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BASIC NEUROPHYSIOLOGY OF EATING BEHAVIOR AND ITS RELATION IN THE PATHOGENESIS OF OBESITY

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ABSTRACT

The regulation of appetite relies on complex hypothalamic neurocircuitry in which the arcuate nucleus and the hormone leptin, ghrelin play important roles. Excess body fat is stored in adipose tissue which forms over 10% of total body weight, but it is now clear that adipocytes have functions other than simple storage cells. The most significant of these appears to be the secretory. Obesity is the result of a sustained disequilibrium between energy intake and energy expenditure. If energy intake is too high or energy expenditure too low, an increase in body weight will develop over time. While in the past the contribution of an increased consumption of high-calorie food has been thought to be the primary factor in the pathogenesis of obesity, reduced physical activity is now thought to be equally or even more important. Even a small difference between these parameters becomes relevant if it is maintained over a prolonged period. It is clear to people living in the Western world that obesity is increasing, probably as a consequence of easily available, fat-rich food and an increasingly sedentary lifestyle and due to this obesity is fast becoming a global epidemic and a potential financial problem for the developing countries. The present review mainly focuses on basic neurological basis of eating behavior and its relation in the pathogenesis of obesity.

Keywords: Appetite, disequilibrium, neurophysiological, obesity.

INTRODUCTION

Obesity, a chronic, relapsing, stigmatized, neurochemical disease that is more prevalent in developing/developed countries and leading to much comorbidity. Multiple factors are involved that contribute to the development of obesity. These may be social, behavioural, environmental and genetic^{1,2}.

Prevalence of obesity is increasing rapidly in developed and developing countries. There is a growing body of evidence that prevalence of overweight and obesity increases in areas where tremendous socioeconomic changes have taken place such as in East Germany. Prevalence of obesity in Indian population is 20% in adults and 10% in children. In Punjab state of India³, frequency of overweight and obesity has found to be more among urban females than in their rural female counterparts. Another similar study reported that the prevalence of overweight (BMI ≥ 25) was high among urban southern Indian children. (17.8% in boys, 15.8% in girls) obesity (BMI ≥ 30 kg/m² in this study) was seen in 3.6% of boys and 2.9% of girls⁴. Level of overall and central adiposity, as well as body fat, was found to be high among Marwari's, as compared with other ethnic populations of India⁵. The prevalence of overweight and obesity among the affluent children in Amritsar was as high or higher as in some

industrialized countries due to life style changes and change in eating behaviour⁶. The prevalence of overweight among affluent Bengali children in Kolkata was higher than those reported from other Asian countries⁷.

Understanding of the pathophysiology of obesity has increased markedly over the last decade, but this knowledge is insufficient for the management of obesity. A better understanding of molecular mechanism of pathogenesis and role of environmental and genetic factors will provide hope for planning the treatment strategies of weight reduction. The present review can be an attempt of unwinding basic neurophysiology of eating behavior and neuropharmacological factors which are involved in pathogenesis of obesity,

NEUROPHYSIOLOGY OF THE REGULATION OF FOOD INTAKE

Energy balance is largely regulated by the central nervous system (CNS), which senses metabolic status from a wide range of humoral and neural signals, and controls energy intake; these systems are also influenced by the sight and smell and texture of food, memory of foods, and the social situation⁸. Much of the integration of this multiplicity of signals occurs in the hypothalamus, which is a key brain region in this respect. However, it is important to

remember that other brain regions play significant roles, particularly the nucleus tractus solitarius and area postrema in the brainstem, parts of the limbic system, the amygdala and the cerebral cortex. This network of neurons is sensitive to short and long-term changes in energy requirements. It acts to control timing of meals, their size and duration, and possibly, under some circumstances, their composition. The metabolism of ingested food is closely linked to the food consumption and is also subject to some neural regulation⁹.

