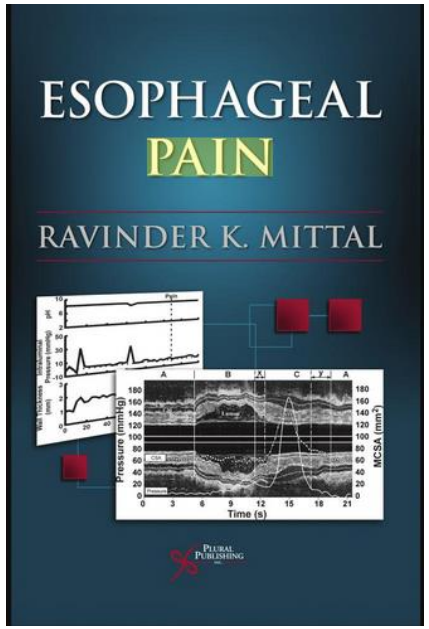

Contents

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Vagal and Splanchnic Distension Sensitive Primary Afferents from the Opossum Esophagus: Implications for Visceral Nociceptors

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INTRODUCTION AND BACKGROUND

Esophageal sensations, like sensations from other viscera, are limited in the variety of their spectrum and precision as compared to cutaneous sensations. All sensory information is coded and transmitted to the CNS by primary sensory afferents. Cutaneous primary afferents convey a variety of sensory information including touch, pressure, pinpoint discrimination, temperature, and pain. Musculoskeletal structures elicit propioceptive sensory information and sensations of pressure and pain. On the other hand, viscera are generally insensitive to touch, heat, or cutting. The viscera respond to distension and the sensory experience depends on the degree of distension. Lipkin and Sleisenger[1] showed that esophageal distension with a compliant balloon in awake persons elicits three types of responses. At small distension pressures, reflex peristaltic contractions in the esophageal body and lower esophageal sphincter relaxation are produced without any sensory perception. At moderate distension pressures, pressure sensation without pain is experienced. But at high distension pressures, subjects experience chest discomfort and pain.[1]

All sensory information from the periphery to the CNS is conveyed by the primary sensory units. A primary sensory unit consists of a bipolar neuron that has a peripheral afferent axon and a central efferent axon. The peripheral afferent axon terminates in specialized nerve endings

that constitute the sensory receptors. The sensory receptors transduce stimuli such as mechanical deformation and severe tissue-injury into electrical spikes. The electrical signals from the sensory receptors are conducted along the peripheral afferent axon to the sensory neuron and then along the central sensory afferent. The central sensory afferents make synapse with other neurons where it releases neurotransmitter to activate the postsynaptic neuron. Thus, the sensory information originating in the sensory receptor is conveyed to the effector neurons that may be motor neurons in case of monosynaptic reflexes, interneurons involved in polysynaptic reflexes or sensory pathways to the CNS for sensory perception.

Esophageal primary afferents, like the other visceral primary afferents, can be divided into intrinsic and excitatory primary afferents based on their location. Intrinsic primary afferents are located within the esophageal wall. The peripheral axons arise from the endings in the esophagus and reach their cell bodies also located within the wall of the esophagus. The "central" afferents from these neurons project onto motor neurons that are also present in the esophageal wall. Because the intrinsic primary afferents have no connections with the CNS, they are not involved in sensory experience of stimuli in the esophagus.

Extrinsic primary afferents, on the other hand, have sensory receptors (nerve endings) located with the esophagus; the peripheral limb of the afferent axon connected to the sensory receptor has an intramural and an extramural course en route to the sensory neurons. The sensory neurons are located in the nuclei of the cranial nerves or the dorsal root ganglia.[2] The central axons project to the target neurons in the brainstem or the spinal cord. Based on their extramural course, the extrinsic primary afferents can be divided into vagal or sympathetic primary afferents. The nerve cell bodies of vagal primary afferents are located in the nodose and the jugular ganglia; their central projections project on to neurons located in the nucleus tractus solitarius (NTS). The NTS neurons, in turn, project onto esophageal motor excitatory and inhibitory neurons located in the vagal nerve nucleus of the brain stem. The vagal extrinsic primary afferents are involved in vagovagal reflexes. On the other hand, splanchnic primary afferents are carried along greater and lesser splanchnic nerves to dorsal root ganglia C8 to L2. Their central axons project onto the segments of the spinal cord (C8 through L2) (Color Plate 1).[2,3]

Our current understanding of the visceral sensory receptors, derived from morphological and functional electrophysiologic studies, is rudimentary and fragmentary. Morphologically, highly specialized sensory receptors similar to those found in the skin are not present in the viscera including the esophagus. Visceral sensory receptors are generally represented by free nerve endings. Relatively recently, careful tracer studies have shown that vagal afferents terminate in nerve endings that are clustered around the myenteric ganglia. These structures have been called intraganglionic laminar endings (IGLE). Another type of ending of vagal afferents is called intramuscular arrays (IMA) that cluster around circular and longitudinal muscles (Color Plate 2). Several different types of sensory nerve endings have been described in the mucosa.[4,5] However, their connections with vagal and splanchnic afferents are not well understood. Sensory endings that

are connected with the splanchnic primary afferents are largely unknown.[6]

