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NEUROGASTROENTEROLOGY

A tale of two neurons — distinct functions of vagal afferents of the gut

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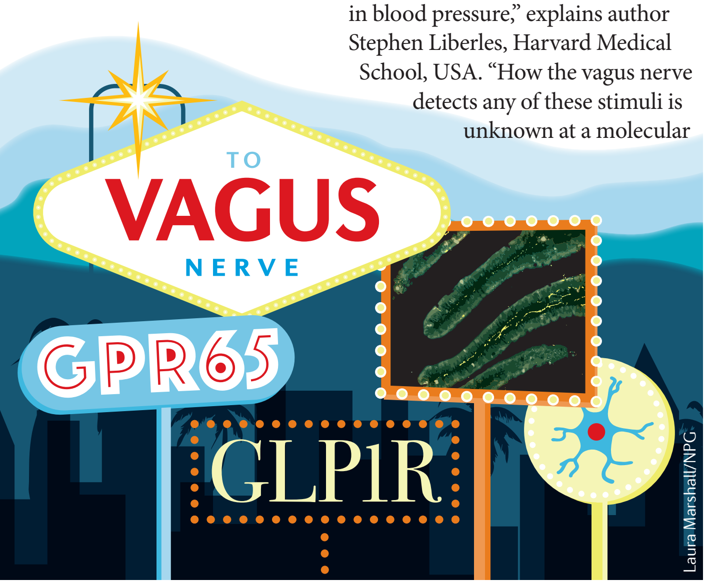
The gut–brain axis is increasingly recognized as a bidirectional communication between these two organs and their associated systems. New research published in *Cell* provides more information on neural control of gastrointestinal physiology, identifying distinct neurons signalling from the gut to the brain: one type detecting nutrients in the intestine, the other type acting as a mechanosensor detecting stretch in the stomach and intestinal muscle.

Vagal sensory neurons have a key role in gastrointestinal physiology in the detection of, among others, gut hormones, nutrients and distension to control digestive function. "The vagus nerve is a fascinating structure that serves as a major conduit between body and brain, controlling several major organ systems, and detecting many vital stimuli — from nutrients in the gastrointestinal tract to stretch of the lungs to changes in blood pressure," explains author Stephen Liberles, Harvard Medical School, USA. "How the vagus nerve detects any of these stimuli is unknown at a molecular level, presenting tremendously important problems in sensory biology and medicine."



GPR65 neuron in an intestinal villus courtesy of E. K. Williams and S. D. Liberles.

The researchers used molecular, imaging and genetic approaches (including optogenetics) to try to deconstruct the sensory system in the gut and provide a more comprehensive analysis of sensory neuron physiology. Experiments focused on *in vivo* evidence from various mouse models, in particular using knock-in mice to examine the role of neurons that express one of two receptors — GLP1R (Glucagon-like peptide 1 receptor) and GPR65 — in response to sensory inputs during digestion.

Liberles and colleagues first focused on *in vivo* calcium imaging of single neuron responses to various stimuli, including stretch (in the stomach, intestine and lungs) and nutrients (in the small intestine). They found that individual vagal sensory neurons had specific response properties depending on the stimuli. Moreover, in terms of position, sensory neurons had no apparent spatial clustering based on response properties and were intermingled throughout vagal ganglia.

Surprisingly, vagal GLP1R neurons were found to act as gastrointestinal mechanoreceptors despite their presumed role in nutrient sensing. These neurons accounted for most neurons responsive to gastric distention (81%) and intestinal distention (67.7%); nutrient responses occurred predominantly in GLP1R-negative neurons. Further experiments mapped neuron anatomy and revealed that the GLP1R neurons densly innervated stomach muscle, forming intraganglionic laminar endings.

Interestingly, most neurons innervating intestinal villi were GLP1R-negative and so optogenetic control of gut motility was used to try to identify these neurons. These experiments indicated that GPR65 neurons receive inputs from the gastrointestinal tract. Indeed, the vagal GPR65 neurons were mapped to the duodenal villi, accounting for 57.4% of vagal innervation in the duodenum. These GPR65 neurons were shown to detect serotonin (a key neurotransmitter) *in vitro* and accounted for most of the neurons (66%) responsive to nutrients, acting as chemoreceptors.

Finally, GLP1R and GPR65 neurons were found to segregate to topographically distinct regions of the posterior nucleus of the solitary tract (NTS) in the brain, suggesting that they potentially engage different neural circuits. Vagal GLP1R neurons targeted the medial NTS subnucleus, whereas GPR65 neurons projected to the NTS commissural zone.

The investigators are now planning further work to examine sensory transduction mechanisms of vagal afferents to determine the key sensory receptors and signalling pathways involved in sensing gastrointestinal inputs, as well as examining the role of GPR65 in modulating nutrient responses in health and disease.

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ORIGINAL ARTICLE Williams, E. K. *et al.* Sensory neurons that detect stretch and nutrients in the digestive tract. *Cell* http://dx.doi.org/10.1016/j.cell.2016.05.011 (2016)

FURTHER READING Brookes, S. J. *et al.* Extrinsic primary afferent signalling in the gut. *Nat. Rev. Gastroenterol. Hepatol.* **10**, 286–296 (2013)