Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Physiology

Inflammatory pain neural plasticity

Carole Torsney

Inflammatory pain comprises bidirectional communication between the immune and nervous system that results in a myriad of changes within the somatosensory system. This results in amplified transmission of nociceptive signals and the unmasking of neural circuits that enable innocuous stimuli to drive central pain circuitry following injury. With increasing use of techniques to genetically ablate or manipulate molecularly defined neuronal subtypes our understanding of nociceptor plasticity mechanisms and the spinal and supraspinal circuits that are recruited is rapidly expanding. Here this inflammatory neural plasticity is reviewed, highlighting recent insights that shed light upon nociceptor and central mechanisms that promote hyperalgesia and also the central unmasking of allodynia circuitry.

Address
Centre for Discovery Brain Sciences, Edinburgh Medical School: Biomedical Sciences, The University of Edinburgh, Edinburgh, EH8 9XD, United Kingdom

Corresponding author: Torsney, Carole (carole.torsney@ed.ac.uk)

Current Opinion in Physiology 2019, **11**:51–57

This review comes from a themed issue on **Physiology of pain**

Edited by **Lucy F Donaldson** and **Cheryl L Stucky**

For a complete overview see the Issue and the Editorial

Available online 8th June 2019

https://doi.org/10.1016/j.cophys.2019.06.001

Introduction

Inflammatory pain that occurs following tissue injury or in chronic inflammatory diseases such as arthritis manifests due to plasticity within both peripheral and central pain pathways, termed peripheral and central sensitisation, respectively. Since the early electrophysiological recordings by Bessou and Perl in 1969 [1] demonstrating the 'decrease in threshold for activation and enhanced response' of nociceptors that is termed peripheral sensitisation and the flexor motor neuron recordings by Clifford Woolf in 1983 [2] demonstrating hyper-excitable spinal responses (novel spontaneous activity, novel innocuous responses and enhanced receptive field sizes) that defined central sensitisation, our knowledge of the mechanisms and neural circuits driving inflammatory pain plasticity has flourished. The resultant inflammatory pain symptoms of allodynia (touch-evoked pain), hyperalgesia (exaggerated pain) and spontaneous (non-evoked) pain are recognised as important protective neural responses to guard injured tissue during the healing process. However, when this neural plasticity persists beyond the healing process then symptoms become maladaptive and there is transition to persistent pain.

This review will summarise peripheral and central plasticity mechanisms underlying inflammatory pain, highlighting recent pertinent studies. There will be a particular focus on nociceptor plasticity, spinal pain circuits and the descending pain modulatory system.

Peripheral plasticity

Neuro-immune interactions

Tissue injury and inflammation results in the release of numerous inflammatory mediators such as bradykinin, Nerve Growth Factor (NGF), prostaglandin E2 (PGE2) and pro-inflammatory cytokines and chemokines from, for example, damaged tissue cells and immune cells [3,4]. These inflammatory mediators act on their respective receptors present on peripheral nociceptor terminals to 'activate' or 'sensitise' the nociceptor terminal. Sensitisation occurs via activation of intracellular signalling pathways (MAP kinase/PKA/PKC/adenylyl cyclase) that drive the phosphorylation and modulation of transducer receptors and voltage-gated ion channels in the nociceptor terminal. This acts to decrease the threshold for action potential firing and via modulation of ion channels such as HCN2 increase nociceptor firing rates [4–6]. These modifications occur rapidly to enable the somatosensory system to dynamically respond to injury. As a result there is ongoing nociceptive afferent drive to the CNS and amplified nociceptive inputs. There is also translational and transcriptional regulation of gene expression that modifies nociceptor phenotype and function that is relevant for pain persistence [7].

It is now increasingly recognised that interactions between the immune and the nervous system in inflammatory pain are bidirectional [8,9]. Nociceptor activity following tissue injury can drive backpropagating action potentials in nociceptors via local axon reflexes and dorsal root reflexes [10]. This concurrent nociceptor antidromic activity induces neurogenic inflammation, via release of factors such as calcitonin gene-related peptide and substance P from peripheral nociceptor terminals that increases vascular permeability and causes oedema. Recent studies demonstrate that these nociceptor derived mediators can also regulate innate and adaptive immune responses that further impacts inflammatory pain [8,9]. Interestingly,

immune cells not only release pro-inflammatory mediators they also produce specialised pro-resolution mediators, such as resolvins and protectins, derived from omega-3 unsaturated fatty acids that not only resolve inflammation but can activate specific receptors on nociceptors to alter their function [11–14].

