Translational Physiology

Quenching the thirst for hunger

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Abstract

Maintenance of energy and water balance is fundamental to survival across organisms. A recent study reveals a unique neuroendocrine node in *Drosophila* that simultaneously surveys systemic caloric and osmotic fluctuations to fine-tune food and water consumption, shedding new neuronal mechanistic insight on anti-diabetes therapeutics with dual glucose/osmolality modulatory actions.
Death from starvation and dehydration are now rare in most of the developed world. Even the word *forthirst*, meaning “dying of thirst”, has become obsolete English, although mortality from either was not uncommon only a century ago and strategies to overcome both are fundamental to survival across animalia. On a physiological level, the hypothalamus plays an integral part in energy and water homeostasis by sensing and reacting to systemic signals of caloric and osmotic fluctuations. However, little is known about the evolutionary footprint of this survival critical neuroendocrine circuitry. Now, Jourjine and colleagues report an energy and water homeostatic co-regulatory neuronal system in *Drosophila* that coordinates food and water consumption juxtaposing at the interplay of a hormone receptor and an ion channel.

In a recent paper, Jourjine set out the goal to identify novel regulators of hunger and thirst in flies (5). Cross-interrogation of brain region-specific gene inhibition in experimentally induced food- and water-seeking flies identified a set of neurons and a cation channel, neither with known roles in energy/fluid homeostasis, actually modulate sugar and water consumption in cooperation. The authors named the neurons in the subesophageal zone (SEZ) that stimulate feeding behaviour the interoceptive SEZ neurons (ISNs), while the cation channel located in the SEZ was identified as the Nanchung (Nan) protein, first described a decade ago for its role in chordotonal mechanotransduction (6). Mining ISN co-expression data in hormone receptor-Gal4 flies pinpointed adipokinetic hormone (AKH), a hunger-sensing peptide, to be one afferent signal of ISNs. Nan SEZ neurons on the other hand fire directly in response to a decrease in hemolymph osmolality.
These findings paved a series of ISN- and Nan-focused experiments proceeding in the parallel universe of food and water investigative neuroscience, at least initially, but the two worlds eventually overlap out of remarkable scientific serendipity: AKH receptor expressing and osmosensitive Nan SEZ neurons are, in fact, the same neurons, and ISNs responded equally to osmolality and AKH changes.

The authors then examined AKH and Nan action within ISNs. In vitro, direct exposure to AKH or hypo-osmotic fluid stimulates ISNs activity; in vivo, ISNs firing heightened in starved flies with high AKH as well as mutant flies with Nan knockdown. Opposing ISN modulation by AKH, the signal of energy depletion, and Nan, the sensor for hypo-osmolality, begs the question of whether hunger and thirst are co-regulated by ISNs through simultaneous AKH and osmolality sensing. This is indeed the case, as illustrated by reciprocal water drinking and sugar consumption in flies governed by starved and water-sated states.

The intriguing studies co-wiring hunger and thirst sensing to behavioural sugar and water consumptive adaptations raise many questions. First, how do identical neurons, the ISNs, effect different consumptive behaviours simultaneously? Second, what is the evolutionary origin of coupled food/water sensing? Finally, in a broader context, what are the implications of these findings to human disease states with perturbations in caloric and osmotic status, such as diabetes mellitus?

Insight to these questions could be drawn by dissecting interactions between ISNs and systemic glucose/solute/hormone interactions. Although the authors found no effect of insulin alone on ISNs, insulin attenuates AKH-stimulated ISN activation, thus
signifying ISN-mediated water/food sensing is likely under multi-level hormonal influences, subsequently modulating drinking and feeding behaviour. In the survival hierarchy, water trumps food and water is required in all energy utilising biochemical processes. Moreover, glucose itself is a primary determinant of serum osmolality, and glycaemic fluxes impact both AKH/insulin balance as well as osmotic states. Although convergence of two mechanisms within one neuronal centre may confer an evolutionary vulnerability, coupling the two homeostatic drives within one locus facilitates direct fine-tuning to satisfy the two survival needs as systemic energy/osmotic status fluctuates, at least in dipterans. In rodents and humans, multiple and sometimes redundant neuroendocrine circuits have evolved to maintain energy/water homeostasis. ISNs in flies have perhaps provided a glimpse at the origin of such homeostatic regulatory machinery in evolutionary history.

