

# THE ROLE OF 5-HT IN POSTOPERATIVE NAUSEA AND VOMITING

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The discovery of potent, selective, 5-HT<sub>3</sub> receptor antagonists (see [17] for review) and the demonstration of their potent antiemetic activity in experimental animals [23] and man [6], has generated considerable interest in the control of the emetic reflex response. Indeed, selective 5-HT<sub>3</sub> receptor antagonists are now used clinically to control emesis induced by chemotherapy or radiotherapy in cancer patients and in postoperative nausea and vomiting (table I).

Both peripheral and central mechanisms are involved in the control of emesis [1]. Evidence for the involvement of 5-HT and 5-HT<sub>3</sub> receptors in such mechanisms is derived from experiments: in the periphery, from measurement of concentrations of 5-HT and 5-HIAA in the gastrointestinal mucosa or urine [12], and from the effects of 2-methyl-5-HT (5-HT<sub>3</sub> receptor agonist) and ondansetron on afferent vagal discharge in the ferret [1]; and in the CNS, from experiments in which the antiemetic effects of 5-HT<sub>3</sub> receptor antagonists have been established after direct injection into the brain stem [15].

Although 5-HT<sub>3</sub> receptor antagonists are potent inhibitors of emesis induced by cytotoxic drugs and radiation, such compounds also exhibit antiemetic activity against a wide spectrum of emetic challenges, thus implicating 5-HT<sub>3</sub> receptors in the broad control of the emetic reflex (table II).

These general antiemetic properties of the 5-HT<sub>3</sub> receptor antagonists, and of ondansetron in particular, led to the clinical evaluation of ondansetron in postoperative nausea and vomiting (PONV). In contrast to the emetic responses to cytotoxic chemotherapy and radiotherapy, relatively little is known about the mechanisms involved in the control of PONV and discussion of such mechanisms is necessarily speculative. Thus, the present discussion considers the mechanisms elucidated from studies using cytotoxic drugs and radiation, and attempts to draw analogies with possible events associated with anaesthesia and surgery. The control of the vomiting reflex is complex, involving both afferent and efferent pathways in the brain stem and also higher centres and the vestibular apparatus [10]. Our present understanding of the control of emesis is derived

principally from studies on the afferent arm, involving both peripheral and central neuronal circuits, and the present discussion concentrates principally on these latter pathways.

## 5-HT<sub>3</sub> RECEPTORS AND PONV

### Peripheral pathways

Emesis induced by cytotoxic drugs and radiation is associated with damage to the gastrointestinal mucosa [5, 27] and the mobilization of 5-HT from mucosal enterochromaffin cells [9, 13]. This 5-HT probably excites 5-HT<sub>3</sub> receptors on mucosal vagal afferents, thereby activating the afferent arm of the vomiting reflex [1]. Indeed, emesis induced by

TABLE I. Present status of 5-HT<sub>3</sub> receptor antagonists as antiemetics. All compounds are potent, 5-HT<sub>3</sub> receptor antagonists with a selectivity ratio of at least 1000 compared with other receptor types [12]

Compound	Approval	Formulations available
Ondansetron	Emesis induced, by cytotoxic chemotherapy, radiotherapy and PONV	I.v. and oral
Granisetron	Emesis induced by cytostatic therapy	I.v.
Tropisetron	Emesis induced by cancer chemotherapy	I.v. and oral

TABLE II. Antiemetic profile of 5-HT<sub>3</sub> receptor antagonists. (\* Inhibition of CuSO<sub>4</sub>-induced emesis by 5-HT<sub>3</sub> antagonists is not a consistent finding (see [8])

Emetic challenge	Species	5-HT <sub>3</sub> antagonist	Reference
CuSO <sub>4</sub>	Ferret	Ondansetron	[11]
	Ferret	Granisetron	[1]
Ipechacuanha	Ferret	Tropisetron	[8]
	Man	Ondansetron	[20]
Emetin	Ferret	Renzapride	[1]
Peptide YY	Dog	Zacopride	[24]

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### KEY WORDS

Serotonin. Vomiting. nausea.

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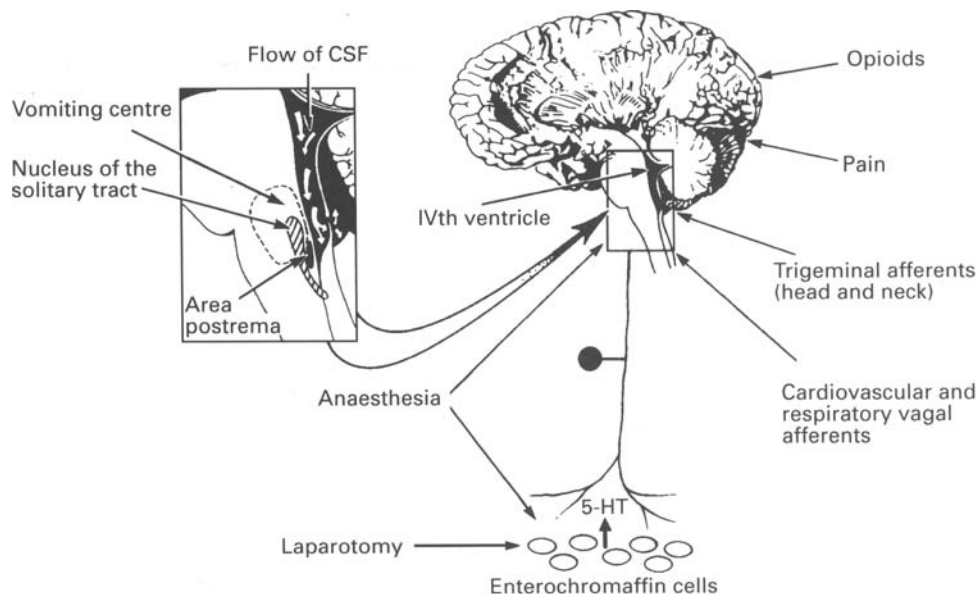


FIG. 1. Proposed scheme summarizing the peripheral and central mechanisms involved in the control of emesis.

cytotoxic drugs and radiation in the ferret is ameliorated by vagotomy [2, 14].

