

## The Ups and Downs of Novel Antiemetic Drugs, Part 2

### An Illustration

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**Issue:** *Novel antiemetic drugs block either neurokinin-1 receptors or serotonin-3 receptors. Research into the neuropharmacology of vomiting is providing insight into the ways substance P and serotonin interact within the central nervous system that could lead to additional applications of neurokinin-1 antagonists for the treatment of depression and stress.*

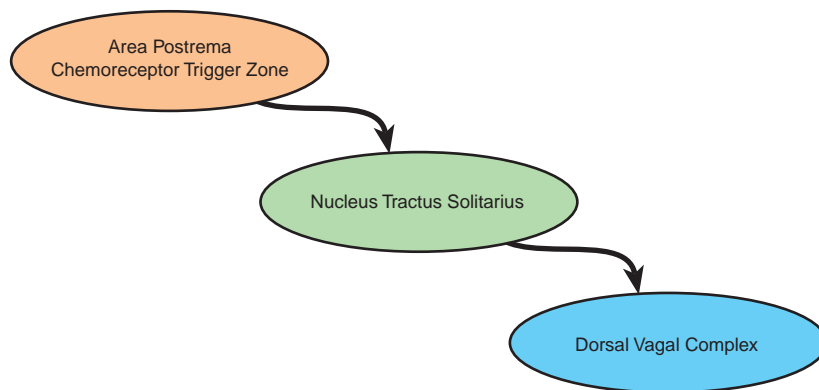
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**T**he concepts of how substance P may interact with serotonin to regulate vomiting<sup>1</sup> and how antagonists of neurokinin-1 receptors and serotonin-3 receptors have become novel antiemetic agents<sup>2</sup> were discussed in last month's BRAINSTORMS<sup>3</sup> and are illustrated here.

#### REFERENCES

1. Diemunsch P, Grelot L. Potential of substance P antagonists as antiemetics. *Drugs* 2000;60: 533–546
2. Navari RM, Reinhardt RR, Gralla RJ, et al. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. *N Engl J Med* 1999;340:190–195
3. Stahl SM. The ups and downs of novel antiemetic drugs, pt 1. *J Clin Psychiatry* 2003;64: 498–499

**Figure 1.** The Brainstem Vomiting Center



Three areas in the brainstem together are sometimes called the vomiting center, including firstly, the area postrema and its associated chemoreceptor trigger zone; secondly, the nucleus tractus solitarius; and thirdly, the dorsal motor nucleus of the vagus also known as the dorsal vagal complex.

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Figure 2. Inputs to the Vomiting Center

Inputs to the vomiting center, such as those provoked by many cancer chemotherapeutic agents, may cause release of substance P in the nucleus tractus solitarius and trigger an emetic response there via neurokinin-1 (NK<sub>1</sub>) receptors. Blocking these inputs can reduce such emetic responses. For example, blocking the final common pathway of substance P actions at its NK<sub>1</sub> receptors in the nucleus tractus solitarius by using an NK<sub>1</sub> antagonist is one way. Another way is to block peripheral input from serotonin-3 (5-HT<sub>3</sub>) receptors in the gut with a 5-HT<sub>3</sub> antagonist. Blocking both central input with an NK<sub>1</sub> antagonist and peripheral input with a 5-HT<sub>3</sub> antagonist may be additive and reduce not only the acute phase but also the delayed phase of chemotherapy-induced nausea and vomiting.

The area postrema can detect toxins like cancer chemotherapy in both blood and cerebrospinal fluid via its chemoreceptor trigger zone and then send this information to the nucleus tractus solitarius to initiate the vomiting reflex. The gut can also detect poisons like some cancer chemotherapies, since they cause the release of serotonin onto 5-HT<sub>3</sub> receptors located on presynaptic sensory vagal afferent fibers within the gut wall, which then send this information to the nucleus tractus solitarius. Other inputs include brain-stem vestibular centers, which can cause

vomiting associated with vertigo, and higher centers in the cerebral cortex, which can produce emesis in response to sensory stimuli (pain, sight, smell) and to emotional stimuli such as memory, anticipation, and fear.

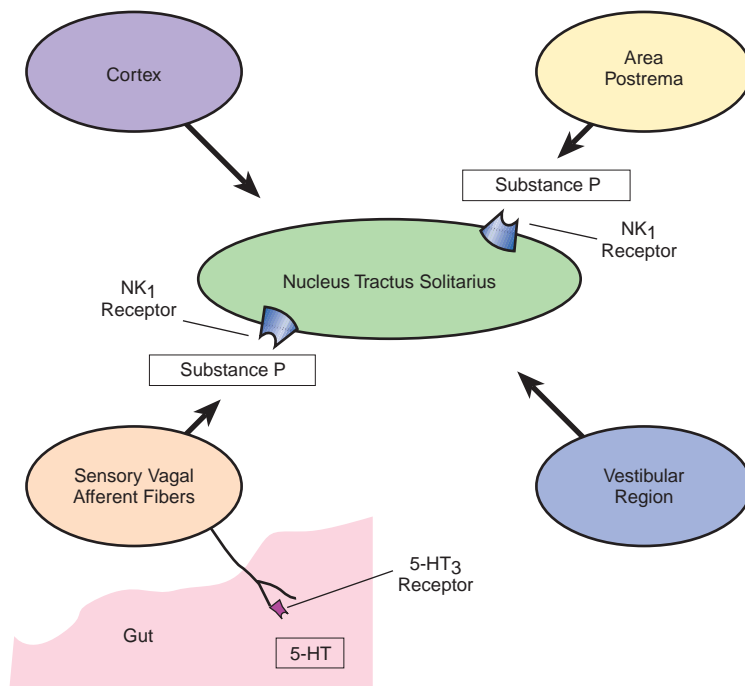
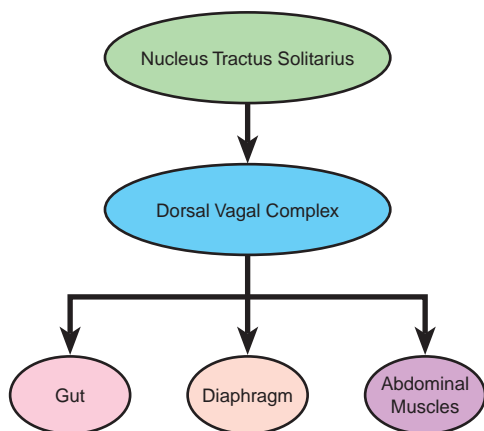


Figure 3. Output From the Vomiting Center



Stimulation of NK<sub>1</sub> receptors by substance P in the nucleus tractus solitarius can cause it to coordinate a vomiting reflex, with output through the dorsal vagal complex. Fibers from this complex go first to the gut to close the pylorus, reduce gastric cardia tone, and open the cardia sphincter while increasing tone in duodenum and jejunum to prepare for vomiting. Then, motor vagal fibers send information via the respiratory muscles to contract the diaphragm via the phrenic nerve and to simultaneously contract abdominal muscles via abdominal motoneurons to expel contents from the gut.