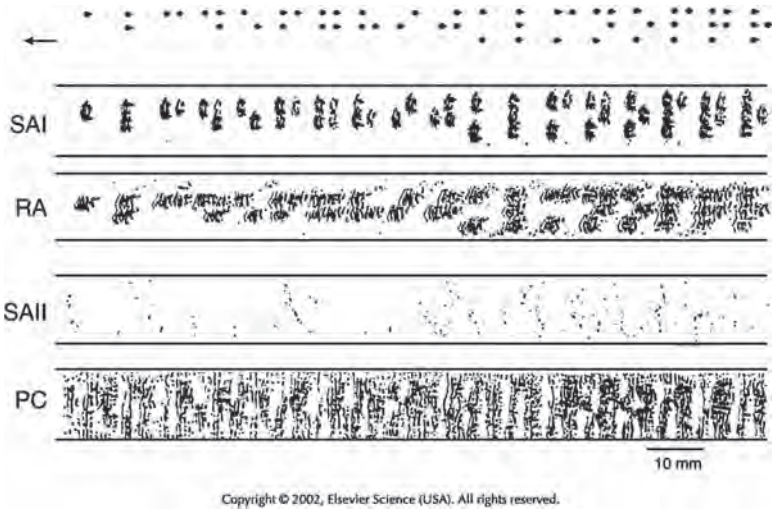

FIGURE 25.4 Response of peripheral axons to a Braille pattern of dots scanned over the surface of a human fingertip at a rate of 60 mm/s, with 200-μm shifts in position after each pass. Dots represent individual action potentials. Only the response of the SAI afferents (Merkel disk receptors) follows the Braille pattern faithfully, whereas RA afferents and Pacinians (PC) produce a response that distorts the input. SAIIs display little response to this stimulus. Adapted from Phillips *et al.* (1990).

dots (6.0 mm high or greater) so accurately as to account for the ability a monkey or a human has in telling one pattern from the next.

Peripheral factors contribute significantly to the SAI's contribution to form and texture perception. One of these factors is the unique sensitivity of SAI afferents to strain energy density, a term that Johnson describes as "the energy required to produce local deformation" per unit volume of skin. Thus rather than responding to the total energy generated by application of a uniform stimulus, SAI afferents respond to even the slight imperfections in that surface and the local deformation of skin they produce. Movement of the skin across a surface, as in scanning Braille, greatly increases the energy produced by any imperfection and leads to a greatly enhanced response by SAI afferents. This finding has a strong intuitive feel to it, given the much greater tactile acuity each of us has when we move a fingertip along a surface with even slight imperfections.

A second peripheral factor is that of surround suppression. Skin mechanics lead not only to local peaks in strain energy density but also to broader troughs. The result for any single SAI afferent are hot spots in its receptive field surrounded by tissue that, when simultaneously probed, leads to a reduction in the response of that afferent. An average terminal domain for an SAI afferent on the finger tip may be as much as 5 mm^2, but the presence of hot spots and surround suppression permits these afferents to signal the presence of a stimulus (such a gap between two elevations) of as little as 0.5 mm.

In contrast to tactile form, texture has relatively few dimensions (rough-smooth, hard-soft, and sticky-slippery are the most prominent) but they are difficult to quantify. Nevertheless, a series of careful studies has documented that for variations in roughness, only the response of SAI afferents matches human perceptual ability. That is, the variation in firing rates among SAI follows precisely the perception human subjects have of surface roughness. Much the same can be said for the detection of surface hardness. Only the response of SAI afferents can account for human perception of how hard or soft is the surface of an object scanned by the fingertips. In summary, a combination of physiological and psychophysical studies leads one to conclude that SAI's provide the central somatosensory system with all the information it needs to detect the shape, hardness, and roughness of objects pressed or scanned across the skin.

