The Molecular Perspective: Morphine

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LEARNING OBJECTIVE

After completing this course, the reader will be able to:

- Describe the role of morphine and the G protein signaling system in pain treatments.

After a century of effort, morphine remains the most effective weapon in the war against pain. Most painkillers, such as aspirin and acetaminophen, have an upper limit to their painkilling level, but morphine blocks more and more pain with increasing doses. Morphine is far from perfect, however: it causes nausea and constipation, it presents a constant danger of life-threatening respiratory depression, and it is strongly addictive. Chemists have tinkered and modified the basic form of the molecule in a continuing effort to make it more potent and to reduce its severe side effects. Heroin was an early attempt to create an improved version of morphine, but it did not reduce the addictive qualities as hoped. Hundreds of compounds have been tested since then, but none have managed to isolate the desirable painkilling properties from the unwanted side effects.

Morphine is so effective because it acts directly at pain-modulating receptors in the nervous system, termed opioid receptors. These receptors respond to natural compounds, such as the enkephalin shown in Figure 1, built by our bodies to control the levels of pain experienced at different times. For instance, endorphins may be produced during heavy exercise, reducing pain levels when those levels inhibit strenuous activity. Morphine mimics these natural compounds, binding to the receptors and artificially blocking the pain messages.

When morphine binds to opioid receptors, the painkilling message is transmitted inside the cell through a G protein cascade, as shown in Figure 2. The G protein system is the most common method of signaling in our cells. There are thousands of different G protein-coupled receptors, each waiting for a different signal. Each system starts with a receptor that recognizes the signaling molecule, which then activates a G protein inside the cell, which in turn activates an enzyme or an ion channel that spreads the signal throughout the cell. In the case of adrenaline, the G protein activates...
adenylyl cyclase, a membrane-bound enzyme. Adenylyl cyclase then floods the cell with cyclic AMP, activating all the components needed to raise the level of metabolism. When morphine binds to its receptors, the G protein in the opioid signaling chain has several targets. It increases conduction through potassium channels, decreases conduction through calcium channels, and inhibits adenylyl cyclase. Together, these changes blunt the effect of signaling systems that transmit pain.

Morphine and other opiates are addictive and have been drugs of abuse for thousands of years. One site where morphine acts is in the reward center of the brain—the area that makes eating and other essential processes feel pleasurable. The brain responds to morphine by building more components for the G protein signaling system. Over time, more and more morphine is needed to have the same effect on the system. When morphine is removed, the normal function of the pleasure system is dulled by the bloated G protein signaling system, leading to severe withdrawal symptoms.

**ADDITIONAL READING**


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**Figure 2. Morphine initiates a signal through a G protein cascade.** When morphine binds to an opiate receptor, the receptor changes shape and interacts with a G protein inside the cell. The activated receptor causes the G protein to expel its GDP molecule and pick up a GTP molecule instead. This causes the G protein to break into two pieces. The half with the GTP molecule then diffuses along the membrane until it finds its target. In the case shown here, it binds to adenylyl cyclase and inhibits the formation of cyclic AMP. In other cases the activated G protein may change the function of an ion channel or another enzyme. After time, the GTP breaks down into GDP, and the entire system returns to a resting, inactive state. Atomic coordinates were taken from entries 1f88, 1got, 1cul and 1tbg at the Protein Data Bank (http://www.pdb.org).