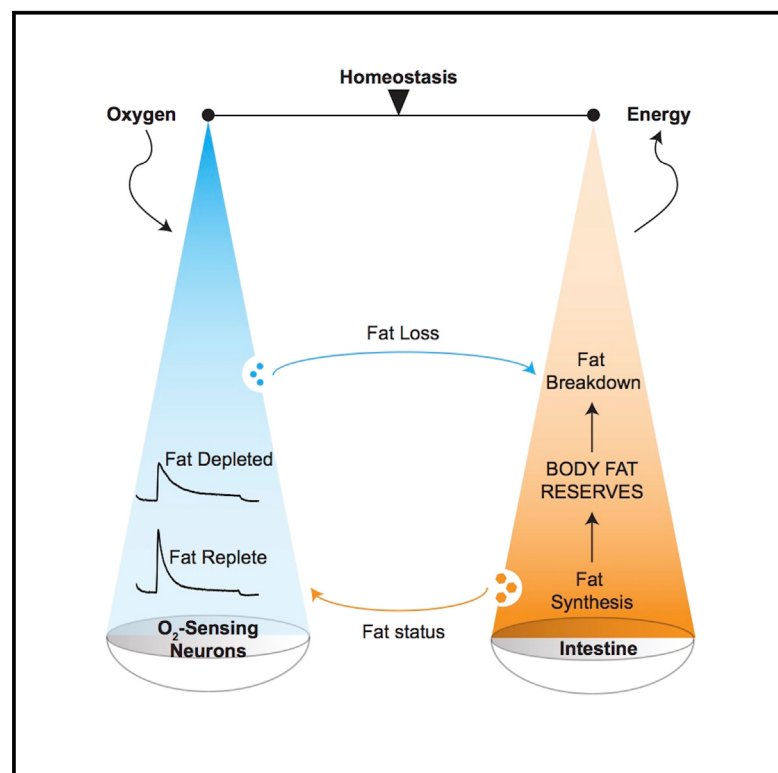


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C. elegans Body Cavity Neurons Are Homeostatic Sensors that Integrate Fluctuations in Oxygen Availability and Internal Nutrient Reserves

Graphical Abstract



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In Brief

Witham et al. show that neuronal oxygen sensing drives fat loss in metabolic tissues in *C. elegans*. In turn, an interoceptive signal relays information to the oxygen-sensing neurons about the available fat reserves. This homeostatic axis sculpts the neuronal drive to stimulate fat loss based on sufficient internal reserves.

Highlights

- Oxygen-sensing neurons regulate body fat metabolism via a neuroendocrine signal
- Fluctuations in normoxic oxygen determine the magnitude of body fat loss
- An interoceptive fat signal controls the tonic activity of oxygen-sensing neurons
- The balance between neuronal oxygen sensing and internal reserves drives fat loss



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SUMMARY

It is known that internal physiological state, or interoception, influences CNS function and behavior. However, the neurons and mechanisms that integrate sensory information with internal physiological state remain largely unknown. Here, we identify *C. elegans* body cavity neurons called URX(L/R) as central homeostatic sensors that integrate fluctuations in oxygen availability with internal metabolic state. We show that depletion of internal body fat reserves increases the tonic activity of URX neurons, which influences the magnitude of the evoked sensory response to oxygen. These responses are integrated via intracellular cGMP and Ca²⁺. The extent of neuronal activity thus reflects the balance between the perception of oxygen and available fat reserves. The URX homeostatic sensor ensures that neural signals that stimulate fat loss are only deployed when there are sufficient fat reserves to do so. Our results uncover an interoceptive neuroendocrine axis that relays internal state information to the nervous system.

INTRODUCTION

The CNS is a major regulator of body fat and energy balance, independent of its effects on food intake. With respect to the sensory nervous system, examples of broad sensory dysfunctions that are accompanied by profound obesity are prevalent in many species. For example, Bardet Biedl syndrome is characterized by defects in sensory processing and extreme obesity stemming from nervous system dysfunction in humans and in model systems (Mykityn et al., 2002; Davis et al., 2007; Lee et al., 2011). Enhanced sensory environments have also been shown to improve metabolic homeostasis (Cao et al., 2011). However, the mechanisms by which a discrete sensory modality is connected to peripheral lipid metabolism have been difficult to

elucidate, in part due to the heterogeneity of sensory dysfunction in mammalian systems. Thus, the role of sensory systems in regulating organismal metabolic control has remained underappreciated.

A body of evidence suggests that, in addition to external sensory cues, interoception or the sensitivity to stimuli originating inside the body is also perceived by the CNS (Cannon, 1932; Craig, 2002). Internal state information is used to modulate behavior in many species. For example, internal sensing of blood glucose regulates feeding behavior (Wang et al., 2008; Mighiu et al., 2013). Intestinal fatty acids are also sensed by the nervous system in mice, *D. melanogaster* and *C. elegans*, and modulate behavior and physiology (Wingrove and O'Farrell, 1999; Kniazeva et al., 2004; Lam et al., 2005; Srinivasan et al., 2008). It follows then that sensory and interoceptive information is integrated by the CNS for an organism to function as a cohesive entity. The complexity and redundancy of sensory and homeostatic functions in mammalian nervous systems make it challenging to decipher the underlying neuronal sites, cellular mechanisms, and the fundamental principles by which this integration occurs. The genetically tractable nematode *C. elegans* is an excellent model system for the study of neural circuits and their role in governing physiology. Many behaviors have been attributed to individual neurons and their mechanisms of action revealed (Bargmann, 2006). Despite these tremendous advances, neural sites of integration between sensory and metabolic information have remained unknown.

Food availability is perhaps one of the most-salient external sensory cues in an animal's environment (Libert and Pletcher, 2007; Berthoud and Morrison, 2008). In *C. elegans*, food sensory cues influence nearly all aspects of behavior and physiology including sensory functions, locomotion, reproduction, metabolism, and lifespan (Lemieux and Ashrafi, 2015; Srinivasan, 2015). Food presence is encoded by two major neuroendocrine systems: serotonin (5-hydroxytryptamine [5-HT]) and transforming growth factor beta (TGF- β) (Entchev et al., 2015). 5-HT synthesis and signaling from a single pair of chemosensory neurons called ADF(L/R) regulates a complex cascade of whole-body metabolic responses that drive peripheral lipid metabolism and fat loss (Srinivasan et al., 2008; Noble et al., 2013). In contrast,

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