

## Review Article

# Induced vomiting: a therapeutic option

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**Abstract:** Vomiting, the basic protective reflexes against ingested toxins, or result from underlying diseases such as inevitable medication side effect or anatomic obstruction, however, in some situations, induced vomiting may be a therapeutic option as reported in bulimia nervosa as a weight control measure. Besides that, many types of researches demonstrate that induced vomiting for treating disease does not have serious negative effects. To well understand the therapeutic effect of induced vomiting, the paper firstly describe the anatomy of brain structures containing the vomiting reflex, including chemoreceptor trigger zone, vomiting center and the specific signal deliver process. Moreover, cardiovascular and respiratory functions changes are essential to the generation of vomiting. Furthermore, the brain-gut connections may play an important role in the vomiting reflex, its bidirectional interaction can be perturbed leading to acute physiological repercussions. In addition to that, vagal afferent activation is also indispensable. Effect of emesis can achieve via vagal fibers in variable methods. Additionally, induced vomiting can change the gastrointestinal homeostasis as well which lead to a recovery of the stomach's function. Finally, this work will briefly illustrate the procedure of induced vomiting, as well as the side effects of induced vomiting and the corresponding control strategies. According to the known acknowledge about the induced vomiting as mentioned above, we draw a conclusion that induced vomiting may be a therapeutic option.

**Keywords:** Induced vomiting, brain-gut connections, vagal fibers, gastrointestinal homeostasis, therapeutic option

## Introduction

Vomiting, the culminating sign of nausea, is a primarily protective reflex involving the gastrointestinal system, respiratory and abdominal muscles, and changes in posture [1-4]. The symptom of vomiting may be associated with a myriad of organic causes, including infections, toxic ingestions, migraine, inevitable medication or post-operative side effect, pregnancy, and increased intracranial pressure, however, vomiting is not always a bad thing existing in the disease, it was known to be a frequent method of purging in patients with bulimia nervosa as a weight control measure in an early time [5, 6]. Besides, many researches has also been reported to demonstrate that induced vomiting for treating disease does not have serious negative effects [7]. Additionally, induced vomiting could also be served as a possible therapeutic option in some diseases. For instance, vomiting can be used to exclude the toxin food, stop migraine attack, or perhaps protect the embryo and mothers. In this paper,

we mainly proposed a hypothesis relating to the topic: induced vomiting, maybe a therapeutic option. And we analyzed the postulation in detail, including the anatomy and physiology of vomiting, the possible mechanisms containing the gut-brain and vagal activation and so on.

## The anatomy and physiology of vomiting

Vomiting is defined as the actual oral expulsion of gastrointestinal contents from the mouth. At the onset of vomiting, intrinsic contractions occur in both the duodenum and the stomach, the lower esophageal sphincter relaxes, and vomitus moves from the stomach into the esophagus. Next, the inspiratory and abdominal muscles contract and expel the vomitus into the mouth [8]. These are basic protective reflexes against ingested toxins, or result from underlying disease that affects the gastrointestinal tract or surrounding structures, metabolic or endocrine function, or the central nervous system [9, 10].

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Vomiting is associated with activation of a matrix of brain structures including the amygdala, periaqueductal gray, putamen, and dorsal pons/locus coeruleus [11]. Among them, the more important are the vomiting center (VC) and the chemoreceptor trigger zone (CTZ). The VC, located in the medulla oblongata, was initially confirmed by Borison and Wang [12]. The VC is the portion of the brain responsible for collecting emetogenic such as emetics stimuli from throughout the body and coordinating the development of nausea and vomiting, which can be activated directly input from multiple mechanisms, including the pharyngeal, vagal, and midbrain afferents and the limbic system [13, 14]. The VC can also be activated indirectly by certain stimuli that activate the CTZ, which is located in the area postrema (AP) on the floor of the fourth ventricle. However, this area lacks a true blood-brain barrier and is exposed to both blood and cerebrospinal fluid. Thus, the CTZ is directly sensitive to stimulation from the transmitters that carried in the blood such as emetics, serotonin, dopamine, histamine, as well as cholinergic, adrenergic, opiate receptors and the substance P [15-18]. Besides, the CTZ could directly identify the harmful stimulation from the stomach and small intestine via vagal afferents. Then the CTZ integrate these information and convey them to VC, which initiates the vomiting reflex [14].

