

FACTORS REGULATING BODY WEIGHT: ROLE OF THE NEURAL PATHWAYS OF INTEGRATION AND COORDINATION OF FEEDING AND ENERGY METABOLISM

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Obesity represents a growing threat for the health of the world population because it leads to a higher risk of developing disorders such as cardiovascular diseases and diabetes. Excess adiposity is a result of prolonged positive energy balance, and genetic and environmental factors are involved in its pathogenesis. In most cases, human obesity does not appear to be due to a single gene defect, but rather to effects of the environment upon a large number of susceptible genes. In addition, a neural network regarded as an "input-integration-output" system, residing in the hypothalamus, is implicated in the regulation of energy homeostasis. This central regulation involves the integration of humoral and afferent neuronal input to some hypothalamic nuclei - the arcuate, paraventricular, ventromedial and dorsomedial, and the dorsolateral area, as well as descending output commands through the brainstem and spinal cord, and via vagal and spinal neurons to the body. The hypothalamic projections to the caudal medulla and the spinal cord have the potential to stimulate or inhibit food intake, and regulate energy balance and ingestive behavior. Since obesity is due to a chronic imbalance between energy intake and energy expenditure, the most important issue in the prevention and treatment of this disorder is our understanding of the molecular mechanisms implicated in energy homeostasis. The complexity of such a neuroendocrine control system gives multiple possible key points of intervention with new drugs, which predominantly target the ingestive behavior. Thus, the behavioral therapy, together with diet and life style changes, is likely to remain the cornerstone ethiological treatment of the common obesity in the foreseeable future.

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INTRODUCTION

Obesity represents a growing threat for the health of the world population. Around the globe, more than half a billion people are overweight (1). Obesity becomes one of the major public health problems, mainly because it is associated with an increased risk of hypertension, cardiovascular diseases and diabetes. Development of effective therapy would require a detailed understanding of the physiology underlying the body weight regulation. Recently, significant advances have been made in our understanding of the mo-

lecular mechanisms regulating food intake and energy homeostasis, including the identification of the appetite regulating hormones, leptin and ghrelin, and their targets in and outside the central nervous system (CNS). By definition, obesity is an excessive accumulation of body fat, and from an anthropometric point of view, which is habitually used in the clinic, a person is considered obese when the body mass index (BMI) (weight (kg)/height (m²)) is equal to or higher than 30 (2). Indeed, obesity is a chronic disease that is much more than excessive fat. It involves genetic predisposition and metabolic, hormonal and behavioral aspects, and results in significant

