catches up

This is not merely:

A MOTILITY EFFECT.

It is:

CHEMICAL LOAD MANAGEMENT.

SECRETIN VS MOTILIN

These peptides offer almost opposite temporal concepts.

MOTILIN

Fasting state



MMC



Propulsive housekeeping contractions

SECRETIN

Fed / digestive acid-response state



Bicarbonate secretion



Acid neutralization + digestive coordination

So:

MOTILIN HELPS ORGANIZE THE GUT BETWEEN MEALS.

Secretin helps organize:

THE CHEMICAL ENVIRONMENT AFTER GASTRIC CONTENT ENTERS THE DUODENUM.

Same GI tract.

Different:

TIME + JOB.

SECRETIN VS GLP-2

GLP-2

Primary identity:

INTESTINAL GROWTH + ABSORPTIVE CAPACITY.

SECRETIN

Primary identity:

ACID-BASE + PANCREATIC DUCTAL PHYSIOLOGY.

So GLP-2 asks:

HOW MUCH FUNCTIONAL INTESTINAL SURFACE DO WE HAVE?

Secretin asks:

IS THE DUODENAL CHEMICAL ENVIRONMENT APPROPRIATE FOR THAT SURFACE TO WORK?

Again:

structure and chemistry are:

DIFFERENT NODES.

PANCREATIC EXOCRINE FUNCTION

Secretin has become extremely useful clinically because its physiology can be:

PROVOKED AND MEASURED.

Administer Secretin.



Healthy pancreas should respond with:

BICARBONATE-RICH FLUID.

If that response is impaired:

it can suggest:

EXOCRINE PANCREATIC DYSFUNCTION.

This led to the:

SECRETIN STIMULATION / PANCREATIC FUNCTION TEST.

Secretin has long been used in studies of exocrine pancreatic secretion and pancreatic function testing.

THE FUNCTION-TEST MODEL

Synthetic Secretin



Pancreatic duct stimulation



Collect / evaluate duodenal
pancreatic secretion



Measure:

VOLUME

and/or:

BICARBONATE

Infer:

PANCREATIC EXOCRINE FUNCTION

This is an elegant diagnostic principle:

DO NOT JUST IMAGE THE ORGAN.

Ask it:

TO PERFORM ITS JOB.

STRUCTURE VS FUNCTION

A pancreas can look:

RELATIVELY NORMAL

- on imaging

and still have impaired:

EXOCRINE FUNCTION.

Conversely:

structural abnormalities do not always perfectly predict:

FUNCTIONAL LOSS.

Secretin testing therefore helped establish a broader diagnostic principle:

ANATOMY $\neq$ FUNCTION.

That is highly consistent with the Praxis approach.

SECRETIN-ENHANCED MRCP

This is one of Secretin's most interesting modern clinical uses.

MRCP - MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY

visualizes:

- pancreatic ducts
- bile ducts

But Secretin can improve the study.



Secretin-enhanced MRCP provides information about both pancreatic duct morphology and exocrine functional response.

THE SECRETIN-MRCP MODEL



DUCT ANATOMY

PANCREATIC FUNCTION

This may be one of the best examples in diagnostic medicine of:

USING A PEPTIDE AS A PHYSIOLOGICAL CHALLENGE TEST.

WHAT SECRETIN-ENHANCED MRCP CAN HELP EVALUATE

Established uses can include assessment of:

- pancreas divisum
- chronic pancreatitis
- anomalous pancreaticobiliary junction
- selected pancreatic duct variants
- subtle pancreatic-duct abnormalities
- duct stenosis
- postoperative pancreatic anatomy

An expert-panel review identifies these among established indications for Secretin-enhanced MRCP.

Again:

Secretin is not:

TREATING THE PANCREAS.

Here it is being used to:

REVEAL PANCREATIC PHYSIOLOGY.

PANCREAS DIVISUM

Pancreas divisum is a developmental ductal variant where:

THE DORSAL AND VENTRAL PANCREATIC DUCT SYSTEMS FAIL TO FUSE NORMALLY.

This can make duct anatomy:

DIFFICULT TO CHARACTERIZE.

Secretin increases pancreatic secretion.



Ducts become more prominent.



MRCP visualization improves.

This is why Secretin can be especially useful when:

STATIC ANATOMY IS SUBTLE.

CHRONIC PANCREATITIS

Chronic pancreatitis can produce:

- fibrosis
- reduced exocrine secretion
- ductal abnormalities
- progressive functional loss

Secretin-enhanced MRCP may reveal:

MORPHOLOGICAL + FUNCTIONAL INFORMATION

that standard imaging alone may miss.

