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Gut peptides: Gastrin Releasing Peptide, Cholecystokinin, and Glucagon-Like Peptide-1 in the Regulation of Food Intake and Satiety: Review Article

Thaer R. Mhalhal[1], Yasmeen J. Mohammed[2], JALA A S ALAHME D[3], Firas A. Alhasson[4]

[1,4]Department of Anatomy and Histology, Veterinary Medicine College, University of Basrah, Basrah, Iraq.
https://orcid.org/ 0000-0001-6104-8516 Tel: 009647718888520
[2]Department of Pathology and Poultry disease, Veterinary Medicine College, University of Basrah, Basrah, Iraq.
https://orcid.org/ 0000-0002-8696-1720 Tel: 009647710788852
[3]Department of Physiology, Pharmacology and Biochemistry, Veterinary Medicine College, University of Basrah, Basrah, Iraq.
https://orcid.org/0000-0003-1033-2626 Tel: 07824000314

Email: [1]thaer.mhalhal@uobasrah.edu.iq, [2]yasmeen.mohammed@uobasrah.edu.iq, [3]jala.salman@uobasrah.edu.iq

Abstract: Obesity is an imbalance between energy intake and energy expenditure. This imbalance is manifested clinically by accumulation of fat primarily in the abdomen, in cases of males, and in the hips, in cases of females. In addition, this world-wide epidemic may lead to several serious, and sometimes deadly, health problems e.g., type 2 diabetes, Cardiovascular disease, osteoarthritis, coronary heart disease (CHD), hypertension, gall bladder disease, sleep apnea and respiratory, cancer and cachexia, irregular menstrual cycles and hormonal imbalances. Gastrin-releasing peptide is a hormonepeptide secreted by gastric and brain neurons, and stimulates gastrin release and regulates gastric acid secretion Gastrin-releasing peptide is a peptide that is structurally similar to the amphibian peptide bombesin (Bn). Bn was isolated from the skin of the fire-bellied toad, Bombina bombina, and Bombina variegate Bombesin-like peptides, discovered in a variety of amphibian skin secretions, have been shown to have a variety of biological functions, including stimulation contraction of smooth muscle and regular of intake food. The short-term control of food intake regulates individual meal size (MS) and the time between two consecutive meals, also known as intermeal interval (IMI). This control is regulated by satiety peptides / hormones secreted by the gastrointestinal (GI) tract. Such peptides / hormones may include gastrin-releasing peptide (GRP), which is secreted by the enteric neurons of the stomach and small intestine, cholecystokinin (CCK), which is secreted by the I cells of the small and the large intestine, glucagon-like peptide-1 (GLP-1), which is secreted by the L cells of the large intestine.

Keywords: Gut peptides, Gastrin Releasing Peptide, Cholecystokinin, Glucagon-Like Peptide-1

1. INTRODUCTION

Gastrin Releasing Peptide

Gastrin-releasing peptide is a hormonepeptide secreted by gastric and brain neurons.(McDonald et al. 1978) and stimulates gastrin release and regulates gastric acid secretion (McDonald et al. 1979). Gastrin-releasing peptide is a peptide that is structurally similar to the amphibian peptide bombesin (Bn). Bn was isolated from the skin of the fire-bellied toad, *Bombina bombina*, and *Bombina variegate* Bombesin-like peptides, discovered in a variety of amphibian skin secretions, have been shown to have a variety of biological functions, including stimulation contraction of smooth muscle and regular of intake food . (Xiaowei Zhou et al 2017). There are numerous bombesin peptides and their precursor cDNAs that have been confirmed from various species' skin secretions.(Bai, B.; Zhang et al 2013).

In mammals, there are two mammalian bombesin-like peptides GRP and neuromedin B (NMB). GRP (gastrin-releasing peptide) and NMB (neuromedin B) are two of the most commonly studied bombesin-like peptides in mammals. Inhibition of food intake, smooth muscle contraction, exocrine and endocrine secretion, thermoregulation, blood pressure, sucrose regulation, and cell growth are just a few examples of these functions. (HIROKO OHKI-HAMAZAKI et al 2005). Amphibian bombesin was used by McDonald to isolate a homologous peptide named GRP from porcine stomach shortly after it was isolated because of its ability to stimulate the release of gastrin from that species. The 29-amino acid peptide in Xenopus laevis' stomach was found to be highly similar to the amino acid sequence of mammalian GRP, and so GRP was thought to be the amphibian bombesin's mammalian homolog for a long time. (Kim et al. 2002). . GRP-29, not GRP-27, is the large molecular form of GRP in rats, according to research. (Nagalla, Gibson, Tang, Reeve, & Spindel, 1992).

