VISCERAL PERCEPTION

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.

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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).[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 secretor motor 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 motor 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 spinothalamic, spinoreticular, and the more recently described dorsal column pathways that are responsible for the phenomenon of

Abbreviations: CCK, cholecystokinin; CGRP, calcitonin gene related peptide; CNS, central nervous system; EC, enteroendocrine cells; IGLE, intraganglionic lamina endings.

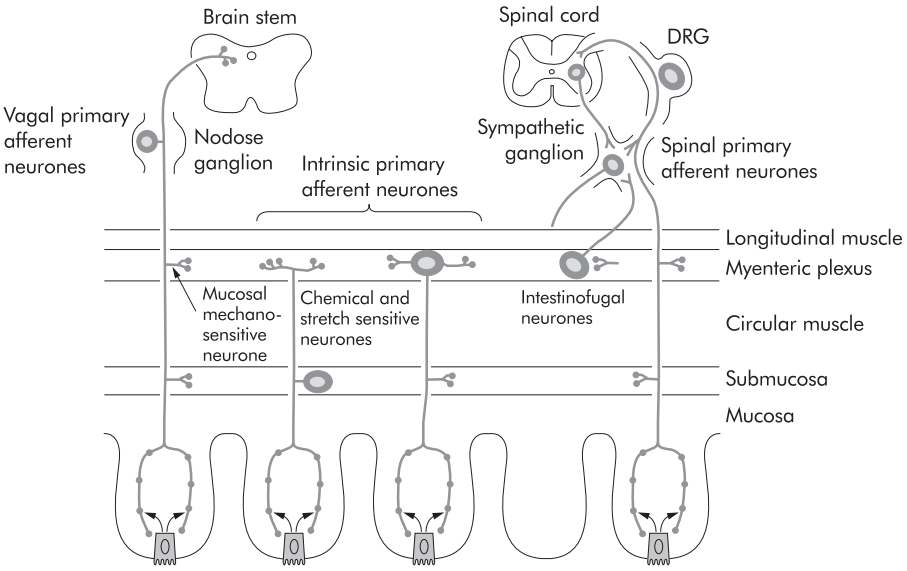

Figure 1 Arrangement of the primary afferent neurones within the intestine. DRG, dorsal root ganglion. Reproduced with permission from Furness and colleagues.[1]

referred pain.[2] Projections from the nucleus tractus solitarus are mainly to hypothalamic and limbic structures associated with behavioural and emotional aspects of sensory processing.[3]

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 serosal and mesenteric attachments are consistent with their responses to stimuli acting at these different sites within the gastrointestinal wall.[4] Nerve terminals in the serosa and in muscle convey mechanosensory information relevant to distension and contraction of the bowel wall. However, the afferent information conveyed by vagal and spinal mechanosensitive afferents is very different, as revealed by direct electrophysiological recordings of afferent traffic en route to the CNS.[5] 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 "efferent" 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 varicose nerve terminals.[6] 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.[7] 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.[8]

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.[9] 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.[10] 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.[11]

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.[12] Previously insensitive afferents have also been shown to develop mechanosensitivity during inflammation. A wide range of chemical mediators are implicated in this sensitisation process.[13]

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.[14] These mediators are implicated in signal transduction from the intestinal lumen, a process referred to as "nutrient tasting".[15] Cholecystokinin (CCK) is one such agent which is released by nutrients, including protein and fat digestion products.

