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Regulation of Food Intake : A Complex Process

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ABSTRACT

Researchers have created a wealth of knowledge about the mechanisms that regulate food intake, appetite and therefore weight control. Appetite regulation is a multifarious mechanism that involves both the physiological and environmental sources. The brain integrates chemical and nervous signals to control hunger and satiety. Other than the signals from glucose metabolism, amino acids or proteins, or adipose tissue, these controls include sensory and gastrointestinal signals, neurotransmitters and neuropeptides. The paper summarizes the existing plethora of the highly convoluted process of appetite regulation and food intake.

Keywords: Food intake; Hormones; Endocrine markers; Appetite regulation

1. INTRODUCTION

Increasing focus on obesity necessitates determination of basic epidemiological evidence and clinical data so as to provide enhanced care and management towards this disease. Psychobiological and neuroendocrine systems involved in regulation of food intake could contribute to a better understanding of obesity. A holistic health care approach encompassing these theoretical and supporting evidences should be adopted for well- being of obese individuals.

2. EATING BEHAVIOUR

The complex interplay between hunger, appetite and satiety reflect about the eating behavior. The concepts of food intake and eating behavior are distinct. While food intake refers to 'what we eat', eating behavior refers to 'how we eat'. Food intake is a biological phenomenon that intends to maintain the energy balance of the body, eating behavior is an environmental phenomenon affecting the dietary preferences and food induced hedonic effect[1,2]. Energy intake is affected by various factors and characteristics of the food environment (Fig. 1) for example the calorie consumption is more when the meals consist of variety of foods, availability of more palatable and energy dense items in menu.

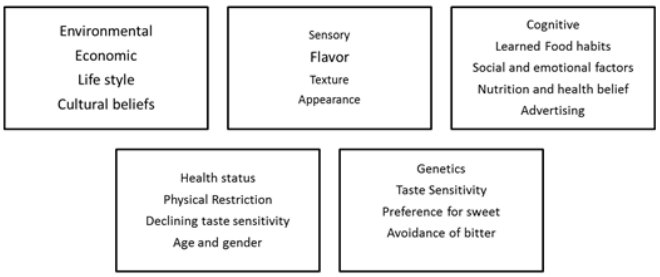

Figure 1. Factors affecting eating behaviour.

The choice of food to be consumed and the amount of food to be eaten are the two basic decisions involved during the process of eating. Different behaviors, signals and physiological mechanisms control food choice and food intake[3]. Studies with animals demonstrate that learning can cause conditioning and result in association of non-food cues with eating for example as seen in Pavlov's experiment with dogs. Humans eat for various reasons; it is not only to satisfy their appetite but also due to sensory hedonics, social pressure, and boredom. The complex interactions between biological mechanisms of appetite control and challenges posed by environment determine our drive to eat. Feeding behavior is controlled by a variety of signals[4]. Cephalic signals such as taste, smell, sight of food and gastrointestinal signals resulting from gut peptide release can have an effect on food intake consumed in the short term.

The synchronous operations of the processes at the three levels of psychobiological system affect appetite. These levels are - psychological episodes and behavioral functions; the level of peripheral physiology and metabolic events and; finally at the brain level. Cravings, perception of hunger and behavioral functions like intake of meals, and macronutrients form the part of psychological episodes and behavioral operations[4]. The lower part of the psychobiological system describes the appetite cascade through behavioral actions which actually form the structure of eating, and prompts the events that stimulate eating as well as occur post consumption of a meal.

'Liking' and 'wanting' are emerging constructs in a conceptual approach to food hedonics. The relationship between hedonic and homeostatic drives arising from biological needs is a key issue in the study of appetite control. Some researchers suggest that a clear distinction between the two concepts may not be possible, as the changes in either of the two, may affect the

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other. Nevertheless, liking and wanting have distinct identities too, which signify their role as major deciding factors, affecting the control on eating and therefore on overconsumption. It is the 'liking' that motivates consumption of food, but once it is held, the construct of 'wanting' in an existing obesigenic environment, promotes excess consumption and consequently could result in weight gain.

With clinical observations now the concepts of hunger and appetite can be distinguished. Hunger is the physiological need for nutritional replenishment, arising out of metabolic reactions beginning at the cellular level for eg. during calorie restriction[5]. Appetites is a function of the brain and the psychological desire to eat.