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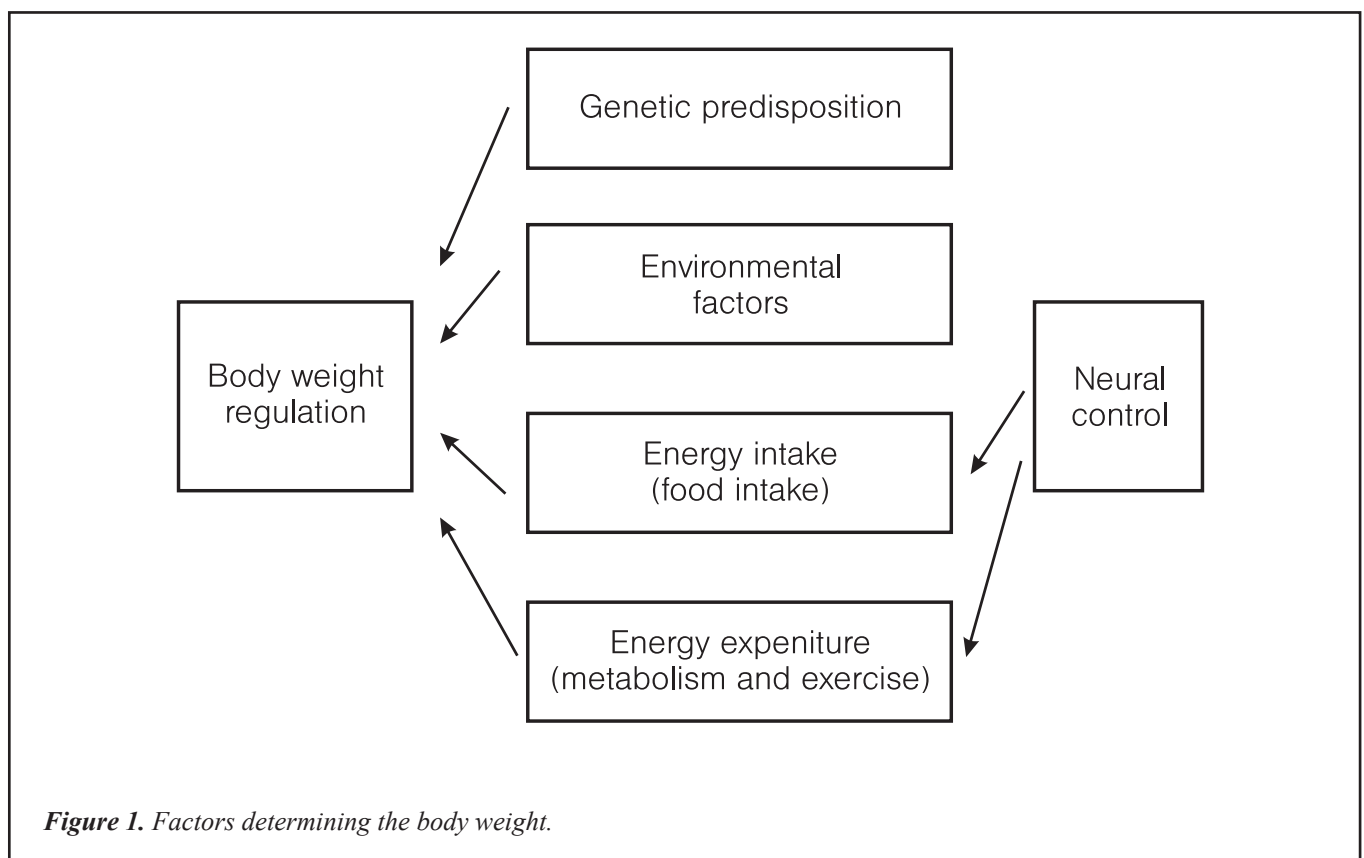
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morbidity, reduced quality of life, discrimination and early mortality. In general, the body weight depends on the genetic predisposition, environmental factors and neural control of metabolism (Fig. 1). It is precisely regulated as part of the process of energy homeostasis, a process whereby energy intake (food intake) is matched to energy expenditure (metabolism and exercise) and the size of the body's energy stores (the fat mass) (3). Feeding behavior involves the complicated integration of a large number of learning, memory, cognitive, emotional, somatosensorimotor and autonomic events. Therefore, obesity is very closely related to changes in the environment and life style.

ROLE OF THE GENETIC FACTORS

Multiple polymorphic genes encoding central and peripheral determinants of energy homeostasis have been revealed over the past decade. Twin, adoption and family studies have shown that genetic factors play a significant role in the pathogenesis of obesity, and heritability can account for as much as 70% of the variation in the BMI (4). The susceptibility to obesity is significantly determined by genetic factors, although an "obesigenic" environment is necessary for its phenotypic expression. From prospective studies in Pima Indians it was concluded that 12% of the variability in BMI are

ascribed to metabolic rate, 5% to fat oxidation, and another around 10% - to the level of spontaneous physical activity, which indicates that at least 40% of the variability in BMI are related to genetic factors involved in the regulation of food intake and/or volitional activity (1). In the last six years, a number of human genes have been identified in which major missense or nonsense mutations are sufficient in themselves to result in severe early-onset obesity, usually associated with the disruption of normal appetite control mechanisms (5). The number of genes and other markers associated with human obesity phenotypes is now well over 200, and many are expressed in the brain (6). Rare mutations in humans and experimental animals indicate that some of the genes involved in pathways regulating energy expenditure and food intake may play a role in the predisposition to obesity. Food intake control may be affected by polymorphism in the genes encoding taste receptors and a number of peripheral signaling peptides such as insulin, leptin, ghrelin, cholecystokinin (CCK) and their corresponding receptors. Polymorphic central regulators of energy intake include hypothalamic neuropeptide Y (NPY), agouti-related protein (AGRP), melanocortin pathway factors, cocaine- and amphetamine-regulated transcript (CART), some other neuropeptides, and receptors for these molecules (7). Potentially important polymorphisms in the genes encoding energy expenditure modulators are al-



