Thirst, hunger and nephrogenic diabetes insipidus

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Thirst is powerful! This is dramatically illustrated by the drinking behaviour of children with nephrogenic diabetes insipidus (NDI), a condition characterised by the unresponsiveness of the kidneys to vasopressin, resulting in large water losses.[1] If water is withheld for any reason, affected children will drink from anything to satisfy the urge: the bathtub, street puddles, flower vases or even the toilet. Other clinical manifestations include an increased incidence of attention deficit hyperactivity disorder (ADHD) and growth failure, the etiology of which is poorly understood[1]. Now, neuroscientists with their sophisticated tools have provided fascinating insights into the neuronal basis of thirst, how it competes with hunger and how these urges affect overall brain activity.

Mechanistically, thirst starts with the excitation of osmoregulatory cells in a brain structure called lamina terminalis located in the anterior wall of the third ventricle. The lamina terminalis contains three nuclei: the subfornical organ (SFO), the organum vasculosum lamina terminalis (OVLT) and the median preoptic nucleus (MnPO). Importantly, SFO and OVLT lack the blood-brain barrier and thus are critical for osmosensing. Optogenetic experiments, a technique where specific cells are genetically modified to express a light-sensitive protein, have identified that excitatory neurons in the MnPO with stimulatory input from SFO and OVLT are critical for eliciting thirst. Stimulation of these neurons with light reliably elicits immediate drinking behaviour even in fully water-satiated animals.[2]

Thirst must elicit behaviours directed at drinking to ensure homeostasis and survival. But how does that happen? Experiments with neuropixels microelectrode arrays, which allow simultaneous recording from thousands of neurons throughout an animal's brain, revealed that thirst gated the activity of a large number of neurons in several different brain areas.[3] Importantly, thirst not only affected behaviour to obtain water, but also the flow of activity throughout the brain in response to a sensory input. These sophisticated experiments reveal the underlying neuronal basis for the powerful nature of thirst and how it affects overall brain activity.

Aristotle already pondered whether an equally hungry and thirsty person would remain stuck between equidistant food and water. Buridan, a 14th century philosopher proposed that an equally hungry and thirsty donkey ("Buridan's ass") placed precisely midway between a stack of hay and a pail of water would die, unable to make any rational decision between the hay and the water. Yet, these were thought experiments that lacked an assay to formally test them. Until the development of "Buridan's assay": a mouse, after an olfactory cue, can get a reward in the form of either food or water.[4] The mice act as expected: food-restricted mice mostly choose food, whereas water-restricted animals mostly choose water. But what if they were both food and water restricted? The answer is simple: they oscillated between food and water until both needs were satisfied. The authors compared and mathematically modelled the transitions between the choices for water and food to diffusion in an energy landscape: the choice would be moving like a ball between "energy wells" (Figure 1a). If both wells are equally deep (equally thirsty and hungry), the ball would be randomly in one well and the animal would start satisfying that need first. Changes in hunger and thirst would then reshape the energy landscape until it favoured the other choice. The animal thus alternates between eating and drinking according to the shifting shape of the energy landscape until both needs are satisfied (Figure 1b).

These results were confirmed with optogenetics: activating the excitatory neurons that initiate thirst increased the likelihood for water as reward choice, even in food-starved mice. Neuropixels recording in these mice again showed that hunger and thirst affected different regions throughout the brain. Indeed, the firing pattern of about 20% of all recorded neurons right before the reward activity (licking for either food or water) provided significant information about the upcoming reward choice.[4] This is again consistent with the idea that a substantial part of brain activity is influenced by the urges hunger and thirst.

Thus, neuroscience has provided fascinating insights into the neuronal basis of basic urges like hunger and thirst and how they affect overall brain activity and behaviour. Translating the results from Buridan's assay back to Buridan's ass suggests that the donkey would certainly not die but go first for either hay or water, based on which energy well the choice happens to be in at the time. He would then alternate between the two for small bouts of drinking and eating, until both needs were completely satisfied.

Intuitively, these results are not unexpected: we all know the powerful nature of thirst and hunger and our language has words like "hangry" that express how overall behaviour is affected when these urges are not satisfied. This likely explains the frequent concomitant diagnosis of attention deficit/hyperactivity disorder (ADHD) and that patients often report difficulties with mental concentration.[5] Because of their constant thirst, brain activity in NDI is focussed on drinking and achieving homeostasis, rather than other specific tasks. It also provides insights into the growth failure in NDI (Figure 1c) which likely reflects a prioritization of water over food: the persistent loss of water and consequent thirst constantly distorts the energy landscape to favour the choice of water over food, analogous to food-starved mice with optogenetic stimulation of the excitatory "thirst" neurons.

Modern neuroscience thus not only appears to have saved Buridan's ass but also explains clinical observations in NDI!

References

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Figures

Fig 1: Buridan's assay and nephrogenic diabetes insipidus

a. Energy wells and the choice between food and water reward in Buridan's assay. Note the "energy landscape" above the mouse with wells for hunger and thirst. If hunger and thirst are equal, the wells will be equally deep and the initial choice could be either. As one urge is being satisfied, the landscape shifts so that the choice is more likely to go for the other urge and the mouse will shift between bouts of licking for food or water until both urges are satisfied (adapted from[4])

b: Example of a Buridan's experiment, performed on a mice starved for food and water. Orange indicates licks for food, blue for water. Note the bursts of licks for food, alternating with water, consistent with a shifting "energy landscape" (adapted from[4])

c: a boy with X-linked nephrogenic diabetes insipidus at presentation. Note the severe cachectic appearance. In analogy to Buridan's assay, malnutrition may be due to persistent deep wells for thirst because of the urinary water losses, favouring water over food intake.