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GASTROINTESTINAL HORMONES: A MINI-REVIEW

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ABSTRACT

The Gastrointestinal hormones (GIH) are a group of hormone secreted by the endocrine cells distributed in the various organs of the digestive system. These GIH are known to control various functions of the digestive organs which includes gastric an intestinal movements and secretions of various digestive juices.[1] Some of these GIH such as secretin, gastrin and cholecystokinin are reported to act as neurotransmitters and neuromodulators in the central and peripheral nervous system.[2,3,4] These GIH have some extra-GI functions , many of which are not yet clearly known. Some of these can regulate the brain to regulate the food intake while others are known to regulate proliferation of certain cells. Receptors of these GIH are reported to be expressed also in various tissues other than in the GI system.GIH have valuable diagnostic and therapeutic uses.[5]

KEYWORDS: Cholecystokinin, Gastrin, Gastrointestinal hormones, neuromodulators, neurotransmitters, secretin.

INTRODUCTION

The Gastrointestinal hormones can be divided into certain main groups based upon their chemical structure. These are, Gastrin–cholecystokinin family, Secretin family , Somatostatin family, Motilin family and Substance P. Gastrin and cholecystokinin belong to the Gastrin-cholesystokinin family. Secretin, glucagon, vasoactive intestinal peptide and gastric inhibitory peptides belong to the Secretin family.[6] Somatostatin family is constituted of certain peptide hormones among which somatostatin is the prime one which is known to inhibit the release of the pituitary somatotropin (growth hormone) and inhibits the release of glucagon and insulin from the pancreas of animals which are starving.[7] Motilin is a 22 amino acid polypeptide hormone and is the prime member of the motilin family of hormones. Motilin is secreted by the M cells, or microfold cells, found in Peyer's patches in the intestine.[8]

These GIH also termed as 'Gut Hormones' have key roles in the regulation of metabolism in our body. These hormones work on various tissues involved in the regulation of intestinal functions. They are known to be associated with the regulation of insulin secretion, nutrient absorbtion, secretion of digestive juices, nutrient assimilation and food intake.[9] These GIH are produced by cells scattered along the entire length of the intestinal epithelium. These enteroendocrine glands are known to secret 30 hormones into the blood stream.[10] The gut hormones generate signals which are related to and also are known to regulate the rate of nutrient absorption in our intestinal lumen.[9,11]

End products of food digestion i.e., amino acids, fatty acids, glucose etc., are known to act as stimulants for local enteroendocrine cells [ECCs] and are thus responsible for regulation of the secretion of GIH. The GI Tract has the ability to sense the composition of the food in our gut. Sensing of nutrients by the ECCs involves a series of signaling pathways which includes ion channels, secondary messenger molecules, G-protein coupled receptors, nutrient transporters etc.[11] EECs are known to respond to certain microbial products produced locally in our gut.[12] EECs also respond to lipid metabolites in the gut and thus provide signals which are actually speak about long-term dietary history.[13]

Studies reveal that based on the type of hormones produced, EECs are broadly categorized into distinct cell types. EECs are known to release two important gut hormones which play significant role in the regulation of glucose homeostasis and appetite. Those are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (formerly known as gastric inhibitory peptide, GIP).[11] EECs which release GIP are classified traditionally as K- cells and those that release GLP-1 are traditionally classified as and L-cells.[14] Various studies reveal that there is a good extent of overlap between EECs in the proximal small intestine which express GLP-1 and GIP. Individual EECs can

express a much broader range of gut hormones than originally believed.[15] The highest number of K-cells which produce GIP are found in the proximal small intestine, primarily in the duodenum. On the other hand, highest density of L-cells which produce GLP-1 are reported to be located in the distal small intestine and colon.[16]

In this review we will briefly discuss about some of the prime GIH and their functions.

