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Pain and itch: insights into the neural circuits of aversive somatosensation in health and disease

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Although pain and itch are distinct sensations, most noxious chemicals are not very specific to one sensation over the other, and recent discoveries are revealing that Trp channels function as transducers for both. A key difference between these sensations is that itch is initiated by irritation of the skin, whereas pain can be elicited from almost anywhere in the body; thus, itch may be encoded by the selective activation of specific subsets of neurons that are tuned to detect harmful stimuli at the surface and have specialized central connectivity that is specific to itch. Within the spinal cord, cross-modal inhibition between pain and itch may help sharpen the distinction between these sensations. Moreover, this idea that somatosensory modalities inhibit one another may be generalizable to other somatosensory subtypes, such as cold and hot. Importantly, just as there are inhibitory circuits in the dorsal horn that mediate cross-inhibition between modalities, it appears that there are also excitatory connections that can be unmasked upon injury or in disease, leading to abnormally elevated pain states such as allodynia. We are now beginning to understand some of this dorsal horn circuitry, and these discoveries are proving to be relevant for pathological conditions of chronic pain and itch.

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Introduction

Pain and itch warn us of physical harm and trigger the appropriate reflex — withdrawal and scratching, respectively — to minimize our exposure to noxious agents. Although pain and itch feel different and elicit separate behavioral responses, these two sensations represent distinct subtypes of aversive somatosensation, and as such they can be viewed as two sides of the same coin.

Despite the fact that pain and itch are unpleasant, it is clear that these sensations are protective, alerting us to a hot flame or a harmful parasite. As evidence, look no further than the example of people with congenital insensitivity to pain, who feel neither pain nor itch, and rarely live beyond thirty, succumbing to injuries, infection, and premature death [1,2]. However, while this extreme example illustrates the utility of acute pain and itch, these sensations ruin one's quality of life when they become chronic conditions. Furthermore, prolonged pain or itch can result in changes in neural circuitry that pathologically magnify the problem. Increasingly, it is recognized that this type of maladaptive synaptic plasticity is a major contributor to persistent pain that represents a disease of the nervous system [3].

Unfortunately, chronic pain and itch are widespread conditions, affecting as many as one in five, and treatments are generally ineffective, pointing to an unmet clinical need [4]. Toward the development of new therapies, it is crucial to gain a better understanding of the neural basis for pain and itch. This review focuses on the recent advances in our understanding of the receptors, neurons and circuits that mediate aversive somatosensation, and how this insight sheds light on the pathological conditions underlying persistent pain and itch.

Trp channels underlie itch as well as pain

While it has been clear for decades that the sensations of pain and itch are initiated by sensory neurons that transmit information from the periphery to the dorsal horn of the spinal cord (or spinal trigeminal nucleus), the manner in which these sensations are encoded remains highly debated [5•]. One of the main current controversies is whether the primary afferents that elicit itch are distinct from those that elicit pain (labeled-line theory) or whether the same primary afferents are capable of triggering both sensations, depending on the pattern or the intensity in which they fire (intensity/pattern theory). The strongest evidence in support of the existence of a labeled-line for itch comes from recordings of individual nerve fibers in humans, which have identified distinct populations of C-fibers (unmyelinated somatosensory neurons) whose activity corresponds to the sensation of itch [6,7]. In addition, spinothalamic neurons that respond to skin application of histamine (which elicits itch) but not mustard oil (which evokes pain) have been identified in cat [8]. Finally, genetic studies in mouse have uncovered an essential role for gastrin releasing peptide receptor (GRPR)-expressing cells in the spinal cord for the

