

Peripheral signalling involved in energy homeostasis control

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Abstract

The alarming prevalence of obesity has led to a better understanding of the molecular mechanisms controlling energy homeostasis. Regulation of energy intake and expenditure is more complex than previously thought, being influenced by signals from many peripheral tissues. In this sense, a wide variety of peripheral signals derived from different organs contributes to the regulation of body weight and energy expenditure. Besides the well-known role of insulin and adipokines, such as leptin and adiponectin, in the regulation of energy homeostasis, signals from other tissues not previously thought to play a role in body weight regulation have emerged in recent years. The role of fibroblast growth factor 21 (FGF21), insulin-like growth factor 1 (IGF-I), and sex hormone-binding globulin (SHBG) produced by the liver in the regulation of body weight and insulin sensitivity has been recently described. Moreover, molecules expressed by skeletal muscle such as myostatin have also been involved in adipose tissue regulation. Better known is the involvement of ghrelin, cholecystokinin, glucagon-like peptide 1 (GLP-1) and PYY_{3–36}, produced by the gut, in energy homeostasis. Even the kidney, through the production of renin, appears to regulate body weight, with mice lacking this hormone exhibiting resistance to diet-induced obesity. In addition, the skeleton has recently emerged as an endocrine organ, with effects on body weight control and glucose homeostasis through the actions of bone-derived factors such as osteocalcin and osteopontin. The comprehension of these signals will help in a better understanding of the aetiopathology of obesity, contributing to the potential development of new therapeutic targets aimed at tackling excess body fat accumulation.

Key words: Peripheral signalling; Energy homeostasis control; Obesity; Adipokines; Cytokines; Hormones

Introduction

The obesity epidemic poses one of the most serious public health challenges. The prevalence of obesity has increased three-fold over the past three to four decades⁽¹⁾. More than half of all adults in Europe and the USA are overweight. Of these, one-third is already obese and figures are increasing⁽²⁾. Obesity is a serious medical problem because it increases the risk of type 2 diabetes mellitus (T2DM), CVD, fatty liver, sleep-breathing disorders, and certain forms of cancer, among others^(3–8). Moreover, obesity adversely affects the quality of life and shortens life expectancy^(9,10).

The alarming prevalence of obesity has led to a greater understanding of the molecular mechanisms that regulate energy homeostasis and body weight control⁽¹¹⁾. Energy balance regulation is an extremely complex process that integrates multiple interacting homeostatic and behavioural

pathways. In recent years, awareness has been raised regarding the increasing number of neuropeptides involved in the hypothalamic integration of peripheral signals derived mainly from the pancreas and adipose tissue⁽¹²⁾. The existing evidence collected over recent years through targeted expression or knockout of specific genes involved in the pathways controlling energy intake, energy expenditure, adiposity or fat distribution has contributed to disentangling the mechanisms controlling energy homeostasis⁽¹³⁾. Thus, regulation of energy intake and expenditure is more complex than previously thought, being influenced by signals from many other peripheral tissues^(14–18). In this sense, a wide variety of peripheral signals derived from different organs contributes to the regulation of body weight and energy expenditure. In addition to the well-known role of insulin (from the pancreas) and adipokines, such as leptin

Abbreviations: AgRP, Agouti-related peptide; AMPK, AMP-activated protein kinase; Ang, angiotensin; ANP, atrial natriuretic peptide; ASP, acylation-stimulating protein; BAT, brown adipose tissue; BNP, brain natriuretic peptide; CCK, cholecystokinin; CCK1R, cholecystokinin-1 receptor; cGMP, cyclic guanosine monophosphate; CNP, c-type natriuretic peptide; ER, oestrogen receptor; FGF, fibroblast growth factor; GIP, glucose-dependent insulinotropic polypeptide; GLP, glucagon-like peptide; GUCY, guanylyl cyclase; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY; SHBG, sex hormone-binding globulin; T2DM, type 2 diabetes mellitus; T3, triiodothyronine; THR, thyroid hormone receptor; vaspin, visceral adipose tissue-derived serpin.

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and adiponectin (from adipose tissue), in the regulation of energy homeostasis, signals from other tissues not previously thought to be involved in body weight regulation have emerged in recent years. The role of emerging proteins produced by the liver such as fibroblast growth factor (FGF) 21 in the regulation of body weight and insulin sensitivity has been described recently. Moreover, molecules expressed by skeletal muscle such as myostatin have also been involved in adipose tissue regulation. Better known is the involvement of ghrelin, cholecystokinin (CCK), glucagon-like peptide (GLP)-1 and peptide YY (PYY)_{3–36}, produced by the gut, in energy homeostasis⁽¹⁹⁾. Even the kidney, through the production of renin, appears to regulate body weight, because mice lacking this hormone exhibit resistance to diet-induced obesity⁽¹⁴⁾. In addition, the skeleton has recently emerged as an endocrine organ, with effects on body weight control and glucose homeostasis through the actions of bone-derived factors such as osteocalcin and osteopontin⁽¹⁵⁾. The cross-talk between adipose tissue and the skeleton constitutes a homeostatic feedback system, with adipokines and molecules secreted by osteoblasts and osteoclasts representing the links of an active bone–adipose tissue axis. The present review summarises the current state of knowledge of the peripherals signals involved in the regulation of energy intake and expenditure.

Signals from adipose tissue

The concept that circulating signals secreted in proportion to body fat stores regulate energy intake and expenditure in a coordinated manner to regulate body weight was proposed more than 50 years ago⁽²⁰⁾. According to this model, changes in energy balance sufficient to alter body fat stores were signalled via one or more circulating factors acting in the hypothalamus for triggering compensatory changes in order to match energy intake to energy expenditure⁽²¹⁾. This was formulated as the 'lipostatic theory', presuming that as adipose tissue mass expands, a factor that operates as a sensing hormone or 'lipostat' in a negative feedback control from adipose tissue to hypothalamic receptors informs the brain about the size of the body fat stores, thereby allowing feeding behaviour and energy expenditure to be coupled to the nutritional state of the organism. Current knowledge has fostered the idea of a far more complex system than initially thought from the formulation of the lipostatic theory, involving the integration of a multitude of factors⁽²¹⁾. This pleiotropic nature relies on the ability of adipocytes to secrete a large number of hormones, growth factors, enzymes, cytokines and matrix proteins, collectively termed as adipokines, which warrant an appropriate feedback response to changes in adipose tissue mass^(22–25).

Leptin

Leptin is an adipokine mainly produced by adipocytes in proportion to fat stores⁽²⁶⁾. It was originally thought to be

only involved in energy intake inhibition and body weight regulation acting at its hypothalamic receptors. This inhibition of appetite takes place mainly through the inhibition of neuropeptide Y (NPY)- and Agouti-related peptide (AgRP)-expressing neurons and the stimulation of pro-opiomelanocortin (POMC)-expressing neurons in the hypothalamic arcuate nucleus⁽²⁷⁾. However, a significant number of leptin receptor-expressing neurons lie outside the hypothalamic arcuate nucleus, suggesting that other brain regions known to modulate energy balance are involved in leptin's anorectic effect⁽²⁸⁾. Although food intake regulation is a major role of leptin, its receptor is expressed in almost all tissues^(29–31), underlining a high functional pleiotropism involving energy homeostasis, glucose metabolism, reproduction, angiogenesis, immunity, gastrointestinal function, wound healing, bone remodelling and cardiovascular function^(32–38). Plasma leptin concentrations are increased in obese patients, being strongly correlated with BMI and the percentage of body fat, as well as with leptin mRNA expression in adipose tissue^(23,39,40). The failure of high leptin concentrations to suppress feeding and mediate weight loss in common obesity defines what has been termed leptin resistance⁽³⁶⁾.

Leptin-deficient *ob/ob* mice and leptin receptor-deficient *db/db* mutants show early-onset obesity, diabetes and reduced energy expenditure⁽⁴¹⁾. Leptin administration induces a dramatic loss of adipose mass in rodents^(42,43). This effect is not only mediated by a reduction in energy intake, but also by a direct effect on adipose tissue⁽⁴³⁾. In this sense, leptin inhibits lipogenesis and stimulates lipolysis in adipocytes through a direct effect^(44,45) or a centrally mediated action⁽⁴⁶⁾ without the release of NEFA, which are intracellularly oxidised⁽⁴⁷⁾. Furthermore, leptin replacement in leptin-deficient mice increases energy expenditure^(42,48). A few leptin-deficient patients who also exhibit severe early-onset obesity and hormonal alterations have been identified^(49,50). Surprisingly, BMR and total energy expenditure were similar to those of age-, sex- and weight-matched controls⁽⁵¹⁾. Leptin replacement in humans reduces body weight mainly at the expense of the fat compartment and reverses metabolic and hormonal alterations^(51–54). Interestingly, the weight loss-associated decrease in energy expenditure that takes place after prolonged negative energy balance was less pronounced in leptin-treated patients than in obese leptin-replete controls following a weight-loss programme^(51,52,55,56). Therefore, leptin prevents the reduction in metabolic rate that is associated with weight loss^(52,55,56).

