SECRETIN

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Primary Disciplinary Field(s): Physiology, Endocrinology, Gastroenterology

1. Core Definition

Secretin is a vital gastrointestinal peptide **hormone** recognized primarily for its regulatory role in digestion, specifically its influence on pancreatic and biliary secretion. Classified within the secretin-glucagon family of peptides, it is synthesized and released by specific enteroendocrine cells--the **S cells**--which are strategically located within the mucosal lining of the upper small intestine, predominantly the **duodenum** and proximal **jejunum**. Its primary function centers on neutralizing the highly acidic gastric chyme that is propelled into the intestine from the stomach during the digestive process.

The release of Secretin is tightly controlled by the pH environment of the duodenal lumen. When the highly acidic chyme (partially digested food containing proteins) enters the duodenum, the low pH acts as a potent stimulus for the S cells. Upon detection of this acidity (typically pH 4.5 or lower), Secretin is rapidly secreted into the bloodstream, establishing it as a classic example of hormonal, rather than purely neural, regulation of physiological functions. This regulatory mechanism ensures that the intestinal environment remains optimal for the action of digestive enzymes which require a near-neutral pH for activity.

The principal target organ of Secretin is the **pancreas**. Secretin acts upon the pancreatic ductal cells, stimulating the release of a large volume of fluid characterized by a high concentration of **bicarbonate ions** (HCO??) and a low concentration of digestive enzymes. This bicarbonate-rich fluid serves as a powerful buffer, quickly raising the pH of the chyme in the small intestine, thereby protecting the delicate duodenal mucosa from acid corrosion and establishing the necessary alkaline environment for enzymatic digestion and absorption of nutrients.

2. Etymology and Historical Development

The study of Secretin holds a foundational place in the history of endocrinology and modern physiology. The term itself is derived from the physiological function it performs: stimulating secretion. However, its true significance lies in its identification in 1902 by the British physiologists **William Maddock Bayliss** and **Ernest Starling**, marking the first time a chemical messenger carried via the bloodstream--a hormone--was definitively demonstrated to regulate an internal bodily function.

Prior to their discovery, physiological regulation was largely attributed to the nervous system. Bayliss and Starling investigated the mechanism controlling pancreatic secretion. They observed that when acidic fluid was introduced into the duodenum, the pancreas secreted digestive juices,

even if all neural connections between the duodenum and the pancreas were severed. They hypothesized that the stimulus must be carried by the blood. They isolated an extract from the duodenal mucosa and demonstrated that injecting this extract intravenously immediately caused pancreatic secretion.

Starling coined the term **"hormone"** in 1905 to describe these new chemical messengers, derived from the Greek word *hormao*, meaning "I excite" or "I set in motion." The identification of Secretin revolutionized biological understanding, shifting the paradigm from purely neural control to recognizing the dual regulatory systems of the nervous and endocrine systems. This seminal discovery established the field of endocrinology and paved the way for the identification of dozens of other crucial hormones regulating metabolism, growth, and reproduction.

Subsequent research refined the understanding of Secretin's molecular nature. The hormone was first purified in 1961, and its complete amino acid sequence was successfully determined in 1971 by Jorpes and Mutt. This work confirmed Secretin as a straight-chain peptide consisting of 27 amino acids, structurally related to other important regulatory peptides like glucagon, vasoactive intestinal peptide (VIP), and gastric inhibitory polypeptide (GIP).

3. Molecular Structure and Synthesis

Secretin is synthesized as a precursor molecule, preprosecretin, which undergoes extensive post-translational processing to yield the mature, biologically active peptide. The gene encoding Secretin is located on the human chromosome 11. The synthesis begins in the S cells (a type of enteroendocrine cell) primarily found in the duodenum and jejunum, where preprosecretin is cleaved to prosecretin, and finally into the 27-amino-acid peptide.

The mature Secretin molecule has a molecular weight of approximately 3,055 daltons. Its structure exhibits significant homology with glucagon, particularly the N-terminal region. For instance, 14 of the first 27 amino acids are identical between Secretin and glucagon. This structural similarity underlies the common evolutionary origin of these peptides and explains why high concentrations of Secretin can sometimes exhibit mild glucagon-like effects, although their primary physiological targets and functions are distinct.

Crucially, the N-terminal end of the Secretin molecule (specifically the His-Ser-Asp-Gly sequence) is essential for its biological activity, particularly binding to the Secretin receptor. The hormone circulates unbound in the plasma, possessing a relatively short half-life of roughly 2 to 8 minutes, ensuring that its regulatory effects are transient and strictly dependent on the continued presence of acidic chyme in the small intestine.

4. Mechanism of Action and Physiological Role

Secretin exerts its regulatory effects by binding to specific, high-affinity **Secretin Receptors** (SR) located on the target cells. These receptors are members of the G protein-coupled receptor (GPCR) family, specifically the Class B (or B1) family, which also includes receptors for VIP and glucagon. The primary functional targets are the ductal cells of the exocrine pancreas and, to a lesser extent, the cholangiocytes (bile duct cells) of the liver.

Upon Secretin binding, the receptor activates adenylate cyclase via a stimulatory G-protein (Gαs). This activation results in a rapid increase in the intracellular concentration of **cyclic adenosine monophosphate (cAMP)**, which acts as the second messenger. Elevated cAMP then activates protein kinase A (PKA). PKA phosphorylation triggers a cascade of events leading to the insertion and activation of ion transporters in the apical membrane of the ductal cells.

