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REVIEW ARTICLE

Revisiting the physiology of nausea and vomiting—challenging the paradigm

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Abstract

Purpose The predominant neurotransmitters and receptors for acute and delayed chemotherapy-induced nausea and vomiting (CINV) are represented in the current paradigm, which reflects successful control of emesis. However, control of nausea (N) lags behind management of vomiting (V). This review aims to re-examine and incorporate new information about the mechanisms of V and N.

Methods The initial literature search focused on CINV. Keywords in articles led to subsequent discovery of publications focused on N&V in other medical and scientific fields (e.g., gastroenterology, neurology, cannabinoid science, neuropharmacology, and motion sickness). Using keywords to identify other sources continued until no further recent, meaningful publications were found.

Results More than 86% of references were from recent non-oncology journals and books, suggesting there are many areas for cross-fertilization research into mechanisms and management of N&V—particularly of N, which involves overlapping and dissimilar CNS areas from V. Information from cited articles was incorporated into visual representation of N&V, which is certainly not exhaustive but supports highly complex processes in the stomach and gut, the vagus nerve and spinal cord neurons, the nucleus tractus solitarii, and the anterior insular cortex and anterior cingulate cortex with input from the amygdala.

Conclusions These data support the idea that mechanisms for N, whatever the cause, must be highly similar. Continued research into nausea, including patient-reported evaluation and outcomes, is important; interventions for nausea could be considered adjuvants to current standard of care antiemetics and be individualized, depending on patient-reported efficacy and adverse effects and preferences.

Keywords Nausea · Vomiting · Gut-brain axis · Insular cortex · Interoception

The evidence-based chemotherapy-induced nausea and vomiting (CINV) paradigm emphasizes serotonin (5HT) and 5HT3 receptors during acute CINV (0–24 h) and substance P (SP) and neurokinin1 (NK1) receptors during delayed CINV (> 24 h) [1]. CINV studies largely did not distinguish nausea (N) from vomiting (V) or include patient ratings of intensity, duration, effects on important activities, and financial toxicity—a "glaring void" [2] of the "neglected symptom" [3]. In one study, > 56% of women reported moderate N for 16 days postchemotherapy—although only 30% received moderately or highly emetogenic regimens [4]. Another sample of 168 breast cancer patients received AC chemotherapy and guideline-recommended antiemetics, but 71% experienced N and 26% V [5]. Patients rated N "most feared chemotherapy side effect," but only 57% with CINV took any rescue antiemetics—only when V was severe. N in advanced cancer is similarly problematic; 10–60% of patients have moderate to severe N in their last weeks to months [6].

Box: Abbreviations in this paper

2-AG: 2-arachidonoylglycerol
5HT: serotonin
5HT3: serotonin subtype 3 receptor
ACC: anterior cingulate cortex
AIC: anterior insular cortex
ANS: autonomic nervous system
AP: area postrema

If you always do what you always did, you'll always get what you always got.

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BBB: blood-brain barrier
CBD: cannabidiol
CBDA: cannabidiolic acid
CPG: central pattern generator
CTZ: chemoreceptor trigger zone
CVO: circumventricular organ
DVC: dorsal vagal complex
DMNV: dorsal motor nucleus of the vagus
eCB: endocannabinoid
ECC: enterochromaffin cell
ECS: endocannabinoid system
EEC: enteroendocrine cell
FAAH: fatty acid amide hydrolase
fMRI: functional magnetic resonance imaging GBA: gut-brain axis
MAGL: monoacylglycerol lipase
MS: motion sickness
NK1: neurokinin subtype 1 receptor
NTS: nucleus tractus solitarii
PBN: parabrachial nucleus
PIC: posterior insular cortex
SP: substance P
THC: delta-9-tetrahydrocannabinol
VEN: von Economo neuron
VIMS: vection-induced motion sickness
VOLT: vascular organ of lamina terminalis

