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Neural pathways of nausea and roles in energy balance

Chuchu Zhang

Our internal sensory systems encode various gut-related sensations, such as hunger, feelings of fullness, and nausea. These internal feelings influence our eating behaviors and play a vital role in regulating energy balance. Among them, the neurological basis for nausea has been the least well characterized, which has hindered comprehension of the connection between these sensations. Single-cell sequencing, along with functional mapping, has brought clarity to the neural pathways of nausea involving the brainstem area postrema. In addition, the newly discovered nausea sensory signals have deepened our understanding of the area postrema in regulating feeding behaviors. Nausea has significant clinical implications, especially in developing drugs for weight loss and metabolism. This review summarizes recent research on the neural pathways of nausea, particularly highlighting their contribution to energy balance.

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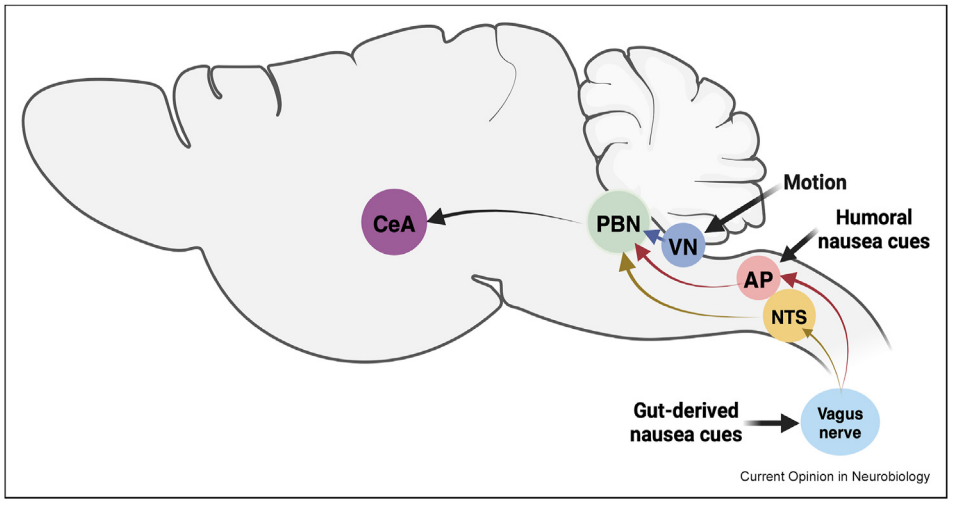
Introduction

Nausea is an unpleasant sensation of visceral malaise often associated with poisoning. Under normal conditions, nausea acts as a warning signal by causing reflexive actions like vomiting (or emesis) in response to potentially noxious stimuli [1]. Apart from visceral poisoning, nausea could also be caused by motion. As a protective mechanism, nausea suppresses appetite and promotes salient aversive learning behaviors critical for survival — future avoidance of poisonous food that may be deadly. In both humans and animals, it manifests as a long-lasting aversion to certain cues, such as flavors, tastes, and odors, that are associated with the experience of nausea.

Although acute nausea serves a protective purpose, experiencing nausea in certain clinical situations, for example, postoperative nausea and vomiting induced by anesthesia, can be highly undesirable and may result in complications [2]. On the other hand, chronic nausea in pathological conditions, such as gastrointestinal diseases, migraines, or as a side effect of cancer chemotherapy medications, loses its protective function and can become a disease of its own [3]. Many commonly used anti-nausea medications, such as those that block serotonin receptors, substance P receptors, and histamine receptors, have shown limited effectiveness for various causes of nausea. There is a lack of clear understanding regarding how these anti-nausea medications work, particularly in relation to their targets in the nervous system that are relevant for treating nausea [3].

As early as the 19th century, physiologists speculated that a "vomiting center" exists in the brainstem [4]. In the 1950s, groundbreaking work by Borison and colleagues demonstrated that the brainstem area postrema functions as the "chemoreceptor trigger zone" for nausea [5]. With fenestrated blood vessels, the area postrema lacks a blood—brain barrier and directly senses humoral signals relevant to nausea [6] — a concept that has become a textbook classic ever since. Only recently have studies gained a deeper understanding of the molecular signals involved in nausea, the anatomy of specific neural circuits, and how targeted changes affect the area postrema. The slow progress is likely due to the challenges of specifically manipulating these brainstem regions and identifying suitable animal models for nausea. Animals capable of vomiting, including ferrets, cats, and shrews [7,8], provide critical insights into the physiology of nausea. However, genetic tools available for non-model organisms are limited. Common laboratory species, such as rodents, lack a vomiting reflex; instead, a conditioned taste aversion test is used to assess nausea association. In rodents, stimuli that promote nausea cause rejection reactions (gapes, chin rubs) and a powerful avoidance of the paired cues [9]. To further explore these nausea-related pathways, innovation in advanced neuroscience techniques is essential. For example, approaches that allow specific targeting and in vivo imaging [10], improved behavioral models in