Paspala[2], *et al.* have described that each meal can be considered as consisting of three phases:

Initiation of food intake - Stomach contractions, food taste and energy levels are the biological mechanisms involved in initiation of a meal. For several years, stomach contractions were regarded as the main stimulus to induce appetite. The taste of the food and food choice play a key role in food preference as well. There are certain signals in the body's circulation that reflect energy reserves and depict energy balance. In obese individuals, however, due to insulin resistance, a misleading signal of lack of food may result in more over consumption.

Meal duration - Duration of a meal depends on internal and external mechanisms. Stimuli from mouth, pharynx and esophagus may cause extension of the meal. While, the exogenous factors that could influence meal duration are the appearance of the food, its taste and smell.

End of meal - The digestion process starts in the stomach where the digestive system hormones control the process and leads to the end of meal. Specialized chemo- and mechano-receptors in the GI system monitor physiological activity and transfer information to the brain. This process might get influenced through the amino acids in the circulation that act as peripheral signals to the brain.

3. APPETITE REGULATION

3.1 Theories Behind Appetite Regulation

3.1.1 The Glucostat Theory

An early attempt to explain the plausible mechanisms controlling hunger and satiety focused on glucose. It was proposed that the hypothalamic nuclei were able to detect changes in blood glucose levels and induced and decreased food intake accordingly during hypoglycemia and hyperglycemia respectively. This hypothesis was called the 'glucostat theory'[6]. When glucose levels fall below the threshold, neuronal activity in the appetite center increases and need for the next meal is felt. The glucostat theory regulates short-term control over appetite. However due the simplicity of the theory it was abandoned.

3.1.2 The Dual-Centre Theory

Describes the occurrence of hunger and satiety as related to the blood glucose levels. It was first formulated in the 1950s and involves two centres of the brain –Ventro medial hypothalamus (VMH) and Lateral hypothalamus (LH). The VMH and LH act as satiety and hunger centres respectively. After a meal, when the glucose levels rise, VMH is activated and initiates satiety, on the other hand LH induces hunger, by producing ghrelin hormone (Fig. 2), when the blood sugar levels drop. Animal experiments have shown that when LH and VMH centres are lesioned, there is an associated decrease in food intake. However, Gold[7]found that lesions on VMH alone did not result in hyperphagia as other regions like the paraventricular nucleus were also involved. Lashley[8] found that rats who had their VMH lesioned had developed over eating which soon led to obesity.

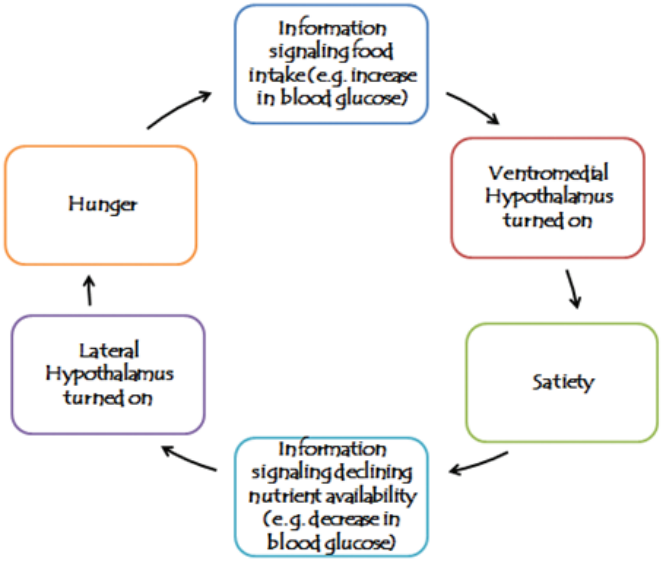

Figure 2. Dual control mechanism as part of the glucostatic theory

Pinel[9] has provided a contemporary view on the role of LH and VMH. He has provided a complementary explanation for the role of the VMH in feeding. He proposed that animals with VMH lesions 'overeat because they become obese'. He argued that VMH lesions increases blood insulin levels thereby triggering lipogenesis. Therefore, a state of energy deficiency sets in because any food that is eaten is rapidly converted into fat. Consequently the food eaten goes in vain to overcome the lack of blood glucose. The 'Dual Control Theory' has not been fully accepted owing to the incongruities of lesion- hypothesis, nevertheless it has given a useful insight of feeding behaviour.