pha- and beta-adrenoceptors, uncoupling proteins, and regulators of adipocyte growth and differentiation (7). However, *in vivo* studies of the variations in uncoupling proteins-2 and -3 have not yet demonstrated a physiological role for them which would explain how they are linked with obesity (8). Although obesity is a common phenomenon, only a small number of obese patients with mutated leptin or leptin receptor genes have been identified (9). An example of the relation of these genes to human obesity is given by the *ob* mouse, which carries a recessive autosomal disorder resulting in an inability of the adipose tissue to secrete leptin. Leptin signals to CNS for both food intake and energy expenditure, and in the homozygous *ob* mouse leptin deficiency resets the control mechanisms to the obese state (10). On the other hand, whilst mutations in leptin and the melanocortin-3 receptor are responsible for rare monogenic forms of obesity, their wider role in the common polygenic obesity remains unknown. For some types of obesity there are no genetic factors involved in their pathogenesis, as Milewicz *et al* (11) have demonstrated for menopausal obesity.

Results that have been replicated in at least three genome-wide scans suggest that key genes related to obesity are located in chromosomes 2p, 3q, 5p, 6p, 7q, 10p, 11q, 17p, and 20q (12). Based on the currently available data, Loos and Bouchard suggest four levels of genetic determination of the increased body weight: genetic obesity, strong genetic predisposition, slight genetic predisposition, and genetically resistant (12). This growing body of information yielded by human genetics provides insights into the critical molecular components of energy balance regulatory systems, pointing the way toward more targeted and effective therapies. It may help in the development of genetic tests to predict the risk for individual abnormal responses to environmental influence.

ROLE OF THE ENVIRONMENTAL FACTORS IN THE BODY WEIGHT REGULATION

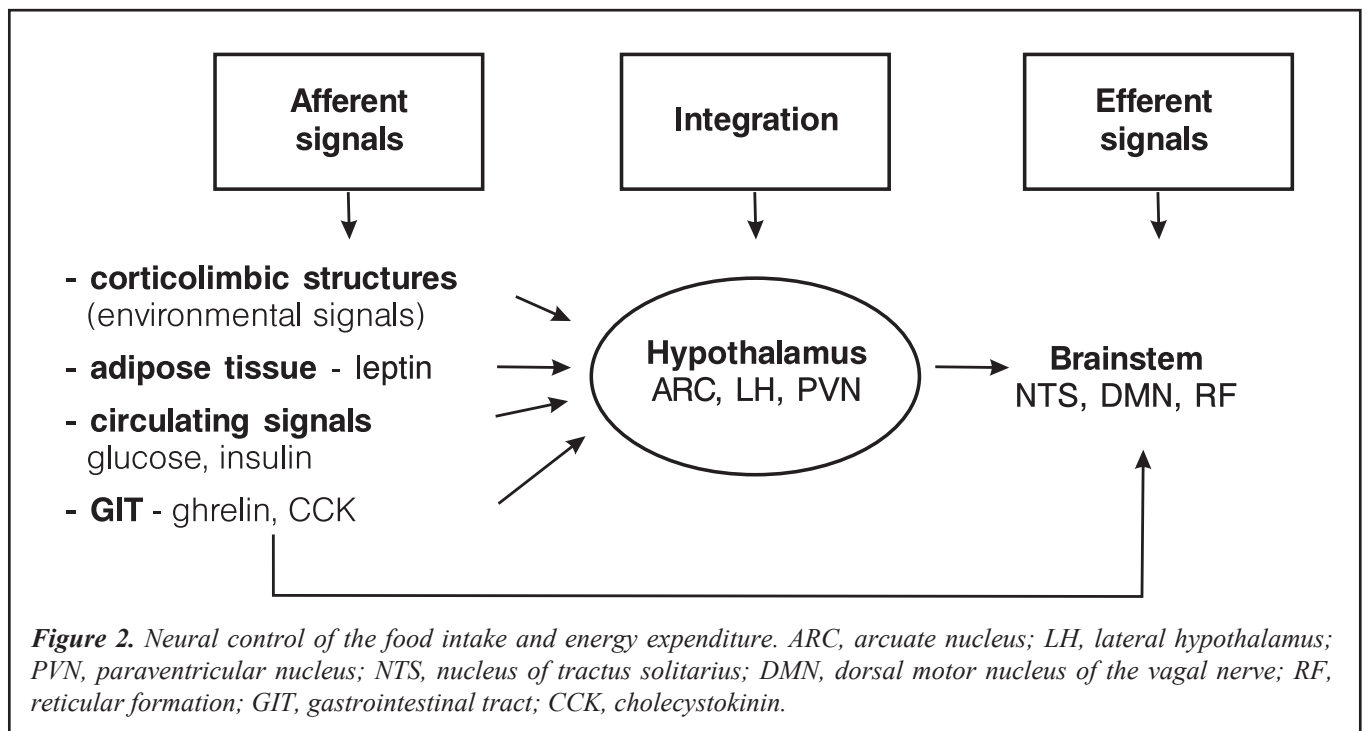
Rather than one single factor or hormone, a number of factors are responsible for the long-term steady energy balance and metabolic fluxes (4,13). In most cases, human obesity does not appear to be due to a single gene defect, but rather to effects of the environment upon a large number of susceptible genes. Thus, obesity should mainly be regarded as an environmental problem, in that the "thrifty genes" that optimized genetic energy assimilation and conservation and were favored for millions of years of relative famine are now a liability in the food-drenched environment of affluent societies (4,14,15). The genetic makeup of human beings, which reflects this long history of relative scarcity of foodstuffs, has run into an age of surfeit, and many people cannot readily adapt. Thus, the increased intake of food does not signal satiety, and there is a gradual increase in energy stores since the intake of energy outpaces one's needs as one grows older

