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Review

Psychobiology of feeding behaviour

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Abstract

Adequate nutrition is essential for survival and therefore is ensured by a complex brain system regulating the levels of various nutrients in the blood and in the body stores. This system includes two distinct mechanisms of control on food intake, i.e. the homeostatic and the hedonic control. Over the last two decades our knowledge of neural circuits and molecules involved in these mechanisms has improved substantially, in large part due to the findings of research in experimental animals and functional neuroimaging in humans. These findings also provide insight into the mechanisms underlying obesity and abnormal feeding behaviour in neuropsychiatric disorders. The hypothalamic network that regulates food intake and energy balance consists of interconnected neurons located in the arcuate (infundibular in humans) nucleus, ventromedial nucleus, paraventricular nucleus, dorsomedial nucleus, and lateral hypothalamic area. Central regulation is mediated by α- and β- melanocyte-stimulating hormone, neuropeptide Y, Agouti-related protein, γ-aminobutyric acid, brain-derived neurotrophic factor, and melanin-concentrating hormone. Peripheral signals that stimulate (orexigenic) or inhibit (anorexigenic) food intake are received by neurons in the medial zones of the hypothalamus, including signals from circulating nutrients (glucose, fatty acids), hormones (insulin, leptin, ghrelin), and gastrointestinal peptides (cholecystokinin and peptide YY3-36). The pleasure of palatable food is associated with activation of the brain reward system, including the ventral tegmental area, dopaminergic system, nucleus accumbens, ventral pallidum, and amygdala. Dopamine release in the nucleus accumbens mediates the motivational aspects of food intake, especially the drive to eat food that is hedonically desirable ("wanting"). Orexin, cocaine- and amphetamine- regulated transcript, and galanin play significant role in hedonic regulation of feeding. The hedonic reaction per se to the pleasure of food reward ("liking") is regulated by endogenous opioids and endocannabinoids. There are homeostatic – hedonic control interactions via functional connections of nucleus accumbens with the prefrontal cortex, amygdala, and lateral hypothalamus, as well as between hypothalamic, cortical, and mesolimbic circuits. There is also a "top-down" control of human feeding behavior: interactions between cognitive and emotional processes could lead to different responses to food cues and changes in food intake.

Keywords: nutrition, homeostatic control, hedonic eating, hypothalamus, reward system.

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INTRODUCTION

Feeding provides the energy that is essential for survival and therefore is subject to intense regulation by human brain. Adequate nutrition is ensured by a complex brain system regulating the levels of various nutrients in the blood and in the body stores. The hypothalamus is the centre of the network of control on food intake and metabolism in response to peripheral signals that reflect the feeding state and energy reserve, i.e. homeostatic control.

Hunger is associated with discomfort providing a strong drive for feeding and satiety is accompanied with satisfaction preventing further consumption of food. However, the rewarding nature of food goes beyond the feelings of hunger and satiety. Modern humans often eat in the complete absence of hunger and nowadays obesity is a serious public health problem. Hedonic eating, i.e. eating based on pleasure rather than energy needs, is controlled by complex neural mechanisms associated with reward. The insular cortex, orbitofrontal cortex, nucleus accumbens, amygdala, and ventral tegmental area have a key role in control of feeding behaviour in response to the hedonic aspects of food.

Over the last two decades our knowledge of neural circuits and molecules involved in homeostatic and hedonic control of food intake, has improved substantially, in large part due to the findings of research in experimental animals and functional neuroimaging in humans. These findings also provide insight into the mechanisms underlying obesity and abnormal feeding behaviour in neuropsychiatric disorders. Only the main aspects of the current knowledge on mechanisms controlling feeding behaviour can be emphasized here.

HOMEOSTATIC CONTROL OF FOOD INTAKE

The hypothalamic network that regulates food intake and energy balance consists of interconnected neurons located in the arcuate (infundibular in humans) nucleus (ARC), ventromedial nucleus (VMH), paraventricular nucleus (PVN), dorsomedial nucleus (DMH), and lateral hypothalamic area (LHA). Peripheral signals that stimulate (orexigenic) or inhibit (anorexigenic) food intake are received by neurons in the medial zones of the hypothalamus, including signals from circulating nutrients (glucose, fatty acids), hormones (insulin, leptin, ghrelin), and gastrointestinal peptides (cholecystokinin and peptide YY_{3-36}) **[1]**. The dorsomedial and lateral hypothalamic neurons receive circadian influences and interact with neural circuits for thermoregulation and arousal **[2]**. The integration between orexigenic and anorexigenic signals proceeds via complex interactions between the hypothalamic nuclei mediated by a variety of neurotransmitters **[3]**. The hypothalamic network exerts control on food intake and peripheral metabolism acting via projections to sympathetic and parasympathetic nuclei (nucleus of the solitary tract, area postrema, dorsal motor nucleus of the vagus, and locus coeruleus) on the endocrine glands and the gastrointestinal system **[4]**. Cognitive and emotional aspects of food intake relay on reciprocal connections of hypothalamus with cortical and mesolimbic circuits, and hippocampus **[5].**

In the following we present the main peripheral and central signals and hypothalamic pathways related to feeding behaviour, which are also briefly displayed in *Table 1*.

