Adiposity signals, genetic and body weight regulation in humans

R Cancellò*, A Tounian*, Ch Poitou, K Clément

SUMMARY
Numerous signals convey information about body fat status from the periphery to the brain areas that control energy homeostasis so that, throughout life, body weight remains nearly stable. These signals mainly originate, either from the adipose tissue, like leptin and to a lesser extent interleukin 6, or from the pancreas, like insulin and amylin. These factors circulate in proportion to body fat mass and they are referred to as “adiposity signals”. It is well established, at least for leptin and insulin, that they enter the brain from the plasma where they induce/repress a network of important neuropeptide regulators of energy intake and expenditure. Beside these endocrine signals, a growing amount of literature show data relative to adipocyte-derived molecules, most of them belonging to the cytokine family, like IL6, TNFα, IL8, IL10 whose secretion also correlates with body fat mass and that may locally regulate fat mass expansion. Others, like Adiponectin, are negatively correlated with body fat mass. These “adiposity molecules” have already been involved in insulin resistance associated with obesity and inflammatory process. They may participate to a complex inter organ dialogue. In this review, we will synthesize data relative to the role played by insulin, leptin and amylin, either alone or through a cross talk, in “energy level sensing” at the brain level. Furthermore, we will develop how “adiposity molecules” through their paracrine and/or autocrine action may contribute to maintain fat mass expansion. Others, like Adiponectin, may locally regulate fat mass expansion. Among these molecules, most of them belonging to the cytokine family, like IL6, TNFα, IL8, IL10 whose secretion also correlates with body fat mass and that may locally regulate fat mass expansion.

Key-words: Adiposity signal • Metabolic signals • Obesity • White adipose tissue • Adipocytes • Inflammation • Insulin • Leptin.

RÉSUMÉ
Signaux d’adiposité, génétique et régulation du poids corporel chez l’homme
De nombreux signaux transmettent au cerveau des informations sur le statut des réserves d’énergie contribuant ainsi au contrôle de la balance énergétique et au maintien d’un poids relativement stable. Ces signaux sont produits par le tissu adipeux comme la leptine et l’interleukine 6 ou par le pancréas, comme l’insuline et l’amyline. Ces facteurs circulent en proportion de la masse graisseuse et sont appelés classiquement des signaux d’adiposité. Il est bien établi, au moins pour la leptine et l’insuline, que ces molécules sont transférées de la circulation vers le cerveau où elles induisent/répriment des circuits neuronaux clés qui contrôlent la prise alimentaire et la dépense énergétique. En dehors de ces molécules endocrines, un nombre croissant de molécules produites par le tissu adipeux sont décrites dans la littérature ; beaucoup d’entre elles appartiennent à la famille des cytokines comme IL6, TNFα, IL8, IL10 ou d’autres comme l’adiponectine. La plupart est exprimé ou sécrété en proportion inverse de la masse graisse et pourraient contribuer à contrôler localement son expansion. L’adiponectine, elle, est synthétisée en proportion inverse de la masse graisse. Ces molécules d’adiposité sont supposées impliquées dans l’insulinorésistance associée à l’obésité et à des processus d’inflammation. Elles participent probablement au dialogue complexe entre les organes. Nous résumons les informations sur le rôle joué par l’insuline, la leptine et l’amyline, soit seules ou via un dialogue complexe impliquant plusieurs d’entre elles, permettant ainsi au cerveau de percevoir les variations des réserves d’énergie. Nous citerons également le rôle d’autres molécules d’adiposité ayant un rôle paracrine et/ou autocrine mais pouvant également contribuer à l’équilibre énergétique. Elles représentent d’une certaine façon des « molécules sigiales d’adiposité ». Enfin, comme toute modification même modérée des circuits contrôlant les réserves d’énergie est susceptible de conduire à des situations pathologiques comme l’obésité, le rôle de polymorphismes situés dans les gènes codant pour ces molécules d’adiposité est discuté.

Mots-clés : Signal d’adiposité • Signaux métaboliques • Obésité • Tissu adipeux blanc • Adipocytes • Inflammation • Insuline • Leptin.

