Santiago Ramón y Cajal described a number of somatosensory structures, including several associated with pain, in his major work on the Histology of the Nervous System of Man and Vertebrates. Our knowledge of such structures has been considerably expanded since Cajal because of the introduction of a number of experimental approaches that were not available in his time. For example, Cajal made several drawings of peripheral mechanoreceptors, as well as of bare nerve endings, but later work by others described additional somatosensory receptors and investigated the ultrastructure of bare nerve endings. Furthermore, the transducer molecules responsible for responses to nociceptive, thermal or chemical stimuli are now becoming known, including a series of TRP (transient receptor potential) receptor molecules, such as TRPV1 (the capsaicin receptor). Cajal described the development of dorsal root and other sensory ganglion cells and related the disposition of their somata and neurites to his theory of the functional polarity of neurons. He described the entry of both large and small afferent fibers into the spinal cord, including the projections of their collaterals into different parts of the gray matter and into different white matter tracts. He described a number of types of neurons in the gray matter, including ones in the marginal zone, substantia gelatinosa and head and neck of the dorsal horn. He found neurons in the deep dorsal horn whose dendrites extend dorsally into the superficial dorsal horn. Some of these neurons have since been shown by retrograde labeling to be spinothalamic tract cells. Cajal clearly described the dorsal column/medial lemniscus pathway, but the presence and course of the spinothalamic tract was unknown at the time.

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1. Introduction

This review is based on a comparison of the description of elements of the somatosensory system by Santiago Ramón y Cajal that can be found in his major work on the Histology of the Nervous System of Man and Vertebrates (Cajal, 1952, 1995 translation) and current views. Many of Cajal’s illustrations are of preparations stained by the Golgi method. Cajal’s observations noted in this review are expanded upon by reference to later work that has employed experimental approaches not available to Cajal, such as retrograde and anterograde labeling of neurons or their projections, immunohistochemistry, ultrastructural studies, electrophysiological recordings and behavioral testing. This review will begin with the peripheral sensory receptors that detect somatosensory stimuli. Emphasis will then be placed on the spinal cord, where somatosensory information from the body is initially processed. Finally, ascending pathways that signal this information to the brain will be introduced. Although it is the brain that provides the means for interpretation of such information in terms of sensory perception (Mountcastle, 1998), this topic is beyond the scope of the present review and will not be discussed.

Fig. 1 – Panel I is a drawing by Cajal of a section of the skin of a human finger. A Meissner corpuscle, E, is shown in a dermal papilla; it is supplied by a large myelinated axon, c. Osmic acid and hematoxylin stain. Panel II is a drawing of a Pacinian corpuscle in human skin. It is also supplied by a large axon, a, that loses its myelin sheath as it enters the capsule of the sense organ and then continues through much of the length of the inner core. Stained by the gold chloride method. (Panels I and II are from Cajal, 1952, 1995 translation.) Panel III shows a number of types of sensory receptors in the epidermis and dermis. Meissner corpuscles are seen in several dermal papilli. Merkel disks are the endings of large myelinated axons in contact with Merkel cells found in the basal layer of the epidermis. Ruffini organs are present in the dermis and a Pacinian corpuscle in the deep dermis (or in subcutaneous tissue) (from Darian-Smith, 1984).
2. Sensory receptors of the somatosensory system

Cajal (1952, 1995 translation) provides a description of some of the sensory receptor organs belonging to the somatosensory system. Most of his emphasis is on the mechanoreceptors, presumably because of their large size and often elaborate organization. For example, Cajal shows drawings of several types of mechanoreceptors, including a Meissner corpuscle (Fig. 1I), a Pacinian corpuscle (Fig. 1II), a frog muscle spindle (Fig. 2I), and a Golgi tendon organ (Fig. 2II). Later work by others has highlighted additional types of cutaneous mechanoreceptors, such as Merkel disks and Ruffini organs (Fig. 1III; reviewed in Darian-Smith, 1984; Willis and Coggeshall, 2004) and has provided detail about the innervation of muscle, including the more complex muscle spindles found in higher vertebrates (Fig. 2III; see reviews by Barker, 1962; Matthews, 1972; Willis and Coggeshall, 2004).