3.1.3 The Lipostat Theory

The hypothesis of this theory is of energy balance. It proposed that adipose tissue generates fatty acids and glycerol by lipolysis, which circulate in the blood and act on the brain to maintain energy expenditure, thereby controlling body weight. Thus, increased lipolysis rates led to eating and a post prandial decrease in lipolysis resulted in its termination[10]. The secretion of leptin hormone also occurs in proportion to the size of the fat cells. It is inferred that the fatter the animal, the more would be the secretion of this hormone and greater should be the satiety. This decreased feeling of hunger would remove the extra weight and return to its set weight.

3.1.4 The Aminostatic Theory

Mellinkoff[11], *et al.* proposed that the amino acids produced after the breakdown of protein stores send signals to the brain for energy balance. This denotes that an increased muscle catabolism would result in raised levels of amino acids and therefore, would

stimulate feeding. On the other hand, diminished amino acid levels signify end of feeding and satiety.

Another model was based on energy rich molecules as ATP and changes in body temperature[12]. Hunger would be a consequence of low ATP production and reduced body temperature. This hypothesis was discarded too as it could not be applied to normal life situations.

3.2 Episodic and Tonic Signals for Appetite Regulation

The short term and long term regulation of appetite, has also been designated as the episodic and tonic signals[13]. As the name suggests, episodic signals are usually generated by episodes of eating and undulate with the eating pattern. They can be excitatory or inhibitory in nature. Tonic signals, arise from tissue stores like adipose tissue and exert a tonic pressure on appetite manifestation. These signals together are integrated within complex brain networks that control the overall expression of appetite.

3.3 Energy Balance Approach

The Energy Balance Approach suggests that the food intake of an individual must match his energy expenditure, in order to regulate the body weight. Taking this view forward, Blundell[14], *et al.* explained in what manner body composition and energy expenditure control hunger and appetite.

The molecular approach for appetite control has an alternative to it now. Fat free mass and resting metabolic rate determine the drive to eat that reflects the body's demand for energy, which is sequentially determined by the tonic inhibition from leptin. Leptin insensitivity also occurs as a result of higher adipose tissue, which reduces the tonic inhibition. Certain GI peptides, released post-prandially, act as episodic signals and suppress the drive to eat. Besides, physical exercise has a dual action on hunger, for instance prolonged exercise may have hunger stimulating effects, whilst also increasing post-prandial satiety signaling[15].

It can be inferred that appetite regulation thus, comprises of tonic drives and tonic inhibition signals as well as episodic signals starting from the mouth and GI tract.

3.4 The Brain/Hypothalamic Circuitry in Central Regulation of Energy Homeostasis

Apart from the psychobiological factors, there is also a brain phase in the food intake process. Discoveries in mammals concerning the endocrine control of appetite and growth have led to a new understanding of how the metabolic demand for energy is regulated in the CNS. Neural circuits integrate the peripheral signals with neurotransmitters within the brain. Brain areas involved in feeding regulation:

Hypothalamus is the regulating center of appetite and energy homeostasis[16].Though most research has been focused on NPY and POMC, the other centers , interconnecting nuclei of the brain are ventromedial nucleus (VMN), lateral hypothalamic area (LHA), arcuate nucleus (ARC), paraventricular nucleus (PVN), and the dorsomedial nucleus (DMN).

The effect of ghrelin and leptin is mediated by NPY/AgRP neurons. Leptin receptors are also found on POMC neurons. Both of these neurons are regulated by leptin in an opposing manner as this hormone inhibits NPY and stimulates POMC. This regulation by leptin is antagonized by ghrelin as these neurons are stimulated by ghrelin[17]. Consequently, GHRL-NPY-AgRP axis controls appetite, while the LEP-POMC-CART axis is thought to control satiety. Signals within the CNS are integrated with peripheral signals in the hypothalamic centers as they adjust to nutrient availability giving information about actual energy stores and needs. The antagonism of each opposing neuropeptide system maintains a sophisticated control. The PVN neurons synthesize and secrete neuropeptides that have a net catabolic action, have neurons which express the anorectic factors, thyrorotropin and corticotropin releasing hormones. Additionally, PVN sends signals to liver and adipose tissue for increased lipolysis[18].

The VMN contains neurons that sense glucose and leptin and it has been shown that destruction of VMN could cause hyperphagia, hyperglycemia and obesity. VMN is considered to generate satiety and glucose homeostasis. Unlike, PVN and VMN, obliteration of LHA causes hypophagia and body weight loss weight. As, LHA contains two neuronal orexigenic peptides, the melanin concentrating hormone and orexin is also considered to be a feeding center[19].

