

Central and peripheral control of food intake

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The maintenance of the body weight at a stable level is a major determinant in keeping the higher animals and mammals survive. The body weight depends on the balance between the energy intake and energy expenditure. Increased food intake over the energy expenditure of prolonged time period results in an obesity. The obesity has become an important worldwide health problem, even at low levels. The obesity has an evil effect on the health and is associated with a shorter life expectancy. A complex of central and peripheral physiological signals is involved in the control of the food intake. Centrally, the food intake is controlled by the hypothalamus, the brainstem, and endocannabinoids and peripherally by the satiety and adiposity signals. Comprehension of the signals that control food intake and energy balance may open a new therapeutic approaches directed against the obesity and its associated complications, as is the insulin resistance and others. In conclusion, the present review summarizes the current knowledge about the complex system of the peripheral and central regulatory mechanisms of food intake and their potential therapeutic implications in the treatment of obesity.

Key words: food intake, gastrointestinal hormones, energy balance, satiety signals, adiposity signals

The maintenance of the body weight at a stable level is a major determinant in keeping the higher animals and mammals survive (Jequier and Tappy 1999). As a compensatory mechanism, hunger increases and energy expenditure decreases the weight loss. However, opposite responses are triggered when body weight increases. Body weight can change only when energy intake is not equal to energy expenditure over a given period of time (Bray et al. 2012). A complex physiological control system is involved in the maintenance of the energy balance. This system includes afferent signals from the periphery about the state of the energy stores and efferent signals that affect the energy intake and expenditure (Sandoval et al. 2008). This regulatory system is formed by multiple interactions between the gastrointestinal tract

(GIT), adipose tissue, and the central nervous system (CNS). It is influenced by behavioral, sensorial, autonomic, nutritional, and endocrine mechanisms (Boguszewski et al. 2010).

Satiety and adiposity signals

The food intake control includes a short-term regulation, which determines the beginning and the end of a meal (hunger and satiation) and the interval between the meals (satiety) and a long-term regulation with factors (signals of adiposity), which help to regulate the body energy depots (Cummings and Overduin 2007).

The satiation means a suppression of the hunger and termination of the food intake after ingestion of

a certain amount of food (Smith 1998). The mechanisms controlling satiation determine the size of the meal. Satiety is a period of time between the meals with no hunger (Strubbe and Woods 2004). This time period is variable and its termination coincides with the refeeling of the hunger accompanied by the consumption of the next meal, thus resuming the cycle of the food intake (Hargrave and Kinzig 2012) (Figure 1).

The mechanisms, which control the size of the meal (satiation) and those controlling the intervals between the meals (satiety), differ (de Graaf et al. 2004; Benelam 2009). The satiation is determined by physiological and psychological mechanisms, which trigger the afferent signals to brain from multiple sites in the GIT, including the stomach, the proximal small intestine, the distal small intestine, and the colon (Ritter 2004; Keenan et al. 2015).

The satiety is affected by short-term signals from GIT (Zac-Varghese et al. 2010) and long-term signals from the body energy store (Woods 2005). The signals from GIT are transmitted primarily via the vagal and spinal nerves to the nucleus of the solitary tract (NTS). Transection of all the gut sensory vagal fibers has been shown to increase the meal size and its duration (Schwartz 2000; Powley et al. 2005). However, the stimulation of the vagus nerve did not result in a weight gain (Koren and Holmes 2006). The long-term signals (adiposity signals) reach the arcuate nucleus (ARC) via the median eminence or by crossing the blood-brain barrier (BBB). There exists, however, a large number of integrations and convergences between these signals mediated by neural connections between the ARC nucleus, NTS, and the vagal afferent fibers (Boguszewski et al. 2010).

The hypothalamus role in the food intake control

The hypothalamus plays a major role in the control of the appetite. In the hypothalamus, afferent signals from the gut and brain stem relied and efferent signals for the food intake control are processed. Within the hypothalamus, there are many nuclei and neuronal circuits involved in the food intake regulation, such as the ARC, a key hypothalamic nucleus in the appetite control, the paraventricular nucleus (PVN), the dorsomedial nucleus (DMN), the ventromedial nucleus (VMN), and the lateral hypothalamic area (LHA) (Wynne et al. 2005).

Arcuate nucleus (ARC) contains two neuronal populations with opposing effects on the food intake, i.e. neurons, which stimulate the food intake co-expressing neuropeptide Y (NPY) and agouti re-

lated peptide (AgRP), and neurons, which suppress the feeding co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). Both types of the neurons project to the hypothalamic areas, which are involved in the control of appetite including the DMN, PVN, and LHA (Suzuki et al. 2010) (Figure 2).

Neuropeptide Y is the most abundant neurotransmitter in the brain. The hypothalamic NPY neuropeptide levels increase during the fasting and decrease after the feeding (Wynne et al. 2005). The NPY integrates a large family of peptides that includes peptide YY (PYY) and pancreatic polypeptide (PP), the effects of which are mediated via the six G-protein-coupled receptors named Y1 to Y6. The orexigenic effect of NPY is mediated by stimulation of the hypothalamic Y1R and Y5R, in addition to the local inhibition of the POMC neurons in the ARC. In addition, AgRP acts as a selective antagonist at MC3R and MC4R in the PVN (Suzuki et al. 2010).

Activation of NPY may explain the easy recovery of weight observed in the obese individuals undergoing treatment, since weight reduction leads to a decrease in the leptin, activation of NPY, and consequently to hyperphagia and reduced energy expenditure (Boguszewski et al. 2010). Regain of the weight, following the weight loss, can be a result of the modified adipose tissue cellularity, endocrine function, and energy metabolism (Ochner et al. 2013).

