Mechanoreceptors in the Gastrointestinal Tract

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Introduction

The upper gastrointestinal tract receives an extensive afferent innervation via both the splanchnic and vagus nerves. At the level of the diaphragm some 30,000 to 50,000 vagal afferent fibres exist, representing between 70 and 95% of the total number of fibres depending upon animal species (Gabella and Pearse, 1973 ; Mei, *et al.*, 1980 ; Pretchl and Powley, 1990). In the major splanchnic nerves the proportion of afferent fibres is considerably less contributing only 10 to 20% of a total count of around 20,000 fibres in the cat (Kuo, *et al.*, 1982). These afferents provides the basis for reflexes which adjust motility and secretion to the digestive needs of the individual, mediate behavioural responses associated with food intake, nausea and vomiting, and are also the source of sensations of gastrointestinal origin. A knowledge of impulse generation in visceral afferents is therefore integral to our understanding of the mechanisms which regulate gastrointestinal function. In this respect the subject of gastrointestinal mechanoreceptors takes in many aspects of visceral muscle activity and its control. In this paper I will specifically consider the morphological arrangement of the afferent endings and the relationship with neural and endocrine structures within the gut wall which determine the stimulus-response characteristics of the sensory afferents.

Methodological approach and some pitfalls

The impulse traffic in vagal and spinal afferents can be recorded using conventional electrophysiological techniques (Grundy and Scratcherd, 1989). However, there are a number of complicating factors that make the interpretation of such studies difficult. First, these are not the only sensory elements in the gut wall. Intrinsic afferents enable reflexes to be organized entirely at the level of the enteric nervous system (Wood, 1989). It is therefore possible that responses recorded in vagal and splanchnic afferents are secondary to effector responses triggered by intrinsic reflexes. One therefore needs to distinguish between primary and secondary effects and the failure to do so has led to a number of anomalies in the literature. In the same way some intrinsic afferents project out of the gut wall to the prevertebral ganglia and evoke reflexes (Szurszewski and King, 1989) which can again make the application of controlled stimuli very difficult.

There is yet another complication to the study of extrinsic afferents. The cell bodies in the nodose and dorsal root ganglia synthesize bioactive peptides and other potential neurotrans-

mitters that are transported to the periphery and are available for release from the terminals of afferent collaterals. Calcitonin gene related peptide (CGRP) and substance P are two such substances (Dockray, 1988). CGRP disappears from the gut wall on extrinsic denervation and is present in over 80% of DRG cells. It can therefore be used as a marker for splanchnic afferents and in this respect, its distribution to the myenteric plexus and submucosal blood vessels suggests an efferent rather than sensory function. Afferent fibres can therefore serve a dual role. Receptor endings generate impulses which are conveyed to the CNS. In addition, these impulse can invade afferent collaterals and cause the release of neurotransmitters and neuromodulators as part of a local reflex pathway. One functional role for such axon reflexes is in gastric mucosal cytoprotection.

Vagal afferent terminal show a similar arrangement but because CGRP is present in only 2% of neurones in the nodose ganglia one must use alternative tracing technique in order to visualize the terminals of vagal afferents. Sato and Koyano, 1987, used autoradiography following the injection of tritiated leucine into the nodose ganglia. Afferent terminals were seen in intimate contact with myenteric neurones suggesting that axon collaterals could innervate the enteric nervous system and mediate local reflexes. Other terminals in the muscle and below the mucosa epithelium were consistent with the more traditional view of afferents as receptor endings. This distribution of vagal afferent terminals has been recently confirmed by Berthoud and Powley (1992) using fluorescent markers injected into the nodose ganglia. Because of the increased resolution of fluorescence microscopy the branching of afferents with separate terminals supplying the muscle and myenteric plexus has been clearly demonstrated.

However, for both vagal and splanchnic afferents the terminals appear as bare nerve endings with none of the morphological specializations evident in the somatic domain. In this respect one might predict that the location of the terminals within the gut wall is important in determining the receptor sensitivity of the endings. From electro-physiological studies of the stimulus/response characteristics of individual afferent fibres this indeed appears to be the case and afferent fibres have been classified as serosal, muscle and mucosal.

