REVIEW ARTICLE

APPETITE REGULATION IN RELATION TO ENERGY PROVISION

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Background: Appetite control is a very complex process which influences the short term feeding behaviour and a long term adaptive process that responds to the energy input. Appetite control and food intake is influenced by a combination of behavioural, psychological and neuro-endocrine influences. **Methods:** For identification of articles search engines of the databases EMBASE, OVID, Pub med and MEDLINE were used for papers published from 2002 to 2015 in English language. **Results:** The higher endogenous peptide YY (PYY) and cholecystokinin (CCK) and lower ghrelin levels are not always associated with subjective feelings of fullness or hunger and a decreased energy intake which highlights the fact that appetite control and food intake is a very intricate process. **Conclusion:** When food is ingested, numerous physiological, hormonal, social and psychological processes are triggered in an intricate manner. Therefore, it can be said that ghrelin, PYY and CCK are just few pieces, which contributes to the process of appetite control and energy intake.

Keywords: Appetite, appetite hormones, ghrelin, CCK, PYY, control of energy intake

J Ayub Med Coll Abbottabad 2016;28(2):392–9

Principles of appetite regulation

The internal driving force for food ingestion is called appetite. Appetite has two definitions; a) that covers the entire field of food intake, selection, preference and motivation b) that refers particularly to the qualitative features of eating, sensory characteristic or receptiveness to the environmental stimulation which can be distinguished with circumstances based on energy deficit or eating in response to physiological stimuli.[1]

Appetite is divided into three components, i.e., hunger, satiation and satiety.[2] Hunger is a motivational state that enhances food intake and reflects the body state in which metabolic fuels for example free fatty acids and glucose, are low and is a principal variable that indicates the drive to eat.[1] Satiation leads to the cessation of eating and it takes place when food is being eaten. It governs the size and duration of the meal. It is also called as intra-meal satiety.[1] Following meal initiation, hunger subsides and satiation is dominant. Then, satiation feelings contribute to eating cessation and a period of eating abstinence begins.

The feelings that determine the inter-meal fasting period is known as satiety, it leads to the inhibition of more eating. It reduces the hunger and enhances fullness after the meal has finished.[1–3] A number of factors influences satiety such as food mass, palatability, energy density and glycaemic index.[4] Satiety is a complex interaction of behavioural, psychological and physiological mechanisms.[4] Satiety leads to increase in fullness and a decline in hunger after the meal has finished.[1] Appetite control is a multifarious process that involves the interaction between the central and peripheral organs. This influences the short term feeding behaviour, as well as the long term adaptive process that responds to the energy input and energy expenditure.[5] A number of different physiological, psychological, cultural, emotional and social factors interact in a very intricate manner. This influences the sensations of hunger, satiety and desire to eat.[6,7] Therefore, appetite control is a complex process, and it involves both central and peripheral organ interaction[5] and is a combination of psychological, neuro-endocrine and behavioural influences which are concerned with the appetite control and food intake.[8]

Role of gut peptides in appetite control

Numerous hormones and peptides produced by the pancreas and the gut are involved in the appetite control. These include peptide YY (PYY), cholecystokinin (CCK), ghrelin and a glucagon -like peptide 1 (GLP-1) which regulates the food intake and directly influences satiety and hunger.[8,9] Gastrointestinal hormones which regulate acute satiety are GLP-1, Peptide YY, Oxyntomodulin and glucose-dependent inhibitory polypeptide.[10] In 1912, stomach contractions were thought to be involved in regulating appetite.

In 1975, the duodenum was considered as the" pituitary of gastrointestinal tract", as it controls gut hormones.[11] After the discovery of gut peptides in the hypothalamus and presence of hypothalamic hormones in the gut, the relationship between the gut and brain became evident.[12] Endocrine cells are scattered throughout the gut mucosa, which ensure the diverse and important endocrinological capacity of the gut. Nutrients in contact with the gut mucosa release gut hormones, which regulate different gastrointestinal functions. Examples of these are; motility, secretion, absorption and positive feedback to the central nervous system in response to the nutrients' availability. All these factors play an imperative role in regulating the food intake.

