telomere structure and/or activity in the somatic cells, as has been observed in ciliates[10].

The overall framework of PDE seems to be conserved between parasitic and free-living nematodes. Therefore, ~135 years of knowledge of PDE from parasitic nematodes should accelerate investigations of PDE mechanisms in free-living nematodes. The two studies also show that, while some aspects of PDE are similar across nematodes, there are also important differences. Comparison of the PDE mechanisms in free-living and parasitic nematodes, as well as identification and characterization of other potential free-living nematodes undergoing PDE, should tell us how PDE has evolved in nematodes and how flexible PDE mechanisms can be in metazoans.

Both *Oscheius* and *Mesorhabditis* belong to the Rhabditidae family, which also includes *C. elegans* (Figure 1). Therefore, many molecular genetic techniques for *C. elegans* can be adapted for these emerging model nematodes. Further investigations of the PDE processes in these genetically tractable free-living nematodes should tell us how the DSB sites for PDE are determined, which enzyme induces DSBs, how germline cells escape from PDE, how DSB formation and *de novo* telomere formation are linked, how eliminated chromosomal fragments are excluded from spindle assembly, and what the role of PDE is. Such studies should also eventually aid in understanding PDE processes in other metazoans.

DECLARATION OF INTERESTS

The author declares no competing interests.

REFERENCES

1. Allen, S.E., and Nowacki, M. (2017). Necessity is the mother of invention: ciliates, transposons, and transgenerational inheritance. Trends Genet. *33*, 197–207.
2. Dockendorff, T.C., Estrem, B., Reed, J., Simmons, J.R., Zadegan, S.B., Zagoskin, M.V., Terta, V., Villalobos, E., Seaberry, E.M., and Wang, J. (2022). The nematode *Oscheius tipulae* as a genetic model for programmed DNA elimination. Curr. Biol. *32*, 5083–5098.
3. Rey, C., Launay, C., Wenger, E., and Delattre, M. (2022). Programmed DNA elimination in the free-living nematodes *Mesorhabditis*. Preprint at bioRxiv, https://doi.org/10.1101/2022.03.19.484980.
4. Boveri, T. (1887). Ueber Differenzierung der Zellkerne wahrend der Furchung des Eies von *Ascaris megalocephala*. Anat. Anz. *2*, 688–693.
5. Dedukh, D., and Krasikova, A. (2022). Delete and survive: strategies of programmed genetic material elimination in eukaryotes. Biol. Rev. *97*, 195–216.
6. Wang, J., Veronezi, G.M.B., Kang, Y., Zagoskin, M., O'Toole, E.T., and Davis, R.E. (2020). Comprehensive chromosome end remodeling during programmed DNA elimination. Curr. Biol. *30*, 3397–3413.
7. Müller, F., and Tobler, H. (2000). Chromatin diminution in the parasitic nematodes Ascaris suum and Parascaris univalens. Internat. J. Parasitol. *30*, 391–399.
8. Gonzalez de la Rosa, P.M., Thomson, M., Trivedi, U., Tracey, A., Tandonnet, S., and Blaxter, M. (2021). A telomere-to-telomere assembly of *Oscheius tipulae* and the evolution of rhabditid nematode chromosomes. G3 (Bethesda) *11*, jkaa020.
9. Wang, J., Gao, S., Mostovoy, Y., Kang, Y., Zagoskin, M., Sun, Y., Zhang, B., White, L.K., Easton, A., Nutman, T.B., *et al*. (2017). Comparative genome analysis of programmed DNA elimination in nematodes. Genome Res. *27*, 2001–2014.
10. Kirk, K.E., and Blackburn, E.H. (1995). An unusual sequence arrangement in the telomeres of the germ-line micronucleus in *Tetrahymena thermophila*. Genes Dev. *9*, 59–71.

Neuroscience: Secretin excites the thirst circuit

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Peptides secreted by internal organs and by neurons in the brain are major regulators of eating and drinking. New work shows that the peptide hormone secretin influences drinking by adjusting the excitability of neurons in the brain's thirst circuit.

Our bodies are constantly generating sensory signals — how much food is in the stomach, how fast the heart is beating, how much air is in the lungs — that allow the brain to precisely track changes in our internal physiological state. These interoceptive signals, for example, make us feel thirsty when we are dehydrated and trigger the feelings of pleasure and satiation that accompany drinking water. Recent work has shown that many of the interoceptive signals for thirst converge onto a single population of dehydration-sensing neurons located in a small forebrain region of the mammalian brain called the subfornical organ (SFO), thereby enabling these cells to integrate information from different organs to generate a holistic representation of the body's hydration state[1,2]. A new study published recently in *Current Biology* by Zhang *et al.*[3] shows that secretin, a peptide hormone that is produced in the gut as well as the brain, influences thirst by adjusting the excitability of these same dehydration-sensing SFO neurons.

Secretin is the original hormone, discovered by Bayliss and Starling in 1902 as a chemical messenger between the intestine and pancreas[4], and endocrinologists have spent the past century dissecting how this 27-amino-acid peptide regulates secretions from the

stomach, pancreas, and other internal organs during feeding and digestion[5]. How did the archetypical digestive hormone become linked to thirst and fluid homeostasis? The strongest evidence has come from experiments using mice that have been genetically engineered to lack either secretin (*Sct*$^{-/-}$) or its receptor (*Sctr*$^{-/-}$) throughout the entire body. At the physiological level, *Sctr*$^{-/-}$ mice have an impaired ability to regulate water reabsorption by the kidneys when they are dehydrated[6]. At the behavioral level, *Sct*$^{-/-}$ and *Sctr*$^{-/-}$ mice both show greatly reduced drinking responses to dehydration and other dipsogenic stimuli, and infusion of secretin directly into the brain is sufficient to trigger drinking in fully hydrated animals[7,8]. Together, these findings suggest that secretin plays a role in maintaining fluid homeostasis in the body.

Zhang *et al.*[3] have now pinpointed the neural population that mediates the effects of secretin on drinking behavior. They began by investigating the SFO, a crucial 'starting point' for the brain's thirst circuit: the SFO lies outside the blood–brain barrier and directly detects circulating signals of dehydration, including the hormone angiotensin II[9], which is produced in the circulation when blood volume or pressure falls, and the osmolarity of the blood[10], which increases during dehydration. Recent optogenetic studies have shown that activation of glutamatergic SFO neurons in particular is both sufficient and necessary for thirst[11,12]. Zhang *et al.*[3] found that these dehydration-sensing glutamatergic SFO neurons — but not other SFO cell types — express the secretin receptor (Figure 1), and furthermore that these neurons are activated by peripheral administration of secretin *in vivo* and by direct application of secretin *ex vivo*.

To directly test whether secretin receptor expression in SFO thirst neurons mediates the hormone's effects on drinking behavior, Zhang *et al.*[3] used a genetic strategy to knock out expression of the receptor specifically in the SFO, while leaving expression in the rest of the brain and body intact. Strikingly, dehydration stimulated less than half as much water intake in these *Sctr*$^{SFO-/-}$ mice compared to controls. This effect is comparable in magnitude to that

