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Regulation of Body Weight in Humans

Introduction

The weight of the human body is influenced by both genetic and environmental factors, and can vary substantially from one person to another. Yet, with the exclusion of fluctuations due to gain and loss of water, the adult body weight remains remarkably stable, despite day to day variations in food intake and energy expenditure. Unaccountable loss or gain of body weight by more than 3% over relatively short time constitutes an alarming indication of a health problem. Loss of weight due to famine or intended caloric restriction is almost always recovered within weeks after the restraints on food intake are removed. Return to initial weight within weeks also occurs after termination of voluntary overeating regimens. Such observations led to the realization that weight stability is a consequence of autonomic mechanisms that act to maintain the reserved energy of the body at a relatively constant value and to resist displacements from this value. Involuntary control of energy homeostasis, which requires routine adjustments in energy intake and expenditure, is thought to be crucial for restraining the compulsive drive to eat when food is readily available. In general, homeostasis or the relative constancy of the internal environment of the body is controlled by the central nervous system (CNS), particularly by the hypothalamus, which regulates both the endocrine and the autonomic nervous systems. Homeostatically controlled variables such as blood pressure, body temperature, heartbeat, osmolarity, as well as energy metabolism and body weight are held to a fixed value called the set point. When a controlled variable assumes different values, various sensing, feedback, and control mechanisms are activated to provide a synchronized response to reestablish the original value. Although the concept of a tightly regulated set point for body weight is strongly supported by the ineffectiveness of periodic dieting to produce sustainable weight change, it is at odds with the accelerated growth of obesity in modern societies. The underlying reasons for this apparent contradiction will be discussed here in the context of our current understanding of brain regulation of energy metabolism.

Central Regulation of Energy Metabolism
(A) Peripheral Inputs (Afferent Signals)

Central regulation of energy homeostasis requires that the brain be constantly informed about the metabolic status of the body. Serving this purpose are various neural and humoral signals that reflect surplus or shortage of metabolic fuel. These metabolic signals are assessed by specialized brain circuits, which integrate them with inputs from the environment (food availability, temperature, etc.) and memory of past experiences (favorable or harmful effects of certain foods, etc.), and then evoke alterations in energy intake and expenditure. A brain area heavily involved in this activity is the hypothalamus, a small nervous tissue (volume of about 4 ml) located in the middle of the base of the brain alongside and partly encapsulating the third ventricle (Figures 1 and 2). Some of this tissue lies outside the blood-brain barrier, enabling it to sense and respond directly to variations in the circulating levels of glucose and other key metabolic signals such as insulin, leptin and ghrelin. It also allows the hypothalamus to control hormonal secretion from the adjacent pituitary gland by secreting hormones called releasing factors into the portal circulation of the pituitary. Additionally, the hypothalamus connects with the pituitary, classically referred to as "the master gland of the body", through a short stalk of nerve fibers. In fact, the hypothalamus has important neural connections to most regions of the CNS, particularly to brain areas which provide ports for neural sensory signals into the CNS, such as the midbrain nucleus of the solitary tract (NST). The neural organization and strategic location of the hypothalamus allow it to control both energy inputs and outputs. Meal-related inputs such as visual appearance, smell, texture, and taste of food are communicated by cranial nerves to the NST and from there to the hypothalamus. The vagus nerve, which innervates most of the gastrointestinal tract, conveys information about gastric distention, the kinds of food present in the gut, their digestibility, flow of nutrients into the blood, etc. Afferent metabolic signals also arise from the liver, white adipose tissue, thyroid, adrenals, reproductive organs, muscle, and other peripheral tissues. The flow of metabolic information is a two way process, in which the brain responds to peripheral inputs by transmitting efferent signals that can alter almost every aspect of energy metabolism. Figure 2 illustrates the flow of peripheral metabolic signals into the CNS, and Table 1 contains data about the source and role of these signals.