Adiponectin

The adipokine adiponectin is highly expressed in adipose tissue and its circulating concentrations are considerably high, accounting for approximately 0.01% of total serum protein^(57–59). Adiponectin exerts a wide variety of physiological roles through the binding of at least three different

receptors called AdipoR1, AdipoR2 and T-cadherin^(60,61). Serum concentrations of adiponectin are decreased in obese subjects^(62,63) and increase with weight loss⁽⁶⁴⁾. Hypoadiponectinaemia is associated with insulin resistance and patients with T2DM are reported to have decreased concentrations of adiponectin^(63,65,66). Patients with CVD also exhibit lower adiponectin concentrations⁽⁶⁷⁾. In addition, administration of adiponectin induces glucose-lowering effects and improves insulin sensitivity in rodent models of obesity-associated diabetes^(68,69). Moreover, adiponectin also exhibits anti-atherosclerotic properties⁽⁷⁰⁾. Adiponectin-deficient mice as well as mice lacking adiponectin receptors confirm the protective effects of this adipokine in the development of insulin resistance and atherosclerosis^(71–73).

Although the insulin-sensitising effects of adiponectin are clear, the effects of this adipokine in energy intake and energy expenditure regulation are still a matter of controversy⁽⁷⁴⁾. A lack of effect of intracerebroventricularly administered adiponectin on energy intake has been described. At the same time, weight-reducing actions through an increase in energy expenditure in normal mice have been shown⁽⁷⁵⁾. These observations are confirmed in the long term after a 4-week treatment⁽⁷⁶⁾. However, other authors have reported that adiponectin increases energy intake through the stimulation of AMP-activated protein kinase (AMPK) in the hypothalamic arcuate nucleus via AdipoR1 with a concomitant decrease in oxygen consumption⁽⁷⁷⁾. Adiponectin- or AdipoR1-deficient mice show no changes in energy intake under a normal diet^(71,73,78) but, when challenged with a high-fat diet, adiponectin knock-out mice show a reduced energy intake accompanied by an increase in oxygen consumption. The absence of lower food consumption in mice lacking adiponectin under a normal diet can be explained by a compensatory increase in the orexigenic pathways in order to avoid excessive weight loss. This reduction in food intake could be detrimental given the increase in energy expenditure observed after adiponectin administration⁽⁷⁷⁾.

Resistin

Resistin is another adipokine which was initially proposed as a link between increased adiposity and T2DM⁽⁷⁹⁾. Resistin has been reported to be highly expressed in adipose tissue in mice. Under physiological circumstances, resistin appears to oppose insulin action in adipocytes and to impair glucose tolerance and insulin sensitivity in mice. Moreover, insulin-stimulated glucose uptake by adipocytes is enhanced by resistin neutralisation and is reduced by resistin treatment^(79,80). Different genetic and dietary models of rodent obesity exhibit increased serum concentrations of resistin^(79,81). Moreover, transgenic overexpression of resistin leads to insulin resistance in mice⁽⁸²⁾ and rats⁽⁸³⁾. In this sense, *ob/ob* mice simultaneously lacking resistin exhibit an improved glucose tolerance and insulin sensitivity⁽⁸⁴⁾.

The exact role of resistin in human physiology and whether or not resistin is involved in the development of insulin resistance still need to be completely elucidated^(80,85,86). Several groups have described increased concentrations of resistin in obesity^(87,88), while others report no existing differences^(89–91). However, cross-sectional and prospective epidemiological investigations reveal that human resistin is not significantly involved in the development of insulin resistance^(92–94) or the metabolic syndrome⁽⁹⁵⁾. Rather than a role in the development of insulin resistance, considerable evidence links resistin to inflammation^(81,85,96). In this respect, it has been reported that resistin markedly up-regulates pro-inflammatory cytokines^(97,98) and that inflammation up-regulates resistin in human macrophages^(99,100). Furthermore, it has been confirmed that resistin is related to markers of inflammation, being a predictive factor of atherosclerosis⁽¹⁰¹⁾, and that it also influences pro-inflammatory cytokine release from human adipocytes⁽¹⁰²⁾. However, the precise physiological role of resistin in the pathogenesis and perpetuation of inflammation and CVD in humans remains unclear⁽⁸¹⁾.

Central administration of resistin induces a short-term decrease in food intake in rats^(103–105), mainly associated with a suppression of the normal fasting-induced increase in the orexigenic neuropeptides NPY and AgRP, and a suppression of the decrease in cocaine and amphetamine-regulated transcript (CART)⁽¹⁰⁶⁾. However, other authors have described an up-regulation of hypothalamic NPY after intracerebroventricular administration of resistin in mice without measuring the potential effect on food intake⁽¹⁰⁷⁾. Furthermore, leptin-deficient *ob/ob* mice lacking resistin exhibit higher body weight and body adiposity than *ob/ob* mice with normal resistin levels⁽⁸⁴⁾. This observation has been attributed to a lower metabolic rate, uncovering a crucial role of resistin in the regulation of thermogenesis. In addition to its inhibitory effect on adipogenesis⁽¹⁰⁸⁾, the anorexigenic and thermogenic effects of resistin underscore the relevance of this molecule as an interesting regulator of energy homeostasis. It still remains to be elucidated whether resistin acts on the brain or peripheral tissues to control metabolic rate. The complex actions of resistin on energy expenditure and the expression of resistin in several hypothalamic nuclei suggest that resistin may act in an autocrine/paracrine fashion for regulating body weight, deserving further research⁽¹⁰⁹⁾.

Acylation-stimulating protein

Acylation-stimulating protein (ASP) is an adipokine predominantly produced by fully differentiated adipocytes⁽¹¹⁰⁾. ASP results from the cleavage of the complement C3 via factor B and adipsin (factor D) interaction producing C3a, which is rapidly desarginated to give ASP (also known as C3adesArg)⁽¹¹¹⁾. ASP increases after a fat-containing meal and stimulates TAG synthesis and storage^(23,112). ASP also stimulates translocation of GLUT1



to the cell surface⁽¹¹³⁾. Differences between adipose tissue depots have been observed, with greater ASP binding and action in subcutaneous compared with omental fat, in females compared with males, and in obese compared with non-obese subjects, suggesting that ASP could be a female lipogenic factor⁽¹¹⁴⁾. Circulating concentrations of ASP have been reported to be increased in obese and T2DM subjects⁽¹¹¹⁾.

Mice lacking complement C3 are deficient in ASP. These mice exhibit a striking phenotype, being leaner in spite of having a significantly increased food intake, which is counterbalanced by increased energy expenditure^(115,116). Similarly, mice lacking the ASP receptor C5L2 showed a phenotype similar to ASP-deficient mice, with delayed postprandial TAG clearance, increased dietary food intake, and increased muscle fatty acid oxidation⁽¹¹⁷⁾. Furthermore, exogenously administered ASP increases energy storage while ASP antibody neutralisation increases whole body energy utilisation in mice⁽¹¹⁸⁾. Recently, it has been suggested that injections of ASP in the third ventricle inhibit food intake in rats through an increase in POMC expression⁽¹¹⁹⁾. Therefore, ASP is pointed out as a potent anabolic hormone that may also be a mediator of energy expenditure. The potential contribution of ASP as a regulator of food intake and energy expenditure in humans remains to be elucidated.

TNF- α

TNF- α is a cytokine involved in the metabolic disturbances of chronic inflammation, playing a major role in pathophysiological processes such as insulin resistance and anorexia^(23,120). In addition, TNF- α is a potent negative regulator of adipocyte differentiation⁽¹²¹⁾. Adipose tissue is both a source of and a target for TNF- α ⁽¹²²⁾. It has been suggested that TNF- α is a candidate mediator of insulin resistance in obesity, as it is overexpressed in the adipose tissue of obese rodents and humans⁽¹²³⁾. This cytokine blocks the action of insulin in adipose tissue and skeletal muscle *in vitro* and *in vivo*. In this sense, TNF- α -deficient mice exhibit protection from the development of obesity-induced insulin resistance⁽¹²⁴⁾.

The anorexigenic and cachexic effects of TNF- α are well known^(125,126). This cytokine modulates the expression of neurotransmitters involved in the control of energy homeostasis, favouring anorexia and energy expenditure⁽¹²⁷⁾. Brown adipose tissue (BAT) is a particular form of adipose tissue, functionally and morphologically distinct from white adipose tissue, specialised in dissipating energy in the form of heat^(128,129). BAT has been suggested to play a role in human energy homeostasis^(129,130). Several controversial studies suggest that TNF- α may modulate the thermogenic capacity of BAT⁽¹²²⁾. Administration of TNF- α increases BAT thermogenic activity⁽¹³¹⁾. This is consistent with the catabolic role of TNF- α . In contrast, other studies suggest that TNF- α decreases the activity of BAT⁽¹³²⁾. Accordingly,

the lack of TNF- α receptor 1 improves the thermoadaptive capacity of obese animals⁽¹³³⁾. However, information regarding the role of TNF- α in energy expenditure in humans, beyond its adipose tissue-mobilising effect, is scarce. Disentangling the exact role of TNF- α action in insulin resistance and energy expenditure in humans may provide the basis for the development of novel strategies for treating obesity and the metabolic syndrome.

IL-6

IL-6 is an inflammatory cytokine with pleiotropic effects on a variety of tissues, including stimulation of acute-phase protein synthesis and regulation of glucose and lipid metabolism^(22,23). Adipose tissue produces IL-6, with circulating levels of IL-6 being proportional to adipose mass and the magnitude of insulin resistance^(134,135). Although increased concentrations of IL-6 have been detected in obese subjects, mice lacking IL-6 develop mature-onset obesity, with the obese phenotype being only partly ameliorated by IL-6 replacement⁽¹³⁶⁾. Interestingly, acute IL-6 treatment has been reported to produce an increase in insulin-stimulated glucose disposal in humans *in vivo* and to induce fatty acid oxidation, glucose transport, and GLUT4 translocation to the plasma membrane *in vitro*⁽¹³⁷⁾. In this sense, IL-6 is considered an auto-crine/paracrine regulator of adipocyte function. Its involvement in the development of insulin resistance is still not completely understood⁽¹³⁵⁾.

