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 (NK_1) receptors. When NK_1 receptors are blocked in the vomiting center of the brainstem, chemotherapy-induced emesis is reduced. It is possible that blocking NK_1 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 NK_1, receptors.[5] Someday, NK_1 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 NK_1 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 centers[6–8] 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

BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry *aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.*

From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102,

5-HT_3 receptors on their presynaptic nerve terminals detect this release of 5-HT and in turn send the information to the NTS in the vomiting center. Here, a key NTS neurotransmitter, substance P, is released and stimulates NK_1 receptors. The NTS, where a high density of NK_1 receptors is present,[3,4,6] thus has sensors stationed distantly in both the gut and the AP of the brain.[6–8] Input from both gut and AP presumably causes substance P to be released and NK_1 receptors to be activated in the NTS, ultimately signaling for a vomiting response. In addition, if any of the toxin is absorbed, it may reach the chemoreceptor trigger zone via the blood, which also helps to set off a vomiting alarm in the NTS.

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.[6] 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 motoneurons 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-HT_3–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.[5,9] Both inputs lead to substance P release at NK_1 receptors in the NTS,[6] 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.[5,6,9]

Not surprisingly, 5-HT_3 antagonists, by blocking the presynaptic 5-HT_3 receptors on sensory vagal fibers in the gut wall, also block the acute phase of CINV.[9] However, 5-HT_3 antagonists do not block the acute phase of CINV completely and are not especially helpful for the delayed phase.[5] NK_1 antagonists give additive benefit with 5-HT_3 antagonists to the acute phase of CINV and also reduce delayed phase CINV.[5] 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,[10] 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 NK_1 receptors in the NTS is the final common pathway. Therapeutic applications for antagonists of substance P at NK_1 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 NK_1 antagonists in psychopharmacology, such as treatment of depression and other stress-related disorders as well as gastrointestinal side effects common in psychopharmacology.

Take-Home Points

- Substance P is a peptide neurotransmitter in the neurokinin (NK) family whose preferred receptor is the NK_1 receptor.
- Substance P regulates emesis in the brainstem vomiting center. Serotonin (5-HT) regulates emesis via presynaptic 5-HT_3 receptors on sensory vagus fibers in the gut. NK_1 antagonists reduce the vomiting frequently caused by many cancer chemotherapeutic agents by blocking NK_1 receptors, especially when combined with an agent that blocks 5-HT_3 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 NK_1 receptors in various CNS circuits may become a novel approach to treating stress-related disorders such as depression.

REFERENCES

1. Stahl SM. J Clin Psychiatry 1999;60:77–78
2. Stahl SM. J Clin Psychiatry 1999;60:140–141
3. Stout SC, et al. Annu Rev Pharmacol Toxicol 2001;41:877–906
4. Harrison S, Geppetti P. Int J Biochem Cell Biol 2001;33:555–576
5. Navari RM, et al, L-754,030 Antiemetic Trials Group. N Engl J Med 1999;340:190–195
6. Diemunsch P, Grelot L. Drugs 2000:60: 533–546
7. Grelot L, Miller AD. News Physiol Sci 1994;9:142–147
8. Borison HL, McCarthy LE. Drugs 1983; 25(suppl 1):8–17
9. DeMulder PH, et al. Ann Intern Med 1990;113: