
Credit: Savushkin/Getty

compulsive drinkers than in the low drinkers. Thus, differences in the neural dynamics of this circuit on day 1 could predict the drinking phenotype many days later.

Last, the authors optogenetically manipulated the activity of mPFC–dPAG neurons in various behavioural assays. Optogenetically inhibiting these neurons as mice drank alcohol mixed with quinine made the animals less deterred by the aversive taste of quinine. Similarly, optogenetic inhibition of these cells also increased animals' latency to withdraw their tails from hot water. However, photoinhibition of the mPFC–dPAG projection was not reinforcing, suggesting this manipulation decreases sensitivity to aversive stimuli. Consistent with this notion, optogenetic stimulation of mPFC–dPAG neurons during alcohol-drinking bouts served as a punishment, leading to long-lasting reductions in alcohol drinking.

Together, these results imply that functional differences in the mPFC–dPAG circuit may disrupt aversive processing and predispose mice to develop compulsive drinking behaviour.

Natasha Bray

ORIGINAL ARTICLE Siciliano, C. A. et al. A cortical-brainstem circuit predicts and governs compulsive alcohol drinking. *Science* **366**, 1008–1012 (2019)

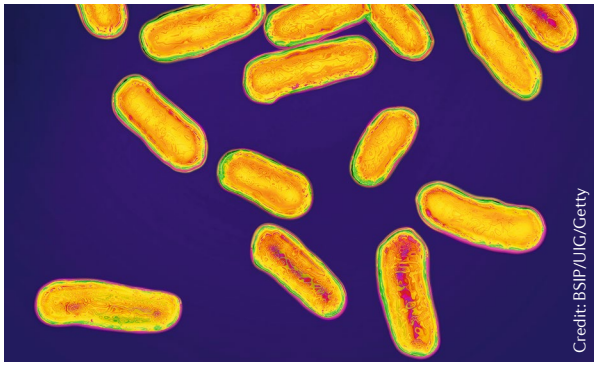

Credit: Yuichiro Chino/Getty

The authors used adeno-associated viral vectors to overexpress genes correlating with resilience or to knock out genes correlating with susceptibility. Increasing *Ucn* expression or decreasing *Crhbp* expression across the whole RGC population substantially increased overall RGC survival rates. The authors then expressed *Timp2* or *Ucn* in RGCs and measured the survival of two susceptible RGC subclasses that do not endogenously express these genes. They found that overexpression of either gene increased survival and axon regeneration in one subclass but not the other, showing that these genes are not universally protective for RGCs.

Together, this study provides a molecular atlas of the responses of different RGC types to injury and identifies specific pro-survival and pro-regeneration genes that might prove useful therapeutically.

Sian Lewis

ORIGINAL ARTICLE Tran, N. M. et al. Single-cell profiles of retinal ganglion cells differing in resilience to injury reveal neuroprotective genes. *Neuron* **104**, 1039–1055.e12 (2019)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NEUROIMMUNOLOGY

Defending the gut

Nociceptors protect the body by detecting noxious stimuli and initiating protective reflexes and behaviours. Gut nociceptors detect gastrointestinal disturbances and drive responses including vomiting, diarrhoea and visceral pain. Chiu and colleagues now show that, in mice, these nociceptors can also regulate mucosal host defence mechanisms.

Salmonella enterica serovar Typhimurium (STm), a major cause of gastroenteritis in humans, invades the body via lymphoid nodules in the ileum known as Peyer's patches (PPs), which also receive sensory innervation. To investigate whether gut nociceptors assist in the defence against STm, the authors used genetic and pharmacological tools to ablate these neurons in mice. Following oral infection with STm, nociceptor-ablated mice exhibited greater PP invasion and systemic STm dissemination than control mice, suggesting an important role for these neurons in host defence against STm.

Commensal bacteria are a vital contributor to host defence. Nociceptor ablation altered ileum commensal bacterial diversity and, in particular, reduced the levels of the segmented filamentous bacteria (SFB) that attach to the epithelium of PP. In mice lacking SFB, nociceptor ablation did not alter STm infection, whereas SFB introduction (via gavage) to SFB-lacking or nociceptor-ablated mice provided protection against STm.

Nociceptor ablation also increased the abundance of PP microfold (M) cells, the main cellular entry point for STm. M cell depletion in these mice restored protection against STm to levels present in wild-type mice and M cell depletion also reduced PP SFB levels. Thus, by regulating M cells, nociceptors may both limit STm entry and boost host resistance to the bacteria. The authors' findings further indicate that both of these effects might be mediated by the neuropeptide CGRP (calcitonin gene-related peptide): STm induced release of CGRP from nociceptors in culture and in vivo, and mice lacking CGRP exhibit increased M cell density and reduced levels of SFB.

These findings indicate an important role for gut-innervating nociceptors in host defence against an invading enteric pathogen. By dissecting some of the cellular mechanisms involved, this study may also contribute to the identification of new targets for therapeutic intervention.

Katherine Whalley

ORIGINAL ARTICLE Lai, N. Y. et al. Gut-innervating nociceptor neurons regulate Peyer's patch microfold cells and SFB levels to mediate *Salmonella* host defence. *Cell* https://doi.org/10.1016/j.cell.2019.11.014 (2019)