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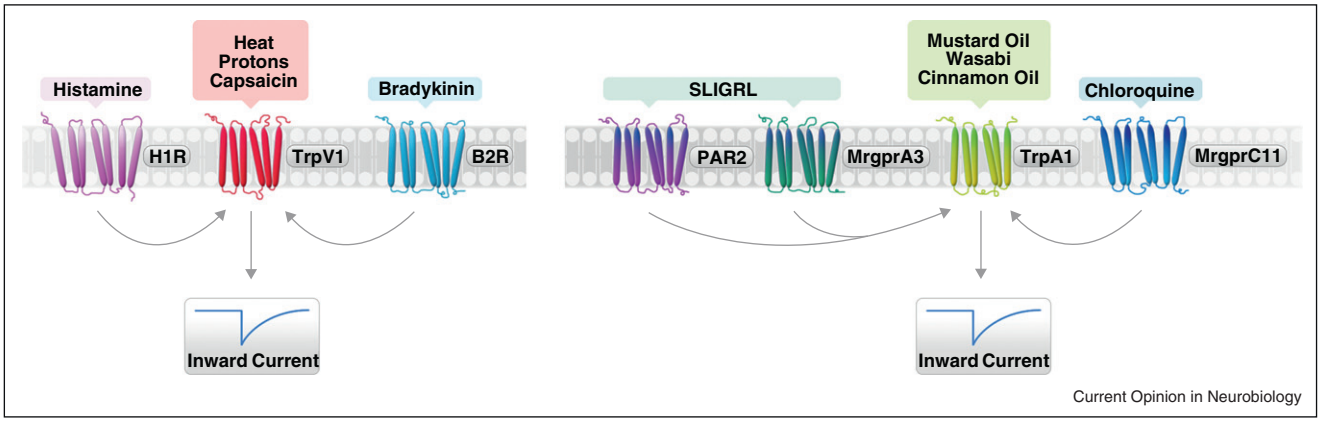
sensation of itch but not pain [9]. Together, these findings argue that there are dedicated peripheral and central neurons that convey itch sensation from the skin to the brain. However, it has been extremely challenging to identify sensory neurons that respond selectively to itch-inducing agents such as histamine but not pain-inducing agents such as capsaicin or mustard oil [10]. So the question remained — how could such neurons specifically convey the sensation of itch if they also respond to painful stimuli?

Recent studies have now clarified this issue by revealing that TrpV1 and TrpA1 — the receptors for capsaicin and mustard oil, respectively — are more than just pain sensors. Rather, it is now emerging that these channels are integrators of diverse noxious stimuli, including those that induce sensations of itch (Figure 1). Specifically, several studies have revealed that TrpV1 and TrpA1 function downstream of a number of itch receptors. For example, the H1 receptor for histamine, a well-known mediator of hives, is coupled to TrpV1 via phospholipase A2 [11,12]. Analogously, several other itch mediators were recently shown to activate G-protein coupled receptors (GPCRs) that couple to TrpA1 [13]. These include Mas-related G protein receptor A3 (MrgprA3), a receptor for the antimalarial drug chloroquine, which causes itch as a side effect, and MrgprC11, a recently identified receptor for itch-inducing peptide, SLIGRL [14••,15•]. The involvement of TrpV1 in both itch and pain is further underscored by the discovery that PIRT, a regulatory subunit of TrpV1, is required for both normal pain and itch [16,17]. Such discoveries imply that antagonists for TrpV1 and TrpA1 should alleviate itch and, at least for TrpV1, this prediction is bearing out [18]. Furthermore, this new insight explains why the ablation of TrpV1-expressing neurons results in the loss of both thermal and itch sensation [12,19,20]. Thus, the seeming paradox that itch-afferents are responsive to capsaicin and/or mustard oil has been resolved, since it turns out that the receptors for these pungent agents are also required for the detection of itch.

Noxious chemicals are not specific to pain or itch

In retrospect, the finding that Trp channels are involved in mediating itch is not altogether surprising, as several other GPCRs that detect noxious stimuli, such as the bradykinin receptor and the protease-activated receptor 2, are likewise known to be coupled to either TrpV1 or TrpA1 [21,22]. Furthermore, the idea that an aversive stimulus can be classified as either an algogen (pain producing) or a pruritogen (itch producing) is increasingly falling by the wayside. Rather, it is beginning to be appreciated that such classifications set up a false dichotomy, because most noxious chemicals can either cause pain or itch, depending on how and where they are applied. For instance, capsaicin, which is considered an algogen, causes itch when it is applied in a punctate fashion to the epidermis [23]. In addition, when capsaicin is applied topically, it initially causes itch, which is followed by sensations of pain [24]. For so-called puritogens, the same is true: histamine causes itch when applied to the surface of the skin, but it elicits pain when it is injected into underlying tissue. This paradigm pertains to a number of other noxious agents including SLIGRL, Bam8-22, serotonin, acetylcholine, bradykinin, endothelin-1, formalin and prostaglandin-E2, to name a few. Indeed, given that the function of both itch and pain is to warn us of noxious agents, it makes sense that these sensory neurons for pain and itch would be tuned to broadly overlapping sets of irritating chemical stimuli (Figure 2a).

