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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".

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).

depending on the brain area observed. This variation is evident when plasma leptin concentrations increase from low to high concentration (30 ng/ml), in this situation the sensitivity of transport mechanism is modified only in certain brain regions. When leptin level is high, the pons and medulla exhibit the higher rates of leptin uptake (Maness et al., 2000), in contrast to the hypothalamus that displays the lowest leptin uptake (Pan and Kastin, 2001). Since leptin's actions differ according to the brain regions considered, it appears that there is an optimum level of leptin, which is different among brain regions. In normal conditions, the hypothalamus has the greatest leptin influx (Ladyman and Grattan, 2005). In contrast, the slowest leptin uptake is observed in the cortex (Zlokovic et al., 2000).

Leptin transport across the BBB is similar to insulin, transferrin, growth factors, vasopressin, endorphins and alpha-MSH transport. At cerebral capillaries, leptin binds to the luminal face of endothelial cells and is transported without any modifications in one direction from the blood to the cerebral parenchyma (Zlokovic et al., 2000) but several studies have also shown that leptin can bind to the abluminal surface of endothelial cells (Mütze et al., 2006). Even if the short form of leptin receptor, LepRa, is present in high density at the cerebral capillaries level, it is not known whether LepRa allows transcytotic transport of leptin (Bjorbaek et al., 1998; Kastin et al., 1999). However transport of leptin across the BBB has not been shown under physiological conditions (Halaas et al., 1997). A saturable transport is only observed with pharmacological concentrations (10–300 ng/ml) Banks et al., 2000. According to these findings, it is reasonable to predict that another transport mechanism exists, maybe more specific, that allows leptin to enter the hypothalamus. For example leptin may enter via the median eminence or tuberoinfundibular zone, resulting in a wave of leptin to gradually spreads from the median eminence to the outer regions of the hypothalamus.

2.1.2. Leptin transport across tanycytes of the median eminence

The main site of leptin's anorexigenic effects is the arcuate nucleus of the hypothalamus (ARH), located next to a circumventricular organ (CVO), the median eminence (ME). CVOs are characterized by a fenestrated endothelium, allowing molecules to freely enter and exit the blood. However, peripheral molecules do not freely diffuse to enter the ARH because this nucleus is protected by a tanycytic barrier (Mullier et al., 2010). Tanycytes are ependymoglial cells lining the floor of the third ventricle and extending processes toward the fenestrated capillaries of the ME (Peruzzo et al., 2004). The cell bodies of tanycytes are linked by tight junctions, preventing passive diffusion of blood-borne molecules (Mullier et al., 2010). However tanycytes are highly polarized and contain vesicular trafficking machinery (Peruzzo et al., 2004), suggesting their involvement in transport mechanisms (Rodríguez et al., 2010). We have recently demonstrated the role played by median eminence tanycytes in leptin transport from the blood to the brain and that the alteration of this transport is a component of leptin resistance in obese mice (Balland et al., 2014). Peripherally injected leptin reaches the median eminence, within a few minutes, where it activates LepRb in tanycytes. Later, leptin is found in the medio-basal hypothalamus (MBH) of lean mice. In obese mice (DIO and db/db mice) leptin accumulates in the ME and does not reach the MBH even 45 min after injection. In vitro experiments on tanycytes primary culture revealed the key role played by ERK signaling pathway in leptin release from leptin-loaded tanycytes. In lean mice, ERK is one of the signaling pathways activated by leptin and this activation in tanycytes allows the released of leptin from tanycytes into the parenchyma of the MBH. Conversely, in DIO mice leptin's ability to activate its signaling pathways in tanycytes is lost, an alteration responsible for the lack of leptin entry in the MBH. The pharmacological activation of ERK in tanycytes of DIO and db/db mice, using epidermal growth factor (EGF), restored leptin entry into tanycytes, and ultimately into the MBH. Ultimately this study reveals the mechanisms of leptin entry in the hypothalamus and a possible target site of action to rescue altered leptin responsiveness (Balland et al., 2014). Nevertheless, further studies are required to investigate the physiological importance of leptin transport across tanycytes and it's involvement in leptins actions.

