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Neural sensing of organ volume

Benjamin D. Umans and **Stephen D. Liberles***

Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA.

Abstract

Many internal organs change volume periodically. For example, the stomach accommodates ingested food and drink, the bladder stores urine, the heart fills with blood, and the lungs expand with every breath. Specialized peripheral sensory neurons function as mechanoreceptors that detect tissue stretch to infer changes in organ volume, and relay this information to the brain. Central neural circuits process this information and evoke perceptions (satiety, nausea), control physiology (breathing, heart rate), and impact behavior (feeding, micturition). Yet, basic questions remain about how neurons sense organ distension, and whether common sensory motifs are involved across organs. Here, we review candidate mechanosensory receptors, cell types, and neural circuits, focusing on the stomach, bladder, and airways. Understanding mechanisms of organ stretch sensation may provide new ways to treat autonomic dysfunction.

Keywords

mechanosensation; Piezo2; ASIC; vagus nerve; dorsal root ganglia; DRG

Internal organ mechanosensation

Mechanosensory neurons detect a variety of forces. External sensory neurons detect forces in the environment, including those that elicit the sensations of touch, hearing, and mechanical pain. Recent advances have revealed key features of external mechanosensory neurons [1], including the identities of some mechanically gated ion channels that function as sensory receptors [2]. Other internal sensory neurons detect a diversity of forces from within the body that can inform for instance about blood pressure changes in the vasculature, urine passing through the urethra, or esophageal expansion during swallowing. Other internal mechanosensory neurons function as proprioceptors or sense mechanical irritants that evoke cough, sneeze, gagging, or pain. This review will highlight a particular class of internal mechanosensory neurons specialized to inform on visceral organ volume changes.

Many organs, including the stomach, heart, lung, bladder, and intestine, periodically fill and empty while carrying out their normal physiological functions. Dedicated sensory neurons report on changes in organ volume to help orchestrate appropriate physiological and

*Correspondence: Stephen_Liberles@hms.harvard.edu, phone: (617) 432-7283, fax: (617) 432-7285.

behavioral responses. While organ distension might seem like a common physical stimulus, there are unique features of volume sensing in different organs related to anatomy, filling rate, force vectors, and organ accommodation and mobility. For example, the bladder fills slowly with urine (liquid) over hours, the stomach fills during a meal (solid and/or liquid) in minutes, and the lungs fill with air (gas) in seconds. To accommodate differing physical parameters, sensory neurons in various organs can display highly specialized terminal morphologies and utilize distinct sensory receptors, although data remain limited in some systems. Perhaps the most progress towards understanding force sensation in internal organs has been made in the airways, with recent studies revealing an essential role for the mechanically gated ion channel Piezo2 [3]. Furthermore, stretch of different organs can evoke different physiological responses, and to achieve this, sensory neurons must engage appropriate neural circuits and be sensitive to distinct neuromodulators. The goal of this Review is to highlight common and unique features of stretch sensation in three different organs: the bladder, stomach, and airways. We note that sensory pathways can vary across species; we try to generalize when possible, but primarily discuss work in the mouse, where genetic approaches have enabled perturbation studies to elucidate the roles of particular genes and neurons.

Airway stretch

During passive breathing, sensory neurons detect airway expansion that occurs with every breath. In 1868, Ewald Hering and Josef Breuer revealed a key physiological role for airway mechanosensation when they reported the now-classical respiratory reflex named after them, the Hering-Breuer inspiratory reflex (HB reflex) [4]. The HB reflex is evoked by increasing gas pressure in the lungs and airways, and is characterized by a reflexive inhibition of inspiration and prolongation of expiration. The HB reflex contributes to normal respiratory rhythms and may also protect the airways from damage associated with overinflation. Additionally, airway stretch regulates smooth muscle tone, vascular tone, and heart rate [5–7]. Furthermore, the HB reflex may be modulated during particular physiological states, such as heavy exercise [8], or impacted during pathologies such as asthma, pulmonary fibrosis, airway obstruction, and lung damage; for excellent reviews on airway sensory neurons, see [9–16].

Airway stretch sensation is mediated by the vagus nerve, which provides the major innervation of the pulmonary system (Figure 1) [11]. Surgical transection of the vagus nerve (vagotomy) eliminates the HB reflex [4], and electrical or optogenetic stimulation of vagal afferents causes a reflexive apnea similar to the HB reflex [15, 17]. Different vagal afferents derive from the neural crest (jugular ganglion) and epibranchial placodes (nodose ganglion), with sensory neurons of the nodose ganglion mediating respiratory responses to airway distension [3]. Vagal afferents in the nodose ganglion relay respiratory inputs to a brainstem region termed the nucleus of the solitary tract (NTS), while jugular ganglion inputs are instead mostly relayed to the paratrigeminal nucleus [18, 19]. Second-order NTS neurons that respond to airway stretch include so-called ‘pump cells’ and ‘inspiratory-β cells’ and are localized to a discrete anterior and ventrolateral region of the visceral NTS (the visceral NTS refers to the NTS division that receives sensory input from internal organs and is caudal to the gustatory NTS involved in taste processing) [20]. Pump cells in turn send

various projections, including to brainstem respiratory nuclei where they interrupt intrinsic oscillations that promote rhythmic inspiration [20].