SAII Afferents

A second slowly adapting afferent in human skin, the SAII afferent, differs from an SAI in the greater size of its receptive field, the reduced sensitivity to simple indentation of the skin, and the greater sensitivity to skin stretch. One surprising feature of these afferents is the less than universal presence of SAIIs across the

short range of well-studied mammals. Direct recordings from the peripheral nerves of humans and of domestic cats show these afferents to be a commonly encountered feature of both species, but they do not exist in monkeys or mice. Just as perplexing is the poor correlation between structure and function with this receptor. The original correlative work in cats found SAII responses to arise from axons terminating in skin as Ruffini endings. These structures were first described in human skin at the turn of the twentieth century, but a twenty-first century study by M. Pare and colleagues found true Ruffini endings in human skin very rarely and only in the bed of fingernails. These findings indicate SAII responses over most of the human hand arise from some other arrangement of mechanoreceptor axon and connective tissue sheath. Recent recordings from human peripheral nerves have added to the conundrum by documenting the presence of a third SA variety—labeled SA3—that has properties intermediate between the other two slowly adapting types. A conservative conclusion from these findings is that some arrangement of nonneural cells, perhaps a classic Ruffini in cats but another configuration in humans, leads to the cardinal feature of SAII afferents, namely a robust response to skin stretch. That configuration could vary from one species to another and from one area of skin surface to the next, but in the end the nonneural tissue serves as a mechanical filter. Given the task of subtracting from the activity of a SAII afferent a response to simple deformation of the skin, the nonneural tissue leaves behind an unambiguous response to anything that stretches the skin.

Hair Follicle Afferents

In addition to receptor types found in glaborous skin, hairy skin is innervated by a separate receptor, called the D-hair receptor or hair follicle afferent (HFA). It is the most sensitive receptor in hairy skin. The HFA threshold is said to be one-tenth that of any other afferent in mouse skin, and displacement of a hair follicle by as little as 1 μm produces robust responses in this population of receptors. Single afferents innervate more than one hair follicle and as a result, the receptive field of an HFA is large (>10 mm^2 in mice). Unlike other mechanoreceptors, HFA's conduct action potentials in the Aδ range, which translates into a velocity of 20–25 m/s for humans but a much lower velocity in mice.

Receptor Density

A plot of SAI and SAII receptors along the human skin surface shows receptive field size and density varies by a factor of four in the short distance from the fingertip to the wrist. As is the case for other sensory systems, wherever receptor density declines receptive field size ascends. This inverse variation in receptive size and density is reflected in the ability of a human subject to discriminate the two-dimensional shape of an object. Human performance in this area has been measured classically as two-point discrimination (Fig. 25.5). Two blunt probes applied to a skin surface can be moved together to produce a perception of a single probe. How close they can be and still produce the percept of two separate probes says something about the receptive field size and density of receptors that underlie the function referred to as fine touch. Normal human subjects are able to detect two probes separated by as little as one millimeter on the surface of the distal pad of the index finger and face. Acuity declines in other regions of the body and is poorest on the back where two points cannot be distinguished from one until they are about 70 mm apart. Regions of high spatial acuity (the hand and face) are where form perception is greatest and are analogous to the fovea of the retina.

Muscle Spindles and Golgi Tendon Organs Are Proprioceptors

The most prominent receptors fulfilling the function of sensing position and movement are muscle

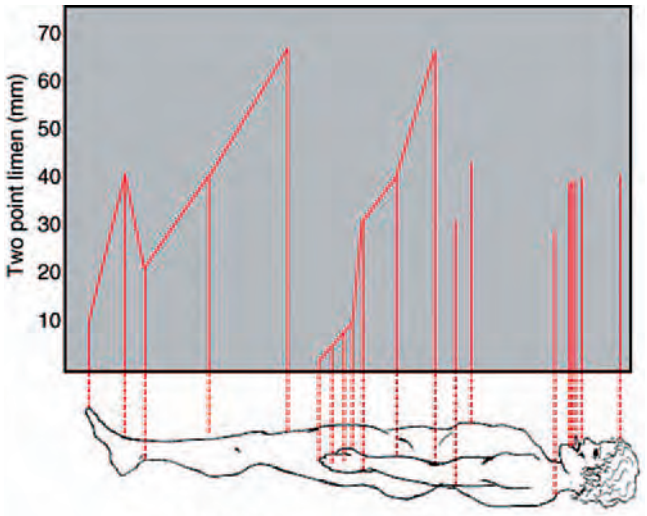

FIGURE 25.5 Variation in two-point limen (threshold) across the body surface. The graph plots the distance necessary for a human subject to detect two blunt probes as separate stimuli. That distance is lowest for the fingertips and mouth (approximately 10 mm) and highest for the legs, shoulders, and back (as much as 70 mm). From Patton, H. D., Sundsten, J. W., Crill, W. E., and Swanson, P. D. (eds.) (1976). "Introduction to Basic Neurology," p. 160. Saunders, Philadelphia.

