Review Article

CONCEPTUALIZATION OF ENDOCRINE FUNCTION OF THE GASTROINTESTINAL TRACT

Abstract

The endocrine and gastrointestinal systems (GIT) are integrated into a well-coordinated complex to ensure the body's metabolic needs are met. The endocrine functions and possible dysfunctions are less emphasized in medical curriculum. Hormones are synthesized and released by different segments of the GIT to perform specific functions. The main sites of synthesis and secretion are the stomach and intestines. The hormones of the GIT are categorized as paracrine, neurocrine, and endocrine.

Endocrine hormones are gastrin, cholecystokinin (CCK), secretin, glucose-dependent insulinotropic peptide or gastrin inhibitory peptide (GIP), and motilin. Paracrine hormones are somatostatin and histamine, while the neurocrine hormones are vasoactive intestinal peptide (VIP), gastrin releasing peptide (GRP), and enkephalins. An additional three work together as endocrine and paracrine hormones (Glucagon-like peptide [GLP-1], pancreatic polypeptide, and peptide-YY). Gastrointestinal tracts hormones play crucial roles in providing satiety, maintaining hormonal secretion and inhibition, and breaking down proteins, fats, and carbohydrates into simple molecules for absorption. There are documented manifestations of hypersecretion or hyposecretion of these hormones. Likewise, there are known medical conditions that can subsequently lead to GIT hormones dysfunction.

Zollinger-Ellison Syndrome, Gastric Outlet Obstruction, Somastinoma ,celiac disease, Crohn's disease, ulcerative colitis, tropical sprue, infective diarrhea, intestinal resection, pancreatic insufficiency, gastric ulcers, and Inflammatory bowel disease(IBS) are few known documented medical conditions that lead to GIT hormonal dysfunctions. The aim of the article is to reiterate endocrine function and dysfunction of the GIT. The review article is part of integrative learning process for students.

1. INTRODUCTION

The Gastrointestinal tract is very essential for the maintenance of life and as human beings, we need to ingest appropriate nutrients for proper energy release, growth, and cell repair. The GI tract is a thought-provoking phenomenon that obscures truth-seekers/readers' understanding concerning the GI mechanism of action. This research will explore the entirety of the GI tract, the hormones involved in that specific system. It will further elucidate to the readers on the embryological development, to the function and diseases arising from it. Furthermore, the research will include the Pathophysiology of all the hormones and the causes, the epidemiology, clinical manifestation, the diagnosis, and the management of the GI Endocrine activity. These interactions will support and contribute towards managing certain gastrointestinal disorders.

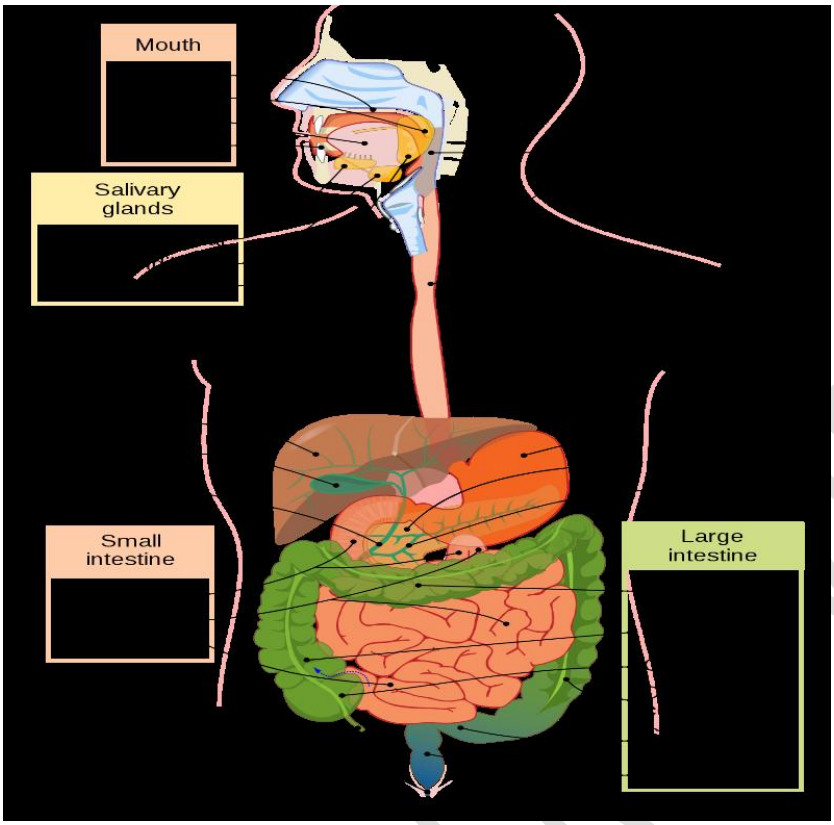

Fig 1: The Gastrointestinal Tract. [Source]

The gastrointestinal tract is also known as the GI tract, digestive tract, or the alimentary canal which can be used interchangeably is considered as the region/tract or the pathway of the digestive system that begins from the mouth to the anus. The GI tract consists of all the major organs within the digestive system, in humans as well as animals, the human GI tract consists of the esophagus, stomach, and intestines upper and lower GI tract. The tract may also be divided into foregut, midgut, and hindgut, reflecting the embryological origin of each segment. In addition, the complete human digestive system is made up of the gastrointestinal tract plus the accessory organs of digestion(the tongue, salivary glands, pancreas, liver, and gallbladder). The whole human GI tract is about nine meters (30 feet) long at autopsy. It is considerably shorter in the living body because the intestines, which are tubes of smooth muscle tissue, maintain constant muscle tone in which it relaxes in spots to allow for local distention. This process is related to the mechanism of how food is moved into the GI tract which is known as a process called peristalsis.

