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Peripheral afferents and spinal inhibitory system in dynamic and static mechanical allodynia

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Mechanical allodynia is a debilitating pain from innocuous mechanical stimuli such as touch. To unravel its mechanism, one approach has been to focus on the fact that different afferent types mediate mechanical allodynia from stimuli ‘moving’ across the skin (e.g., brushing) and from stimuli ‘fixed’ on a certain spot (e.g., gentle pressure or weak punctate stimulation); the former type of allodynia being designated ‘dynamic’ and the latter, ‘static’ [23; 39] (these terms, however, differentiate mechanical allodynia by ‘stimulation mode’, not by afferent type). Thus, since the stimulation mode differs between dynamic and static mechanical allodynia, different afferent inputs are presumably generated and then differentially processed in the spinal cord. In this regard, recent literature suggests that inhibitory processing of afferent inputs by glycine- and γ -aminobutyric acid (GABA) transmission differs between dynamic and static mechanical allodynia, respectively [36; 41]. In addition to the dynamic/static stimulation mode, factors such as the size/depth of stimulated area (e.g., large pressure probe *vs.* von Frey filament) and the stimulation velocity/duration can influence mechanical allodynia because of spatial/temporal summation, counteraction between afferents [2; 34], and afferents’ adaptation properties.

Since the nature of afferent inputs and the spinal inhibitory processing seem to differ in the 2 types of mechanical allodynia, this review summarizes what we know of these issues in various pathologic and experimental pain conditions. In this review, as a caveat, we do not deal with ‘mechanical hyperalgesia’, a pain from a mechanical stimulus that normally provokes pain.

1. Peripheral afferents mediating dynamic and static mechanical allodynia

Most A β -fibers are low-threshold mechanoreceptors, while the majority of mechanosensitive A δ /C-fibers are high-threshold, leading to the generalization that A β -fibers are touch sensors, whereas mechanosensitive A δ /C-fibers are mechanical nociceptors. Although there are A δ /C low-threshold mechanoreceptors functioning as light touch sensors in the hairy skin, their exact role in mechanical allodynia in humans remains unclear [29; 38].

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As mechanical allodynia is evoked by low-intensity stimulation, it must be initiated by excitation of touch sensors or sensitized mechanical nociceptors that become responsive to low-intensity stimulation (for nociceptor sensitization, see [17]). Literature shows that blocking A-fiber conduction abolishes dynamic mechanical allodynia [22; 23; 39; 52]; in two studies, the abolition coincided with touch sensory loss, suggesting A β -fibers as the symptom-mediating afferents. In contrast, static mechanical allodynia appears to be mediated by various afferent types in different pathologic or experimental conditions (Table 1).

1.1. Afferents mediating static mechanical allodynia in peripheral neuropathy

Piezo2 is a mechanosensitive ion channel that confers low-threshold mechanosensitivity to A-fibers. The loss of Piezo2 causes significant defects in touch sensation without affecting normal mechanical nociceptive behaviors evoked by pressure/punctate stimulation [47]. When mechanical allodynia to punctate stimulation developed in mice after peripheral nerve injury, downregulating Piezo2 expression alleviated the allodynia, suggesting that low-threshold A-fibers mediate the allodynia [10]. Similarly, neuropathic mechanical allodynia to punctate stimulation was temporarily relieved by delivering the lidocaine derivative QX-314 selectively into A-fibers in mice [56]; and the allodynia was only mildly attenuated when the anesthetic was delivered into a subpopulation of A δ /C-nociceptors expressing Transient Receptor Potential channel V1 (TRPV1).

By contrast, blocking A-fiber conduction did not abolish pressure-evoked mechanical allodynia in 15 of 18 neuropathic pain patients, suggesting that C-fibers mediate the allodynia in these patients [39]. Also in rats exhibiting mechanical allodynia to punctate stimulation after nerve injury, the allodynia was alleviated when TRPV1-expressing nociceptors were ‘desensitized’ by multiple doses of intraplantar capsaicin or ‘silenced’ by QX-314 [4; 13].