The anorexigenic effect of POMC has been proven by an increase in the food intake and adiposity as a result of POMC gene mutations in humans (Krude

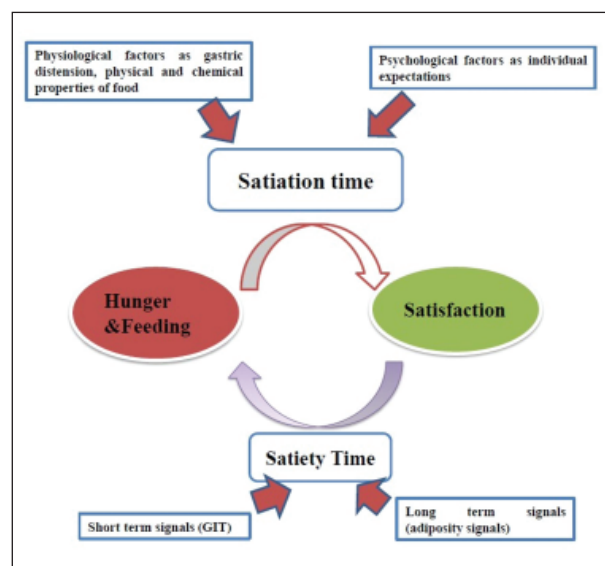


Figure1. Food intake cycle.

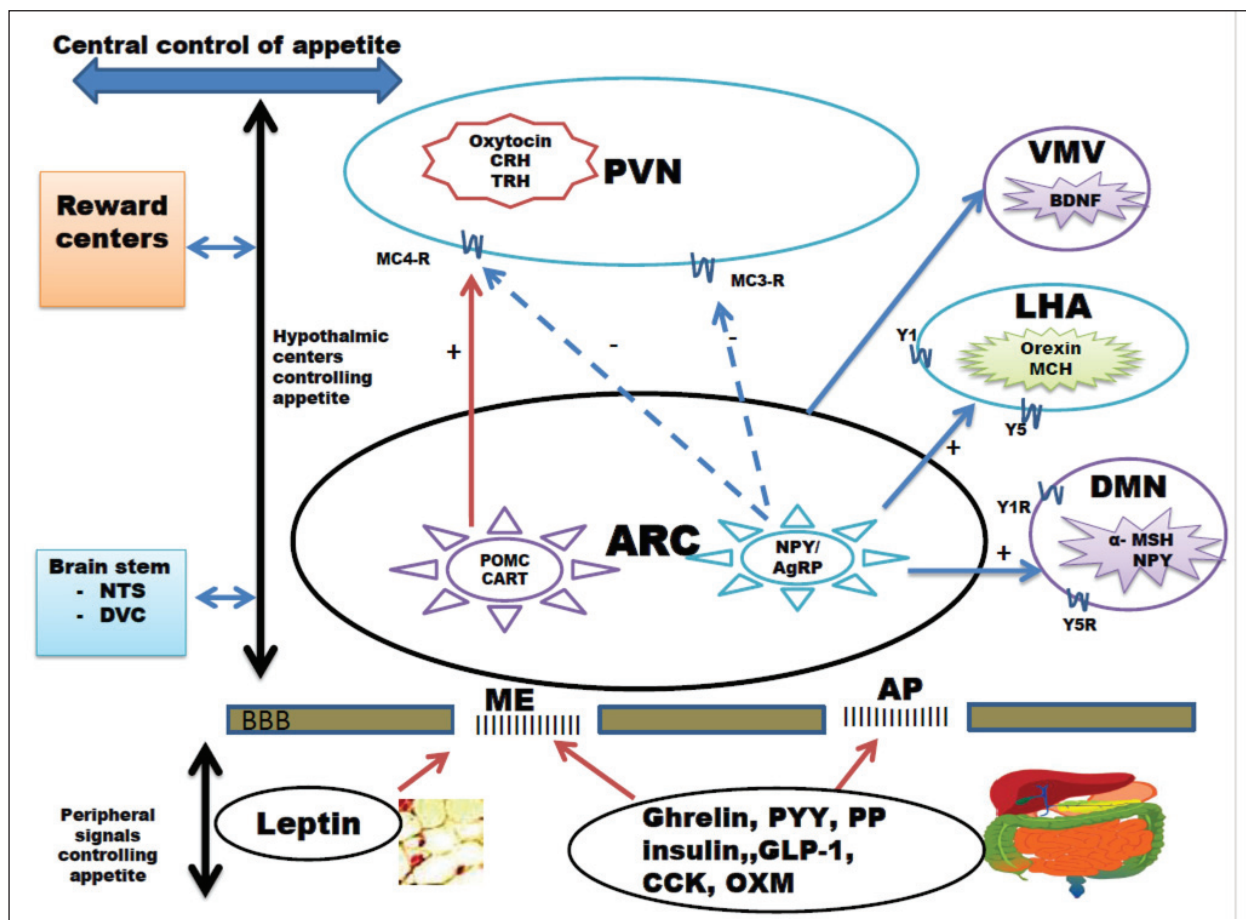


Figure 2. Short and long signals for food intake control. Abbreviations: ARC – arcuate nucleus; NPY/AgRP – neuropeptide Y and agouti related peptide; POMC/CART – pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript; PVN – paraventricular nucleus; LHA – lateral hypothalamic area; DMN – dorsomedial nucleus; VMN – ventromedial hypothalamic nucleus; ME – median eminence; AP – area postrema; GLP-1 – glucagon-like peptide-1; CCK – cholecystokinin; PP – pancreatic polypeptide; PYY – peptide YY; OXM – oxyntomodulin; BBB – blood-brain barrier; MCH – melanin-concentrating hormone; α -MSH – alpha melanocyte stimulating hormone; BDNF – brain derived neurotrophic factor; CRH – corticotrophin releasing hormone; NTS – nucleus tractus solitaries; DVC – dorsal vagal complex; TRH – thyroid releasing hormone; MC4-R – melanocortin receptor 4; MC3-R – melanocortin receptor 3; Y1R & Y5R – neuropeptide Y receptors 1 & 5

et al. 1998) and gene deletion in canine (Raffan et al. 2016). In the ARC nucleus, the cleavage of POMC results in the production of melanocortin peptides including adrenocorticotrophic hormone (ACTH) and α -melanocyte-stimulating hormone (α -MSH) that exert their effects by binding to G-protein coupled melanocortin receptors (MC-Rs). From five, two melanocortin receptors are expressed in the brain, MC4-R and MC3-R. Hyperphagia and obesity result from the targeted deletion of MC4-R in mice (Huszar et al. 1997). The higher fat content that have been noticed in MC3-R knockout mice (Chen et al. 2000) reflects the importance of these two receptors in controlling the appetite. The inhibitory effect of the melanocortinergic neurons is antagonized by AgRP

at MC4-R and MC3-R (Bagnol et al. 1999). The products of POMC cleavage, the five different subtypes of G-protein-coupled receptors, and the endogenous antagonists, AgRP and Agouti constitute the melanocortin system that is involved in many important physiological processes. In addition to food intake, the melanocortin system is involved in the regulation of pigmentation, adrenocortical steroidogenesis, natriuresis, erection, and exocrine secretion (Cone 2005; Wynne et al. 2005).