Again:

this reinforces:

DISEASE IS NOT JUST WHAT AN ORGAN LOOKS LIKE.

It is:

WHAT THE ORGAN CAN STILL DO.

GASTRINOMA / ZOLLINGER-ELLISON SYNDROME

Secretin also has a remarkable diagnostic relationship with:

GASTRINOMA.

Normally:

Secretin is not expected to produce a dramatic rise in:

GASTRIN.

But gastrinoma cells can respond paradoxically.

Administer Secretin.**In gastrinoma:****GASTRIN CAN RISE MARKEDLY.**

This forms the basis of the:

SECRETIN STIMULATION TEST

used in selected patients being evaluated for:

ZOLLINGER-ELLISON SYNDROME.

Secretin has historically been used diagnostically in gastrinoma syndrome.

THE GASTRINOMA MODEL

**Patient with suspected
gastrinoma****Baseline gastrin****Secretin administered****If gastrinoma present:**

Potential:

PARADOXICAL GASTRIN RISE

- Supports diagnosis in appropriate clinical context

Again:

this is another case where Secretin is valuable not as:

A THERAPY

but as:

A PHYSIOLOGICAL PROBE.

WHY THIS IS SO INTERESTING

Most peptides are discussed in medicine as:

TREATMENTS.

Secretin shows another possibility.

A peptide can be used to:

ASK A BIOLOGICAL QUESTION.

Can the pancreas secrete bicarbonate?

Does the duct expand normally?

Does a gastrinoma respond paradoxically?

That transforms peptide medicine from:

GIVE SIGNAL → CHANGE SYSTEM

into:

GIVE SIGNAL → OBSERVE SYSTEM.

That is an important PPI concept.

SECRETIN AND THE KIDNEY

One of the more surprising modern developments is Secretin's role in:

RENAL BICARBONATE HOMEOSTASIS.

Secretin receptors have been identified on:

- β -INTERCALATED CELLS

in the collecting duct.

Experimental work suggests Secretin can stimulate urinary:

BICARBONATE EXCRETION

through pathways involving:

- pendrin

CFTR

SCTR

This has led to a broader model of Secretin as a hormone involved in:

WHOLE-BODY HCO_3^- HOMEOSTASIS.

That significantly expands its classical identity.

THE RENAL MODEL



ACID-BASE HOMEOSTASIS

This research is newer and much of the mechanistic work is:

PRECLINICAL.

But conceptually it is extremely interesting.

The same hormone helping deliver bicarbonate into:

THE GI LUMEN

may also help regulate bicarbonate loss through:

THE KIDNEY.

SECRETIN AS A BICARBONATE-HOMEOSTASIS HORMONE

This gives us a broader model:

DIGESTIVE SYSTEM

Secretin



Bicarbonate into:

PANCREATIC JUICE

BILE

DUODENAL SECRETIONS

RENAL SYSTEM

Secretin



Potential bicarbonate excretion into:

URINE

So the peptide may help determine:

WHERE BASE GOES.

That is far more sophisticated than:

“SECRETIN STIMULATES THE PANCREAS.”

CENTRAL NERVOUS SYSTEM

Secretin and its receptor are also present within:

THE CENTRAL NERVOUS SYSTEM.

Research has explored possible roles in:

- hypothalamic function
- neuroendocrine signaling
- behavioral regulation
- water balance
- synaptic biology

The existence of central Secretin signaling is well documented, although its physiological significance remains far less completely defined than its pancreatic role.

This provides a useful evidence distinction:

RECEPTOR PRESENT

does not mean:

THERAPEUTIC INDICATION ESTABLISHED.

SECRETIN AND AUTISM - A MAJOR EVIDENCE LESSON

Secretin has a unique and important history in:

AUTISM.

In the late 1990s, anecdotal reports suggested children with autism experienced improvements after Secretin administration.

The story spread rapidly.

Families understandably became interested.

Secretin began receiving substantial attention as a potential:

AUTISM TREATMENT.

Then randomized controlled trials were performed.

And the results repeatedly failed to show:

MEANINGFUL BENEFIT OVER PLACEBO.

A 60-child double-blind trial of synthetic human Secretin found no significant improvement in standardized autism outcomes compared with placebo.

A separate 95-participant randomized trial also found no significant improvement in language or autistic behaviors.

Multisite and crossover trials likewise failed to demonstrate efficacy.

WHY THE SECRETIN-AUTISM STORY MATTERS

This should not be framed as:

“SECRETIN WAS A FRAUD.”

That misses the lesson.

