Regulation of Energy Intake

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Obesity is considered one of the leading health issues and is becoming a global epidemic that is rising worldwide [1]. Overweight and obesity depend on the unbalance between energy intake and expenditure, and there is no doubt that food intake is controlled by internal signals [2]. Since food and then energy intake is a behaviour, it must be mediated by the brain. Although many different regions of the brain have been shown to be involved in the control of daily intake, several studies have demonstrated that two main regions, the ventromedial hypothalamus (VMN) and the lateral hypothalamus (LH), are critically involved in the control of food intake and body weight [2]. The dual-centre hypothesis in the central control of energy balance originates from the first observations performed more than six decades ago with specific brain regions damage and stimulation experiments. On the basis of these studies the "satiety centre" was located in the ventromedial hypothalamic nucleus (VMN), since lesions of this region caused overfeeding and excessive weight gain, while its electrical stimulation suppressed eating. On the contrary, damage or stimulation of the lateral hypothalamus (LH) elicited the opposite set of responses, thus leading to the conclusion that this region represented the "feeding centre" [3, 4]. The subsequent expansion of our knowledge of specific neuronal subpopulations involved in energy homeostasis has replaced the notion of specific "centres" controlling energy balance with that of discrete neuronal pathways fully integrated in a more complex neuronal network [5].

The advancement of our knowledge on the anatomical structure and the function of the hypothalamic regions reveals the great complexity of this system. In this brief overview, we will focus on the knowledge of the main central and neurohormonal mediators involved in the control of energy balance and their possible role in the pathophysiology of obesity.

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2.1 Control of Energy Metabolism by Circadian Clocks

In the vast majority of living organisms, synchronous oscillations of biological parameters can be detected, most of them paralleling the night and day, sleep and waking, rest and activity and feeding and fasting cycles. This is an intrinsic characteristic of each cell of the body to coordinate and integrate all the metabolic, hormonal, immune, neurological and many other functions of the body with the environmental daily, monthly or yearly rhythmic oscillation and cycles. This finely tuned mechanism in humans and all other living organisms involves an intrinsic machinery that tracks time in approximately 24-h cycles being controlled by a series of genes that are down- and upregulated in a closely coordinated feedback loop. The importance of the circadian clock in the control of energy metabolism has been clearly demonstrated, but the detailed mechanisms are far to be elucidated. The complexity of mammalian circadian system is explained by the presence of multiple cellular clocks located in the different tissues. In the hierarchical organization, the master regulator is the suprachiasmatic nuclei (SCN), which synchronizes the downstream organs and tissue clocks using neuronal, endocrine and metabolic signalling pathways that influence the molecular machinery of cellular clocks. Disruption in this synchronization may contribute to the development of diseases such as obesity. This disruption could arise from insensitivity of the suprachiasmatic nucleus and the pineal clock to sense the light and release melatonin according to the circadian cycle. Peripheral hormones as ghrelin, leptin, insulin, corticosteroids and adrenalin affect or are affected by the master clock and a reciprocal alteration could result in a disruption of the coordinated cycling of the metabolic control during the day. Moreover metabolic fuels as glucose, fatty acids, amino acids, lactate and ketone bodies could act as signals having deep influence in the right functioning of the central clock which in turn could influence peripheral organ metabolism throughout specific neuronal connections. In order to understand the clock systems, a useful distinction in three major steps could be taken into account both at the cellular and at the systemic level: (1) the input to the system, (2) the intrinsic mechanisms linked to the clock function and (3) the output system. The clock mechanism consists of two main parts: (1) a transcriptional–translational feedback loop (TTL) consisting of a positive and a negative branch and (2) oscillating post-translational modification of gene products in the TTL, which regulate degradation and/or nuclear localization of these proteins. The positive and negative branches are intertwined via clock protein-driven nuclear receptors and their interactions with period circadian protein homolog 2 (PER2), a component of the negative limb. Per2 is an integral component of a glucocorticoid regulatory pathway involving peripheral clock selectively required for some actions of glucocorticoids. A metabolic oscillator is driven by the TTL and feeds back on it via SIRT1 which stands for sirtuin (silent mating type information regulation 2 homolog) 1, an enzyme that deacetylates proteins that contribute to cellular regulation. The promoter elements in clock-controlled genes (CCGs) are regulated either directly or indirectly. (1) Direct regulation via Circadian Locomotor Output Cycles Kaput (BMAL/CLOCK) functions as an essential activator of downstream elements in the pathway critical to the