In 2014, the large form of GRP in rats is GRP-29 and the small form is GRP-10 (Reeve et al. 2014). In addition, both forms reduced MS, prolonged the IMI length and increased the SR when administered intravenously (i.v) (Reeve et al. 2014).

Furthermore, the intraperitoneal i.p. injections of GRP-27 and GRP-29 reduce MS, prolong the IMI length and increase the SR (Washington, Wright, et al. 2011). In 2012, Wright et. al. found that the vagus and the splanchnic nerves are necessary for reducing MS by GRP-29 and that the enteric nervous system in the duodenum is necessary for prolongation of the IMI length by this peptide (Wright, Washington, Garcia, & Sayegh, 2012). In 2014, Washington and colleagues found that intravenous (i.v.) administration of GRP-27 causes a decrease in MS while Bn prolonged the IMI, suggesting different binding sites for these peptides (Washington, Salyer, Aglan, & Sayegh, 2014). In addition, GRP-10, GRP-27 and GRP-29 reduced MS, prolonged the IMI length and increased the SR similarly in lean and obese Zucker rats (Washington, Park, & Sayegh, 2014). Finally, the gastrointestinal sites of action regulating MS and IMI length by GRP-27 and GRP-29 are located in the stomach and / or upper duodenum (Washington, Aglan, & Sayegh, 2014).

Washington et. al. found that Roux-en-Y gastric bypass improves the feeding responses evoked by exogenous GRP-10 and GRP-29 (Washington, Mhalhal, Johnson-Rouse, et al. 2016) and the BB2 receptor in the stomach and upper duodenum is necessary for GRP-29's reduction of food intake and prolongation of the IMI (Washington, Mhalhal, et al. 2016a). Mhalhal et. al. found that CCK-8, GRP-29 and the combination of the two peptides reduce body weight in the diet-induced obese rat model when administered directly to the gastrointestinal sites of action (T. R. Mhalhal, M. C. Washington, K. Newman, J. C. Heath, & A. I. Sayegh, 2017c).

Peptide Bombasin, found in the skin of the frog Bombina, is a possible antibacterial agent. Animals have been found to produce two closely related (bombesin-like) peptides: gastrin-releasing peptide (GRP) and neuromedin B (NMB). GRP/bombesin receptor

evolution in vertebrates has received scant attention in the wake of their discovery because of this. (Asuka Hirooka et al 2021).

found a GRP neuropeptide in amphioxus that could interact with the GRP receptor, activate PKC/PKA pathways as well as Gh/IGF/VEGF expression; this GRP neuropeptide was found to be functional. In addition, the transcription level of amphioxus grp was affected by temperature and light, indicating its role in the regulation of energy balance and circadian rhythms. Amphioxus grp was also detected in the cerebral vesicle, which has been proposed to be a homologous organ for the vertebrate brain's cerebral cortex.(PengWang et al 2020)

Forms and Receptors

There are three forms of GRP, GRP-10, GRP-27 and GRP-29. Gastrin-releasing peptide-10 is present in all species, GRP-27 is present in all species except the rat and GRP-29 is found only in the rat (McDonald et al. 1978; Minamino, Kangawa, & Matsuo, 1984; Orloff, Reeve, Ben-Avram, Shively, & Walsh, 1984; Spindel et al. 1984). Bombesin and GRP evoke many responses by activating three receptors distributed centrally and peripherally. They bind to three G-protein coupled receptors, BB1 (GRP receptor), BB2 (NMB receptor) and BB3 (BRS-3 receptor) (McDonald et al. 1978; Seidita et al. 2008). The BB1 (neuromedin-B receptor) receptor is found in the CNS, the BB2 (gastrin- releasing peptide receptor) receptor and the BB3 (bombesin receptor subtype-3) are found in the alimentary tract and the CNS (Sayegh, 2013a; Washington, Mhalhal, & Sayegh, 2016a). The ligand for the BRS-3 receptor is unknown.