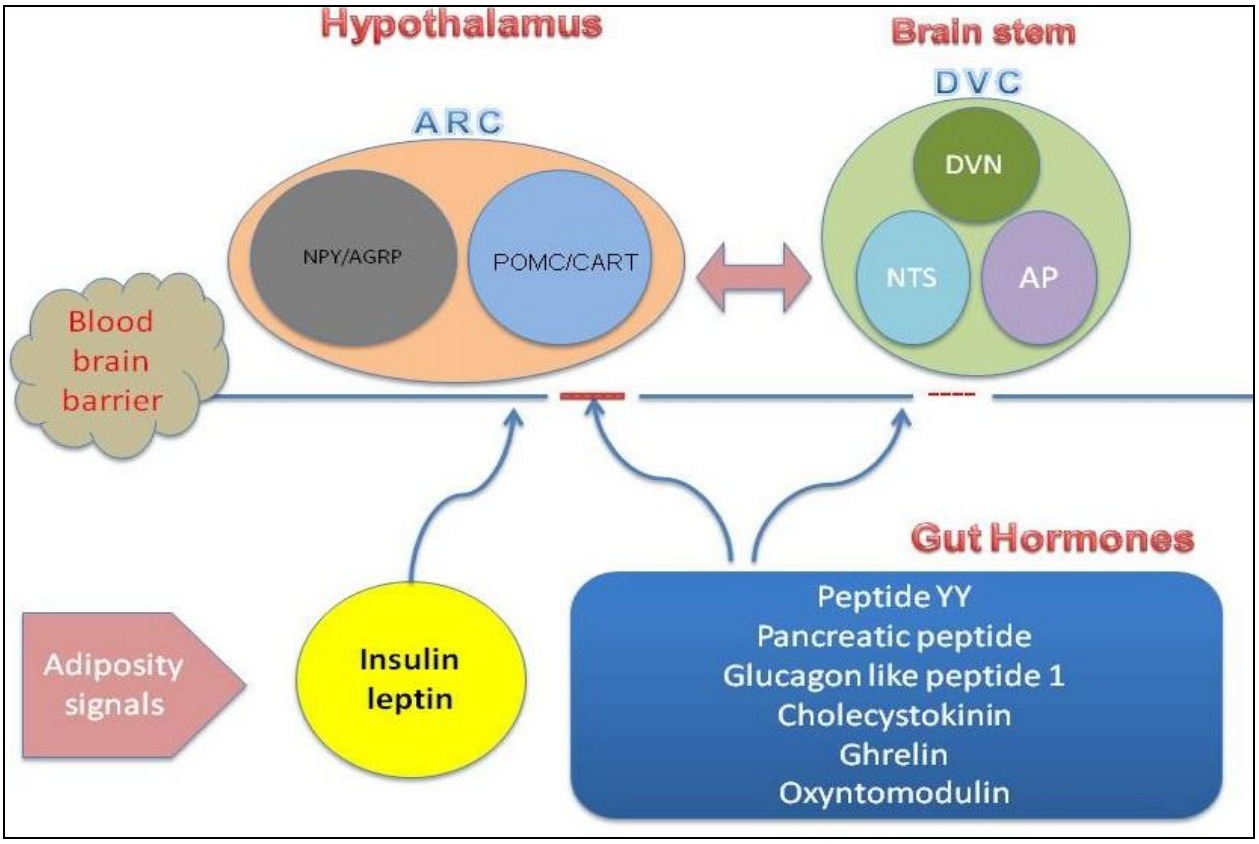

Figure-1: Schematic diagram of appetite regulation by central appetite circuits and circulating factors. Abbreviations: ARC- Arcuate Nucleus, NPY- Neuropeptide Y, AgRP - Agouti-Related Peptide, CART- Cocaine Amphetamine Regulated Transcripts, POMC-proopiomelanocortin, DVC- Dorsal Vagal Complex, consisting of dorsal motor nucleus, AP- Area Postrema and NTS- Nucleus Tractus Solitarius

Ghrelin

Ghrelin is the only endogenous peripheral hormone that has powerful orexigenic properties (appetite stimulant; which induces hunger and increases food intake). In 1996, the growth hormone secretagogue (GHS) receptor was identified, and surprisingly ghrelin was discovered.[13] Ghrelin is a 28- amino acid peptide released primarily by the oxyntic glands of the gastric mucosa, and from the duodenum, ileum, caecum and colon.[8,9,14] Ghrelin was also isolated from tissues of the hypothalamus[12], anterior pituitary gland[15], lungs[16], pancreas[17], kidneys, adrenal glands, thyroid, placenta, gonads, lymphatic tissue, myocardium, adipose tissues, and the bones[8]. This widespread distribution of ghrelin may explain its many endocrine and non-endocrine effects.