The large, hollow organs of your GI tract contain a layer of muscle that enables their walls to move. The movement pushes food and liquid through your GI tract and mixes the contents within each organ. The muscle behind the food contracts and squeezes the food forward, while the muscle in front of the food relaxes to allow the food to move. The duodenum serves a mixing function as it combines digestive secretions from the pancreas and liver with the contents expelled from the stomach. The start of the jejunum is marked by a sharp bend, the duodenojejunal flexure. It is in the jejunum where most of the digestion and absorption occur. The final portion, the ileum, is the longest segment and empties into the caecum at the ileocecal junction. The small intestine performs most of the digestion and absorption of nutrients. The functions of the large intestine include the accumulation of unabsorbed material to form feces. It also aids some digestion by bacteria and the bacteria are responsible for the formation of intestinal gas. Reabsorption of water, salts, sugar, and vitamins also occurs in the large intestine.

The GI hormones classify as endocrine, paracrine, and neurocrine based on the method by which the molecule gets delivered to its target cell(s). Endocrine hormones are secreted from enteroendocrine cells directly into the bloodstream, passing from the portal circulation to the systemic circulation, before being delivered to target cells with receptor-specificity for the hormone. The five GI hormones that qualify as endocrines are gastrin, cholecystokinin (CCK), secretin, glucose-dependent insulinotropic peptide (GIP), and motilin. Enteroendocrine cells also secrete paracrine hormones, but they diffuse through

the extracellular space to act locally on target tissues and do not enter the systemic circulation. Two examples of paracrine hormones are somatostatin and histamine. Additionally, some hormones may operate via a combination of endocrine and paracrine mechanisms. These “candidate” hormones are glucagon-like peptide-1 (GLP-1), pancreatic polypeptide, and peptide YY. Lastly, neurocrine hormones get secreted by postganglionic non-cholinergic neurons of the enteric nervous system. Three neurocrine hormones with significant physiologic functions in the gut are vasoactive intestinal peptide (VIP), gastrin release peptide (GRP), and enkephalins. [1]

ANATOMY & PHYSIOLOGY OF GI ENDOCRINE HORMONES

The main sites of hormone synthesis and secretion are in the stomach and intestines. There are no exocrine hormones produced by the mouth, pharynx, esophagus, rectum, and anus.

Stomach

primarily released in response to vagal and gastrin-releasing peptide (GRP) stimulation secondary to the ingestion of peptides, amino acids, gastric distention, and an elevated stomach pH. Conversely, gastrin release is

It is the most dilated part of the GI tract, having a capacity of 1000-1500ml in the adult. It is located at the L1-L2 vertebrae at the upper left side of the abdomen, inferior to the diaphragm. It functions to store masses of food, secretes hydrochloric acid, mucus, and digestive enzymes required to further break down and digest the food.[2]

Gastrin Releasing Peptide

It is produced by the G cells in the antrum and duodenum with its genetic location on chromosome 17. The stimuli for its release are protein (phenylalanine, tryptophan) and stomach distention (from eating). It functions to stimulate gastrin release in the stomach. [3]

Gastrin

Gastrin is a linear peptide that is synthesized as a preprohormone and is post-translationally cleaved to form a family of peptides with identical carboxyterminal. Gastrin receptors are found on parietal cells and enterochromaffin-like cells (ECL) also bear gastrin receptors as recent evidence indicates that this cell may be the most important target of gastrin concerning regulating acid secretion.

decreased in response to paracrine inhibition by somatostatin and decreased stomach pH.

The main functions of Gastrin are enhancing gastric mucosal growth, gastric motility, and

secretion of hydrochloric acid (HCl) into the stomach.

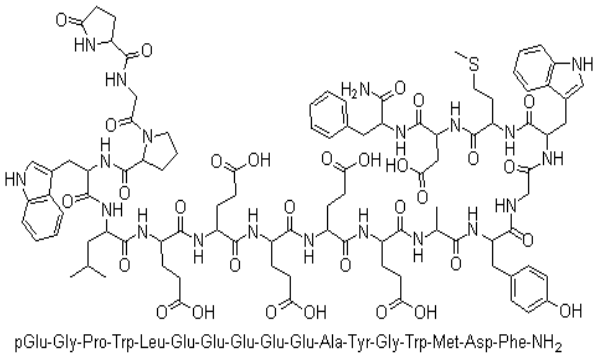

Fig 2: Molecular Arrangement of Gastrin [Source]

Urogastrone

It is secreted by the stomach. It reduces gastric acid secretion and increases oxyntic gland growth. Its stimulus is not yet known.[26]

Intestine

The intestine is composed of the small and large intestines. These are also divided into regions known as the duodenum, jejunum, ileum, cecum, and colons.

