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Making connections: recent advances in spinal cord dorsal horn circuitry

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1. Introduction

As the first point where sensory information enters the central nervous system, the cell types and connections in the dorsal horn are of great interest. Correct processing of sensory information within the dorsal horn relies on the balance of excitation and inhibition, although the cell types and circuitry underlying normal transmission of sensory information are still poorly understood. Despite this, there is significant evidence that changes occur in the dorsal horn in pain states, making it an attractive target for novel analgesics to stop aberrant sensory information before it reaches the brain. Progress in this area has been hindered, however, because we do not have a clear picture of how information is modulated within the dorsal horn in naive conditions, let alone in the context of injury. A number of recent studies have used genetic tools to target subpopulations of spinal neurons with the goal of understanding their function within the context of somatosensory integration. These discoveries provide important new insights, yet force us to grapple with a new of level complexity. We also need to remember that most studies to date use mouse models, and future experiments will be required to address whether these organization principles hold true in other species. In this review, we highlight some major themes that are emerging, as well as the issues that need to be addressed for a clearer understanding of the spinal processing of itch and pain, and the logic through which this information is conveyed to the brain.

2. Organization within the spinal cord

The fundamental organizational principle of the spinal cord is the manner in which information is organized with respect to sensory subtype (modality) and body region (somatotopy). The information from distinct sensory afferent subtypes is organized by lamina across the dorsoventral axis, whereas information from distinct body parts is organized by location across the rostrocaudal and mediolateral axes. This organization can be conceptualized as a microcircuit column, repeating along the rostrocaudal and mediolateral axes of the dorsal horn. These columns of spinal microcircuits represent the fundamental processing units of initial somatosensory integration (**Fig. 1**). Of course, it is important to understand that these repeating stacks of microcircuit columns will certainly have some key differences. For example, columns in regions that receive more input from cutaneous structures will have a slightly different organization and cell types than columns that receive input from visceral structures. Nevertheless, once we have a broad picture of how all the neurons within a spinal microcircuit are connected, we can begin to model how they integrate somatosensory information, and how this integration changes in the context of injury.

Dorsoventral organization of both primary afferent input and neuron populations intrinsic to the spinal cord is often viewed as an intensity gradient, with noxious stimuli being processed superficially, whereas innocuous (nonpainful) information enters deeper (although this notion is a generalization, because cool-sensing afferents, at least, seem to be the most superficial of all). Early work assigned functional classes to different populations of primary afferents by expression of various neurochemical markers, responses to natural stimuli, and conduction velocity. These analyses revealed a modality-segregated spread along the dorsoventral axis of the spinal cord. In general, Trpm8+ (cool/cold sensing) and unmyelinated peptidergic afferents enter into to lamina I,[5,32] Mrgpra3+, nonpeptidergic (eg, Mrgprd+), and C-LTMRs are organized dorsoventrally within lamina II,[8,17,38] Aδ-LTMRs synapse in lamina III, and Aβ-LTMRs enter into LIV.[17] Recent sequencing studies have identified yet more populations, such as Somatostatin+ neurons[10,16,24,37]; nevertheless, it is likely that this modality-specific organization will still hold, albeit, with a more detailed view of afferent populations.

Although we do not yet understand all the nuanced details of interneuron organization and function within the dorsal horn, the broad categorization of functional populations along the dorsoventral axis is known and unsurprisingly follows a similar pattern as the primary afferent input. Neurons in more superficial (dorsal) regions respond to pain, heat, cold, and itch stimuli, whereas neurons that lie deeper within the dorsal horn are more likely to respond to nonpainful stimuli (**Fig. 1**). Along the mediolateral and rostrocaudal axes of the dorsal horn, primary afferent input is organized somatotopically. In the mediolateral extent information is organized in a distal/proximal manner (more distal regions enter medially and proximal areas enter laterally in the dorsal horn; **Fig. 1**). However along the rostrocaudal axis of the spinal cord, information from the neck and trunk enter more rostrally than information from the feet and legs (**Fig. 1**). With this picture of discrete microcircuit columns, the major challenge now is to understand how somatosensory information is transformed within these columns before ultimately being relayed to the brain.