Changes in cardiovascular and respiratory functions are essential for the generation of vomiting. Vomiting is associated with the increase in blood pressure and a coordinated contraction of respiratory muscles. The coordinated activity of respiratory muscles (diaphragm, abdominal, intercostal) is essential to the production of increased thoracic and abdominal pressures required for vomiting. Unlike normal respiration, during emetic-like behavior the diaphragm and abdominal muscles co-contract accompanied by contraction of the external (inspiratory) intercostal muscles and relaxation of the internal (expiratory) intercostal muscles [19-21]. When vomiting, some of these coordinated reflex events are a reduction in gastric motility, retrograde movement of gut contents from the proximal intestine to the stomach, and relaxation of the gastro-esophageal junction followed by expulsion of gastric contents brought about by forceful contractions of the diaphragm and abdominal muscles, and closure of the glottis to protect the airways [1, 3, 22].

During the vomiting phase, salivation and swallowing increase, gastric tone decreases, and pallor, diaphoresis, and tachycardia occur. The act of vomiting can produce a transiently elevated heart rate followed by decreased heart rate, and additionally causes continued peripheral vasoconstriction [23]. This phase is mediated by the vagus nerve and the neurotransmitter acetylcholine [24].

### The practical application of induced vomiting

Extensive research has been reported to demonstrate that several treatments for disease do not have negative effects, such as nausea and induced vomiting [7]. Induced vomiting has also been conducted by some patients to be therapeutic. Generally speaking, vomiting was used as an additional therapeutic schedule for dealing with an unhealthy meal or dangerous ingested toxins, playing a significant role in subsequent levels of defense. Vomiting, along with diarrhea, contributes to ridding the gastrointestinal tract of dangerous contents [7]. Additionally, certain events such as emesis appear to completely abort migraine, such as reported, patients found that the most striking terminator (because the effects can be almost instantaneous) is emesis [25]. Then vomiting proved to stop a migraine attack [26]. Further, previous report also proposed an embryo protection hypothesis, which stated the benefit of vomiting were the expulsion of dangerous foodborne chemicals and the subsequent avoidance of these chemical via learned aversions to the food that triggered illness [27].

### The possible therapeutic mechanisms of vomiting

There are obvious instances, such as when it is in response to the ingestion of toxic or irritating substances when vomiting is in the best interest of the patient and should be encouraged rather than suppressed. Besides that, as mentioned above, induced vomiting can also be a treatment for some diseases. Here, we proposed some possible mechanisms of induced vomiting as a therapy option.

#### *Vomiting as an adaptive reaction and, in turn modulating the action*

The gastrointestinal system could be viewed as an important organ system with the physiologi-

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cal challenge of absorbing nutrients while maintaining a delicate balance between defense and tolerance against foreign antigens and pathogens that enter with the food and in maintaining homeostasis [28]. As the stomach plays a key role in the homeostatic mechanism, when vomiting, the gastrointestinal homeostasis could be changed. Thus, the resultant emptying of the stomach actually leads to the recovery of the stomach's function. This is consistent with Solomon's theory which states that a reaction to an event will automatically produce the opposite reaction [29].

Given our knowledge of gastrointestinal and autonomic function, active rather than passive regulation of homeostasis should not be surprising [30]. In the body, feed-forward and feedback loops are obligatory components of any homeostasis system, among of them, the negative feed-back loops are more important. When diseases occur, internal environment disturbance would be disturbed. The focus on the treatment is the terminations of pathological reactions, restoration the internal environment homeostasis. Shapiro reported that if the mechanisms for active termination exist, they may lie within neural networks that also subserve the initiation of emesis [31]. In summary, vomiting may be an adaptive action to maintain the internal environment homeostasis and inhibit diseases development.

### *The role of the brain-gut axis in vomiting*

An increasing number of experts held that the gut and the brain are closely connected through direct and indirect wiring. The transmission of information from the gut to the brain relies on multiple information carriers, including the vagal and the spinal afferent system, gut hormones, and gut-microbiota derived signaling [32]. While output from the CNS to the gut primarily through a myriad of neural, hormonal and immunological routes, these include the sympathoadrenal axis and hypothalamic-pituitary-adrenal (HPA) axis, the two branches of the autonomic nervous system (ANS), and the monoaminergic pathways, which modify dorsal horn excitability and spinal reflexes [33].

