The Future of GI and Liver Research: Editorial Perspectives

IV. Visceral afferents: an update

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Raybould, Helen E. The Future of GI and Liver Research: Editorial Perspectives. IV. Visceral afferents: an update. Am J Physiol Gastrointest Liver Physiol 284: G880–G882, 2003; 10.1152/ajpgi.00123.2003.—The number of articles published in American Journal of Physiology Gastrointestinal and Liver Physiology over the last 15 years on visceral afferents has increased dramatically. This reflects our growing ability to study the characteristics and function of visceral afferents and also the recognition of their importance in the maintenance of homeostasis and also in a number of pathophysiologic conditions. However, there are several key unanswered questions concerning the function of visceral afferents that await further investigation.

Vagal; afferents; sensory transduction

THE LAST 15–20 years have seen an explosion in the number of Journal articles on the topic of visceral afferents. By searching the Journal's database using “afferent” as a keyword, there were only 18 articles with this keyword in the title or abstract between January 1987 and 1992, which increased dramatically between January 1992 and 1997 to 48 and then to 65 in the next five years. Indeed, visceral afferents have also been the subject of several articles in five of the themes series (Neural injury, Repair, and Adaptation in the GI tract; Nutrient Tasting and Signaling Mechanisms in the Gut; Receptors and Transmission in the Brain-Gut Axis; Pathobiology of Visceral Pain: Molecular Mechanisms and Therapeutic Implications; Musings on The Wanderer: What's New in Our Understanding of Vago-Vagal Reflexes) over the last 5 years (1–6, 8, 10, 14, 16). In this short article, I very briefly outline some of the recent, most intriguing advances in our understanding of visceral afferents and also highlight some of the areas in which our understanding remains far from complete.

One of the areas in which there has been considerable progress is in the description of the morphology of vagal afferent terminals in the gastrointestinal tract. As pointed out in the themes article by Powley and Philips (14), sensory transduction events have largely been inferred from the data obtained in functional studies or electrophysiological experiments and that a detailed knowledge of the morphology of terminals will assist greatly in our understanding of their physiology. In this manner, several groups have described the complex morphology of vagal afferent terminals in the muscle layers of the gut wall and of the terminals situated between the muscle and the myenteric plexus. These observations have led directly to an elegant demonstration of the sensory transduction mechanism in slowly adapting vagal mechanoreceptors innervating the gastric wall and esophagus. With the use of a combination of morphological and electrophysiological techniques, Zagorodnyuk et al. (18) demonstrated that the neuronal structures underlying the receptive fields of slowly adapting stretch-sensitive afferents were the intraganglionic laminar endings. These studies did not provide any evidence to suggest that the other type of terminal structure of vagal afferents in the wall of the gastrointestinal tract, the intramuscular arrays, were mechanosensitive. Similar studies on vagal terminals in other locations, such as the mucosa, have not been performed and, although technically demanding, such studies would undoubtedly help in our understanding of sensory transduction in the key modality of chemoreception in the gastrointestinal tract.

It is well established that gastrointestinal afferents subserve an efferent role by release of neurotransmitters from their varicose nerve terminals. This has been shown to be of major importance in cytoprotection of gastric mucosa (9) and also in inflammatory processes (6). However, what is not so well established and may be of particular significance is the ability of effector peptides released from visceral afferent nerve terminals to drive intrinsic neurons. It has been shown that visceral afferents, vagal afferents in particular, terminate within the myenteric plexus, and it has recently been shown that these terminals are functionally significant. A recent study (17), using c-Fos to determine activation of neurons, showed activation of myenteric neurons in response to lumenal acid via a capsaicin-sensitive afferent pathway. This communication between afferent nerve terminals and myenteric motor neurons may be important in other changes in effector function thought to involve visceral afferents and raises many interesting possibilities on the modulation of enteric reflexes.

It is also well established that visceral afferents express receptors for a number of different peptide hormones and neurotransmitters (10). For the peptide hormones, it can be demonstrated that ligand-induced activation of these receptors on peripheral nerve terminals activates afferent firing and produces a number of different functional responses including changes in gastric motor and secretory function, pancreatic secre-
tion, and also changes in feeding behavior. The use of specific receptor antagonists to a number of these neuroactive hormones and chemicals in experiments using a change in physiological function has revealed that these neuroactive agents and their receptors may be involved in the sensory transduction process for nutrients and other stimuli such as acid or osmotically active solutions.

