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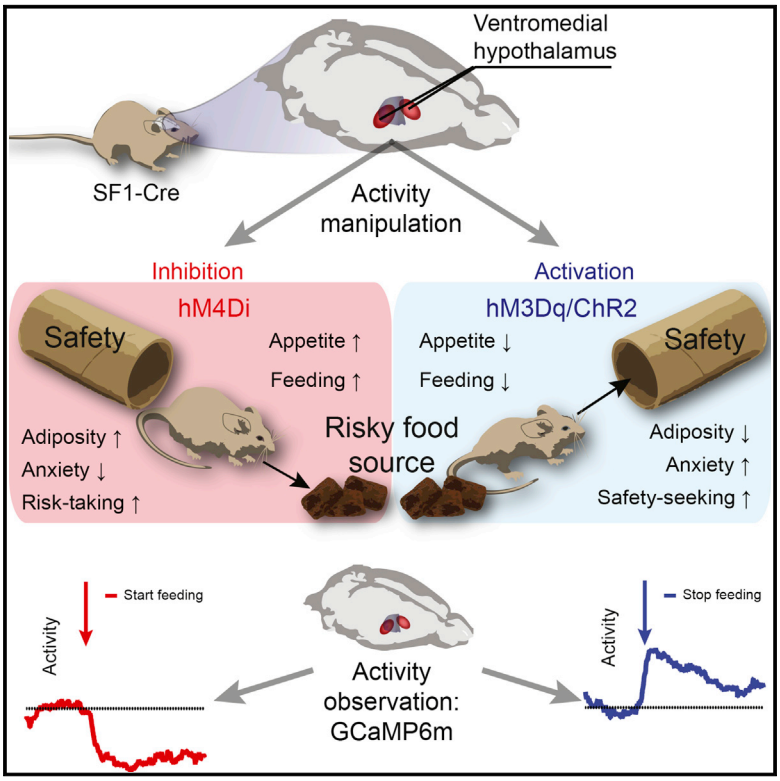
Modulation of SF1 Neuron Activity Coordinately Regulates Both Feeding Behavior and Associated Emotional States

Graphical Abstract



Highlights

- Intrinsic SF1 neuron activity is low during feeding and increases when feeding stops
- Manipulating SF1 neuron activity controls food intake and related behaviors
- Response to SF1 neuron activity is sensitive to energy status
- SF1 neural circuitry integrates feeding and emotional states

Authors

Paulius Viskaitis, Elaine E. Irvine, Mark A. Smith, ..., Mark A. Ungless, Graeme Milligan, Dominic J. Withers

Correspondence

d.withers@imperial.ac.uk

In Brief

Viskaitis et al. show that hypothalamic SF1 neurons act as a nutrient-sensitive switch between feeding and anxiety states. They identify a key circuit that permits feeding and related behaviors when its activity is low but primes the animal to stop feeding and to face potential stresses when activity is high.

Viskaitis et al., 2017, Cell Reports *21*, 3559–3572
December 19, 2017
https://doi.org/10.1016/j.celrep.2017.11.089

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Modulation of SF1 Neuron Activity Coordinately Regulates Both Feeding Behavior and Associated Emotional States

Paulius Viskaitis,[1,2] Elaine E. Irvine,[1,2] Mark A. Smith,[1,2] Agharul I. Choudhury,[1,2] Elisa Alvarez-Curto,[3] Justyna A. Glegola,[1,2] Darran G. Hardy,[1,2] Silvia M.A. Pedroni,[1,2] Maria R. Paiva Pessoa,[1,2] Anushka B.P. Fernando,[1,2] Loukia Katsouri,[1,2] Alessandro Sardini,[1,2] Mark A. Ungless,[1,2] Graeme Milligan,[3] and Dominic J. Withers[1,2,4,*]

