NEUROGASTROENTEROLOGY

A thirst-quenching gut–brain signal

A new study in mice has revealed a gut–brain signal that relays measurements of ingested fluid osmolarity in the gastrointestinal tract to regions of the brain. The integration and processing of these signals is key to determining thirst satiation and drinking behaviour.

Thirst was previously thought to be a negative-feedback response to changes in the blood. However, some behaviours such as thirst satiation occur before ingested water can be absorbed into the blood. This understanding suggests thirst cannot be controlled by blood composition alone and has led to studies of other ways the brain controls thirst.

“In 2016, we reported the first in vivo recordings of ‘thirst neuron’ activity during behaviour,” says first author of the latest study, Chris Zimmerman. “These recordings revealed that, in addition to directly monitoring the osmolarity of the blood, the ‘thirst neurons’ also receive sensory signals from the mouth and throat during drinking.” These oropharyngeal signals provided the brain cues on the volume of liquid ingested but not its composition, which is also crucial for fluid homeostasis. Now, the investigators have revealed the mechanism that tracks the osmolarity of fluids ingested during drinking.

The new study combined optical techniques for monitoring neural activity in awake mice with surgical manipulation of the gastrointestinal tract and peripheral nervous system. “To monitor neural activity, we expressed a fluorescent calcium indicator in several populations of thirst-driving neurons as well as in vasopressin (antidiuretic hormone)-releasing neurons in the mouse brain,” explains Zimmerman. “We then implanted optical fibres above these neural populations to record either population-level activity using a technique called fibre photometry or the activity of individual neurons by mounting a miniature microscope on the mouse’s head.” By implanting intragastric catheters in these mice, fluids containing water, salts and sugars could be infused directly into the stomach while neural dynamics were monitored in real-time in awake, behaving animals.

Using these techniques, the team demonstrated that an osmosensory signal from the gastrointestinal tract is necessary and sufficient to satiate thirst. “This gut-to-brain signal encodes the osmolarity of ingested fluids and rapidly travels through the vagus nerve to neurons in the forebrain that orchestrate thirst and vasopressin secretion,” reports Zimmerman. Using microendoscopic imaging, the researchers also show how individual neurons in regions of the brain’s fluid homeostasis system integrate gut-derived osmosensory signals with oropharyngeal and blood-derived signals.

“In this paper, we reveal the existence and mechanism of the ‘missing’ third signal from the gastrointestinal tract that tells the brain about the osmolarity of the fluids we drink,” says Zimmerman. The researchers propose a three-step mechanism that promotes thirst satiation: first, a signal detecting the volume of liquid ingested is generated in the mouth; a second gut-derived signal reports the osmolarity; and finally, the absorption of water into the bloodstream leads to signals that are monitored by the brain directly.

The investigators are now interested in how the gastrointestinal tract senses osmolarity. “Right now, we don’t know the identity of the protein that transforms extracellular osmolarity into intracellular biochemical signals in this system, we don’t know which cell types in the gastrointestinal tract express this protein and we don’t know how these cells talk to nearby nerve fibres,” says Zimmerman. “The approach we use in this paper offers a promising roadmap for future studies.”

Iain Dickson

ORIGINAL ARTICLE Zimmerman, C. A. et al. A gut-to-brain signal of fluid osmolarity controls thirst satiation. *Nature* **568**, 98–102 (2019)

Liver lobule. Image courtesy of H. Zhu, Children’s Medical Center Research Institute at UT Southwestern, USA.

acted as a model of liver damage and regeneration in the context of chronic disease. Crucially, this screen validated the functional relevance of *Pkd1*, *Kmt2d* and *Arid1a*. Conditional deletion of these genes from hepatocytes in various floxed mice confirmed their role in promoting hepatocyte fitness or liver regeneration in liver injury assays.

The researchers hope their conclusions might be explored in other tissues to determine whether they also harbour mutations that are adaptive rather than maladaptive, and they hope to further develop their screens in the liver to identify potential novel therapeutic targets.

Katrina Ray

ORIGINAL ARTICLE Zhu, M. et al. Somatic mutations increase hepatic clonal fitness and regeneration in chronic liver disease. *Cell* **177**, 608–621.e12 (2019)

...the number and volume of clones carrying mutations increased as a function of fibrosis stage and level of liver damage

Credit: Image courtesy of S. Babaee, Massachusetts Institute of Technology, USA. Image design: L. Marshall, Springer Nature Ltd.

fenestrated spherical shape in the stomach, residing there for weeks. Endoscopic application of warm water triggered device disintegration for easy passage through the gut.

“[The research] helps establish a route toward potentially safer in situ device disintegration in the gastrointestinal tract with subsequent excretion of the smaller individual segments,” notes Babaee. “However, additional testing will be needed to characterize heat dissipation in humans,” he cautions, with the researchers currently identifying and prioritizing conditions to optimize this new approach.

Katrina Ray

ORIGINAL ARTICLE Babaee, S. et al. Temperature-sensitive biometamaterials for gastrointestinal applications. *Sci. Transl. Med.* **11**, eaau8581 (2019)

...the biomaterials within changed shape or disassembled for easier passage through the gastrointestinal tract