N is often considered a lower level antecedent of V [7]—reflected in study response criteria of antiemetic complete response: "no emetic episodes, no or little N, and no rescue therapy." Considering "no rescue," a surrogate for no/mild N without patient input often miscalculates occurrence and exaggerates clinical benefit [8]. Patients underreport CINV to not bother their physician or nurse, for fear chemotherapy will be stopped, thinking CINV is part of chemotherapy to be tolerated, to "save" expensive antiemetics for absolutely necessity, or because of adverse antiemetic effects [2]. Oncology professionals amplify the problem by using suboptimal antiemetics, underestimating CINV in *their* patients, not using antiemetic guidelines, using data that overrate antiemetic efficacy, or having insufficient knowledge about N mechanisms [5, 9]. N and V are largely separate processes initiated in the same peripheral or central nervous system (CNS) afferents, with distinctive and overlapping integration in the CNS and efferent output manifestations [10].

Mechanisms of nausea and vomiting

N and V are highly conserved responses and survival advantages in vertebrate animals. V is a primitive, low-threshold, brainstem response that allows fish, amphibians, reptiles, birds, and mammals (except rodents and rabbits) to purge the gastrointestinal (GI) tract of orally consumed noxious substances [7]. Stimuli for V (e.g., emetogenic chemotherapy, bacterial toxins in the gut, food poisoning, epigastric radiation, opioids, anesthesia, and motion or compression of GI structures) usually cause N (Fig. 1) [7, 11].

N is multidimensional, has higher brain center cognitive, emotional, and interoceptive domains [12], and is more common, disabling, and more difficult to control than V [3]. N is a warning signal that serves no adaptive purpose. Emetic stimuli cause interrelated endocrine, GI, and autonomic nervous system (ANS) prodromal stress responses [3, 11, 13]. Endocrine actions increase plasma vasopressin 20–30 times than usual—maybe to conserve body water and vasoconstrict GI blood vessels and impede circulatory dispersal of toxins. GI responses (after cisplatin, motion sickness [MS], or gastroparesis) are proximal stomach relaxation, gastric dysrhythmia, decreased ghrelin, retrograde flow of small intestine contents, and decreased GI motility [13]. Mild or brief gastric dysrhythmia might not trigger perceived N, and decreased N accompanies gastric dysrhythmia cessation. The stomach secretes ghrelin, the "hunger hormone" that signals the CNS to regulate gastric acid secretion and emptying [14]. Cisplatin induces significant ghrelin decreases for up to 27 days [15]; ghrelin agonists speed gastric emptying, improve eating and weight after chemotherapy, enhance antiemetic control of palonosetron ± netupitant, and decrease N&V with motion and cisplatin [16, 17].

ANS (sympathetic and parasympathetic) responses accompanying N include cold sweats, salivation, pallor, fatigue, and altered heart rate [11, 13]. Other ANS responses are awareness of imminent V, appetite loss, anxiety, lethargy, and disinterest in usual activities. Prodromal manifestations may be related to N severity although none are specific; symptom clusters are stronger evidence for emetic stimulus-induced N.

Whether animals experience "nausea" akin to humans cannot be directly confirmed. Rats cannot vomit but experience emetogen-induced proxy behaviors for N—increased salivation, pica, and conditioned gaping that causes rodents to avoid substances (or contextual cues) previously paired with gaping [18, 19]. Animals also experience gastric dysrhythmia and delayed stomach emptying after cisplatin (worsens with chronic administration), elevated plasma vasopressin, and malaise.

Due to severe or persistent N after chemotherapy, humans may develop anticipatory N that recurs with contextual cues (e.g., thinking about coming to the clinic, odors or sights encountered) before subsequent chemotherapy [7]. People use different words for N or may find it difficult to describe it, complicating assessment. For example, one patient said "… Because nausea is 'I feel I'm going to be sick,' then there's *this* (emphasis added) nausea …" [2]. Humans have a dynamic threshold for N, depending on interactions between inherent individual influences and malleable psychological states (anxiety, anticipation, expectation, and adaptation) [3].