The feeding circuitry involves certain parts of the forebrain region which are essential in integrating feeding, reward, and motivation to eat. These are telencephalic areas, amygdala, hippocampus and prefrontal cortex and the lateral hypothalamus. Correspondingly, amygdalar circuitry supports termination of feeding[20].

Brain stemplays an important role in food intake and hence energy balance. Dorso-vagal complex situated in the brain stem relays peripheral signals of satiety from the gastrointestinal tract to the hypothalamus. Both ascending and descending brain stem-hypothalamus pathways are important in control of food intake. The hindbrain has equal importance in energy homeostasis. The lesions of the area postrema or vagotomy have effects of various gut hormones and attenuate their effect on food intake. Collectively, these findings suggest that food intake is controlled through brainstem-mediated mechanisms. Vagus nerve also plays a central role in regulating the feeding through variety of receptors within the brain stem. The gut hormone signals such as CCK, ghrelin, PYY are also transmitted through the vagus nerve[20,21].

3.5 Biomarkers of Satiation in CNS Neuropeptide Y (NPY)

NPY is a 36 amino acid peptide which is widely spread throughout the brain as well as the peripheral nervous system where it is often co-localized with nor epinephrine and other neurotransmitters. There are five receptors for NPY and its related peptides present in mammals:–It increases in the peripheral blood after a meal. NPY expression has been shown to be increased in ARC of the hypothalamus, in food restricted animals[23]. Findings from comprehensive studies have suggested that NPY exhibits a lesser role in regulation of food intake under normal laboratory conditions but could be imperative for fasting induced re-feeding[24]. NPY acts at multiple sites within the brain like PVN and LH to increase food intake, besides it is the level

of different Y receptors present at the time of NPY release that causes downstream effects of NPY.

α – Melanocyte stimulating hormone (α- MSH) - This is a cleavage product of pro-opiomelanocortin gene. It has two receptors in the brain: MC3R and MC4R. Although evidence suggests both these receptors are involved in appetite regulation, the MC4R is usually considered more important in this context[25].

Agouti related peptide (AgRP) - AgRP acts as an antagonist at the α- MSH receptors, and thus stimulates appetite even in the absence of α- MSH. Under the influence of an obesigenic factor, over expression of AgRP leads to obesity. However, there are opposing views regarding the physiological role of this peptide on feeding[26].

3.6 Peripheral Signals

The gut has an essential function, in maintaining energy homeostasis along with its digestive and absorptive functions in the body. It is regarded as the largest endocrine organ.

3.6.1 Gut Hormones

Cholecystokinin (CCK) - Cholecystokinin is known to be the foremost gut hormone which has implications in appetite control. Though synthesised in the small intestine and is secreted post-prandially, it mediates satiety through CCK receptors spread all over the central nervous system. Research has shown that intravenous injection of CCK reduces meal size and duration in rats as well as in case of humans. Other physiological functions of CCK are stimulating the release of enzymes, promoting gastrointestinal motility, and delaying gastric emptying. CCK along with leptinproduces short term inhibition in food consumption and long term reduction of body weight; as a result it has been investigated as a potential therapeutic target for obesity[22].

Ghrelin - Ghrelin is a 28 amino acid peptide and the only orexigenic gut hormone identified till date. Ghrelin appears in two forms – total ghrelin which does not possess any endocrine action and octanoylated ghrelin which exerts its action on gastrointestinal function and appetite. Ghrelin is produced in the stomach mainly from the fundic region and is a growth hormone releasing agent. Ghrelin also induces feeding and modifies body energy composition. Ghrelin synthesis is regulated by nutritional status. Plasma ghrelin concentrations are in proportion to the amount of calories ingested, in contrast to other gastrointestinal hormones[27]. The blood levels increase in fasting , and in starvation and anorexia nervosa, and after acute caloric intake levels decrease. Ghrelin increases rapidly before eating and therefore acts as a meal initiator and declines when food is ingested. The suppression of ghrelin occurs in response to administration of nutrients into the stomach, duodenum and carbohydrate and protein appear to be more potent suppressors of ghrelin than fat[28]. Intravenous glucose but not lipid has been known to suppress ghrelin secretion[29]. Ghrelin via effect on neurons in the hypothalamus stimulates hunger.