Recent nociceptor insights

Silent nociceptors are a special class of nociceptors, long appreciated to be mechano-insensitive but have the capacity to acquire mechanical sensitivity under inflammatory pain conditions. Recently Prato *et al.* [15•] have discovered the molecular mechanism by which this unsilencing occurs. First they identified a molecular marker, the nicotinic acetylcholine receptor subunit alpha-3 (CHRNA3) that defines this mechano-insensitive subset of peptidergic C-fibre nociceptors that innervate viscera and deep somatic tissue. Then they demonstrated that the inflammatory mediator NGF confers mechanical sensitivity in these neurons that is mediated by the mechanically-gated ion channel Piezo2. What remains to be elucidated is why these silent nociceptors lack mechanical sensitivity despite expressing PIEZO2 under control conditions and the mechanism by which NGF unmasks this Piezo2 mediated mechanosensation.

Studies of peripheral pain plasticity have mainly focussed on the processes that alter the sensitivity of the nociceptor terminal, within inflamed tissue, but less so on the transmission of action potentials from the peripheral nociceptor terminal along afferent fibres to their central terminals in the spinal cord dorsal horn. However, recent work highlights plasticity at both the cell body and afferent fibre level that can regulate nociceptive drive to the CNS. Using *in vivo* confocal imaging to monitor DRG neuronal calcium responses, Kim *et al.* [16••] revealed coupled activation of DRG neurons, via electrical gap junctions, during tissue inflammation that by amplifying afferent input to the CNS contributes to inflammatory mechanical hyperalgesia. In addition to DRG neuronal electrical transmission Du *et al.* [17] has provided evidence for GABAergic neurochemical transmission that regulates action potential propagation through the DRG and thereby nociceptive input to the spinal cord. It will be of interest to learn whether this DRG GABAergic communication is modified following injury. Furthermore, we have demonstrated that the temporal relay of pain signals in nociceptive C-fibre afferents is altered in inflammatory pain [18], consistent with prior studies of the inflammatory mediator NGF [19,20] including in humans [21]. Specifically, peripheral inflammation reduces activity-dependent slowing of C-fibre conduction velocity, interestingly in a sex-dependent manner. We show that this tightens up synaptic transmission of nociceptive inputs and promotes spinal summation that we propose contributes to hyperalgesia.

To date there is fairly limited understanding of the primary sensory neuron subtypes that drive and mediate inflammatory pain symptoms. Beyond the seminal observation, using genetic neuronal ablation, that NaV1.8 expressing neurons are required for inflammatory pain [22] confirmed with optogenetic silencing [23], subsequent neuronal ablation studies suggest differential involvement of the MRGPRD subset in inflammatory mechanical hypersensitivity and GINIP-expressing neurons in formalin evoked pain [24–26]. Given the revolution in our understanding of the different subclasses of DRG neurons and their molecular signatures through transcriptomic studies [27••,28] this will undoubtedly be exploited in future studies employing genetic ablation, optogenetic or chemogenetic approaches to further our understanding of the nociceptor subtypes key for inflammatory pain. Another area of significant future interest is the involvement of epidermal cells in somatosensory transduction. Evidence suggests that both Merkel cells and keratinocytes transduce mechanical stimuli and communicate with sensory afferents via serotonergic and ATP-P2X4 signalling, respectively, to facilitate mechanosensation [29,30] but it is not yet known whether these processes are involved or regulated in inflammatory pain [31].

