# Role of Neuro-Endocrine System in Obesity

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## Energy and Life

Energy is needed for every manifestation of life such as to run various biosynthetic pathways, active transport, generation of nerve impulses, muscular contractions and motility etc. The energy is derived from the oxidation of nutrients. One of the greatest source of energy is sun (solar energy), absorbed by the plants to synthesize the energy rich chemical compounds (carbohydrates, lipids etc.). These carbohydrates and lipids are used by the human beings and other animals to synthesize their own type of compounds such as glycogen, lipids, and high energy compounds like adenosine triphosphate (ATP). ATP is an energy rich chemical used for various physiological activities such as muscular contraction (mechanical work), generation of nerve impulses (electrical work), transport against the gradient (osmotic work) etc. In plants the solar energy is converted to chemical energy, which is converted by humans and higher animals into mechanical energy, electrical energy, osmotic energy and other form of chemical energy. This confirms the first law of thermodynamics in living cells that energy can neither be created, nor be destroyed but transformed from one to the other form.

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## Energy Cycle Body Mass and Obesity

Whenever the energy intake and output ratio increases, there is a conservation of energy in the body stores as carbohydrates and lipids. The normal proportion among them gets disturbed in the total body mass. This imbalance initially leads to overweight, and if not controlled causes obesity. The simple, easy and commonly used method to calculate and differentiate between overweight and obesity in human is the measurement of Body Mass Index (BMI) which is the body weight (in Kg) divided by the square of height (in meters) or $Kg/m^2$. According to WHO, BMI of 25 or over is overweight and greater than 30 or over is obesity [1].

In recent years the importance of obesity has drawn extraordinary attention due to its association with metabolic imbalance. Obesity is one of the most common metabolic diseases and greatest threat to the health because of the possibility of numerous complications and elevated risk such as Type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disorders and cancer [2]. T2 DM in turn gives rise to several different complications (see Chap. 12). Development of effective tools for treatment of obesity by drugs or elective surgery demands complete understanding of the mechanisms of appetite control and the evaluation of disorders resulting in obesity.

Obesity is reaching to an alarming stage and in United States alone up to 33 % of adults are



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suffering from this disease [3]. In 1998 WHO has declared obesity as a chronic medical disease because of the risk of serious complications, which prompted extensive studies on its pathogenesis in order to apply appropriate treatment before the serious disorders develop [4, 5].

## Gastrointestinal Hormones, Neuron Systems, Satiety and Body Weight

Our body has highly synchronized systems regulated by various hormonal and neuronal processes. It is believed that the central nervous system (CNS), particularly hypothalamic region together with other regions is involved in the feedback regulation of energy homeostasis, i.e., food intake and satiety.

The hypothalamus plays a pivotal role by exerting its influence on hunger center situated laterally and satiety center at ventromedial nucleus. Also the paraventricular and arcuate nuclei are the sites in guts and adipose tissues from where multiple hormones are released and used to regulate food intake and energy utilization.

Two distinct types of neurons in arcuate nuclei that regulate food intake are: (a) Proopiomelanocortin (POMC) neurons, activated by α-melanocyte stimulating hormone (α-MSH) which is released from arcuate nuclei and suppresses appetite at the satiety center and (b): neurons stimulated by ghrelin which induces and releases neuropeptide-Y (NPY) and Agouti Related Peptide (AgRP) at hunger center with the increase of appetite.

Arcuate nucleus integrates neural and humoral inputs and determines a physiological role in regulating appetite and satiety, such as the neural via vagal and mostly hormonal via anorexigenic (cholecystokinin, polypeptide YY, glucagon like peptide-I, oxyntomodulin, leptin and others) peptides and orexigenic enteropeptides (ghrelin and other orexins). The adiposity signaling and control of appetite is mediated through peripheral and central humoral mechanisms involving specific receptors.

When food intake is in excess the resulting unused energy is stored mostly as fat in adipocytes in subcutaneous tissues and in the intraperitoneal cavity. Recent studies show that the new adipocytes may differentiate from fibroblast-like preadipocytes at any time in life and the development of obesity in adults is accompanied by increased numbers as well as increased size of adipocytes; this contravenes earlier thinking [1]. The hypothalamus is the key region in CNS which controls the feedback mechanism of appetite and food intake, though other regions also play their roles. Nucleus Tractus Solitarius in the brain stem is the gateway for neural signals from the gastrointestinal tract to the hypothalamus feeding centers. Also the Amygdala, cortex prefrontalis, as well as area postrema have been held responsible for feeding disorders and inadequate conservation or storage of energy. In addition both the nucleus arcuatus (ARC) and the nucleus paraventricularis (PVN) are important centers [1].

