Republic of Iraq
Ministry of Higher Education
& Scientific Research
University of Al-Qadisiyah
College of Veterinary Medicine

Role of Cholecystokinin in regulation of Gastrointestinal motor function

A Graduation Project Submitted to the Department Council of the Internal and Preventive Medicine-College of Veterinary Medicine/ University of Al-Qadisiyah in a partial fulfillment of the requirements for the Degree of Bachelor of Science in Veterinary Medicine and Surgery.

By
_____ Omer Munther ghaib _____

Supervised by
_____ Dr.Khetam abdalsada ali alhilali _____

2021 A.D. 1441 A.H.

فَتَعَٰلَى ٱللَّهُ ٱلْمَلِكُ ٱلْحَقُّ ۗ وَلَا تَعْجَلْ بِٱلْقُرْءَانِ مِن قَبْلِ أَن يُقْضَىٰٓ
إِلَيْكَ وَحْيُهُۥ ۖ وَقُل رَّبِّ زِدْنِى عِلْمًا ﴿١١٤﴾

صَدَقَ اللهُ العَظِيمُ

من سورة طه

We certify that the project entitled (Role of Cholecystokinin in regulation of Gastrointestinal motor function) was prepared under our supervision by omer munther ghaib at the College of Veterinary Medicine / University of Al-Qadisiyah.

Supervisor

Khetam Alhilali

Dept. of Basic science / pharmacology

College of Dentistry

Univ. of Al-Qadisiyah.

22 / 5 / 2021

Certificate of Department

We certify that omer munther ghaib has finished his Graduation Project entitled (Role of Cholecystokinin in regulation of Gastrointestinal motor function) and candidate it for debating.

Instructor

Dr. Muthanna H. Hussain

-- / -- / 2020

Head of Dept of Int. and Prev. Med.

-- / -- / 2020

Dedication

To our country …peace and safety

The light of my eyes …. My mother

List of Contents

List of Figures (Optional)

Abstract

This research talks about the effect of the stomach hormone (cholecystokinin) on the movement of the gastrointestinal tract, its effect on the digestion of fats, as well as its effect on gastric emptying, as well as the sympathetic effects and parasympathetic ,the effect of the hormone on the pancreas and gallbladder.

Influencing intestinal motility and food ability by affecting satiety. Therefore, this hormone is one of the most important hormones in the gastrointestinal tract, in addition to other hormones such as secretin and gastrin. This hormone is characterized by its strong effect on the pancreas and its secretions, and it helps in the digestion of proteins and fats in the intestine through digestive juices. , Which is what distinguishes this hormone

Chapter one

Introduction

Introduction

Cholecystokinin (CCK or CCK-PZ; from Greek chole, "bile"; cysto, "sac"; kinin, "move"; hence, move the bile-sac (gallbladder)) is a peptide hormone of the gastrointestinal system responsible for stimulating the digestion of fat and protein.[1] Cholecystokinin, officially called pancreozymin .[2][3][4] This hormone strongly contracts the gallbladder, expelling bile into the small intestine, where the bile in turn plays important roles in emulsifying fatty substances,[5] and allowing them to be digested and absorbed. CCK also inhibits stomach contraction moderately.[6][7][8] Therefore, at the same time that this hormone causes emptying of the gallbladder, it also slows the emptying of food from the stomach to give adequate time for digestion of the fats in the upper intestinal tract.[9] CCK also inhibits appetite to prevent overeating during meals by stimulating sensory afferent

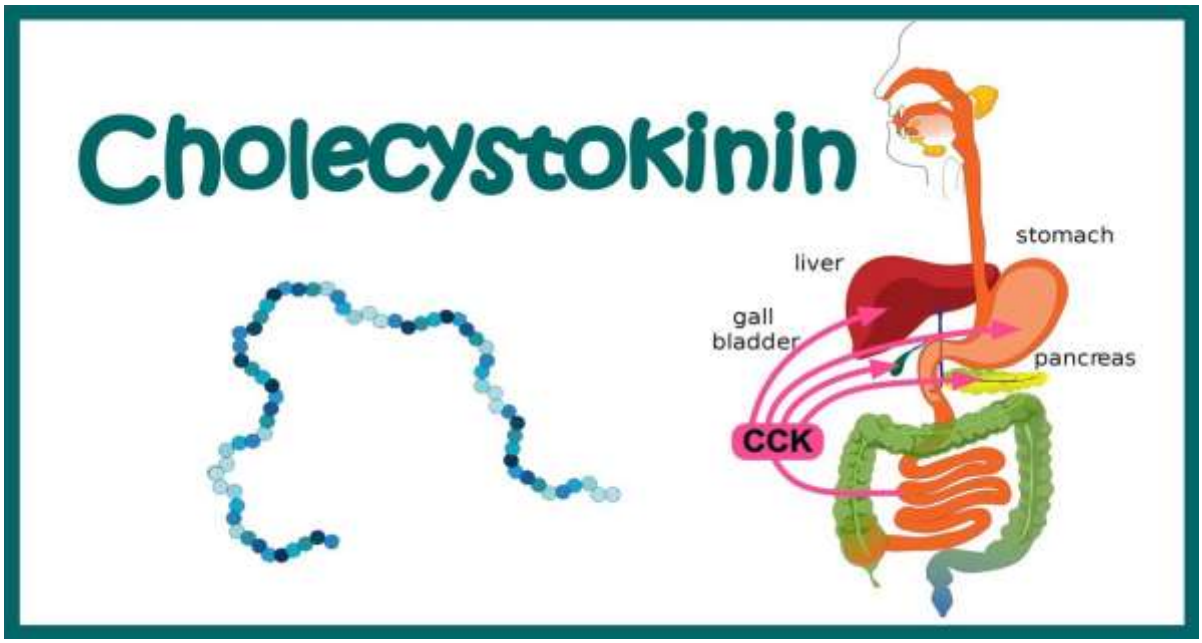

Figure1 [10]CCK function on tomach , pancras , liver,gall bladder and intestine

nerve fibers in the duodenum CCK synthesized and secreted by enteroendocrine cells in the duodenum, the first segment of the small intestine.[11] Its presence causes the release of digestive enzymes and bile from the pancreas and gallbladder, respectively, and also acts as a hunger suppressant When food, especially fat-containing food,[12] [13] reaches the duodenum, the GI endocrine cells are stimulated to secrete CCK Cholecystokinin (CCK) is secreted by "I" cells in the mucosa of the duodenum and jejunum mainly in response to digestive products of fat, fatty acids, and monoglycerides in the intestinal contents[14][15] ، Cholecystokinin stimulates the pancreas ، Pancreatic

secretion contains multiple enzymes for digesting all of the three major types of food: proteins, carbohydrates, and fats. It also contains large quantities of bicarbonate ions,[16] [17] which play an important role in neutralizing the acidity of the chyme emptied from the stomach into the duodenum [6] ‘Cholecystokinin is important in the movement of the gut ‹ Gastrointestinal (GI) motility is an essential function of digestive and absorptive processes of the gut,[18] [19] [20] [21] required for propelling intestinal contents, mixing them with digestive juices, and preparing unabsorbed particles for excretion.[22] the action of CCK can be learned from , Dexloxiglumide **Dexloxiglumide** is a selective cholecystokinin type A (CCKA) receptor antagonist in phase III testing by Rottapharm in Europe only, as U.S. trials have been discontinued. As the D-isomer of loxiglumide, it retains all pharmacological properties of loxiglumide but is more potent[23] [24] [25] [26] loxiglumide CCKA antagonists target receptors in the gastrointestinal system to increase gastric emptying and intestinal motility, as well as modulate intestinal sensitivity to distension.[27] [28] [29] [30]