Similarly to TNF- α , IL-6 has been shown to trigger catabolic effects⁽¹²⁵⁾. In this sense, IL-6 exerts anti-obesity effects centrally by increasing energy expenditure⁽¹³⁸⁾, with mice lacking IL-6 exhibiting adult-onset obesity^(136,139) through decreased expression of corticotrophin-releasing hormone (CRH) and oxytocin in the hypothalamus. Due to the fact that CRH is known to stimulate energy expenditure and oxytocin has anorexigenic effects, a reduction in both neuropeptides may be contributing to the obese phenotype of mice lacking IL-6⁽¹⁴⁰⁾. In humans, exogenous administration of IL-6 increases energy expenditure and activates the hypothalamic–pituitary–adrenal axis, thereby suggesting that CRH may be mediating this effect, as is observed in mice^(141,142). Moreover, a polymorphism in the IL-6 gene has been shown to influence energy expenditure⁽¹⁴³⁾. It seems clear that IL-6 regulates energy expenditure; however, its exact involvement in the development of obesity in humans and its potential therapeutic utility remain to be fully elucidated. It should be noted that the treatment of obesity with IL-6 is not currently under way due to potential major side effects and the lack of knowledge regarding the relative contribution of different target organs to IL-6-induced thermogenesis⁽¹⁴⁴⁾.

Visfatin

Visfatin, previously identified as nicotinamide phosphoribosyl transferase and colony-enhancing factor of pre-B

cells, was originally identified as a modulator of B cell differentiation expressed in lymphocytes, bone marrow, skeletal muscle and liver⁽¹⁴⁵⁾. It was named visfatin because it is highly secreted by visceral fat of both mice and humans and its expression levels in serum increase during the development of obesity^(145,146). Visfatin was first reported to have insulin-like activity⁽¹⁴⁶⁾. However, these findings are currently controversial, with the authors having been forced to retract some of their original conclusions⁽¹⁴⁷⁾. Surprisingly, plasma visfatin correlates with measures of obesity but not with visceral fat mass or variables of insulin sensitivity in humans. Furthermore, visfatin mRNA expression does not differ between visceral and subcutaneous adipose tissue^(148,149). Nicotinamide phosphoribosyl transferase is thought to play an important role in insulin secretion by pancreatic β -cells⁽¹⁵⁰⁾ and appears to also be involved in the regulation of the inflammatory response⁽¹⁵¹⁾.

There is little information regarding the effect of visfatin on energy homeostasis. Central administration of visfatin to Sprague–Dawley rats decreased food intake and locomotor activity, and also increased body temperature⁽¹⁵²⁾. These effects resemble those produced by other pro-inflammatory cytokines and they take place via the melanocortin pathway⁽¹⁵²⁾. Undoubtedly, more studies are needed in order to fully understand the real implications of visfatin in glucose metabolism and energy homeostasis^(93,153).

Visceral adipose tissue-derived serpin

Visceral adipose tissue-derived serpin (vaspin) is a member of the serine protease inhibitor family. Vaspin is highly expressed in adipocytes of visceral adipose tissue at the same time that obesity and insulin levels peak in Otsuka Long-Evans Tokushima fatty (OLETF) diabetic obese rats. Administration of vaspin to obese insulin-resistant mice improves glucose tolerance and insulin sensitivity. These findings indicate that vaspin exerts an insulin-sensitising effect in states of obesity⁽¹⁵⁴⁾. Human vaspin mRNA expression in adipose tissue is not detectable in lean normoglycaemic individuals, but is induced by increased fat mass and decreased insulin sensitivity, which could represent a compensatory mechanism associated with obesity and T2DM⁽¹⁵⁵⁾. However, no differences in the levels of vaspin between individuals with normal glucose tolerance and T2DM have been detected⁽¹⁵⁶⁾. The potential involvement of vaspin in glucose homeostasis certainly requires further investigation⁽¹⁵⁷⁾.

Vaspin mRNA in adipose tissue decreases after fasting and its levels are partially recovered after leptin treatment⁽¹⁵⁸⁾. Circulating vaspin concentrations follow a meal-related circadian variation in humans, similar to that seen for ghrelin, suggesting a role for vaspin in the regulation of food intake. Serum vaspin levels exhibit a preprandial rise followed by a rapid decline after meals⁽¹⁵⁹⁾. Both peripheral and central vaspin administration decrease

food intake in mice⁽¹⁶⁰⁾. Furthermore, intrahypothalamic vaspin administration reduces food intake in rats, decreasing NPY and increasing POMC mRNA expression⁽¹⁶¹⁾. Therefore, vaspin exhibits anorexigenic and glucose-lowering effects, suggesting its potential use as a therapeutic tool for the treatment of obesity and related diseases. However, the effect of vaspin on energy expenditure needs to be addressed.

Chemerin

Chemerin, also known as retinoic acid receptor responder 2, is a secreted chemoattractant protein with an important role in adaptive and innate immunity^(25,162). Chemerin has been recently described as an adipokine associated with obesity and the metabolic syndrome^(163,164). Furthermore, chemerin contributes to inflammation by stimulating macrophage adhesion to extracellular matrix proteins and by promoting chemotaxis⁽¹⁶⁵⁾. Increased mRNA expression of chemerin has been found in mouse and human adipocytes, while the knockdown of chemerin indicates a major role for this adipokine in regulating adipogenesis and metabolic homeostasis in the adipocyte⁽¹⁶⁴⁾. Increased circulating levels of chemerin have been found in morbidly obese patients, with a significant decrease after bariatric surgery^(166,167).

Central administration of chemerin does not modify food intake 24 h after treatment in rats⁽¹⁶¹⁾. However, chemerin treatment increases both AgRP and POMC mRNA expression in the hypothalamus. This could lead to a null effect, considering that AgRP is orexigenic and POMC is anorexigenic, but it suggests a role of chemerin in the regulation of neuropeptides involved in food intake regulation⁽¹⁶¹⁾. The changes in chemerin concentrations after weight loss may merely reflect the reduction in body adiposity, but also a putative role in body weight homeostasis^(166,167).

Omentin

Omentin, also named intelectin or intestinal lactoferrin receptor, is another recently described visceral fat depot-specific adipokine^(25,168). It is a secreted protein likely to act as both an endocrine factor to modulate systemic metabolism and an autocrine/paracrine factor to regulate adipocyte biology locally^(168,169). Obesity negatively regulates omentin expression and its release into the circulation, with reduced plasma omentin levels having been observed in obese subjects⁽¹⁷⁰⁾. Omentin increases insulin action by enhancing insulin-mediated glucose transport in isolated adipocytes^(168,169). Omentin has also been related to inflammation, exerting an anti-inflammatory action and displaying beneficial effects on the metabolic syndrome⁽¹⁷¹⁾.

Little is known regarding the role of omentin in energy homeostasis. Central administration of omentin produces

a slight but non-significant increase in food intake in rats⁽¹⁶¹⁾. In humans, circulating omentin concentrations change oppositely to what takes place in energy balance, thereby rising after prolonged negative energy balance, as is the case after dietary-induced weight loss⁽¹⁷²⁾. Further studies are necessary in order to gain more insight regarding the involvement of omentin in the regulation of appetite and energy expenditure.

Angiotensin II

Murine models of obesity show increased local formation of angiotensin (Ang) II due to elevated secretion of its precursor, angiotensinogen, from adipocytes^(23,173,174), with deficiency or overexpression of angiotensinogen affecting body weight regulation⁽¹³⁾. Given the close relationship between Ang II and insulin resistance and the fact that the renin–Ang system is inappropriately activated in obesity^(175,176), the participation of the adipose tissue–renin–Ang system in the development of insulin resistance and the metabolic syndrome is conceivable in humans, but has to be evaluated in more detail^(173,177).

Mice lacking angiotensinogen or any of its two major receptor subtypes, type 1 (AT1R) and type 2, show protection against the development of obesity without notable changes in food intake^(178–180). By contrast, it is clear that these knockout mice exhibit higher energy expenditure, particularly when a high-fat diet is consumed^(179,180). Furthermore, mice deficient in Ang-converting enzyme (ACE), which is responsible for the conversion of Ang I to the bioactive peptide Ang II, also have increased energy expenditure, with reduced fat mass and improved glucose clearance⁽¹⁸¹⁾. Paradoxically, administration of Ang II to rats by means of subcutaneous osmotic minipumps produces a maintained reduction of food intake with a transient decrease in oxygen consumption^(182,183). Furthermore, ACE inhibition with captopril reduces food intake and protects against the development of diet-induced obesity and glucose intolerance in rats⁽¹⁸⁴⁾. However, Ang II may exert different effects on metabolism, depending on the tissues of action. In this sense, accumulating evidence suggests that increased Ang II activity locally within the brain promotes negative energy balance^(185,186). Taken together, these studies suggest that reduced systemic Ang II signalling protects against diet-induced adipose tissue enlargement by increasing energy expenditure in rodents⁽¹⁷³⁾. In humans, although ACE inhibitors and AT1R blockers are widely used as antihypertensive agents and are beginning to be used for promoting insulin sensitivity, there is minimal evidence that these agents significantly affect energy homeostasis⁽¹⁸⁷⁾.