Ghrelin has numerous physiological effects on the human body due to its extensive expression in various tissues (Table 1). Through GHSR-1a activation, it is a powerful releasing stimulator of growth hormones from the anterior pituitary gland. Ghrelin also influences the secretion of the other endocrine hormones such as cortisol (18) and insulin.[19,20] The most important function of ghrelin is the regulation of food intake and energy balance. Ghrelin also increases pancreatic exocrine secretion, gastric acid secretion and enhances gastric motility.[21,22] After binding to its receptors GHSR-1a, it stimulates neurons expressing AgRP and NPY, which are orexigenic peptides.[9]

Ghrelin secretion from the stomach is largely dependent upon the nutritional state. Under fasting conditions before a meal ghrelin, plasma concentration is highest, suggesting its role in meal initiation.[23] Its level decreases tremendously after a meal (within 15–20 minutes of food intake) and again, its plasma concentration increases before the next meal after gastric emptying.[24] Ghrelin responses are dose dependently associated to the amount of calories ingested. They are also dependent on the type and composition of the macronutrient ingested.[25] Ghrelin is more effectively suppressed by proteins and carbohydrates as compared to isocaloric-rich fat meals.[26,27] Prolonged suppression of ghrelin after consumption of dietary proteins is found in many studies showing relationship between higher satiety and high protein intake.[28,29]

Table-1: Main neuropeptides and peripheral appetite regulating hormones and their role in appetite regulation neuropeptides and neurotransmitters

Neuropeptides and Neurotransmitters	Main site of synthesis/ production	Action on appetite	Other functions	Effect of peripheral peptides on food intake
Anorexigenic factors				
PYY	Ileum and colon (gastrointestinal L cells)	• Inhibition of gastric emptying • Increases absorption of fluid and electrolytes from ileum after meal • May acts as "illeal brake" • Direct appetite suppressing effect on brain by activation of anorexigenic POMC neurons and inhibition of NPY neurons	• Inhibits bile acid secretion • Inhibits secretion of digestive enzymes • Inhibits gall bladder emptying	↓
CCK	Duodenum and proximal jejunum (Intestinal I cells)	• Inhibits gastric emptying • Appetite suppressing action on brain (hypothalamus through neural pathway to brain stem). • CCK1 receptors are present in the areas of CNS involved in food regulation such as dorsomedial hypothalamus, NTS and AP	• Stimulates gallbladder contraction • Stimulates release of digestive enzymes • Stimulates pancreatic enzyme secretion • Regulates nutrient delivery rate from stomach to small intestine • CCK has numerous effects on memory, analgesia, sexual behaviour, anxiety and seizure threshold • May be involved in long-term body weight regulation.	↓
GLP-1	Ileum and colon (gastrointestinal L cells)	• Inhibits gastric emptying • Important role in "illeal brake" • Direct appetite suppressing action on brain. It exert its effects via GLP-1 receptors containing neurones of NTS project to POMC/CART neurones in arcuate nucleus and to dorsomedial and para-ventricular nucleus. The central effect of GLP-1 are mediated through AP and ascending brain stem pathway.	• Stimulates glucose dependent insulin secretion and inhibits glucagon release	↓
Oxyntomodulin	Ileum and colon (gastrointestinal L cells)	• Delays gastric emptying • Inhibit gastric acid secretion	• Glucose dependent insulin release	↓
Pancreatic Polypeptide	Peripheries of pancreatic islets (endocrine type F cells)	• Stimulation of gastrointestinal motility • Stimulation of gastric acid secretion	• Inhibit pancreatic exocrine function • Inhibit gall bladder contraction	↓
Leptin	Adipocytes	• Signals the brain stem and arcuate nucleus of hypothalamus when fat stores are low • Regulate body weight and energy homeostasis. It inhibits NPY and AgRP and activates α-MSH. It also acts on IGF-1 and growth hormone • Involved in neuroendocrine response to starvation	• Expression of NPY and AgRP is up-regulated in leptin deficiency due to fasting • Regulation of lipid metabolism • Regulation of inflammatory response • Glucose homeostasis • Puberty and ovulation • Fetal growth and metabolism • Bone metabolism	↓
Orexigenic Factors				
Ghrelin	Gastric mucosa (X/A like cells)	• Direct appetite stimulating effect. It stimulates neurons expressing AgRP and NPY, which are orexigenic peptides. • Increase gastric emptying • It also increases gastric motility gastric acid secretion and pancreatic exocrine secretion	• Powerful releasing stimulator of growth hormones from anterior pituitary gland • It also influences secretion of other endocrine hormones like cortisol and insulin	↑
Orexin A and B	Cell bodies of lateral hypothalamic area	• Excitatory neuropeptides • Appetite stimulating neuropeptides		↑
NPY	Arcuate nucleus of hypothalamus	• Stimulate food intake	• Decrease energy expenditure	↑
AgRP	Arcuate nucleus of hypothalamus	• Stimulate food intake		↑