2.2. Central leptin resistance

Changes in the ability of peripheral leptin to access hypothalamic nuclei contributes to the development of central leptin resistance. Indeed, leptin resistance occurs firstly in ARH, a nucleus more sensitive to leptin than other hypothalamic nuclei (Faouzi et al., 2007). Later in the development of central leptin resistance, VMH, DMH and PVH decrease gradually their sensitivity to leptin (Munzberg et al., 2004). However it is of importance to note that these nuclei become resistant to the appetite suppressing effects of leptin but not to all its other functions. For instance hyperleptinemia seen in obesity is responsible for the development of hypertension, due to leptins action on the DMH (Simonds and Cowley, 2013; Simonds et al., 2014). The DMH remains leptin responsive in obesity, it has been shown by electrophysiology (Lee et al., 2013), unaltered leptin-induced pSTAT3 positive DMH neurons in DIO mice (Balland et al., 2014; Enriori et al., 2011) and leptin-induced thermogenesis (Enriori et al., 2011). Interestingly, the sequential occurrence of central leptin resistance among hypothalamic nuclei reflects leptin accessibility pattern, moreover hyperleptinemia was demonstrated to be required for the development of central leptin resistance (Knight et al., 2010). Older studies from Scarpace's group demonstrated that over-expression of leptin (rAAV-leptin) in the brain had no effect on DIO mice but surprisingly the same treatment caused significant weight loss in lean mice (Wilsey et al., 2003). Under these conditions, we would have expected to see an altered leptin responsiveness caused by central hyperleptinemia. The opposite effects observed could be explained by the length of the treatment, mice received rAAV-leptin for 30 days, which may not be long enough to alter leptin sensitivity. Indeed, a study from the same group demonstrated that rats with chronically infused rAAV-leptin in the brain for a longer period of time (14 months) displayed cellular leptin resistance (Matheny et al., 2011). All together, these results suggest that long-term excess of central leptin level could be responsible for the development of loss of leptin responsiveness. Central leptin resistance is simply revealed by the decrease or the absence of cellular and physiological responses to central leptin administration (Widdowson et al., 1997; El-Haschimi et al., 2000; Lin et al., 2000). Finally leptin access to the brain is not the only mechanism leading to leptin resistance but it's also clear that central sensitivity to leptin is modified.

2.2.1. Leptin receptor expression

Although in most physiological situations, there is no major change in LepR expression and no difference between lean and obese brain, changes in lepR can alter the response to leptin. The decreased LepRb-associated signaling pathways in response to leptin, seen in chronic obesity, could be caused by a decrease of LepRb expression at the level of cell surface (Wilsey and Scarpace, 2004; Wilsey et al., 2003). This hypothesis is supported by the observation that repression in ARH of OB-RGRP, a negative regulator of LepR gene, prevents the development of obesity when mice consume a HFD (Couturier et al., 2007). However, LepRb-associated signaling pathways are more likely to be altered in case of leptin resistance rather than the level of expression of the receptor itself. A study conducted by Bjorbaek's group supports this idea and

showed that mice over-expressing leptin receptors in POMC neurons are more sensitive to diet-induced obesity (Gamber et al., 2012).

