RESEARCH ARTICLE

NEUROSCIENCE

A gut-brain neural circuit for nutrient sensory transduction

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Premise of paper

- It is known that the gut communicates with the brain, but mechanism is unknown
- Enteroendocrine cells were previously thought to interact with nerves through hormone signaling
- However, hormone signaling is slower than the brain is thought to respond to gut signals, and enteroendocrine cells have neuron-like properties and form synapses
- Thus, **the authors hypothesized that enteroendocrine cells synapse with the vagus nerve to communicate with the brain**

Vagus nerve

- Longest cranial nerve and longest nerve of autonomic nervous system
- Deals with parasympathetic control of heart, lungs, digestive tract

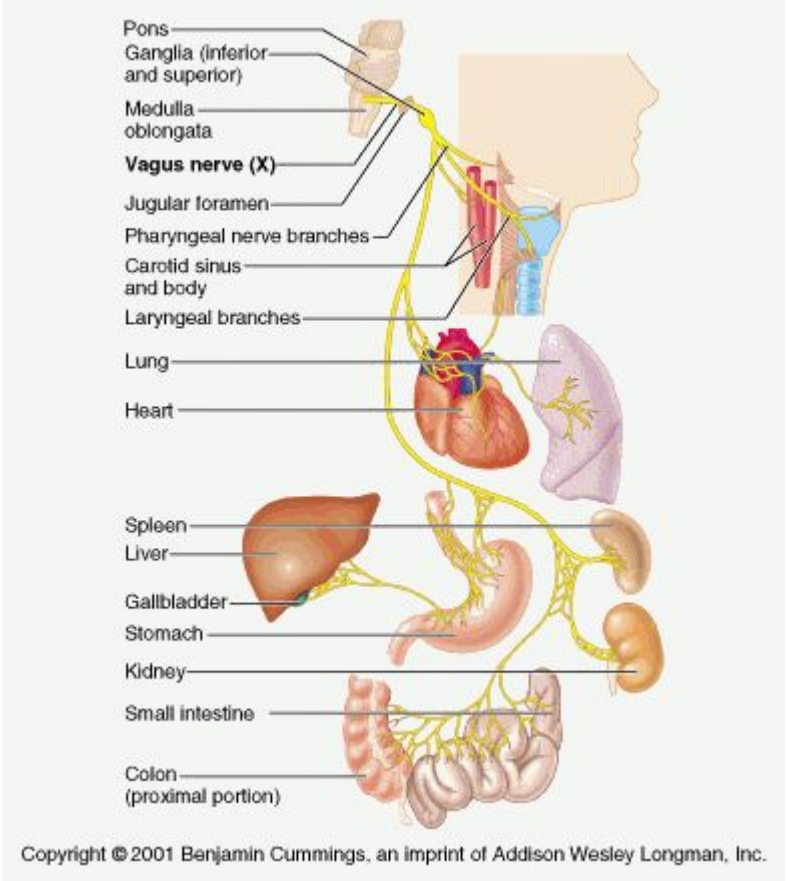
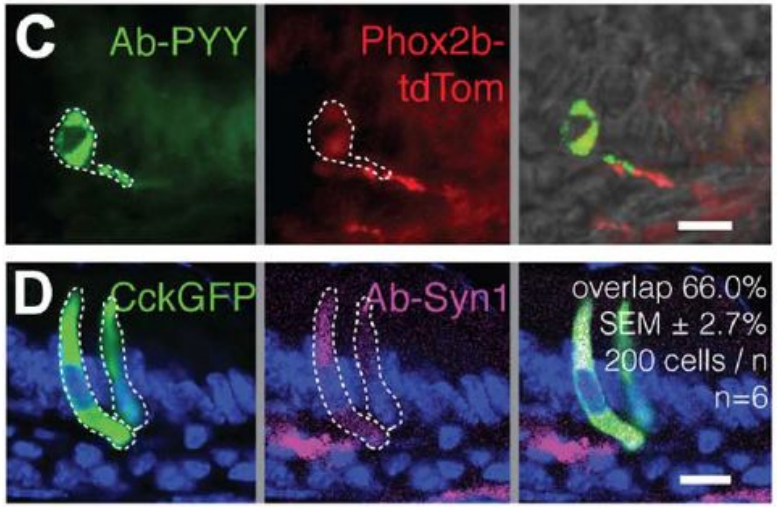
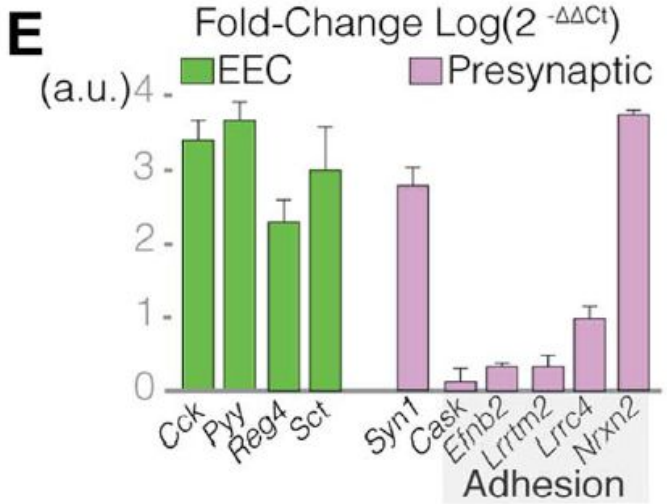