Hypothalamic lesions in experimental animals and in human autopsies with morbid obesity led to "dual center hypothesis" suggesting that ventromedial nuclei (VMN) act as the satiety center and the lateral hypothalamic area (LHA) as the hunger center, that when stimulated result in hyperphagia and subsequently hypothalamic induced obesity [6, 7].

It seems that appetite center is instinctively active and only inhibited for a short term basis by the satiety center just after the meal. The destruction of feeding center in animal models leads to anorexia and cachexia. Signals from the receptors in oropharyngeal and gastric area are conveyed to nucleus tractus solitarius (NTS) in brain stem through afferent nerves. In addition to mechanical stimulation, the chemical stimulation of receptors in gastrointestinal mucosa by nutrients contributes to the peripheral signaling from gastrointestinal tract (GIT) and pancreas with orexigenic and anorexigenic properties [1].

Various enteropeptides and enteric nervous system (ENS) which have their two way connections with CNS mainly via vagal nerves and peripheral neurohormonal component reflects an active regulatory process termed "energy homeostasis" conserving the stability of the amount of the body fat stores [8–10].

The stimulation of appetite is obtained via ARC to hypothalamus by the neurons containing

neuropeptide Y (NPY) and AgRP and inhibition of appetite by neurons containing pro-opiomelanocortin (POMC) derived α-MSH and Cocaine & Amphetamine Regulated Transcript (CART) peptide to hunger centers in LHA, the satiety center in the medial hypothalamus [11]. Thus the coordination of feeding and energy expenditure in response to constantly altered energy balance is managed via NTS to CNS. Moreover, NTS itself gathers and assimilates numerous neural and hormonal impulses from peripheral organs like gastrointestinal mucosa and fat tissues and accordingly transfers to CNS.

## Ghrelin

Ghrelin, a potent orexigenic hormone, released from the empty stomach; its plasma level reaches to peak in fasting and lowest after feeding, and this cycle goes on with empty and full stomach [12, 13]. Its peripheral input is routed through ARS and leads to NTS, releasing growth hormone, and regulating energy balance and its metabolic control via hypothalamus [12, 14]. Target of ghrelin are neurons in arcuate resulting in release of NPY and AgRP to express orexigenic effects in brain [11, 15]. It seems to inhibit POMC derivative α-MSH and its anorexigenic effects in the PVN [10, 11, 16]. Experiments have shown that the ghrelin is a mediator of altered energy balance [17–19]. Increased food desire, combined with increased gastrointestinal motility and gastric acid secretion, is associated with higher levels of ghrelin in plasma [20].

Exogenous ghrelin reduces release and action of leptin and vice versa, in that soon after starting of food intake leptin reduces the plasma level of ghrelin [21]. Increased levels of ghrelin in plasma in fasting and weight loss are proposed to be due to diminished or inhibitory effect of leptin and also by peptide YY (PYY). It seems as if the weight reducing effects of leptin are mediated not only centrally via hypothalamus but also peripherally by inhibiting release and actions of ghrelin. Studies of immune-neutralization of ghrelin and leptin with anti-ghrelin and ant-leptin IgG on rats suggest the existence of "Argentinian ghrelin-leptin tango" [21].

The neuropeptide orexin A (OXA) and orexin B (OXB) are implicated in stimulation of food intake [22]. Plasma levels of OXA are increased in humans during fasting, and lowered in obese as compared to normal weight subjects [23, 24]. This suggests that peripheral OXA modulates food intake as an orexigenic agent [25].

The vagal afferent receptors receiving satiety signals from GIT and hypothalamic ARC inhibit the food intake at the satiety center and inhibit the feeding center [10]. The duodeno-jejunal endocrine-I cells secrete cholecystokinin (CCK) [26–29]. This hormone has several isoforms and has five same amino acids at the C-terminal. CCK is also produced in other peripheral nerves and brain neurons, in addition to intestinal mucosa [30]. Physiological mediation of satiety is likely to be obtained by CCK and works well in connivance with the mechanoreceptors of the gut as observed during distension, after food intake, to the brain via vagal afferents. Subdiaphragmatic vagotomy thwarts the effects of exogenous CCK as was found earlier. Also CCK-receptors and vagal nerves limit food intake, and loxiglumide by blocking CCK-receptors abandons the anorexigenic activity of both the exogenous and endogenous hormone [31]. The development of tolerance to CCK and its analogues diminishes its utility as an appetite reducing agent and thus obesity on long term basis as compared to its short term use [32]. Moreover, removing the gene for CCK-receptors could not increase the appetite, instead, resulted in the decreased sensitivity of these animals to anorexigenic action of exogenous CCK [33]. Exogenous CCK injection retains its efficacy, only intermittently, tendency to overeat compensatorily occurs; thus its utility as anti-obesity therapeutic agent becomes questionable.

