Challenges and Opportunities of Defining Clinical Leptin Resistance

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The widespread use of the inadequately defined term “leptin resistance” led the National Institutes of Health to convene a workshop aimed at developing a quantitative definition of this term that would facilitate mechanistic research into leptin’s actions in human health and disease. Although leptin-responsive conditions are recognized, the field is limited by a lack of robust, easily quantifiable behavioral or metabolic biomarkers of the hormone’s action. Further advances require biomarkers that can be used to identify patients who may benefit from leptin therapy and that are useful for understanding the determinants of clinical leptin responsiveness.

Overview
The phrase “leptin resistance” arose not long after the discovery of this adipose tissue-derived hormone in late 1994 (Frederich et al., 1995a; Zhang et al., 1994). Found in more than 4,000 citations since (Figure 1), “leptin resistance” appears to connote diverse meanings in distinct contexts and to different investigators, including obesity in the face of hyperleptinemia, and the failure of pharmacologic leptin to suppress feeding (Froy et al., 2011; Miyazaki et al., 2009; Stradecki and Jaworski, 2011).

The disparate and confusing usage of the term “leptin resistance” led the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health (NIH) to hold a workshop, “Toward a Clinical Definition of Leptin Resistance,” on February 25, 2011. The goal of the expert attendees (see the Supplemental Information available online) at the meeting was to explore current usage of the phrase “leptin resistance” and to work toward a quantifiable, clinically useful definition that could be used to identify patient populations that would benefit from leptin therapy. Some of the questions discussed at the 1 day workshop were as follows:

- The term “leptin resistance” has been applied diversely to mean different things in different contexts. Can a general definition be found?
- What studies need to be done to establish a useful definition of leptin resistance in people?
- Do appropriate tools exist to measure leptin resistance in human subjects?
- What clinical populations are candidates for leptin therapy? Are there therapies that can increase leptin sensitivity?
- Is obesity always accompanied by leptin resistance?

This perspective summarizes the general conclusions of the meeting (Box 1).

Leptin Biology
Leptin, a 16 kDa cytokine, is produced by adipose tissue in approximate proportion to adipose tissue mass (Considine et al., 1996; Frederich et al., 1995a, 1995b). Thus, circulating leptin concentrations generally reflect the status of long-term adipose tissue energy stores, and are usually greater in obese compared to lean individuals (Considine et al., 1996; Frederich et al., 1995a, 1995b). Leptin modulates a host of physiologic processes and behaviors in line with the need for these reserves (Ahima et al., 1996; Myers et al., 2009). For instance, adequate fat stores/leptin concentrations diminish the drive to feed, while enabling energy expenditure via a variety of neuroendocrine axes and autonomic outputs. Conversely, inadequate or falling leptin concentrations diminish the drive to eat, decreases energy utilization, and promotes a variety of behavioral adaptations to diminished energy stores. Leptin also supports reproductive competence and immune function and contributes to the regulation of metabolic homeostasis (by modulating insulin secretion, hepatic glucose production, and lipid metabolism), as well as some aspects of bone biology (Ducy et al., 2000; Farooqi et al., 2002; Kulkarni et al., 1997; Liang and Tall, 2001; Minokoshi et al., 2002; Nogueiras et al., 2007; Pocai et al., 2005; Stafford et al., 2008; Wang et al., 2010). The biological effects of leptin action suggest its potential therapeutic utility in a variety of pathologic states, including obesity and diabetes and their comorbid diseases. Indeed, leptin effectively treats the metabolic complications of lipodystrophy syndromes and restores menstruation in hypothalamic amenorrhea (Kelesidis...
Multiple LEPR isoforms that result from alternative splicing of the Lepr mRNA, the LEPR-B form of the receptor mediates essentially all known physiologic effects of leptin (Chua et al., 1996, 1997; Tartaglia et al., 1995). LEPR-B is a type 1 cytokine receptor that mediates intracellular signaling via an associated Janus family tyrosine kinase (Jak2) (Baumann et al., 1996; Robertson et al., 2008). Major intracellular signaling pathways emanating from activated LEPR-B include the phosphorylation and activation of signal transducer and activator of transcription (STAT) proteins (STAT3 and STAT5), the PTPN11 → extracellular regulated kinase (ERK) pathway, and the feedback inhibition pathway mediated by the suppressor of cytokine signaling-3 (SOCS3) (Bjorbaek et al., 1998; Robertson et al., 2008). Another inhibitory pathway involves pyruvate dehydrogenase kinase 1 (PDHK1) (Bjorbaek et al., 1998; Robertson et al., 2008). Both SOCS3 and PTP1B decrease leptin sensitivity and response in vitro and in vivo (Bjorbaek et al., 1998, 1999; Bjorbaek et al., 2000; Bjornholm et al., 2007; Zabolotny et al., 2002) (Figure 2).

