Intrinsic Sensory Neurons of Mouse Gut—Toward 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 (Bornstein et al. 2002; Thomas and Bornstein 2003; 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 by Mao et al. 2006 in this issue of Journal of Neurophysiology (p. 998–1010), 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.

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 ≥15 mV) afterhyperpolarizing 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 (Bertrand et al. 1997; Kunze et al. 1999) 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; Nurgali et al. 2004; Ren et al. 2003), rat (Brookes et al. 1988), pig (Cornelissen et al. 2000) and human (Brookes et al. 1987; Dogiel 1899) 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. Although other neuronal subtypes may share this function, as in gut regions beyond the small intestine in the guinea pig, 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 behavior 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 enteric nervous system and set the scene for further studies in the favored species for studies of transgenic and mutant animals.

REFERENCES