Concerning what seems to be an inconsistent role of TRPV1-expressing nociceptors in mediating neuropathic static mechanical allodynia, we should consider species differences in mechanosensory function of TRPV1-expressing cutaneous afferents. These afferents have little or no mechanosensory function in normal mice [6; 26; 37], unlike rats and humans [3; 33]. Therefore, in mice, we may expect no significant contribution of TRPV1-expressing nociceptors to static mechanical allodynia unless they acquire such mechanosensitivity, or other mechanosensitive afferents start expressing TRPV1 in pathological conditions. Such abnormal function/expression of TRPV1 after nerve injury [12; 32; 54; 55] would confound the afferent type identification based on afferents’ reactivity to TRPV1 agonists/antagonists. Interestingly, ‘neonatal ablation’ of TRPV1-expressing nociceptors in rats did not prevent static mechanical allodynia after nerve injury in adulthood [48]. It would be interesting to examine whether abnormal expression of TRPV1 by nerve injury would contribute to the allodynia in this rat model.

1.2. Afferents mediating static mechanical allodynia in inflammation

When inflammatory mechanical allodynia to pressure/punctate stimulation developed after complete Freund’s adjuvant (CFA) injection, a TRPV1 antagonist, or silencing of TRPV1-

expressing nociceptors by QX-314, significantly alleviated the allodynia in rats [4; 16]. However, as expected based on the difference between rats and mice in TRPV1-expressing cutaneous nociceptors, inflammatory static mechanical allodynia in mice was not affected when TRPV1 itself or TRPV1-expressing afferents were inhibited [5; 6; 28; 37]. Instead, in CFA-injected mice, targeting TRPA1-expressing nociceptors before or 2–3 days after the inflammation prevented or alleviated the allodynia [15; 28]. These results may seem to contradict the findings that inhibiting A-fibers in mice by Piezo2 downregulation (initiated 1 day post-CFA) significantly alleviated the inflammatory static mechanical allodynia 4 days post-CFA [49]. However, Piezo2 downregulation initiated 3 days before CFA injection did not prevent static mechanical allodynia 1 day post-CFA [47; 49]. Collectively, it appears that TRPA1-expressing afferents mediate mouse inflammatory static mechanical allodynia early after the inflammation develops (3 days post-CFA), whereas A-fibers do so later (4 days post-CFA).

1.3. Afferents mediating static mechanical allodynia in primary and secondary zones of skin injury

Static mechanical allodynia develops inside (primary zone) and outside (secondary zone) injured skin areas. Blocking A-fiber conduction failed to abolish pressure-evoked mechanical allodynia in the primary zone injured by topical capsaicin or freezing, suggesting C-fibers are the symptom-mediating afferents [22; 23]. On the contrary, in the secondary zone of capsaicin-injected human skin area, static mechanical allodynia to punctate stimulation (at an intensity normally below the 50% pain threshold) was abolished by blocking A-fiber conduction [59].

The above findings suggest that dynamic mechanical allodynia is consistently mediated by touch sensors and static mechanical allodynia by either touch sensors or sensitized mechanical nociceptors, depending on pathological/experimental conditions. Concerning the role of sensitized mechanical nociceptors in static mechanical allodynia, no clear evidence of 'decreased nociceptor mechanical thresholds' has been obtained [1; 19; 28; 50] despite that static mechanical allodynia is characterized by a decreased pain threshold. Sensitized mechanical nociceptors rather show increased firing upon suprathreshold stimulation. It seems necessary to compare the mechanical thresholds for nociceptor excitation with those for pain perception/behaviors in static mechanical allodynia conditions. In one exemplary study using rats, normal mechanical thresholds for nociceptive behavior were significantly higher than those for nociceptor excitation (which supports the idea that suprathreshold nociceptor activity is necessary to evoke normal mechanical pain sensations in humans [18]). After incision injury, the behavioral thresholds dropped to within the threshold range of mechanical nociceptors [44]. Therefore, it could be that nociceptor sensitization to suprathreshold stimulation is manifested as static mechanical allodynia in some conditions or simple nociceptor excitation at threshold intensity, which is normally insufficient to activate spinal nociceptive neural circuits, becomes able to do so because the circuits are sensitized to afferent inputs (for central sensitization, see [25]). In the following, we address the literature reporting spinal disinhibition as one of the key central sensitization mechanisms for mechanical allodynia.