Sex steroids

Adipose tissue expresses different sex steroid-metabolising enzymes that promote the conversion of oestrogens from androgenic precursors, which are produced by the

gonads or adrenal glands, thereby regulating the synthesis and bioavailability of endogenous sex steroids, oestrogens and androgens, through different mechanisms^(188–191). In this sense, in men and postmenopausal women, adipose tissue is the main source of oestrogen synthesis, and circulating levels of oestrogens are directly related to BMI. Sex steroid hormones play a critical role in adipose tissue metabolism, distribution and accretion^(188,189). In women, menopause-induced oestrogen deficiency and increased androgenicity are associated with increased visceral obesity and with the subsequent cardiometabolic alterations⁽¹⁸⁸⁾. Moreover, hormone replacement therapy with oestradiol treatment for 1 year decreased intra-abdominal fat⁽¹⁹²⁾. Ageing in men is associated with a progressive deficit in androgen production and reduced concentrations of testosterone have been related to increased visceral obesity and the metabolic syndrome^(193,194). Therefore, treating middle-aged obese men with testosterone reduces abdominal fat⁽¹⁹⁵⁾.

In females, oestrogens regulate energy homeostasis via oestrogen receptor (ER) α and ER β , by reducing food intake^(18,190,196) and adiposity⁽¹⁹⁷⁾, enhancing energy expenditure^(198,199), and improving insulin sensitivity⁽¹⁹⁹⁾. In males, testosterone is converted to oestrogen and controls energy homeostasis via ER and androgen receptors, which share related functions for increasing energy expenditure, reducing fat accumulation⁽²⁰⁰⁾ and ameliorating glucose homeostasis⁽¹⁹¹⁾. It has been recently reported that distinct hypothalamic neurons mediate oestrogenic effects on food intake and energy homeostasis. Food intake is regulated by ER α in POMC neurons while energy expenditure and fat accumulation is controlled by ER α in steroidogenic factor-1 neurons⁽²⁰¹⁾.

Signals from the pancreas

The major physiological function of the endocrine pancreas is the maintenance of glucose homeostasis. The pancreas senses the concentration of glucose in blood and, through the release of insulin and glucagon, regulates glucose uptake and utilisation by peripheral tissues. However, insulin and glucagon, as well as pancreatic polypeptide (PP) and amylin, also exert a regulatory effect on energy homeostasis⁽²⁰²⁾.

Insulin

Insulin was the first hormone to be involved in the control of body weight by the central nervous system^(202–204). To date, insulin and leptin are the only hormones that fulfil the criteria to be considered an adiposity signal. Both hormones circulate at concentrations proportional to the amount of body fat and enter the central nervous system where leptin and insulin receptors are expressed by neurons involved in energy homeostasis; administration of either molecule into the brain reduces food intake,

whereas its deficiency does the opposite^(27,205). The breeding of mice with brain-specific insulin receptor deficiency, which translates into an increased food intake and diet-sensitive obesity, demonstrated a critical role for brain insulin signalling in the central regulation of energy disposal and fuel metabolism⁽²⁰⁴⁾. The central effect of insulin on the reduction of food intake is mainly mediated through an inhibition of NPY/AgRP neurons and the stimulation of POMC neurons^(27,202). Besides these basic homeostatic circuits, food palatability and reward are thought to be major factors involved in the regulation of food intake elicited by insulin and leptin⁽²⁰⁶⁾. Although it was initially considered that the effect of insulin was dose dependent, with low doses stimulating thermogenesis and high doses decreasing it⁽²⁰⁷⁾, further studies have shown the thermogenic effect of insulin^(208,209).

Glucagon

Glucagon is secreted by the α -cells of the pancreatic islets. It has catabolic properties, functioning as a counter-regulatory hormone opposing the actions of insulin. Glucagon maintains blood glucose concentrations during fasting by promoting glycogenolysis and gluconeogenesis as well as by inhibiting glycogenesis and glycolysis in the liver, thereby preventing hypoglycaemia^(210,211). Obese patients exhibit increased glucagon levels^(212,213). Inappropriately elevated concentrations of insulin and glucagon, together with insulin resistance, contribute to the obesity-associated impaired glucose homeostasis⁽²¹⁴⁾.

Glucagon exerts many extrahepatic actions. It increases lipolysis in adipose tissue and reduces food intake, acting as a satiety factor in the brain⁽²¹¹⁾. In humans, pharmacological doses of glucagon decrease the amount of food that is eaten⁽²¹⁵⁾. Although this effect was initially attributed to an indirect action of glucagon via the increase in portal glucose levels⁽²¹⁶⁾, it has been clearly demonstrated that glucagon has central actions in the brain to reduce food intake⁽²¹⁷⁾. Administration of glucagon has been shown to produce weight loss in humans and rats^(218,219). This can be explained by the fact that glucagon causes an increase in energy expenditure⁽²²⁰⁾ via activation of BAT⁽²¹⁹⁾. The effect of glucagon on human BAT remains to be fully clarified. However, this effect of glucagon promoting energy expenditure contrasts with the phenotype observed in glucagon receptor knockout mice that exhibit lower adiposity, despite having normal growth rates, body weight, food intake and resting energy expenditure⁽²²¹⁾. Similar striking observations are reported for mice lacking synaptotagmin-7, a Ca sensor for insulin and glucagon granule exocytosis, which show normal insulin concentrations but severely reduced glucagon levels. This mouse model exhibits a lean phenotype with increased lipolysis and energy expenditure⁽²²²⁾. A potential counter-regulatory increase in GLP-1 in mice lacking glucagon signalling could explain these discrepancies⁽²²³⁾.

Pancreatic polypeptide

PP is a thirty-six-amino acid peptide belonging to the family of peptides including NPY and PYY, which is secreted postprandially under vagal control by pancreatic islet PP cells^(19,224). Circulating levels of PP are apparently normal in obese patients^(225,226) but the rapid increase in response to a meal observed in healthy subjects is significantly impaired in obese individuals^(227,228).

Peripheral administration of PP acutely reduces food intake and gastric emptying and increases energy expenditure in mice, whereas repeated administration during 2 weeks leads to reductions in body weight gain⁽²²⁹⁾. Similar effects are observed in transgenic mice overexpressing PP⁽²³⁰⁾. The anorectic effect is mediated through Y4 receptors and is associated with reduced expression of NPY and orexin mRNA in the hypothalamus, being dependent on intact vagal signalling⁽²²⁹⁾. In humans, intravenous infusion of PP leads to delayed gastric emptying and reduced cumulative 24 h food intake^(231,232). To our knowledge, there are no data reporting the effect of PP on energy expenditure in humans.

Amylin

Amylin, a peptide co-secreted with insulin postprandially by pancreatic β -cells and, therefore, also named islet amyloid polypeptide, was firstly isolated from diabetic human pancreas⁽²³³⁾. Amylin inhibits gastric emptying as well as gastric acid and glucagon secretion^(19,234,235). Increased circulating concentrations of amylin have been reported in obese rats and humans, suggesting a role for amylin in the pathophysiology of obesity⁽²³⁶⁾.

Central or peripheral administration of amylin decreases meal size and food intake by promoting meal-ending satiation⁽²³⁵⁾. The anorectic effects of amylin, in contrast to other gut peptides, take place primarily in the area postrema, showing synergy with PYY, CCK and leptin⁽²³⁷⁾. Mechanistic studies in rodents suggest that amylin reduces body weight in a fat-specific manner, preserving lean mass⁽²³⁷⁾. The synthetic amylin analogue pramlintide is prescribed for the treatment of diabetes but also causes mild progressive weight loss in humans⁽²³⁸⁾. Furthermore, pramlintide also exhibits synergic effects with leptin after 20 weeks of treatment in overweight and obese volunteers⁽²³⁹⁾. In addition to its role eliciting satiety, amylin appears to influence energy balance by increasing energy expenditure^(240–242). Amylin administration increases lipid utilisation, as indicated by a lower respiratory quotient, reducing adiposity⁽²⁴³⁾. Finally, it has been suggested that amylin could prevent the compensatory decrease in energy expenditure that typically takes place during or after weight loss⁽²³⁵⁾.

Signals from the gut

The gastrointestinal tract is the largest endocrine organ in the body, representing an important source of regulatory

hormones⁽²⁴⁴⁾. The gut uses neural and endocrine pathways to coordinately regulate food intake and energy expenditure in the hypothalamus⁽²⁴⁵⁾. Ghrelin is considered the only circulating orexigenic hormone, which seems to act as a meal initiator⁽²⁴⁶⁾. Satiety signals derived from the gut include GLP-1, PYY, CCK and oxyntomodulin, among others^(234,244,245,247,248). Recently, the existence of another peptide, prouroguanylin, produced by the intestine and with satiating effects has been reported⁽¹⁶⁾.

Ghrelin

Ghrelin is a twenty-eight-amino acid peptide secreted by oxyntic cells in the stomach fundus. Ghrelin was first characterised as a natural ligand of the growth hormone secretagogue receptor⁽²⁴⁹⁾. In subsequent studies ghrelin was shown to participate in the complex entero-hypothalamic control of food intake signalling⁽²⁵⁰⁾. Central or peripheral administration of ghrelin increases food intake and adiposity in rodents^(251,252) and humans^(253,254). In humans, plasma ghrelin concentrations have been shown to rise shortly before and fall quickly after every meal, suggesting a role in meal initiation⁽²⁵⁵⁾. Ghrelin concentrations are decreased in human obesity⁽²⁵⁶⁾, which has been explained as a physiological adaptation to the positive energy balance associated with obesity, and increase in response to diet-induced weight loss⁽²⁵⁷⁾. However, many studies have shown that ghrelin concentrations do not increase after surgically induced weight loss following procedures that compromise the functionality of the fundus^(258,259), while other studies have reported an increase in ghrelin levels following bariatric surgery⁽²⁶⁰⁾.