2.2.2. Leptin signaling alteration

LepRb-associated signaling pathways activation in response to exogenous leptin is dramatically decreased in ARH of DIO mice while others nuclei maintain a certain sensitivity to the hormone. This may be the consequence of the hierarchical installation of leptin resistance in hypothalamic nuclei, described by Munzberg et al. (2004). The diminished leptin-induced signaling capacities affecting the ARH, notably in POMC and AgRP neurons, are associated with an alteration in the release of these neuropeptides (Enriori et al., 2007). In DIO mice, there is no further increase in the number of pSTAT3-positive neurons in the ARH following exogenous leptin injection (Munzberg et al., 2004). However it is of importance to note that the basal level of STAT3 activation, in absence of exogenous stimulation is significantly higher in the ARH of DIO mice (Martin et al., 2006; Enriori et al., 2011). In parallel, ARH displays an increased expression of suppressor of cytokine signaling 3 (SOCS3), increasing the inhibition of leptin signaling pathways (Munzberg et al., 2004; Gamber et al., 2012; Enriori et al., 2007). However, genetic enhancement of STAT3 activation in POMC neurons does not prevent leptin resistance. In contrary, transgenic mice expressing a constitutively active form of STAT3 become obese on normal chow diet consequently to the increase of negative feedback inhibition played by SOCS3 on leptin signaling (Ernst et al., 2009). In opposite, SOCS3 deficiency in the brain (Mori et al., 2004) and specifically in POMC neurons (Kievit et al., 2006) increased leptin-induced body weight loss and protected again the development of obesity when mice were fed a HFD. Similarly to SOCS3, depletion of others negative regulators of LepRb-associated signaling pathways like PTP1B (Bence et al., 2006), TCPTP (Loh et al., 2011) and SHIP2 (Sleeman et al., 2005) phosphatases involved in the inhibition of leptin signaling (Fig. 1), enhance leptin sensitivity and attenuate weight gain under a HFD. Besides STAT3 signaling, PI3K pathway is also required for the metabolic action of leptin (Niswender et al., 2001; Zhao et al., 2002; Hill et al., 2008). Not surprisingly, PI3K is impaired in DIO (Metlakunta et al., 2008; Sahu and Metlakunta, 2005). However, STAT3 and PI3K pathways appear to be differentially affected by DIO and central hyperleptinemia. PI3K signaling is impaired more rapidly than STAT3 signaling. This was shown in rats with chronic central leptin infusion in which PI3K pathway was altered within 2 days, whereas STAT3 signaling remained unchanged (Sahu and Metlakunta, 2005). Accordingly, the study from Scarpace's group previously cited, showed that 30 days of leptin over-expression in the brain was insufficient to provoke changes in STAT3 signaling or downstream gene expression (Wilsey et al., 2003). In line with these findings, another study identified differences in the time of appearance of alterations between STAT3 and PI3K signaling following HFD exposure. After 4 weeks of HFD, mice failed to display a leptin-induced increase in PI3K activity, while pSTAT3 was still increased by the same treatment (Metlakunta et al., 2008). As a transcription factor, STAT3 is involved in the genomic effects of leptin on metabolism (Baumann et al., 1996; Allison and Myers, 2014). On the other hand, PI3K signaling mediates the acute effects of leptin by regulating the cell excitability of POMC neurons (Hill et al., 2008) and acting on short-term regulation of leptin-mediated food-intake