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“Adiposity signals” in the context of body weight regulation

Throughout life, body weight in humans varies within a very narrow range despite large day-to-day fluctuations in food intake [1]. Energy expenditure, classically, adjusts to energy intake and thanks to this mechanism energy balance remains stable over long periods of time [2, 3]. It has been suggested that individuals possess a predefined energy store status, referred to as body weight set point, determined by the combination of environmental and genetic factors. Any attempt to move away from the body weight set point remains vain [4]. The existence of this regulatory system implies a permanent and complex dialogue between the brain and peripheral tissues, including adipose tissues, but also other organs, such as the pancreas, the liver and muscles, that reflect the status of energy stores. The brain, and especially the hypothalamic nuclei, integrates this information from the periphery and in return, coordinates the adaptive response to energy imbalance. The hypothesis of the existence of an endocrine feedback loop, implying factors that circulate in proportion to body-fat content and act in the brain to reduce food intake was confirmed by the discovery of leptin ten years ago [5]. The fact that adiposity signals exist could thus no longer be doubted. To be considered as an adiposity signal, a molecule has to be secreted into the plasma in proportion to the body fat stores, be transported into the brain from the bloodstream, trigger expression of signal-transducing molecules in well-characterized hypothalamic and brainstem centres that regulate energy homeostasis and exert long-acting catabolic effects by decreasing food intake and increasing energy expenditure [6, 7]. Although these molecules have different modes of action in peripheral tissues, three of them meet the “classic” criteria of adiposity signals; insulin and amylin produced by the pancreatic β-cells and the hormone leptin, secreted by the adipose cells. Reproductive hormones have also been considered as adiposity signals but we will mainly focus on adipose tissue and pancreas produced signals. Genetic screening of the adiposity signal genes led to the discovery of genetic variations in their coding or regulatory regions that were sometimes associated with the modulation of adiposity signal circulating levels. This opened the question of the genetic contribution of adiposity signals to the control of body weight. Growing knowledge of adipose tissue biology and the possibility of studying gene expression on a large scale in human adipose tissue has offered — or will offer — new targets to be considered as adipocyte-derived signals. These factors can bear properties of adiposity signals and thus intervene in the long-term control of body weight. However for many of these new adiposity signals, proof of their role in a feedback loop of body weight regulation and especially their role at the brain level, is still to be provided. In this review, we will report data regarding well-known adiposity signals, mainly insulin, leptin and amylin and discuss the fact that there are also grounds for considering new molecules as possible adiposity signals, i.e. peptide hormones and cytokines that the adipocyte secretes and the fluctuation in the secretion of which reflects the variations in adipose state. The knowledge contributed by the discovery of genetic variation in these adiposity signals is also discussed.

Recognized adiposity signals

Leptin

While historically insulin was the first adiposity signal discovered, the “gold standard” in the field remains leptin, discovered ten years ago [5]. This adipocyte-derived hormone fully satisfies the criteria for an adiposity signal. In healthy animals [8], as in humans [9], circulating concentrations of leptin are highly correlated with body fat mass, it crosses the blood-brain barrier and interacts with neurons known to decrease food intake and stimulate thermogenesis [10]. The physiologically active isoforms of the leptin receptor (LEPR) are expressed in these neurons receiving the leptin signal from the periphery. Since its discovery, an increasing amount of knowledge has been gained in particular regarding the mode of action of leptin in the brain. Several brain pathways targeted by leptin have been described. Leptin globally activates anorexigenic neurons (such as proopiomelanocortin [POMC] derived neurons) through a neural network in the hypothalamic nuclei while it inhibits orexigenic neurons (such as NPY/AGRP neurons).

However, the simple model of negative feedback existing between body fat and the brain carried by leptin, that would avoid obesity development, appears more complicated than at first suggested. Substantial data suggest that the basal levels of leptin in the fed state represent a signal of energy sufficiency [10] (Fig 1). A relatively short-term period of food restriction, independent of reduction of fat stores, produces a clear-cut decrease in leptin levels. Reduced leptin levels trigger a neural response characteristic of starvation with food seeking behaviour, efficient metabolism and an array of neuroendocrine responses that help survival in periods of food scarcity [10]. In the brain, the response to weight loss induced decreased leptin leads to the activation of anabolic pathways and the inhibition of catabolic pathways. Conversely, circulating leptin concentrations rapidly increase after reintroduction of energy supplies [11] or overfeeding [12], and the process cited is immediately aborted. However, the neuronal responses to weight loss are more efficient than the response to weight gain since at basal state (stable weight) catabolic responses to weight loss are more efficient than the response to weight gain since at basal state (stable weight) catabolic pathways are already activated and anabolic pathways suppressed.

In parallel to its central action on food intake and energy expenditure, leptin may also be endowed with direct peripheral effects that limit fat accumulation in non-adipose tissue (muscle, liver) [13]. Thus leptin appears as the survival hormone, which aims at maintaining energy balance. In the
light of these observations leptin first appeared as a great hope for obesity treatment. Unfortunately, except for the rare forms of monogenic obesity due to genetic leptin deficiency, the majority of cases of human obesity are associated with high levels of leptin generally related to the degree of adiposity in each case. The idea that patients are resistant to the action of leptin [14] was then brought to the fore, even though the genesis of leptin resistance still remains to be discovered. Human trials performed with leptin treatment have shown that most subjects are unlikely to respond to pharmacological treatment with the hormone [15]. Several assumptions have been made to explain the concept of leptin resistance and the inefficiency of leptin treatment. Decreased leptin transport into the CNS has been suggested since obese people have lower leptin levels in the cerebrospinal fluid than in the plasma [16]. Since the leptin transport mechanism is saturated at low plasma leptin concentrations, it might limit the effectiveness of peripherally administered hormone. In addition, the molecular events downstream of the receptor in key hypothalamic neurons have been under focus [17]. The binding of leptin to its full-length receptor triggers the activation of the Janus kinase family (Jak2), which leads to the translocation of STAT3 to the nucleus where it regulates gene transcription. Concomitantly, the activation of the leptin receptor induces the expression of a “suppressor of cytokine signalling” (SOCS-3). While putative alterations in the JAK-STAT signalling either in animal or human obesity are still to be highlighted, the SOCS-3 could appear as a potential mediator of leptin resistance in obesity. The expression of SOCS-3 mRNA in the arcuate and dorsomedial hypothalamic nuclei is for example increased in Ay/a mice, a model of leptin-resistant murine obesity [18]. For leptin to have therapeutic potential, it either needs to be modified or the transport system by which leptin enters the brain needs to be upregulated to allow leptin to enter the brain more easily. It may also be necessary to overcome “central leptin insensitivity” by developing agents that act downstream of leptin activity. In this regard, the CNTF ciliary neurotrophic factor (rhvCNTF) that acts through leptin-like pathways in the hypothalamus, bypassing leptin resistance, is being used in different human trials [19].

**Insulin**

Insulin was the first putative adiposity signal discovered but it took time to consider it as such since the action of the hormone in the peripheral systems is the opposite of that in the central systems. While insulin shows unambiguously anabolic effects in peripheral tissues, the hormone contributes to food intake control in the brain. Experiments performed in animals proved very conclusive in the field. In the late 1970s, Woods and Porte first proposed that insulin could be a long-term regulator of food intake and energy stores [20]. Continuous intracerebroventricular infusions of insulin in free-feeding baboons clearly reduced food intake and...
Amylin

Amylin is a 37 amino acid protein mainly secreted by the pancreas and is co-secreted with insulin in response to food intake [28, 29]. The involvement of amylin in short and long-term effects of the regulation of food intake and body weight is well documented [30]. Evidence for the role of amylin in the regulation of food intake mostly stems from the central or peripheral administration of a low dose of amylin in rodents that potently reduced food intake in a dose-dependent manner [31]. Amylin crosses the blood-brain barrier and binds to receptors located in different brain areas involved in the regulation of energy homeostasis (nucleus of the solitary tract (NTS), nucleus accumbens and hypothalamus) [32, 33]. Amylin acts only as a humoral signal since neither vagotomy nor destruction of capsaicin-sensitive sensory afferents affect the biological hormone effect [34]. Besides its short-term effect on food intake regulation, amylin probably controls energy balance over the longer term. While an acute bolus of amylin in the 3rd ventricle decreases food intake in a dose-dependent manner, the effect seems to persist for 7 days after the administration. Animals treated with amylin lose weight compared with controls [31]. A tonic elevation of central amylin over 10 days or repeated daily injections over 6 days in rodents leads to a marked alteration in food intake with considerable weight loss due to the reduction of body adiposity. Although the exact nature of amylin receptors remains still to be determined, amylin binding sites have been identified [32, 33] and specific antagonists have been developed. When rats were given an acute intracerebroventricular administration of an amylin antagonist, a significant increase in energy intake was observed [31]. The tonic inhibition of any central amylin signal led to a body fat increase of about 30% in treated rats as compared with controls [31]. A tonic elevation of central amylin over 10 days or repeated daily injections over 6 days in rodents leads to a marked alteration in food intake with considerable weight loss due to the reduction of body adiposity. Although the exact nature of amylin receptors remains still to be determined, amylin binding sites have been identified [32, 33] and specific antagonists have been developed. When rats were given an acute intracerebroventricular administration of an amylin antagonist, a significant increase in energy intake was observed [31]. The tonic inhibition of any central amylin signal led to a body fat increase of about 30% in treated rats as compared with controls. These experiments have placed amylin among the adiposity signals since the crucial difference between a short-term satiety signal and long-term energy homeostasis regulators resides in the fact that repeated administrations of amylin do not alter body weight because of a compensatory increase in meal frequency.

