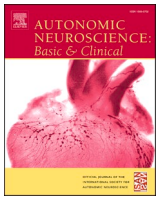
Autonomic Neuroscience: Basic and Clinical 268 (2026) 103507



Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu



Review

Vagal mechanoreceptors controlling gastrointestinal function☆

Elijah David Lowenstein [a,*], Carmen Birchmeier [b,*]

[a] Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02215, USA
[b] Neurowissenschaftliches Forschungszentrum, NeuroCure Cluster of Excellence, Charité, and Max-Delbrück-Centrum für Molekulare Medizin in der Helmholtz-Gemeinschaft, Berlin, Germany

ARTICLE INFO

Keywords:
Vagal mechanoreceptors
Vagal afferents and vagus nerve
Vagal mechanoreception
Gut
Gastrointestinal tract
GI mechanoreception
Piezo2
Glp1r
Oxtr
Prox2
Runx3 vagal sensory neurons
Esophagus
Esophageal
Stomach mechanosensation
Nodose neurons controlling gut stretch or distension

ABSTRACT

The vagus nerve innervates internal organs, in particular the gastrointestinal tract, and is a major communication route between the gut and brain. Most vagal fibers are viscerosensory, but vagal motor axons also travel with the nerve. Vagal sensory neurons can detect mechanosensory information arising from the gastrointestinal tract such as stretch or pressure, and transmit this information to the nucleus of the solitary tract in the brain. Recent technological advances have opened new routes for studying vagal mechanosensation. Single-cell transcriptomic atlases have revealed substantial heterogeneity among vagal sensory neurons and now guide targeted analysis of individual subtypes. Viral and genetic approaches based on molecular profiling enable anatomical tracing, electrophysiological recordings, and selective ablation, silencing, or activation of defined neuronal populations. Recent work has revealed subtypes of vagal mechanoreceptors defined by expression of Prox2, Runx3, Glp1r, and Oxtr, which form intraganglionic laminar endings in the muscle layer of the gut. These mechanoreceptors detect distension in the gastrointestinal tract, such as a bolus moving through the esophagus or the filling of the stomach, and initiate coordinated peristalsis. Together, these mechanosensory pathways enable precise monitoring of gastrointestinal mechanics to support digestive function.

1. Viscero- and somatosensory neurons - an introduction

Sensory neurons (also called afferent neurons) are specialized to detect stimuli and relay this information to second-order sensory neurons located in the central nervous system. Viscerosensory, or interoceptive, neurons – located largely in the vagal ganglia – innervate major organ systems, including the digestive, cardiovascular, and respiratory systems, whereas the urogenital tract and lymphatic organs apparently lack vagal innervation (Prescott and Liberles, 2022). They detect diverse sensory information such as mechanical forces, metabolites, pH, pathogens, and temperature, and transmit this information to the hindbrain (Jänig, 1996; Prescott and Liberles, 2022; Undem and Weinreich, 2005). This interoceptive information is largely processed unconsciously, although we may become aware of it when the stimulus is sufficiently strong. In contrast, the somatosensory neurons located in the dorsal root ganglia (DRGs), and the cranial, trigeminal and jugular ganglia, detect inputs from the external environment through specialized nerve endings in the skin, transmitting conscious information about touch, temperature, texture, and pain through the spinal cord to the brain (Koch et al., 2018). It should be noted, however, that a small number of DRG neurons also innervate the viscera (Jänig, 1996).

Most sensory neurons are pseudounipolar, with cell bodies located in ganglia that extend a single process that bifurcates into two branches: a peripheral branch that terminates in an internal organ or the skin, and a central branch that projects into the central nervous system (Undem and Weinreich, 2005). Both viscero- and somatosensory information is processed centrally, where motor outputs generate movement: internally, as the digestive tract mechanically breaks down food in the stomach and passes the bolus to the intestine, or externally, as we move through our environment.

2. Viscero- and somatosensory neuron development

Viscero- and somatosensory neurons are located in peripheral

☆ This article is part of a Special issue entitled: 'Autonomic gastrointestinal dysfunction' published in Autonomic Neuroscience: Basic and Clinical.

* Corresponding authors.
E-mail addresses: elowens1@bidmc.harvard.edu (E.D. Lowenstein), cbirch@mdc-berlin.de, carmen.birchmeier@charite.de (C. Birchmeier).

https://doi.org/10.1016/j.autneu.2026.103507
Received 2 March 2026; Received in revised form 21 August 2026; Accepted 16 October 2026
Available online 17 October 2026
1566-0702/© 2026 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Open access funding enabled and organized by Projekt DEAL.

sensory ganglia, where they are closely associated with resident glial cells. Although both neurons and glia in most sensory ganglia derive from the neural crest, viscerosensory neurons and their accompanying glia in cranial ganglia have distinct embryonic origins (Rao and Jacobson, 2005; Undem and Weinreich, 2005). Specifically, viscerosensory neurons arise from the epibranchial placodes, specialized regions of the ectoderm, whereas the associated glial cells are derived from the cranial neural crest (Narayanan and Narayanan, 1980; Ayer-Le Lievre and Le Douarin, 1982; D'Amico-Martel and Noden, 1983; Vermeiren et al., 2020).

The homeodomain transcription factor Phox2b is a critical determinant of autonomic nervous system development and function. Phox2b is expressed in all vagal viscerosensory neurons and plays a key role in regulating their specification and differentiation (Pattyn et al., 1999, 1997; Vermeiren et al., 2020). Interestingly, Phox2b specifies all key neuronal components of the gut to brain circuit, from the enteric neurons that line the entire gastrointestinal tract, to the nodose neurons that contact them, and the 2nd order sensory neurons of the nucleus of the solitary tract in the hindbrain (Espinosa-Medina et al., 2017; Morin et al., 1997; Pattyn et al., 1999; Sungeelee et al., 2025). Genetic approaches commonly rely on recombinases to eliminate gene expression in specific cell populations. Genetically modified transgenic mouse strains expressing recombinases (e.g., Cre, FlpO) under the control of Phox2b regulatory elements are available and have frequently been used to analyze viscerosensory neuron function and development (D'Autréaux et al., 2011; Hirsch et al., 2013; Lowenstein et al., 2024).

The sensory vagal ganglion comprises two components: the superior (jugular) and the inferior (nodose) ganglia. Neurons from both extend their peripheral axons through the vagus nerve. In mice, these two ganglia are fused and collectively referred to as the vagal ganglion, whereas in humans they remain anatomically distinct (Undem and Weinreich, 2005). Phox2b+ viscerosensory neurons are located in the nodose portion of the vagal ganglion and derive from the epibranchial placode, while Prdm12+ somatosensory neurons are molecularly and functionally distinct (Kupari et al., 2019; Vermeiren et al., 2020). They are located in the jugular portion of the vagal ganglion and originate from the neural crest. As the majority of the studies discussed here rely on mice as the model organism, we use the term viscerosensory vagal neurons to refer to the neurons of the nodose ganglion.

3. Viscero- and somatosensory mechanosensory neurons

Sensory neurons that are specialized to detect mechanical stimuli such as touch, pressure, tension, stretch, vibration, and sound are referred to as **mechanoreceptive** neurons or **mechanoreceptors**. Most research thus far deals with the cutaneous mechanoreceptors in the dorsal root ganglia that mediate conscious sensations arising from the external world (Handler and Ginty, 2021). In comparison, viscerosensory vagal mechanoreceptors in the nodose ganglia receive less attention, largely because their rarity has made them difficult to study: mice only have one pair of viscerosensory vagal ganglia, compared to the 31 pairs of somatosensory DRGs. Only recently, single-cell mRNA sequencing (scRNA-seq) technologies defined the exact molecular identity of vagal neurons and revealed their vast heterogeneity (see also below). Both vagal and cutaneous mechanoreceptors detect various types of mechanical stimuli and convert them into electrical signals that are relayed to the central nervous system. This is accomplished mainly by activating mechanosensitive ion channels, the best studied being Piezo1/2 (Ranade et al., 2015).

A role for ion channels in sensing mechanical forces has been proposed for decades (Katz, 1950), but their molecular identity remained elusive until the discovery of Piezo channels by Ardem Patapoutian and colleagues. In their seminal 2010 study, Piezo1 and Piezo2 were identified and characterized as rapidly adapting, mechanically activated cation channels (Coste et al., 2010). These channels are evolutionarily conserved and are expressed not only in mechanosensory neurons, but in numerous other cell types across the animal kingdom and even in plants (Hill et al., 2026; Ma et al., 2018; Mousavi et al., 2021; Nakamichi et al., 2022; Schappe et al., 2024). The lack of homology between Piezo proteins and previously known ion channels initially made their structural prediction challenging. More recently, their architecture was resolved using cryo-electron microscopy, revealing that Piezo channels form homotrimeric, propeller-shaped structures, with each subunit containing at least 26 transmembrane helices (Ge et al., 2015; Saotome et al., 2018; Wang et al., 2019).

Piezo2 is required for rapidly adapting mechanically activated currents in DRG neurons, and its function has also been characterized in several subtypes of vagal neurons. In vagal afferents innervating the lung, Piezo2 serves as the primary mechanotransducer detecting stretch during lung inflation (Nonomura et al., 2017). In those that innervate the esophagus, Piezo2 is likewise essential for detecting mechanical stimuli (Nair et al., 2024). In contrast, the baroreceptor reflex in the cardiovascular system requires both Piezo1 and Piezo2 (Zeng et al., 2018). Another mechanically activated ion channel, ELKIN1, was recently identified in DRG neurons where it is required for light-touch sensation in a subset of mechanoreceptors (Chakrabarti et al., 2024). Although it is expressed in viscerosensory neurons, including in subtypes that project to the gastrointestinal tract, its potential role in viscerosensation remains unknown.

Our review focuses on vagal mechanoreceptors but we briefly introduce cutaneous mechanoreceptors, as much of the physiological classification and terminology in the field originates from their study. The 2nd order sensory neurons in the nucleus of the solitary tract that process vagal mechanosensory information were recently discussed by others (Huang et al., 2025; Ly et al., 2026; Ran et al., 2022; Rinaman, 2010).

4. Functional characteristics of mechanoreceptors

Mechanoreceptors detect distinct types of mechanical stimuli. Some are highly sensitive to mechanical forces (low-threshold mechanoreceptors), whereas others are less sensitive and respond to noxious, i.e., potentially harmful, stimuli (high-threshold mechanoreceptors). Their functional characteristics were classically defined via electrophysiological approaches. Mechanical threshold is commonly used to classify viscero- and somatosensory mechanoreceptors (Abraira and Ginty, 2013; Lechner and Lewin, 2013; Wang et al., 2020). Myelination represents an additional distinguishing feature: low-threshold mechanoreceptors are typically myelinated, whereas high threshold receptors are either unmyelinated or thinly myelinated. The degree of myelination has important consequences for conduction velocity in both vagal and DRG neurons. Heavily myelinated axons (Aβ fibers) transmit signals rapidly, while thinly myelinated or unmyelinated axons conduct more slowly (Aδ and C fibers, respectively; the fiber nomenclature was introduced by Joseph Erlanger and Herbert S. Gasser in the 1930's). Another key classification criterion is adaptation speed. Some mechanoreceptors are rapidly adapting, firing primarily at the onset and offset of a mechanical stimulus, whereas slowly adapting mechanoreceptors continue to fire throughout sustained stimulation (Mountcastle, 1957).