The mechanosensitive receptors are activated by mechanical deformation that cause depolarization of the endings and elicit spike discharge mediated by calcium channels. The spike discharges are then conducted along the afferent axon. A single afferent axon may be connected to several receptors which generally are of the same type; however, some afferents may be connected with receptors of different types and located at different sites. Based on their myelination and diameters, these afferent axons can be divided into: (1) nonmyelinated C fibers; (2) thinly myelinated Aδ fibers; and (3) well-myelinated Aβ fibers. Electrophysiologically, these fibers can be identified by measuring their conduction velocities. C fibers have conduction velocity of less than 2.5 m/s; Aδ fibers have conduction velocity of 2.5 to 25 m/s and Aβ fibers have fast conduction velocity of greater than 33 m/s. The afferent axons from the viscera including the esophagus are carried along the vagus and the splanchnic nerves. Electrical recordings from the afferent axons provide information on electrical activity generated in the sensory receptor to which they are connected.

The sensory nerve endings contain and release neurotransmitters that modulate their activity. Nociceptors are activated by products of tissue damage such as bradykinin and prostaglandins. Because all forms of stimuli that cause tissue damage activate these receptors, they are multimodal in nature. Nociceptors usually contain and release tachykinins such as substance P; they also possess capsaicin receptors and are activated by capsaicin. Chemical mediation of visceral sensory receptors is currently an active field of study, but it is outside the scope of this review (see also Page & Blackshaw).[4]

Activation of sensory receptors produces a host of biochemical and electrical responses along the entire sensory pathway and ultimately in sensory experiences such as pain or discomfort. The stimulus response studies of sensory experience can only be done in conscious human subjects. Studies in awake-humans have shown that distension pressures greater than 40 to 45 mm Hg for greater than 10 s in the esophagus or the colon is experienced as painful.[1] In anesthetized animals, distension of the gut with pressures greater than 40 to 45 mm Hg elicit pseudo-affective responses.[7] These studies indicate that distension pressures greater than 40 to 45 mm Hg can be considered as noxious. Such studies, however, do not provide information on the precise electrical signaling by the sensory receptors.

In experimental animals, stimulus response studies of the sensory receptors may be performed directly by quantifying electrical spike discharges in the sensory receptors elicited by appropriate stimuli. This requires identification of the putative receptor. However, this is almost never possible because location and identity of the receptors are not usually known. However, the spike discharges from the sensory receptors can be monitored by recordings made from primary sensory afferents that are connected with the sensory receptors. Such recordings can be made from the peripheral sensory axon, sensory neuron or the central sensory axon (see Color Plate 1). The electrical spike activity from the primary sensory afferent in response to a known stimulus has been recorded in many different ways. However, recording from a single sensory fiber or sensory neuron is very

tedious and time consuming, but is necessary to obtain the most reliable results.

A putative sensory receptor can not be identified unless an appropriate and adequate stimulus for the activation of the sensory receptor is applied. For example, a search stimulus of less than 40 mm Hg distension would overlook all nociceptors. Furthermore, proper characterization of the receptors require acquisition of data showing the quantitative changes in responses to application of graded intensities of the stimuli, similar to obtaining dose response curves in pharmacologic investigations. There have been several studies of visceral and esophageal sensory receptors connected to the primary afferents. However, quantitative stimulus response studies of distension-sensitive receptors connected to different nerves from several different viscera were not reported until late 1980s. These included studies of distension sensitive receptors connected to vagal afferent in the dog[8] and the opossum.[9] Distension-sensitive receptors located in the splanchnic nerve have also been studied in the opossum,[10] dog colon,[11] guinea-pig ureter[12] and urinary bladder.[13]

ESOPHAGEAL DISTENSION SENSITIVE RECEPTORS CONNECTED TO VAGAL PRIMARY AFFERENTS: LOW THRESHOLD MECHANORECEPTORS (PURE MECHANORECEPTORS)

Stimulus Response Characteristics

Sengupta et al[9] published a detailed study of quantitative stimulus response characteristics involving graded esophageal distension by recording electrical spike discharges in single afferent axons in the opossum (Fig 4–1).[14] In this study, fibers in the peripheral end of the decentralized vagal nerve trunk were teased to isolate single fibers to ensure that only the afferent fibers were being studied. Fibers that responded to esophageal balloon distension of greater than 80 mm Hg were included in the study. Distension pressure of greater than 80 mm Hg was considered to represent adequate stimulus for all distension sensitive non-nociceptive and nociceptive mechanoreceptors. The balloon used for esophageal distension was highly compliant so that the recorded pressure reflected true pressure exerted on the esophageal wall. In mechanosensitive single afferent fiber so identified, stimulus-response relationship (rate of spike discharge as a function of various degrees of esophageal distension) was established to determine the threshold value of the pressure that activates the sensory receptor and the pressure that elicits peak discharge rate.