Cholecystokinin (CCK)

Cholecystokinin is a member of the gastrin/cholecystokinin family of peptide hormones and is very similar in structure to gastrin, sharing the same 5 C-terminal amino acids. This hormone is found on chromosome 3. It is produced by the I cell of the duodenum and jejunum. CCK plays important physiological roles both as a neuropeptide in the central nervous system and as a peptide hormone in the gut. I cells are concentrated in the proximal small intestine which secret CCK into the blood upon the ingestion of food. The physiological actions of CCK include stimulation of pancreatic secretion and gallbladder contraction, regulation of gastric emptying, and induction of satiety. [3][7]

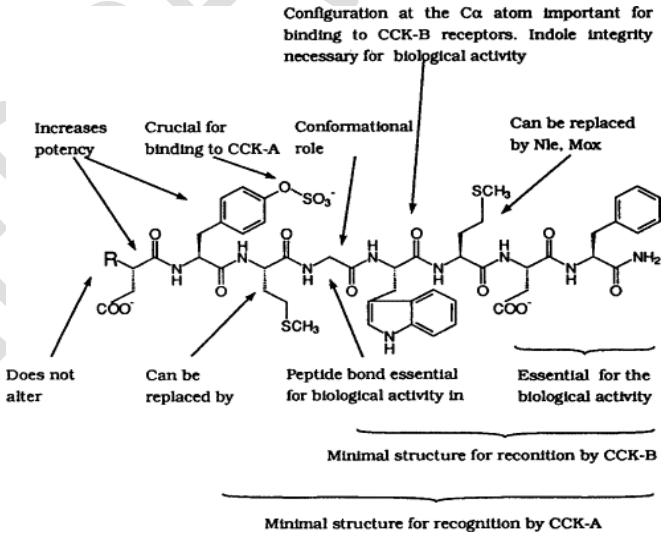

Fig 3: Molecular Composition of Cholecystokinin. [Source

Secretin

Secretin is initially synthesized as a 120 amino acid precursor protein known as prosecretin. This precursor contains an N-terminal signal peptide, spacer, secretin itself (residues 28–

54), and a 72-amino acid C-terminal peptide. It is produced by the S cells of the duodenum and in smaller numbers by the jejunum. It is mainly stimulated in response to the arrival of gastric contents that decrease the duodenal pH to a range between 2-4.5. Secretin increases bicarbonate and pancreatic fluid secretion to neutralize the acid. It may also function to increase hepatic bile secretion. [6]

Serotonin

Serotonin is a monoamine neurotransmitter. Peripheral serotonin is produced in all regions of the GIT by enterochromaffin (EC) cells which produce about 90% of the total body serotonin. It can function to inhibit gastric acid secretion and stimulate the production of gastric and colonic mucus.

Motilin

Motilin is a 22-amino-acid peptide synthesized in endocrine cells (Mo cells) of the duodenal and jejunal mucosae. Motilin is the hormone that is cyclically released during the fasted state and is released by the entero-endocrine cells (Mo cells) in the upper small intestine. Motilin stimulates gastric and small intestine motility, causing undigested food in these regions to move into the large intestine. They are the reason for "growling" sounds occur.

Neurotensin

Neurotensin is synthesized and released by the N cells of the jejunum and ileum. It is stimulated by the presence of fats and gastrin-releasing peptides. Its main function is to stimulate pancreatic and biliary secretions while also suppressing the motility of the small intestine.

Bombesin

Bombesin is homologous to the gastrin-releasing peptide (G cells). It is mediated by gastrin in the antrum and regulates the release of GI hormones. [3]

Peptide-YY

This hormone is produced in the L cells in the distal portion of the small intestine on chromosome 17. It exists as a 36-chain amino acid. It is stimulated by the presence of fats and protein. It inhibits acid and pepsin secretion from the stomach and the exocrine function of the pancreas. [3]

Gastrin Inhibiting Hormone

It is produced by the K cells of the duodenum and the upper jejunum. It is located on chromosome 17. Its stimuli include glucose, amino acids, and fatty acids. It inhibits gastric acid secretion and stimulates insulin secretion. [3]

Glucagon-like peptide

It is secreted by the L cells in the small intestine, colon, and partly by the rectum. Its

stimuli include glucose and fats. It inhibits gastric motility and encourages insulin release.

Vasoactive Intestinal peptide

This is commonly produced by the enteric nerves. This hormone is located on chromosome 6. The pattern of stimulation for this hormone is not yet known. It functions to relax the lower esophageal sphincter and fundus of the stomach. It also stimulates biliary and pancreatic secretions.