Majority of the neurons that express POMC also co-express CART mRNA. The fasting decreases CART expression (Kristensen et al. 1998). Animal studies have shown a decrease in the food intake upon the intracerebroventricular (ICV) administra-

tion of CART (Aja et al. 2001; Rohner-Jeanrenaud et al. 2002) and its increase after ICV injection of CART antiserum (Kristensen et al. 1998). However, recent studies have shown an increase in the food intake after injection of CART into the hypothalamic nuclei in streptozotocin-diabetic rats (Hou et al. 2010). This suggests that CART can be orexigenic or anorexigenic, based on the neural circuit that is stimulated. It has been suggested that decreased expression of CART mRNA in ARC and PVN regions may contribute to the development of high-fat diet-induced obesity in mice. In addition, CART in the DMN and LH may be involved in the activation of the orexigenic effect (Yu et al. 2008).

Neurotensin (NT), a peptide expressed in the brain and GIT, plays a role in the regulation of food intake as evidenced by the inhibition of the food intake following the central and peripheral NT administration (Ratner et al. 2016). Transient increase in the food intake has been shown following pharmacological NT antagonism in a rat Roux-en-gastric bypass model (Ratner et al. 2016). It has been shown that peripheral NT administration inhibits the food intake by increasing the POMC mRNA in the ARC (Ratner et al. 2016). The anorexigenic effect of NT is mediated by neurotensin receptor-1 (Ntsr1), as it has been evidenced by Kim and Mizuno (2010). Other peptides that act on Ntsr1 and inhibit food intake include neuropeptide U (Kim and Mizuno 2010) and xenin, a peptide that is released from the small intestine (Sterl et al. 2016).

The hypothalamic paraventricular nucleus (PVN) contains several neurons that secrete anorexigenic substances such as corticotropin-releasing hormone (CRH), oxytocin, and thyrotropin-releasing hormone (TRH). Each of these peptides acts to decrease food intake, increase the metabolic rate, or both (Morton et al. 2012; Blevins et al. 2015; Moore et al. 2015). The CRH is a 41 amino acid peptide, which is widely distributed throughout the brain, but is particularly abundant in the medial parvocellular division of the PVN (Sawchenko et al. 1985). In addition to its role in controlling the activity of the pituitary-adrenal axis, CRH controls the food intake too. Within the brain, CRH with its two receptor types, CRH type 1 (CRH1-R) and CRH type 2 α (CRH2 α -R), its binding protein, and its closely related peptide urocortin, forms a network of neuronal pathways that is capable of interacting with other circuitries controlling the food intake (Mastorakos and Zapaniti 2004). It has been shown that CRH mediates the anorexigenic effect of α -MSH in fish (Matsuda et al. 2008) and ELABELA in the adult mouse (Santoso et

al. 2015). ELABELA, a novel hormone consisting of 32 amino acid peptides, found in humans and other vertebrates, is considered to play an important role in the circulatory system. It has been shown that ICV injection of ELABELA reduces food intake and activates the arginine vasopressin (AVP) and CRH neurons in the PVN in a dose dependent manner (Santoso et al. 2015).

A defect in the synthesis and release of the CRH has been implicated in the development of the obesity in laboratory animals (Mastorakos and Zapaniti 2004). Moore et al. (2015) have reported a beneficial effect of CRH1-R antagonism in the attenuation of the stress-induced consumption of palatable diets in female rhesus monkeys. It has been suggested that anorexigenic effect of CRH is conferred by CRH1R (Hotta et al. 1999). However, it has been observed that CRH is able to decrease the food intake in CRH1R knockout mice as much as in wild type littermates suggesting that both CRH1-R and CRH2-R may mediate the food intake inhibitory effect of CRH and urocortin but at different time course (Sekino et al. 2004).

Oxytocin, a hypothalamic peptide, is released into the circulation through the posterior pituitary and also directly acts on the central nervous receptors. In addition to its role in regulation of reproductive functions, such as mother-infant interaction and lactation, it is a potent modulator of social behaviors including attachment and sexual behavior (Meyer-Lindenberg et al. 2011). Moreover, animal studies and pilot experiments in humans have indicated that oxytocin might have a role in the regulation of eating behavior and metabolism in normal weight as well as with diet-induced obesity. Oxytocin administration in animals and humans inhibits food intake, increases energy expenditure, and reduces glucose levels (Morton et al. 2012; Ott et al. 2013; Blevins et al. 2015; Lawson et al. 2015). Interestingly, there are experiments, which suggest that the metabolic effects of oxytocin may be even enhanced in diet-induced obese in comparison to control weight (Thienel et al. 2016) with absent or minimal side effects. This makes oxytocin a promising pharmacological intervention in obesity (Blevins and Baskin 2015; Zhang et al. 2013). A recent study has shown that central oxytocin acts via an oxytocin receptor that is expressed in the nucleus accumbens core to decrease food intake driven by hunger and reward in rats offered a meal in a non-social setting (Herisson et al. 2016).