Cajal also illustrated cutaneous free nerve endings that end in the dermis or that extend into the epidermis (Fig. 3). "Free nerve endings" of either finely myelinated axons (Aδ cutaneous or group III muscle and joint afferent fibers) or unmyelinated axons (C cutaneous or group IV muscle or joint afferent fibers) have been described much more fully by later investigators (Perl, 1984; Mense, 1996). Heppelmann et al. (1990, 1995) showed...
Fig. 3  
(I) Nerve endings in the epidermis of the paw skin in a kitten. Golgi method. The cornified epidermis is shown in panel A, the granular layer in panel B and the basal layer in panel C. Nerve fascicles in the dermis are seen in a, collaterals of these fibers in b, and terminals entering the epidermis in c and d (from Cajal, 1952, 1995 translation). (II) On the left are drawings of the “bare nerve endings” of two sensory receptors in the knee joint. One was a finely myelinated group III fiber and the other an unmyelinated group IV fiber. Terminal branches of these fibers are shown in the upper panels at the right. The axons have a series of swellings called “axon beads”, and the axon terminals are imbedded in Schwann cells along most of their length. However, the lower panel on the right shows that the axon membrane is exposed to the extracellular space along regions called “bare areas.” The surface membranes of the bare areas of the axons are thought to contain receptor sites containing transducer molecules and associated channels (from Schaible and Schmidt, 1996).
ultrastructural evidence that most of the surface membrane of such endings (Fig. 3II) is actually covered by the processes of Schwann cells. Only in restricted regions is the terminal membrane freely exposed to the extracellular space. It was suggested that such regions of membrane are likely to contain the receptors and channels that transduce sensory stimuli. Therefore, the term “free nerve ending” is an exaggeration.

The terminations of an Aδ mechanical nociceptor in the basal layer of the epidermis are illustrated in Fig. 4IA. Electrophysiological recordings from individual afferent axons during stimulation of their receptive fields have allowed afferent fibers to be classified as mechanoreceptors, thermoreceptors, or nociceptors (Perl, 1968; Bessou and Perl, 1969; Iggo and Ogawa, 1971). The responses depend on the transducer mechanism that is present in a particular sensory ending. Nociceptors were defined by Sherrington (1906) as receptors that respond selectively to stimuli that cause damage or threaten to cause damage. Some nociceptors selectively res-
pond to particular kinds of noxious stimuli, such as noxious mechanical or noxious thermal stimuli. Other nociceptors, such as the polymodal nociceptors, are activated by various combinations of intense mechanical, thermal (heat and/or cold), and/or chemical stimuli (e.g., Bessou and Perl, 1969; Torebjörk, 1974; see Willis and Coggeshall, 2004).

The responses of a mechanical nociceptor recorded in a monkey are shown in Fig. 4IB–D (Perl, 1968), and the receptive fields of 3 similar mechanical nociceptors are indicated in the drawings at the right in Fig. 4IE. The responses of a human C polymodal nociceptor to mechanical, thermal and chemical stimuli (Torebjörk, 1974) are illustrated in Fig. 4II. The receptive fields of several such receptors are shown on the drawing of the foot at the left. The human recordings were done using microneurography.

Although most mechanoreceptors are supplied by large or medium-sized myelinated fibers, some are associated with finely myelinated axons (e.g., afferents from down hair follicles; Brown and Iggo, 1967; Burgess and Perl, 1967) or even with unmyelinated axons (C mechanoreceptors; Iggo, 1960; Bessou et al., 1971). Conversely, although most nociceptors are associated with fine afferents, some have large myelinated axons (Burgess and Perl, 1967; Djouhri and Lawson, 1999). Thermoreceptors have small myelinated or unmyelinated axons (see Willis and Coggeshall, 2004).