generation of circadian rhythms by binding at E-boxes or via the nuclear receptors REV-ERB and retinoic acid receptor-related orphan receptors (RORs), which are involved in many physiological processes, including regulation of metabolism, development and immunity as well as the circadian rhythm, by binding at RORE elements and (2) Indirect regulation via binding of clock-regulated circadian transcription of proline- and acidic amino acid-rich basic leucine zipper (PAR-B-ZIP) transcription factors like Dbp (D-element-binding protein) on D-elements or via protein–protein interactions between period circadian protein homolog 2 (PER2) and nuclear receptors at nuclear receptor elements (NREs) such as ROREs [6]. The light–dark cycle is for sure one of the major determinant of the circadian clock. Light signals are directly conveyed to three units in the brain: (1) centres which control timing, such as the SCN and pineal gland; (2) centres devoted to the metabolic integration, such as the subparaventricular zone (sPVZ); and (3) centres which control rewarding, such as the habenula (HB). Light sensing and the subsequent neuronal messages are indirectly transmitted from the SCN which in turn projects to areas devoted to the metabolic integration including the paraventricular nucleus (PVN), sPVZ, dorsomedial hypothalamus (DMH) and arcuate nucleus (ARC). The pineal gland also transmits light information to the HB. Anorexigenic signals as leptin and orexigenic signals as ghrelin primarily affect the ARC, which is important for the metabolic integration of feeding signals, and the ventral tegmental area (VTA), which is important for the integration of reward. The centres important for metabolic and reward integration exchange information with each other and can affect the SCN and pineal gland timing centres. Light and feeding signals combine and contribute to motor coordination and activity [7]. It is therefore well defined that circadian programming mechanisms regulating food intake are crucial in maintaining energy homeostasis [8] and that the development of most of the metabolic disorders could be due to clock genes disruption [9].

2.2 The Arcuate Nucleus

The arcuate nucleus (ARC) is one of the most important brain regions involved in the control of energy homeostasis. It is located in the mediobasal hypothalamus, adjacent to the floor of the third ventricle. Neurons in the ARC express receptors for a variety of hormones known to affect food intake, such as leptin, cortisol, oestrogen, progesterone and growth hormone [10], and the permeability of blood–brain barrier of this part of the brain [11] allowing the passage of these signalling molecules into the brain. Moreover the ARC, like other hypothalamic nuclei (dorsomedial hypothalamic nucleus [DMH], paraventricular nucleus [PVN], VMH and LH), contains neurons that are thought to represent the central glucose sensor element [12], but their action may also be affected by other circulating metabolites, such as FFA [13]. Then the ARC may be viewed as a “metabolic sensor”, since it receives and integrates endocrine and metabolic information arriving from periphery concerning the body nutritional and energetic status.

The ARC houses a number of neurons which can be differentiated on the basis of their signalling molecule expression. A first population of cells co-express two neuropeptides which have been strongly implicated in the control of food intake and energy homeostasis that are NPY and AgRP [14]. Two other important signalling molecules, POMC and CART, are co-localized in a distinct, but adjacent, subset of ARC neurons [15].

2.3 Neuropeptide Y

NPY is a 36 amino acid orexigenic peptide with many other endocrine and behavioural effects [16]. It belongs to the pancreatic polypeptide (PP) family, and it is considered the most abundant neuropeptide in the brain [17], the ARC nucleus being the major hypothalamic site of NPY expression. A dense projection is directed to the PVN, but other less dense projections are directed into other nuclei [18]. PVN also receive afferent NPY-containing fibres from catecholaminergic nuclei in the brainstem [19]. NPY is also released locally in the ARC and regulates the NPY/AgRP neurons in a ultrashort loop feedback acting on NPY-Y2/NPY-Y4 receptors [20].