receptors and tendon receptors. These two have in common their sensitivity to stretch and the large diameter of the axons that carry the receptors' activity into the CNS. The manner in which they are arranged, however, makes all the difference in the world. Muscle receptors are arranged in parallel with the muscle fibers and as a result, these afferents respond when the muscle is stretched. As a common occurrence, muscle fibers stretch when load is added to them in the form of weight or resistance. The resulting stretch of the extrafusal or work muscle fibers produces a simultaneous stretch of the much smaller intrafusal muscle fibers. The intrafusal fibers have their own motor innervation and a sensory innervation from the largest diameter axons in a sensory nerve (Fig. 25.6). These sensory axons are called Ia afferents and they end in one of two configurations around the noncontractile portion of an intrafusal muscle fiber, where they signal the static or dynamic aspects of muscle stretch. All of these—sensory axons, intrafusal muscle fibers, and motor axons—are surrounded by a connective tissue capsule to form a muscle spindle. The contribution of the motor axons to all this is rather simple to envision—by adjusting the contractile state of the intrafusal muscle fiber, they adjust the sensitivity of the muscle afferent. When the intrafusal fiber is contracted

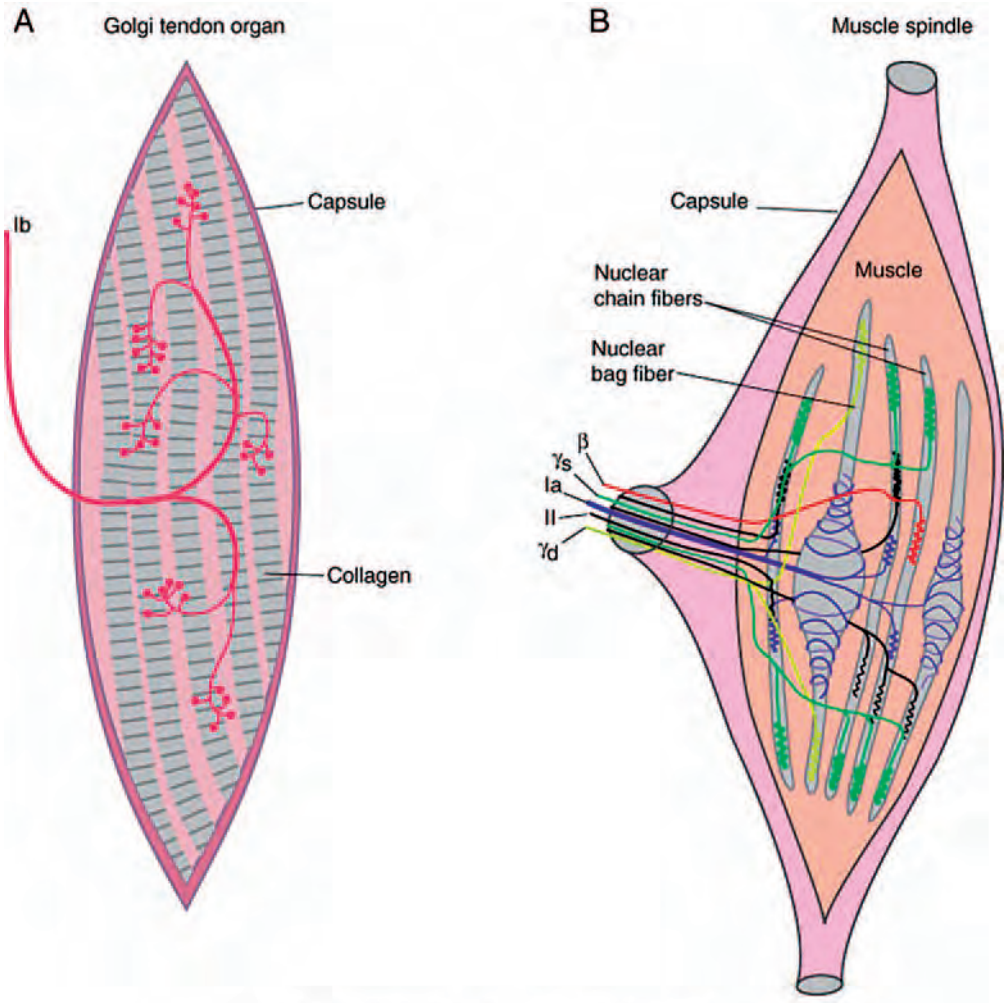

FIGURE 25.6 Proprioceptive afferents. (A) Golgi tendon organs and their termination along collagen fibers of the tendon capsule. These afferents respond when the entire capsule is stretched, usually by overvigorous contraction of the muscle. (B) Muscle spindle afferents (Ia and II) terminate on the noncontractile portions of intrafusal muscle fibers. They are arranged in parallel with work muscle fibers and respond to stretch of the entire muscle. Specialized motoneurons (γ) provide the motor innervation of the intrafusal muscle fibers and control the overall sensitivity of the muscle spindle.

the spindle is at its most sensitive and when the intrafusal fiber is relaxed, the spindle is least sensitive.