Most known leptin action is attributable to its effects in the brain, where LEPR-B is predominantly expressed (Cohen et al., 2001; de Luca et al., 2005; Elmqquist et al., 1998; Myers et al., 2009). Leptin action and LEPR-B expression have also been reported in a variety of tissues outside of the brain, including some cells of the immune system (Matarese et al., 2005). There is little evidence to support a role for peripheral LEPR-B expression in the control of whole-body energy balance or glucose homeostasis, however. CNS leptin has been shown to mediate most leptin actions, including control of neuroendocrine axes, the autonomic nervous system, satiety, and the limbic system, as well as numerous behaviors. A great deal of research in this area has focused on important neurons of the hypothalamic arcuate nucleus that express proopiomelanocortin or Agouti-related peptide, but direct leptin action on these neurons accounts for only a fraction of total leptin action, and LEPR-B is highly expressed in several other brain regions associated with the control of feeding-related behaviors and energy expenditure—including multiple hypothalamic, midbrain, and brainstem nuclei (Myers et al., 2009; Patterson et al., 2011; Scott et al., 2009).

**Leptin Resistance**

**Definitions**

The biology of leptin, as outlined above, was elucidated by studying leptin deficiency and examining the effects of leptin repletion on low-leptin states in animal models and humans. These leptin-deficient states include not only genetic leptin deficiency (very rare in humans) and caloric restriction (including anorexia), but also other conditions associated with diminished fat stores and their consequently low or falling leptin concentration, whose production is expected to be increased in this condition. Furthermore, leptin retains physiologic relevance even when elevated in obesity, and alterations in leptin action may or may not be primary to the genesis of obesity. Thus, referring to the coexistence of hyperleptinemia in obesity as “leptin resistance” imbues the term with little meaning.

Despite some utility of the term as used to describe relative insensitivity to exogenous leptin, “leptin resistance” implies neither a single specific mechanism nor a specific metric of leptin action. Because of the pluripotent effects of leptin and the numerous ways in which its action is studied, the universal application of a narrow definition of leptin resistance appears unlikely to be practical or useful in most contexts.

Pragmatically, when considering leptin as a potential clinical therapeutic agent, predictors of therapeutic responsiveness to exogenous leptin rather than a precise universal “leptin resistance” definition represent the most important consideration.

We currently lack good predictors of, and acute assays to define, leptin responsiveness in humans. Such tools are needed to identify those who might be helped by leptin administration. The performance of studies to define potentially sensitive groups, with rapid dissemination of the resultant data, represents a high priority.

Further clinical studies are also required to examine mechanisms by which leptin sensitivity may potentially be increased, and to determine predictors that identify individuals who may benefit most from such sensitizing treatments.
Figure 2. Potential Sites/Mechanisms Interfering with the Regulation of Energy Balance to Produce Obesity

Leptin is transported across the blood-brain barrier (BBB) to access first-order LEPR-B-expressing neurons, which connect with downstream neurons to eventually modulate food intake and energy expenditure. Other circuits, including those not modulated by leptin, also contribute to the control of feeding and energy expenditure. Interference (red) with any of these processes, including BBB transport of leptin; cellular processes in LEPR-B neurons (such as LEPR-B signaling); or alterations in the neural function, “wiring,” or plasticity in any of the leptin-regulated or leptin-independent circuits that contribute to energy balance are expected to promote obesity (and increase circulating leptin concentrations).

et al., 2010; Oral et al., 2002; Shimomura et al., 1999; Wang et al., 2010; Welt et al., 2004; Zhang et al., 1994). Administration of exogenous leptin mitigates the increased appetite, decreased energy expenditure, and neuroendocrine dysfunction associated with each of these states of leptin insufficiency. Leptin also attenuates the hyperglycemia caused by uncontrolled insulin-deficient diabetes and lipodystrophy syndromes (Kelesidis et al., 2010; Wang et al., 2010).