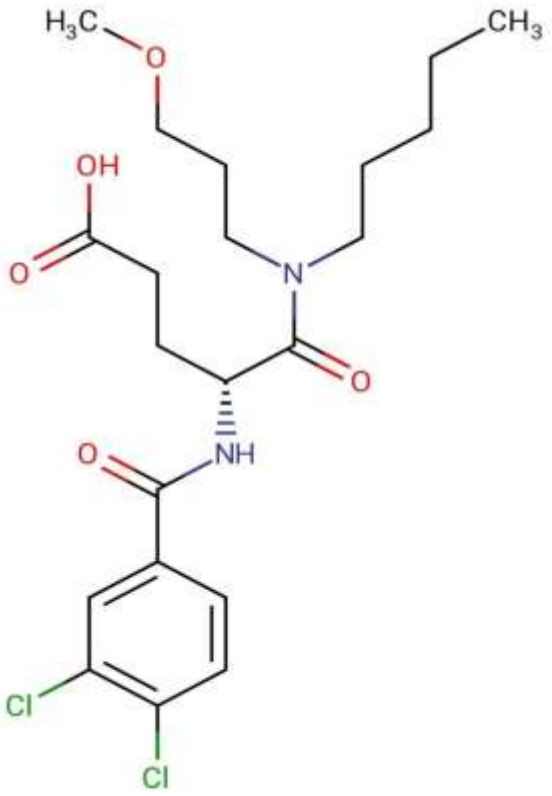

Figure 2 loxiglumide structure[31]

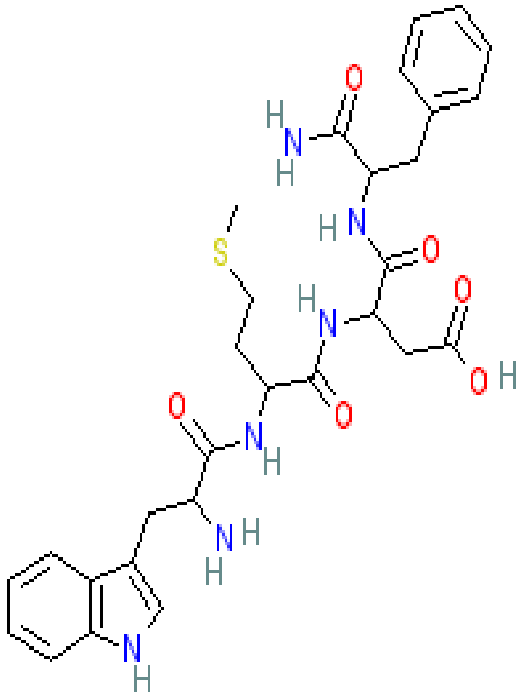

Figure 3CCK 4 structure [32]

Chapter two

Review and literatures

Cholecystokinin, is synthesized and secreted by enteroendocrine cells in the duodenum, the first segment of the small intestine.[33] Its presence causes the release of digestive enzymes and bile from [34] [35] the pancreas and gallbladder Cholecystokinin (CCK) is secreted by "I" cells in the mucosa of the duodenum and jejunum mainly in response to digestive products of fat, [33] [36] fatty acids, and monoglycerides in the intestinal contents. CCK plays important physiological roles both as a neuropeptide in the central nervous system and as a peptide hormone in the gut[38] . It participates in a number of processes such as digestion, satiety and anxiety. When food begins to be digested in the upper gastrointestinal tract, the gallbladder begins to empty, especially when fatty foods reach the duodenum about 30 minutes after a meal. The mechanism of gallbladder [39]. CCK, a polypeptide containing 33 amino acids, to be released from yet another group of cells, the I cells, in the mucosa of the duodenum and upper jejunum. [40] [41] This release of CCK results especially from the presence of proteoses and peptones (products of partial protein digestion) and long-chain fatty acids in the chyme coming from the stomach[42] [43]. CCK, like secretin, passes by way of the blood to the pancreas but instead of causing sodium bicarbonate secretion causes mainly secretion of still much more pancreatic digestive enzymes by the acinar cells[42] [44] [45]. This effect is similar to that caused by vagal stimulation but even more pronounced, accounting for 70

to 80 percent of the total secretion of the pancreatic digestive enzymes after a meal[46]. The differences between the pancreatic stimulatory effects of secretin and CCK, which demonstrates (1) intense sodium bicarbonate secretion in response to acid in the duodenum, stimulated by secretin; (2) a dual effect in response to soap (a fat); and (3) intense digestive enzyme secretion (when peptones enter the duodenum)

stimulated by CCK[47] [48] [49] . Stomach Emptying of the stomach is controlled only to a moderate degree by stomach factors such as the degree of filling in the stomach and the excitatory effect of gastrin on stomach peristalsis[50] [51]. Probably the more important control of stomach emptying resides in inhibitory feedback signals from the duodenum,[52] including both enterogastric inhibitory nervous feedback reflexes and hormonal feedback by CCK[53].

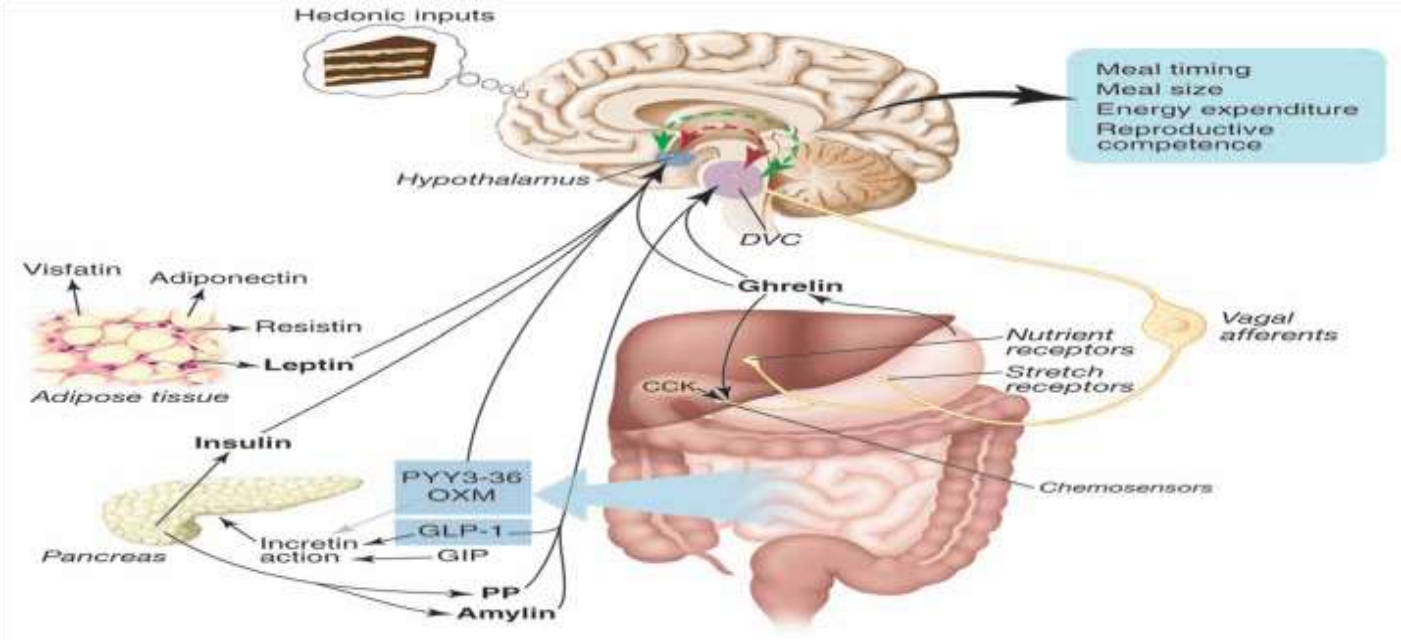

Figure4 CCK The mechanics of hormones to work together and influence the nervous system

These feedback inhibitory mechanisms work together to slow the rate of emptying when

(1) too much chyme is already in the small intestine or (2) the chyme is excessively acidic, contains too much unprocessed protein or fat [54] [55] [14] , is hypotonic or hypertonic, or is irritating. In this way, the rate of stomach emptying is limited to that amount of chyme that the small intestine can process[56] .