Pancreatic polypeptide (PP) - This peptide is secreted from the pancreatic islets of Langerhans post meal consumption. It is also known to act through the vagus nerve, as vagotomy in rodents have exhibited the anorectic effects of PP. Peripheral administration of PP for acute and chronic duration reduces food intake in mice and in humans. Furthermore, it has been observed that the plasma PP levels are lower in early morning and highest in the morning[30].

Peptide Tyrosine Tyrosine (PYY) – This peptide has a typical Tyrosine (Y) residue, depicting its name. It is secreted from the ileum, rectum and colon and its release is increased in proportion to calorie intake. It acts directly through the hypothalamic region. While the circulating levels of PYY are low in fasted state, they increase rapidly after a meal, and persist raised up for several hours[31].

Glucagon like Peptide-1 (GLP-1) - GLP-1 is secreted along with PYY from the ileum and colon. Verdich et al.[32]has shown reduction in food intake in lean and obese subjects on intravenous infusion of GLP-1. Its effects are exerted through GLP-1 receptor which is widely distributed in brain, GI tract and pancreas. GLP-1 also acts on pancreatic β-cells and stimulates glucose-dependent insulin secretion. Its levels are known to rise in anticipation of a meal[33].

Oxyntomodulin (OXM) - OXM is a 37-amino acid peptide, secreted by the L-cells of the distal gastrointestinal tract as a response to food intake and proportionate caloric load. Though it exhibits glucagon like activity in liver, it has moderate anorexigenic actions in rodents and humans but with a much lower potency when compared with GLP-1[22].

3.6.2 Adiposity signals

Adiposity signals are produced in proportion to adipose stores. The increased levels of leptin and insulin reflect these. They reduce the food intake by stimulating POMC neurons in the brain.

Leptin - Leptin is a 16 kDalton peptide synthesized by adipocytes, its main source being adipose tissue. Early experiments in rodents revealed that the absence of leptin causes obesity in the *ob/ob* mouse. Leptin has antagonist actions on NPY, melanin concentrating hormone (MCH) and AgRP which results in an increase of NPY concentration and augmented appetite. The anorectic neuropeptides that are up-regulated by leptin are POMC, CART and corticotrophin releasing hormone. Early research has proved Recombinant leptin therapy successful in humans with an extreme obese phenotype.In normal population, women have higher serum levels than men indicating an increased fat mass in women[34]. Leptin levels are low during fasting state but increase following the food intake. In obese individuals leptin has a diminished effect at its hypothalamic target which results in leptin resistance[35]. Leptin levels are increased by insulin and cortisol. However, when leptin acts with insulin centrally, together they bring satiety by stimulating POMC and preventing NPY action[36].

Adiponectin - It is a 244- amino acid protein secreted from adipose tissue. The hormone, Adiponectin is produced by fat cells in inverse proportion to the body fat. The molecule is postulated to regulate energy homeostasis. It regulates metabolic functions of glucose regulation and fatty acid catabolism. The adiponectin receptors also control the metabolic rate at cellular level by targeting AMP-activated protein Kinase (AMPK), downstream. The enzyme, AMPK is activated by diminished Adenosine triphosphate (ATP) or increased Adenosine monophosphate

(AMP) levels. Sequentially, this activates catabolic processes like fatty acid breakdown and glycolysis and closes ATP-consuming processes such as lipogenesis[37]. Studies show that expression of these receptors and also plasma adiponectin levels correlate with insulin levels[38]. Calorie restriction in rodents and weight loss due to calorie deficit diets have shown to increase adiponectin levels significantly. According to Shklyaev[39], *et al.* the effects that adiponectin exerts are improving insulin resistance, glucose metabolism that are not completely understood but are thought to be mediated through metabolic pathways of gluconeogensis, lipogenesis and through regulation of food intake. With the persistent associations of adiponectin with obesity and diabetes, studies now support the molecule as a potent antidiabetic hormone[40].

Insulin - Insulin along with leptin positively correlates with adipose tissue mass within the body. It is believed to have a similar lipostatic role to that of leptin. Similar to leptin, circulating insulin levels are proportional to the degree of adiposity[41]. Insulin is synthesized by β cells in the pancreas. Its release is induced in response to elevated glucose and amino acid concentrations. Through the blood brain barrier insulin reaches the hypothalamus and the receptors regulate glucose homeostasis. This is achieved by hormone binding to its cell surface receptors[42]. Lipid metabolism is also influenced, by increased lipid synthesis in adipocytes[43]High insulin levels are found in over weight individuals generally, though it is also considered that adiposity might in fact be a consequence of insulin resistance itself. Both insulin and leptin resistance exists in obese people mostly.