Mucosal terminals are likely involved in the sensory transduction of nutrient stimuli, yet we know little about the morphology or specialization of these terminals. It has been shown that they are widely distributed in the lamina propria and are situated around intestinal crypts. Vagal afferents also extend into each individual villus of the mucosa where they divide into terminal processes. Within the villi, the afferents run in conjunction with fibroblasts and terminate close to the basolateral surface of the epithelial cells, including enteroendocrine cells and enterochromaffin cells. As pointed out by Powley and Phillips (14), we know little about the extent of individual mucosal vagal afferents in terms of the area they innervate, whether any specialization of endings occurs, and any possible features that provide them with specificity for particular modalities.

It is possible that there are no specializations of mucosal terminals and that specificity is determined by the location of the free nerve terminal, for example, proximity of the terminal to a particular endocrine cell or the receptors expressed on the terminals. The latter would appear to be unlikely given the information that the majority of vagal afferent nodose cell bodies innervating the upper gastrointestinal tract express cholecystokinin-A receptors (CCK-ARs) (12) or 5-HT3 receptors (5-HT3R) (7). This does not take into consideration the possibility of selective axonal transport of receptor to terminal fields. Mucosal terminals respond to a number of different chemicals that may be involved in the transduction process, but it is not clear whether this is an obligatory role or involves changes in afferent terminal sensitivity. Activation of vagal afferents by fatty acid in the jejunum depends on an action of CCK at a CCK-AR, because afferent response to fatty acids in the jejunal lumen was blocked by a CCK-AR antagonist (11, 15). Likewise, activation of duodenal vagal afferent fiber discharge by glucose depends on 5-HT3 receptors (19). However, it is possible that CCK and 5-HT act to alter the sensitivity of these afferents to the nutrient stimuli rather than playing an obligatory role in sensory transduction. This will be a difficult concept to demonstrate experimentally, but it is critical to our understanding of the function of visceral afferents and chemoreception.

Another apparent paradox in the physiology of visceral afferents is the observations that suggest that a single afferent pathway, the vagus nerve for example, and a single neuroactive agent, 5-HT, can mediate a number of different responses. 5-HT acting at 5-HT3 receptors has been implicated in mediating the inhibition of gastric emptying and stimulation of pancreatic secretion in response to physiological levels of glucose and hypertonic solutions in the intestinal lumen, emesis, and nausea associated with chemotherapeutic agents and also visceral pain. All three of these responses have been shown to be mediated by extrinsic vagal afferents and 5-HT acting at 5-HT3 receptors, and it is difficult to reconcile how the same afferent pathway may be differentially activated in a number of different conditions. It is possible that the response to glucose and hypertonic solutions is part of the spectrum of a response, with either the number of afferent impulses or recruitment of more afferents altering the strength of the signal-activating central pathways.

It is an intriguing possibility that there is specificity of vagal afferents conferred either by morphological or functional specialization of the terminals or by differences in the location of the terminal field. Electrophysiological studies from dissociated vagal afferents have shown differences in the active and passive electrophysiological properties. In addition, intracellular recordings from intact nodose ganglia have shown that some neurons, located within the midcaudal pole of the nodose ganglion of the guinea pig, show a slow after-hyperpolarization after firing. However, as pointed out in the themes article by Browning and Mendelowitz (2), because of the blind nature of these types of studies, it is not clear whether any functional specialization exists between vagal afferents innervating the same or different organs or within the different modalities that activate terminal endings. Another possibility is that there is functional specialization of enterochromaffin cells; for example, it has recently been shown that not all enterochromaffin cells express 5-HT3Rs, at least as determined with immunocytochemistry. This is certainly an area that will require further experimentation.

One potentially interesting area for further study is the significance of receptor expression on the cell bodies of vagal afferents. Recent experiments (13) showed that stimulation of a subpopulation of nodose neurons could enhance the activity of unstimulated neighbors. This suggests that communication between afferent cell bodies in the nodose ganglion does occur.

REFERENCES


