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Review

Spinal ascending pathways for somatosensory information processing

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The somatosensory system processes diverse types of information including mechanical, thermal, and chemical signals. It has an essential role in sensory perception and body movement and, thus, is crucial for organism survival. The neural network for processing somatosensory information comprises multiple key nodes. Spinal projection neurons represent the key node for transmitting somatosensory information from the periphery to the brain. Although the anatomy of spinal ascending pathways has been characterized, the mechanisms underlying somatosensory information processing by spinal ascending pathways are incompletely understood. Recent studies have begun to reveal the diversity of spinal ascending pathways and their functional roles in somatosensory information processing. Here, we review the anatomic, molecular, and functional characteristics of spinal ascending pathways.

Highlights

The somatosensory system detects and processes diverse types of information from the external and internal environment, and is critical for animal survival.

The ascending pathway originating from spinal projection neurons is crucial for transmitting the various subtypes of somatosensory information to multiple brain areas, and is involved in perception, emotion, motivation, and cognition.

Although most spinal projection neurons target contralateral brain regions, spinal projection neurons with bilateral targets have also been described.

The diverse projection patterns of spinal projection neurons are likely determined by their molecular properties.

Given the heterogeneity of spinal projection neurons, it is possible that different subpopulations of spinal projection neurons and spinal ascending pathways are differentially involved in diverse submodalities of somatosensation and its distinct components.

Spinal ascending pathways of the somatosensory system

The somatosensory system has important roles in processing diverse types of sensory information and, thus, is critical for detecting potential danger and maintaining the integrity of the organism. It encodes spatial, temporal, and intensity dimensions for discriminative modalities, and also carries information about the affective component.

The peripheral and spinal mechanisms underlying somatosensory processing have been well studied. At the peripheral level, the molecular mechanisms underlying the signal transduction of mechanical, thermal, and chemical stimuli have been identified. Transient receptor potential (TRP) channels and piezo channels are important for thermal and mechanical signal transduction, respectively [1–4]. G-protein-coupled receptors (GPCRs) expressed in primary sensory fibers have been shown to be involved in chemical signal transduction [5–7]. Distinct neuronal subtypes have been defined by transcriptomic studies in sensory ganglia [8–10]. Some of these have been shown to be involved in processing diverse modalities of somatosensory information. At the spinal level, the gate control theory of pain has been proposed [11,12], and recent studies have revealed critical components of the neural circuit for processing nociceptive information [13,14]. In addition, several distinct groups of excitatory interneuron, including spinal gastrin-releasing peptide receptor-positive (GRPR$^+$) interneurons and urocortin 3-positive (Ucn3$^+$) interneurons, have been identified to be important for transmitting chemical and mechanical itch [15–17], and have been shown to be tightly gated by local inhibitory neurons [13,14,18–20]. Progress in understanding the mechanisms underlying periphery and spinal neural circuit of pain, itch, touch, and temperature has been reviewed elsewhere [21–27]. One of the most important nodes of the somatosensory system is the spinal projection neuron, a key element in the pathway conveying somatosensory information from the spinal cord to the brain. In addition, anatomic and electrophysiological studies have revealed supraspinal targets of spinal ascending pathways and their important roles in processing of touch, temperature, pain, and itch [28–34].

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Here, we review the spinal ascending pathways from anatomical, molecular, and functional perspectives. We also discuss important roles of the ascending pathways in somatosensory processing, including sensory discrimination, as well as affective and motivational components of somatosensation. Early anatomical and electrophysiological studies exploring the properties of spinal projection neurons were often carried out in rats, cats, and, sometimes, nonhuman primates. However, because many molecular markers are identified in mice and many transgenic mouse lines are available, most recent studies of the function of spinal projection neurons have been performed in mice. In this review, we discuss studies from these different species.

Anatomical features of spinal ascending pathways

Spinal projection neurons are widely distributed in the spinal dorsal horn. Early studies in rats, cats, and monkeys determined the soma distribution pattern of spinal projection neurons using retrograde approaches [21,31,35–39]. Spinal projection neurons are primarily located in the superficial layer (lamina I) of the spinal dorsal horn, with some scattered throughout deep layers (lamina III–VIII, X) and the lateral spinal nucleus (LSN). Spinal projection neurons in lamina I and lamina III–V exhibit morphological heterogeneity in their somatodendritic architecture. There are at least three subtypes of lamina I projection neurons classified based on their morphology, including pyramidal (~10%), fusiform (~80%), and multipolar (or flattened, ~10%) neurons [32,40–43], whereas lamina III–V projection neurons are mainly multipolar [44–46] (Figure 1). Spinal projection neurons send axonal projections to multiple brain areas, and the projection pattern of spinal projection neurons has been examined extensively (Figure 1). The axons of most spinal projection neurons cross the midline to the anterolateral funiculus and terminate in many brain areas, including the forebrain, pons, midbrain, and medulla [47–52]. Whereas most spinal projection neurons project to contralateral brain regions, a small population sends ascending axons to bilateral brain areas [35,49].

The thalamus is one of the primary targets of spinal projection neurons, which mainly project to the contralateral thalamus. Most studies of spinal ascending pathways focused on the superficial (lamina I) spinal dorsal horn. Afferent fibers originating from spinal projection neurons in lamina I in rats and monkeys mainly terminate in the ventral posterolateral nucleus of the thalamus or the ventral posteromedial nucleus of the thalamus (VPL/VPM), posterior group thalamic nuclei (Po), the posterior triangular thalamic nucleus (PoT), ventral posterior parvicellular (VPPC) thalamic nuclei, and ventral medial nucleus (VMpo) [37,48,49,53,54]. These pathways are likely involved in encoding the spatial, temporal, and intensity aspects of somatosensation, because these thalamic regions act, in part, as relay stations to convey information to somatosensory cortex [55].