The gut-brain axis

The gut-brain axis (GBA) is a continuous, bidirectional neural and endocrine communication network between the GI tract

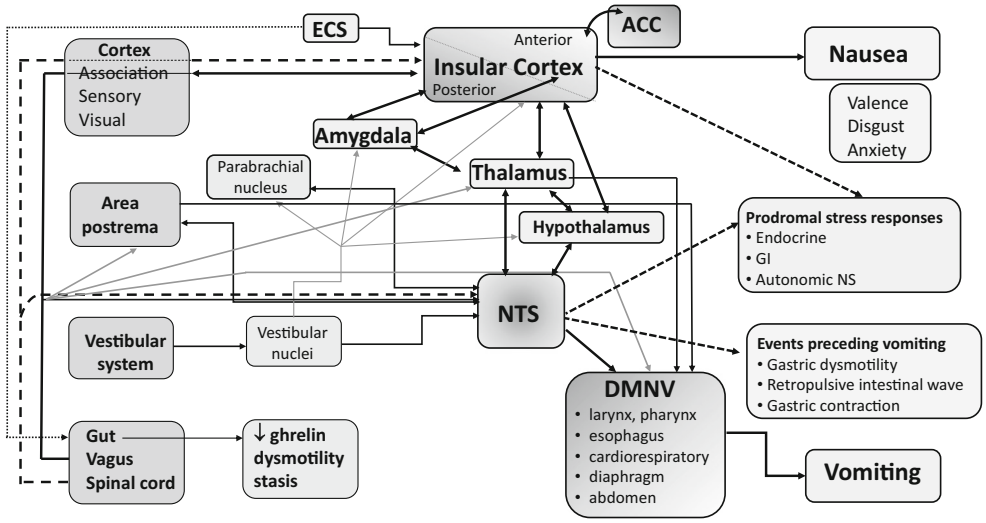

Fig. 1 Proposed mechanisms of nausea and vomiting. Abbreviations: ECS—endocannabinoid system; ACC—anterior cingulate cortex; NTS—nucleus tractus solitarii; DMNV—dorsal motor nucleus of the vagus. This proposed model incorporates information synthesized from numerous publications. It should be apparent from this representation that these are highly complex and interactive processes that are far from being fully understood. N&V involve the GI tract and other inputs, the gut-brain axis, medullary structure (area postrema, NTS, and DMNV), and higher brain centers (insular cortex, anterior cingulate cortex, and amygdala plus sensory and visual cortices, thalamus, and other limbic regions)

and the brain that is crucial to GI regulation and physical and emotional integration [20]. The GBA probably plays roles in N&V from any cause and includes the enteric nervous system (ENS)—the myenteric and submucosal plexuses, sensory and motor neurons and interneurons, and the afferent and efferent vagus and spinal cord, the brainstem, limbic and interoceptive regions, and ANS and motor outputs.

The brain mediates the gut, monitors enteric processes, and maintains functional homeostasis, GI visceral sensations (e.g., appetite, nausea, and pain), and symptoms (e.g., diarrhea, constipation, or cramping) [20]. The ENS ("second" brain) initiates afferent vagal communication with cognitive and emotional brain regions. Even if the vagus is severed, the ENS can independently trigger gut reflexes to maintain appropriate GI responses [21]. Spinal visceral afferents (the spinothalamic tract) are more important in tissue damage–induced N&V [22].

GI enteroendocrine cells (EECs), 1% of the gut epithelium, are sensing cells sparsely scattered from the stomach to the rectum. EECs constitute the largest endocrine organ (cell numbers) and modulate numerous processes [23]. EECs synthesize ≥ 1 of 20+ peptides (e.g., ghrelin, somatostatin, and motilin), stored in cytoplasmatic granules and released by chemical, neural, or mechanical stimuli [24]. EECs are open or closed type. Open EECs have microvilli projecting to the intestinal lumen to sense contents. Closed EECs do not communicate with the lumen and concentrate secretory granules at the cell base. Secretory products act as paracrine hormones on nearby EECs or other cells, as neurotransmitters at adjacent nerve endings, or as humoral hormones at distant targets [23, 25].