Figure 1



Trp channels underlie pain and itch. TrpV1 and TrpA1 are calcium-permeable cation channels that are directly activated by a variety of noxious stimuli, including heat, acid and capsaicin (TrpV1) and mustard oil, wasabi and cinnamon oil (TrpA1). In addition, numerous GPRCs that are involved in detecting itch and pain stimuli are coupled to either TrpV1 or TrpA1, including the histamine receptor (H1R), the bradykinin receptor (B2R) the protease-activated receptor 2 (PAR2), MrgprA3, and MrgprC11.

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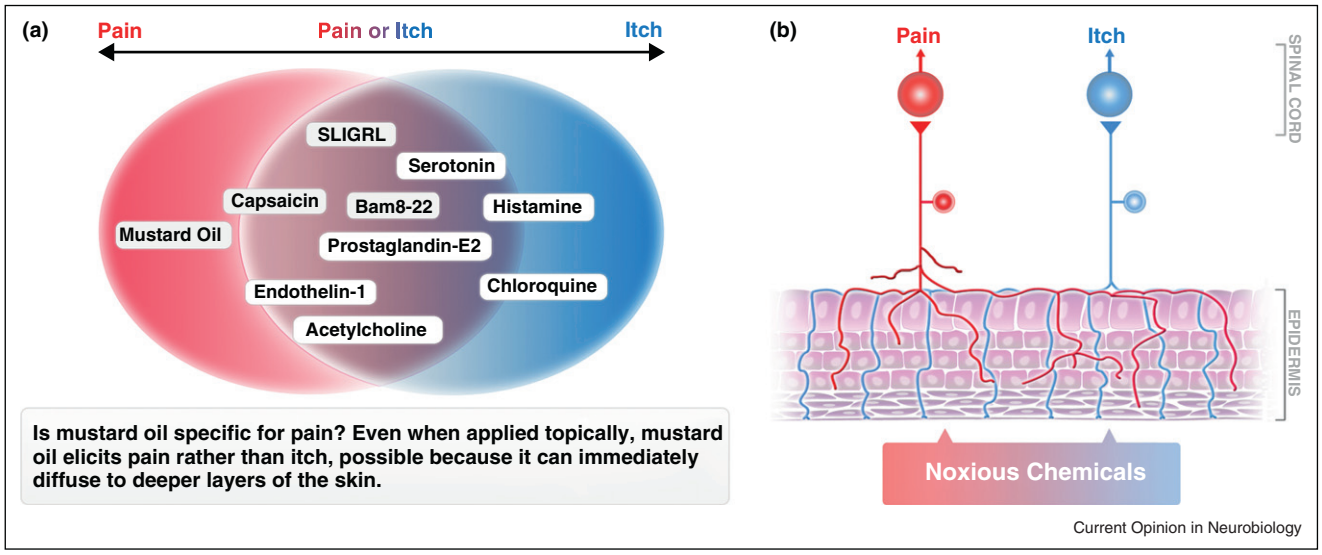
Figure 2



Primary afferents may selectively convey pain or itch, even if noxious chemicals lack specificity. **(a)** Almost all noxious chemicals can, depending on how they are applied, elicit either pain or itch. **(b)** Model: discrimination between itch and pain may be achieved, in part, via sensory afferents with differential distribution of free-nerve endings and specialized central connectivity. Noxious chemicals could either elicit pain or itch depending on which subset of primary afferents are predominantly activated by a given stimulus.

However, the idea that neurons that convey pain and itch respond to overlapping stimuli brings us back to square one — how are these distinct sensations discriminated from one another? This dilemma is the focus of ongoing research, and for now we can only speculate. One proposed explanation is that pain and itch may be elicited by common primary afferents. For instance, it has recently been suggested that a given polymodal C-fiber could potentially use distinct second messenger pathways to distinguish between pain and itch stimuli in the periphery [25]. Others have suggested that distinct neurochemical mediators released at central terminals, namely glutamate and gastrin-releasing peptide, may be selective for pain and itch, respectively [26,27]. However, these explanations appear to be at odds with the observation that, when itch is evoked by the activation of select nerve fibers in the skin, changing the stimulus intensity does not change the sensory percept — it is always itch, not pain, that is elicited, suggesting that an individual nerve fiber is either wired to convey pain or itch, not both [28].

