Neuroanatomy of visceral nociception: vagal and splanchnic afferent

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Afferent fibres convey sensory information from the upper gastrointestinal tract to the central nervous system but the nature of this information is different for vagal and spinal pathways. Vagal afferents convey predominantly physiological information while spinal afferents are able to encode noxious events. Because of the different response profiles following activation of these pathways, it is likely that vagal and splanchnic afferents play different roles in mediating sensation.

SUMMARY
The rich sensory innervation of the gastrointestinal tract comprises intrinsic sensory neurones contained entirely within the gastrointestinal wall, intestinofugal fibres that project to prevertebral ganglia, and vagal and spinal afferents that project into the central nervous system (CNS). Vagal mechanosensitive fibres extend into the muscle where, together with intraganglionic lamina endings (IGLE), they form a transduction site for mechanosensitivity. These afferents are responsible for low threshold activity. They both facilitate and inhibit sensory transmission through the spinal cord and are probably involved in emotional and behavioural aspects rather than pain cognition. The spinal afferents encode both physiological and supraphysiological levels of intestinal pressure and therefore form the main pathway for mediating pain perception. Spinal afferents releasing calcitonin gene related peptide (CGRP) are closely associated with blood vessels and ganglia, indicating that they modulate local reflex traffic and regulate blood flow. These mechanisms probably have a cytoprotective effect in the event of injury or inflammation. Spinal afferents have a more promiscuous type of chemosensitivity as opposed to a specific chemical sensitivity that may be involved in signal transduction of vagal afferents. Because of the different response profiles and different distribution patterns of second order neurones activated by these pathways, it is likely that vagal and splanchnic afferents play different roles in mediating sensation.

INTRODUCTION
Afferent fibres convey sensory information from the upper gastrointestinal tract to the CNS via vagal and splanchnic nerve pathways. In the case of the vagus nerve, afferent fibres outnumber efferent fibres by 10 to 1. The density of splanchnic afferents is more scant with <7% of sensory cell bodies in the thoracolumbar region of the spinal cord projecting to the viscera. However, even when both vagal and spinal afferents are considered together, these are greatly outnumbered by the millions of sensory neurones that are part of the enteric nervous system (fig 1). These intrinsic afferents provide the basis for local reflexes that control and coordinate gastrointestinal function. However, as these intrinsic afferents do not project beyond the bowel wall, they do not contribute to visceral sensations except indirectly as a consequence of changes in secretomotor activity. Intestinofugal fibres of myenteric origin project to the prevertebral ganglia and reflexly influence the sympathetic innervation to the intestinal wall, again without being involved in visceral perception.

Thus there is a dense intrinsic sensory innervation that serves to control motility and secretory function in response to the local environment in the gastrointestinal wall or lumen. Sensory information is conveyed to the CNS by a relatively small number of vagal and spinal nerves. This allows the CNS to construct a “global picture” of events in the bowel and provides the afferent limb of sympathetic and parasympathetic reflexes to coordinate regions of the gastrointestinal tract that can be physically metres apart. These extrinsic afferents are also involved in behavioural responses associated with feeding and illness and also mediate sensations including pain and discomfort.

THE AFFERENT INNERVATION

Neurophysiology
The cell bodies of vagal and spinal visceral afferents are contained within the nodose and dorsal root ganglia. Central projections of these neurones enter the brain stem and spinal cord, respectively, and make synaptic connection with second order neurones that distribute visceral information throughout central neuronal structures. In particular, ascending spinal pathways project ultimately to thalamic nuclei involved in cognition. The receptive fields of neurones responding to visceral stimuli also respond to stimulation of somatic receptive fields indicating that both visceral and somatic information converge on to spinohalamic, spinoreticular, and the more recently described dorsal column pathways that are responsible for the phenomenon of
referred pain. Projections from the nucleus tractus solitarius are mainly to hypothalamic and limbic structures associated with behavioural and emotional aspects of sensory processing.