Enterochromaffin cells (ECCs), 50% of EECs, synthesize > 90% of the body's 5HT, and most also synthesize SP—hormones fundamental to GI motility, water and electrolyte balance, and N&V. Some ECCs synthesize other signaling molecules (e.g., secretin, CCK, and somatostatin) [26, 27], and > 60% are mechanosensors, activated during abnormal gastric distention, GI dysrhythmia, or dysmotility. This causes 5HT release and vagal binding that induce N [28]. ECCs are closed type with cytoplasmic extensions extending into basement connective tissues. Chemical, mechanical, or neurological emetogenic stimuli induce receptors to release calcium (Ca^{2+}), which stimulates 5HT and SP release from ECCs [25, 29, 30]. ECCs have synaptic-like contacts with afferent vagal receptors (5HT3, 5HT4 or 5HT1b, or NK1) [7]. Some 5HT (in platelets) and SP are taken up into the bloodstream and carried to the CNS and other organs.

After cisplatin administration, some patients have increased 5HT release during the first 24 h, while serum SP is measurable > 24 h in patients with delayed CINV [31]. SP increases ~ 600% at 36 h and persists for 2–5 days. Rats experience a cisplatin-induced inflammatory response for 72 h, with the same pattern of increased 5HT-producing ECCs by 24 h and SP ECCs by 72 h [27, 32]. Methotrexate induces more transient hyperplasia of 5HT- and SP-containing ECCs with moderate ileal mucosal inflammation [33].

Afferent fibers are 80–90% of the vagus nerve. Most of these terminate in the nucleus tractus solitarii (NTS) and the dorsal motor nucleus of the vagus (DMNV), and fewer project to the thalamus and thence to interoceptive regions [10, 34].

The vestibular system

The vestibular system is largely disregarded in oncology literature, but MS provides insights into neural mechanisms of N. MS is a subjective response to sufficiently intense and enduring motion—real (e.g., car, sea, or air sickness) or apparent (illusory motion induced by an altered visual field [vection]) [35]. Ambiguous or incongruent sensory information about body position stimulates labyrinth cells to propagate afferent impulses toward brainstem vestibular nuclei to trigger MS [36]. Vestibular nuclei project to multiple brain areas, including the NTS, parabrachial nucleus (PBN), hypothalamus, amygdala, and insular cortex [37]. V is rare with MS, but N is universal and accompanied by endocrine, GI, and sympathetic manifestations: delayed gastric emptying, stomach discomfort, feelings of imminent V, increased salivation, pallor, diaphoresis, profound drowsiness, and fatigue [35, 36].

The area postrema

The area postrema (AP)—the chemoreceptor trigger zone (CTZ)—is a small, sensory circumventricular organ (CVO) in the midline floor of the fourth ventricle near the NTS [38, 39]. It is the first site for integration of afferent medullary signals that trigger N, V, MS, and perhaps anorexia [30]. Chemoreceptors monitor neural and bloodstream environments to maintain metabolic, fluid balance, cardiovascular, and immune system homeostasis [39, 40]. Another sensory CVO, the vascular organ of lamina terminalis (VOLT), has osmosensory cells for serum osmolality and regulates thirst and vasopressin release [22].

A blood-brain barrier (BBB) protects neurons from exposure to harmful or fluctuating blood constituents. CVOs have an incomplete BBB with size-selective, low-permeability, fenestrated capillaries [40]. AP blood vessels form large loops surrounded by perivascular areas (Virchow-Robin spaces) that optimize diffusion and prolong exposure to circulating substances; a 150-fold increase in surface area permeability ratio and a 50% higher plasma flow allow larger molecules (peptides, chemical messengers, and hormones) to directly pass bidirectionally between the bloodstream and the AP [41]. Specialized neurons respond relatively rapidly to systemic, blood-borne stimuli [40]. The AP basement membrane has tight capillary junctions to prevent circulating substances from diffusing into the adjacent NTS and other areas [42]. Neurotransmitters diffusing into the AP might act on neurons projecting to the NTS or stimulate other neurotransmitters to convey impulses [30, 40].