3.7 Endocrine Markers of Nutritional Status

Insulin like Growth Factor-1

IGF-1 is a small peptide hormone about 7.5 kDa present in the blood at high concentrations structurally resembling proinsulin. Liver in response to high calorie intakes also increase its production. IGF-1 in the liver cells maintains blood glucose homeostasis for glycogen synthesis. The levels of IGF-1 are regulated by nutritional status and energy intake. Low IGF-1 levels are seen in fasting and signify catabolism. Decline in serum IGF-1 levels and IGFBP-3 levels have also been seen on 50 per cent reduction in calorie intake and 30 per cent reduction in protein intake[44]. IGF-1 may indirectly influence hunger by inhibiting leptin through IGFBP-1 levels[45].

Thyroid hormones - Thyroid hormones and glucocorticoids both have a role in the regulation of energy homeostasis. Thyroid hormones are known to regulate energy expenditure through effects on basal metabolism and adaptive thermogenesis. Thyroid hormones in brown adipose tissue (BAT) are essential for diet-induced thermogenesis. In addition to effects on heat generation, thyroid hormone has effects on lipogenesis and appetite regulation. Studies show that HPT axis may have outcomes on appetite control unrelated to energy expenditure. Typically, thyroid-stimulating hormone (TSH) released from the anterior pituitary gland, stimulates the secretion of triodothyronine (T3) and thyroxine (T4). These peptides can directly influence food intake[46]. Local regulation of thyroid hormones in the CNS may physiologically regulate appetite. More research needs to be done to identify the mechanisms through which thyroid hormones regulate energy balance. T3 increases expression of genes coding for lipogenic enzymes such as malic enzyme, glucose 6-phosphate dehydrogenase and acetyl-coenzyme A carboxylase[47] that use fatty acids derived from adipose tissue as the primary source of substrate and is well known to increase food intake.

Corticosterone - Any disturbance in the body evokes a stress response. Corticosterone controls sensitivity of the system's response to stress and maintains the basal activity of the HPA axis thereby coordinating sleep/awake cycle, food intake, etc. It increases hepatic gluconeogenesis, and also increases cellular concentrations of enzymes and the substrates for gluconeogenesis[48]. Along with the established effects of glucocorticoids on blood glucose, corticosterone has also shown to directly inhibit insulin release from pancreatic β cells.This transitory decrease of the insulin response to hyperglycemia, may possibly be a regulatory mechanism to meet the glucose needs of the brain during stress[49]. Glucocorticoids also have a role in adipose tissue and regulate several processes including metabolic activity, production and secretion of leptin. In the recent years, the effects of excess or reduced corticosterone levels in adipose tissue have been extensively studied. The evidence of the effects of corticosterone on food intake is controversial. Levay[50], *et al.* showed that calorie restriction of different levels results in increased serum corticosterone in a dose-response trend in adult rats. In another study, higher levels of plasma corticosterone and lower levels of plasma ACTH were found in calorie-restricted rats compared with isolated or group-caged controls, during the light phase of the daily cycle. Higher levels of plasma corticosterone and lower levels of plasma ACTH were found in calorie-restricted rats compared with isolated or group-caged controls. However, as observed in precocial chicks corticosterone treatment may also affect growth by reducing appetite[51] and possibly increase maintenance of energy expenditure. The glucocorticoid in man, cortisol has been known to increase leptin levels, stimulate insulin secretion and promote gluconeogenesis but decrease insulin sensitivity.

4. CONCLUSION

This paper elucidated the mechanisms that are involved in appetite control. The three phases of any meal viz. the initiation of food intake, duration of meal and end of the meal act as crucial points for meal regulation, in turn controlled by stomach contractions, internal and external mechanisms and specialized chemo- and mechano-receptors. Appetite regulation requires a balance of processes occurring at the brain, digestive tract and adipose tissue, much regulated centrally by the brain stem and hypothalamus. Peptides from the gut and adipose tissue, control energy balance. In addition, the urge or reluctance to eat or not eat, are governed by the tonic and episodic signals. To a large extent, environmental cues and life style factors create an obesigenic environment for the individual. For these reasons, to control the epidemic of obesity, the intricate process of appetite regulation has to be understood so as to effectively utilize the targeted pharmacological or therapeutic agents for obesity.

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