The control of body weight is actually a concern limited to control of adipose tissue. Adipose tissue acts as a depot for huge amount of energy. Adipocytes produce the leptin, a peripherally active appetite inhibiting hormone. Leptin acts directly on ARC neurons enhancing satiety via specific receptors (Ob-R) on afferent vagal neurons [33, 34]. Leptin is also produced in the stomach, protecting gastric mucosa against topical

irritant and as ulcerogen. It acts at least partly by increasing the blood flow due to increased production of nitric oxide (NO) achieved by the upregulation of NO synthase as well as the brain-gut axis pathways [35, 36]. Also brain gut axis is involved in releasing leptin, in sham feeling, with excitation of vagal nerves [36]. Thus it seems that gastro-protective and hyperemic effects are centrally mediated at least partly by the activation of sensory vagal fibers [37].

Gastric ghrelin antagonizes leptin release in stomach, probably through brain-gut axis, called as "leptin-ghrelin tango", and thus leptin together with insulin acts as lipostatic substance playing their roles in adiposity signaling [1, 38]. It has been observed that insulin applied intracerebroventricularly (ICV) decreases appetite and antibodies to insulin administered ICV increases appetite and body weight. Also insulin, like leptin, seems to inhibit NPY/AgRP neurons in ARC region and enhances satiety [39, 40]. Thus leptin, like insulin, induces an adiposity signal decreasing appetite via hypothalamic receptors through POMC and CART neuronal pathways stimulating satiety center, and decreasing hunger by inhibiting activity of NPY/AgRP neurons.

### Conclusion

Obesity is one of the most common metabolic diseases and greatest threat of the health because of the possibility of numerous complications. Development of effective tool of treatment of obesity by drugs or elective surgery demands complete understanding of the mechanisms of appetite and satiety control and a pinpoint evaluation of disorder(s) resulting in obesity.

## References


1. WHO fact sheet No. 311 updated Jan 2015.
2. Konturek SJ, Konturek PC, Konturek JW, Czesnikiewicz-Guzik M, Brzozowski T, Sito E. Neuro-hormonal control of food intake; basic mechanism and clinical implication. J Physiol Pharmacol. 2005;56 Suppl 6:5–25.
3. Visscher TL, Seidell JC. The public health impact of obesity. Annu Rev Public Health. 2001;22:355–75.
4. World Health Organisation. Obesity. Preventing and managing the global epidemic. Geneva: WHO; 1998.
5. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA. 1999;282(16):1532–29.
6. Druce MR, Small CK, Bloom SR. Minireview: gut peptides regulating satiety. Endocrinology. 2004;145: 2660–5.
7. Vettor R, Fabris R, Pagano C, Federspil G. Neuroendocrine regulation of eating behavior. J Endocrinol Invest. 2002;25:836–54.
8. Wingate DL, Ewart WR. The brain-gut axis. In: Yamada T, Alpers DH, Owyang C, Powell DW, Silverstein FE, editors. Textbook of gastroenterology. Philadelphia: B. Lippincott Co; 1981. p. 50–60.
9. Dockray GJ. Luminal sensing in the gut; an overview. J Physiol Pharmacol. 2003;54 Suppl 4:9–18.
10. Konturek SJ, Konturek JW, Pawlik T, Brzozowski T. Brain- gut axis and it role in control of food intake. J Physiol Pharamcol. 2004;55 Suppl 1:137–54.
11. Currie PJ, Mirza A, Fuld R, Park D, Vasselli JR. Ghrelin is an orexigenic and metabolic signaling peptide in the arcuate and paraventricular nuclei. Am J Physiol. 2005;289:R353–8.
12. Kojima M, Hosoda H, Dae Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402: 656–60.
13. Cummings DE, Purnell JQ, Frayol RS, Schmidova K, Wisse BE, Weigle DS. A peripheral rise in plasma ghrelin levels suggests a role in meal initiation in human. Diabetes. 2001;50:1714–9.
14. Takaya K, Ariyasu H, Kanamoto N, et al. Ghrelin strongly stimulates growth hormone release in humans. J Clinical Endocrinol Metab. 2000;85: 4908–11.
15. Nakazato M, Murakami N, Date Y, et al. A role of ghrelin in the central regulation of feeding. Nature. 2001;409:194–8.
16. Riediger T, Traebert M, Schmidt HA, Scheel C, Lutz TA, Scharrer E. Site specific effects of ghrelin on the neuronal activity in the hypothalamic arcuate nucleus. Nuerosci Lett. 2003;341:151–5.
17. Cummings DE, Clement K, Purnell JQ, et al. Elevated plasma ghrelin levels in Prader-Willi syndrome. Nat Met. 2002;8(7):643–4.
18. DelParigi A, Tschop M, Heiman ML, et al. High circulating ghrelin: a potential cause for hyperphagia and obesity in Prader-Willi syndrome. J Clin Endocrinol Metab. 2002;87:5464.
19. Faraj M, Havel PJ, Phelis S, Blank D, Sniderman AD, Cianflone K. Plasma acylation-stimulating protein, adiponectin, leptin and ghrelin before and after weight loss induced by gastric bypass surgery in morbidity obese subjects. J Clin Endocrinol Metab. 2003;88: 1594–602.
20. Konturek PC, Konturek SJ, Ochmanski W. Endocrinology of gastric H and duodenal HCO3 secretion the role of grain-gut axis. Eur J Pharmacol. 2004;499:15–27.

