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Leptin: at the crossroads of energy balance and systemic inflammation

Alexandre A. Steiner[a] and **Andrej A. Romanovsky**[a,*]

aSystemic Inflammation Laboratory, Trauma Research, St. Joseph's Hospital and Medical Center, Phoenix, AZ 85013, USA

Abstract

In addition to playing a central role in energy homeostasis, leptin is also an important player in the inflammatory response. Systemic inflammation is accompanied by fever (less severe cases) or hypothermia (more severe cases). In leptin-irresponsive mutants, the hypothermia of systemic inflammation is exaggerated, presumably due to the enhanced production and cryogenic action of tumor necrosis factor (TNF)-α. Mechanisms that exaggerate hypothermia can also attenuate fever, particularly in a cool environment. Another common manifestation of systemic inflammation is behavioral depression. Along with the production of interleukin (IL)-1β, this manifestation is exaggerated in leptin-irresponsive mutants. The enhanced production of TNF-α and IL-1β may be due, at least in part, to insufficient activation of the anti-inflammatory hypothalamo-pituitary-adrenal axis by immune stimuli in the absence of leptin signaling. In experimental animals and humans that are responsive to leptin, suppression of leptin production under conditions of negative energy balance (*e.g.*, fasting) can exaggerate both hypothermia and behavioral depression. Since these manifestations aid energy conservation, exaggeration of these manifestations under conditions of negative energy balance is likely to be beneficial.

Keywords

adipose tissue; obesity; leptin receptor; lipopolysaccharide; LPS; immune-to-brain signaling; fever; hypothermia; sickness behavior; behavioral depression; anorexia

1. Introduction

Inflammation is an important host-defense response [1]. However, when the inflammatory response becomes overwhelming, it disrupts vital homeostatic processes and ultimately results in multiple organ failure and death [2]. It is not surprising, therefore, that severe forms of inflammation are major medical problems. A common complication in hospitalized patients is sepsis (systemic inflammation due to infection). Mortality rate is extremely high in septic patients: it ranges from 30% in those patients that do not develop shock to 70% in those patients that do [3-6]. Sepsis becomes an even more serious threat in view of the fact that its incidence is increasing fast, *i.e.*, at an annual rate of 9% in the United States [7]. The increasing incidence of sepsis seems to be associated with, among other factors, the escalating incidence of metabolic disorders, particularly obesity [8-10]. Clearly, understanding how the mechanisms involved in obesity (and energy homeostasis in general) affect systemic inflammation is important.

*Corresponding author.** Tel.: +1-602-406-5059; fax: +1-602-406-4113 *E-mail address:* aromano@chw.edu (A.A. Romanovsky).

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The adipocyte-derived hormone, leptin, plays a central role in energy homeostasis, and resistance to its actions is associated with obesity [11-13]. Since it also modulates inflammation [14,15], leptin may integrate energy balance and systemic inflammation. In the present article, we examine this issue. A succinct review of the roles played by leptin in energy homeostasis is followed by an in-depth analysis of the roles of leptin in common physiological manifestations of systemic inflammation. These manifestations include fever (or hypothermia), behavioral depression, and anorexia; they jointly form the so-called sickness syndrome.

2. Leptin and energy homeostasis

2.1. Leptin and its receptors

It has been known for many decades that mice carrying the homozygous *obese* mutation (*ob/ob* mice) develop a syndrome that resembles human morbid obesity. However, it was not until the last decade that the *obese* mutation was identified, and the gene that carries such a mutation was isolated by positional cloning [16]. In wild-type animals, this gene encodes a 167-amino-acid, 16-kDa protein that is produced and secreted primarily by adipocytes [16-19]. Because its absence accounts for the obese phenotype of *ob/ob* mice, this protein was named leptin (from the Greek, *leptós*, which means *thin*); see Ref. 20. Leptin is highly conserved among species [16,17], and its structure resembles that of cytokines, especially interleukin (IL)-6 [21,22].

Not long following the discovery of leptin, the leptin receptor (LR) gene was identified [23-25]. The mRNA encoded by the LR gene is subject to extensive splicing, and each splicing variant is responsible for the translation of a distinct LR isoform. Six LR isoforms have been identified to date (Fig. 1), all of which have identical or nearly identical extracellular domains but differ in their transmembrane and intracellular domains (for reviews, see Refs. 11,12,26). The LR*e* isoform lacks the transmembrane and intracellular domains altogether and is found dissolved in the extracellular fluid. LR*e* is thought to sequester circulating leptin, thus limiting its action [27]. The LR*a*, *c*, *d*, and *f* isoforms have a transmembrane domain, but these membrane-bound isoforms lack a full intracellular domain and display no signal transduction capabilities. These isoforms, especially LR*a*, appear to be involved in the internalization, transport, and degradation of leptin [28,29]. LR*b* is the only isoform with complete transmembrane and intracellular domains. It is a class-I cytokine receptor and, as such, signals primarily *via* the JAK2-STAT3 pathway [30,31]. LR*b* has been implicated in most biological effects of leptin [32-34]. Importantly, several widely used rodent models of obesity — *viz.*, *db/db* mice [24,35,36], Zucker *fa/fa* rats [36-38], and Kotetsky *f/f* rats [39,40] — carry mutations in the LR gene that result in either absence or dysfunctionality of LR*b* (Table 1).

LR*b* is expressed in the brain, especially in areas that are involved in the regulation of appetite and metabolism, such as the arcuate, ventromedial, and dorsomedial hypothalamic nuclei (for a review, see Ref. 41). Circulating leptin crosses the blood-brain barrier and gains access to these areas *via* a specific, saturable transport mechanism that is believed to involve LR*a* [42]. Alternatively, leptin can enter the brain *via* the median eminence. This structure is characterized by a leaky blood-brain barrier, and it is strategically located at the boundaries of the arcuate, ventromedial, and dorsomedial hypothalamic nuclei [43].

2.2. Role of leptin in energy homeostasis

The concentration of leptin in the blood plasma is maintained between 1 and 20 ng/ml in lean animal and human subjects, but it may be as high as 100 ng/ml in obese subjects [44,45]. The circulating level of leptin reflects its production by white adipocytes, and it exhibits both long-term (days) and short-term (hours) changes. Mechanisms that drive changes in fat storage regulate long-term changes in leptin production, as evident from the strong positive correlation between the total size of the body fat stores and the plasma concentration of leptin [44-46]. Not only are more adipocytes expected to produce more leptin, but also adipocytes containing more fat synthesize more leptin [47]. Short-term changes in leptin levels occur independently of body fat mass gain or loss. For example, leptin production is decreased a few hours after initiation of fasting, and refeeding restores its production to prefasting levels [48-52]. The mechanisms of these short-term changes appear to involve insulin, as evidenced by the positive correlation between the plasma levels of leptin and insulin [50,52,53] and by the ability of insulin treatment to increase leptin production [48,54,55].