2. Dysfunction of spinal inhibitory system in dynamic and static mechanical allodynia

Because nociceptors already have connections to nociceptive neural circuits in the spinal dorsal horn of naïve animals, nociceptors can easily evoke allodynia when they are sensitized and/or the spinal nociceptive circuits are sensitized to their inputs. However, since touch sensors are normally unable to activate nociceptive circuits, altered processing of their inputs must take place for their excitation to evoke allodynia.

The nociceptive circuits in the spinal cord are under strong inhibition, an important component of which are interneurons releasing the inhibitory neurotransmitters GABA and glycine. Many pathological pain conditions are associated with decreased spinal inhibition [58], and experimentally suppressing GABAergic/glycinergic inhibition makes excitation of spinal dorsal horn neurons to brush, pressure, and pinch stimulations greater than normal [42] and reveals novel A-fiber excitatory inputs to the spinal nociceptive circuits [53].

In the rodent spinal dorsal horn, glycine is mostly detected in GABAergic neurons, and fast inhibitory synaptic transmission in this area is often composed of both GABAergic (GABA_A receptor-mediated) and glycinergic components [21; 45; 46; 51]. Accordingly, intrathecal injection of blockers of GABA_A (bicuculline or picrotoxin) and glycine receptors (strychnine) produces mechanical allodynia [40; 57]. Recent studies show that the disinhibition of each system differentially affects spinal neuronal responses to A β -inputs and behaviors to dynamic and static mechanical stimulations.

In the rat spinal cord, A β -inputs excite inhibitory interneurons that in turn suppress the activation of protein kinase C γ (PKC γ)-expressing excitatory interneurons by the same A β -inputs. This feed-forward inhibition was removed by strychnine but not by bicuculline [31]. In line with these findings, rats treated with intracisternal strychnine showed dynamic mechanical allodynia to air puffing on the face in a PKC γ antagonist-dependent manner [35]. Notably, these rats did not show static mechanical allodynia to punctate stimulation of the face. In contrast, rats treated with intracisternal bicuculline showed static but not dynamic mechanical allodynia [36]. Collectively, these studies suggest that glycinergic disinhibition in the rat medullary dorsal horn (spinal trigeminal nucleus) allows dynamic stimulation-generated A β -inputs to activate nociceptive circuits but does not abnormally process static stimulation-generated afferent inputs. On the other hand, suppression of GABA_A receptor-mediated inhibition in the same region activates nociceptive circuits by the latter afferent inputs but not by the former. To better understand this differential processing of mechanosensory inputs by the two inhibitory systems at a circuit level, it will be necessary to identify the nature of afferent inputs mediating the bicuculline-induced static mechanical allodynia in the rat face.

In other body parts of rats and mice and in the mouse face, however, have been obtained results that speak against the differential role of glycinergic and GABAergic disinhibition in the development of dynamic and static mechanical allodynia (Table 2). For instance, either intrathecal strychnine or targeted silencing of spinal glycinergic neurons resulted in static mechanical allodynia to punctate stimulation in the rat and mouse hindpaw [14; 31]. In

addition, intracisternal bicuculline produced dynamic mechanical allodynia in the mouse face [27] and intrathecal bicuculline similarly in the flank of both rats and mice [20; 40]. The combination of intrathecal bicuculline and strychnine was synergistic in producing dynamic mechanical allodynia in rats [30].

As possible explanations for the above discrepancy, it should be noted that GABAergic and glycinergic inhibitory systems are not mutually exclusive. Spinal dorsal horn inhibitory interneurons construct an interacting neural network, feeding GABAergic and glycinergic fast inhibitory inputs to themselves [24]. That similar blockage of GABA_A receptor-mediated inhibition either in the rat spinal cord vs. medullary dorsal horn or in the rat vs. mouse medullary dorsal horn produces different results, warrants studies examining regional and species differences in the degree of GABAergic and glycinergic inhibitory interactions suppressing mechanosensory afferent inputs generated by these various stimulation modes.