21. Konturek SJ, Pepera J, Zabieiski K, et al. Brain-gut axis in pancreatic secretion and appetite control. J Physiol Pharmacol. 2003;54:293–317.
22. Kirchgessner AL. Orexins in the brain-gut axis. Endocr Rev. 2002;23:1–15.
23. Komaki G, Matsumoto Y, Nishikarata H, et al. Orexin-A and leptin change inversely in fasting non-obese subjects. Eur J Endocrinol. 2001;144: 645–51.
24. Adam JA, menheere PP, van Dielen PM, Soeters PB, Buurman WA, Greve JW. Decreased plasma orexin-A levels in obese individuals. Int J Obes Relat Metab Disord. 2002;26:274–6.
25. Nalund E, Schmidt PT, Hellstrom PM. Gut peptide hormones: importance for food intake Scand. J Gastroenterol. 2005;40:250–8.
26. Kissileff HR, Pi-Sunyer FX, Thornton J, Smith GP. Cholecystokinin decreases food intake in man. Am J Clin Nutr. 1981;34:154–60.
27. Ballinger A, McLoughlin L, Medback S, Clark M. Cholecystokinin is a satiety hormone in humans as physiological post-prandial concentrations. Clin Sci. 1995;89:375–81.
28. Lieverse RJ, Jansen JB, Masclee AA, Lamers CB. Satiety effects of a physiological dose of cholecystokinin in humans. Gut. 1995;36:176–9.
29. Muurahainen N, Kissileff HR, Derogatis AJ, Pi-Sunyer FX. Effects of cholecystokinin-oktapeptide (CCK_8) on food intake and gastric emptying in man. Physiol Behav. 1988;44:644–9.
30. Ehfeldt JF. Clinical endocrinology and metabolism. Cholecystokinin. Best Pract Res Clin Endocrinol Metab. 2004;18:569–86.
31. Garlicki J, Konturek PC, Majka J, Kwiecien N, Konturek SJ. Cholecystokinin receptors and vagal nerves in control of food intake in rats. Am J Physiol. 1990;258:E40–5.
32. Crawley JN, Beinfeld MC. Rapid development of tolerance to the behavioural actions of cholecystokinin. Nature. 1983;302:703–5.
33. Schwartz GJ, Whitney A, Skoglund C, Castonguay TW, Moran TH. Decreased responsiveness to dietary fat in Otsuka Long-Evans Tokushima fatty rats lacking CCk-A receptors. Am J Physiol. 1999;277: R1144–51.
34. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1983;372: 425–32.
35. Mantzoros CS, Flier JS. Editorial: leptin as a therapeutic agent-trials and tribulations. J Clin Endocrinol Metab. 2000;85:4000–2.
36. Kontured JW, Konturek SJ, Kwiecien S, et al. Leptin in the control of gastric secretion and gut hormones in humans infected with Helicobacter pylori. Scand J Gastroenterol. 2004;36:1148–564.
37. Konturek PC, Konturek SJ, Zabielski R, Konturek JW, Czarnecki J. Neuroendocrinology of the pancreas: role of brain-axis in pancreatic secretion. Eur J Pharmacol. 2003;481:1–14.
38. Cummings DE, Foster KE. Ghrelin-leptin tango in body-weight regulation. Gastroenterology. 2003;124: 1532–5.
39. Air EL, Benoit SC, Blake Smith KA, Clegg DJ, Woods SC. Acute third ventricular administration of insulin decreases food intake in two paradigms. Pharmacol Biochem Behav. 2002;72:423–9.
40. Morely JE, Levine AS, Grace M, Kneip J. Peptide YY (PYY), a potent orexigenic agent. Brain Res. 1985; 341:200–3.