"ISN't Thirst Sweet?" Says the Fly

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How food and water intake is reciprocally regulated to maintain homeostasis is unclear. New findings by Jourjine and colleagues identify four neurons in the *Drosophila* brain that receive both water and sugar abundance signals and oppositely regulate hunger and thirst.

To lose weight, a common recommendation is to drink a lot of water. For example, drinking a glass of water before a meal makes you feel more full and eat less. Even though many studies have associated chronic dehydration with obesity and increased water intake with weight loss (Thornton, 2016), the mechanism that explains the interplay between hydration and feeding is not clear. In this issue of *Cell*, through a set of elegant experiments in flies, Jourjine et al. (2016) uncover a mechanism by which eating and drinking are reciprocally regulated.

Hunger and thirst are two essential, innate mechanisms for survival. Osmoregulator animals like mammals and insects maintain both systems under strict homeostatic control and regulate water and food consumption based on internal nutrient abundance. Different signaling pathways sense their internal metabolic state (Bourque, 2008; Efeyan et al., 2015; Pool and Scott, 2014; Woods et al., 1998), but despite intense research, our understanding of nutrient-sensing and intake mechanisms is incomplete. In particular, how the nervous system integrates diverse nutrient signals so that homeostatic drives of hunger and thirst match the metabolic demand remains unclear.

To address this question, Jourjine et al. (2016) began by carrying out two independent screens for new food and water signaling pathways. They identified four previously uncharacterized neurons in the subesophageal zone (SEZ) of the adult *Drosophila* brain, which they named interoceptive SEZ neurons (ISNs), that function as the convergence point for two different internal nutrient signals: sugar and water. Using well-designed genetic and behavioral experiments, as well as diverse calcium imaging assays, they demonstrated that ISNs balance food and water intake by sensing internal sugar levels through the G-protein-coupled receptor adipokinetic hormone receptor (AKHR) and water levels via the osmolality-sensitive TRPV cation channel Nanchung (Nan).

AKH is a peptide whose metabolic function has been widely studied in *Drosophila* and is analogous to mammalian glucagon, since it promotes sugar and lipid release into the hemolymph upon nutrient depletion (Kim and Rulifson, 2004). The authors showed that starvation or AKH treatment induced ISN firing, which in turn significantly promoted feeding, whereas AKHR reduction decreased ISN activation and reduced sugar consumption. Furthermore, in line with the opposing functions of AKH and insulin in sensing nutrient abundance, insulin treatment indirectly inhibited AKHR-induced response in ISNs. Therefore, these data suggest that ISNs use AKHR to receive both starvation and satiety cues and regulate feeding. Nan belongs to the conserved family of TRPV (transient receptor potential vanilloid) channel (Kim et al., 2003), and reduction of Nan in ISNs significantly increased water consumption upon dehydration (high osmolality). Water satiety (low osmolality) caused Nan-induced ISN firing, which in turn reduced drinking, suggesting that the function of Nan in ISNs is to restrict water intake. Taken together, these data point to ISNs as the integrator of pathways sensing internal sugar and water abundance in the fly.

Distinguishing the neuronal from the metabolic function of AKH and identifying Nan, potentially the first described internal hemolymph osmolality sensor, are by themselves important discoveries. However, arguably the most significant finding is how these two signals interact in ISNs and their functions in the homeostatic drives of hunger and thirst. Jourjine et al. (2016) showed that, even though AKH signaling and osmolality initiate different downstream pathways in ISNs, they both control ISN depolarization. As a result, they oppose each other's output behavior, with reduction of AKHR in ISNs increasing water intake and reduction of Nan decreasing sugar consumption. Thus, ISN activation, either through AKH increase or low osmolality, leads to high food consumption and low water intake, whereas ISNs silencing, either through AKH reduction, insulin increase, or high osmolality, leads to low food consumption and high water intake (Figure 1).