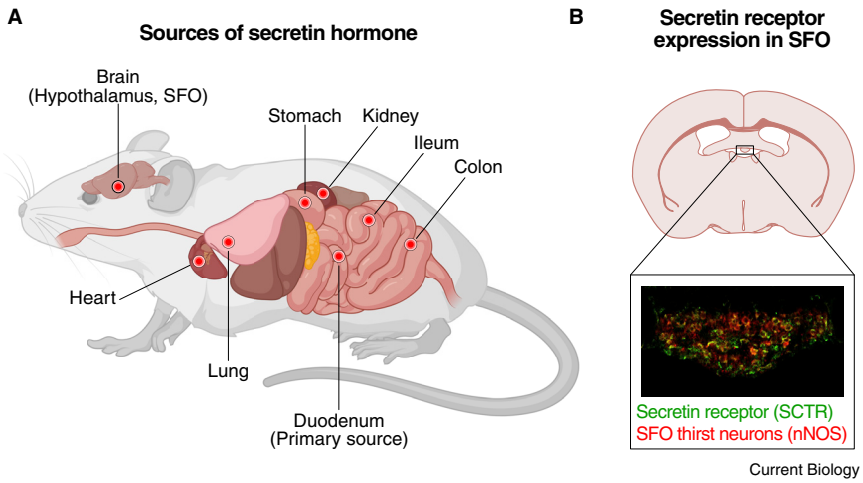

Figure 1. Secretin in the body and the brain.
(A) The duodenum is the body's primary source of secretin, although secretin-producing cells can be found in many organs and there is evidence for secretin production (based on expression of the *Sct* gene or of the active peptide) in several brain regions, including the subfornical organ and the pituitary-projecting paraventricular and supraoptic nuclei of the hypothalamus. The source of secretin that influences the activity of thirst-promoting SFO neurons remains unclear. (B) The secretin receptor is expressed by thirst-promoting glutamatergic SFO neurons, but not by other SFO cell types. Here, the secretin receptor (SCTR) is labeled in green and SFO thirst neurons are labeled in red (based on expression of the marker protein nNOS). The schematics were created with BioRender and the histology image is reproduced from Zhang *et al.*[3].

observed in global *Sct*$^{-/-}$ and *Sctr*$^{-/-}$ knockout mice, which suggests that the SFO is the critical site in the brain at which secretin influences thirst. On the other hand, SFO secretin receptor deletion had no effect on salt appetite or sodium intake. This is an important control because a subpopulation of glutamatergic SFO neurons has been shown to play a key role in salt appetite[13], and this result indicates that secretin may specifically target the thirst-promoting subset of excitatory SFO neurons.

Dehydration-sensing SFO neurons trigger thirst via their projection to the median preoptic nucleus (MnPO)[12,14]. Zhang *et al.*[3] further showed that ablating expression of the secretin receptor exclusively in MnPO-projecting SFO neurons inhibited dehydration-induced drinking to a similar degree as observed in SFO-wide and global knockouts. This suggests that secretin modulates the well-established SFO→MnPO pathway that drives thirst in response to most forms of dehydration, rather than operating through a new circuit.

Does secretin convey a specific interoceptive signal for thirst to the SFO? To gain insight into this question, Zhang *et al.*[3] used fiber photometry to record the responses of SFO neurons of wild-type or *Sctr*$^{SFO-/-}$ mice to several forms of dehydration. They found that *Sctr*$^{SFO-/-}$ mice had blunted responses to every stimulus tested. This suggests that rather than mediating a specific thirst signal like 'low blood volume' or 'food in the gastrointestinal tract', basal levels of secretin receptor signaling are necessary to maintain the excitability of SFO thirst neurons and permit them to respond to more specific inputs from other hormones and neural pathways. Alternatively, it remains possible that the timing of secretin's actions at the SFO will reveal a more specific role — for example, if secretin receptor signaling in thirst neurons is elevated only under specific circumstances, either due to a local increase in hormone levels or receptor levels. Tools for directly monitoring the dynamics of secretin receptor signaling *in vivo* would help to distinguish these possibilities but do not yet exist.

Where does the secretin that acts on SFO thirst neurons originate? The body's primary source of secretin is the duodenum, where it is released during digestion, but secretin is also produced by several internal organs as well as by neurons in the brain (Figure 1). Indeed, secretin is released into the bloodstream during dehydration by

pituitary-projecting neurons in the hypothalamus[15] and expression of the *Sct* gene has even been observed directly in the SFO[7]. If secretin originating from a single organ or brain region is responsible for increasing the excitability of the thirst circuit, this could provide a foothold for understanding whether the hormone plays a specific or permissive role in regulating thirst under normal physiological conditions.

The new study by Zhang *et al.*[3] comes at an exciting time for the thirst field. Recent work has uncovered several new interoceptive signals that arise in the periphery and then converge in the brain to regulate thirst during eating and drinking[1,2], and this has led to a renewed interest in the neural and hormonal pathways that might convey these signals. For example, SFO thirst neurons are activated during feeding to drive prandial thirst[12], but the mechanism underlying this activation remains unknown and feeding-triggered hormones like secretin represent promising candidates. Combining tissue-specific deletion of hormones and their receptors with *in vivo* recordings of thirst neuron activity, as in this study, will be a powerful strategy for identifying hormonal pathways that may encode these interoceptive signals.

DECLARATION OF INTERESTS

The author declares no competing interests.