Much as muscle receptors are sensitive to muscle stretch, tendon receptors (referred to as Golgi tendon organs) are sensitive to tendon stretch and provide information about muscle force. Because tendons are arranged in series with the muscles, so too are tendon receptors. What stretches the tendon is muscle contraction. In this regard, muscle spindles and Golgi tendon organs signal the opposite trends. Spindles fire when a muscle is relatively inactive and stretched whereas tendon organs fire when the muscle is most active and contracted.

Proprioception Involves More Than Proprioceptors

By a definition of proprioception as an awareness of the position of the body and limbs, the two most prominent proprioceptors are necessary but not sufficient. More than just muscle and tendon receptors are at work. The related sense of kinesthesia, or awareness of position of moving body parts, is equally complex. Often used interchangeably for position sense, these two are complex percepts that require the contribution of receptors in muscle, skin, and joints as well as a sense of muscle exertion. Studies of the 1950s and 1960s focused on the contribution of joint afferents to a sense of limb position. The connective tissue and bones of joints are richly innervated and would seem to be in an ideal location to signal limb position. Yet a series of findings in the 1970s made clear that a sense of position survived joint removal; and the joint afferents, themselves, responded only at the extreme limits of joint flexion. With no response in the usual, midrange of joint movement, these afferents could not signal position under most circumstances.

Studies of more recent vintage have dealt principally with muscle spindle afferents as a major source of the position signal. Since all muscles are organized as antagonistic pairs, contraction of one delivers a robust stimulus to afferents of the antagonistic, stretched muscle. From these sorts of inputs, limb position and movement would appear to require a simple neural computation. That position sense is significantly affected by stimulation, anesthesia and disengagement of spindle afferents adds weight to the argument that the burden of signaling limb position and movement falls on these receptors. Perhaps the most convincing data are from studies of illusory movements produced by tendon vibration. This type of stimulus selectively activates spindle afferents and leads to the perception of limb movement when none has occurred. Illusory movement is muscle specific, so that activation of arm flexors gives rise to the percept of an arm that has extended (a movement that normally produces activation of flexor muscle afferents). The illusion is so strong it gives rise to the Pinocchio effect: if arm flexor afferents are activated when a subject is touching his or her nose with an index finger, the nose itself, is perceived to grow.

Only in the past several years has proper attention been paid to the role of cutaneous receptors in position sense. In recording from peripheral nerve axons of human subjects, B. Edin has made a strong case for a unique response by an ensemble of SAII afferents to any position a limb or digit might adopt. Particularly compelling is the role these skin stretch receptors play in signaling the position of fingers. For the hand and fingers, therefore, a conscious sense of position appears to arise from the cooperative activity of SAII afferents, muscle afferents, and (at the extremes of movement) joint afferents.

NOCICEPTION, THERMORECEPTION, AND ITCH

Nociceptors Respond to Noxious Stimuli

For most purposes anything that has produced tissue damage or that threatens do so in the immediate future can be defined as noxious and the type of axon that responds selectively to the noxious quality of a stimulus is, by definition then, a nociceptor. These are not pain receptors because nociception is not pain just as sensitivity to the wavelength of light is not color perception. Both are CNS constructs of peripheral events. Unlike color, pain has not only a perceptual component that involves comparison across receptors but also rich psychological and cognitive components. We will deal with those elements of pain perception but for now the most important principle to grasp is also intuitively obvious: the range of stimuli that are perceived as painful is very broad, from heat above 42°C to acids below pH6, from a sharp pinch on the fingertip to a swollen ankle. Each of these is tied to the activity in a variety of nociceptors.

True for all nociceptors is the simple morphology of their axon terminations. These are usually described as free nerve endings because unlike mechanoreceptive afferents, nociceptors end in no specialized capsule of nonneural cells. Another way of looking at this relationship is to notice that nothing extraneuronal serves as a filter or buffer between the nociceptive axon tip and its immediate environment. The only thing that

determines the response of a nociceptor, then, is the type of protein receptor it inserts into its membrane.