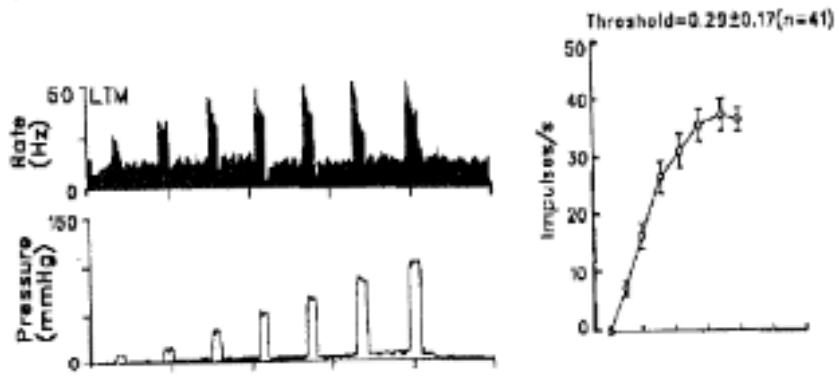

Fig 4–1. Vagal low threshold mechanoreceptor (LT-M). Differential sensitivity to bradykinin of esophageal distension-sensitive mechanoreceptors in vagal and sympathetic afferents of the opossum. From Sengupta et al.[14]

All vagal afferents had spontaneous activity varying from 1.2 to 23 Hz with a mean value of 7.3 ± 1.0 Hz. Threshold pressure to elicit electrical spike discharge in the vagal afferent fibers was low with a mean value of 0.29 ± 0.17 mm Hg. The spike rate increased with increasing distension pressures, reaching a peak discharge rate of 46 to 59 Hz depending on the type of distension and increased no more with further distension. The distension pressure at which peak discharge rate was achieved was called the saturation pressure. The saturation pressure of distension sensitive vagal receptors was 70 mm Hg with stepwise and 56 mm Hg with graded distension.

These results were similar to those reported by Satchell[8] and revealed that functional behavior of vagal distension sensitive esophageal sensory receptors in dog and opossum esophagus were similar. They were characterized by: (1) low threshold of activation; (2) a narrow stimulus response relationship in which the unit discharge rate increases with increasing esophageal distension pressure; and (3) the discharge rate reaches a peak (saturates) at pressures within the physiologic range and further increase in pressure does not modify their discharge rate.

Other Characteristics

1. Distension sensitive vagal sensory receptors are in-series muscle tension receptors. Tension receptors in the somatic (striated) muscles have been broadly divided into in-series and in-parallel receptors that are present in series or in parallel with the contractile elements. Golgi tendon organ in the striated muscle represent in-series tension receptors whereas muscle spindles represent in-parallel tension receptors. In-series tension receptors monitor muscle contraction whereas in-parallel tension receptors monitor stretching of the tissues around the muscles. The in-series tension receptors are active during muscle contraction as well as stretch whereas in-parallel tension receptors are active during stretch but are inactive during muscle contraction. Esophageal distension may activate both in-series and in-parallel tension sensory receptors. Sengupta et al[9] investigated whether the vagal sensory receptors were in parallel or in series tension receptors by investigating their activation by muscle contraction. They found that the vagal receptors were fully activated by esophageal peristaltic contraction suggesting that they are in-series muscle tension receptors.

2. Some distension sensitive muscle tension receptors and mucosal receptors may share a common vagal afferent axon, the distension sensitive vagal sensory

receptors could be located in the mucosa responding to mucosal stretch or pressure or the muscle responding to tension. Studies by Sengupta et al[9] showed that the vagal distension sensitive receptors also responded to contraction of esophageal muscles, suggesting that the sensory receptors may be primarily associated with the muscles and not the mucosa. However, Medda et al[15] found that esophageal perfusion increased spontaneous activity of one third of the vagal mechanosensitive receptors. These observations suggest that a proportion of distension sensitive vagal axons are branching in nature and are connected to both muscle and mucosal receptors. These observations are consistent with those reported earlier by Page et al[4,16] who showed in their studies, in an in vitro system, that a proportion of circular stretch sensitive vagal receptors were also activated by mucosal stroking with a von Frey brush.