Bulbogastrone

It is a candidate hormone secreted in the duodenum. It reduces gastric acid secretion and is stimulated by gastrin. [26]

PATHOPHYSIOLOGY

Gastrin

Hypersecretion of Gastrin:

1. **Zollinger-Ellison Syndrome:**

Hypersecretion of gastrin usually occurs in a disorder known as Zollinger-Ellison Syndrome (AKA gastrinoma). It is a rare syndrome that also is associated with peptic ulcers caused by a gastrin-secreting neuroendocrine tumor or multiple tumors (gastrinoma) of the pancreas or duodenum. Increased secretion of gastrin causes excess secretion of gastric acid, resulting in gastric and duodenal ulcers, gastroesophageal reflux with abdominal pain, and diarrhea.

The annual incidence of gastrinoma is 0.5-2 per million population. Most patients are diagnosed between the ages of 20 and 50, with a higher incidence in males as compared with females. Approximately 80% of gastrinomas are sporadic, but 20-30% occur in association with Multiple Endocrine Neoplasia type 1 (MEN1). Approximately 50 to 88 percent of patients with sporadic ZES, and 70 to 100 percent of patients with ZES associated with MEN1, have duodenal gastrinomas. Duodenal gastrinomas are predominantly found in the first part of the duodenum. As compared with pancreatic gastrinomas, duodenal gastrinomas are usually small (<1 cm), are often multiple, and are less likely to have metastasized to the liver at diagnosis (0 to 10 versus 22 to 35 percent). In 5 to 15 percent of patients, gastrinomas arise in non-pancreatic, non-duodenal abdominal (stomach, peripancreatic lymph nodes, liver, bile duct, ovary), and extra-abdominal (heart, small cell lung cancer) locations. [11]

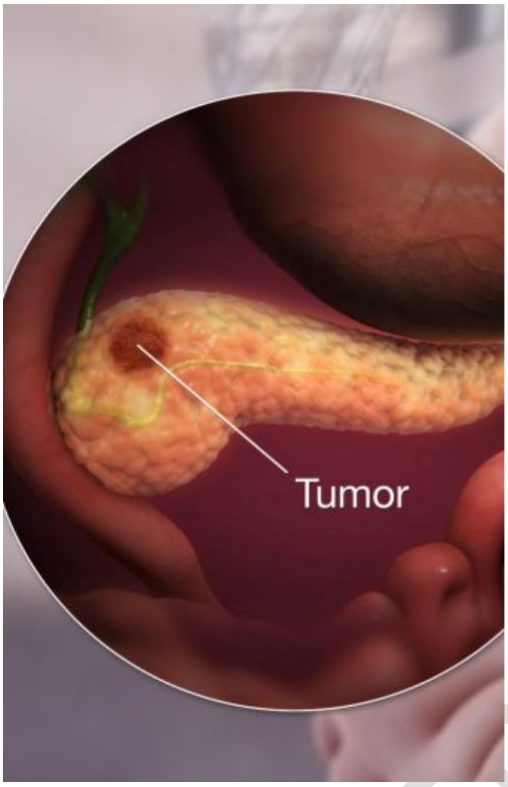

Fig 4: Zollinger-Ellison Syndrome [Source]

Typical clinical manifestations include:

- Ulcers that are refractory to standard therapy
- Multiple ulcers
- Giant ulcers, larger than 2 cm
- Recurrent ulcers
- Ulcers with unexplained diarrhea
- Strong family history of ulcers
- Hypercalcemia
- A duodenal ulcer that is not related to *Helicobacter pylori* infection or nonsteroidal anti-inflammatory drug use

i. **Helicobacter pylori infection:**

H. pylori is a type of bacteria that can colonize the stomach and cause ulcers. Some people with an H. Pylori infection may also have high stomach acid.

2. **Gastric outlet obstruction:**

When the path leading from the stomach to the small intestine is blocked, it can result in increased stomach acid.

Investigative procedures include:

- Blood tests such as Fasting gastrin test and secretin stimulation test in ZES. Also, test for bacteria and neutrophilia.
- Imaging tests (i.e., scintigraphy, MRI, and CT scan) to locate and determine the size of gastrinoma
- Endoscopy to check for ulcers

Management of hypersecretion:

- Injecting drugs into the tumor to relieve cancer symptoms.
- Using chemotherapy to try to slow tumor growth.
- In H.pylori Infection, treat with the triple-therapy regimen that comprises a proton pump inhibitor and 2 antibacterials
- Sometimes surgery may be recommended, such as removal of gastrinomas in people with Zollinger-Ellison syndrome.[8]

Hyposecretion of Gastrin:

Low gastrin levels are rare but when they do occur, the condition can increase the risk of infection in the digestive system and limits the stomach's ability to absorb nutrients.

