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Current Opinion in Neurobiology

Interoception 2025

Zachary A. Knight and Stephen D. Liberles

Current Opinion in Neurobiology 2025, **95:**103122

This review comes from a themed issue on **Interoception 2025**

Edited by **Stephen Liberles** and **Zachary Knight**

https://doi.org/10.1016/j.conb.2025.103122

Zachary A. Knight

Zachary Knight is a Professor of Physiology at University of California, San Francisco and an Investigator of the Howard Hughes Medical Institute. Dr. Knight received his B.A. in Chemistry from Princeton and his Ph.D. in Chemistry from UCSF, where he performed research with Kevan Shokat. He then performed postdoctoral studies with Jeffrey Friedman at Rockefeller before returning to UCSF to start his independent lab.
Dr. Knight's lab studies the neural mechanisms that control hunger and thirst. A general discovery from this work has been that homeostatic neurons in the hypothalamus and brainstem—which are traditionally thought to react to physiologic imbalances in the body—instead utilize sensory cues from the outside world to anticipate bodily changes and adjust behavior preemptively.

Our sensory systems enable us to perceive the environments around us and within us. While the key sensory receptors and circuit motifs that underlie our external senses of touch, taste, vision, smell, and hearing have been extensively studied, the sensations from within our body—known as interoception—are less well understood. Interoceptive mechanisms are fundamental as they control our most basic physiology, change mood and behavior, and elicit perceptions to maintain homeostasis and survival. Harnessing body–brain signals also has tremendous therapeutic power—from control of breathing, heart rate, and blood pressure to alleviation of sickness, nausea, and obesity, the latter through a new generation of gut hormone mimetics. In the past decade, a resurgence of study into mechanisms of body–brain communication has revealed diverse sensory neurons that innervate the respiratory, cardiovascular, digestive, and immune systems. New neuron types, sensory pathways, and reflexes have been uncovered, as well as receptors and circuit mechanisms that underlie classical reflexes discovered over a hundred years ago.

There are two principal neural pathways that relay information from the body to brain. One consists of cranial afferents, notably including the vagus nerve which has cell bodies in nodose and jugular ganglia and directly connects the gut, airways, and vasculature to the caudal brainstem. The other pathway involves spinal afferents, which have cell bodies in dorsal root ganglia and connect the viscera to the spinal cord. Review articles in this issue highlight recent advances in the study of both systems. Yin Liu discusses the diversity of vagal sensory neurons in the respiratory system, which includes neurons that ensure the constancy of breathing throughout life and others that protect the airways through reflexes like cough and swallow. A complementary review by Hans Rudolf-Berthold discusses the vagal sensory neurons that innervate the stomach and intestines and are important for detecting gastrointestinal stretch, nutrients, toxins, and microbial products. Jose Lopez Barneo reviews recent advances in understanding the carotid body, a sensory tissue innervated by the glossopharyngeal nerve that detects low circulating oxygen and in response, triggers the hypoxic ventilatory response. The hypoxic ventilatory response promotes breathing and gas exchange and is triggered, for example, during a hike at a high altitude. The axons from these vagal and glossopharyngeal afferents terminate in two small structures in the caudal brainstem—known as the area postrema (AP) and nucleus of the solitary

Stephen D. Liberles

Dr. Liberles is a Professor and Howard Hughes Medical Institute Investigator in the Cell Biology Department at Harvard Medical School who focuses on the molecular neuroscience of sensory systems. He discovered nonclassical families of olfactory receptors and charted how the vagus nerve controls physiology and behavior. His studies of sensory neurons in the respiratory, cardiovascular, and digestive systems led to the identification of novel body–brain reflexes, sensory receptors and mechanisms underlying classical reflexes, and key features of how inputs from the interoceptive nervous system are organized in the brain.

tract (NTS)—and two reviews in this issue discuss these important gateways for interoceptive information. Chen Ran gives an overview of the organizational principles of the NTS, which is important for myriad bodily functions including the regulation of food intake, gut motility, breathing, and blood pressure. Chuchu Zhang reviews the nearby AP and its role in nausea behaviors. Finally, Darleen Sandoval discusses how these brainstem structures and vagal pathways are altered after bariatric surgery, which is the most effective intervention for weight loss and yet remains mysterious at the level of molecular and cellular mechanisms.