In lean animal [56-58] and human [59-61] subjects, reduction in plasma leptin (usually to < 4 ng/ml) during fasting or other conditions of negative energy balance (*e.g.*, calorie restriction) is associated with suppression of metabolic rate and stimulation of appetite. These adaptive responses are abolished by supplementation with recombinant leptin at doses that typically elevate the plasma leptin of fasted or calorie restricted subjects to a level that is similar to that found in well-fed subjects, *i.e.*, 4-20 ng/ml [56-58,60,62]. The same doses of leptin, however, produce modest or no effect when given to well-fed subjects [20,56,63-65]. Only when injected at doses known [66] to produce supraphysiological rises in its plasma level (to > 100 ng/ml) does leptin cause marked hypermetabolic and anorexic responses in fed subjects [67,68]. These observations lead to two conclusions: (i) that a fall in circulating leptin during conditions of negative energy balance works as an anti-starvation signal, a signal that suppresses energy expenditure and stimulates appetite; and (ii) that a rise in circulating leptin to a level above that found in lean, fed individuals produces little or no physiological response; see Fig. 2.

With a few exceptions [69-73], obese patients have plasma levels of leptin that are above those found in lean, fed individuals [44,45]. These patients are even more resistant than lean individuals to the hypermetabolic and anorexic effects of recombinant leptin [74-76]. Likewise, rodents with diet-induced obesity exhibit high plasma leptin and resistance to the hypermetabolic and anorexic effects of leptin [77,78]; see Fig. 2. Resistance to these weight-reducing effects of leptin can contribute to the progression of obesity. Irresponsiveness to leptin appears to involve decreased leptin transport across the blood-brain barrier and impairment of LR*b* signaling (for a review, see Ref. 13). It may also be due to mutations in the LR gene, but these mutations have been found to be extremely rare in humans [79].

3. Leptin production in inflammation

Parenteral administration of lipopolysaccharide (LPS), a constituent of the outer envelope of Gram-negative bacteria, is commonly used to induce systemic inflammation experimentally. In 1996, Grunfeld and colleagues [80] reported that hamsters respond to intraperitoneal LPS with increases in both the expression of the leptin gene in white fat and the circulating level of leptin. Since then, the effect of LPS on leptin production has been well characterized in mice and rats [81-90]. It is now known that: (i) a rise in plasma leptin may occur as early as 1 h post-LPS; (ii) the rise may last for several hours; (iii) the magnitude of the rise is directly proportional to the LPS dose until a ceiling level of leptin is reached; (iv) as in non-inflammatory states, the ceiling level of leptin is ~20 ng/ml in lean animals, but it may be higher in obese animals; and (v) the leptin response to LPS occurs in both fasted and fed animals, but the peak leptin level achieved in fasted animals is lower, possibly due to their already reduced basal production of leptin. Inflammatory stimuli other than LPS, specifically turpentine [84] and carrageenan [91], also stimulate leptin production. It is not surprising, therefore, that plasma leptin was found to be high in mice and humans with bacterial sepsis [92,93] as well as in those patients who developed post-surgical inflammation [94].

The fact that many effects of LPS and other microbial products are mediated by pro-inflammatory cytokines [95,96] propelled several studies on the roles of tumor necrosis factor

(TNF)-α and IL-1β in the leptin response to inflammatory stimuli. It has been shown that the plasma leptin response of mice to LPS is preceded by an increased production of TNF-α [82]; that systemic administration of TNF-α to mice or hamsters increases the expression of the leptin gene in white fat as well as the circulating level of leptin [80-83]; and that administration of IL-1β to mice, hamsters, or humans increases leptin production [80,81,97]. It has also been shown that the plasma leptin response to LPS or bacterial peritonitis does not occur in mice treated with the TNF-binding protein [92], in mice that lack the IL-1β gene [84], or in rats administered with the IL-1 soluble receptor [98]. These lines of evidence indicate that TNF-α and IL-1β mediate the inflammatory increase in leptin production.

To determine whether LPS and cytokines increase leptin production by acting on adipocytes directly or indirectly, Finck and colleagues [83] treated cultured mouse adipocytes with LPS or TNF-α. They found that only TNF-α is capable of inducing leptin production in their *in-vitro* model, in spite of the fact that both LPS and TNF-α increase leptin production when administered *in vivo*. This finding is consistent with the notion that LPS-induced leptin production involves recognition of LPS by cells other than adipocytes (presumably immunocytes), and that TNF-α produced by these cells acts directly on adipocytes to stimulate leptin production. Immune activation of leptin production may also involve neuroendocrine mechanisms [89,99], but these mechanisms remain poorly explored.

Based on the large body of evidence showing that inflammatory insult stimulates leptin production, an involvement of leptin in at least some components of the inflammatory response can be anticipated. Below, we analyze whether and how leptin participates in some of the most common physiological manifestations of systemic inflammation.

4. Leptin and thermoregulatory manifestations of systemic inflammation

4.1. Fever and hypothermia: overview

So strongly is systemic inflammation associated with changes in deep body temperature (T_b) that an altered T_b is included in all definitions of systemic inflammation and sepsis [100-102]. Whereas the majority of septic patients (∼90%) are febrile, a number of them (∼10%) develop hypothermia [3,6]. Importantly, hypothermia occurs in the most severe cases of sepsis, and it is often associated with circulatory shock [3,6]. As humans, experimental animals respond to intravenous administration of LPS with fever or hypothermia; the direction and pattern of the T_b response depends on the LPS dose and ambient temperature (for a review, see Ref. 103). In a thermally neutral environment, fever is the prevailing response; fever is monophasic when the dose of LPS is low (just supra-threshold), but it turns into polyphasic as the dose increases; see Fig. 3 and Refs. 104-107. Three febrile phases have been identified in the rat [107-111] and mouse [106,112,113]. Interestingly, when an LPS dose that normally causes polyphasic fever at a neutral ambient temperature is given to a rat in a cool environment, it causes hypothermia (which may or may not be followed by fever); see Fig. 3 and Refs. 105,110,111,114. More recently, we studied [115,116] the thermoregulatory responses to two doses of LPS in rats that were allowed to select their preferred ambient temperature in a thermally heterogeneous environment, a more natural condition. Whereas a lower dose caused warmth-seeking behavior and polyphasic fever, a higher dose caused cold-seeking behavior and hypothermia. At a later stage of the response to the higher dose, when most of the injected LPS has been cleared from the circulation, warmth-seeking behavior and fever were observed. These data indicate that fever is a natural response to a weaker inflammatory insult, whereas hypothermia is a natural response to a stronger inflammatory insult.