To date, a growing body of data is converging to prove that amylin possesses many characteristics in common with well-known adiposity signals and also show that it seems to act in cooperation with them. Like insulin and leptin, amylin is rapidly and efficiently transported to brain areas involved in the regulation of energy balance. Amylin secretion and plasma amylin concentrations correlate with the degree of body adiposity [35]. Lastly, amylin, like leptin and insulin, potently reduces food intake without aversive consequences, and the signal it conveys to the brain grows in importance when it is remembered that sub-threshold doses of amylin and insulin, with no effect on food intake when infused individually, significantly reduce intake when administered together. Even though many points regarding amylin (nature of the receptors, signalling pathways, interactions with other
adiposity signals, etc.) still remain to be elucidated, all these findings pave the way for amylin analogs as new anti-obesity drugs [36], all the more so since body weight gain observed after administration of these compounds was entirely due to fat accumulation.

**Inflammatory cytokines as “adiposity signals”?**

Among the cytokines/chemokines that are produced by adipose tissue, are some that may contribute to signalling the amount of fat mass and its variation to the brain. Recent data show that several pro-inflammatory cytokines (such as interleukin-6, interleukin-1, interleukin-8) and chemokines may participate in the control of feeding during physiological conditions, as reviewed recently by Plata-Salaman [37]. Among the cytokines, interleukin-6 (IL6) is probably the one that best displays many characteristics in common with insulin, leptin and amylin as an adiposity signal. During inflammation, IL6 is released from immune cells and elicits pro-inflammatory effects [38-40]. Its secretion is modulated by immune, hormonal and metabolic stimuli in a cell-specific manner. In physiological conditions, the adipose tissue (especially the omental tissue) provides about one third of the circulating levels of IL6 [41]. Besides its role in the immune response, IL6 is characterized by the capacity to regulate energy balance in the short and long-term. IL6 serum levels correlate with adipose tissue mass in animals and humans to the same extent as leptin, and in the brain, it favours a negative energy balance since it decreases food intake and enhances energy expenditure. Rodent IL6 and its receptor are expressed, among other nuclei, in the dorsomedial and ventromedial hypothalamus, two brain areas involved in the regulation of energy balance [42] and there is substantial evidence that this observation can be extended to humans [43]. IL6 is also produced by several parts of the brain [42, 44-46]. Mice lacking the IL6 gene develop mature-onset obesity and obesity-related metabolic disturbances with an increase mainly in subcutaneous adipose tissue [47]. These animals exhibit increased absolute food intake that is corrected by long-term intracerebroventricular administration of IL6 but not by intraperitoneal injection [48]. While the effect of an ICV IL6 treatment on caloric ingestion has duration-dependent effects) the animals all exhibited body weight reduction. IL6 injections also decrease body weight with an increase mainly in subcutaneous adipose tissue [47].

Besides IL6, both in mice and humans, adipose tissue produces and secretes a large number of other cytokines including interleukins, chemokines and related substances with their level of expression and/or synthesis directly correlated with the degree of adiposity. These molecules could be involved in processes mediating adiposity and insulin resistance. We will only cite some of them. Tumour necrosis factor alpha (TNF-α) is among these. Studies on obese human patients have demonstrated a positive correlation between levels of TNF-α, the extent of obesity, and the level of hyperinsulinaemia observed [59-61]. In vitro cell culture studies have suggested that TNF-α is able to render cells insulin resistant through regulation of the synthesis of the insulin responsive glucose transporter as well as through interference with insulin signalling [62]. Other molecules discovered could also belong to this class of factors [63-65]. Circulating levels of the anti-inflammatory cytokine IL-10, for example, are raised in obese women. Adipocyte production, modulation and secretion of interleukin 8 (IL8), another adipocyte-derived cytokine, has been well described in vitro [66], and in vivo relationships between IL8 levels and obesity have been observed [67]. An increase in plasma IL-8 concentrations after glucose load in obese impaired glucose tolerance subjects in comparison with normoglycaemic weight-matched individuals, also suggests a modulating role both by sympathetic nerve system leading to an increase in thermogenesis in brown adipose tissue.

A straight extrapolation of this mechanism to humans, in whom the physiological role of brown adipose tissue is still debated, is questionable. A lot remains to be discovered about the impact of IL6 on energy balance in humans [54]. In obese subjects, serum IL6 levels correlate positively with body mass index [55-57] but cerebrospinal fluid (CSF) IL6 levels correlate negatively with total body fat. Unlike the observation with leptin the CSF levels of which, even if lower than serum ones, remain correlated with body weight [16], CSF IL6 seems to be regulated independently of serum IL6. This observation suggests that CSF IL6 is not serum-derived but could be locally produced. However, the possibility that the blood-brain barrier in obese subjects may become, for reasons still to be discovered, dramatically “IL6-tight” cannot be ruled out. Indeed, it is clearly acknowledged that IL6 crosses the blood-brain barrier by a unidirectional (blood-to-brain) influx system which can be saturated [58]. Taken together, these data provide indications of a role for IL6 in the regulation of energy balance over the long-term. The origin of CNS IL6, the exact brain sites involved and the possible interactions with other adiposity signals are, at present, under investigation.