Nociceptors are of particular interest because, when activated, they may evoke pain sensation. Morphological features are being found that allow the recognition of at least some types of nociceptors, and their electrophysiological responses help account for their properties. For example, cutaneous nociceptors often have TRPV1 receptors in their surface membranes. TRPV1 receptors are transducer molecules that respond to noxious heat, lowered pH and certain pain-provoking chemicals, notably capsaicin and resiniferotoxin (Caterina and Julius, 2001). Other cutaneous nociceptors contain TRPV2 receptors, which are activated by high intensities of noxious heat stimuli, but not by capsaicin or heat (Caterina et al., 1999). Acid-sensing ion channels (ASICs) are activated by lowered pH (Habelt et al., 2000; Immke and McCleskey, 2001; Sutherland et al., 2001). Other transducer molecules, perhaps belonging to the class of ENaC sodium channels (Price et al., 2000; García-Añoveros et al., 2001), appear to be responsible for the responses of nociceptors to strong mechanical stimuli.

Nociceptors can often be sensitized, with the consequence that they become much more sensitive to noxious stimuli or even to normally innocuous stimuli (Bessou and Perl, 1969; see review by Willis and Coggeshall, 2004). For example, Fig. 5B illustrates the enhancement of the responses of a C polymodal nociceptor that supplied monkey skin to graded heat stimuli before and 10 min after a mild burn (LaMotte et al., 1983). A parallel change in the human pain ratings associated with comparable heat stimuli is shown in Fig. 5A. Another example would be the nociceptors that can be called “silent nociceptors.” These are normally unresponsive to mechanical stimuli, but when sensitized, they become highly responsive to even very weak mechanical stimuli (Schaible and Schmidt, 1985, 1988; Handwerker et al., 1991; Meyer et al., 1991).

Sensitization of nociceptors is often the result of exposure of their terminals to irritant chemicals (such as capsaicin, formalin or mustard oil), to inflammatory mediators (bradykinin, prostaglandins and other products of arachidonic acid metabolism, growth factors such as nerve growth factor), or a variety of neurotransmitters (excitatory amino acids, neurokinins, serotonin, norepinephrine, histamine or other agents.

Fig. 5 – The records in panel A show the pain ratings given by a human subject who was exposed to a graded series of noxious heat stimuli applied to an area of skin on the arm. The pain ratings provide an estimate of the time course of the pain experienced during each stimulus. The lower records were taken before the skin was mildly burned in the stimulated area, and the upper records show the enhanced pain responses to the same stimuli after the burn. In panel B, recordings were made from a C mechanoheat (CMH) nociceptor in a monkey subjected to the same series of heat stimuli. The responses were enhanced and the heat threshold lowered by the burn (from LaMotte et al., 1983).
transducer molecules (Carlton and Coggeshall, 2001).

Sensitization of primary afferent nociceptors (also known as "peripheral sensitization") seems to depend in part on the activation of second messenger systems that cause the phosphorylation of transducer proteins, such as TRPV1, in the surface membranes of the receptors (Kress and Guenther, 1999; Bhave and Gereau, 2004; Cortright and Szallasi, 2004; see review by Willis, 2006) or an increased expression of such transducer molecules (Carlton and Coggeshall, 2001).

Like nociceptors, thermoreceptors are supplied by finely myelinated or unmyelinated afferent axons, and their responses have now been suggested to result from the activation of their own special transducer proteins. Warm receptors contain several TRP receptors, TRPV3 and TRPV4, which are activated by warming stimuli. Cold receptors contain TRPM8 and/or ANKTM1 (also known as TRPA1), which, respectively, respond to cooling (and menthol) and to cold (and to a variety of chemical substances) (Patapoutian et al., 2003; McKemy et al., 2002; Peier et al., 2002; Nealen et al., 2003; Bandell et al., 2004).