4.2. Leptin and thermoregulation in the absence of inflammation

Before discussing the function of leptin in the thermoregulatory manifestations of systemic inflammation, it is important to consider a few points regarding the role of leptin in thermoregulation under non-inflammatory conditions. Activation of metabolic heat production (nonshivering thermogenesis) is vital for homeothermic organisms (especially small animals) to maintain their T_b at a normothermic level in the cold [117,118]. Therefore, substances that affect metabolic rate invariably have an impact on thermoregulation [119]. In small rodents, leptin raises energy expenditure by increasing the sympathetic outflow to brown adipose tissue [120], which is the primary source of nonshivering thermogenesis in these animals [118]. Elimination of leptin signaling impairs chronic activation of thermogenesis in a cool environment [33,63,64,121,122]. As a result, *ob/ob* mice [63,64,123], *db/db* mice [33,65, 121,123], Koletsky *f/f* rats [110], and Zucker *fa/fa* rats [122,124,125] are hypothermic in a regular laboratory environment, which is often cool for small rodents [126]. The magnitude of the hypothermia varies from a few tenths of a degree Celsius to several degrees; it is inversely proportional to the ambient temperature (as predicted by the Fourier's law for conductive heat transfer). In a thermally neutral environment, T_b is regulated not by activation/inactivation of thermogenesis, but by constriction/dilation of skin vessels [126]. In such an environment, elimination of leptin signaling does not result in hypothermia [110,125].

It is important to note that, despite its critical role in chronic activation of thermogenesis during long-term cold exposure, leptin is apparently uninvolved in acute thermogenic responses. This is evident from the fact that young adult (7-10 week-old) Zucker *fa/fa* rats are capable of mounting vivid thermogenic responses to short-term cold exposure [127-129], in spite of their irresponsiveness to leptin. Only at an older age (> 10 week-old) do Zucker *fa/fa* rats display attenuation of acute thermogenic responses, but such an attenuation coincides with involution of the brown adipose tissue [130]. Once this secondary trait is manifested, the thermogenic responses of Zucker *fa/fa* rats are compromised altogether, regardless of whether or not the responses involve leptin.

4.3. Role of leptin in the fever and hypothermia of systemic inflammation

Activation of thermogenesis is important for fever production, especially in a cool environment [131,132]. It is then natural to ask: can the thermogenic action of leptin contribute to fever production? The answer to this question is probably negative for two reasons. First, whereas fever is brought about by acute activation of thermoeffectors [103], leptin appears to be unimportant for acute activation of thermogenesis [127-129]. Second, the febrile response to LPS is least manifest [133-136] under the condition (negative energy balance) that is most propitious for activation of thermogenesis by a rise in circulating leptin [56-58,60,62]. Most likely, a participation of leptin in fever or hypothermia would be related to the mechanisms of immune-to-brain signaling.

Rosenthal and colleagues [137] were the first to demonstrate that the febrile response to LPS is largely attenuated in Zucker *fa/fa* rats at room temperature. The attenuation of fever may result from alteration of a leptin-related mechanism of immune-to-brain signaling, but it may also result from factors unrelated to immune-to-brain signaling. As discussed in the previous section, Zucker *fa/fa* rats of more than 10 weeks of age have an atrophic brown adipose tissue [130]. This trait might result in attenuation of fever at room temperature, because room temperature is often subneutral for rats [126], and because rats develop fever in a subthermoneutral environment by activating thermogenesis [131]. It should be noted, however, that exhaustion of thermogenic reserves is not required for leptin-irresponsive animals to show attenuated febrile responses. This is evident from the fact that young (9 week-old) Koletsky *f/f* rats do not have exhausted thermogenic reserves, yet their overall febrile response to LPS is attenuated in a cool environment [110]. Excessive fat accumulation and hyperlipidemia are traits that are common to Zucker *fa/fa* and Koletsky *f/f* rats, and that might account for their attenuated febrile responses. Each of these traits is independently found in leptin-responsive rat strains: fat accumulation is a characteristic of Otsuka Long-Evans Tokushima fatty rats, and hyperlipidemia is a characteristic of Nagase analbuminemic rats. Since the T_b responses of these rat strains to LPS are not attenuated [138-140], fat accumulation and hyperlipidemia cannot explain the low-grade febrile responses of Zucker *fa/fa* and Koletsky *f/f* rats. Therefore, altered immune-to-brain signaling in Zucker *fa/fa* and Koletsky *f/f* rats appears to be the most plausible explanation for their attenuated fever. Altered immune-to-brain signaling can also explain the inability of wild-type rats treated with an anti-leptin antibody to mount a full-blown febrile response to LPS [141].

The mechanisms of immune-to-brain signaling can be febrigenic (increase T_b) or cryogenic (decrease T_b). These mechanisms compete with each other, and the balance between the two determines the resulting T_b response [95,142]. Febrigenic mechanisms can inhibit heat loss and activate thermogenesis [143]. Therefore, these mechanisms can drive T_b responses in both cool and warm environments; in the cold, heat loss (which is already at its minimum) cannot be inhibited, but thermogenesis (which is already activated) can be further activated; in the warmth, heat loss (which is already activated) can be inhibited, and thermogenesis (which is at its minimum) can be activated. Cryogenic mechanisms drive strong inhibition of thermogenesis, but have little effect on heat loss [143]. Therefore, they can drive T_b responses in a cool environment (in which thermogenesis is already activated and can be inhibited), but not in a warm environment (in which thermogenesis is at its minimum and cannot be further inhibited). An example of a substance that plays key roles in immune-to-brain signaling is TNF-α. This pro-inflammatory cytokine can be either febrigenic or cryogenic: it mediates the second and later phases of the polyphasic fever to lower LPS doses [144,145]; it also mediates the hypothermic response (and counteracts the febrile response) to higher LPS doses [146-149]. Such a dual role of TNF-α is consistent with the fact that the thermoregulatory response to TNF-α administration shifts from fever to hypothermia as the dose administered increases [150].