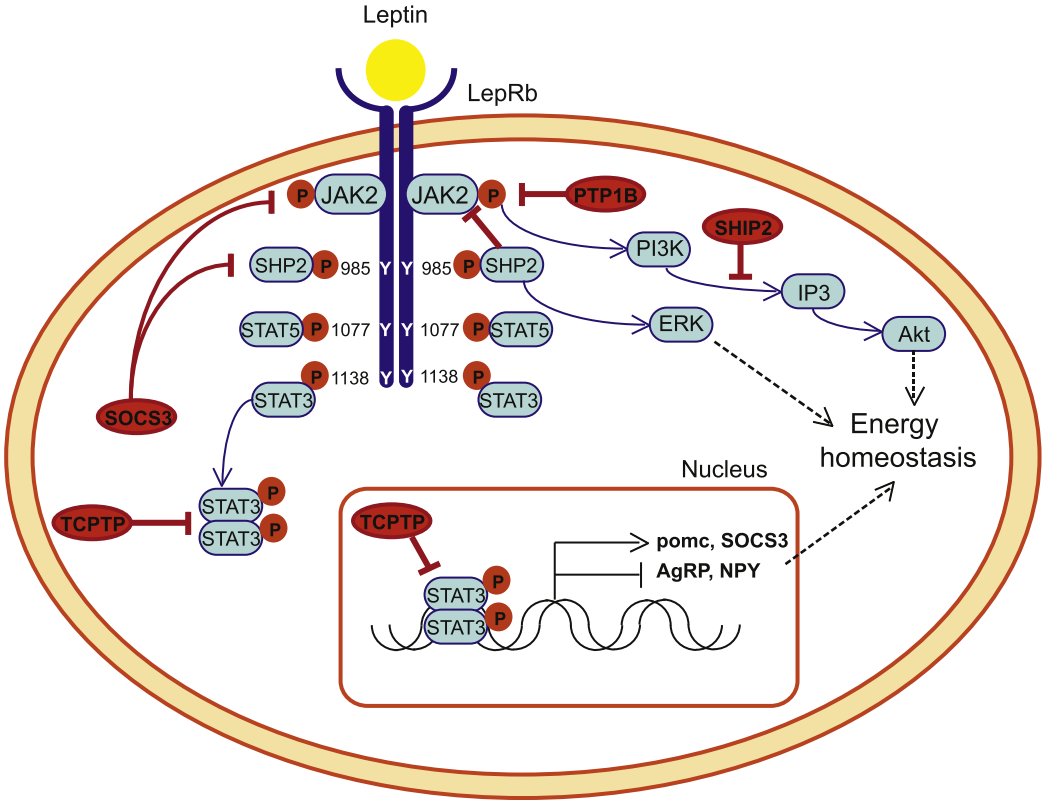

Fig. 1. LepRb-associated signaling pathways and inhibitions. After leptin binding on LepRb dimers, JAK2 are phosphorylated. Phosphorylated JAK2 activates PI3K signaling pathway and also phosphorylates LepRb on several tyrosine residues: Y985, Y1077 and Y1138. SHP2 tyrosine-phosphatase binds to phosphorylated Y985 and activates ERK signaling pathway but also inhibit JAK2 phosphorylation. STAT5 and STAT3 respectively binds Y1077 and Y1138 phosphorylated by JAK2. Dimers of phosphorylated STAT3 enter the nucleus to acts as a transcription factor to regulates leptin target genes to mediate its metabolic effects. SOCS3 acts as a feedback loop to inhibit leptin signaling through the dephosphorylation of JAK2 and Y985. PTP1B and TCPTP respectively dephosphorylate JAK2 and STAT3 dimers. Another phosphatase, SHIP2, inhibits the conversion of PI3K to IP3, blocking this signaling cascade.

(Niswender et al., 2001). The observation that leptin-dependent STAT3 and PI3K signaling pathways are differentially affected by DIO, together with their different roles in mediating the actions of leptin, highlights the need to study the effects of DIO specifically in individual leptin signaling pathways.

Altogether these findings suggest that an alteration of leptin signaling specifically in the arcuate nucleus of the hypothalamus is responsible for a part of the physiopathology of leptin resistance, a phenomenon that maintains obesity. Nevertheless, leptins action does not exclusively rely on the ARH and involves a complex network including other hypothalamic and extra-hypothalamic nuclei (Scott et al., 2009; Myers et al., 2009). Interestingly, a recent study demonstrated that DIO mice retain endogenous leptin action (Ottaway et al., 2015). Ottaway and colleagues used a leptin receptor antagonist (LA) and showed that central and peripheral delivery of LA in DIO mice triggered a decrease in food intake and body weight to a similar extend seen in lean mice receiving the same treatment. This study is the first to show that in spite of the apparent "leptin resistance", characterized by an absence of response to exogenous leptin and the failure of the high endogenous leptin levels to regulate body weight, endogenous leptin still played a role in energy homeostasis of DIO mice. Several hypothesizes could underlie this phenomenon: one is that the high number of pSTAT3 activated neurons observed in basal conditions in DIO mice are in a state of constant response to endogenous leptin and are playing a role in the regulation of energy balance. Another hypothesis, which do not exclude the first one and others, is that hypothalamic and extra-hypothalamic nuclei that remains leptin responsive in obesity are responsible for the regulation of energy balance that is modified by LA administration.

