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Review article

New insights in leptin resistance mechanisms in mice

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ABSTRACT

Leptin resistance is one of the main challenges of obesity. To date, two levels of resistance have been identified, first a decreased rate of leptin uptake into the brain and secondly a diminished central response to leptin. New findings have identified the mechanisms of leptin transport and demonstrated that it can be rescued in obesity, but it did not overcome the problem of central resistance. Alteration in the actions of leptin following diet-induced obesity (DIO) appears to be a multifactorial condition. Several phosphatases are inhibiting leptin signaling pathways in a pathological way. Besides, hypothalamic inflammation alters the neuronal circuits that control metabolism. Recent studies describing both mechanisms (inhibition of leptin signaling and inflammation), have provided key insights to potential new targets for treatment. However, recent data showing that DIO mice may conserve a cellular and physiological response to endogenous leptin, highlights the need to redefine the concept of "leptin resistance".

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1. Obesity: from human to mice models

The body weight of an individual is determined by the long-term balance of energy intake and output. In this context, obesity is caused by a chronically positive energy balance resulting in increased fat mass (Stunkard, 1996; Surwit et al., 1988; Weiser et al., 1997). Although genetic and epigenetic factors can predispose an individual to store more fat, it is commonly accepted that hyperphagia is the major cause of obesity (WHO – «Overweight and Obesity» – Atlanta, Georgia, USA, 2006). Increased adiposity is typically associated with increased levels of leptin, a key hormone involved in body weight regulation by decreasing food intake and increasing energy expenditure. However, unlike what their high leptin level could predict, obese individuals do not respond to leptin in an adequate manner (Considine et al., 1996; Maffei et al., 1995). Indeed, in animals model of obesity, hyperleptinemia induced by high fat diet fails to decrease food intake (Ogus et al., 2003). Moreover, exogenous leptin administration, even at high doses, does not trigger any food intake nor body weight decrease, except in cases of leptin deficiency in obese animals and humans (Bluher and Mantzoros, 2009). These observations lead to the concept of leptin resistance, defined by the inability of obese individuals (humans or animals) to respond to an elevated levels of endogenous or exogenous leptin (Myers et al., 2010).

It has been established that leptin administration in leptin deficient mice (*ob*/*ob*) decreases food intake and body weight (Campfield et al., 1995; Halaas et al., 1995; Pelleymounter et al., 1995), however this genetic model of obesity is not particularly relevant in the context of human obesity as monogenic syndromes are responsible for only very few case of obesity in human (Farooqi and O'Rahilly, 2005). Indeed, most obese individuals exhibit highly elevated serum levels of leptin, directly linked to the increased adiposity (Maffei et al., 1995). As a consequence, the study of leptin resistance is more relevant in animal models in which obesity is induced by feeding, better reflecting human obesity. The most commonly used model is diet-induced obesity (DIO) in mice and rats (Van Heek et al., 1997). It has been shown that in this model, several weeks of exposure to a high fat diet (45–60% of energy intake from fat) is linked to the development of obesity and reduced responses to leptin (Van Heek et al., 1997; Widdowson et al., 1997).

2. "Leptin resistance in diet-induced obesity

The present review, will describe the cellular mechanisms that alters leptins action in the context of hyperleptinemic diet-induced obesity. "Leptin resistance" commonly refers to a state in which DIO mice do not display an adapted response to their high endogenous leptin levels as they maintain body weight excess. Besides the altered response to endogenous leptin in DIO, resistance to exogenous leptin is also observed at several structural levels, from the cell to the organism. At the cellular level, "leptin resistance" can

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be observed by the absence of leptin-induced pSTAT3 expression in neurons, a marker of leptin receptor (LepRb) activation Baumann et al., 1996. At the physiological level, "leptin resistance" in DIO mice is evident by a lack of decrease in body weight and food intake, that otherwise occurs in lean mice following exogenous leptin administration (Halaas et al., 1995).

In humans, elevated leptin has no effect on body weight of obese individuals (Considine et al., 1996; Maffei et al., 1995). This phenomenon, that has been widely studied since the identification of the leptin receptors (Tartaglia et al., 1995), is still not fully understood.

Four mechanisms have been proposed:

- First, a decrease in leptin transport from the blood to the hypothalamus, a critical site for leptin actions, has been demonstrated (Van Heek et al., 1997).
- Another mechanism responsible for leptin resistance involves central leptin signaling. The long form of leptin receptor, LepRb, is the relevant form for signaling and is known to activate JAK/STAT and PI3K signaling pathways (Vaisse et al., 1996). Leptin capacity to activate STAT3 and PI3K is decreased in DIO mice (El-Haschimi et al., 2000; Metlakunta et al., 2008). Several proteins can reduce the signaling from cytokine receptors, by interfering with signal transduction. The first of these was SOCS-3, and since then PTP1B, TCPTP, SHIP2 and others have been shown to be negative regulators of leptin receptor signaling, and possibly elevated in obesity. It has been suggested that suppression of LepRb-associated signaling pathways could be responsible for central leptin resistance.
- Unfolded protein response (UPR) has been shown to modulate the sensitivity to DIO and to be linked to leptin responsiveness.
- DIO was proved to cause hypothalamic inflammation, altering the neuronal pathway involved in energy homeostasis.