To make sense of these disparate ideas, it is important to note that the key difference between pain and itch is not the nature of the stimulus but rather its location — itch is perceived at the very surface of the skin, whereas pain can be elicited from almost anywhere in the body. It follows therefore that the salient feature that distinguishes neurons that mediate pain from those that mediate itch is their peripheral location and central connectivity (Figure 2b). Thus, itch-mediating neurons may be distinct from other C-fibers that elicit pain because they have peripheral terminals exclusively in the most superficial aspects of the skin and central terminals in the dorsal horn that can selectively activate specific second-order projection neurons that transfer itch inputs to the brain. In other words, itch afferents are unique because they are wired to elicit itch. If you activate this subset exclusively (even if you do so using capsaicin as the agonist) you will feel itch, rather than pain or heat, because these afferents show cellular specificity for itch, despite lacking molecular specificity in terms of receptor expression.

According to this model, the neurons that convey pain and those that convey itch are likely to express many common receptors (such as TrpV1), and thus it will be challenging to prove that primary afferents for pain and itch are separate populations that convey distinct sensations. To do so will likely require the discovery of some distinguishing molecular feature to enable the genetic identification and regulation of itch-specific afferents as distinct from a larger subset that mediate pain responses. In this regard, select members of the recently identified family of Mrgprs, such as MrgprA3 and MrgprC11, may be good candidates.

Specific modalities are subserved by labeled lines that project to distinct layers of the dorsal horn

Beyond noxious chemicals, there are a number of other types of physical harm — too hot, too cold, and too sharp — that also elicit pain, and increasingly it appears that these distinct sensations are mediated by specific subsets of neurons with specialized termination zones in

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the dorsal horn of the spinal cord. This general idea — that different types of somatosensory neurons convey different sensations — is not new. For instance, it is well known that primary afferent neurons mediate pain project mainly to laminae I and II of the dorsal spinal cord, whereas those mediate innocuous touch project predominantly to laminae III–V [29•,30]. However, whether an analogous logic existed among C-fibers was unknown. As of a few years ago, although many distinct subtypes of C-fibers had been classified based on their response properties, only two main classes had been identified with neurochemical markers (peptidergic and non-peptidergic), and the functional significance of these two classes remained unclear.

Recent discoveries have begun to shed light on this issue through the genetic labeling of several new subtypes of C-fibers that appear to underlie different aspects of sensation, namely cold (Trpm8-expressing neurons), mechanical pain (MrgprD-expressing neurons), and C-fiber mediated light touch (Vglut3/tyrosine hydroxylase-expressing neurons), not to mention MrgprB4-expressing neurons, whose function remains to be identified [31–34,35••]. Furthermore, new evidence from cell ablation studies in the adult points to the possibility that two main types of pain, thermal and mechanical, may be primarily mediated by distinct subsets of fibers with largely non-overlapping termination zones (those that express TrpV1 and those that express MrgprD, respectively) [19]. Thus, it is looking increasingly as if the dorsal horn of the spinal cord is stratified by somatosensory modality, with different populations of primary sensory neurons representing labeled-lines for discrete aspects of somatosensation.

Neural circuits of pain and itch

The finding that the neurons underlying specific modalities and submodalities of somatosensation are generally arranged in particular lamina of the dorsal horn imply that there are characteristic connections within and between the laminae in the spinal cord that form the basis of neural circuits. Consistent with this idea, it appears that distinct somatosensory modalities are coupled across laminae both through inhibitory circuits, which may aid in stimulus discrimination, and through excitatory circuits, which (though normally silent) can be unmasked upon injury and in disease. Because chronic pain and itch result partly from maladaptive changes in these spinal cord circuits, there is a pressing need to understand the fundamental logic of wiring within the spinal cord and uncover the principles that govern their plasticity.

