of tundra ecosystems. The original drainage experiment[3] a decade earlier did indeed examine the impact of drainage on both CO_2 and methane fluxes. A follow-up study would be useful to fill the gap in the current findings.

Kwon and co-workers' results illustrate the value of long-term studies in the Arctic, but they also highlight the paucity of long-term data, which limits our ability to predict the effect of environmental change on greenhouse-gas fluxes in tundra ecosystems. Observations and manipulations over decades and across a variety of sites in the Arctic are required to understand and predict more fully the long-term effects of climate change on ecosystem functions. That would enable a better assessment of the applicability of research results such as those of Kwon and colleagues.

Unfortunately, given the costs of doing research in this region, funding agencies tend to support projects of only 3–5 years — hardly long enough to provide even a first glimpse of the impact of climate change. Long-term studies would be possible only through a collaboration of research groups, with several funding agencies sharing the financial burden.

Maintaining long-term research across the Arctic should be a priority. Large-scale collaborative projects could be the way forward. For example, in the INTAROS project, which is funded by the European Union, various research groups are joining forces to develop an integrated Arctic observation system that extends, improves and unifies existing systems in different regions of the Arctic. It is to be hoped that this effort will be followed by increased collaboration between other funding agencies and research groups across the area. ■

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1. Liljedahl, A. K. *et al. Nature Geosci.* **9,** 312–318 (2016).
2. Kwon, M. J. *et al. Biogeosciences* **13,** 4219–4235 (2016).
3. Merbold, L. *et al. Glob. Change Biol.* **15,** 2599–2614 (2009).
4. Zona, D. *et al. Glob. Biogeochem. Cycles* **26,** GB2004 (2012).
5. Stow, D. A. *et al. Remote Sens. Environ.* **89,** 281–308 (2004).
6. Naito, A. T. & Cairns, D. M. *Prog. Phys. Geogr.* **35,** 423–442 (2011).
7. Mastepanov, M. *et al. Biogeosci. Discuss.* **9,** 15853–15900 (2012).
8. Oechel, W. C., Laskowski, C. A., Burba, G., Gioli, B. & Kalhori, A. A. M. *J. Geophys. Res. Biogeosci.* **119,** 323–339 (2014).
9. Zona, D. *et al. Proc. Natl Acad. Sci. USA* **113,** 40–45 (2016).

PHYSIOLOGY

Forecast for water balance

Disturbances in internal water equilibrium can be debilitating for mammals. Two studies pinpoint areas of the mouse brain that respond to and anticipate thirst, preserving systematic fluid regulation. SEE LETTERS P.680 & P.685

MICHAEL J. KRASHES

When I feel thirsty, I drink water. But given the prominence of water intake in my daily life, I dedicate very little time to understanding the biology behind it. Why do I feel relieved almost immediately after drinking a glass of cold water? Why do I drink with every meal? Why do I find myself drinking at particular times each day? In this issue, Zimmerman *et al.*[1] and Gizowski *et al.*[2] shed light on these questions by defining the neuronal subtypes that mediate anticipatory thirst in mice.

In 1953, a pioneering study[3] demonstrated that injections of salty solutions into the hypothalamus of goats' brains elicited copious drinking behaviour, implicating the brain in thirst regulation for the first time. Later, pharmacological and lesion manipulations[4,5] revealed the importance of brain structures called the circumventricular organs (CVOs) to drinking behaviour. These organs have extensive vasculature and lack the normal blood–brain barrier — as such, they are a site of integration between the central nervous system and peripheral blood, allowing any water imbalance to be readily relayed to the brain.

A study last year[6] revealed that manipulation of populations of neurons in a CVO called the subfornical organ (SFO) can promote or preclude water intake in satiated or thirsty mice, respectively. However, the activity of these populations under physiological conditions remained elusive. In the first of the current studies, Zimmerman *et al.* (page 680) used a monitoring technique that allows for real-time recordings of molecularly defined groups of neurons in freely moving mice. These recordings revealed that overnight water restriction, which leads to a fluid imbalance, robustly stimulated activity in thirst-regulating neurons in the SFO.