Somatostatin

Hypersecretion of Somatostatin (Somastatinoma):

Somatostatinomas often simultaneously produce other hormone products, including insulin, gastrin, VIP,

glucagon, corticotropin (previously adrenocorticotropic hormone [ACTH]), calcitonin, pancreatic polypeptide, etc. Duodenal somatostatinomas may be associated with neurofibromatosis, which is an autosomal dominant disorder characterized by abnormalities of growth and differentiation of the nervous system. Somatostatinomas occur with an annual incidence of 1 case per 40 million population. Somatostatinomas occur sporadically in 93% of cases, and 7% of cases are seen in conjunction with multiple endocrine neoplasia type 1 (MEN 1) syndromes. MEN 1 involves parathyroid, pancreatic, and pituitary neoplasms. Neurofibromatosis and pheochromo cytoma are associated with the duodenal form of somatostatinomas. Risk factors can also include Von Hippel-Lindau disease and tuberous sclerosis.

Somatostatinoma may present as:

- pain in the abdomen (most common symptom)
- Diabetes
- unexplained weight loss
- Gallstones
- Steatorrhea, or fatty stools
- Bowel blockage
- Diarrhea
- Jaundice, or yellowing skin.

Investigative measures include:

- Endoscopic ultrasound
- CT Scan
- Octreoscan (which is a radioactive scan)
- MRI scan

Management of somatostatinoma involve surgical procedures and antineoplastic agents

Cholecystokinin

Hypersecretion of CCK:

High levels of CCK can increase the effectiveness of how fast gastric emptying occurs, and it does this by increasing the excitatory effect it has on both the small and large intestine, which leads to movement in the bowels or by improving the tension of the pyloric sphincter. Cholecystokinin has been associated with increased anxiety and panic attacks.[12]

In a primary-care study from the UK, the overall age- and sex-adjusted incidence rate of BN decreased during the second half of the 1990s from 12.2 per 100,000 person-years in 1993 to 6.6 per 100,000 person-years in 2000. However, the incidence rate of BN in women aged 10–19 years remained relatively stable around 40 per 100,000 person-years in 1993 as well as in 2000. Several studies suggest that the age at onset of BN is decreasing. In a sample of 793 Italian BN patients referred to an eating disorders outpatient unit between 1985 and 2008, subjects born in 1970–1972 had a mean age at onset of 18.5 years, compared to 17.1 years in subjects born between 1979–1981. It is unclear whether this reflects a true earlier age at onset or rather earlier detection of BN cases.

CCK is a well-established trophic factor in pancreatic growth. It is therefore believed that CCK may affect the proliferation of pancreatic tumors. Recent studies have shown that CCK enhances induction of pancreatic carcinogenesis and has growth-promoting actions on GI cancers, especially pancreatic carcinomas

Hyposecretion of CCK:

Low levels of cholecystokinin may contribute to reduced feelings of fullness and difficulty in losing weight in very obese people.

Obesity blunts the effect of CCK, which means vagal afferent neurons are insensitive to CCK. This reduced expression of CCK accounts for a reduced effect on satiety and the fact that most obese people always complain about feeling hungry. Consumption of high-fat diets with diminished expression of the CCK-1 receptor increases the levels of ghrelin in plasma. This increases food intake, and it does this by suppressing the expression of satiety peptide cocaine and amphetamine-regulated transcript (CART) in vagal afferent neurons. CCK is also involved in metabolic regulation and lipid absorption. They link the inactivation of the CCK signaling pathway to reduced weight gain. Inactivation increases energy expenditure and lowers energy extraction. Complications from bulimia can include:

- kidney failure
- heart problems
- gum disease
- tooth decay
- digestive issues or constipation
- ulcers and stomach damage
- dehydration
- nutrient deficiencies
- electrolyte or chemical imbalances

Secretin

Hypersecretion of Secretin:

Pancreatic secretion is governed by neural and hormonal mechanisms. The hormones responsible for regulation are secretin and cholecystokinin (CCK). Secretin is secreted in response to acid in the duodenum, causing duct cells to release water and bicarbonate; CCK is secreted in response to protein and fat in the small intestine, stimulating acinar cells to release the pancreatic enzymes. The adverse effects of excessive secretin are mainly nausea, flushing, abdominal pain, and vomiting and can be seen in up to 5% of patients. Acute pancreatitis is listed as a contraindication to secretin administration. [10]

A common cause of hypersecretion is Exocrine Pancreatic Insufficiency (EPI). EPI has multiple possible causes and is not usually recorded as a medical statistic; its prevalence and demographics cannot be established with certainty at present. In a German-based study, one of the most common causes of EPI had an age-adjusted prevalence of 8 per 100,000 for

males and 2 per 100,000 for women; these numbers are probably relatively close to the prevalence of EPI in most developed countries. No other reliable data are currently available.

Clinical manifestations include steatorrhea, weight loss, flatulence, and abdominal pain.

Hyposecretion of Secretin:

Hyposecretinemia, or a blood secretin level below normal, has been found in patients with untreated adult celiac disease or achlorhydria. Secretin concentrations in patients with celiac disease fail to increase after exogenous duodenal acidification or after a mixed meal. In contrast, patients with achlorhydria present reduced secretin levels after a mixed meal, although the response to duodenal acidification remains normal.