**Other adipose tissue-derived molecules as adiposity signals?**

Besides IL6, in physiological conditions, the adipose tissue is among the cytokines that may participate in the control of feeding during physiological conditions, as reviewed recently by Plata-Salaman [37]. Among the cytokines/chemokines that are produced by adipose tissue, are some that may contribute to signalling the amount of fat mass and its variation to the brain. Recent data show that several pro-inflammatory cytokines (such as interleukin-6, interleukin-1, interleukin-8) and chemokines may participate in the control of feeding during physiological conditions, as reviewed recently by Plata-Salaman [37]. Among the cytokines, interleukin-6 (IL6) is probably the one that best displays many characteristics in common with insulin, leptin and amylin as an adiposity signal. During inflammation, IL6 is released from immune cells and elicits pro-inflammatory effects [38-40]. Its secretion is modulated by immune, hormonal and metabolic stimuli in a cell-specific manner. In physiological conditions, the adipose tissue (especially the omental tissue) provides about one third of the circulating levels of IL6 [41]. Besides its role in the immune response, IL6 is characterized by the capacity to regulate energy balance in the short and long-term. IL6 serum levels correlate with adipose tissue mass in animals and humans to the same extent as leptin, and in the brain, it favours a negative energy balance since it decreases food intake and enhances energy expenditure. Rodent IL6 and its receptor are expressed, among other nuclei, in the dorsomedial and ventromedial hypothalamus, two brain areas involved in the regulation of energy balance [42] and there is substantial evidence that this observation can be extended to humans [43]. IL6 is also produced by several parts of the brain [42, 44-46]. Mice lacking the IL6 gene develop mature-onset obesity and obesity-related metabolic disturbances with an increase mainly in subcutaneous adipose tissue [47]. These animals exhibit increased absolute food intake that is corrected by long-term intracerebroventricular administration of IL6 but not by intraperitoneal injection [48]. While the effect of an ICV IL6 treatment on caloric ingestion has duration-dependent effects) the animals all exhibited body weight reduction. IL6 injections also decrease body weight with an increase mainly in subcutaneous adipose tissue [47].

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insulin sensitivity and glucose tolerance [68]. Interestingly, IL8 was detected in CSF and a role in decreasing food intake and weight was shown several years ago in rodents [69]. Up to now there are, however, few arguments regarding the contribution of TNFα and others as direct messengers between adipose tissue and the brain in physiological conditions. Many authors believe that TNFα has an effect on body weight regulation and that it acts probably through a local action on adipose tissue, although interactions between the brain and the cytokines produced in the periphery are described [58].

Several adipocyte-derived molecules may also participate in the complex dialogue between organs involved in body weight regulation. Adipocyte cells use polypeptide hormones to influence metabolic processes at distant sites, other than the brain. Adiponectin exclusively synthesized in adipose tissue is probably the best example of such a type of molecule. There are, however, weak requirements for considering adiponectin as an adiposity signal, as classically defined above. Adiponectin could then fall into this category of signalling molecules since this adipocytokine contributed to the description of a key role for adipose tissue in fine-tuning hepatic and muscle insulin responsiveness. Contrasting with other molecules, adiponectin plasma levels decrease proportionally with the accumulation of adipose tissue, especially in the visceral depot [70] and with the development of insulin resistance. When administered to mice, it enhances insulin sensitivity and glucose tolerance [68]. Interestingly, when administered to mice, it enhances insulin sensitivity and glucose tolerance [68].

Genetic studies to identify the contribution of adiposity signal genes

The first gene identification in obese human subjects was linked with screening for genes encoding leptin and leptin receptor. Homozygous carriers of a loss of function mutation in the leptin gene or in the leptin receptor exhibit morbid obesity with onset in the first months of life, hypogonadotropic hypogonadism and central hypothyroidism [73]. Three sisters bearing the leptin receptor mutation also display significant growth retardation due to impaired growth hormone secretion. Affected subjects continuously seek food and eat considerably more than their siblings [73]. A leptin deficient child has been treated successfully by leptin replacement. In this nine-year-old girl, daily subcutaneous injection of recombinant human leptin for a year was well tolerated and led to an important and sustained fat mass loss and an age-appropriate improvement in function of the reproductive axis [74]. Although exceptional, these situations of monogenic obesity have greatly contributed to validating the role of the leptin axis not only in body weight regulation but also in the control of several endocrine functions. Efforts to identify candidate genes for common obesity have concentrated on adiposity signal genes. Association studies have been conducted to identify the association between obesity or obesity-related phenotypes and genetic variants (single nucleotide polymorphisms or SNPs) located in gene-encoding adiposity signal genes. In addition, researchers have looked for regions in the genome including the location of adiposity signal genes [75]. In association studies, the frequency of DNA variations between groups of subjects (i.e. obese vs. non obese) is evaluated on a measurable phenotype (body mass index, fat mass, skin folds, waist/hip ratio, as well as circulating levels of adiposity signal proteins) in subjects carrying or not carrying the given polymorphism being...
compared. These association studies have been conducted in children and obese populations in Europe and in North America. Gene-gene and gene-environment interactions have begun to emerge.

