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REVIEW ARTICLE

NEUROENDOCRINE REGULATION OF FEEDING BEHAVIOUR

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ABSTRACT

Several hypothalamic peptides that participate in the control of ingestive behavior are produced in neuronal cell bodies of the arcuate nucleus and/ or the lateral hypothalamic area. Apart from producing orexigenic or anorexigenic compounds of peptidergic nature, these neurons also produce excitatory and inhibitory amino acid neurotransmitters. The role of GABA and glutamate in regulating energy balance has received less attention in comparison to neuropeptides. The arcuate nucleus median eminence area, a region with a weak blood–brain barrier, contains at least two neuronal cell populations that exert opposing actions on energy balance.some other nucleus and other neuropeptides secreted from the hypothalamus regulate the feeding behaviour.

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INTRODUCTION

Most organisms function in environments with marked seasonal and, on a less predictable basis, climactic changes in nutrient availability. Species survival is dependent on systems that are remarkably adept at balancing food intake with the fluctuations in energy expenditure and with the amount of energy stored as triacylglycerol (TAG) in adipocytes. Neural and endocrine regulatory systems affecting feeding behavior must respond to short-term cues, such as the ability to sense and respond to stomach contents, along with signals concerning the long-term status of energy balance over periods of days. The main regions of the hypothalamus involved in feeding and satiety were, arcuate nucleus, paraventricular nucleus, ventromedial nucleus, dorsomedial hypothalamic nucleus, the lateral hypothalamic area and the brain stem (Arora *et al.,* 2006). In this review we will dicuss about the neuro endocrine factors regulating the feeding behaviour.

Arcuate nucleus

The arcuate nucleus of the hypothalamus (ARH) plays a central role in a variety of homeostatic circuits and is a particularly important site for the central regulation of food intake, energy expenditure, and body weight. The arcuate nucleus of the hypothalamus contains at least two populations of neurons that continuously monitor signals reflecting energy status and promote the appropriate behavioral and metabolic responses to changes in energy demand. Activation of neurons making pro-opiomelanocortin (POMC) decreases food intake and increases energy expenditure through activation of G protein-coupled melanocortin receptors via the release of α-melanocyte-stimulating hormone. Cansell *et al.* (2012) stated that the neighboring neurons [agouti-related protein (AgRP) neurons] co-expressing the orexigenic neuropeptides, AgRP, and neuropeptide Y increase feeding by opposing the anorexigenic actions of the POMC neurons.

AgRP and POMC Neurons

Agouti-related protein was discovered as an endogenously released neuropeptide that acts as an inverse agonist for the melanocortin receptors, MC3R/MC4. AgRP is co-expressed in hunger activated neurons with NPY, another peptide that stimulates food intake and regulates weight gain. AgRP neurons are located in the ARC subdivision of the hypothalamus at the bottom of the third ventricle close to a circumventricular organ called median eminence (ME). The blood–brain barrier in this region is fenes- trated and allows for facilitated blood–brain exchange (Friedman and Halaas, 1998). As a result, neurons that reside there are referred to as "first

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order neurons" because they would be the first to respond to the circulating signals of hunger and satiety. Neuron sintheARC that make pro- opio melanocortin (POMC) and cocaine-and amphetamine-related transcript (CART) secrete the melanocortin peptides adrenocorticotropichormone (ACTH) and α, β, and γ-melanocyte-stimulating hormone (MSH),which are derived frompost- Translational processing of POMC. POMC and AgRP neurons are considered to be two functionally opposed components of the"central melanocortin system. Thus arcuate nucleus is a privileged site which can sample the peripheral circulation through semi-permeable capillaries in the underlying median – eminence and is the ideal position to integrate hormonal signals for energy homeostasis.

The Paraventricular Nucleus (PVN)

PVN is adjacent to the superior part of the third ventricle in the anterior hypothalamus. The PVN is the main site of corticotropin releasing hormone (CRH) and thyrotropin releasing hormone (TRH) secretion. Numerous neuronal pathways implicated in energy balance converge in PVN, including major projections from NPY neurons of the ARC, Orexins, POMC derivative a-melanocyte stimulatinghormone (a-MSH) and the appetite stimulating peptide galanin. Thus PVN plays a role in the integration of nutritional signals with the thyroid and hypothalamic- pituitary axis (Neary *et al*., 2004).