3. Classification of neuron populations

A variety of different approaches have been used to try classifying cell types in the dorsal horn. These include morphology (eg, islet

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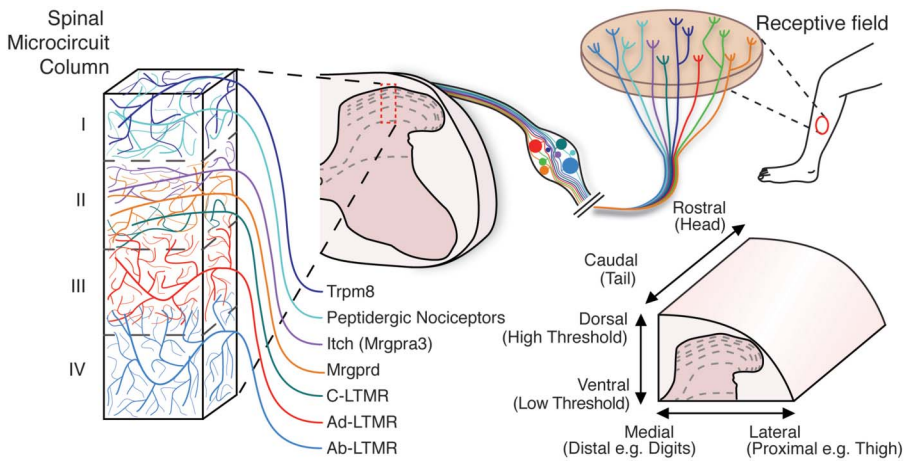

Figure 1. Primary afferent entry to the dorsal horn can be conceptualized as a series of microcircuit columns. In the dorsoventral axis, primary afferents are organized along an intensity gradient with noxious and temperature-sensitive fibers entering superficially (TRPM8, peptidergic nociceptors, and itch sensitive afferents), whereas low-threshold mechanoreceptors (LTMRs) enter deeper within the dorsal horn (Left). Along the rostrocaudal and mediolateral axes of the spinal cord, primary afferents are organized according to somatotopy (body region). A single microcircuit column will receive afferent input from a single receptive field (top right). Bottom right shows a "map" of afferent input to different parts of the dorsal horn.

cells, central, radial, and vertical), physiology (eg, tonic, delayed, initial bursting, and single spiking action potential firing in response to current injection), specific connectivity patterns (eg, axoaxonic synapses on primary afferents, axodendritic synapses onto local interneurons), and the expression of neurochemical markers (eg, Pvalb, Tac1, Grpr). In some cases, these features have all come together to define a clear cell type. For example, PV neurons are tonic-firing islet cells that mediate presynaptic inhibition onto primary afferents.[3,12] But this example is the exception rather than the rule. For the majority of neurons in the dorsal horn, we have, as of yet, only pieces of the puzzle, and which cells constitute true "cell types" remains unknown.

The recent advent of single-cell sequencing approaches is helping to disambiguate the problem of cell types. As an example of a success story, consider the insight that has been gained into primary afferent populations through major sequencing efforts. Zeisel et al. pooled sensory neurons across the body (L1-C6 dorsal root ganglia), whereas other teams focused their analyses on specific subsets of afferents: those that innervate the leg[16,36], the face,[24] or the colon.[10] Most recently, a comprehensive developmental profile was performed that gives a beautiful picture of how distinct primary afferents emerge from a common lineage.[31] Regardless of the study, the fundamental primary populations that emerge are remarkably similar. Indeed, with the exception of proprioceptors (which are absent from trigeminal ganglia because proprioceptors for this region have their cell bodies in the mesencephalic trigeminal nucleus located at the mesopontine junction[15]), there was outstanding correspondence between populations from trigeminal and dorsal root ganglia, challenging the dogma that these afferents have distinct developmental origins, and instead arguing for a common lineage (ie, neural crest), at least in mouse. Together, these efforts are converging on the idea that, insofar as gene expression can define a cell type, there are ~14 major groups of abundant primary afferents.

