Signal Transduction Pathways for Leptin
An Embarrassment of Riches

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Leptin is a critical regulator of energy balance in mammals and has served as a launch point for innumerable studies examining the regulation of food intake and energy expenditure (1). At high physiological concentrations, leptin causes a decrease in food intake, an increase in energy expenditure, and a shift to increased fatty acid oxidation. These physiological shifts lead to a decrease in body weight and body fat content. Conversely, a lack of leptin leads to obesity due to hyperphagia and increased lipogenesis. In leptin signaling deficiencies, brown adipose tissue, a major thermogenic organ in small rodents, loses its thermogenic capacity due to diminished sympathetic nervous system activity. In this issue of *Diabetes*, Rahmouni et al. (2) present a new molecular mechanism by which leptin stimulates anorectic and thermogenic responses in rodents.

Given that most of leptin's actions with regard to energy balance occur within the central nervous system, it is currently accepted that a distributed network of leptin receptor–bearing neurons within the hypothalamus are responsible for mediating a concerted response to fluctuations of energy stores within adipose tissue (3). Leptin receptor–bearing neurons are found throughout the hypothalamus, and some of them are chemically defined: arcuate nucleus (proopiomelanocortin [POMC] neurons and agouti-related peptide/neuropeptide Y neurons), ventromedial nucleus (SF1 neurons), and lateral hypothalamus (neurotensin neurons). Other types still must be identified and characterized thoroughly. Analysis of the workings of this distributed network has led to the finding of intriguing and (maddeningly) idiosyncratic properties of the system. For example, leptin is known to cause phosphorylation of signal transducer and elevator of transcription (STAT)3 by the activation of janus kinase (JAK)2 for all cell types studied to date (4). However, leptin causes depolarization of POMC neurons but leads to hyperpolarization of agouti-related peptide/neuropeptide Y neurons (5). This differential response also applies to activation of phosphoinositol-3 kinase (PI3K) within the same two cell types (6). The basis of this differential activation between the two neuronal types remains to be determined.

Electrophysiological responses to leptin occur within several minutes, a span of time that is too short to be mediated via transcriptional responses, as would occur with STAT3 activation. Thus, the search for alternative signal transduction pathways for leptin remains an interesting enterprise. Although several traditional signal transduction pathways for leptin were invoked during studies with cultured cells (JAK2-STAT3, Src homology–containing tyrosine phosphatase 2 [Shp2]—extracellular signal–regulated kinase [ERK], and JAK2–phosphoinositol-3 kinase) (6,7), an article in this issue of *Diabetes* indicates a highly specific role for ERK signaling in leptin's stimulation of anorectic mechanisms and thermogenesis in rodents (1). The authors show that leptin activates ERK signaling specifically in POMC neurons only, greatly simplifying the interpretation of subsequent experiments wherein delivery of ERK pathway inhibitors prevents the anorexia and sympathetic nervous system stimulation of brown adipose tissue after leptin infusion. As ERK is only activated in POMC neurons, the inhibitors are presumably active specifically within POMC neurons.

With the plethora of intracellular signal transduction mechanisms that have been shown to be crucial to or involved in mediating leptin's actions, one is in a quandary to assign relative weights to each claim. However, the criterion of necessity for a phenomenon is different from the criterion of sufficiency. Thus, although the authors have shown that ERK signaling is necessary for leptin-induced anorexia, the test of sufficiency has not been applied in this case. Stripped of all other signaling pathways, the test of sufficiency is to determine whether ERK signaling (or any other candidate) solely is responsible for leptin's anorectic and thermogenic responses. It may be necessary to compare the delivery of a cocktail of inhibitors that block all of the known signal transduction mechanisms with a cocktail in which one or more inhibitors has been omitted. Such an experimental paradigm would be useful if all known players have been identified; the same paradigm could also be used to obtain evidence that other unidentified players are involved. Although performing such studies in intact model organisms is challenging, it is the only means to identify the needed components and circuitry for a neuron-mediated response. One particularly complex possibility is that multiple signal transduction pathways are needed for a given physiological response, making the reductionist chase for the sole responsible actor a Sisyphean effort.

An important consideration for elucidating the mechanisms of leptin response is the time scale, as mentioned previously. Although immediate responses on a scale of minutes are typically encountered in a neural response, it is well-known that some of leptin's effects are long acting and persistent over several hours. With transcriptional responses, taking into account the

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hours-long scale for protein products to be synthesized, it is not unreasonable to suggest that some of the responses to leptin might not appear until hours after the initial exposure. The synaptic plasticity of leptin receptor–bearing neurons is one prime example of such a long-lived and persistent response (5). The formation of new synapses could involve prolongation and enhancement of the initial response to leptin, as is seen in the recordings of sympathetic nerve activity after leptin treatment. The next challenge will be to fully examine potential alterations in neuronal circuitry associated with genetic manipulations that could invoke developmental adaptations along with tests of sufficiency for a given intracellular pathway and neural circuit.

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REFERENCES

1. Leibel RL, Chung WK, Chua SC Jr: The molecular genetics of rodent single gene obesities. *J Biol Chem* 272:31937–31940, 1997
2. Rahmouni K, Sigmund CD, Haynes WG, Mark AL: Hypothalamic ERK mediates the anorectic and thermogenic sympathetic effects of leptin. *Diabetes* 58:536–542, 2009
3. Leinninger GM, Myers MG Jr: LRb signals act within a distributed network of leptin-responsive neurones to mediate leptin action. *Acta Physiol* 192:49–59, 2008
4. Myers MG Jr: Leptin receptor signaling and the regulation of mammalian physiology. *Recent Prog Horm Res* 59:287–304, 2004
5. Pinto S, Roseberry AG, Liu H, Diano S, Shanabrough M, Cai X, Friedman JM, Horvath TL: Rapid rewiring of arcuate nucleus feeding circuits by leptin. *Science* 304:110–115, 2004
6. Xu AW, Kaelin CB, Takeda K, Akira S, Schwartz MW, Barsh GS: PI3K integrates the action of insulin and leptin on hypothalamic neurons. *J Clin Invest* 115:951–958, 2005
7. Banks AS, Davis SM, Bates SH, Myers MG Jr: Activation of downstream signals by the long form of the leptin receptor. *J Biol Chem.* 275:14563–14572, 2000