Table 1: Main signals and mechanisms for homeostatic control of food intake

Signal	Source	Target (receptors)	Effect	Mechanisms of action
Peripheral (hormones)				
Insulin	Pancreas	Hypothalamus (Insulin Receptors, IR)	↓Food intake	Activation of POMC neurons in ARC Activation of BDNF neurons in VMH Inhibition of LHA neurons

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Cholecystokinin Peptide YY_{3-36}	Gut	Hypothalamus via vagus nerve (CCK-1, Y2)	↓Food intake	Stimulation of vagus nerve – signals via NTS and PBN projections to POMC neurons in ARC
Leptin	Adipose tissue	Hypothalamus (Leptin Receptors, OB-R)	↓Food intake ↑Metabolism	Activation of POMC neurons in ARC Activation of BDNF neurons in VMH Inhibition of LHA neurons
Ghrelin	Stomach	Hypothalamus (GHR1)	↑Food intake	Activation of Neuropeptide Y, Agouti-related peptide, and GABA neurons in ARC
Central				
α- and β-MSH	ARC	Hypothalamus (MC4R)	↓Food intake	Agonists of MC4R in PVN and VMH
Agouti-related peptide	ARC	Hypothalamus (MC4R)	↑Food intake ↓Metabolism	Inverse agonist of MC4R in PVN
Neuropeptide Y	ARC	Hypothalamus (Y1, Y2, Y5)	↑Food intake ↓Metabolism	Direct activation of PVN Inhibition of POMC neurons in ARC
BDNF	VMH	Hypothalamus (Tropomyosin receptor kinase B, TrkB)	↓Food intake	Agonist of TrkB and MC4R in PVN and VMH
Melanin-concentrating hormone	LHA	Hypothalamus, VTA (MCH1 and MCH2)	↑Food intake ↓Metabolism	Agonist of MCH receptors in hypothalamus and VTA
Orexin/hypocretin	LHA	Hypothalamus (OX1 and OX2)	↑Food intake	Agonist of OX1 and OX2 in PVN (short-term regulation of energy balance)
Endocannabinoids	LHA	Hypothalamus (cannabinoid-1 receptors, CB1)	↑Food intake ↓Metabolism	Inhibition of anorexigenic signals via CB1

Abbreviations: ARC, arcuate (infundibular in humans) nucleus; BDNF, brain-derived neurotrophic factor; GABA, γ-aminobutyric acid; LHA, lateral hypothalamic area; MC4R, Melanocortin 4 receptor; MSH, melanocyte-stimulating hormone; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; VMH, ventromedial nucleus; VTA, ventral tegmental area.

Central regulation of feeding and energy balance

The ARC is a key regulator of food intake and energy balance containing a group of neurons that synthesizes α- *and* β- *melanocyte-stimulating hormone (MSH)*, neuropeptides derived from *pro-opiomelanocortin (POMC)*, and another group of neurons synthesizing *neuropeptide Y (NPY), Agouti-related protein (AgRP),* and γ-*aminobutyric acid (GABA)*. A- and β- MSH decrease food intake and increase energy expenditure acting on melanocortin 4 receptors (MC4R) in the PVN and VMH **[6].** By contrast, NPY via Y1, Y2, Y5 receptors and AgRP acting as an inverse agonist of MC4R in the PVN increase food intake and reduce energy expenditure **[3].** Moreover, the same group of neurons can inhibit POMC neurons in the ARC via GABA and NPY projections **[7].** Thus, the ARC mediates both orexigenic and anorexigenic signals from periphery and regulates feeding and energy metabolism integrating these mutually opposing influences.

Neurons in the VMH that synthesize *brain-derived neurotrophic factor (BDNF)* receive signals from POMC neurons of the ARC and they also respond to glucose and leptin reducing food intake and increasing energy metabolism **[8]**. Groups of neurons in the PVN receiving signals from the ARC synthesize hormones

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with anorexigenic effects – corticotrophin releasing hormone (CRH), thyrotrophin releasing hormone (TRH), and oxytocin **[7].**