The ability of exogenous leptin to reduce food intake/body weight (and to modulate metabolism and endocrine function) in the face of replete adipose stores, especially in obese individuals, has proven to be more limited, however (Harmsfield et al., 1999; Mantzoros and Flier, 2000). Indeed, commensurate with their large adipose mass, obese individuals exhibit elevated circulating leptin concentrations relative to lean subjects (Considine et al., 1996), but these elevated leptin concentrations fail to return body adiposity to the normal range. In rare instances, genetic mutations may abrogate LEPR function (here, circulating leptin is increased to concentrations above those observed in “normal” obese humans of similar fat mass) (Clement et al., 1998). These instances are similar to classical hormone resistance/insensitivity syndromes (growth hormone insensitivity, type A insulin resistance, etc.), in which genetic alterations of the hormone receptor prevent hormone action (Moller and Flier, 1991; Savage et al., 2006).

In the vast majority of human obesity, however, Lepr is unper- turbated, and obesity and any diminished responsiveness to leptin must result from other mechanisms. The poor efficacy of elevated endogenous leptin concentrations to promote leanness in obese subjects has given rise to the notion of functional “leptin resistance,” which is often compared to the concept of insulin resistance in type 2 diabetes—where diminished cellular and metabolic insulin responsiveness coexist with the hypersecretion of insulin (Myers et al., 2010; Spiegelman and Flier, 2001). Implicit in the concept of leptin resistance is the idea that processes that promote and/or result from obesity impair leptin action, thereby facilitating the occurrence of obesity and attenuating the potential efficacy of therapy with exogenous leptin. Understanding mechanisms that may underlie “leptin resistance” is thus crucial both for determining the causes of obesity and identifying potential mechanisms that can be targeted for therapy.

While the goal of this NIH conference was to generate a universal, quantifiable definition of leptin resistance, the common application of “leptin resistance” to label both the presence of hyperleptinemia in obesity and the failure of exogenous leptin administration to provide therapeutic benefit suggests the difficulty of identifying such a universal definition. Regarding the use of “leptin resistance” to label hyperleptinemia in obesity, due to their increased adipose tissue mass, virtually all obese humans and animal models (except some animal strains and extraordinarily rare patients with genetic leptin deficiency) display elevated circulating leptin concentrations relative to lean controls (Considine et al., 1996; Frederick et al., 1995a, 1995b). Additionally, processes other than those attendant to leptin action and/or LEPR-B signaling per se likely contribute to the determination of adiposity and etiology of obesity in each person—including the function and/or anatomic variation of numerous neural circuits. While some of these circuits may be directly modulated and/or developmentally programmed by leptin, many are not (Berthoud, 2007; Bouret et al., 2004; Hill et al., 2008; Horvath and Bruning, 2006; Myers et al., 2010; Pinto et al., 2004; Ring and Zelis, 2010) (Figure 2). Furthermore, the finding that even very obese individuals exhibit changes in hunger and energy expenditure upon moderate weight loss, and that these changes are blunted by the administration of leptin, suggests that the elevated levels of leptin in obese individuals may be functionally relevant (Rosenbaum et al., 2002). Thus, defining leptin resistance as the coexistence of hyperleptinemia in obesity merely serves to note the elevated concentration of a single hormone whose production is expected to be increased in this condition. Furthermore, leptin retains physiologic relevance even when elevated in obesity, and alterations in leptin action may or may not be primary to the genesis of obesity. Thus, referring to the coexistence of hyperleptinemia in obesity as “leptin resistance” imbues the term with little meaning.