Ventromedial Nucleus of Hypothalamus (VMH)

VMH is mainly acting as satiety centre. It has been identified as a key target for leptin, which acts on the hypothalamus to inhibit feeding, stimulate energy expenditure and cause weight loss. Lesions of either ventromedial hypothalamic nuclei or PVN produce syndromes of hyperphagia and obesity (Satoh *et al.,* 1997).

The Dorsomedial Hypothalamic Nucleus (DMH)

DMH has extensive connections with other medial hypothalamic nuclei and the lateral hypothalamus and serves the function of integration and processing of information from these nuclei (Elmquist *et al.,* 1998).

The Lateral Hypothalamic Area (LHA)

LHA is the classical 'feeding centre', also contains glucose-sensitive neurons that are stimulated by hypoglycemia (by ascending pathways from brainstem) and it is crucial in mediating the marked hyperphagia which is normally induced by hypoglycaemia (Bernardis and Bellinger, 1996).

Orexigenic Neuropeptides Secreted by Hypothalamus
Neuropeptide Y (NPY)

NPY is one of the most abundant peptides of the hypothalamus and one of the most potent orexigenicfactors.The ARC is the major site of expression for NPY within neurons in the hypothalamus that project to PVN, DMH, LHA, and other hypothalamic sites.

Five G-protein coupled NPY receptors have been identified – Y1, Y2, Y4, Y5 and Y6.Y5 receptors have been implicated as important receptors that mediate the feeding effects of NPY.The Y5 receptor is expressed at relatively high levels in the LHA, close to the site where NPY acts most potently to stimulate feeding.NPY synthesis in the ARC and its release into the PVN, are regulated by afferent signals such as leptin, insulin (both inhibitory), and glucocorticoids (stimulatory).The NPY neurons are potential hypothalamic targets for leptin.A primary physiological role of the ARC NPY neurons may thus be to restore normal energy balance and body fat stores (Marsh *et al.*, 1998 and Pedrazzini *et al.,* 1998).

Melanin-concentrating hormone

Melanin-concentrating hormone (MCH) is an orexigenic neuropeptide. It is cleaved from its precursorprepro-MCH.The cell bodies of MCH-containing neurons are mainly present in the lateralhypothalamusand zonaincerta that are recognized as the feeding center of mammalian brain. MCH signals in the brain through two types of G protein-coupled receptors, namely MCH-1R and MCH-2R. The MCH system is thought to play a role in stimulatory effect on feeding behaviour (Inui, 2000).

Orexins

Orexin A and orexin B are 33- and 28-amino acid peptides, respectively, Localized in neurons in the dorsal and lateral hypothalamic areas and perifornical hypothalamus.Orexin neurons project throughout the central nervous system (CNS) to nuclei known to be important in the control of feeding.The orexins activate two closely related and highly conserved G-protein coupled receptors termed OX_1R and OX_2R. OX_1R is expressed widely in the hypothalamus including ARC, VMH and SCN, OX_2R is found mainly in PVN. Orexin neurons are regulated by metabolic cues, including leptin, glucose, and ghrelin.Orexin mRNA expression is up-regulated by fasting and insulin-induced hypoglycemia.Orexin-A increases food intake by delaying the onset of a behaviorally normal satiety sequence.Orexin may also play a role as a peripheral hormone involved in energy homeostasis. Orexinneurons,expressing both orexin and leptin receptors, have been identified in the gastrointestinal tract, and appear to be activated during starvation. Orexin is also expressed in the endocrine cells in the gastric mucosa, intestine and pancreas (Sakurai, 2003 and Dyer *et al.*, 1999).

Agouti-related peptide

AGRP is expressed only in the ARC of the hypothalamus in the brain, and all of the AGRP-producing neurons co-secrete NPY and project to various hypothalamic (such as PVN and DMH) and extra hypothalamic sites.Leptin inhibits the release of AGRP. Like NPY, expression of AGRP is up-regulated in leptin deficiency due to fasting.AGRP is a potent and selective antagonist of MC-3 and MC-4 receptors, the melanocortin receptors implicated in control of energy balance. The inhibition of melanocortin receptors may thus lead to the obese phenotype that is associated with hyperphagia, decreased

thermogenesis, and increased caloric efficiency (Wilson, 2000).

