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Multifunctional mechanosensitive neurons in the enteric nervous system

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ABSTRACT

One of the most intriguing abilities of the gut is to function in isolation. This is possible because the gut's own nervous system, the enteric nervous system, contains the necessary elements to control reflex behaviors. Much progress has been made in identifying those neurons that encode mechanical or chemical stimuli. Thus, muscle behaviors in the small and large intestines depend on mechanosensitive neurons which encode a variety of mechanical stimuli, ranging from brief deformation of the neurons soma or processes to sustained tissue stretch. Mechanosensitivity has been recorded in a wide variety of neurons which behave like rapid or slowly adapting mechanosensors. Strikingly, mechanosensitive neurons do not appear to belong to a distinct class of highly specialised neurons but rather differ in their electrophysiology, neurochemistry and morphology. While some mechanosensitive neurons may respond to one stimulus type others appear to be polymodal. Available data would suggest that mechanosensitive enteric neurons are multitasking and hence belong to multifunctional circuits. This review summarises the main arguments in favour of this concept, discusses the stimulus modalities, the response patterns and the functional role of mechanosensitive enteric neurons and concludes with identifying future challenges.

1. Stimulus encoding pathways in the enteric nervous system

The enteric nervous system (ENS) is a ganglionated network located within the gut wall and consists of about 100 million nerve cells. The ENS can function independently of the central nervous system (CNS) because it contains the full reflex pathways that control gastrointestinal functions such as motility and secretion. Many nerve evoked reflexes are intrinsic to the intestinal wall, as they are preserved following extrinsic denervation (Furness et al., 1995). The purpose of this review is to summarise current views on sensory processing within the ENS with particular focus on the concept that many mechanosensitive enteric neurons are in fact multifunctional. Multifunctional circuits account for the capability of individual neurons to generate a wide variety of activity patterns depending on their state of modulation, synaptic input, and plasticity (Briggman and Kristan, 2008). According to this concept organ behaviors may be driven by the concerted actions of multifunctional neurons as opposed to simple pathways dedicated to one function only. The correlation of neuronal activity with sensory input and behavioral output has revealed that information is often encoded in the activity of many neurons across a population, that is, a neural population code is used.

Neuroanatomical tracing techniques in combination with multiple-labelling immunohistochemistry have been helpful to reveal functional classes of enteric neurons and their possible role in reflex behavior (Brookes, 2001). Based on characteristic combinations of morphological features, projections, biophysical properties, neurochemical profile, and receptors such studies identified different classes of neurons, including sensory neurons, muscle motor neurons, interneurons, secretomotor and vasomotor neurons. Such studies were the basis to suggest that reflex behaviors in the gut can be attributed to a direct pathway from sensory neurons via interneurons to motor neurons. The current concept suggests existence of hard-wired motor programs; such a circuit consists of chemo- and/or mechanosensitive neurons that activate via interneuronal pathways ascending excitatory and descending inhibitory muscle motor neurons. However, there is now evidence for far more distributed interactions, in particular at the pre-effector level. The identification and characterisation of sensory neurons have received particular attention in order to conceptualise the intriguing capability of the gut to function in isolation. Moreover, understanding of sensory pathways in the ENS has a translational aspect as it may reveal novel strategies to normalise impaired sensory functions that occur in gastrointestinal disorders.

Based on their electrophysiological properties one can distinguish two main classes of enteric neurons, notwithstanding existence of additional subtypes and some plasticity in their behavior (see Nurgali, 2009). The first class is named AH because of its prominent slow hyperpolarisation following spikes which are primarily carried by calcium influx. AH neurons receive slow, but rarely, fast synaptic input. Most AH neurons have multiple long processes and this morphology classifies them as Dogiel type II neurons. The second class

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is referred to as S neurons because these neurons receive numerous fast excitatory synaptic potentials in addition to receiving slow synaptic input. Their action potentials are mainly carried by sodium influx. Most S neurons are Dogiel type I neurons because they have only one long process, presumably the axon, and several short processes which very likely are dendrites.

Stimulus encoding enteric neurons have been termed intrinsic sensory neurons, enteric sensory neurons or intrinsic primary afferent neurons (IPANs), the latter being extensively used (Bornstein, 1994; Bertrand and Thomas, 2004; Furness et al., 2004; Gershon, 2005). A lot of confusion arose around the concept of sensory transmission in the ENS, mainly because of misconception, false extrapolations of concepts derived from guinea-pig ileum to other gut regions or species, and unnecessary arguments about semantics. Those issues have been discussed in detail elsewhere (Grundy and Schemann, 2005; Blackshaw et al., 2007). Another issue is the misconception that the stimulus encoding neuron in the ENS ought to be a highly specialised neuron which therefore must fulfil the same criteria described for dedicated sensory neurons in other nervous systems. Therefore, it appears inappropriate to apply the terminology "sensory" to enteric neurons, despite its rather broad use in neuroscience (Kandel et al., 1995). In order to avoid further confusion, we recommend the use of terms that specify stimulus modalities and response patterns of those enteric neurons that directly respond to mechanical stimulation rather than generic terms.