The nucleus tractus solitarii and dorsal motor nucleus of the vagus

The GI tract and other visceral sensory impulses are transmitted on unmyelinated, slow-conducting vagal C-fibers, and stimuli from the vestibular system and higher brain centers project to the AP and NTS [38]. The NTS and the DMNV, the main elements of the dorsal vagal complex (DVC), regulate gastric motility and mediate vomiting [7, 43]. 5HT3 receptor antagonist application to the AP, NTS, or DMNV reduces CINV, suggesting both central and peripheral 5HT effects [30]. NK1 receptors are also highly concentrated in the NTS and the DMNV.

It is unknown if the NTS or DMNV is the "vomiting center"; both may be a central pattern generator or vomiting region—a network of NTS neural connections and specific DMNV motor nuclei that coordinate laryngeal and pharyngeal, esophageal, diaphragmatic, gastric, and abdominal motor patterns for V [7, 9, 30, 38]. The NTS, viscerotopically laid down cranial nerve subnuclei, includes the afferent vagus that terminates in the NTS and the DMNV. Emetogen-evoked cytoplasmic Ca^{2+} in the NTS stimulates neurotransmitter release and binding at NK1 and 5HT3 receptors [31]. Events resulting in N&V, including MS, are accompanied by increased c-fos immunoreactivity (a marker of neural activation) in regions that control the motor aspects of V [30, 33]. Afferent inputs from the AP and spinal nerves project to the NTS, and some conveying tastes and visceral sensations project from the NTS to the thalamus [22, 38]. Other secondary NTS afferents project to the PBN and to brain regions involved in higher cognitive function, emotional responses, and perceptions of N [30, 38, 44].

Most sensory information the DMNV receives comes from the NTS. The DMNV integrates other inputs from the AP, olfactory system, amygdala, hypothalamus, and other regions [38, 45]. Cisplatin administration causes dose-dependent SP binding to DMNV NK1 receptors in rats, with enhanced gastric contractility and motility. Most (> 80%) efferent vagal motor and sympathetic DVNM fibers project to the gut and influence gastric and bowel motility [30]. The emetic reflex induces the large retropulsive intestinal wave and gastric contraction that precede V.

Brain areas involved in the sensation of nausea

Increasing evidence supports N formation in the insular cortex (or insula)—particularly the anterior insular cortex (AIC), with input from the anterior cingulate cortex (ACC), the posterior insular cortex (PIC), and the amygdala [9, 19, 46, 47]. Neuroimaging, especially functional magnetic resonance imaging (fMRI), is used to visualize brain areas activated during

neural events and clearly links nausea to interoceptive brain regions [37, 48]. Briefly, most vection-induced MS (VIMS) studies found that fMRIs of ~ 70% of N-sensitive individuals showed activation in regions processing stress and fear (amygdala, ventral putamen, and dorsal pontine) with slowly increasing N during a phasic period [49]. Sustained activation in the AIC, ACC, and somatosensory cortices and ANS activation followed in subjects who then reported "severe nausea and strong stomach awareness." Others also confirmed increased anxiety and ANS activity, but only activation of the left ACC in individuals with VIMS [47].

The insular cortex and cingulate cortex

A neural interoceptive network—the insula, ACC, and somatosensory and somatomotor cortices—is essential to homeostasis and monitors all body states. Interoception is the sensations of all tissues of the body, of physiological conditions or internal states, and of self-awareness [47]. For example, an individual about to give an important speech might be aware of their rapidly beating heart, sweaty palms, or "butterflies" in their stomach—interoceptive sensations that would not typically arise to awareness.