3. Dorsal root ganglia

Cajal (1952; 1995 translation) illustrates the developmental changes that he observed in vertebrate dorsal root ganglion cells as they progressed from a bipolar configuration to a pseudounipolar one (Fig. 6I). He discusses his theory that activity in neurons normally passes in only one direction, from dendrites through the cell body to the axon (“axopetal” functional polarity). Primary sensory neurons are the only neurons that have a direct connection with a sensory surface, such as the skin. When these cells have a bipolar form during development, the peripheral process conducts impulses toward the cell body, and the impulses are then conducted through the central process to the spinal cord. However, in the pseudounipolar dorsal root ganglion cells of adults, the nerve impulse can propagate from the peripheral process directly into the central process and thence to the spinal cord (Fig. 6II). This confers an advantage in that the conduction time for sensory propagation is minimized. Fig. 6II shows Cajal’s diagram of this mode of propagation in an adult mammalian spinal ganglion sensory cell (D and C). However, Cajal also shows in this drawing a “fiber giving rise to a pericellular arborization around the cell body of a ganglion cell” (Fig. 6IIE) that could evoke a discharge that passes along the central process (Fig. 6IIC) to the spinal cord (Fig. 6IIM). Cajal later states that “the cell body of spinal ganglion cells also receives impulses delivered by autonomic fibers,” and he illustrates such a connection in his Fig. 169. Baskets of sympathetic terminals have since been demonstrated in association with the cell bodies of dorsal root ganglion cells following peripheral nerve lesions (Fig. 6IIL; see McLachlan et al., 1993; Chung et al., 1996). Under such circumstances, it is possible for stimuli applied to the sympathetic nervous system to activate dorsal root ganglion cells (Devor et al., 1994). However, despite Cajal’s assertion, it is unclear that this arrangement occurs other than under pathological conditions.

Although Cajal admits the possibility under abnormal conditions of retrograde conduction in the axons of primary sensory neurons, the discovery of dorsal root reflexes (which are initiated at the synaptic terminals of primary afferents in the spinal cord and which then propagate antidromically out to the periphery) had to wait for many years (see review by Willis, 1999).

4. Dorsal root entry zone and Lissauer’s tract

Fig. 7I is a drawing by Cajal (1952; 1995 translation) of a cross-section of the visceral spinal cord. The entry of large afferents in the medial part of a dorsal root into the spinal cord dorsal horn is indicated in B; these afferents are also shown to contribute to the cuneate fasciculus (C). The lateral course of the fine afferents into Lissauer’s tract is seen in F. Terminals of the large afferents course into the neck of the dorsal horn (c) and into the ventral horn (h) whereas the fine afferents are destined for the substantia gelatinosa (a) and the head of the dorsal horn (b).

More details concerning the large afferent projections are seen in Fig. 7II. Collaterals reaching the intermediate nucleus are shown on the left in A and on the right in B; terminals in the head of the dorsal horn in panel C, and “deep” terminals in the substantia gelatinosa in c. A “sensory-motor” bundle is shown in a, as well as “arborizations in the motor nucleus” in B. The destination of fine afferents is seen more clearly in Fig. 7III, where they pass from the dorsal root (A) laterally through the marginal plexus (B), while giving off collaterals (C), that terminate in the substantia gelatinosa.

The path followed by fine afferent fibers of the dorsal root into Lissauer’s tract has been described by a number of investigators (Lissauer, 1885; Ranson and Billingsley, 1916; Sindou et al., 1974). However, Lissauer’s tract includes not only primary afferent fibers but also the axons of neurons intrinsic to the dorsal horn (Coggeshall et al., 1981).