Four different NPY receptors have been recognized in human named NPY-Y1, NPY-Y2, NPY-Y4 and NPY-Y5 that are widely distributed in the hypothalamus [21]. Selective receptor antagonists and the administration of antisense oligonucleotides directed against the different Y receptor subtypes were recognized to inhibit both NPY-induced food intake and the abnormalities of feeding behaviour present in genetically obese animal models [22] although conflicting results have been obtained with other experimental approaches using different putative selective antagonists [23].

2.4 Neuropeptide YY

Neuropeptide YY (PYY) belongs to the NPY and PP family [24]. It is 70 % identical to NPY in mammals, and it was first identified as a gastrointestinal hormone, but it has subsequently been found to occur in neurons. Peptide YY3-36 (PYY3-36) is released from the gastrointestinal tract postprandially in proportion to the calorie content of a meal [25].

In contrast to the well-established functions of NPY, the role of PYY in the nervous system remains obscure. Experiments carried out in humans by intravenous injection of physiological doses of PYY3-36 lead to a significant reduction of appetite and food intake. All these data taken together lead to hypothesize that the elevation of PYY3-36 observed after a normal meal may act through the ARC Y2 receptor to inhibit feeding, thus suggesting at that time the existence of a new important gut–hypothalamic axis as demonstrated successively (see below).

2.5 Agouti-Related Protein

Agouti-related protein (AgRP) is a peptide with orexigenic properties [26], which mRNA and protein can be found in virtually all NPY-expressing cells of the ARC, but not in any other brain region [18]. As with NPY, AgRP synthesis is increased in response to leptin deficiency and during fasting and is inhibited by leptin treatment [17]. The icv AgRP administration, as well as the overexpression of AgRP in transgenic mice, stimulates feeding and induces obesity, and its expression is significantly elevated in genetic models of obesity in mice [27]. AgRP is thought to influence feeding by blocking the action of α-MSH at the melanocortin receptors MC4 and possibly MC3 [28]. However, AgRP's orexigenic action is still potent at long term after melanocortin receptor blockade, indicating the existence of alternative mechanisms for its orexigenic action.

2.6 Pro-opiomelanocortin

Pro-opiomelanocortin (POMC) is the precursor of a number of peptides, including α-MSH and ACTH. It is expressed in the ARC, and many of its effects on energy balance appear to be mediated by α-MSH, which exerts its action by binding to members of a family of melanocortin receptors [29]. In rodents, stimulation of MC3 and MC4 receptors suppresses feeding behaviour, whereas binding of these receptors with synthetic ligands stimulates eating [30]. Moreover the POMC-null mutant mice progressively develop obesity [31], which can also be obtained by targeted deletion of melanocortin receptor gene MC3 and MC4 [32]. In humans abnormalities in both the MC4-R gene and the POMC gene are associated with severe obesity [33] indicating that tonic signalling by MC4 receptor limits food intake and body fat mass. The deletion of the MC3-R gene leads to a different phenotype, having the mutant mice a weight close to the wild-type animals but an altered body composition characterised by an increased fat mass and reduced lean mass. Thus, contrary to what is observed in the MC4-deficient mice, the obesity due to MC3 receptor gene deletion results more from altered metabolism and energy partitioning than to feeding changes. Current available data suggest that MC3 and MC4 receptors have different nonredundant functions in energy homeostasis. As a matter of fact, mice lacking both types of receptors are more obese than the MC4-R-deficient mice, showing therefore additive effects of the two deletions.

2.7 Cocaine- and Amphetamine-Regulated Transcript

Cocaine- and amphetamine-regulated transcript (CART) is a anorectic factor, which is produced in the ARC but also in the PVN, dorsomedial (DMN) and other hypothalamic nuclei [34] and inhibits feeding when administered icv. Hypothalamic

CART peptide and mRNA levels are decreased in fasted rats, genetically obese ob/ob mice, which are leptin deficient, and fa/fa Zucker rats, characterized by a defective leptin receptor [35]. CART is co-expressed with POMC in a subpopulation of neurons in the ARC and distributed to the LH, PVN and preganglionic sympathetic neurons in the thoracic spinal cord. These neurons respond directly to circulating leptin, and it is possible that CART and POMC mediate the inhibitory effect of leptin on food intake.