Mechanosensitive vagal afferents innervating the digestive tract were first recorded in the anesthetized cat (Paintal, 1954) and goat (Iggo, 1955). As in vitro electrophysiological preparations improved, it became possible to dissect out the esophagus or stomach attached to the vagus nerve and perform recordings. These experiments revealed that vagal afferents were largely slowly adapting, low-threshold mechanoreceptors (Page et al., 2002; Page and Blackshaw, 1998). Later experiments aimed to combine in vitro electrophysiology with morphological analysis to identify the type of ending responding to mechanical cues in the guinea pig esophagus, stomach and small intestine. Thus, after identifying mechanosensory transduction sites, researchers applied a dye locally and found that labeled sensory endings displayed the morphology of intraganglionic laminar endings (Tassicker et al., 1999;

Zagorodnyuk et al., 2003, 2001; Zagorodnyuk and Brookes, 2000). These endings display branched structures that appear to wrap around enteric neurons (Fig. 1).

An alternate approach to study viscerosensory neuron responses to mechanical stimuli uses Ca^{2+} imaging. Genetically encoded calcium indicators, such as GCaMP, can be expressed in vagal neurons either via viral delivery or through transgenic strategies (Tian et al., 2009; Williams et al., 2016). After anesthesia, the vagal ganglia can be surgically exposed for ex vivo imaging while preserving their peripheral and central connections. Subsequent stimulation of peripheral end organs, e.g. gastric or intestinal distension, while recording changes in GCaMP fluorescence, allows for the analysis of neuronal activity patterns. Combining these imaging approaches with post-hoc RNAscope reveals the molecular identity of the responding neuron (Zhao et al., 2022). Restricting GCaMP expression to specific vagal subtypes using transgenic animals was used to characterize responses of gastric vagal Glp1r+ and Oxtr+ neurons to the distension of stomach and intestine, respectively (Rafael et al., 2026; Williams et al., 2016).

5. Physiological roles of mechanosensation in the digestive tract

As food and liquid pass through the digestive tract, they exert pressure outwards and generate shear forces. The gastrointestinal tract does not behave as a passive hollow tube; rather, it generates mechanical forces of its own by actively distending and contracting to propel the bolus through the alimentary canal in a process known as peristalsis (Mercado-Perez and Beyder, 2022). Proper coordination of digestive behaviors requires the nervous system to continuously monitor the mechanical state of the gastrointestinal tract (Kim et al., 2022). This monitoring is mediated by specialized mechanoreceptors. Although enteric neurons and spinal afferents innervating the gastrointestinal tract also possess mechanosensitive properties, many of the key specialized mechanoreceptors are vagal afferents - specifically those afferents forming intraganglionic laminar endings and intramuscular arrays (Brookes et al., 2013).

5.1. Esophagus

Swallowing (deglutition) is an active process that transports food and liquids from the mouth to the stomach via the esophagus. The esophageal phase of swallowing depends on coordinated peristaltic contractions of the esophageal wall, mediated by reflex circuits involving Crhr2+ nucleus ambiguus vagal motor neurons, Prox2+/Runx3+ vagal viscerosensory neurons and enteric ganglia within the esophagus (Coverdell et al., 2022; Ertekin and Aydogdu, 2003; Goyal and Chaudhury, 2008; Lowenstein et al., 2023). Esophageal motility disorders are characterized by dysphagia and frequently occur as comorbidities of aging and age-related neurological diseases (Aslam and Vaezi,

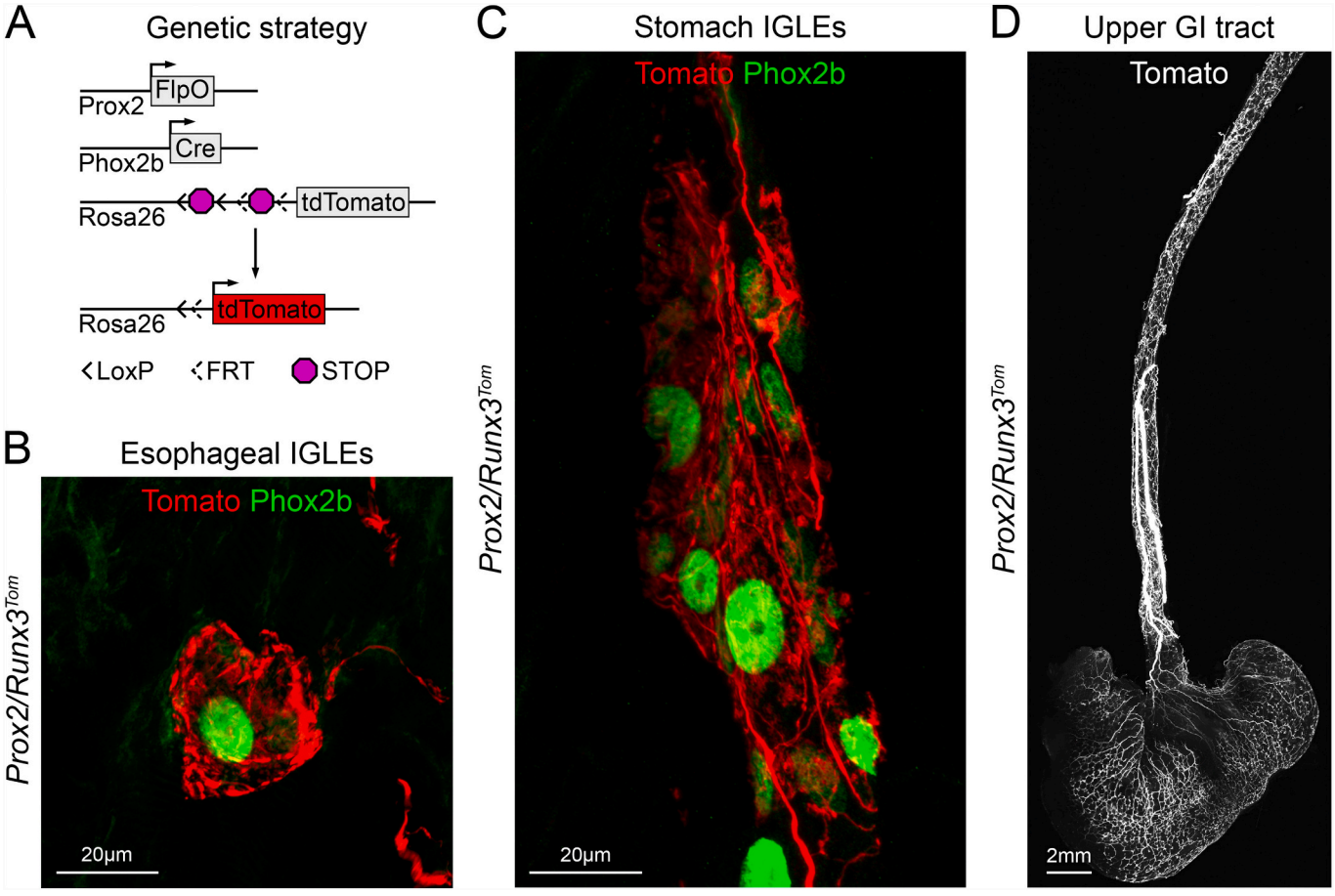


Fig. 1. Prox2/Runx3 neurons form intraganglionic laminar endings in the upper gastrointestinal tract.
(A) Intersectional genetic strategy used to label Prox2/Runx3 neurons with tdTomato by generating *Prox2FlpO;Phox2bCre;Ai65 (Prox2/Runx3^{Tom})* mice. (B, C). Immunohistology of the esophagus (A) and stomach (B) of mice expressing tdTomato in Prox2/Runx3 neurons using antibodies directed against tdTomato (red) and Phox2b (green). tdTomato was expressed after Cre- and Flp- dependent recombination, and the Cre and FlpO recombinase were driven by Phox2b and Prox2 regulatory sequences (to label Prox2/Runx3 neurons) or by Runx3 and Prox2 regulatory sequences (to label Runx3 neurons). (C) Light-sheet image of the esophagus and stomach of mice expressing tdTomato in Prox/Runx3 neurons after tissue clearing. Projections were visualized by immunostaining using anti-tdTomato antibodies. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2013; Aziz et al., 2016; Suttrup and Warnecke, 2016). The etiology of dysphagia remains largely unknown (Kloepper et al., 2020).

The first investigations of esophageal physiology were conducted in the late 19th century (Kronecker, 1883). In subsequent decades, it was debated whether activity of the hindbrain swallowing centers (i.e., the vagal motor nuclei and the nucleus of the solitary tract) is sufficient to generate esophageal peristalsis, or whether vagal sensory feedback is also required (Janssens et al., 1976; Jean, 1984; Kronecker, 1883). Later studies provided evidence for a critical role of sensory feedback in esophageal function (Falempin et al., 1986; Frazure et al., 2021; Lang, 2009). However, many classical experiments relied on blunt vagus nerve dissection, thereby affecting both vagal sensory and motor fibers. In addition, most studies assessed swallowing under anesthesia, which is known to alter esophageal peristalsis (Lang, 2009). Only recently has it become possible to investigate swallowing in behaving animals using videofluoroscopic swallowing studies (Haney et al., 2019; Hinkel et al., 2016; Lever et al., 2015; see also below).

5.2. Stomach

Based on anatomical structure and physiological function, in mice, the stomach is divided into non-glandular and glandular regions, while in humans it is entirely glandular. The non-glandular stomach serves primarily as a reservoir and contributes to gastric accommodation, whereas the glandular stomach is responsible for digestion and gastric emptying (Janssen et al., 2011; Umans and Liberles, 2018). Gastric accommodation and emptying both depend on coordinated stretching and contraction of the stomach, largely mediated by vago-vagal reflexes, i.e. vagal motor neurons residing in the dorsal motor nucleus of the vagus for reflex execution (Powley, 2021; Tao et al., 2021).

5.3. Summary

Although mechanosensation is clearly essential for food intake and digestion, the relative contributions of distinct neuronal populations remain poorly defined. Vagotomy affects multiple aspects of esophageal and gastric function; however, it is unclear whether these effects result from impaired vagal sensory signaling, disrupted vagal motor output, or a combination of both (Powley, 2021).

6. Anatomy of vagal afferents innervating the gastrointestinal tract

Vagal sensory afferents innervating the gastrointestinal tract are physiologically and morphologically heterogeneous, with distinct terminal specializations that enable the detection of mechanical, chemical, or polymodal cues (Brookes et al., 2013; Wang et al., 2020). These afferents can be broadly grouped into three classes based on their target layer and terminal morphology: intraganglionic laminar endings, intramuscular arrays, and mucosal polymodal afferents.