Targeted manipulations of specific spinal dorsal horn neurons reveal critical roles of phenotypically diverse inhibitory interneurons in the feed-forward suppression of A β -input-evoked nociceptive circuit activation [8; 9; 43] where a population of spinal excitatory interneurons transiently expressing vesicular glutamate transporter 3 (VGLUT3) participate in dynamic but not static (punctate) mechanical allodynia, while somatostatin-expressing ones do in both [7]. It would be interesting to examine whether GABAergic and glycinergic inhibition differentially affect responses of these two excitatory neuronal populations to mechanosensory afferent inputs.

3. Concluding remarks

In general, dynamic mechanical allodynia is mediated by A β -fibers in pathological conditions, whereas static mechanical allodynia is mediated by various afferent types depending on the pain conditions. Spinal disinhibition allows abnormal processing of these afferent inputs to produce mechanical allodynia, and there seem to be regional/species differences in glycinergic and GABAergic inhibitory processing of afferent inputs generated by dynamic/static stimulation.

Since dynamic and static mechanical allodynia can differ in their peripheral and central neural substrates, their sensitivities to therapeutics could also differ. Indeed, for example, dynamic mechanical allodynia was significantly attenuated by μ -opioid agonists, whereas no consistent effect was seen on static mechanical allodynia, in neuropathic pain patients [11]. In contrast, morphine was effective only on static mechanical allodynia in animals [7; 13]. Therefore, with species differences being considered, investigating both types of mechanical allodynia is necessary to better understand the pathological mechanisms and ultimately develop mechanism-based, more efficacious treatments.