The insula, an "island" of distinct but hidden cortical lobe, folded within each lateral sulcus below the frontal, parietal, and temporal lobes—the opercula or "lids" (Fig. 2) [49]. It is grossly divided into anterior (dysgranular) and posterior (visceral or granular) regions, each having different structures and functions. The PIC receives the vestibular, spinal cord, and brainstem input (via the thalamus) and association cortices; information is re-represented in the mid-insula and then again in the AIC, where all body sensations are integrated and location of the "sentient self" is located [37, 44, 50, 51]. Other neural inputs, sensory environmental, motivational, and social information, are integrated in this general to increasingly complex processing; emotional valence—good, bad, or neutral—is added to refined frontal cortex perceptions. According to Craig [52], interoception with increasingly layered PIC to AIC neural processing, integration, and interpretation is unique to humans (and a few other animals) with large brains and intelligence, proportionately larger and more complex interoceptive cortices and thalami, self-awareness, social sophistication, and von Economo spindle neurons (VENs) that form extensive connections and rapidly conduct neural information between brain regions [44, 52].

Many interoceptive stimuli (e.g., nausea, hunger, thirst, dyspnea, warmth, sensual touch, pain, itch, heart rate, or visceral distension) can activate the ACC and AIC. These complementary regions are activated together during subjective or emotional feelings (e.g., love—maternal or romantic, anger, fear, sexual arousal, sadness or happiness, disgust, or empathy) [51]. The AIC integrates emotional, cognitive, and motivational impulses from the amygdala and other areas. The ACC, in the medial wall of each cerebral hemisphere, mediates cognitive influences on emotion, integrates emotional and cognitive neuronal crosstalk, and influences autonomic functions [47]. Both have numerous robust reciprocal connections with areas involved in emotion, memory, motivation, sensory, and autonomic functions [44, 49–51]. Top-down autonomic visceral control originates in the AIC via projections to the NTS, hypothalamus, and PBN [50].

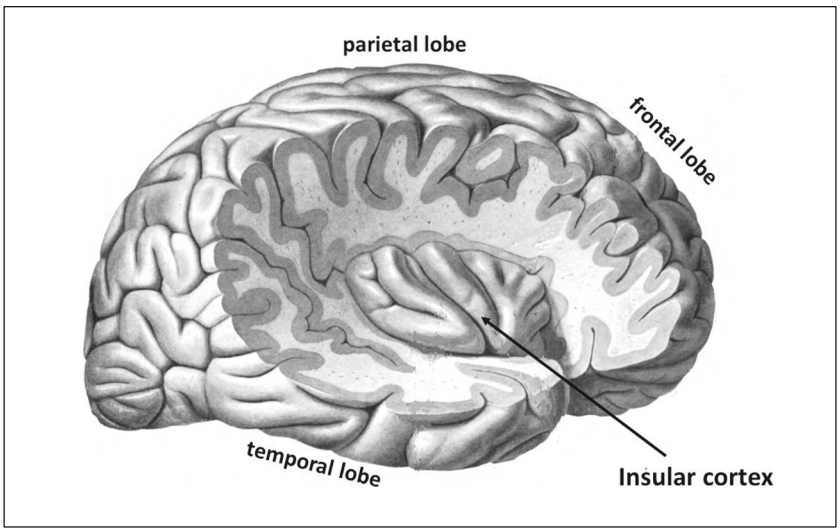

Fig. 2 The insular cortex. The right and left insular cortices are folded and entirely hidden beneath the opercula ("lids")—the frontal, parietal, and temporal lobes. The insula is primarily involved in homeostasis and incorporating the internal states or conditions of all body tissues, that is, interoception. Along with the anterior cingulate cortex and the amygdala, the anterior insula actualizes physical conditions with subjective or emotional feelings that contribute to the sentient self. Modified from Sobotta J, Sobotta's Textbook and Atlas of Human Anatomy 1908, Public Domain, https://commons.wikimedia.org/w/index.php?curid=29190135

The amygdala

Emotional learning (Pavlovian conditioning) is attributed to the amygdala, deep within the temporal lobe. The amygdala can rapidly detect and adapt to fearful or aversive external or internal environmental stimuli or situations that promote or inhibit dread and anxiety [53]. It also collects external environmental information via the sensory cortices and thalamus and has extensive reciprocal cortical, sensory association, and hippocampal connections with the insula [50, 51]. fMRI studies confirm the amygdala, insula, and perhaps somatosensory cortices are activated during anticipatory nausea, which may also be related to epigastric signals and gastric arrhythmia that accompany nausea [53].