Stimulus-response characteristics of vagal and spinal afferent fibres innervating the upper gastrointestinal tract

A great number of studies have investigated the stimulus-response characteristics of vagal and spinal afferents supplying the oesophagus, stomach and small intestine (Grundy and Scratcherd, 1989). However, because of species differences, different recording techniques and different methods of applying stimuli to the gut wall, it is often difficult to compare directly the properties of one group of afferents with another. However, a recent series of studies by Sengupta, *et al.*, 1990, is unique in that it used the same preparation to investigate the stimulus/response characteristics of both vagal and spinal afferents supplying the smooth muscle portion of the oesophagus of the North American Opossum. Figure 1 is a summary of their data.

Three types of afferent fibre were distinguished on the basis of the response of individual afferent fibres to increasing levels of balloon distension. These were low threshold mechanoreceptors (LTM), high threshold mechanoreceptors (HTM), and wide-dynamic range mechanoreceptors (WDM), although the difference between the latter two may simply reflect differences

Fig. 1. Stimulus-response curves for oesophageal mechanoreceptors. Discharge frequency is plotted against distension pressure for 3 types of mechanoreceptor. (See text for details. From Sengupta, *et al.*, 1990).

in the location of the oesophageal balloon relative to the receptor ending of the afferent. Vagal afferents were always low threshold while the high-threshold and wide dynamic range afferents projected to the spinal cord.

During peristalsis the vagal fibres fired maximally showing that tension generated passively by distension and actively during contraction are equally effective stimuli for vagal mechanoreceptors. During contraction WDR splanchnic afferents fired at only 20% of that obtained during maximal balloon distension at 120 mmHG while HTR did not respond. Sengupta *et al.* concluded that spinal afferents signal noxious events while vagal fibres operate in the physiological range to monitor peristalsis and act as a trigger for secondary peristalsis.

This threshold difference between vagal and splanchnic afferent responses to distension appears to hold true throughout the gastrointestinal tract but has not been systematically studied in the same preparation as it has for the oesophagus.

In the colon splanchnic afferents were demonstrated to have receptive fields in the serosa at the level of the mesenteric connections. These splanchnic afferents responded to distension with different fibres showing either phasic or tonic components (Haupt, *et al.*, 1983).

The wide-dynamic range of sensitivity of these fibres is consistent with the intensity theory for the mediation of visceral pain (Janig and Morrison, 1986). That is that the same population monitors normal activity and mediates reflex control but as the intensity increases these also signal noxious events and cause pain. The alternative hypothesis is that there are specific nociceptors but their presence in the gastrointestinal tract remains controversial.

In contrast to the relatively high threshold for activation of splanchnic afferents, vagal afferents respond to more physiological stimuli (Andrews, Grundy and Scratcherd, 1980). Fig. 2 shows recordings from two vagal mechanoreceptors innervating the stomach. Antral mechanoreceptors discharge action potentials in phase with peristaltic contractions and tend not to respond to distension except in association with the augmented motility that often accompany such stimulation. Corpus mechanoreceptors, in contrast, respond readily to dis-

Fig. 2. Actual records of afferent discharge from two ferret vagal mechanoreceptors. The upper panel is an antral mechanoreceptor generating a burst of impulses as a contraction (indicated by pressure trace) passes over the receptive field. Below is a corpus mechanoreceptor responding to a ramp distension upto 50 ml.

tenion. However, these differences between antral and corpus mechanoreceptors are a reflection of regional differences in motor activity rather than of specific receptor types. The corpus functions as a distensible reservoir for ingested food while the antrum is a muscular pump to break up solid food and deliver it in a controlled way into the duodenum. Both antral and corpus mechanoreceptors will respond to stretch and contraction if appropriately stimulated; characteristics that led Iggo in 1957 to coin the term "in-series tension receptor".

The counterpart of the in-series ending is the "in parallel" receptor which in skeletal muscle is the muscle spindle of which there is no equivalent in gastrointestinal smooth muscle. There is a tendency to describe reflex responses which show no obvious relationship between volume and tension as being mediated by "in-parallel" receptors. However, because of the orientation of the longitudinal and circular muscle layers at right angles to each other this distinction is difficult to make especially since contraction at one point will inevitably stretch adjacent regions.

