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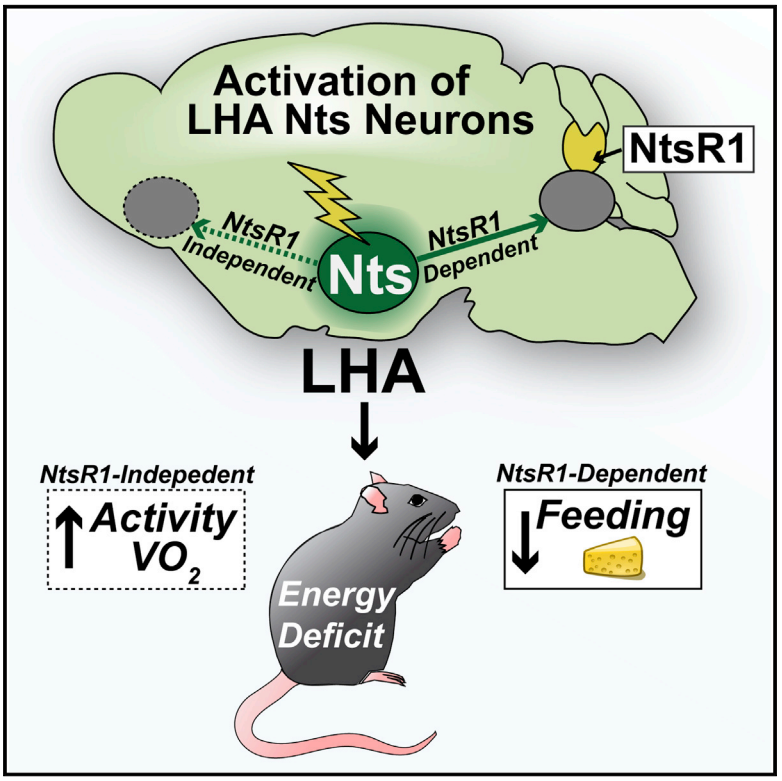
Lateral Hypothalamic Neurotensin Neurons Orchestrate Dual Weight Loss Behaviors via Distinct Mechanisms

Graphical Abstract



Highlights

- LHA Nts neurons suppress feeding and promote weight loss via NtsR1
- Enhanced LHA Nts action does not restrain palatable food intake in obesity
- LHA Nts neurons suppress feeding and weight gain in food-deprived mice

Authors

Hillary L. Woodworth, Bethany G. Beekly, Hannah M. Batchelor, Raluca Bugescu, Patricia Perez-Bonilla, Laura E. Schroeder, Gina M. Leinninger

Correspondence

leinning@msu.edu

In Brief

Woodworth et al. demonstrate that neurotensin (Nts) neurons in the lateral hypothalamic area (LHA) suppress food intake while increasing energy expenditure, resulting in weight loss. Enhanced LHA Nts action does not restrain free intake of palatable food in sated mice, but it suppresses feeding and weight gain in food-deprived animals.

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Lateral Hypothalamic Neurotensin Neurons Orchestrate Dual Weight Loss Behaviors via Distinct Mechanisms

Hillary L. Woodworth,[1] Bethany G. Beekly,[1] Hannah M. Batchelor,[1] Raluca Bugescu,[1] Patricia Perez-Bonilla,[2] Laura E. Schroeder,[1] and Gina M. Leinninger[1,3,*]
[1]Department of Physiology
[2]Department of Pharmacology and Toxicology
Michigan State University, East Lansing, MI 48824, USA
[3]Lead Contact
*Correspondence: leinning@msu.edu
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SUMMARY

The central mechanism by which neurotensin (Nts) potentiates weight loss has remained elusive. We leveraged chemogenetics to reveal that Nts-expressing neurons of the lateral hypothalamic area (LHA) promote weight loss in mice by increasing volitional activity and restraining food intake. Intriguingly, these dual weight loss behaviors are mediated by distinct signaling pathways: Nts action via NtsR1 is essential for the anorectic effect of the LHA Nts circuit, but not for regulation of locomotor or drinking behavior. Furthermore, although LHA Nts neurons cannot reduce intake of freely available obesogenic foods, they effectively restrain motivated feeding in hungry, weight-restricted animals. LHA Nts neurons are thus vital mediators of central Nts action, particularly in the face of negative energy balance. Enhanced action via LHA Nts neurons may, therefore, be useful to suppress the increased appetitive drive that occurs after lifestyle-mediated weight loss and, hence, to prevent weight regain.