Chronic central or peripheral administration of ghrelin increases cumulative food intake and decreases energy expenditure, resulting in body weight gain^(250,251,253,261). The orexigenic effect of ghrelin is mediated by the activation of NPY/AgRP, since ghrelin does not stimulate feeding in NPY and AgRP double knockout mice⁽²⁶²⁾, and it is also mediated by the inhibition of hypothalamic fatty acid biosynthesis⁽²⁶³⁾. In this sense, the absence of ghrelin or its receptors protects against the development of early-onset obesity^(264,265) and mice lacking simultaneously ghrelin and its receptor exhibit an increased energy expenditure⁽²⁶⁶⁾. Therefore, ghrelin signalling inhibition has been suggested as a potential therapeutic tool in obesity treatment, whereas a direct therapeutic application of ghrelin can be contemplated for the treatment of cachexia and anorexia⁽²⁴⁸⁾. In this sense, intravenous administration of ghrelin results in weight gain in patients with cardiac cachexia and chronic obstructive pulmonary disease^(267,268).

Glucose-dependent insulinotropic polypeptide

Insulin secretion is higher in response to orally administered than to intravenous glucose administration. This is

known as the incretin effect⁽²⁶⁹⁾. Originally named gastric inhibitory polypeptide, glucose-dependent insulinotropic polypeptide (GIP) was the first incretin identified⁽²⁷⁰⁾. The major stimulus for GIP secretion is nutrient intake. GIP is mainly secreted by K cells in the duodenum and jejunum^(269,271). Circulating concentrations of GIP are low in the fasting state and rise within minutes following food intake. Moreover, GIP levels increase after a high-fat diet, with postprandial GIP secretion being significantly higher in obese subjects than in age-matched lean individuals^(271,272). In addition to its role in regulating insulin secretion, GIP stimulates β -cell replication and mass expansion at the same time as it stimulates glucagon secretion^(273,274). In addition, GIP inhibits gastric acid secretion and gastric emptying, although only at supraphysiological doses⁽²⁷⁵⁾.

The GIP receptor (GIPR) is present in adipose tissue, regulating adipocyte growth, and there is a large body of biochemical and animal data suggesting that GIP signalling promotes fat accumulation^(271,276–278). Chemical or genetic ablation of GIP signalling or targeted reduction of GIP-secreting cells does not modify food intake^(278–281). However, the absence of GIP signalling produces a significant increase in energy expenditure, protecting from high-fat diet-induced obesity and insulin resistance^(278,279,281). Moreover, peripheral administration of synthetic human GIP reduces energy expenditure in healthy subjects but not in patients with T2DM⁽²⁸²⁾. Furthermore, emerging evidence suggests that the rapid resolution of diabetes in morbidly obese patients undergoing bypass surgery is mediated, at least in part, by surgical removal of GIP-secreting cells in the upper small intestine⁽²⁸³⁾. Although inhibiting GIP/GIPR signalling may be beneficial as a treatment for obesity⁽²⁷¹⁾, the mechanisms involved in the regulation of food intake and energy expenditure elicited by GIP in humans remain to be fully understood.

Glucagon-like peptide 1

Through action of prohormone convertases, proglucagon is processed to glicentin, oxyntomodulin, intervening peptides 1 and 2, GLP-1 and GLP-2. To date, only GIP and GLP-1 are considered to be incretin hormones in humans, being responsible for as much as 50% of postprandial insulin secretion^(274,284). GLP-1 is mainly produced by L-cells in the ileum after meals; in addition to its role as an insulinotropic hormone it participates actively in regulating gastric motility, islet β -cell neogenesis, neuronal plasticity and the suppression of plasma glucagon concentrations^(285,286). Although a clear role for GLP-1 in the aetiology of T2DM has not been proved, a common view states that GLP-1 secretion in patients with T2DM is deficient⁽²⁸⁷⁾. Similarly, some controversies exist regarding the involvement of GLP-1 in obesity pathophysiology. It has been suggested that obesity is associated with reduced secretion of GLP-1^(288–290), which is restored to normal



levels after weight loss⁽²⁹¹⁾, particularly following malabsorptive bariatric surgery⁽²⁹²⁾.

GLP-1 has an important role in food intake regulation, promoting satiety^(293–295) even in obese men^(296,297), acting as a short-term satiation signal, limiting the amount of food eaten and prolonging time between meals⁽²⁹⁸⁾. Another important action of this incretin in relation to energy homeostasis is the inhibition of gastric emptying following GLP-1 administration, with the vagus nerve playing an important role^(286,297). Intravenous administration of GLP-1 increases postprandial energy expenditure via the lower brainstem and the sympathoadrenal system in rats⁽²⁹⁹⁾. Exogenous administration of GLP-1 to humans reduces postprandial thermogenesis, which can be explained by a reduction in meal size⁽²⁹⁷⁾. However, higher fasting plasma concentrations of GLP-1 are associated with higher resting energy expenditure and fat oxidation rates in humans⁽³⁰⁰⁾. Data regarding energy expenditure from mice deficient in GLP-1 signalling are conflicting, with some studies finding that loss of function protects against the development of diet-induced obesity by increasing energy expenditure^(281,301,302), while others show that loss of GLP-1 signalling increases fat accumulation^(303,304). These differences may be related to species-specific differences and effects on locomotor activity⁽³⁰⁵⁾.

GLP-1 signalling is a potential target for the treatment of both T2DM and obesity. In this sense, liraglutide, a GLP-1 analogue with a prolonged half-life initially developed for the treatment of T2DM, has shown additional beneficial features for body weight control^(306,307). In this context, activation of the GLP-1 receptor is currently proposed as the most effective drug for treating the metabolic syndrome⁽³⁰⁸⁾.

GLP-2 has also been involved in the regulation of food intake⁽³⁰⁹⁾. However, deletion of GLP-2 receptor signalling in *ob/ob* mice impairs the normal islet adaptive response needed for maintaining glucose homeostasis but has no effect on body weight or food intake⁽³¹⁰⁾. GLP-2 has also been associated with gut hypertrophy and intestinal crypt cell proliferation after gastric bypass⁽³¹¹⁾ but has no effect on energy expenditure⁽²⁹⁹⁾.

Further evidence of the important involvement of incretins in energy homeostasis arises from studies involving dipeptidyl peptidase 4 (DPP-4). DPP-4 is a member of the prolyl oligopeptidase family of peptidases and is the key enzyme responsible for cleaving and inactivating GIP and GLP-1⁽³¹²⁾. Mice lacking DPP-4 exhibit improved glucose tolerance and insulin sensitivity as well as resistance to diet-induced obesity, which can be explained by reduced food intake and increased energy expenditure⁽³¹³⁾.

Peptide YY

PYY is a thirty-six-amino acid gut hormone so called after the tyrosine residues at each terminus of the peptide that belongs to the NPY family^(314,315). It is secreted mainly from specialised enteroendocrine cells, called L-cells, of

the distal gut, with the highest production being in the ileum and colon. Two main endogenous forms of PYY exist, PYY_{1–36} and PYY_{3–36}. PYY_{3–36} is the dominant circulating form of the peptide both in the fasted and fed states, accounting for 60% of postprandial circulating PYY^(316,317). Circulating concentrations of PYY rise within 15 min after nutrient ingestion. PYY_{1–36} has specificity for Y1 and Y5 receptors, increasing food intake. However, PYY_{3–36} binds preferentially to Y2 receptors, thereby stimulating anorectic pathways⁽³¹⁸⁾. Lower levels of PYY_{3–36} have been reported in obese individuals, suggesting that this gut hormone has a role in the pathophysiology of obesity⁽³¹⁹⁾.

Peripheral injection of PYY_{3–36} has been shown to reduce food intake and to induce a negative energy balance in mice and rats⁽³²⁰⁾, monkeys⁽³²¹⁾ and humans⁽³²⁰⁾, even in obese patients⁽³¹⁹⁾. This occurs through modulation of different cortical and hypothalamic brain areas⁽³²²⁾. However, these anorexigenic effects of PYY_{3–36} have not been confirmed by others⁽³²³⁾. Furthermore, despite the effects of PYY_{3–36} on food intake inhibition, mice lacking Pyy do not exhibit a clear phenotype, showing normal feeding behaviour, growth and energy expenditure^(324,325), or even obesity^(326,327). Intravenous administration of PYY_{3–36} increases lipolysis and energy expenditure in humans⁽³²⁸⁾, with total PYY being significantly correlated with postprandial energy expenditure⁽³²⁹⁾. However, this association has not been unequivocally found⁽³³⁰⁾. The extent of PYY_{3–36} involvement in the regulation of energy homeostasis and the underlying mechanisms mediating the effects of PYY_{3–36} on energy expenditure in humans are still not fully understood.

Cholecystokinin

CCK is secreted mainly by I-cells in the proximal small intestine in response to lipids and proteins in the meal^(19,234,331). The predominant circulating forms of CCK in rodents include CCK octapeptide (CCK-8) and CCK-22, whereas larger molecular forms are also present in human plasma⁽³³²⁾. CCK is involved in modulating intestinal motility, stimulating pancreatic enzyme secretion, enhancing gallbladder contraction and regulating meal size but not meal frequency⁽³³³⁾. A total of two CCK receptors have been cloned so far: CCK1R and CCK2R. Selective CCK1R antagonists block the anorectic effect of CCK, whereas selective antagonism of CCK2R has no effect on food intake^(234,334–336).

The satiating effect of CCK was first described more than three decades ago⁽³³⁷⁾, with vagotomy suppressing the anorectic effects of peripheral CCK⁽³³⁸⁾. In humans, intravenous infusion of CCK induces a dose-dependent suppression of food intake⁽³³⁹⁾. Administration of CCK before the start of a meal does not delay the onset of eating, but rather reduces the amount of food consumed once eating begins⁽¹²⁾.