The ascending pathway from superficial spinal cord of rodents also extensively terminates in the pons, midbrain, and medulla [47,49,51,52,56,57]. Terminals of superficial spinal projection neurons are found bilaterally in several nuclei in the pons and midbrain [49]. In the pons, dense terminals of spinal projection neurons terminate in the parabrachial nucleus (PBN) [47,49,51,52,57] and the caudal part of the pontine reticular nucleus (PnC) [49]. The somatosensory projection from spinal cord to the PBN is topographically organized [51]. Neurons in the superficial dorsal horn of cervical segments project not only specifically to the external part of the lateral PBN, (LPBE), but also to other lateral PBN nuclei, albeit more sparsely. By contrast, neurons in superficial dorsal horn of thoracic and lumbar segments project mainly to the dorsal part (LPBD) and central part (LPBC) of lateral PBN [47]. In the midbrain, moderate terminals of spinal projection neurons are distributed in the cuneiform nucleus (CnF) [49], the lateral and ventrolateral parts of the periaqueductal gray (PAG) and the intermediate gray layer of the superior colliculus (InG). In the medulla, the caudal ventrolateral medulla (CVLM) and the nucleus of the solitary tract (NTS) also receive dense projections from the spinal cord [21,35,56,58].

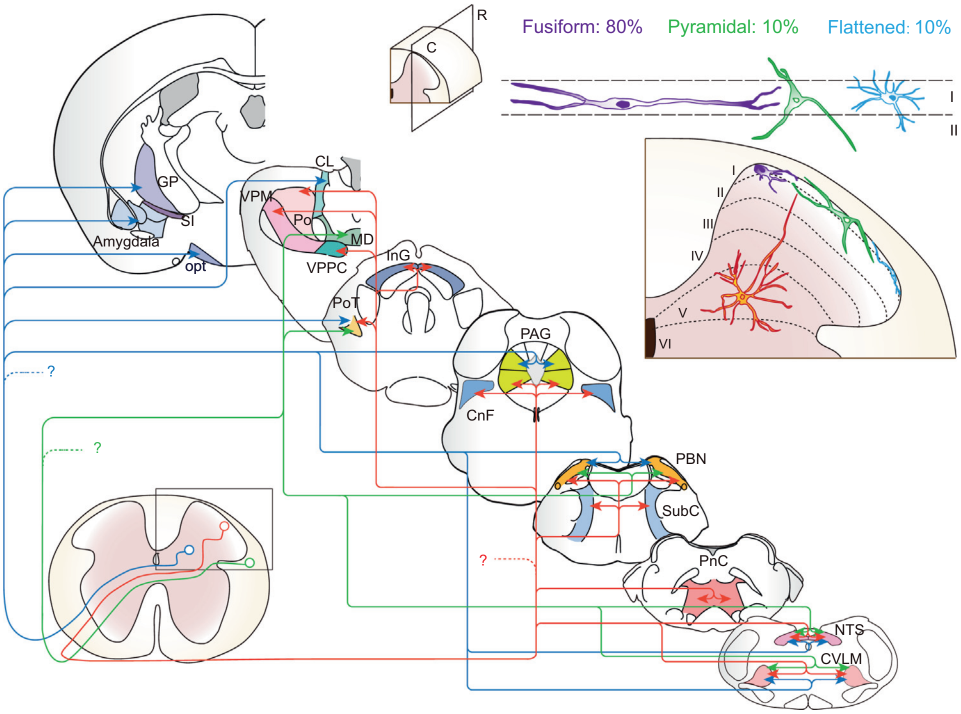

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Figure 1. Anatomical features of spinal projection neurons. Somatodendritic architecture of projection neurons in the superficial and deep layer of the spinal dorsal horn (upper right). Anatomical data of spinal projection neurons was obtained from mice, rats, cats, as well as monkeys. In the superficial layer, there are three major categories of spinal projection neuron: fusiform (purple); pyramidal (green); and multipolar (or flattened, blue) neurons. Projection neurons in lamina III–V are mainly multipolar (orange). The dendrites of some of these neurons extend up to lamina I. The schematic sections through the rodent brain illustrate the different connectional patterns of projection neurons in superficial dorsal horn (red), deep lamina (blue), and lateral spinal nucleus (LSN; green, left bottom). Abbreviations: CL, central lateral nucleus of the thalamus; CnF, cuneiform nucleus; CVLM, caudal ventrolateral medulla; GP, globus pallidus. InG, intermediate gray layer of superior colliculus; MD, mediodorsal thalamus; NTS, nucleus of solitary tract; PAG, periaqueductal gray; PBN, parabrachial nucleus; PnC, caudal part of pontine reticular nucleus; Po, posterior group thalamic nuclei; PoT, posterior triangular thalamic nucleus; SI, substantia innominata; SubC, subcoeruleus nucleus; VPM, ventral posteromedial nucleus; opt, optic tract; VPPC, ventral posterior nucleus, parvicellular part.

