Chapter 14

Medicinal Chemistry

THE MAIN IDEA

Medicines are like keys that unlock various biological responses.

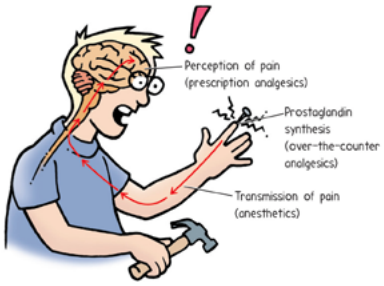
14.6 Pain Relievers

Physical pain is a complex body response to injury. On the cellular level, pain-inducing biochemicals are rapidly synthesized at the site of injury, where they initiate swelling, inflammation, and other responses that get your body's attention. These pain signals are sent through the nervous system to the brain, where the pain is perceived. Drugs act at various stages of this process to alleviate pain, as shown in **Figure 14.40**.

Anesthetics prevent neurons from transmitting sensations to the brain. *Local anesthetics* are applied either topically to numb the skin or by injection to numb deeper tissues. These mild anesthetics are useful for minor surgical and dental procedures. As described earlier, cocaine was the first medically used local anesthetic. Others having fewer side effects soon followed, such as the ones shown in **Figure 14.41**.

A general anesthetic blocks out pain by rendering the patient unconscious. As discussed in Section 12.4, diethyl ether was one of the first general anesthetics. Sevoflurane and nitrous oxide, shown in **Figure 14.42**, are two of the more popular gaseous general anesthetics used by anesthesiologists today. When inhaled, these compounds enter the bloodstream and are distributed throughout the body. At certain blood concentrations, general anesthetics render the individual unconscious, which is useful for invasive surgery. General anesthesia must be monitored very carefully, however, to avoid a major shutdown of the nervous system and consequent death.

Analgesics are a class of drugs that help us to tolerate pain without abolishing nerve sensations. Over-the-counter analgesics, such as aspirin, ibuprofen, and acetaminophen, inhibit the formation of *prostaglandins*. As **Figure 14.43** illustrates, prostaglandins are biochemicals the body quickly synthesizes to generate pain signals. These analgesics also reduce fever, because of the role prostaglandins play in raising body temperature. In addition to reducing pain and fever, aspirin and ibuprofen act as



∧ Figure 14.40

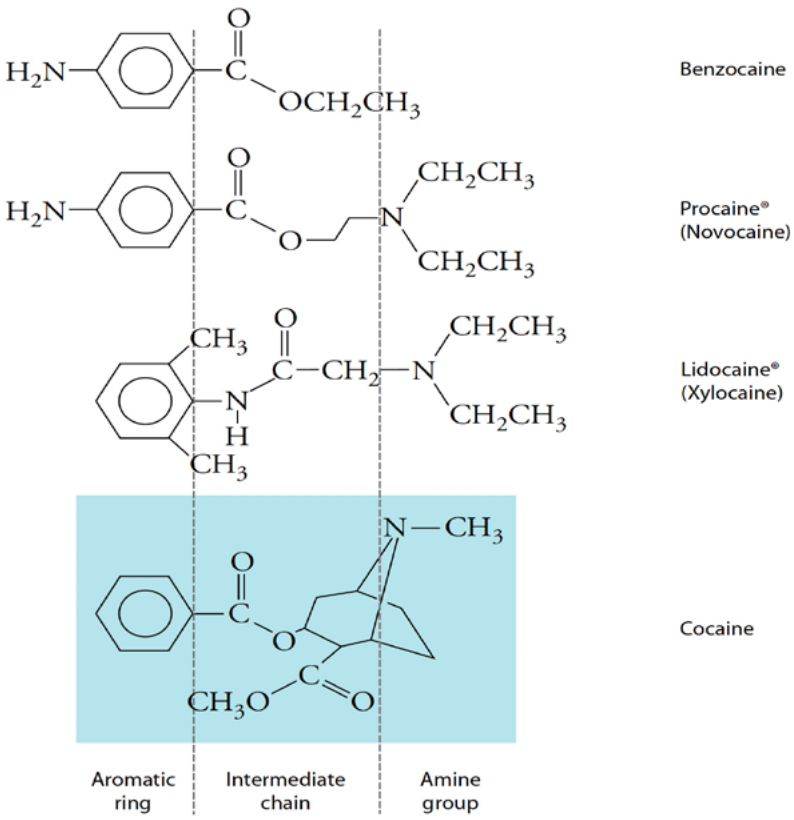
Injury to tissue causes the transmission of pain signals to the brain. Pain relievers prevent this transmission, inhibit the inflammatory response, or dampen the brain's ability to perceive the pain.