3. Separate populations of distension sensitive vagal receptors are associated with circular and longitudinal muscle layers. Sengupta et al[9] investigated whether the vagal in-series tension receptors were associated with circular, longitudinal or both muscle layers. During a swallow, both circular and longitudinal muscle layers of the esophagus contract. The circular muscle segments contract for a shorter duration than the longitudinal muscle, the latter contracts throughout the peristaltic sequence. Sengupta et al[9] observed that during swallow induced peristalsis, vagal afferent units showed two types of spike discharges. (1) A short duration (~3 sec) spike discharge correlated with circular muscle contraction; and (2) a long duration (~10 sec) spike discharge that correlated with longitudinal muscle contraction. These observations show that separate populations of vagal sensory receptors are present in circular and longitudinal muscle layers and suggest that precise information regarding contraction of circular and longitudinal muscle layers is sent to the CNS. This information may be important in the modulation of peristaltic activity.

4. Bradykinin chemosensitivity of the vagal sensory receptors: Bradykinin is an algogenic compound and responsiveness to bradykinin (BK) is sometimes used to distinguish between non-nociceptive and nociceptive receptors. However, this response was not very sensitive in experiments reported by Sengupta et al.[14] Only 66% of the receptors responded and the maximal response was only 33% of the maximal response to esophageal distension. There was no tachyphylaxis. The bradykinin response on the vagal sensory receptors was suppressed by inhibition of the muscle contraction. These data suggested that BK does not stimulate the vagal sensory receptors directly, but only indirectly by stimulating longitudinal muscle contraction.[14] These studies emphasize the importance of dose response studies and exclusion of indirect effect of nociceptive chemicals that may be used to identify nociceptive sensory receptors. Sengupta also made an intriguing and potentially important observation that bradykinin causes contraction of longitudinal but not the circular esophageal muscle and only the vagal sensory receptors associated with the esophageal longitudinal muscle layer were indirectly activated by bradykinin.

5. Morphologic identity of esophageal distension sensitive vagal sensory receptors:

The electrophysiologic studies described above and other studies show that esophageal distension identifies a single population of in series muscle tension receptors. However, morphologic studies have shown that the vagal afferents end in two different types of specialized endings associated with the muscle layers.[3] These have been called intraganglionic laminar endings (IGLE)[17,18] and intramuscular arrays (IMA).[19] Correlative structure function studies have shown that IGLEs are sites of mechanosensitive signal transduction.[20] Although similar studies are not available for IMA, it can be assumed that they also represent vagal mechanosensory receptors. Whether the functionally defined in series muscle tension are connected to IGLEs or IMA or both has not been clear. Based on the distribution of the two morphologic vagal receptor types, it has been argued that IGLEs and not IMA transduce in series muscle tension receptors and may represent electrophysiologic distension sensitive in series tension receptors.[21] IGLEs are present in and around the myenteric plexus in the plane between the longitudinal and circular muscle layers.[17,18] As such, this location is not suitable for their function as in series muscle tension receptors. It has been suggested that they are activated by shearing stress caused by the contraction of the longitudinal and the circular muscle layers. However, existence of such shearing stress is highly speculative and has not been defined or documented. Moreover, observations that separate populations of distension sensitive receptors may be associated with longitudinal muscle and circular muscle contractions, cannot be explained by the role of IGLEs as in series tension receptors.[3] IMAs have been proposed as in parallel muscle tension receptors.[19,21] However, in-parallel muscle tension receptors have not been clearly identified in the electrophysiologic studies. This may be due to the fact that the same vagal afferent is connected with IGLEs and IMAs. Although this may be case in a small number of cases, it is not a common occurrence.[21] We believe that the most likely reason for not finding in parallel tension receptor is that they have not been properly explored using stimuli that are adequate and specific for activation of in parallel tension receptors. It is clear that further studies are needed to determine functional behavior of IGLEs and IMAs.

6. Other types of vagal sensory receptors: Apart from the distension sensitive in-series tension receptors, vagal afferents connected to other sensory receptors are also present but all of them have not yet been characterized. Functional identity of in parallel tension receptors remains to be established. Yu et al[22] investigated electrical discharges in vagal (nodose and jugular) ganglion cells in the upper esophagus of the guinea pig in a carefully designed in vitro system. They found that apart from the low threshold mechanoreceptors with primary sensory neurons present in the nodose ganglia, there were also receptors with properties of wide dynamic range receptors with cell bodies present the jugular ganglion. Several other types of vagal polymodal receptors have been identified in the upper esophagus that may mediate nocifensive reflexes and affective component of pain (eg, nausea). However, at the present time there is no evidence to suggest that the conscious discriminative sensation of pain is mediated via the vagal receptors.[5] Several types of mucosal receptors are also connected to vagal afferents that are stimulated by esophageal distension.