Now, the challenge is to correlate these newly described transcriptomic populations with well-established functional classes of sensory neurons. For abundant afferents, such as peptidergic nociceptors, there seems to be a greater diversity of molecular classes than (as-of-yet described) functional subtypes. What could these clusters represent at the level of cell type? It may be that distinct transcriptomic populations reflect afferent subtypes with different targets of innervation (eg, endothelial vs epithelial), or different efferent functions in tissue homeostasis and repair. For rare afferents, the situation is the opposite: there is much greater functional diversity than is evident among transcriptomic populations. For instance, the afferents that mediate sexual pleasure are completely unknown. Thus, more extensive sequencing together with targeted efforts will be required to identify these and other rare populations of primary afferents.

Although there has been some effort to perform the same single-cell sequencing in the dorsal horn, our understanding of cell types here is not yet as granular. Part of the challenge may be that, relative to primary afferents, the spinal cord populations are not as transcriptionally distinct from one another, and so it is challenging to use sequencing information alone to define populations. Nevertheless, one concept that has emerged is that many of the markers that have previously been used to define "cell types" comprise more than one population. One such example is excitatory substance P (Tac1)-expressing interneurons. Dickie et al.[6] showed that this was a largely homogenous population through careful electrophysiological and morphological characterization. By contrast, Häring et al.,[9] showed Tac1 neurons in 2 clusters (GLUT10 and 11) suggesting there are at least 2 molecularly distinct groups within this population.[6,9] Whether this means distinct functional roles for these populations remains to be seen. Although we are unsure if the neuron populations proposed by the sequencing studies constitute "true" functional populations, or if deeper sequencing analysis is required, these efforts have given us invaluable information as to the many other molecular markers each population expresses. An important step now will be to see if any of these markers change after injury. Although these new sequencing studies will no doubt bring more clarity to our grasp of dorsal horn organization, it is important to remember that understanding the function and connectivity patterns of individual populations is key if we are to begin to target the spinal cord for therapeutic benefit.

4. Functional role of dorsal horn neurons

One of the approaches to address the question of cell function is through loss-of-function and gain-of-function studies that target distinct cell types in the spinal cord. These experiments typically involve molecular genetic tools such as optogenetic or chemogenetic approaches to activate, inhibit, or ablate a population of neurons that is defined genetically through expression of Cre (and/or Flp) recombinase. Importantly when discussing a presumed function for a population of neurons, it is important that we look at the circuit as a whole, considering the entirety of the connectome (whole spinal cord) including, where possible, descending fibers and sensory afferent inputs.

One way to assess the modality specificity of different dorsal horn neurons is through simultaneous electrophysiological recordings and peripheral stimulation, such as that performed by our group.[7] In that study, we adapted an ex vivo preparation[14] to allow whole-cell patch-clamp recordings from superficial dorsal horn neurons while simultaneously applying natural stimulation to the skin in a continuous preparation. In doing so, we were not only able to quantify the modality tuning of projection neurons and interneuron populations using retrograde labelling or Cre reporter lines, but we were also able to look at connectivity patterns of defined populations. Other groups have used optogenetic activation of dorsal horn populations in awake and behaving animals as a way to understand their functional role. Both somatostatin-expressing and calretinin-expressing neurons were shown to generate nocifensive behaviors and conditioned place aversion when optogenetically activated in awake animals.[4,33] Furthermore, activating calretinin neurons using DREADDs also produced a behavior consistent with mechanical hypersensitivity.[27] Although both the somatostatin and calretinin populations likely have several smaller subgroups, these data provide valuable insight into what these neurons are capable of, and highlight techniques that can be used to assess function of dorsal horn neurons. More recent work has also used a combination of slice electrophysiology and in vivo optogenetics to look at how and what spinal neurons receive itch information. Zeilhofer's group showed that the transmission of itch information required MrgprA3 afferents to fire at specific frequencies onto gastrin-releasing peptide (GRP) neurons in the dorsal horn to cause animals to scratch.[1,25] These studies provided important information into how itch is transmitted, adding to a significant body of literature discussed in the next section.

Although it is tempting to assume distinct roles for each population of neurons, there are several important factors that need to be considered before making certain assumptions. Despite many attempts over the past few decades to define true populations of dorsal horn neurons, we are still not there. Recent sequencing efforts are pushing the field forward in this way calling into question previously defined populations and beginning to provide more clarity as to "true" neuron subtypes. Careful consideration must also be taken when choosing tools to investigate neuron function. An interesting phenomenon that has emerged is that different tools can lead to different behavior outcomes. This concept is illustrated in a recent study that shows scratching behavior after DREADD activation of Mrgpra3 afferents but nocifensive behavior after optogenetic activation the same population,[30] raising the intriguing possibility that different kinds of neuronal "activation" (second messenger signaling vs action potentials) give rise to very different effects.