Afferent signals reflecting size and composition of body energy stores, as well as those reflecting nutrient
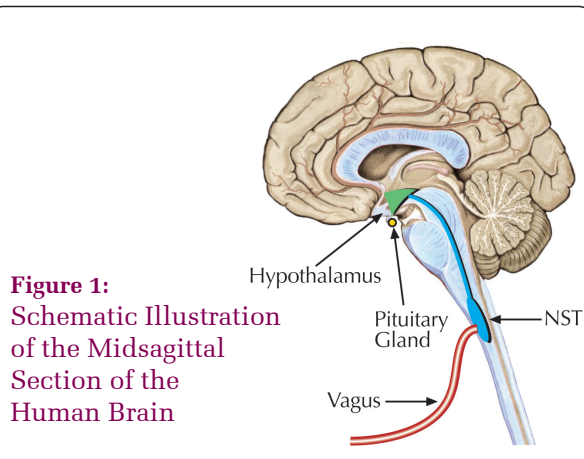

Figure 1:
Schematic Illustration of the Midsagittal Section of the Human Brain

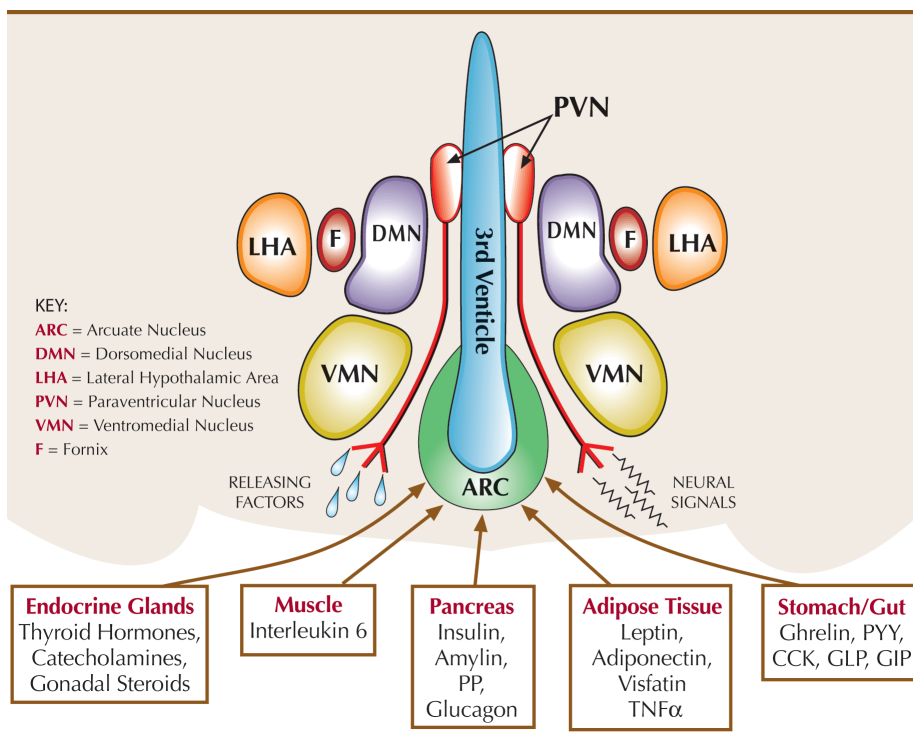Hypothalamus

Pituitary Gland

NST

Vagus

intake and acute metabolic requirements are processed in the hypothalamic arcuate nucleus (ARC), which is situated adjacent to the floor of the third ventricle (Figure 2). The ARC is one of at least twelve distinct hypothalamic nuclei which collectively regulate a variety of bodily functions including circadian rhythm, sexual activity, and emotional responses, and whose variability can greatly affect energy metabolism. The ARC contains two primary groups of neurons called POMC and NPY/AgRP, which exert opposite effects on energy balance. The POMC neurons respond to afferent signals reflecting energy surplus by expressing the precursor protein pro-opiomelanocortin (POMC). Post-translational processing of POMC liberates melanocortin peptides such as adrenocorticotrophin and α-melanocortin stimulating hormone. Binding of these peptides to melanocortin receptors (MC3-R and MC4-R) expressed by neurons within the ventromedial nucleus of the hypothalamus (VMN) induces a powerful anorectic effect. The melanocortin signaling system is considered to be one of the most important pathways for controlling appetite. Mutations within this system are the most common cause of genetic obesity in humans, and mice with impaired melanocortin signaling due to defects in POMC neurons eat excessively and become obese. Many POMC neurons also produce a neuropeptide precursor protein called cocaine and amphetamine-regulated transcript (CART), which like POMC is proteolytically processed to yield potent anorectic peptides. CART expression is upregulated after cocaine or amphetamine administration, two stimulant drugs that have a powerful appetite suppressant effect but are no longer prescribed to treat obesity because of dependence and abuse problems. The catabolic action of CART appears to be mediated by neurons located within the third and forth ventricles, two brain areas that are involved in processing stress and reward signals. The recent finding that blocking central GLP-1 signaling with a potent GLP-1 receptor antagonist abolishes CART-induced suppression of food intake, suggests that CART peptides exert their anorectic effect, at least in part, by stimulating central expression of GLP-1 and/or GLP-1 receptors [1]. The NPY/AgRP neurons respond to afferent signals reflecting energy deficits (e.g. low blood glucose) by co-expressing neuropeptide Y (NPY) and Agouti-related peptide (AgRP), which exert orexigenic effects, i.e. increased food intake and decreased energy expenditure. The appetite-stimulating effect of AgRP is elicited through binding to melanocortin receptors, particularly MC4-R. This interaction reversibly inhibits anorectic signaling by the melanocortin system. The recent finding that genetic variation in the human AgRP gene (Ala67Thr) is