ESOPHAGEAL SENSORY RECEPTORS CONNECTED TO SPLANCHNIC PRIMARY AFFERENTS

Stimulus Response Characteristics

Splanchnic sensory receptors displayed stimulus response relationships that were very different from the vagal sensory receptors. As compared to the vagal sensory receptors, splanchnic receptors were characterized by: (1) no or very low level spontaneous activity 0.28 ± 0.06 (range 0–2.6 Hz); (2) high threshold pressure for activation (mean 16.2 + 2.86 mm Hg); (3) the spike discharge increased with increasing esophageal distension up to 120 mm Hg without any distinct saturation pressure; and (4) low discharge rate (14.87 ± 1.5 Hz) even at pressures of 120 mm Hg.

A careful examination of the data revealed that although the saturation pressures of these units were vary close together, they had a very widely divergent threshold pressures, varying from 0 to 50 mm Hg. Distribution of the threshold pressures suggested that there may be at least two different populations of the nociceptors (Fig 4–2).[10] Based on their threshold pressures they were divided into low threshold and high threshold types. The low threshold type active over a very wide range of distension pressures from non-noxious to noxious and were therefore called wide dynamic range mechano-nociceptors (WDR-MN). The high threshold units were active primarily in the range of noxious distension pressures and were therefore called high threshold nociceptors (HT-N) or specific nociceptors.

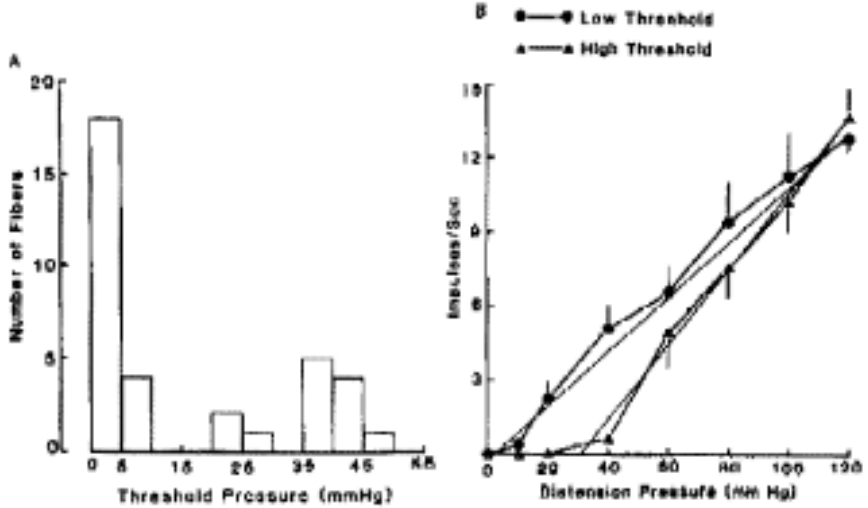

Fig 4–2. A. Frequency histogram of threshold of 35 splanchnic I nerve units. Two peaks of the distribution plot indicate 2 separate populations of fibers in respect to their pressure threshold. First group of fibers is low threshold ranging from 0 to 10 mm Hg and 2nd group of fibers is high threshold with a range of 19 to 50 mm Hg. B. Least-squares linear regression plot of low- and high-threshold fibers. Regression lines were originated from Y-calculated values derived from mean frequency response (impulse/s) of fibers. Lines were extrapolated to ordinate (mm Hg) to obtain threshold pressure. Average threshold pressures for low- and high-threshold fibers were 2.89 ± 0.75 and 33.26 ± 0.54 mm Hg, respectively. From Sengupta et al.[10]

Wide Dynamic Range Mechano-Nociceptors (WDR-MN)

The WDR-MN were either silent or had a low spike discharge rate of 0.5 ± 0.13 at rest; their threshold pressure was 2.89 ± 0.75 mm Hg (range 0–7 mm Hg) (Fig 4–3).[14] The spike discharge increased progressively with increasing distension pressure up to a pressure of 120 mm Hg without showing any signs of saturation. The spike discharge rate at 120 mm Hg distension pressure was 12.8 ± 2 Hz. All receptors were stimulated by bradykinin with a large sensitivity. The action of bradykinin was exerted directly on the sensory receptor and showed partial tachyphylaxis. Bradykinin exerted its effect via bradykinin 2 type receptor.

Response of these receptors to physiologic peristaltic contraction showed that they were activated during peristaltic contractions. However, all the units tested were found to be in association with the longitudinal muscle; no unit associated with circular muscle was found. A larger sample size is needed to draw firm conclusions, but these observations suggest that WDR-MN may primarily be present as in-series tension receptors in the longitudinal muscle layer of the esophagus. The morphologic identity of WDR-MN is not known.