Intraganglionic laminar endings terminate on enteric ganglia located between muscle layers where they form lamellar terminal plates with leafy processes that intercalate among enteric neurons (Fig. 1; see also Umans and Liberles, 2018; Wang et al., 2020). First described in the dog esophagus nearly a century ago (Lawrentjew, 1929; Nonidez, 1946) and later named by Rodrigo (Rodrigo et al., 1975), these endings have myelinated main axons with unmyelinated terminal processes contacting enteric neurons. Based on the speed with which they respond to the mechanical stimulus, and because the neuronal activation persisted in spite of blocking synaptic transmission, it was proposed that the vagal afferent itself is mechanosensory and does not rely on the enteric neurons to detect mechanical information (Zagorodnyuk et al., 2001).

Intraganglionic laminar endings are widespread along the gastrointestinal tract, including the esophagus, stomach, and intestine, and were analyzed in multiple species (Bai et al., 2019; Iggo, 1955; Kim et al., 2022; Lawrentjew, 1929; Lowenstein et al., 2023; Mercado-Perez and Beyder, 2022; Paintal, 1954; Wang et al., 2020; Zhao et al., 2022). In mice, their density decreases along the rostral-to-caudal axis, with the highest concentration in upper segments (Bai et al., 2019; Berthoud and Patterson, 1996; Fox et al., 2000; Zhao et al., 2022). Single vagal axons can form intraganglionic laminar endings across multiple enteric ganglia (Berthoud and Powley, 1992; Phillips and Powley, 2000). They have been described as “in-series tension receptors”, reminiscent of Golgi tendon organs in skeletal muscle (Iggo, 1955; Phillips and Powley, 2000).

Although vagal neurons forming intraganglionic laminar endings are pseudounipolar, electron microscopy and immunohistochemistry revealed presynaptic contacts from intraganglionic laminar endings onto enteric neurons, and the co-localization of presynaptic markers vGlut2 and synaptophysin (Lowenstein, 2023; Neuhuber, 1987; Raab and Neuhuber, 2003). However, electrical stimulation of vagal afferents produces limited c-fos activation in enteric neurons (Zheng et al., 1997), leaving open questions about whether intraganglionic laminar endings act as local effectors, communicate with other myenteric cell types, or simply use enteric neurons as scaffolding.

Intramuscular arrays terminate within the longitudinal or circular muscle layers and form elongated terminal arrays aligned parallel to smooth muscle fibers and interstitial cells of Cajal (Lowenstein et al., 2023; Powley et al., 2016, 2008; Powley and Phillips, 2011; Zhao et al., 2022). Interstitial cells of Cajal are specialized pacemaker cells that coordinate gut motility by forming gap junctions with smooth muscle and establishing close contacts with intramuscular arrays, creating a functional interface between the nervous system and smooth muscle (Powley et al., 2008; Sanders et al., 2006; Sanders and Ward, 2006). The intramuscular arrays-interstitial cell of Cajal complex structurally resembles a proprioceptive sensory neuron-muscle spindle unit, supporting the hypothesis that intramuscular arrays function as stretch receptors (Phillips and Powley, 2000; Powley and Phillips, 2011). Intramuscular arrays are not evenly distributed along the gut. They are concentrated in sphincter regions and are also present in the non-glandular stomach (Powley et al., 2016, 2014). Their molecular identity and physiological roles remain largely unknown, though esophageal intramuscular arrays have been characterized as Piezo2+/Grm5+/Slit2+ neurons that respond to muscle stretch (Zhao et al., 2022).

Mucosal polymodal afferents innervate the lamina propria of the esophagus, stomach, and intestine and are generally considered to be chemosensory, although many also respond to gentle mechanical stimulation, making them polymodal (Berthoud et al., 2004, 1995; Li et al., 2018; Page et al., 2002; Page and Blackshaw, 1998; Wang et al., 2020; Wank and Neuhuber, 2001). While primarily studied in the intestine, similar free nerve endings exist in the esophagus (Harsanyiova et al., 2020). In the intestine, these afferents were suggested to form direct synaptic contacts with specialized enteroendocrine cells capable of nutrient sensing, providing a direct gut-to-brain pathway (Buchanan et al., 2022; Kaelberer et al., 2018; Waise et al., 2018). Recent work has challenged this view as vagal endings in the intestinal or proximal colon mucosa very rarely form close physical contact with resident enteroendocrine cells, suggesting that they communicate instead in a paracrine fashion (Cao et al., 2024; Spencer et al., 2024a, 2024b).

In summary, intramuscular arrays, intraganglionic laminar endings, and mucosal polymodal afferents represent complementary vagal pathways that integrate mechanical and chemical information from the gastrointestinal tract, enabling precise regulation of gut motility, nutrient sensing, and gut-brain communication.

7. Molecular heterogeneity of viscerosensory neurons

The extensive heterogeneity of vagal sensory neurons has only recently been resolved at the molecular level through the use of single-cell RNA sequencing (scRNA-seq) (Bai et al., 2019; Buchanan et al., 2022; Cheng et al., 2025; Kupari et al., 2019; Liu et al., 2025;

Lowenstein et al., 2023; Prescott et al., 2020; Welch et al., 2025; Zhao et al., 2022). These transcriptomic approaches have identified approximately 20–30 molecularly distinct vagal neuron subtypes, with subtypes comprising between 20 and 200 neurons. Thus, specific viscerosensory modalities may be mediated by remarkably small populations of neurons. While the viscerosensory system contains relatively few neurons compared to the somatosensory system, it exhibits extraordinary molecular and functional diversity. The physiological roles of a small number of molecularly defined subtypes have been characterized, but the functions of the majority remain unknown.

One study profiled vagal sensory neuron heterogeneity at postnatal day 4 (P4), during the first week of life (Lowenstein et al., 2023). Bioinformatic analysis identified 22 neuronal subtypes at this developmental stage, including four jugular subtypes, nine mechanosensory-like nodose subtypes, and nine chemosensory-like nodose subtypes. Integration of this dataset with others published prior to 2022 enabled the meta-analysis of vagal neurons using established data-integration frameworks (Fig. 2; see also Lowenstein et al., 2023). Such integration enhances subtype annotation robustness and facilitates the detection of rare populations. The resulting meta-analysis included 4,442 vagal neurons organized into 27 subtypes: six jugular (defined by *Prdm12* expression), 10 mechanosensory nodose (defined by *Phox2b* and *Piezo2* expression), and 11 chemosensory nodose subtypes (defined by *Phox2b* and *TrpV1* expression; Fig. 2A, B). This meta-analysis of vagal neurons is

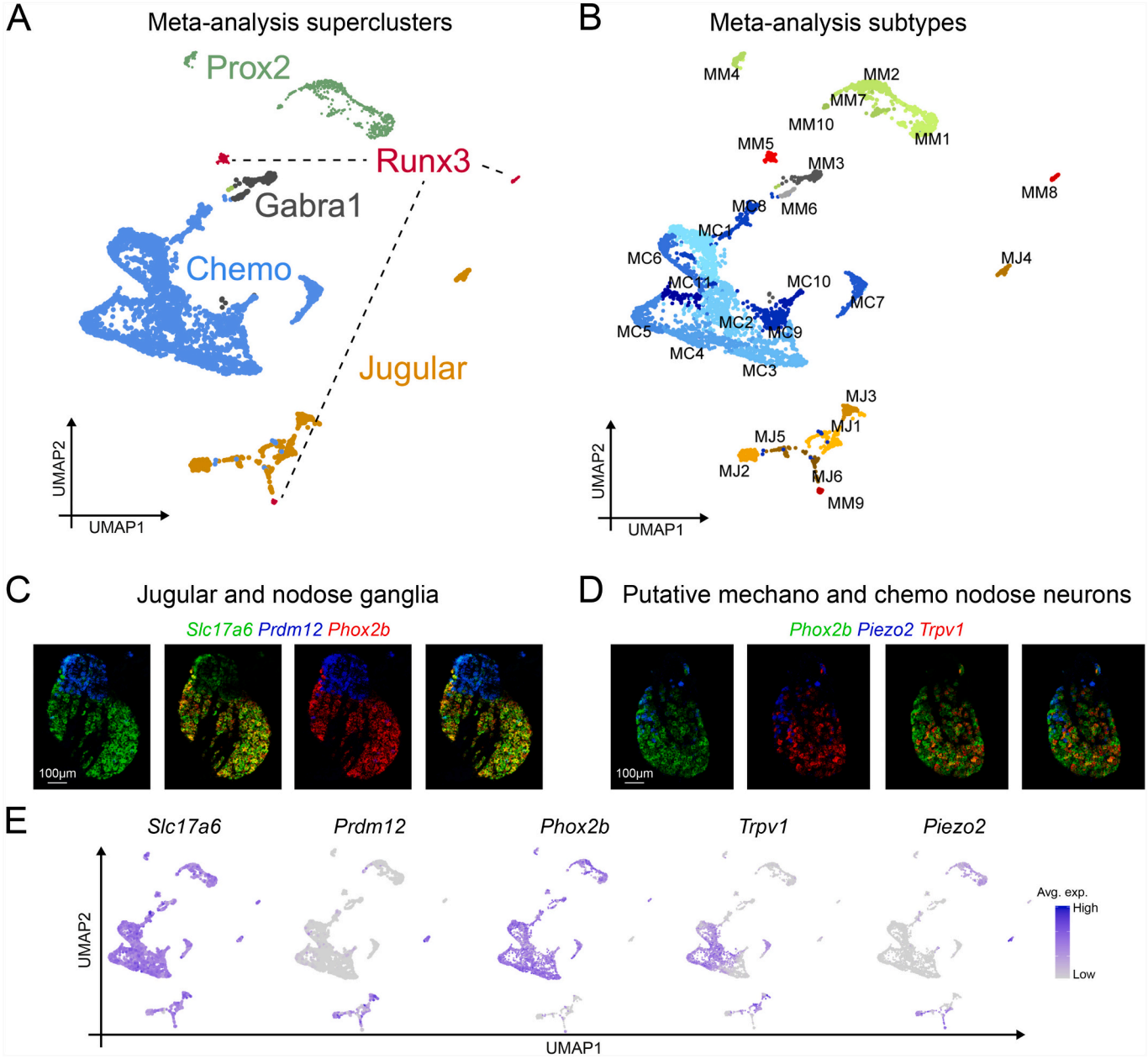


Fig. 2. Meta-analysis of vagal neurons identified the Prox2+ and Runx3+ superclusters of putative mechanoreceptors.
(A, B). UMAP plot based on a meta-analysis of scRNA-seq data (Kupari et al., 2019; Bai et al., 2019; Lowenstein et al., 2023) showing the various superclusters: Prox2, Runx3, Gabra1, Chemo and Jugular. Two Piezo2+ superclusters can be identified that express Prox2 or Runx3 which encompass 8 subtypes: MM1, MM2, MM4, MM7 and MM10 (Prox2+) and MM5, MM8, MM9 (Runx3+). (C) In situ hybridization (smFISH) showing that all vagal neurons are glutamatergic (i.e. all express *Slc17a6* that encodes vGlut2); they also express either *Prdm12* or *Phox2b* that distinguish the jugular and nodose ganglia, respectively. (D) In situ hybridization (smFISH) showing that nodose *Phox2b* + neurons express *Piezo2* or *Trpv1* that mark putative mechanosensory and chemosensory neurons, respectively. (E) UMAP plots for *Slc17a6*, *Prdm12*, *Phox2b*, *Trpv1* and *Piezo2*.

freely available online, and researchers can search and visualize gene expression across all vagal sensory neuron subtypes: https://shiny.mdc-berlin.de/VGIE/. Neurons from each dataset contributed to all major subtypes, indicating that the full complement of vagal neuron subtypes is already present by early postnatal life, although maturation-dependent transcriptional changes occur in the early postnatal period (Lowenstein et al., 2023; McCoy and Kamitakahara, 2023).

