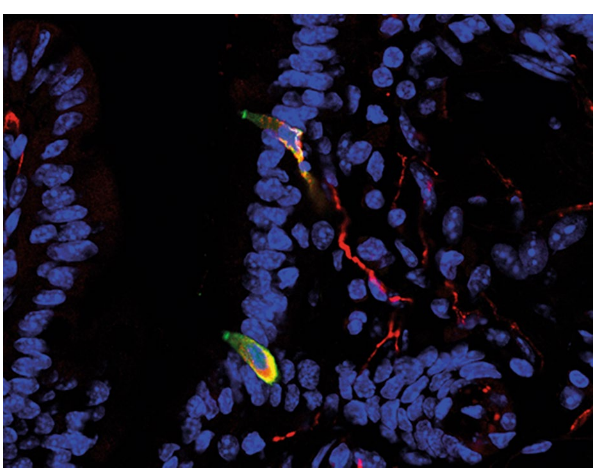
NEUROGASTROENTEROLOGY

A gut–brain neural connection for rapid nutrient sensing

> …sensory signals arising in the gut lumen are only one synapse away from the brainstem

Although gut–brain communication has been recognized for a long time, the underlying neural circuits and sensory transducers have not been well-defined. Now, in a study published in *Science*, a team of researchers have demonstrated that a type of gut epithelial cell they call the neuropod cell synapses with vagal neurons to directly connect the gut with the brainstem, enabling the rapid transduction of nutrient stimuli.

The brain is thought to sense nutrient stimuli indirectly via the release of gut hormones from putative gut epithelial sensors, the enteroendocrine cells (EECs). The gut hormone cholecystokinin, for example, has been proposed as a key signal of satiety, but this hormone peaks in the circulation several minutes after food is ingested and often after a meal has ended. "In fact, it is a mystery what happens from the seconds that nutrients reach the intestinal wall to the minutes that it takes to stop eating," explains senior author Diego Bohórquez. "This dichotomy suggests the gut and the brain exchange signals from nutrients in very fast time scales."



Innervated neuropod cell in a mouse ileum. Neuropeptide Y is stained red, nuclei are blue. Image courtesy of D. Bohórquez, Duke University, North Carolina, USA.

Previously, Bohórquez and colleagues had shown that EECs can synapse with nerves in the gastrointestinal tract, and others had shown that hypothalamic neurons controlling food intake were silenced within seconds of nutrients reaching the intestine. "These findings suggest that, like the nose or the tongue, the gut should have a neural circuit capable of rapidly transducing sensory signals to the brain," says Bohórquez. "To overturn a dogma and uncover the neural basis of a new sense, we knew we had to thoroughly demonstrate the mechanism."

To trace the hypothetical neuroepithelial circuit, the team used a modified fluorescent rabies virus that infects EECs and spreads through synapses onto nerves. After the virus was given to mice by enema, it was observed to spread to nerve fibres in the colon as well as vagal nodose neurons projecting into the nucleus tractus solitarius of the brainstem. These findings demonstrated that sensory signals arising in the gut lumen are only one synapse away from the brainstem.

"We also developed an in vitro system to recapitulate the neural circuit in isolation," reports Bohórquez. "This helped to dissect the neurotransmission mechanisms." Using their in vitro system in electrophysiology experiments, the researchers tested the function of the neuroepithelial circuit to establish whether sugar is sensed by the vagus nerve directly or via EECs. They found that vagal nodose neurons cultured alone did not respond to a glucose stimulus; however, when the neurons were co-cultured with EECs, visible connections between the two cell types were made and glucose now stimulated excitatory postsynaptic currents (EPSCs) and action potentials in the neurons.

Next, the researchers used optogenetic techniques in vitro and in vivo to characterize specificity and transduction speed. In vitro, with vagal neurons connected to EECs expressing a light-excitatory ion channel, a photostimulus elicited EPSCs as fast as 60 ms. Then, in mice bred with EECs that expressed a light-inhibitory channel, nutrient-stimulated activity in the vagal neurons was abolished in the presence of a photostimulus. Together these findings indicate that EECs are required to rapidly transduce a glucose stimulus.

Finally, the investigators tested the hypothesis that glutamate is used by EECs as a neurotransmitter. Using a 'sniffer protein' that fluoresces in the presence of glutamate, EECs were shown to release glutamate in the presence of a glucose stimulus. Additionally, in vagal neurons connected to light-sensitive EECs, photostimulated EPSCs were abolished in the presence of glutamate receptor blockers. Together, these findings show that synaptic glutamate is used by EECs to rapidly transduce luminal stimuli to the brain. In light of these data and because the name 'enteroendocrine' might obscure the role of some synaptically connected EECs as transducers, the researchers refer to these cells as neuropod cells.

"These findings open a field of possibilities," concludes Bohórquez. "For instance, what is the role of this neural circuit in multiple behaviours that rely on food detection, how do neuropod cells sort and encode signals from different nutrients or gut bacteria and, importantly, which gut pathogens hijack this pathway to alter brain function and health?"

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