Galanin

Galanin is found in the brain and the gut. It modulates a variety of physiological processes including feeding behavior.Its actions are mediated via Gi-protein-coupled receptors and ion channels, through inhibition of gastric neuropeptides via potassium channels. Galanin coexists with NPY in several regions of the brain. Hypothalamic galanin (GAL) has a variety of functions related to energy and nutrient balance, body weight regulation, reproduction, water balance, and neuroendocrine regulation. Many galanin-positive fibers as well as galanin-positive neurons have been demonstrated in the dorsal vagal complex, suggesting that galanin produces its effects by involving vagal neurons. The nucleus of the solitary tract is the major source of the galanin terminals in the dorsal vagal complex (Leibowitz, 1995).

Galanin-Like Peptide (GALP)

GALP is produced by a discrete population of neurons within the basomedialarcuate nucleus (and median eminence) that send projections to the anterior paraventricular nucleus.

Endogenous opioids

b-endorphin, dynorphin, and enkephalins.l-opioid receptor, j-opioid receptor, and d-opioid receptor.Opioid peptides mediate the hunger component in the control of food intake (Levine and Billington, 1989).

Endocannabinoids

Anandamide, 2-arachidonoylglycerol (2-AG), noladinether andvirodhamine). Receptors for endocannabinoidsare CB1 and CB2 receptors. Pleasure centers of the central nervous system, hypothalamus and the gastrointestinal tract. The endocannabinoids appear to regulate energy balance and food intake at four functional levels within the brain and periphery were, limbic system (for hedonic evaluation of foods), hypothalamus and hindbrain (integrative functions), intestinal system, and adipose tissue. At each of these levels, the endocannabinoid system interacts with a number of other neuropeptides involved in appetite and weight regulation, including leptin, ghrelin, and the melanocortins (Wenger and Moldrich, 2002).

Anorectic neuropeptides secreted by hypothalamus

Cocaine and Amphetamine Regulated Transcript (CART)

The CART peptides are localized in specific areas of the hypothalamus including the periventricular nucleus, paraventricular nucleus, dorsomedial nucleus, perifornical regions, lateral nucleus, and the arcuate nucleus. In the paraventricular nucleus. (Li *et al*., 2002)

Melanocortins

The melanocortins are bioactive peptides derived from the precursor molecule pro-opiomelanocortin (POMC) via tissue-specific post-translational cleavage. The stimulatory effect of AGRP is inhibited by a-MSH (Rossi *et al*., 1998).

Glucagon-like peptides

Secreted by a-cells in the pancreas, L cells in the gut, and neurons in the brain stem nucleus of the solitary tract (NTS). GLP family includes Glicentin, oxyntomodulin, glucagon-like peptide (GLP)-1, and GLP-2. GLP-1 and GLP-2 are both involved in a wide variety of peripheral functions, such as glucose homeostasis, gastric emptying, intestinal growth, insulin secretion as well as the regulation of food intake.After a meal, GLP-1 and GLP-2 are secreted in parallel in the circulation.GLP-1 containing nerve fibres and the GLP-1 receptor are found predominantly in hypothalamic midline nuclei (Vrang *et al.,* 2003).

Corticotropin releasing factor (CRF) and related peptides

The major physiological regulator of pituitary ACTH secretion. CRF is an endogenous anorectic and thermogenic agent. CRF secretion modulates food intake in the absence of stress by exerting an inhibitory tone on appetite.Receptor subtypes CRF is CRF-1 and CRF-2. CRF-2 receptor is primarily involved in the feeding-suppressive and thermogenicrespons. Both CRF and NPY may exert local site-specific effects on feeding behavior within the PVN relative to the extra hypothalamic site to CRF and CRF-related peptides.In addition to coordination of anorectic and thermogenic effects, CRF is also sensitive to the action of peripheral peptides signaling the brain about the fluctuations in energy reserves especially leptin (Richard Denis, 1999).