Not surprisingly, when the authors presented thirsty mice with water, the animals promptly began drinking. Remarkably, however, SFO neurons were significantly inhibited as soon as the animal engaged in drinking behaviour. Unlike hypothalamic hunger neurons[7,8], which respond when an animal merely sees or anticipates food, rapid silencing of SFO neurons was not observed if the dehydrated subject could not directly access the water source — neither the sight of water, nor conditioned cues associated with water reward, altered the activity of the

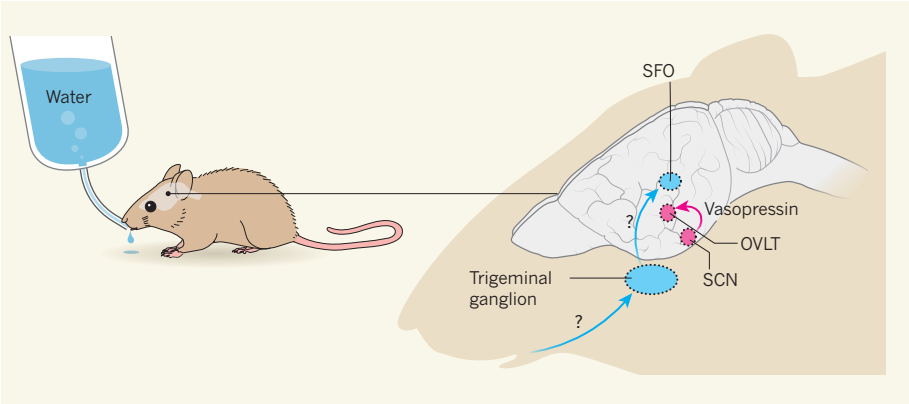

Figure 1 | Bring a mouse to water. Two studies reveal how water balance is maintained in mice by neural pathways that mediate thirst. Zimmerman *et al.*[1] report that neurons in a brain region called the subfornical organ (SFO) mediate anticipatory thirst (pathway indicated in blue). SFO neurons are activated when mice are dehydrated. This activity is almost immediately inhibited by drinking, owing to unknown signals that stem from the oral cavity, and which might act through a region called the trigeminal ganglion. Gizowski *et al.*[2] find that signalling by the hormone vasopressin from the brain's suprachiasmatic nucleus (SCN) to the organum vasculosum lamina terminalis (OVLT) promotes thirst before sleeping (pathway in red).

SFO population. Furthermore, licking in the absence of water had no effect. Thus, something about the ingestion of water seems to be crucial for inhibiting SFO neuronal activity.

Next, Zimmerman and colleagues offered thirsty mice saline, which triggers physiological responses to fluid ingestion without restoring water balance. Consumption of this hypertonic solution initially attenuated SFO neural activity in a manner indistinguishable from normal water intake, but activity quickly returned to baseline 'thirsty' levels. This led the researchers to conclude that the rapid anticipatory thirst response comprises at least two distinct phases — an instantaneous indicator of fluid ingestion and a deferred signal that encodes fluid tonicity. The authors confirm the mouth's role in facilitating these responses, finding that the decline in SFO neural activity was higher for cold than for warm water, and was recapitulated to a lesser degree by the application of cold metal directly to the oral cavity.

In most animals, there is a close association between feeding and drinking, due both to physiological needs and to learned associations between particular food smells and specific fluid requirements. Accordingly, Zimmerman *et al.* showed that food consumption rapidly ramped up the activity of SFO neurons, even before food-dependent alterations in blood composition — a result that reveals a neural explanation for why we drink while we eat. Finally, suppression of these SFO neurons drastically reduced water consumption following dehydration, demonstrating the absolute necessity of the cells for orchestrating drinking behaviour.

Together, Zimmerman and colleagues' results outline a mechanism by which water balance is encoded in the brain and preemptively corrected before fluid disturbances occur (Fig. 1). But how is thirst regulated over the course of the day to ensure accurate water balance? Another structure in the brain called the suprachiasmatic nucleus maintains behavioural rhythms such as the sleep cycle[9]. Gizowski *et al.* (page 685) found that, like many humans coming up to bedtime, mice elevate their water intake before sleeping, safeguarding against dehydration. This outcome hinges on the activity of a defined neural population in the suprachiasmatic nucleus and its output to another CVO, the organum vasculosum lamina terminalis (OVLT).