Central plasticity

Spinal circuits

Primary hyperalgesia that develops at the site of an injury is considered to result from the peripheral sensitisation mechanisms described above in combination with homosynaptic potentiation of nociceptor spinal synapses [32]. Secondary hyperalgesia that develops outwith the injury site and widespread allodynia is generally regarded to result from central spinal plasticity [32,33]. Since the discovery of central sensitisation, it has been known that activity in C-fibre nociceptors is the necessary 'trigger' to elicit this enhanced excitability within spinal sensory pathways [2]. C-fibres induce plasticity via elevated glutamatergic and neuropeptide neurotransmission with spinal neurons that raises intracellular calcium and induces kinase activation (PKA/PKC/CamKII/ERK) that drives rapid post-translational and also longer term translational and transcriptional changes [7]. This plasticity manifests as increased local excitatory control [32,34], decreased local inhibitory control [35,36] as well as altered descending control [37–39]. Importantly, there are also bidirectional neuronal-glial interactions that are integral to this central plasticity [40,41]. As a result of this C-fibre driven spinal hyperexcitability, it is believed that thinly myelinated Aδ-fibre primary afferents and touch-sensitive myelinated Aβ-fibres are now able to gain access to specific spinal circuitry, via heterosynaptic facilitatory mechanisms, enabling these afferents to 'mediate' the sensations of mechanical

hyperalgesia and mechanical allodynia, respectively [32,33]. I have observed unmasking of monosynaptic Aδ inputs to lamina I nociceptive output neurons under inflammatory pain conditions that potentially may be relevant for mechanical hyperalgesia [42]. Furthermore, we identified a putative 'allodynia' circuit — a polysynaptic circuit between Aβ fibres and lamina I nociceptive output neurons that is normally under local inhibitory control [43].

Identification of this spinal allodynia circuit that provides a route for communication between touch-sensitive afferents and ascending pain pathways, has been an area of significant research focus [31,44–49,50••,51••,52–55,56•]. Recent optogenetic, chemogenetic and genetic neuronal ablation studies have begun to identify the excitatory interneurons within this polysynaptic circuit and provide insight into their connectivity and also the inhibitory interneurons that regulate this circuit. VGlut3, transiently expressing lamina III neurons, somatostatin lamina II/III neurons, calretinin lamina II neurons and potentially cholecystokinin deep dorsal horn neurons [57••] are excitatory interneurons within allodynia circuits recruited under inflammatory pain conditions [50••,51••,52]. These excitatory allodynia circuits are gated by superficial dynorphin inhibitory neurons [50••] and also early RET+ deep dorsal horn inhibitory neurons [53]. Interestingly, overlapping yet distinct allodynia circuits are thought to be recruited in inflammatory versus neuropathic pain conditions [51••,54]. Following nerve injury, excitatory lamina IIi PKCγ neurons, that are gated by lamina II/III parvalbumin inhibitory neurons [55] are recruited rather than the calretinin neurons engaged in inflammatory pain [51••]. Moreover, there is evidence for distinct circuitries for dynamic versus punctate mechanical allodynia in both inflammatory and neuropathic pain [56•]. In the future similar studies will likely capitalise on the recent transformation in our understanding of molecularly defined dorsal horn neuronal subtypes [58••,59] to further our understanding of the allodynia circuits recruited following injury.

Recent findings have shed light on the myelinated Aβ-fibre mechanoreceptors that activate these spinal allodynia circuits following injury. There is compelling evidence that low threshold mechanoreceptors expressing the stretch-gated ion channel Piezo2 are required to activate spinal allodynia circuits in both inflammatory and neuropathic conditions [60,61•] and these may include mechanoreceptors expressing the delta opioid receptor [62]. TrkB expressing A-fibre mechanoreceptors are required for neuropathic allodynia but they do not appear to be required for inflammatory allodynia [63,64]. Development of therapeutic strategies to selectively block activity in A-fibres driving allodynia circuits has only been explored thus far for neuropathic pain [63,65,66].

