The Ups and Downs of Novel Antiemetic Drugs, Part 1
Substance P, 5-HT, and the Neuropharmacology of Vomiting

Stephen M. Stahl, M.D., Ph.D.

Issue: Novel antiemetic agents such as the newly approved aprepitant (Emend) target receptors for substance P, known as neurokinin-1 (NK₁) receptors. When NK₁ receptors are blocked in the vomiting center of the brainstem, chemotherapy-induced emesis is reduced. It is possible that blocking NK₁ receptors elsewhere in the CNS will lead to therapeutic actions in depression and other stress-related disorders.

 Neuropharmacology of the peptide neurotransmitter substance P is just now being unraveled.¹⁻⁴ An interesting and somewhat surprising therapeutic application, namely prevention of cancer chemotherapy-induced nausea and vomiting (CINV), has recently been approved for aprepitant (Emend), an agent that blocks the receptors for substance P, known as neurokinin-1, or NK₁, receptors.⁵ Someday, NK₁ antagonists may also become novel psychotherapeutic agents for depression and other stress-related conditions.²⁻³ For now, an understanding of these agents may be enhanced by a review of the neuropharmacology of emesis, including how substance P helps to regulate this reflex within the central nervous system (CNS) via NK₁ receptors in the brainstem vomiting center.

THE BRAINSTEM VOMITING CENTER

Vomiting is a reflex orchestrated by the CNS. Together, 3 areas in the brainstem are sometimes called the vomiting center: the area postrema (AP) and its associated chemoreceptor trigger zone; the nucleus tractus solitarius (NTS); and the dorsal motor nucleus of the vagus (DMV), also known as the dorsal vagal complex.⁶⁻⁸

The Area Postrema

The AP, located near the floor of the fourth ventricle, is bathed in both blood and cerebrospinal fluid. It lies functionally outside the blood-brain barrier, so it can detect numerous drugs and toxins in both of these fluids via its chemoreceptor trigger zone and then send this information to the NTS to initiate the vomiting reflex.⁶⁻⁸ Pharmacologic sensitivity in the chemoreceptor trigger zone is not equivalent to neurotransmitter receptor specificity but is a much more generalized response to chemicals, toxins, and irritants. Detecting systemic poisoning coming from the blood in this way and causing a reflex action to expel chemicals and poisons that have been ingested is a long-preserved evolutionary survival technique for many species, including man.

The Nucleus Tractus Solitarius

Because the NTS is inside the blood-brain barrier, it must rely on the AP to detect poisons in the blood. It also receives input directly from 3 other sources: (1) Sensory and emotional inputs from higher cortical centers⁶⁻⁸ can produce emesis in response to sensory stimuli (pain, sight, smell) and emotional stimuli (memory, conditioning, anticipation, fear). (2) Brainstem vestibular centers can cause nausea and vomiting to occur (for unclear benefit) when there is vertigo, dizziness, or visuospatial disorientation.⁶⁻⁸ (3) Chemosensors in the gut can detect chemicals, drugs, and toxins and cause enterochromaffin cells to release various emetogenic substances, especially serotonin (5-HT). Embedded in the gut wall,⁷ sensory vagal afferent fibers with...
The Dorsal Motor Nucleus of the Vagus

After the NTS, the headquarters of the vomiting center, integrates input from central and peripheral sensors, it determines whether or not the vomiting reflex will be triggered. The DMV is the effector of that decision and carries it out through motor (efferent) outputs to the gut, diaphragm, and abdominal muscles. Fibers from the motor vagal 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 motor-neurons to expel contents from the gut.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Cancer chemotherapy is frequently associated with nausea and vomiting because it not only triggers release of 5-HT, and thus sensory vagal 5-HT3–mediated input to the vomiting center, but also acts as a toxin directly in the chemoreceptor trigger zone in the brainstem, thus providing central input to the vomiting center as well. Both inputs lead to substance P release at NK1 receptors in the NTS, thus causing, in turn, the 2-phase response of CINV—an acute phase of several hours mediated by both 5-HT and substance P and a delayed phase over a few days mediated more by substance P than by 5-HT.

Not surprisingly, 5-HT3 antagonists give additive benefit with 5-HT3 antagonists to the acute phase of CINV and also reduce delayed phase CINV. Thus, these agents are used together to maximize antiemetic benefit. Interestingly, 5-HT and substance P are colocalized in the sensory vagal fibers and in many CNS serotonergic neurons, so therapeutic interaction of antagonists of both neurotransmitters is not too surprising.

SUMMARY

Although the circuits involving vomiting are incompletely defined, substance P acting at NK1 receptors in the NTS is the final common pathway. Therapeutic applications for antagonists of substance P at NK1 receptors are now evolving, with the first use to reduce the nausea and vomiting associated with administering cancer chemotherapy. This research has helped to clarify the central role of substance P as a neurotransmitter in the brainstem vomiting center and may shed light on potential additional applications of NK1 antagonists in psychopharmacology, such as treatment of depression and other stress-related disorders as well as gastrointestinal side effects common in psychopharmacology.

REFERENCES


Take-Home Points

- Substance P is a peptide neurotransmitter in the neurokinin (NK) family whose preferred receptor is the NK1 receptor.
- Substance P regulates emesis in the brainstem vomiting center. Serotonin (5-HT) regulates emesis via presynaptic 5-HT1 receptors on sensory vagus fibers in the gut. NK1 antagonists reduce the vomiting frequently caused by many cancer chemotherapeutic agents by blocking NK1 receptors, especially when combined with an agent that blocks 5-HT2 receptors.
- Substance P is often colocalized in neurons along with 5-HT and may also be an important regulator of emotions, behaviors, and stress. Blocking NK1 receptors in various CNS circuits may become a novel approach to treating stress-related disorders such as depression.