Abbreviations: Cholecystokinin, CCK; neuropeptide Y, NPY; agouti-related peptide, AgRP; peptide YY, PYY; glucagon-like peptide 1, GLP-1; insulin like growth fator-1, IGF-1; Growth hormone, GH; proopiomelanocortin, POMC; α-melanocyte-stimulating hormone, α-MSH; area postrema, AP; nucleus tractus solitaries, NT

Plasma ghrelin levels are higher in lean people, low in obese people, and its level increases with the loss of weight in obesity.[30] There is a difference in appetite regulation and ghrelin in overweight and lean subjects.[31] In obese subjects fasting ghrelin levels are reduced[32] and post-prandial ghrelin levels are not suppressed in obese subjects, which demonstrates that ghrelin may be involved in obesity[33]. Moreover, intravenous administration of ghrelin in obese subjects resulted in the consumption of more food showing that obese subjects are not resistant to ghrelin.[34] On the other hand, ghrelin levels rises when weight loss is associated with cachexia and anorexia.[35,36]

An understanding of the fundamental role of ghrelin, in appetite regulation, in humans, comes mainly from two independent clinical trials. One in which synthetic ghrelin was intravenously administered to the subjects and then appetite and food intake was measured prior to, during and after infusion which was then compared with the infusion of placebo (saline). In other trials, the ghrelin was investigated in pre-load studies in which ghrelin concentrations were studied prior to, during and after consumption of a pre-load, and then compared with the reference product. In healthy subjects intravenous administration of ghrelin caused 28% increase in energy intake from *ad libitum* buffet breakfast, and increased the subjective ratings of hunger.[37]

Similarly, intravenous infusion of ghrelin in lean and obese humans has shown increased energy intake from buffet meals. In healthy lean and obese individuals intravenous administration of ghrelin at doses of 1 pmol/kg/min (low dose) and 5 pmol/kg/min (high dose) increased the mean energy intake by 36.6±9.4% and 70.1±15.5% respectively in obese subjects. However, in the lean subjects, the mean increase in energy intake on the low dose day and on the high dose day was 20.2 ±10.8% and 20.1±10.6% respectively[34,38], demonstrating its relevance to food intake behaviour[5].

Studies have documented, that after ghrelin infusion, the palatability of the food was increased.[34] Moreover, ghrelin administration increased the neural response to food pictures.[36] The pre-load studies also demonstrated that suppression of ghrelin resulted in decreased energy intake from subsequent an *ad libitum* buffet meal. In lean and obese subjects, it was observed that high protein and adequate protein meals resulted in decreased energy intake by approximately 14 and 22% respectively from subsequent an *ad libitum* buffet meal, which was associated with the suppression of ghrelin.[40] In overweight male subjects, consumption of a glucose based liquid pre-load, compared with lactose, resulted in higher *ad libitum* energy intake and an earlier return of ghrelin to pre-prandial concentrations.[28]

There are some studies where this is not the case. This suggests that ghrelin suppression may postpone initiation of the next meal. However, evidence also suggests that ghrelin levels are conditioned by the habitual patterns of meals and rises in anticipation of a meal.[41] On the other hand, studies have documented that time-blinded natural meal requests are not directly related to the ghrelin response. When the macronutrient distribution, volume and other features are kept constant, and the caloric content of meals is varied, the duration and depth of ghrelin suppression are related to the number of calories ingested.[42] Therefore, it can be suggested that large meals suppresses ghrelin and hunger both more comprehensively as compared to small meals. Additionally, the degree of the consequent pre-prandial recovery of ghrelin has also been associated with the number of calories consumed in the following meal.[42,43]

Peptide tyrosin-tyrosin

Peptide tyrosin-tyrosin (PYY) was first isolated from porcine jejunal mucosa by Tatemoto and his colleagues.[8] Peptide YY is a thirty-six amino acid peptide which is synthesized and released from endocrine cells (L-cells) of the intestine.[5,9] Peptide YY is present throughout the gastrointestinal tract, but its highest concentration is present in the distal segment of gastrointestinal tract, i.e., ileum, colon and rectum. It is also found in the pancreas and hypothalamus. Peptide YY is co-secreted with glucagon like peptide 1.[8,44] PYY affects gastrointestinal motility and inhibits gastric acid secretion, pancreatic enzyme secretion and gall bladder emptying.[44–46] PYY also act as part of the "ileal brake".[8]