The first comprehensive scientific theory of brain-viscera interactions was formulated in the 1880s by William James and Carl Lange and was based on the central concept that

stimuli that induce emotions such as fear, anger or love initially induce changes in visceral function through autonomic nervous system output, and that the afferent feedback of these peripheral changes to the brain is essential in the generation of specific emotional feelings [34]. The symptoms of nausea and vomiting may be considered phenomena emerging from a complex interaction of the central nervous system (CNS), autonomic nervous system (ANS), and enteric nervous system (ENS), where vomiting may be a terminal event of these interactions.

The ENS interfaces closely with our largest body surface (the intestinal surface area, which is approximately 100 times larger than the surface area of the skin), with the largest population of commensal microorganisms of all body surfaces (100 trillion microorganisms from 40,000 species with 100 times the number of genes in the human genome) [35], with the gut-associated immune system (containing two-thirds of the body's immune cells) and with thousands of enteroendocrine cells (containing more than 20 identified hormones). Apart from this, the gastrointestinal tract has been revealed as the largest endocrine organ in the body. More than 30 different gastric-derived peptides are secreted from enteroendocrine cells in response to ingested food regulating, in addition to digestive functions, energy balance [36]. Among the novel gastric systems requiring central integration that directly or indirectly participates in the regulation of energy balance by the brain-stomach connection, the endocannabinoid, ghrelin and nesfatin systems together with the intracellular mTOR/S6K1 pathway have become key factors. Based on its size, complexity and similarity in neurotransmitters and signaling molecules with the brain, even though it is now considered the third branch of the autonomic nervous system, the ENS has been referred to as the 'second brain'.

Most experts would probably maintain that the gut-brain interaction is bidirectional and complex, and certainly extends beyond simply the maintenance of daily digestion [37]. Accumulating evidences suggest that the bidirectional brain-gut interaction can be perturbed leading to acute physiological repercussions. The plasticity of the brain-gut axis during acute and chronic perturbation of homeostasis, including

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changes in the gut to brain signaling that is associated with increased consumption of fat-rich diets and neuroplastic changes in visceral afferent pathways associated with gut inflammation [38, 39]. These unparalleled relationships between the gastrointestinal tract and the brain, with multiple bidirectional and often interacting interoceptive communication systems, emphasize the importance of this system in the maintenance of homeostasis, which also implicating gut-brain communication regulated under neural and hormonal control, the stomach-brain connection has been revealed to be one of the most promising targets for treating disease [40].

### *Vagal afferents activation during vomiting modulates diseases*

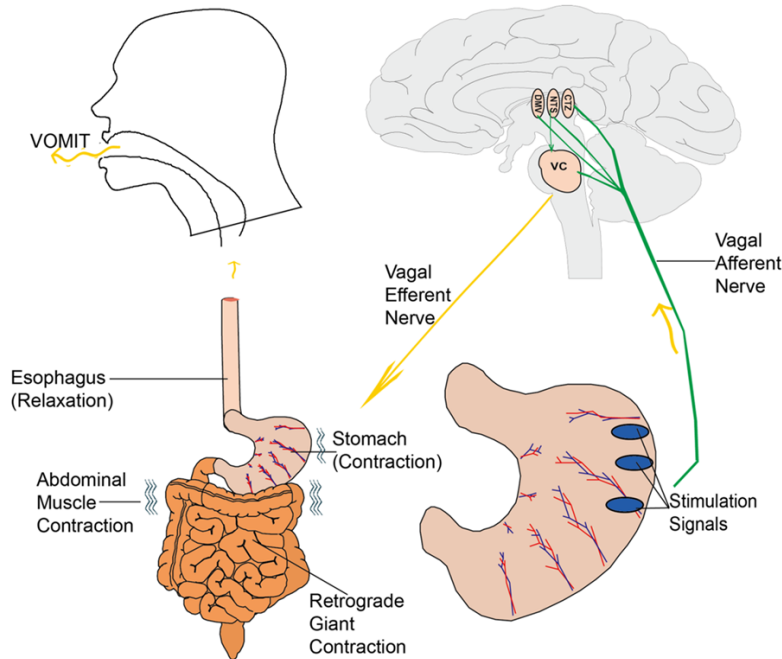
Vagal afferents are extensively distributed in the digestive tract from the esophagus to the colon. They are involved in the reflex control of normal gastrointestinal (GI) tract function (e.g. secretion and motility) as well as reflexes more characteristic of diseases such as functional dyspepsia and gastroesophageal reflux disease (e.g. vomiting, disordered lower esophageal sphincter relaxation and gastric accommodation). They are also implicated in signaling non-painful sensations (e.g. nausea and early satiety) associated with disease [41]. Substantial experiments have demonstrated that gastrointestinal vagal afferent fibers play a critical role in the induction of nausea and the generation of vomiting [23], and the integrity of the abdominal vagus is essential for the generation of emesis. In 1951, Wang and Borison demonstrated that vagotomy can prevent the emesis [42] and electrical stimulation of the abdominal vagus was known to induce an emetic response that includes an increase in blood pressure, increased activity of the abdominal muscles and an increased intragastric pressure [43]. Furthermore, in ferrets, stimulation of mucosal chemoreceptors in the stomach or the duodenum results in a long latency but sudden increase in vagal efferent discharge associated with the prodrome of vomiting, suggesting that activation of vagal afferents is involved in the generation of vomiting [44]. The involvement and importance of vagal neurocircuitry in the generation of vomiting have been well defined across several species including humans [7, 22, 23, 41].