Studies utilizing anterograde axonal transport of markers injected intracellularly into large myelinated afferent fibers indicate that the axons shown in Fig. 7II include group Ia and II fibers from muscle spindles that terminate in the intermediate region and motor nucleus and group Ib fibers from Golgi tendon organs that end in the intermediate nucleus (Brown, 1981; Brown and Fyffe, 1978, 1979; see Willis and Coggeshall, 2004). The axons that terminate in the neck of the dorsal horn would include a variety of mecanoreceptors. Those that recurve dorsally from the neck of the dorsal horn to end more superficially are likely to be hair follicle afferents (Brown et al., 1977). A difficulty in much of Cajal’s work is that he often used material from very young animals. This may have led to misinterpretation of what arrangements persist into adulthood. However, it has been shown in electrophysiological experiments that neurons in lamina II can be activated either by noxious or innocuous mechanical stimuli (Kumazawa and Perl, 1976, 1977, 1978). The recordings were from interneurons, since the cells could not be activated antidromically from rostral levels of the spinal cord. The input from mecanoreceptors to neurons of the substantia gelatinosa may have been relayed through dorsal horn circuits or perhaps by fine
terminal branches of mechanoreceptors not readily visualized at the light microscopic level.

Light and Perl (1979) injected Aδ (group III) axons intracellularly with an anterograde marker. Figs. 8A and B show the distribution pattern of the terminals of two different Aδ mechanical nociceptors in the dorsal horn, and Fig. 8C shows the endings of an axon that supplied a down hair follicle receptor.

Fig. 6 – Panel I is a drawing by Cajal of a longitudinal section through a dorsal root ganglion from a chick embryo, stained by the reduced silver nitrate method. Unipolar dorsal root ganglion neurons are indicated by A and B. Forms transitional between uni- and bipolar neurons are indicated by C, D, F, and G. A bipolar neuron is pointed out by E. Panel II shows the direction of nerve impulse propagation in a dorsal root ganglion neuron. A is the cell body of the neuron, B is the unipolar neurite, C the central process, and D the peripheral process. E is a nerve fiber forming a pericellular arborization around the ganglion cell soma; this nerve fiber presumably originates from a sympathetic ganglion. The sensory receptor terminals at P are in the skin, and the central terminals at M are in the spinal cord. The arrows show the direction of action potential propagation. (Panels I and II are from Cajal, 1952, 1995 translation.) Panel III illustrates a sympathetic pericellular arborization (stained for tyrosine hydroxylase) around a large dorsal root ganglion neuron in an animal with a peripheral neuropathy (Chung et al., 1996).
Since it is very difficult to make intracellular impalements of unmyelinated afferent fibers, Sugiura’s group instead injected an anterograde marker into individual cell bodies of dorsal root ganglion cells in a small animal, the guinea pig. They were then able to follow the afferent fibers to their terminals in the dorsal horn. Fig. 9I shows the pattern of terminations of a cutaneous C polymodal nociceptor in laminae I and II of the dorsal horn (Sugiura et al., 1986), and Fig. 9II illustrates the more widespread distribution of the terminals of a visceral C afferent fiber. Visceral afferent nociceptors were found to be distributed rostrocaudally over as many as six segments, in contrast to cutaneous no-
ciceptors, which had a more limited longitudinal distribution (Sugiura et al., 1989).

5. Dorsal horn neurons

Cajal (1952, 1995 translation) was able to distinguish between a number of different kinds of neurons in the spinal cord dorsal horn using the Golgi stain. In Fig. 10IA is his illustration of a large neuron in lamina I, the marginal zone. This type of cell is often called a Waldeyer cell, after the person who described such neurons in the spinal cord of the gorilla (Waldeyer, 1888). Other, smaller neurons are also found in lamina I (Lima and Coimbra, 1988; Zhang and Craig, 1997; Zhang et al., 1996). Cajal also illustrated several types of neurons that he saw in the substantia gelatinosa, including "limiting" and "central" cells (Figs. 10IIC and D). These were renamed "stalked" and "islet" cells, respectively, by Gobel (1978) in his investigation of the neurons of the spinal nucleus of the trigeminal, pars caudalis.