Physiological Response

Internally, GRP causes the release of various peptides such as pancreatic polypeptide, insulin-like growth factor 1, enteroglucagon and pancreatic glucagon, as well as contraction of smooth muscle. (Ghatei et al. 1982; Gibbs et al. 1979; Gibbs, Kulkosky, & Smith, 1981; McDonald et al. 1983; Porreca, Burks, & Koslo, 1985; Stein & Woods, 1982; Tache & Gunion, 1985). Direct injections of GRP in the NTS decreased meal size (MS) (Johnston & Merali, 1988) and infusion of a highly selective GRP antagonist (BN-ME) in the third (Johnston & Merali, 1988) and fourth ventricles blocked this effect. (Ladenheim & Ritter, 1991; Ladenheim, Taylor, Coy, Moore, & Moran, 1996). G-cells secrete more gastrin in the presence of Helicobacter pylori gastritis, likely due to the loss of D-cells and the subsequent dysregulation of gastrin secretion by G-cells.When this imbalance occurs, the gastric mucosa is overwhelmed, which can lead to gastric mucosal damage and the development of peptic ulcers. Jordon G. Prosapio and colleagues.(Jordon G. Prosapio et al 2022).

Effect of GRP on Food Intake

Intraperitoneal (i.p.) injections of GRP-27 and GRP-29 reduced first MS, extended IMI length, and increased satiety ratio (IMI divided by MS, the amount of food consumed per unit of time) in rats when GRP-10 failed to elicit these effects. (Washington, Wright, et al. 2011).

GRP-27 and GRP-29, the large forms of this peptide, activated the duodenal myenteric neurons while only GRP-29 activated the duodenal submucosal plexus, according to one study. According to the authors (Washington and Sayegh, 2011). It is possible that GRP reduces food intake by activating vagal and / or splanchnic innervations, which may be activated by the AP as well. The fact that GRP activates enteric neurons suggests that these neurons are either directly or indirectly involved in the peptide's ability to reduce food intake. The Fos-LI, a neuronal activation marker, was also increased by GRP in the gut's enteric

nervous system (ENS) as well as the DVC (Washington & Sayegh, 2011). This suggests that GRP's ability to reduce food intake may be mediated by the ENS. (Washington, Wright, et al. 2011). GRP, or GRP agonists like bombesin, can reduce the size of a meal in both animals and humans when given orally or intravenously. The stomach, according to studies on local administration, is the most important site for secretion and action. In this way, GRP may mediate some of the satiating effect of the mechanical stimuli that are generated when ingested food fills the stomach. Through both vagal and spinal visceral afferents (which project to the NTS), GRP exerts its effect on the brain's peripheral nervous system.(NoriGeary 2004).

Cholecystokinin

It was discovered in 1902 by Bayliss and Starling that the mucosa of the upper small intestine contains CCK, a peptide hormone that stimulates pancreatic secretion and bile flow. (Bayliss & Starling, 1902). Significant discoveries have been made since that lead to learning more about CCK. In 1919, Braga and Campos found that a preparation similar to Bayliss and Starling's preparation caused contraction of the gallbladder. In 1928, Ivy and Oldberg named the substance which stimulated gallbladder contraction cholecystokinin (CCK) (Ivy AC, 1928).

To stimulate pancreatic enzyme secretion, Harper and Raper in 1943 discovered a substance. (Harper & Raper, 1943). They named the substance pancreozymin (Harper & Raper, 1943). In 1948, Wang and Grossman found a substance which is similar in functions to both pancreozymin and CCK (Wang & Grossman, 1948). In 1966, Jorpes and Mutt suggested that purified pancreozymin, similar to CCK, stimulates both pancreatic secretion and gallbladder contraction (Jorpes & Mutt, 1966). As a result, they kept the original name CCK.

Johnson and Magee found that CCK reduces intragastric pressure (L. P. Johnson & Magee, 1965), while in 1967, Unger and colleagues found that CCK activates insulin secretion in dogs (Unger, Ketterer, Dupre, & Eisentraut, 1967).

Sayegh & Ritter in 2000, it has been shown that CCK-8 activates the CCK1 receptors in the myenteric plexus (Sayegh & Ritter, 2000) and that CCK-8 activation of myenteric neurons doesn't depend on activation of the vagus nerve or capsaicin-sensitive neurons (Sayegh & Ritter, 2000). In 2003, Sayegh and colleagues found that CCK-8 activates specific enteric neurons in the upper small intestine, and CCK-8 actives inhibitory motor neurons in the myenteric plexus (Sayegh & Ritter, 2003).