The role of vagal afferents stimulation exerts the effect of the vomiting sensation via the following methods. Vomiting can be triggered by toxic materials within the gastrointestinal lumen which stimulate dorsal brainstem via vagal afferents, absorbed toxins or drugs which act directly on the dorsal vagal complex, pathologies in the gastrointestinal tract or other visceral organs (e.g. renal or cardiac) which stimulate vagal afferents, stimuli within the central nervous system (CNS) including cerebral cortex and limbic system; and disturbance of the vestibular nuclei and cerebellum [45, 46].

The specific process is that, the afferent vagus nerve is responsible for relaying a vast amount of sensory information such as acidity, alkalinity, hypertonic fluids, temperature extremes, and irritants from thoracic and abdominal organs to the nucleus of the solitary tract (NTS), which is thought to be the main site for the termination of vagal afferents from the gut and receives not only inputs from peripheral sensory but have direct or indirect connections with several other hindbrain, midbrain and forebrain structures responsible for the coordination of the multiple organ systems. From here, information is disseminated to autonomic motor nuclei, such as the dorsal motor vagal nucleus (DMV) and 'higher' regions of the brain including the parabrachial nucleus, hypothalamus, amygdala and insular cortex. The efferent vagus nerve which output from the DMV relays the integrated and coordinated output response to several peripheral organs responsible for emesis [18]. Activity within vagal efferent pathways during emetic reflexes results in a large retropulsive wave of intestinal motility accompanied by gastric contraction. Together with temporally coordinated relaxation of the antral/pyloric sphincter and the lower esophageal sphincter accompanied by contraction of the abdominal and intercostal muscles, this results in expulsion of gastric contents from the stomach and upper intestine [21, 47-49]. The CTZ is also the point of vagal afferent entry. Serotonin is thought to be the major neurotransmitter involved in vagal stimulation [14]. Serotonin binds to 5-hydroxy tryptamine (5-HT<sub>3</sub>) receptors on vagal afferent fibers, and conveys impulses to the CTZ [50]. The CTZ conveys these impulses to the vomiting center, stimulating the vomiting reflex. Additionally, the sensory signals from CTZ are also sent to DMV and cen-



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**Figure 1.** Activation of vagal afferents involved in the processing of vomiting.

tral pattern generators via nucleus of the solitary tract and moderate the motor and prodromal activities which mediate nausea and vomiting [22, 51]. Abdominal and other vagal afferents might also be involved in the genesis of fatigue associated with cancer and its treatment [52].

Activation of vagal afferents involved in the processing of vomiting (**Figure 1**). Input signals such as the stimulation of toxin, acidity, alkalinity, hypertonic fluids, or temperature extremes from the gastrointestinal (GI) tract are respectively transferred to the DMV, NTS, and CTZ through the afferent vagus nerve. Then, the efferent vagus nerve coordinates GI function based on the processed data in the brainstem. The reaction of GI including intrinsic contractions occurs in both the duodenum and the stomach, the lower esophageal sphincter relaxes, and vomitus moves from the stomach into the esophagus. Next, the inspiratory and abdominal muscles contract and expel the vomitus into the mouth.