2.2.3. Unfolded protein response

Increasing number of studies suggest that inflammation is also involved in leptin resistance mechanisms. Notably, it has been suggested that endoplasmic reticulum stress (ER stress) acts as a part of leptin resistance. ER is required for protein synthesis in the cell. After synthesis, proteins are modified in the ER lumen to adopt their final bioactive conformation. Proteins that do not display a correct conformation are directed to the proteasome to be degraded. The accumulation of unfolded proteins at a higher level than ER folding machinery capacity triggers ER stress (Vembar and Brodsky, 2008). ER stress involves unfold protein response (UPR) activating a large number of intracellular signaling cascades. Long-term ER stress triggers apoptosis in cells (Ron and Walter, 2007). In obesity, ER stress is highly increased, particularly in the brain (Zhang et al., 2008). Excessive food intake stimulates mTOR signaling which in turn creates ER stress (Ozcan et al., 2008). Moreover, ER stress inhibition in hypothalamus (with genetic or pharmacological approaches) restores leptin sensitivity and decreases food intake in mice (Ozcan et al., 2008). Interestingly, ER stress is able to inhibit leptin signaling in vitro whereas pharmacological suppression of ER stress allows an increase of leptin signaling (Ozcan et al., 2008; Hosoi et al., 2008). The relationship between ER stress and leptin responsiveness could be mediated by many different factors and therefore requires further studies to investigate which pathways of the UPR response are potentially beneficial or deleterious in regard of leptin sensitivity. Recently, Williams and colleagues studied the constitutive expression of Xbp1s, a transcription factor responsible for the activation of UPR response, specifically in POMC neurons and showed that it was sufficient to increase leptin sensitivity and protect mice against DIO when fed with HFD (Williams et al., 2014). Finally, it appears that ER stress contributes to central leptin responsiveness through the activation of signaling cascades associated to UPRs, modulating leptin signaling pathways.

2.2.4. Hypothalamic inflammation

Inflammatory processes can also be responsible for structural changes in the hypothalamus, making the hypothalamic circuits inefficient in controlling food intake. A few years ago, Horvath and colleagues showed differences in hypothalamic synaptic organization of mice and rats based on their sensitivity to diet-induced obesity (Horvath et al., 2010). This study highlighted the role played by reactive astrocytes in the ensheathment of anorexigenic POMC neurons, decreasing the number of synapses and isolating these neurons from blood-borne signals. A pro-inflammatory state of glial cells is an early response to HFD exposure and occurs within few days prior to detection of significant changes in body weight (Thaler et al., 2012; García-Cáceres et al., 2013). The proliferation of reactive astrocytes and microglial cells during HFD, a phenomenon known as gliosis, is then responsible not only for structural modifications (Horvath et al., 2010; Thaler et al., 2012) but also for functional alterations of the hypothalamus in response to an increased level of pro-inflammatory cytokines (Thaler et al., 2012, 2014). The early inflammatory response that appears during the first days of HFD displays a short-term neuroprotective effect (Thaler et al., 2014). However the maintenance of a chronic inflammatory response could then become responsible for hypothalamic changes involved in the loss of leptin responsiveness (Thaler et al., 2012, 2014). Recent data generated by deleting leptin receptors in GFAP-expressing cells, suggests a direct link between astrocytes and leptin sensitivity, (Kim et al., 2014). The absence of lepR in astrocytes was associated with an altered glial morphology and modification of synaptic output, similarly to the modification previously observed in DIO animals (Horvath et al., 2010). In parallel, mice lacking LepR expression in astrocytes also displayed a decreased sensitivity to leptin (Kim et al., 2014). Not only astrocytes, but also microglia activation has been linked to POMC neurons dysfunction induced by HFD (Gao et al., 2014). More evidence is required to further understand the role played by glial cells in leptin resistance and whether this occurs due to direct actions on neurons themselves or their immediate environment. Importantly, more studies are necessary to better identify the role of gliosis in leptin resistance and to understand if it is a cause or a consequence.