Pancreatic secretion contains multiple enzymes for digesting all of the three major types of food: proteins, carbohydrates, and fats[57] [58]. It also contains large quantities of bicarbonate ions, which play an important role in neutralizing the acidity of the chyme emptied from the stomach into the duodenum[52] [39] [14]. The most important of the pancreatic enzymes for digesting proteins are trypsin, chymotrypsin, and carboxypolypeptidase. Basic Stimuli That Cause Pancreatic Secretion Three basic stimuli are important in causing pancreatic[55] [59]
secretion:

1. Acetylcholine, which is released from the parasympathetic vagus nerve endings and from other cholinergic nerves in the enteric nervous system [60] [59]
2. Cholecystokinin, which is secreted by the duodenal and upper jejunal mucosa when food enters the small intestine [61]
3. Secretin, which is also secreted by the duodenal and jejunal mucosa when highly acidic food enters the small intestine [45]

The first two of these stimuli, acetylcholine and cholecystokinin, stimulate the acinar cells of the pancreas, causing production of large quantities of pancreatic digestive enzymes but relatively small quantities of water and electrolytes to go with the enzymes[62] [63] . Without the water, most of the enzymes

remain temporarily stored in the acini and ducts until more fluid secretion comes along to wash them into the duodenum[51]. Secretin , in contrast to the first two basic stimuli, stimulates secretion of large quantities of water solution of sodium bicarbonate by the pancreatic ductal epithelium[55].

Chemical Composition of cholecystokinin Hormones

Gastrin, cholecystokinin (CCK), and secretin are all large polypeptides with approximate molecular weights, respectively, of 2000, 4200, and 3400. The terminal five amino acids in the gastrin and CCK molecular chains are the same[51] . The functional activity of gastrin resides in the terminal four amino acids[64] [65], and the activity for CCK resides in the terminal eight amino acids[66]. All the amino acids in the secretin molecule are essential. A synthetic gastrin, composed of the terminal four amino acids of natural gastrin plus the amino acid alanine, has all the same physiologic properties as the natural gastrin[67] [68] . This synthetic product is called pentagastrin.

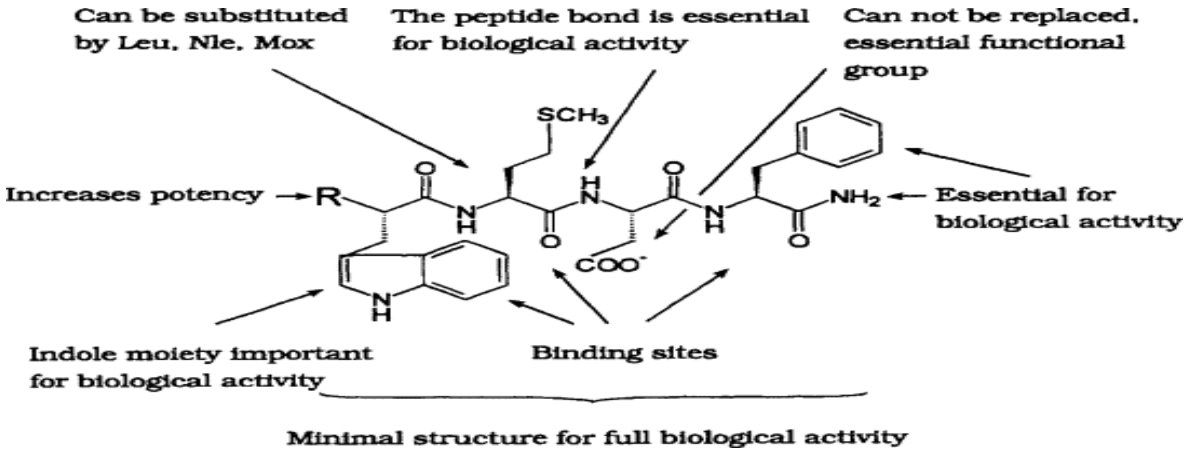

Figure5 CCKChemical Composition of cholecystokinin Hormones

Regulation of Stomach Emptying

The rate at which the stomach empties is regulated by signals from both the stomach and the duodenum. However[69] [70], the duodenum provides by far the more potent of the signals, controlling the emptying of chime into the duodenum at a rate no greater than the rate at which the chyme can be digested and absorbed in the small intestine[71] . Gastric Factors That Promote Emptying

Effect of Gastric Food Volume on Rate of Emptying. Increased food volume in the stomach promotes increased emptying from the stomach. But this increased emptying does not occur for the reasons that one would expect[72][73][61]. It is not increased storage pressure of the food in the stomach that causes the increased emptying because[74][35], in the usual normal range of volume, the increase in volume does not increase the pressure much[75]. However, stretching of the stomach wall does elicit local myenteric reflexes in the wall that greatly accentuate activity of the pyloric pump and at the same time inhibit the pylorus[76] [77].

Basic Mechanisms of Stimulation of the Alimentary Tract Glands

Contact of Food with the Epithelium Stimulates Secretion—Function of Enteric Nervous Stimuli[78][79]. The mechanical presence of food in a particular segment of the gastrointestinal tract usually causes the glands of that region and adjacent regions to secrete moderate to large quantities of juices [80]. Part of this local effect, especially the secretion of mucus by mucous cells,