Electrical recordings of the vagus nerve revealed at least three major classes of sensory neurons that innervate the lungs and upper airways: slowly adapting stretch receptors (SARs), rapidly adapting stretch receptors (RARs), and chemoreceptors [11]. SARs are myelinated fast-conducting A fibers that display low-threshold and graded responses to airway stretch [21]. *In vivo* calcium imaging within the mouse nodose ganglion revealed that SAR responses occur in only ~4% of nodose sensory neurons, or about 90 neurons per ganglion [22]. Airway stretch responses are similarly evoked by infusion with ambient air, oxygen, or the inert gas nitrogen, consistent with a mechanical response [22, 23]. SARs are activated by increases in lung volume that occur with each inhalation during relaxed (eupneic) breathing [22, 23].

Similar to SARs, RARs are also stretch-sensitive myelinated A fibers [21], but their frequency can vary across species [24]. RARs display high threshold responses, are not richly active during eupneic breathing, and are also activated by lung deflation [11]. Additionally, RARs may contribute to irritant responses, such as cigarette smoke- induced cough [25, 26]. Chemoreceptors are slower conducting C fibers that function in airway defense, with potential roles in cough [27], airway hypersensitivity [28], and modulation of immune function [29]. Chemical or optogenetic activation of airway C fibers causes rapid and shallow breathing [17, 30], perhaps to limit toxin absorption [11]. Sensory neurons from dorsal root ganglia (DRG) also innervate the airways, although more sparsely than vagal afferents, and their function remains largely uncharacterized.

The morphology of force-sensing neurons in the airways that mediate the HB reflex is unclear. Attempts to quantify SARs in different regions of the airways by focal pressure application have suggested a distributed anatomy with variable results about their location in trachea, extrapulmonary bronchi, and intrapulmonary airways [13]. Adding complexity, while some electrophysiological approaches suggested that SARs are abundant in large extrapulmonary airways, other studies suggested that the HB reflex is more powerfully evoked by mechanical input in smaller airways [11, 13]. Some variation may be due to species of study, but it is also possible that neurons with mechanoreceptive fields in different airway regions display different activities during respiration, with intrapulmonary receptors blocking inspiration and upper airway receptors promoting expiration [11]. Higher resolution anatomical studies of afferent nerve terminals suggested that SARs reside near airway smooth muscle [31], although alternative sites of airway mechanosensation have also been proposed [11,32]. Additional studies are needed to clarify the location and architecture of force-sensing structures in the airways.

Recent progress revealed that the mechanically gated ion channel Piezo2 is essential for airway mechanosensation and the HB reflex [3]. Piezo2 is an enormous protein, comprised of over 2000 amino acids and at least 26 transmembrane α-helices, that forms an ion channel intrinsically gated by mechanical force [33]. High resolution cryo- electron microscopy revealed that the related channel Piezo1 forms a trimeric propeller blade structure with a central pore embedded in curved membrane; one model posits that

membrane tension flattens the central membrane, allowing for allosteric gating of the channel pore [34, 35]. Piezo2 is expressed in some DRG sensory neurons [36], where it mediates gentle touch and limb proprioception [33], as well as in a subset of vagal sensory neurons [17]. Piezo2-expressing vagal afferents in the airways are SARs, and optogenetically activating them acutely inhibits breathing, trapping animals in a state of exhalation [3]. Global knockout of Piezo2 is lethal due to respiratory distress, but mice with selective elimination of Piezo2 from epibranchial placode-derived cells (*Phox2b-Cre; Piezo2*$^{fl/fl}$ mice, herein named *Piezo2*^{epKO} mice) survive [3], allowing for interrogation of Piezo2 function in nodose ganglion neurons. *Piezo2*^{epKO} mice fail to display both vagal afferent responses to airway stretch across a range of stimulus intensities (Figure 1B), as well as the HB reflex. Furthermore, conditional ablation of Piezo2 in adult animals using a tamoxifen-inducible Cre driver line diminishes airway stretch-evoked nerve responses and respiratory reflexes, suggesting that Piezo2 functions directly in stretch sensation rather than in afferent neuron development [3]. Intriguingly, human patients with loss of Piezo2 function can survive, but display a spectrum of dramatic physiological impairments that includes respiratory complications during infancy [37]. Taken together, these findings indicate a key role for Piezo2 in neurons that sense airway stretch. *Piezo2*^{epKO} mice should allow for a better understanding of the role of lung volume sensing in health and disease.