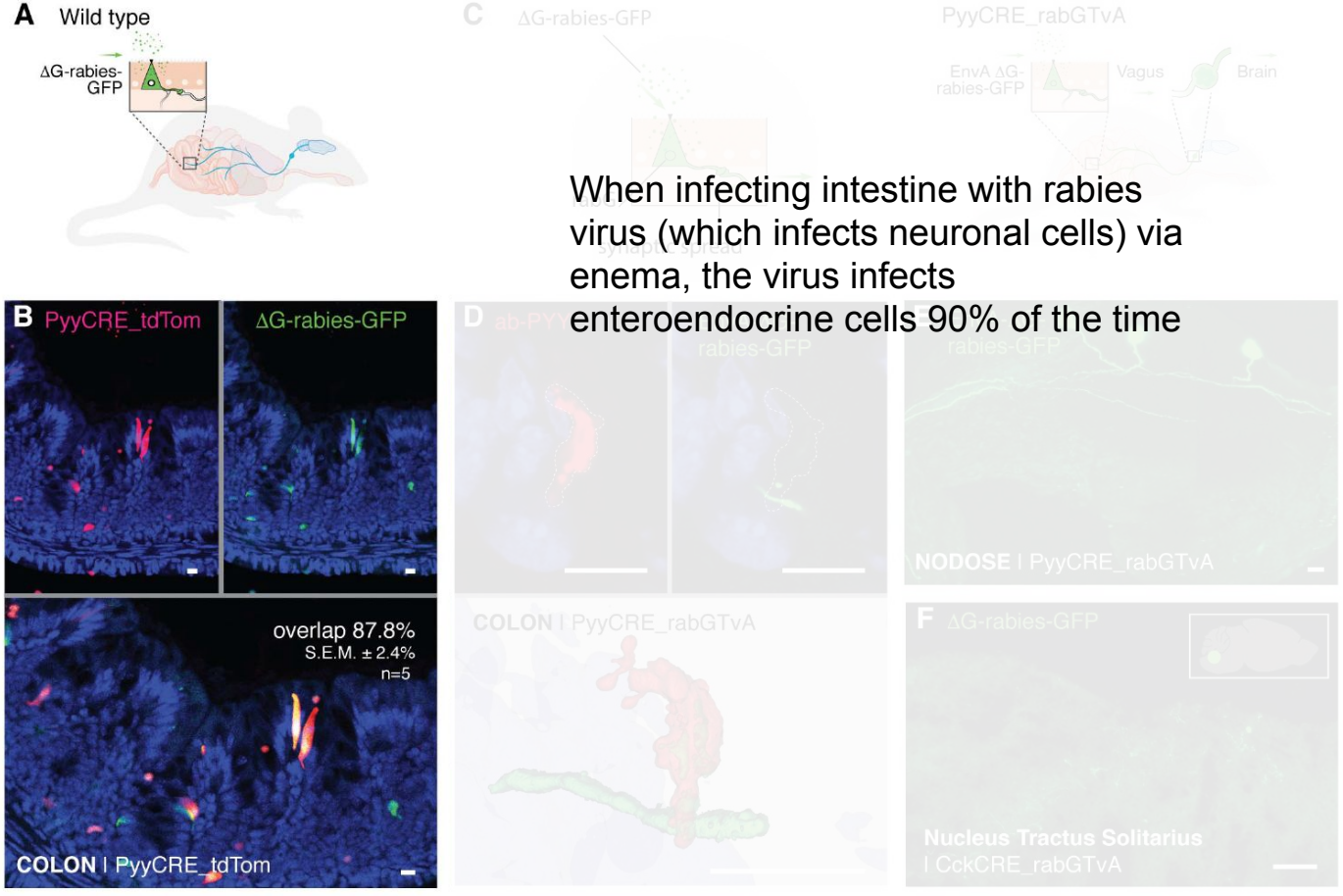
Fig 1: Enteroendocrine cells contact nerve fibers and have neuron-like properties