(16). Aggressive advertisement and the availability of highly palatable and calorically dense foods are some of the components of a new obesigenic environment (17) that may overwhelm endogenous systems regulating energy homeostasis. The "liking" and "wanting" associated with this increased awareness and availability of food is thought to be processed in corticolimbic structures such as the prefrontal cortex, amygdala and ventral striatum (18), whereas homeostatic controls have been mainly assigned to the hypothalamus (19). Therefore, "crosstalk" between the two systems might be critical for the understanding how environmental factors can overrule the neuronal regulatory mechanisms (20).

ROLE OF THE NEURAL CONTROL IN THE FOOD INTAKE AND ENERGY EXPENDITURE

The body weight and composition depend on three inter-related and self-controlled components: (i) food intake, (ii) nutrient turnover and thermogenesis, and (iii) body fat stores (21). Although obesity has strong genetic determinants, it is generally accepted that it results from an imbalance between nutrient intake and daily physical activity. In addition, it was only recently that studies identified important new molecular mechanisms involved in the regulation of body weight. The main organ regulating the body mass is the brain, although multiple organ systems are implicated in this process. The basic principles of the neural control mechanisms are elegantly outlined in a review by Berthoud (4), where these are depicted as an "input-integration-output" setup (Fig. 2), despite the difficulties to determine any clear boundaries between these three parts of the regulatory system. The neural control can be illustrated with the hourglass: a large degree of convergence of sensory inputs has to pass through a narrow part or bottleneck (processing), followed by a wide divergence of motor outputs (4). Considering that the major cause of the most human obesities is the modern lifestyle, it may be assumed that "the battle" is between brain areas controlling internal metabolic homeostasis and those dealing with cognitive and emotional processing of external information, i.e. the interaction between the homeostatic and non-homeostatic systems (22).

Research in mammals has established the existence of a neuronal network that resides in the hypothalamus and regulates appetite and energy homeostasis (23,24). Specific neuronal peptidergic populations in the medial hypothalamus can be considered metabolic integrators sensing both short- and long-term availability of fuels, and in turn connecting with various other brain regions to orchestrate adaptive responses through changes in food intake, as well as with endocrine and autonomic responses (22). The ventromedial hypothalamus (VMH) was identified as the satiety center and the lateral hypothalamus (LH) as the hunger center (25). Other areas of the brain known to play a role in the regulation of food intake



in animals include the thalamus, a relay center for taste perception and learning, and the limbic areas, related to behavioral regulation (20) and arousal during a meal (26). Little is known about the regions of the human brain involved in the control of food intake, and the bulk of information has been inferred from pathological conditions (27). It has been shown that the anterior and middle parts of the insular cortex are involved in the response to hunger or satiation (28), while the dorsolateral and medial prefrontal cortex participate in the inhibition of excessive food consumption (29). Using positron emission tomography Tataranni *et al* found postmeal neuronal activity in parts of the brain, not previously associated with the regulation of food intake, such as the putamen and cerebellum (30).