Stomach stretch

During a meal, the stomach expands to accommodate ingested food and drink. Neurons sense increases in stomach volume, and trigger neural circuits that inhibit feeding behavior and promote digestion [38]. Small increases in stomach volume evoke the sensation of satiety or fullness, while larger increases in stomach volume evoke distinct sensations of nausea and pain [39]. The stomach consists of discrete anatomical regions, with stretch-induced meal accommodation occurring primarily in the forestomach or fundus (Figure 2). It is conceivable that pharmacological strategies to stimulate or enhance stomach stretch responses will become available once the underlying sensory transduction mechanism is understood at a molecular level, possibly providing much-needed therapeutic approaches to curb appetite [40].

The stomach receives dense innervation from vagal, DRG, and enteric neurons [41]. The vagus nerve is thought to mediate responses to stomach stretch associated with fullness, as surgical vagotomy below the diaphragm blocks fullness from gastric distension [42, 43]; DRG neurons also detect stomach stretch [44, 45], but their role in perception and behavior is less clear. Vagal afferents respond to stomach stretch and tension in a graded manner with thresholds that correspond to volume changes that occur during a meal, and with little or no adaptation [46, 47]. Vagal afferents display at least three types of terminal morphologies within the stomach: intraganglionic laminar endings (IGLEs), intramuscular arrays (IMAs) and mucosal endings (Figure 2) [41]. IGLEs are located near mechanosensory hotspots in the stomach [48], where they appose enteric ganglia between layers of stomach muscle [49]. Genetic approaches revealed that vagal afferent subtypes containing GLP1R (in *GlpIr-ires-Cre* mice) both respond to stomach stretch and form IGLE terminals (Figure 2), directly linking neuron response properties and anatomy [22]. IGLE terminals are observed not just in the stomach but also in the esophagus (vagal), proximal small intestine (vagal), and colon

(DRG) [41, 50]. IMAs appear as long, parallel fibers within a muscle layer, resembling muscle spindle afferents, and are closely associated with interstitial cells of Cajal [51]; however, methods for selective interrogation of IMAs are lacking, and a mechanosensory role for IMAs has not been experimentally demonstrated [52].

IGLEs are proposed to be intrinsically mechanosensitive based on response kinetics, as stretch evokes fast responses that occur within 6 milliseconds and persist in calcium- free media [53]. However, this short latency does not strictly preclude synaptic transmission, which can occur on faster time scales at some synapses. It also remains unclear why IGLEs form such intimate contacts with enteric neurons. IGLE architecture in colon (from DRG neurons) can be disrupted in mutant mice that lack enteric ganglia, yet these extrinsic neurons still retain some stretch sensitivity [54], suggesting that mechanosensation does not require a stereotyped structure within an IGLE. Instead, electron microscopy of IGLE terminals within esophagus suggested that extrinsic sensory afferents are presynaptic to enteric neurons [55], although functional evidence for sensory neuron to enteric neuron communication within IGLEs has not been demonstrated. Together, these findings raise the possibility of a model where IGLE- forming extrinsic afferents are intrinsically mechanosensitive, relay inputs to the brain to control behavior, and communicate within IGLEs to enteric neurons, perhaps for local control of gut motility and/or digestion. Other possible models are that IGLE-forming extrinsic neurons are second-order to other primary mechanosensory cells, or that both extrinsic neurons and enteric neurons are intrinsically mechanosensitive.

The molecular mechanism by which IGLEs sense stomach stretch is unknown. Pharmacological studies indicated that high concentrations of benzamil (100 μM), an inhibitor of ENaC/ASIC channels (but also other ion channels at this concentration), blocked mechanical responses in an *ex-vivo* esophagus preparation rich in IGLE terminals [53], ASIC channels are expressed by vagal sensory neurons, although IGLE mechanical responses persist in individual ASIC knockout mice [56], Stomach stretch responses were reduced but not eliminated in ASIC2 and ASIC3 knockout mice, but increased in ASIC1 knockout mice [56], The residual mechanosensory responses in ASIC knockout mice suggest that either ASICs are redundant, or that there is another principal mechanosensor. Piezo2 has also been proposed to function as a mechanoreceptor in tissue culture cells derived from enterochromaffin cells [57], but an *in vivo* role for Piezo2 in gastrointestinal stretch sensation has not been shown.

Glp1r-ires-Cre mice enable genetic tagging of stomach-stretch responsive neurons for direct analysis of peripheral and central neuron anatomy, physiological function (e.g., by optogenetics), conduction velocity, neuromodulation, gene expression, and other properties [22]. GLP1R neurons additionally account for intestine stretch-responsive IGLEs, as well as some other neuron types. Cellular imaging and optogenetics-assisted conduction velocity measurements revealed that vagal GLP1R neurons are predominantly capsaicin-sensitive, slow-conducting C fibers [22]. *In vivo* calcium imaging within vagal ganglia indicated that 17% of vagal sensory neurons respond to stomach stretch, and that 81 % of stomach stretch-responsive neurons contain GLP1R [22].