Splanchnic WDR-MN are easily distinguished from the vagal LT-M because of their lower spontaneous discharge rate at background, higher threshold pressure, activity at a wide range of pressures in non-noxious to noxious range, saturation pressure greater than 120 mm Hg and a

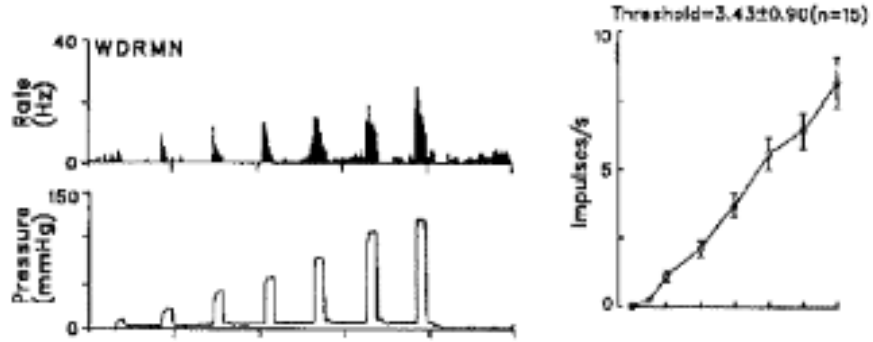

Fig 4–3. Splanchnic wide dynamic range mechano-nociceptor (WDR-MN). Differential sensitivity to bradykinin of esophageal distension-sensitive mechanoreceptors in vagal and sympathetic afferents of the opossum. From Sengupta et al.[14]

slower discharge rate at all distension pressures compared to LT-M (Fig 4–4 and Table 4–1).[10] Moreover, WDR-MNs were only weakly activated by physiological peristaltic contractions and they appeared to be primarily associated with longitudinal muscle layer.

High Threshold Nociceptors (HT-N) or Specific Nociceptors

The HT-N had small spontaneous activity of 0.15 ± 0.07 Hz and threshold pressure of 33.26 ± 0.96 mm Hg (19–50 mm Hg) (Fig 4–5).[14] The spike discharge increased progressively with increasing distension pressure up to a pressure of 120 mm Hg without showing any signs of saturation. The spike discharge rate at 120 mm Hg distension pressure was 13.87 ± 1.24 (see Fig 4–4 and Table 4–1).[10] All receptors were stimulated by bradykinin with extreme sensitivity. The action of bradykinin was exerted directly on the sensory receptor and showed partial tachyphylaxis. Bradykinin exerted its effect via bradykinin 2 type receptor. Response of these receptors to physiologic peristaltic

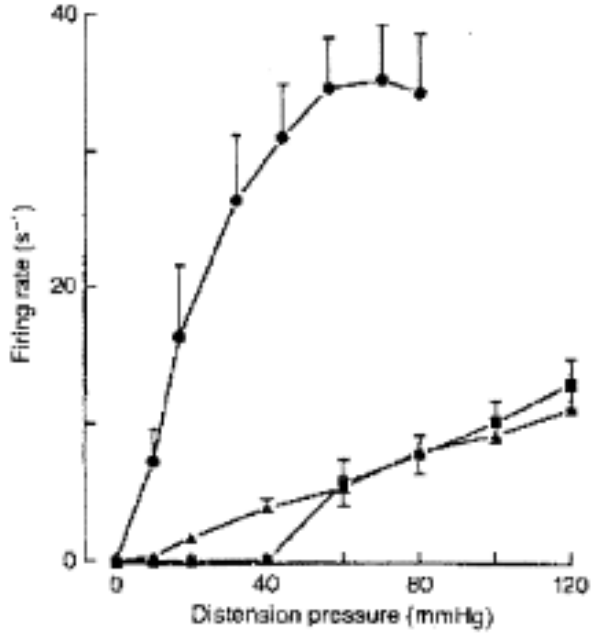

Fig 4–4. Three types of esophageal distension sensitive receptors. Stimulus response function studies of esophageal mechanosensitive nociceptors in sympathetic afferents of opposum. From Sengupta et al.[10]

Table 4–1. Summary of Esophageal Distension-Sensitive Sensory Receptors

	LTM	WDR-MN	HT-N
Location of afferents	vagal	spinal	spinal
Fiber diameter	Aδ or C	Aδ or C	Aδ or C
Spontaneous activity	yes	silent or low	silent or very low
Threshold pressure	very low	low	high
Saturation pressure	<60 mm Hg	>120 mm Hg	>120 mm Hg
Max. discharge rate	60 Hz	12 Hz	10 Hz
Activation by esophageal peristalsis	yes	sometimes	no
In series or in parallel	in series	in series	N/A
Association with muscle layer	Separate for CM and LM	LM	N/A
Response to BK sensitivity	low	high	very high
Direct or indirect effect	via muscle contraction	direct	direct
Tachyphylaxis	none	partial	partial
Receptor type	B4 (B1)	B2	B2
Proposed function	Pure mechanoceptors	Both mechano- and nociceptors	Specific nociceptors

LTM, low threshold mechanoceptor; WDR-MN, wide dynamic range mechanonociceptor; HT-N, high threshold nociceptor.

contraction showed that none of receptor examined were activated during peristaltic contractions. However, HT-N responded to strong longitudinal muscle stretch. Further studies are needed to draw firm conclusions, but these observations suggest that HT-N may primarily be present as in-series tension receptors in the longitudinal muscle layer of the esophagus. The morphologic identity of HT-N is not known.