However, long-term CCK1R stimulation failed to produce significant weight loss in obese patients due to the rapid development of tolerance^(340,341), thereby questioning the potential of CCK as an anti-obesity target⁽²³⁴⁾.

Rats deficient in CCK1R show increased meal size and obesity⁽³⁴²⁾. However, mice lacking CCK or CCK1R exhibit a normal food intake and body weight, apparently indicating that CCK is not essential for the long-term maintenance of body weight^(333,335). Interestingly, CCK knockout mice fed on a high-fat diet develop protection against obesity despite having a normal food intake, probably through decreased lipid absorption and increased energy expenditure⁽³³⁶⁾.

Oxyntomodulin

Oxyntomodulin is another cleavage product of proglucagon secreted by intestinal L-cells after meals in proportion to the energy content of foods^(343,344). It was named oxyntomodulin after its inhibitory action on the oxyntic glands of the stomach⁽³⁴⁵⁾. Oxyntomodulin inhibits gastric acid secretion and pancreatic enzyme secretion⁽³⁴⁶⁾. Although no oxyntomodulin receptor has been identified yet, it appears that the actions of oxyntomodulin are mediated via the GLP-1 receptor⁽³⁴⁷⁾, since the anorectic effect of oxyntomodulin is abolished in GLP-1 receptor-deficient mice⁽³⁴⁸⁾. However, GLP-1 and oxyntomodulin appear to activate different hypothalamic pathways⁽³⁴⁹⁾ and, therefore, a separate unidentified oxyntomodulin receptor may exist⁽³¹⁵⁾.

Central or peripherally administered oxyntomodulin inhibits food intake in fasted and non-fasted rats^(350,351). However, the anorectic effect in mice is only observed after intracerebroventricular administration⁽³⁴⁸⁾. Intravenous administration of oxyntomodulin suppresses appetite and reduces food intake in humans⁽³⁵²⁾. Furthermore, subcutaneous injections of oxyntomodulin resulted in weight loss and a change in the levels of adipokines consistent with a loss of body fat over a 4-week period in overweight and obese subjects⁽³⁵³⁾. Central administration of oxyntomodulin increases energy expenditure and causes a disproportionate reduction in body weight compared with pair-fed rats^(351,354). In humans, 4 d subcutaneous self-administration of pre-prandial oxyntomodulin three times per d promotes a negative energy balance, increasing energy expenditure while reducing energy intake⁽³⁵⁵⁾. However, the acute thermogenic effect of oxyntomodulin observed in rats and humans has not been reproduced in mice⁽³⁴⁸⁾. Further studies are needed in order to investigate whether the effect of oxyntomodulin on energy expenditure in humans is maintained in the long term, but data presented above support the role of oxyntomodulin as a potential anti-obesity tool.

Uroguanylin

Guanylin and uroguanylin have been well-known key paracrine players in intestinal ion and water balance for

over 20 years, acting as endogenous ligands of guanylyl cyclase (GUCY) 2C and increasing cyclic guanosine monophosphate (cGMP) production⁽³⁵⁶⁾. They are secreted by intestinal epithelial cells as prohormones, requiring proteolytic enzymic conversion into active hormones in the target tissue⁽³⁵⁷⁾. Physiological functions for these molecules include the modulation of epithelial cell balance in the intestinal epithelium and the regulation of Na balance through actions on the kidney⁽³⁵⁸⁾. Recently, Valentino *et al.*⁽¹⁶⁾ revealed a new endocrine role for uroguanylin in energy homeostasis. The uroguanylin precursor, prouroguanylin, is secreted into the circulation after meals in both mice and humans; it can then be cleaved to uroguanylin in the hypothalamus to activate GUCY2C for decreasing food intake⁽¹⁶⁾. Deletion of GUCY2C in mice disrupts appetite regulation specifically by impairing satiation, producing hyperphagia associated with obesity and glucose intolerance⁽¹⁶⁾. No changes in cold-induced thermogenesis assessed by core body temperature were observed⁽¹⁶⁾. However, the role of uroguanylin in the modulation of energy expenditure needs to be addressed in both rodents and humans. Furthermore, it has been suggested that uroguanylin could exert a direct effect on adipose tissue, regulating lipolysis⁽³⁵⁹⁾, given the fact that cGMP is a second messenger known to be involved in the lipolytic effect of natriuretic peptides, which are closely related to uroguanylin⁽³⁶⁰⁾. The uroguanylin–GUCY2C endocrine axis may offer a novel therapeutic target for regulating food intake and a weapon against obesity^(16,359).

Fibroblast growth factor 19

The family of fibroblast growth factors (FGF) regulates a plethora of processes including organ development, the maintaining of bile acid homeostasis and the activation of hepatic protein and glycogen synthesis^(361,362). FGF19 is expressed in the distal small intestine, with the concentration of circulating FGF19 increasing in response to feeding. Transgenic mice expressing human FGF19 exhibit an increased metabolic rate and decreased adiposity despite having increased food intake with an increase in fatty acid oxidation^(363,364). However, in addition to its metabolic actions FGF19 also has proliferative effects, with transgenic mice developing hepatocellular carcinoma within 1 year, thereby rendering FGF19, *a priori*, unsuitable as a candidate for combating obesity⁽³⁶⁵⁾.

Signals from the liver

The liver plays an important role in energy homeostasis⁽³⁶⁶⁾. Due to its anatomical position the liver has rapid access to incoming nutrients from intestinal absorption. In addition to its role in regulating glucose and fatty acid metabolism, the liver produces several proteins involved in peripheral control of energy homeostasis.

Insulin-like growth factor system

Members of the insulin-like growth factor (IGF) system are functionally related to insulin. The IGF regulatory system consists of IGF (IGF-I and IGF-II), type I and type II IGF receptors, and IGF-binding proteins (IGFBP-1–6)^(367,368). IGF are ubiquitously expressed, although the main source of circulating IGF-I is the liver. They exert actions in almost all tissues and are among the major regulators of growth^(368,369). While insulin is a short-term regulator of glucose homeostasis, IGF have been suggested to exert long-term regulation of glucose homeostasis^(370–372). Insulin and IGF-I show cross-reactivity at the receptor level. After ligand binding-induced autophosphorylation, insulin receptor and IGF-I receptor catalyse the phosphorylation of cellular proteins such as members of the insulin receptor substrate family⁽³⁷³⁾. Other functions in which IGF play a critical role are the regulation of growth, neuroprotection, tumorigenesis and longevity^(372,374,375). Adipose tissue levels of IGF-I have been shown to be higher in both rodent and human obesity⁽³⁷⁶⁾, although the IGF-I-induced signalling cascade is impaired in obese mice⁽³⁷⁷⁾.

IGF-I treatment by osmotic minipumps at adult age reduces hyperphagia, obesity, hyperinsulinaemia, hyperleptinaemia and hypertension in rats programmed to develop the metabolic syndrome by fetal programming⁽³⁷⁸⁾. However, IGF-I administration does not exhibit anorectic effects in sheep⁽³⁷⁹⁾. Singularly, another study reported that central injection of IGF-II, but not IGF-I, reduces short-term food intake in rats⁽³⁸⁰⁾. It has been recently reported that IGF-I may play an important role in thermogenesis⁽³⁷⁵⁾. Administration of IGF-I to the preoptic area, a hypothalamic region involved in the control of thermoregulation, produces hyperthermia involving activation of BAT in mice⁽³⁷⁵⁾. This thermogenic effect was accompanied by a switch from glycolysis to fatty acid oxidation and appears to be dependent of the insulin receptor, since it is absent in mice lacking the neuronal insulin receptor. These findings suggest a more important role of the IGF system in energy expenditure than previously thought⁽³⁷⁵⁾.

Although IGFBP are generally thought to inhibit the action of IGF through high-affinity binding which prevents interaction with IGF receptors, IGFBP can potentially either inhibit or enhance IGF actions^(368,381). Overexpression of IGFBP2 by adenovirus prevents weight gain and hyperglycaemia in diet-induced obese mice⁽³⁸²⁾. Moreover, it reverses diabetes at the same time as reducing food intake and inhibits body weight gain in insulin-resistant *ob/ob* mice by unexplored mechanisms⁽³⁸³⁾.

Fibroblast growth factor 21

FGF21 is a pleiotropic hormone-like protein that has emerged as a major regulator of energy homeostasis⁽³⁸⁴⁾.

Production of FGF21 takes place mainly in the liver⁽³⁸⁵⁾ and is regulated by PPAR α ⁽³⁸⁶⁾. FGF21 has been shown to be a major regulator of hepatic lipid metabolism in ketotic states, being up-regulated during fasting^(386,387). FGF21 transgenic mice are resistant to diet-induced obesity, with FGF21 administration reducing serum glucose and TAG levels in obese and diabetic *ob/ob* and *db/db* mice⁽³⁸⁸⁾. In humans, FGF21 correlates with BMI and may be a novel biomarker for fatty liver⁽³⁸⁹⁾. Since the expected beneficial effects of endogenous FGF21 for improving glucose tolerance and reducing TAG levels are absent in obese mice and men, obesity has been proposed to be a FGF21-resistant state⁽³⁹⁰⁾.