Alongside vagal afferents, spinal sensory neurons are an important, but comparatively understudied, source of interoceptive signals. Rachel Wolfson discusses the diversity of spinal afferents that innervate the colon and evoke sensations like constipation and pain. Kara Marshall discusses spinal afferents that innervate the bladder, sense fullness, and elicit the urge to urinate. Rose Hill reviews other spinal afferents in the kidney, which are relevant for fluid homeostasis, sodium excretion, and renal pain. Finally, our ability to study spinal and vagal pathways is greatly dependent on the tools that are available to monitor and manipulate these distributed sensory neurons, and Polina Anikeeva provides an overview of the latest technologies for interoception research.

Gut–brain communication is intimately connected to the control of ingestion, and several articles in this issue discuss the control of eating and drinking. Amber Alhadeff reviews the gut–brain pathways that detect ingested nutrients and describes how this information is used by the brain to determine what and how much we eat. A complementary review by Nilay Yapici explores what is known about these same pathways in *Drosophila*. Enteroendocrine cells (EECs) are the primary chemosensors in the gastrointestinal tract that detect ingested nutrients, and Fiona Gribble discusses sensory mechanisms in these cells. EECs release gut hormones like glucagon-like peptide 1, and manipulating these gut-brain signals has led to powerful therapies for obesity and nausea, highlighting the therapeutic potential of controlling interoception. In addition to sensing ingested food, EECs are important for sensing microbial products, and Chrisopher Thaiss gives an overview of the microbial regulation of interoception. Finally, Yuki Oka focuses on peripheral sensory pathways and central neural circuits that regulate bodily fluid homeostasis and the sensation of thirst.

All of these interoceptive pathways ultimately terminate in the brain, where they provide sensory signals that alter perception, mood, physiology, and behavior. Accordingly, several reviews in this issue discuss the central processes by which interoceptive cues impact motivation, learning, and emotion. Qili Liu discusses the neural basis of nutrient-specific appetites, which refers to the ability of the brain to detect the bodily deficiency of a single nutrient, such as sodium or protein, and then generate a specific hunger for that missing nutrient. She provides an overview of what has been learned about nutrient-specific appetites in invertebrates, where cellular and molecular mechanisms are beginning to come into focus, and compares this to our understanding in mammals.

One of the most important roles of interoception is the control of cardiopulmonary function, with control of physiology achieved through autonomic brain–body motor neurons. Kevin Yackle highlights how interoceptive cues from the respiratory system impinge on key breathing control centers in the brain that drive respiratory rhythms. Ritchie Chen provides an overview of the mechanistic studies of the bidirectional crosstalk between interceptive signals and emotional responses, while Philip Tovote discusses models for the central control of brain-to-heart channels during emotional stress. Carrie Boychuk discusses the organization of parasympathetic motor neurons that control the cardiovascular system, and a review by Wenwen Zeng discusses the function of sympathetic neurons.

While nutrient-specific appetites are innate, most of our decisions about what to eat and drink are guided by learning, and two reviews in this issue discuss how bodily signals enable reinforcement of actions and preferences. Mitchell Roitman provides an overview of how the dopamine system, which is important for learning associations between cues and rewards, is modulated by changes in fluid and energy homeostasis. He suggests that the internal state should be viewed as an 'occasion setter' that determines the magnitude of phasic dopamine responses to exterosensory cues. On the other hand, **Dana Small** discusses the mechanisms by which postingestive nutrients shape both our preferences for different foods and our motivation to consume them. She integrates findings from rodent studies, where it is possible to investigate detailed sensory mechanisms, with the results of human behavioral and neuroimaging research. Finally, emotions such as stress are intimately connected to our internal state, as they can both modulate visceral processes and be modulated by them. Sahib Khalsa integrates these ideas from rodents and humans to propose a multidisciplinary neurobiology of interoception and mental health.

Declaration of competing interest

None.