The peripheral terminals of vagal and spinal afferents can be localised within the gastrointestinal wall using antegrade tracing techniques. Their location in mucosal layers, muscle, and in the serosa and mesenteric attachments are consistent with their responses to stimuli acting at these different sites within the gastrointestinal wall. Nerve terminals in the serosa are believed to convey mechanosensory information respective to distension and contraction of the bowel wall. However, the afferent information conveyed by vagal and spinal mechano-sensitive afferents is very different, as revealed by direct electrophysiological recordings of afferent traffic en route to the CNS. Vagal afferents have low thresholds of activation and reach maximal responses within physiological levels of distension. In contrast, spinal afferents, although many have corresponding thresholds for activation, are able to respond beyond the physiological range and encode both physiological and noxious levels of stimulation. This different stimulus-response profile is consistent with the hypothesis that vagal afferents are involved in physiological regulation while spinal afferents are responsible for mediating pain. However, recent evidence implicates vagal afferents both in the mediation of sensation and in the modulation of sensory experience (see below).

**Inflammation and injury**

The morphological appearance of afferent terminals in the gastrointestinal wall, visualised by fluorescent microscopy, suggests that these endings may also subserve an “effector” sensorimotor function. Gastrointestinal afferents are thought to have collateral branches that supply blood vessels and innervate the enteric ganglia where they have the potential to modulate blood flow and enteric reflex pathways as a consequence of release of transmitters from their varicos nerve terminals. In the case of spinal afferents, the main transmitters present in these sensory nerves are CGRP and substance P. Both peptides are implicated in gastrointestinal inflammation and both contribute to neurogenic inflammation. In this respect sensory ablation with capsaicin or receptor antagonist to CGRP both attenuate the inflammation induced by *Clostridium difficile* toxin A. The visceral afferents are believed to play a cytoprotective role in more proximal regions of the gastrointestinal tract. The injury response to stomach acid is exacerbated by ablation of sensory nerves or treatment with CGRP. This cytoprotective function is believed to arise from the ability of afferents to increase blood flow to the mucosa.

**Mechanosensitivity**

The terminals of vagal afferents form elaborate structures within the gastrointestinal wall. Two types of vagal ending have been attributed to mechanosensory function. The first is the intramuscular array found in both circular and longitudinal muscle layers where vagal afferents branch extensively to run parallel with the smooth muscle nerve bundles. These have been suggested to be “in series tension receptor endings” that respond to muscle tension generated during passive stretch or active contraction of the muscle. However, more recently this mechanosensory property has been attributed to the second type of vagal sensory ending referred to as IGLE which are found as basket-like structures surrounding myenteric ganglia. It is proposed that it is at this site that IGLE are exposed to stresses and strains generated by muscle stretch or contraction. Evidence supporting this view has been elaborated recently by mapping the receptor fields of vagal afferent endings in the oesophagus and showing morphologically that these “hot spots” correspond to the location of IGLE.

Mechanosensitivity, particularly that of spinal afferents, is not fixed but can be influenced by a wide range of chemical mediators released as a consequence of injury and inflammation (fig 2). Bradykinin and prostaglandins interact in a potentiating way to modulate the sensitivity of spinal afferent endings, reducing the threshold for activation to cause hypersensitivity. Previously insensitive afferents have also been shown to develop mechanosensitivity during inflammation. A wide range of chemical mediators are implicated in this sensitisation process.

**Response to nutrients**

In contrast to this promiscuous chemical sensitivity of spinal mechanoreceptors, other afferent endings, particularly those supplying the mucosa and those running in vagal pathways, are involved in specific sensitivity to mediators released from enteroendocrine cells (EC) in the gastrointestinal mucosa. These mediators are implicated in signal transduction from the intestinal lumen, a process referred to as “nutrient tasting”. Cholecystokinin (CCK) is one such agent which is released by nutrients, including protein and fat digestion products.
endogenous signals generated from within the gastrointestinal tract, in particular those activated by low levels of mechanical stimulation and nutrients. This suggests that normal postprandial vagal activity may also play a role in regulating the threshold for nociceptive signals generated through spinal afferent pathways.

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