associated with inherited leanness [2] highlights the role of AgRP in the regulation of body weight. Unlike AgRP whose expression is confined to the medial part of the ARC, NPY is widely expressed throughout the CNS and is one of the most abundant neurotransmitters in the brain. The NPY levels within the ARC are increased during fasting and are chronically elevated in genetically obese rodents (e.g. ob/ob mice). Binding of NPY to Y receptors expressed by neurons within the lateral hypothalamus area (LHA) increases food intake and decreases energy expenditure. However, although NPY appears to be an important orexigenic signal, NPY-null mice have

Table 1: Afferent Signals Effecting Energy Balance (EB)

Signal	Produced by	Stimuli	Effect on EB	Comments
ghrelin	stomach/CNS	fasting/low BMI	*positive*	An endogenous regulator of food intake
Peptide YY (PYY)	intestine	food intake	*negative*	Inhibits gastric emptying and food intake
cholecystokinin (CCK)	intestine/CNS	fat/protein intake	*negative*	Slows gastric emptying and reduce food intake. Acts both directly and through the vagus
gastric inhibitory peptide (GIP)	intestine	food intake	*negative*	Stimulate insulin release
glucagon-like peptide 1 (GLP-1)	intestine/brain	nutrient ingestion	*negative*	Stimulate insulin release, inhibits food intake
oxyntomodulin (OXM)	intestine	nutrient ingestion	*negative*	Stimulate energy expenditure and reduces food intake
oleylethanolamide	small intestine	fatty meals	*negative*	Reduce food intake by shortening mealtime
apo A-IV (chylomicrons)	small intestine	fatty meals	*negative*	Acts in the CNS to inhibit food intake
Enterostatin	stomach/intestine	fatty meals	*negative*	Inhibits food intake
gastric releasing peptide (GRP)	GI tract	gastric mucosa	*negative*	Stimulate release of CCK, insulin, and gastrin
insulin	pancreas	glucose/high BMI	*negative*	Interacts with hypothalamic insulin receptors to suppress appetite
amylin	pancreas	blood glucose	*negative*	Inhibits food intake and delays gastric emptying
pancreatic polypeptide (PP)	pancreas	caloric load	*negative*	Inhibits both food intake and energy expenditure
glucagon	pancreas	cephalic response		Decreases meal size, acts on vagal afferents
leptin	adipose tissue	high BMI	*negative*	Interacts with hypothalamic Ob-R receptors to suppress appetite and stimulates thermogenesis
adiponectin	adipose tissue	fasting/low BMI	*negative*	Stimulates fatty acid oxidation
Visfatin	adipose tissue	high BMI	*negative*	Interacts with insulin receptors. May play a leptin-like role.
thyroid hormones	thyroid	pituitary signals (TSH)	*negative*	Stimulate energy expenditure
catecholamines	adrenals	pituitary signals	*negative*	Stimulate energy expenditure
Steriod hormones	Gonadal glands	pituitary signals	*negative*	Stimulate fat catabolism
inflammatory cytokines	macrophages	inflammation	*negative*	Suppress appetite and cause nausea

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KEY:
ARC = Arcuate Nucleus
DMN = Dorsomedial Nucleus
LHA = Lateral Hypothalamic Area
PVN = Paraventricular Nucleus
VMN = Ventromedial Nucleus
F = Fornix