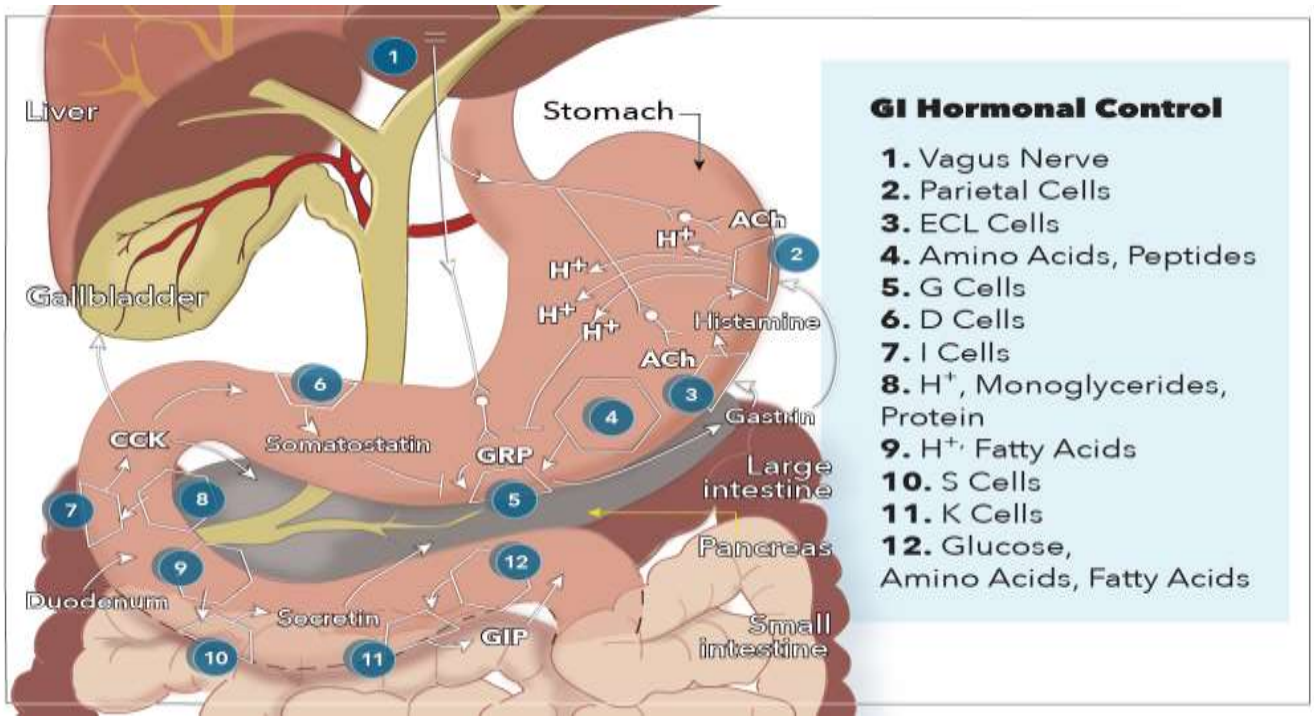

Figure6 Gi hormonal control and CCK no.7 showing its effect and its please in GI

results from direct contact stimulation of the surface glandular cells by the food[81][82]. In addition, local epithelial stimulation also activates the enteric nervous system of the gut wall. The types of stimuli that do this are (1) tactile stimulation, (2) chemical irritation, and (3) distention of the gut wall[83]. The resulting nervous reflexes stimulate both the mucous cells on the gut epithelial surface and the deep glands in the gut wall to increase their secretion[84][85].

Autonomic Stimulation of Secretion Regulation of Glandular Secretion by Hormones.

In the stomach and intestine, several different gastrointestinal hormones help regulate the volume and character of the secretions[85][76]. These hormones are liberated from the gastrointestinal mucosa in response to the presence of food in the lumen of the gut[86]. The hormones are then absorbed into the blood and carried to the glands, where they stimulate secretion. This type of stimulation is particularly valuable to increase the output of gastric juice and pancreatic juice when food enters the stomach or duodenum[87][88]. Chemically, the gastrointestinal hormones are polypeptides or polypeptide derivatives

Basic Mechanism of Secretion by Glandular Cells

Secretion of Organic Substances[89]. Although all the basic mechanisms by which glandular cells function are not known, experimental evidence points to the following principles of secretion. 1. The nutrient material needed for formation of the secretion must first diffuse or be actively transported by the blood in the capillaries into the base of the glandular cell. 2. Many mitochondria located inside the glandular cell near its base use oxidative energy to form adenosine triphosphate (ATP). 3. Energy from the ATP, along with appropriate substrates provided by the nutrients, is then used to synthesize the organic secretory substances[90][91][87]; this synthesis occurs almost entirely in the endoplasmic reticulum and Golgi complex of the glandular cell. Ribosomes adherent to the reticulum are specifically responsible for formation of the proteins that are secreted. 4. The secretory materials are transported through the tubules of the endoplasmic reticulum, passing in about 20 minutes all the way to the vesicles of the Golgi complex. 5. In the Golgi complex, the

materials are modified, added to, concentrated, and discharged into the cytoplasm in the form of secretory vesicles, which are stored in the apical ends of the secretory cells. 6. These vesicles remain stored until nervous or hormonal control signals cause the cells to extrude the vesicular contents through the cells' surface. This probably occurs in the following way: The control signal first increases the cell membrane permeability to calcium ions, and calcium enters the cell. The calcium in turn causes many of the vesicles to fuse with the apical cell membrane. Then the apical cell membrane breaks open, thus emptying the vesicles to the exterior; this process is called exocytosis.[92][93]

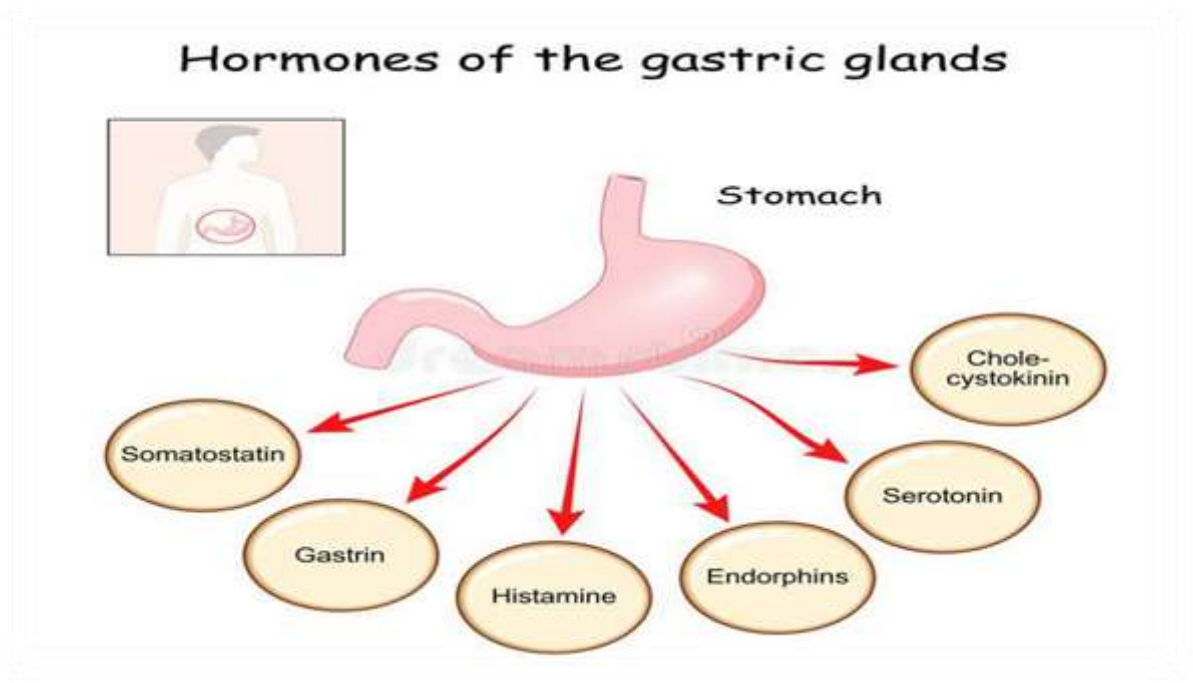

Figure7 hormone of the gastric glands that effect on digestion

Parasympathetic Stimulation Increases Alimentary Tract Glandular Secretion Rate.

Stimulation of the parasympathetic nerves to the alimentary tract almost invariably increases the rates of alimentary glandular secretion[94]. This is especially true of the glands in the upper portion of the tract (innervated by the glossopharyngeal and vagus parasympathetic nerves) such as the salivary glands, esophageal glands[95][87], gastric glands, pancreas, and Brunner's glands in the duodenum. It is also true of some glands in the distal portion of the large intestine, innervated by pelvic parasympathetic nerves[96]. Secretion in the remainder of the small intestine and in the first two thirds of the large intestine occurs mainly

Sympathetic Stimulation Has a Dual Effect on Alimentary Tract Glandular Secretion Rate[94]. Stimulation of the sympathetic nerves going to the

gastrointestinal tract causes a slight to moderate increase in secretion by some of the local glands[97]. But sympathetic stimulation also results in constriction of the blood vessels that supply the glands. Therefore, sympathetic stimulation can have a dual effect: (1) sympathetic stimulation alone usually slightly increases secretion and (2) if parasympathetic or hormonal stimulation is already causing copious secretion by the glands[98][89], superimposed sympathetic stimulation usually reduces the secretion, sometimes significantly so, mainly because of vasoconstrictive reduction of the blood supply

Hormonal Feedback from the Duodenum Inhibits Gastric Emptying—Role of Fats and the Hormone Cholecystokinin.