5. Connectivity within the dorsal horn

Despite the surge in data identifying molecularly distinct neuron classes, it is important to remember that it is the connectivity among dorsal horn populations in addition to the neurons themselves that determines "what" and "how much" information is transmitted to the brain. Our current understanding of connectivity within the dorsal horn draws from many functional and anatomical studies, which makes gaining a comprehensive understanding of the circuits that transmit pain and itch information somewhat difficult to understand. Significant work has been done looking at the connectivity of neurochemically defined dorsal horn populations; however, the biggest limitation of most of these experiments is the lack of clearly defined, functionally distinct populations. Understanding how these pathways normally function will help us understand how this circuitry is subverted in altered pain states.

6. Functional circuits

Historically, connectivity among dorsal horn neurons was studied using paired electrophysiology recordings.[19,20] Now, integration of optogenetic techniques into the field is rapidly increasing our understanding of specific connectivity patterns within the dorsal horn. There is evidence in the literature that suggests connectivity patterns are somewhat cell type-specific. Perhaps, the best example is the circuitry underlying mechanical allodynia whereby, through many studies, it was shown that a polysynaptic pathway exists between Aβ primary afferents and lamina I projection neurons through a series of dorsally projecting connections. Initial work on this pathway identified a polysynaptic circuit between Aβ primary afferents and lamina I projection neurons that required disinhibition of PKCγ cells allowing them to send excitatory connections through vertical cells to projection neurons.[18,21,23,28] However, it seems that as we look deeper into this phenomenon, more complex circuitry arises, which now involves neuropeptide Y1 receptor (NPY1R), cholecystokinin (CCK), and parvalbumin (PV)-expressing neurons.[22,28]

One circuit that has received significant attention in recent years is the circuit(s) involved in the transmission of itch information. Perhaps, the most important discovery here was the role of GRP-expressing neurons in the superficial dorsal horn. This seminal work identified that GRP neurons (releasing GRP onto GRPR neurons) is required for chemical itch.[2,34,35] More recent work has expanded this circuit to include a population of primary afferent neurons (Mrgpra3 expressing). Pagani et al.[25] and Albisetti et al.[1] show that MrgprA3 afferents form monosynaptic connections with GRP neurons and that when the afferents fire at specific frequencies, are able to drive GRP release, ultimately resulting in scratching behavior.[1,25]

Although it is important to understand these excitatory pathways, spinal cord circuits also have a significant inhibitory component, able to stop or dampen certain information from ascending the neuroaxis. Work has also been done on the inhibitory circuits of itch. Work from our laboratory revealed that transcription factor Bhlhb5 is required for the survival of a group of inhibitory interneurons in laminae I and II in the dorsal horn. These inhibitory neurons, which were termed B5-I neurons, were found to be required to inhibit itch. In mice that lacked them, abnormal itch ensued.[29] Subsequently, we discovered that B5-I neurons are made up of 2 cell types—those that express Nos1 and those that express Pdyn. Although we did not know at the time which ones were involved in the inhibition of itch, we speculated that the Pdyn subset was involved because they release dynorphin, a kappa opioid receptor agonist that inhibits itch.[13] This idea has since been substantiated in a recent study that looked directly at the function of each population, thereby revealing that Pdyn neurons inhibit itch.[11] Other work on the inhibition of itch has used

current treatments, such as the inhibition of itch by counterstimuli, to identify novel spinal circuits. One such example is the inhibition of itch by cold stimuli. This has recently been shown to require the activation of cool sensing afferents (Trpm8 positive) that synapse with B5-I inhibitory interneurons in the dorsal horn.[26] Together, these studies are suggesting a mechanism that may mediate the inhibition of itch by counterstimuli.