In vagal afferents, GLP1R is frequently co-expressed with several other receptors for gut hormones including cholecystokinin (CCK) and peptide YY (PYY) [22]. GLP-1, CCK, and PYY are all satiety hormones, and GLP-1 is a powerful incretin used in the clinic to promote insulin release in diabetic patients [58]. These and other feeding-control hormones such as ghrelin and leptin have been proposed to modulate stomach stretch responses [59, 60], perhaps providing integration of mechanical and chemical signals. CCK, GLP1, and other gut hormones activate distinct intracellular signaling pathways, and additional studies are needed to understand the consequences of activating these various pathways in stomach stretch sensors. Of gut hormones analyzed, CCK is sufficient to stimulate stomach stretch-responsive afferents *in vitro* [22, 61, 62]. Yet, intestinal nutrients, which promote CCK release, do not activate gastric mechanoreceptors *in vivo*, as calcium imaging of vagal ganglia revealed that gastric mechanoreceptors and intestinal chemoreceptors are distinct cell populations [22]. Perhaps *in vivo*, CCK provides subthreshold sensitization of mechanoreceptors to promote satiety signaling when physiologically appropriate, such as during a meal.

Stomach stretch sensors activate neural circuits that reduce appetite and control digestive physiology. Genetically guided anatomical mapping approaches revealed that vagal GLP1R neurons project to a discrete brainstem region in the medial NTS and adjacent area postrema [22]. Furthermore, neurons intrinsic to this region express the immediate early gene cFos after gastric distension [63]. The projection domain of stomach stretch-responsive neurons is distinct from NTS regions that receive airway input, consistent with a topographic map in the brainstem for visceral input [17, 20, 22, 64]. cFos induction in the NTS increases with the extent of gastric distension [63], and similarly located neurons also express cFos following exposure to nutrients, leptin, or nausea-inducing chemicals [65, 66]. Additional studies are needed to understand whether the NTS differentially represents satiety and nausea through discrete neural pathways, or through changing activity patterns in a ‘labeled line’ constituted by the same neurons. Future studies are needed to understand how information about gastric distension is routed to control behavior, presumably by altering activity in appetite- control neurons of the hypothalamic arcuate nucleus [67] and/or aversion-promoting neurons in the parabrachial nucleus [68].

Bladder stretch

Neurons that sense bladder volume are essential for proper control of micturition (urination) [69–73]. The bladder is a hollow organ that fills slowly and progressively with urine, and increasing bladder volume (and thereby stretch) promotes the drive to urinate. In humans, bladder pressures of 5–15 mmHg elicit the sensation of bladder fullness, 20–25 mmHg induce urgency, and 30 mmHg evoke pain [72]. Inappropriate bladder control can be common in the young and old, and dysfunction of neural circuits that control the bladder can cause medical problems such as uncontrollable urination (incontinence).

Bladder sensory neurons detect bladder stretch, and relay this information to brainstem regions that drive micturition [74]. Bladder sensory neuron soma reside in lumbar and sacral DRG, rather than vagal ganglia, and access the bladder through the hypogastric, pelvic, and pudendal nerves [74, 75]. Sensory input from the bladder is transmitted through the spinal

cord, triggering both local spinal reflexes and ascending input to the brainstem [74]. Low levels of bladder stretch trigger spinal cord circuits that activate a sympathetic response resulting in bladder accommodation [74]. Increasing bladder stretch blocks sympathetic responses, and promotes micturition drive primarily through ascending input to two key brainstem regions: the periaqueductal gray (PAG) and the pontine micturition center (PMC) [74, 76, 77]. Together, the PAG and PMC form a bistable system that switches between 'guarding' when the bladder fills with continence and 'voiding' [74]. Many brain regions provide input to the PAG and PMC, allowing for integration of bladder volume information with forebrain circuits relevant for voluntary induction or restraint of micturition [78]. For example, when the bladder is in a low- volume state, forebrain circuits can suppress micturition until a socially appropriate opportunity arises [74], or promote micturition in animals that use urinary scent marks for pheromone-based social communication [79]. High bladder volumes can override forebrain circuits, leading to uncontrollable and reflexive micturition.

The PMC is a command center that communicates with motor efferent pathways to the urinary tract, and bilateral PMC lesions impair micturition [80]. Single unit recordings revealed that activity in most PMC neurons (70–80%) is tightly linked to motor function, including 'direct neurons' that fire before and during reflexive bladder contractions, and 'inverse neurons' that fire between bladder contractions [81, 82]. PMC direct neurons express CRH and glutamate, and optogenetic activation of direct neurons promotes micturition, while genetically silencing them suppresses micturition [83]. PMC direct neurons initiate voiding through descending motor programs that contract bladder smooth muscle and relax the urethral sphincter.