Spinal projection neurons in LSN and deep lamina have different projection patterns compared with projection neurons in superficial lamina. Projection neurons of rats in LSN send projections to mediodorsal thalamus (MD) [48,49]. Neurons in deeper lamina mainly project to the central lateral nucleus of the thalamus (CL) and have moderate projection to the PoT, with only weak projection to the remaining thalamic nuclei [48]. Furthermore, spinal projection neurons in deep lamina project substantially to the substantia innominate (SI) and the globus pallidus (GP), with weaker projection to the amygdala and hypothalamus. Given that these brain regions are important for emotion and motor processing, this projection pattern suggests that projection neurons in deep lamina are related to the emotional and motor components of pain and itch [48,49,53]. In addition, spinal projection neurons in deep lamina and LSN also innervate regions in the pons, midbrain, and medulla [30,36]. Projection neurons in LSN of all spinal segments project almost exclusively to the internal part of lateral PBN (LPBI) [47], suggesting a topographic organization. Since spinal projection neurons in superficial and deep lamina have different targets in the forebrain, including the thalamus and the pallidum [48], it will be interesting to define how spinal projection neurons in the deep lamina are differentially involved in processing diverse components of somatosensation.

Quantitative studies have investigated the projection pattern of spinal projection neurons, and suggest that most individual spinal projection neurons innervate multiple brain areas with diverse projection patterns [30,35,37]. A retrograde tracing study in rats showed that ~85% of spinal projection neurons in lumbar spinal lamina I can be labeled from either the CVLM or LPB, and >90% of projection neurons that project to PAG also send axons to CVLM or LPB [35]. All spinothalamic lamina I neurons could also be virtually retrogradely labeled from LPB, and more than one-third could be labeled from PAG. These thalamus-projecting neurons have larger somas than those that project to PBN, and most are multipolar [30]. In addition, retrograde labeling experiments showed that ~90% of spinal neurons labeled from ipsilateral PBN are also labeled from contralateral PBN [35,44], suggesting a bilateral projection pattern of some spinal projection neurons. However, traditional tracing methods using anterograde and retrograde tracers cannot provide a complete picture of organizing principles of spinal projection neurons at a single cell resolution. Determining the connectome of spinal projection neurons at a single cell resolution with newly developed technologies, including fluorescence micro-optical sectioning tomography (fMOST) [59] and brain-wide individual animal connectome sequencing (BRICseq) [60], would help to reveal the wiring principle of spinal projection neurons.

Molecular features of spinal projection neurons

Several molecular markers have been identified for multiple subtypes of spinal projection neuron. The neurokinin 1 receptor (NK1R) marks ~80% of projection neurons in lamina I of rodents [21,35,36,61]. A recent study in mice found the number of GPCR83-positive (Gpr83$^+$) spinoparabrachial (SPB) neurons was comparable with NK1R$^+$ SPB neurons, and that these two population were largely nonoverlapping [62]. Gpr83$^+$ and NK1R$^+$ spinal projection neurons innervate the pons, thalamus, and most subregions of the midbrain and medulla with similar patterns, whereas NK1R$^+$ neurons send more axons to InG and Gpr83$^+$ neurons uniquely innervate the dorsal fold of the dorsal accessory olive (DAOdf) [61–63]. In addition, Gpr83$^+$ and NK1R$^+$ neurons that innervate the thalamus, midbrain, and PBN are likely distinct populations [62]. Preprotachykinin 1 also marks a population of spinal projection neurons (Tac1-lineage neurons, referred to as Tac1$^+$ neurons hereafter) that may correspond to the small subset of spinal projection neurons that express both NK1R and Gpr83 [61,62]. A recent study in mice found that fibers of Tac1$^+$ neurons pass through the area lateral to LPBE and the dorsoventral lateral PBN (PBdvl) and terminate in the superior lateral PBN (PBsl) [61]. Tac1$^+$ spinal projection neurons also project to the medial thalamic complex with rare innervation in VPL [61], suggesting the unique projection patterns of different spinal projection neurons. Recent single cell RNA-sequencing studies in mice also identified several important molecular markers of spinal neurons, including LY6/PLAUR domain-containing 1 (Lypd1), and zinc finger homeobox 3 (Zfhx3) [64,65]. Lypd1 marks SPB neurons with greater reliability than does NK1R, whereas the projection patterns of Lypd1$^+$ spinal projection neurons remain unknown [65]. Zfhx3$^+$ spinal neurons of mice were shown to innervate the lateral reticular nucleus, thalamus, and cerebellum [64]. Additional molecular markers of NK1R$^+$ SPB neurons of mice, including cholecystokinin (Cck), neuronal pentraxin 2 (Nptx2), neuromedin (Nmb), and corticotropin-releasing hormone (Crh), have also been recently identified [66]. However, because these genes are also expressed in spinal interneurons neurons, it is still challenging to specifically label subpopulations of spinal projection neurons.

Functional roles of the spinal ascending pathways

The diverse anatomical and molecular features of spinal projection neurons provide the basis for their functional roles in encoding and processing different modalities of somatosensory information. Here, we summarize recent progress in understanding the functional roles of spinal ascending pathways that convey diverse somatosensory information.