Galanin-like peptide (GALP) is a neuropeptide expressed in several brain areas including hypothalamic nuclei involved in the appetite regulation such

as ARC, PVN, and median eminence (Wodowska and Ciosek 2015). GALP seems to be a promising peptide in the obesity treating. GALP administration has been effective in ameliorating the obesity in mice, where it has been shown that brain uptake of GALP is higher after intranasal than intravenous administration (Hirako et al. 2016; Kageyama et al. 2016). Administration of GALP in mice, but not rats, resulted in an acute orexigenic effect that may be explained by an NPY input to GALP neurons from the ARC NPY-containing neurons and orexin-containing neurons in LHA, in addition to fibers that project from GALP neurons to orexin and melanin-concentrating hormone (MCH) ones in the LHA (Takenoya et al. 2005). However, this orexigenic effect was transient and followed by a chronic anorexigenic effect and decrease of the body weight. It has been suggested that GALP expression is regulated by leptin and insulin as evidenced by the presence of leptin receptors in more than 85% of GALP neurons (Hirako et al. 2016). The expression of GALP in the brain has been found to be increased after administration of the leptin in fasted rats as compared with controls (Lawrence and Fraley 2011). GALP expression has been found to be restored in diabetic rats after insulin administration (Fraley et al. 2004).

The lateral hypothalamic area (LHA). Orexin A and B, a pair of neuropeptides, are produced in cells located in the hypothalamic lateral and perifornical areas. Orexin A has been found to enhance the food intake when injected into certain hypothalamic nuclei such as LHA, PVN, DMN, and the perifornical area. However, orexin B has been found to be ineffective when injected to any of the hypothalamic nuclei (Dube et al. 1999). Hypocretin-1 (HC, Orexin A) is a neuropeptide that is involved in the regulation of many physiological functions, such as sleep, appetite, and arousal. Recently, a study on rats has shown an increase in the food consumption after intranasal administration of HC (Dhuria et al. 2016). In addition to orexin expressing cells, LHA contains MCH expressing cells that extend in a wider area. These two types of cells are targets for NPY and AgRP projections coming from the ARC (Broberger et al. 1998).

The ventromedial nucleus (VMN). In addition to the large population of glucoresponsive neurons in the VMN, the brain-derived neurotrophic factor (BDNF) is also highly expressed. Central infusion of BDNF reduces food intake and induces weight loss in rats (Pellemounter et al. 1995). The VMN receives NPY, AgRP, and POMC neuronal projections from the ARC and it is thought that POMC neurons from the ARC play a role in activating BDNF neurons in

VMN to decrease the food intake (Xu et al. 2003).

The dorsomedial nucleus (DMN) contains a high level of NPY and α -MSH terminals originating in the ARC. From DMN, α -MSH fibers project to the TRH-containing neurons in the PVN (Mihaly et al. 2001). Destruction of the DMN results in hyperphagia and obesity (Bernardis and Bellinger 1986).

Role of the brainstem

The dorsal vagal complex (DVC), located within the brainstem, is a crucial in the interpretation and relaying of peripheral signals from the gut to the hypothalamus. The DVC consists of the dorsal motor nucleus of the vagus (DVN), the area postrema (AP), and the NTS within which POMC neurons exist (Schwartz 2010). Receptors for a variety of hormones controlling food intake have been found to be expressed in the brainstem vagal afferent neurons including cholecystokinin (CCK) 1R and CCK 2R at which both CCK and gastrin act (Moriarty et al. 1997), insulin receptors, GLP-1 (Nakagawa et al. 2004) and GLP-2R (Nelson et al. 2007), growth hormone secretagogue receptor (GHS)-R1 at which ghrelin acts (Date et al. 2002), the orexin receptor, OX-R1 (Burdyga et al. 2003), and leptin (Burdyga et al. 2002).

Role of the reward system

Different brain circuits involved in the reward, as the hippocampus, amygdala, pre-frontal cortex, and midbrain, have been found to be activated by food and food-related cues (Palmiter 2007; Kenny 2011). Dopamine is a neurotransmitter that is released from the neurons in the mesolimbic system and mediate emotions and pleasure (reviewed by Nutt et al. 2015). It has been demonstrated that with food intake dopamine release is enhanced in the circuits that mediate the pleasurable aspects of the eating (Volkow et al. 2011). However, decreased body weight after chronic food deprivation has been shown to be associated with a decrease of dopamine levels (Pothos et al. 1995). This suggests that increased food intake after chronic food deprivation and weight loss may represent a compensatory mechanism to restore the baseline dopamine levels (Cota et al. 2006).

The endogenous opioid and endocannabinoid systems play important role in the reward-related feeding (Pomorska et al. 2016). The endogenous opioid peptides such as β -endorphins derived from POMC, which is a precursor of opioids, bind to opioid receptors that are distributed in the hypothalamic regions controlling the food intake (reviewed by Kenny 2011).

Some studies have shown that infusions of μ -opioid receptor agonists stimulate feeding behavior in rats, while opioid receptor antagonists infused decrease the consumption of the preferred food without affecting the intake of the less palatable alternatives (reviewed by Goodman 2008). In addition, systemic injection of a μ -opioid antagonist prevents the stimulatory effect of palatable food on dopamine release in the nucleus accumbens, which confirms the excitatory effects of opioids on the dopamine system (Tanda and di Chiara 1998).

Role of the endocannabinoid system

The plant-derived cannabinoids such as Δ^9 -tetrahydrocannabinol (THC) as well as their synthetic analogues, act in the organism by activating specific cell-surface receptors that are normally engaged by a family of endogenous ligands; the endocannabinoids. The first endocannabinoid discovered was named anandamide (AEA), the amide of arachidonic acid (AA) and ethanolamine (Et) (Devane et al. 1992). A second arachidonic-acid derivative is the 2-arachidonoylglycerol (2-AG) that binds to cannabinoid receptors was subsequently described (Mechoulam et al. 1995).