In 2005, Gulley and others found that chemical sympathectomy by guanethidine sulfate attenuates myenteric activation but not DVC activation in response to CCK-8 (Webb et al. 2005) and that CCK-8 increases activation in the brainstem and myenteric neurons of the jejunum through CCK1 receptors (Webb et al. 2005). They also found that Sprague Dawley rats had more activation in the AP than standard Long-Evans and Long-Evans Tokushima Otsuka rats in response to CCK-8, and Otsuka Long-Evans Tokushima Fatty rats (rats lacking the CCK1 receptor) which had no activation (Webb et al. 2005). Webb and others found that i.p. injection of CCK-8 is more potent in increasing activation of the DVC than the i.v. route (Webb et al. 2005).

Raboin and colleagues found that a sympathectomy and demedullation could increase activation in the DVC and myenteric plexus by CCK-8 (Raboin, Gulley, Henley, Chan, et al. 2006) and there is an interaction of CCK-8 activation in the myenteric plexus and adrenal gland secretions (Raboin, Gulley, Henley, Chang, et al. 2006). In 2007, Sullivan and others

found that endogenous / peripherally produced CCK reduces food intake by a central mechanism that involves the vagus and CCK1 receptors (Sullivan et al. 2007).

In 2008, Cooper and colleagues found that CCK-58 and CCK-8 activate the myenteric plexus and the DVC in similar patterns (Cooper, Reeve, Raboin, et al. 2008), but CCK-33 is more efficient in reducing food intake and activating the DVC and myenteric plexus than CCK-8 (Cooper, Reeve, Abdalla, et al. 2008). In 2010, Larsen and colleagues found that CCK-8 increases the satiety ratio more than CCK-33 in diabetic rats (Larsen, Washington, & Sayegh, 2010) (Larsen et al. 2010).

Lateef and colleagues found that camostat, a non-nutrient releaser of endogenous CCK, reduces MS and prolongs the IMI length (Lateef, Washington, & Sayegh, 2011). However, Washington and others found that CCK-33 and CCK-8 reduce MS, whereas CCK-33 prolongs the IMI length and increases the satiety ratio (Washington, Coggeshall, & Sayegh, 2011). Brown and others found that CCK-8 mediates the feeding responses through the vagus and splanchnic nerves (Brown, Washington, Metcalf, & Sayegh, 2011) and Metcalf and others found that performing an ileal interposition attenuates reduction of food intake by CCK-8 (Metcalf et al. 2011) and Washington and others found that CCK-8 activated the DVC in 4-, 14-, 21-, and 35- day old rats and CCK-8 activated the myenteric neurons in 21- and 35- day old rats (Washington, Murry, et al. 2011).

Lateef and colleagues found that the CCK1 receptor is located mainly in the duodenum and that a myotomy blocked reduction of MS and prolongation of the IMI by endogenous CCK (Lateef et al. 2012).

In 2014, Sayegh and colleagues found that all forms of CCK do not have the same bioactivity due to the fact that CCK-58 prolongs the IMI when CCK-8 shortens it, and in 2015 they found that the gastrointestinal tract contains sites of action for regulation of MS and IMI length by CCK-58 (Sayegh et al. 2015).

Washington and others found that CCK-8 regulates MS through the celiac artery, which supplies the stomach and upper duodenum, and regulates the IMI length through the cranial mesenteric artery, which supplies the small and part of the large intestine. This suggested different regulatory sites for CCK-8 in the gut (Washington, Mhalhal, & Sayegh, 2016b) and the different forms of CCK e.g. CCK-33 have different gastrointestinal regulatory sites than CCK-8 (Washington, Mhalhal, et al. 2016b).

Forms

In 1968 and 1971, Mutt and Jorpes described the first molecular form of CCK in the porcine upper intestine (Mutt & Jorpes, 1968; Mutt, Jorpes, & Magnusson, 1970). After that point many scientists isolated various molecular forms of CCK e.g. CCK-5, CCK-7, CCK-8, CCK-12, CCK-18, CCK-22, CCK-25, CCK-33, CCK-39, CCK-53, CCK-58 and CCK-83.

Way found that CCK reduces gastric secretion in the cat (Way, 1971). In 1973 Gibbs, Young and Smith found that intraperitoneal (i.p.) administration of CCK-8 reduces food intake in rats during the first 30-60 minute after injection (Gibbs, Young, & Smith, 1973). Also in 1973 Fisher and Lipshutz found that CCK-8 increases pyloric contraction (Fisher, Lipshutz, & Cohen, 1973).

In 1975, Debas and Farooq found that CCK-8 inhibits gastric emptying (Debas, Farooq, & Grossman, 1975). There is CCK-8 in the mucosa of the duodenum and jejunum in humans, according to the findings of Polak and Bloom that year. (Polak et al. 1975) and in 1976 Buffa and Solcia confirmed this finding (Buffa, Solcia, & Go, 1976). In 1977 Egberts and Johnson found that CCK causes contraction of the colon (Egberts & Johnson, 1977).

