

## New Vistas in the Pathophysiology of Vomiting

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Vomiting (emesis) is currently viewed as a complex multi-transmitter protective reflex mechanism which has developed in diverse species to different degrees to remove toxic agents from the gastrointestinal tract prior to their absorption. Not all animals are capable of vomiting and despite extensive research, the reflex is only partially characterized [1]. Nausea is an unpleasant sensation of gastrointestinal discomfort and may accompany or precede vomiting (a forceful expulsion of gastrointestinal contents). However, both events can be experienced separately and remain a significant clinical problem. Although several animal models of emesis are available in the laboratory, only few such models exist for the study of nausea. Thus, our knowledge of nausea, its related brain-gut circuit(s), associated neurotransmitters, and pathophysiology is even more limited with no noteworthy anti-nausea agent available in the clinic. In fact the severity of chemotherapy-induced vomiting can be controlled to a significant extent by combined antiemetic regimens, but control of nausea still remains a persistent problem. Retching is rhythmically alternating abdomino-thoracic contractions (with the glottis closed), and is also associated with emesis. Nausea, retching and vomiting are hallmarks of several gastrointestinal disorders including gastroenteritis, anorexia nervosa, bulimia, hyperemesis gravidarum, and cyclic vomiting syndrome. Conditions such as pregnancy, motion, space sickness, and surgery are also accompanied by nausea, retching and vomiting. Likewise, vomiting and associated behaviours can develop as a specific response to treatments such as radiation or chemotherapy, or appear as side effect of numerous clinically used drugs such as antidepressants, opiates, cholinesterase inhibitors, L-DOPA, phosphodiesterase inhibitors, and cardiac glycosides. In addition, vomiting can be a response generated by cognitive, visual, flavour or CNS disorders including anxiety and stress. Prolonged emesis induces severe dehydration, electrolyte imbalance and even death which are features for human rotavirus disease as well as cholera and staphylococcal food-borne infections. The current literature identifies no specific antiemetic that works for all types of vomiting, or in all patients suffering from a specific type of emesis. Thus, treatment tends to be based on individual clinicians' experience and time after time combination antiemetic regimens are needed to manage patients successfully. Even with combination regimens certain kinds of emesis such as chemotherapy-induced nausea and vomiting (CINV) can only be completely controlled in 70-80% of cancer patients receiving chemotherapy.

Vomiting can be induced via the activation of several cell membrane bound receptors including: serotonergic 5-HT<sub>3</sub> and 5-HT<sub>4</sub>, tachykinergic NK<sub>1</sub>, dopaminergic D<sub>2</sub> and D<sub>3</sub>; muscarinic M<sub>1</sub>; histaminergic H<sub>1</sub>;  $\mu$  opioid; cysteinyl leukotriene 1; prostaglandin DP, FP, and EP; thromboxane TP; glucagon peptide 1, and vanilloid TRPV1 [1]. These proemetic receptors are found both in the brainstem and in the gastrointestinal tract (GIT) emetic loci where induction of emesis and associated behaviours involve cross-talk between the peripheral and the central nervous systems. The enteric nervous system (ENS) in the GIT contains about 100 million neurons which are sensory, inter- and motor neurons. Following stimulation by different emetogens (e.g. hyperosmolarity, chemotherapeutics, cholera/staphylococcal/viral enterotoxins, etc.), the gastrointestinal enterochromaffin cells (EC) and/or mast cells mobilize intracellular Ca<sup>2+</sup> to release emetic neurotransmitters including 5-HT, substance P (SP), dopamine, prostaglandins (PGs) and/or histamine to activate the ENS as well as the extrinsic vagal afferents to the brainstem [1]. Thus, in the periphery emetogens may act directly in the GIT, and/or indirectly by activating the central nervous system (CNS) emetic nuclei through stimulation of vagal afferents whose somata are

in the nodose ganglion. Nodose neurons project extensively branched afferent fibers in both ascending and descending directions, such that the same neurons innervate both the brainstem dorsal vagal complex (DVC) and a segment within the ENS. The vagus contains afferent as well as efferent nerves and acts as a communication circuit between the brainstem and the GIT. The secreted emetic transmitters may act locally to stimulate their corresponding (e.g. 5-HT<sub>3</sub>- and NK<sub>1</sub>-) receptors present on vagal afferent terminals in the GIT, thus potentiating vagal afferent activity and subsequently the DVC emetic nuclei in the brainstem. Other proemetic signals such as prostanoids can also increase vagal afferent activity and in fact PGE<sub>2</sub> receptors are present in nodose ganglionic cells. Vagal afferents are glutamatergic and appear to co-release SP, thus providing excitatory input to much of the emetic reflex arc. Absorbed or released emetogens may also act more distantly via the bloodstream to stimulate the DVC directly. In the CNS, both the DVC and a more ventrolaterally localized group of cells that make up the central pattern generator (CPG) are key sites in the mediation of emesis. The DVC is a cluster of nuclei in the dorsomedial medulla comprising the area postrema (AP), the nucleus of the solitary tract (NTS), and the dorsal motor nucleus of the vagus (DMNX). The AP comprises the chemoreceptor trigger zone (CTZ), a circumventricular organ that allows blood borne chemicals absorbed or secreted (e.g. SP) from the intestinal mucosa to bypass the blood-brain-barrier and stimulate the DVC directly. The medial NTS (mNTS) is the key integrative site for CNS modulation of the emetic reflex. It receives input from the AP, vagal afferents, the posterior paraventricular hypothalamic nuclei, and the serotonergic raphe nuclei. After integrating the central and peripheral signals relating to emesis or other GI activity, the NTS neurons project in to the DMNX as well as to the CPG. The DMNX motor neurons project to various parts of the GIT, including the stomach, lower esophageal sphincter, duodenum, and jejunum which completes the act of vomiting (Figure 1).

