CCK- and leptin-induced vagal afferent activation: a model for organ-specific endocrine modulation of visceral sensory information

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The vagus nerve supplies sensory innervation to nearly all of the viscera, including the heart, respiratory passages, great vessels of the thoracic cavity, esophagus, stomach, small intestine, cecum, colon, pancreas, and liver (29). Although the vagus supplies the majority of parasympathetic motor innervation to these structures, 75–90% of the axons in the monogastric vagi actually are sensory fibers (25). The thoracic vagal sensory innervation participates in reflex control of cardiovascular and ventilatory function, whereas the abdominal vagal afferents are involved in control of gastrointestinal (GI) activities, such as pancreatic secretion (15), gut motility (26), and GI blood flow (34). In addition, it is now well demonstrated that vagal sensory neurons participate in control of food intake through detection of intestinal chemicals (31, 35), endocrine signals (18, 30), and monitoring of gastric distension (24). Extracellular recordings from teased vagal sensory fibers or from neurons in the nucleus of the solitary tract, where vagal sensory fibers synapse in the brain, indicate that subpopulations of vagal sensory neurons increase their firing in response to gastric distension (12, 19), as well as intestinal infusion of nutrients or osmotically active substances (9, 28). Thus the sensory vagus seems to monitor the mechanical and chemical milieu of the GI tract and provides information to the brain. Recordings from teased vagal fibers and from the nucleus of the solitary tract also indicate that vagal afferents respond to a wide variety of substances, including peptide hormones, such as CCK, leptin, ghrelin, glucagon-like peptide (27), cytokines, such as TNF, IL-2 (6, 10, 11), amines (3, 14), and purines (5). Vagal afferent sensitivity to these substances suggests humoral modulation of sensory function or even humoral transduction of sensory signals. In this context, it is important that we do not know with certainty whether all vagal afferent neurons are capable of responding to all of these various humoral stimuli or whether sensitivities to specific substances are expressed in functionally or anatomically discrete subpopulations. In the case of CCK and leptin, anatomical studies and previous electrophysiological results suggest that hormone sensitivity may not be present in all vagal afferents, but only in subpopulations. For example, CCK-1 receptor mRNA is only found in a little over one-third of all vagal afferents (2), and leptin receptor (Ob-R) transcripts were found in ~16% of nodose ganglia cells that innervate the stomach (20). The distribution of CCK and leptin sensitivity to various innervations has not been determined. In other words, it is not known whether all CCK-sensitive afferents go to a specific set of organs or whether the vagal afferent innervation to every organ includes the same proportion of CCK-sensitive afferents. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Peters and colleagues (23) report on an extension of their work with isolated vagal afferent neurons (21, 22), in this case, specifically examining the hormonal sensitivity of neurons that innervate the upper GI tract. They report that the vagal afferent population that innervates the stomach and duodenum contains a much higher proportion of neurons that increase their firing in response to the gut hormone CCK than do neurons in the general vagal afferent population, which includes afferents that innervate structures like the heart and lungs, as well as GI structures. In fact, the proportion of CCK-sensitive afferents is enriched by ~200% in the innervations of the stomach and duodenum, compared with the general population of vagal afferents. Likewise, the population of vagal afferents sensitive to leptin is almost double that of the general population.

There are several inferences that can be drawn from these results. The first is that CCK-sensitive vagal afferents innervate mostly, perhaps entirely, upper GI organs. This suggests that CCK sensitivity is primarily involved in GI functions. Leptin sensitivity also is more concentrated in vagal afferents innervating the upper GI tract. However, leptin’s prevalence in the duodenal and gastric innervations is not enriched as greatly as that of CCK, suggesting that leptin-sensitive afferents are distributed more widely than CCK-sensitive afferents. This might indicate that vagal afferents that respond to leptin are involved in reflexes involving organs outside the upper GI tract. One can imagine, for example, that leptin, which reflects body fat mass, might modulate baroreceptive afferents, as well as GI afferents.

The second interesting inference from these results is regarding the mode of action of CCK. CCK sensitivity is equally prevalent in gastric and duodenal afferent populations. CCK is secreted by the duodenum, so it is reasonable to suggest that these afferents might respond to CCK as it is secreted into the intestinal extracellular space, i.e., in a paracrine manner. On the other hand, the stomach does not secrete CCK (1), and gastrin is not an agonist at CCK-1 receptors (13). Therefore, gastric afferents must be activated by endocrine CCK. Peters et al. (23) did not compare the sensitivity of gastric and duodenal vagal afferents. However, one would predict that afferents activated by endocrine CCK, which circulates at picomolar concentrations, would be more sensitive than those adapted to responding to the peptide at paracrine concentrations. A careful examination of peptide sensitivity would be a welcome addition to future studies.

A third interesting aspect of the results described above is the close relationship between CCK and leptin sensitivity in upper GI afferents. Virtually all leptin-sensitive afferents that innervate the stomach or duodenum are also sensitive to CCK. This suggests prominent functional cooperation between CCK and leptin. Indeed, several investigators have reported such cooperation in the control of food intake. For example, CCK amplifies the suppression of food intake, as well as body weight, by leptin (8, 16, 32). In addition, electrophysiological data show that leptin acts peripherally to increase gastric vagal afferent activity and that CCK modulates the sensitivity of gastric afferents to leptin (21, 33). Peters et al. (22) previously have also demonstrated that leptin and CCK-sensitive vagal afferents can affect food intake.
In a broader context, the results from Peters et al. (23) suggest that specific populations of vagal afferents are modulated or “tuned” by hormones that are specific to the functions of the organs they innervate. If this is so, we should expect to find a wide variety of hormone-sensitive vagal afferent phenotypes that are selectively modulated by hormones that influence the activities of specific organ systems. These afferents might represent similar modalities but be selectively influenced by different hormones. For example, there are stretch receptors in both gut and arteries. The ones in the arteries might be tuned by angiotensin, whereas the ones in the gut might be tuned by CCK. On the other hand, some hormones might have modulatory effects on a variety of modalities in several organ innervations. A broad sensitivity might be appropriate for leptin, for example.

Finally, the study by Peters et al. (23) lays the foundation for identifying and characterizing the neurochemical phenotypes of visceral sensory neurons (e.g., mechanoresponsive, chemoresponsive) and to reveal the mechanisms by which these sensory stimuli are detected and modulated. For example, immunohistochemical staining of the nodose ganglia has revealed that vagal sensory neurons express a variety of distinct neuropeptide, enzymatic, membrane, and cytoskeletal traits (4, 7, 17). It is becoming apparent that some of these traits identify mutually exclusive membrane, and cytoskeletal traits (4, 7, 17). It is becoming apparent that some of these traits identify mutually exclusive populations of sensory neurons. It is quite probable that distinctive immunohistochemical traits can be associated with specific sensory modalities and/or with vagal sensory innervation of particular organs, such as the stomach and intestine. Therefore, identifying the functional phenotype of the sensory afferents mediating humoral signals, such as CCK and leptin, becomes important.

REFERENCES