What is important to remember when studying neural circuitry is that connections within the dorsal horn (and the central nervous system as a whole) are dynamic. Connectivity is not hardwired, and any perturbations to incoming somatosensory information are able to alter the way in which neurons in this region process sensory information. In addition to the complexity surrounding normal and abnormal signaling, there are also further complications when trying to understand modality-specific circuits. Interaction of pain and itch information calls into question the specificity/labelled line theory. Although itch specific circuitry has been identified with MgrprA3 afferents and GRP dorsal horn neurons, there does seem to be significant cross-talk between these 2 modalities suggested by the inhibition of itch by painful stimuli.

7. Conclusion

As we move closer towards finally understanding the precise, functional populations that comprise the dorsal horn, it is important to remember that we need to study the dorsal horn as a whole—incorporating not just individual populations, but also their connections and how they affect overall processing—to gain a complete understanding of how the dorsal horn is able to integrate and process sensory information. This will not be possible without several advancements in our understanding of dorsal horn organization. First, until we have a clear understanding of bona fide cell types in the dorsal horn (as well as genetic tools that allow them to be targeted with precision), it is difficult to interpret behavior data that are observed upon manipulation of disparate neuronal subpopulations. Second, we need to understand how cell types are connected together and to begin thinking of a cell function in the context of a circuit. Finally, although activating and inhibiting neurons may tell us what neural circuits can *do*, this type of artificial manipulation can only take us so far in terms of understanding what neural circuits actually *do*. For this fundamental insight into coding, it is critical to visualize the activity of the network of neurons as they respond and integrate natural stimulation. To take this insight further, it is important to go down to the fundamentals—what are the cell types and how are they connected?—to begin understanding the computations that are performed within a spinal microcircuit column. Although daunting, these goals are now within our reach.

8. Learning objectives

Understand the functional organization of dorsal horn circuitry with respect to somatotopy and modality integration.

Appreciate the challenge of defining cell types in the dorsal horn.

See a few examples of how genetic tools help us infer cell type function.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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References