A more recent study expanded this approach by combining new single-nucleus RNA-seq (snRNA-seq) data with published scRNA-seq datasets, generating a meta-analysis of over 100,000 cells, including neurons, glia, fibroblasts, and other cell types of the ganglion (Cheng et al., 2025). This analysis identified 27 neuronal subtypes: five jugular and 22 nodose, which were classified as mechanoreceptors (10/27), chemoreceptors (11/27), or mixed (6/27). Putative mechanoreceptors are defined by expression of the voltage-gated sodium channel Scn1a (Nav1.1), and the mechanosensitive ion channel Piezo2 (Cheng et al., 2025).

A recent and particularly comprehensive study combined molecular profiling with anatomical tracing and functional analyses. Retrograde viral tracers, each labeled with a unique barcode, were injected into seven major organs, followed by scRNA-seq of more than 14,500 Phox2b+ neurons (Zhao et al., 2022). The study demonstrated that individual neuronal subtypes typically innervate a specific organ and tissue layer. Moreover, neurons innervating similar tissue layers across organs shared molecular features. For example, intraganglionic laminar endings of the esophagus and proximal stomach were closely related, and resembled each other more than intraganglionic laminar endings of the duodenum, highlighting region-specific molecular specialization.

In summary, sc/snRNA-seq studies have revealed the remarkable molecular diversity of vagal viscerosensory neurons. The absolute number of identified subtypes varies across studies and depends on sequencing depth, clustering parameters, dataset integration strategies, and whether anatomical target information is incorporated into subtype definitions. Relying only on molecular data, these studies report ~20 viscerosensory subtypes, of which about half are mechanoreceptive subtypes. We will subsequently use the terminology introduced in the meta-analysis reported by Lowenstein and colleagues, and refer to viscerosensory mechanoreceptor subtypes by their nomenclature: Meta-analysis putative Mechanoreceptor subtypes 1–10 (MM1-MM10).

Together, these studies establish the molecular characteristics of viscerosensory neurons and pave the way for their further analysis, helping to assign specific roles to a particular sensory subtype.

8. Molecularly defined vagal mechanoreceptor subtypes: anatomy, physiology and functions of intraganglionic laminar endings

Advances in transcriptomics, genetics, and anatomical tracing have begun to unify the molecular, structural, and functional organization of vagal viscerosensory neurons. Increased knowledge about their molecular characteristics has made it possible to use genetic tools for the study of defined neuronal subtypes, characterizing their anatomy, electrophysiological properties and function.

8.1. *Prox2/Runx3 neurons*

scRNA-seq identified the transcription factors Prox2 and Runx3 as key markers of vagal mechanoreceptors (Lowenstein et al., 2023). Prox2+ and Runx3+ neurons together account for ~85% of all Piezo2+ neurons in the nodose ganglion, representing the vast majority of vagal mechanosensory neurons. The small population of Piezo2+ neurons that express neither Prox2 nor Runx3 appears to correspond to polymodal afferents (Lowenstein et al., 2023).

Prox2+ and Runx3+ neurons share a developmental lineage. Lineage-tracing studies indicate that all vagal mechanosensory neurons arise from Prox2-expressing cells (Lowenstein et al., 2023). While most neurons within this lineage maintain Prox2 expression postnatally, a subset downregulates Prox2 and instead expresses Runx3. To selectively investigate these mechanoreceptors, an intersectional genetic strategy was developed in mice. This approach combines FlpO recombinase driven by *Prox2* regulatory elements with Cre recombinase under control of *Phox2b* regulatory sequences (Fig. 1A). Because Phox2b is broadly expressed in viscerosensory neurons, this intersection increases specificity for vagal mechanoreceptors. Reporter alleles requiring both recombinases (e.g. tdTomato expressed by the *Ai65* allele) enable analysis of the mechanosensory lineage. Due to their shared developmental origin, labeling occurs in both Prox2+/Phox2b+ and Runx3+/Phox2b+ neurons in the adult nodose ganglion.

Visualization of labeled axons revealed that Prox2/Runx3 mechanoreceptors innervate multiple thoracic and upper gastrointestinal organs, including the esophagus, stomach, larynx, lung, and heart (Fig. 1; see also Lowenstein et al., 2023). Combining genetic labeling with retrograde tracing enabled assignment of molecular subtypes to specific organs. This demonstrated that three subtypes - MM1, MM2, and MM8 - form intraganglionic laminar endings in the esophagus and stomach. Comparison with published analyses suggests that three additional Prox2/Runx3 mechanoreceptors subtypes can be assigned: MM9 and MM10 innervate the lung, whereas MM5 likely corresponds to laryngeal afferents (Chang et al., 2015; Liu et al., 2025; Prescott et al., 2020). The identity of cardiac-innervating Prox2/Runx3 subtypes remains unresolved (see Min et al., 2019 for an analysis of vagal afferents innervating the heart).

8.2. *Electrophysiological characteristics of Prox2/Runx3 neurons*

The esophagus of transgenic mice expressing channelrhodopsin in Prox2/Runx3 neurons was used to characterize the electrophysiological properties of these neurons. For this, the esophagus was isolated as an "open book" preparation, and single nerve fibers were recorded from the attached vagus nerve (Fig. 3A). Vagal fibers were classified as Prox2/Runx3-positive or -negative based on whether they fired action potentials in response to blue light (Fig. 3B; see also Lowenstein et al., 2023). Notably, all vagal fibers in the esophagus that were mechanically sensitive at low threshold also responded to blue light, indicating that Prox2/Runx3-positive neurons constitute the sole population of vagal esophageal mechanoreceptors (Fig. 3B, C). Within this population, Prox2/Runx3-positive neurons segregated into type I and type II mechanoreceptors, which exhibited slow and rapid adaptation, respectively (Fig. 3D). Based on unit abundance, MM2 was assigned as the slowly adapting esophageal type I mechanoreceptor, whereas MM8 corresponded to the rapidly adapting esophageal type II mechanoreceptor (Lowenstein et al., 2023). These findings suggest that MM2 and MM8 neurons may encode distinct features of esophageal distension. Esophageal distension triggers reflexes that lead to contraction of the upper esophageal sphincter, and these reflexes respond differentially to slow versus rapid distension (Lang, 2009; Lang et al., 2001). The relative contributions of these two mechanoreceptor subtypes to esophageal reflex control warrant further investigation.

A similar experimental approach was applied to characterize the electrophysiological properties of gastric Prox2/Runx3 neurons (Lowenstein et al., 2023). As in the esophagus, this revealed both slowly and rapidly adapting mechanoreceptive neuronal types. The slowly adapting gastric type I receptors likely correspond to MM1, which closely resembles the esophageal MM2 slowly adapting receptor in its molecular profile. In contrast, esophageal and gastric type II rapidly adapting receptors exhibited similar electrophysiological properties and correspond to the MM8 subtype. Consistent with these findings, a recent study measuring calcium activity in vagal neurons during gastric and esophageal distension identified Piezo2+/Glp1r+/Rbp4+ and Piezo2+/Grm5+/Slit2+ subtypes as low threshold mechanoreceptors with slowly adapting responses. These populations appear to correspond to Prox2/Runx3 type I mechanoreceptors, namely, the MM1 and MM2

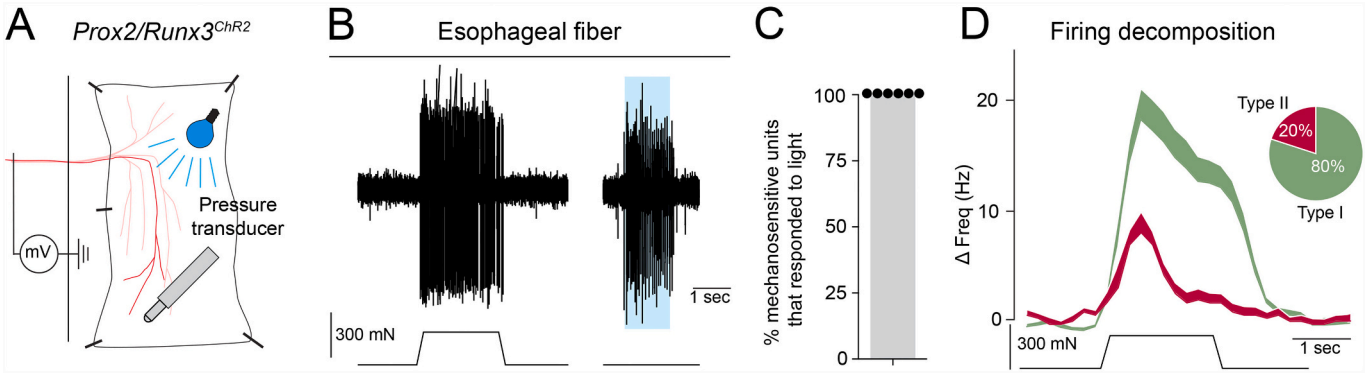


Fig. 3. Prox2/Runx3 neurons are esophageal mechanoreceptors.
(A) Scheme of the esophagus-vagus nerve ex vivo preparation. For the preparation, transgenic mice that express channelrhodopsin in Prox2/Runx3 neurons were used (channelrhodopsin was expressed after Cre- and Flp- dependent recombination, and the Cre and FlpO recombinases were driven by Phox2b and Prox2 regulatory sequences). (B) A Vagal fiber responding to mechanical stimuli (left); the same fiber also responded to blue light in the absence of a mechanical stimulus (right). (C) Quantification of mechanosensitive units in the esophagus show that all are sensitive to blue light, i.e. correspond to Prox2/Runx3-positive units ($N = 6$, $n = 30/30$). (D) Decomposition of Prox2/Runx3-positive unit firing patterns revealed two types of mechanosensory neurons, type I (slowly adapting, green) and II (quickly adapting, red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

subtypes (Zhao et al., 2022).

Prox2/Runx3 neurons encompass all vagal Piezo2+ fibers innervating the stomach. However, only about half of the vagal mechanoreceptors that respond to gastric distension belong to the Prox2/Runx3 population, indicating the presence of Piezo2-negative gastric mechanoreceptors (Lowenstein et al., 2023). Notably, Piezo2+ Prox2/Runx3 fibers exhibit higher firing rates in response to mechanical stimulation than Piezo2-negative fibers. The mechanosensory ion channel(s) responsible for stretch detection in the Piezo2-negative neuronal populations remain unknown.