Within the arcuate nucleus (ARC) of the hypothalamus, there are two neuronal populations with opposing effects on food intake: neurons which co-express neuropeptide Y (NPY) and agouti related peptide (AgRP) stimulate food intake, whereas neurons co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) suppress feeding. Within POMC neurons, α -melanocyte-stimulating hormone (α -MSH) is produced and this binds to melanocortin-4 (MC4R) receptors in the PVN to suppress food intake¹⁰. Within the brainstem, the dorsal vagal complex (DVC) is crucial in the interpretation and relaying of peripheral signals such as vagal afferents from the gut to the hypothalamus¹¹. The DVC consists of the dorsal motor nucleus of vagus (DMN), area postrema (AP), and the nucleus of the

tractus solitarius (NTS). Vagal afferents from the gut convey information such as gastric distension, gut hormone levels and fatty acids. Gut hormones act peripherally to modulate digestion and absorption of nutrients. However, they also act as neurotransmitters within the central nervous system to control food intake^{12, 13}.

Satiety signals and adiposity signals

There are various types of signals that influence food intake. Although it is an oversimplification, these signals can be separated into three major categories: satiety signals, adiposity signals, and central effectors.

Satiety signals

Satiety signals are those arising from the GI tract and related organs during a meal. These signals influence eating behavior by activating neurons in the nucleus of the solitary tract (NTS) in the hindbrain. Although there are minor variations in the exact pattern, most satiety signals interact with specific receptors on peripheral nerves passing from the GI tract to the hindbrain, especially the vagus nerves (e.g., CCK and glucagon), or else circulate to the hindbrain via the blood and interact with local receptors there (e.g., amylin)¹⁴.

As food interacts with the lining of the stomach and intestine, a complex array of gut peptides and other signals that function to coordinate and optimize the digestive

process are secreted. Some of these enter the lumen to interact with the food directly, others are secreted into the local interstitial fluid to influence neighbouring cells in a paracrine fashion, and still others enter the blood as hormones to influence more distant target organs such as the liver, pancreas, or brain¹⁴. These signals collectively ensure that the appropriate mix of enzymes and other factors are added to the ingested food in the right sequence and that the mixture is passed along the GI tract at the appropriate speed. Some of these same signals also provide information to the central nervous system and thereby function as satiety signals. Table 1 lists the peptides secreted from the digestive system that have been found to alter meal size. By monitoring signals that are correlated with ingested calories, the brain is able to terminate a meal when ample calories have been ingested but well before they have entered the blood in significant amounts. This ability is important for preventing the body from becoming overwhelmed by a flood of newly ingested glucose and lipids if too large a meal is consumed^{15, 16}.

Cholecystokinin (CCK)

Any endogenous factor that causes a sensation of fullness and reduces the size of an ongoing meal is called a satiety signal, and several different GI peptides are thought to meet this criterion. Different signals are

secreted in response to specific carbohydrates, fats, proteins, or mixtures of these macronutrients, and it is the specific mix or cocktail of signals that presumably informs the brain as to what precisely has been eaten¹⁴.

When food containing fat or protein is consumed and enters the duodenum, CCK is secreted from I cells of the small intestine into the circulation with a plasma half-life of a few minutes. CCK enters the blood and has hormonal influences on gut motility, contraction of the gallbladder, pancreatic enzyme secretion, gastric emptying, and gastric acid secretion.¹⁷⁻¹⁹ There are two CCK receptor subtypes: CCK1 and CCK2, both receptors being widely distributed in the brain including the brainstem and hypothalamus²⁰. The anorectic action of CCK appears to be mostly mediated through CCK1R on vagal afferents²¹. Through this mechanism a message, generally that ingested fat/protein is being processed and will soon be absorbed, is conveyed to the hindbrain and relayed to the hypothalamus where it is integrated into the composite information on energy homeostasis^{22, 23}.

Other satiety signals

Besides CCK, there are other peptides secreted from the gastrointestinal system that have been reported to reduce meal size [Table 1].

Table 1: Gastrointestinal peptides that influence food intake.