Not only do nervous reflexes from the duodenum to the stomach inhibit stomach emptying, but hormones released from the upper intestine do so as well[99][100][83]. The stimulus for releasing these inhibitory hormones is mainly fats entering the duodenum, although other types of foods can increase the hormones to a lesser degree[59][85]. On entering the duodenum, the fats extract several different hormones from the duodenal and jejunal epithelium, either by binding with "receptors" on the epithelial cells or in some other way[38][33]. In turn, the hormones are carried by way of the blood to the stomach, where they inhibit the pyloric pump and at the same time increase the strength of contraction of the pyloric sphincter[101]. These effects are important because fats are much slower to be digested than most other foods. Precisely which hormones cause the hormonal feedback inhibition of the stomach is not fully clear. The most potent appears to be cholecystokinin (CCK), which is

released from the mucosa of the jejunum in response to fatty substances in the chime[101][102]. This hormone acts as an inhibitor to block increased stomach motility caused by gastrin. Other possible inhibitors of stomach emptying are the hormones secretin and gastric inhibitory peptide (GIP), also called glucose-dependent insulinotropic peptide[104][96][7]. Secretin is released mainly from the duodenal mucosa in response to gastric acid passed from the stomach through the pylorus[3]. GIP has a general but weak effect of decreasing gastrointestinal motility. GIP is

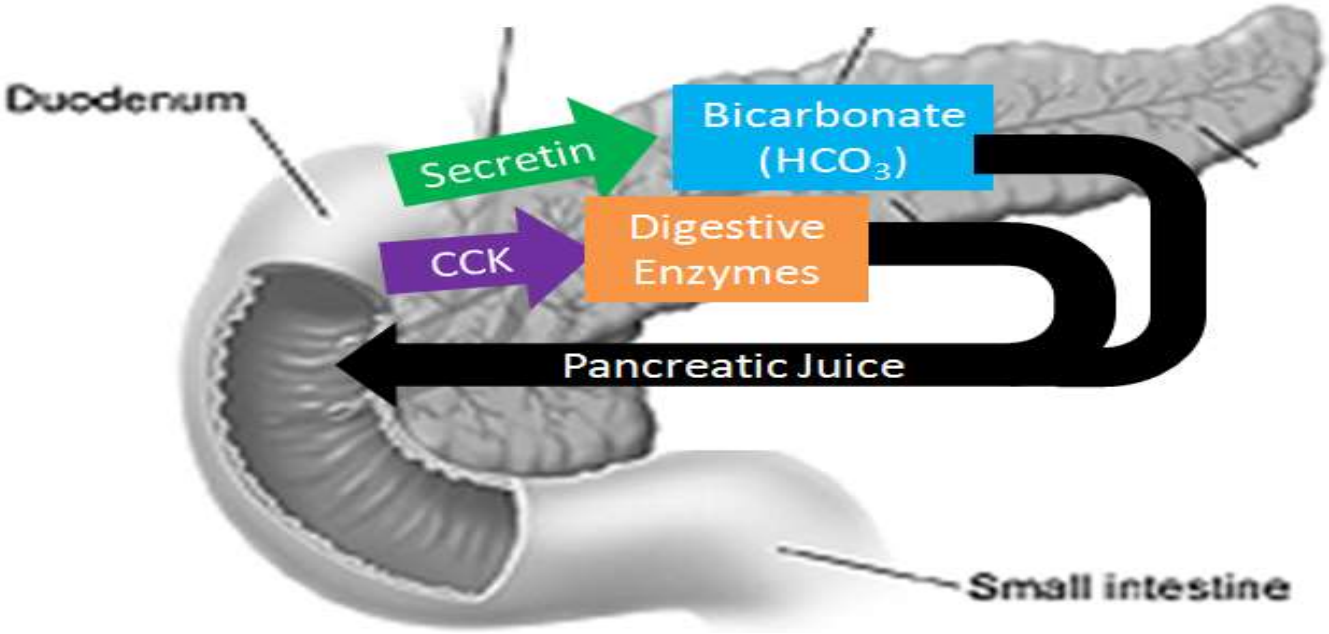

Figure8 pancreatic juice in the small intestine

released from the upper small intestine in response mainly to fat in the chyme, but to a lesser extent to carbohydrates as well. Although GIP inhibits gastric motility under some conditions, its main effect at physiologic concentrations is probably mainly to stimulate secretion of insulin by the pancreas[87] . In summary, hormones, especially CCK, can inhibit gastric emptying when excess quantities of chyme, especially acidic or fatty chyme, enter the duodenum from the stomach.[105]

Summary of the Control of Stomach Emptying

Emptying of the stomach is controlled only to a moderate degree by stomach factors such as the degree of filling in the stomach and the excitatory effect of gastrin on stomach peristalsis. Probably the more important control of stomach emptying resides in inhibitory feedback signals from the duodenum, including both enterogastric inhibitory nervous feedback reflexes and hormonal feedback by CCK[106][13][87]. These feedback inhibitory mechanisms work together to slow the rate of emptying when (1) too much chyme is already in the small intestine or (2) the chyme is excessively acidic, contains too much unprocessed protein or fat, is hypotonic or hypertonic, or is irritating[13][107]. In this way, the rate of stomach emptying is limited to that amount of chyme that the small intestine can process.[88]

Control of Peristalsis by Nervous and Hormonal Signals.

Peristaltic activity of the small intestine is greatly increased after a meal. This is caused partly by the beginning entry of chyme into the duodenum causing stretch of the duodenal wall[108]. Also, peristaltic activity is increased by the so-called gastroenteric reflex that is initiated by of the stomach and conducted principally through the myenteric plexus from the stomach down along the wall of the small intestine[109][89]. In addition to the nervous signals that may affect small intestinal peristalsis, several hormonal factors also affect peristalsis. They include gastrin, CCK, insulin, motilin, and serotonin, all of which enhance intestinal motility and are secreted during various phases of food processing[110][87].

Conversely, secretin and glucagon inhibit small intestinal motility. The physiologic importance of each of these hormonal factors for controlling motility is still questionable[111][87]. The function of the peristaltic waves in the small intestine is not only to cause progression of chyme toward the ileocecal valve but also to spread out the chyme along the intestinal mucosa. As the chyme enters the intestines from the stomach and elicits peristalsis, this immediately spreads the chyme along the intestine; and this process intensifies as additional chyme enters the duodenum[88][83]. On reaching the ileocecal valve, the chyme is sometimes blocked for several hours until the person eats another meal; at that time, a gastroileal reflex intensifies peristalsis in the ileum and forces the remaining chyme through the ileocecal valve into the cecum of the large intestine.[87][89][85]