Normal sensation: inhibitory circuits between somatosensory modalities sharpen sensory acuity

Everyone is familiar with the idea that itch is relieved (at least temporarily) by scratching — that is why we scratch. Studies using human subjects have revealed that itch can likewise be reduced by application of heat, cold or pain-inducing chemicals. Furthermore, this type of inhibition by so-called counter-stimuli is not limited to itch — cold lessens the sting from a bee whereas gentle rubbing reduces the unpleasant tingle of bumping one's 'funny bone'. A key feature of this inhibition between sensory modalities is that counter-stimuli can work at a distance of many centimeters, outside the receptive field of the primary stimulus, suggesting that central neurons are involved in mediating this effect [36]. This cross-inhibition between a variety of somatosensory modalities and submodalities may function to sharpen sensory acuity just as, for instance, inhibition between red-sensitive and green-sensitive neurons in the retina improves color discrimination [37].

We now have a concrete example of this type of cross-inhibition through an important study that begins to unravel the neural circuits through which menthol soothes pain [38•]. When the interconnections between dorsal horn neurons were mapped through extensive paired-cell recordings, it turned out that different inhibitory interneuron subtypes receive input from distinct types of C-fiber afferents. Specifically, primary afferents that express TrpM8, the receptor for menthol, synapse selectively onto a specific subtype of inhibitory interneuron in the dorsal horn (tonic central interneurons) and not another (islet interneurons) that receives input from other C-nociceptors. Moreover, these two interneuron subtypes reciprocally inhibit one another (Figure 3a). Thus, this circuitry provides the neural substrate through which cold and pain signals could inhibit one another within the dorsal spinal cord.

Inhibition between somatosensory subtypes may be particularly important for pain versus itch to help determine the appropriate behavioral response. If only a small subset of predominantly itch-mediating fibers are activated by a mosquito bite, itch may dominate over pain and elicit scratching, whereas if a larger subset of predominantly pain-mediating neurons are activated by a stepping on a sharp stone, pain may dominate over itch and trigger withdrawal. This concept, which is termed the selectivity theory, has recently gained more attention following the identification of a specific subset of inhibitory interneurons that may help to distinguish pain from itch [39••]. These interneurons are found in the superficial laminae of the dorsal horn, and they can be defined by their developmental expression of the transcription factor, Bhlhb5. Mice lacking Bhlhb5 interneurons in the dorsal horn show normal behavior in response to painful stimuli, but dramatically elevated scratching in response to itch-inducing agents, implying that these neurons normally function to inhibit itch.

Further evidence supporting the existence of neural circuits that mediate the inhibition of itch by pain comes

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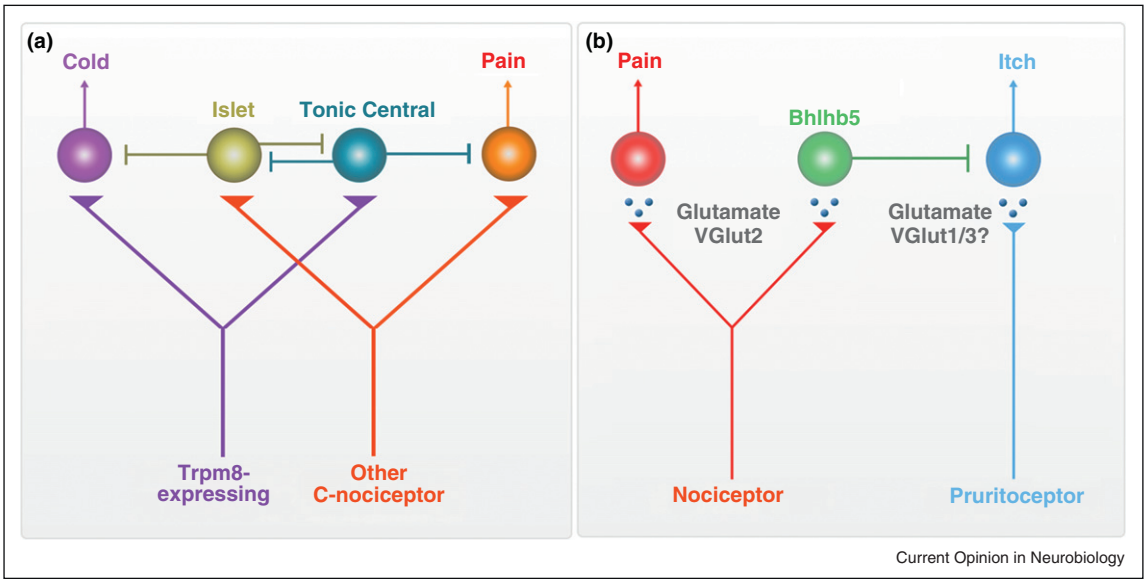
Figure 3



