Intrinsic sensory neurons of mouse gut – towards a detailed knowledge of enteric neural circuitry across species.

Focus on “Characterization of myenteric sensory neurons in the mouse small intestine”

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The enteric nervous system of the gut is largely self-contained and includes intrinsic sensory (or primary afferent) neurons, a variety of interneurons and several classes of motor neurons (Bornstein et al 2002; Furness et al 2004a). Detailed studies of guinea pig ileum have identified all of these neurons and allowed construction of a model neural circuit that accounts for some intestinal behaviors (Bornstein et al 2002; Furness et al 2004a). Computer simulations indicate that complex behaviors can arise from neural interactions within this circuit and are starting to clarify the regulation of intestinal movements (Thomas and Bornstein 2003; Thomas et al., 2004). The central elements of this model are the intrinsic sensory neurons, which form recurrent excitatory networks (Thomas and Bornstein 2003; Bornstein et al 2002; Thomas et al 2004). Inflammation enhances firing in these neurons (Palmer et al 1998), which have therefore been identified as prime targets for drug therapies directed at gut disorders (Clerc et al 2002). However, despite their importance, no direct evidence as to the identity of intrinsic sensory neurons in other species has been available until now. This highlights the significance of the study reported in this issue of *Journal of Neurophysiology* (page numbers), which shows that a specific morphological and physiological subclass of neurons in mouse small intestine has mechanosensitive processes within the myenteric plexus and are virtually identical to an equivalent neuronal class in the guinea pig (Mao et al 2006).

Correlated electrophysiological, immunohistochemical and morphological studies of myenteric neurons that respond directly to physiological stimuli have identified intrinsic sensory neurons in guinea pig small intestine. These all have large smooth cell bodies and multiple axonal processes, most have very few dendrites and their axons typically project circumferentially around the intestine. In guinea pig, this
morphological class of neurons, Dogiel type II neurons, have common
electrophysiological properties (Bornstein et al 1994). Their action potentials are
followed by prolonged (> 4 s duration) and substantial (often up to 15 mV) after-
hyperpolarizing potentials (AHPs). They are termed AH neurons from this
characteristic. Neurons with the Dogiel type II shape were postulated to have a
sensory function over century ago (Dogiel 1899), while the suggestion that AH
neurons are sensory dates back to 1974 (Hirst et al 1974). However, it was only
recently shown that AH/Dogiel type II neurons respond directly to physiological
stimuli. Acid and neutral acetate applied to the mucosa (Kunze et al 1995; Bertrand
et al 1997), maintained increases in muscle tension (Kunze et al 1998, 1999) and
mechanical deformation of myenteric ganglia (Kunze et al 2000), all evoke action
potentials in these neurons independently of synaptic input.

AH neurons and/or neurons with Dogiel type II morphology are seen in mouse
(Furukawa et al 1986; Ren et al 2003; Nurgali et al 2004), rat (Brookes et al 1988),
pig (Cornelissen et al 2000) and human (Dogiel 1899; Brookes et al 1987) as well as
in gut regions beyond the small intestine in the guinea pig. However, several studies
challenge extrapolation of conclusions from guinea pig small intestine to other
preparations. Colonic AH neurons in guinea pig do not fire during maintained stretch;
the neurons that do fire appear to be orally directed interneurons (Spencer and Smith
2004). Further, Dogiel type II neurons in pig small intestine rarely exhibit prominent
AHPs (Cornelissen et al 2000). Similarly, the neurochemistry of the AH/Dogiel type II
neuron in guinea pig and mouse is distinctly different with the latter expressing
calcitonin gene-related peptide, although the former do not (Furness et al 2004b).
However, although some properties of Dogiel type II neurons clearly vary between
preparations, there has been no test of whether these variations reflect changes in
the basic properties (e.g. mechanosensitivity) needed for them to be intrinsic sensory
neurons.

Mao et al (2006) used whole cell and sharp electrode recordings to characterize
myenteric AH neurons of mouse small intestine. They confirmed that these neurons
have Dogiel type II morphology via intracellular injection of Neurobiotin. They are
almost identical in membrane properties, and the ion channels they express, to the
equivalent neurons in guinea pig small intestine (Rugiero et al 2002). However, the
key finding is that probing the preparation’s surface with a calibrated von Frey hair
evoked bursts of action potentials in the AH/Dogiel type II neurons, even during
synaptic blockade. Thus, these neurons have mechanosensitive processes within
the myenteric plexus, providing powerful support for the conclusion that Dogiel type II
neurons are mechanosensory neurons wherever they are found. While other
neuronal subtypes may share this function, as in the guinea pig colon, the findings of
Mao et al (2006) indicate that Dogiel type II neurons are likely to be the major
population of intrinsic sensory neurons in all parts of the intestine.

Mao et al (2006) also found that murine AH/Dogiel type II neurons respond to
stimulation of interganglionic connectives with slow excitatory synaptic potentials.
This is an essential feature of recent computational models of neural circuits in
guinea pig small intestine (Thomas and Bornstein 2003; Thomas et al 2004).
Together with the strong similarity in membrane properties of AH/Dogiel type II
neurons in mouse and guinea pig, these data suggest that the models can make
reliable predictions about circuit behaviour across different species. Thus, the results
of Mao et al (2006) provide a key confirmation of the general relevance of the already published studies of guinea pig ENS, and set the scene for further studies in the favored species for studies of transgenic and mutant animals.

References


Cornelissen W, de Laet A, Kroese ABA, Van Bogaert P-P, Scheuermann DW, and Timmermans J-P. Electrophysiological features of morphological Dogiel type II