A majority of both NPY/AgRP and POMC/CART neurons co-express leptin receptors. NPY/AgRP neurons are inhibited by leptin and activated by low leptin levels. Similarly these neurons seem to be activated also by insulin deficiency [36], and insulin receptors have been found to be highly concentrated in the ARC [37]. On the contrary, conditions characterized by insulin or leptin deficiency inhibit POMC and CART expression in the ARC, while the administration of these hormones can prevent or reduce these neuropeptide responses [38]. Taken together, these data indicate that the ARC represents a major site for transducing peripheral adiposity signals, such as leptin and insulin, into a neuronal response.

2.8 Neurotransmitters and Peptides Mediating Appetite Stimulation

Urocortins are a family of CRH-related peptides identified in humans, rodents and other mammalian species. The administration of urocortin into the PVN decreases feeding [39]. Urocortin III distribution in the brain differs from that of CRH and includes the VMH, lateral septum and other areas known to express high levels of CRH-R2, suggesting that urocortin III is the endogenous ligand for this receptor in these areas [40].

TRH, apart from its role in pituitary–thyroid axis, inhibits feeding and drinking when injected icv; its metabolite cyclo(His-Pro) produces a long-lasting reduction in food intake and body weight in rats [41]. The NPY-TRH connection is thought to be mediated through the Y1 receptor, and it has been shown that icv NPY administration can decrease plasma levels of thyroid-stimulating hormone, which links TRH with the thyroid hormones [42].

Orexins A and B are encoded by the same gene and produced in the same regions by a population of neurons separate from MCH. Icv injection of orexin stimulates feeding, and its gene expression increases in response to fasting and leptin deficiency [43]. On the contrary, icv administration of orexin A had no effect on body weight in rats [44]; moreover genetic ablation of orexin-sensitive neurons in mice caused late-onset obesity despite a decrease in food intake [45]. These results may be explained by the observation that orexin A, beyond its stimulation on food intake, increases oxygen consumption and energy expenditure, thus preventing weight gain [46]. Glucose, another signal that is essential in initiating and terminating feeding [47], also appears to regulate orexin neuronal activity since orexin neurones are stimulated by falling blood glucose levels but are inhibited by feeding-related signals, such as signals from the gut as well as a rise in blood glucose [48].

GABA stimulates carbohydrate-rich food intake after injection in the PVN through interaction with GABA-A receptors [49] and benzodiazepines, which are agonists of GABA, beyond their action on anxiety, increase food consumption by potentiating taste palatability of food [50].

2.9 Neurotransmitters and Peptides Mediating Appetite Suppression

Neurotensin, which is produced in the ARC, PVN and DMN, inhibits food intake after icv injection. Leptin stimulates neurotensin synthesis in the hypothalamus; moreover genetically obese ob/ob mice and fa/fa rats exhibit a decreased neurotensin expression, suggesting that neurotensin could mediate, at least in part, the anorectic effect of the ob gene product.

Bombesin-like peptides include gastrin-releasing peptide (GRP), neuromedin B (NMB) and glucagon-like peptide (GLP)-1. Either peripheral or central administration of bombesin-like peptides inhibits food intake by acting on satiety [51]. This effect appears to be mediated through three different receptors: the GRP receptor, the NMB receptor and the bombesin receptor subtype 3 (BRS-3). These receptors share about 50 % amino acids sequence identity but show different affinities for the bombesin-like peptides [52].

2.10 The Cannabinoid System

Epidemiological evidence reporting an orexigenic activity of cannabinoids and the insights into the molecular mechanisms underlying cannabinoid action have suggested a role for this neuromodulatory system in the pathophysiology of obesity. The observation that exogenous cannabinoid derivatives may influence food intake was extensively studied in the 1970s [53]. However, the demonstration in the 1990s of the existence of a new class of endogenous ligands and of specific receptors binding to cannabinoids led to a substantial advancement of the knowledge of this new pathway of regulation of food intake and other central and peripheral functions. Exogenous cannabinoids act by binding two specific receptors, cannabinoid receptor 1 (CB1), abundantly expressed in brain areas involved in feeding behaviour [54], and cannabinoid receptor 2 (CB2) which is mostly expressed in cells of the immune system.