The spinothalamic pathway

The spinothalamic pathway was traditionally thought to be important for sensory-discriminative components of somatosensation (Figure 2). Early electrophysiological studies examined the coding properties of spinothalamic tract (STT) neurons. Electrophysiological recordings in rats showed that STT neurons respond to noxious mechanical stimulation [67,68], consistent with results obtained in cats [69]. STT neurons also participate in temperature processing, as evidenced by the finding that these neurons in cats can be activated by thermal stimulation [69]. In line with this, spinal cord lamina I neurons projecting to the VMpo of the monkey also respond to innocuous cooling stimulation [54]. In primates, STT neurons were shown to respond

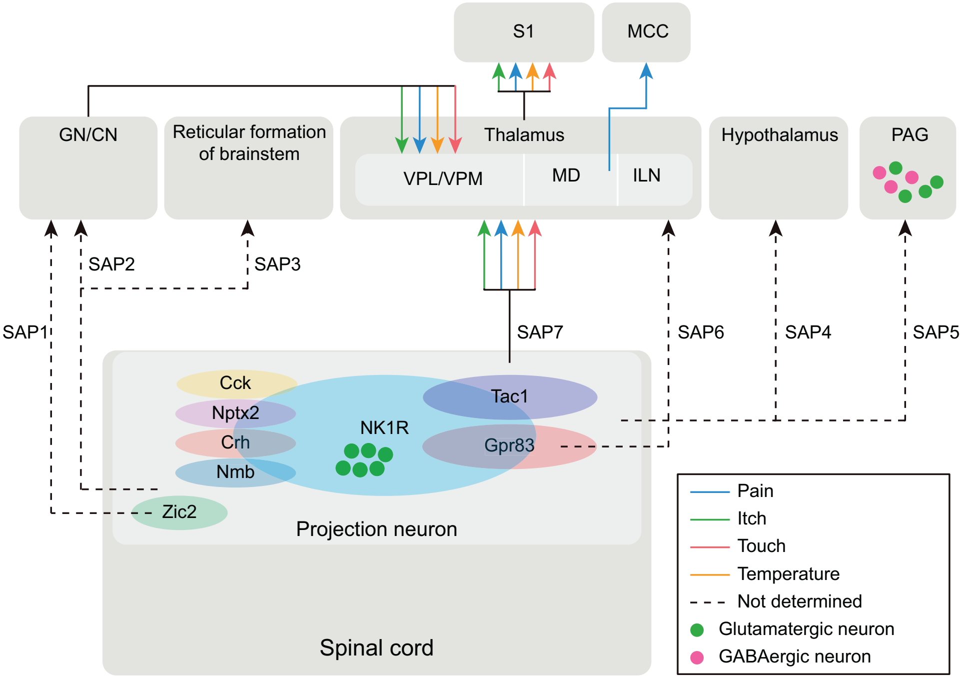

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Figure 2. Major spinal ascending pathways that process sensory components of somatosensation. For clarity, ascending pathways are numbered (e.g., spinal ascending pathway 1, SAP1), and some of their properties are discussed below. Zic family member 2 (Zic2)-positive postsynaptic dorsal column (PSDC) neurons are sensitive to light touch stimuli and, thus, may convey sensory information of touch to either the gracile (GN) or cuneate nucleus (CN) (via SAP1). PSDC neurons also respond to noxious stimuli, suggesting that the PSDC–GN/CN pathway (SAP2) may transmit sensory information of pain, although the molecular identities of these neurons have not yet been determined. Sensory information of various modalities is further sent from the GN/CN to the ventral posterolateral nucleus of the thalamus or the ventral posteromedial nucleus of the thalamus (VPL/VPM). The spinoreticular pathway (SAP3), spinohypothalamic pathway (SAP4), and spino-PAG pathway (SAP5) respond to various somatosensory modalities, but direct evidence is largely lacking to support the notion that they are involved in processing sensory components of somatosensation. The spinothalamic pathway (SAP7) has been demonstrated to transmit the sensory information of pain, itch, touch, and temperature. In turn, the thalamus sends somatosensory information to higher order brain areas. In addition, G-protein-coupled receptor 83-positive (Gpr83$^+$) spinal projection neurons send axon to the thalamus (SAP6), but the role of this pathway in sensory components of somatosensation processing remains unclear. Solid lines represent the spinal ascending pathways involved in sensory components of different somatosensory modalities. Dashed lines represent spinal ascending pathways the functions of which in processing specific components of somatosensory information remain unclear. The arrows that originate from individual cluster of projection neurons represent spinal ascending pathways labeled by specific molecular markers (such as Tac1, Gpr83, and Zic2). The arrows that originate from the large gray box of projection neurons represent spinal ascending pathway without cell specificity. Abbreviations:Cck, cholecystokinin; Crh, corticotropin-releasing hormone; ILN, intralaminar thalamic nuclei; NK1R, neurokinin 1 receptor; Nmb, neuromedin; Nptx2, neuronal pentraxin 2; MD, mediodorsal thalamus; MCC, midcingulate cortex; NK1R, neurokinin 1 receptor; Nmb, neuromedin; Nptx2, neuronal pentraxin 2; PAG, periaqueductal gray; S1, primary somatosensory cortex; Tac1, preprotachykinin 1.

to capsaicin application [70], further supporting the critical role of the spinothalamic pathway in pain processing. Periphery injury could evoke hyperexcitability in the spinothalamic pathway and thalamus of rats [71–73], suggesting that this ascending pathway contributes to chronic pain. In addition, STT neurons of primates also process pruritic information, because they also respond to histamine and cowhage [74]. Recently, by using a dual retrograde tract-tracing strategy combined with immunohistochemical staining in mice, spinal projection neurons targeting the dorsal midline/intralaminar thalamic complex (dMITC) were demonstrated to be activated by histamine [75], supporting the critical role of the spinothalamic pathway in itch processing. Together, these data demonstrate that the spinal ascending pathway conveys pain, itch, touch, and temperature information to the thalamus.