8.3. Physiological roles of Prox2/Runx3 neurons

Genetic ablation of Prox2/Runx3 neurons demonstrated their critical role in the esophageal phase of swallowing. This was achieved by combining *Prox2FlpO* and *Phox2bCre* driver lines with a transgene that expresses the diphtheria toxin receptor following Cre and Flp recombination. Mice are normally resistant to diphtheria toxin as its receptor (e.g. heparin-binding EGF-like growth factor) has amino acid substitutions that prevent binding of the toxin. However, cells engineered to express the human diphtheria toxin receptor become susceptible, and a single systemic injection of the toxin suffices to ablate them. Ablation of vagal Prox2/Runx3 neurons resulted in a marked increase in esophageal bolus transit time and led to a megaesophagus (Fig. 4; see also Lowenstein et al., 2023). The animals also rapidly lost weight, reflecting severe impairment of swallowing. In this study, swallowing was assessed in awake, freely behaving rodents using videofluoroscopic swallowing studies (Fig. 4A).

Together, the targeted ablation of a defined vagal sensory neuron population, combined with analysis of freely behaving mice demonstrated that sensory feedback is essential for proper esophageal peristalsis and identified Prox2/Runx3 neurons as a key vagal sensory subtype underlying this regulation.

8.4. Glp1r and Oxtr vagal mechanoreceptors

Recent work identified Glp1r+ and Oxtr+ vagal sensory neurons as major molecularly defined populations that form intraganglionic laminar endings and function as key gastrointestinal mechanoreceptors (Bai et al., 2019; Williams et al., 2016). By using *Glp1rCre* transgenic animals and viral delivery of a Cre dependent tdTomato, Glp1r+ vagal afferents were shown to largely form stomach intraganglionic laminar endings (Bai et al., 2019). In order to understand the response properties, a Ca^{2+} indicator, GCaMP3, was expressed in Glp1r+ neurons. Imaging of the vagal ganglion revealed Ca^{2+} transients in response to stomach stretch (Williams et al., 2016). Optogenetic activation of these neurons (i.e. viral delivery of Cre-dependent channelrhodopsin to the vagal ganglion of *Glp1rCre* transgenic mice and exposure of the vagal ganglion to blue light) increases gastric pressure and suppresses food intake, supporting a role in regulating gastric tone and satiation.

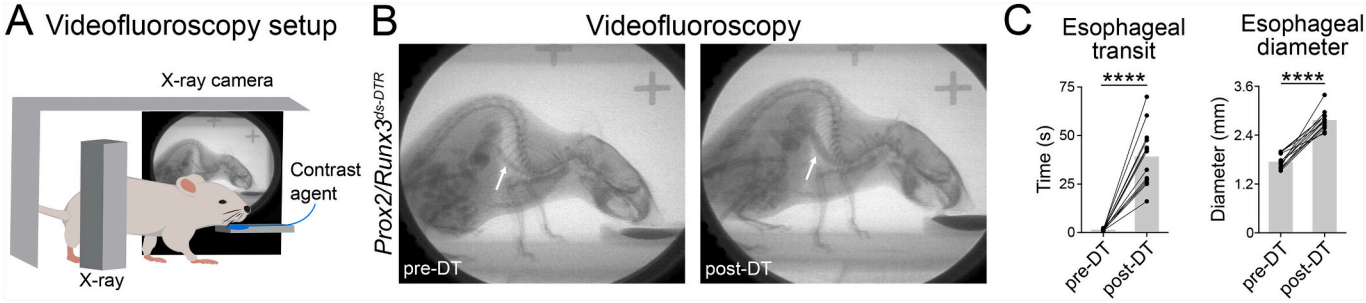


Fig. 4. Ablation of Prox2/Runx3 neurons impairs esophageal motility in freely behaving animals.
(A) Scheme of the videofluoroscopy setup. Mice are licking and swallowing a liquid containing a contrast agent. The movement of the bolus is followed by X-ray. (B) X-ray images taken from the same mouse expressing the human diphtheria toxin receptor gene in Prox2/Runx3-positive neurons mouse before (left, pre-DT) and after (right, post-DT) administration of diphtheria toxin e.g. ablation of Prox2/Runx3 neurons. The arrow points towards the esophagus that is enlarged after Prox2/Runx3 neuron ablation. (C) Quantifications of the transit time of a bolus through the esophagus before (pre-DT) and after (post-DT) ablation of Prox2/Runx3 neurons (left); quantifications of the esophageal diameter before (pre-DT) and after (post-DT) ablation of Prox2/Runx3 neurons (right).

However, Glp1r+ neurons exhibit heterogeneous physiological responses to stretch. scRNA-seq analyses identified at least two distinct Prox2/Runx3-positive Glp1r+ subtypes (MM1 and MM8) that display distinct electrophysiological properties, shedding light on this heterogeneity (Lowenstein et al., 2023). Additional diversity is suggested by the existence of Glp1r+ extraganglionic neurons along the vagus nerve, but the function of such extraganglionic neurons remain unclear (Leon-Mercado et al., 2023). Glp1r+ neurons have also been identified in the human nodose ganglion, although whether similar subtype specialization exists in humans is unknown (Merchant et al., 2026).

Oxtr expression also marks multiple vagal mechanoreceptor populations with region-specific roles along the gastrointestinal tract. Injection of a Cre-dependent tdTomato virus into nodose ganglia of *OxtrCre* animals was used to label Oxtr+ vagal projections, and showed that they form intraganglionic laminar endings in the intestine and esophagus (Lowenstein et al., 2023; Bai et al., 2019). Further, in vivo imaging of Oxtr+ vagal neurons expressing GCaMP demonstrates that at least a subset of Oxtr+ vagal neurons responds to intestinal distension (Rafael et al., 2026). Artificial activation of Oxtr+ vagal neurons via either chemogenetics (by expressing the excitatory DREADD in Oxtr+ neurons followed by CNO treatment) or optogenetics (by expressing channelrhodopsin in Oxtr+ neurons and blue light delivery to central terminals in the nucleus of the solitary tract) strongly suppressed feeding and engaged central satiety circuits (Bai et al., 2019).

Oxtr+ intraganglionic laminar endings in the esophagus correspond to the MM2 subtype and are mechanosensitive, but the molecular identity of the Oxtr+ neurons projecting to the stomach remains open (Lowenstein et al., 2023; Zhao et al., 2022). Recent work ablated oxytocin signaling by injecting a short hairpin RNA targeting *Oxtr* into the vagal ganglion of rats (Asker et al., 2025). *Oxtr* downregulation resulted in impaired esophageal transit, altered luminal diameter, and reduced food intake - phenotypes resembling those seen after ablation of the vagal Prox2/Runx3 mechanoreceptor populations (Asker et al., 2025; Lowenstein et al., 2023).

Together, analysis of Glp1r+, Oxtr+, and Prox2/Runx3+ neurons reveal substantial molecular and functional heterogeneity among vagal mechanoreceptors that monitor the gastrointestinal tract. Importantly, many of these populations have a shared developmental origin defined by expression of the transcription factors Prox2 and Runx3. This Prox2/Runx3 lineage comprises multiple mechanosensory subtypes, among them subtypes that innervate distinct gastrointestinal regions and form specialized intraganglionic laminar endings. These neurons detect mechanical cues - such as stretch produced by a bolus within the esophageal wall or gastric distension during filling - and trigger reflexes essential for bolus movement and digestion.

9. Outlook

Single-cell sequencing technologies have transformed the study of viscerosensation. Rather than relying primarily on anatomical and electrophysiological approaches that characterize heterogeneous and often poorly defined neuronal populations, researchers can now perform genetically guided analyses of specific vagal sensory neuron subtypes. Because single-cell RNA sequencing (scRNA-seq) datasets provide detailed gene expression profiles for individual neuronal populations, they enable systematic identification of candidate molecular targets for therapeutic intervention. Such targets could be used to modulate vagal sensory activity in disorders involving altered visceral signaling, including gastrointestinal motility disorders and cardiovascular disease. Given that viscerosensory neurons also regulate satiety and participate in stress-related responses, pharmacological manipulation of defined vagal subtypes may have broader therapeutic applications.

More than twenty molecularly distinct viscerosensory neuron subtypes have been identified, yet the physiological roles of only a small subset - primarily mechanoreceptors - have been functionally characterized. Although substantial progress has been made in understanding vagal chemosensation, the specific molecular subtypes responsible for most chemosensory functions remain unclear. Emerging technologies, including thin and flexible optogenetic interfaces (Sahasrabudhe et al., 2024), will increasingly enable selective activation or inhibition of vagal axon terminals in awake, freely moving animals. Such approaches allow manipulation of specific sensory input - for example, at defined sites along the gastrointestinal tract - and will be instrumental in defining the physiological roles of individual viscerosensory neuron subtypes.

CRediT authorship contribution statement

Elijah David Lowenstein: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Carmen Birchmeier:** Writing – review & editing, Writing – original draft, Conceptualization.

Acknowledgements

We would like to thank Dr. Thomas Müller from the Max Delbrück Center for Molecular Medicine in Berlin for his critical reading of the manuscript. Figs. 1–4 are modified versions of those originally published by Lowenstein et al. (2023). Portions of the text have been adapted from the doctoral dissertation of the first author, Elijah Lowenstein, which is available at: https://refubium.fu-berlin.de/handle/fub188/38267. This work was supported by grants of the NeuroCure Cluster of Excellence, Charité (to CB), the Max-Delbrück-Centrum für Molekulare Medizin in der Helmholtz-Gemeinschaft (to CB), and an American Diabetes Association Postdoctoral Fellowship (1-26-PDF-1107, to EDL).

References

Abraira, V.E., Ginty, D.D., 2013. The sensory neurons of touch. Neuron 79, 618–639. https://doi.org/10.1016/j.neuron.2013.07.051.

Asker, M., Krieger, J.-P., Maric, I., Bedel, E., Steen, J., Börchers, S., Wen, Y., Longo, F., Aronsson, P., Winder, M., Doyle, R.P., Hayes, M.R., Skibicka, K.P., 2025. Vagal oxytocin receptors are necessary for esophageal motility and function. JCI Insight 10. https://doi.org/10.1172/jci.insight.190108.

Aslam, M., Vaezi, M.F., 2013. Dysphagia in the elderly. Gastroenterol. Hepatol. 9, 784–795.

Ayer-Le Lievre, C.S., Le Douarin, N.M., 1982. The early development of cranial sensory ganglia and the potentialities of their component cells studied in quail-chick chimeras. Dev. Biol. 94, 291–310. https://doi.org/10.1016/0012-1606(82)90349-9.

Aziz, Q., Fass, R., Gyawali, C.P., Miwa, H., Pandolfino, J.E., Zerbib, F., 2016. Functional esophageal disorders. Gastroenterology. https://doi.org/10.1053/j.gastro.2016.02.012. S0016-5085(16)00178–5.

Bai, L., Mesgarzadeh, S., Ramesh, K.S., Huey, E.L., Liu, Y., Gray, L.A., Aitken, T.J., Chen, Y., Beutler, L.R., Ahn, J.S., Madisen, L., Zeng, H., Krasnow, M.A., Knight, Z.A., 2019. Genetic identification of vagal sensory neurons that control feeding. Cell 179, 1129–1143.e23. https://doi.org/10.1016/j.cell.2019.10.031.