The LHA has also a key role in regulation of feeding and metabolism, integrating signals from the periphery (i.e., glucose, leptin, ghrelin) and interacting with other hypothalamic areas and the mesolimbic system **[4] [9] [10]**. A group of neurons in the LHA synthesizing *orexin* (or *hypocretin*) plays a significant role in the short-term regulation of energy balance. Orexin neurons are inhibited by glucose and stimulated during fasting and they promote food intake acting on specific receptors (OX1 and OX2) in the PVN **[11]** up of LHA neurons synthesizes *melanin-concentrating hormone (MCH)* and they act on specific receptors (MCH1 and MCH2) increasing food intake and decreasing energy metabolism **[12].** The function of LHA on food intake is related to sleep-wake cycle: the MCH neurons are active during slow-wave sleep while the orexin neurons are activated in wakefulness **[7].**

Peripheral factors regulating food intake and metabolism

Gut peptides (cholecystokinin, peptide YY$_{3-36}$) are released after a meal and suppress food intake and meal size activating via vagal afferents the nucleus of the solitary tract, which signals fullness to the hypothalamus and other brain regions, initiating satiety and resulting in meal termination **[13], [9].** Another gut peptide under investigation with similar effects on food intake and a significant role in the control of glucose and energy homeostasis is *glucagon-like peptide-1* **[14].** On the other hand, *ghrelin* is the hormone that is released from the stomach during fasting and provokes hunger and meal initiation. Ghrelin, acting on the growth hormone secretagogue receptor (GHSR) in the ARC, stimulates NPY, AgRP and GABA neurons **[15].** *Leptin* is a hormone synthesized in the adipose tissue that circulates at levels proportional to the amount of fat. Leptin, acting on specific receptors in the ARC, stimulates POMC neurons and inhibits the release of NPY and AgRP, thus contributing in long-term weight and glucose homeostasis **[16], [14]**. It also produces anorexigenic effect stimulating BDNF neurons in VMH while inhibiting LHA neurons **[16].** *Insulin*, the hormone released by beta-cells in pancreas and regulating glucose homeostasis, has also anorexigenic effects possibly through similar mechanisms of action as those of leptin **[17], [14].**

HEDONIC CONTROL OF FEEDING BEHAVIOUR

Many aspects of human behaviour, like seeking for pleasant food, cooking, or obesity, indicate that feeding is not controlled solely by homeostatic mechanisms but is also influenced by the rewarding nature of food.

Gustatory regulation of feeding

Food reward is associated with palatability qualities, particularly taste and smell. Animals consume sweet and salty food beyond their homeostatic needs and avoid sour or bitter food even if they are hungry. In human brain, taste information passes via the nucleus of the solitary tract and parabrachial nucleus to the thalamus, the lateral frontal cerebral cortex, the central nucleus of amygdala, and several hypothalamic areas, including LHA. Although gustatory thalamus is critical for hedonic aspects of taste, other subcortical areas also mediate the motivational qualities of palatable food cues **[2].**

Reward system for feeding

The pleasure of palatable food is associated with activation of many areas of the brain reward system, including the ventral tegmental area (VTA) dopaminergic system, nucleus accumbens (NAc), ventral pallidum, and amygdala **[10], [18].** Dopamine release in the NAc mediates the motivational aspects of food intake, especially the drive to eat food that is hedonically desirable ("wanting") **[19]**. As yet, the mechanisms by which food stimulates dopamine release are not well understood. It has been found that food can stimulate dopamine signalling independent of the processing of taste information **[20].**

Release of *orexin* during feeding directly stimulates dopamine neurons in the VTA increasing dopamine release in the NAc **[21]**. Other hypothalamic neuropeptides may also play a

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role in hedonic regulation of feeding influencing dopamine release. The *cocaine- and amphetamine- regulated transcript (CART)* which is found in several hypothalamic areas decreases food intake possibly inhibiting dopaminergic neurons in VTA. However, the anorexigenic effect of CART is associated with its multiple actions in hedonic and homeostatic regulating systems, which are not clear yet **[22].** By contrast, *galanin* stimulates food intake, in particular the intake of fat, possibly acting on specific receptors in the PVN. However, it still remains unknown which of the multiple central and peripheral effects of galanin might be related with this effect **[23].**

The hedonic reaction *per se* to the pleasure of food reward ("liking") is regulated by *endogenous opioids* and *endocannabinoids* acting via μ-type opioid receptors and CB1 receptors respectively, within the shell of the NAc and possibly within the ventral pallidum **[10].** Although 'liking' and 'wanting' are needed together for complete food reward, are mediated by interacting but partially independent neural substrates.

Interactions of homeostatic and hedonic regulatory mechanisms

The stability of body weight over adult life in spite of the availability of highly palatable and energy dense food, as well as the discrepancies from normal eating, e.g. overweight, obesity and eating disorders, indicate an interface between the metabolic and hedonic drives of eating. Therefore, the possible neural circuits and mechanisms that underlie interactions between homeostatic and hedonic regulation of feeding have been a focus of research during the last two decades.