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References

1. Andrew D, Greenspan JD. Mechanical and heat sensitization of cutaneous nociceptors after peripheral inflammation in the rat. *J Neurophysiol.* 1999; 82(5):2649–2656. [PubMed: 10561434]
2. Arcourt A, Gorham L, Dhandapani R, Prato V, Taberner FJ, Wende H, Gangadharan V, Birchmeier C, Heppenstall PA, Lechner SG. Touch Receptor-Derived Sensory Information Alleviates Acute Pain Signaling and Fine-Tunes Nociceptive Reflex Coordination. *Neuron.* 2017; 93(1):179–193. [PubMed: 27989460]
3. Binshok AM, Bean BP, Woolf CJ. Inhibition of nociceptors by TRPV1-mediated entry of impermeant sodium channel blockers. *Nature.* 2007; 449(7162):607–610. [PubMed: 17914397]
4. Brenneis C, Kistner K, Puopolo M, Segal D, Roberson D, Sisignano M, Labocha S, Ferreirós N, Strominger A, Cobos EJ, Ghasemlou N, Geisslinger G, Reeh PW, Bean BP, Woolf CJ. Phenotyping the function of TRPV1-expressing sensory neurons by targeted axonal silencing. *J Neurosci.* 2013; 33(1):315–326. [PubMed: 23283344]
5. Bölcskei K, Helyes Z, Szabó A, Sándor K, Elekes K, Németh J, Almási R, Pintér E, Petho G, Szolcsányi J. Investigation of the role of TRPV1 receptors in acute and chronic nociceptive processes using gene-deficient mice. *Pain.* 2005; 117(3):368–376. [PubMed: 16150543]
6. Cavanaugh DJ, Lee H, Lo L, Shields SD, Zylka MJ, Basbaum AI, Anderson DJ. Distinct subsets of unmyelinated primary sensory fibers mediate behavioral responses to noxious thermal and mechanical stimuli. *Proc Natl Acad Sci U S A.* 2009; 106(22):9075–9080. [PubMed: 19451647]
7. Cheng L, Duan B, Huang T, Zhang Y, Chen Y, Britz O, Garcia-Campmany L, Ren X, Vong L, Lowell BB, Goulding M, Wang Y, Ma Q. Identification of spinal circuits involved in touch-evoked dynamic mechanical pain. *Nat Neurosci.* 2017; 20(6):804–814. [PubMed: 28436981]
8. Cui L, Miao X, Liang L, Abdus-Saboor I, Olson W, Fleming MS, Ma M, Tao YX, Luo W. Identification of Early RET+ Deep Dorsal Spinal Cord Interneurons in Gating Pain. *Neuron.* 2016; 91(6):1413. [PubMed: 27657453]
9. Duan B, Cheng L, Bourane S, Britz O, Padilla C, Garcia-Campmany L, Krashes M, Knowlton W, Velasquez T, Ren X, Ross S, Lowell BB, Wang Y, Goulding M, Ma Q. Identification of spinal circuits transmitting and gating mechanical pain. *Cell.* 2014; 159(6):1417–1432. [PubMed: 25467445]
10. Eijkelkamp N, Linley JE, Torres JM, Bee L, Dickenson AH, Gringhuis M, Minett MS, Hong GS, Lee E, Oh U, Ishikawa Y, Zwartkuis FJ, Cox JJ, Wood JN. A role for Piezo2 in EPAC1-dependent mechanical allodynia. *Nat Commun.* 2013; 4:1682. [PubMed: 23575686]
11. Eisenberg E, McNicol ED, Carr DB. Efficacy of mu-opioid agonists in the treatment of evoked neuropathic pain: Systematic review of randomized controlled trials. *Eur J Pain.* 2006; 10(8):667–676. [PubMed: 16337151]
12. Facer P, Casula MA, Smith GD, Benham CD, Chessell IP, Bountra C, Sinisi M, Birch R, Anand P. Differential expression of the capsaicin receptor TRPV1 and related novel receptors TRPV3, TRPV4 and TRPM8 in normal human tissues and changes in traumatic and diabetic neuropathy. *BMC Neurol.* 2007; 7:11. [PubMed: 17521436]
13. Field MJ, Bramwell S, Hughes J, Singh L. Detection of static and dynamic components of mechanical allodynia in rat models of neuropathic pain: are they signalled by distinct primary sensory neurones? *Pain.* 1999; 83(2):303–311. [PubMed: 10534603]
14. Foster E, Wildner H, Tudeau L, Haueter S, Ralvenius WT, Jegen M, Johannssen H, Hösli L, Haenraets K, Ghanem A, Conzelmann KK, Bösl M, Zeilhofer HU. Targeted ablation, silencing, and activation establish glycinergic dorsal horn neurons as key components of a spinal gate for pain and itch. *Neuron.* 2015; 85(6):1289–1304. [PubMed: 25789756]
15. Garrison SR, Stucky CL. Contribution of transient receptor potential ankyrin 1 to chronic pain in aged mice with complete Freund's adjuvant-induced arthritis. *Arthritis Rheumatol.* 2014; 66(9):2380–2390. [PubMed: 24891324]
16. Gavva NR, Tamir R, Qu Y, Klionsky L, Zhang TJ, Immke D, Wang J, Zhu D, Vanderah TW, Porreca F, Doherty EM, Norman MH, Wild KD, Bannon AW, Louis JC, Treanor JJ. AMG 9810 [(E)-3-(4-t-butylphenyl)-N-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl)acrylamide], a novel vanilloid