One of the key questions is how spinal projection neurons process different submodalities of somatosensation. A study using extracellular recordings in cats found that a distinct class of STT neurons were selectively excited by histamine [76], suggesting that there is a subpopulation of STT neurons that selectively transmit itch information. A study in primates also described a small population of lamina I STT projections to Vmpo that specifically respond to cooling stimulation [54]. These results suggest that there are some modality-specific STT neurons, which is in line with the ‘labeled-line’ theory [26]. However, another study in monkeys showed that pruriceptive neurons were also sensitive to gentle stroking and noxious stimulation [70], indicating that STT neurons are polymodal. This is also observed in several other studies in rats and cats [68,69], supporting the notion that STT neurons encode different submodalities of somatosensation with a population coding approach. Thus, the coding principle of somatosensory information needs further investigation. However, these electrophysiological recording studies were conducted in anesthetized animals and, thus, it remains to be examined whether this is also the case in awake animals.

The projection from the spinal cord to the thalamus also processes affective and motivational components of somatosensation (Figure 3). Optogenetic activation of terminals derived from spinal Tac1^{+} neurons around the medial thalamus evoked avoidance behaviors in mice, which provides direct evidence to support the idea that this pathway has an important role in the negative affective component of somatosensation [61]. Anatomically, this is supported by the connection patterns of the medial thalamus, which sends projections to prefrontal cortical areas, the midbrain, and limbic system [77]. The MD receives nociceptive inputs from the spinal cord and is the major sources of nociceptive information to the anterior cingulate cortex (ACC), which has been demonstrated to be crucial for the negative affect of pain in both mice and humans [78,79]. In addition, a study in mice showed that the projection from MD to ACC contributes to chronic pain-related aversion [80]. Thus, the potential roles of the spinal projection neurons targeting the medial thalamus in emotional and motivational behavior would of interest for further investigation.

The spinohypothalamic pathway

The hypothalamus, which receives direct input from the spinal cord, is a brain region crucial for various functions that are vital for organism survival. Electrophysiological recordings combined with retrograde tracing in rats found that spinal neurons projecting to the hypothalamus preferentially responded to innoxious tactile and noxious mechanical stimulation [67,68,81,82]. These neurons showed more vigorous responses to noxious stimulation [67]. These findings suggest that the spinohypothalamic pathway processes information associated with touch and pain. Consistent with the functional role of the hypothalamus in regulating body temperature, spinohypothalamic tract (SHT) neurons were demonstrated to be responsive to thermal stimulation [68], including noxious heat and cooling stimulation. Interestingly, some SHT neurons of rats