The in-series receptor in skeletal muscle is the Golgi tendon organ. However unlike the Golgi, vagal tension receptors are low threshold. Also because vagal tension receptors are spontaneously active they are able to signal both increases and decreases in tone (Blackshaw and Grundy, 1987). By analogy with the Golgi tendon organ the vagal mechanoreceptor may be associated with the intraseptal bundles of connective tissue which are the smooth muscle equivalent of the tendon. There is some recent morphological evidence from Bertoulet and Powley (1992) which supports this concept.

The third category of mechanoreceptor have their terminations within the gastrointestinal mucosa (Grundy and Scratcherd, 1989). Interestingly, mucosal receptors which are in parallel with the muscle layers respond to neither contraction nor distension. Instead they monitor the physical and chemical environment within the lumen. The adequate mechanical stimulus to these endings is mucosal deformation achieved experimentally by stroking the mucosa with a fine probe.

In addition to this mechanical sensitivity, vagal mucosal afferents respond in a slowly adapting manner to luminal perfusions with a range of different chemical solutions. Responses to acids and hypertonic solutions have been best characterized but in general it appears that these mucosal mechanoreceptors respond whenever the luminal environment changes from neutrality, isotonicity or contains nutrients. These afferents are therefore referred to as multimodal chemoreceptor.

The sensitivity to both mechanical stimuli such as stroking and chemosensitivity to luminal chemicals has important implications for the understanding of signal transduction in these endings. It is possible that for both the adequate stimulus is mucosal deformation. This would occur directly during stroking and indirectly following chemical stimulation either because of osmotic effects on interstitial water content, obligatory water movements accompanying nutrient absorption or following local reflexes regulating the muscularis mucosae.

An alternative possibility arises because mucosal afferents respond to chemicals delivered systemically. CCK and 5HT both mediate relaxation of the stomach via a vagally dependent mechanism (Andrews, *et al.*, 1990, Raybould, *et al.*, 1987). In addition endogenous CCK modulates feeding behaviour (Shillabeer and Davison, 1984) and 5HT is implicated in the stimulation of nausea and vomiting by cancer chemotherapy agents (Andrews, *et al.*, 1990). Both these affects are mediated via vagal afferents. Despite earlier suggestions that CCK in particular acts on vagal mechanoreceptors (Davison and Clark, 1988, Schwartz, *et al.*, 1991) it is now apparent that it is the mucosal receptor that has a primary sensitivity to both CCK and 5HT and that mechanoreceptor responses to these compounds are secondary to motor responses (Blackshaw and Grundy, 1990, 1991). Fig. 3 illustrates the response of a single vagal

Fig. 3. Recording of a vagal mucosal afferent from the ferret following the close-arterial injection of 100 pmol of CCK-8.

mucosal afferent fibre responding to CCK and demonstrates to intense nature of the response to CCK.

The finding that mucosal afferents are sensitive to systemic agents like CCK and 5HT has implications beyond their role in food intake, nausea and vomiting despite the obvious therapeutic possibilities (Sanger, 1990). More important from the viewpoint of this discussion is the possible involvement of endogenous CCK and 5HT in the process of afferent transduction. The suggested involvement of enteroendocrine cells in the activation of mucosal afferents is based on the morphological features of these cells (Fujita *et al.*, 1979). A microvillus tuft exposed to the gut lumen is proposed to recognise luminal stimuli, in response to which, secretory granules are released across the basolateral membrane. These peptides and amines have access to nerve fibres within the lamina propria which, because they disappear after intranodose vagotomy, are considered to be afferent (Schofield, 1960).

It is possible to examine the role of CCK and 5HT in signal transduction using relatively specific receptor antagonists. The effect of CCK on mucosal afferent fibres is mediated by the CCK-A receptor since the effect of systemic CCK is blocked by L364718. Similarly, granisetron, a potent 5HT₃ receptor antagonist completely blocks the response to systemic 5HT (Fig. 4). The effect of these antagonists on mucosal afferent responses to luminal stimuli has only recently started to be addressed (Blackshaw and Grundy, 1991). However, even in these preliminary studies it is clear that the mechanosensitivity of mucosal afferents and the ability to respond to luminal acid and hypertonic saline still persists after blockade of the CCK-A and 5HT₃ receptor. Thus the responses of mucosal afferents to CCK and 5HT represents an extension of the polymodal sensitivity of these endings rather than an obligatory event in signal transduction.