GASTRIN

Gastrin is a peptide hormone. This hormone was first identified in 1906 by Ekins.[11] This hormone stimulates secretion of acid mainly HCl that is secreted by the parietal cells of the stomach and aids in gastric motility. It is primarily released by G cells located in the gastric pits in the pyloric antrum of the stomach, during a meal [Fig.1].[17] Gastrin secretion is known to be induced by vagal stimulation, distention and digested protein.[18] Endocrine cells in the pancreas, the pituitary and the extrantral G cells are also known to produce gastrin.[17-19] Studies show that the prime targets of gastrin are the parietal cells of the stomach which produce HCl. The other prime targets of gastrin are the enterochromaffin-like (ECL) cells which produce histamine. Gastrin works either directly or by binding to its receptors.[20,21] Gastrin is also known to be a key 'growth regulator' in the gut mucosa and is associated with the development of various GI cancers.[22]

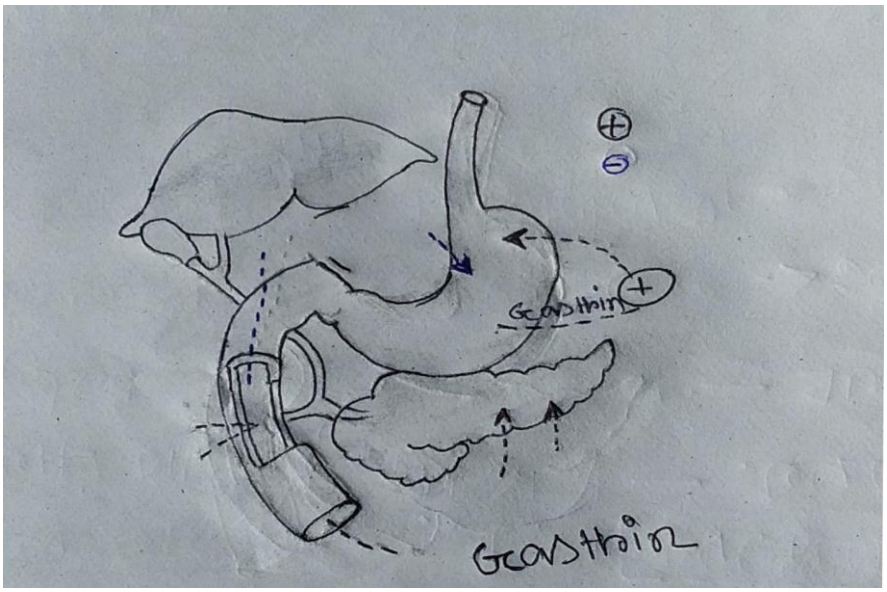

Fig. 1: Cite of secretion of gastrin and its action.

Calcium, small peptides and aromatic amino acids in a meal are the stimulants for secretion of gastrin.[23] Negative regulation of gastrin depends on the low pH level following acid secretion.[24] Studies show that gastrin is stored as progastrin in the G cells.[25] It is also reported that all forms of gastrin have equal effects on the gastrin receptors leading to the deduction that post transcriptional modification has no effect on the function or effectiveness of the peptide hormone.[26] The biologically active form of gastrin are the G-17 and G-34 amino acid peptides containing tyrosine residues at carboxyl terminus.[26]

SECRETIN

Secretin is also a polypeptide hormone. It contains 27 amino acids residues.It was identified by Bayliss and Starling in 1902.[27] It is secreted by the duodenal mucosa in response to the presence of chyme from stomach [Fig.2.]. The prime function of seretin is the regulation of the secretion of pancreatic juice [Fig.2.]. It regulates pancreatic exocrine secretion of fluid and bicarbonate.[28] It regulates gastric acid secretion, gastric motility and secretion of the biliary epithelium in the liver.[29] Studies report presence of extra antral secretin. Secretin has been found to be present in the hypothalamo-hypophyseal axis and this secretin is known to regulates water homeostasis throughout in the body.[30] Secretin is structurally similar to that of glucagon with respect to the position of amino acid residues and is a polypeptide hormone.[29] Secretin is also structurally similar to vasoactive intestinal peptide (VIP) and gastric inhibitory peptide (PHI-27), which are the members of the secretin family.[31,32] Secretin is known to exert trophic effects in several cell types.[29] The hormone is known to exert pharmacological impacts on a number of organs which include the heart, kidney, lung, and brain.[33] Secretin is reported to have inhibitory effects on the gastric acid secretion and also on food-stimulated gastrin release.[34] Secretin has inhibitory effects on upper small intestinal motility and lower esophageal sphincter pressure.[34] Studies reveal that Secretin plays an important role in management of blood glucose following ingestion of glucose. Secretin induces the release of insulin from the pancreatic endocrine cells following ingestion of glucose.[35]