Endocannabinoids are produced by a variety of cell types including endothelial cells (Gauthier et al. 2005), adipocytes (Pagano et al. 2008), glial cells (Gonthier et al. 2007), macrophages (Di Marzo et al. 1999), and Purkinje cells (Maejima et al. 2001). The endocannabinoid system (ECS) consists of the endogenous cannabinoid ligands, the enzymatic machinery involved in their synthesis uptake and degra-

dation, the G-protein-coupled cannabinoid receptors type 1 and 2 (CB1 and CB2) (Kogan and Mechoulam 2006; Quarta et al. 2011). CB1 has been found to be widely and abundantly distributed in tissues involved in the energy homeostasis, including the hypothalamus, brainstem, mesolimbic region, and peripheral tissues such as the GIT, fat, liver, muscle, thyroid, and pancreas (Matias et al. 2006). CB2 is well known in his immune modulatory effect (Cabral and Griffin-Thomas 2009). However, recently it has been found that CB2 plays a role in the energy homeostasis and food intake (Verty et al. 2015) (Figure 3).

The ECS is involved in the regulation of food intake and energy balance as evidenced by the following: 1) binding of endocannabinoids to CB1 receptors results in an increased appetite, weight gain, lipogenesis, and lower insulin sensitivity (Horvath 2003); 2) an increased food intake after central administration of cannabinoids mediated by CB1 activation (Jamshidi and Taylor 2001; Verty et al. 2005) and its suppression by blocking the cannabinoid receptor that has been found to have a direct participation of sympathetic nervous system, ghrelin, or leptin (Alen et al. 2013; Silvestri and Di Marzo 2013); 3) increased endocannabinoid hypothalamic levels in rodents with diet-induced or genetic obesity (Quarta et al. 2011). The endocannabinoids increase the production of the hypothalamic appetite stimulating transmitters and reduce the production of the appetite-suppressing signals. In the reward center of the mesolimbic region, the endocannabinoids promote the motivation to eat palatable food (Di Marzo and Matias 2005).

Food intake has been found to be suppressed by genetic deletion or pharmacological CB1 blockade in the lean and obese starved animals (Verty et al. 2009; Quarta et al. 2010; Quarta et al. 2011; Rorato et al. 2013). However, other studies have shown that CB1 blockade may result in a food intake independent decrease in fat mass mainly through lipolysis (Jbilo et al. 2005; Nogueiras et al. 2008; Quarta et al. 2010). As a consequence, CB1 blockade has been shown to be effective in ameliorating the obesity-related metabolic disorders (Cota et al. 2003; Ravinet Trillou et al. 2004; Quarta et al. 2011).

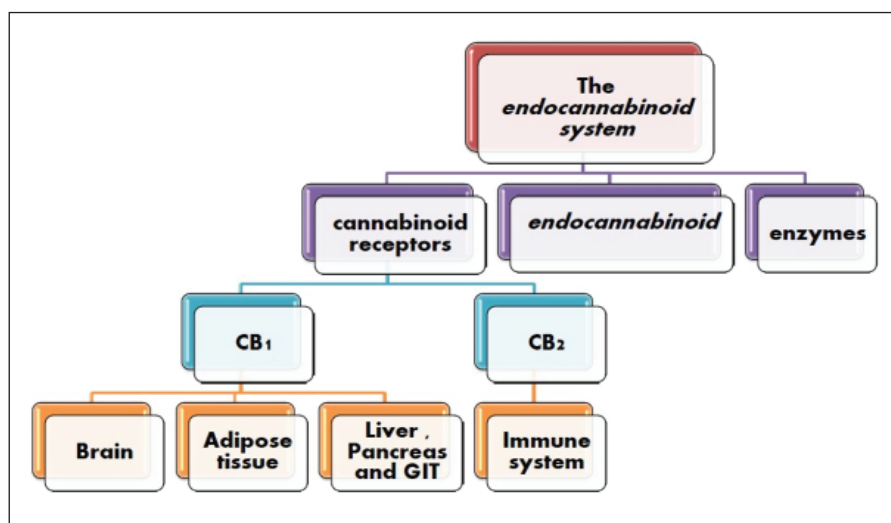


Figure 3. The endocannabinoid system.

The activation of ECS has been found to promote energy storage (Bermudez-Silva et al. 2010; Quarta et al. 2010; Bermudez-Silva et al. 2012). Physiologically, ECS is activated in response to stressful stimuli helping the affected tissues to restore their steady state (Pagotto et al. 2006). Ingestion of food, CCK and other gastric peptides decrease the activity of the ECS. In contrast, increased circulating levels of ghrelin in situations of the food deprivation are associated with higher endocannabinoid activity, suggesting that the orexigenic effect of ghrelin occurs, at least in part, by activation of the endocannabinoid system (Boguszewski et al. 2010). Leptin produced from the adipose tissue reduces the levels of endocannabinoids due to interference with 2-AG synthesis and increased anandamide degradation (Di Marzo and Matias 2005).

Is the over-activity of ECS a cause of obesity?

The sustained hyperactivity of the ECS could lead to hyperphagia with a progressive and excessive accumulation of fat and subsequent development of obesity (Ravinet Trillou et al. 2004), insulin resistance, and disturbed lipid profile (Foster-Schubert and Cummings 2006). Obesity has been found to be associated with a dysregulation of the ECS. CB1 has been found to be less in obese and returned to the normal after weight loss (Bennetzen et al. 2011). Blocking of CB1 in humans using rimonabant, as a treatment for obesity, resulted in psychiatric side effects, which resulted in withdrawal of the drug (Lee et al. 2009). However, targeting the peripheral CB1 receptors has been found to safely alleviate the cardio-metabolic disorders associated with the obesity (Tam et al. 2010).

The effectiveness of CB1 receptor blockade in decreasing body weight and amelioration of the obesity related metabolic disorders may be mediated by elimination of ECS effects on the appetite, increase in adiponectin levels, which is thought to result in increased fat metabolism and an improvement in glucose metabolism (Scheen et al. 2006) and increase in the mitochondrial biogenesis in white adipocytes by inducing the expression of nitric oxide (NO) produced by endothelial NO synthase (eNOS), which is linked to the prevention of high-fat diet-induced fat accumulation, without concomitant changes in food intake (Tedesco et al. 2008).