- receptor 1 (TRPV1) antagonist with antihyperalgesic properties. *J Pharmacol Exp Ther.* 2005; 313(1):474–484. [PubMed: 15615864]
17. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. *Nat Med.* 2010; 16(11): 1248–1257. [PubMed: 20948530]
 18. Greenspan JD, Thomadaki M, McGillis SL. Spatial summation of perceived pressure, sharpness and mechanically evoked cutaneous pain. *Somatosens Mot Res.* 1997; 14(2):107–112. [PubMed: 9399411]
 19. Hillery CA, Kerstein PC, Vilceanu D, Barabas ME, Retherford D, Brandow AM, Wandersee NJ, Stucky CL. Transient receptor potential vanilloid 1 mediates pain in mice with severe sickle cell disease. *Blood.* 2011; 118(12):3376–3383. [PubMed: 21708890]
 20. Ishikawa T, Marsala M, Sakabe T, Yaksh TL. Characterization of spinal amino acid release and touch-evoked allodynia produced by spinal glycine or GABA(A) receptor antagonist. *Neuroscience.* 2000; 95(3):781–786. [PubMed: 10670445]
 21. Keller AF, Coull JA, Chery N, Poisbeau P, De Koninck Y. Region-specific developmental specialization of GABA-glycine cosynapses in laminae I-II of the rat spinal dorsal horn. *J Neurosci.* 2001; 21(20):7871–7880. [PubMed: 11588160]
 22. Kilo S, Schmeltz M, Koltzenburg M, Handwerker HO. Different patterns of hyperalgesia induced by experimental inflammation in human skin. *Brain.* 1994; 117(Pt 2):385–396. [PubMed: 8186964]
 23. Koltzenburg M, Lundberg LE, Torebjörk HE. Dynamic and static components of mechanical hyperalgesia in human hairy skin. *Pain.* 1992; 51(2):207–219. [PubMed: 1484717]
 24. Labrakakis C, Lorenzo LE, Bories C, Ribeiro-da-Silva A, De Koninck Y. Inhibitory coupling between inhibitory interneurons in the spinal cord dorsal horn. *Mol Pain.* 2009; 5:24. [PubMed: 19432997]
 25. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain.* 2009; 10(9):895–926. [PubMed: 19712899]
 26. Lawson JJ, McIlwrath SL, Woodbury CJ, Davis BM, Koerber HR. TRPV1 unlike TRPV2 is restricted to a subset of mechanically insensitive cutaneous nociceptors responding to heat. *J Pain.* 2008; 9(4):298–308. [PubMed: 18226966]
 27. Lee IO, Lim ES. Intracisternal or intrathecal glycine, taurine, or muscimol inhibit bicuculline-induced allodynia and thermal hyperalgesia in mice. *Acta Pharmacol Sin.* 2010; 31(8):907–914. [PubMed: 20686515]
 28. Lennertz RC, Kossyrev EA, Smith AK, Stucky CL. TRPA1 mediates mechanical sensitization in nociceptors during inflammation. *PLoS One.* 2012; 7(8):e43597. [PubMed: 22927999]
 29. Liljencrantz J, Björnsdotter M, Morrison I, Bergstrand S, Ceko M, Seminowicz DA, Cole J, Bushnell MC, Olsson H. Altered C-tactile processing in human dynamic tactile allodynia. *Pain.* 2013; 154(2):227–234. [PubMed: 23290550]
 30. Loomis CW, Khandwala H, Osmond G, Hefferan MP. Coadministration of intrathecal strychnine and bicuculline effects synergistic allodynia in the rat: an isobolographic analysis. *J Pharmacol Exp Ther.* 2001; 296(3):756–761. [PubMed: 11181903]
 31. 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(9):4050–4062. [PubMed: 23979158]
 32. Ma W, Zhang Y, Bantel C, Eisenach JC. Medium and large injured dorsal root ganglion cells increase TRPV-1, accompanied by increased alpha2C-adrenoceptor co-expression and functional inhibition by clonidine. *Pain.* 2005; 113(3):386–394. [PubMed: 15661448]
 33. Magerl W, Fuchs PN, Meyer RA, Treede RD. Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. *Brain.* 2001; 124(Pt 9):1754–1764. [PubMed: 11522578]
 34. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science.* 1965; 150(3699):971–979. [PubMed: 5320816]
 35. Miraucourt LS, Dalle R, Voisin DL. Glycine inhibitory dysfunction turns touch into pain through PKCgamma interneurons. *PLoS One.* 2007; 2(11):e1116. [PubMed: 17987109]