To determine whether leptin affects febrigenic or cryogenic mechanisms, we have studied the T_b responses of Zucker *fa/fa* or Koletsky *f/f* rats injected with lower or higher doses of LPS in a thermally neutral or cool environment. We have found that Zucker *fa/fa* rats [125] and Koletsky *f/f* rats [110] respond to lower doses of LPS with normal polyphasic fever in a thermally neutral environment (in which only those T_b responses that are driven by febrigenic mechanisms are revealed), but with attenuated fever in a cool environment (in which T_b responses driven not only by febrigenic mechanisms, but also by cryogenic mechanisms are revealed). Additionally, we have found that Koletsky *f/f* rats respond to higher doses of LPS in a cool environment with a dramatically exaggerated hypothermia [110]; see Fig. 4. The exaggerated LPS hypothermia in Koletsky *f/f* rats is associated with an enhanced rise in the plasma level of TNF-α (Fig. 5). The cryogenic effect of intravenous TNF-α is also markedly prolonged in Koletsky *f/f* rats. It is concluded from these results that elimination of leptin signaling does not affect febrigenic mechanisms, but it exaggerates cryogenic mechanisms. Among the mechanisms exaggerated in the absence of leptin signaling are the production and the cryogenic action of TNF-α.

Because leptin stimulates TNF-α production by monocytes and macrophages *in vitro* [151-154], elimination of a direct action of leptin on immune cells is expected to suppress rather than enhance TNF-α production. Other factors must account for the enhanced production of this cytokine in Koletsky *f/f* rats treated with LPS. A possible link between leptin and the immune response *in vivo* is the hypothalamo-pituitary-adrenal (HPA) axis. Compared to their leptin-responsive counterparts, undisturbed Koletsky *f/f* rats [110] and other leptin-irresponsive rodents [85,155] have slightly elevated plasma levels of corticotropin and corticosterone (two major components of the HPA axis). The mechanisms of such an abnormality are not completely understood but may include elimination of leptin signaling in the hypothalamus [156,157] and adrenals [158]. Although the basal activity of their HPA axis is slightly elevated, Koletsky *f/f* rats are unable to further activate the HPA axis in response to LPS; see Fig. 5 and Ref. 110. Activation of the HPA axis has multiple anti-inflammatory actions [96], and lack of such activation in the Koletsky *f/f* rats is likely to contribute to their exaggerated production of TNF-α in response to LPS and to their hypersensitivity to the cryogenic action of this cytokine. The revealed irresponsiveness of the HPA axis to LPS in Koletsky *f/f* rats agrees with the fact that LPS does not activate the HPA axis in *ob/ob* mice [85], and that corticosterone responses of wild-type mice and rats to LPS and IL-1β are enhanced by leptin administration [87,159,160]. Because leptin can trigger the release of corticotropin-releasing factor by hypothalamic neurons [161,162], and because several substances only stimulate the release of corticotropin-releasing factor in the presence of a functional leptin-LR system [163,164], it is possible that the participation of leptin in the immune activation of the HPA axis is related to regulation of the production and release of corticotropin-releasing factor.

5. Leptin and non-thermoregulatory manifestations of systemic inflammation

5.1. Leptin and behavioral depression

The thermoregulatory manifestations of systemic inflammation are not isolated events. They occur within the sickness syndrome, along with its behavioral manifestations [165,166]. As proposed by Romanovsky and colleagues [104,167,168], the sickness syndrome is a dynamic entity, *i.e.*, its symptoms change drastically as the syndrome progresses. Like the thermoregulatory manifestations, the behavioral manifestations of systemic inflammation are dynamic. At the onset of a systemic inflammatory response (*e.g.*, associated with a viral infection), humans feel uncomfortable and restless. As the disease progresses, this hyperactive state turns into a longer-lasting hypoactive state characterized by general weakness, sleepiness, and inability (or unwillingness) to perform normal daily routines. A similar behavioral pattern exists in experimental animals. Locomotor excitation has been occasionally reported in LPS-treated rats [104] and guinea pigs [169]. This excitation is short-lasting; it occurs during the course of the inflammatory response to low (just supra-threshold) doses of LPS or during the early phase of the response to moderate and high doses; and it coincides with monophasic fever or the first phase of polyphasic fever [104]. Behavioral excitation belongs to the so-called early sickness syndrome, which is aimed at actively fighting infection [104,167,168]. Most frequently, however, experimental animals challenged with microbial products, including LPS, are reported to have reduced locomotor activity and to spend more time sleeping [170-178]. This behavioral depression is long-lasting; it occurs during the later stages of the inflammatory response to moderate and high LPS doses; and it coincides with the second and subsequent phases of polyphasic fever or with hypothermia [104]. Behavioral depression belongs to the so-called late sickness syndrome, which is aimed at energy conservation [104,167,168].

Leptin is involved in the regulation of locomotor behavior. The spontaneous locomotor activity of *ob/ob* and *db/db* mice is depressed in several experimental paradigms [33,63,179-182]. As expected, leptin supplementation reverses the locomotor depression of *ob/ob* mice, but not that of *db/db* mice [63,179]. O'Connor and colleagues [183] determined how intraperitoneal administration of LPS affects exploratory behavior to introduction of a new cage mate in *db/db* mice or wild-type mice. In the wild-type mice, LPS caused a dose-dependent depression of exploratory behavior. In the *db/db* mice, LPS also induced behavioral depression, but this response was augmented in both magnitude and duration when compared to the response of the wild-type mice (Fig. 6). In a separate experiment, O'Connor and colleagues [183] showed that the augmented behavioral depression of *db/db* mice is associated with enhanced production of IL-1β (Fig. 6), a known mediator of LPS-induced depression [184,185].

Because exaggeration of the hypothermic and TNF-α responses to LPS in Koletsky *f/f* rats is associated with inability of these animals to respond to inflammatory stimuli with activation of the HPA axis [110], it is reasonable to conjecture that exaggeration of the behavioral and IL-1β responses to LPS in *db/db* mice is also related to the HPA axis. Compared to wild-type mice, the circulating level of corticosterone is higher in *db/db* mice before inflammatory challenge, but it tends to be lower after challenge with a lethal dose of LPS [85], thus suggesting that LPS-induced HPA axis activation in *db/db* mice is less pronounced. Perhaps, such an activation is even less pronounced when non-lethal doses of LPS are used, like the doses used in the study by O'Connor and colleagues [183]. It should be considered, however, that HPA axis-unrelated factors might also contribute to the exaggeration of the IL-1β response, as suggested by the *in-vitro* observation that *db/db* mice-derived macrophages produce more IL-1β than wild-type macrophages in response to LPS [183].

