

ESSAY How Do Viagra[®], Levitra[®], and Cialis[®] Work?

In the United States alone, 30 million men are estimated to suffer from erectile dysfunction—the inability to produce and sustain an erection when sexually stimulated. In recent years, drugs that treat this disorder effectively have appeared on the

The development of this drug therapy grew out of a detailed understanding of a signal transduction pathway.

market. Among them are molecules that are marketed under the trade names Viagra, Levitra, and Cialis. How do these drugs work?

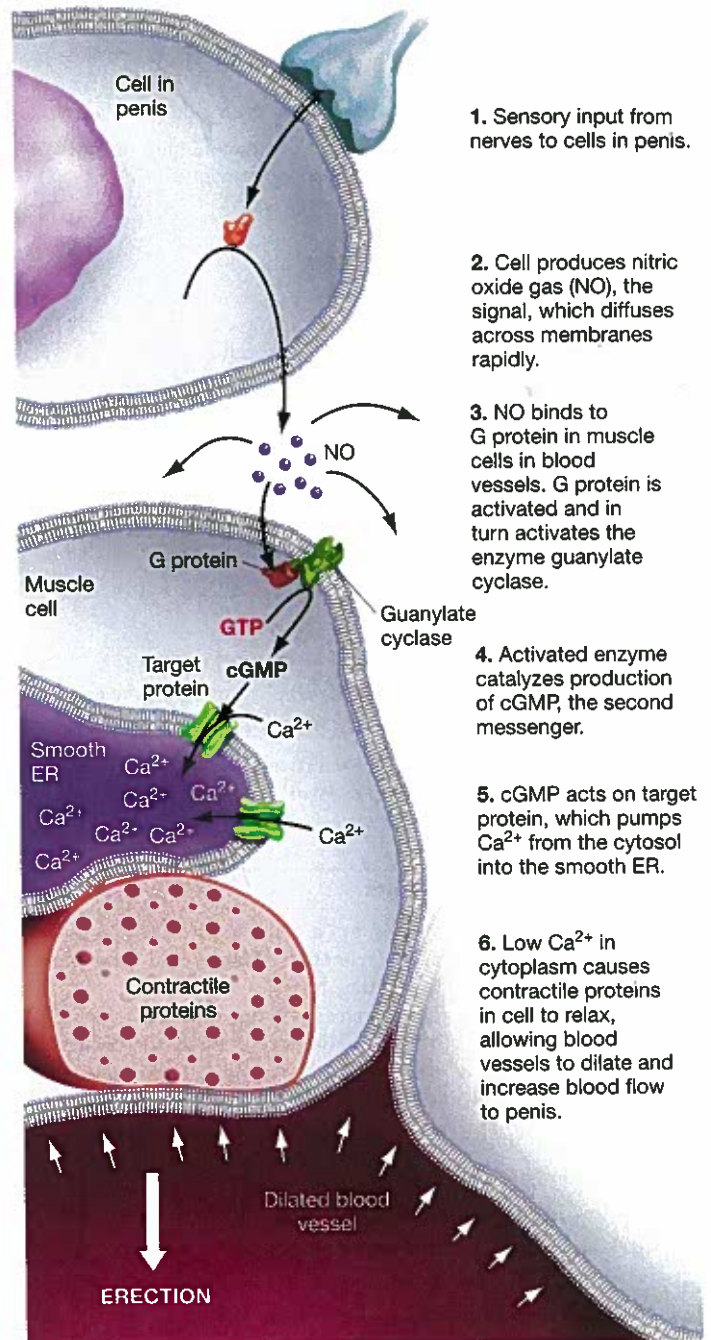
The answer to this question is found in the cell-cell signaling system that leads to erection in males. Figure 8.17 outlines the sequence of events. When a man is sexually stimulated, nerve impulses from the brain or direct physical contact lead to the release of the chemical messenger nitric oxide (NO) gas from blood-vessel cells in his

penis. NO acts as an intercellular signal. Its targets are muscle cells that surround the blood vessels throughout the penis. When it arrives at one of these muscle cells, the NO diffuses through the plasma membrane and binds to the enzyme guanylate cyclase. The activated enzyme catalyzes the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). cGMP acts as a second messenger. It binds to and activates a protein kinase. This kinase then phosphorylates a protein in the membrane of the smooth ER.

When that protein is activated, it begins pumping calcium ions (Ca^{2+}) out of the cytosol and into the lumen of the smooth ER. When Ca^{2+} levels in the cytoplasm of the muscle cells are low, the muscle tissue that contains these cells relaxes. When muscles that surround blood vessels relax, the vessels widen. As a result, blood flow through the vessels increases. As muscles in the penis relax, blood flows into chambers in the structure and fills them, causing an erection.

How do the drugs Viagra, Levitra, and Cialis fit into this signaling pathway? The muscle cells of the penis contain an enzyme called phosphodiesterase 5 (PDE5), which turns off the NO-induced system. More specifically, PDE5 catalyzes the conversion of cGMP to an inactive form. Because it removes the second messenger, PDE5 diminishes the cells' response to the original signal. Viagra, Levitra, and Cialis inhibit PDE5. When these drugs are in the cytoplasm, the cell's mechanism for deactivating the signal is inhibited and cGMP levels tend to stay high. Because this second messenger is present at a high concentration, each cell's response to the signal tends to be stronger and of longer duration. The development of this drug therapy grew out of a detailed understanding of a signal transduction pathway.

CELL-CELL SIGNALING DURING ERECTIONS



1. Sensory input from nerves to cells in penis.

2. Cell produces nitric oxide gas (NO), the signal, which diffuses across membranes rapidly.

3. NO binds to G protein in muscle cells in blood vessels. G protein is activated and in turn activates the enzyme guanylate cyclase.

4. Activated enzyme catalyzes production of cGMP, the second messenger.

5. cGMP acts on target protein, which pumps Ca^{2+} from the cytosol into the smooth ER.

6. Low Ca^{2+} in cytoplasm causes contractile proteins in cell to relax, allowing blood vessels to dilate and increase blood flow to penis.

FIGURE 8.17 A Signal Transduction Pathway in Male Reproductive Tissue

EXERCISE The enzyme PDE5 converts cGMP to an inactive molecule. Circle the step in the signal transduction pathway that is affected by PDE5. What effect does PDE5 activity have on the response?