The real sequence was:

**Anecdotal
observation**



Hypothesis



Public enthusiasm



Controlled trials



**Hypothesis did not
reproduce reliably**

That is:

SCIENCE WORKING.

The correct response to an interesting clinical observation is:

TEST IT.

Not:

BELIEVE IT AUTOMATICALLY.

And not:

DISMISS IT BEFORE TESTING.

Secretin therefore provides one of the best examples in this entire library of:

EVIDENCE CALIBRATION.

ANECDOTE VS CONTROLLED EVIDENCE

An anecdote can tell us:

SOMETHING INTERESTING MAY HAVE HAPPENED.

It cannot reliably tell us:

WHY IT HAPPENED.

Potential explanations include:

- placebo effect
- concurrent treatment
- observer expectation
- true drug effect
- natural variation
- regression toward the mean
- real responder subgroup

A randomized trial helps:

SEPARATE THESE POSSIBILITIES.

With Secretin in autism:

multiple controlled studies did not support:

A REPRODUCIBLE THERAPEUTIC EFFECT.

That is the correct evidence conclusion.

THE CORE MECHANISM MAP

GASTRIC ACID ENTERS DUODENUM → Duodenal S cells → SECRETIN → SCTR → cAMP SIGNALING → PANCREAS

BICARBONATE-RICH FLUID ↑

BILIARY SYSTEM

BICARBONATE / FLUID ↑

BRUNNER GLANDS

ALKALINE SECRETION ↑

STOMACH

Potential:

ACID DELIVERY / MOTILITY MODULATION

DUODENAL PH RESTORED



Potential:

MUCOSAL PROTECTION + PANCREATIC ENZYME FUNCTION + DIGESTION

The core concept is:

SECRETIN COORDINATES THE BODY'S RESPONSE TO ACID ENTERING THE SMALL INTESTINE.

WHAT THIS MECHANISM MAY SUGGEST

Mechanistically and diagnostically, Secretin deserves interest in:

- pancreatic exocrine physiology
- pancreatic duct abnormalities
- secretin-enhanced MRCP
- gastrinoma evaluation
- biliary bicarbonate secretion
- selected renal bicarbonate research
- chronic pancreatitis evaluation
- pancreas divisum
- pancreatic function testing
- duodenal bicarbonate physiology
- acid-base physiology

Its strongest established modern roles are predominantly:

PHYSIOLOGICAL AND DIAGNOSTIC

rather than:

GENERAL THERAPEUTIC PEPTIDE USE.

WHAT THIS MECHANISM DOES NOT PROVE

Secretin biology does not prove that it:

- treats every digestive disorder
- treats GERD simply because acid is involved
- treats autism
- treats every form of malabsorption
- improves CNS function simply because SCTR exists in the brain
- corrects all pancreatic insufficiency
- repairs chronic pancreatitis
- should be used whenever bicarbonate is low
- treats every pancreatic duct abnormality
- should be chronically administered to improve digestion

Again:

PHYSIOLOGICAL IMPORTANCE $\neq$ THERAPEUTIC INDICATION.

THE EVIDENCE, POTENTIAL APPLICATIONS, AND LIMITATIONS

ENDOGENOUS PHYSIOLOGY

VERY STRONG

Secretin is a foundational gastrointestinal hormone with established effects on:

- pancreatic bicarbonate
- pancreatic fluid
- gastric regulation

biliary and duodenal physiology.

RECEPTOR BIOLOGY

STRONG

The Secretin receptor is a well-characterized class-B GPCR signaling prominently through: cAMP.

PANCREATIC PHYSIOLOGY

VERY STRONG

Exogenous Secretin reliably stimulates pancreatic:

BICARBONATE-RICH FLUID SECRETION.

That physiological response forms the basis for:

- pancreatic function testing

Secretin-enhanced MRCP.

DIAGNOSTIC EVIDENCE

STRONG IN APPROPRIATE APPLICATIONS

Secretin-enhanced MRCP can improve visualization of:

- | | |
|-------------------------|--|
| • pancreatic ducts | • side branches |
| • subtle duct pathology | • pancreatic secretion into the duodenum |

and can provide information about:

MORPHOLOGY + FUNCTION.

NEUROBEHAVIORAL THERAPEUTIC EVIDENCE

NEGATIVE FOR AUTISM

Multiple randomized, placebo-controlled trials failed to demonstrate meaningful therapeutic efficacy of Secretin for autism.

This is an important evidence boundary.

- Research

EXOCRINE PANCREATIC FUNCTION

This is Secretin's most obvious clinical physiology domain.

If the pancreas cannot produce adequate:

BICARBONATE-RICH FLUID,

the duodenal environment may remain excessively acidic.