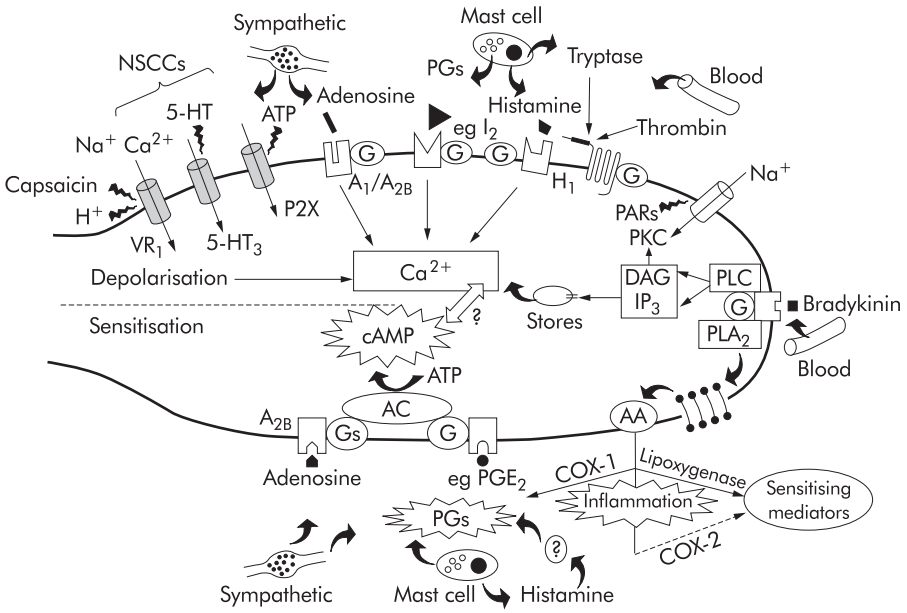

Figure 2 Potential receptor mechanisms underlying activation (depolarisation) and sensitisation of visceral sensory afferents. Some mediators, for example, serotonin (5-HT) acting on $5\text{-}HT_3$ receptors, cause activation while some (prostaglandin E_2 (PGE_2)) cause sensitisation. Others, for example adenosine, cause both stimulation and sensitisation. Bradykinin has a self sensitising action, stimulating discharge through activation of phospholipases (PLs) and enhancing excitability via PGs. Inflammatory mediators can be released from a variety of cell types (for example, sympathetic varicosities, mast cells, and blood vessels) present in or around the afferent nerve terminal. 5-HT, adenosine triphosphate (ATP), and capsaicin can directly activate non-selective cation channels (NSCCs) while adenosine, histamine, PGs (not PGE_2), and proteases such as tryptase and thrombin act on G protein coupled receptors leading to a Ca^{2+} dependent modulation of ion channel activity. Sensitisation may be mediated via cyclic adenosine 3,5-monophosphate (cAMP). Adenosine and PGE_2 can generate cAMP directly through G protein coupled stimulation of adenyl cyclase (AC). In contrast, histamine may act indirectly through generation of PGs. The actions of cAMP downstream are currently unknown but may involve modulation of ion channels, interaction with other second messengers, such as Ca^{2+}, or even changes in receptor expression. COX, cyclooxygenase; DAG, diacylglycerol; IP_3, inositol 1,4,5-triphosphate; PARs, protease activated receptors; PLC, phospholipase C; PLA_2, phospholipase A_2; PKC, protein kinase C. Modified from Kirkup and colleagues.[12]

The nerve terminals of vagal afferents in the lamina propria are found in close proximity to the EC and have been shown to respond both to exogenous CCK and to luminal nutrients by a CCK dependant process.[16] Information concerning nutrients is used as the basis of reflex mechanisms via the vagus to control gastrointestinal motor and secretory function but this information is also implicated in the regulation of food intake. Serotonin mediates a similar process, particularly in the presence of bacterial toxins, which trigger vagal mechanisms to dilute and expel the potentially harmful luminal contents.[17]

Much of the sensory information, particularly in vagal afferent information, fails to reach the level of conscious perception. This is consistent with observations in patients who have suffered a spinal injury and have lost all bowel sensations.[18] However, some vagal afferents project into the cervical region of the spinal cord and these fibres may be involved in transmitting sensation to thalamic nuclei. Vagal afferents are also implicated in nociception as they are known to activate CNS structures that have a descending influence on spinal nociceptive transmission.

Thus on the one hand vagal afferents have been shown to facilitate nociceptive transmission and these pathways are believed to be implicated in the hyperalgesia that arises as a consequence of illness behaviour triggered by some cytokines, especially interleukin 1β.[19] However, vagal afferents also influence descending pathways that inhibit nociceptive transmission, a phenomenon termed antinociception.

Morphine at low doses produces its analgesic action in part by activating vagal afferents.[20] Consistent with this view is the observation that opioid receptors are expressed on vagal sensory neurones, and agonists acting at μ and δ receptors can activate vagal afferent pathways.[21] This activation occurs at doses of opioids that are well below analgesic levels. Moreover, fibres that respond to opioids also respond to other 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.

CONCLUSIONS

Afferent fibres convey a vast amount of sensory information to the brain stem and spinal cord 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. These spinal nociceptors are influenced by peripherally acting chemicals which are released during inflammation and injury and they are thought to trigger the processes leading to sensitisation and increased nociceptive activity. Other chemicals act in a more selective way to activate vagal afferents and are implicated in nutrient signalling from the gastrointestinal tract.

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