[1] Albisetti GW, Pagani M, Platonova E, Hösli L, Johannssen HC, Fritschy JM, Wildner H, Zeilhofer HU. Dorsal horn gastrin-releasing peptide expressing neurons transmit spinal itch but not pain signals. J Neurosci 2019;39:2238–50.
[2] Bourane S, Duan B, Koch SC, Dalet A, Britz O, Garcia-Campmany L, Kim E, Cheng L, Ghosh A, Ma Q, Goulding M. Gate control of mechanical itch by a subpopulation of spinal cord interneurons. Science (New York, NY) 2015;350:550–4.
[3] Boyle KA, Gradwell MA, Yasaka T, Dickie AC, Polgár E, Ganley RP, Orr DPH, Watanabe M, Abraira VE, Kuehn ED, Zimmerman AL, Ginty DD, Callister RJ, Graham BA, Hughes DI. Defining a Spinal Microcircuit that Gates Myelinated Afferent Input: Implications for Tactile Allodynia. Cell reports 2019;28:526–540.e526.
[4] Christensen AJ, Iyer SM, François A, Vyas S, Ramakrishnan C, Vesuna S, Deisseroth K, Scherrer G, Delp SL. In vivo interrogation of spinal mechanosensory circuits. Cell Rep 2016;17:1699–710.
[5] Dhaka A, Earley TJ, Watson J, Patapoutian A. Visualizing cold spots: TRPM8-expressing sensory neurons and their projections. J Neurosci 2008;28:566.
[6] Dickie AC, Bell AM, Iwagaki N, Polgár E, Gutierrez-Mecinas M, Kelly R, Lyon H, Turnbull K, West SJ, Etlin A, Braz J, Watanabe M, Bennett DLH, Basbaum AI, Riddell JS, Todd AJ. Morphological and functional properties distinguish the substance P and gastrin-releasing peptide subsets of excitatory interneuron in the spinal cord dorsal horn. PAIN 2019;160:442–62.
[7] Hachisuka J, Baumbauer KM, Omori Y, Snyder LM, Koerber HR, Ross SE. Semi-intact ex vivo approach to investigate spinal somatosensory circuits. eLife 2016;5:e22866.
[8] Han L, Ma C, Liu Q, Weng HJ, Cui Y, Tang Z, Kim Y, Nie H, Qu L, Patel KN, Li Z, McNeil B, He S, Guan Y, Xiao B, Lamotte RH, Dong X. A subpopulation of nociceptors specifically linked to itch. Nat Neurosci 2013;16:174–82.
[9] Häring M, Zeisel A, Hochgerner H, Rinwa P, Jakobsson JET, Lönnerberg P, La Manno G, Sharma N, Borgius L, Kiehn O, Lagerström MC, Linnarsson S, Ernfors P. Neuronal atlas of the dorsal horn defines its architecture and links sensory input to transcriptional cell types. Nat Neurosci 2018;21:869–80.
[10] Hockley JRF, Taylor TS, Callejo G, Wilbrey AL, Gutteridge A, Bach K, Winchester WJ, Bulmer DC, McMurray G, Smith ESJ. Single-cell RNAseq reveals seven classes of colonic sensory neuron. Gut 2019;68:633–44.
[11] Huang J, Polgár E, Solinski HJ, Mishra SK, Tseng P-Y, Iwagaki N, Boyle KA, Dickie AC, Kriegbaum MC, Wildner H, Zeilhofer HU, Watanabe M, Riddell JS, Todd AJ, Hoon MA. Circuit dissection of the role of somatostatin in itch and pain. Nat Neurosci 2018;21:707–16.
[12] Hughes DI, Sikander S, Kinnon CM, Boyle KA, Watanabe M, Callister RJ, Graham BA. Morphological, neurochemical and electrophysiological features of parvalbumin-expressing cells: a likely source of axo-axonic inputs in the mouse spinal dorsal horn. Journal of Physiology 2012;590:3927–51.
[13] Kardon AP, Polgár E, Hachisuka J, Snyder LM, Cameron D, Savage S, Cai X, Karnup S, Fan CR, Hemenway GM, Bernard CS, Schwartz ES, Nagase H, Schwarzer C, Watanabe M, Furuta T, Kaneko T, Koerber HR, Todd AJ, Ross SE. Dynorphin acts as a neuromodulator to inhibit itch in the dorsal horn of the spinal cord. Neuron 2014;82:573–86.
[14] Koerber HR, Woodbury CJ. Comprehensive phenotyping of sensory neurons using an ex vivo somatosensory system. Physiol Behav 2002;77:589–94.
[15] Lazarov NE. Neurobiology of orofacial proprioception. Brain Res Rev 2007;56:362–83.
[16] Li CL, Li KC, Wu D, Chen Y, Luo H, Zhao JR, Wang SS, Sun MM, Lu YJ, Zhong YQ, Hu XY, Hou R, Zhou BB, Bao L, Xiao HS, Zhang X. Somatosensory neuron types identified by high-coverage single-cell RNA-sequencing and functional heterogeneity. Cell Res 2016;26:967.