READING CHECK

How does a general anesthetic knock out pain?

Figure 14.41 >

Local anesthetics have similar structural features, including an aromatic ring, an intermediate chain, and an amine group. Ask your dentist which ones she uses for your treatment.



fyi FOR YOUR INFORMATION

The 19th-century chemist Felix Hoffmann created, acetylsalicylic acid (aspirin) by adding the acetyl functional group to salicylic acid (see Chapter 12). Two weeks later, he applied the same chemistry to morphine to create diacetylmorphine. The company he was working for, Bayer, named and marketed this product "heroin" for the "heroic" feeling it inspired in users. It was erroneously advertised as being a nonaddictive alternative to morphine. More importantly, however, heroin is a powerful cough suppressant. At the time, tuberculosis and pneumonia were the leading causes of death. Heroin became a much welcomed medicine, as it allowed people sick from these diseases to obtain a restorative night's sleep. By 1913, the negative aspects of heroin became widely known and Bayer stopped producing it, focusing instead on selling aspirin.

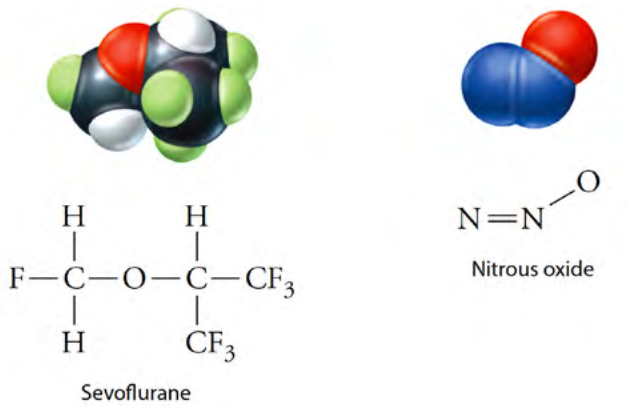
anti-inflammatory agents, because they block the formation of a certain type of prostaglandin responsible for inflammation. Acetaminophen does not act on inflammation. These three analgesics are shown in **Figure 14.44**.

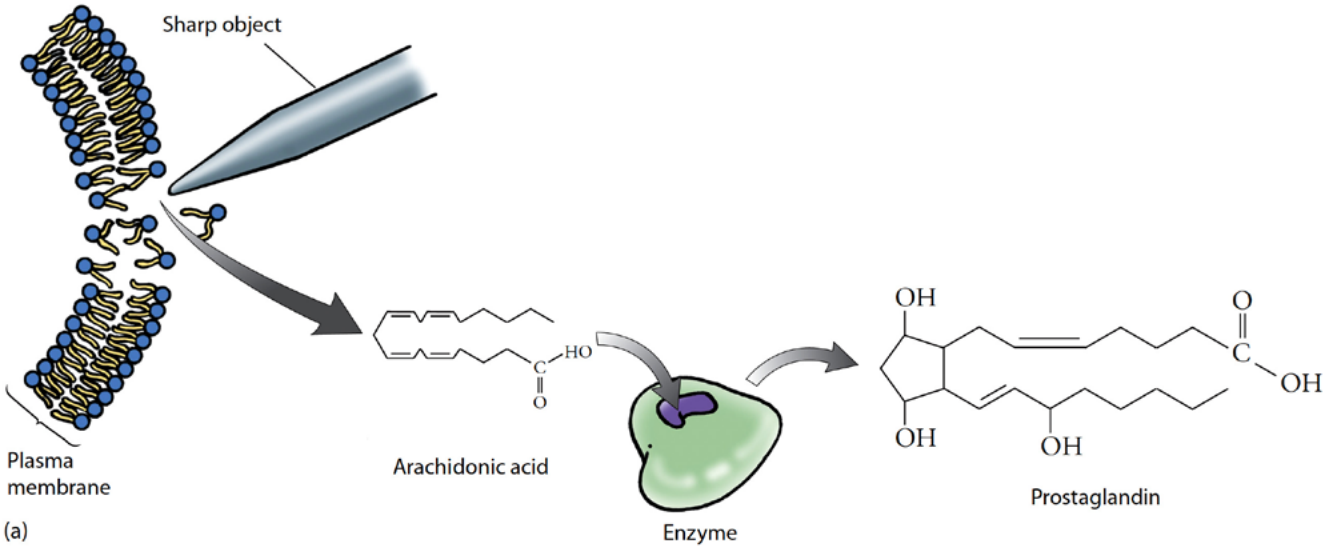
The more potent opioid analgesics—morphine, codeine, and heroin—alter the brain's perception of pain by binding to receptor sites on neurons in the central nervous system, which includes the brain and spinal column. Initial discovery of these receptor sites raised the question of why they exist. At the time, some hypothesized that opioids mimic the action of a naturally occurring brain chemical. *Endorphins*, a group of large biomolecules that have strong opioid activity, were subsequently isolated from brain tissue. It has been suggested that endorphins evolved as a means of suppressing awareness of pain that would otherwise be incapacitating in life-threatening situations. The "runner's high" experienced by many athletes after a vigorous workout is caused by endorphins.