INTRODUCTION

Obesity is a formidable health concern, yet non-surgical treatments, including lifestyle modification and pharmacotherapy, provide limited long-term weight loss (Khera et al., 2016). Individuals who lose weight experience compensatory increases in appetite and diminished metabolic rate and, as a result, most regain weight (Sumithran et al., 2011; Wing and Hill, 2001). Understanding how the brain coordinates feeding and energy expenditure is therefore crucial to identify strategies to support sustained weight loss.

The neuropeptide neurotensin (Nts) acts centrally to suppress feeding in hungry and obese rodents, and it holds potential to counteract increased appetitive drive that thwarts sustained weight loss (Boules et al., 2000; Cooke et al., 2009; Feifel et al., 2010; Hawkins, 1986b; Kim et al., 2008; Luttinger et al., 1982). Nts can signal via the G-protein-coupled Nts receptors-1 and -2 (NtsR1 and NtsR2), and NtsR1 has been specifically implicated in mediating anorectic effects (Kim et al., 2008; Remaury et al., 2002). However, Nts and NtsR1 are broadly distributed throughout the brain and also regulate analgesia, thermoregulation, and blood pressure (Geisler et al., 2006), and it remains unclear which Nts neurons specifically modify energy balance. For example, Nts in the nucleus accumbens blunts physical activity with no effect on feeding or body weight (Ervin et al., 1981; Kalivas et al., 1984), while Nts in the ventral tegmental area (VTA) limits feeding and promotes locomotor activity, dual behaviors that could support weight loss (Cador et al., 1986; Hawkins, 1986a; Stanley et al., 1983). These data indicate that specific, yet-to-be-defined Nts neurons promote weight loss behaviors, in part via Nts release to the VTA. Establishing the precise Nts population that modifies energy balance and the requirement for signaling via NtsR1 is necessary to design therapies to support weight loss without disrupting other Nts-mediated physiology.

Nts-expressing neurons within the lateral hypothalamic area (LHA) are positioned to potentiate weight loss, consistent with the role of the LHA in coordinating ingestive and locomotor behaviors (Brown et al., 2015; Opland et al., 2013). The large population of LHA Nts neurons is distinct from orexigenic melanin-concentrating hormone or orexin/hypocretin neurons (Brown et al., 2017), and, although some LHA Nts neurons co-express GABA (Jennings et al., 2015; Patterson et al., 2015), they do not provoke the voracious feeding response that occurs with the activation of all LHA GABA neurons (Jennings et al., 2013, 2015; Navarro et al., 2016; Nieh et al., 2015). Instead, LHA Nts neurons are physiologically activated by signals that suppress feeding, such as dehydration anorexia (Watts and Sanchez-Watts, 2007) or the appetite-suppressing hormone leptin (Leinninger et al., 2011). However, only 15% of LHA Nts neurons mediate leptin action (Brown et al., 2017; Leinninger et al., 2011), yet the overall role of the large population of LHA Nts neurons, and Nts signaling from them, is unclear. Since LHA Nts neurons release Nts to the VTA, where NtsR1-expressing dopamine (DA) neurons have been implicated in coordinating feeding and locomotor activity (Opland et al., 2013; Patterson et al., 2015; Woodworth et al., 2017), LHA Nts neurons might support NtsR1 and/or DA-mediated weight loss behaviors. Indeed, experimental activation of LHA Nts neurons increases