That can impair:

DIGESTIVE ENZYME FUNCTION.

Secretin allows clinicians and researchers to ask:

HOW MUCH FUNCTIONAL DUCTAL RESPONSE REMAINS?

CHRONIC PANCREATITIS

Chronic pancreatitis can progressively damage:

- acinar tissue
- ductal architecture
- exocrine function

Secretin-enhanced imaging may be especially useful when:

EARLY DUCTAL ABNORMALITIES ARE SUBTLE.

It may improve duct visualization while simultaneously providing information about:

PANCREATIC SECRETORY RESPONSE.

Again:

ANATOMY + FUNCTION.

PANCREAS DIVISUM

Secretin-enhanced MRCP can improve visualization of:

DORSAL PANCREATIC DUCT ANATOMY

and other structural variants.

This can be valuable in selected patients with:

- unexplained pancreatitis
- suspected ductal anomaly
- complex pancreatic anatomy

Again:

the peptide is being used to:

MAKE PHYSIOLOGY VISIBLE.

GASTRINOMA

The Secretin stimulation test remains a fascinating example of:

PARADOXICAL TUMOR PHYSIOLOGY.

A tumor may respond to a hormone:

DIFFERENTLY THAN NORMAL TISSUE.

So instead of asking only:

“WHAT IS THE GASTRIN LEVEL?”

we ask:

“WHAT DOES THE GASTRIN-SECRETING TISSUE DO WHEN CHALLENGED WITH SECRETIN?”

That is functional endocrinology.

DUODENAL ACID DISORDERS

Secretin physiology is relevant wherever:

ACID DELIVERY

and:

BICARBONATE DEFENSE

become imbalanced.

But the cause must still be identified.

Potential problems can involve:

- excess gastric acid
- impaired ductal function
- altered gastric emptying
- inadequate pancreatic secretion
- pancreatic insufficiency

Again:

same duodenal acidity.

Different:

UPSTREAM CAUSE.

CYSTIC FIBROSIS - CONCEPTUALLY IMPORTANT

Cystic fibrosis disrupts:

CFTR FUNCTION.

CFTR is central to:

- chloride transport
- bicarbonate secretion
- pancreatic duct fluid

So Secretin may successfully:

SEND THE SIGNAL

while the ductal transport machinery remains:

IMPAIRED.

This illustrates a powerful concept:

NORMAL HORMONE + BROKEN EFFECTOR = POOR PHYSIOLOGICAL RESPONSE.

Again:

high-quality signaling cannot compensate for:

A DEFECTIVE DOWNSTREAM MACHINE.

THE SIGNAL-EFFECTOR MODEL

Secretin normal



SCTR normal



cAMP signal normal

But:

CFTR / duct transport impaired



Bicarbonate response remains poor

This gives us another PPI principle:

RECEPTOR ACTIVATION $\neq$ FUNCTION IF THE DOWNSTREAM EFFECTOR CANNOT RESPOND.

GASTRIC ACID HYPERSECRETION

Secretin historically helped reveal relationships among:

- | | |
|-----------------------|----------------------|
| • duodenal acidity | • gastric secretion |
| • pancreatic response | • gastrin physiology |

But chronic gastric acid disorders should not be reduced to:

SECRETIN DEFICIENCY.

Potential drivers include:

- H. pylori
- medication changes
- histamine signaling
- gastrinoma
- parietal-cell regulation
- gastrin abnormalities

Again:

ONE OUTPUT $\neq$ ONE CAUSE.

BILIARY DISEASE

Secretin's cholangiocyte and bicarbonate effects make biliary biology interesting.

But evidence for therapeutic Secretin use across chronic biliary disease remains far less developed than:

THE PHYSIOLOGY.

This is another place where:

MECHANISM SHOULD NOT OUTFRAN APPLICATION EVIDENCE.

RENAL ACID-BASE PHYSIOLOGY

The emerging renal Secretin story could substantially broaden how the hormone is understood.

Experimental data suggest:

- SCTR-dependent urinary bicarbonate excretion

contributes to rapid adaptation to:

BASE LOAD.

This means Secretin may participate in:

WHOLE-BODY ACID-BASE INTEGRATION.

But the human clinical significance of this newer renal pathway remains:

LESS ESTABLISHED

than pancreatic Secretin physiology.

Again:

INTERESTING MECHANISM $\neq$ ESTABLISHED THERAPY.

AUTISM - WHAT THE EVIDENCE ACTUALLY SHOWED

This deserves a dedicated research section because it is such a valuable example.

Anecdotal reports generated considerable excitement.