Volume sensing in the bladder is essential for the voiding reflex, but underlying mechanisms are incompletely understood [69–73]. Anatomically, the interior bladder surface consists of an epithelial layer termed the urothelium (Figure 3). The urothelium forms a tightly sealed barrier to confine bladder contents, but also functions as a sensory structure [84]. Specialized 'umbrella cells' constitute the urothelium surface; as bladder volume increases, umbrella cells change shape dramatically - like an opening umbrella - to accommodate volume increases by expanding epithelial surface area. Basally, the basement membrane of the urothelium is penetrated by sensory afferents, with particularly dense innervation in bladder regions near the urethral opening. Sensory neurons that terminate near the basal urothelium include those that sense bladder stretch; other bladder sensory neurons are urethral mechanoreceptors, innervate the vasculature, form antenna-like endings in muscle, and function as nociceptors [71,85].

Bladder distension activates urothelium-innervating A-delta fibers in a graded manner, with response thresholds of 5–15 mmHg similar to sensation thresholds [86]. Neurons with low and high response thresholds are reported [87], suggesting that increases in bladder volume evoke variable perceptions (from filling to discomfort to pain) by activating additional classes of sensory neurons. Neurons with low-threshold and high- threshold responses would presumably evoke distinct sensations by coupling to different higher-order neural circuits. An alternative model is that stretch-responsive neurons collectively function as a rheostat, with increasing signal intensity across the sensory neuron repertoire differentially read by

central neural circuits to increase micturition drive and change evoked perception. Separate from A fibers, slow- conducting C-fibers display high threshold responses or are silent during bladder stretch, but can be sensitized by chemical modulators that may enhance mechanical responses during injury or inflammation [74].

Sensory neurons that respond to bladder stretch may be first-order neurons intrinsically sensitive to force and/or second-order neurons that receive input from urothelial stretch sensors. Stretch responses persist in some but not all bladder sensory neurons after surgical removal of the urothelium, or (in some studies), in low-calcium conditions where synaptic release is reduced [88]. These findings suggest that at least some neurons do not require urothelial input to fire but may instead be intrinsically mechanosensitive. Pharmacological studies revealed that these neurons, like esophageal IGLEs, are sensitive to high concentrations of benzamil, but not to blockers of other candidate mechanoreceptors [88]. However, the identity of mechanoreceptors utilized by afferent nerves remains unclear.

Bladder stretch also triggers mechanical responses in the urothelium, leading to release of chemical transmitters that can activate afferent nerves. For example, stretch promotes a 10- to 50-fold increase in ATP release from the urothelium [89, 90], with a response threshold of ~4 mmHg and a response magnitude that correlates with the extent of stretch [91]. ATP applied *in vitro* activates bladder afferents through the ionotropic ATP receptors P2X2 and P2X3 [92]. It is difficult to quantify ATP levels *in vivo* near afferent terminals, and pharmacological studies have produced conflicting results about the role of purinergic receptors in physiological stretch sensation [88, 93]. Knockout of P2X2 and P2X3 in mice alters bladder function, increasing bladder capacity and decreasing voiding frequency [92]. ATP-mediated control of bladder accommodation may involve purinergic receptor-dependent mobilization of vesicular trafficking in umbrella cells to change bladder surface area [94]. Afferent nerve responses to bladder stretch persist in P2X2/P2X3 double knockouts [92], suggesting another redundant or dominant mechanosensory pathway; the administered volume that triggers a threshold nerve response is increased [92], but this effect may be explained by altered bladder accommodation. Notably, ATP release is further enhanced following injury and inflammation, and perhaps purinergic signaling sensitizes stretch responses during these conditions to decrease accommodation and promote early voiding [95, 96]. Adding complexity, ATP is just one of many factors that influences bladder afferent activity, with roles for nitric oxide, acetylcholine, prostaglandins, and peptide hormones also reported [71, 97, 98].

Mechanoreceptors that sense force in the urothelium, like those in bladder sensory afferents, are unknown. Several candidates have been proposed, including channels of the ENaC, TRP, and Piezo families [88, 99, 100]. The TRPV4 ion channel is a candidate to contribute to stretch-evoked responses in the urothelium, where it is abundantly expressed [99]. TRPV4 agonism promotes calcium increases in bladder urothelium and ATP release, and TRPV4 knockout mice display incontinence-like behavior with reduced (but not eliminated) calcium mobilization and ATP release in bladder urothelium after stretch [99, 101, 102]. TRPV4 can be gated by osmolarity changes, heat, chemical agonists, and other stimuli [103], but its precise biochemical function in urothelial cells requires elucidation. More generally, additional studies are essential to understand the primary force-sensing apparatus in the

bladder that ultimately results in afferent nerve activity. Understanding mechanisms of bladder stretch sensation may offer new ways to treat bladder dysfunction.