Several surgical procedures may also affect these peripheral afferent pathways. The anaesthetic itself could disrupt mucosal enterochromaffin cells and induce release of paracrine transmitters, including 5-HT, resulting in afferent vagal firing and initiation of the vomiting reflex. A similar mechanism of cell disruption may be induced also by gastrointestinal distention caused by diffusion of nitrous oxide into the lumen of the gastrointestinal tract [7]. In addition, laparotomy, involving manipulation and irritation of the gastrointestinal tract, could activate vagal afferents via mucosal 5-HT release. Although these peripheral mechanisms are speculative, the involvement of 5-HT from enterochromaffin cells is likely and would provide a rational explanation for the antiemetic effect of ondansetron in PONV.

It is particularly interesting to speculate on how other peripheral systems, outside the gastrointestinal tract, may interact with the emetic pathways to modify the vomiting reflex. Gastric vagal afferents terminate principally in the medial subnucleus of the tractus solitarius [16] and vagal afferents from other abdominal and thoracic systems, namely the heart and respiratory tract, also terminate in distinct, adjacent regions of the nucleus tractus solitarius [16]. Therefore, it is possible that central connections exist between these "nuclei" controlling gastrointestinal, cardiac and respiratory function. Thus cardiovascular or respiratory perturbations, arising principally from hypertension and hypoxia, with or without tracheal irritation associated with surgery and anaesthesia, may sensitize the vomiting system through neuronal pathways involving 5-HT of central origin and 5-HT<sub>3</sub> receptors. On this basis, ondansetron would attenuate these responses. However, it must be pointed out that endogenous 5-HT and 5-HT<sub>3</sub> receptors do not appear to be involved directly in the control of cardiovascular or respiratory function as ondansetron has no effect on these systems [19, 26].

It has been noted that patients undergoing surgery in the head and neck region are particularly susceptible to PONV [7]. In this context, it is known that sensory afferent fibres of the trigeminal nerve (the largest cranial nerve and predominantly sensory) terminate in the nucleus tractus solitarius [3], and 5-HT<sub>3</sub> receptors are present in the spinal trigeminal nerve complex [4]. Thus, we may speculate that surgery in the region of the head and neck sensitizes the nucleus tractus solitarius to induce a vomiting response via stimulation of trigeminal afferents. This sensitization of the nucleus tractus solitarius involves 5-HT pathways and 5-HT<sub>3</sub> receptors because ondansetron is effective in controlling this aspect of PONV.

#### Central pathways

Gastrointestinal vagal afferents terminate in the area postrema and nucleus of the solitary tract and these two medullary structures are known to be important in the control of the vomiting reflex; indeed the area postrema is the locus of the chemoreceptor trigger zone [1]. Furthermore, the area postrema and nucleus tractus solitarius contain a high concentration of 5-HT<sub>3</sub> receptors [22] which are located on presynaptic terminals [18, 21]. Block of these central 5-HT<sub>3</sub> receptors by the discrete injection of ondansetron into the region of the area postrema and nucleus tractus solitarius inhibits cisplatin-induced emesis in the ferret [15]. It is therefore pertinent to consider the possible role of the area postrema and nucleus tractus solitarius in the control of PONV.

The area postrema is a circumventricular organ located outside the blood-brain barrier, and is therefore uniquely placed to "sample" both blood and CSF. It is possible that an anaesthetic substance in the blood, CSF, or both, could stimulate neurones (or cause disinhibition of a moderating influence) within the area postrema and activate the vomiting reflex via a 5-HT pathway. Similarly, the anaesthetic could affect the vomiting reflex via 5-HT containing

neurones, or interneurones, in the nucleus tractus solitarius and other components in the vomiting system, namely the parvicellular reticular formation and visceral and somatic motor nuclei.

Pain in the postoperative period may also predispose patients to PONV. Painful stimuli from the viscera are transmitted to the CNS in the splanchnic nerves. In this context it is interesting to note that sectioning of the splanchnic nerves in the ferret, while having no effect itself on the emetic response to cisplatin, enhanced the antiemetic effect of vagotomy [14]. Thus it is likely that painful stimuli induce discharge of splanchnic afferents which in turn contribute to the initiation of the vomiting reflex. Because ondansetron completely blocks the emetic response to cisplatin in the ferret [25], it is possible that 5-HT<sub>3</sub> receptors are involved in the splanchnic component of the vomiting reflex.

#### SUMMARY

In this review it has been speculated that PONV is induced by the anaesthetic and by the trauma and perturbations associated with surgery. Indeed, it is unlikely that PONV is caused by any one pathophysiological input, but is multifactorial in origin. These perturbations may be peripheral, central, or both, and involve direct effects on the vomiting system together with afferent inputs in the vagal, splanchnic and trigeminal nerves. A proposed scheme summarizing these inputs is given in figure 1. The precise mechanisms through which 5-HT and 5-HT<sub>3</sub> receptors contribute to the control of PONV is unknown, but their involvement is demonstrated by the antiemetic effect of ondansetron.

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