Supraspinal circuits

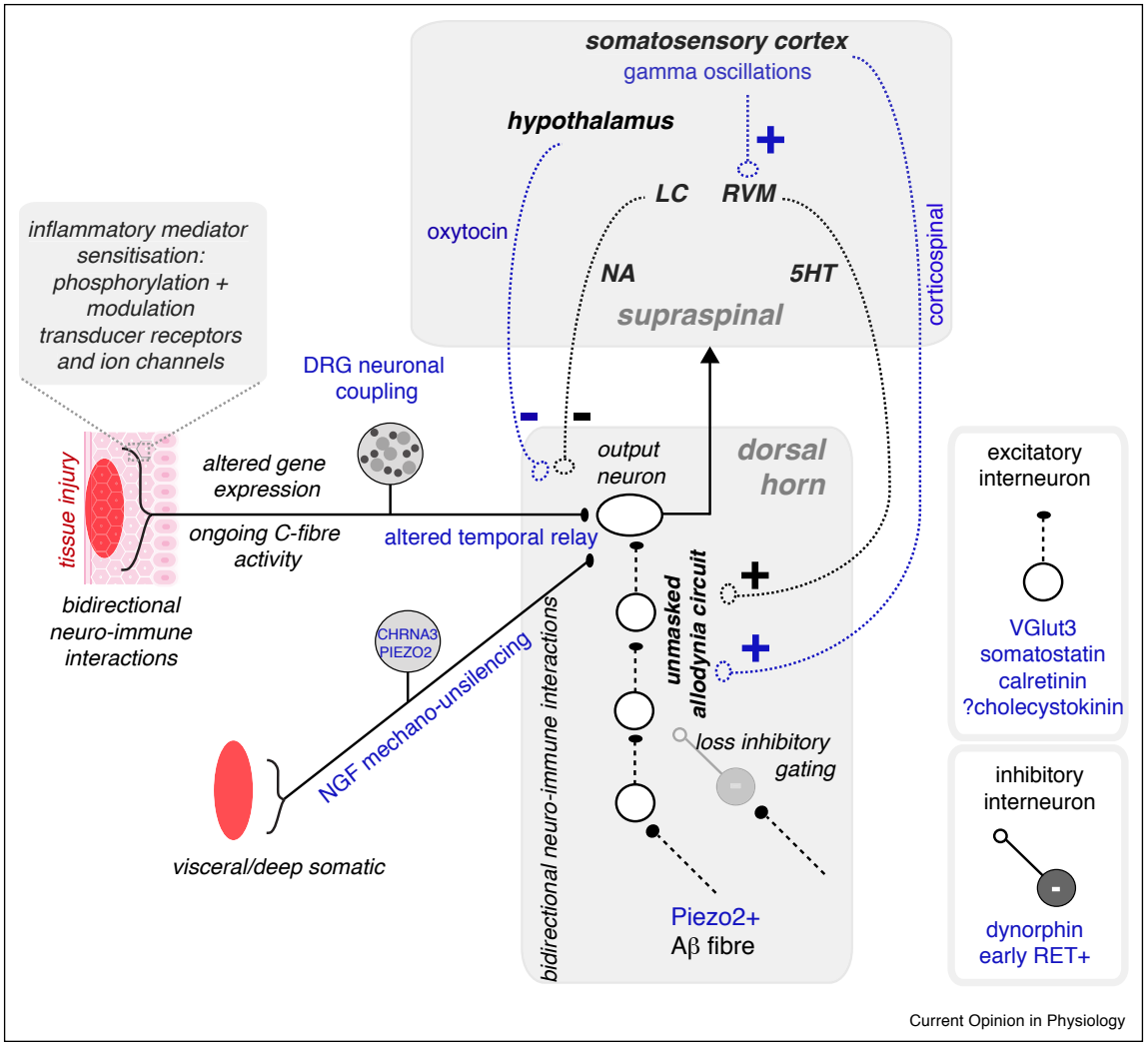
Spinal output neurons project to a number of sites including the thalamus, parabrachial area and the periaqueductal grey region (PAG) [67]. From the thalamus there are projections to the somatosensory cortex and insular cortex likely relevant for discriminative and affective aspects of sensory processing, respectively. Projections from the parabrachial area target the amygdala and hypothalamic components of the limbic system and are also likely important for the affective pain component. Recently it was discovered that the parabrachial area directly relays nociceptive information to the rostral ventromedial medulla (RVM) [68,69]. The RVM is long known to receive strong input from the PAG and drive descending serotonergic pathways to bi-directionally modulate spinal pain circuits whereas descending noradrenergic pathways from the locus coeruleus exert inhibitory spinal control [39]. Plasticity occurs within these various supraspinal regions and their connections in inflammatory pain conditions [38,70–72]. Dysregulation in the descending pain modulatory system has received much attention [37–39] with descending serotonergic systems promoting inflammatory mechanical hypersensitivity [73,74] and descending noradrenergic systems limiting inflammatory thermal hyperalgesia and formalin-induced pain behaviours [75]. Interestingly, it has been shown that descending dopaminergic circuits are particularly important for the transition from acute to chronic inflammatory pain [76]. In this final section I will highlight three innovative studies identifying novel descending control systems relevant for inflammatory pain.