Concluding Remarks

Many internal organs change volume dynamically while they temporarily fill with food (stomach), urine (bladder), blood (heart), and air (lungs). Dedicated sensory neurons monitor the volumetric state of internal organs- as reflected by tissue stretch or pressure - to help control basic physiological functions such as breathing, heart rate regulation, digestion, micturition, and feeding behavior.

Much remains to be discovered about how different mechanosensory neurons sense forces associated with internal organ stretch (see ‘Outstanding Questions’). Extrinsic afferents in stomach and bladder display intimate but poorly understood contacts with local cells: enteric neurons and urothelial cells respectively. It remains unclear also which cell types first sense force in the bladder and stomach to initiate afferent signals to the brain, and what sensory receptors they utilize. Airway sensory neurons that mediate the HB reflex are first-order mechanoreceptors and utilize Piezo2, but additional studies are needed to understand the architecture of force-sensing terminals in the airways. Extrinsic sensory neurons are also sensitive to various hormones, including CCK (stomach), GLP1 (stomach), and ATP (bladder, stomach, airways) and hormones may sensitize sensory responses, modulate presynaptic neurotransmitter release, or evoke other cellular responses. Additional work is required to understand hormone-activated signaling pathways in sensory neurons, and the consequences on physiology and behavior. Furthermore, while this Review focused on some of the best studied systems and pathways, less is known about other mechanosensors, such as DRG neurons in the stomach and RARs in the airways, as well as stretch sensing mechanisms in other organs such as the heart and intestine.

Available evidence appears to indicate a high degree of sensory neuron specialization across organ systems, with sensory neurons in each organ displaying many unique features (Table 1). Low-threshold gastric and airway distension activates vagal afferents, while bladder stretch activates DRG afferents. Airway stretch sensors, and likely gastric stretch sensors, are intrinsic first-order mechanosensors, while bladder afferents may function as primary or secondary neurons during normal bladder filling. IGLE terminals near enteric neurons sense forces throughout the alimentary canal, including in the esophagus, stomach, duodenum, and colon. Force in the bladder is sensed in the urothelium by epithelial cells and/or by free sensory endings, while force in the airways may involve endings in smooth muscle [31]. Together, these findings indicate that bladder, stomach, and airway stretch sensors can display at least some variations related to neuron morphology, response properties, receptor utilization, and neuromodulation.

Some common features of sensory perception across different organs are also apparent. For example, changing stimulus intensity can alter perception, with high- magnitude distension of both stomach and bladder evoking discomfort and pain. It is unclear how such volume increases are functionally coded by afferent network activity. Perhaps high organ volumes shift perceptions by recruiting high-threshold mechanoreceptors with different central

connectivity. Alternatively, activity across the sensory neuron repertoire may be integrated to measure the extent of volume filling. Different strategies for intensity coding are used by other sensory systems. In the olfactory system, increasing odor concentration can recruit separate low-affinity olfactory receptors that may change odor perception [104]. In the gustatory system, however, sensors for bitter and sweet (but not salt) are more homogenous, with variable signal intensity likely encoded within a single labeled line rather than by discrete low- and high-threshold sensing pathways [105].

Why have unique sensory mechanisms evolved in each organ for stretch sensation? A comparative analysis of primary force-sensing receptors may provide insights into how evolution independently solved related problems in mechanosensation. Piezo2 is a mechanically gated ion channel essential for airway stretch sensation [3], and we await a similar characterization of stretch sensing receptors and pathways in the bladder, stomach, and other internal organs like the esophagus, intestine, heart, and vasculature. The availability of powerful genetic approaches for cell type-selective gene manipulation should enable definitive loss-of-function studies for receptor identification. Understanding basic principles of stretch sensation across organs should enable new ways to treat dysfunctions of the autonomic nervous system.

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Outstanding questions

1. What receptors and pathways underlie sensation of stretch in the bladder, stomach, and other organs?
2. What is the location and architecture of primary force-sensing terminals in the airways and bladder?
3. What is the importance of interactions between afferent neurons and resident enteric neurons (stomach) and urothelial cells (bladder)?
4. How are mechanosensory neurons modulated by hormones and other extracellular signals (like GLP1, CCK, and ATP)?
5. How do DRG and enteric neurons contribute to internal organ sensation?
6. How do ascending sensory networks distinguish low-intensity and high-intensity stretches, known to evoke different perceptions?
7. How do neural circuits route stomach stretch inputs to higher-order brain centers that control feeding and/or nausea?
8. What features of stretch sensation are common across sensory organs, and what are specialized?
9. Are sensory mechanisms conserved across evolution in species with different internal organ anatomy and function?