Endorphins are also implicated in the *placebo effect*, in which patients experience a reduction in pain after taking what they believe is a drug but is

Figure 14.42 >

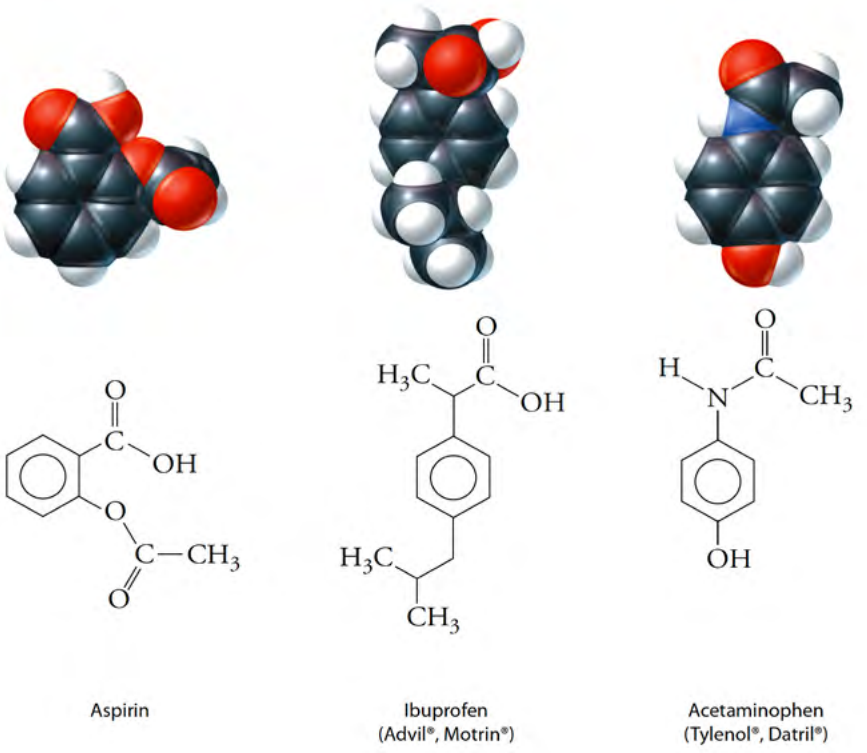
The chemical structures of sevoflurane and nitrous oxide.





∧ Figure 14.43

(a) Prostaglandins, which cause pain signals to be sent to the brain, are synthesized in response to injury. The starting material for all prostaglandins is arachidonic acid, which is found in the membranes of all cells. Arachidonic acid is transformed to prostaglandins with the help of an enzyme. There are a variety of prostaglandins, each having its own effect, but all have a chemical structure resembling the one shown here. (b) Analgesics inhibit the synthesis of prostaglandins by binding to the arachidonic acid receptor site. With no prostaglandins, no pain signals are generated.



< Figure 14.44

Aspirin and ibuprofen block the formation of the prostaglandins responsible for pain, fever, and inflammation. Acetaminophen only blocks the formation of the prostaglandins responsible for pain and fever.

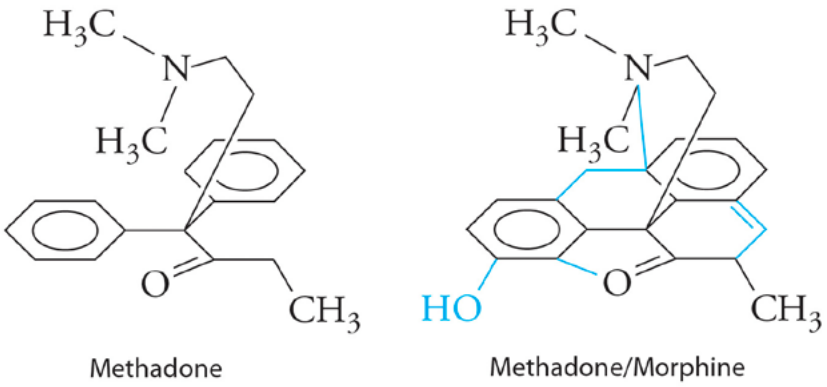


Figure 14.45 >

The structure of methadone (black) superimposed on that of morphine (blue and black).

actually a sugar pill. (A *placebo* is any inactive substance used as a control in a scientific experiment.) Through the placebo effect, it is the patient's belief in the effectiveness of a medicine rather than the medicine itself that leads to pain relief. The involvement of endorphins in the placebo effect has been demonstrated by replacing the sugar pills with drugs that block opioids or endorphins from binding to their receptor sites. Under these circumstances, the placebo effect vanishes.