The suggestion that these sites have a role in the circadian control of thirst is supported by the finding that neural activity in both the suprachiasmatic nucleus and the OVLT was vastly magnified during the anticipatory period before sleep compared with a preceding time period. Moreover, the mechanism of communication between these regions was dependent on intact signalling from the suprachiasmatic nucleus by vasopressin, a hormone known to reduce the production of dilute urine (Fig. 1). Gizowski and colleagues showed that this pathway can both promote and prevent thirst — neural activation augmented drinking during normal periods of low water intake, whereas neural silencing reduced drinking during normal periods of high water consumption.

These studies have made substantial strides towards illuminating the neural mechanisms of anticipatory thirst. However, several avenues remain to be explored. First, putative osmoreceptors must respond to cellular dehydration in the mouth and send signals to the brain — how is this information relayed? One potential pathway for transmission of this somatosensory information is by way of a nerve cluster called the trigeminal ganglion. And what might be the contribution of the stomach or small intestine to this pre-absorptive mechanism?

It remains unclear why the anticipatory response evolved — perhaps it prevents animals from overhydrating, which can have detrimental effects on health. It might also serve to expedite drinking behaviour, limiting the amount of time an animal is exposed to predation or harsh environmental conditions.

Another area for investigation is whether the population-level neural activity seen in the current studies reflects identical responses by all neurons in the population or the combined action of differently responding neurons. Finally, the roles of the environment, previous experience and daily rhythms in shaping these neural networks have yet to be determined. For instance, might the simple expectation of food influence thirst-responding neurons? Future experiments aimed at answering these questions, and at further unravelling the complex neural circuitry involved in drinking behaviour, will enhance our understanding of this essential motivational drive. ■

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1. Zimmerman, C. A. *et al. Nature* **537,** 680–684 (2016).
2. Gizowski, C., Zaelzer, C. & Bourque, C. W. *Nature* **357,** 685–688 (2016).
3. Anderson, B. *Acta Physiol. Scand.* **28,** 188–201 (1953).
4. Johnson, A. K. & Epstein, A. N. *Brain Res.* **86,** 399–418 (1975).
5. Rolls, B. J. & Rolls, E. T. *Thirst (Problems in the Behavioural Sciences)* Ch. 7 (Cambridge Univ. Press, 1982).
6. Oka, Y., Ye, M. & Zuker, C. S. *Nature* **520,** 349–352 (2015).
7. Chen, Y., Lin, Y.-C., Kuo, T.-W. & Knight, Z. A. *Cell* **160,** 829–841 (2015).
8. Betley, J. N. *et al. Nature* **521,** 180–185 (2015).
9. Mills, J. N. *Physiol. Rev.* **46,** 128–171 (1966).

CHEMISTRY

Small molecular replicators go organic

The emergence of complex, dynamic molecular behaviour might have had a role in the origin of life. Such behaviour has now been seen in a reaction network involving small, organic, self-replicating molecules of biological relevance. SEE LETTER P.656

ANNETTE F. TAYLOR

A hallmark of life is its ability to self-replicate at every level, from individual molecules to whole organisms. The first prebiotic molecular replicators were probably RNA-like, but other, non-genetic self-replicators might have had a role in the emergence of life. On page 656, Semenov *et al.*[1] report the self-replication of a small organic molecule in an autocatalytic process — one that produces its own catalysts — and demonstrate that their system can display complex, nonlinear responses to changes in environmental conditions. This is the first experimental example of autocatalysis and complex behaviour in a reaction network that contains only simple organic compounds of biological relevance.

Models of biological systems involving autocatalysis appeared as early as 1910, and were proposed to explain oscillations in population dynamics[2], the origin of homochirality[3] (the single 'handedness' of biological molecules such as amino acids) and shape formation in cellular systems[4]. However, despite the physicist Charles Frank's suggestion[3] that "a laboratory demonstration might not be impossible", it proved difficult to find real autocatalytic chemical reactions to replace the artificial (and sometimes impossible) processes suggested in these biological models.

A breakthrough came in the 1950s, when the chemist Boris Belousov discovered oscillations in a chemical system while trying to create an inorganic analogue of the Krebs cycle[5],