The endogenous cannabinoids. The most common endogenous ligand binding to cannabinoid receptors are anandamide and 2-arachidonoyl glycerol [55], which are produced within the brain by the phospholipid precursor N-arachidonoyl phosphatidylethanolamine by the action of a phospholipase D. Anandamide binds with a higher affinity to CB1 and is present at highest concentration in the hypothalamus, cortex, thalamus and cerebellum of different species including humans. Other endogenous ligands for CB1 and CB2 are docosatetraenoyl ethanolamide, di-homo-γ-linolenoyl ethanolamide and 2-arachidonyl glyceryl ether. Interestingly all these

compounds are polyunsaturated fatty acid derivatives. Anandamide and CB1 are present in the hypothalamus in centres known to regulate food intake and body weight regulation.

Extensive data are available on the effects of cannabinoids on food intake in animals. Anandamide administration was demonstrated to induce overeating in rodents, and this effect was mediated by CB1 receptors [56]. A specific CB1 receptor antagonist (SR141716) has been previously synthesized reducing food intake in rats, mice and marmosets. This effect was selective for sweet food, sucrose and ethanol. Interestingly SR141716 inhibition of food intake was present also in NPY-stimulated food intake, thus indicating a neuronal pathway independent from the hypothalamic NPYergic neuronal circuit [57].

Hypothalamic endocannabinoids are elevated in leptin signalling-deficient rodents (*ob*/*ob* and *db*/*db* mice, *fa*/*fa* rats), while leptin administration in normal and *ob*/*ob* mice reduces anandamide and 2-arachidonoyl glycerol [58]. Moreover knockout mice for CB1 receptor eat less food than wild-type littermates. Taken together, available data on exogenous and endogenous cannabinoids administration, knockout model and endocannabinoid regulation in experimental obesity is strongly suggestive for a role of this biological system in the regulation of feeding behaviour, and an effective antagonist of the CB1 receptor has been recently marketed for obesity treatment although it has been successively retired due to its side effects.

2.11 Signals from Gastrointestinal Tract

Nutrient ingestion stimulates secretion of numerous gastroenteropancreatic hormones into the bloodstream that regulate digestive function. However, it has been proposed that these hormones may play a role also as feedback regulators of meal ingestion and in particular of meal size.

Cholecystokinin (CCK) is present in the brain and the endocrine cells of the duodenum and jejunum. It is released into the bloodstream in response to the presence of food in the intestinal lumen. In addition to its actions on gastrointestinal system, several experimental evidences in different species show that CCK administration reduces food intake [59]. However, the inhibition of food consumption induced by CCK seems to be limited to the reduction of meal size without any significant effect on daily food intake and body weight. Two CCK receptors have been identified. Type A CCK receptor is more abundant in peripheral tissues including pancreas, pyloric sphincter and afferent vagal fibres but is present also in CNS structures. Type B CCK receptors are widely distributed throughout the brain. Type A receptor inhibition, but not type B, prevents the satiety action of administered CCK and increases basal food intake in rats by inhibiting the action of endogenous CCK [60].

Peripheral CCK administration appears to promote satiety by both inhibition of gastric emptying, that indirectly activates vagal afferent signals, and direct activation of a vagal afferent pathway driving to the hypothalamic effector pathways

through specific CCK receptors present on vagus nerve fibres. Both these mechanisms require the integrity of the vagus nerve [61].

Ghrelin is a gastrointestinal peptide with a peculiar structure characterized by an octanoic acid chain esterified on a serine residue. It is synthesized in the stomach, intestine, placenta, pituitary and hypothalamus. Ghrelin binds to a specific transmembrane G-protein linked receptor of 366 amino acids belonging to the rhodopsin family [62]. Circulating ghrelin mainly derives from the stomach, and its plasma concentration is influenced by acute and chronic changes in nutritional state [63]. A postprandial reduction of ghrelin is observed in humans, and infusion of ghrelin leads to short-term increase in hunger [64], thus suggesting that ghrelin inhibition shortly after a meal may be responsible for meal cessation. Moreover in obese humans, ghrelin is markedly reduced compared to lean subjects, but it is not further inhibited by feeding [65]. Low ghrelin levels in human obesity exclude that fat excess is determined by an increased activity of this orexigenic pathway. It is of interest that diet-induced weight loss, but not weight loss obtained by gastric surgery, increases ghrelin thus suggesting a link between the persistence of low ghrelin levels and the more effective and prolonged weight loss after gastric bypass surgery [66]. In summary, available data suggest that ghrelin is an orexigenic signal starting in the stomach and acting on CNS by activating hypothalamic effector mechanisms that induce eating and a positive energy balance although other studies are needed in order to better clarify the role of ghrelin in the pathophysiology of human obesity.