[17] Li L, Rutlin M, Abraira VE, Cassidy C, Kus L, Gong S, Jankowski MP, Luo W, Heintz N, Koerber HR, Woodbury CJ, Ginty DD. The functional organization of cutaneous low-threshold mechanosensory neurons. Cell 2011;147:1615–27.
[18] Lu Y, Dong H, Gao Y, Gong Y, Ren Y, Gu N, Zhou S, Xia N, Sun YY, Ji RR, Xiong L. A feed-forward spinal cord glycinergic neural circuit gates mechanical allodynia. J Clin Invest 2013;123:4050–62.
[19] Lu Y, Perl ER. A specific inhibitory pathway between substantia gelatinosa neurons receiving direct C-fiber input. J Neurosci 2003;23:8752–8.
[20] Lu Y, Perl ER. Modular organization of excitatory circuits between neurons of the spinal superficial dorsal horn (laminae I and II). J Neurosci 2005;25:3900–7.
[21] Miraucourt LS, Dallel R, Voisin DL. Glycine inhibitory dysfunction turns touch into pain through PKCgamma interneurons. PLoS One 2007;2:e1116.
[22] Nelson TS, Fu W, Donahue RR, Corder GF, Hökfelt T, Wiley RG, Taylor BK. Facilitation of neuropathic pain by the NPY Y1 receptor-expressing subpopulation of excitatory interneurons in the dorsal horn. Scientific Rep 2019;9:7248.
[23] Neumann S, Braz JM, Skinner K, Llewellyn-Smith IJ, Basbaum AI. Innocuous, not noxious, input activates PKCgamma interneurons of the spinal dorsal horn via myelinated afferent fibers. J Neurosci 2008;28:7936–44.
[24] Nguyen MQ, Wu Y, Bonilla LS, von Buchholtz LJ, Ryba NJP. Diversity amongst trigeminal neurons revealed by high throughput single cell sequencing. PLoS One 2017;12:e0185543.
[25] Pagani M, Albisetti GW, Sivakumar N, Wildner H, Santello M, Johannssen HC, Zeilhofer HU. How gastrin-releasing peptide opens the spinal gate for itch. Neuron 2019;103:102–17.e105.
[26] Palkar R, Ongun S, Catich E, Li N, Borad N, Sarkisian A, McKemy DD. Cooling relief of acute and chronic itch requires TRPM8 channels and neurons. J Invest Dermatol 2018;138:1391–9.
[27] Peirs C, Williams SP, Zhao X, Walsh CE, Gedeon JY, Cagle NE, Goldring AC, Hioki H, Liu Z, Marell PS, Seal RP. Dorsal horn circuits for persistent mechanical pain. Neuron 2015;87:797–812.
[28] Petitjean H, Pawlowski SA, Fraine SL, Sharif B, Hamad D, Fatima T, Berg J, Brown CM, Jan LY, Ribeiro-da-Silva A, Braz JM, Basbaum AI, Sharif-Naeini R. Dorsal horn Parvalbumin neurons are gate-keepers of touch-evoked pain after nerve injury. Cell Rep 2015;13:1246–57.
[29] Ross SE, Mardinly AR, McCord AE, Zurawski J, Cohen S, Jung C, Hu L, Mok SI, Shah A, Savner EM, Tolias C, Corfas R, Chen S, Inquimbert P, Xu Y, McInnes RR, Rice FL, Corfas G, Ma Q, Woolf CJ, Greenberg ME. Loss of inhibitory interneurons in the dorsal spinal cord and elevated itch in Bhlhb5 mutant mice. Neuron 2010;65:886–98.
[30] Sharif B, Ase AR, Ribeiro-da-Silva A, Séguéla P. Differential coding of itch and pain by a subpopulation of primary afferent neurons. Neuron 2020;106:940–951.e4.
[31] Sharma N, Flaherty K, Lezgiyeva K, Wagner DE, Klein AM, Ginty DD. The emergence of transcriptional identity in somatosensory neurons. Nature 2020;577:392–8.
[32] Skofitsch G, Jacobowitz DM. Calcitonin gene-related peptide coexists with substance P in capsaicin sensitive neurons and sensory ganglia of the rat. Peptides 1985;6:747–54.
[33] Smith KM, Browne TJ, Davis OC, Coyle A, Boyle KA, Watanabe M, Dickinson SA, Iredale JA, Gradwell MA, Jobling P, Callister RJ, Dayas CV, Hughes DI, Graham BA. Calretinin positive neurons form an excitatory amplifier network in the spinal cord dorsal horn. eLife 2019;8:e49190.
[34] Sun YG, Chen ZF. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. Nature 2007;448:700–3.
[35] Sun YG, Zhao ZQ, Meng XL, Yin J, Liu XY, Chen ZF. Cellular basis of itch sensation. Science 2009;325:1531–4.
[36] Usoskin D, Furlan A, Islam S, Abdo H, Lönnerberg P, Lou D, Hjerling-Leffler J, Haeggström J, Kharchenko O, Kharchenko PV, Linnarsson S, Ernfors P. Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. Nat Neurosci 2015;18:145–53.
[37] Zeisel A, Hochgerner H, Lönnerberg P, Johnsson A, Memic F, van der Zwan J, Häring M, Braun E, Borm LE, La Manno G, Codeluppi S, Furlan A, Lee K, Skene N, Harris KD, Hjerling-Leffler J, Arenas E, Ernfors P, Marklund U, Linnarsson S. Molecular architecture of the mouse nervous system. Cell 2018;174:999–1014.e1022.
[38] Zylka MJ, Rice FL, Anderson DJ. Topographically distinct epidermal nociceptive circuits revealed by axonal tracers targeted to Mrgprd. Neuron 2005;45:17–25.