The concept that humoral signals generated in proportion to body energy stores provide negative feedback to brain areas controlling food intake and energy expenditure was first proposed by Gordon Kennedy some 50 years ago (31). Two classes of feedback signals are involved in the regulation of the body weight as a result of food ingestion (32). One type is related to the amount and quality of food ingested, and consists of neural afferent signals from the gastrointestinal tract and psychosocial conditioning factors. These short-term signals operate on a meal-to-meal basis and determine the amount of food ingested in a single meal (satiety signals). The second type of feedback signals is also sensitive to nutrient intake but is modulated by adipose tissue mass (adiposity signals)(33), referred to as long-term controllers of adiposity (34). Circulating adiposity signals are integrated with the sa-

tiety signals to control energy homeostasis (35). Insulin and leptin are hypothesized to be adiposity signals for the long-term regulation of body weight by the brain. Leptin (from Greek *leptos*, meaning thin) belongs to the group of adipokines (adipose tissue-secreted molecules) (36) which constitute a complex network of multifunctional mediators implicated in various neuroimmune, adipoimmune, inflammatory, vascular and metabolic events (37,38). Leptin was discovered at the end of 1994 (39), and was recently described in the human subcutaneous preadipose cells at a very early stage of embryogenesis (6-10 weeks), which suggests its significance to the fat mass formation (40).

In addition to leptin and insulin, another hormone, ghrelin, was established as a signal participating in body-weight regulation (41,42). Ghrelin (*ghre-* is the proto-Indo-European root of the word *grow*), is a 28-amino acid acylated peptide produced primarily by enteroendocrine cells in the stomach, probably the X/A-like cells. The latter represent a major endocrine cell population in the oxyntic mucosa, whose hormonal product has not previously been clarified (43). Ghrelin displays strong growth hormone (GH)-releasing activity mediated by activation of the GH secretagogue receptor 1A (44). It may be a crucial element of the neurohumoral system, serving to integrate the energy needs of the body and the growth process. Studies in rodents indicate that this hormone plays an important role in signaling hypothalamic centers which regulate feeding and caloric state (45), and its

orexigenic (appetite stimulating) and adipogenic activities contribute to energy balance (46). In 75% of treated subjects, ghrelin enhanced the sensation of hunger and reduced fat depot utilization, increasing carbohydrate consumption through the mediation of gamma-aminobutyric acid (GABA) and the inhibition of anorexigenic substances such as alpha-melanocyte stimulating hormone (α -MSH) (46). This humoral orexigen participates in meal initiation, and ingested nutrients acutely suppress ghrelin levels (47). Because its circulating levels increase before and decrease after each meal, ghrelin is implicated in the short-term control of pre-meal hunger (48). Ghrelin is the only gastrointestinal peptide which stimulates food intake and is active even if administered peripherally, while the other orexigenic peptides are devoid of action *via* peripheral mechanisms (46). Ghrelin had been thought to enter the brain across the blood-brain barrier, although a recent study demonstrates that intraperitoneal ghrelin administration after vagotomy does not stimulate food intake (49). In rodents, exogenous ghrelin induces weight gain by increasing food intake and reduction of fat utilization (50,51). In humans, circulating ghrelin levels are decreased in chronic (obesity) and acute (feeding) states of positive energy balance, while its plasma levels are increased during fasting and in patients with *anorexia nervosa* (52). These actions are GH-independent and are most likely mediated by a specific CNS neuronal network that is also modulated by leptin: ghrelin and leptin might be complementary partners in the regulatory system that informs CNS about the status of energy balance (50,51). The observation that in obesity leptin levels are elevated while ghrelin levels are decreased compared to age-matched lean control subjects, suggests their adaptation to the positive energy balance rather than an involvement in the etiology of obesity (53). In addition, ghrelin plasma concentrations are significantly lower in Pima Indians than in Caucasians (51).

Substantially lower amounts of ghrelin are produced by the small intestine, pancreas, kidney, placenta, testis, ovaries, and hypothalamus (50). Besides its GH-releasing and orexigenic actions, ghrelin exerts other remarkable effects, including control of gastric motility and acid secretion, cardiovascular actions, antiproliferative effects in neoplastic cell lines, influence on pancreatic function and glucose metabolism, stimulation of lactotroph and corticotroph secretion, influence on sleep, and action on gonadal activity (50,54,55). Recent results indicate that at least some of the feeding and energy regulatory effects of ghrelin might be mediated by brain-derived ghrelin, rather than ghrelin from the stomach (56). Cowley *et al* (57) showed that ghrelin is expressed in a previously uncharacterized group of neurons in the hypothalamus, located in the space between the lateral hypothalamic, the arcuate (ARC), ventromedial (VMN), dorsomedial (DMN) and paraventricular (PVN) hypothalamic nuclei, and

they send projections to several of these nuclei as well as outside the hypothalamus. Adiponectin is another hormone recently discovered in adipose tissue, which exhibits the same effect as ghrelin in enhancing hunger and carbohydrate metabolism. Adiponectin, however, increases insulin sensitivity and reduces hyperglycemia, whereas ghrelin suppresses insulin secretion (58).