The levels of plasma PYY are lowest in the morning in the fasted state, rise after breakfast, increase more after lunch, and peak after the evening meal.[5,9] PYY is secreted into the circulation after the intake of food and its levels are elevated within 30 minutes of food reaching the small intestine.[9,47] This implies neural regulation of PYY in the intestine as the majority of PYY is released from the intestine in advance of the arrival of the nutrients to the intestine. The highest plasma concentration of PYY occurs postprandially, one hour after the meal[47,48], and its levels remain high for about 6 hours after the meal[9,47].

The increase in PYY levels is directly proportional to caloric intake.[9,49] The size of the meal is also important in relation to the PYY response.[49,50] PYY release is stimulated more by fat intake than protein and carbohydrate meals with similar energy content.[8,44,51] The maximum elevation in PYY levels

is observed by the intake of protein rich meals as compared to other macronutrients.[9,52]

Evidence for the causal role of PYY in appetite regulation in humans mainly comes from two independent clinical trials; one in which synthetic PYY was exogenously administered to the subjects and then appetite was measured (appetite ratings and or *ad libitum* food intake after fixed time period) prior to, during and after infusion which was then compared with the infusion of a placebo (saline). In other clinical trial the PYY was investigated in pre-load studies in which serum PYY concentrations were studied prior, during and after consumption of test meals and then compared with the reference product.[53]

Peripheral administration of PYY_{1-36} in both rodents and man, inhibited food intake for several hours.[48,54] Similarly, a study by Sloth *et al* (2007) on 12 lean and 12 obese males observed a decreased energy intake of 19% during lunch. This was compared to PYY_{1-36} and a 22% decrease in the energy intake after saline infusion. A statistically significant lower rating of perceived ability to eat were observed after both PYY_{3-36} and PYY_{1-36} infusion but no significant differences were observed in other ratings of appetite.[55] The impact of exogenous administration of PYY_{3-36} was also studied in both obese and lean subjects. After 2 hours of intravenous administration of $PYY3_{-36,}$ the energy intake at an *ad libitum* buffet was reduced by 31% in lean subjects and 30% in obese.[47] Lower fasting plasma levels of PYY have been reported in obese people in comparison with lean subjects.[47,50] Several other studies have also demonstrated reduction in energy intake following exogenous PYY administration.[49,56]

All the above mentioned exogenously administered PYY studies demonstrate that the intravenous infusion of PYY reduced food intake. However, evidence regarding the role of endogenously produced PYY on energy intake is less conclusive and is less frequently studied.[44] Duocet *et al* observed no association between *ad libitum* energy intake and PYY levels in twenty-five pre-menopausal women.[57] Guo *et al* observed that fasting and postprandial PYY levels were not associated with the *ad libitum* food intake over 24 hours in twenty-nine non-diabetic subjects.[58] However, in another study, it was found that β-glucan enriched bread (βGB) resulted in a 16% higher PYY response, resulting in 19% decreased energy intake at an *ad libitum* lunch following βGB, comparison to the control bread.[59] There is also controversy regarding the role of endogenous PYY on appetite control. With some studies showing that plasma PYY is positively correlated with the feelings of fullness and inversely related with the feelings of hunger[58], while other studies report that PYY levels were not associated with the feelings of fullness and hunger.[60–64] The fact that higher endogenous PYY levels are not always associated with a decreased energy intake, or subjective ratings of fullness, or hunger, highlights the fact that appetite control is a very complex process. When food is ingested, numerous physiological, hormonal, social and psychological processes are triggered in a very complex manner. Therefore, it can be said that PYY is just one piece, which contributes to the complex process of appetite control.