RELEASING FACTORS

NEURAL SIGNALS

PVN

3rd Venticle

Endocrine Glands
Thyroid Hormones, Catecholamines, Gonadal Steroids

Muscle
Interleukin 6

Pancreas
Insulin, Amylin, PP, Glucagon

Adipose Tissue
Leptin, Adiponectin, Visfatin TNFα

Stomach/Gut
Ghrelin, PYY, CCK, GLP, GIP

normal body weight and adiposity, suggesting that the alternative orexigenic signaling via AgRP is an effective compensatory pathway. The interplay between POMC/CART and NPY/AgRP neurons in controlling energy balance is underscored by their opposite response to changes in the plasma levels of leptin and insulin, two hormones signaling metabolic affluence, which stimulate expression of POMC/CART and inhibit NPY/AgRP expression. The magnitude of the anabolic and catabolic effects of NPY/AgRP and POMC/CART, respectively, is directly proportional to the released amount of the corresponding neuropeptides.

(B) Brain Outputs (Efferent Signals)

Efferent signals controlling energy balance include hormonal, behavioral and neural outputs. An important element in the efferent networks underlying these outputs is the hypothalamic paraventricular nucleus (PVN), which provides important outlets for both neural and hormonal signals. Individual neurons within the PVN secrete specific releasing factors which control hormonal secretion from the pituitary gland, which in turn regulates the secretion of peripheral endocrine hormones. The classical endocrine axes, consisting of hypothalamic releasing/inhibitory factors, pituitary hormones/releasing hormones, and peripheral endocrine signals, affect energy metabolism primarily by modulating the metabolic rate and the ratio between fat and glycogen stores. Such adjustments are particularly important whenever the routine pattern of energy intake and/or expenditure is altered, e.g. due to changes in physical activity and/or eating habits, which subsequently result in alteration in the relative usage of fatty acids and glucose as metabolic substrates for ATP synthesis.

Other PVN neurons convey neural signals controlling the activity of the autonomic nervous system via direct projections to preganglionic neurons in the spinal cord intermediolateral cell column (sympathetic), and the dorsal motor nucleus of the vagus (parasympathetic). Both the sympathetic and parasympathetic nervous systems are important mediating structures from the brain to the periphery, and play an essential role in adjusting energy balance according to acute and chronic requirements. In general, the activity of the parasympathetic system promotes anabolism by facilitating digestion and absorption of nutrients, whereas that of the sympathetic system, which prepares the body for a "flight or fight response", enhances catabolism by stimulating energy expenditure and inhibiting food intake. Although the two systems exert opposite physiological effects, they usually act in conjunction even at times when the activity of one system predominates that of the other. For example, the massive autonomic response to a sharp drop in blood glucose includes accelerated heart beat, trembling, anxiety, and sweating (sympathetic) as well as hunger (parasympathetic).

Feeding Behavior and Eating Disorders

Central regulation of eating behavior is aimed primarily at restraining the powerful and perpetual drive to eat. To meet this challenge, the CNS employs a meticulously interconnected circuitry consisting of multiple appetite-controlling pathways with significant redundancy. Overcompensation by these mechanisms may result in anorexia, whereas shortcoming may lead to overeating and obesity. Such inadequacies may result from failure of either afferent or efferent networks to generate appropriate satiety signals, e.g. weak afferent signals in response to overload of a high-caloric nutrient such as fructose. When searching for the link between feeding behavior and eating disorders it should also be taken into consideration that eating is as much a matter of attaining pleasure and reward as it is a means for satisfying nutritional needs. Seeking and attaining pleasure and reward are powerful urges in human behavior, and coupling them with eating may override normal satiety mechanisms, resulting in overeating. The concept of pleasure is intimately linked to that of addiction, and it has been suggested that non-genetic obesity results from an addiction to food (3). On the other hand, emerging evidence from numerous studies strongly suggest that the marked increase in the prevalence of

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obesity during the past three decades is a consequence of metabolic disturbances elicited by dietary changes, in particular the dramatic increase in fructose consumption during the same time frame (reviewed in reference 4). For many years fructose was considered to be a healthy sweetener and superior to glucose because of its much lower Glycemic Index, and wide occurrence in natural products such as fresh fruits and honey. Commercial production of fructose in the form of high-fructose corn syrup (HFCS) began in 1974 and has steadily increased thereafter to meet increasing consumer demands for HFCS-sweetened soft drinks and other "goodies". Recent estimates suggest that the contribution of fructose to the daily caloric intake per capita in the U.S has increased by more than 8-fold during the past three decades. As discussed below, over consumption of this seemingly harmless sugar may lead to obesity, which in turn is associated with a cluster of pathologies including insulin resistance, dyslipidemia, hypertension, and atherosclerosis.

