sunburned skin, in which severe pain can be produced by a gentle slap on the back or a warm shower.

Sensitization is of particular importance for pain and tenderness in deep tissues. Viscera are normally relatively insensitive to noxious mechanical and thermal stimuli, although hollow viscera do generate significant discomfort when distended. In contrast, when affected by a disease process with an inflammatory component, deep structures such as joints or hollow viscera characteristically become exquisitely sensitive to mechanical stimulation.

A large proportion of Aδ and C fiber afferents innervating viscera are completely insensitive in normal noninjured, noninflamed tissue. That is, they cannot be activated by known mechanical or thermal stimuli and are not spontaneously active. However, in the presence of inflammatory mediators, these afferents become sensitive to mechanical stimuli. Such afferents have been termed *silent nociceptors*, and their characteristic properties may explain how, under pathologic conditions, the relatively insensitive deep structures can become the source of severe and debilitating pain and tenderness. Low pH, prostaglandins, leukotrienes, and other inflammatory mediators such as bradykinin play a significant role in sensitization.

Nociceptor-Induced Inflammation Primary afferent nociceptors also have a neuroeffector function. Most nociceptors contain polypeptide mediators that are released from their peripheral terminals when they are activated (Fig. 18-2). An example is substance P, an 11-amino-acid peptide. Substance P is released from primary afferent nociceptors and has multiple biologic activities. It is a potent vasodilator, degranulates mast cells, is a chemoattractant for leukocytes, and increases the production and release of inflammatory mediators. Interestingly, depletion of substance P from joints reduces the severity of experimental arthritis. Primary afferent nociceptors are not simply passive messengers of threats to tissue injury but also play an active role in tissue protection through these neuroeffector functions.

CENTRAL MECHANISMS

The Spinal Cord and Referred Pain The axons of primary afferent nociceptors enter the spinal cord via the dorsal root. They terminate in the dorsal horn of the spinal gray matter (Fig. 18-3). The terminals of primary afferent axons contact spinal neurons that transmit the pain signal to brain sites involved in pain perception. When primary afferents are activated by noxious stimuli, they release neurotransmitters from their terminals that excite the spinal cord neurons. The major neurotransmitter released is glutamate, which rapidly excites dorsal horn neurons. Primary afferent nociceptor terminals also release peptides, including substance P and calcitonin gene-related peptide, which produce a slower and longer-lasting excitation of the dorsal horn neurons. The axon of each primary afferent contacts many spinal neurons, and each spinal neuron receives convergent inputs from many primary afferents.

The convergence of sensory inputs to a single spinal pain-transmission neuron is of great importance because it underlies the phenomenon of referred pain. All spinal neurons that receive input from the viscera and deep musculoskeletal structures also receive input from the skin. The convergence patterns are determined by the spinal segment of the dorsal root ganglion that supplies the afferent innervation of a structure. For example, the afferents that supply the central diaphragm are derived from the third and fourth cervical dorsal root ganglia. Primary afferents with cell bodies in these same ganglia supply the skin of the shoulder and lower neck. Thus, sensory inputs from both the shoulder skin and the central diaphragm converge on pain-transmission neurons in the third and fourth cervical spinal segments. *Because of this convergence and the fact that the spinal neurons are most often activated by inputs from the skin, activity evoked in spinal neurons by input from deep structures is mislocalized by the patient to a place that roughly corresponds with the region of skin innervated by the same spinal segment.* Thus, inflammation near the central diaphragm is often reported as shoulder discomfort. This spatial displacement of pain sensation from the site of the injury that produces it is known as *referred pain*.

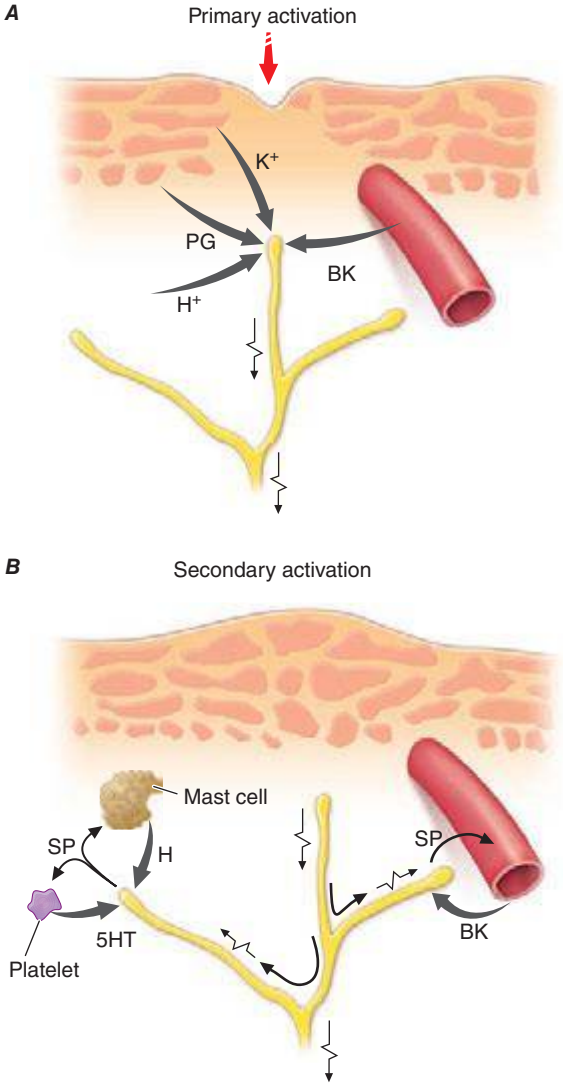

FIGURE 18-2 Events leading to activation, sensitization, and spread of sensitization of primary afferent nociceptor terminals. ***A.*** Direct activation by intense pressure and consequent cell damage. Cell damage induces lower pH (H^+) and leads to release of potassium (K^+) and to synthesis of prostaglandins (PG) and bradykinin (BK). Prostaglandins increase the sensitivity of the terminal to bradykinin and other pain-producing substances. ***B.*** Secondary activation. Impulses generated in the stimulated terminal propagate not only to the spinal cord but also into other terminal branches where they induce the release of peptides, including substance P (SP). Substance P causes vasodilation and neurogenic edema with further accumulation of bradykinin (BK). Substance P also causes the release of histamine (H) from mast cells and serotonin (5HT) from platelets.

Ascending Pathways for Pain A majority of spinal neurons contacted by primary afferent nociceptors send their axons to the contralateral thalamus. These axons form the contralateral spinothalamic tract, which lies in the anterolateral white matter of the spinal cord, the lateral edge of the medulla, and the lateral pons and midbrain. The spinothalamic pathway is crucial for pain sensation in humans. Interruption of this pathway produces permanent deficits in pain and temperature discrimination.

Spinothalamic tract axons ascend to several regions of the thalamus. There is tremendous divergence of the pain signal from these thalamic sites to several distinct areas of the cerebral cortex that subserve different aspects of the pain experience (Fig. 18-4). One of the thalamic projections is to the somatosensory cortex. This projection mediates the purely sensory aspects of pain, i.e., its location, intensity, and quality. Other thalamic neurons project to cortical regions that are linked