

Appetite Regulating Hormones

Nirmala, G.C., Suchitra, B. R* and Pavankumar, K. N.

Dept. of Pharmacology and Toxicology,
Veterinary College, Hebbal, Bangalore-24

* Veterinary Officer, Veterinary Dispensory, Hanabe, Bangalore
Corresponding author email : nirmala_gc@yahoo.co.in

All higher life forms exhibit a desire to eat food known as appetite which is felt as hunger. Appetite is required to regulate adequate energy intake and to maintain metabolic needs. It is regulated by a close interplay between the digestive tract, adipose tissue and the brain. Decreased desire to eat is termed as anorexia, while polyphagia or hyperphagia is increased eating. Dysregulation of appetite may either contribute to cachexia or obesity.

Better understanding of appetite regulation improves understanding of the etiology of debility or obesity. Manipulation of this homeostatic system offers potentially useful treatments for obesity and anorexia (Druce and Bloom, 2006).

Appetite regulation

Appetite regulation is an immensely complex process involving:

1. Hypothalamic neuropeptides
2. peripheral signals like adipokines and gut hormones

Hypothalamic neuropeptides

Hypothalamus, posses several neuronal centers such as that in lateral hypothalamic nuclei considered to be "hunger" center and in ventromedial nuclei serving as the "satiety" center. In addition, paraventricular and arcuate hypothalamic nuclei (ARC) are the sites where multiple hormones, released from the gut and adipose tissue, converge to regulate food intake and energy expenditure. *Nucleus tractus solitarius* (NTS) in the brain stem serves as gateway for neural signals from the gastrointestinal tract to the hypothalamic feeding centers. Also the *amygdala*, the *cortex prefrontalis*, as well as the *area postrema* have been held responsible for feeding disorders and inadequate conservation or storage of energy.

There are two distinct types of neurons in ARC that are important in control of food intake;

- (1) Neurons activated by orexigenic peptides such as ghrelin that release the substances including neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP) in hunger center.
- (2) Neurons activated by anorexigenic hormones and

releasing alpha-melanocyte-stimulating hormone (α -MSH) from the polypeptide preopiomelanocortin (POMC) or the cocaine and amphetamine regulated transcript (CART) in satiety center.

ARC integrates neural (mostly vagal) and humoral inputs such as enteropeptides including orexigenic (ghrelin and orexins) and anorexigenic peptides (cholecystokinin, polypeptide YY, glucagon-like peptide-1, oxyntomodulin, leptin and others) that exert a physiological role in regulating appetite and satiety. The peripherally (gut, adipose tissue) and centrally expressed modulators of appetitive behavior act through specific receptors in the afferent (mostly vagal) nerves and hypothalamic neurons implicated in adiposity signaling and regulation of food intake (Konturek *et al.*, 2005).

The hypothalamus with its key regions, including ARC, LHA and closely related PVN, serving as the feeding or hunger center, VMN acting as the satiety center and NTS conveying the peripheral signals, particularly from the gut to the feeding centers, are implicated in appetitive behavior. Thus, CNS receives (through NTS) numerous neural impulses and hormones from peripheral organs, especially from the gastrointestinal mucosa, and fat tissue that are involved in short and long-term coordination of feeding and energy expenditure in response to constantly altered energy balance. The gut peptides signaling to the hypothalamus act via the ARC to mediate the appetite stimulation (+) effect through the activation of neurons containing neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP) or appetite-inhibitory effects (-) via neurons containing the pro-opiomelanocortin (POMC)-derived α -melanocyte stimulating hormone (α -MSH) and cocaine and amphetamine regulated transcript (CART) peptide to hunger centers in the LHA, the satiety center in PVN in the medial hypothalamus (Currie *et al.*, 2005).

Generally, there are two systems that operate in the regulation of the quantity of food intake; short-term regulation, which is concerned primarily with preventing overeating at each meal. It is regulated

CCK, ghrelin, and long term regulation, which is primarily related with the maintenance of normal quantities of energy stores in the form of fat in the body. It is regulated by hormones like insulin and leptin.

Neuropeptide Y (NPY)

- NPY is part of the pancreatic polypeptide (PP) family of peptides with 36 amino acids.
- Bind to seven-transmembrane-domain G-protein-coupled receptors, designated Y_1 - Y_6 , Y_1 , Y_2 , Y_4 , and Y_5 receptors are found in the hypothalamus which mediates the orexigenic effects of NPY.
- NPY may inhibit the arcuate POMC neuron via ARC NPY Y_1 receptors.
- Hypothalamic levels of NPY reflect the body's nutritional status.
- The levels of hypothalamic NPY mRNA and NPY release increase with fasting and decrease after refeeding.
- Repeated icv inj. of NPY into the PVN causes hyperphagia and obesity.