It seems to have been previously known that enteroendocrine cells synapse with nerves, so this is probably just a confirmation that motivates the rest of the paper.

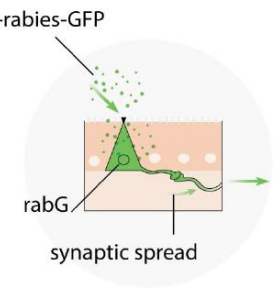
Fig 2: Tracing neurons that enteroendocrine cells synapse with

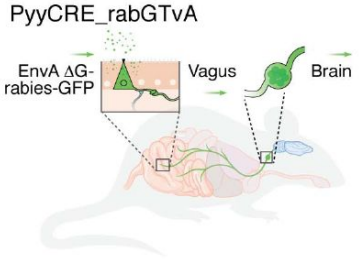


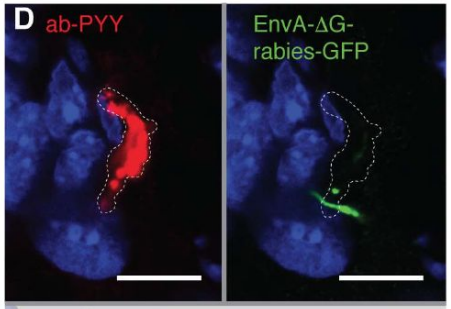
When infecting intestine with rabies virus (which infects neuronal cells) via enema, the virus infects enteroendocrine cells 90% of the time

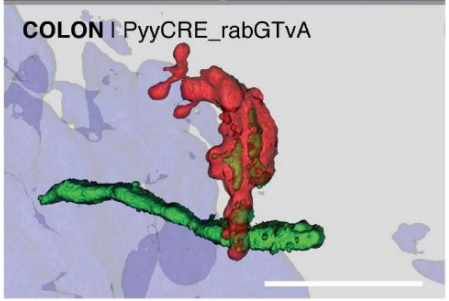
Fig 2: Tracing neurons that enteroendocrine cells synapse with

When enteroendocrine cells express rabG, rabies can transsynptically spread









Restricted rabies infection to enteroendocrine cells using EnvA coating on rabies virus and TvA expression in enteroendocrine cells

Fig 2: Tracing neurons that enteroendocrine cells synapse with

Infection leads to labeling of vagal neurons in nodose ganglion…

But only in 2 out of 9 mice. Is this significant?