According to Gobel, the dendrites of stalked cells descend from the cell body ventrally into deeper parts of lamina II and into lamina III and even IV. The axon has terminations in lamina I. The dendrites of islet cells are oriented longitudinally in lamina II, and their axons project for a distance of up to 1 mm and end within lamina II. Also shown in Figs. 10IB and IIA are several "antenna neurons" (Schoenen, 1982) whose cell bodies are in deep layers of the dorsal horn, but whose dendrites ascend dorsally into lamina II and even into lamina I. Retrogradely labeled neurons belonging to the spinothalamic tract (Fig. 10III; Surmeier et al., 1988) and the postsynaptic dorsal column pathway (Fig. 10IV; Brown and Fyffe, 1981) often have such dorsally projecting dendrites.

6. Tracts ascending from the spinal cord to the brain

A number of tracts originate in the spinal cord and ascend to the brain (see Willis and Coggeshall, 2004; Willis and
Some of these tracts are involved in sensory functions, whereas others operate at a subconscious level and often influence motor functions (e.g., the dorsal and ventral spinocerebellar tracts). Several of the ascending tracts that convey sensory information to the brain include the spinoreticular, spinomesencephalic, and spinohypothalamic tracts. These pathways are likely to participate in motivational-affective behaviors, including arousal and attention, as well as in somatic motor, autonomic and endocrine responses. Somatosensory discrimination appears to depend on the dorsal column-medial lemniscus system (including the postsynaptic dorsal column pathway), the spinocervicothalamic pathway, and the spinothalamic tract. Various types of pain responses are triggered by activation not only of the

Fig. 9 – Panel I shows the projection of a cutaneous C polymodal nociceptor into the spinal cord of a guinea pig. Phaseolus leukoagglutinin (PHA-L) was injected intracellularly into the soma of the dorsal root ganglion neuron that gave rise to the axon; the label was allowed to be transported centrally and then the axon was followed into the spinal cord histologically. The terminals were mostly in laminae I and II, as shown in panels A and B at different magnifications (from Sugiura et al., 1986). Panel II shows the projection of a visceral afferent C fiber into the spinal cord. The soma of the DRG neuron was injected with PHA-L, as in panel I, and followed histologically. The endings were in several laminae, and branches of the axon crossed to the contralateral side of the cord. The axon was distributed over 6 segments (from Sugiura et al., 1989).
Fig. 10 – Panel I shows a drawing by Cajal (1952; 1995 translation) of several neurons in the dorsal horn of the spinal cord in a chick embryo stained by the Golgi method. A is a large, horizontally disposed neuron in the marginal zone that can be considered a “Waldeyer” cell of lamina I. B is another large neuron whose cell body is located in the head of the dorsal horn and whose widely dispersed dendrites include branches that extend dorsally into laminae I and II. The axons of both of these neurons, a and b, are shown to enter the lateral funiculus. Another neuron, C, is located in the interstitial nucleus of the lateral funiculus, presumably in what is now known as the lateral spinal nucleus. Its axon, c, follows a medially directed course. Panel II is a transverse section of the cervical spinal cord of a newborn kitten, stained using the Golgi method. A variety of types of neurons are depicted by Cajal. A is a large neuron whose cell body is in the deep layers of the dorsal horn. It has dendritic projections that extend dorsally into the substantia gelatinosa. Its axon, a, extends laterally in the direction of the lateral funiculus. Neurons of the substantia gelatinosa include a limiting cell, C and a central cell, D. The axon terminals indicated by F are collaterals of axons that first enter the deep dorsal horn and then recurve to end in the substantia gelatinosa. (Panels I and II are from Cajal, 1952; 1995 translation.) Panel III illustrates a spinothalamic tract neuron in the dorsal horn of a monkey. The neuron was injected intracellularly with horseradish peroxidase. Its dendrites ramify widely in the dorsal horn, and include branches that ascend into laminae I and II. The axon, arrow, crossed the midline near the level of the cell body. The responses of this neuron to graded intensities of mechanical stimuli are shown below the drawing of the foot; the drawing shows the receptive field in black. The spinothalamic neuron responded to tactile, as well as to noxious, mechanical stimuli. (Panel III is from Surmeier et al., 1988.) Panel IV is a reconstruction of a postsynaptic dorsal column neuron. The cell body was in lamina III, and the dendritic tree extended dorsally into lamina I. The axon (dashed line) passed medially to enter the dorsal column (from Brown and Fyffe, 1981).
spinothalamic and spinoreticular tracts, but also of the postsynaptic dorsal column pathway, and the spinocervical, spinoparabrachial, and spinoamygdalar tracts. A surprising recent finding is that visceral nociception depends more on the postsynaptic dorsal column pathway than on the spinothalamic tract (Fig. 12; Hirshberg et al., 1996; Al-Chaer et al., 1996a,b, 1998, 1999, Wang et al., 1999; Willis et al., 1999; Nauta et al., 2000; Houghton et al., 2001; Palecek et al., 2002), although the latter does convey information concerning painful visceral stimuli (Milne et al., 1981; Al-Chaer et al., 1999). Of especial interest is that midline myelotomies in humans that interrupt axons presumably belonging to this postsynaptic dorsal column visceral pain system relieve the pain associated with pelvic cancer (Hirshberg et al., 1996; Nauta et al., 1997, 2000).