Gastric Inhibiting Hormone

Hypersecretion of GIH:

Although hyper- or hyposecretion of GIP is not causally related to the pathogenesis of diseases, the secretion of GIP is altered in the following disease states:

Type 2 Diabetes Mellites:

An abnormal incretin effect occurs in pathological glucose intolerance. Patients with type-2 diabetes mellitus either have lower levels of GIP or beta-cell resistance to GIP as compared to healthy individuals that demonstrate a dose-dependent incretin response to oral glucose. Since incretins contribute to approximately 70% of the insulin response post meals, the reduced incretin effect is responsible for the glucose intolerance seen in diabetics. [9]

I. Obesity:

GIP plays a vital role in lipid metabolism and the development of obesity. Hyperplasia of K-cells and increased GIP levels are observed in obesity as fat is a potent stimulus of GIP secretion. As mentioned above, GIP is an anabolic hormone that inhibits lipolysis and stimulates lipogenesis. [9]

II. Food-Induced Cushing Syndrome:

GIP, like ACTH, can cause hypersecretion of cortisol after mixed meals leading to food-induced Cushing syndrome or ACTH-independent macronodular adrenal hyperplasia (AIMAH). GIP-R are present in the zona fasciculate of the adrenal cortex. Following a meal, GIP concentration increases in the blood which causes an increase in cortisol even in the presence of low ACTH. Treatment of AIMAH involves the use of somatostatin analogs such as octreotide. [9]

ASSOCIATED DISEASES

CELIAC'S DISEASE

Patients with untreated coeliac disease have a relative failure of release of both GIP and secretin, two hormones -localized to the area of maximal mucosal damage in coeliac disease [14]. A failure of cholecystokinin release has also been reported which

would fit with the observed diminished pancreatic endocrine and exocrine response to intraduodenal stimuli. [25]

In their studies, the release of gastrin and pancreatic polypeptide, whose tissues of origin are unaffected, was entirely normal. Plasma motilin levels were slightly increased above normal, following a tendency for this peptide to be raised in steatorrhea conditions. Plasma enterglucagon levels, in contrast, were greatly raised.

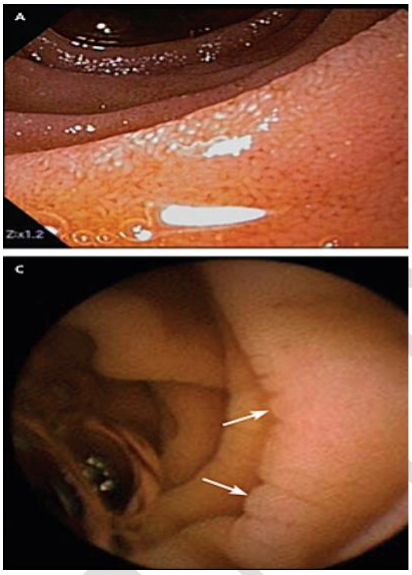

Fig 5: Gross & Histological appearance of Celiac Disease. [Source]

TROPICAL SPRUE (MALABSORPTION)

Eight patients with severe tropical sprue were studied. There was a significant diminution of both GIP and insulin release associated with a delayed and impaired rise in blood glucose. In contrast, however, plasma motilin levels were greatly raised. Basal plasma enteroglucagon concentrations were also much higher than in normal, with only a small further rise after the test breakfast. This pattern differs from that seen in coeliac disease, possibly reflecting the different pathophysiological processes and the greater area of gut involved in tropical malabsorption. Gastrin, neurotensin, and pancreatic polypeptide responses were all similar to normal. [15]

CROHN'S DISEASE

In an experiment studying fourteen patients with Crohn's disease, it was noticed that after the test breakfast, the release of the upper small intestinal hormone GIP was increased, in contrast to the poor rise found in coeliac disease and acute tropical sprue. Motilin, however, showed the greatest response, though there was also an augmented pancreatic polypeptide response. Fasting plasma enteroglucagon levels in these patients and the postprandial response were greater than normal, but lower order of magnitude than in coeliac disease. [14]

ULCERATIVE COLITIS

In 24 patients with ulcerative colitis, the response of GIP after the test breakfast was entirely normal. Basal plasma motilin levels were significantly raised. An augmented gastrin response might be secondary to hypochlorhydria (acid studies were not performed) or possibly due to loss of some colonic gastric inhibitory substance secondary to the pathological damage. Both enteroglucagon andpancreatic polypeptide, as in Crohn's disease, showed a moderately raised response. [14]

Fig 6: Side-by-side comparison of Crohn's Disease and Ulcerative Colitis [Source]

INFECTIVE DIARRHEA

The responses of pancreatic polypeptide and GIP were normal. In contrast, augmented responses of gastrin, motilin, and enteroglucagon were found. These may relate to compensatory mechanisms occurring in the gut to diarrhea. As diarrhea abated basal motilin levels fell in parallel. [15]

PANCREATIC INSUFFICIENCY

In these patients, the GIP response was entirely normal in contrast to the diminished release in coeliac disease and acute tropical sprue, in both of which the malabsorption is secondary to mucosal damage. The gastrin response was diminished but both the motilin and enteroglucagon responses were increased. However, the increased enteroglucagon release was much less than that found in association with the atrophic small intestinal mucosa. This could suggest that the grossly raised levels in coeliac disease and acute tropical sprue are not merely secondary to the steatorrhea (fat is a potent stimulant of enteroglucagon release) as this is much greater in the patients with pancreatic insufficiency.

