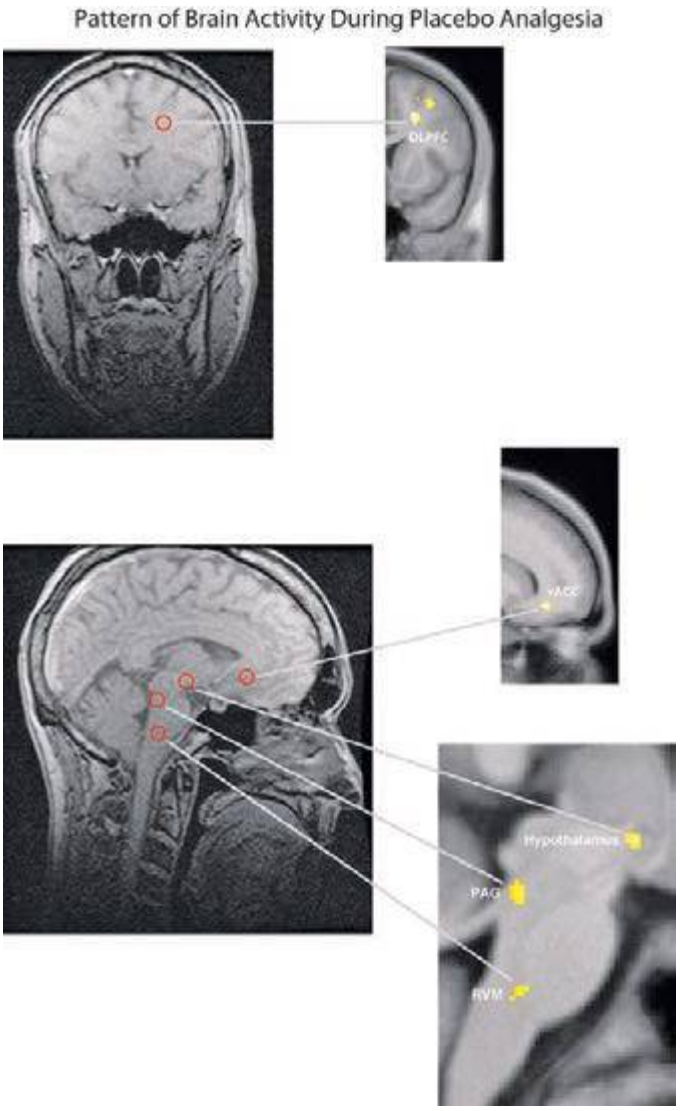

FIGURE 18-5 Functional magnetic resonance imaging (fMRI) demonstrates placebo-enhanced brain activity in anatomic regions correlating with the opioidergic descending pain control system. *Top panel:* Frontal fMRI image shows placebo-enhanced brain activity in the dorsal lateral prefrontal cortex (DLPFC). *Bottom panel:* Sagittal fMRI images show placebo-enhanced responses in the rostral anterior cingulate cortex (rACC), the rostral ventral medullae (RVM), the periaqueductal gray (PAG) area, and the hypothalamus. The placebo-enhanced activity in all areas was reduced by naloxone, demonstrating the link between the descending opioidergic system and the placebo analgesic response. *(Adapted with permission from F Eippert et al: Neuron 63:533, 2009.)*

or mild nociceptive stimuli, is also characteristic of neuropathic pain; patients often complain that the very lightest moving stimulus evokes exquisite pain (allodynia). In this regard, it is of clinical interest that a topical preparation of 5% lidocaine in patch form is effective for patients with postherpetic neuralgia who have prominent allodynia.

A variety of mechanisms contribute to neuropathic pain. As with sensitized primary afferent nociceptors, damaged primary afferents, including nociceptors, become highly sensitive to mechanical stimulation and may generate impulses in the absence of stimulation. Increased sensitivity and spontaneous activity are due, in part, to an increased concentration of sodium channels in the damaged nerve fiber. Damaged primary afferents may also develop sensitivity to norepinephrine. Interestingly, spinal cord pain-transmission neurons cut off from their normal input may also become spontaneously active. Thus, both CNS and peripheral nervous system hyperactivity contribute to neuropathic pain.

Sympathetically Maintained Pain Patients with peripheral nerve injury occasionally develop spontaneous pain in the region innervated by the nerve. This pain is often described as having a burning quality. The pain typically begins after a delay of hours to days or even weeks and is accompanied by swelling of the extremity, periarticular bone loss, and arthritic changes in the distal joints. The pain may be relieved by a local anesthetic block of the sympathetic innervation to the affected extremity. Damaged primary afferent nociceptors acquire adrenergic sensitivity and can be activated by stimulation of the sympathetic outflow. This constellation of spontaneous pain and signs of sympathetic dysfunction following injury has been termed *complex regional pain syndrome* (CRPS). When this occurs after an identifiable nerve injury, it is termed CRPS type II (also known as posttraumatic neuralgia or, if severe, *causalgia*). When a similar clinical picture appears without obvious nerve injury, it is termed CRPS type I (also known as *reflex sympathetic dystrophy*). CRPS can be produced by a variety of injuries, including fractures of bone, soft tissue trauma, myocardial infarction, and stroke (Chap. 446). CRPS type I typically resolves with symptomatic treatment; however, when it persists, detailed examination often reveals evidence of peripheral nerve injury. Although the pathophysiology of CRPS is poorly understood, the pain and the signs of inflammation, when acute, can be rapidly relieved by blocking the sympathetic nervous system. This implies that sympathetic activity can activate undamaged nociceptors when inflammation is present. Signs of sympathetic hyperactivity should be sought in patients with posttraumatic pain and inflammation and no other obvious explanation.

TREATMENT ACUTE PAIN

The ideal treatment for any pain is to remove the cause; thus, while treatment can be initiated immediately, efforts to establish the underlying etiology should always proceed as treatment begins. Sometimes, treating the underlying condition does not immediately relieve pain. Furthermore, some conditions are so painful that rapid and effective analgesia is essential (e.g., the postoperative state, burns, trauma, cancer, or sickle cell crisis). Analgesic medications are a first line of treatment in these cases, and all practitioners should be familiar with their use.

ASPIRIN, ACETAMINOPHEN, AND NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDs)

These drugs are considered together because they are used for similar problems and may have a similar mechanism of action (Table 18-1). All these compounds inhibit cyclooxygenase (COX), and, except for acetaminophen, all have anti-inflammatory actions, especially at higher dosages. They are particularly effective for mild to moderate headache and for pain of musculoskeletal origin.

Because they are effective for these common types of pain and are available without prescription, COX inhibitors are by far the most commonly used analgesics. They are absorbed well from the gastrointestinal tract and, with occasional use, have only minimal side effects. With chronic use, gastric irritation is a common side effect of aspirin and NSAIDs and is the problem that most frequently limits the dose that can be given. Gastric irritation is most severe with aspirin, which may cause erosion and ulceration of the gastric mucosa leading to bleeding or perforation. Because aspirin irreversibly acetylates platelet cyclooxygenase and thereby interferes with coagulation of the blood, gastrointestinal bleeding is a particular risk. Older age and history of gastrointestinal disease increase the risks of aspirin and NSAIDs. In addition to the well-known gastrointestinal toxicity of NSAIDs, nephrotoxicity is a significant problem for patients using these drugs on a chronic basis. Patients at risk for renal insufficiency, particularly those with significant contraction of their intravascular volume as occurs with chronic diuretic use or