As shown in tables I and II, several studies have shown indications of linkage and/or association between adiposity signal (or adipocyte produced molecule) gene variants and obesity related phenotypes. This was particularly the case for leptin gene studies where many linkage studies in independent populations and a meta-analysis suggested that the leptin gene locus is associated with obesity phenotypes [76] (Fig 2). An impressive genome wide scan performed in thousands of subjects also found a peak of linkage in this region [77]. However no functional mutation has been discovered to explain these findings. As shown in Tables I and II, the results observed have not always been consistent for the markers tested. These studies met with difficulties of interpretation related to statistical power, biased population stratification, false positive results due to multiple testing and the suppression of negative results.

### Table I
Examples of association studies between recognized adiposity signal gene variants and obesity phenotypes.

<table>
<thead>
<tr>
<th>Adiposity signal</th>
<th>Polymorphisms</th>
<th>Population</th>
<th>Association with Studied phenotypes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>nucleotide repeat</td>
<td>Japanese</td>
<td>Hypertension (+)</td>
<td>[88]</td>
</tr>
<tr>
<td>Leptin</td>
<td>25CAG</td>
<td>Japanese</td>
<td>Obesity (+)</td>
<td>[89]</td>
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<tr>
<td>Leptin</td>
<td>G-2548A</td>
<td>French</td>
<td>Weight response to caloric restriction (+)</td>
<td>[79]</td>
</tr>
<tr>
<td>Leptin</td>
<td>A19G</td>
<td>French</td>
<td>Obesity (–)</td>
<td>[78]</td>
</tr>
<tr>
<td>Leptin</td>
<td>C(-188)A</td>
<td>Finns</td>
<td>Weight (–)</td>
<td>[90]</td>
</tr>
<tr>
<td>EPR</td>
<td>K109R, Q223R, K656N</td>
<td>Dutch</td>
<td>High leptin level (+)</td>
<td>[91]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Americans</td>
<td>Weight gain (+)</td>
<td>[92]</td>
</tr>
<tr>
<td></td>
<td>Q223R, K656N</td>
<td>British</td>
<td>Obesity (–)</td>
<td>[93]</td>
</tr>
<tr>
<td></td>
<td>3'-UTR ins/del</td>
<td>French</td>
<td>Morbid obesity (–)</td>
<td>[94]</td>
</tr>
<tr>
<td>LEPR</td>
<td>K109R, Q223R, K656N</td>
<td>African-American, Caucasian, Danish, Finns, Canadian and Nigerian</td>
<td>BMI (+)</td>
<td>[95]</td>
</tr>
<tr>
<td>LEPR</td>
<td>K109R, Q223R, K656N, base repeats</td>
<td>Caucasian</td>
<td>BMI (+), Fat mass (+)</td>
<td>[96]</td>
</tr>
<tr>
<td>LEPR</td>
<td>Q223R</td>
<td>Pima Indians, Americans</td>
<td>Adiposity (+)</td>
<td>[97]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Energy Expenditure (+)</td>
<td>[98]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Glucose metabolism (+)</td>
<td>[98]</td>
</tr>
<tr>
<td>LEPR</td>
<td>Q223R</td>
<td>Caucasian women</td>
<td>BMI, fat mass, serum leptin (+)</td>
<td>[99]</td>
</tr>
<tr>
<td>LEPR</td>
<td>Q223R</td>
<td>Greeks</td>
<td>predict BMI and percentage fat mass</td>
<td>[100]</td>
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<tr>
<td>LEPR</td>
<td>K109R, Q223R, K656N</td>
<td>Caucasian women</td>
<td>Insulin glucose metabolism, fat mass, energy expenditure (+)</td>
<td>[101, 102]</td>
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<td>T+70C</td>
<td>French</td>
<td>BMI, Fat mass (+)</td>
<td>[103]</td>
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<td>LEPR and leptin</td>
<td>Q223R, P1019P</td>
<td>Nauruans</td>
<td>Adiposity (+)</td>
<td>[104; 105]</td>
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<tr>
<td></td>
<td>Leptin variants</td>
<td></td>
<td>Insulin resistance (+)</td>
<td>[104; 105]</td>
</tr>
<tr>
<td>LEPR and leptin</td>
<td>LEP: A19G, LEPR Q223R, P1019P</td>
<td>Caucasians</td>
<td>BMI (+)</td>
<td>[106]</td>
</tr>
<tr>
<td>IL6</td>
<td>CA repeat</td>
<td>Caucasians</td>
<td>BMI, fat mass (+)</td>
<td>[81]</td>
</tr>
<tr>
<td>IL6</td>
<td>C-174G</td>
<td>Finns</td>
<td>Energy expenditure insulin sensitivity (+)</td>
<td>[83; 107]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>French-Canadians</td>
<td>Waist either insulin or glucose (+)</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spanish Caucasians</td>
<td>Glucose metabolism, type-2 diabetes (+)</td>
<td>[108; 109]</td>
</tr>
<tr>
<td>BMI Body Mass Index. (+) refers to positive association while (–) refers to negative association.</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
More importantly, some association between the genetic variations of adiposity signals and the level of expression of the blood circulation levels of their substrates has been found. For example, although no polymorphisms were detected in the coding region of the leptin gene, a single A-to-G transition and a 2548G-A were found respectively in the untranslated first exon and in the regulatory region. Hager et al. showed that patients homozygous for the G allele of the exon 1 variant had significantly lower fasting leptin levels compared with subjects who were either heterozygous (AG) or homozygous for the A allele despite a similar BMI [78]. Men carriers of the 2548 G allele variant had lower leptin concentrations adjusted for fat mass [79]. In 2001, Farooqi et al. studied 13 subjects who were homozygous for the frame shift mutation delta-G133 of the leptin gene [80]. Their serum leptin concentrations were lower than in controls with a similar sex distribution and age. Lower leptin levels in these subjects were characterized by an increased prevalence of obesity. Similar observations were made between insulin gene variation and insulin circulating levels. Gene polymorphisms in the region of the INS gene were studied in obese children. The authors found that obese patients homozygous for class I VNTR (variable nucleotide tandem repeat polymorphism) alleles secreted more insulin than those with other genotypes [125]. Genetic polymorphisms of the IL-6 gene have also been described [81]. Lower expression of cellular constructs containing the -174C change was found when comparing with the 174G constructs. The IL6 -174G/C polymorphism is associated with some indices of body composition and parameters of glucose and insulin homeostasis [82] but no study has determined relationships between this variant and circulating levels of IL6.