Berthoud, H.R., Blackshaw, L.A., Brookes, S.J.H., Grundy, D., 2004. Neuroanatomy of extrinsic afferents supplying the gastrointestinal tract. Neurogastroenterol. Motil. 16 (Suppl. 1), 28–33. https://doi.org/10.1111/j.1743-3150.2004.00471.x.

Berthoud, H.R., Kressel, M., Raybould, H.E., Neuhuber, W.L., 1995. Vagal sensors in the rat duodenal mucosa: distribution and structure as revealed by in vivo DiI-tracing. Anat. Embryol. (Berl.) 191, 203–212. https://doi.org/10.1007/BF00187819.

Berthoud, H.R., Patterson, L.M., 1996. Anatomical relationship between vagal afferent fibers and CCK-immunoreactive entero-endocrine cells in the rat small intestinal mucosa. Acta Anat. (Basel) 156, 123–131. https://doi.org/10.1159/000147837.

Berthoud, H.R., Powley, T.L., 1992. Vagal afferent innervation of the rat fundic stomach: morphological characterization of the gastric tension receptor. J. Comp. Neurol. 319, 261–276. https://doi.org/10.1002/cne.903190206.

Brookes, S.J.H., Spencer, N.J., Costa, M., Zagorodnyuk, V.P., 2013. Extrinsic primary afferent signalling in the gut. Nat. Rev. Gastroenterol. Hepatol. 10, 286–296. https://doi.org/10.1038/nrgastro.2013.29.

Buchanan, K.L., Rupprecht, L.E., Kaelberer, M.M., Sahasrabudhe, A., Klein, M.E., Villalobos, J.A., Liu, W.W., Yang, A., Gelman, J., Park, S., Anikeeva, P., Bohórquez, D.V., 2022. The preference for sugar over sweetener depends on a gut sensor cell. Nat. Neurosci. 25, 191–200. https://doi.org/10.1038/s41593-021-00982-7.

Cao, N., Merchant, W., Gautron, L., 2024. Limited evidence for anatomical contacts between intestinal GLP-1 cells and vagal neurons in male mice. Sci. Rep. 14, 23666. https://doi.org/10.1038/s41598-024-74000-8.

Chakrabarti, S., Klich, J.D., Khallaf, M.A., Hulme, A.J., Sánchez-Carranza, O., Baran, Z. M., Rossi, A., Huang, A.T.-L., Pohl, T., Fleischer, R., Fürst, C., Hammes, A., Bégay, V., Hörnberg, H., Finol-Urdaneta, R.K., Poole, K., Dottori, M., Lewin, G.R., 2024. Touch sensation requires the mechanically gated ion channel ELKIN1. Science 383, 992–998. https://doi.org/10.1126/science.adl0495.

Chang, R.B., Strochlic, D.E., Williams, E.K., Umans, B.D., Liberles, S.D., 2015. Vagal sensory neuron subtypes that differentially control breathing. Cell 161, 622–633. https://doi.org/10.1016/j.cell.2015.03.022.

Cheng, S., Dowsett, G.K.C., Rainbow, K., Norton, M., Roberts, A.G., Phuah, P., Bewick, G. A., Lam, B.Y.H., Yeo, G.S.H., Murphy, K.G., 2025. NodoMap: A Spatio-cellular Map of the Mouse Nodose Ganglia. https://doi.org/10.1101/2025.05.11.653249.

Coste, B., Mathur, J., Schmidt, M., Earley, T.J., Ranade, S., Petrus, M.J., Dubin, A.E., Patapoutian, A., 2010. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. Science 330, 55–60. https://doi.org/10.1126/science.1193270.

Coverdell, T.C., Abraham-Fan, R.-J., Wu, C., Abbott, S.B.G., Campbell, J.N., 2022. Genetic encoding of an esophageal motor circuit. Cell Rep. 39, 110962. https://doi.org/10.1016/j.celrep.2022.110962.

D'Amico-Martel, A., Noden, D.M., 1983. Contributions of placodal and neural crest cells to avian cranial peripheral ganglia. Am. J. Anat. 166, 445–468. https://doi.org/10.1002/aja.1001660406.

D'Autréaux, F., Coppola, E., Hirsch, M.-R., Birchmeier, C., Brunet, J.-F., 2011. Homeoprotein Phox2b commands a somatic-to-visceral switch in cranial sensory pathways. Proc. Natl. Acad. Sci. 108, 20018–20023. https://doi.org/10.1073/pnas.1110416108.

Ertekin, C., Aydogdu, I., 2003. Neurophysiology of swallowing. Clin. Neurophysiol. 114, 2226–2244. https://doi.org/10.1016/s1388-2457(03)00237-2.

Espinosa-Medina, I., Jevans, B., Boismoreau, F., Chettouh, Z., Enomoto, H., Müller, T., Birchmeier, C., Burns, A.J., Brunet, J.-F., 2017. Dual origin of enteric neurons in vagal Schwann cell precursors and the sympathetic neural crest. Proc. Natl. Acad. Sci. 114, 11980–11985. https://doi.org/10.1073/pnas.1710308114.

Falempin, M., Madhloum, A., Rousseau, J.P., 1986. Effects of vagal deafferentation on oesophageal motility and transit in the sheep. J. Physiol. 372, 425–436. https://doi.org/10.1113/jphysiol.1986.sp016017.

Fox, E.A., Phillips, R.J., Martinson, F.A., Baronowsky, E.A., Powley, T.L., 2000. Vagal afferent innervation of smooth muscle in the stomach and duodenum of the mouse: morphology and topography. J. Comp. Neurol. 428, 558–576. https://doi.org/10.1002/1096-9861(20001218)428:3%253C558::aid-cne11%253E3.0.co;2-m.

Frazure, M.L., Brown, A.D., Greene, C.L., Iceman, K.E., Pitts, T., 2021. Rapid activation of esophageal mechanoreceptors alters the pharyngeal phase of swallow: evidence for inspiratory activity during swallow. PLoS One 16, e0248994. https://doi.org/10.1371/journal.pone.0248994.

Ge, J., Li, W., Zhao, Q., Li, N., Chen, M., Zhi, P., Li, R., Gao, N., Xiao, B., Yang, M., 2015. Architecture of the mammalian mechanosensitive Piezo1 channel. Nature 527, 64–69. https://doi.org/10.1038/nature15247.

Goyal, R.K., Chaudhury, A., 2008. Physiology of normal esophageal motility. J. Clin. Gastroenterol. 42, 610–619. https://doi.org/10.1097/MCG.0b013e31816b444d.

Handler, A., Ginty, D.D., 2021. The mechanosensory neurons of touch and their mechanisms of activation. Nat. Rev. Neurosci. 22, 521–537. https://doi.org/10.1038/s41583-021-00489-x.

Haney, M.M., Sinnott, J., Osman, K.L., Deninger, I., Andel, E., Caywood, V., Mok, A., Ballenger, B., Cummings, K., Thombs, L., Lever, T.E., 2019. Mice lacking brain-derived serotonin have altered swallowing function. Otolaryngol. Head Neck Surg. 161, 468–471. https://doi.org/10.1177/0194599819846109.

Harsanyiova, J., Ru, F., Zatko, T., Kollarik, M., Hennel, M., 2020. Vagus nerves provide a robust afferent innervation of the mucosa throughout the body of the esophagus in the mouse. Dysphagia 35, 471–478. https://doi.org/10.1007/s00455-019-10051-8.

Hill, R.Z., Nelson, J.W., Gyarmati, G., Medrano, S., Shirvan, S., McCormick, J.A., Burquez, S., Ahmed, J., Eng, D.G., Wysocki, J., Dubin, A.E., Servin-Vences, M.R., Lakshmanan, A., Gomez, R.A., Sequeira-Lopez, M.L.S., Shankland, S.J., Batlle, D., Miner, J.H., Peti-Peterdi, J., Patapoutian, A., 2026. Renal PIEZO2 is an essential regulator of renin. Cell 189, 161–178.e22. https://doi.org/10.1016/j.cell.2025.11.013.

Hinkel, C.J., Sharma, R., Thakkar, M.M., Takahashi, K., Hopewell, B.L., Lever, T.E., 2016. Neural mechanisms contributing to dysphagia in mouse models. Otolaryngol. Head Neck Surg. 155, 303–306. https://doi.org/10.1177/0194599816640261.

Hirsch, M.-R., d'Autréaux, F., Dymecki, S.M., Brunet, J.-F., Goridis, C., 2013. A Phox2b:: FLPo transgenic mouse line suitable for intersectional genetics: transgenic line Phox2b::FLPo. Genesis 51, 506–514. https://doi.org/10.1002/dvg.22393.

Huang, T.X., Wang, S., Ran, C., 2025. Interoceptive processing in the nucleus of the solitary tract. Curr. Opin. Neurobiol. 93, 103021. https://doi.org/10.1016/j.conb.2025.103021.

Iggo, A., 1955. Tension receptors in the stomach and the urinary bladder. J. Physiol. 128, 593–607. https://doi.org/10.1113/jphysiol.1955.sp005327.

Jänig, W., 1996. Neurobiology of visceral afferent neurons: neuroanatomy, functions, organ regulations and sensations. Biol. Psychol. 42, 29–51. https://doi.org/10.1016/0301-0511(95)05145-7.

Janssen, P., Vanden Berghe, P., Verschueren, S., Lehmann, A., Depoortere, I., Tack, J., 2011. The role of gastric motility in the control of food intake. Aliment. Pharmacol. Ther. 33, 880–894. https://doi.org/10.1111/j.1365-2036.2011.04609.x.

Janssens, J., De Wever, I., Vantrappen, G., Hellemans, J., 1976. Peristalsis in smooth muscle esophagus after transection and bolus deviation. Gastroenterology 71, 1004–1009.

Jean, A., 1984. Brainstem organization of the swallowing network. Brain Behav. Evol. 25, 109–116. https://doi.org/10.1159/000118856.

Kaelberer, M.M., Buchanan, K.L., Klein, M.E., Barth, B.B., Montoya, M.M., Shen, X., Bohórquez, D.V., 2018. A gut-brain neural circuit for nutrient sensory transduction. Science 361, eaat5236. https://doi.org/10.1126/science.aat5236.

Katz, B., 1950. Depolarization of sensory terminals and the initiation of impulses in the muscle spindle. J. Physiol. 111, 261–282. https://doi.org/10.1113/jphysiol.1950.sp004479.

Kim, M., Heo, G., Kim, S.-Y., 2022. Neural signalling of gut mechanosensation in ingestive and digestive processes. Nat. Rev. Neurosci. 23, 135–156. https://doi.org/10.1038/s41583-021-00544-7.

Kloepper, A., Arnold, J., Ruffolo, A., Kinealy, B., Haxton, C., Nichols, N., Takahashi, K., Lever, T.E., 2020. An experimental swallow evoked potential protocol to investigate the neural substrates of swallowing. OTO Open 4, 2473974X20913542. https://doi.org/10.1177/2473974X20913542.