Yamagishi and Debas (1978) found that CCK inhibits gastric emptying by acting on the pylorus and the proximal stomach.

Effect of CCK on Food Intake

In 1981 Smith and Jerome found that CCK reduces the satiety (feeling full after eating) in rats via the gastric branch of the vagus nerve (G. P. Smith, Jerome, Cushin, Eterno, & Simansky, 1981). In the same year, they found that abdominal vagotomy blocked the feeding effects of CCK-8, therefore providing the first evidence for CCK-8 working peripherally (G. P. Smith, Jerome, et al. 1981). In 1984 and in 1986 Smith and colleagues found that CCK receptors reside in the alimentary tract and the brain of rats (Moran, Robinson, Goldrich, & McHugh, 1986; G. T. Smith et al. 1984) and they adopted the names CCKA for the alimentary receptor and CCKB for the brain receptor.

Smith and Moran determined that CCK-8 inhibits gastric emptying by relaxing the circular smooth muscle of the pyloric sphincter (G. T. Smith et al. 1984). In the same year, Tatemoto and Jornvall found that CCK-58 stimulates gallbladder contraction (Tatemoto, Jornvall, Siimesmaa, Hallden, & Mutt, 1984). In 1985, Smith and Jerome found that vagotomy results in decreaseing of gastric empting and reduction of food consumption. (G. P. Smith, Jerome, & Norgren, 1985). In 1988, Eberlein et al. found that CCK's primary molecule in the dog circulation is CCK-58 (Eberlein, Eysselein, & Goebell, 1988). Additionally, Raybould and Tache found that CCK-8 inhibits gastric motility via a vagal afferent pathway in the same year. (Raybould & Tache, 1988).

Melville and Smith found that devazepide, a specific CCKA receptor antagonist, attenuates reduction of food intake by CCK-8 (Melville, Smith, & Gibbs, 1992). In the same year, Fraser and Davison demonstrated that CCK-8 increases Fos-like immunoreactivity (Fos-L), a marker for neuronal activation, in hindbrain feeding areas such as nucleus tractus solitaries (NTS), area postrema (AP) and dorsal motor nucleus of vagal nerve (DMV), and in the paraventricular nucleus of the hypothalamus (Fraser & Davison, 1992). In 1993, Corwin and Smith found that CCK-8 stimulates gastric secretion following CCKA and CCKB receptor blockade (Corwin & Smith, 1993).

Receptors

In 1994, Jensen and Wank found that CCKA receptor, also known as CCK_1 receptor, is a 429- amino acid peptide, and CCKB receptor also known as CCK_2 receptor, is a 453-amino acid peptide (Jensen et al. 1994). In 1996, Richards et al. determined that CCK-8 stimulates neurons by activating CCK_1 receptors on vagal afferents (Richards, Hillsley, Eastwood, & Grundy, 1996). Schutte and Akkermans found in 1997 that CCK-8 activates the neurons by both CCKA and CCKB receptors (Schutte, Akkermans, & Kroese, 1997). These results showed that some neurons have only one of the CCK receptors and some neurons have both receptors.

Barrachina and colleagues found that CCK-8 and leptin reduce food intake synergistically in mice (Barrachina, Martinez, Wang, Wei, & Tache, 1997). In 1998 Kennedy and Mawe found that in the guinea pig a myenteric neurons projecting from the duodenum to the sphincter of Oddi contain CCK (Kennedy & Mawe, 1998). In addition, in 2000 Sayegh and Ritter found that CCK-8 increases Fos-LI in the myenteric neurons of the small intestine in the rat by activating CCKA receptors (Sayegh & Ritter, 2000).

Reeve and colleagues in 2003 found that the major endocrine form of CCK in the rat is CCK-58(Reeve, Green, Chew, Eysselein, & Keire, 2003). This is an important finding because there are differences between the different forms of CCK. For instance, CCK-58

stimulates pancreatic secretion while CCK-8 does not (Yamamoto, Reeve, & Green, 2007; Yamamoto, Reeve, Keire, & Green, 2005). Cholecystokinin-58 increased Fos-like immunoreactivity in the hindbrain and submucosal plexus (Cooper, Reeve, Raboin, et al. 2008; Raboin, Reeve, Cooper, Green, & Sayegh, 2008) while CCK-8 increased it in the hindbrain, myenteric and submucosal plexuses (Cooper, Reeve, Raboin, et al. 2008; Raboin et al. 2008). It has also been shown that CCK-58 and CCK-33 can reduce MS and prolong the IMI whereas, CCK-8 can reduce only MS (Glatzle, Raybould, Kueper, Reeve, & Zittel, 2008; Goebel-Stengel et al. 2012; Sayegh, Washington, Raboin, Aglan, & Reeve, 2014).