Cajal had little to say about somatosensory pathways that ascend to the brain from the spinal cord. Most of these pathways were discovered only after anterograde and retrograde tracing techniques became available. However, Cajal does illustrate the dorsal column-medial lemniscus pathway (and also the lateral corticospinal tract), as shown in Fig. 11. Cajal states that the “somatosensory pathway or medial lemniscus of Reil terminates entirely in the ventral nucleus [of the thalamus], and its freely ending terminal arborizations contact particular cells that give rise to the rostral or thalamocortical somatosensory pathway.” (This opinion was based on observations on the brains of the mouse and the rabbit in Golgi preparations.) Neurons with short axons were found by Cajal “only in the somatosensory nucleus of the cat” (apparently not in that of mice). The recently described dorsal column visceral pain pathway is shown in Fig. 12.

It appears that Cajal (1995 translation; see also Cajal, 1933) did not recognize the existence of a spinothalamic tract, although this pathway had been described in the late 1880s by Edinger (1889, 1890) and by Mott (1895). The likely role of the spinothalamic and associated tracts that ascend in the anterolateral white matter of the spinal cord in pain has been inferred from observations made by many clinical investigators (e.g., Brown-Séquard, 1860; Foerster and Gagel, 1932; Head and Thompson, 1906; Spiller, 1905; Spiller and Martin, 1912; Gybels and Sweet, 1989). The discoveries of other pathways that may contribute to pain sensation were made at much later times (for example, the spino-cervicalthalamic pathway by Morin (1955); the postsynaptic dorsal column pathway by Uddenberg (1968); the spino-parabrachioamygdaloid pathway by Bernard and Besson (1990), and several spino-limbic pathways by Giesler and his colleagues, including the spino-hypothalamic tract (Burstein and Giesler, 1989; Burstein et al., 1987, 1990; Cliffer et al., 1991)). Details concerning these pathways are reviewed in Willis and Coggeshall (2004).

7. Summary and conclusions

In his major work on the Histology of the Nervous System of Man and Vertebrates, Santiago Ramón y Cajal discusses a number of structures belonging to the somatosensory system, including structures since shown to be involved in responses to painful stimuli. However, later work has greatly expanded on the work of Cajal, in large part because of the introduction of a number of experimental approaches that were not available to him.

Cajal describes some of the sensory receptors that signal information derived from stimuli applied to the body surface or to deep tissues, such as muscles. However, more recent
observations have led to the discovery of additional sense organs and to electrophysiological and behavioral studies that have helped to demonstrate the functional role of the various somatosensory receptors.