Glucagon-like peptide-1 (GLP-1) is a gut hormone secreted after food intake. This hormone greatly increases glucose-stimulated insulin secretion while inhibiting glucagon production [67]. It is also synthesized in the NTS and released in the PVN and DMH. It has anorexigenic effects after central administration; it also has some important role in the regulation of glucose homeostasis. The majority of these actions are probably mediated by the GLP-1 receptor (GLP-1-R). However, data coming from GLP-1-R-knocked-out mice are consistent with a minor role of GLP-1 in the control of satiety [68].

Glucagon-like peptide-2 (GLP-2) is a newly discovered anorectic hormone that is expressed in the NTS and released in the DMH [69]. It is co-secreted with GLP-1 from enteroendocrine cells in the small and large bowels. GLP-2 secretion is regulated by food nutrients, mainly fat and carbohydrates, and targets receptors in the gastrointestinal tract, from the stomach to the colon. The major known actions of GLP-2 are mucosal growth (especially in the proximal bowel, increasing villous height and crypt cell proliferation and inhibiting apoptosis in both the crypt and villous compartments) and increase of the uptake of intestinal nutrients [70]. GLP-2 also increases mesenteric blood flow, thus providing another mechanism to facilitate digestion and absorption of nutrients [71].

GLP-2 may also influence food intake since icv administration of GLP-2 reduces food intake in rats [72] although to date, studies in humans have not demonstrated a decrease in food intake after peripheral GLP-2 administration [73]. The clear demonstration of GLP-2R expression in the nonrodent brain is still lacking, and then the role of this hormone in the central regulation of food intake is still under consideration.

2.12 Signals from Adipose Tissue

Leptin. Several years ago, Coleman and Hummel first hypothesized the existence of a humoral factor, produced by adipose tissue, involved in the monitoring of lipid stores and regulation of body weight. The discovery of leptin then confirmed the theory of the so-called "adipostatic model". Leptin is synthesized mainly in the adipose tissue at levels proportional to body fat content and enters the CNS via a saturable process [74]. Leptin role in energy homeostasis is critical, since the genetic deficiency of either leptin or its receptor causes profound hyperphagia, morbid obesity and several neuroendocrine and metabolic abnormalities both in rodents and in humans. Leptin receptors are expressed by brain neurons involved in energy intake. Neuronal targets for leptin have been identified in the ARC, VMN, DMH and other brain regions [75]. Leptin receptors are also expressed in many peripheral tissues, implying that the role of leptin is much broader than that of a circulating satiety factor [76]. The dramatic effects of leptin administration to ob/ob mice raised expectations that human obesity might also be a leptin-deficient state, and so that the exogenous administration of the hormone might be effective in the treatment of the disease as demonstrated successively [77]. However, most obese subjects have increased leptin levels, indicating that obesity is a leptin-resistant state in the majority of cases. A leptin receptor defect caused by a mutation, similar to that described in some rodent models of obesity, was found in obese members of two unrelated families [78], but the frequency of similar mutations in the general population is thought to be very low. Other potential mechanisms of leptin resistance include impaired transport into the brain and defective intracellular leptin signalling. Saturable transport of leptin through the blood–brain barrier may be a rate-limiting step [79]; however, brain leptin transport appears to be saturated even at the low leptin levels found in lean individuals [80].