Inhibition between modalities may sharpen somatosensory acuity. **(a)** Model for the cross-inhibition between cold and pain. TrpM8-expressing primary afferents, which are thought to convey cold, directly synapse onto tonic central interneurons, but not islet cells, which receive other C-fiber input. Furthermore, tonic central and islet cells show reciprocal inhibition. This reciprocal inhibition may help discriminate between cold and other types of pain. **(b)** Model for the inhibition of itch by pain. Many pain-afferents express VGlut2, whereas itch-afferents may express Vglut1 or Vglut3. Within the spinal cord, interneurons defined by the developmental expression of Bhlhb5 inhibit itch, but not pain. According to the selectivity theory, when both nociceptors and pruritoceptors are activated, pain will dominate over itch due to this inhibition.

from two recent studies involving the selective ablation of the vesicular glutamate transporter type 2 (Vglut2) in either all or in subsets of primary sensory neurons in the dorsal root ganglia (DRG) [40•,41•]. Because Vglut2 is the only glutamate transporter expressed in many DRG neurons, this genetic manipulation effectively silences excitatory neurotransmission in subsets of primary afferents, but not others that express either Vglut1 or Vglut3. Importantly, loss of Vglut2 in all DRG neurons resulted in mice that were less sensitive to pain but more sensitive to itch. Assuming that itch-afferents use glutamate, rather than a neuropeptide, to signal itch (which appears likely in light of new evidence [42•]), these findings imply that itch is mediated by a subpopulation of DRG neurons that express Vglut1 or Vglut3 instead of Vglut2. Moreover, these studies suggest a model in which Vglut2-containing primary afferents are the input neurons of a spinal circuit that both triggers pain and inhibits itch (Figure 3b).

Finally, direct evidence in favor of the idea that the activation of pain-afferents inhibits itch is provided by electrophysiological studies revealing that scratching inhibits the activity of histamine-responsive projection neurons in the dorsal spinal cord [43], likely via GABAergic and glycinergic interneurons [44]. Together, these data suggest a neural circuit in which inhibitory interneurons, possibly those that express Bhlhb5, mediate the inhibition of itch by pain in the spinal cord, thereby sharpening sensory discrimination (Figure 3b). Furthermore, there is good evidence that opioid systems appear act in parallel with inhibitory neurotransmitters to mediate cross inhibition between pain and itch. For instance, activation of mu-opioid receptors in the spine with morphine provides relief from pain, but evokes itch [27], thereby enhancing the discrimination between these sensations. Recent studies have revealed the molecular basis for phenomenon, showing that morphine's opposite effects on itch and pain are mediated by distinct isoforms of the mu-opioid receptor [45••].

Disease conditions: disinhibited excitatory circuits cross somatosensory modalities to mediate pain sensitization

Once you have pain, a broad range of somatosensory stimuli can trigger more pain, even those that are normally innocuous. Importantly, this increase in pain sensitivity is not simply due to peripheral inflammation [46]. Instead, there is good evidence that excitatory circuits within the spinal cord become unmasked by sustained noxious input, leading to the blurring of somatosensory modalities. For instance, sunburn causes pain in response to innocuous stimuli such as gentle touch, a phenomenon called allodynia. Analogously, following application of histamine, gentle stroking of the skin evokes abnormal itch sensations in the surrounding region, so-called itchy skin [47]. Further evidence for such cross-modal facilitation is evidenced in