In laboratory animal models, the hypothalamus was shown to be a major center for the regulation of food intake (59). Different parts of the hypothalamus are involved in energy balance albeit ARC is generally thought to be the most likely CNS site for leptin adiposity signaling to the brain (4,60). Indeed, the signaling is mediated by more than a dozen peptides that individually exert anabolic or catabolic effects when experimentally administered into the brain (35). ARC has leptin binding sites (61) and appears to be a special CNS location where leptin has access to the brain by a saturable system independent of insulin (62). Specific targets of leptin in ARC are neurons expressing NPY, AGRP, pro-opiomelanocortin (POMC), and CART. Leptin inhibits expression of NPY and AGRP (63,64), both of which are potent stimulators of food intake. On the other hand, leptin increases the expression of the POMC-derived peptide α -MSH (64,65), and CART (66), which induce an anorexic response. Insulin also inhibits ARC expression of NPY and has central anorexic effects (67), but its effects on the other hypothalamic signaling systems are not well known (68). Insulin may potentially influence food intake by acting on brain catecholaminergic pathways (69). The hormone acts on the presynaptic norepinephrine (NE) and dopamine (DA) transporters, which interrupt NE and DA signaling in the presynaptic nerve endings (70) since insulin decreases NE uptake (71) and facilitates DA uptake (72). Specific effects of NE and DA on the regulation of body weight have not been identified, although effects on the food intake by the manipulation of these transmitter systems have been described (73). DA transmission is important in the rat brain for the rewarding and motivational components of food intake (74). Insulin may also influence food intake by acting on other non-peptide classical neurotransmitter systems including GABA, glutamate, and serotonin systems (68).

Other hypothalamic areas sensitive to leptin and insulin and involved in the food intake regulation with their multisynaptic projections to the brainstem are VMN and DMN (75). Furthermore, leptin binding sites are found in the rat cerebral cortex, pyriform cortex and thalamus (60). Similarly, insulin receptors are widely distributed in non-hypothalamic brain regions including the olfactory bulb, hippocampus and dentate gyrus, cerebral cortex, cerebellum, and brainstem (76). The physiological roles of leptin and insulin in these non-hypothalamic regions have not been extensively studied, and it is not certain yet whether their action there has any relationship to food intake and body weight (68).

Specific targets of ghrelin are neurons in ARC and LH (77). Ghrelin activates approximately 40% of the NPY/AGRP-positive ARC neurons (42), which express ghrelin receptor mRNA (78). Ghrelin receptor mRNA is also present in the LH of rats (79). Intraventricular administration of ghrelin induces activity in 23% of orexin (hypocretin)-immunoreactive neurons, but not in melanocyte concentrating hormone (MCH)-expressing hypothalamic cells, and this activation of orexinergic neurons is in a manner independent of NPY (77). Therefore, ghrelin is likely to interact with both NPY and orexin systems to induce feeding. Centrally administered ghrelin strongly induces neuronal activity in the hypothalamus, brainstem, hippocampus and dentate gyrus, and piriform cortex (42), which suggests that ghrelin may regulate feeding and energy homeostasis not only through direct activation of orexin and NPY pathways, but also *via* effects on other events integrated in the feeding behavior, such as learning, memory, mood and emotions.

HYPOTHALAMIC CONNECTIONS WITH OTHER BRAIN AREAS

LH, traditionally viewed as a phylogenetic continuation of the reticular formation, governs many functions such as feeding, blood pressure, neuroendocrine axis, thermoregulation, sleep-waking cycle, emotion, sensorimotor integration and reward processes (80). Of all its diverse roles, feeding behavior regulation is a major one, which is strongly supported by the recent discovery that LH contains at least two major orexigenic peptides, orexins (81) and MCH (82). Energy metabolism is also thought to be critically controlled by LH, as it contains a population of neurons which are sensitive to glucose levels and are activated by hypoglycemia (80). It may be that some orexin-positive neurons are the anatomical substrate of the hypothalamic glucostate (83,84) rather than the formerly suspected MCH neurons (85).

