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Leptin Keeps Working, Even in Obesity

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The concept of leptin resistance posits that elevated endogenous leptin fails to decrease food intake in obese animals due to diminished leptin signaling. In this issue, Ottaway et al. (2015) use leptin antagonists to reveal persistence (or even elevation) of endogenous leptin signaling and physiologic action in diet-induced obesity.

Although common (mis)perceptions hold that obesity results from poor volitional behavior, body weight is dictated by biologically encoded processes; the dysregulation of these processes leads to obesity (Myers et al., 2012). The discovery of the adipose tissue-derived hormone leptin and its ability to decrease food intake and body weight in lean (as well as leptin-deficient obese) animals not only identified a crucial mediator of energy balance, but also suggested the therapeutic potential of leptin (Zhang et al., 1994). The findings that obese individuals exhibit elevated circulating leptin concentrations (commensurate with their increased adipose mass) and that exogenous leptin poorly suppresses food intake and body weight in obesity blunted the initial enthusiasm for leptin as a therapeutic agent, however. Indeed, these observations suggested that impaired leptin action ("leptin resistance") might play a role in the initiation and/or maintenance of obesity (Myers et al., 2012).

The absence of leptin receptor (LepRb) mutations in the overwhelming majority of obese people (and animals) revealed that obesity does not represent a classical hormone resistance syndrome (in which the receptor is mutated or absent), however (Myers et al., 2012). Indeed, in diet-induced obesity (DIO; which presumably mirrors human obesity), obese animals are genetically identical to their lean controls, but made obese by the provision of highly palatable fat- and sucrose-laden food. Nonetheless, the inability of pharmacologic leptin to stimulate LepRb signals (such as the phosphorylation of the LepRb second messenger, STAT3 [pSTAT3]) and promote catabolic responses in DIO and other obese animals is consistent with impaired LepRb function in the obese state. Understanding how leptin works (and may be impaired) during obesity will reveal potential mechanisms of leptin resistance; it will also suggest how altered leptin action might contribute to the development or maintenance of obesity.

While it is clear that the response to exogenous leptin is diminished in DIO and other forms of obesity, the function of endogenous leptin has generally not been examined, largely because modulating endogenous leptin is difficult. In this issue of *Cell Metabolism*, Ottaway et al. have cleverly taken advantage of an engineered leptin analog (LA) that binds LepRb without promoting receptor activation; LA competes with native leptin for LepRb binding, acting as a competitive antagonist. As expected, LA does not alter food intake or body weight in animals null for leptin, LepRb, or melanocortin action (melanocortin signaling is a crucial mediator of energy balance that operates downstream of leptin/LepRb), but either peripheral or i.c.v. LA increases feeding and body weight in lean mice. Importantly, DIO animals also eat more and gain weight in response to LA. While DIO animals are slightly less sensitive to low doses of peripherally administered LA (consistent with increased leptin that competes with LA for LepRb occupancy in DIO animals), the maximal response to i.p. or i.c.v. LA in DIO animals is the same as for lean mice. Thus, not only does endogenous leptin suppress food intake and body weight gain in DIO as well as lean animals, it does so to the same extent in DIO and lean mice.

Similarly, the analysis of cellular leptin action revealed that LA blocks pSTAT3, as well as decreasing the hypothalamic expression of two major leptin target genes, *Pomc* and *Socs3* (Ottaway et al., 2015). While *Pomc* (which encodes melanocortin peptides that are crucial for leptin action) expression is controlled by a number of convergent pathways, *Socs3* is directly controlled by LepRb → STAT3 signaling and represents the best known readout of cell-autonomous transcriptional control by leptin (Allison et al., 2015; Bjørbaek et al., 1998). While LA suppresses *Pomc* expression similarly in DIO and lean animals, the inhibition of pSTAT3 and *Socs3* expression by LA is actually greater in DIO animals than in lean controls, because (in the absence of LA) pSTAT3 and *Socs3* expression are increased in DIO mice; the final (suppressed) levels are similar in the two LA-treated groups (Ottaway et al., 2015). These data are not only consistent with the similar physiologic actions of LA in DIO and lean animals, but also reveal increased LepRb signaling in DIO animals. Thus, cellular leptin action is increased in DIO animals in response to the elevated circulating leptin concentrations in these animals, and it is difficult to blame obesity on decreased LepRb signaling.