5.2. Leptin and anorexia

Another prominent manifestation of systemic inflammation is anorexia. Loss of appetite and consequent decrease in food intake is commonly observed in humans with infections of different etiologies. Likewise, a reduction in food intake has been reported in rats, mice, sheep, and pigs challenged with microbial products, including LPS (for reviews, see Refs. 165,186, 187). In rats, suppression of food intake usually starts 2-4 h after LPS administration [188-191], and it is associated with symptoms of the late sickness syndrome, *viz.*, the second and subsequent phases of polyphasic fever and behavioral depression [188,191]. Importantly, though, LPS-induced suppression of feeding is not a result of fever or behavioral depression, since it can occur even when the febrile or behavioral response is experimentally abolished [188,191,192]. In fact, the inflammatory suppression of feeding is related to a specific aspect of appetite regulation, as evident from the fact that peripheral LPS reduces meal frequency, but does not affect meal size or duration [193]. Like other manifestations of the sickness syndrome, anorexia is a well-defined strategy to cope with infection [165,194,195]. A decreased motivation for food reduces the possibility of predation while an animal is less vigilant due to disease [165]. Another benefit of anorexia may lie in the fact that the plasma levels of trace metals that are essential for bacterial growth drop abruptly upon suppression of food intake [196]. Additional benefits are likely to exist, considering that anorexia is a phylogenetically conserved host-defense response.

Leptin may participate in the anorexia of systemic inflammation in at least two distinct ways. First, leptin may mediate inflammatory anorexia; it can do so by acting directly on the hypothalamic neurons involved in appetite regulation [41]. Second, leptin may counteract inflammatory anorexia; it can do so by promoting activation of the HPA axis [85,110] and, consequently, limiting the production and action of cytokines (*e.g.*, TNF-α, and IL-1β) that mediate inflammatory anorexia. Whether these mechanisms are involved in inflammatory anorexia is unknown. It is unclear why the anorexic effect of LPS was suppressed in *db/db* mice, whereas it was enhanced in *ob/ob* mice under the same experimental conditions [197]. It is also unclear why LPS-induced anorexia was unaffected in Zucker *fa/fa* rats [198], but was attenuated in wild-type rats treated with an anti-leptin antibody [141]. Future studies are clearly necessary to determine what role, if any, leptin plays in the anorexia of systemic inflammation.

6. An integrated view: leptin, energy balance, and systemic inflammation

6.1. When leptin and its receptors function normally

A fall in the circulating level of leptin during conditions of negative energy balance (*e.g.*, calorie restriction and fasting) works as an anti-starvation signal, and this is believed to be the main physiological function of leptin (see section 2.2). Conditions of negative energy balance also reduce the peak level of leptin achieved during systemic inflammation [87]. It is, therefore, tempting to speculate that the roles of leptin in systemic inflammation may be generally related to regulation of energy balance.

At doses that are highly febrigenic in fed animals, LPS produces low-grade fever or hypothermia in fasted animals [133-136]. A shift from fever to hypothermia in fasted animals may be related to their lowered leptin production, as suggested by the fact that fever is often attenuated and hypothermia is exaggerated in leptin-irresponsive mutants (see section 4.3). As in leptin-irresponsive mutants, LPS-induced TNF-α production is enhanced in fasted animals whose plasma leptin is allowed to drop [87]. It remains to the determined, however, whether this enhanced TNF-α production accounts for prevalence of hypothermia over fever in fasted animals. Regardless of the mechanisms involved, a shift from fever to hypothermia is likely to be adaptive under conditions of negative energy balance. Although fever has antimicrobial and immunostimulating effects [199,200], its benefits may be offset by the high energetic cost associated with maintaining a high T_b [167,201,202]. On the other hand, lowering T_b is an energy conservation strategy that is widely used by vertebrates and invertebrates under conditions of imminent or enduring energy deficit [167,203,204].

Like hypothermia, behavioral depression is a manifestation of systemic inflammation that is augmented in the absence of leptin signaling (see section 5.1) and aimed at energy conservation [104,165,167]. It is, therefore, possible that suppression of leptin production under conditions of negative energy balance augments behavioral depression as well. This possibility has not yet been tested in a direct experiment, but it finds support in the observation that malnourished rats respond to LPS with an exaggerated production of IL-1β [205], a key mediator of behavioral depression [184,185]. The key role of leptin in regulating both energy balance and systemic inflammation is illustrated in Fig. 7.

6.2. Leptin irresponsiveness

Humans with idiopathic obesity and experimental animals with diet-induced obesity are typically irresponsive to leptin, and this irresponsiveness seems to be a cause of their low energy expenditure and relentless hunger (see section 2.2). Whereas inhibition of energy expenditure and stimulation of appetite are adaptive under conditions of negative energy balance, they are maladaptive in obesity, a persistent state of positive energy balance. Likewise, exaggeration of inflammation-associated hypothermia and behavioral depression looses its purpose in obese subjects. However, obese subjects may suffer from the detrimental effects of an exaggerated production of some inflammatory mediators. Indeed, LPS is more lethal in *ob/ob* mice than in their lean counterparts [85]. The *ob/ob* mice respond to LPS with an excessive production of TNF-α [85]. They are also more sensitive to the detrimental effects of TNF-α, as are *db/db* mice and Zucker *fa/fa* rats [206,207]. These findings are consistent with clinical studies [8-10,208,209] showing that obesity is often associated with a poor outcome in inflammatory disorders such as sepsis, lupus erythematosus, and severe pancreatitis.

7. Summary

- **i.** Mutant rats that are irresponsive to leptin due to an absent or a dysfunctional LR*b* show attenuated fever or exaggerated hypothermia in a cool environment, but not in a warm environment. This shift from fever to hypothermia is likely to be due to amplification of cryogenic signaling. Indeed, both the production and cryogenic action of TNF-α are enhanced in leptin-irresponsive mutants.
- **ii.** In mutant mice that are irresponsive to leptin due to an absent LR*b*, the behavioral depression of systemic inflammation is exaggerated. This exaggeration is associated with enhancement of IL-1β production.

iii. Leptin-irresponsive mutants are unable to fully activate the HPA axis in response to inflammatory stimuli. The HPA axis has multiple anti-inflammatory actions, and its incomplete activation may account for the exaggerated production of TNF-α and IL-1β in leptin-irresponsive rats and mice.

iv. In lean subjects (experimental animals and humans), the leptin-LR system is functional. When energy balance in these subjects is negative (*e.g.*, during fasting or calorie restriction), leptin production is suppressed, which can exaggerate both the hypothermia and behavioral depression of systemic inflammation. The biological value of this exaggeration is likely to be energy conservation (Fig. 7).

v. Experimental animals with diet-induced obesity and humans with idiopathic obesity are irresponsive to leptin. This dysfunctionality can result in augmentation of the hypothermia and behavioral depression of systemic inflammation. These manifestations, however, aid no benefit in obesity, a persistent state of positive energy balance.

vi. An involvement of leptin in inflammatory anorexia is also possible, but decisive evidence for such an involvement is still missing.

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Abbreviations

HPA, hypothalamo-pituitary-adrenal; IL, interleukin; LPS, lipopolysaccharide; LR, leptin receptor; TNF, tumor necrosis factor; T_b, deep body temperature.