The most striking finding in patients with pancreatic insufficiency was the gross failure of pancreatic polypeptide release following the test breakfast [15]. This probably reflects the extensive damage to pancreatic tissue as the pancreatic polypeptide cells are scattered throughout the pancreatic parenchyma.

INTESTINAL RESECTION

The subsequent effects of surgical removal of a length of intestine depend on the site and the length of gut resected. The loss of absorptive area may give rise to severe malabsorption, even when only a short length of distal ileum has been resected (for example failure of vitamin B12 and bile salt absorption). After small intestinal resection, there is villous hypertrophy of the mucosa of the remainder [21]. This compensatory mechanism is probably stimulated by a humoral agent, enteroglucagon being a possibility. We have studied patients who have undergone varying degrees of gut resection for several different pathological states [14]. The commonest indication for surgery was Crohn's disease when most patients had between one and two meters of terminal ileum resected. Partial resection of the ascending or transverse colon or both was carried out for Crohn's disease or ulcerative colitis. Neoplasia, trauma, and post-radiation fibrosis were fewer common reasons.

There was no significant difference between the effects of partial ileal and partial colonic resection in the responses of gastrin, pancreatic polypeptide, GIP, and neurotensin. The post-breakfast release of both gastrin and pancreatic polypeptide was greater than normal in both groups of patients. Raised gastrin levels after intestinal resection have been reported by others [23] and this may be relevant to the

gastric acid hypersecretion which occurs in these patients [22] The GIP and neurotensin responses, in contrast, were similar to normal. There was, however, a striking difference in the responses of motilin and enteroglucagon between the two groups of patients. The patients with partial resection of the colon had only mildly raised motilin responses and even a somewhat decreased enteroglucagon release. Those with partial resection of the ileum had a greatly augmented motilin response and a substantially increased release of enteroglucagon.

IRRITABLE BOWEL SYNDROME

This common diagnosis is made by exclusion of demonstrable organic disease and is usually regarded as a 'functional' disorder. Abnormalities of intestinal motility have been described [24] and abnormal gut hormone release has been postulated as an etiological factor [13].

A total of 42 patients with IBS were studied. Nineteen had abdominal pain and frequency of bowel action, 11 had pain and constipation, and 12 had pain but normal bowel function. All had been thoroughly investigated and no organic disease was found. In contrast to all other disease groups studied, these patients had entirely normal responses of all the gut hormones measured.

GASTRIC (PEPTIC) ULCERS

Enhanced HCl secretion resulting from increased parietal cell stimulation (gastrin in gastremia), decreased PGE2 secretion resulting in a. Increased HCl secretion b. Decreased mucus production (example as induced by aspirin) resulting in epithelial-cell damage by HCl; enhanced vagal (cholinergic stimulation; enhanced histamine secretion).

GASTRIC-RELATED PEPTIDE (GRP)

This is a homolog of bombesin (BBS). Peptides of the BBS have a wide spectrum of biological effects on the GIT, pancreas, and CNS. In addition to their actions as neurotransmitters in CNS, these peptides stimulate the contraction of smooth muscle in the GIT and the release of various GI hormones- gastrin, somatostatin, CCK, pancreatic polypeptide, insulin, enteroglucagon, pancreatic glucagon, and GIP as well as the exocrine secretion in the pancreas.

On cancers, in recent years several studies have shown that BBS may serve as a growth factor in colon cancer cells. GRP receptor mRNAs are present in gastric cancer cell lines.

Hence, in general, the effect of these peptides in GI cancer is stimulatory, but they also inhibit the growth of some specific cell types.

CONCLUSION

From our literature review, it is evident that there is a broad range of causes of GI hormone imbalances, that can occur when the endocrine glands fail to function properly. However, these

hormones can also be seen to naturally fluctuate throughout life as we age or enter new phases, like obesity.

Understanding the GIT response to foods and meals is critical to understanding the metabolic effects of functional foods. Each hormone has specific effects on digestive functions. Changes in plasma hormone concentrations after a meal related to changes in digestive function encourage a natural correlation. It is necessary to relate changes in endogenous hormone concentrations to digestive function. It would be valuable to assess digestive function in groups with altered circulating concentrations of gastrointestinal hormones. The elevated plasma concentrations of these hormones in patients with gastrointestinal cause poor digestive function, which results in poor nutritional status. Gastrointestinal endocrinology is beginning to reveal the complexity of hormonal involvement indigestion. [27]

Abbreviations

AIMAH - ACTH-Independent Macronodular Adrenal Hyperplasia
BBS – Bombesin
CCK – Cholecystokinin
EPI - Exocrine Pancreatic Insufficiency
GIP – Gastrin-Inhibiting Peptide
GIT – Gastrointestinal Tract
GRP – Gastrin-Releasing Peptide
HCl – Hydrochloric Acid
PPIs – Proton Pump Inhibitors