Cholecystokinin

Cholecystokinin (CCK) was discovered by Ivy and old berg in 1928. It is a hormone that contracts the gall bladder.[8] In 1973, Gibbs and his colleagues discovered that CCK had impact on the appetite. CCK is a gut hormone found in the duodenum and jejunum. CCK is also present in some parts of brain and acts as a neurotransmitter.[5,8,9]

The main effect of CCK on the gastrointestinal system is to enhance nutrient absorption and pancreatic enzyme secretion, stimulate gall bladder contraction and slow gastric emptying. The nutrient delivery rate from the stomach to the small intestine is regulated by CCK.[5,46,65] (Table-1)

Cholecystokinin levels increase 10–30 minutes after the initiation of a meal. The levels fall gradually and require 3–5 hrs to return to baseline levels. Proteins and fats (rather than equal calories of carbohydrates) have been shown to stimulate the release of CCK.[5]

It has been reported that fasting CCK levels were higher in obese women as compared to lean women. In anorexia nervosa fasting CCK levels were found to be lowered.[66] Results of another study are at variance.[67] In one study on Prader-Willi Syndrome (PWS), which is characterised by hyperphagia, it was found that the fasting CCK levels were not significantly different from non PWS obese subjects, which suggests that CCK may not be associated with the hyperphagia of PWS.[68]

As with PYY, evidence for the causal role of CCK in appetite regulation comes mostly from two types of clinical trials, infusion studies and pre-load studies. Intravenous infusion of physiological doses of CCK in humans reduces food intake and also increases the perception of fullness.[9] Several studies have been performed regarding the impact of CCK on appetite. A study by Ballinger *et al* observed a statistically significant reduction of 20% in food intake, after administration of CCK-8. This produced a similar plasma concentration to that of the meal.[69] Similarly, an infusion of CCK-33 also reduced food intake in the subsequent meal by 20%.[70] Brennan *et*

al also demonstrated that exogenous administration of CCK-8 in the nine healthy males increased the subjective rating of fullness, decreased ratings of desire to eat and subsequent energy intake at the *ad libitum* buffet meal.[71] Exogenous administration of CCK-8 in ten healthy men decreased energy intake during an *ad libitum* buffet meal, and reduced the desire to eat after 90 minutes of the intravenous administration of CCK-8.[72]

Evidence also suggests that the intravenous administration of CCK-8 in healthy older adults also suppressed energy intake significantly at a subsequent *ad libitum* buffet meal by 11%.[73] This indicates that CCK has a fundamental role in appetite regulation.[5] Generally, all these studies provide a consistent picture that CCK suppresses food intake. The suppression of food intake varied considerably between 0% and 63% depending upon the subject characteristics, dose and other experimental conditions. For the appetite suppressing impact of CCK a full stomach is considered to be a necessary condition, which indicates that the delayed gastric emptying may be the possible mechanism by which CCK suppresses appetite.[74]

Evidence regarding the role of the endogenously produced CCK on the energy intake and appetite is controversial, with some demonstrating, that the higher CCK levels, compared to the reference, was associated with decreased energy intake during an *ad libitum* meal, and decreased ratings of hunger and increased fullness.[75,76] While some studies demonstrated no effect of CCK on satiety[77] another demonstrated the opposite effect[78]. Hall *et al* 2005 demonstrated that there was significantly less energy intake from the *ad libitum* buffet meal after 90 minutes, after whey protein, compared to casein pre-load, with a 60% increase in the plasma CCK and greater subjective feeling of satiety.[75] In another pre-load study, performed on overweight subjects, it was observed that the higher responses of CCK were correlated with satiety, but had no impact on energy intake.[28]

The exogenous administration of CCK may achieve concentrations above physiological values (the increase in blood levels may be larger than that which can be evoked by food) and therefore we see a link between CCK, appetite and food intake. However, the higher endogenous CCK levels are not always associated with increased subjective ratings of fullness, or decreased hunger, or decreased energy intake, which identifies the fact, that when food is ingested numerous physiological processes are triggered, including hormonal responses which interact in a very complex manner. Therefore, we can say that CCK is just a single factor, which also contributes to the complex process of appetite control.

CONCLUSION

Appetite control and energy intake is a very complicated process which is influenced by a number of behavioural, psychological and neuro-endocrine influences. However, evidence suggests that ghrelin may acts as a meal initiator, while endogenous PYY and CCK levels are not always associated with subjective feelings of satiety and hunger or decreased energy intake which suggests that appetite hormones are just the few pieces which contributes to the mechanisms of energy intake and appetite control.

AUTHORS' CONTRIBUTION

SF, FF, SW: Contributed to concept development and drafted the manuscript; SF, SW, NA revised manuscript. None of the authors had a personal or financial conflict of interest to disclose.

ACKNOWLEDGEMENT

This review was conducted as a part of the PhD of Dr Sadia Fatima, funded by Khyber Medical University (Pakistan).

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