HT-N could not be distinguished from WDR-MN based on spontaneous spike discharge, saturation pressure or peak discharge at 120 mm Hg, their response to bradykinin, or conduction velocity of the vagal afferent. However, they could be easily distinguished from the WDR-MN from their threshold value and the pressure range of their activity and response to peristaltic contraction (see Fig 4–4 and Table 4–1).[10]

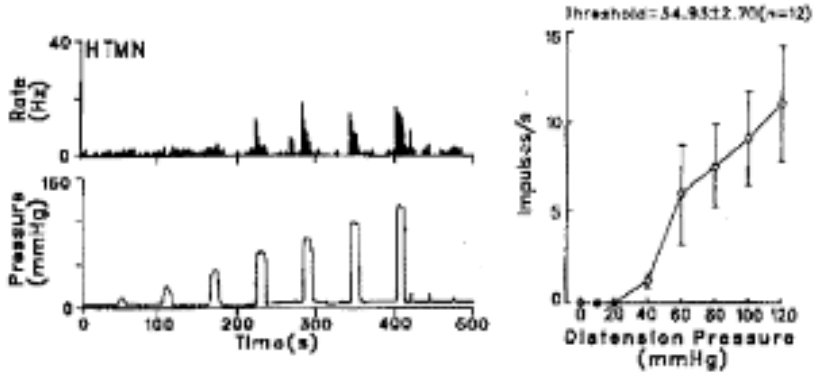

Fig 4–5. Splanchnic high threshold nociceptor (HT-N). Differential sensitivity to bradykinin of esophageal distension-sensitive mechanoreceptors in vagal and sympathetic afferents of the opossum. From Sengupta et al.[14]

Physiologic and Clinical Implications of Two Types of Nociceptors

1. Specificity and intensity theories of visceral nociceptors: Nature of the visceral nociceptors has been a subject of controversy in the past. There have been two theories regarding the nature of the visceral nociceptors, called specificity and the intensity theories.[23] The specificity theory proposed the existence of specific nociceptors that only transduce nocioception and a different set of non-nociceptive receptors that transduce non-nociceptive stimuli. On the other hand, the intensity theory assumed that the viscera had only one type of sensory receptor that transduce non-nociceptive stimuli at low intensity stimulation and nocioceptive stimuli at high intensity stimulation. Quantitative stimulus response studies that monitor electrical spike discharges generated in a sensory receptor in response to graded stimuli that span non-noxious as well as noxious ranges have helped resolve the controversy regarding the nature of the nociceptors.[23] Studies in the opossum esophagus that are elaborated in the preceding paragraphs showed that sensory receptors consistent with both the theories were present. The wide dynamic range mechano-nocioceptors were active during both non-noxious and noxious range of esophageal distension and the high threshold nociceptors were active only in noxious range of esophageal distension. Both these types of nociceptors were connected to axons in the splenchnic nerves (see Fig 4–4).[10] Although, existence of the two types of nociceptors in the same organ has not been demonstrated, other studies have shown presence of WDR-MN in the heart[24] and colon,[11] and HT-N in the ureter[12] and urinary bladder.[15,25]

2. HT-N and silent nociceptors: Habler et al[15] reported that a small number of nonmyelinated afferents from the urinary bladder had high threshold for stimulation and had no or a very low activity with distension of healthy urinary bladder distension. However, sensitivity of these units markedly increased after inflammation so that their activity can be recorded at lower distension pressures. This behavior was similar to the receptors described in the joints.[25] These receptors have been called visceral silent nocioceptors and may represent HT-N with very high thresholds and that show sensitization with inflammation. Further studies are needed to determine if the silent receptors constitute a distinct population of HT-N.

SUMMARY AND CONCLUSIONS

This review reveals that the current information on the nature of the esophageal primary sensory receptors is rudimentary. Information on the functional behavior of the sensory receptors has often been derived from studies of the electrical discharges in the afferent fibers that are presumably connected with the receptors. Most of the available information is focused on the receptors that respond to esophageal distension. Quantitative studies of electrical responses in single afferent fibers responsive to graded esophageal balloon distension have identified three different types of mechanosensitive receptors, namely, low threshold mechanoreceptors, wide dynamic range mechanonociceptors and high threshold nociceptors. The low threshold mechanoreceptors respond to non-nociceptive esophageal distension and may mediate physiologic reflexes. The wide dynamic range mechanonociceptors may respond to both non-nociceptive and nociceptive distensions. The high threshold nociceptors are specific nociceptors. The afferents of low threshold mechanoreceptors are carried in the vagus nerves. On the other hand, the afferents of the nociceptors, wide dynamic range mechanonociceptors and high threshold nociceptors, are carried along the splanchnic nerves. Some nociceptive afferents from the upper esophagus may also be carried in the vagus nerves.