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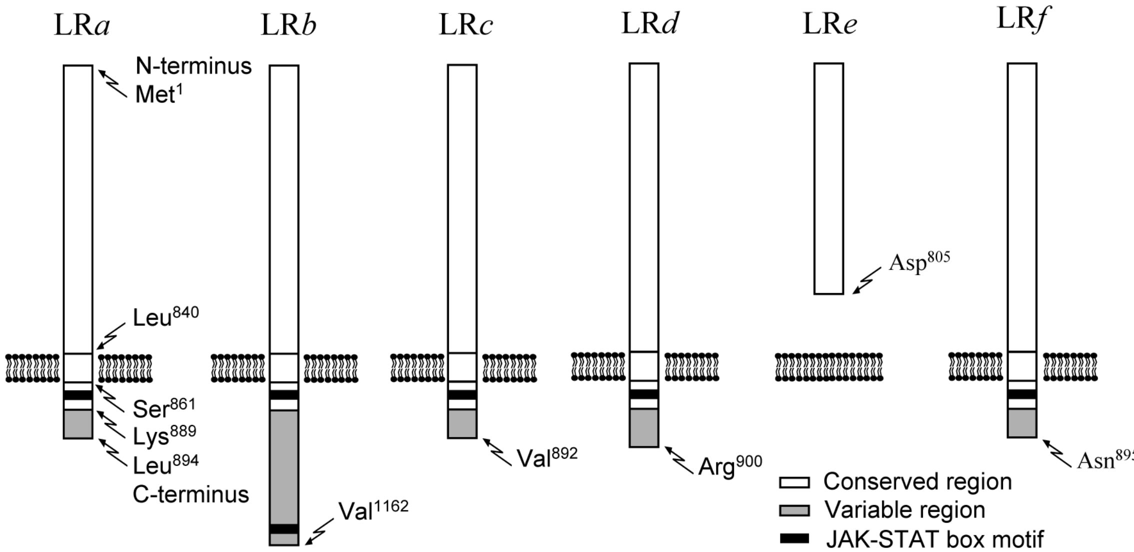

Fig 1.

Structures of LR isoforms. All isoforms are products of splicing variants of a single transcript. Each isoform has a conserved region, and may or may not have a variable region. The conserved region forms the extracellular and transmembrane domains as well as a small portion of the intracellular domain; the aminoacid sequence of this region is always constant, although it may be truncated. The variable region forms a large portion of the intracellular domain; the aminoacid sequence in this region is highly sensitive to splicing. The first or last aminoacid of each region and domain are listed at the first (left to right) diagram that contains this region or domain; amino acid numbering is based on the published sequences of mouse LR*a-e* [23,24] and rat LR*f*[25]. Box motifs for JAK-STAT phosphorylation are marked. Only when two JAK-STAT box motifs are present (as in LR*b*) does LR display full signal transduction capability.

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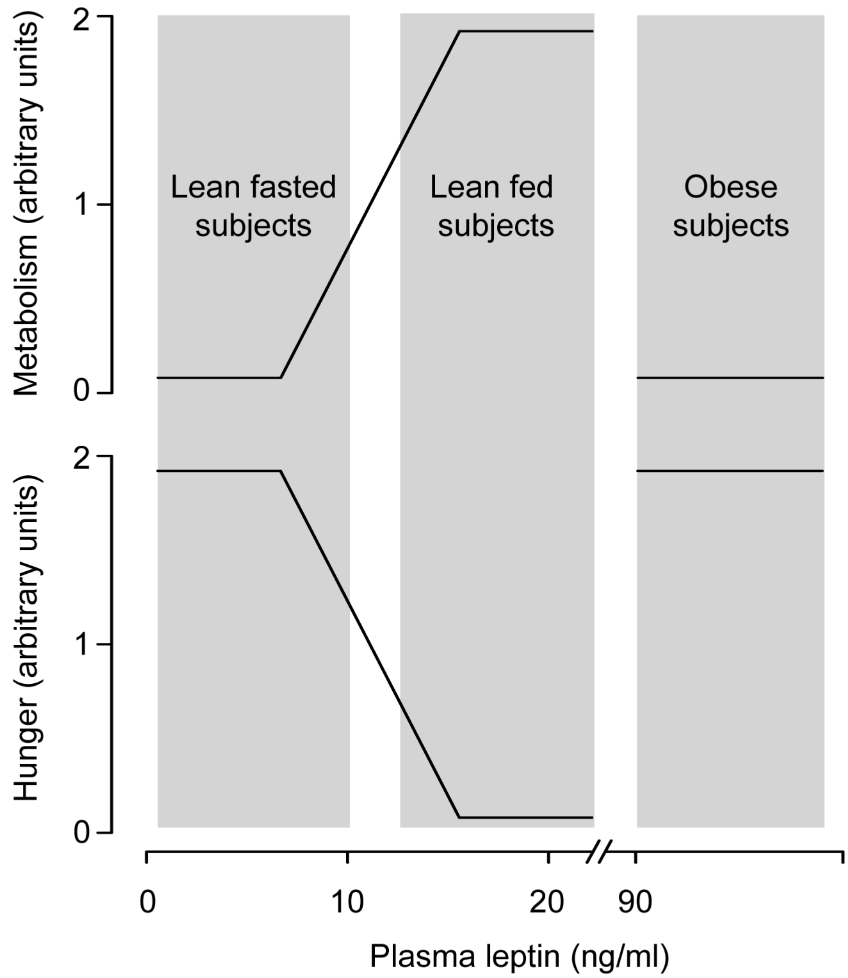

Fig 2.
A simplified schematic of the relationships among plasma leptin, metabolism, and hunger in lean and obese subjects. Please note that quantitative aspects of the relationships shown should be looked upon with great skepticism.