However, a recent study conducted by Ottaway and colleagues demonstrated that DIO mice retain endogenous leptin action (Ottaway et al., 2015). This new data, together with older studies, will be further discussed in the section describing alterations in leptin signaling.

2.1. Peripherally-administrated leptin resistance: leptin transport alteration

Studies conducted in humans shown a strong decrease in the capacity of peripheral leptin to enter the brain. Peripheral (serum) and central (CSF) leptin levels have been measured in obese and lean individuals. In obese individuals, peripheral leptin level is dramatically increased (10 ng/ml in lean, 40 ng/ml in obese). The results were normalized based on the CSF/serum leptin level ratio for each of the individuals. This analysis revealed that in obese individuals, this ratio was diminished by 3–4-fold compare to lean individuals (Lin et al., 2000). This result suggests that the capacity of leptin to be transported from blood to brain is decreased in obesity, although absolute concentrations of leptin in the brains of obese individuals is higher compare to lean humans (Caro et al., 1996). This finding is further highlighted by the inability of peripheral administration of exogenous leptin at supra-physiological doses, to activate leptin signaling pathways in the CNS of DIO mice (El-Haschimi et al., 2000). Development of leptin resistance can be described in three steps. (1) The beginning of high fat feeding triggers a fat mass increase, although mice are still sensitive to leptin as a peripheral administration of exogenous leptin is able to decrease their food intake. (2) An intermediary step consist in peripheral leptin resistance but central leptin response is intact as leptin directly delivered in CNS induce a decrease in food intake, which is not the case if leptin is peripherally injected (Van Heek et al., 1997; El-Haschimi et al., 2000; Lin et al., 2000). (3) In more advanced stages, mice display a central leptin resistance demonstrated by the absence of leptin effects on STAT3 phosphorylation, food intake, or body weight when leptin is injected into the cerebral ventricles or into the brain parenchyma, even at high doses (El-Haschimi et al., 2000; Lin et al., 2000). The development of leptin resistance is summarized in Table 1.

The study from Lin et al. (2000) clearly demonstrates that leptin resistance gradually develops and is linked to increased body weight and adiposity. The first alteration observed is a disruption of leptin uptake from the blood to the brain, more precisely to the hypothalamus, the target area of leptin's anorexigenic effects. Another study followed the accumulation and activity of peripherally-delivered leptin in various hypothalamic nuclei and revealed that leptin accessibility differs between hypothalamic nuclei (Faouzi et al., 2007). Indeed the arcuate nucleus of the hypothalamus (ARH) displays a faster and stronger response following peripheral leptin injection, even with low doses (evaluated through STAT3 phosphorylation), compared to other hypothalamic nuclei. The authors of this study demonstrated a gradual leptin response first in the ARH and later in VMH, PVH and DMH. In contrast, when leptin is centrally delivered, the gradual access of leptin to the different nuclei is abolished and all regions are activated simultaneously (Faouzi et al., 2007). All together these results show that hypothalamic nuclei have varying levels of access to peripheral leptin, highlighting again the necessity to determine the precise mechanisms of leptin transport from the blood to the brain. Moreover, the hypothalamus itself displays a different level of leptin accessibility compared to other brain regions that also express leptin receptors (Banks et al., 2000).

2.1.1. Leptin transport: generalities

There is a non-linear relationship between plasma leptin levels and leptin entry into the brain (Schulz et al., 2004). Leptin uptake in the brain occurs quickly in low leptin conditions but does not increase proportionally following an increase of plasma leptin level, highlighting a saturable leptin transport mechanism (Banks, 2004). The saturation of this transport is also variable

Table 1
Timing of development of leptin resistance in mice.

1 week HFD	BW +5.2% Fat content +6.7% Serum leptin +18%	Sensitivity to 2 mg/kg peripheral leptin injection is conserved	Sensitive to leptin
8 weeks HFD	BW +11.4% Fat content +68.1% Serum leptin +223%	Sensitivity to 2 mg/kg peripheral leptin injection is lost Sensitivity to 0.1 μg icv leptin injection is conserved	Resistant to peripheral leptin Sensitive to central leptin
19 weeks HFD	BW +30.5% Fat content +141% Serum leptin +458%	Sensitivity to 0.1 μg icv leptin injection is lost Sensitivity to 2 μg icv leptin injection is reduced	Resistant to peripheral and central leptin

Adapted from Lin (El-Haschimi et al., 2000).

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