Intraperitoneal injections or central administration of FGF21 increases energy expenditure, improves insulin sensitivity and reverses hepatic steatosis in diet-induced obese mice⁽³⁹¹⁾ and rats⁽³⁹²⁾. The thermogenic effect may be related to the activation of BAT, since it has been reported that this adipose depot may be a source of FGF in response to cold, exhibiting an autocrine role in the stimulation of thermogenesis⁽³⁹³⁾. Although the wide interindividual variation in serum FGF21 observed in humans raises some doubts regarding its therapeutic relevance⁽³⁸⁴⁾, the reported metabolic effects of FGF21 highlight the need for more research in order to assess the use of FGF21 for treating metabolic diseases.

Sex hormone-binding globulin

Sex hormone-binding globulin (SHBG) transports androgens and oestrogens in blood and regulates their access to target tissues⁽³⁹⁴⁾. SHBG is mainly produced by hepatocytes and its secretion fluctuates, being primarily influenced by metabolic and hormonal factors⁽³⁹⁴⁾. Obesity results in reduced hepatic synthesis and blood concentrations of SHBG, with blood levels of SHBG correlating negatively with energy expenditure in postmenopausal women⁽³⁹⁵⁾ and with fat accumulation in men⁽³⁹⁶⁾. Moreover, low circulating concentrations of SHBG are a strong predictor of the risk of T2DM in men and women⁽³⁹⁷⁾ as well as of the metabolic syndrome in non-obese men⁽¹⁹⁴⁾. This finding has been related to the suppressive effect of insulin on SHBG. Furthermore, the combined effect of increased levels of sex hormones previously mentioned, together with the reduced concentrations of SHBG, leads to an increase in the bioavailable androgens and oestrogens which may promote cellular proliferation and inhibit apoptosis in target cells, thereby being involved in the increased risk of cancer associated with obesity⁽³⁹⁸⁾.

Signals from skeletal muscle

In humans, skeletal muscle represents 40% of the total body mass and accounts for approximately 20–30% of the total resting oxygen uptake⁽³⁹⁹⁾. A large part of the adaptive thermogenic response is determined by skeletal



muscle via the process of mitochondrial uncoupling⁽⁴⁰⁰⁾. Furthermore, skeletal muscle secretes myostatin, which has been shown to play a role in energy homeostasis⁽¹⁷⁾. Exercise is well known to exert beneficial effects on energy balance control. Recently, irisin has been identified as an exercise-induced hormone secreted by skeletal muscle that promotes brown adipocyte recruitment in white fat, thereby increasing energy expenditure⁽⁴⁰¹⁾.

Myostatin

Myostatin is a secreted member of the transforming growth factor- β (TGF- β) family that acts as a negative regulator of skeletal muscle growth by signalling through activin receptors⁽⁴⁰²⁾. During adulthood, the myostatin protein is produced by skeletal muscle, circulates in the blood, and limits muscle mass⁽⁴⁰²⁾. Myostatin is expressed almost exclusively in skeletal muscle, although detectable levels of myostatin mRNA are also present in adipose tissue. Myostatin overexpression in mice induces a dramatic loss of muscle and adipose tissue mass with normal food intake⁽⁴⁰³⁾. The loss of fat is concordant with the capacity of myostatin to block adipogenesis⁽⁴⁰⁴⁾. As can be expected, mice lacking myostatin exhibit increased muscle mass but, surprisingly, show reduced adiposity⁽⁴⁰⁵⁾. This finding can be explained by an increased fatty acid oxidation in peripheral tissues through the stimulation of enzymes involved in lipolysis and in mitochondrial fatty acid oxidation⁽⁴⁰⁶⁾. The decreased fat mass of myostatin-null mice can be further explained by a concomitant stimulation of thermogenesis through the activation of BAT⁽⁴⁰⁶⁾. Inhibition of myostatin signalling either in skeletal muscle or adipose tissue evidenced that body fat loss is an indirect result of metabolic changes in skeletal muscle⁽⁴⁰⁷⁾, apparently mediated by increased energy expenditure and leptin sensitivity⁽¹⁷⁾. Interestingly, skeletal muscle myostatin protein levels and plasma concentrations were higher in extremely obese women, with the former being correlated with the severity of insulin resistance⁽⁴⁰⁸⁾. Leptin replacement increases muscle mass of *ob/ob* mice, and this effect is associated with a leptin-induced reduction in the skeletal muscle expression of myostatin⁽⁴⁰⁹⁾. However, leptin administration to hypoleptinaemic women did not decrease serum levels of myostatin, suggesting that leptin is not probably involved in the regulation of the myostatin axis in humans, although expression of myostatin in skeletal muscle was not measured⁽⁴¹⁰⁾. Recently, the association of myostatin gene polymorphisms with obesity in humans has been reported, although the pathophysiological mechanisms remain to be elucidated⁽⁴¹¹⁾.

Signals from the kidney

Under normal circumstances the kidney is not directly involved in energy homeostasis. However, it exerts a notable role in the peripheral control of energy

metabolism, secreting primary molecules that participate in the renin–Ang system⁽¹⁷⁴⁾.

Renin

As mentioned previously, an overactive renin–Ang system has been involved in the development of obesity-associated co-morbidities as well as in energy homeostasis⁽¹⁷⁴⁾. Renin catalyses the rate-limiting step of Ang II production⁽¹⁷⁴⁾. Mice lacking renin exhibit lower blood pressure and undetectable plasma levels of renin, Ang I and Ang II⁽⁴¹²⁾. Unexpectedly, these mice are resistant to diet-induced obesity via an increased metabolic rate and partly through a gastrointestinal loss of dietary fat, but not from increased locomotor activity or reduced food intake⁽¹⁴⁾. Some, but not all, of the observed alterations were reversed after Ang II administration. Furthermore, it has been reported that transgenic rodents overexpressing renin eat significantly more after 24 h than controls⁽⁴¹³⁾ and develop obesity⁽⁴¹⁴⁾ by mechanisms not related to Ang II⁽⁴¹⁵⁾. These findings suggest that renin inhibitors may be a therapeutic tool against obesity, insulin resistance and their cardiometabolic co-morbidities.

Signals from the heart

The discovery of atrial natriuretic peptide (ANP) showed that the heart is not only a mechanical organ pumping blood through the blood vessels, but also an endocrine organ involved in the regulation of the cardiovascular–renal system and energy metabolism⁽⁴¹⁶⁾.

Atrial natriuretic peptides

ANP and brain natriuretic peptide (BNP) are synthesised in the heart and they are considered to exert their predominant effects in lowering blood pressure, controlling blood volume and reducing heart overgrowth in pathological conditions⁽⁴¹⁷⁾. Another related peptide, C-type natriuretic peptide (CNP) is expressed mainly in the central nervous system but also in the vascular endothelial cells and chondrocytes⁽⁴¹⁸⁾. ANP and BNP preferentially bind to GUCY-A, promoting the production of cGMP and the activation of protein kinase G⁽⁴¹⁹⁾. CNP is the physiological ligand for GUCY-B.

All members of the system (natriuretic peptides and their receptors) are expressed in adipose tissue, while their expression levels are altered in obesity^(417,420–423). ANP and BNP, but not CNP, have been reported to induce potent lipolytic effects in human adipocytes similar to those exerted by the β -adrenoceptor agonist isoproterenol^(360,424). Moreover, ANP inhibits human visceral adipocyte growth in culture at physiological concentrations⁽⁴²⁵⁾. ANP availability is decreased in obesity, with BMI being inversely correlated to circulating ANP and BNP concentrations⁽⁴²⁶⁾.



Besides their physiological role as lipid-mobilising agents, natriuretic peptides are also involved in the regulation of food intake and energy expenditure. CNP suppresses oxygen consumption in BAT in mice by attenuating the sympathetic nervous system activity, possibly under the control of the hypothalamus⁽⁴²⁷⁾. Furthermore, it has been shown that natriuretic peptides can promote muscle mitochondrial biogenesis and fat oxidation, preventing the development of obesity and insulin resistance in mice⁽⁴²⁸⁾. In this sense, intravenously administered ANP induces postprandial lipid oxidation in humans and increases energy expenditure⁽⁴²⁹⁾. These findings suggest that natriuretic peptides may represent a promising therapeutic tool for combating obesity and T2DM.

Signals from the thyroid gland

The thyroid gland, through the production of thyroid hormones, is a major determinant of overall energy expenditure and BMR⁽⁴³⁰⁾.

Thyroid hormones

The thyroid gland produces the parental form of thyroid hormone, thyroxine (T₄), and lower amounts of the major active form of thyroid hormone, triiodothyronine (T₃)⁽⁴³¹⁾. T₃ is produced by deiodination of T₄ in target cells by specific deiodinases. Secretion of T₄ by the thyroid gland is stimulated by thyroid-stimulating hormone secreted by the pituitary gland⁽⁴³²⁾. Thyroid hormones bind to thyroid hormone receptor (THR) α and THR β , which are members of the nuclear hormone receptor family⁽⁴³³⁾. Thyroid hormones affect numerous cellular processes that are relevant for energy homeostasis⁽⁴³⁰⁾. Thyroid-stimulating hormone is usually moderately increased in obesity, which is a consequence rather than a cause of obesity⁽⁴³⁴⁾. Alterations in thyroid hormones affect body weight. Hypothyroidism is frequently associated with a modest weight gain, decreased metabolic rate and cold intolerance, whereas hyperthyroidism is related to weight loss despite increased appetite and elevated metabolic rate^(434,435).