Glucagon Like Peptide-1

In addition to the enteroendocrine L cells, pancreatic cells, and NTS neurons, GLP1 is also produced by the posttranslational processing of the proglucagon gene in the enteroendocrine L cells, pancreas cells, and NTS neurons (Kreymann 1988 #301; Eissele 1992 #304; Brubaker and Anini 2003). Proteolytic cleavage and amidation of the initial product, GLP-1 (1–37), produce two biologically active forms, GLP-1 (7–36) amide and GLP-1 (7–36) (7–37). The enzyme dipeptidyl peptidase-4 rapidly degrades both forms in the bloodstream (DPP4). (Orskov, Bersani, Johnsen, Hojrup, & Holst, 1989).

Glucagon like peptide-1 proglucagon is expressed in various tissues e.g. intestinal enteroendocrine L-cells, α-cells of the islets of Langerhans in the pancreas and neurons of the caudal brainstem and hypothalamus. The hormone glucagon, a counter-regulatory hormone, the growth factor GLP2, a gastric acid inhibitor, and the oxyntomodulin proglucagon derivative are all examples of other proglucagon-derived products. Fasting and hypoglycemia promote proglucagon expression in the pancreas, while insulin tends to inhibit pancreatic expression of proglucagon. Intestinal expression of the proglucagon is inhibited by hypoglycemia but stimulated by ingestion of food e.g. fat and carbohydrates (Marathe, Rayner, Jones, & Horowitz, 2013).

To get the biologically active GLP-1, endopeptidase cleaves proglucagon (78–107) into GLP-1 (1–37), which is the endogenous GLP-1 Amidation of the C-terminal arginine, on the other hand, results in GLP-1 (7–36) amide, which is just as potent as GLP-1. The vast majority of GLP-1 secreted by humans is amidated, whereas in other species a significant portion of GLP-1 remains as GLP-1(Holst, 2007).

Glucagon like peptide-1 exerted its effects through binding to a G protein coupled receptor GLP1R (Maida, Lovshin, Baggio, & Drucker, 2008). GLP1R is expressed on vagal afferents, the gut, pancreas, brainstem and the hypothalamus (Holst, 2004 #309;Vilsboll, 2004 #316;Turton, 1996 #312;Tang-Christensen, 1996 #310; Drucker, 2006). K. E. Williams in 2016 , it has been shown that the small and large intestines contain sites of action that reduce MS, prolong the IMI length and increase the satiety ratio by GLP-1 (K. E. Williams et al. 2016).

Physiological Response

It has been shown that GLP-1 stimulates glucose-dependent insulin release, inhibits glucagon secretion, promotes pancreatic cell growth, and suppresses necrosis. It is also important to note that GLP-1 is a key component of the ileal brake system. ingested food activates distal-intestinal signals, which inhibit proximal GI motility and gastric emptying and reduce food intake in a positive feedback phenomenon. (Pironi et al. 1993; Holst, 2004 #309;Vilsboll, 2004 #316; Turton, 1996 #312; Tang-Christensen, 1996 #310).

Effect of GLP-1 on Food Intake

Glucagon-like peptide-1 can act centrally and peripherally to reduce food intake (Abbott et al. 2005; Baggio, Huang, Brown, & Drucker, 2004; Ruttimann, Arnold, Hillebrand, Geary, & Langhans, 2009; Turton et al. 1996). For example, when GLP-1 is administered via an intracerebroventricular (ICV) route, feeding was decreased (Turton et al. 1996), and this inhibition was reversed when exendin (9-39), a GLP-1R antagonist, was administered by the same route (Turton et al. 1996). In addition, when albugon, a GLP-1-albumin fusion protein that does not cross the blood brain barrier was infused systemically, food intake was inhibited (Baggio et al. 2004). Exendin (9-36) given i.p. decreased food intake (D. L. Williams, Baskin, & Schwartz, 2009) and i.p. injections of GLP-1 in vagotomized rats blocked this inhibition (Abbott et al. 2005; Ruttimann et al. 2009).