In addition to the regulation of nervous system, the vomiting could also be triggered by the release of the neurotransmitter serotonin (5-HT) from the Enterochromaffin (EC) cells, which stimulates the vagus nerve via 5-HT<sub>3</sub> receptors [41, 53, 54]. The vagus nerve is the

primary afferent nerve of the GI tract. Most of the messages from the gut transmitted via the vagus nerve may involve the neurotransmitter serotonin. In fact, 80% of the serotonin in the body is located in EC cells [55]. These cells mediate messages from the brain to the nucleus tractus solitarius (NTS) via the vagus nerve. Messages from the EC cells can also activate reflexes to regulate secretion of digestive enzymes and peristalsis in the gut. Serotonin, along with several tachykinins, can have direct local physiological effects, such as smooth muscle relaxation, vasodilation, and secretion of water and electrolytes.

### Procedure of induced vomiting

Induced vomiting is achieved most effectively through manual stimulation of the gag reflex [56]. To induce vomiting, patients need to drink a large number of the emetics, such as mild water, salt water and vinegar water [57], to increase the stomach volume in a short period of time. And then, the materials such as a spoon handle, spatula, chopsticks or a plume would be used to stimulate the posterior pharyngeal wall or tongue root, causing the vomiting reflex. Generally, the total number of operation times is four times. The whole operation process needs about one hour. According to reports, the vomitus consisted of food remnants initially, often changing almost entirely to saliva, gastric. To get the best effect of induced vomiting, patients are usually intended to try their best in the vomiting process until they spit out the sticky mucus. If the process of stomach emptying was slow, the intestinal tract could increase the volume of absorption of water, which could easily lead to water intoxication.

There are some other emetics, for example, traditional medicine, western medicine and other drugs to operate the induced-vomiting procedure [57]. The whole operation can force the patients to spit out all of the contents of the stomach, throat, trachea, lots of mucus and

other foreign matter can be emptied. Vomiting may be accompanied by nausea, sweating, palpitation and rapid pulse, which can cause a positive feedback to increase the process of secretion.

### The side effects of induced vomiting and control strategies

Induced vomiting would result in diverse side effects. It has been reported that vomitus is mainly composed of acidic substances and gastrointestinal fluid, and a significant amount of these contents loss could give rise to metabolic alkalosis, hyponatremia and hypokalemia [58]. And previous study indicated that the gastric acid in vomitus will induce esophageal burns, chronic pharyngitis and teeth decay [59]. Induced vomiting might breaks the dynamic equilibrium of gastric mucosal damage and self-healing, and thus leading to severe gastric mucosal injury and stomach bleeding [60]. Moreover, Chevalier N, et al confirmed that violent vomiting would increase intra-abdominal pressure, duodenal contents reflux, and further cause acute pancreatitis [61]. Excessive induced vomiting contributes to the over-stimulation and laxity of esophagus sphincter, which may cause the symptom of nausea, and induce vomiting during normal stomach contractions, and lead to mild esophagitis and even gastroesophageal reflux disease [62, 63]. In addition, it has been found that induced vomiting could lead to hoarseness, rough skin and a yellow face color [64, 65].

Through summarizing the previous studies and our clinical experiences, we found some effective treatment methods for aforementioned complications. For the esophageal reflux disease, cessation of vomiting behavior is the best way to control the heartburn symptoms [66]. And if the symptoms were not eliminated, patients can take the omeprazole correctly [67]. During or before the induced vomiting, eating some fruits (bananas, oranges, or watermelons) or drinking fruit juice, which are rich in potassium, can prevent electrolyte imbalance [68]. According to our clinical experiences, taking some light victuals such as porridge, instead of food difficult to digest is benefit to protecting the gastric mucosa. Additionally, vitamin B12 could be regarded as adjuvant drug to repair the gastric mucosa. Besides these, the frequency of induced vomiting procure should be strictly controlled.

### Conclusion

Vomiting is one of the most frequent co-existing symptoms in many diseases, yet it has also been reported by some patients to abort or improve their performance, for instance, headache. Induced vomiting may exert its effects by fulfilling its fundamental goal of connecting the brain-gut bid-interaction, or, activating vagal nerve, or changing the gastrointestinal homeostasis to break the internal environment disturbance. Vomiting may exert multiple autonomic, chemical, and vascular effects to diminish diseases. Though induced vomiting might give rise to some serious side effects, we can take effective treatment strategies to prevent these complications. Taken together, more studies should be performed to elucidate the underlying mechanism of the therapeutic effects of vomiting in future.

### Disclosure of conflict of interest

None.

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