Hyperthyroidism in humans and rodents causes increased food intake but reduced body weight compared with euthyroid controls due to increased energy expenditure. The increase in oxygen consumption and body temperature is accompanied by enhanced fatty acid oxidation⁽⁴³¹⁾. Evidence of the critical role of thyroid hormones on energy homeostasis arises from genetic mouse models lacking THR^(436,437). Mice lacking THR α ⁽⁴³⁸⁾ or THR β ⁽⁴³⁹⁾ exhibit reduced thermogenesis as well as other metabolic alterations. Although the involvement of thyroid hormones in energy homeostasis is critical, the physiological mechanisms explaining this effect remain elusive. The thermogenic effect of thyroid hormones has been related

to accelerated ATP turnover and reduced efficiency of ATP synthesis as well as to changes in the efficiency of metabolic processes downstream from the mitochondria 'futile and substrate cycles'^(430,435). Peripheral administration of T₃ increases food intake but also energy expenditure⁽⁴⁴⁰⁾. An increase in hypothalamic AMPK may be mediating the orexigenic effect of T₃⁽⁴⁴¹⁾. Similarly, it has been recently described that besides the critical role of T₃ stimulating thermogenesis in skeletal muscle⁽⁴³⁰⁾, thyroid hormone-induced modulation of AMPK activity and lipid metabolism in the hypothalamus and subsequent thermogenic activation of BAT is a major regulator of whole-body energy homeostasis⁽⁴⁴²⁾. Although the information available makes the thyroid system an interesting field for the development of therapeutic drugs in the fight against obesity, available data regarding effectiveness of thyroid hormone therapy for treating obesity are inconclusive⁽⁴⁴³⁾.

Signals from bone

Both body fat mass and fat-free mass correlate directly with bone mineral density. Obesity has been proposed to exert a protective role in the development of osteoporosis⁽⁴⁴⁴⁾. On the contrary, low BMI is a risk factor for low bone quality and osteoporosis which is largely independent of age and sex⁽⁴⁴⁵⁾. There is a putative 'endocrine' interplay between adipose tissue and bone, with adipokines and molecules secreted by osteoblasts and osteoclasts (osteokines) being the links of a bone–adipose tissue axis⁽¹⁵⁾. In this sense, recent findings suggest that osteokines may exert an endocrine regulation on glucose homeostasis and body weight^(15,446).

Osteopontin

Osteopontin, also known as secreted phosphoprotein-1, bone sialoprotein-1 and early T lymphocyte activation (Eta-1) is a phosphoprotein expressed by a wide variety of cell types, such as osteoclasts, macrophages, hepatocytes and vascular smooth muscle cells, among others⁽⁴⁴⁷⁾. Osteopontin exerts important actions on bone turnover, serving as attachment for osteoclasts activating resorption^(447,448). In addition to bone remodelling, osteopontin is also involved in several pathophysiological processes including inflammation, immunity, neoplastic transformation, progression of metastases, wound healing and cardiovascular function⁽⁴⁴⁷⁾. Osteopontin has been shown to be also produced by adipocytes and to play an important role in obesity and obesity-associated insulin resistance^(39,449–453). Expression of osteopontin is dramatically increased in adipose tissue from obese individuals^(449,454,455), suggesting the important role that this protein has in the molecular alterations that take place during adipose tissue enlargement. Moreover, osteopontin has been suggested to play a pivotal role linking obesity to

insulin resistance development by promoting inflammation and the accumulation of macrophages in adipose tissue^(450,453,456). Higher levels of expression of osteopontin have been shown to be related to macrophage accumulation in adipose tissue and to liver steatosis in morbidly obese subjects⁽⁴⁵⁷⁾, which promote fibrosis progression in non-alcoholic steatohepatitis⁽⁴⁵⁸⁾. Furthermore, it has been recently shown that osteopontin expression is increased in omental adipose tissue of colon cancer patients, suggesting a potential role of osteopontin linking increased inflammation in visceral adiposity with neoplastic processes⁽⁴⁵⁹⁾.

Osteocalcin

Osteocalcin is a non-collagenous protein marker of osteoblastic activity thought to play a role in mineralisation and Ca homeostasis⁽⁴⁶⁰⁾. Osteocalcin is secreted mainly by osteoblasts and its levels decrease in malnutrition, starvation and anorexia nervosa. Osteocalcin has been traditionally considered as a biological marker of bone formation⁽⁴⁶⁰⁾ but now has also been shown to play a

role in the regulation of metabolism and in the development of CVD^(461–463).

The regulation of bone remodelling by leptin led to the hypothesis that bone exerts a role in the feedback control of energy homeostasis⁽⁴⁶⁴⁾. In this sense, mice lacking the osteoblast-secreted molecule osteocalcin exhibit an increased adiposity and insulin resistance^(464,465). Osteocalcin is able to improve glucose tolerance *in vivo* through the stimulation of the expression of insulin and β -cell proliferation and the induction of the expression of adiponectin and genes involved in energy expenditure in adipocytes^(464,466). In this sense, administration of osteocalcin improves glucose metabolism and prevents the development of T2DM in mice^(466,467).

Serum osteocalcin levels are positively associated with insulin sensitivity and secretion in non-diabetic subjects as well as in patients with type 2 diabetes^(462,468). Interestingly, osteocalcin concentrations are reduced in obese individuals and increase after weight loss in parallel to the reduction in visceral fat mass⁽⁴⁶⁹⁾. Finally, a recent work suggests that further molecules secreted by bone, yet to be identified, affect energy metabolism⁽⁴⁷⁰⁾.

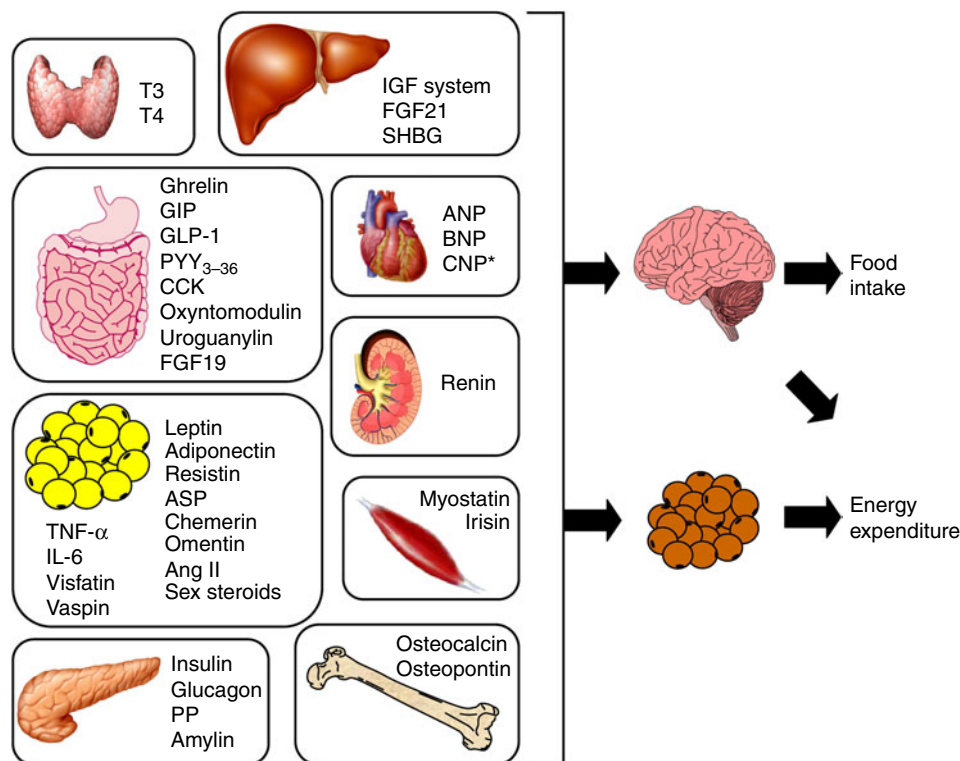


Fig. 1. Peripheral factors exerting a direct effect on energy homeostasis grouped by source organ or system. Although due to their multiple production organs some of the elements might be included in more than one organ or system, they have been included only under one organ or system for simplicity reasons. These molecules play an important role in energy homeostasis mainly, but not uniquely, through direct actions on the brain regulation of food intake and on the thermogenic activity of brown adipose tissue (BAT). In some cases, the effect on BAT activation is mediated via the hypothalamus. Ang II, angiotensin II; ANP, atrial natriuretic peptide; ASP, acylation-stimulating protein; BNP, brain natriuretic peptide; CCK, cholecystokinin; CNP, c-type natriuretic peptide; FGF19, fibroblast growth factor-19; FGF21, fibroblast growth factor-21; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; IGF, insulin-like growth factor; PP, pancreatic polypeptide; PYY₃₋₃₆, peptide YY (peptide tyrosine-tyrosine); SHBG, sex hormone-binding globulin; T3, triiodothyronine; T4, thyroxine. * Although CNP is mainly expressed in the central nervous system, it is also expressed in vascular cells (A colour version of this figure can be found online at <http://www.journals.cambridge.org/nrr>).

Conclusions

In summary, adipose tissue mass and energy homeostasis are regulated by a wide array of molecules derived not only by adipose tissue and the pancreas but also by the gut, liver, skeletal muscle, kidney, heart, thyroid gland and bone. This implies that the control of energy homeostasis is more complex than previously described and that the hypothalamus integrates hundreds of signals from many different peripheral organs. Moreover, many of these signals are able to stimulate thermogenesis in organs such as BAT and skeletal muscle (Fig. 1). The comprehension of these signals will help to better understand the aetiopathology of obesity and will contribute to the development of new therapeutic targets aimed at tackling excess body fat accumulation. More exact and precise knowledge regarding the complex interplay between the diverse and numerous peripheral signals as well as the pathophysiological alterations that take place in the different organs will lead to a better understanding of energy homeostasis and the causes and pathogenesis of obesity.

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