It is possible that a relatively small decrease in this adiposity signal production, associated with the genetic variations, may be sensed by the homeostatic feedback system that controls energy balance and may in turn contribute to some dysregulation in energy balance. This was suggested by Fa-

Table II
Examples of association study between molecules produced by the adipocyte and obesity phenotypes.

<table>
<thead>
<tr>
<th>Adiposity signal</th>
<th>Polymorphisms</th>
<th>Population</th>
<th>Association with studied phenotypes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF α -857C/A</td>
<td>adipose tissue TNF secretion (+)</td>
<td>[86]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF α -863C/A</td>
<td>BMI (+)</td>
<td>[110]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF α G-308A</td>
<td>Swedish, Finnish subjects, Fat accumulation (+)</td>
<td>[83, 85]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF α G-238A</td>
<td>Polish Caucasians, Australian Metabolic parameters (+)</td>
<td>[107, 112, 113]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF α G-308A</td>
<td>Danish Insulin resistance (+)</td>
<td>[114]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF α A + 252G G-308A</td>
<td>decreased waist/hipBMI (–)</td>
<td>[115]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF α Nco I</td>
<td>Insulin resistance (–)</td>
<td>[116, 117]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF α G-308A</td>
<td>Japanese, Chinese Obesity, metabolic parameters (–)</td>
<td>[11-120]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF β T29C</td>
<td>Swedish men Obesity (+)</td>
<td>[121]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin T94G</td>
<td>BMI (+)</td>
<td>[122]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin T45G</td>
<td>Cholesterol, waist circumference (+). Blood glucose, BMI, diastolic blood pressure, sagittal diameter (+)</td>
<td>[123]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin haplotype TGFβ and -11377, 5′ sequence rare non-synonymous mutations of exon 3 45T → G, 276G → T</td>
<td>type 2 diabetes (+)</td>
<td>[124]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI Body Mass Index. (+) refers to positive association while (–) refers to negative association.
rooqi et al. when analysing the phenotypes of the frame shift mutation delta-G133 carrier with relatively decreased leptin. It was suggested that in these subjects fat mass would be increased in an attempt [80] to restore leptin levels to some “set” point.