Insulin was the first hormonal signal to be implicated in the control of body weight by the CNS, acting there to reduce energy intake [81]. Insulin receptors are expressed by brain neurons involved in energy intake, and the administration of the pancreatic hormone directly into the brain reduces food intake, whereas its deficiency does the opposite [36]. These effects appear to be mediated, at least in part, by NPY, since insulin suppresses NPY mRNA expression, while its deficiency has been associated with increased hypothalamic NPY levels [82]. Finally the disruption of the brain insulin receptor gene produced a modest but significant increase in food intake and body weight in mice [83].

Glucocorticoids exert a permissive effect on feeding and adiposity, as confirmed by the presence of hyperphagia and obesity in Cushing's syndrome and anorexia in Addison's disease. Moreover most experimental obesities in rodents are associated with hypercorticism and prevented by adrenalectomy [84]. The effects of glucocorticoids on food intake could be mediated by orexigenic peptides, such as NPY, and there is significant overlap in neuronal targets of glucocorticoids, leptin and insulin, raising the possibility that these hormones act in a coordinated fashion to regulate feeding and energy balance [85]. Indeed glucocorticoids enhance leptin production

both in vitro and in vivo [86]. Moreover glucocorticoids can act at the CNS level by reducing the anorectic action of leptin [87] inducing a relative leptin resistance, which in turn may be responsible for the fat deposition observed in hypercorticism. On the other hand, leptin seems to regulate glucocorticoid levels by directly inhibiting cortisol release, but the existence of a feedback between leptin and glucocorticoids in humans has not been demonstrated [88].

Sex steroids are able to influence food intake, body weight and composition, as well as leptin production; conversely sex steroid are related to body fat. Androgens stimulate appetite and increase lean mass, while oestrogens tend to decrease feeding and body weight. Oestrogen deficiency in rats causes impaired central leptin sensitivity and increased hypothalamic NPY production [89]. Sex steroid effects are probably mediated through the regulation of the synthesis of neuropeptides such as NPY, POMC and MCH in similar hypothalamic targets as leptin [90].

Pro-inflammatory cytokines, such as tumour necrosis factor- α (TNF-α), interleukin (IL)-1 and IL-6, which are produced in response to infections and cancer, have been implicated in anorexia and wasting syndrome associated with these conditions. These cytokines can be transported from periphery to the CNS across the blood–brain barrier, where they can act on neuronal pathways and modulate eating behaviour and energy balance [91]. Moreover TNF-α can directly induce ob gene expression in rodents as well as in man [92]; furthermore IL-1 seems to increase leptin levels both directly and through the increase of the hypothalamus–pituitary–adrenal axis activity [93]. IL-6 is expressed both in adipose tissue and in hypothalamic nuclei that regulate body composition. Mice lacking the gene encoding for IL-6 develop mature-onset obesity, altered carbohydrate and lipid metabolism, increased leptin levels and decreased responsiveness to leptin treatment. Icv, but not ip, IL-6 administration was able to increase energy expenditure, partly reversing obesity [94].

Ciliary neurotrophic factor (CTNF), a neurocytokine, decreases body weight and fat depot by inhibiting food intake and increasing energy expenditure [95]. As for leptin, CTNF acts through the Jak–STAT signal transduction pathway; however, hypothalamic targets of CTNF differ from those of leptin [96].

2.13 Monoamine Neurotransmitters

Aminergic neurotransmitter systems provide important targets for drug treatment of obesity. However, these pathways exert ambiguous effects on food intake and their role is complex.

Noradrenaline is synthesized in dorsal vagal complex and locus ceruleus. These areas project to the spinal cord, hypothalamus, thalamus and cortex. In some of these neurons and particularly in those projecting to the PVN, noradrenaline is co-localized with NPY. Like NPY, icv administration of noradrenaline increases food intake and weight gain [97]. Moreover noradrenaline levels in the PVN of ob/ob mice are elevated, suggesting that leptin may inhibit its release in this brain area, as confirmed by in vitro studies using rat hypothalamus [98, 99].

Dopamine signalling is thought to play a relevant role in the regulation of food intake, since pharmacological depletion or genetic disruption of its synthesis deeply alters food intake [100, 101], even if the interpretation of these finding is complicated by motor impairments associated with dopamine deficiency. Mesolimbic dopamine pathways seem to contribute to the "rewarding" aspects of palatable foods [102], while dopamine signalling in the hypothalamus seems to inhibit food intake [3].