Then multiple trials were conducted.

A randomized trial of 60 children found no significant treatment benefit with synthetic human Secretin.

Another randomized trial involving 95 children found no significant difference in language or autistic behaviors.

Another multicenter crossover study likewise found no evidence of efficacy.

So the conclusion is not:

“SECRETIN BIOLOGY IN THE BRAIN DOES NOT EXIST.”

The conclusion is:

SECRETIN ADMINISTRATION DID NOT DEMONSTRATE REPRODUCIBLE THERAPEUTIC EFFICACY FOR AUTISM IN CONTROLLED TRIALS.

That wording matters.

WHAT WE KNOW

Secretin is a 27-amino-acid gastrointestinal peptide hormone.

It is secreted primarily from duodenal S cells in response to acid entering the proximal small intestine.

Its defining physiological action is stimulation of pancreatic bicarbonate-rich fluid secretion.

Secretin acts through the Secretin receptor - SCTR.

SCTR is a class-B GPCR in the Secretin/VIP/glucagon receptor family.

Its classical signaling pathway involves Gs, adenylyl cyclase, and cAMP.

Secretin stimulates pancreatic ductal bicarbonate secretion.

It also stimulates bicarbonate-rich secretion from the biliary tract and Brunner glands.

These responses help neutralize acidic gastric contents entering the duodenum.

Secretin also participates in regulation of gastric acid secretion and gastric motility.

Secretin can be used diagnostically to provoke pancreatic exocrine secretion.

Secretin-enhanced MRCP improves visualization of pancreatic duct anatomy and provides functional information about pancreatic secretion.

Established S-MRCP indications include selected ductal variants, chronic pancreatitis, stenosis, and complex pancreatic anatomy.

Secretin has also been used in the diagnostic evaluation of gastrinoma syndrome.

Emerging experimental work suggests Secretin may also participate in renal bicarbonate excretion and whole-body acid-base homeostasis.

Secretin and SCTR are present in the CNS, but central physiological roles remain less clearly defined than pancreatic actions.

Multiple randomized controlled trials failed to demonstrate meaningful efficacy of Secretin as a treatment for autism.

WHAT WE THINK MAY BE HAPPENING

Secretin may be best understood as:

THE BODY'S “TOO MUCH ACID JUST ARRIVED” SIGNAL.

The stomach does its job.



Acidic chyme enters the duodenum.



Now the digestive system faces a different problem.

The small intestine needs:

A DIFFERENT CHEMICAL ENVIRONMENT.

So S cells detect:

ACID.

Secretin rises.



The pancreas receives the message:

SEND BICARBONATE.

The biliary system receives:

SEND ALKALINE FLUID.

The duodenum receives:

PROTECT THE SURFACE.

The stomach receives feedback:

DO NOT DELIVER MORE ACID TOO QUICKLY.

And digestion shifts from:

GASTRIC ACID PHYSIOLOGY

into:

INTESTINAL ENZYME PHYSIOLOGY.

In that model:

Secretin is not simply:

A PANCREATIC STIMULANT.

It is:

A PHASE-TRANSITION HORMONE BETWEEN TWO DIFFERENT CHEMICAL ENVIRONMENTS OF DIGESTION.

WHAT REMAINS CONTEXT-DEPENDENT

Important questions include:

What exact luminal signals dominate Secretin release in humans?

How much does vagal signaling contribute to normal secretion?

How do intestinal Secretin-releasing peptides contribute physiologically?

How strongly does insulin modify Secretin's pancreatic effects?

Which pancreatic disorders show impaired Secretin signaling versus impaired ductal response?

Can Secretin-response patterns help identify earlier chronic pancreatitis?

Which S-MRCP measurements best quantify pancreatic exocrine reserve?

How should S-MRCP findings be standardized across centers?

How much of Secretin's biliary biology is clinically actionable?

What is the full importance of SCTR signaling in cholangiocytes?

Does renal Secretin physiology meaningfully regulate human acid-base balance?

Which clinical acid-base disorders alter Secretin concentrations?

How much of central Secretin signaling is truly endocrine versus locally neuronal?

What does CNS Secretin regulate physiologically in humans?

How does Secretin interact with VIP?

How does Secretin interact with CCK?

How does pancreatic CFTR dysfunction alter the Secretin response?

Can Secretin testing better phenotype exocrine pancreatic insufficiency?

Which patients with suspected gastrinoma gain most from Secretin stimulation testing?

Can future SCTR agonists or antagonists become therapeutic rather than primarily diagnostic?

Are there pancreatic or biliary phenotypes where chronic receptor modulation would be useful?