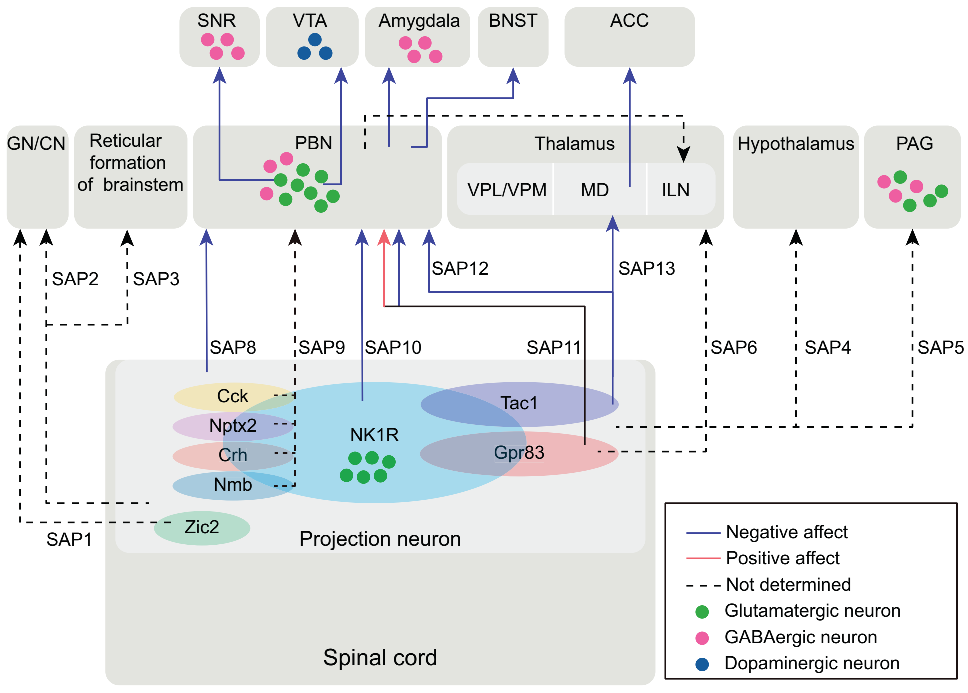

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Figure 3. Major spinal ascending pathways that process affective components of somatosensation. Ascending pathways are numbered for clarity (e.g., spinal ascending pathway 1, SAP1). The Zic family member 2 (Zic2)-labeled postsynaptic dorsal column (PSDC) pathway (SAP1) is sensitive to light touch stimuli, but its role in affective valence is unclear. The postsynaptic dorsal column (SAP2), spinoreticular (SAP3), spinohypothalamic (SAP4) and spino-PAG (SAP5) pathways respond to multiple somatosensory modalities, while their roles in affective valence are unclear. The spinoparabrachial (SPB) pathway has been demonstrated to transmit emotional valence (positive effects in blue, negative effects in red). Some evidence for involvement in emotional valence coding was found for the population of SPB neurons (SAP8), and some studies implicated SPB neurons labeled by specific molecular markers, such as neurokinin 1 receptor (NK1R; SAP10) and G-protein-coupled receptor 83 (Gpr83; SAP11). Other pathways emanating from cholecystokinin (Cck)-, neuronal pentraxin 2 (Nptx2)-, and neuromedin (Nmb)-labeled SPB neurons are likely to process emotional components of somatosensation (SAP9), although direct evidence is lacking. Gpr83$^+$ spinal projection neurons also innervate the thalamus (SAP6), but the function of this ascending pathway remains unknown. The parabrachial nucleus (PBN) further projects to multiple downstream brain areas, including intralaminar thalamic nuclei (ILN), midbrain areas, amygdala and bed nucleus of the stria terminalis (BNST), thereby transforming signals into autonomic, affective, and motivational responses. Tac1$^+$ spinal projection neurons send axons to both the PBN (SAP12) and mediodorsal thalamus (MD; SAP13), which are involved in processing negative emotional aspects of somatosensation. The MD–anterior cingulate cortex (ACC) pathway contributes to pain-related aversion. Solid lines represent spinal ascending pathways involved in emotional components processing. Dashed lines represent pathways likely to process emotional components of somatosensation, but direct evidence is largely lacking. The arrows that originate from individual clusters of projection neurons represent spinal ascending pathways labeled by specific molecular markers (such as Tac1, Gpr83, and Zic2). The arrows that originate from the large gray box of projection neurons represent spinal ascending pathways without cell specificity. Abbreviations: CN, cuneate nucleus; Crh, corticotropin-releasing hormone; GN, gracile nucleus; PAG, periaqueductal gray; SNR, substantia nigra pars reticulata; VPL/VPM, ventral posterolateral nucleus/ventral posteromedial nucleus; VTA, ventral tegmental area.

responded to increasing intensity of heat with graded increases in their firing rate [81,82], indicating that the spinohypothalamic pathway participates in processing of body temperature information. Notably, although most SHT neurons in rats respond to both noxious and innocuous stimuli, small subsets that specifically respond to noxious mechanical stimuli or innoxious tactile stimuli were also described [67,68,81,82] (Figure 2). Thus, both monomodal and polymodal SHT neurons are present. However, partly due to the small number of spinohypothalamic neurons, functional examination of the spinohypothalamic remains limited.

The spino-PAG pathway

Anatomical studies in rats revealed that ~20% of lamina I projection neurons project to the PAG [36,83]. This anatomical organization suggests that PAG represents one of the key nodes of the spinal ascending pathway. PAG has been known to be important for many physiological functions and behaviors, including aggression [84,85], defensive behavior [86,87], and descending modulation of pain and itch [88–90]; thus, the spino-PAG pathway could contribute to these diverse functions.

Spino-PAG neurons display distinct electrophysiological characteristics. Compared with SPB neurons, spino-PAG neurons exhibit a higher firing rate during early life in rats, as well as a preferential burst firing pattern [83,91,92]. Spino-PAG neurons are likely involved in the development of chronic inflammatory pain. In spinal cord slices from rats, low-frequency stimulation modified synaptic strength in spinal lamina I neurons projecting to the PAG and induced a robust long-term potentiation (LTP) [93] (Figure 2). However, the functional role of spino-PAG ascending pathway remains to be further explored.

The spinoparabrachial pathway

The PBN is important for processing information about multiple somatosensory modalities. Much progress has been made in revealing the properties and functional roles of the spinal ascending pathway targeting PBN. In particular, it has been shown that the spinoparabrachial pathway is critical for processing pain and itch. Noxious heat or cold stimuli were shown to induce upregulation of *Fos* in SPB neurons of rats [94], suggesting that this pathway is involved in processing nociceptive information. Recent studies have begun to reveal the functional role of the spinoparabrachial pathway. It has been shown that activation of terminals of spinal projection neurons in the PBN could elicit pain-related behaviors, such as licking and flinching, in mice [63,95,96]. Conversely, silencing of the spinoparabrachial pathway suppressed pain-related licking behaviors but not nocifensive reflexing behaviors [96]. Thus, the spinoparabrachial pathway is critical for pain processing, especially for pain-evoked coping behaviors. Additionally, a recent study in mice discovered that a subpopulation of SPB neurons receives direct inputs from spinal itch-selective GRPR$^+$ neurons. SPB neurons are activated by pruritic stimuli [97]. Furthermore, photoinhibition of the spinoparabrachial pathway reduced pruritogen-evoked scratching behaviors [97], suggesting that the ascending spinoparabrachial pathway is required for itch transmission.

The molecular identity of the spinoparabrachial neuronal population has also been revealed. NK1R marks SPB neurons [98] and early studies in rats showed that spinal NK1R$^+$ neurons have a pivotal role in the processing of nociceptive information [99,100]. Consistently, chemogenetic and optogenetic activation of NK1R$^+$ SPB neurons in mice elicited pain-related behaviors [95]. Moreover, electrophysiological studies in rats suggest that NK1R$^+$ SPB neurons are involved in hyperalgesia during inflammation [93,101]. Thus, NK1R$^+$ SPB neurons appear to be essential for both acute and chronic pain. In addition, ablation of NK1R$^+$ neurons in the superficial spinal dorsal horn was reported to significantly attenuate behavioral signs of acute and chronic itch in rats and mice [102–104]. Since the expression level of NK1R in spinal interneurons is lower than in spinal projection neurons, these effects of ablation are more likely to be caused by the loss of NK1R$^+$ SPB neurons, although these ablation experiments did not specifically target projection neurons in the spinal cord. This is further supported by a recent study in mice showing that ablation of Tac1-labeled spinal projection neurons, which substantially overlap with NK1R$^+$ spinal projection neurons in the superficial spinal cord, impaired sustained pain-evoked licking behaviors, as well as pruritogen-induced scratching behaviors [61]. Since the NK1R$^+$ spinal projection neurons could transmit both nociceptive and pruritic information, one outstanding question is whether these two signals are transmitted by the same group of neurons, or by two separate subgroups. By combining *in situ* hybridization with *Fos*-based assay, a recent study in mice indicated that Cck$^+$-, Nptx2$^+$-, Nmb$^+$-, and Crh$^+$-labeled NK1R$^+$ projection neurons transmit both pain- and itch-relevant signals to the PBN, whereas other subsets are more selective to pain or itch [66]. Thus, the NK1R$^+$ SPB neurons are rather heterogeneous. Another group of SPB neurons, labeled by Gpr83, only partially overlap with NK1R$^+$ neurons. This subset of spinal projection neurons receives input from Mrgprb4$^+$ mechanosensory neurons and Ntrk2$^+$ Aδ-low threshold mechanoreceptive neurons [63]. Thus, Gpr83$^+$ spinal projection neurons are critical for transmitting mechanical information to the PBN. Behaviorally, high-intensity stimulation of Gpr83$^+$ projection terminals in the PBN induced nocifensive responses in mice [63]. Therefore, Gpr83$^+$ SPB neurons likely convey both noxious and innocuous mechanical information in a stimulus intensity-dependent manner.