Serotonin (5-HT) is synthesized in the dorsal raphé nucleus (DRN) and is distributed to the PVN, VMN and other forebrain regions [112]. It inhibits eating in spontaneously feeding and food-deprived animals. 5-HT agonists reduce body weight in humans by suppressing appetite and increasing energy expenditure, probably acting at the 5-HT2C receptor subtype level [103].

2.14 Nutrient Sensing in the Hypothalamus

In addition to hormones and neurotransmitters, the brain also directly responds to nutrients, such as glucose, fatty acid and amino acids. Within specific hypothalamic nuclei, subsets of neurons with specific neurobiological phenotypes are responsive to nutrients that act as signalling molecules to engage a complex set of neurochemical and neurophysiological responses, thereby regulating energy intake.

Brain glucose sensing. Two different glucose-responsive neurons have been described within the hypothalamus depending on the effect of altered glucose concentration: glucose-excited (GE) neurons, abundant in the lateral hypothalamus (LH), and glucose-inhibited (GI) neurons which are more abundant in the ventromedial hypothalamus (VMH) [104]. Different nutrient-sensing mechanisms and intracellular signal transduction pathways have been implicated in the ability of nutrient-sensing neurons to monitor the amount of available fuel in the body. ATP production and the associated changes in the ADP/ATP ratio have long been considered as the main metabolic signals of nutrient availability although other mechanisms have been suggested in the last years [98, 105].

Brain lipid sensing. Despite the fact that the brain does not use fatty acids (FA) as a major fuel source, there is growing evidence that FA metabolism within distinct hypothalamic regions can function as a sensor for nutrient availability. It has been previously shown that FA, particularly long-chain FA, activate LH neurons [106] and modify neuronal firing rate in ARC [107]. However, the idea that increases in brain FA levels act as a satiety signal to inhibit feeding contrasts with the fact that plasma FA levels do not rise substantially after food ingestion but rise significantly during fasting [108]. Another problem concerning the view of FA directly acting on neurons as a satiety signal is the fact that the vast majority of FA oxidation in the brain occurs in astrocytes rather than neurons [109]. So there must be a mechanism by which alterations in astrocyte FA metabolism can provide a signal to neurons. Hypothalamic glia responds to increases in extracellular glucose levels through an increase in glycolytic ATP production, which induces lactate release from astrocytes [110], and hypothalamic lactate sensing has been shown to regulate food intake [111].

Brain amino acid sensing. Recent data demonstrate that ARC neurons can also sense changes in amino acid availability and implicate this sensing in the regulation of energy balance. Leucine administration into the mediobasal hypothalamus reduces food intake, both through a rapid reduction in meal size and a longer-term reduction in meal number, leading to a reduction in body weight gain [112]. This effect is blunted by rapamycin, a pharmacological inhibitor of the serine–threonine kinase mammalian target of rapamycin (mTOR) [113], a protein kinase activated by states of positive energy balance that is expressed in POMC and AgRP neurons in the ARC, where they respond to insulin, leptin and nutrient levels and exert potent effects on feeding and energy balance [114].

Conclusions

The survival of higher organisms depends on the ability to efficiently acquire, use and conserve energy. Humans and other mammals have developed complex mechanisms to ensure a constant supply of energy for cellular functions in an attempt to fight against the periods of energy deprivation. Like other biological parameters, body weight is usually maintained within a narrow range of variations for long time periods. To ensure the stability of this parameter, calories intake must equal energy needs, and even small environmental reduction in energy availability, food intake and body weight may be perceived as an emergency situation that activates a wide spectrum of events teleologically directed to the survival of the individuals and of the species. The anatomical and functional structure regulating feeding behaviour evolved in an energy-deficient environment. Therefore, at present time the great and easily available quantity of food present in the western countries may be considered an abnormal situation in evolutionary terms, and the immense complexity of these mechanisms adapts poorly to these conditions, explaining at least in part the overwhelming increase in the prevalence of obesity in our population. The complete understanding of all pathophysiological mechanisms regulating energy metabolism in human will lead to the discovery of new medical approaches to treat obesity and related diseases.

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