Reduce Meal Size/ Food intake	Increase Meal Size/ Food intake
Cholecystokinin (CCK)	Ghrelin
Bombesin family (bombesin, gastrin releasing peptide (GRP), and neuromedin B)	β -Casomorphin
Glucagon	
Glucagon-like peptide-1	
Somatostatin	
Enterostatin	
Peptide YY-(3–36)	
Amylin	
Oxyntomodulin	
Exendin-4	
Apolipoprotein A-IV	

Adiposity signals

Adiposity signals, in contrast, are hormones secreted into the blood. The two adiposity signals that are best known are insulin and leptin. Both hormones are transported through the blood-brain barrier (BBB) and gain access to neurons in the hypothalamus and elsewhere in the brain to influence energy homeostasis. Although many areas of the brain are sensitive to insulin and leptin, neurons in the arcuate nucleus of the hypothalamus have particularly high levels of their receptors¹⁷.

Insulin

Plasma insulin levels also reflect more-acute changes in energy status. Insulin is synthesized in the β cells of the pancreas and secreted rapidly after a meal and any other condition of positive energy balance and decreases during fasting and other periods of negative energy balance. The major stimulant of insulin secretion is an increase of local glucose levels in the

pancreas. The degree of glucose-stimulated insulin secretion is a direct function of body fat. Circulating insulin crosses the BBB in a dose-dependent manner by a saturable receptor mediated mechanism and acts at the ARC where insulin receptors are highly expressed²⁴. One mechanism by which insulin may participate in energy homeostasis is via its effect to inhibit hypothalamic expression of NPY^{24,25}. Central insulin infusion also potentiates the satiety effect of peripherally administered cholecystokinin²⁶. Elevated brain insulin concentrations may therefore promote a state of negative energy balance both by inhibiting anabolic effector pathways (e.g., NPY) and by increasing sensitivity to peripheral satiety signals such as cholecystokinin²⁷.

Leptin

Leptin is secreted by from white adipocytes (as well as the stomach and other tissues) with circulating levels proportional to fat

mass²⁸. Leptin is transported across the BBB by a saturable system and exerts its anorectic effect via the ARC. In the ARC, both NPY/AgRP and POMC/ CART neurons express leptin receptors²⁹. Leptin inhibits NPY/AgRP neurons and activates POMC/ CART neurons resulting in reduced food intake and increased energy expenditure. Among the three types of leptin receptors, the Ob-Rb receptor, which is highly expressed in the hypothalamus, is thought to be the main receptor involved in appetite regulation³⁰. However, obesity in humans is often associated with high leptin levels and failure to respond to exogenous leptin. This leptin resistance may be attributable to reduced leptin receptor signal transduction³¹ or an impaired ability of the BBB to transport leptin³². The ability of insulin and leptin to function as adiposity signals to the brain has been reviewed several times³³. Consistent with this, if exogenous insulin or leptin is added locally into the brain, the individual responds as if excess fat exists in the body; *i.e.* food intake is reduced and body weight is lost. Analogously, if either the leptin or the insulin signal is reduced locally in the brain, the individual responds as if insufficient fat is present in the body, more food is eaten, and the individual gains weight³⁴.

Central effectors

Central effector signals arise from circuits that receive inputs from satiety signals and

adiposity signals and integrate them with inputs from several other brain areas. In this way, factors such as learning and habits, the social situation, stress and emotions, and many others are able to interact with metabolic factors to influence food intake³⁵. Central effector pathways can be defined as either anabolic or catabolic, terms that reflect the overall effect on energy balance brought about through stimulation of the pathway. Elevated neuronal activity in anabolic pathways promotes a state of positive energy balance by stimulating the ingestion and storage of energy, whereas stimulation of catabolic pathways causes a net loss of energy from the body. Anabolic systems act primarily by increasing the drive for food intake, although they may also decrease energy expenditure, alter the peripheral metabolic environment to favor assimilation and storage of ingested energy, or both. In contrast, catabolic effector systems promote the mobilization of stored fat and cause weight loss by reducing food intake, increasing lipolysis and thermogenesis, or both. Available evidence suggests that the peripheral metabolic effects of central neuropeptides and monoamines are mediated by efferent autonomic activity. As a general rule, elevated sympathetic nervous system (SNS) outflow promotes catabolic effects and a decreased SNS outflow favors anabolic

actions³⁶, whereas the reverse applies to efferent activity of the parasympathetic nervous system³⁷.