The NAc plays a key role in the integration of homeostatic, hedonic, and cognitive aspects of food intake via its connections with the prefrontal cortex, amygdala, and lateral hypothalamus **[10], [24]**. There are also multiple functional connections between hypothalamic, cortical, and mesolimbic circuits mediated by POMC, orexin and MCH that may play a role in homeostatic – hedonic control interactions **[18].** Hormones involved in homeostatic regulation of feeding, such as leptin, insulin, and ghrelin, also exert effects on motivation to obtain food through their influence on mesolimbic dopamine signalling, especially on the dopaminergic neurons in the VTA **[25].** Leptin decreases the firing rate of the VTA dopaminergic neurons. Insulin increases dopamine release and the firing rate of dopaminergic neurons but reduces dopamine levels in the VTA probably by upregulation of the dopamine active transporter (DAT). Ghrelin enhances signalling from the VTA to the NAc increasing the activation of dopamine D_1 and D_2 receptors and dopamine levels.

Like ghrelin, other factors involved in meal-to-meal regulation of feeding may also affect food reward in a way that even highly palatable food may be unpleasant after satiation. There is evidence that the rewarding effects of food are potently modulated by indicators of satiety, such as peptide YY_{3-36} that was found to elicit a switch of activation from the hypothalamus to the orbitofrontal cortex and diminished orbitofrontal activation in response to the rewarding aspects of food **[26].** The main pathways related to hedonic control of feeding behaviour are briefly displayed in *Table 2*.

Table 2: Main signals and mechanisms for hedonic control of eating behaviour

Signal	Source	Target (receptors)	Effect	Mechanisms of action
Peripheral (hormones)				
Leptin	Adipose tissue	VTA (Leptin Receptors, OB-R)	↓ Food intake ↑ Metabolism	Inhibition of dopaminergic neurons in VTA
Insulin	Pancreas	VTA (Insulin Receptors, IR)	↓ Food intake	Reduction of dopamine levels in VTA probably by upregulation of DAT
Central				

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Ghrelin	ARC	VTA (GHR1)	↑ Food intake	Activation of dopaminergic neurons in VTA Increase of the activation of dopamine D1 and D2 receptors and dopamine levels in NAc
Orexin/hypocretin	LHA	VTA (OX1 and OX2)	↑ Food intake	Activation of dopaminergic neurons in VTA
Endocannabinoids	Local	Nucleus accumbens (cannabinoid-1 receptors, CB1)	↑ Food intake ↓ Metabolism	Enhancement of dopamine effect on nucleus accumbens
Endogenous opioids	Local	Nucleus accumbens (μ-opioid receptors)	↑ Food intake	Increase of dopamine release in nucleus accumbens
CART	ARC, LHA	Hypothalamus, Mesolimbic system	↓ Food intake	Unknown
Galanin	ARC	Hypothalamus, especially PVN (GALR)	↑ Food intake	Unknown

Abbreviations: ARC, arcuate (infundibular in humans) nucleus; CART, cocaine- and amphetamine- regulated transcript; DAT, dopamine active transporter; LHA, lateral hypothalamic area; NAc, nucleus accumbens; PVN, paraventricular nucleus; VTA, ventral tegmental area.

COGNITIVE AND EMOTIONAL CONTROL OF FEEDING BEHAVIOUR

Homeostatic and hedonic mechanisms controlling feeding behaviour described above only partially operate outside awareness. However, there is also a "top-down" control of human feeding behavior: interactions between cognitive and emotional processes could lead to different responses to food cues and changes in food intake **[27].** Thus, humans can voluntary inhibit their drive to eat or develop involuntary changes in their appetite and body weight related to emotional states.

Cognitive control of feeding behaviour involves integration of peripheral signals related to energy status of the body, food-related signals in the form of sensory and environmental cues, and memory of past feeding experiences **[7].** The insular, orbitofrontal, and anterior cingulate cortical areas have a key role in the processing of interoceptive and food-related information and participate in motivational aspects of feeding behaviour **[28], [29], [2].**

There is now evidence from preclinical studies that emotional factors influence both hedonic and homeostatic aspects of food intake, altering the activation of many mediators such as ghrelin, orexin and leptin. For example, chronic stress may influence feeding and body weight independent of palatability of food or energy status of the individual **[19].** This is more obvious in human behaviour, since changes in appetite and body weight are frequent symptoms and one of the core diagnostic features of major depressive disorder. Furthermore, the association rate between mood disorders and obesity is about 25% **[30].** Influences of mood on hedonic and homeostatic control of feeding may partially mediated by the effects of serotoninergic system, e.g. action of serotonin on POMC neurons in ARC via $5HT_{2C}$ receptors **[31].** Aside from depression, serotonin dysfunctions are also implicated in the pathophysiology of eating disorders, i.e. anorexia nervosa and bulimia nervosa **[32].**

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