There has been no equivalent of the vagal mucosal afferent recorded in the splanchnic nerves. This prompts the question how are mucosal events encoded as noxious? It is unlikely

Fig. 4. Histogram showing the discharge of a ferret vagal mucosal afferent in response to the intra-arterial injection of increasing doses of 5HT. After granisetron (0.5 mg/kg) the response to 5HT was completely abolished.

that pain is mediated via the vagus since clinical data has shown that electrical stimulation of the abdominal vagus can cause vomiting but not pain. However, vagal afferent information, on reaching the brainstem, is widely disseminated. The NTS and area postrema are the major recipients of vagal afferent inputs (Leslie, 1982) although there is some evidence for monosynaptic connections with neurones in the DMVN (Rinaman, *et al.*, 1989). Reflex connections within the brainstem provide the basis for vago-vagal reflexes involved in the control of gastrointestinal motor and secretory function. Other projections ascend through the midbrain and reticular nuclei to higher centres (Sawchenko, 1983). The parvocellular reticular formation is involved in the activation and coordination of vomiting for which vagal afferents are a powerful trigger (Brizzee and Mehler, 1986). The projection to the hypothalamus is involved in specific behavioural patterns such as food intake (Anand and Pillai, 1967; Barone, *et al.*, 1979; Jeanningros, 1983; Yuan and Barber, 1992). Pathways through which gastrointestinal vagal afferents reach the thalamus and cortex have also been established but the functional implications of this pathway is not known (Sawchenko, 1983). Vagal representation is found on the orbital surface of the frontal lobe (see Newman, 1974) rather than the sensory cortex as for splanchnic afferents, suggesting that vagal afferent are not involved in pain but may mediate behavioural responses.

The alternative to mucosal pain being mediated via the vagus is that it is a splanchnic phenomenon. This could occur either directly through splanchnic mucosal afferents that have yet to be identified electrophysiologically or indirectly via the already characterized serosal mechanoreceptor. In either case one must bear in mind observations such as those by Wolf (1965) on his gastric stoma patient Tom Little. He demonstrated that the healthy mucosa is insensitive to noxious stimuli such as strong pinch or faradic stimulation. However, when the mucosa is inflamed the same stimuli causes pain.

It is possible that splanchnic mucosal afferents would only be active when inflamed. In this respect serosal receptors become sensitized following ischaemia such that they respond at lower distension levels generating higher levels of discharge (Haupt, *et al.*, 1983). Prostaglandins appear to be involved in this process (Longhurst, *et al.*, 1991). Moreover, recent experimental studies have indicated that some sensory receptors are only activated by persistent damage or inflammation. These "silent" nociceptors are normally unresponsive to physiological stimulation and therefore would not be encountered in electrophysiological studies unless inflammation had been experimentally induced.

Another possibility is that mucosal sensations are not mediated by mucosal afferents at all. Instead sensations could arise secondary to motor events triggered by intrinsic reflexes. Short chain fatty acids (SCFA) infused into the ileum mimic the effect of reflux from the colon and have a marked stimulatory effect on motility which serves to clear the refluxed material from the ileum. In human volunteers infusion of SCFA into the ileum stimulate propagating power contractions which evoke symptoms of cramp, bloating and pain (Kamath, *et al.*, 1988).

Afferent recordings from mesenteric nerve bundles have demonstrated an exquisite sensitivity to SCFA with an order of potency; butyrate > propionate > acetate (Richards, *et al.*, 1991). This is the inverse of their concentrations in the colon which may be of physiological significance. The response to SCFAs consists of two components, a peak and a plateau, which

can be separated pharmacologically by cholinergic antagonists. The powerful peak response and an associated motor response is blocked by cholinergic blockade leaving the smaller plateau response intact. It appears therefore, that SCFAs stimulate a local reflex which triggers a motor response. Motor response stimulates extrinsic mechanoreceptors which have the potential to activate spinal nociceptive pathways. The plateau response is independent of motility and may reflect the activation of mucosal afferents.

Conclusion

Vagal and splanchnic afferents relay centrally an enormous volume of information relating to the gastrointestinal tract. Through mucosal, muscle and serosal mechanoreceptors information on the physical and chemical environment within the gastrointestinal lumen together with information on the amplitude and waveform of every contraction that occurs is available. In this way, the everchanging environment within both the lumen and wall of the gastrointestinal tract is reflected in the afferent inflow to the central nervous system which enables the various motor and secretory activities to be adjusted to the needs of the individual.

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