The PVN, LH with the adjacent perifornical area (PFA), and VMH receive a rich innervation from ARC, and thus they are related to the ingestive behavior, energy balance and body-mass regulation. The concept developed is that of a dual-control center of feeding, with LH more closely associated with the initiation of eating (thus being the feeding center) and VMH responsible for its cessation (satiety center) (80). The parvocellular part of the paraventricular nucleus (pPVN) is also included in the suppressing mechanism (86). LH and PFA have neuronal populations expressing orexin (hypocretin) and MCH. Orexin-A and orexin-B are two novel neuropeptides discovered in 1998 (81,87), proteolytically derived from the same precursor protein (81). They facilitate feeding behavior and also play important roles in maintaining energy metabolism, hormone homeostasis, cardiovascular function, and sleep-wake regulation (81,88). Orexin-producing neurons are almost exclusively distributed within and around LH, DMH and PFA (87), although orexin-immuno-

reactivity (IR) is also reported in the enteric nervous system, the pancreas (89), and the testis (81). Central orexin administration stimulates feeding (81) and drinking (90), and affects behavioral satiety (91). Although orexinergic perikarya are restricted exclusively to the LH, their fibers are broadly distributed in CNS (92). These results indicate that orexinergic neurons link hypothalamic control regions to many other essential autonomic brain centers, and LH plays an important role in the integration of the complex physiology underlying feeding behavior and other autonomic functions (94). The hypothalamic orexinergic projections reach the brainstem mesencephalic trigeminal nucleus (MTN) and the trigeminal motor nucleus (Vmo) (92,95), where Zhang and Luo (96) have demonstrated synaptic contacts on the trigeminal sensory and motoneurons. These MTN and Vmo neurons innervate the jaw-closing and a part of the jaw-opening muscles, and they constitute a neuronal circuit of the mastication control (97), an executive part of feeding behavior. These studies suggest that the masticatory behavior is under a direct control of the hypothalamic orexinergic neurons (96).

Another target for the hypothalamic orexin-containing neurons is the nucleus of *tractus solitarius* (NTS), located in the dorsomedial medulla oblongata and widely accepted as a pivotal brain region involved in the integration of cardiovascular, respiratory, gustatory, hepatic, and renal control mechanisms (98). NTS has bi-directional connections to the hypothalamus and to many other CNS areas including essential autonomic control centers in the midbrain and spinal cord (99).

MCH is a cyclic heptadecapeptide, first isolated from the pituitary of the teleost, where it plays a role in adaptive changes in the pigmentation of this lower vertebrate (100). MCH may be used as a marker to probe the topographical connectivity of LH and *zona incerta* in relation to the complexity of their functional organization (101). MCH axonal projections ramify broadly throughout CNS reaching nuclei in the medial septum, which are considered as part of the limbic system and implicated in processes such as motivation, ingesting behavior, learning (102), emotion (103), and regions in the spinal cord participating in somatosensory, autonomic and somatomotor functions (104). MCH cells directly innervate critical regions of the amygdala, thalamus, autonomic preganglionic neurons, and the cerebral cortex, thus linking the mediobasal satiety and lateral hypothalamic feeding centers (105). These projections may underlie some of the extremely complex responses associated with hunger, food intake and satiety. Orexin and MCH stimulate food intake, show an increased expression under leptin-deficient conditions (32), and are inhibited by leptin (106). Indeed, in both areas there is an abundance of NPY containing fibers adjacent to orexin and MCH neurons (107). Some of the NPY/AGRP- and POMC/CART- positive fibers originate

from ARC, although NPY input to LH and PVN probably also arises in the medulla where NPY is co-localized with catecholamines (108).