Fructose Metabolism and Obesity

Although fructose and glucose are monosaccharides with the same empirical formula ($C_6H_{12}O_6$), their metabolism is substantially different. An important step in the metabolism of hexoses (6-carbon sugars) is their uptake by cells, which requires the presence of distinct membrane-imbedded transporter (GLUT) proteins, as well as specific hexose-phosphorylating enzymes, such as glucokinase and fructokinase. Phosphorylation of internalized monosaccharides by these enzymes renders the sugars unrecognizable by GLUT proteins and prevents their exportation from the cell. Fructose, which exists predominantly as a 5-member furanose ring, is not recognized by the ubiquitous GLUT proteins (e.g. GLUT 4) that provide transport systems for glucose and other 6-member ring monosaccharides (e.g. galactose). Consequently, fructose metabolism can occur only in cells that express fructokinase as well as specific fructose transporter proteins such as GLUT 5. Both GLUT 5 and fructokinase are abundantly and predominantly expressed in the liver (in men they are also expressed in spermatozoa). Interestingly, the fructokinase activity in the liver is usually higher than the combined glucokinase and hexokinase activities. The abundance of hepatic fructokinase and GLUT 5 enables the liver to readily absorb large quantities of fructose from the portal vein; accounting for the low plasma levels of fructose after relatively high intake of this simple carbohydrate. In the liver, fructose is rapidly phosphorylated to fructose-1-phosphate which, unlike glucose-6-phosphate and other hexose-6-phosphates, cannot be catabolized by glycolysis. Instead, it is primarily utilized as a substrate for triglyceride (fat) synthesis (de-novo lipogenesis). The conversion of fructose to fat consumes ATP and explains the low Glycemic Index (GI) of fructose (5-fold lower than that of glucose). The GI of nutrients, a measure of their ability to elevate blood glucose levels, is inversely proportional to their effect on appetite reduction in the short-term (5). Hence, consumption of low GI nutrients (e.g. fructose and fat) induces satiety slower than intake of isocaloric amounts of high GI nutrients (e.g. glucose and starch), resulting in longer mealtime and increased food intake. The de-novo lipogenesis elicited by high dietary fructose also explains the similarity between the metabolic effects of high fructose intake and consumption of high-fat meals (6). Thus, similar to fat but unlike glucose, fructose does not stimulate pancreatic β-cells secretion of insulin, which in turn enhances leptin secretion from white adipose tissue. Insulin and leptin are important afferent signals conveying energy surplus and a decrease in their circulating levels is associated with increased caloric intake and body adiposity both in humans and animals. A comparison between the effects of high dietary fructose and glucose (served in mixed-nutrient meals as beverages sweetened with either fructose or glucose) showed that consumption of high fructose, but not high glucose reduces circulating insulin and leptin, increases plasma triglycerides, and attenuates postprandial suppression of ghrelin (6). Ghrelin is a stomach-derived orexigenic peptide whose plasma levels increase during fasting, decrease in response to food ingestion, and remain unchanged following consumption of water. This pattern suggests that ghrelin levels are regulated by ingested nutrients but not by gastric distension (7). The postprandial decrease in the circulating levels of ghrelin is slower in obese subjects than in lean individuals, which may contribute to differences in food intake (8). Elevated plasma ghrelin levels are found in Prader-Willi syndrome, which is associated with increased caloric intake and obesity (9). Human subjects who receive ghrelin intravenously demonstrate a 28% increase in food intake (10). Taken together, these findings suggest that ghrelin is an important stimulator of food intake, and that failure to suppress its postprandial levels may lead to overeating. They also implicate high dietary fructose, especially when derived from HFCS-sweetened beverages, as a major contributor to the accelerated rates of obesity in modern societies.

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