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GUT–BRAIN COMMUNICATION

# Making contact

> enterochromaffin cells exhibit characteristics typical of peripheral sensory cells

The gut epithelium is the major interface between the digestive and neural systems and has an important role in the modulation of physiological processes in response to intestinal signals. Bellono *et al.* now provide insight into the mechanisms that mediate this link, showing that a rare subtype of gut epithelial cell — enterochromaffin cells — responds to physiologically relevant stimuli and can modulate the function of nearby neurons.

Enterochromaffin cells produce most of the body's serotonin and are thought to contribute to the regulation of several physiological and pathological processes; however, because these cells are small and represent a tiny fraction of all gut epithelial cells, it has been difficult to determine their specific properties. Bellono *et al.* therefore generated intestinal organoids in which enterochromaffin cells were labelled with green fluorescent protein, allowing them to examine the function of individual enterochromaffin cells.

Through electrophysiological analysis, the authors showed that enterochromaffin cells exhibit characteristics typical of peripheral sensory cells, including the presence of voltage-gated sodium and calcium channels and excitability in response to depolarization. Furthermore, the cells responded to several physiologically important compounds, including allyl isothiocyanate (AITC; a mustard plant component that has been linked to visceral inflammatory pain), isovalerate (a product of gut microbiota that has been associated with gastrointestinal disorders) and the catecholamine noradrenaline (which is released by sympathetic nerve fibres in the gut and has been linked to gastrointestinal injury and stress).

Next, the authors considered the mechanisms by which the enterochromaffin cells detect and respond to these stimuli. Transcriptional profiling revealed that they express sensory receptors, including transient receptor potential cation channel A1 (TRPA1; a receptor for AITC), the olfactory receptor OLFR558 (which the authors showed could be activated by isovalerate) and TRPC4 (a component of the catecholamine signal-transduction pathway). Pharmacological or genetic modulation of the signal-transduction pathways used by these receptors confirmed their role in the detection and transduction of specific signals. Using an *ex vivo* preparation in which 'biosensor' cells expressing the serotonin receptor 5-$HT_3$R were placed close to enterochromaffin cells, the authors showed that application of adrenaline (which activates the same receptors as noradrenaline) to the gut epithelium induces serotonin release from enterochromaffin cells.

Which cells are affected by this serotonin release? Imaging of intestinal preparations showed that many 5-$HT_3$R-expressing neurons innervate the gut epithelium and make contacts with enterochromaffin cells that are characterized by colocalization with synaptic markers. Furthermore, when the authors recorded from mechanosensory nerve fibres in an *ex vivo* colonic preparation, they found that application of noradrenaline or isovalerate to the epithelium evoked large, 5-$HT_3$R-mediated responses in the sensory neurons that were dependent on enterochromaffin cell-mediated transduction.

This work shows that enterochromaffin cells are chemosensors that respond to a range of stimuli that are indicative of gastrointestinal injury or stress, and provides insight into the mechanisms by which such signals may modulate neural function.

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**ORIGINAL ARTICLE** Bellono, N. W. *et al.* Enterochromaffin cells are gut chemosensors that couple to sensory neural pathways. *Cell* **170**, 185–198 (2017)