Endocrine control of feeding behavior

Peripheral orexigenic mechanisms

Ghrelin

Major GI hormone with potent orexigenic property is ghrelin.It is a 28 aminoacid peptide Produced by enteroendocrine cell types known as A/D cells. Food intake and appetite regulation is mediated through peripheral input at the ARC and further spread to the NTS.Neurons and in ARC that express and release NPY and AgRP in the Antagonizes the leptin induced inhibition of food intake and also inhibit the neurons in the ARC that contain POMC derivative α MSH that mediate the anorexigenic effect in the PVN. Receptor for ghrelin belongs to the family of the G-protein coupled receptors.Predominantly detected in the pituitary,hypothalamicnuclei, stomach, he--art, lungs, kidneys, gut, the adipose and many other tissues. Stimulates the release of GH in the pituitary. Induces rise in the serum conc of ACTH, cortisol, aldosterone, catecholamineand prolactin (Jain *et al*., 2014)

Orexin

Orexin A&B, the novel neuropeptides were found to play the role in the stimulation of food intake. OXA has been deducted in the mucosa & neuronal plexus of the GI tract & in the LHA.Actions of orexins are mediated via two types of GPCRs.OX1R & OX2R.

Anorectic peripheral peptides

Peptide YY:

Peptide YY is a 36 a.a peptide belonging to PP family. (NPY,PYY,PP). Produced by the intestinal L cells. Circulating PYY exists in two major forms were, PYY1-36 and PYY3-36. PYY3-36 peripherally active anorectic signal.Acts on Y receptors(shows high affinity for Y2 receptor).Following food intake PYY is released into the circulation &peak plasma levels appear post prandially after 1-2 hr. PYYconc are proprotional to meal energy content. PYY causes a delay in gastric emptying.Increases the absorption of fluids and electrolytes from the ileum after a meal (Ekblad and Sundler, 2002).

Cholecystokinin

Endogenous peptide found in the GI tract &brain.It is present in multiple bioactive forms including CCK-58,CCK-33,CCK-8.CCK sensitive brain sites lie not only in the hypothalamus but also in the medial pons,lateral medulla and NTS (Gibbs *et al.,* 1973). The function of CCK were, stimulation of pancreatic secretion, gallbladder contraction, intestinal motility, memory enhancement and inhibition of gastric motility. There are two types of cck receptors (CCK-A and CCK-B). CCK receptors are G protein coupled receptors. The satiety actions of CCK are mediated by CCK-A receptors not CCK-B (Roux and Bloom, 2005).

Leptin

Leptin, the "satiety hormone," is a hormone made by adipose cells that helps to regulate energy balance by inhibiting hunger. Leptin is opposed by the actions of the hormone ghrelin, the "hunger hormone". Both hormones act on receptors in the arcuate nucleus of the hypothalamus to regulate appetite to achieve energy homeostasis (Oswal *et al*., 2010)

Insulin

Insulin is a peptide hormone produced by beta cells in the pancreas, It regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose from the blood to skeletal muscles and fat tissue and by causing fat to be stored rather than used for energy. Insulin also inhibits the production of glucose by the liver (Wilcox *et al*., 2005)

Amylin

Amylin, or islet amyloid polypeptide (IAPP), is a 37-residue peptide hormone. It is cosecreted with insulin from the pancreatic β-cells in the ratio of approximately 100:1. Amylin plays a role in glycemic regulation by slowing gastric emptying and promoting satiety, thereby preventing post-prandial spikes in blood glucose levels (Bhavsar *et al.,* 1998).

Bombesin

Bombesin family (Bombesin, neuromedin B and gastrin-releasing peptide). It stimulates gastrin release from G cells. It activates three different G-protein-coupled receptors known as BBR1, 2, and 3. It also activates these receptors in the brain. Together with cholecystokinin, it is the second major source of negative feedback signals that stop eating behaviour (Rampal, 1986).

Oxyntomodulin

Oxyntomodulin is a naturally occurring 37-amino acid peptide hormone found in the colon, produced by the oxyntic (fundic) cells of the oxynti (fundic) mucosa. It has been found to suppress appetite. It is known to bind both the GLP-1receptor and the glucagon receptor.

Enterostatin

Pentapeptide derived from a proenzyme in the gastrointestinal tract called procolipase. An increased high fat diets will cause the procolipase gene transcription and enterostatin to release into the gastrointestinal lumen. Enterostatin appears in the lymph and circulation after a meal. Enterostatin has been shown to selectively reduce fat intake during a normal meal.

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