[1]MRC London Institute of Medical Sciences, Du Cane Road, London W12 0NN, UK
[2]Institute of Clinical Sciences, Faculty of Medicine, Imperial College London, Du Cane Road, London W12 0NN, UK
[3]Centre for Translational Pharmacology, Institute of Molecular, Cell and Systems Biology, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8QQ, UK
[4]Lead Contact
*Correspondence: d.withers@imperial.ac.uk
https://doi.org/10.1016/j.celrep.2017.11.089

SUMMARY

Feeding requires the integration of homeostatic drives with emotional states relevant to food procurement in potentially hostile environments. The ventromedial hypothalamus (VMH) regulates feeding and anxiety, but how these are controlled in a concerted manner remains unclear. Using pharmacogenetic, optogenetic, and calcium imaging approaches with a battery of behavioral assays, we demonstrate that VMH steroidogenic factor 1 (SF1) neurons constitute a nutritionally sensitive switch, modulating the competing motivations of feeding and avoidance of potentially dangerous environments. Acute alteration of SF1 neuronal activity alters food intake via changes in appetite and feeding-related behaviors, including locomotion, exploration, anxiety, and valence. In turn, intrinsic SF1 neuron activity is low during feeding and increases with both feeding termination and stress. Our findings identify SF1 neurons as a key part of the neurocircuitry that controls both feeding and related affective states, giving potential insights into the relationship between disordered eating and stress-associated psychological disorders in humans.

INTRODUCTION

Feeding involves a complex series of actions that an animal must undertake in order to procure nutrients in a timely and safe manner. In the wild, feeding is often associated with exploration of novel and potentially dangerous environments. As a result, the systems controlling feeding behavior have evolved under a requirement for swift selection of situationally appropriate behaviors and accurate metabolic tuning. This involves integration of internal homeostatic signals, external environmental stressors, motivational drives, and learned associations to consolidate conflicts between risk mitigation and the requirement to feed. Consistent with these observations, the neurocircuitry and whole-body physiological processes underlying energy homeostasis have substantial functional overlap with the systems controlling responses to stressful situations (Sweeney and Yang, 2017; Ulrich-Lai and Ryan, 2014). For example, arcuate nucleus agouti-related peptide (AgRP), lateral hypothalamic, and amygdalar neurons have important roles in the incorporation of various emotional aspects into the regulation of feeding (Sweeney and Yang, 2017). In experimental models and humans, both disordered eating behavior and obesity have a significant association with stress-related behavioral changes, such as anxiety and depression (Anderson et al., 2001; Faith et al., 2002; Gariepy et al., 2010; Hryhorczuk et al., 2013; Stunkard et al., 2003).

The ventromedial hypothalamus (VMH) is a key brain region involved in the control of feeding, metabolism, and the manifestation of stress and anxiety-related behaviors. Lesioning and electrical stimulation studies implicate the VMH in the regulation of feeding, body weight, and defensive behaviors (King, 2006), and a role in the link between appetitive and affective responses has also been suggested (Grossman, 1966). Recent studies manipulating nutrient- and hormone-sensing-signaling pathways in steroidogenic factor 1 (SF1) neurons have confirmed the role of the VMH in the regulation of body weight and metabolism. However, somewhat surprisingly, the studies have in general not detected effects on acute food intake (Cardinal et al., 2014; Cheung et al., 2015; Dhillon et al., 2006; Kim et al., 2012; Klöckener et al., 2011; Ramadori et al., 2011; Xu et al., 2010, 2011). Pharmacogenetic and optogenetic manipulations of SF1 neurons have shown that these cells regulate defensive social states (Silva et al., 2013, 2016) and profound escape behaviors (Kunwar et al., 2015; Wang et al., 2015), and a recent study has shown that the activation of SF1 neurons can suppress acute feeding but through indeterminate mechanisms (Coutinho et al., 2017). Despite these observations, the precise relationships among SF1 neuronal activity, acute feeding regulation, and other behaviors associated with the VMH function remain unclear.

Here we find that SF1 neurons alter feeding via direct changes in appetite and by altering locomotion, exploration, anxiety,