Nociceptors also differ from mechanoreceptors in how broadly the terminals of the peripheral axon branch as they reach target. Take the tip of the human index finger as an example. An individual SAI and SAII axon ends in a well-confined cluster of terminals over a distance as small as a few millimeters. Terminals of a single C fiber, by contrast, end over an area of more than a dozen millimeters. This is the first of several anatomical features along the nociceptive pathway that, together, produce a much coarser spatial sense for pain than exists for mechanosensation. Only the simultaneous activation of mechanoreceptors as occurs with puncture wounds or damaging compression permits a person to accurately detect the location of a nociceptive stimulus.

The afferents that make up the nociceptive population can be subdivided into groups that are named by their axon conduction velocity (Aδ vs. C) and the response to noxious mechanical stimuli and noxious heat. Thus, an AM receptor conducts in the Aδ range and responds to intense mechanical stimuli whereas a CMH receptor conducts in the C range and responds to both noxious mechanical energy and noxious heat (Fig. 25.1). Other permutations of conduction velocity and response type are evident in the peripheral nerves of humans and other mammals, but these two are most common. They are frequently referred to as specific mechanical nociceptors and polymodal nociceptors.

First and Second Pain

Many afferents responding specifically to a mechanical stimulus (AM receptors) carry the more rapid signals into the CNS, whereas those responding to the broad range of noxious stimuli (CMH receptors) conduct action potentials more slowly. These are the peripheral components to the two very different qualities of pain perceived by humans (Fig. 25.7). First pain or epicritic pain is rapidly perceived and carries with it much that is discriminative. A person can quickly and with some ease figure out what has happened and where it has happened when he or she drops a heavy object onto a toe or touches a hot stove surface with a couple of fingers on the right hand. First pain is informative and the peripheral component of it is the population of Aδ nociceptors. What follows later is second pain or protopathic pain. This is agonizing pain that carries much less information about location or source of energy. Second pain is punishing pain that serves to change the behavior of a person. Its peripheral component is the population of C nociceptors.

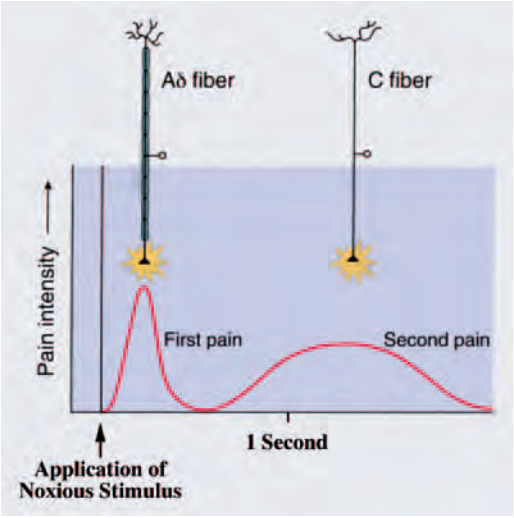

FIGURE 25.7 The two classes of nociceptors that conduct action potentials in the C and Ad ranges are peripheral components for two types of pain. First pain carried by Ad axons reaches consciousness rapidly and is discriminative. Both the location and the subjective intensity of the stimulus can be judged with relatively good precision in first pain. Second pain, in contrast, is much slower and is agonizing pain, with greatly reduced discriminative value.

Two varieties of C nociceptors are found in mammalian skin. One of these is characterized by the presence of fluoride-resistant acid phosphatase (FRAP) in its cytoplasm and cell-surface glycoproteins recognized by the isolectin I-B4 and the monoclonal antibody LA4. As none of these proteins is known to contribute to the physiological features of this C fiber type their presence is currently a convenient feature that allows anyone studying them to recognize and target them. The situation is very different in the second type of C nociceptor. Present in its cytoplasm are two neuroactive peptides, calcitonin gene-related peptide (CGRP) and substance P. These play major roles in the function of the peptide-containing type of C nociceptor.

The Axon Reflex

Release of neuropeptides from the second type of C nociceptor is responsible for the axon reflex (Fig. 25.8). Injury to the skin surface is often well confined, as happens with a paper cut, for example. Yet within a short time of that injury, tissue surrounding the cut becomes reddened in what is referred to as flair and edema or swelling sets in as the tissue fills with fluid. Most importantly, the region surrounding a punctate wound becomes painful to touch even though it is outside the zone of direct damage.