There is strong evidence for the existence of mechanosensitive neurons in the ENS and their relevance for adjusting reflex muscle behavior. This conclusion is based on the discovery that interneurons (Kirchgessner et al., 1992; Furness et al., 2004; Smith et al., 2007) and probably even motor neurons (Mazzuoli et al., 2008; Mazzuoli and Schemann, 2009) exhibit mechanosensitivity. Nevertheless, one cannot disregard the possibility that reflex behavior is initiated by specialised non-neuronal cells that function as primary sensory cells. This has been well documented for neuronal representation of chemical stimuli. Changes in the chemical milieu are coded by chemosensory enteroendocrine cells of the mucosa that activate endings of enteric neurons following the release of their mediators (Kirchgessner et al., 1992; Bertrand et al., 1997). On the other hand, there is evidence that some myenteric AH and S neurons directly respond to nutrients and protons (see method section in Schemann and Kayser, 1991; Bertrand et al., 1997; Neunlist et al., 1999). It remains controversial whether this reflects chemosensitivity or merely another way to modulate neuronal activity.

2. Anatomical basis for multifunctional enteric neurons

A substantial proportion of enteric neurons are multifunctional or multitasking as opposed to the classical view that a sole function can be assigned to a particular neuronal population. As discussed below, this seems also and in particular true for those neurons that encode mechanical stimuli. The concept of multifunctional enteric neurons has already been proposed in the 70s where spontaneously active enteric neurons (pacemaker units) were suggested to be multifunctional providing input to both neurons and muscle (Wood, 1970). In the myenteric plexus of the stomach, multitargeted neurons with projections to the muscle layers, mucosa and other myenteric neurons have been identified (Schemann and Schaaf, 1995). That they are multitasking is indicated by the target specific projections of collaterals that all arise from one long process, presumed to be the axon. The same is true for Dogiel type II neurons in the myenteric plexus (Furness et al., 1988). This type of neuron, which makes up about 30% of enteric neurons, has a large smooth cell body and multiple long processes, most of which project to other neurons, some to the mucosa and few to the muscle layer. Thus, Dogiel type II neurons make interneuronal connections and are important to gate excitability spread in enteric networks (Wood, 2004).

3. Mechanosensitive enteric neurons

Mechanical activity is almost constantly present in the gut. Since the myenteric plexus is sandwiched in between two muscle layers, any muscle movement will cause distortion of ganglia in all axes. Thereby, cell bodies and processes of enteric neurons are exposed directly to the mechanical forces that they control. In the 70s extracellular recordings from myenteric ganglia that have been mechanically stimulated by pressing a probe onto the ganglion surface revealed mechanosensitive neurons. This stimulus had to produce a visible dimple in the ganglia in order to evoke action potentials suggesting that light touch of a ganglion is ineffective. Mechanical distortion of myenteric ganglia, but not of interganglionic fiber tracts, for only a couple of seconds caused spike discharge in some neurons but was not a general property of all myenteric neurons (Wood, 1970). In fact, in this study only 1–2 neurons per ganglion responded to ganglion distortion. Mechanosensitive neurons belonged to three classes based on their discharge patterns: rapidly adapting neurons which fired spikes only during the initial period of distortion, slowly adapting neurons which discharged spikes throughout the deformation stimulus and tonic type neurons whose spike discharge outlasted the deformation stimulus for several seconds (Wood, 1970; Wood and Mayer, 1974). The temporal association of discharge patterns suggested that phasic type mechanosensitive neurons trigger activity in tonic type neurons (Wood and Mayer, 1974).

Intracellular recording techniques allowed further electrophysiological characterisation of the mechanosensitive neurons. Most mechanosensitive neurons in the myenteric plexus of the guinea-pig and mouse small intestine have Dogiel type II morphology (Kunze et al., 1998; Mao et al., 2006). These neurons are AH neurons because they exhibit a long lasting after spike hyperpolarisation. Most neurons in the guinea-pig ileum myenteric plexus responding to both stretch and contraction with an ongoing action potential discharge are AH/Dogiel type II neurons (Kunze et al., 1998; Kunze and Furness 1999). The neuronal discharge pattern suggests activation of slowly adapting mechanosensors. The response to sustained stretch depends on an increase in smooth muscle tension because action potentials were abolished by drugs that paralyse the muscle despite maintained stretch (Kunze et al., 1998; Kunze and Furness, 1999; Kunze et al., 2000). The signals associated with increase in muscle tension are transmitted by yet unknown mechanisms to mechanosensitive structures on AH/Dogiel type II neurons. Other myenteric AH/Dogiel type II neurons are activated during tissue stretch by synaptic transmission (Kunze et al., 1999), reemphasizing the concept that these neurons are part of a self reinforcing network. Interestingly, AH/Dogiel type II neurons, as well as S Dogiel type I neurons, respond, even in paralysed tissue, to rapid stretch with a discharge pattern typical of fast adapting mechanosensors (Kunze et al., 1999). This finding emphasizes the importance of the stimulus modality to evoke action potentials in mechanosensitive neurons. Thus, rapid deformation, that more closely mimics changes in contracting tissue than sustained stretch does, exerts effective forces onto neurons. The results suggest that mechanosensitive AH/Dogiel type II neurons in the myenteric plexus of the ileum are able to directly encode dynamic changes but do not respond to sustained stretch of the ganglion network, except when the muscle is allowed to develop tension which leads to activation of mechanosensitive structures.

In line with this conclusion, AH/Dogiel type II neurons respond to mechanical deformation of myenteric ganglia with a von Frey hair in the mouse small intestine (Mao et al., 2006). The response remains after synaptic blockade. Their discharge pattern would suggest activation of rapidly adapting mechanosensors. Apparently, responses are elicited only when probing processes of the neuron. Distortion of extraganglionic areas that even causes movement of the soma did not evoke any response. These findings suggest that responses to