How should structural imaging and functional Secretin responses be integrated?

Again:

these are the questions needed to move from:

CLASSICAL GI HORMONE

to:

PRECISION PANCREATIC AND ACID-BASE PHYSIOLOGY.

THE PRAXIS LENS

DO NOT BEGIN WITH SECRETIN

Begin with:

WHAT PART OF ACID-BASE, PANCREATIC, OR DUODENAL PHYSIOLOGY IS ACTUALLY FAILING?

Then:

PHYSIOLOGY

PATTERN



MECHANISM



EVIDENCE



RISK



MONITORING



DECISION

PHYSIOLOGY

Healthy duodenal digestion requires:

- appropriate gastric acid delivery
- bicarbonate secretion
- pancreatic enzymes
- coordinated gastric emptying
- pancreatic duct function
- biliary secretion
- mucosal integrity

Secretin appears especially relevant to:

BICARBONATE + DUCTAL FLUID + ACID NEUTRALIZATION.

PATTERN

What is actually present?

pancreatic insufficiency?

chronic pancreatitis?

pancreatic duct abnormality?

pancreas divisum?

excessive gastric acid?

impaired bicarbonate secretion?

suspected gastrinoma?

malabsorption?

cystic-fibrosis-related pancreatic dysfunction?

Again:

“BAD DIGESTION” IS NOT A SECRETIN DIAGNOSIS.

MECHANISM

Does Secretin physiology match:

THE DOMINANT BOTTLENECK?

If pancreatic enzymes are low because:

ACINAR TISSUE HAS BEEN DESTROYED,

Secretin cannot magically restore:

THE LOST ACINAR MASS.

If the pancreatic duct cannot transport bicarbonate because:

CFTR IS DYSFUNCTIONAL,

the problem is not necessarily:

INADEQUATE SECRETIN.

If the patient has:

ANATOMICAL DUCTAL DISEASE,

Secretin may be especially useful as:

A DIAGNOSTIC CHALLENGE.

Again:

SIGNAL

and:

ABILITY TO RESPOND

are separate questions.

EVIDENCE

Ask:

WHAT ARE WE USING SECRETIN FOR?

Pancreatic physiology?

VERY STRONG.

Secretin-enhanced MRCP?

ESTABLISHED DIAGNOSTIC USE IN SELECTED SETTINGS.

Gastrinoma testing?

ESTABLISHED PHYSIOLOGICAL DIAGNOSTIC CONCEPT.

Autism?

CONTROLLED TRIALS DO NOT SUPPORT THERAPEUTIC EFFICACY.

Renal bicarbonate therapy?

INTERESTING MECHANISM, EARLY TRANSLATION.

Again:

SAME PEPTIDE. DIFFERENT EVIDENCE CLASS.

RISK

For diagnostic Secretin administration, considerations can include:

- transient nausea
- flushing or other infusion-related effects
- interpretation errors if pretest conditions are inappropriate
- abdominal discomfort
- application-specific contraindications

But perhaps the largest conceptual risk is:

USING SECRETIN TO TREAT A CONDITION SIMPLY BECAUSE SECRETIN IS BIOLOGICALLY PRESENT IN THAT SYSTEM.

Again:

PATHWAY INVOLVEMENT $\neq$ THERAPEUTIC EFFICACY.

MONITORING

Monitoring should follow:

THE SECRETIN QUESTION.

PANCREATIC FUNCTION

- bicarbonate output
- pancreatic exocrine function
- fluid response
- nutritional consequences of insufficiency

SECRETIN-ENHANCED MRCP

- duct caliber
 - duodenal filling
 - structural abnormalities
- side-branch visualization
 - ductal compliance

GASTRINOMA

- fasting gastrin
 - gastric-acid context
- Secretin-stimulated gastrin response
 - disease-specific imaging

DIGESTIVE FUNCTION

- steatorrhea
 - fat-soluble vitamins
 - pancreatic-enzyme requirement
- weight
 - nutritional status

Again:
monitor:

WHAT SECRETIN IS SUPPOSED TO REVEAL OR CHANGE.

THE PRAXIS 5

MECHANISM

Secretin's central pathway is:
DUODENAL ACID → SECRETIN → SCTR → cAMP → BICARBONATE-RICH SECRETION.
Its primary biological identity is:

ACID-BASE COORDINATION IN DIGESTION.

EVIDENCE

Endogenous physiology:

VERY STRONG.

Receptor biology:

STRONG.

Pancreatic function:

VERY STRONG.

Diagnostic pancreatic use:

STRONG.

Renal bicarbonate biology:

EMERGING.