36. Miraucourt LS, Moisset X, Dallel R, Voisin DL. Glycine inhibitory dysfunction induces a selectively dynamic, morphine-resistant, and neurokinin 1 receptor-independent mechanical allodynia. *J Neurosci*. 2009; 29(8):2519–2527. [PubMed: 19244526]
37. Mishra SK, Tisel SM, Orestes P, Bhangoo SK, Hoon MA. TRPV1-lineage neurons are required for thermal sensation. *EMBO J*. 2011; 30(3):582–593. [PubMed: 21139565]
38. Nagi SS, Rubin TK, Chelvanayagam DK, Macefield VG, Mahns DA. Allodynia mediated by C-tactile afferents in human hairy skin. *J Physiol*. 2011; 589(Pt 16):4065–4075. [PubMed: 21727219]
39. Ochoa JL, Yarnitsky D. Mechanical hyperalgesias in neuropathic pain patients: dynamic and static subtypes. *Ann Neurol*. 1993; 33(5):465–472. [PubMed: 8388678]
40. Onaka M, Minami T, Nishihara I, Ito S. Involvement of glutamate receptors in strychnine- and bicuculline-induced allodynia in conscious mice. *Anesthesiology*. 1996; 84(5):1215–1222. [PubMed: 8624016]
41. Peirs C, Bourgois N, Artola A, Dallel R. Protein Kinase C γ Interneurons Mediate C-fiber-induced Orofacial Secondary Static Mechanical Allodynia, but Not C-fiber-induced Nociceptive Behavior. *Anesthesiology*. 2016; 124(5):1136–1152. [PubMed: 26745451]
42. Peng YB, Lin Q, Willis WD. Effects of GABA and glycine receptor antagonists on the activity and PAG-induced inhibition of rat dorsal horn neurons. *Brain Res*. 1996; 736(1–2):189–201. [PubMed: 8930324]
43. 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(6):1246–1257. [PubMed: 26527000]
44. Pogatzki EM, Gebhart GF, Brennan TJ. Characterization of Adelta- and C-fibers innervating the plantar rat hindpaw one day after an incision. *J Neurophysiol*. 2002; 87(2):721–731. [PubMed: 11826041]
45. Polgár E, Durrieux C, Hughes DI, Todd AJ. A quantitative study of inhibitory interneurons in laminae I–III of the mouse spinal dorsal horn. *PLoS One*. 2013; 8(10):e78309. [PubMed: 24205193]
46. Punnakal P, von Schoultz C, Haenraets K, Wildner H, Zeilhofer HU. Morphological, biophysical and synaptic properties of glutamatergic neurons of the mouse spinal dorsal horn. *J Physiol*. 2014; 592(4):759–776. [PubMed: 24324003]
47. Ranade SS, Woo SH, Dubin AE, Moshourab RA, Wetzel C, Petrus M, Mathur J, Bégay V, Coste B, Mainquist J, Wilson AJ, Francisco AG, Reddy K, Qiu Z, Wood JN, Lewin GR, Patapoutian A. Piezo2 is the major transducer of mechanical forces for touch sensation in mice. *Nature*. 2014; 516(7529):121–125. [PubMed: 25471886]
48. Shir Y, Seltzer Z. A-fibers mediate mechanical hyperesthesia and allodynia and C-fibers mediate thermal hyperalgesia in a new model of causalgiform pain disorders in rats. *Neurosci Lett*. 1990; 115(1):62–67. [PubMed: 2216058]
49. Singhmar P, Huo X, Eijkelkamp N, Berciano SR, Baameur F, Mei FC, Zhu Y, Cheng X, Hawke D, Mayor F, Murga C, Heijnen CJ, Kavelaars A. Critical role for Epac1 in inflammatory pain controlled by GRK2-mediated phosphorylation of Epac1. *Proc Natl Acad Sci U S A*. 2016; 113(11):3036–3041. [PubMed: 26929333]
50. Smith AK, O'Hara CL, Stucky CL. Mechanical sensitization of cutaneous sensory fibers in the spared nerve injury mouse model. *Mol Pain*. 2013; 9:61. [PubMed: 24286165]
51. Todd AJ. Neuronal circuitry for pain processing in the dorsal horn. *Nat Rev Neurosci*. 2010; 11(12):823–836. [PubMed: 21068766]
52. Torebjörk HE, Lundberg LE, LaMotte RH. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *J Physiol*. 1992; 448:765–780. [PubMed: 1593489]
53. Torsney C, MacDermott AB. Disinhibition opens the gate to pathological pain signaling in superficial neurokinin 1 receptor-expressing neurons in rat spinal cord. *J Neurosci*. 2006; 26(6):1833–1843. [PubMed: 16467532]