Agouti-related peptide (AgRP)

- AgRP is expressed in the medial part of the ARC.
- The levels of AgRP mRNA are increased during fasting.
- Potent inhibitor of MC3R and MC4R.
- AgRP induces hyperphagia when administered icv or when over expressed in transgenic mice.
- Exogenous administration of AgRP in rodents predisposes to high fat and high sugar intakes (Loos *et al.*, 2005).
- Induced selective ablation of AgRP-expressing neurons in adult mice results in acute reduction of feeding (Gropp *et al.*, 2005).

The melanocortin system

- The anorexigenic neurons in the arcuate nucleus produce α -MSH from the polypeptide precursor POMC.
- They bind to melanocortin receptor family of which MC3R and MC4R are important.
- POMC mRNA levels are reduced in fasted animals and increased by exogenous administration of leptin, or restored by refeeding after 6h.
- MC3R and MC4R are the receptors found in the ARC, VMH and PVN which play a role in energy homeostasis.
- The MC3R/MC4R antagonist, AgRP is able to increase food intake in MC4R deficient mice.
- Lack of MC4R leads to hyperphagia and obesity in rodents.
- The main endogenous ligand for the MC3R/MC4R is α -MSH.

Cocaine and amphetamine regulated transcript (CART)

- CART is coexpressed with α -MSH in the ARC, also found in LHA and PVN.
- Food deprived animals show a reduction in CART mRNA.
- Peripheral administration of leptin to leptin deficient *ob/ob* mice results in a stimulation of CART mRNA expression.
- CART (1-102) and CART (82-103) icv inhibit the normal and NPY stimulated feeding response.
- Antiserum against CART peptide (1-102) and CART peptide fragment (82-103) icv in rats increased hunger.

Orexins

Greek- Orexis: appetite.

- Orexins are the novel neuropeptides play a role in the stimulation of food intake and energy homeostasis (Kirchgessner, 2002).
- The two highly-related peptides (Orexin A and B, or Hypocretin-1 and -2) are produced by cleavage of a single precursor protein secreted by the cells in the LHA. Orexin-A is a 33-residue peptide with two intramolecular disulfide linkages. Orexin-B is a linear 28-residue peptide.
- OXA has been detected in the mucosa and neuronal plexuses of the gastrointestinal tract.
- Plasma levels of OXA are increased during fasting in humans and are lower in obese subjects than normal-weight people (Adam *et al.*, 2002), suggesting that peripheral OXA modulates food intake as an orexigenic peptide.

Peripheral signals controlling appetite

Hormones of adipose tissue (Adipokines)

- Insulin
- Adiponectin
- Leptin

Hormones of GIT.

- Ghrelin
- Cholecystokinin
- Glucagon like peptide-1 (GLP-1)
- Oxyntomodulin
- PYY3-36

Insulin

- Insulin is produced by the pancreas in relation to the adiposity and blood glucose levels.
- It acts on the insulin receptors in the ARC of hypothalamus to inhibit the eating behavior:
 - inhibits the release of NPY/AgRP.
 - stimulate α -MSH and CART.
- Insulin applied intra-cerebro-ventricularly (icv) inhibits food intake and body weight in rats.

- icv administration of insulin antibodies increased food intake and body weight.

Adiponectin

- It is a peptide hormone (adipokine) with 224 amino acids secreted by the white adipose tissue (Trayhurn, 2005).
- Peripheral administration of adiponectin results in the attenuation of body-weight gain without affecting food intake.
- Increases oxygen consumption by inducing the expression of gene *c-fos* in the PVN and involving melanocortin system.
- Increased after food restriction in rodents and after weight loss induced by a calorie-restricted diet.

Leptin

leptos: thin. Leptin is an anorexigenic adipokine with 167 amino acids.

Production sites:

- a. adipose tissue
 - b. nonadipose tissue: stomach, placenta, skeletal muscle and mammary epithelium
- Combine with the Ob-R on afferent vagal nerves and directly on the ARC to enhance satiety.
 - Inhibits the expression of orexigenic NPY/AgRP hypothalamic neurons.
 - Also stimulates the anorexigenic POMC neurons in ARC.

