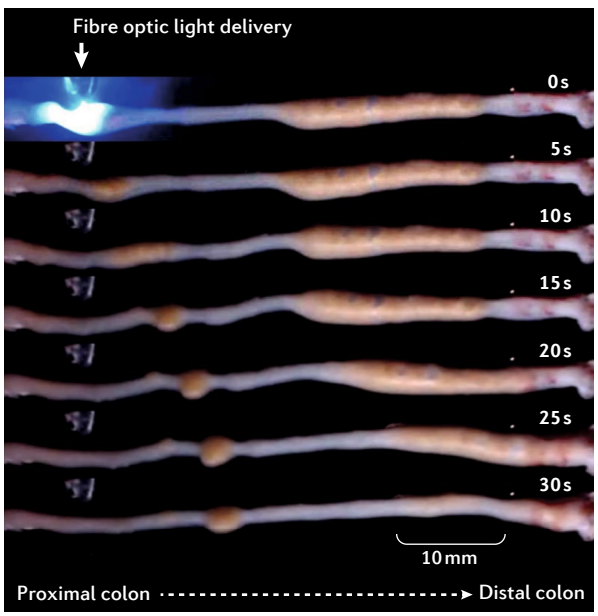
NEUROGASTROENTEROLOGY

Wireless optogenetic control of gut motility

> Focal light stimulation resulted in polarized motor reflexes along the entire length of the colon

A new study published in the journal *Gastroenterology* provides the first demonstration that optogenetic control of enteric nervous system (ENS) activity can evoke propagating contractions of the entire colon in vitro and in vivo. These findings offer the potential of improving gut motility and transit using wireless technologies rather than conventional pharmacological agents that can have unwanted effects.

A unique feature of the gastrointestinal tract is its nervous system. Known as the ENS, it is able to coordinate complex behaviours independently of the central nervous system (CNS). For example, isolated segments of the gastrointestinal tract are capable of producing contractile, propulsive motility without CNS input. This understanding provides opportunities for targeting specific ENS neurons to improve colonic transit for the benefit of patients with chronic constipation. In the latest study, researchers led by Nick Spencer and Hongzhen Hu aimed to establish whether optogenetics could be used for this goal.



In vitro light-evoked motility in colon preparations from optogenetic transgenic mice. Adapted with permission from Hibberd, T. J. et al. (2018), Elsevier.

Optogenetics is a technique in which specific wavelengths of light are used to excite or inhibit cells, typically neurons. To enable such control, neurons are genetically modified to express light-sensitive ion channels; for example, channelrhodopsin-2 (ChR2), which functions as a sensory photoreceptor in algae. "Optogenetics has been around for about 10 years, and many laboratories have been using it to stimulate or inhibit neurons in the brain," explains Spencer. "We realized this approach had not been done in the ENS and there was a major benefit to millions of people if we could offer a new technique that does not have all the unwanted side effects of current drugs used to treat chronic constipation."

First, the investigators bred two different transgenic mice together, generating mice with Cre-mediated expression of ChR2 in calretinin neurons — a subset of myenteric excitatory neurons involved in gut motility. In isolated neurons from the colons of these transgenic mice, the investigators demonstrated light-evoked transmembrane currents and light-evoked depolarization and action potential discharge. Complementing these electrophysiological data, calcium imaging experiments also confirmed that the transgenic mice expressed light-sensitive channels.

Next, using electrophysiological and mechanical recordings of intact whole colon preparations from the transgenic mice, the investigators showed that focal light stimulation resulted in polarized motor reflexes along the entire length of the colon. These reflexes were characterized by proximal contractions and distal relaxations relative to the light-exposed stimulation site and were not seen in control mice or when a neurotoxin was included.

Isolated mouse colons were also set up in an in vitro organ bath with the natural colonic content kept intact. "By applying pulses of blue light to the colon we could activate only the excitatory neurons to cause muscle contraction, leading to the propulsion of colonic content," reports Spencer. After 15 minutes of light stimulation to the mid-proximal colon, a significantly greater proportion of natural faecal pellets were expelled in preparations from the transgenic mice compared with controls.

To demonstrate the efficacy of the optogenetic technique in vivo, the researchers implanted wireless blue-light-emitting diodes (LEDs) into transgenic mice, positioned opposing the proximal colon wall. Following recovery, the mice were put into recording chambers and, after an acclimation period, the LEDs were activated for 1 h. Following light stimulation, the researchers observed significantly increased pellet output in the transgenic mice compared with controls, suggesting that colonic transit can be enhanced in conscious, free-moving mice using a wireless optogenetic approach.

"The most exciting aspect of our future studies is that we can use optogenetics to stimulate the gut in non-transgenic animals," concludes Spencer. "To do this, we use harmless viruses to express ChR2 in enteric neurons. This means we can stimulate the gut in any mammal with an ENS, including humans."

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ORIGINAL ARTICLE Hibberd, T. J. et al. Optogenetic induction of colonic motility in mice. *Gastroenterology* https://doi.org/10.1053/j.gastro.2018.05.029 (2018)