54. Urano H, Ara T, Fujinami Y, Hiraoka BY. Aberrant TRPV1 expression in heat hyperalgesia associated with trigeminal neuropathic pain. *Int J Med Sci.* 2012; 9(8):690–697. [PubMed: 23091405]
55. Vilceanu D, Honore P, Hogan QH, Stucky CL. Spinal nerve ligation in mouse upregulates TRPV1 heat function in injured IB4-positive nociceptors. *J Pain.* 2010; 11(6):588–599. [PubMed: 20015699]
56. Xu ZZ, Kim YH, Bang S, Zhang Y, Berta T, Wang F, Oh SB, Ji RR. Inhibition of mechanical allodynia in neuropathic pain by TLR5-mediated A-fiber blockade. *Nat Med.* 2015; 21(11):1326–1331. [PubMed: 26479925]
57. Yaksh TL. Behavioral and autonomic correlates of the tactile evoked allodynia produced by spinal glycine inhibition: effects of modulatory receptor systems and excitatory amino acid antagonists. *Pain.* 1989; 37(1):111–123. [PubMed: 2542867]
58. Zeilhofer HU, Wildner H, Yévenes GE. Fast synaptic inhibition in spinal sensory processing and pain control. *Physiol Rev.* 2012; 92(1):193–235. [PubMed: 22298656]
59. Ziegler EA, Magerl W, Meyer RA, Treede RD. Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. *Brain.* 1999; 122(Pt 12):2245–2257. [PubMed: 10581220]

Table 1
Afferent types mediating dynamic and static mechanical allodynia in various pain conditions

Pain condition	Species	Stimulation	Afferent type	Identification approach	Ref
peripheral neuropathy	mouse	punctate	A	Piezo2 knockdown	10
			A	QX-314 with flagellin	56(a)
	rat	punctate	TRPV1(+)	capsaicin-induced desensitization	13(b)
inflammation	human	pressure	TRPV1(+)	QX-314 with capsaicin	4
			C	compression nerve block	39
			A	compression nerve block	39
inflammation	mouse	punctate	TRPA1(+)	TRPA1 antagonist (2–3 days post-CFA)	28
			TRPA1(+)	QX-314 with cinnamaldehyde (2–3 days post-CFA)	28
			TRPA1(+)	TRPA1 knockout (2 days–2 weeks post-CFA)	15(c)
			A	Piezo2 knockdown (4 days post-CFA)	49(d)
1° zone	rat	pressure	TRPV1(+)	TRPV1 antagonist	16
			TRPV1(+)	QX-314 with capsaicin	4
2° zone	human	pressure	C	compression nerve block	22, 23
			A	compression nerve block	22, 23
			A	compression nerve block	59
			A	compression nerve block	22, 52

QX-314; lidocaine N-ethyl bromide, TRPV1: Transient Receptor Potential Channel V1, TRPA1: Transient Receptor Potential Channel A1.

(a) QX-314 with capsaicin had only a mild effect in this model;

(b) In comparison, neonatal capsaicin-induced ablation of TRPV1(+)-afferents did not prevent neuropathic static mechanical allodynia [48]; (

(c) These young (3–6 month-old) TRPA1 knockout mice later developed static mechanical allodynia unlike their aged (18 months) counterpart;

(d) This approach was ineffective at 1 day post-CFA as in [47].

Table 2
Effects of glycinergic vs. GABAergic (GABA_A-mediated) disinhibition on mechanical nociceptive responses

Species	Body part	Stimulation type	Glycinergic disinhibition	GABAergic disinhibition	Ref
rat	face	brush/air puff	dynamic allodynia	no nociceptive response	35, 36
		punctate	no nociceptive response	static allodynia	36
	flank	brush	dynamic allodynia	dynamic allodynia	20
mouse	plantar	punctate	static allodynia	-	31
	face	brush	-	dynamic allodynia	27
	flank	brush	dynamic allodynia	dynamic allodynia	40
	plantar	brush	-	dynamic allodynia	27
		punctate	static allodynia	-	14

GABA, γ -aminobutyric acid