Control of Food Intake

Finding possible methods to prevent and treat obesity is necessary. However, in order to accomplish this goal, understanding the mechanisms that control food intake becomes a requirement. There are two mechanisms that control food intake, a long-term mechanism and a short-term mechanism (Sayegh, 2013a, 2013b; Stanley, Wynne, McGowan, & Bloom, 2005). The long-term control of food intake maintains energy homeostasis and preserves body weight over longer periods (Sayegh, 2013a, 2013b; Stanley et al. 2005). The long term control of food intake over long periods of time such as days or years is controlled by hormonal signals such as insulin and leptin (Sayegh, 2013a).

The short-term control of food intake regulates individual meal size (MS) and the time between two consecutive meals, also known as intermeal interval (IMI) (Sayegh, 2013a, 2013b; Stanley et al. 2005). This control is regulated by satiety peptides / hormones secreted by the gastrointestinal (GI) tract. Such peptides / hormones may include gastrin-releasing peptide (GRP), which is secreted by the enteric neurons of the stomach and small intestine, cholecystokinin (CCK), which is secreted by the I cells of the small and the large intestine, glucagon-like peptide-1 (GLP-1), which is secreted by the L cells of the large intestine and peptide tyrosine tyrosine (PYY), which is secreted by the L cells of the small and the large intestine (Sayegh, 2013a, 2013b; Simpson, Martin, & Bloom, 2009; Stanley et al. 2005; Suzuki, Jayasena, & Bloom, 2012; Suzuki, Simpson, Minnion, Shillito, & Bloom, 2010).

The previous peptides are secreted in response to ingesting a meal (G. P. Smith, Gibbs, et al. 1981), they activate their specific receptors and stimulate central food control areas in the hypothalamus of the midbrain and / or the dorsal vagal complex (DVC) of the hindbrain to reduce MS and/or to prolong the IMI (Prinz & Stengel, 2017; Sayegh, 2013a; Schwartz, Woods, Porte, Seeley, & Baskin, 2000; Suzuki et al. 2012).