Figure 1



Sensory pathways for nausea. Visceral pathways comprise the vagus nerve, responsible for detecting nausea signals from the gut, and the area postrema (AP), which directly senses humoral cues and may receive secondary inputs from the vagus nerve. The vestibular pathway encompasses the vestibular nucleus (VN) that mediates motion sickness. It seems that all sensory pathways converge at the parabrachial nucleus (PBN) and central amygdala (CeA), which are crucial for aversive learning. Created in BioRender. Zhang, C. (2025) https://BioRender.com/r58i192.

non-emetic species, and genetic or similar manipulations in non-model vomiting species.

Growing evidence indicates that the neural pathways of nausea are closely linked to feeding and metabolic regulation. Many anorexia-related weight loss medications induce nausea, particularly glucagon-like peptide-1 (GLP-1) receptor agonists [11,12]. This raises questions about whether increasing satiety, the gratified feeling of being fed, will result in nausea or whether separating these two pathways is possible. On the other hand, cancer cachexia, which is characterized by chronic involuntary body weight loss [13], activates the neural pathways of nausea to induce anorexia and peripheral catabolic metabolism [14]. We will review recent discoveries on the neural mechanisms of nausea, particularly highlighting their contribution to feeding and metabolism.

Sensory pathways for nausea

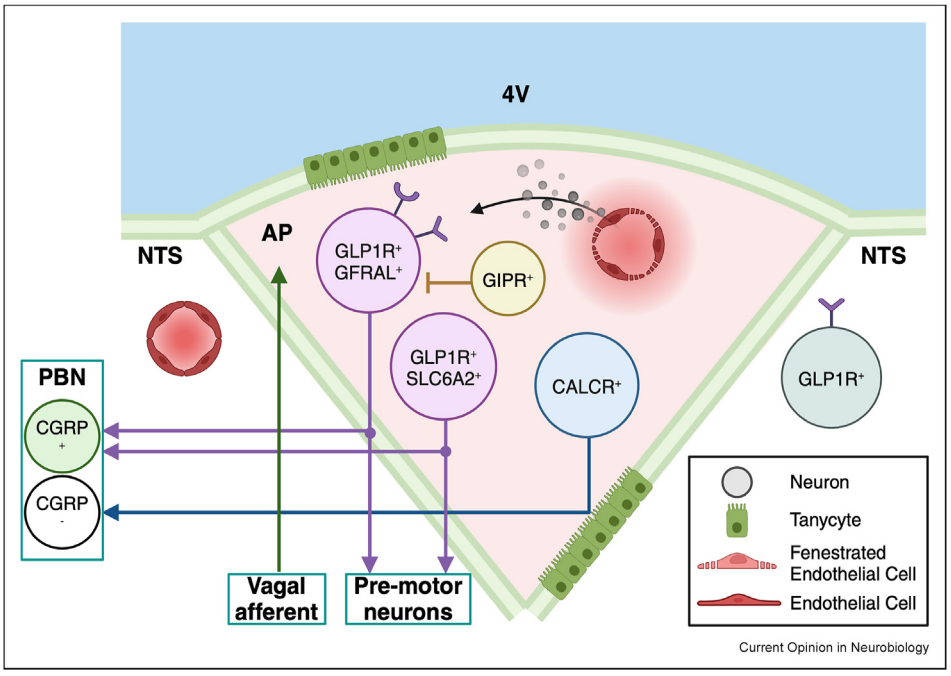
As with many exteroceptive sensations like olfaction and somatosensation, nausea — an interoceptive sensation — is evoked first by peripheral sensory pathways, which then activate the central nervous system. There are two main peripheral pathways responsible for nausea: the visceral pathway, which mediates poisoning, and the vestibular pathway, which causes motion sickness. For motion sickness, it is driven by conflicts between movement-related vestibular and visual inputs, which are processed in the vestibular nuclei [15]. For visceral poisoning, which is the main focus of this review, it involves mainly the brainstem area postrema and the vagal afferent pathway (Figure 1).