3. Reversibility of leptin resistance

Both stages of leptin resistance development, that consists of alterations in leptin transport and loss of central leptin sensitivity, can be reversed by body weight loss.

3.1. Sensitivity to peripherally injected leptin

The rapid body weight loss caused by reduced dietary fat intake leads to a decrease in body weight but is not sufficient to rapidly rescue leptin transport into the brain (Balland et al., 2014; Enriori et al., 2007). In the study of leptin transport and resistance conducted by Balland et al., sensitivity to peripherally injected leptin is restored in DIO mice (initially fed with HFD for 8–9 weeks) after being fed with standard chow for 10 weeks, when their body weight is similar to mice fed with chow-diet. Interestingly, when leptin transport across tanycytes is pharmacologically restored in DIO mice, body weight loss and leptin sensitivity rescue (as measured by leptin-induced body weight loss and pSTAT3 signaling) are accelerated. This recovery occurs only within 4 weeks of consuming the chow-diet, despite animals still presenting greater body weight compare to lean control mice (Balland et al., 2014). This former result highlights the therapeutic potential of leptin transport across tanycytes to treat obesity. However, as hyperleptinemia may be a major cause of diminished leptin

responsiveness, a treatment that favors leptin entry in the brain should only be used in the context of significant weight loss. Nevertheless, the control of leptin transport across tanycytes could then be used as a target to prevent central hyperleptinemia.

3.2. Central leptin sensitivity

A study from Enriori et al. demonstrated that the central leptin resistance acquired after 20 weeks on HFD, is characterized by an elevated level of the leptin signaling inhibitor SOCS3. In these DIO mice, leptin fails to modulate peptide secretion from the leptin-responsive neurons in ARH (Enriori et al., 2007). As others showed previously (Munzberg et al., 2004), central leptin resistance occurs mainly in ARH. Enriori and colleagues confirmed and described this result showing that the downstream melanocortin system is still sensitive to melanocortin agonists in 20 weeks HFD DIO mice. Decreasing the fat content of the diet in these mice, by giving them back a chow-diet, decreased their body weight (matching chow-diet fed mice) and allowed them to recover central leptin sensitivity. In this study the recovery of central leptin sensitivity was observed through the response to centrally administrated leptin, excluding leptin transport alteration issues. The restoration of central leptin resistance is a long process, mice were initially fed with HFD for 20 weeks, after this period, 17 weeks of standard diet feeding were necessary to observe the complete restoration of central leptin sensitivity (Enriori et al., 2007).

3.3. Concluding remarks

Finally it is clear that "leptin resistance", a state defined by a lack of response (cellular and physiological) to exogenous leptin and an attenuated response to an elevated level of endogenous leptin, is a multifactor pathophysiological state and occurs in different stages. The first alteration observed, a decreased leptin uptake in the brain, could act as a protective mechanism to prevent the hypothalamus from being exposed to high leptin levels which can in turn be toxic and trigger inflammation and cellular signaling alterations (up-regulation of phosphatases). A similar early protective mechanism occurs within the hypothalamus, with the proliferation of glial cells, that first exerts an acute protective role but becomes toxic in a chronic situation. After some time, if leptin levels remain high, the hypothalamus itself is altered. However, endogenous leptin actions appear to be conserved in obesity and new obesity therapies should focus on finding mechanisms that improve the effects of endogenously available leptin. The next challenge would be to understand the link between the different mechanisms and the precise sequence of appearance of the alterations, discriminating between the causes and the consequences of "leptin resistance". This knowledge could lead to new treatment options in obesity, acting simultaneously and possibly synergically at different levels.

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