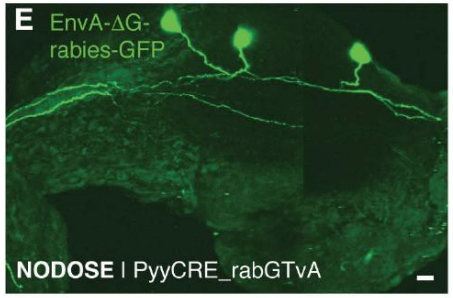
9 mice

5 with visible infection of nerve fibers in colon

4 without

2 with visible infection in vagal nodose

But vagal nodose neurons synapsed with enteroendocrine cells in intestinal organoids which helps to confirm vagal neuron connection.



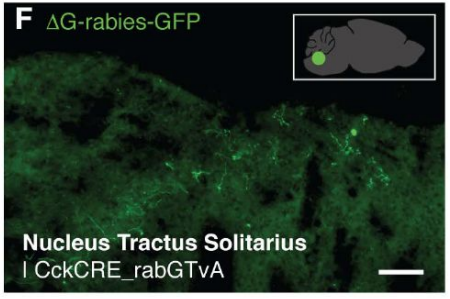
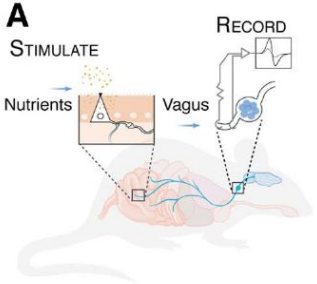
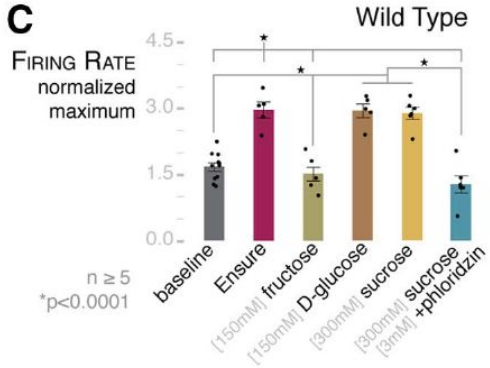


Fig 3: Enteroendocrine cells stimulate vagal nodose neurons in response to glucose

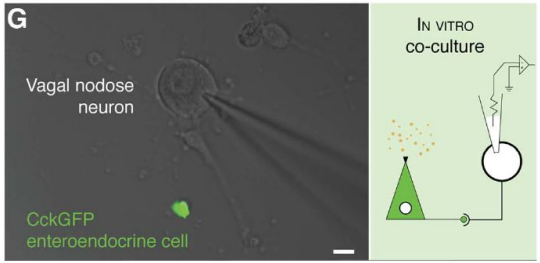
Feeding mice: Vagal nodose neuron firing specific to glucose, as opposed to fructose

- (sucrose = fructose + glucose)





Coculture of vagal nodose neuron + enteroendocrine cell in presence of glucose: vagal nodose neuron firing



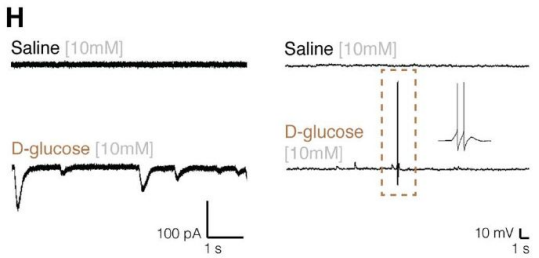


Fig 4: Timing and specificity of enteroendocrine to vagal neuron firing

- Bred a mouse where enteroendocrine cells express channel rhodopsin 2 (ChR2)
- Stimulated coculture with 470nm light (ChR2 specific)
- Measured time delay in firing of vagal neurons: 60-800 ms