Area postrema neural pathway

The area postrema is a sensory circumventricular organ with direct access to peripheral circulation and cerebrospinal fluid [6]. Capillaries in the area postrema are highly permeable, allowing rapid humoral access to peptides and metabolites. Historically known as the chemoreceptor trigger zone for nausea, the area postrema is anatomically privileged to sense nausea-related stimuli in the blood to induce vomiting [6,16]. Several classical emetic stimuli (for example, apomorphine) have been shown to require the area postrema to induce emesis, while other types of stimuli (for example, veratrum alkaloid toxins) do not [17]. These suggest that the area postrema plays a crucial role in nausea, potentially in recognizing endogenous nausea triggers, whereas the other pathway may be more relevant for ingested nausea toxins (see the vagal route below).

Recent single-cell transcriptomics combined with functional studies have helped us better understand the area postrema neural pathways for nausea and feeding regulation [18,19] (Figure 2). The area postrema is composed of both excitatory and inhibitory neurons. Among the excitatory neurons, there are at least two largely divided populations with distinct anatomical projections and behavioral effects. One marked by the GLP-1 receptor (GLP1R) contains at least two smaller excitatory clusters. This includes one subpopulation

Figure 2



Area postrema cell types and circuits. The area postrema is located in the brain near the 4th ventricle, lined by specialized tanycyte. Endothelial cells within the area postrema form fenestrated vessels, allowing direct access to humoral cues such as hormones, immune signals, and GLP1R agonists. Single-cell sequencing experiments have revealed two largely segregated excitatory populations marked by CALCR and GLP1R in the area postrema. GLP1R$^+$ neurons can be further separated based on receptor expression. Inhibitory neurons also express markers, such as the GIP receptor. Area postrema GLP1R$^+$ population project to the PBN CGRP$^+$ neurons while CALCR$^+$ population project to the PBN CGRP$^-$ region. They also project to parasympathetic and sympathetic premotor regions in the brainstem. Peripheral vagal afferent nerves innervate the area postrema and NTS. NTS GLP1R$^+$ neurons can detect GLP1R agonists to suppress feeding via the non-aversive PVH pathway. Created in BioRender. Zhang, C. (2025) https://BioRender.com/d22p624.

that expresses the GDNF family receptor alpha-like (GFRAL), a receptor for the growth differentiation factor 15 (GDF15) [20], and another subpopulation that expresses solute carrier family 6 member 2 (SLC6A2). Activation of these smaller (SLC6A2$^+$ or GFRAL$^+$) or large (GLP1R$^+$) neuronal populations evokes conditioned flavor avoidance in mice [18]. In addition, specific genetic ablation of these neuronal populations in the area postrema abolishes avoidance conditioned to nausea-related cues, including exendin-4 (GLP1R agonist), bacterial lipopolysaccharide, and lithium chloride (gut irritant) [18]. Another area postrema excitatory population marked by calcitonin receptor (CALCR) suppresses food intake without evoking avoidance behavior [18,19]. Inhibitory neurons in the area postrema also express specific receptors and are interconnected with excitatory neurons in a cell-type-specific manner to modulate network excitations [21].

Both the avoidance-promoting (GLP1R$^+$) and non-aversive neuronal populations (CALCR$^+$) project to the parabrachial nucleus (PBN), a midbrain hub that relays the majority of the somatosensory and interoceptive sensory information [15,22–24]. However, only the GLP1R$^+$ area postrema population densely innervates the PBN neurons expressing calcitonin gene-related peptide (CGRP) [18], which is central in transmitting threat signals and mediating meal termination and aversive learning behaviors [25–28]. PBN CGRP$^+$ neurons form monosynaptic connections in the central amygdala (CeA), a critical site for anorexia and malaise-induced conditioned avoidance of novel flavors [27,28]. Novel flavors activate these amygdala regions and are specifically reactivated and stabilized by malaise signals through the PBN CGRP$^+$ neuronal inputs, which enables learned avoidance of the novel flavors despite the delayed malaise responses [29].