Autism therapy:

NEGATIVE CONTROLLED EVIDENCE.

RISK

The major conceptual mistake is:

ASSUMING AN IMPORTANT PHYSIOLOGICAL HORMONE MUST BE A USEFUL THERAPY FOR ANY CONDITION INVOLVING THAT ORGAN SYSTEM.

Secretin's physiology is:

UNDENIABLE.

But therapeutic usefulness is:

APPLICATION SPECIFIC.

MONITORING

Monitor:

THE FUNCTIONAL RESPONSE.

If the question is pancreatic:

did bicarbonate or fluid secretion occur?

If the question is MRCP:

did pancreatic ductal anatomy become clearer?

If the question is gastrinoma:

did gastrin respond paradoxically?

Again:

MEASURE THE HYPOTHESIS.

PATIENT CONTEXT

A patient with:

PANCREAS DIVISUM

is not identical to:

someone with:

EXOCRINE PANCREATIC INSUFFICIENCY.

A patient with:

CYSTIC FIBROSIS

may receive the Secretin signal but have:

IMPAIRED DOWNSTREAM DUCTAL TRANSPORT.

A patient with:

ZOLLINGER-ELLISON SYNDROME

uses Secretin diagnostically in an entirely different way.

And a child with:

AUTISM

should not receive Secretin simply because early anecdotal reports once generated enthusiasm.

Same peptide.

Different:

BIOLOGICAL QUESTION.

SEVEN QUESTIONS TO ASK BEFORE SECRETIN

1. WHAT SYSTEM ARE WE ACTUALLY TRYING TO EVALUATE OR CHANGE?

pancreatic?
biliary?
gastric?
acid-base?
renal?
neuroendocrine?

2. WHAT IS THE PRIMARY PHYSIOLOGICAL FAILURE?

inadequate bicarbonate?
duct obstruction?
acinar insufficiency?
excess acid?
gastrinoma?
abnormal pancreatic anatomy?

3. IS THE PROBLEM THE SECRETIN SIGNAL - OR THE TISSUE'S ABILITY TO RESPOND?

This is one of the most important questions.

4. IS SECRETIN BEING USED THERAPEUTICALLY OR DIAGNOSTICALLY?

Those are entirely different applications.

5. WHAT TYPE OF EVIDENCE SUPPORTS THE USE?

established physiology?
function testing?
imaging?
tumor-provocation test?
speculative CNS pathway?

6. WHAT WILL WE MONITOR?

bicarbonate?
pancreatic duct response?
gastrin?
nutritional function?
organ-specific outcome?

7. WHAT WOULD DEFINE SUCCESS?

Not:

"SECRETIN WAS GIVEN."

But:

THE EXPECTED PHYSIOLOGICAL RESPONSE OCCURRED, CLARIFIED THE DIAGNOSIS, OR CORRECTED A SPECIFIC SECRETIN-RESPONSIVE FUNCTION IN A MEASURABLE WAY.

KEY TAKEAWAYS

Secretin is a 27-amino-acid gastrointestinal peptide hormone.

It is released primarily from duodenal S cells when acidic gastric contents enter the proximal small intestine.

Its defining physiological role is stimulation of bicarbonate-rich pancreatic fluid.

Secretin acts through the Secretin receptor - SCTR.

SCTR is a class-B G-protein-coupled receptor within the Secretin/VIP/glucagon receptor family.

The classical pathway involves Gs, adenylyl cyclase, and cAMP.

Secretin is especially important for pancreatic duct cells rather than simply pancreatic enzyme-producing acinar cells.

That distinction matters because pancreatic digestion requires both enzymes and bicarbonate-rich fluid.

Secretin provides the bicarbonate side of that partnership.

CCK more strongly provides the enzyme-secretion side.

Together, Secretin and CCK demonstrate how peptide systems cooperate rather than functioning in isolation.

Secretin stimulates bicarbonate secretion from the pancreas, biliary system, and Brunner glands.

These responses help neutralize gastric acid entering the duodenum.

Secretin also participates in negative feedback on gastric acid delivery and gastric motility.

This means the body solves duodenal acidity by both adding base and limiting additional acid exposure.

Secretin is clinically important as a diagnostic peptide.

It can be used to stimulate pancreatic exocrine secretion and assess pancreatic function.

Secretin-enhanced MRCP uses the normal pancreatic secretory response to improve visualization of pancreatic ducts.

This allows anatomy and physiology to be evaluated together.

Secretin-enhanced MRCP can be useful in selected cases of pancreas divisum, chronic pancreatitis, duct stenosis, anatomical variants, and complex postoperative anatomy.