The most significant physiological role is the secretion of **bicarbonate**. Secretin drives the movement of bicarbonate ions, synthesized within the ductal cells, into the pancreatic juice. This mechanism relies on the activity of the cystic fibrosis transmembrane conductance regulator (CFTR) channel, which facilitates chloride efflux, and the Cl?/HCO?? exchanger. The resultant fluid is isotonic and highly alkaline, achieving pH levels of 8.0 or higher, which is critical for two reasons: 1) protecting the duodenal mucosa from acid erosion, and 2) optimizing the environment for pancreatic digestive enzymes (like trypsin and lipase), which are rendered inactive at the low pH arriving from the stomach.

Beyond the pancreas, Secretin also stimulates bile flow (choleretic effect) by promoting bicarbonate secretion by the liver cholangiocytes, contributing further to intestinal neutralization. Furthermore, Secretin is known to inhibit gastric acid secretion and reduce gastric emptying, providing a coordinated delay that allows the small intestine adequate time to neutralize and process the incoming chyme load.

5. Regulation of Secretin Release

The secretion of Secretin is governed by a highly sensitive feedback loop, making it one of the most precisely regulated digestive hormones. The primary stimulus, as established by Bayliss and Starling, is the presence of **acidic chyme** in the duodenum.

Stimulation: The key trigger is luminal pH. S cells are activated when the pH drops below 4.5, with maximum Secretin release occurring at pH 3.0 or lower. The acid detection mechanism is highly specialized, although the exact sensor remains a subject of ongoing research, involving potential activation of proton-sensing G-protein coupled receptors. The presence of fatty acids and partially digested proteins also potentiates (enhances) the response to acid, although acid remains the essential direct trigger.

Inhibition: Once Secretin has stimulated the pancreas to release sufficient bicarbonate, the pH of the duodenal lumen quickly rises, typically above 4.5. This neutralization removes the primary stimulus, thereby halting further Secretin release. This negative feedback mechanism ensures that Secretin levels only rise when needed and return rapidly to basal levels once homeostasis is restored.
Neural Influence: While Secretin is defined as a hormone acting via blood transport, neural signals, particularly those mediated by the vagus nerve (e.g., acetylcholine), can potentiate the effects of Secretin on pancreatic bicarbonate secretion, illustrating the complex interplay between the endocrine and nervous systems in digestive regulation.

6. Clinical Significance

Secretin plays a crucial role in clinical diagnosis and is relevant in several pathological conditions related to the gastrointestinal tract and pancreas.

The **Secretin Stimulation Test** (or Secretin Test) is a gold standard diagnostic procedure used primarily to evaluate pancreatic exocrine function and to diagnose certain gastrointestinal tumors. The test involves intravenously administering synthetic Secretin and then measuring the pancreatic fluid output, specifically the volume and bicarbonate concentration, via a nasogastric tube placed near the duodenum. A reduced volume or depressed bicarbonate concentration suggests severe pancreatic disease, such as chronic pancreatitis or pancreatic cancer, where the ductal cells are compromised.

Conversely, Secretin is essential in the diagnosis of **Zollinger-Ellison Syndrome (ZES)**. ZES is characterized by the excessive production of the hormone gastrin, usually due to a gastrin-secreting tumor (gastrinoma). Normally, Secretin inhibits gastrin release. However, in patients with ZES, administering Secretin paradoxically causes a large increase in circulating gastrin levels. This anomalous response is highly specific to ZES and provides a powerful diagnostic marker for confirming the presence of a gastrinoma.

Furthermore, dysregulation of Secretin release or responsiveness may contribute to conditions like functional dyspepsia or irritable bowel syndrome (IBS), although the direct etiological link is complex. The balance between acid delivery and bicarbonate neutralization is paramount for overall digestive health, and Secretin is the key physiological regulator maintaining this critical equilibrium.

7. Key Characteristics

Classification: Member of the Secretin-Glucagon peptide family.
Origin: Enteroendocrine S cells located primarily in the duodenum and jejunum.
Primary Stimulus: Luminal acidity (pH < 4.5) of the chyme entering the small intestine.

Mechanism: Acts via G-protein coupled Secretin Receptors (SR) to increase intracellular cAMP.
Principal Action: Stimulates the pancreatic ductal cells and liver cholangiocytes to secrete a large volume of **bicarbonate-rich fluid**, neutralizing gastric acid.
Historical Importance: Recognized as the **first substance ever demonstrated to be a hormone**, defining the field of endocrinology.

8. Significance and Impact

Secretin's significance extends far beyond its specific role in acid neutralization. Its discovery fundamentally redefined the understanding of physiological control, demonstrating the existence of the endocrine system as a parallel regulatory pathway to the nervous system. The work of Bayliss and Starling provided the conceptual framework for all subsequent hormone research, including the identification of insulin, thyroid hormones, and sex hormones.

In the context of digestive physiology, Secretin is the essential protective mechanism for the upper small intestine. Without the robust, Secretin-mediated release of bicarbonate, the highly acidic gastric contents would cause severe chemical burns to the duodenal mucosa, leading to ulceration and impaired nutrient absorption. It ensures that the critical transition from gastric digestion (low pH, pepsin activity) to intestinal digestion (neutral/alkaline pH, pancreatic enzyme activity) occurs smoothly and efficiently.

Its structure and function also serve as a model for understanding peptide hormones. The structural homology between Secretin and glucagon highlights key principles of molecular evolution, where peptides sharing similar sequences often utilize similar signaling pathways (GPCR/cAMP) but evolve specific target tissues to regulate distinct physiological needs--metabolism versus digestion.

Further Reading

Secretin - Wikipedia
William Maddock Bayliss - Wikipedia
Ernest Starling - Wikipedia
Secretin: ScienceDirect Overview