CHOLECYSTOKININ

Cholecystokinin (CCK) is a peptide hormone of the intestinal system responsible for stimulating the digestion of fat and protein.[36] Cholecystokinin , officially called pancreozymin, is synthesized and secreted by EECs in the duodenum , the first segment of the small intestine and is secreted into the blood following intake of a meal.[37] Circulating CCK act by binding with its receptors expressed on various organs including the gall bladder, pancreas, smooth muscle etc. The main functions of CCK are gall bladder contraction, relaxation of sphincter of Oddi, increased pancreatic enzyme secretion and decreased gastric emptying [Fig.2.].[38] CCK receptors are of two types mainly, CCK- A and CCK- B**.** CCK- A is found to be primarily located in GI tract whereas CCK-B is located mainly in the central nervous system (CNS). CCK is known to be responsible for inducing satiety sensation in the hypothalamus. CCK is reported to have tropic effect on pancreas.[38]

Initially CCK was identified as a 33 amino acid peptide but later on , various length of CCK have been isolated from the brain, intestine and blood. All forms of CCK have been reported to be expressed by the same gene. CCK ranging in size from CCK-58 to CCK-8 have similar biological activities.[39]

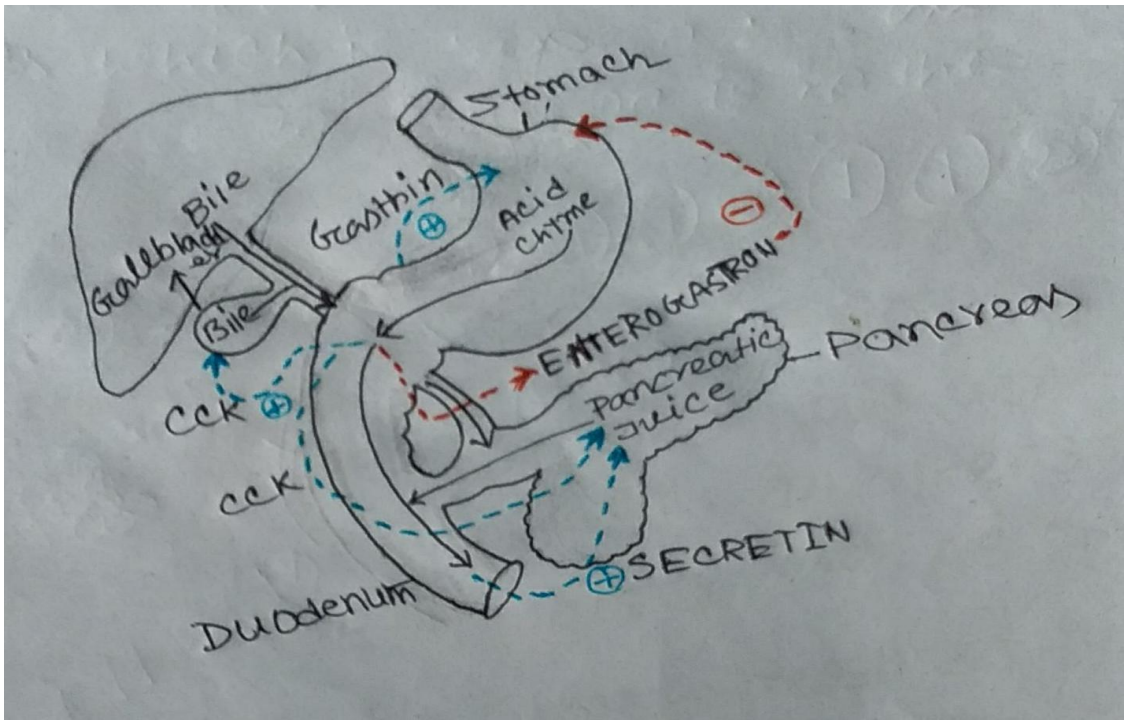

Fig. 2: Stimulatory (+) effects of Secretin, Cholecystokinin (CCK) and Gastrin and inhibitory (-) effect of Enterogastron.

SOME OTHER GUT HORMONES

Caerulein

Caerulein is a ten amino acid oligopeptide that stimulates smooth muscle and increases digestive secretions. Caerulein is deceptive with biological activity on GI smooth muscle contraction and pancreatic and gastrin secretion . It was first observed in the skin of Australian green frog , later it was identified in the South American Hylid frog.

It is a ten amino acid oligopeptide that stimulates smooth muscle and increases digestive secretions . It stimulates gastrin, biliary and pancreatic secretion and certain smooth muscle. It is generally used in humans for the contraction of gallbladder during cholecystography.[40]

Gastrone