When focusing on the potential therapeutic utility of leptin, the limited ability of exogenous leptin to promote desired outcomes represents the central issue, and it is this aspect of the leptin resistance concept that we will focus on in this review. This encompasses a multitude of situations, however, from assays of leptin action as diverse as the induction of STAT3 phosphorylation in the brain (in animal models) and other tissues, to the attenuation of feeding and the restraint of body weight and adiposity (in either animals or humans). These may be assayed following acute or long-term treatment with leptin doses ranging from the approximately physiologic to the heroically pharmacologic. Practically speaking, therefore, “leptin resistance” is a term so broadly applied and context dependent that there can be no universal, quantifiable, clinically useful definition of “leptin resistance.”
Potential Mechanisms

Studies in animal models have suggested a number of basic mechanisms that may underlie attenuated responsiveness to leptin. Many of these are processes engaged during or promoted by overnutrition and obesity, including changes in circulating leptin-binding proteins, reduced transport of leptin across the blood-brain barrier, and/or the provocation of processes that diminish cellular LEPR-B signaling (inflammation, ER stress, feedback inhibition, etc.) (Bjorbaek et al., 1998, 1999; Bjornholm et al., 2007; Levin et al., 2004; Lou et al., 2010; Ozcan et al., 2009; Zabolotny et al., 2002; Zhang and Scarpace, 2009; Zhang et al., 2008). Alterations in the development of leptin-regulated neurons and other components of the circuitry that mediates leptin action could also blunt leptin action throughout life (Bouret et al., 2004). While differing in their specifics, these potential explanations for the decreased efficacy of leptin all postulate that nutritional alterations, obesity (including increased ambient leptin concentrations themselves [Knight et al., 2010; Qiu et al., 2001]), or other developmental events impair leptin action. Indeed, interference with many of the cellular mechanisms that attenuate LEPR-B signaling improves leptin action in cells and animal models, revealing that these mechanisms decrease leptin action in vivo, as well as suggesting the potential utility of these processes as points of therapeutic intervention (Bjorbaek et al., 2000; Howard et al., 2004; Ozcan et al., 2009; Zabolotny et al., 2002). Thus, while it is not possible to precisely define leptin resistance in a universal, precise, and quantifiable manner, it is clearly useful to identify and understand mechanisms that may attenuate leptin action in vivo.

The “normal” response to exogenous leptin, against which leptin resistance is often defined (especially in rodents), most often results from the attainment of circulating leptin concentrations thousands of times higher than physiological (Faouzi et al., 2007), and the anorectic response to these doses is modest and subject to relatively rapid tachyphylaxis. During evolution, undernutrition presumably represented a greater threat to survival than did overnutrition, with the result that the defense against starvation (low and/or falling leptin) produces stronger responses than does the defense against nutritional surplus (high leptin). A similar line of reasoning posits that the efficacy of leptin may be near maximal at the concentrations found in most obese people at baseline, and that the addition of exogenous leptin may, therefore, raise circulating leptin concentrations without substantially increasing leptin action. While a related hypothesis suggests that obesity was also selected by factors including the likelihood of predation (Krol and Speakman, 2007), the ability of palatable calorically dense diets to promote obesity in most animals and the failure of elevated leptin levels to reduce body weight in obese animals suggests that leptin may not play a major role at this end of the spectrum. The possibility that leptin action may be near its physiological maximum in states of obesity and the notion that obesity attenuates leptin action are not mutually exclusive—both mechanisms may contribute.

Clinical Issues

In human subjects, it is generally not possible to examine the molecular mechanisms associated with or underlying “leptin resistance.” Rather, the state must be operationally defined as decreased responsiveness to leptin by certain criteria. As noted, however, there is no standard for the definition of human “leptin resistance.” Is leptin resistance defined by the response to a high or low dose of leptin, given once for a short time or chronically over weeks to months, in patients at baseline or following some amount of weight reduction? What is the attenuated response by which we define leptin resistance: decreased food intake, weight loss, alterations in blood glucose or lipids, hepatic triglycerides, immune function, etc.? Since the efficacy of leptin for the control of many metabolic parameters (e.g., weight, glucose, lipids, hepatic steatosis, etc.) is likely to be of interest, leptin responsiveness must be defined in terms of the response of specific parameters, individually, to leptin treatment.