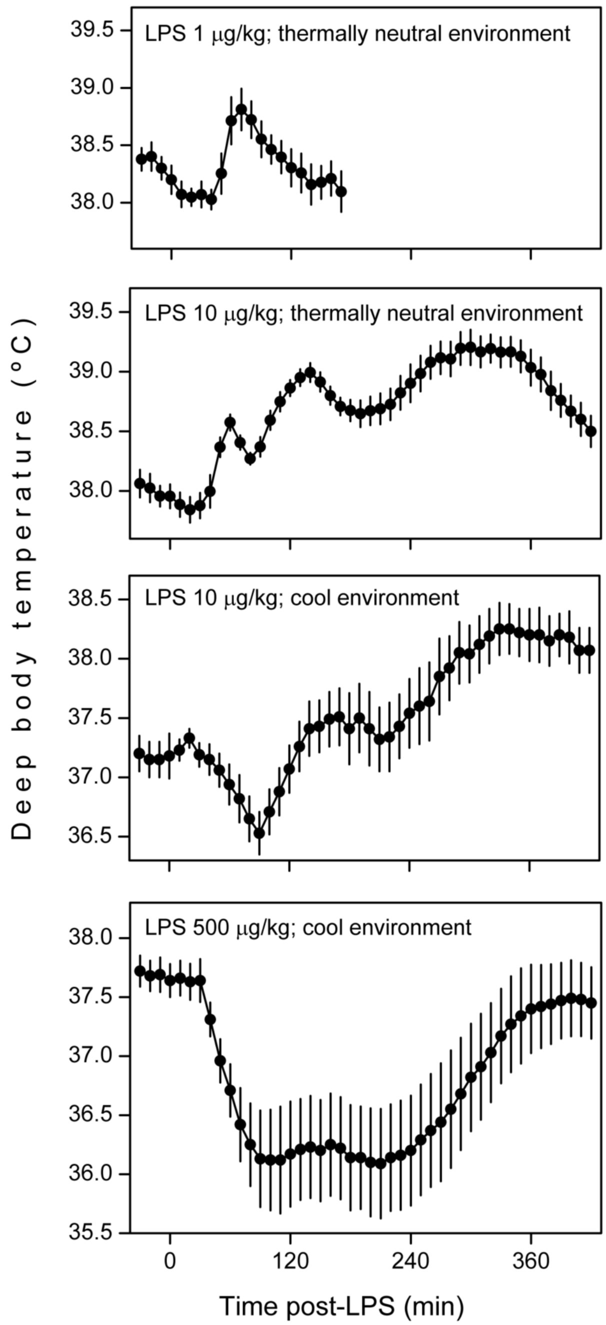

Fig 3.

Thermoregulatory responses of the rat to intravenous injection of LPS (doses indicated) in thermally neutral and cool environments. From top to bottom: monophasic fever, polyphasic fever, hypothermia followed by fever, and long-lasting hypothermia. Note that fever prevails when the LPS dose is lower or the environment is warmer, whereas hypothermia prevails when the LPS dose is higher or the environment is cooler. Adapted from Refs. 105,107,108,110 by permissions from the American Physiological Society and the Federation of American Societies for Experimental Biology.

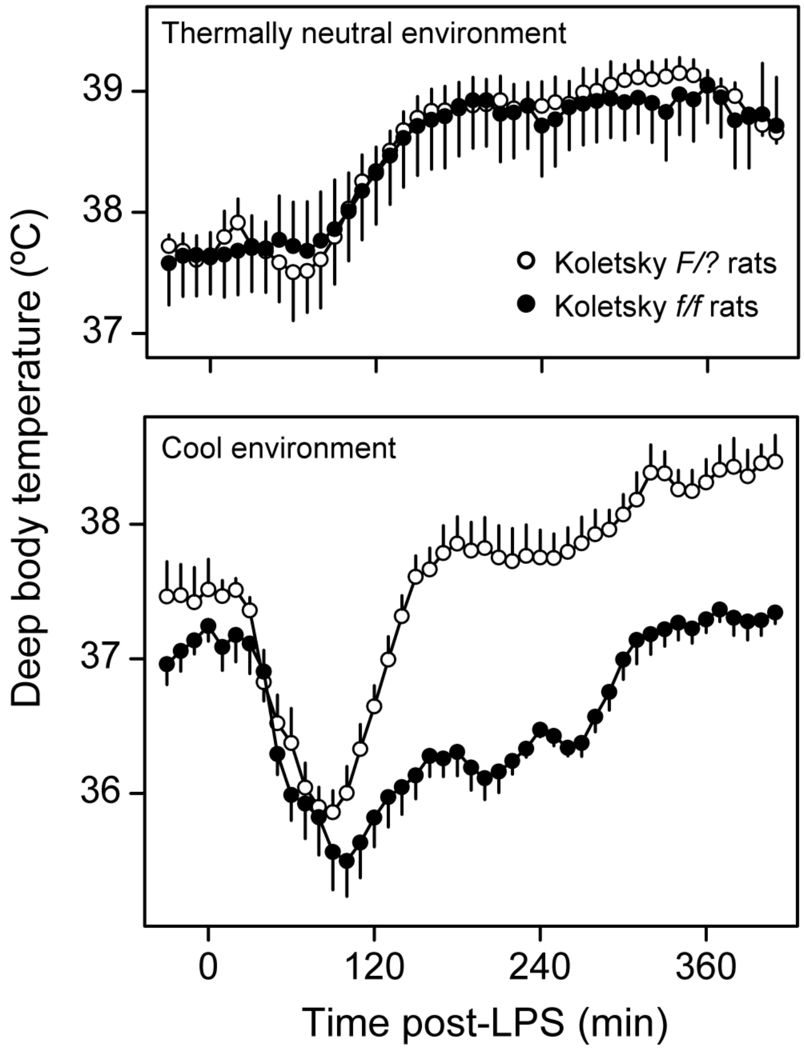

Fig 4.

Thermoregulatory responses of Koletsky *f/f* rats (lack all LR isoforms) and *F/?* rats (possess all LR isoforms) to intravenous LPS (100 μg/kg) in thermally neutral and cool environments. Reproduced from Ref. 110 by permission from the Federation of American Societies for Experimental Biology.

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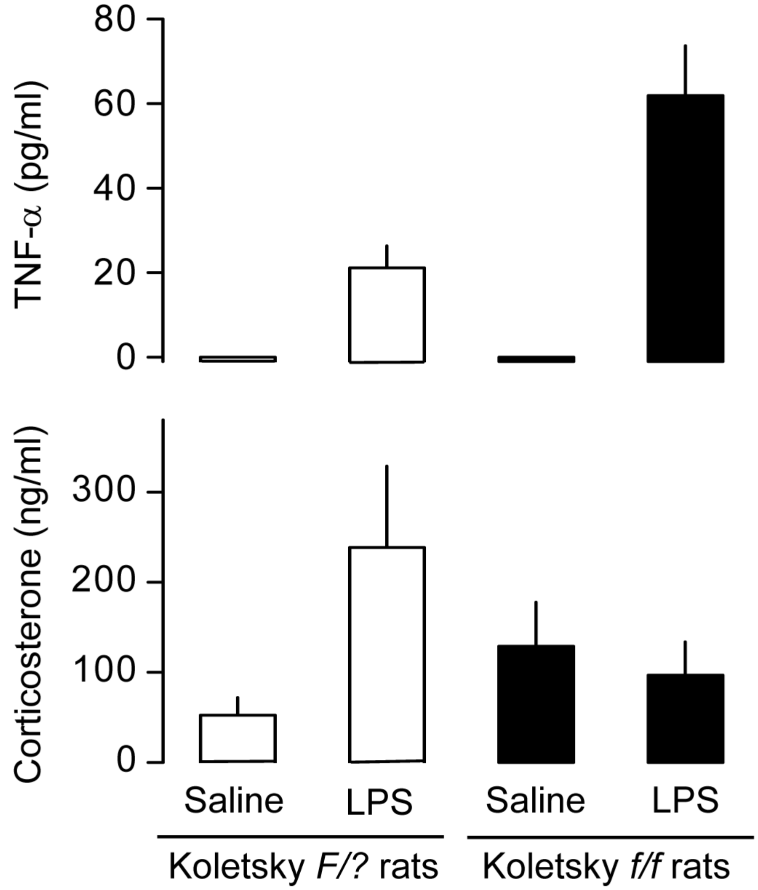