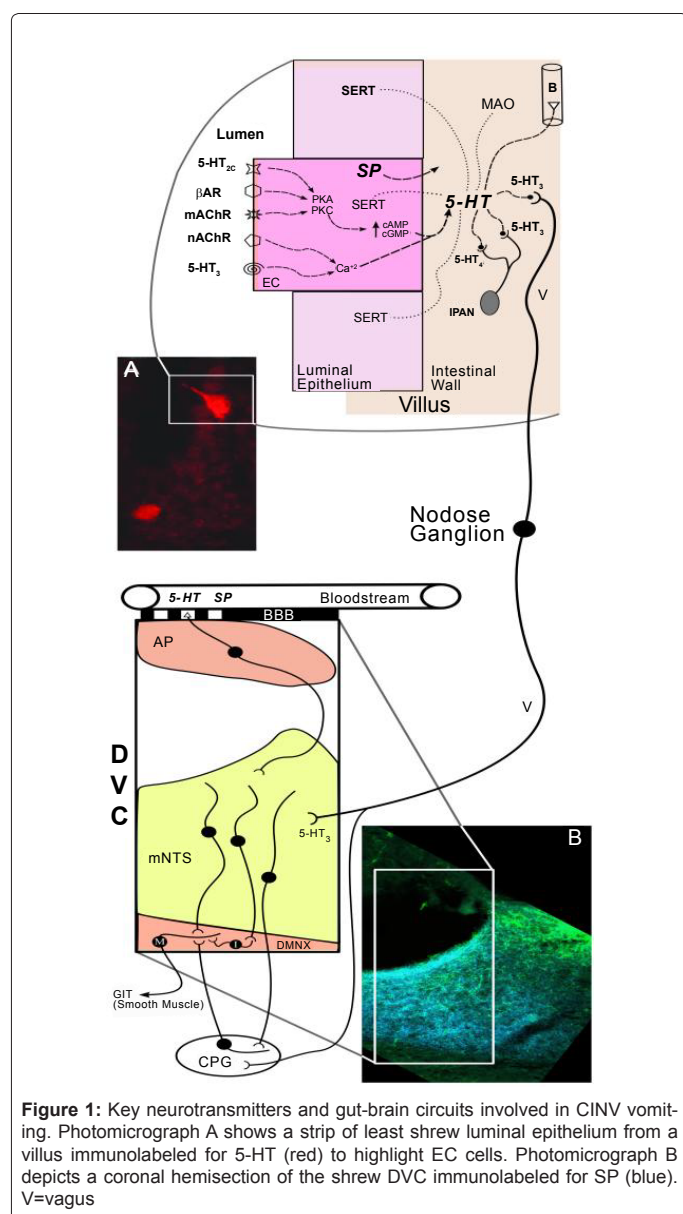
Antiemetics such as scopolamine, diphenhydramine, promethazine, droperidol, haloperidol, metoclopramide, ondansetron, and aprepitant are generally classified according to the predominant receptor on which they are proposed to act and many exhibit varying affinities for several receptors. Older antiemetics such as histamine (e.g. diphenhydramine), dopamine (droperidol) and muscarinic scopolamine) receptor antagonists are nonselective and possess side effects such as sedation, drowsiness, blurred vision, dry mouth and/or extrapyramidal symptoms. Thus far, the most aggressive research effort in antiemetic drug development has focused on producing receptor-selective antagonists that possess antiemetic efficacy with fewer side-effects such as the currently used 5-HT<sub>3</sub> (e.g. ondansetron)- and NK<sub>1</sub> (e.g. aprepitant)-receptor antagonists. Development of NK<sub>1</sub> receptor antagonists opened the potential of an universal antiemetic, at

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least in the realm of larger emesis competent animals, but unfortunately this universality failed to translate either to the clinic for humans nor in the laboratory for the smaller animal, the least shrew, against several types

of emetogens. Development of universal antiemetics can be possible if one targets either: i) a critical emetic signalling pathway which many of the cited diverse emetogens share downstream of their corresponding receptors. In fact we have recently demonstrated that cisplatin-induced peak acute- and delayed-phase vomiting are associated not only with temporally specific increases in the expression levels of tachykinin NK1 receptor mRNA and its protein, but also with the activation of its downstream signals such as phosphorylation of both ERK1/2 and PKA [2]; or ii) a common essential signal which can cross-talk between signalling transduction pathways such as  $Ca^{2+}$ . Indeed, we have recently demonstrated in the least shrew [3] that emetic serotonergic 5-HT<sub>3</sub>- and tachykinergic NK1 receptors cross-talk through their downstream signalling probably at the level of intracellular calcium [4]. Their corresponding selective antagonists produce synergistic antiemetic effects when concurrently used against emesis caused by a selective agonist of either receptor.

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