The adiposity hormones insulin and leptin elicit a net catabolic response in the brain.

Many neuropeptides and monoamines synthesized and released along discrete neuronal pathways within the brain can modify food intake when administered to the CNS [Table 2].

Table 2: Some candidate signalling molecules used by central effector pathways involved in the hypothalamic control of energy balance.

	Effect on Food intake / meal size	Effect on Sympathetic Nervous System (SNS) activity
Anabolic		
Neuropeptide Y ³	↑↑	↓↓
Melanin concentrating hormone ³	↑	?
Agouty-related protein ³	↑	?
Orexin A and B ³	↑	?
Galanin	↑	?
B-Endorphin	↑	↓
Dynorphin	↑	?
Growth hormone-releasing hormone	↑	↓
Noradrenaline	↑	↓
Catabolic		
Corticotropin-releasing hormone ²	↓↓	↑↑
α-MSH ²	↓	?
CART ²	↓	?
Bombesin	↓	↑
Somatostatin	↓	?
Cholecystokinin	↓	↑
Thyrotropin-releasing hormone	↓	?
Calcitonin-gene-related peptide	↓	↑
Neurotensin	↓	↑
Serotonin	↓	↑

¹↑, increase; ↓, decrease; ?, not established; double arrows indicate robust effects; SNS, sympathetic nervous system; MSH, α-melanocyte stimulating hormone; CART, cocaine- and amphetamine-regulated transcript.

² Pathways that are stimulated by leptin.

³ Pathways that are inhibited by leptin, activated by fasting, or both.

Therefore, signals from the periphery have pivotal roles in transmitting information via afferent vagal fibres to the caudal brainstem

or directly to the hypothalamus to modify appetite. Table 3 lists several peripheral appetite-related signals and their roles.

Table 3: Summary of the main gut hormones and adiposity signals that influence food intake and body weight.

	Feeding	Receptor	Major secretion site	Other Action
Gut hormones				
PYY (3-36)	↓	Y2	Ileum, colon, rectum	Delays gastric emptying
PP	↓	Y4, Y5	Endocrine pancreas	-
GLP-1	↓	GLP-1	L cells in gut	Incretin, decreases blood glucose, delays gastric emptying, neurotrophic effect
GLP-2	-	GLP-2	L cells in gut	Intestinal trophic effect
OXM	↓	GLP-1	L cells in gut	
Glucagon	↓	GCGR	Pancreatic α cells	Increases blood glucose levels and insulin secretion
CCK	↓	CCK 1, 2	I cell of small intestine	Gall bladder contraction, relaxation of sphincter of Oddi, pancreatic enzyme secretion
Ghrelin	↑	GHS	stomach	Growth hormone secretion
Amylin	↓	AMY1-3	pancreatic β cells	Decreases blood glucose levels
Adiposity signals				
Insulin	↓	Insulin	pancreatic β cells	Decreases blood glucose levels, stimulates glycogen synthesis
Leptin	↓	Leptin (Ob-R)s	Adipocyte	Regulation of energy metabolism
Adiponectin	↓	Adipo R1, R2	Adipose tissue	-

PYY, peptide YY; PP, pancreatic polypeptide; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; OXM, oxyntomodulin; CCK, cholecystokinin; GCGR, glucagon receptor.

Pathophysiology of obesity

Modulation of the amount of energy that we take in as food involves several mechanisms and networks that connect the brain with the gut, this process being key to the regulation of body weight over time, as well

as to the modification of long-term eating behaviours. Obesity is characterized by an increase in subcutaneous adipose tissue. Its metabolic consequences, such as insulin resistance, are primarily attributable to

increased fat deposition at sites such as the omentum, liver, and skeletal muscles.

Body weight regulation is at both, short term (day to day) and long term basis. Obesity occurs as a result of imbalance in energy input and expenditure. If energy intake is too high or energy expenditure too low, an increase in body weight will develop over time. While in the past the contribution of an increased consumption of high-calorie food has been thought to be the primary factor in the pathogenesis of obesity, reduced physical activity is now thought to be equally or even more important^{38, 39}. For weight regulation there is a set point in every individual. A lot of information is available regarding genes, peptides, neurotransmitters, and receptors in the hypothalamus and neighbouring areas which regulate appetite and body weight⁴⁰ that is discussed above.