Fig 5.
Concentrations of TNF-α and corticosterone in the plasma of Koletsky *f/f* rats and their wild-type (*F/?*) counterparts 120 min after intravenous administration of LPS (100 μg/kg) or saline in a cool environment. This time point (120 min) corresponds to the maximal rate of divergence between the hypothermic responses of the *f/f* and *F/?* rats shown in Fig. 4. These data suggest that the exaggerated hypothermia of Koletsky *f/f* rats is associated with an enhanced rise in plasma TNF-α and a lack of activation of the HPA axis. Adapted from Ref. 110 by permission from the Federation of American Societies for Experimental Biology.

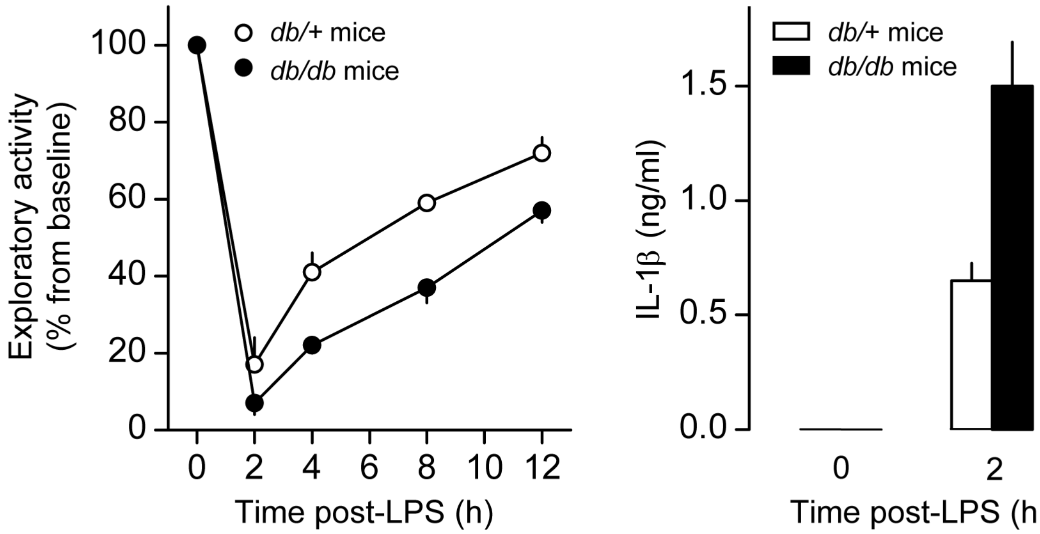

Fig 6.

Exploratory behavior and level of IL-1β in the peritoneal lavage of *db/db* mice (lack LR*b*) and *db/+* mice (possess LR*b*) injected intraperitoneally with LPS (5 μg/mouse). Reproduced from Ref. 183; copyright 2005 by the American Association of Immunologists, Inc.

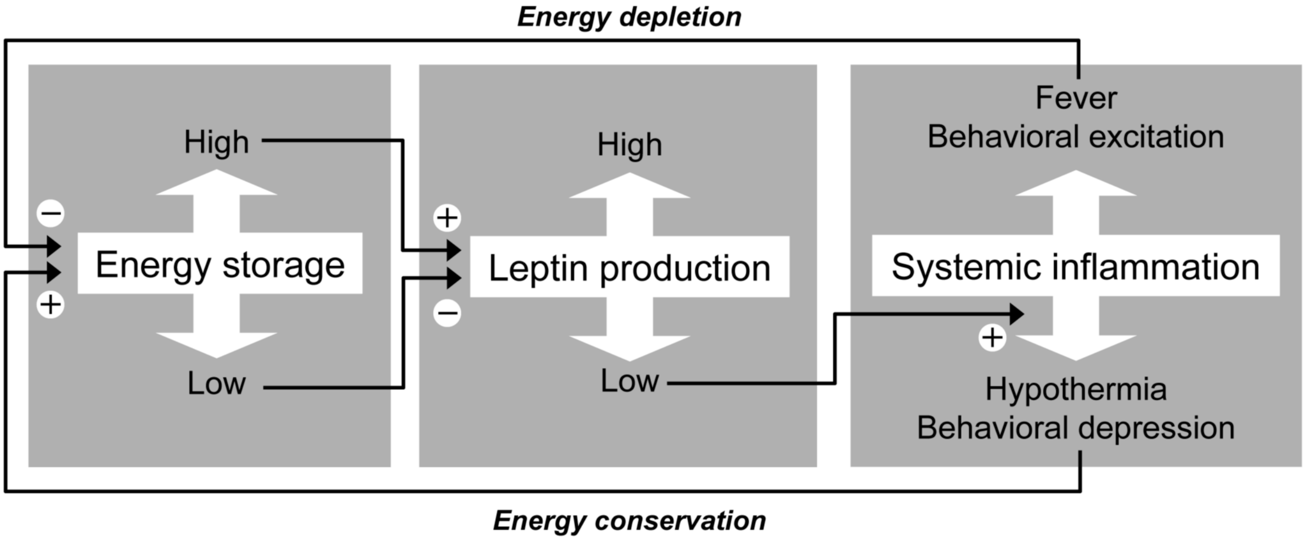

Fig 7.
Mechanisms of energy balance and systemic inflammation are interconnected *via* leptin. The fat white arrows show changes or manifestations of the processes indicated. The thin black arrows show stimulating (+) or inhibitory (−) effects.

Table 1

LR isoforms in three mutant models of obesity

Mutant	DNA level	mRNA level	Protein level	
			LR*b*	**LR*a*, LR*c-f***
db/db mouse	G → T at the region encoding the intracellular domain	Abnormal splicing	Absent	Functional
Zucker *fa/fa* rat	A → C at the region encoding the extracellular domain	Glu → Pro codon conversion	Dysfunctional	Functional
Koletsky *f/f* rat	T → A at the region encoding the extracellular domain	Early stop codon	Absent	Absent