Early studies in rodents examined the coding properties of SPB neurons and tested their responsiveness to various stimulation paradigms, including chemical, mechanical, and thermal stimulation [34,105,106]. Electrophysiological studies in rats showed that SPB neurons that responded to cold stimuli were also responsive to noxious mechanical and noxious heat stimuli [107]. Emerging evidence using *in vivo* imaging in anesthetized mice further suggested that a large subset of SPB neurons responds to multiple sensory modalities, including pinch, heat, and cold [108]. These data suggest polymodal properties of the spinoparabrachial pathway [34]. However, an early study in rats showed that lamina I SPB neurons were activated by innocuous cooling or warming stimuli, but not by other stimulus modalities [107]. Recently, a study using patch-clamp recordings in mice also found that a subset of cold-selective SPB neurons was significantly different from other SPB neurons in many aspects, suggesting that cold information is conveyed from the periphery to the PBN through a distinct population of 'SPB-cold' neurons [105]. In line with this, an *in vivo* imaging study in anesthetized mice also found a small subset of SPB neurons that exclusively respond to the innocuous cooling stimulation [108]. In addition, in rats, another single-unit extracellular recording study found a population of nociceptive-specific SPB neurons [109]. These results were further supported by a recent study in mice showing that Gpr83$^+$ SPB neurons in the spinal cord were sensitive to mechanical stimuli, while NK1R$^+$ SPB neurons were more sensitive to noxious heat and cold stimulation [63]. Collectively, these data indicate that there are likely modality-specific SPB neurons, although SPB neurons are predominantly polymodal.

The PBN projects to multiple downstream brain areas, including the amygdala, bed nucleus of the stria terminalis (BNST), midbrain, and thalamus [57,96,110]. Thus, PBN has been recognized as a critical brain region that transforms sensory signals into autonomic, affective, and motivational responses (Figure 3). Photostimulation of SPB neurons is sufficient to induce avoidance behaviors in mice, suggesting that the PBN processes the affective value of somatosensation [61,63,96]. Interestingly, a recent study found that activation of Gpr83$^+$ SPB neurons can evoke either positive reinforcement or avoidance behaviors in mice, depending on stimulus intensity [63]. This is consistent with the broad projection pattern of the PBN. Recent studies have begun to reveal the functional role of downstream pathway of PBN [57,110]. A recent study in mice described an ascending spinoparabrachial pathway relaying nociceptive signals to substantia nigra pars reticulata (SNR) and ventral tegmental area (VTA) [57]. Given that inhibition of VTA dopaminergic neurons promotes behaviors associated with aversion [111], the spinal–parabrachial–midbrain pathway likely contributes to the negative emotional or motivational components of pain.

The postsynaptic dorsal column pathway

Of interest, but sometimes overlooked, are the postsynaptic dorsal column (PSDC) neurons, which locate in laminae III/IV and X and project through dorsal columns (DC) to either the gracile

(GN) or cuneate nucleus (CN) [112] (Figures 2 and 3). A study in patients found that lesions in the medial part of the posterior column could eliminate pelvic pain caused by cancer [113]. The role of the PSDC neurons in mediating visceral nociceptive inputs was also examined in early extracellular recording studies in rats, showing that these neurons are responsive to noxious visceral stimuli [113,114]. Consistently, later electrophysiological and immunohistochemical studies found that PSDC neurons in the T3–T4 spinal cord of anesthetized rats respond to mechanical somatic stimuli and chemical stimulation of cardiac inputs [115,116]. Relatedly, *Fos* expression in PSDC neurons was increased after distention of the ureter [117]. These data suggest that the ascending PSDC pathway has an important role in transmitting sensory information from visceral organs. Interestingly, by retrograde tracing from the gracile nucleus, studies in rats found that *Fos* expression was increased in PSDC neurons after plantar incision or intradermal injection of capsaicin [117,118]. These results suggest that activation of PSDC neurons is involved in cutaneous pain. In addition to pain, a recent study using a Zic2cre^{ER} mouse line showed that chemogenetic activation of PSDC neurons marked by zic family member 2 (Zic2) increased sensitivity to light touch stimuli [119], indicating that the dorsal column projection transmits tactile information from the spinal cord to the brain. In addition, single-unit extracellular recordings in anesthetized rats showed that dorsal horn neurons that were retrogradely labeled from the GN responded to both thermal nociceptive stimulation and innocuous brush stimulation applied to the hindpaw [117]. These results reveal that the ascending PSDC pathway transmits cutaneous nociceptive and mechanical information in a polymodal manner [120].