Located outside the blood–brain barrier, area postrema neurons can directly detect humoral cues through receptors expressed in the cell surface. Consistent with the primary role of the area postrema in regulating feeding, several gut hormones, including GLP-1, amylin, ghrelin, peptide YY, and glucose-dependent insulinotropic polypeptide (GIP), target this region [18,21,30–33]. Peripherally injected gut hormones or long-acting analogs activate the area postrema; however, it is unclear whether physiologically produced gut

hormones modulate the area postrema similarly. Other secreted factors that also engage neurons in this area include angiotensin [34] and GDF15 [35]. GDF15 is a cell stress signal that is elevated during numerous conditions, such as cancer, liver injury, mitochondrial diseases, and exercise [35]. The currently identified receptor GFRAL is located only in the area postrema and the adjacent nucleus of the solitary tract (NTS) [20]. Activation of the GDF15-GFRAL pathway causes hypothermia [36], alters systemic glucose and triglyceride metabolism [36,37], and directly induces vomiting in species capable of emesis [38]. Genetic variants of GDF15 underline severe nausea and vomiting during pregnancy [39]. In addition, GDF15 plays a role in food allergy-induced aversion [40]. Finally, there are emerging roles of immunological signals that target the area postrema. For example, cancer-induced interleukin-6 (IL-6), a key mediator of cancer cachexia, has been shown to act on the area postrema [41] (see below). IL-1beta and other cytokines for anti-microbial type-3 responses also activate the area postrema, leading to corticosterone responses through the NF-kB pathway and COX2 expression [42].

Vagal neural pathway

The vagus nerve is a key body-brain connection. Vagal sensory neurons are genetically heterogeneous and functionally distinct [43–46]. Different vagal neuron types innervate the gut, forming intraganglionic laminar endings, intramuscular array endings, and mucosal endings [45,46]. The vagal afferent pathway is primed to detect nutrients and nausea-related stimuli in the gastrointestinal tract. Several classic emetic stimuli, including plant-derived irritants, bacterial toxins, and viral proteins, require the vagus nerve for nausea responses [47–49]. Though the exact mechanisms by which the vagus nerve detects these stimuli are unclear, they possibly involve direct sensing or indirect signaling with the gastrointestinal mucosal barrier [47,48,50,51]. The mucosal barrier is formed by epithelial cells and specialized sensory cells, including the enteroendocrine cells and enterochromaffin cells. These sensory cells play a significant role in detecting chemical cues, including nutrients [52] and irritants [53,54]. They are "excitable" cells with a wide variety of cell-surface receptors for nutrients and irritants, which, upon stimulation, can release hormones and neurotransmitters, including cholecystokinin, GLP-1, serotonin, and substance P [52–54]. Vagal afferent terminals express receptors, including serotonin receptors, the substance P receptor, cysteinyl leukotriene receptors, and interleukin receptors, and detect diffused signaling cues [43,54]. Many commonly used anti-nausea medications, such as those that block serotonin and substance P receptors, are thought to act on the vagus nerve. However, as some of the receptors are also expressed in the brainstem [19,55], targeted loss-of-function studies are essential to identify the sites of action of these known antiemetics. This will help clarify the contributions of these antiemetic-sensitive vagal or brainstem neurons to nausea.

The sensory vagal neurons centrally relay visceral information to the brainstem NTS and the area postrema [46], with specific visceral inputs engaging distinct brainstem domains and cell types [46,56]. One possibility is that nausea-related vagal sensory neurons converge onto the same area postrema neurons implicated in nausea responses. The types of vagal sensory nerves that directly influence the area postrema and their roles in food intake, nausea, and other autonomic functions, such as cardiac reflexes [57], are still unclear. It is also possible that there are additional vagal pathways that induce nausea independently of the area postrema [58] (Figure 1). Further research on these critical questions will help to reveal the peripheral neural mechanisms of nausea involving the vagus nerve.

GLP1R agonists: relationship of satiety and nausea

Feeling satiated suppresses eating without any negative valence. Contrary to nausea, which is aversive and typically arises during non-homeostatic conditions, satiety plays a crucial role in meal termination during physiological feeding behaviors [59]. When mechanisms regulating satiety go wrong, conditions such as obesity can develop.

Recently, GLP1R agonists have emerged as the most successful weight-loss therapeutics [60], with an impressive 16 % reduction in body weight in clinical trials [11,12] and other meaningful health benefits beyond weight loss [61]. By far, the most common adverse side effects of GLP1R agonists are nausea and vomiting, with up to 60 % of patients reporting these effects, limiting adherence and efficacy [11,12]. This raises questions as to whether nausea can be functionally dissociated from satiety-promoting obesity therapeutics.