Mucous membrane of human stomach contains a substance called gastrone . It's secretion is stimulated by the histamine and gastrin. Pharmacological dose of gastrone is reported to improve digestion naturally.[41]

Urogastrone

It is a polypeptide hormone that has been isolated mainly from men and dog urine. Urogatrone is a potent inhibitor of gastric acid secretion. It is known to intercept the gastric secretion in response to cholinergic drugs.[41]

Villikinin

This hormone is secreted from the mucosa of the upper small intestine. It stimulates villi in the small intestine.[42]

Enterocrinin

This hormone is also postulated to be secreted from the intestinal lumen .It is known to stimulate the intestinal glands and increase the secretion of intestinal juice.[43]

CONCLUSION

Gut hormones are locally secreted in our gut. Though their main functions are associated with the regulation of secretion, motility, cellular permeability of the various components of our enteric system yet, almost all of the GIH are known to be having various types of physiological effects on different organ systems in our body. These GIH have significant role in maintaining the glucose homeostasis in our body and are intimately associated with the maintenance of the metabolism. These hormones are not only produced in the intestine but also are produced in other parts of our body. Also, they have diverse type of physiological functions. Explorng this ectensive physiological impact of these GIH, they can be of immense therapeutic and pharmacological significance. Further studies and detailed research is necessary to elucidate the therapeutic role and applications of the GIH. Studies reveal that neurohormes like melatonin have healing and protective roles against oxidative stress induced damages in stomach duodenum and spleen in murine model.[43] Investigations targeting the healing properties and antioxidant role of these small physiological peptides are awaiting exploration and can pave new paths for GIH induced gut therapies.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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REFERENCES