Role of the gastrointestinal tract peptides

The gastrointestinal (GI) tract is the largest endocrine organ in the body where many hormone genes are expressed and bioactive peptides are produced (Rehfeld 1998). Many of these hormones and peptides

are involved in the peripheral control of the food intake by controlling the initiation and termination of the meal. Besides the role of peptides in satiation and satiety, gastric distension has a satiating effect that forms the basis of gastric balloon use in humans as a treatment for obesity (Martin et al. 2007).

Cholecystokinin (CCK) was the first gut hormone shown to modulate the food intake (Bray and York 1972). CCK is secreted postprandial from I cells of the small intestine into the circulation with a plasma half-life of a few minutes. CCK levels rise rapidly reaching a peak within 15 minutes after a meal. It is also reported to reduce food intake in humans and rodents (Liddle et al. 1985). The action of CCK is mediated by two CCK receptor subtypes: CCK1 and CCK2, which are widely distributed in the brain including the brainstem and the hypothalamus (Moran et al. 1998). The anorectic action of CCK has been found to be mostly mediated through CCK1R on vagal afferents (Moran et al. 1997). There are various forms of CCK with various effects on the meal size and the intervals between meals. While CCK 58 and CCK-8 both stimulate satiation, thereby reducing meal size, CCK-58 consistently exerts a satiety effect (Overduin et al. 2014). Similar results have been reported with CCK-33, which has been found to reduce the food intake by prolonging the inter-meal interval (Washington et al. 2011; Lateef et al. 2012).

Peptide tyrosine tyrosine (PYY) is a member of the pancreatic polypeptide (PP) family (Lin et al. 2004). There are two circulating forms of PYY released by L cells in the distal gut: PYY (1–36) and PYY (3–36). PYY (3–36), the major circulating form, is produced by cleavage of the N-terminal Tyrosine-Proline residues from PYY (1–36) by the enzyme dipeptidyl-peptidase-IV (DPP-IV) (Wynne et al. 2005). Currently, the DPP-IV inhibitors are being evaluated for their effects on the obesity and metabolic traits (Martin et al. 2015).

PYY (3–36) binds with highest affinity to the hypothalamic Y2R causing a reduction in food intake. It also binds to other Y receptors, although with much lower affinity. In addition to PYY's anorectic effect on food intake, it also increased the energy expenditure (Boey et al. 2008) and delayed gastric emptying in mice (Talsania et al. 2005). The low level of PYY in obese subjects and their blunt increase after a meal possibly results in impaired satiety and hence greater food intake (le Roux et al. 2006). However, this was not supported by the findings of another study that has shown no differences in the levels of PYY between lean and the obese (Pfluger et al. 2007). Weight regain after Roux-en-Y gastric bypass (RYGB) has been

found to be attributed to the failure to sustain a high level of PYY indicating that combining RYGB with pharmacologic stimulation of PYY secretion in patients after RYGB who exhibit inadequate PYY concentration may increase long-term success of surgical weight reduction in morbidly obese adults (Meguid *et al.* 2008).

Pancreatic polypeptide (PP) is a hormone released from the pancreas in response to food ingestion. PP plasma levels are reduced by obesity and increased by anorexia nervosa. The peripheral administration of PP has been shown to decrease the food intake in rodents and humans (Batterham *et al.* 2003; Jesudason *et al.* 2007). PP is thought to reduce food intake through the following mechanisms 1) stimulation of Y4 and Y5 receptors in the dorsal vagal complex, including the area postrema (AP), the nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus (DMV) (Whitcomb *et al.* 1997; Lin *et al.* 2009); 2) sending anorexigenic signals via the brainstem and hypothalamic neuropeptides (Hankir *et al.* 2011); 3) modulation of the expression of other peripheral peptides such as ghrelin, and 4) delay in gastric emptying that seemed to occur only in animal models and not in humans. The anorectic effects of PP and PYY (3–36) are abolished in abdominal vagotomised rats, suggesting that PP and PYY (3–36) induce anorexia via vagal afferent nerves (Iwasaki *et al.* 2013).

Enterostatin and apolipoprotein A-IV. Enterostatin is a peptide secreted from the exocrine pancreas in response to fat intake to facilitate its digestion (Cummings and Overduin 2007). Both peripheral and central enterostatin administrations have been found to decrease dietary fat intake in animals, conversely enterostatin-receptor antagonists have been found to do the opposite (Okada *et al.* 1992). Apolipoprotein A-IV (APO AIV) is a glycoprotein secreted from the intestine in response to fat absorption and chylomicron formation to be used in packaging of digested lipids in transit through lymphatic to blood. It has been hypothesized that APO AIV represents a link between the short- and long-term regulations of lipid-related energy balance (Qin and Tso 2005) based on the following findings: 1) APO AIV is produced in the hypothalamic arcuate nucleus (Tso *et al.* 2004) and 2) exogenous administration of APO AIV has been found to decrease meal size, food intake, and weight gain in rats, whereas APO AIV-specific antibodies have been found do the opposite (Fujimoto *et al.* 1993).

Glucagon-like peptide-1 (GLP-1). The pro-glucagon gene is cleaved into different products by the en-

zymes convertase 1 and convertase 2, a process that varies among the tissues. In the pancreas, the main product of this cleavage is glucagon, whereas in the intestine the GLP-1 and GLP-2. GLP-1 is released into the circulation after meals, physiologically acting as an incretin that promotes increased pancreatic insulin secretion and consequently influences the glucose homeostasis (Holst 2004).

DPP-IV degradation and renal clearance rapidly inactivate and remove GLP-1 from the plasma circulation, resulting in a half-life of 1–2 minutes (Mentlein *et al.* 1993). GLP-1 has two biologically active forms, GLP-1 (7–37) amide and GLP-1 (7–36) amide, the latter being the major circulating form in humans. GLP-1R expression is widely distributed particularly in the brain, GIT, and pancreas (Baggio and Drucker 2014). Circulating GLP-1 levels rise after a meal and fall in the fasted state. GLP-1 reduces food intake (Parker *et al.* 2013), suppresses glucagon secretion (Hare 2010), and delays gastric emptying (Little *et al.* 2006).