Actions of leptin

1. Thermogenesis
2. Decrease in Food intake

Thermogenesis

Stimulate the transcription of mitochondrial uncoupling protein (UCP) or thermogenin, which forms a channel in the inner mitochondrial membrane that allows protons to reenter the mitochondrial matrix without passing through the ATP synthase complex. This permits the continual oxidation of fuel (fatty acids in an adipocyte) without ATP synthesis, dissipating energy as heat and consuming dietary calories or stored fats in potentially very large amounts (Nelson and Cox 2005).

Decrease in food intake:

- Combine with the Ob-R on afferent vagal nerves and directly on the ARC to enhance satiety.
- Inhibits the expression of orexigenic NPY/AgRP hypothalamic neurons.
- Also stimulates the anorexigenic POMC neurons in ARC.

Leptin - insulin lipostat

Although there is rather low local expression of leptin in the stomach, probably responsible for local antagonism of gastric release of ghrelin and named

“leptin/ghrelin tango” operating along the brain-gut axis, leptin belongs together with insulin to a “lipostat” substances that play a role in adiposity signaling. Insulin, like leptin, is thought to inhibit NPY/AgRP neurons in ARC region of the hypothalamus and reduce food intake. This is supported by the observations that insulin applied intra-cerebro-ventricularly (icv) inhibits food intake. Accordingly icv administration of insulin antibodies increased food intake and body weight (Air *et al.*, 2002). Thus, leptin-like insulin, represents adiposity signal inhibiting food intake by interacting with hypothalamic receptors activated through POMC and CART neuronal pathways stimulating satiety center, and reducing the activity of NPY/AgRP neurons driving the appetitive behavior.

Peptide YY3–36 (PYY)

- A peptide hormone (34 amino acids) that is secreted postprandially, in response to food entering from the stomach.
- Endocrine L cells lining the ileal and colon mucosa (Judith Korner *et al.*, 2003).
- PYY3-36, acts via Y1, Y2, Y3 and Y5 receptors.
- Peripheral administration: Decrease appetite and cause weight loss by inhibiting ARC expressions of NPY/AgRP (Hagan, 2002).
- Central administration: stimulate food intake by enhancing the expression of NPY/AgRP.

Ghrelin

ghre: grow. Ghrelin is a potent orexigenic hormone with 28 amino acids secreted from X/A cells in the fundus mucosa of empty stomach (Rindi *et al.*, 2002).

Biological activities:

1. Stimulation of GH secretion through GHS-R.
2. Regulation of energy balance/appetite.

1. Stimulation of growth hormone secretion: Ghrelin, as the ligand for the growth hormone secretagogue receptor, potently stimulates the secretion of the growth hormone. The ghrelin signal is integrated with that of the growth hormone-releasing hormone and somatostatin to control the timing and magnitude of growth hormone secretion.

2. Regulation of energy balance: In rodents and humans, ghrelin functions to increase hunger through its action on the hypothalamic feeding centers. The plasma ghrelin concentrations increase during fasting. Humans injected with ghrelin reported sensations of intense hunger. Ghrelin also appears to suppress fat utilization in the adipose tissue, which is somewhat paradoxical considering that the growth hormone has the opposite effect. Overall, ghrelin seems to be one of several hormonal signals that communicate the state

of energy balance in the body to the brain.

Regulation of appetite

- The primary hypothalamic target for ghrelin are neurons in ARC that express and release NPY and AgRP in the PVN and LHA to mediate orexigenic effect in the brain.
- It may also inhibit the neurons in the ARC that contain POMC-derivative α -MSH that mediate the anorexigenic effect in the PVN (Currie *et al.*, 2005).

Other effects of ghrelin include stimulation of gastric emptying and a variety of positive effects on cardiovascular function (e.g. increased cardiac output). It is not yet clear whether the cardiovascular effects are due to a direct effect of ghrelin or an indirect effect of ghrelin's ability to stimulate growth hormone secretion. The concentration of ghrelin in blood peaks just before a meal and drops suddenly just after the meal.

Prader-Willi syndrome: It is a disorder relevant to ghrelin. Affected patients develop extreme obesity associated with an uncontrollable and voracious appetite. The plasma ghrelin levels are exceptionally high in comparison to patients similarly obese due to other causes.

Ghrelin as a drug target: People who lose weight have higher blood levels of ghrelin, than they did when they were fat. This also supports the concept that the body tends to maintain its ideal weight and when one loses weight, the body should produce more ghrelin to stimulate to regain the lost weight. Therefore ghrelin makes one fatter by causing hunger to eat more and slowing metabolism to burn fewer calories.