1. Parikh A, Thevenin C. Physiology, Gastrointestinal Hormonal Control. [Updated 2021 May 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537284/
2. Rehfeld J F. Cholecystokinin and the hormone concept. *Endocr Connect*. 2021;10(3):R139-R150. doi:10.1530/EC-21-0025.
3. Cholecystokinin and Gastrin Receptors. https://www.sigmaaldrich.com/IN/en/technical-documents/technical-article/protein-biology/protein-expression/cholecystokinin-and-gastrin-receptors. [Accessed on 08.03.2022]
4. Csillag V, Vastagh C, Liposits Z, Farkas I. Secretin Regulates Excitatory GABAergic Neurotransmission to GnRH Neurons via Retrograde NO Signaling Pathway in Mice. *Front Cell Neurosci.* 2019; 23(13): 371. doi: 10.3389/fncel.2019.00371. PMID: 31507377; PMCID: PMC6716020.
5. Ahmed M, Ahmed S. Functional, Diagnostic and Therapeutic Aspects of Gastrointestinal Hormones. *Gastroenterology Res*. 2019; 12(5): 233-244. doi:10.14740/gr1219.
6. Burtis CA, Ashwood ER, Bruns DE (2012-10-14). *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 5th edition*. Elsevier Saunders. ISBN 978-1-4160-6164-9.
7. De Lecea L, Danielson PE, Criado JR, Prospero-garcia O, Gautvik KM, Schweitzer P, Dunlop CL, Siggins GR, Henriksen SJ, Sutcliffe JG (1996). "A cortical neuropeptide with neuronal depressant and sleep-modulating properties". *Nature* 381 (6579): 242–245.
8. Poitras P, Peeters TL (February 2008). "Motilin". *Current Opinion in Endocrinology, Diabetes and Obesity*. 15(1): 54–7.
9. Gribble FM, Reimann, F. Function and mechanisms of enteroendocrine cells and gut hormones in metabolism. *Nat Rev Endocrinol* 2019; 15: 226–237.
10. The new biology of gastrointestinal hormones. *Rehfeld JF Physiol Rev.* 1998; 78(4): 1087-108.
11. Lu VB, Gribble FM, Reimann F. Nutrient-Induced Cellular Mechanisms of Gut Hormone Secretion. *Nutrients*. 2021; 13(3): 883. doi:10.3390/nu13030883.
12. Cummings JH, Pomare EW, Branch WJ, Naylor CP, Macfarlane GT. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut* 1987; *28(10): 1221-7.*
13. Panaro BL, Yusta B, Matthews D, Koehler JA, Song Y, Sandoval DA, Drucker DJ. Intestine-selective reduction of Gcg expression reveals the importance of the distal gut for GLP-1 secretion. *Mol Metab.* 2020; 37: 100990.
14. Mortensen K, Christensen LL, Holst JJ, Orskov C. GLP-1 and GIP are colocalized in a subset of endocrine cells in the small intestine. *Regul Pept.* 2003; 114(2-3): 189-96.
15. Theodorakis MJ, Carlson O, Michopoulos S, Doyle ME, Juhaszova M, Petraki K, Egan JM. Human duodenal enteroendocrine cells: source of both incretin peptides, GLP-1 and GIP. *American J Physiol - Endocrinol Metab*. 2017; 3: 16219666.
16. Buchan AM, Polak JM, Capella C, Solcia E, Pearse AG. Electronimmunocytochemical evidence for the K cell localization of gastric inhibitory polypeptide (GIP) in man.*Histochemistry* 1978; 56(1): 37-44.
17. http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/gi/gastrin.html (Accessed on 08.03.2022).
18. Brand SJ, Andersen BN, Rehfeld JF. Complete tyrosine-O-sulphation of gastrin in neonatal rat pancreas. *Nature* 1984. 309: 456–8.10.1038/309456a0.
19. Larsson LI, Rehfeld JF. Pituitary gastrins occur in corticotrophs and melanotrophs. *Science* 1981; 213: 768–70,.10.1126/science.6266012.
20. Brand SJ, Klarlund J, Schwartz TW, Rehfeld JF. Biosynthesis of tyrosine-O-sulfated gastrins in rat antral mucosa. J Biol Chem 259: pp. 13246–52, 1984

21. Evers BM, Townsend CM. Growth factors, hormones and receptors in GI cancers. In: Molecular Mechanisms in Gastrointestinal Cancer, edited by Evers BM; Landes, Austin, TX, pp. 1–19, 1999.
22. Evers BM. Gastrointestinal growth factors and neoplasia. *Am J Surg* 2005; 190: 279–84, 2005.10.1016/j.amjsurg.2005.05.027.
23. Feng J, Petersen CD, Coy DH, et al. Calcium-sensing receptor is a physiologic multimodal chemosensor regulating gastric G-cell growth and gastrin secretion. *Proc Natl Acad Sci U S A*. 2010; 107(41): 17791-17796. doi:10.1073/pnas.1009078107.
24. Prosapio JG, Sankar P, Jialal I. Physiology, Gastrin. [Updated 2021 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534822/.
25. Walsh JH. Gastrointestinal hormones. In: Physiology of the Gastrointestinal Tract. 3rd ed., edited by Johnson LR, Alpers DH, Christensen J, Jacobson ED, and Walsh JH; Raven Press, New York, pp. 1–128, 1994
26. Dockry G, Dimaline R, Varro A. Gastrin: old hormone, new functions. *Pflugers Arch* 2005; 449: 344–55, 2005.10.1007/s00424-004-1347-5.
27. Bayliss HP, Starling EH. Mechanism of pancreatic secretion. *J Physiol Lond* 1902; 28: 325–53.
28. William CY, Ta-Min C. Secretin, 100 years later. *J Gastroenterol* 2003; 38: 1025–35, 2003.
29. Afroze S, Meng F, Jensen K, et al. The physiological roles of secretin and its receptor. *Ann Transl Med*. 2013; 1(3): 29. doi:10.3978/j.issn.2305-5839.2012.12.01
30. Chu JY, Lee LT, Lai CH, et al. Secretin as a neurohypophysial factor regulating body water homeostasis. *Proc Natl Acad Sci U S A*. 2009; 106(37): 15961-15966. doi:10.1073/pnas.0903695106
31. Williams RH. eds. Textbook of endocrinology. 6th ed. Philadelphia: Saunders, 1981: xxiii, 1270.
32. DeGroot LJ. eds. Endocrinology. 2nd ed. Philadelphia: Saunders, 1989.
33. Straus E, Greenstein AJ, Yalow RS. Effect of secretin on release of heterogeneous forms of gastrin. *Gut.* 1975 Dec; 16(12): 999-1005.
34. Hubel KA. Secretin: a long progress note. *Gastroenterol.* 1972; 62(6): 318-41.
35. Kraegen EW, Chisholm DJ, Young JD, Lazarus L. The gastrointestinal stimulus to insulin release. II. A dual action of secretin. *J Clin Invest.* 1970; 49(3): 524-9.
36. https://go.drugbank.com/drugs/DB08862 (Accessed on 08.03.2022).
37. Latorre R, Sternini C, De Giorgio R, Greenwood-Van Meerveld B. Enteroendocrine cells: a review of their role in brain-gut communication. *Neurogastroenterol Motil*. 2016; 28(5): 620-630. doi:10.1111/nmo.12754
38. https://www.drbeen.com/uncategorized/hormones-of-the-gastrointestinal-tract/ (Accessed on 08.03.2022).
39. Niederau C, Ferrell LD, Grendell JH. Caerulein-induced acute necrotizing pancreatitis in mice: protective effects of proglumide, benzotript, and secretin. Gastroenterol. 1985; 88(5 Pt 1): 1192-204. doi: 10.1016/s0016-5085(85)80079-2. PMID: 2984080.
40. Balanzo JT, Glass GB. Bioassay of inhibitory activity of gastrone on basal HCl secretion in rats with chronic gastric fistula. *Digestion* 1975; 13(6): 334-43. doi: 10.1159/000197731. PMID: 130273.
41. Gregory H, Preston BM. The primary structure of human urogastrone. *Int J Pept Protein Res.* 1977; 9(2): 107-18. doi: 10.1111/j.1399-3011.1977.tb03470.x. PMID: 300079.
42. "Villikinin." *Merriam-Webster.com Medical Dictionary*, Merriam-Webster, https://www.merriam-webster.com/medical/villikinin. (Accessed 8 Mar. 2022).
43. Mishra S, Ghosh D, Dutta M, Chattopadhyay A, Bandyopadhyay D. Melatonin protects against lead-induced oxidative stress in stomach,duodenum and spleen of male wistar rats. JPR:BioMedRx: An International Journal 2013; 1(11): 997-1004.