Koch, S.C., Acton, D., Goulding, M., 2018. Spinal circuits for touch, pain, and itch. Annu. Rev. Physiol. 80, 189–217. https://doi.org/10.1146/annurev-physiol-022516-034303.

Kronecker, H., 1883. Der Schluckmechanismus, seine Erreggnung und seine Hemmung. Arch. Anat. Physiol. Physiol. Abt. 328–360.

Kupari, J., Häring, M., Agirre, E., Castelo-Branco, G., Ernfors, P., 2019. An atlas of vagal sensory neurons and their molecular specialization. Cell Rep. 27, 2508–2523.e4. https://doi.org/10.1016/j.celrep.2019.04.096.

Lang, I.M., 2009. Brain stem control of the phases of swallowing. Dysphagia 24, 333–348. https://doi.org/10.1007/s00455-009-9211-6.

Lang, I.M., Medda, B.K., Shaker, R., 2001. Mechanisms of reflexes induced by esophageal distension. Am. J. Physiol. Gastrointest. Liver Physiol. 281, G1246–G1263. https://doi.org/10.1152/ajpgi.2001.281.5.G1246.

Lawrentjew, B.I., 1929. Experimentell-morphologische Studien uber den feineren Bau des autonomen Nervensystems. Uber den Aufbau der Ganglien der Speiserohre nebst einigen Bemerkungen uber das Vorkommen und die Verteilung zweier Arten von Nervenzellen im autonomen Nervensystem, pp. 233–262.

Lechner, S.G., Lewin, G.R., 2013. Hairy sensation. Physiology (Bethesda) 28, 142–150. https://doi.org/10.1152/physiol.00059.2012.

Leon-Mercado, L., Tinajero, A., Gautron, L., 2023. Evidence of extraganglionic vagal mechanoreceptors in the mouse vagus nerve. J. Anat. 243, 936–950. https://doi.org/10.1111/joa.13925.

Lever, T.E., Braun, S.M., Brooks, R.T., Harris, R.A., Littrell, L.L., Neff, R.M., Hinkel, C.J., Allen, M.J., Ulsas, M.A., 2015. Adapting human videofluoroscopic swallow study methods to detect and characterize dysphagia in murine disease models. J. Vis. Exp., 52319 https://doi.org/10.3791/52319.

Li, H., Kentish, S.J., Wittert, G.A., Page, A.J., 2018. Apelin modulates murine gastric vagal afferent mechanosensitivity. Physiol. Behav. 194, 466–473. https://doi.org/10.1016/j.physbeh.2018.06.039.

Liu, Y., Kinsey, L., Arce, A.J.D. de, Krasnow, M.A., 2025. Molecular, Anatomical, and Functional Organization of Lung Interoceptors. https://doi.org/10.1101/2021.11.10.468116.

Lowenstein, E.D., 2023. Connecting the Esophagus to the Brain: Examining the Role of Prox2 and Runx3 Vagal Sensory Neurons in Swallowing. https://doi.org/10.17169/refubium-37986.

Lowenstein, E.D., Misios, A., Buchert, S., Ruffault, P.-L., 2024. Molecular characterization of nodose ganglia development reveals a novel population of Phox2b+ glial progenitors in mice. J. Neurosci. 44. https://doi.org/10.1523/JNEUROSCI.1441-23.2024.

Lowenstein, E.D., Ruffault, P.-L., Misios, A., Osman, K.L., Li, H., Greenberg, R.S., Thompson, R., Song, K., Dietrich, S., Li, X., Vladimirov, N., Woehler, A., Brunet, J.-F., Zampieri, N., Kühn, R., Liberles, S.D., Jia, S., Lewin, G.R., Rajewsky, N., Lever, T. E., Birchmeier, C., 2023. Prox2 and Runx3 vagal sensory neurons regulate esophageal motility. Neuron 111, 2184–2200.e7. https://doi.org/10.1016/j.neuron.2023.04.025.

Ly, T., Yi, X., Lee, G.R., Grove, J.C., Sibih, Y.E., Oh, Y.Y., Qiu, L., Namkung, H., Sivakumar, N., Knight, Z.A., 2026. Cellular coding of ingestion in the caudal brainstem. BioRxiv. https://doi.org/10.64898/2025.11.30.691333. Prepr. Serv. Biol. 2025.11.30.691333.

Ma, S., Cahalan, S., LaMonte, G., Grubaugh, N.D., Zeng, W., Murthy, S.E., Paytas, E., Gamini, R., Lukacs, V., Whitwam, T., Loud, M., Lohia, R., Berry, L., Khan, S.M., Janse, C.J., Bandell, M., Schmedt, C., Wengelnik, K., Su, A.I., Honore, E., Winzeler, E.A., Andersen, K.G., Patapoutian, A., 2018. Common PIEZO1 allele in African populations causes RBC dehydration and attenuates plasmodium infection. Cell 173, 443–455.e12. https://doi.org/10.1016/j.cell.2018.02.047.

McCoy, M.E., Kamitakahara, A.K., 2023. Ontogeny and trophic factor sensitivity of gastrointestinal projecting vagal sensory cell types. eNeuro 10. https://doi.org/10.1523/ENEURO.0511-22.2023. ENEURO.0511-22.2023.

Mercado-Perez, A., Beyder, A., 2022. Gut feelings: mechanosensing in the gastrointestinal tract. Nat. Rev. Gastroenterol. Hepatol. 19, 283–296. https://doi.org/10.1038/s41575-021-00561-y.

Merchant, W., Mackaaij, C., Cleypool, C.G.J., Gautron, L., 2026. Glucagon-like peptide-1 targets in the human nodose ganglion. J. Comp. Neurol. 534, e70135. https://doi.org/10.1002/cne.70135.

Min, S., Chang, R.B., Prescott, S.L., Beeler, B., Joshi, N.R., Strochlic, D.E., Liberles, S.D., 2019. Arterial baroreceptors sense blood pressure through decorated aortic claws. Cell Rep. 29, 2192–2201.e3. https://doi.org/10.1016/j.celrep.2019.10.040.

Morin, X., Cremer, H., Hirsch, M.R., Kapur, R.P., Goridis, C., Brunet, J.F., 1997. Defects in sensory and autonomic ganglia and absence of locus coeruleus in mice deficient for the homeobox gene Phox2a. Neuron 18, 411–423. https://doi.org/10.1016/s0896-6273(00)81242-8.

Mountcastle, V.B., 1957. Modality and topographic properties of single neurons of cat's somatic sensory cortex. J. Neurophysiol. 20, 408–434. https://doi.org/10.1152/jn.1957.20.4.408.

Mousavi, S.A.R., Dubin, A.E., Zeng, W.-Z., Coombs, A.M., Do, K., Ghadiri, D.A., Keenan, W.T., Ge, C., Zhao, Y., Patapoutian, A., 2021. PIEZO ion channel is required for root mechanotransduction in *Arabidopsis thaliana*. Proc. Natl. Acad. Sci. USA 118, e2102188118. https://doi.org/10.1073/pnas.2102188118.