Oxyntomodulin (OXM) is another product of the proglucagon gene, which is released from the intestinal cells into the circulation in proportion to caloric intake (Ghatei *et al.* 1983). OXM has been found to reduce the food intake and promote increased energy expenditure resulting in negative energy balance that supports the role of oxyntomodulin as a potential anti-obesity therapy (Cohen *et al.* 2003; Wynne *et al.* 2006). The most likely mechanism of OXM action on energy homeostasis is through its binding to the GLP-1 receptor as GLP-1 receptor antagonists have been found to reduce the food intake (Dakin *et al.* 2004). Although OXM binds the GLP-1 receptor with lower affinity than GLP-1 by approximately 50 fold less strongly than GLP-1, they are equally effective in causing anorexia. Thus, differences in the biological effects of OXM and GLP-1 may be due to variations in the tissue penetration, degradation, or intracellular signaling pathways (Fehmann *et al.* 1994; Baggio *et al.* 2004).

Glucagon is produced by alpha cells of the pancreatic islets. In contrast to GLP-1 and insulin, hypoglycemia causes an increase in the glucagon secretion resulting in hepatic glycogenolysis. Peripheral as well as central administration of glucagon in rats reduced food intake and meal size in addition to reducing body weight gain (Geary *et al.* 1993; Honda *et al.* 2007). Combination of glucagon and GLP-1 agonists has been found to be beneficial as a treatment of obesity rodents have been demonstrated (Pocai *et al.* 2009) as GLP-1 prevented the hypoglycemia induced by glucagon (Parker *et al.* 2013).

Insulin and amylin. Insulin, a peptide secreted from beta cells of the pancreas after a meal and its amount along with leptin has been found to be directly proportional to white fat (Considine et al. 1996) that may reflect the important role of both as an adiposity signals from adipose tissue to the hypothalamic centers controlling energy balance. Although there is a controversy in the issue whether insulin can cross the blood brain barrier and whether it is synthesized by the brain itself (Woods et al. 2003; Gerozissis 2004). It has been found that central administration of insulin caused a decrease in food intake and weight loss in animals (Woods et al. 1979; Riedy et al. 1995) whereas opposite effect has been found when insulin antibodies were administered in or near the mediobasal hypothalamus (McGowan et al. 1992) where insulin receptors are highly expressed (Halmos and Suba 2011).

Amylin is a peptide co-secreted with insulin, inhibits gastric emptying, gastric acid and glucagon secretions, and reduces food intake and meal size in animals (Young and Denaro 1998). The anorectic action of amylin has been found to be mediated by decreasing the expression of orexigenic neuropeptides (Lutz 2009). The effect of chronic administration of amylin in increasing energy expenditure has been demonstrated (Wielinga et al. 2007). Acute administration of amylin agonist, salmon calcitonin but not amylin significantly stimulated energy expenditure in fasted animals (Roth et al. 2006).

Ghrelin is the only known orexigenic gut peptide secreted mainly from the stomach. The pre-prandial elevation of ghrelin levels and its fall after meals led to the notion that ghrelin is a 'hunger' hormone responsible for meal initiation. Ghrelin is involved in short-term regulation of the food intake and long-term regulation of bodyweight through decreasing fat utilization (Castaneda et al. 2010). The effect of ghrelin on food intake is mediated through the growth hormone secretagogue receptor 1a (GHS-R1a), which is highly expressed in the hypothalamic cell populations that regulate the feeding and the body weight homeostasis. This was evidenced by lack of the orexigenic effect of ghrelin in GHS-R knocked out mice (Sun et al. 2004). Ghrelin's orexigenic effect is mediated by specific modulation of AgRP/NPY neurons in the ARC without demonstrated change in the mRNA levels of the other feeding-promoting neuropeptides such as melanocyte stimulating hormone (MCH) and pre-pro-orexin (OX) (Cowley et al. 2003). Recent data have indicated that the orexigenic effect of ghrelin is mediated by its modulation of the hypothalamic adenosine monophosphate (AMP)-activated protein

kinase (AMPK) enzyme activity (Kola et al. 2008). The detection of the ghrelin receptors on the vagal afferent neurons in the rat suggests that ghrelin signals from the stomach are transmitted to the brain via the vagus nerve (Date 2012). However, the findings regarding effect of vagotomy on the orexigenic effect of ghrelin in animal models and humans is not universal. The vagal afferents cut was not necessary for the orexigenic effect of the peripherally injected ghrelin in rats (Arnold et al. 2006) as well as gastrectomy in humans accompanied by vagotomy did not prevent the orexigenic effects of ghrelin treatment, indicating that intact vagus is not required for its orexigenic effects (Adachi et al. 2010). The orexigenic and lipogenic effect of ghrelin provide a potential use of ghrelin antagonists or reverse agonists in the treatment of the obesity (Alvarez-Castro et al. 2013). However, studies in this area have shown conflicting results (Costantini et al. 2011; Abdel-Hakim et al. 2014).

Role of peripheral adiposity signals

Adiposity signals are signals that inform the brain about the mass of the adipose tissue. Basal levels of insulin and leptin are widely accepted to be adiposity signals. Amylin, ghrelin, and peptide YY have been hypothesized to be adiposity signals (reviewed by Hillebrand and Geary 2010).

Leptin is a peptide hormone produced by the *ob* gene and secreted mainly by the adipose tissue, playing a key role in the energy homeostasis (Klok et al. 2007). The production of leptin is higher in the subcutaneous than in visceral fat, and its level in the blood correlate directly with the amount of body fat. The secretion of leptin is reduced during periods of fasting and increased after meals. It is influenced by several metabolic and hormonal factors (Friedman 2004).

Leptin is transported across the BBB by a saturable system and exerts its anorectic effect in the ARC via inhibition of NPY/AgRP neurons and activation of POMC/ CART neurons resulting in reduced food intake and increased energy expenditure. The Ob-Rb receptor, which is highly expressed in the hypothalamus, is thought to be the main receptor involved in the appetite regulation. Ob-Rb receptor belongs to the type I cytokine receptor family and exists in five distinct isoforms (splice variants) named as Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, and Ob-Re. Only the Ob-Rb isoform contains a long intracellular domain essential for the biological actions of leptin (Suzuki et al. 2010).