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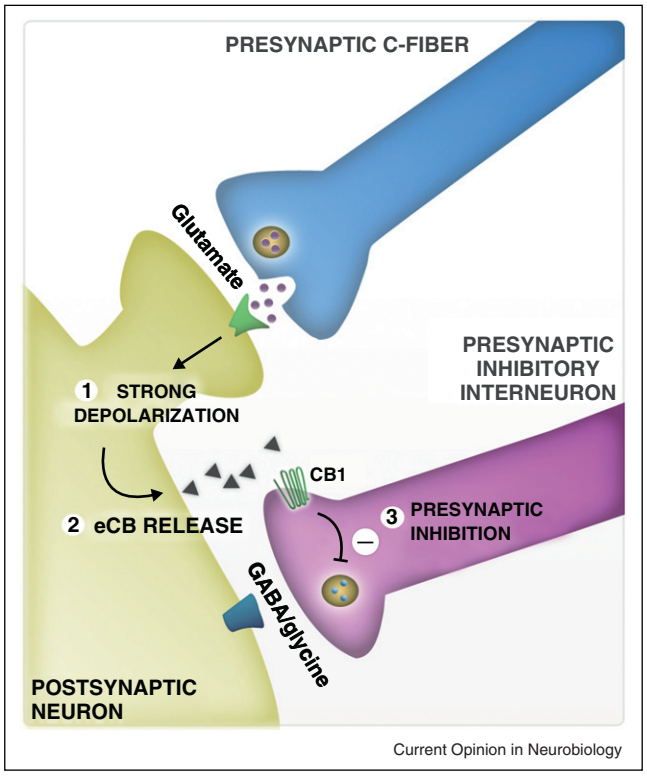
disease states. Thus, histamine induces primarily pain rather than itch in people suffering from neuropathic pain, and conversely bradykinin induces primarily itch rather than pain in people suffering from atopic dermatitis [48,49]. These types of hypersensitivity are caused, in part, by central sensitization due to neural plasticity within the dorsal spinal cord. While we still do not fully understand the neural circuits that are mediating these effects, there is increasing evidence that they involve excitatory neural connections that reach across labeled-lines. Consistent with this, recent studies have provided direct evidence for the existence of such circuits and revealed the neural basis for mechanical allodynia.

To a large degree, pain is conveyed from the spinal cord to the brain via lamina I projection neurons in the dorsal spinal cord. Since low threshold touch sensations are received in laminae III–V, the connection between these two sensations was not clear. Electrophysiological studies have now revealed the existence of polysynaptic circuits that couple low threshold input from deeper lamina onto lamina I output neurons [50•]. Under normal conditions, transmission of this information is silenced by inhibitory interneurons. However, sustained noxious input results in release of this inhibition, likely through multiple mechanisms acting in parallel, and this type of central sensitization can occur within hours of injury [51]. Recently, one of these mechanisms has been elucidated in detail, revealing a molecular basis for activity-dependent disinhibition in the dorsal horn [52••]. Specifically, when C-fiber input into the dorsal horn is abnormally sustained as the result of injury, this strong, persistent activity in nociceptors results in the release of endocannabinoids from the post-synaptic target, and these endocannabiniods act upon nearby inhibitory neurons to inhibit neurotransmitter release. As a consequence, endocannabinoid-mediated disinhibition allows low threshold input to activate pain circuits in the superficial dorsal horn, resulting in allodynia (Figure 4).

Figure 4



Endocannabinoid-mediated disinhibition leads to touch-evoked pain. In response to prolonged C-fiber input, strong depolarization of the post-synaptic neuron results in the release of endocannabinoids (eCB), which bind to CB1 receptors on inhibitory interneurons. Activation of CB1 receptors causes inhibition of neurotransmitter release, thereby decreasing inhibition. This disinhibition allows low-threshold input to activate pain circuits, leading to the blurring of touch and pain.

Conclusions

Dissecting these and other neural circuits in the dorsal spinal cord is key to our understanding of the pathology that accompanies chronic pain, irrespective of the cause. Thus, whether persistent pain is the result of ongoing activity in C-fibers, as in inflammatory conditions such as rheumatoid arthritis, or whether it is caused by damage to nerve fibers themselves, as in neuropathic states such as diabetic neuropathy, the abnormal sensory input can modulate circuits within the dorsal horn. Similarly with itch, inflammatory conditions like atopic dermatitis and neuropathic conditions like post-herpetic itch can both result in pathological changes in the dorsal spinal cord that represent a disease state. Fortunately, advances in molecular genetic approaches are allowing these circuits to be studied with greater ease, and so the future promises a clearer picture of the neural circuits underlying aversive somatosensation in both health and disease.

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- •• of outstanding interest

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