

EDITORIAL COMMENTARY

FROM 'MACRO' TO 'MICRO': MAPPING THE NEURONAL CIRCUITS OF THE INTESTINE

The gastrointestinal (GI) tract is the main organ for the digestion and absorption of food, as well as contributing to water balance and immune function. It is also a very long organ, running more than 6 m in the human. Coordinating the complex functions of such an extended organ is a difficult task. Fortunately, the GI tract comes with its own network of neurons, which are present within the wall of the intestine and are known collectively as the enteric nervous system (ENS). The GI tract is unique among the organs of the body in having a large degree of freedom from central control. The central nervous system, by way of the sympathetic and parasympathetic nervous systems, provides overall modulation of the intestine, but we now know that the ENS is responsible for the moment-to-moment coordination of whole organ behaviours. One outstanding question is how we get from the whole organ or 'macro' level to the 'micro' level of individual neurons and muscle?

Studies of GI motility at the macro level began more than a hundred years ago. Small segments of intestine were examined and found to contain everything required for sustaining simple reflexes. Consequently, important patterns of GI motility were identified, such as peristalsis, segmentation and the migrating motor complex, all of which rely on the ENS for initiation, integration and propagation (for a review, see Bornstein *et al.*¹). In the 1970s, new electrophysiological methods were introduced that allowed investigations to focus on the micro level of GI function. With these intracellular techniques, individual neurons were recorded and fast ligand-gated and slow G-protein-coupled synaptic transmission were demonstrated (for reviews, see Galligan² and Wood and Kirchgessner³). Similar recordings from smooth muscle cells have revealed many of the neurotransmitters that control GI motility⁴ and have helped determine neuronal projection lengths.^{5,6} These later studies used a fixed stimulating electrode and manually moved a single recording electrode to identify the functional projections of the enteric motor neurons. Although elegant in design, data collection with these methods was painstaking and inefficient. Moreover, the link between the single cell recordings and the behaviour of the whole organ was lost.

The paper by Sibaev *et al.*⁷ in the current issue of the Journal has made an excellent attempt to overcome these limitations and relate observations at a macro level with the activity of individual cells at a micro level. They did this by using an innovative 12-channel array of stimulation electrodes mounted within an organ bath. This allowed them to use a single recording electrode to make multiple recordings of junction potentials over different distances. This significantly increased the efficiency in identifying the functional distances that myenteric neurons project. With this new technique, the investigators have shown that in proximal mouse colon the excitatory neural input from the ascending neuronal microcircuit to

the smooth muscle cells is entirely via nicotinic neurotransmission and have deduced that the maximal distance the ascending myenteric neurons can reach functionally is approximately 20 mm. The total length that the ascending signal travels in a single motor neuron (i.e. without a synapse) is just over 10 mm. These values agree well with previous studies from guinea-pig ileum and were obtained without errors in manual placement of the stimulating or recording electrode.

A very interesting observation in the study of Sibaev *et al.*⁷ is that an orally transmitted inhibitory input to the smooth muscle cells can be recorded up to a distance of 10 mm. If these mechanisms occur physiologically, they may be involved in phenomena such as retrograde propulsion. Another important achievement is that the investigators correlated their electrophysiological data, which shows that the ascending reflex is primarily nicotinic, to an *in vivo* whole organ study, in which colonic expulsion is delayed significantly by a nicotinic receptor antagonist.

One limitation of the study of Sibaev *et al.*⁷ is that the inhibitory input to the smooth muscle cells in the ascending microcircuitry was not examined further. The authors have made a very plausible argument that this input is from the terminals of the orally projecting inhibitory motor neurons that are antidromically excited by electrical stimulation. It will be interesting to see whether this inhibitory transmission in the ascending microcircuit exists when more physiological stimuli, such as distension of the gut wall, are used.

Overall, this study on enteric motor pathways has provided a glimpse into processes that bridge the gap between whole intestinal segments and individual neurons and muscle that are contained therein. We hope that, in future, it will be possible to combine the advances made here with further technical improvements that use multiple, simultaneous recording sites on the smooth muscle. These types of data are critical for an understanding of how single nerves and muscle conspire to control the actions of the GI tract.

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