Is SNP in other signal molecules associated with modification of their transcription, production or circulating levels and does this perhaps influence body weight regulation? There is evidence for association between the -308A polymorphism located in the promoter of the TNF-α gene and obesity, with high rates of glucose oxidation in normal weight subjects and with lipid storage in overweight subjects [83-85]. Another polymorphism described in the promoter region of the TNF-α gene (a C → A substitution at position -863) is associated with lower transcriptional activity and with down-regulation of the basal rate of transcription of the TNFα gene in vitro. In men (carriers of the rare A allele having a significantly lower TNF-α level), the -863C/A polymorphism seems to be associated with serum TNFα concentrations [86, 87]. Nevertheless, these polymorphisms have not been sufficiently investigated in human obesity to date. Adiponectin gene variations have also been studied in different populations. A combination of SNPs (haplotype including 2 5-prime SNPs) was associated with adiponectin levels. The results have been quite consistent in different populations (Tab III).

Table III
Examples of the study of association between genetic variants of molecules produced by the adipocyte (either adiposity signal or adipocyte produced molecules) and circulating levels.

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Gene variant and type of study</th>
<th>Population</th>
<th>Genetic association or linkage with circulating levels</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>G-2548A Association</td>
<td>French</td>
<td>Serum leptin levels (+)</td>
<td>[79; 126]</td>
</tr>
<tr>
<td>Leptin</td>
<td>A19G Association</td>
<td>French</td>
<td>Serum leptin levels (+)</td>
<td>[78]</td>
</tr>
<tr>
<td>Leptin</td>
<td>Lep -2, 549 Association</td>
<td>Caucasians</td>
<td>Relationship between serum leptin and body fatness</td>
<td>[127; 128]</td>
</tr>
<tr>
<td>Leptin</td>
<td>Linkage Estimation of heritability</td>
<td>Monozygotic and dizygotic twins</td>
<td>Serum leptin levels (estimated heritability 55%)</td>
<td>[129]</td>
</tr>
<tr>
<td>Leptin</td>
<td>CA repeat D2S1788 Genome wide scan</td>
<td>Mexicans Americans</td>
<td>Serum leptin levels (lod score 4.95)</td>
<td>[130]</td>
</tr>
<tr>
<td>LEPR</td>
<td>K109R, Q223R, K656N Association</td>
<td>Dutch</td>
<td>Serum leptin levels (+)</td>
<td>[91]</td>
</tr>
<tr>
<td>IL6</td>
<td>G-597A, G-572C, G -174C, -373A(n)T(n) Association</td>
<td>Spanish women</td>
<td>Interleukine 6 levels (+)</td>
<td>[131]</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>-1139 &amp; -11377 haplotypes one non-synonymous mutation in exon 3</td>
<td>Caucasians</td>
<td>Serum adiponectin levels (+)</td>
<td>[124]</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Missense mutation (R112C) in exon 3 G/T polymorphism in exon 2 Association</td>
<td>Japanese</td>
<td>Serum adiponectin levels (+) Serum adiponectin R112C (-)</td>
<td>[132]</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Missense mutation (I164T) Association</td>
<td>Japanese</td>
<td>Serum adiponectin levels (+)</td>
<td>[133]</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>PolyCA Linkage analysis</td>
<td>Pima population</td>
<td>Serum adiponectin levels (QTL on chromosomes 2, 3, 9, 10)</td>
<td>[134]</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>PolyCA Linkage analysis</td>
<td>Northern European ancestry</td>
<td>Serum adiponectin levels (LOD score: 4.06 on chromosome 5 and 3.2 on chromosome 14)</td>
<td>[135]</td>
</tr>
</tbody>
</table>

QTL = quantitative trait linkage.
(+ ) refers to positive association while (- ) refers to negative association.
It is possible that combinations of polymorphisms, encoding adiposity signal genes and signalling molecules that may contribute to the complex dialogue between organs, may intervene in the accuracy and synergy of signal transmission. Slight modification of this molecule expression and production by the peripheral organ may bias the way the brain senses the amount of fat mass and its variation. Similarly at the peripheral level, slight modification of circulating molecules may interfere with inter-organ dialogue. Systematic analysis of these gene variants and genotype combinations (haplotype) on a large scale may be necessary to explore this hypothesis especially in the context of the dynamic variation of body weight. Up to now most genetic studies include the search for genotype/phenotype associations without taking into account the influence of the environment (diet) in the relationship. Among the limitations, the availability of large sample numbers should be mentioned, as well as the bio-informatics tools that are still in their infancy for accessing the question of multiple interactions with no “a priori hypothesis”. This picture will probably change rapidly in the future. Large databases and DNA and biological sample banks will be available with updated environmental information and precise phenotypes especially thanks to European working groups. The capacity for accessing multiple genes at once at the level of DNA or RNA is rapidly growing. Finally, tremendous (rapid) progress in bio-informatics will allow information of different natures to be integrated (biological sources) (i.e. environment, phe-

References

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83. Kubaszek A, Pihlajamaki J, Komarovsky V, et al. Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. Diabetologia, 2003, 46, 1898-1900.