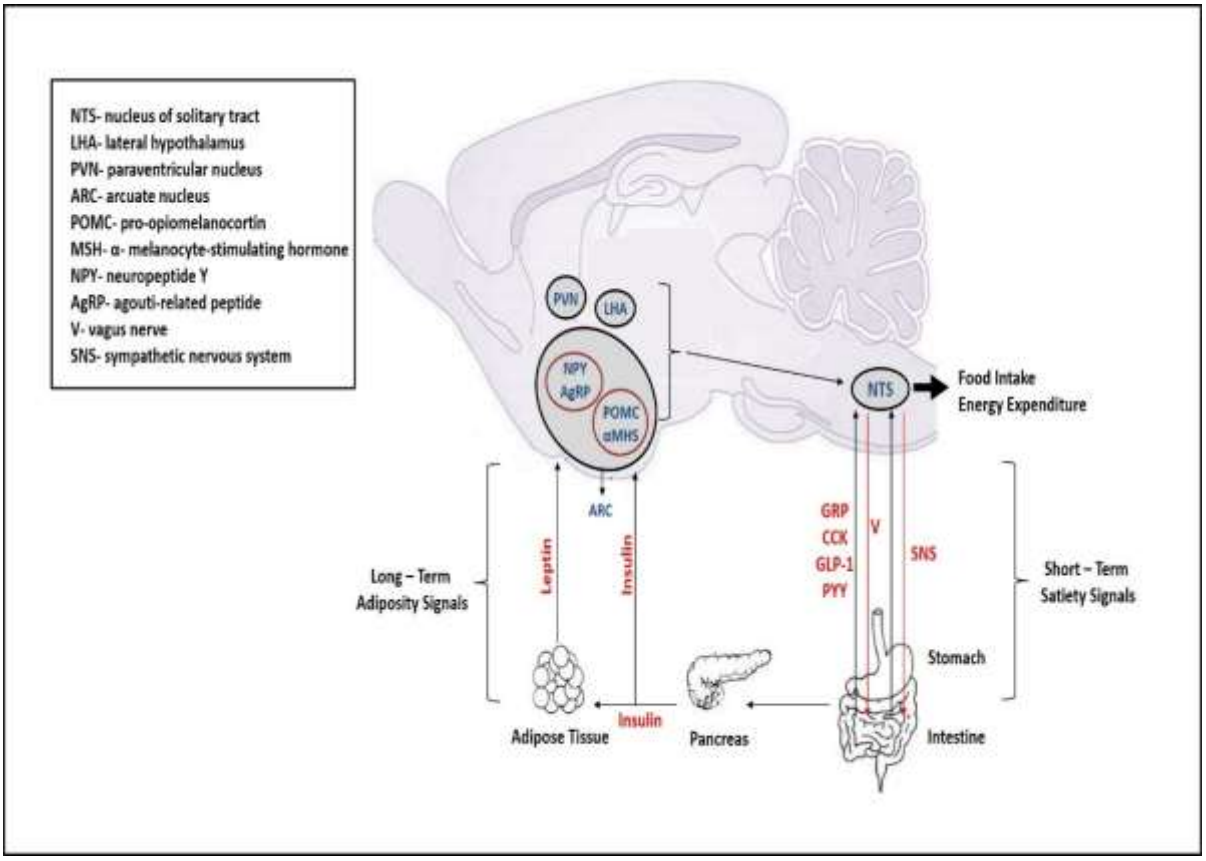

Diagram 1.1. Summary of the Long and Short-Term Controls of Food Intake

The long-term control of food intake is the mechanism that extends over long periods of time (days and/or years). This mechanism is controlled by hormonal signals such as insulin and leptin. IN addition, it involves higher brain centers that control metabolism and energy homeostasis. Insulin stimulates pro-opiomelanocortin (POMC) and α-melanocyte-stimulating hormone (α-MSH) neurons but inhibits neurons that express neuropeptide Y (NPY) and agouti-related protein (AgRP) in the arcuate nucleus (ARC) of the hypothalamic. Insulin also stimulates adipose tissue to secrete leptin, which in turn stimulates POMC and α-MSH neurons but inhibits neurons that express NPY and AgRP in the ARC that exert stimulatory (orexigenic) or inhibitory (anorexigenic) influence on food intake and energy metabolism, this called adiposity signals. These neurons project to second-order neurons in adjacent hypothalamic nuclei, including the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA). serving as the feeding or hunger center, ventromedial nuclei (VMN) acting as the satiety center and nucleus tractus solitaries (NTS) conveying the peripheral signals, particularly from the gut to the feeding centers, are implicated in appetitive behavior.

The short-term control of food intake regulates meal size (MS) and time between two consecutive meals, also known as the intermeal interval (IMI). When the animal starts eating, food goes to the gut where local hormones and peptides are secreted e.g. gastrin releasing peptide (GRP), cholecystokinin (CCK) and glucagon- like peptide-1 (GLP-1). These peptides send satiety signals by vagal afferents and / or sympathetic nerves to hindbrain areas such as the nucleus tractus solitaries (NTS) in the brain stem serves as gateway for neural signals from the gastrointestinal tract to the hypothalamic feeding centers. Also, the amygdala, the cortex prefrontalis, as well as the area postrema have been held responsible for feeding

disorders and inadequate conservation or storage of energy, to determine food intake and energy expenditure.

In the hypothalamus, the arcuate (ARC) nucleus is a key site for controlling food intake (Prinz & Stengel, 2017; Sayegh, 2013a, 2013b; Schwartz et al. 2000; Suzuki et al. 2012). When the neurons of the ARC nucleus are stimulated they secrete neurotransmitters such as pro-opiomelanocortin (POMC) and cocaine- and amphetamine- regulated transcript (CART), which inhibit food intake, or peptides such as neuropeptide Y (NPY) and agouti-regulated peptide (AgRP) which stimulate food intake (Sayegh, 2013a, 2013b; Simpson et al. 2009).

The DVC consists of three feeding control areas, area postrema (AP), nucleus tractus solitaries (NTS) and dorsal motor nucleus of the vagus (DMV) (Sullivan et al. 2007; Washington, Wright, & Sayegh, 2011). The DVC receives signals from the gut, via the vagus or the sympathetic nerves (Konturek, Konturek, Pawlik, & Brzozowski, 2004), and excites the NTS neurons, which is directly connected to the DMV and the AP. This in turn evokes reduction of food intake (Schwartz et al. 2000; Stanley et al. 2005; Suzuki et al. 2012). In addition, the AP and portions of the NTS lack the blood-brain barrier, which allows circulating peptides e.g. GRP, CCK to enter the central nervous system causing direct reduction of food intake (Fenstermacher et al. 1988; Pardridge, 1983). Furthermore, there are POMC neurons in the NTS, which suggests that the forebrain and the hindbrain may work together to control food intake (Prinz & Stengel 2017; Schwartz et al. 2000; Suzuki et al. 2012).

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