Highlights

- Sensory neurons detect stretch of bladder, stomach, and airways to inform on organ volume and enable appropriate physiological and behavioral responses.
- Piezo2 mediates airway stretch sensation and the Hering-Breuer inspiratory reflex.
- Stomach stretch is sensed by IGLE terminals between layers of stomach muscle.
- Primary mechanoreceptors that underlie afferent nerve responses to bladder and stomach stretch sensation are unknown.

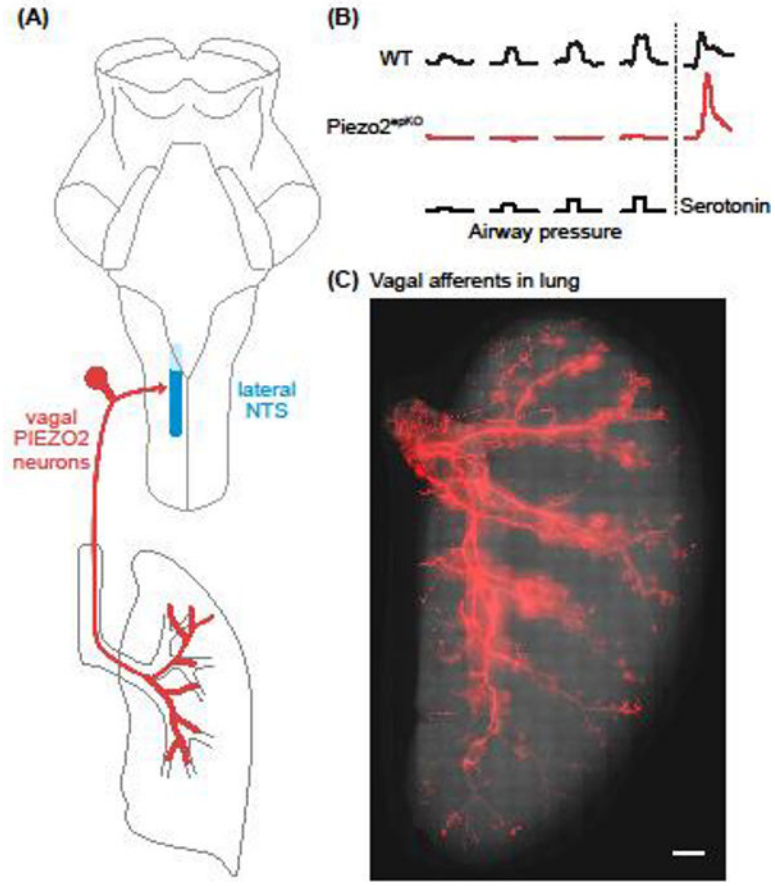

Figure 1. Sensory innervation of the lungs.

(A) Vagal sensory neurons send afferent fibers to the lungs (red) as well as central projections to the anterolateral portion of the visceral NTS (dark blue), caudal to the gustatory NTS (light blue). Nodose ganglion- derived Piezo2 neurons sense airway stretch, although sensory terminal morphology awaits additional characterization. **(B)** Whole vagus nerve electrophysiological responses to airway stretch are lost in Piezo2^{epko} mice. Adapted from [3] **(C)** Genetically guided anatomical mapping of vagal sensory afferents in a lobe of the mouse lung (scale bar = 1 mm), adapted from [6].

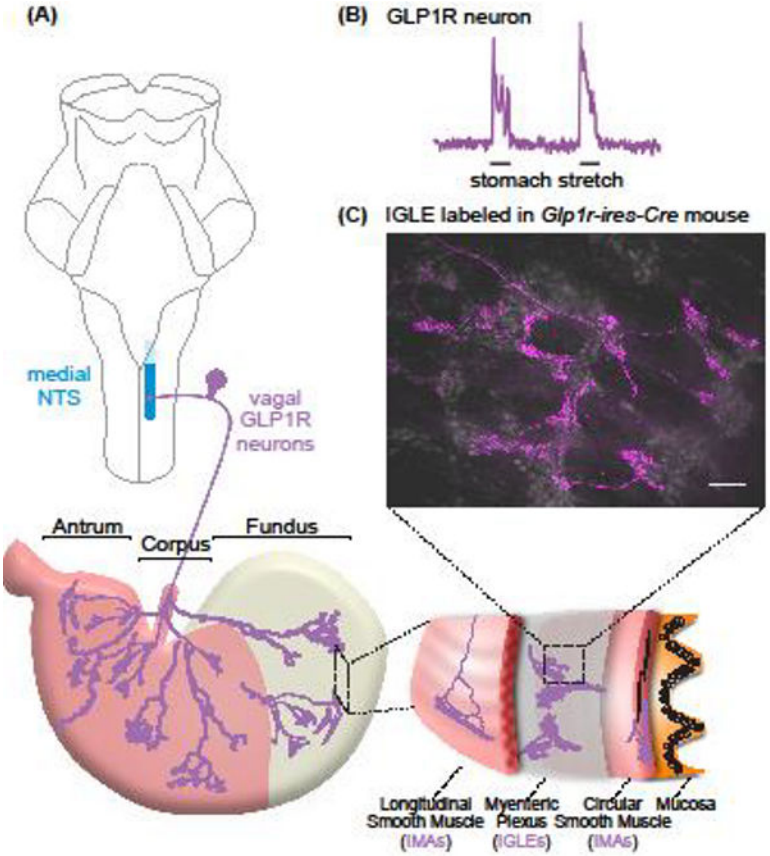

Figure 2. Sensory innervation of the stomach.