Human obesity is generally associated with high serum levels of leptin and less efficient transport

across the BBB, consistent with a state of central resistance to leptin. This resistance may be secondary to obesity or vice versa, and genetic factors, age, diet, sedentary lifestyle, and stress might contribute to the development of defects in the transport of leptin across the BBB or might lead to abnormalities in leptin signaling (Paz-Filho *et al.* 2009).

Adiponectin and resistin. The adipose tissue produces numerous other factors that may directly or indirectly influence the energy balance and body weight. Adiponectin is one of these factors. The physiological effect of adiponectin is to increase energy expenditure and to protect against insulin resistance and atherosclerosis (Trujillo and Scherer 2006). Studies have shown that adiponectin activates signal transduction pathways similar to leptin and insulin in the hypothalamus, reinforcing its role in the central control of energy homeostasis (Coope *et al.* 2008). In humans, serum adiponectin levels are inversely related to adiposity and insulin resistance, increasing after weight loss induced by diet or bariatric surgery (Ahima and Lazar 2008). In contrast, resistin is a peptide produced by adipocytes and increases insulin resistance *via* paracrine actions. Serum levels of resistin are increased in obesity (Banerjee *et al.* 2004).

Other adipocytokines involved in energy balance. Tumor necrosis factor- α is correlated with the amount of body fat, inhibits feeding, increases metabolic rate, and induces cachexia (Galic *et al.* 2010). Another potential adipocytokine involved in energy homeostasis is interleukin-6 (IL-6). Several data have suggested a potential protective role of IL-6 against the development of obesity (Wallenius *et al.* 2003). However, the data are not consistent between different research groups and the actual involvement of IL-6 in controlling the energy balance requires additional studies (Ahima and Lazar 2008). In addition, it has been demonstrated that atrial natriuretic peptide (ANP) is expressed and secreted by human pre-adipocytes. ANP is not only a strong hypotensive, but also a lipolytic compound (Garruti *et al.* 2008).

Role of catecholamines

Norepinephrine (NE), synthesized in both the central and peripheral nervous system, is involved in food intake regulation of both mammals and chickens. NPY, a potent orexigenic peptide, is co-localized with NE in the central and peripheral nervous system, suggesting an interaction (Katayama *et al.* 2010). The effect of NE on the food intake is a point of great controversy. Some studies have demonstrated an increase in the food intake following central NE injection

in the anterior and medial hypothalamus, and explained the increase in feeding following ovariectomy by increase in NE (Simpson and Dicara 1973). In contrast, several studies have demonstrated a dose-dependent decrease in food intake following ICV injection of NE in rats and chickens (Katayama *et al.* 2010). Another study evidenced that noradrenergic neurons in the area postrema mediate at least part of the hypophagic action of amylin (Potes *et al.* 2010).

In the lateral hypothalamus (LH), Leibowitz (1978) has found that epinephrine, NE or dopamine had an anti-feeding effect. Beta-adrenergic or dopaminergic drugs injected into the LH tend to inhibit feeding. Similarly, drugs that release catecholamines also inhibit feeding (Hoebel 1985). Several studies have

Table 1
Summary of central and peripheral orexigenic and anorexigenic hormones/ peptides

Orexigenic hormones/ peptides		Anorexigenic hormones/ peptides	
Central	Peripheral	Central	Peripheral
NPY	Ghrelin	POMC	CCK
AgRP		CART	PYY
Orexin A		BDNF	PP
MCH		ACTH	Enterostatin
Dopamine "Reward- related feeding"		α -MSH	Apolipoprotein A-IV
Endogenous opioids "Reward-related feeding"		Neurotensin	Neurotensin
		CRH	GLP-1
		Oxytocin	Oxyntomodulin
		TRH	Glucagon
		ELABELA	Insulin
		GALP	Amylin
			Leptin

Abbreviations: ACTH – adrenocorticotrophic hormone; NPY – neuropeptide Y; AgRP – agouti related peptide; CRH – corticotrophin releasing hormone; TRH – thyroid releasing hormone; POMC – pro-opiomelanocortin; CART – cocaine-amphetamine regulated transcript; CCK – cholecystokinin; MCH – melanin- concentrating hormone; PYY – peptide tyrosine tyrosine; PP – pancreatic polypeptide; GALPn – galanin-like peptide; GLP-1 – glucagon-like peptide 1; BDNF – brain derived neurotrophic factor; α -MSH – alpha melanocyte stimulating hormone

suggested that the anorexic action of amphetamine is mediated by releasing of catecholamines in LH (Leibowitz 1978) and so amphetamine loses its effect after killing the catecholamine terminals in the LH with 6-hydroxydopamine. Without these LH catecholamines the animal a) overeats; b) self-stimulates faster; c) becomes moderately obese, d) is less responsive to amphetamine treatment (Hoebel 1985).

In the medial hypothalamus (MH), NE input does the opposite. It inhibits the satiety. In front of the MH, the PVN, which lies along the sides of the third ventricle, is the most sensitive site for effect of NE on feeding where injection of NE or NE mimetics will initiate and also prolong the meal. Amphetamine-induced feeding may sound paradoxically, but it is easily observed and explained when the amphetamine is applied locally into the PVN, where it could inhibit

satiety (Leibowitz 1978). Summary of central as well as peripheral orexigenic and anorexigenic hormones/peptides are shown in Table 1.

Conclusion

Food intake is controlled centrally by the hypothalamus, brainstem, reward system, and endocannabinoids. The peripheral control of the food intake includes signals from the gastrointestinal tract and adipose tissue. The GIT hormones affecting food intake include ghrelin, an orexigenic peptide that act to increase food intake and anorexigenic hormones that act to decrease food intake and leads to satiation. The agonists for the anorexigenic and antagonist for the orexigenic peptides have been investigated in the treatment of obesity.

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