Such a remarkable discovery opens a wide field of questions for future studies. For instance, what are the downstream targets of ISNs? Upon ISN firing, is the low water intake and high sugar consumption mediated by different downstream targets (e.g., neuropeptides)? Interestingly, a water-taste sensor acting together with AKH signaling has been found to regulate longevity in *Drosophila* (Waterson et al., 2014). Since ISNs function as a node for both those signals, it would be interesting to test whether ISNs alone affect lifespan.

Given the conservation of neuronal mechanisms between flies and mammals, it will be exciting to see whether a similar principle exists in the mammalian brain. The hypothalamus or ghrelin-responding neurons are perhaps a good place to start, since hypothalamic neurons receive satiety, adiposity, and osmolality signals (Bourque, 2008; Woods et al., 1998).

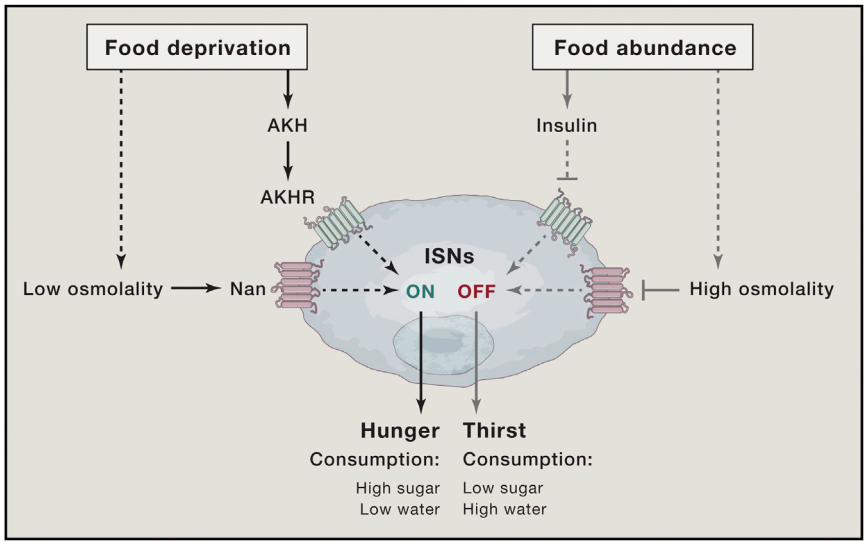

Figure 1. Integration of Nutrient Signals by ISNs for Homeostatic Regulation of Feeding and Drinking

The hunger signal AKH and low osmolality detected by the Nan channel activate ISNs, leading to high sugar and low water consumption. Opposing signals such as insulin and high osmolality instead limit firing of ISNs, causing lower sugar and higher water consumption.

Further, the ghrelin peptide has been found to regulate food consumption and, in some thirst-inducing conditions, water intake (Mietlicki et al., 2009).

The neuronal networks that integrate internal nutrient abundance signals and couple them to homeostatic behaviors remain largely unexplored, and yet disruption of this machinery could potentially contribute to the onset of homeostatic disorders like obesity-linked diabetes. Hence, the work of Jourjine et al. (2016) provides an excellent stepping stone for future research in this direction.

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Look Out Autophagy, Ubiquilin UPS Its Game

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Mutations in Ubiquilin-2 are linked to the onset of amyotrophic lateral sclerosis, but its connection to disease processes has remained unknown. Hjerpe et. al now report that Ubiquilin-2 enables the ubiquitin proteasome system (UPS) to single-handedly clear aggregated proteins, a cellular function previously thought to rely at least partially on autophagy.

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurological disease caused by motor-neuron degeneration in the brain and spinal cord, leading to paralysis and death typically within 2–5 years of onset. As with many other neurodegenerative diseases, the remarkable complexity of ALS etiology has historically stifled all attempts at a mechanistic understanding of ALS, let alone therapeutic design. Recent years, however, have seen a seismic shift in the appreciation of the molecular underpinnings of the disease, mainly thanks to systematic sequencing of patient genomes, combined with new cell biological insight (Chesi et al., 2013). As it is currently understood, most cases of ALS are pathologically related to a cell biological feature, namely neuronal aggregates of TDP-43, an RNA-binding protein. These aggregates, in turn, can often be traced to genetic mutations in TDP-43 or functionally related RNA-binding proteins,