NAD^+ biology research into clinical application.

Acknowledgments

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Spotlight

'Et Tu, Leptin?'

Diego Perez-Tilve[1,*]

Leptin promotes adequate caloric intake and glycemia in healthy lean individuals, harnessing the benefits of the ideal therapy against metabolic syndrome. Yet, new evidence demonstrates an unexpected causal role for leptin in obesity-associated hyperglycemia. Like the betrayal of Julius Caesar by Brutus, insulin did not see that coming from leptin.

The hormones leptin and insulin are cornerstones of the control of energy homeostasis. Individually, leptin primarily regulates energy stores, whereas insulin maintains tissue fuel availability, and together they provide an intertwined contribution to optimal metabolic control. Their circulating levels are tightly regulated by changes in energy status, each dropping to a minimum during severe energy deprivation and each increasing during energy surplus. These synchronous increases enable insulin to maintain adequate fuel deposition and utilization as leptin reduces further energy intake. These activities are coordinated by the action of both hormones on discrete neurons of the brain, including hypothalamic arcuate neurons expressing agouti-related protein (AGRP) that integrate many aspects of the control of energy intake and whole-body glucose metabolism [1].

During unrestricted access to normal food, circulating levels of both insulin and leptin are modest, yet efficacious at maintaining a stable body weight. In contrast, in conditions favoring chronic energy surplus, such as having access to a highly palatable energy-dense diet, both adipose tissue mass and plasma glucose gradually increase concomitantly with an increase of circulating leptin and insulin and an apparent reduction in their ability to curb energy intake and maintain glucose control. The cause of the apparent reduction of leptin and insulin efficacy has stimulated intense research activity to discover novel targets for treating obesity and type 2 diabetes.

With this in mind, Balland *et al*. [2] tested the hypothesis that elevated circulating leptin is causally linked to the reduction of the ability of insulin to act in the brain to maintain glucose control in diet-induced obese (DIO) mice. They focused on the interplay between leptin and insulin action directly at AGRP neurons. To dissociate the effect of elevated brain leptin from other obesity-induced factors, they administered a leptin-receptor antagonist (LAN) locally into the brain prior to performing a euglycemic-hyperinsulinemic clamp to assess whole-body insulin action. Reducing leptin action from the brain of DIO mice resulted in an increase in the glucose-infusion rate during the clamp, associated with a suppression of hepatic glucose production, signifying improved efficacy of circulating insulin to regulate glucose metabolism (i.e., in the obese state, ongoing leptin signaling actively countered the ability of insulin to restrain hyperglycemia). Importantly, LAN was ineffective when coadministered with an insulin antagonist to blunt insulin signaling in the brain. Intracerebral coadministration of LAN with an inhibitor of protein-tyrosine phosphatase-1B (PTP1B), a negative regulator of both insulin- and leptin-receptor signaling, resulted in a comparably improved glucose infusion rate during the insulin clamp without additive benefits. Consistent with this, DIO mice lacking PTP1B expression uniquely in AGRP neurons had comparably improved glucose control, as occurred with intracerebral LAN administration. Based on these results, the authors propose that chronic brain exposure to increased leptin reduces insulin signaling in AGRP neurons in a PTP1B-dependent manner, compromising the ability of insulin to suppress hepatic glucose production.

This conclusion may be viewed with skepticism since many reports indicate that exogenous leptin acts in the brain to dramatically reduce energy intake and improve glycemic control. Importantly, this occurs in subjects with absent or low endogenous leptin levels. Indeed, Balland *et al*. also found that brain administration of LAN to lean normoleptinemic mice worsened glucose control. Thus, leptin appears to improve glycemic control in lean animals but worsen it during obesity.

Current consideration of the beneficial effects of leptin on energy homeostasis are likely biased by a certain degree of 'theory-ladenness', positing that the only expected outcome from increased brain leptin action should be hypophagia and improved glycemic control. Failure to confirm such a prediction, which often occurs in hyperleptinemic conditions, is too-often interpreted as the result of reduced leptin signaling (i.e., leptin resistance). However, consistent with Balland's results, reducing brain leptin action in the context of hyperleptinemia has also unveiled normal or even increased leptin action regulating feeding [3] and blood pressure [4] in DIO mice previously thought to have leptin resistance. The collective results from Balland and others indicate that, far from a reduction or preservation of action due to excess signaling, chronic hyperleptinemia promotes gain of a new function, reduced hypothalamic insulin signaling with a consequent detrimental impact on glucose control.

Excessive leptin action due to hyperleptinemia is well accepted in the context of the proinflammatory effects of leptin on specific cellular contexts [5] that are apparently refractory to leptin resistance. This proinflammatory activity has been linked to the significant association of hyperleptinemia and other features of the metabolic syndrome in human obesity. In this context, the results by Balland *et al*. provide a plausible mechanism to some of those associations, such as the significant impairment of glycemic control and hyperleptinemia in obese individuals [6].

Remaining questions pertain to the mechanisms whereby hyperleptinemia promotes this PTP1B-dependent reduction of hypothalamic insulin signaling, and whether they are solely contributed by cell-autonomous signaling events at AGRP neurons or by indirect mechanisms, perhaps derived from the proinflammatory activity of leptin within the neuronal environment [7]. It is noteworthy that the impact of acute blockade of leptin action on the glycemic control of wild type lean and/or DIO mice appears to be of a lesser magnitude than the overt diabetic phenotype exhibited by leptin-receptor or leptin-deficient mice, or to the normoglycemia induced by leptin replacement in the latter [8]. Aside from baseline differences due to the congenital loss of leptin [9], it is possible that the negative effect of hyperleptinemia on insulin signaling overlaps with lasting signaling events conveying the benefits of leptin on glucose metabolism. This raises the possibility that blockade of the former, or activation of the latter mechanisms, may underlie the benefits of drugs selected based on their ability to increase leptin action [10].

Regardless of the potential molecular mechanisms involved, this unexpected active contribution of hyperleptinemia to the impaired glycemic control in obesity provides a missing critical insight that challenges our understanding of the control of energy homeostasis and may generate novel opportunities to refine approaches using leptin-regulated pathways for the treatment of metabolic disease.

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