(A) Patterns of vagal sensory neuron innervation in mouse stomach are drawn (magenta) based on observations from anatomical tracing experiments [22]. Vagal fibers enter along the esophagus and radiate over the stomach surface. A cross-section (parallelogram) of stomach tissue is depicted (bottom right), showing mucosal layers, and two orthogonal layers of stomach muscle. Enteric neurons of the myenteric plexus reside between muscle layers and are innervated by IGLEs. IMAs are found in each muscular layer in parallel with muscle and near interstitial cells of Cajal. The stomach also receives input from DRG sensory neurons, and additional vagal sensory neurons that access stomach mucosa (not shown). **(B)** A single vagal GLP1R neuron responds to stomach stretch, as measured by *in vivo* calcium imaging in vagal ganglia. Adapted from [22]. **(C)** Vagal GLP1R neurons form IGLE terminals, as visualized by genetically guided anatomical mapping (scale bar = 100 μm) [22]. Note the proximity of IGLE terminals (magenta) to enteric ganglia (gray).

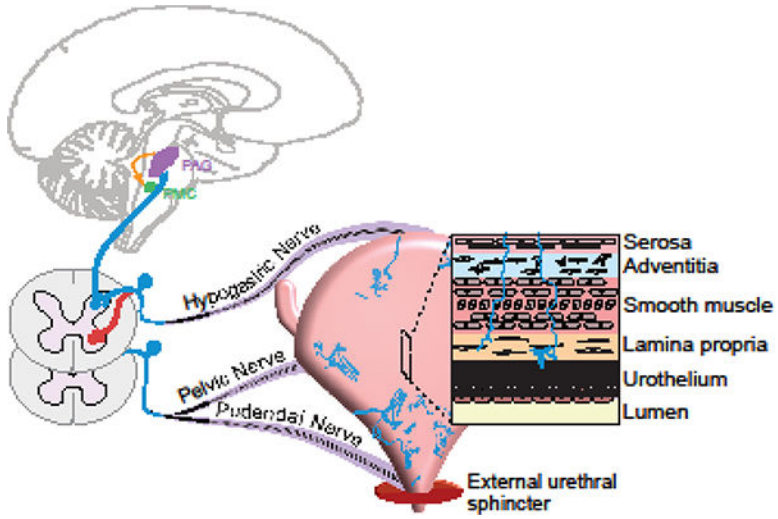

Figure 3. Sensory innervation of the bladder.

The bladder is innervated by three spinal nerves, with sensory neuron soma located in dorsal root ganglia from the sacral and lumbar spinal cord. The outer layers of the bladder include serosa and adventitial connective tissue surrounding three layers of smooth muscle, collectively named the detrusor muscle, arrayed in alternating orientations. The lamina propria contains vasculature and interstitial cells of Cajal, similar to the gastrointestinal tract. The mucosa consists of a transitional epithelium overlying a basement membrane, with umbrella cells facing the lumen to form an expandable membrane surface. Nerve terminals are particularly concentrated in the lamina propria and the basal layer of the urothelium. Afferent sensory neurons communicate locally within the spinal cord (red) and provide ascending input to the brainstem (blue). PAG: periaqueductal grey; PMC: pontine micturition center.

Table 1.

Key features of sensory neurons that detect distension of the airways, stomach, and bladder.

	Airways	**Stomach**	**Bladder**
Physiological responses to stretch	apnea (HB reflex), cardiovascular tone	satiety (medium), digestion, pain (high)	accommodation (low), micturition (medium), pain (high)
Afferent nerve type	vagal (HB reflex)	vagus (satiety), spinal (unknown function), enteric (digestion)	spinal
Primary sensory cell	extrinsic neuron	proposed: extrinsic neuron; role of enteric neurons unknown	proposed: urothelial cells and/or extrinsic neuron
Anatomy of sensory Terminal	proposed: terminals near smooth muscle	IGLE	terminals in urothelium
Sensory neuron modulators	proposed: respiratory gases	gut hormones (e.g. CCK)	inflammatory cues (e.g. ATP)
Central targets	NTS	NTS	dorsal spinal cord, PAG, PMC
Primary stretch-activated sensory receptor for afferent nerve signaling	Piezo2	?	?