The spinoreticular pathway

Spinal projection neurons targeting the reticular formation of brainstem are another neural population that merits attention (Figures 2 and 3). The soma of spinoreticular neurons are scattered throughout laminae VII and VIII [121]. This ascending pathway is likely an alternate pathway for nociceptive information processing. Early studies in rats, cats, and monkeys found that spinoreticular neurons were activated by noxious stimulation, such as cutaneous pinching [122–125], indicating a potential role of the spinoreticular pathway in nociception. In addition, extracellular recordings in the spinal cords of anesthetized monkeys found that innocuous mechanical stimulation could also activate spinoreticular neurons [124]. This suggests that the spinoreticular pathway also conveys tactile information to the brain. In addition, studies in cats showed that tactile stimulation of the pinna that evoked scratching behaviors could modulate the activity of spinoreticular neurons [126], suggesting that this pathway processes part of the itch sensation. However, the functional role of spinoreticular neurons needs to be further investigated.

Concluding remarks

Spinal projection neurons are highly heterogeneous and target multiple brain areas. Much progress has been made in deciphering the functional roles of spinal projection neurons. The discovery of both contralateral and bilateral projection patterns of spinal ascending pathways has expanded our understanding of somatosensory system organization. Early electrophysiological studies revealed the role of the spinal ascending pathway in chemical, mechanical, and temperature information processing, while later studies revealed differential functional roles of several subgroups of spinal projection neurons, although some of these subgroups anatomically partially overlap. In addition, recent studies have provided growing evidence that the spinal ascending pathway processes both sensory and emotional information. However, current knowledge of the spinal ascending pathway is still incomplete (see Outstanding questions).

Dissecting the modality coding property of spinal projection neurons is critical for understanding the somatosensory system. Emerging evidence has shown that, while some spinal projection neurons are selectively activated by some types of somatosensory stimulation and exhibit

Outstanding questions

Although recent single cell-sequencing studies have partially revealed the transcriptomic signature of some spinal projection neurons, a complete map of molecular profiles of spinal projection neurons is still lacking. Can subpopulations of spinal projection neurons be distinguished based on their molecular profiles?

Dynamic control of excitability of spinal projection neurons is critical for somatosensory processing. How are spinal projection neurons modulated at both the molecular and circuit level? To fully address this question, it will also be crucial to map the local connectome in the spinal cord, which will help determine how local interneurons modulate spinal projection neurons.

Spinal projection neurons exhibit both polymodal properties and submodality selectivity in coding somatosensation. What are the coding principles underlying processing somatosensory information at the spinal projection neuron level? Are different components of somatosensation processed by parallel or convergent pathways?

Spinal projection neurons target multiple brain areas and display diverse projection patterns. However, a single cell-resolution ‘projectome’ of spinal projection neurons remains lacking, and general principles underlying spinal ascending pathway organization are unknown. What is the functional role of different spinal ascending pathways? What is the relationship among the molecular identity, projection pattern, and function of spinal projection neurons?

Neural plasticity and epigenetic modifications could be important underlying mechanisms for chronic pain. Is neural plasticity along the spinal ascending pathway involved in pain or itch chronicity? What are the roles of epigenetic regulation at the spinal projection neuron level in dysfunctions of somatosensation?

modality-specific coding properties, in line with the classic 'labeled-line' theory, most spinal projection neurons respond to more than one somatosensory stimulation type, indicating that somatosensory modalities are processed in a population coding manner in spinal projection neurons. Thus, the general principles by which spinal projection neurons process somatosensory information remain to be further explored. It will also be important to examine the properties of spinal projection neurons in awake animals and using large-population recordings.

Many molecular markers of spinal projection neurons have been discovered, and this facilitates progress in deciphering the functional roles of different subpopulations of spinal projection neurons in somatosensory information processing. However, comprehensive molecular profiling of spinal projection neurons is still lacking. Such a transcriptomic map of spinal projection neurons would further advance our knowledge of the functional roles of these neurons.

From a behavioral and cognitive perspective, the affective component of somatosensation is critical for animals and humans to produce quick and suitable reactions to the external environment and modulate information storage, which is critical for both survival and social function. In somatosensation, increasing evidence, especially from tactile research, supports the notion that valence-coded signals propagate into the central nervous system in channels distinct from those for discriminative sensation [127]. However, it remains largely unknown how sensory and affective components are distinguished and interact with each other along ascending pathways, and whether affective components are modality general or modality specific. There is need to dissect the neural networks underlying the affective component of somatosensation and understand the interaction between the discriminative and affective dimensions. Developing new paradigms to distinguish and measure the sensory and emotional aspects will be key to addressing these questions.

Finally, the relationship between dysregulation of the ascending pathway and chronic disease remains to be further explored. Recently, for instance, the pre- and postsynaptic mechanisms underlying LTP induction in chronic pain at the spinal level have been investigated [93,101,128]. The study of synaptic plasticity along the spinal ascending pathway will be critical for better understanding of pain and itch chronicity. In addition, injury-induced changes in chromatin structure can alter gene expression and neural function at the spinal cord, leading to chronic pain [129–131]. Thus, further investigation of epigenetic modulation along the spinal ascending pathway would also be of great interest for understanding disorders such as chronic pain and itch, and could help guide the development of new therapeutic approaches for somatosensation dysfunction.

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Declaration of interests

The authors declare no competing interests in relation to this work.

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