Given this response to endogenous leptin in DIO, how are we to understand the failure of exogenous leptin to promote pSTAT3 (as well as decreased feeding and body weight) in DIO? The answer may lie partly with *Socs3* itself, which encodes the suppressor of cytokine signaling-3 (SOCS3, which binds to activated LepRb to inhibit its activity) (Figure 1; Bjørbaek et al., 1998; Björnholm et al., 2007). The present data suggest that while elevated *Socs3* may limit the maximal amplitude of LepRb signaling in DIO mice, it does not reduce LepRb signaling below baseline. Indeed, since *Socs3* expression is restricted to LepRb neurons in the hypothalamus and results from leptin → LepRb → STAT3 signaling

(Figure 1; Allison et al., 2015; Bjørbaek et al., 1998; Myers et al., 2012), how could *Socs3* be elevated if LepRb signaling is decreased? What SOCS3 can do, though, is limit the maximum response to leptin; thus, while LepRb signaling is increased compared to lean animals in the face of elevated endogenous leptin in DIO, LepRb signaling in DIO is not as high as it might be in the absence of SOCS3, and SOCS3 likely limits the response to pharmacologic leptin (Figure 1; Björnholm et al., 2007; Mori et al., 2004). Consistent with this notion, the constant infusion of leptin into leptin-deficient *ob/ob* animals revealed that leptin treatment itself, rather than obesity, blunts the response to pharmacological leptin (Knight et al., 2010).

How, then, do we define and understand leptin resistance? Since DIO animals demonstrate an appropriately elevated response to high endogenous leptin, we can't say that they are obese due to decreased leptin action. Such animals are expected to respond poorly to exogenous leptin, however, because leptin-induced SOCS3 limits any additional LepRb signaling. Thus, while there is no pathophysiologic decrease in endogenous leptin action that could promote obesity, leptin resistance could be defined as the failure of pharmacologic leptin to increase LepRb signaling and physiologic responses in hyperleptinemic obesity. Similarly, while hypothalamic inflammation and ER stress have also been suggested to mediate leptin resistance in DIO (Ozcan et al., 2009; Zhang et al., 2008), the persistence of endogenous leptin action in DIO animals also indicates that these processes do not diminish LepRb signaling or cellular leptin action below baseline, although they could theoretically contribute to the impaired response to pharmacologic leptin that defines leptin resistance.

This does leave important questions, though. Is there some blockage in the system downstream of the cellular response to leptin in DIO that prevents the translation of elevated cellular leptin action into a catabolic drive capable of deceasing adiposity to baseline? Or is the level of obesity achieved in DIO merely the point at which the hedonic drive to eat palatable food is balanced by the increased catabolic drive promoted by hyperleptinemia?

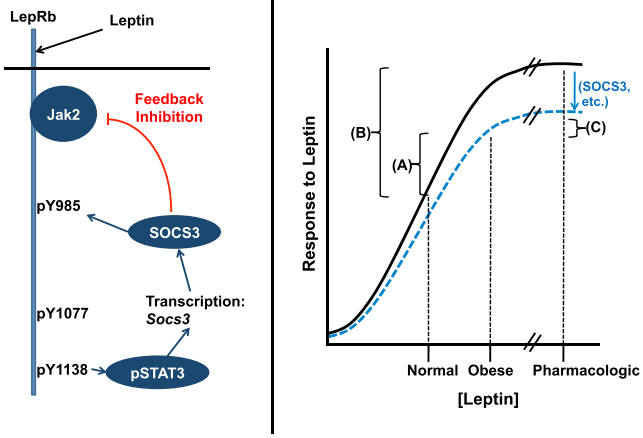

Figure 1. Feedback Inhibition and the Response to Endogenous and Exogenous Leptin

Left: Shown is a schematic of crucial element of LepRb signaling. Leptin binds to the extracellular domain of LepRb, causing a conformational change that activates the associated Jak2 tyrosine kinase, which then phosphorylates the indicated residues on the intracellular domain of LepRb. Phosphorylated Tyr1138 (pY1138) recruits the latent transcription factor, STAT3, leading to its phosphorylation (pSTAT3) and transcriptional activation. STAT3 increases the expression of a variety of genes in LepRb neurons, including *Socs3*. *Socs3* expression directly indicates the strength of the intracellular LepRb → STAT3 signal. SOCS3 protein mediates feedback inhibition on LepRb, however, by binding pY985 on LepRb and inhibiting Jak2. Right: A graphical representation of the strength of overall leptin action (as read out by pSTAT3, Socs3 expression, or leptin-dependent suppression of food intake and body weight) at circulating leptin concentrations found in normal (lean) animals, obese (e.g., DIO) animals, and in response to pharmacologic leptin. The curve shown in black is the predicted response in the absence of SOCS3 accumulation (as well as any other LepRb-inhibiting parameters in obese, hyperleptinemic animals). The dashed blue curve demonstrates the response to leptin in the presence of SOCS3 and other inhibitors of LepRb action in DIO mice. The brackets show: (A) the predicted and observed increase in leptin action in DIO compared to lean mice at endogenous leptin concentrations; (B) the increase in leptin action during the acute response to pharmacological leptin in lean mice, and (C) the much smaller increase in leptin action during the acute response to pharmacologic leptin in DIO mice.

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