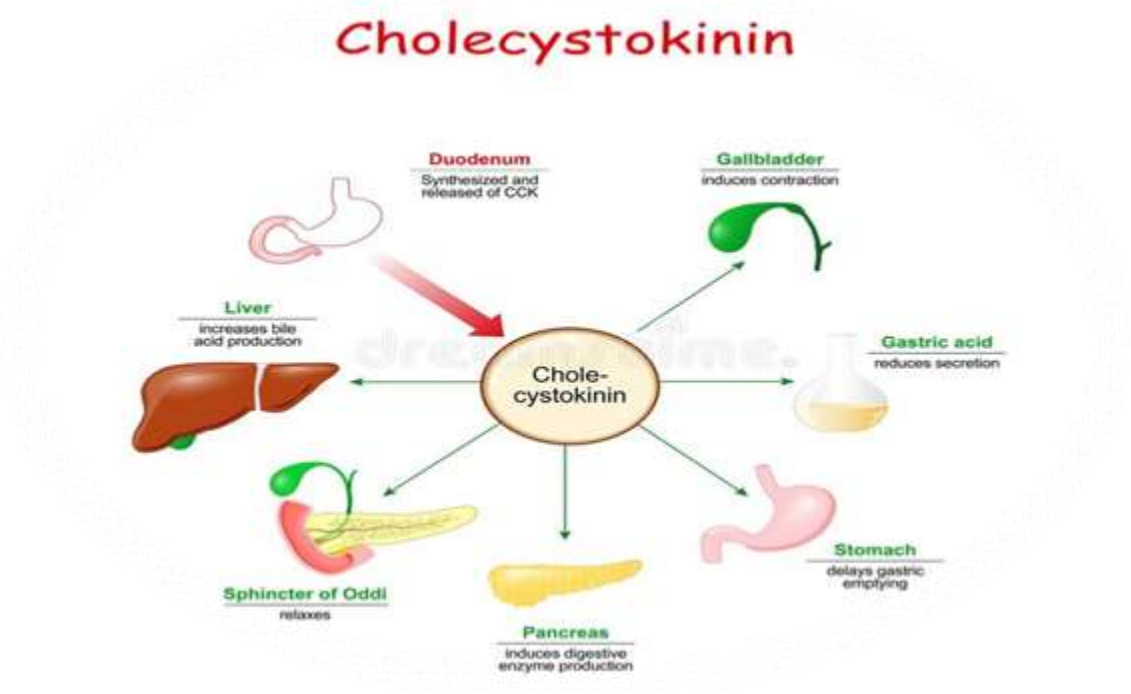

Figure9 CCK physiology effect of CCK on the body organs

Chapter three

Conclusion

Conclusion

1. CCK it is a peptide hormone of the gastrointestinal system responsible for stimulating the digestion of fat and protein
2. This hormone strongly contracts the gallbladder, expelling bile into the small intestine
3. CCK slows the emptying of food from the stomach to give adequate time for digestion of the fats in the upper intestinal tract
4. CCK also inhibits appetite to prevent overeating during meals by stimulating sensory afferent nerve fibers in the duodenum
5. (CCK) is secreted by “I” cells in the mucosa of the duodenum and jejunum mainly in response to digestive products of fat, fatty acids, and monoglycerides in the intestinal contents[
6. CCK stimulates the pancreas , Pancreatic secretion contains multiple enzymes for digesting all of the three major types of food: proteins, carbohydrates, and fats.

7. Cholecystokinin is important in the movement of the gut , Gastrointestinal (GI) motility is an essential function of digestive and absorptive processes

Chapter four

References

References

1. Yamazaki, T., Morimoto-Kobayashi, Y., Koizumi, K., Takahashi, C., Nakajima, S., Kitao, S., ... & Ogawa, Y. (2019). Secretion of a gastrointestinal hormone, cholecystokinin, by hop-derived bitter components activates sympathetic nerves in brown adipose tissue. The Journal of nutritional biochemistry, 64, 80-87.
2. Jorpes, E., & Mutt, V. (1966). Cholecystokinin and pancreozymin, one single hormone?. Acta physiologica Scandinavica, 66(1- 2), 196-202.
3. JORPES, J. E., & MUTT, V. (1961). The gastrointestinal hormones, secretin and cholecystokinin-pancreozymin. Annals of internal medicine, 55(3), 395-405.
4. Liddle, R. A. (1989). Integrated actions of cholecystokinin on the gastrointestinal tract: use of the cholecystokinin bioassay. Gastroenterology clinics of North America, 18(4), 735-756.
5. ^ Barrett TD, Yan W, Freedman JM, Lagaud GJ, Breitenbucher JG, Shankley NP (April 2008). "Role of CCK and potential utility of CCK1 receptor antagonism in the treatment of pancreatitis induced by biliary tract obstruction". British Journal of Pharmacology. 153 (8): 1650–8. doi:10.1038/bjp.2008.44. PMC 2438255. PMID 18297100.
6. Johnson LR (2013). Gastrointestinal Physiology (Eighth ed.). Philadelphia: Elsevier/Mosby. ISBN 978-0-323-10085-4.

7. Rehfeld, J. F. (1999). The Cholecystokinin—Gastrin Family of Peptides and Their Receptors. Regulatory Peptides and Cognate Receptors, 293-321.
8. Harvey, R. F., & Oliver, J. M. (1981). Hormonal content and effect on gallbladder of commercial preparations of cholecystokinin-pancreozymin. Hormone and Metabolic Research, 13(08), 446-450.
9. Ondetti, M. A., Rubin, B., Engel, S. L., Pluščec, J., & Sheehan, J. T. (1970). Cholecystokinin-pancreozymin. The American journal of digestive diseases, 15(2), 149-156.
10. https://go.drugbank.com/drugs/DB08862
11. Miyasaka, K., & Funakoshi, A. (2003). Cholecystokinin and cholecystokinin receptors. Journal of gastroenterology, 38(1), 1-13.
12. Spellman, S. J., Shaffer, E. A., & Rosenthall, L. (1979). Gallbladder emptying in response to cholecystokinin: a cholescintigraphic study. Gastroenterology, 77(1), 115-120.
13. Edholm, P. (1958). Emptying of the human gallbladder under the stimulus of cholecystokinin. Acta radiologica, 50(6), 521-532.
14. Owyang, C., Louie, D. S., & Tatum, D. (1986). Feedback regulation of pancreatic enzyme secretion. Suppression of cholecystokinin release by trypsin. The Journal of clinical investigation, 77(6), 2042-2047.
15. Schjoldager, B., Molero, X., & Miller, L. J. (1989). Functional and biochemical characterization of the human gallbladder muscularis

cholecystokinin receptor. Gastroenterology, 96(4), 1119-1125.
16. Wahlin, T., Bloom, G. D., & Danielsson, Å. (1976). Effect of cholecystokinin-pancreozymin (CCK-PZ) on glycoprotein secretion from mouse gallbladder epithelium. Cell and tissue research, 171(4), 425-435.
17. Kerstens, P. J. S. M., Lamers, C. B. H. W., Jansen, J. B. M. J., De Jong, A. J. L., Hessels, M., & Hafkenscheid, J. C. M. (1985). Physiological plasma concentrations of cholecystokinin stimulate pancreatic enzyme secretion and gallbladder contraction in man. Life sciences, 36(6), 565-569.
18. Matzinger, D., Gutzwiller, J. P., Drewe, J., Orban, A., Engel, R., D'Amato, M., ... & Beglinger, C. (1999). Inhibition of food intake in response to intestinal lipid is mediated by cholecystokinin in humans. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 277(6), R1718-R1724.
19. MacIntosh, C. G., Horowitz, M., Verhagen, M. A., Smout, A. J., Wishart, J., Morris, H., ... & Chapman, I. M. (2001). Effect of small intestinal nutrient infusion on appetite, gastrointestinal hormone release, and gastric myoelectrical activity in young and older men. The American journal of gastroenterology, 96(4), 997-1007.
20. Cottrell, D. F., & Iggo, A. (1984). The responses of duodenal tension receptors in sheep to pentagastrin, cholecystokinin and some other drugs. The Journal of physiology, 354(1), 477-495.
21. Anattomy&physiology ; the unit of form and function 3rd edition