- Showed that enteroendocrine cell signaling is essential for vagal neuron sensing of glucose

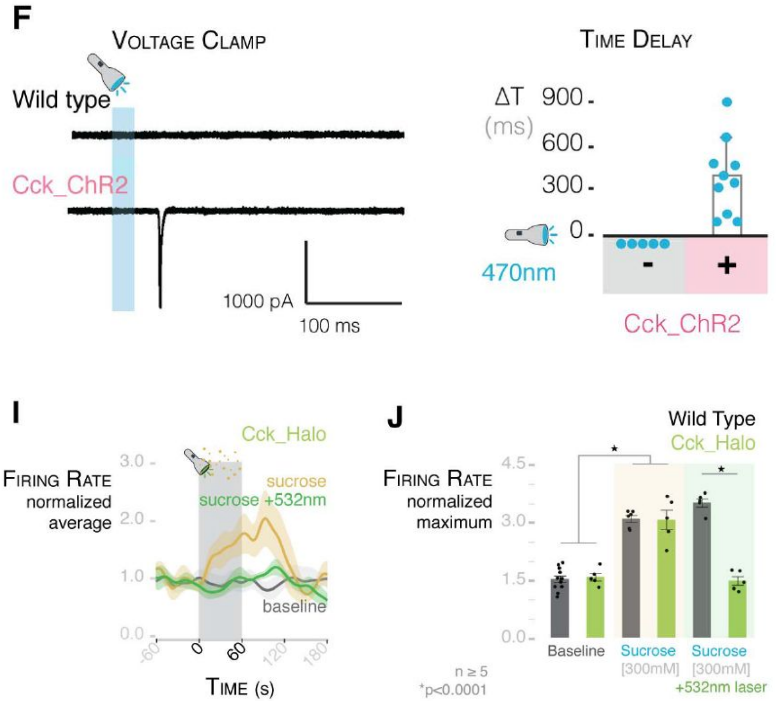
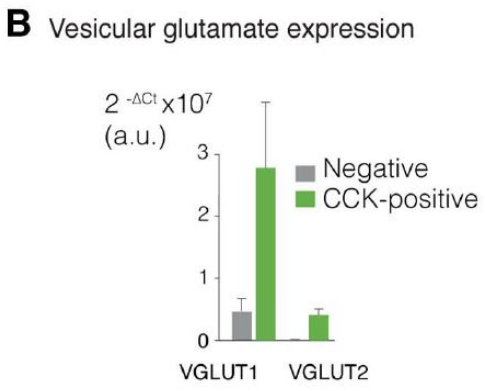
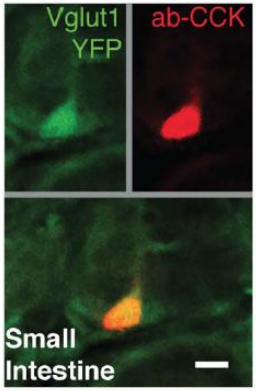


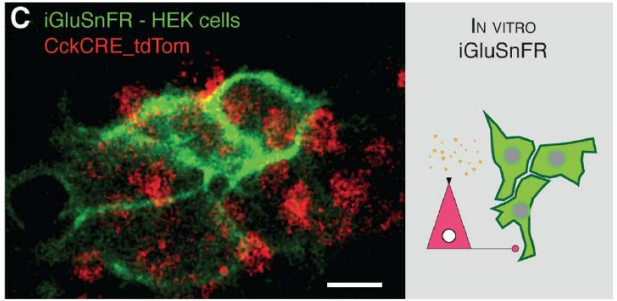
Fig 5: Glutamate is a neurotransmitter between enteroendocrine cells and neurons