While GLP1R agonists have various peripheral effects, such as reducing blood glucose through the pancreas, the suppression of feeding primarily originates from targets in the central nervous system [62,63]. Studies have identified GLP1R^{+} neural circuits that suppress feeding, with candidate brain regions including the hypothalamus and the brainstem [60,64–67]. These regions are conveniently located either outside the blood–brain barrier or in close proximity to the circumventricular organs in the brain, allowing peptide GLP1R agonists to access them [68]. In the area postrema, targeted genetic deletion and rescue of the receptor are sufficient and necessary for the avoidance responses induced by GLP1R agonists, suggesting that

GLP1R in the area postrema mediates nausea [10,18]. On the other hand, feeding suppression is prominent despite the loss of avoidance [10,18]. This supports the idea that the nausea pathway is not necessary for effective weight loss by GLP1R-agonists-based drugs. Additional GLP1R$^+$ neurons account for the appetite suppression of GLP1R agonists, with the NTS GLP1R$^+$ neurons being the most important [10] (Figure 2). *In vivo* imaging of these neurons shows that they are tuned to respond to GLP1R agonists and nutrients rather than aversive nausea signals [10]. NTS GLP1R$^+$ neurons inhibit feeding through a non-aversive pathway involving the paraventricular hypothalamus (PVH) [10], unlike the area postrema GLP1R$^+$ neurons, which activate the PBN CGRP$^+$ neurons [18]. When both the NTS and area postrema GLP1R$^+$ neurons are lost, GLP1R agonists-induced feeding suppression is eliminated [10]. This suggests that brainstem GLP1R$^+$ neurons play a critical role in the weight loss functions of GLP1R agonists: the area postrema promotes nausea-induced anorexia, while the NTS promotes non-aversive appetite suppression. It is unclear whether these neurons detect endogenously produced GLP-1, either from the gut or from brainstem glucagon neurons, a major source of GLP-1 neuropeptide in the brain [69]. Other GLP1R$^+$ neurons in the brain may have additional roles in regulating feeding. For instance, GLP1R$^+$ neurons in the dorsomedial hypothalamus control preingestive satiation, which is commonly observed in patients using GLP1R agonists [70].

Nausea, anorexia, and metabolism

Recent studies have also indicated a connection between the area postrema neural pathway for nausea and the regulation of metabolism [14,36,37,41,71]. This connection is especially prominent in the metabolic syndrome associated with cancer cachexia, or wasting syndrome, which impacts up to 80 % of cancer patients [13]. The key characteristics of cancer cachexia include extreme loss of appetite and reduction in skeletal muscle mass. One of the mediators for cancer cachexia, IL-6, acts on neurons of the area postrema in several cancer models [41]. As cancer progresses, humoral IL-6 reaches the area postrema and elevates neuronal activity [41]. The activation of the network of area postrema neurons and their downstream targets leads to anorexia.

Interestingly, area postrema also drives weight loss via active catabolic activities independent of feeding suppression [41]. Consistent with this observation, a different study shows that acute activation of the area postrema GFRAL neurons induces lipid oxidation, ketogenesis, and hypothermia [36]. As the neurons in the area postrema project to the pre-motor and motor regions of the sympathetic and parasympathetic systems [18], their influence on metabolism may be partly attributed to the activation of these peripheral pathways. Insight into how the area postrema controls peripheral metabolism and how the circuit behaves in chronic (e.g., cancer) versus acute (e.g., GLP1R agonist injection) conditions may help inform strategies for potentially targeting the area postrema for therapeutic purposes.

Conclusion and perspectives

The area postrema is a crucial sensory pathway for nausea, integrating signals from the blood and potential vagal-mediated peripheral cues. Neurons in the area postrema project to the higher brain regions for aversive learning, but also communicate with the peripheral pathways that control body physiology. Together, activation of the area postrema sensory pathway may lead to aversion, visceral malaise, anorexia, and changes in metabolism.

The area postrema also emerges as an important player in controlling energy balance. It plays a key role in nausea induced by GLP1R agonists, as well as in cancer-related cachexia. Studying the neural pathways of nausea in the area postrema can help us understand how to achieve weight loss with fewer negative side effects. Additionally, the area postrema shows promise as a target for treating cancer-related weight loss and potentially other metabolic disorders.

There are still many fundamental questions that remain unanswered. For example, are there distinct mechanisms for nausea, such as those related to food poisoning, pregnancy, cancer chemotherapy, and food allergy? Are there additional signaling molecules, other than GDF15 and IL-6, that contribute to the mechanisms of nausea? What is the role of the vagus nerve in mediating nausea? By understanding context-dependent nausea mechanisms, we hope to uncover new pathways for intervention in clinical conditions.

Declaration of competing interest

The author declares no conflicts of interest.

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Data availability

No data was used for the research described in the article.

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