22. Wank, S. A. (1995). Cholecystokinin receptors. American Journal of Physiology-Gastrointestinal and Liver Physiology, 269(5), G628-G646.
23. Scarpignato, C., Kisfalvi, I., D'Amato, M., & Varga, G. (1996). Effect of dexloxiglumide and spiroglumide, two new CCK- receptor antagonists, on gastric emptying and secretion in the rat: evaluation of their receptor selectivity in vivo. Alimentary pharmacology & therapeutics, 10(3), 411-419.
24. Varga, G. (2002). Dexloxiglumide Rotta Research Lab. Current opinion in investigational drugs (London, England: 2000), 3(4), 621-626.
25. Webber, C., Roth, A., Persiani, S., Peard, A. J., Makovec, F., Kapil, R. P., ... & Rovati, L. C. (2003). Pharmacokinetics and metabolism of the cholecystokinin antagonist dexloxiglumide in male human subjects. Xenobiotica, 33(6), 625-641.
26. Tolle- Sander, S., Grill, A., Joshi, H., Kapil, R., Persiani, S., & Polli, J. E. (2003). Characterization of dexloxiglumide in vitro biopharmaceutical properties and active transport. Journal of pharmaceutical sciences, 92(10), 1968-1980.
27. ^ Cremonini F, Camilleri M, McKinzie S, Carlson P, Camilleri CE, Burton D, et al. (March 2005). "Effect of CCK-1 antagonist, dexloxiglumide, in female patients with irritable bowel syndrome: a pharmacodynamic and pharmacogenomic study". The American Journal of Gastroenterology. 100 (3): 652–63. PMID 15743365.
28. ^ Galligan JJ, Vanner S (October 2005). "Basic and clinical pharmacology of new motility

promoting agents". Neurogastroenterology and Motility. 17 (5): 643–53. doi:10.1111/j.1365-2982.2005.00675.x. PMID 16185302.
29. Herranz, R. (2003). Cholecystokinin antagonists: pharmacological and therapeutic potential. Medicinal research reviews, 23(5), 559-605.
30. ^ Maselli MA, Mennuni L (September 2003). "CCK1 receptor antagonist, dexloxiglumide: effects on human isolated gallbladder. Potential clinical applications". Minerva Gastroenterologica e Dietologica. 49 (3): 211–6. PMID 16484960.
31. go.drugbank.com/structures/DB04856/image.svg
32. www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=861
33. Liddle, R. A. (1997). Cholecystokinin cells. Annual review of physiology, 59(1), 221-242.
34. Moran, T. H., & Kinzig, K. P. (2004). Gastrointestinal satiety signals II. Cholecystokinin. American Journal of Physiology-Gastrointestinal and Liver Physiology, 286(2), G183-G188.
35. Liddle, R. A. (2000). Regulation of cholecystokinin secretion in humans. Journal of gastroenterology, 35(3), 181-187.
36. Polak, J. M., Bloom, S. R., Rayford, P. L., Pearse, A. G. E., Buchan, A. M. J., & Thompson, J. C. (1975). Identification of cholecystokinin-secreting cells. The Lancet, 306(7943), 1016-1018.
37. go.drugbank.com/drugs/DB04856
38. The gastrointestinal system ; gastrointestinal , nutritional & hepatobiliary physiology

39. Grider, J. R. (1994). Role of cholecystokinin in the regulation of gastrointestinal motility. The Journal of nutrition, 124(suppl_8), 1334S-1339S.
40. Beglinger, C., Fried, M., Whitehouse, I., Jansen, J. B., Lamers, C. B., & Gyr, K. (1985). Pancreatic enzyme response to a liquid meal and to hormonal stimulation. Correlation with plasma secretin and cholecystokinin levels. The Journal of clinical investigation, 75(5), 1471-1476.
41. Williams, J. A., & Blevins Jr, G. T. (1993). Cholecystokinin and regulation of pancreatic acinar cell function. Physiological reviews, 73(4), 701-723.
42. Jorpes, J. E., & Mutt, V. (1973). Secretin and cholecystokinin (CCK). In Secretin, cholecystokinin, pancreozymin and gastrin (pp. 1-179). Springer, Berlin, Heidelberg.
43. Sayegh, A. I. (2013). The role of cholecystokinin receptors in the short-term control of food intake. Progress in molecular biology and translational science, 114, 277-316.
44. Debas, H. T., & Grossman, M. I. (1973). Pure cholecystokinin: pancreatic protein and bicarbonate response. Digestion, 9(6), 469-481.
45. Herzig, K. H. (1998). Cholecystokinin-and secretin-releasing peptides in the intestine—a new regulatory interendocrine mechanism in the gastrointestinal tract. Regulatory peptides, 73(2), 89-94.
46. Dockray, G. J. (2006). Gastrointestinal hormones: gastrin, cholecystokinin, somatostatin and ghrelin. Physiology of the gastrointestinal tract. Amsterdam, Elsevier Inc, 91-120.

47. Hirschberg, A. L., Lindholm, C., Carlström, K., & Von Schoultz, B. (1994). Reduced serum cholecystokinin response to food intake in female athletes. Metabolism, 43(2), 217-222.
48. Hirschberg, A. L., Byström, B., Carlström, K., & von Schoultz, B. (1996). Reduced serum cholecystokinin and increase in body fat during oral contraception. Contraception, 53(2), 109-113.
49. Thompson, J. C., Fender, H. R., Ramus, N. I., Villar, H. V., & Rayford, P. L. (1975). Cholecystokinin metabolism in man and dogs. Annals of surgery, 182(4), 496.
50. Dufresne, M., Seva, C., & Fourmy, D. (2006). Cholecystokinin and gastrin receptors. Physiological reviews, 86(3), 805-847.
51. Rehfeld, J. F. (1978). The measurement of cholecystokinin. Journal of Clinical Pathology. Supplement (Ass. Clin. Path.), 8, 26.
52. Liddle, R. A. (1994). Regulation of cholecystokinin synthesis and secretion in rat intestine. The Journal of nutrition, 124(suppl_8), 1308S-1314S.
53. Manual of endocrinology & metabolism 5th edition
54. Dodd, J., & Kelly, J. S. (1981). The actions of cholecystokinin and related peptides on pyramidal neurones of the mammalian hippocampus. Brain research, 205(2), 337-350.
55. The manual of endocrinology & physiology 5th edition
56. Lal, S., McLaughlin, J., Barlow, J., D'Amato, M., Giacovelli, G., Varro, A., ... & Thompson, D. G. (2004). Cholecystokinin pathways modulate

sensations induced by gastric distension in humans. American Journal of Physiology-Gastrointestinal and Liver Physiology, 287(1), G72-G79.
57. Zeng, Q., Ou, L., Wang, W., & Guo, D. Y. (2020). Gastrin, cholecystokinin, signaling, and biological activities in cellular processes. Frontiers in endocrinology, 11, 112.
58. Crona, D., & MacLaren, R. (2012). Gastrointestinal hormone concentrations associated with gastric feeding in critically ill patients. Journal of Parenteral and Enteral Nutrition, 36(2), 189-196.
59. Sartor, D. M., & Verberne, A. J. (2006). The sympathoinhibitory effects of systemic cholecystokinin are dependent on neurons in the caudal ventrolateral medulla in the rat. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 291(5), R1390-R1398.
60. Sartor, D. M., & Verberne, A. J. (2008). Abdominal vagal signalling: a novel role for cholecystokinin in circulatory control?. Brain research reviews, 59(1), 140-154.
61. Reidelberger, R. D. (1994). Cholecystokinin and control of food intake. The Journal of nutrition, 124(suppl_8), 1327S-1333S.
62. CARE, A. D., BRUCE, J. B., BOELKINS, J., KENNY, A. D., CONAWAY, H., & ANAST, C. S. (1971). Role of pancreozymin-cholecystokinin and structurally related compounds as calcitonin secretogogues. Endocrinology, 89(1), 262-271.
63. 2 Jansen, J. B. M. J., & Lamers, C. B. H. W. (1983). Molecular forms of cholecystokinin in human plasma during infusion of bombesin. Life sciences, 33(22), 2197-2205.