Secretin also has a diagnostic role in gastrinoma physiology because gastrinoma cells can produce a paradoxical gastrin increase following Secretin stimulation.

Secretin's biology may extend into renal bicarbonate handling.

Experimental research suggests renal SCTR signaling can increase urinary bicarbonate excretion through β -intercalated-cell pathways involving pendrin and CFTR.

That has expanded the concept of Secretin toward whole-body bicarbonate homeostasis.

Secretin and its receptor also exist in the central nervous system.

But receptor presence and neurobiological plausibility do not prove a therapeutic application.

The Secretin-autism story provides a particularly important evidence lesson.

Early anecdotes created substantial enthusiasm.

Then randomized controlled trials repeatedly failed to demonstrate meaningful benefit over placebo.

That does not mean the original observations should never have been investigated.

It means the hypothesis was tested and did not reproduce convincingly.

This is exactly why mechanism, anecdote, and controlled therapeutic evidence must remain separate evidence classes.

- The best question is not “what does Secretin do?”

The better question is “what acid-base or pancreatic function is being challenged, is the Secretin signal deficient or is the responding tissue unable to execute the signal, and can Secretin administration reveal or improve a specific measurable physiological function?”

THE BOTTOM LINE

Secretin may be one of the most historically important peptides in medicine because it helped teach us that:

ORGANS TALK TO EACH OTHER CHEMICALLY.

The stomach produces:

ACID.

That acid enters:

THE DUODENUM.

The duodenum recognizes:

THIS ENVIRONMENT IS NOW TOO ACIDIC.

And instead of fixing the problem locally:

it sends:

A SIGNAL THROUGH THE BLOOD.

That signal is:

SECRETIN.

The pancreas receives the message:

SEND BICARBONATE.

The biliary system contributes:

MORE ALKALINE FLUID.

The duodenum increases:

PROTECTIVE SECRETIONS.

The stomach receives feedback:

SLOW DOWN THE ACID LOAD.

And the entire digestive system changes state.

That is:

ENDOCRINE COORDINATION.

But Secretin teaches an even deeper lesson.

A peptide can be medically valuable without being:

A DAILY TREATMENT.

Sometimes its greatest value is:

TO ASK THE BODY A QUESTION.

Give Secretin.

Then ask:

CAN THE PANCREAS RESPOND?

Use Secretin-enhanced MRCP.

Then ask:

WHAT DOES THE PANCREATIC DUCT ACTUALLY DO UNDER STIMULATION?

Give Secretin during a gastrinoma evaluation.

Then ask:

DOES THIS TISSUE BEHAVE ABNORMALLY WHEN CHALLENGED?

That is a completely different way to think about peptide medicine.

Not simply:

PEPTIDE → THERAPY.

But:

PEPTIDE → PHYSIOLOGICAL PROBE → INFORMATION.

And then there is the autism story.

An anecdote created a hypothesis.

The hypothesis was plausible enough to test.

Researchers tested it.

Repeated randomized trials failed to show meaningful efficacy.

That is not:

SCIENCE FAILING.

That is:

SCIENCE DOING ITS JOB.

So the Praxis question becomes:

“WHAT physiology is Secretin actually controlling, is the failure occurring at the level of peptide release, receptor signaling, pancreatic duct transport, organ structure, or somewhere else entirely, and would administering Secretin change the system - or simply reveal where the system can no longer respond?”

That is the difference between:

CALLING SECRETIN A PANCREATIC HORMONE

and:

UNDERSTANDING FUNCTIONAL ENDOCRINE PHYSIOLOGY.

FINAL RECALL

SENSE Duodenal acid triggers the signal	NEUTRALIZE Pancreas, bile, and glands deliver bicarbonate-rich fluid	TEST Use the response to reveal function when appropriate
---	--	---

STOP MEMORIZING PEPTIDES. START UNDERSTANDING THE SYSTEM.

Praxis Peptide Institute provides educational information and is not a substitute for individualized medical diagnosis or treatment. Secretin is an endogenous 27-amino-acid gastrointestinal hormone with established roles in pancreatic ductal bicarbonate secretion, duodenal acid neutralization, biliary and intestinal secretion, gastric regulation, and pancreatic diagnostic physiology. Exogenous Secretin is also used in selected pancreatic function and imaging applications, including Secretin-enhanced MRCP, and has historical use in gastrinoma testing. Its relevance depends on whether the biological problem involves Secretin release, receptor signaling, downstream ductal transport, pancreatic structure, acid load, biliary physiology, or another mechanism. Central and renal Secretin biology remains an important research area, while controlled trials do not support Secretin as an effective autism therapy.