A rise or fall in ghrelin is not observed in patients who had gastric bypass surgery, before or after they eat. Their levels of ghrelin remain low all the time. This shows that stomach cells produce ghrelin only when food passes into the stomach. An empty stomach causes stimulation of ghrelin secretion while food in the stomach stops production of ghrelin. However, when no food enters the stomach for a long time, stomach cells stop producing ghrelin and a person stops being hungry. That is why when it is long past normal mealtime a person stops feeling hungry. So drugs that can block ghrelin will be very effective to overcome obesity without much disturbance in the physiological homeostasis of our body. Intense research is going on in this regard for a breakthrough drug in obesity (Madan, 2005).

Cholecystokinin (CCK)

Among the anorexigenic peptides, the first recognized inhibitor of food intake in rodents and then in humans was cholecystokinin (CCK).

- Secreted by duodeno-jejunal endocrine I cells

and cells in peripheral nerves and neurons of the brain.

- Acts via CCK₁ receptors on vagal afferent nerves.
- Hormone exists in the mucosa and circulation in several molecular forms such as CCK-8, CCK-33, CCK-39 and CCK-58.

All these molecular forms derive from a single CCK gene through posttranslational processing and have the same C-terminal five amino acid sequence (Rehfeldt, 2004).

CCK is the likely candidate for the physiological mediation of short-term inhibition of food intake. It cooperates with signals originating from the mechanoreceptors of the gut that are generated by the distention of the gut and transmitted to the brain through vagal afferents. This is in keeping with earlier findings that sub-diaphragmatic vagotomy abolishes anorexigenic activity of exogenous CCK and, as we found it for the first time and the blockage of CCK₁ receptors with loxiglumide abolishes the anorexigenic effects of both exogenous and endogenous hormone. The clinical usefulness of CCK as an anti-obesity, appetite reducing agent was found, however, to be transient due to the development of tolerance to CCK and its analogs (Crawly and Beinfeld, 1983). Furthermore, even removal of gene for CCK₁ receptors, (CCK₁ receptor knockout mouse) failed to increase the food intake, but resulted in the lack of the sensitivity of these animals to anorexigenic action of exogenous CCK. Since CCK only intermittently preserves its anorexigenic activity between injections of exogenous CCK, compensatory overeating occurs, so it is unlikely that this peptide could be useful in anti-obesity therapy.

Glucagon-like peptide-1 (GLP-1)

- Glucagon-like peptide-1 (GLP-1) is a anorexigenic peptide secreted by endocrine L-cells in the ileal and colonic mucosa in response to food intake.
- Increase satiety and decrease food intake in normal-weight subjects, diabetes patients and obese subjects (Gutzwiller *et al.*, 1999).
- GLP-1 reduces the postprandial demand of insulin to maintain euglycemia after a meal (Imeryuz *et al.*, 1997).
- GLP-1 on gastrointestinal functions are mediated through its distinct receptors on vagal nerves.

Oxyntomodulin (OXM)

- Oxyntomodulin (OXM) is produced by the same L-cells as GLP-1 in the distal portion of the gut and also in the brain.
- It is a 37 amino acid peptide released after ingestion of meal.
- Involved in the short-term suppression of food

intake.

- The mechanism of anorexigenic action of OXM is not known but it may involve the suppression of plasma ghrelin levels (Cohen *et al.*, 2003).
- OXM, act through GLP-1 receptors.

Obestatin

Latin: Obedere- to devour, Statin- suppression.

Ghrelin, a circulating appetite-inducing hormone, is derived from a prohormone by posttranslational processing. On the basis of the bioinformatic prediction that another peptide also derived from proghrelin exists, they have isolated a hormone from rat stomach and named it obestatin-a contraction of obese, from the Latin "obedere," meaning to devour, and "statin," denoting suppression. Contrary to the appetite-stimulating effects of ghrelin, treatment of rats with obestatin suppressed food intake, inhibited jejunal contraction, and decreased body-weight gain. Obestatin bound to the orphan G protein-coupled receptor GPR39. Thus, two peptide hormones with opposing action in weight regulation are derived from the same ghrelin gene. After differential modification, these hormones activate distinct receptors (Zhang *et al.*, 2005).

Conclusion

The better understanding of hormonal control of appetite improves understanding of the etiology of debility or obesity. Manipulation of this homeostatic system by pharmacological intervention offers potentially useful treatments for anorexia and obesity.

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