There are four hypotheses regarding afferent mechanisms involved in appetite regulation. According to lipostatic hypothesis adipose tissue produces a hormonal signal that is proportionate to the amount of fat. Obesity is also said to be an inflammatory condition of the body. A growing list of adipocytokines involved in inflammation (IL-1beta, IL-6, IL-8, IL-10, IL-18⁴¹ TNF-alpha, TGF-beta,) and the acute-phase response (serum amyloid A, PAI-1) have been found to be increased in the metabolic syndrome.

From white adipose tissue, there is release of leptin and resistin which decrease appetite. There is also release of adiponectin and adipocytokines like tumor necrosis factor- α and interleukin-6 (IL-6) which increase appetite. Brown adipose tissue also releases PPAR- γ and uncoupling protein (UCP-1) which are responsible for high metabolic rate and thus, for weight reduction.

Gut peptide hypothesis determines release of peptides like GRP from the stomach. Glucagon and somatostatin from pancreas which decrease appetite and control weight. Some more peptides like CCK and PYY released from intestine and colon also are responsible for appetite and body weight regulation. Polypeptide ghrelin is released from stomach. It exerts orexogenic effect through NPY/AGRP pathway in the arcuate nucleus^{42,43}.

Glucostatic hypothesis holds that reduced blood glucose level increases appetite, frequent fasts lead to reduction in basal metabolic rate and increase in adiposity.

Thermostatic hypothesis postulates that fall in body temperature below set point stimulates appetite and above set point inhibits.

CONCLUSION:

Obesity develops when energy intake exceeds energy output, leading to accumulation of adipose tissue. Energy

balance is maintained through the control of appetite and metabolism. Appetite regulation is a complex process, influenced by peripheral and central signals. In the gastrointestinal tract, ghrelin and decreasing concentrations of nutrients such as glucose, fatty acids and amino acids stimulate hunger. Following a meal, gastric and duodenal distension produce the feeling of satiety, aided by release of gastrointestinal peptides such as cholecystokinin, glucagon-like peptide 1 and peptide YY 3-36. Glucagon-like peptide is also secreted in response to nutrients in the intestines and increases satiety. Signals regarding appetite regulation are received centrally by the brainstem and hypothalamus; these central control centres are linked by projections from brain stem neurons to the paraventricular nucleus and lateral hypothalamus. The brainstem receives information concerned with satiety via afferent vagal fibres shortly after meals, whereas the hypothalamus integrates short term and long term signals from the brain, gastrointestinal tract and peripheral circulation.

Leptin levels are directly proportional to levels of adipose tissue. In severely obese individuals, subcutaneous adipose tissue concentrations of leptin mRNA are 80% higher than in controls, and plasma levels are also high. Plasma concentrations of

leptin are reduced when weight loss occurs due to diet restriction. Insulin-induced alterations in adipocyte metabolism are thought to stimulate production of leptin. A diminution of adipose tissue results in reduced leptin release which stimulates appetite and restores the energy deficit. The central nervous system responds to a lack of leptin as it would to an absence of adipose tissue stores, by increasing food intake and decreasing energy expenditure. Conversely, an increase in adipose tissue stimulates leptin release, thus reducing appetite and promoting weight gain. Physiologic responses to decreased leptin are more pronounced than responses to increased levels of leptin, leading to speculation that the primary role of leptin is to adapt to a negative energy balance rather than to prevent obesity. The feedback mechanism is not completely understood. Adipose tissue mass may not be the sole determinant of leptin release and it has been suggested that leptin resistance may occur. Many other signals such as ghrelin and cholecystokinin may have a role in long term regulation of appetite and energy, thus increasing the complexity of the feedback mechanism.

Thus after understanding basic neurophysiology of eating behavior various treatment strategies can be applied by neurological ways to reduce development and progression of obesity.

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