Nair, S.N., Hadley, S., Patil, M., Taylor-Clark, T., 2024. Nodose afferent fibers require PIEZO2 for esophageal mechanosensation. Physiology 38. https://doi.org/10.1152/physiol.2023.38.S1.5734530.
Nakamichi, R., Ma, S., Nonoyama, T., Chiba, T., Kurimoto, R., Ohzono, H., Olmer, M., Shukunami, C., Fuku, N., Wang, G., Morrison, E., Pitsiladis, Y.P., Ozaki, T., D'Lima, D., Lotz, M., Patapoutian, A., Asahara, H., 2022. The mechanosensitive ion channel PIEZO1 is expressed in tendons and regulates physical performance. Sci. Transl. Med. 14, eabj5557. https://doi.org/10.1126/scitranslmed.abj5557.
Narayanan, C.H., Narayanan, Y., 1980. Neural crest and placodal contributions in the development of the glossopharyngeal-vagal complex in the chick. Anat. Rec. 196, 71–82. https://doi.org/10.1002/ar.1091960108.
Neuhuber, W.L., 1987. Sensory vagal innervation of the rat esophagus and cardia: a light and electron microscopic anterograde tracing study. J. Auton. Nerv. Syst. 20, 243–255. https://doi.org/10.1016/0165-1838(87)90153-6.
Nonidez, J.F., 1946. Afferent nerve endings in the ganglia of the intermuscular plexus of the dog's oesophagus. J. Comp. Neurol. 85, 177–189. https://doi.org/10.1002/cne.900850204.
Nonomura, K., Woo, S.-H., Chang, R.B., Gillich, A., Qiu, Z., Francisco, A.G., Ranade, S.S., Liberles, S.D., Patapoutian, A., 2017. Piezo2 senses airway stretch and mediates lung inflation-induced apnoea. Nature 541, 176–181. https://doi.org/10.1038/nature20793.
Page, A.J., Blackshaw, L.A., 1998. An in vitro study of the properties of vagal afferent fibres innervating the ferret oesophagus and stomach. J. Physiol. 512 (Pt 3), 907–916. https://doi.org/10.1111/j.1469-7793.1998.907bd.x.
Page, A.J., Martin, C.M., Blackshaw, L.A., 2002. Vagal mechanoreceptors and chemoreceptors in mouse stomach and esophagus. J. Neurophysiol. 87, 2095–2103. https://doi.org/10.1152/jn.00785.2001.
Paintal, A.S., 1954. The response of gastric stretch receptors and certain other abdominal and thoracic vagal receptors to some drugs. J. Physiol. 126, 271–285. https://doi.org/10.1113/jphysiol.1954.sp005208.
Pattyn, A., Morin, X., Cremer, H., Goridis, C., Brunet, J.-F., 1997. Expression and interactions of the two closely related homeobox genes *Phox2a* and *Phox2b* during neurogenesis. Development 124, 4065–4075. https://doi.org/10.1242/dev.124.20.4065.
Pattyn, A., Morin, X., Cremer, H., Goridis, C., Brunet, J.-F., 1999. The homeobox gene Phox2b is essential for the development of autonomic neural crest derivatives. Nature 399, 366–370. https://doi.org/10.1038/20700.
Phillips, R.J., Powley, T.L., 2000. Tension and stretch receptors in gastrointestinal smooth muscle: re-evaluating vagal mechanoreceptor electrophysiology. Brain Res. Brain Res. Rev. 34, 1–26. https://doi.org/10.1016/s0165-0173(00)00036-9.
Powley, T.L., 2021. Brain-gut communication: vagovagal reflexes interconnect the two "brains". Am. J. Physiol. Gastrointest. Liver Physiol. 321, G576–G587. https://doi.org/10.1152/ajpgi.00214.2021.
Powley, T.L., Hudson, C.N., McAdams, J.L., Baronowsky, E.A., Martin, F.N., Mason, J.K., Phillips, R.J., 2014. Organization of vagal afferents in pylorus: mechanoreceptors arrayed for high sensitivity and fine spatial resolution? Auton. Neurosci. Basic Clin. 183, 36–48. https://doi.org/10.1016/j.autneu.2014.02.008.
Powley, T.L., Hudson, C.N., McAdams, J.L., Baronowsky, E.A., Phillips, R.J., 2016. Vagal intramuscular arrays: the specialized mechanoreceptor arbors that innervate the smooth muscle layers of the stomach examined in the rat. J. Comp. Neurol. 524, 713–737. https://doi.org/10.1002/cne.23892.
Powley, T.L., Phillips, R.J., 2011. Vagal intramuscular array afferents form complexes with interstitial cells of Cajal in gastrointestinal smooth muscle: analogues of muscle spindle organs? Neuroscience 186, 188–200. https://doi.org/10.1016/j.neuroscience.2011.04.036.
Powley, T.L., Wang, X.-Y., Fox, E.A., Phillips, R.J., Liu, L.W.C., Huizinga, J.D., 2008. Ultrastructural evidence for communication between intramuscular vagal mechanoreceptors and interstitial cells of Cajal in the rat fundus. Neurogastroenterol. Motil. 20, 69–79. https://doi.org/10.1111/j.1365-2982.2007.00990.x.
Prescott, S.L., Liberles, S.D., 2022. Internal senses of the vagus nerve. Neuron 110, 579–599. https://doi.org/10.1016/j.neuron.2021.12.020.
Prescott, S.L., Umans, B.D., Williams, E.K., Brust, R.D., Liberles, S.D., 2020. An airway protection program revealed by sweeping genetic control of vagal afferents. Cell 181, 574–589.e14. https://doi.org/10.1016/j.cell.2020.03.004.
Raab, M., Neuhuber, W.L., 2003. Vesicular glutamate transporter 2 immunoreactivity in putative vagal mechanosensor terminals of mouse and rat esophagus: indication of a local effector function? Cell Tissue Res. 312, 141–148. https://doi.org/10.1007/s00441-003-0721-5.
Rafael, O., Shtiglitz, S., Miller, J., Prilutski, Y., Talpir, I., Lavi, A., Livneh, Y., 2026. A Cortical Basis for Perception of Internal Gut Sensations. https://doi.org/10.64898/2026.02.11.705298.
Ran, C., Boettcher, J.C., Kaye, J.A., Gallori, C.E., Liberles, S.D., 2022. A brainstem map for visceral sensations. Nature 609, 320–326. https://doi.org/10.1038/s41586-022-05139-5.
Ranade, S.S., Syeda, R., Patapoutian, A., 2015. Mechanically activated ion channels. Neuron 87, 1162–1179. https://doi.org/10.1016/j.neuron.2015.08.032.
Rao, M.S., Jacobson, M., 2005. Developmental Neurobiology, 4th ed. Springer US.
Rinaman, L., 2010. Ascending projections from the caudal visceral nucleus of the solitary tract to brain regions involved in food intake and energy expenditure. Brain Res. Neural Mech. Ingestive Behav. Obes. 1350, 18–34. https://doi.org/10.1016/j.brainres.2010.03.059.
Rodrigo, J., Hernández, J., Vidal, M.A., Pedrosa, J.A., 1975. Vegetative innervation of the esophagus. II. Intraganglionic laminar endings. Acta Anat. (Basel) 92, 79–100. https://doi.org/10.1159/000144431.
Sahasrabudhe, A., Rupprecht, L.E., Orguc, S., Khudiyev, T., Tanaka, T., Sands, J., Zhu, W., Tabet, A., Manthey, M., Allen, H., Loke, G., Antonini, M.-J., Rosenfeld, D., Park, J., Garwood, I.C., Yan, W., Niroui, F., Fink, Y., Chandrakasan, A., Bohórquez, D.V., Anikeeva, P., 2024. Multifunctional microelectronic fibers enable wireless modulation of gut and brain neural circuits. Nat. Biotechnol. 42, 892–904. https://doi.org/10.1038/s41587-023-01833-5.
Sanders, K.M., Koh, S.D., Ward, S.M., 2006. Interstitial cells of cajal as pacemakers in the gastrointestinal tract. Annu. Rev. Physiol. 68, 307–343. https://doi.org/10.1146/annurev.physiol.68.040504.094718.
Sanders, K.M., Ward, S.M., 2006. Interstitial cells of Cajal: a new perspective on smooth muscle function. J. Physiol. 576, 721–726. https://doi.org/10.1113/jphysiol.2006.115279.
Saotome, K., Murthy, S.E., Kefauver, J.M., Whitwam, T., Patapoutian, A., Ward, A.B., 2018. Structure of the mechanically activated ion channel Piezo1. Nature 554, 481–486. https://doi.org/10.1038/nature25453.
Schappe, M.S., Brinn, P.A., Joshi, N.R., Greenberg, R.S., Min, S., Alabi, A.A., Zhang, C., Liberles, S.D., 2024. A vagal reflex evoked by airway closure. Nature 627, 830–838. https://doi.org/10.1038/s41586-024-07144-2.
Spencer, N.J., Kyloh, M.A., Travis, L., Hibberd, T.J., 2024a. Identification of vagal afferent nerve endings in the mouse colon and their spatial relationship with enterochromaffin cells. Cell Tissue Res. 396, 313–327. https://doi.org/10.1007/s00441-024-03879-6.
Spencer, N.J., Kyloh, M.A., Travis, L., Hibberd, T.J., 2024b. Mechanisms underlying the gut-brain communication: how enterochromaffin (EC) cells activate vagal afferent nerve endings in the small intestine. J. Comp. Neurol. 532, e25613. https://doi.org/10.1002/cne.25613.
Sungeelee, S., Mailhes-Hamon, C., Chettouh, Z., Bokiniec, P., Eymael, A., McMullan, S., Léna, C., Dempsey, B., Brunet, J.-F., 2025. A genetically defined pontine nucleus essential for ingestion in mice. Proc. Natl. Acad. Sci. USA 122, e2411174122. https://doi.org/10.1073/pnas.2411174122.
Suttrup, I., Warnecke, T., 2016. Dysphagia in Parkinson's disease. Dysphagia 31, 24–32. https://doi.org/10.1007/s00455-015-9671-9.
Tao, J., Campbell, J.N., Tsai, L.T., Wu, C., Liberles, S.D., Lowell, B.B., 2021. Highly selective brain-to-gut communication via genetically defined vagus neurons. Neuron 109, 2106–2115.e4. https://doi.org/10.1016/j.neuron.2021.05.004.
Tassicker, B.C., Hennig, G.W., Costa, M., Brookes, S.J., 1999. Rapid anterograde and retrograde tracing from mesenteric nerve trunks to the guinea-pig small intestine in vitro. Cell Tissue Res. 295, 437–452. https://doi.org/10.1007/s004410051250.
Tian, L., Hires, S.A., Mao, T., Huber, D., Chiappe, M.E., Chalasani, S.H., Petreanu, L., Akerboom, J., McKinney, S.A., Schreiter, E.R., 2009. Imaging neural activity in worms, flies and mice with improved GCaMP calcium indicators. Nat. Methods 6, 875–881.
Umans, B.D., Liberles, S.D., 2018. Neural sensing of organ volume. Trends Neurosci. 41, 911–924. https://doi.org/10.1016/j.tins.2018.07.008.
Undem, B.J., Weinreich, D. (Eds.), 2005. Advances in Vagal Afferent Neurobiology. CRC Press, Boca Raton. https://doi.org/10.1201/9780203492314.
Vermeiren, S., Bellefroid, E.J., Desiderio, S., 2020. Vertebrate sensory ganglia: common and divergent features of the transcriptional programs generating their functional specialization. Front. Cell Dev. Biol. 8, 587699. https://doi.org/10.3389/fcell.2020.587699.
Waise, T.M.Z., Dranse, H.J., Lam, T.K.T., 2018. The metabolic role of vagal afferent innervation. Nat. Rev. Gastroenterol. Hepatol. 15, 625–636. https://doi.org/10.1038/s41575-018-0062-1.
Wang, L., Zhou, H., Zhang, M., Liu, W., Deng, T., Zhao, Q., Li, Y., Lei, J., Li, X., Xiao, B., 2019. Structure and mechanogating of the mammalian tactile channel PIEZO2. Nature 573, 225–229. https://doi.org/10.1038/s41586-019-1505-8.
Wang, Y.B., de Lartigue, G., Page, A.J., 2020. Dissecting the role of subtypes of gastrointestinal vagal afferents. Front. Physiol. 11, 643. https://doi.org/10.3389/fphys.2020.00643.
Wank, M., Neuhuber, W.L., 2001. Local differences in vagal afferent innervation of the rat esophagus are reflected by neurochemical differences at the level of the sensory ganglia and by different brainstem projections. J. Comp. Neurol. 435, 41–59. https://doi.org/10.1002/cne.1192.
Welch, H.F., Sankaranarayanan, I., Hong, V.M., Qavi, H., Mazhar, K., Kolber, B.J., Price, T.J., Thorn, C.A., 2025. Molecular and functional asymmetry in Cckar-expressing vagal sensory neurons. Cell Rep. 44, 116507. https://doi.org/10.1016/j.celrep.2025.116507.
Williams, E.K., Chang, R.B., Strochlic, D.E., Umans, B.D., Lowell, B.B., Liberles, S.D., 2016. Sensory neurons that detect stretch and nutrients in the digestive system. Cell 166, 209–221. https://doi.org/10.1016/j.cell.2016.05.011.
Zagorodnyuk, V.P., Brookes, S.J., 2000. Transduction sites of vagal mechanoreceptors in the guinea pig esophagus. J. Neurosci. 20, 6249–6255. https://doi.org/10.1523/JNEUROSCI.20-16-06249.2000.
Zagorodnyuk, V.P., Chen, B.N., Brookes, S.J., 2001. Intraganglionic laminar endings are mechano-transduction sites of vagal tension receptors in the guinea-pig stomach. J. Physiol. 534, 255–268. https://doi.org/10.1111/j.1469-7793.2001.00255.x.
Zagorodnyuk, V.P., Chen, B.N., Costa, M., Brookes, S.J.H., 2003. Mechanotransduction by intraganglionic laminar endings of vagal tension receptors in the guinea-pig oesophagus. J. Physiol. 553, 575–587. https://doi.org/10.1113/jphysiol.2003.051862.
Zeng, W.-Z., Marshall, K.L., Min, S., Daou, I., Chapleau, M.W., Abboud, F.M., Liberles, S.D., Patapoutian, A., 2018. PIEZOs mediate neuronal sensing of blood pressure and

the baroreceptor reflex. Science 362, 464–467. https://doi.org/10.1126/science.aau6324.
Zhao, Q., Yu, C.D., Wang, R., Xu, Q.J., Dai Pra, R., Zhang, L., Chang, R.B., 2022. A multidimensional coding architecture of the vagal interoceptive system. Nature 603, 878–884. https://doi.org/10.1038/s41586-022-04515-5.
Zheng, H., Lauve, A., Patterson, L.M., Berthoud, H.R., 1997. Limited excitatory local effector function of gastric vagal afferent intraganglionic terminals in rats. Am. J. Phys. 273, G661–G669. https://doi.org/10.1152/ajpgi.1997.273.3.G661.