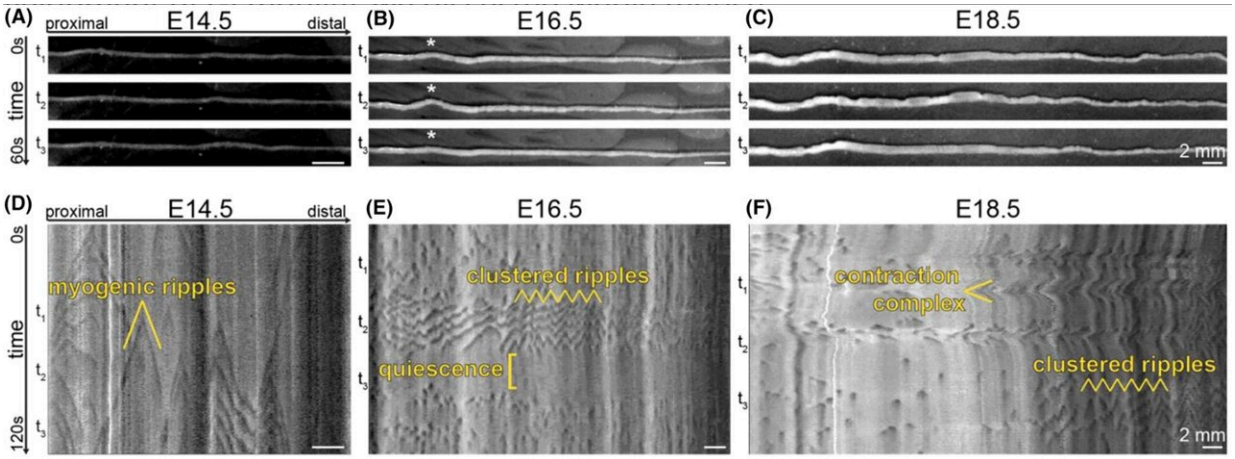
Medical Xpress

Discovery sheds light on a key step in nervous system control over gut motility

September 5 2024, by Nicholas Weiler



Wu Tsai Neurosciences Institute researchers studied isolated mouse intestines (A–C) to identify different patterns of GI motility during embryonic development. Spatiotemporal maps of GI motility revealed the onset of "clustered ripples" around embryonic day 16.5. Credit: Stanford University

Wu Tsai Neurosciences Institute researchers have uncovered a previously unknown pattern of intestinal contractions in developing mouse embryos. The new findings shed light on the earliest development of the nervous system that controls our digestive tract and could have implications for understanding and treating gastrointestinal (GI) disorders in premature infants.

The team published their results August 8, 2024 in the journal *Neurogastroenterology and Motility*.

The enteric nervous system (ENS), sometimes referred to as the "second brain," is a complex network of neurons embedded in the walls of the GI tract. This system autonomously controls various digestive functions, including the rhythmic contractions that propel food along the gut.

Proper ENS development is critical for healthy digestion, and its dysfunction can lead to severe conditions such as Hirschsprung's disease, a life-threatening form of extreme constipation in newborns caused by the lack of neural innervation in parts of the intestine.

Despite its importance, the early development of the ENS and its role in initiating GI motility patterns have remained poorly understood. Julia Kaltschmidt, a Wu Tsai Neurosciences Institute Faculty Scholar and associate professor of neurosurgery, aimed to bridge this knowledge gap by investigating spontaneous neuronal activity in the developing gut.

"Our lab had been able to visually discern a new form of motility in the embryonic mouse intestine. However, to prove that it was truly a distinct form of motility that disappeared when neurons were silenced, we needed to computationally characterize this motility pattern," said Lori Dershowitz, who led the study as an MD/Ph.D. candidate in the Kaltschmidt lab.

To achieve this result, Dershowitz and colleagues struck up a collaboration with Wu Tsai Neuro Faculty Scholar Todd Coleman, an associate professor of bioengineering. "The Coleman lab are experts in computationally assessing GI motility in humans, so we worked together to develop a new analysis in the mouse."

"I am especially excited about this work because it is one of our first

publications with a neighbor here at Wu Tsai Neuro," Kaltschmidt said. "The institute is a very collaborative trans-disciplinary environment, and I think this publication, spanning neurosurgery and bioengineering, nicely showcases the importance of such multi-group collaborations."

A novel discovery: Clustered ripples

Using advanced ex vivo GI motility assays and sophisticated computational analyses, the researchers identified a novel pattern of contractions driven by ENS activity, which they dubbed "clustered ripples."

These contractions could be observed as early as embryonic day 16 in mice, and are the earliest known case of the ENS driving GI motility. Unlike mature motility patterns, clustered ripples consist of dynamic clusters of contractions that occur simultaneously across the length of the small intestine, followed by periods of quiescence.

The team demonstrated that these clustered ripples are driven by spontaneous activity in enteric neurons and are dependent on the neurotransmitter acetylcholine. When they blocked neural signaling pharmacologically, the ripples disappeared.

"These waves depend on ENS activity, yet they precede all propulsive forms of GI motility," said Dershowitz, now a postdoctoral scientist at Massachusetts General Hospital. "To us, this suggests that clustered ripples are a precursor to mature forms of motility. "

Implications for pediatric GI disorders

The study highlights a critical period in ENS development where spontaneous neuronal activity plays a pivotal role in establishing GI

motility patterns. The discovery of clustered ripples has significant implications for pediatric health care, particularly for preterm infants who often exhibit immature GI motility.

"Understanding the development of GI motility is clinically significant, as immature GI motility is a major source of mortality for preterm infants," Kaltschmidt explained. "Pro-motility drugs used in adults have failed to enhance GI motility in the preterm population."

The findings in mice are likely to have direct relevance to human physiology, the authors argue.

"It was exciting to realize that the motility pattern we are characterizing is reminiscent of a pattern we previously noted in humans," Dershowitz said. "At the time, we did not understand what we were observing, but now we can show that the development of mouse and human GI motility are very similar."

Understanding these early motility patterns could lead to new therapeutic strategies to enhance GI function in preterm infants, the researchers say, potentially improving their survival and quality of life.

Future directions

While this study provides valuable insights into the early development of the ENS, further research is needed to explore the functional significance of clustered ripples and their potential as therapeutic targets.

"We are excited to test whether drugs that are safe to use in human neonates can accelerate development of GI motility," Dershowitz said.

More information: Lori B. Dershowitz et al, Spontaneous enteric nervous system activity generates contractile patterns prior to maturation

of gastrointestinal motility, *Neurogastroenterology & Motility* (2024).
DOI: 10.1111/nmo.14890