What can we learn from ISNs of flies to further understanding of human health and disease? The hallmark of diabetes mellitus is hyperosmolar hyperglycaemia. If a similar ISN-like coupling mechanism exists in humans, one would expect low glucagon (mammalian equivalent to AKH) from energy repletion and relative hyperosmolality induced by hyperglycaemia to constitute an innate cap on appetite-driven weight gain operated via ISNs. Insulin and its secretagogue (i.e. sulphonylurea) are traditional glucose-lowering therapies. While efficacious, the drawback is weight gain, generally attributed to an increase in appetite, albeit poor understanding of the underlying mechanism. Through the lens of ISNs, the balance between thirst vs. hunger would be expected to gravitate towards food consumption as osmolality falls following pharmacological glucose lowering. In addition, sulphonylurea exhibits an antidiuretic effect reducing free water clearance (8). The net result is relative hypo-
osmolality that could trigger an ISN-mediated orexigenic response. It is tempting to speculate whether ISN-like neurophysiology, should it exist in humans, could potentially explain, at least partly, the long-recognised weight gain phenomenon observed during insulin/sulphonylurea treatment. In contrast, the new class of oral hypoglycaemic agent, sodium-glucose co-transporter 2 (SGLT2) inhibitors, reduce glucose by inducing glycosuria, which is accompanied by an osmotic diuresis (1). The lack of hyperphagia despite caloric loss upon SGLT2 inhibitor therapy has puzzled many but could hypothetically be a result of repressed ISN-mediated hunger signal from relative hyper-osmolality [Figure 1].

Conceptually, the corollary of these implications may also be applicable to weight loss benefits associated with renin-angiotensin-aldosterone (RAA) antagonism. While various central mechanisms have been postulated (2, 7), weight reduction from RAA blockade could potentially emanate from augmented osmolality lessening ISNs hunger signal. Emerging evidence is spotlighting astrocytes as salt sensors (3, 9) and kidney as a diabetes treatment target (4). ISNs neurophysiology in *Drosophila* sheds new insight on how water/solute homeostasis could wire to energy balance through an ancient coupled hormone-channel neuro-sensor, poised for further experimentations in rodents/humans.

Overall, this exciting study by Jourjine and colleagues uncovers a neuroendocrine centre capable of juggling water and caloric needs by integrating hunger/water satiety signals. Coupling of energy/osmolality sensing centrally illuminates pathophysiology and therapeutic responses in human disease states characterised by caloric and water balance disturbances. By unveiling a previously underappreciated layer of neuronal
input to satiety control from osmotic status, this unexpected insight from *Drosophila*
opens avenues in therapeutics research exploring interactive manipulation of energy and solute/water balance, centrally and peripherally, in our ongoing combat against diabetes/obesity.
References:

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The interoceptive subesophageal zone neurons (ISNs) are specialised sensors in *Drosophila* capable of simultaneously sensing systemic energy and water balance through input from adipokinetic hormone (AKH) and osmolality sensing by NaN ion channel, respectively. High AKH (signifying energy depletion) and low osmolality both drive feeding behaviour through ISNs activation while high osmolality promotes water drinking by repressing ISNs. This ancient conserved loop coupling energy/osmolality sensing may underlie appetite stimulation during glucose-lowering therapies in humans that also reduce osmolality, such as insulin and sulphonylurea. Conversely treatment that reduce glucose but induce osmotic diuresis, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors could lessen ISN-mediated orexigenic response limiting weight gain.
Low osmolality
High AKH

Hunger

Thirst

ISNs

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<th>Medication</th>
<th>Glucose</th>
<th>Osmolality</th>
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<tr>
<td>Sulphonylurea</td>
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<td>Insulin</td>
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