The vagal afferent fibers are the major neuroanatomical link between the alimentary tract and NTS in the hindbrain, where the afferent input is integrated with descending hypothalamic input and ascending output to the hypothalamus is produced (109,110). The meal-related satiety signals are transmitted to NTS *via* the vagal nerve or to the hypothalamus *via* the bloodstream. The afferent vagal discharge is suppressed by ghrelin, whereas CCK, an anorectic peptide produced by enteroendocrine cells in the intestine (111) stimulates it (112). The satiety action of CCK is enhanced by leptin and insulin (113-115), and results in smaller meals with the cumulative effect of reduced body weight. This suggests the existence of central autonomic pathways between the hypothalamus and the caudal brainstem that specifically integrate the reception of insulin and leptin adiposity signals in ARC with the processing of vagally-mediated meal-related signals to the caudal brainstem. Based on this, Baskin *et al* (68) hypothesized that the mechanism of this interaction involves the primary action of leptin and insulin on subsets of NPY- and POMC-IR neurons in ARC projecting to PVN and LH, which have direct descending connections to caudal brainstem centers regulating the meal size (116,117). These PVN and LH perikarya projecting directly to NTS in the medulla have been identified as oxytocin (OXY)- and corticotropin releasing hormone (CRH)- IR neurons (117). Another subpopulation of LH neurons projecting directly to the medulla has been identified as orexin- and MCH- IR (93,118).

The brainstem is sensitive to the neuronal and humoral signals from the gastrointestinal tract. It is able to react and regulate the size of an individual meal even if it is completely transected and disconnected from the hypothalamus (119), an effect which is blocked by vagotomy (120). Food ingestion elicits a burst of rapidly-acting neural, endocrine, and duodenal nutrient signals converging on the caudal brainstem and resulting in the termination of a meal (121). Meal-related signals are conveyed to NTS and the dorsal motor nucleus of the vagus (DMN) *via* the vagus nerve and other routes (121). The intestinal enterochromaffin cells release CCK, which binds to vagal terminals in the gut (122) ending in the caudal brainstem (123), and this consequently leads to meal termination (124). Intraventricular or intraperitoneal infusion of insulin (125) or leptin (113) enhances the satiety response to CCK. Furthermore, reduced leptin signaling attenuates the satiety effect of CCK (126). It is hypothesized that leptin- and insulin-responsive circuits in the hypothalamus project to the caudal brainstem neuronal groups and these hypothalamic projections potentially increase the brain's motor and autonomic responses, leading to smaller individual meals, reduced cumulative food intake, and lower body weight (33).

Thus, the communication between the hypothalamic circuits that respond to changes in adiposity signals, and those in the caudal brainstem that respond to meal-generated signals are essential for the long-term regulation of energy homeostasis and adipose tissue mass (68).

The central melanocortin system is an important component in the regulation of the energy balance and manipulations on this pathway can lead to the development of obesity in several animal models (127). Melanocortins are small peptides such as α -, β - and γ -MSH, ACTH, β - and γ -endorphin encoded by the POMC gene (128,129). The peptides most strongly implicated in this regulatory process are AGRP and α -MSH. Recent evidence suggests that the hypothalamic melanocortin system is directly influenced by leptin to regulate food intake (65). Together with the genes encoding NPY, vasoactive intestinal peptide (VIP) and prepro-orexin, POMC gene expression is very sensitive to fasting. AGRP gene expression and the NPY gene response are stimulated by food deprivation (130). This implies an important role for this signaling pathway in the control of energy balance during the vertebrate evolution. In contrast, no significant change in POMC gene expression is observed after fasting in birds (131), while in mammals food deprivation has no effect on the POMC gene activation (132). There is a lack of *VIP* or *orexin* gene expression after fasting in birds, which may reflect interspecies differences in the regulation of carbohydrate metabolism, and suggests that orexin may fulfill different physiological functions in birds (131).

CONCLUSIONS: THERAPEUTIC IMPLICATIONS

The neuroendocrine control system upon energy homeostasis is complex, with multiple possible points of intervention. Drug treatments have so far had limited efficacy and some have shown serious side effects. Most types of treatment tried over the years produce a rapid decrease in body weight before a plateau is reached. This plateau occurs because, as body weight decreases, the metabolic rate also decreases and there are reduced levels of adiposity signals feeding back to the brain, which tends to cause increased food intake (3). Because of this complexity of the energy control system, therapeutic plans involving two or more processes will be more effective than those that intervene at one point only. The existing adiposity signals communicating the status of fat stores to the brain are obvious targets for novel drugs that could address either obesity or wasting disorders, conditions for which existing therapies are remarkably limited and ineffective. It should be remembered, however, that pharmacotherapy for obesity is unlikely to provide a "magic bullet", which can strike the central control mechanism and make permanent changes in the body weight with either no adverse effects, or so few side effects that the biological price would be acceptable. Therefore, diet and lifestyle changes are likely

to remain the cornerstones in the treatment of obesity in the foreseeable future.

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