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REFERENCES

1. Lipkin M, Sleisenger MH. Studies of visceral pain: measurement of stimulus intensity and duration associated with the onset of pain in esophagus, ileum and colon. *J Clin Invest.* 1958;37:28–34.
2. Collman PI, Tremblay L, Diamant NE. The distribution of spinal and vagal sensory neurons that innervate the esophagus of the cat. *Gastroenterology.* 1992;103:817–822.
3. Sengupta JN. Esophageal sensory physiology. *GI Motility online.* 2006;doi:10.1038/gimo16
4. Page AJ, Martin CM, Blackshaw LA. Vagal mechanoreceptors and chemoreceptors in mouse stomach and esophagus. *J Neurophysiol.* 2002;87:2095–2103.
5. Lennerz JKM, Deutsch C, Bernardini N, Hummel T, Neuhuber WL, Reeh PW. Electrophysiological characterization of vagal afferents relevant to mucosal nociception in the rat upper oesophagus. *J Physiol.* 2007;582:229–242.

6. Mazzia C, Clerc N. Ultrastructural relationships of spinal primary afferent fibres with neuronal and non-neural cells in the myenteric plexus of the cat oesophagogastric junction. *Neuroscience*. 1997;80:925–937.
7. Ammons WS, Foreman RD. Responses of T2–T4 spinal neurons to stimulation of the greater splanchnic nerves of the cat. *Exp Neurol*. 1984;83:288–301.
8. Satchell PM. Canine oesophageal mechanoreceptors. *J Physiol*. 1984;346:287–300.
9. Sengupta JN, Kunvar D, Goyal RK. Characteristics of vagal esophageal tension-sensitive afferent fibers in the opossum. *J Neurophysiol*. 1989;61:1001–1010.
10. Sengupta JN, Saha JK, Goyal RK. Stimulus-response function studies of the esophageal mechanosensitive nociceptors in sympathetic afferents of opossum. *J Neurophysiol*. 1990;64:796–812.
11. Janig W, Morrison JFB. Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. *Prog Brain Res*.1986;67:87–114.
12. Cervero F. Neurophysiology of gastrointestinal pain. *Balli Clin Gastroenterol*. 1988;2:183–199.
13. Habler HJ, Janig W, Koltzenburg M. Activation of unmyelinated afferent fibers by mechanical stimuli and inflammation of the urinary bladder in the cat. *J Physiol*. 1990;425:545–562.
14. Sengupta JN, Saha JK, Goyal RK. Differential sensitivity of bradykinin to ED-sensitive mechanoreceptor in vagal and sympathetic afferents of the opossum. *J Neurophysiol*. 1992;68:1053–1067.
15. Medda BK, Sengupta JN, Lang IM, Shaker R. Response properties of the brainstem neurons of the cat following intra-esophageal acid-pepsin infusion. *Neuroscience*. 2005;135:1285–1294.
16. Page AJ, Blackshaw LA. An in vitro study of the properties of vagal afferent fibres innervating the ferret oesophagus and stomach. *J Physiol*. 1998;512:907–916.
17. Nonidez JF. Afferent nerves in the intermuscular plexus of the dog's esophagus. *J Comp Neurol*.1946;85:177–189.
18. Rodrigo J, Hernandez CJ, Vidal MA, Pedrosa JA. Vegetative innervation of the esophagus II: intraganglionic laminar endings. *Acta Anat*. 1975;9:79–100.
19. Berthoud HR, Powley TL. Vagal afferent innervation of the rat fundic stomach: morphological characterization of the gastric tension receptors. *J Comp Neurol*. 1992;319:195–276.
20. Zagorodnyuk VP, Chen BN, Costa M, Brookes SJH. Mechanotransduction by intraganglionic laminar endings of vagal tension receptors in the guinea-pig oesophagus. *J Physiol*. 2003;553:575–587.
21. Phillips RJ, Powley TL. Tension and stretch receptors in gastrointestinal smooth muscle: re-evaluating vagal mechanoreceptor electrophysiology. *Brain Res Rev*. 2000;34:1–26.
22. Yu S, Undem BJ, Kollarik M. Vagal afferent nerves with nociceptive properties in guinea-pig oesophagus. *J Physiol*. 2005;563:831–842.
23. Cervero F, Janig W. Visceral nociceptors: a new world order. *TINS*. 1992;15:374–378.
24. Malliani A, Lombardi F. Consideration of the fundamental mechanisms eliciting cardiac pain. *Am Heart J*. 1982;103:575–578.
25. Schaible, H-G, Schmidt, RE Time course of mechanosensitivity changes in articular afferents during a developing experimental arthritis. *J Neurophysiol*. 1988;60:2180–2195.