With respect to pain mechanisms, important findings include the characterization of several types of nociceptors (receptors that specifically respond to noxious stimuli), the observation that these receptors contain transducer molecules, such as TRPV1 (the capsaicin receptor), TRPV2 and acid-sensing ion channels (ASICs), which allow the nociceptors to respond to particular kinds of noxious stimuli. Another major advance is an analysis of the possible mechanisms by which nociceptors can be sensitized and hence altered in such a way as to respond more vigorously to stimuli. Of particular note are the sensitizing actions of inflammatory mediators, such as bradykinin, prostaglandins and other chemical substances.

Thermoreceptors have also been shown to contain transducer molecules that allow them to detect warming or cooling stimuli. These include TRPV3 and TRPV4, which are activated by warming, and TRPM8 and ANKTM1, which are activated by cooling or noxious cold (as well as by certain chemical substances).

Cajal relates the morphology of the cell bodies of primary afferent neurons in the dorsal root ganglia to his theories of functional polarity of neurons. He mentions his observation that some dorsal root ganglion cells are contacted by pericellular arborizations that appear to derive from postganglionic sympathetic nerve fibers. Such arborizations have since been described following peripheral nerve injuries. Experiments have shown that stimulation of sympathetic nerves can activate some dorsal root ganglion neurons in neuropathic animals, presumably in part because of such connections. However, it is unclear if such connections occur in the absence of pathology.

Large afferents are observed to enter the spinal cord through the medial part of the dorsal roots, whereas fine afferent fibers enter through the lateral part and then enter Lissauer’s tract. The large afferents project into the deep layers of the dorsal horn and or into the ventral horn, whereas most fine afferents terminate in laminae I and II. These observations have been enlarged upon in more recent studies in which an anterograde label has been injected intracellularly into the axons, allowing identified primary afferent axons to be traced to their terminals. The afferents that have been traced in this fashion include Aβ and Aδ afferents from the skin and groups Ia, Ib and II fibers from stretch receptors. The projections of unmyelinated (C) afferent fibers have also been traced, but in a more indirect way. The anterograde label is injected into the identified cell bodies of dorsal root ganglion cells, and then the label is traced into the spinal cord to the terminals. It is desirable to do such experiments in a small animal, such as the guinea pig, so as to minimize the distance required for anterograde axonal transport of the label.

Cajal was able to demonstrate a number of different types of neurons in the dorsal horn, using the Golgi stain. These included marginal neurons (Waldeyer cells), limiting and central cells of the substantia gelatinosa, and neurons of the deep dorsal horn whose dendrites extend dorsally into the

**Fig. 12** – Representation of the dorsal column visceral pain pathway. A representative nociceptive visceral afferent from a pelvic visceral organ, the colon, is shown to enter the lumbosacral spinal cord over a dorsal root at L6-S1 and synapses on postsynaptic dorsal column (PSDC) neurons. The PSDC neurons project rostrally in the midline dorsal column to synapse in the medial part of the nucleus gracilis. A comparable nociceptive visceral afferent fiber from the stomach projects to the thoracic spinal cord, where it synapses on PSDC neurons that project to the junction of the gracile (Gr) and cuneate (Cu) nuclei. These axons are at the boundary between the gracile and cuneate fasciculi. The neurons in the dorsal column nuclei that receive noxious visceral input then project contralaterally through the medial lemniscus to the ventral posterolateral nucleus of the thalamus (Th) (from Willis et al., 2004).
superficial dorsal horn. Some of the latter neurons have since been shown to be spinothalamic or postsynaptic dorsal column neurons.

Cajal provides an accurate picture of the course of the dorsal column-medial lemniscus pathway in the spinal cord, through the brain stem and to its termination in the thalamus. Work by others has led to a description of the spinothalamic tract and of other pathways that convey somatosensory information (including pain) to the brain.

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