The parabrachial nucleus

The bilateral PBN on the dorsolateral pons is not involved with vomiting but is the first relay for general visceral and taste afferents (indirectly via the NTS) and interoceptive information from the AIC, ACC, hypothalamus, and amygdala. The PBN is essential to single-trial acquisition of conditioned gaping: if an animal ingests an innocuous substance (e.g., saccharin) followed immediately by lithium chloride (always induces conditioned gaping [nausea]), the animal will subsequently *always* avoid the *innocuous agent* that will induce gaping [37, 44, 54]. This may occur in humans, to some degree: patients who experience N&V often develop a negative association between food intake and CINV and appetite loss [55].

The endocannabinoid system

The endocannabinoid system (ECS), a ubiquitous, neuromodulatory system, was identified around 1990. The ECS is important to homeostasis in most organ systems and to many disorders (e.g., inflammation, pain, neurological diseases, psychiatric illnesses, immune dysfunction, and cancer) [56]. It includes two G protein-coupled cannabinoid receptors (CB1 and CB2), endogenous ligands (anandamide and 2-arachidonoylglycerol [2-AG]), and enzymes for ligand synthesis, transport, and degradation [57]. CB1 receptors are most common in the CNS and CB2s in the periphery.

The ECS is the body's only retrograde neurotransmitter signaling system. Postsynaptic cells release endocannabinoids (eCBs), which travel backward (against usual synaptic transmitter flow), to act at presynaptic target cell receptors [57]. Specific signals cause postsynaptic cells to synthesize anandamide and 2-AG "on demand" that act as a synaptic "circuit breakers": they are released, rapidly cross the synaptic cleft and bind to presynaptic CB1 receptors, modulate Ca^{2+} channels, and suppress neurotransmitter release. Less often, anamide and 2-AG bind to and act at postsynaptic neurons or have autocrine feedback effects at neighboring astrocytes. eCB effects may also be mediated by binding at serotonin, β-adrenergic, mu-opioid, or other receptors. After receptor binding, eCB actions rapidly end, and ligands are taken up into presynaptic cells and recycled. Monoacylglycerol lipase (MAGL) hydrolyzes 2-AG, whereas fatty acid amide hydrolase (FAAH) can degrade anandamide and 2-AG [57].

The ECS influences V and N [9, 46]. Activation of CB1 receptors in the NTS and DMNV induces V that can be blocked by administering a CB1 inverse agonist (e.g., rimonabant) [58]. The ECS has a greater role in regulating nausea. PIC neurons respond to emetic stimuli by releasing 5HT, which binds to postsynaptic 5HT3 receptors and triggers nausea [10]. In response, the ECS causes postsynaptic neurons to release 2-AG, which (briefly) bind at presynaptic CB1 receptors in the PIC to suppress 5HT release and decrease nausea. Therapies that can suppress 5HT in the insula for a longer period are thus needed. MAGL inhibitors (investigational agents) prevent 2-AG hydrolysis and suppress 5HT in the PIC for up to 24 h. They may be effective for acute and anticipatory N, MS, and postanesthesia N [9, 19, 46].

Marijuana (cannabis), which contains > 100 phytocannabinoids and other compounds, is the plant for which the ECS was named. Both delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), the most abundant phytocannabinoids in cannabis, have antiemetic properties. THC has psychoactive effects (may cause a "high") and is a partial agonist that binds to and activates presynaptic CB1 receptors, which inhibits 5HT release and decreases nausea [57, 58]. CBD (and cannabidiolic acid [CBDA], its 1000 times stronger precursor) do not bind to eCB receptors but are *5HT1A* receptor agonists that bind in the insula to reduce 5HT and thereby decrease nausea [52, 57]. Corticosteroids may also act, in part, on the ECS to decrease N&V. MS may alter eCB synthesis in the CNS and intestine, decrease CNS levels of 2-AG, and increase CB1 receptor expression in the DVC; effects blocked by dexamethasone preventing "nausea" in an animal model [59].