REFERENCES

1. Lowell, B.B. (2019). New neuroscience of homeostasis and drives for food, water, and salt. N. Engl. J. Med. *380*, 459–471.
2. Zimmerman, C.A., and Knight, Z.A. (2020). Layers of signals that regulate appetite. Curr. Opin. Neurobiol. *64*, 79–88.
3. Zhang, F., Mak, S.O.K., Liu, Y., Rao, F., Yung, W.H., Zhang, L., and Chow, B.K.C. (2022). Secretin receptor deletion in the subfornical organ attenuates the activation of excitatory neurons under dehydration. Curr. Biol. *32*, 4832–4841.e5.
4. Bayliss, W.M., and Starling, E.H. (1902). The mechanism of pancreatic secretion. J. Physiol. *28*, 325–353.
5. Chey, W.Y., and Chang, T.-M. (2003). Secretin, 100 years later. J. Gastroenterol. *38*, 1025–1035.
6. Chu, J.Y., Chung, S.C., Lam, A.K., Tam, S., Chung, S.K., and Chow, B.K. (2007). Phenotypes developed in secretin receptor-null mice indicated a role for secretin in regulating renal water reabsorption. Mol. Cell. Biol. *27*, 2499–2511.
7. Lee, V.H.Y., Lee, L.T.O., Chu, J.Y.S., Lam, I.P.Y., Siu, F.K.Y., Vaudry, H., and Chow, B.K.C. (2010). An indispensable role of secretin in mediating the osmoregulatory functions of angiotensin II. FASEB J. *24*, 5024–5032.
8. Lee, L.T.O., Ng, S.Y.L., Chu, J.Y.S., Sekar, R., Harikumar, K.G., Miller, L.J., and Chow, B.K.C. (2014). Transmembrane peptides as unique tools to demonstrate the in vivo action of a cross-class GPCR heterocomplex. FASEB J. *28*, 2632–2644.
9. Simpson, J.B., and Routtenberg, A. (1973). Subfornical organ: site of drinking elicitation by angiotensin II. Science *181*, 1172–1175.
10. Lind, R.W., Thunhorst, R.L., and Johnson, A.K. (1984). The subfornical organ and the integration of multiple factors in thirst. Physiol. Behav. *32*, 69–74.
11. Oka, Y., Ye, M., and Zuker, C.S. (2015). Thirst driving and suppressing signals encoded by distinct neural populations in the brain. Nature *520*, 349–352.
12. Zimmerman, C.A., Lin, Y.-C., Leib, D.E., Guo, L., Huey, E.L., Daly, G.E., Chen, Y., and Knight, Z.A. (2016). Thirst neurons anticipate the homeostatic consequences of eating and drinking. Nature *537*, 680–684.
13. Matsuda, T., Hiyama, T.Y., Niimura, F., Matsusaka, T., Fukamizu, A., Kobayashi, K., Kobayashi, K., and Noda, M. (2017). Distinct neural mechanisms for the control of thirst and salt appetite in the subfornical organ. Nat. Neurosci. *20*, 230–241.
14. Augustine, V., Gokce, S.K., Lee, S., Wang, B., Davidson, T.J., Reimann, F., Gribble, F., Deisseroth, K., Lois, C., and Oka, Y. (2018). Hierarchical neural architecture underlying thirst regulation. Nature *555*, 204–209.
15. Chu, J.Y., Lee, L.T., Lai, C.H., Vaudry, H., Chan, Y.S., Yung, W.H., and Chow, B.K. (2009). Secretin as a neurohypophysial factor regulating body water homeostasis. Proc. Natl. Acad. Sci. USA *106*, 15961–15966.

Plant nutrition: An architect of nitrate-hunger cues

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Nitrate perception and uptake are critical for plant well-being. A known actor in nitrate signaling, the transcription factor NLP7, has now been reported to have a new role: as a nitrate sensor. The latter function has been characterized and exploited to generate a fluorescent nitrate biosensor.

Nitrogen (N) is an essential macroelement for life, acting as a building block in DNA and proteins and in molecular currencies such as ATP. For plants, crucial processes require N at many levels, including for the structure of chlorophyll, which is at the heart of photosynthesis. However, plants do not utilize N_2 from the air, but instead readily take up inorganic forms, such as nitrate fixed by soil bacteria, through the roots. Shifts in nitrate levels are detected by the plant, triggering widespread transcriptional, metabolic, hormonal and developmental reprogramming[1,2]. Although this ensemble of responses supports acclimatization of the plant to varying nitrate conditions, crops still require large inputs of synthetic nitrogenous fertilizers, which are expensive, energetically costly and environmentally destructive[3,4]. Exacerbated by the conflict in Ukraine, scientists, UN officials and farmers have sounded the alarm bells: we are currently