In addition to acting as analgesics, opioids can induce euphoria, which is why they are so frequently abused. With repeated use, individuals develop a tolerance to these drugs: they must take larger and larger doses to achieve the same effect. These people can also become physically dependent on opioids, which means they must continue to take them to avoid severe withdrawal symptoms, such as chills, sweating, stiffness, abdominal cramps, vomiting, weight loss, and anxiety. Most notable are the craving that addicts experience. It's this constant craving that makes treatment of opioid addiction particularly challenging. Interestingly, when opioids are used primarily for pain relief rather than for pleasure, the withdrawal symptoms are much less dramatic—especially when the patient does not know he has been on these drugs. Yet, over-prescription of these opioids for pain relief remains the predominate gateway to full-blown addiction.

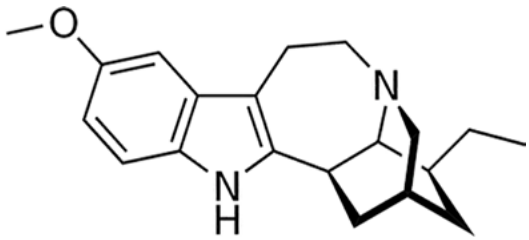
Currently, a widely used approach to treating opioid addiction is Medically Assisted Therapy (MAT) in which the patient is treated with a milder opioid such as Methadone, Seboxone, or Buprenorphine. As an example, *Methadone*, shown in **Figure 14.45**, is a synthetic opioid derivative that has most of the effects of other opioids, including euphoria, but differs in that it retains much of its activity when taken orally. This means that doses are easier to control and monitor. The withdrawal symptoms of methadone are also less severe, and the patient may be slowly weaned off the opioid without excessive stress. Yet, the patient may require methadone treament for many years because withdrawal symptoms from these sorts of "milder" opioids are still most challenging. What does this mean? It means they need to get themselves to the clinic for daily treatment—a process that takes time and energy away from life activities, such as work and caring for their family. Because of its long-term nature, MAT is very expensive. Further, the psychological dependence and craving for opioids usually persists throughout the individual's life, which is why the relapse rate is high.

For opioid addiction, one area of promising research are treatments centered around the molecule Ibogaine, shown in **Figure 14.46**. This naturally-occurring alkaloid is isolated from the root of the iboga shrub, found in central Africa. Indiginous peoples would use this hallucinogenic agent to

FOR YOUR INFORMATION

Oxycodone and hydrocodone are two derivatives of morphine available by prescription for pain management. According to the Centers for Disease Control and Prevention, abuse of these prescription painkillers is a fast-growing epidemic currently resulting in more than 15,000 deaths in the United States each year. That makes these agents the second-leading cause of injury death after motor vehicle crashes.

Iboga Shrub



Ibogaine

Λ Figure 14.46

Ibogaine, found found within the iboga shrub native to central Africa, has potential for the treatment of opioid addiction.

enter a trance allowing them to remain still for extended periods of time. This is due to the action this agent has on skeletal muscles at low doses. With a weapon in hand, they could wait for game to pass by—an unusual form of hunting. At stronger doses, the Ibogaine moves the user into a self-reflective hallucinogenic experience, but acting in a way very different from LSD. Under proper medical supervision and counseling, the user comes out of the Ibogaine treatment with an often deeper persepective on their life. In a number of ways, their outlook has been "reset." After a single session, any cravings they might have for opioids are greatly diminished or absent. Without these cravings, the chances for a cure are largly enhanced.

The professional supervision is most important because 1) This drug has some cardiotoxicity, 2) The patient must be confirmed 100 percent free of opioids. This is rather difficult because most opioids today are laced with the super powerful opioid fentanyl, which lingers in the body for many weeks, and 3) Psychological counseling is needed to help address the challenging and complex life issues people addicted to opioids tend to face.

This area of research is greatly hindered by present drug laws that classify Ibogaine as an illegal substance of no known medical use. The reasons for this classification are more political than scientific. While politics and science are two different areas of human activity, they nonetheless remain very interconnected. To keep the two moving in productive directions requires citizens who are both politically aware and scientifically literate.

CONCEPT **CHECK**

Distinguish between an anesthetic and an analgesic.

CHECK YOUR ANSWER An anesthetic blocks pain signals from reaching the brain. An analgesic facilitates the ability to manage pain signals once they are received by the brain.