64. Wang, Y., Chandra, R., Samsa, L. A., Gooch, B., Fee, B. E., Cook, J. M., ... & Liddle, R. A. (2011). Amino acids stimulate cholecystokinin release through the Ca2+-sensing receptor. American Journal of Physiology-Gastrointestinal and Liver Physiology, 300(4), G528-G537.
65. Lamers, C. B. H., Jansen, J. B. M. J., & Woutersen, R. A. (1990). Cholecystokinin and gastrointestinal cancer. The Journal of steroid biochemistry and molecular biology, 37(6), 1069-1072.
66. Rehfeld, J. F. (2021). Cholecystokinin and the hormone concept. Endocrine Connections, 10(3), R139-R150.
67. Rehfeld, J. F., Friis-Hansen, L., Goetze, J. P., & Hansen, T. V. (2007). The biology of cholecystokinin and gastrin peptides. Current topics in medicinal chemistry, 7(12), 1154-1165.
68. Johnsen, A. H. (1998). Phylogeny of the cholecystokinin/gastrin family. Frontiers in neuroendocrinology, 19(2), 73-99.
69. Wank, S. A., Pisegna, J. R., & De Weerth, A. (1992). Brain and gastrointestinal cholecystokinin receptor family: structure and functional expression. Proceedings of the National Academy of Sciences, 89(18), 8691-8695.
70. Gibbs, J., Young, R. C., & Smith, G. P. (1973). Cholecystokinin decreases food intake in rats. Journal of comparative and physiological psychology, 84(3), 488.
71. Sturdevant, R. A., & Goetz, H. (1976). Cholecystokinin both stimulates and inhibits human food intake. Nature, 261(5562), 713-715.

72. Rehfeld, J. F. (2017). Cholecystokinin—from local gut hormone to ubiquitous messenger. Frontiers in endocrinology, 8, 47.
73. Rehfeld, J. F. (1981). Four basic characteristics of the gastrin-cholecystokinin system. American Journal of Physiology-Gastrointestinal and Liver Physiology, 240(4), G255-G266.
74. Teitelbaum, D. H., Han- Markey, T., Drongowski, R. A., Coran, A. G., Bayar, B., Geiger, J. D., ... & Schork, M. A. (1997). Use of cholecystokinin to prevent the development of parenteral nutrition- associated cholestasis. Journal of Parenteral and Enteral Nutrition, 21(2), 100-103.
75. Bergh, C., Sjöstedt, S., Hellers, G., Zandian, M., & Södersten, P. (2003). Meal size, satiety and cholecystokinin in gastrectomized humans. Physiology & behavior, 78(1), 143-147.
76. Kissileff, H. R., Carretta, J. C., Geliebter, A., & Pi-Sunyer, F. X. (2003). Cholecystokinin and stomach distension combine to reduce food intake in humans. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 285(5), R992-R998.
77. Santangelo, A., Peracchi, M., Conte, D., Fraquelli, M., & Porrini, M. (1998). Physical state of meal affects gastric emptying, cholecystokinin release and satiety. British Journal of Nutrition, 80(6), 521-527.
78. Miller, L. J., Jardine, I., Weissman, E., Go, V. L. W., & Speicher, D. (1984). Characterization of cholecystokinin from the human brain. Journal of neurochemistry, 43(3), 835-840.

79. Anika, S. M., Houpt, T. R., & Houpt, K. A. (1981). Cholecystokinin and satiety in pigs. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 240(5), R310-R318.
80. Dockray, G. J. (2009). Cholecystokinin and gut–brain signalling. Regulatory peptides, 155(1-3), 6-10.
81. ^ Roberts DJ, Banh HL, Hall RI (August 2006). "Use of novel prokinetic agents to facilitate return of gastrointestinal motility in adult critically ill patients". Current Opinion in Critical Care. 12 (4): 295–
302. doi:10.1097/01.ccx.0000235205.54579.5d. PM ID 16810038.
82. ^ Jump up to:[a] [b] Bowen R (28 January 2001). "Cholecystokinin". Colorado State University. Archived from the original on 17 March 2016. Retrieved 6 November 2015.
83. Physiology_Osama_Abo_El_Nasr_Year_2_Concise_Medical_Physiology_3rd edition
84. Esentials of anatomy and physiology 6th edition
85. Medical physiology ; the big picture
86. Meyer, B., Beglinger, C., Jansen, J. M., Rovati, L., Werth, B., Hildebrand, P., ... & Stalder, G. (1989). Role of cholecystokinin in regulation of gastrointestinal motor functions. The Lancet, 334(8653), 12-15.
87. Guyton_and_Hall_Textbook_of_Medical physiology 12th edition
88. ross and wilson anatomy and physiology in health & illness 11th edition
89. endocrine and reproductive physiology

90. Gastrointestinal physiology ; development , principles & mechanisms of regulation
91. Gastrointestinal anatomy & physiology the essentials
92. Principles of Translational neuroendocrinology
93. Ganong's review of medical physiology 26th edition
94. Clinical anatomy and physiology for veterinary technicians 3rd edition
95. Fisher, R. S., DiMarino, A. J., & Cohen, S. I. D. N. E. Y. (1975). Mechanism of cholecystokinin inhibition of lower esophageal sphincter pressure. American Journal of Physiology-Legacy Content, 228(5), 1469-1473.
96. Cunningham's_Textbook_of_Veterinary physiology 5th edition
97. Beinfeld, M. C. (1983). Cholecystokinin in the central nervous system: a minireview. Neuropeptides, 3(6), 411-427.
98. Straus, E., & Yalow, R. S. (1978). Species specificity of cholecystokinin in gut and brain of several mammalian species. Proceedings of the National Academy of Sciences, 75(1), 486-489.
99. Smith, G. P., & Gibbs, J. (1994). Satiating Effect of Cholecystokinin a. Annals of the New York Academy of Sciences, 713(1), 236-241.
100. Beinfeld, M. C., Meyer, D. K., & Brownstein, M. J. (1981). Cholecystokinin in the central nervous system. Peptides, 2, 77-79.
101. Glick, Z., Thomas, D. W., & Mayer, J. (1971). Absence of effect of injections of the intestinal hormones secretin and cholecystokinin-

pancreozymin upon feeding behavior. Physiology & behavior, 6(1), 5-8.
102. Tripathi, S., Flobak, Å., Chawla, K., Baudot, A., Bruland, T., Thommesen, L., ... & Lægreid, A. (2015). The gastrin and cholecystokinin receptors mediated signaling network: a scaffold for data analysis and new hypotheses on regulatory mechanisms. BMC systems biology, 9(1), 1-15.
103. Hoyda, T. D., Smith, P. M., & Ferguson, A. V. (2009). Gastrointestinal hormone actions in the central regulation of energy metabolism: potential sensory roles for the circumventricular organs. International journal of obesity, 33(1), S16-S21.
104. Renny, A., Snape Jr, W. J., Sun, E. A., London, R., & Cohen, S. (1983). Role of cholecystokinin in the gastrocolonic response to a fat meal. Gastroenterology, 85(1), 17-21.
105. Saito, A., Sankaran, H., Goldfine, I. D., & Williams, J. A. (1980). Cholecystokinin receptors in the brain: characterization and distribution. Science, 208(4448), 1155-1156.
106. Beinfeld, M. C. (2001). An introduction to neuronal cholecystokinin. Peptides, 22(8), 1197-1200.
107. Liddle, R. A. (1995). Regulation of cholecystokinin secretion by intraluminal releasing factors. American Journal of Physiology-Gastrointestinal and Liver Physiology, 269(3), G319-G327.
108. SILVENTE- POIROT, S., Dufresne, M., Vaysse, N., & Fourmy, D. (1993). The peripheral cholecystokinin receptors. European journal of biochemistry, 215(3), 513-529.

109. Guilloteau, P., Le Meuth-Metzinger, V., Morisset, J., & Zabielski, R. (2006). Gastrin, cholecystokinin and gastrointestinal tract functions in mammals. Nutrition research reviews, 19(2), 254-283.
110. Morisset, J. (2005). The gastrointestinal cholecystokinin receptors in health and diseases. Rocz Akad Med Bialymst, 50, 21-36.
111. Liddle, R. A. (2003). Cholecystokinin: its role in health and disease. Current Opinion in Endocrinology, Diabetes and Obesity, 10(1), 50-54.