References

1. Parikh A, Thevenin C. Physiology, Gastrointestinal Hormonal Control. 2021 May 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.
2. Daniels I.R., Allum W.H. (2005) The Anatomy and Physiology of the Stomach. In: Upper Gastrointestinal Surgery. Springer Specialist Surgery Series. Springer, London. [Article]
3. Wittert G.A., Fraser R., Morley J.E. (1997) The Endocrine System of the Gastrointestinal Tract. In: Conn P.M., Melmed S. (eds) Endocrinology. Humana Press, Totowa, NJ. [Article]
4. Rao JN, Wang JY. Regulation of Gastrointestinal Mucosal Growth. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. Role of GI Hormones on Gut Mucosal Growth. [Article]
5. "Gastrin." *Pathophysiology of the Endocrine System*, Colorado State University. [Article]
6. Afroze S, Meng F, Jensen K, McDaniel K, Rahal K, Onori P, Gaudio E, Alpini G, Glaser SS. The physiological roles of secretin and its receptor. Ann Transl Med. 2013 Oct;1(3):29.
7. *Rehfeld, Jens F. (March 2021). "Cholecystokinin and the hormone concept". Endocrine Connections. 10 (3): R139–R150. [Article]*
8. Seladi-Schulman, Jill. "High Stomach Acid Symptoms: Side Effects, Causes & Treatment." *Healthline*, Healthline Media, 11 May 2020, [Article]
9. Gupta K, Raja A. Physiology, Gastric Inhibitory Peptide. [Updated 2021 Sep 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. [Article]

10. Samer Al-Kaade, MD. “Exocrine Pancreatic Insufficiency.” *Practice Essentials, Anatomy, Pathophysiology*, Medscape, 12 Aug. 2021, [Article]
11. Bergsland, Emily. “Zollinger-Ellison Syndrome (Gastrinoma): Clinical Manifestations and Diagnosis.” Edited by Mark Feldman and Shilpa Grover, *UpToDate*, 30 Nov. 2021. [Article]
12. Bradwejn J, Koszycki D: Cholecystokinin and panic disorder: past and future clinical research strategies. Scand J Clin Lab Invest Suppl. 2001;234:19-27. [Article]
13. Harvey, R. F. (1977). The irritable bowel syndrome; hormonal influences. Clinics in *Gastroenterology*, 6, 631-641.
14. Besterman, H. S.(1978). Gut hormones in gastrointestinal disease journal of clinical pathology(*Ass. Clin. Path.*), 8,76-84.
15. Adrian, T. E., Besterman, H. S., Mallinson, C. N., Garalotis, C., and Bloom, S. R. (1979). Impaired pancreatic polypeptide release in chronic pancreatitis with steatorrhoea. Gut, 20, 98-101.
16. Norman S.Track. The Gastrointestinal endocrine system (1980). *Can Med Assoc J*; 122(3): 287-292.
17. Barbara O. Schneeman. Gastrointestinal physiology and function (2002). *British Journal of Nutrition,* Volume 88, Issue S2. pp. S159-S163.
18. Marx M., Gomez G., Lonovics J., Thompson J.C. (1987) Cholecystokinin. In: Thompson JC, Greeley Jr GH, Rayford PL, Townsend CM Jr, eds. Gastrointestinal Endocrinology. McGraw Hill, New York, pp. 213~222.
19. Rehfeld J. F., Solinge W. W. (1994) The tumor biology of gastrin and cholecystokinin. *Adv Cancer Res* 63:295~347.
20. Axelson J., Ihse I., Hakanson R. (1990) Pancreatic cancer: the role of cholecystokinin? *Scand J Gastroenterol* 27:993-998.
21. Porus, R. L. (1965). Epithelial hyperplasia following massive small bowel resection in man. *Gastroenterology*, 48, 753-757.
22. Osborne, M. P., Frederick, P. L., Sizer, J. S., Blair, D., Cole, P., and Thum, W. (1966). Mechanism of gastric hypersecretion following massive intestinal resection: clinical and experimental observations. *Annals of Surgery*, 64, 622-634.
23. Straus, E., Gerson, C. D., and Yalow, R. S. (1974). Hypersecretion of gastrin is associated with short bowel syndrome. Gastroenterology, 66, 175-180.
24. Misiewicz, J. J. (1974). Muscular disorders of the colon. *British Journal of Hospital Medicine,* 11, 191-202.
25. DiMagno, E. P., Go, V. L. W., and Summerskill, W. H. J. (1972). Impaired cholecystokinin-pancreozymins secretion, intraluminal dilution, and maldigestion of fat in sprue. *Gastroenterology,* 63, 25-32.
26. Kim, Nam Deuk. “Chapter 7 Gastrointestinal Hormones.” [Article]
27. Barbara O. Schneeman. Gastrointestinal physiology and function (2002). *British Journal of Nutrition,* Volume 88, Issue S2. pp. S159-S163.