- Suspected glutamate as neurotransmitter because
  - Other sensory epithelial cells use glutamate to transduce
  - Expression of glutamate transporter genes (VGLUT1 and VGLUT2) in enteroendocrine cells





- In presence of glucose, HEK cells transfected with membrane protein that fluoresces green in presence of glutamate turns green



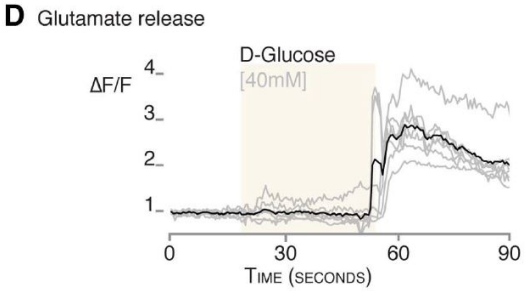
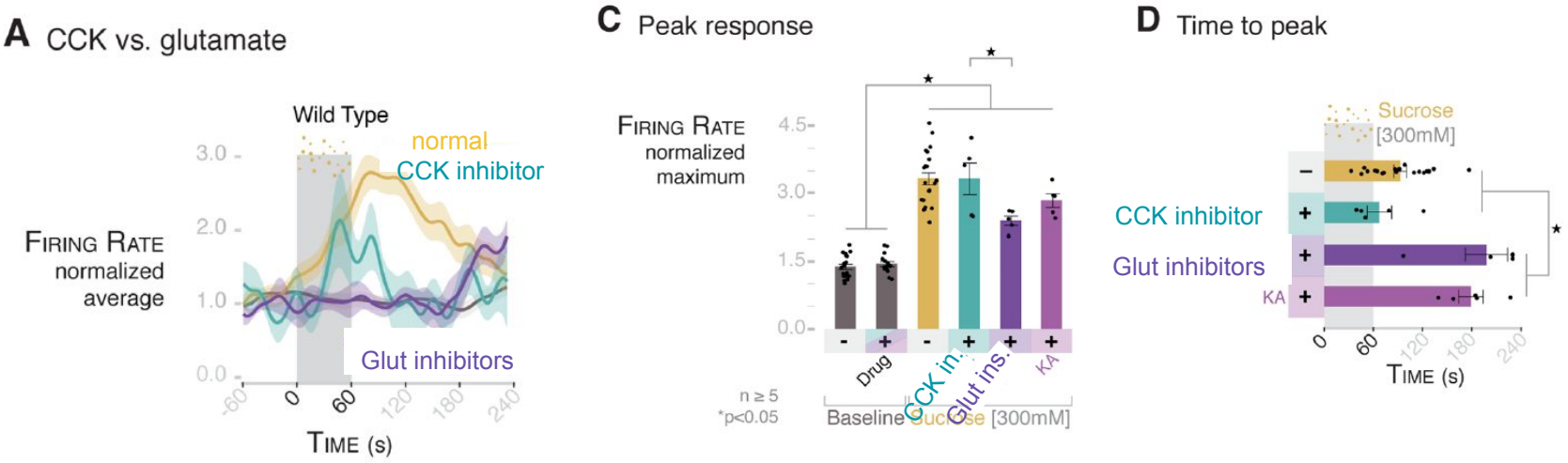


Fig 6: Vagal firing is caused by glutamate (neurotransmitter), not CCK (hormone)



- Using two glutamate receptor blockers significantly inhibits normal vagal firing, whereas a CCK receptor inhibitor does not yield significant changes. This indicates that glutamate, not CCK, is used for enteroendocrine cells to communicate with the CNS via vagal neurons.

Implications of the study

- Neuropod cell = enteroendocrine cells that synapse with nerves (coined by the authors)

- Can lead to studies about
  - How quantity/contents of ingested food affect vagal nodose neuron firing
  - Characterizing sensory information in different regions of GI tract
  - Localized plasticity
  - Monitoring vagus nerve as a way of monitoring GI sensory changes