In the 1970s and 1980s, a number of small studies included adult cancer patients receiving emetogenic chemotherapy. Most studies compared THC (dronabinol or nabilone) with placebo or prochlorperazine, domperidone, or chlorpromazine and led to approval of dronabinol and nabilone for CINV inadequately controlled with conventional antiemetics (and cachexia in AIDS). Nabiximols (Sativex, 1:1 THC and CBD sublingual spray) is indicated for neuropathic pain and spasticity. Recent meta-analyses and reviews have concluded cannabinoids are favored for nausea control, are preferred by patients, and are effective for CINV (and for pain) [60, 61]. The USA and the United Nations Convention on Narcotic Drugs consider botanical cannabis (marijuana) a schedule I drug (illegal, no medical use, and high abuse potential). The EU's modified regulatory framework now allows medically

prescribed, pharmacy-prepared cannabis products (in accordance with member countries' pharmacopeia). Medical marijuana/cannabis programs are approved in 34 states, 3 US territories, and Washington D.C., but the federal government still considers cannabis illegal, essentially squelching cannabis research.

Conclusions

Antiemetic research of targeted 5HT3 and NK1 receptor antagonists has vastly increased the understanding of acute and delayed CINV, but these are more efficacious for V than N—particularly for delayed N, an impactful and persistent problem that decreases overall quality of life, impairs usual activities, leads to nutritional deficits, and alters social interactions [2, 4, 55, 62]. If the NTS is the only hub for N, antiemetics that prevent V would also prevent N. On the other hand, the idea that N largely **o**ccurs in higher brain centers (with less involvement of the GI tract and the NTS) is congruent with Napadow and others' [12] characterization of N as multidimensional, with cognitive, emotional, and interoceptive domains occurring in higher brain centers. That is, the sensation of N comes about in the AIC and the ACC, where the sentient self interprets all internal states, the amygdala adds negative valence, such as disgust, anxiety, and dread, and other cortical and limbic regions incorporate learning and memory.

A great deal of evidence for antiemetic control of V has been generalized from animal data, but using the same approach for N is problematic. Andrews and Sanger [63] argue studies claiming to investigate and "interpret" nausea in animals are controversial and may not be generalizable to humans; there are no validated models of "nausea" in animals, and VIM studies identifying interoceptive regions in N may not represent N initiated via other primary inputs. However, they recognize that N induced by gastric distension, apomorphine, ipecacuanha, or vection may activate the same areas (AIC, ACC orbitofrontal, prefrontal, and inferior frontal gyrus). It would probably be difficult (if not impossible) to substantiate these findings in patients with CINV. However, some patients with persistent delayed CIN might be willing and able to undergo fMRI.

Drugs with prokinetic effects, such as metoclopramide, mirtazapine, or investigational agents (motilin or ghrelin receptor agonists), might be useful for N associated with delayed gastric emptying (common with CINV) [63, 64] or investigational MAGL inhibitors, which act in interoceptive regions to decrease 5HT release and action and thereby decrease N [46, 56–58, 60, 61]. Interventions for N might be "adjuvants" to guideline-recommended antiemetics, and patients and clinician decide together which adjuvant to use first.

And finally, considering how to improve on-time assessment and intervention adjustments is warranted. Ideally, patient ratings (initial and subsequent) of N and V and of intervention efficacy would be incorporated into routine assessment. For example, the MASCC antiemesis tool (MAT), a validated screening tool for acute and delayed CINV, could be useful in the clinic to help patients estimate N and V ratings that would trigger notifying their clinician (and a clinician response)—particularly during chemotherapy cycles 1 and 2. Patient teaching should stress the importance of preventing V and N, and patients are coached to complete the MAT at the end of each day they experience N or V. Clinicians could complete the screen by asking patients if N control and V control are "good enough or could be better," and if they have new side effects from interventions.

Compliance with ethical standards

Conflict of interest Rita J. Wickham has received speaker's honoraria from Insys Therapeutics and advisory board compensation from Helsinn Healthcare SA. There is no primary data associated with this manuscript.

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