Clinical Leptin Responsiveness

While clinical “leptin resistance” may be captured in a general way as poor responsiveness to exogenous leptin, for the reasons outlined above, it is not possible to define clinical leptin resistance in a precise manner that can be assessed with a single, universal assay. A pragmatic approach to leptin resistance and therapeutic leptin action thus focuses not on defining clinical leptin resistance in a universal manner, but rather on assessing which individuals are likely to respond to and/or can be sensitized to leptin. While this may seem, on the surface, to be a semantic argument, it acknowledges that there can be no universal definition of leptin resistance, and focuses instead on the more tangible goal of determining whom we can effectively treat and the parameters of effective treatment.

How to assess leptin sensitivity effectively in the clinical setting is not currently clear. The available information suggests that, in general, leptin sensitivity is greatest in those with low adiposity and low endogenous circulating leptin (Bluher and Mantzoros, 2009). Body adiposity and leptin concentration are unlikely to represent the only predictors for leptin sensitivity, however, as each individual is likely to exhibit an idiosyncratic response to overnutrition or obesity (i.e., in terms of genetic differences or ER stress or other responses that might limit leptin action). Indeed, the sexual dimorphism in circulating leptin concentrations suggests underlying differences in leptin production and/or action by sex (Considine et al., 1996). Similarly, circulating free leptin concentrations are determined not only by leptin production but by its clearance and by levels of circulating soluble LEPR (Zhang and Scarpace, 2009). Furthermore, adiponectin and other circulating factors may predict aspects of the therapeutic efficacy of leptin (Iannucci et al., 2007). Thus, it will be crucial to assess and report measures of leptin responsiveness in large samples of individuals in the context of a variety of parameters that may affect leptin sensitivity (e.g., age, sex, BMI, adiposity, fat distribution, circulating levels of leptin, and other factors, etc.). Also, leptin is manufactured in multiple forms, each with different pharmacodynamics parameters and potentially distinct determinants of efficacy.

In addition to the modulation of body weight and adiposity, the examination of other potentially useful outcomes of leptin therapy (e.g., glucose homeostasis, lipid metabolism, hepatic lipid content, etc.) will be important. Furthermore, as the relationship between potential measures of acute leptin action (e.g., 24 hr food intake, energy expenditure, leptin-stimulated STAT3 phosphorylation in peripheral blood monocytes, or brain imaging) and the potential therapeutic chronic effects of leptin
are unclear, it would be useful to examine both acute and long-term responsiveness of individuals to determine the potential predictive value of acute studies.

**Can Leptin Responsiveness Be Increased?**

Some investigators have suggested that pharmacologic interruption of the cellular mechanisms apparently attenuating LEPR-B signaling could increase leptin sensitivity (Ozcan et al., 2009). Indeed, early attempts have met with preliminary success in animal models. Furthermore, the finding that some compounds (e.g., the amylin derivative, pramlintide) augment leptin action in some individuals suggests that it may be possible to increase the sensitivity of some individuals to therapeutic leptin administration (Turek et al., 2010). Whether such a result is a consequence of the initial weight loss induced by a nonleptin drug or by direct impact of such a drug on leptin receptor signaling, or mediated by other phenomena remains unclear. Certainly, however, combinatorial approaches appear to hold some promise for clinical leptin therapy. As above, for responsiveness to leptin alone, it will be important to determine traits and/or acute assays and endpoints that predict the responsiveness of patients to leptin to many types of potential leptin-sensitizing therapies.

**Conclusions**

While no universal, quantifiable, and clinically useful definition of the term “leptin resistance” is feasible, defining populations of patients and/or disease processes that are potentially responsive to leptin therapy will be important. Leptin treatment has proven therapeutically useful for several clinical indications, including lipodystrophy syndromes, and is likely to be useful to leptin treatment will be important. Leptin treatment has proven therapeutically useful for several clinical indications, including lipodystrophy syndromes, and is likely to be useful for numerous others. Identifying predictors of leptin responsiveness for numerous clinical indications represents an important research priority.

**SUPPLEMENTAL INFORMATION**

Supplemental Information includes the list of workshop attendees, “Toward a Clinical Definition of Leptin Resistance,” National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, February 25, 2011, and can be found with this article online at doi:10.1016/j.cmet.2012.01.002.

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**REFERENCES**