It has recently been shown that hindpaw inflammation induces gamma oscillations in the primary somatosensory (S1) cortex [77••]. Interestingly evidence suggests that this oscillatory activity, likely through direct connections with the RVM, drives descending serotonergic pathways to specifically facilitate mechanical allodynia. Moreover, direct corticospinal connections, originating in primary and secondary somatosensory cortex that target deep dorsal horn neurons, including cholecystokinin interneurons, have recently been identified and shown to be required for recruiting spinal allodynia circuits in neuropathic conditions and likely also inflammatory pain [57••]. Furthermore descending oxytocin projections from hypothalamic paraventricular parvocellular neurons that target deep dorsal horn wide dynamic range neurons, alongside collateral projections to the supraoptic nucleus that drive peripheral oxytocin release have been identified that are proposed to limit inflammatory hyperalgesia [78].

Conclusion

Our understanding of the plasticity and neural circuits that underlie inflammatory pain is rapidly expanding with increased interrogation of neuro-immune interactions and genetic manipulation of neuronal subtypes within pain circuitry (summarised Figure 1). These approaches can be further exploited to carefully dissect the neuronal mechanisms essential for induction versus maintenance of inflammatory pain and also identify the circuits that mediate specific symptoms. The timing of activity within

Figure 1



Inflammatory pain neural plasticity schematic. Overview of the most recent insights in to inflammatory pain mechanisms and circuits illustrated in blue text/connections. Black text/connections denote prior established inflammatory pain mechanisms and circuits. Excitatory interneurons within spinal allodynia circuits and the inhibitory interneurons that gate these circuits are listed. LC, locus coeruleus; NA, noradrenaline; RVM, rostral ventromedial medulla; 5HT, serotonin.

these pain transmitting and gating circuits will also be of significance [79,80]. It will be of interest to further appreciate how different mechanisms and circuits are differentially activated by various types of injury and how these are influenced by sex, environmental and genetic factors [81]. Moreover, it will be key to identify the interactions and circuits most relevant for persistence of inflammatory pain following tissue healing.

Conflict of interest statement

Nothing declared.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Bessou P, Perl ER: **Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli**. *J Neurophysiol* 1969, **32**:1025-1043.

2. Woolf CJ: **Evidence for a central component of post-injury pain hypersensitivity**. *Nature* 1983, **306**:686-688.

3. Matsuda M, Huh Y, Ji RR: **Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain**. *J Anesth* 2019, **33**:131-139.

4. Gold MS, Gebhart GF: **Nociceptor sensitization in pain pathogenesis**. *Nat Med* 2010, **16**:1248-1257.

5. Emery EC, Young GT, Berrocoso EM, Chen L, McNaughton PA: **HCN2 ion channels play a central role in inflammatory and neuropathic pain**. *Science* 2011, **333**:1462-1466.

6. Emery EC, Young GT, McNaughton PA: **HCN2 ion channels: an emerging role as the pacemakers of pain**. *Trends Pharmacol Sci* 2012, **33**:456-463.

7. Khoutorsky A, Price TJ: **Translational control mechanisms in persistent pain**. *Trends Neurosci* 2018, **41**:100-114.

8. McMahon SB, La Russa F, Bennett DL: **Crosstalk between the nociceptive and immune systems in host defence and disease**. *Nat Rev Neurosci* 2015, **16**:389-402.

9. Pinho-Ribeiro FA, Verri WA Jr, Chiu IM: **Nociceptor sensory neuron-immune interactions in pain and inflammation**. *Trends Immunol* 2017, **38**:5-19.

10. Carlton SM: **Nociceptive primary afferents: they have a mind of their own**. *J Physiol* 2014, **592**:3403-3411.

11. Ji RR, Chamessian A, Zhang YQ: **Pain regulation by non-neuronal cells and inflammation**. *Science* 2016, **354**:572-577.

12. Ji RR, Xu ZZ, Gao YJ: **Emerging targets in neuroinflammation-driven chronic pain**. *Nat Rev Drug Discov* 2014, **13**:533-548.

13. Xu ZZ, Zhang L, Liu T, Park JY, Berta T, Yang R, Serhan CN, Ji RR: **Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions**. *Nat Med* 2010, **16**:592-597 591p following 597.

14. Dickie AC, Torsney C: **The chemerin receptor 23 agonist, chemerin, attenuates monosynaptic C-fibre input to lamina I neurokinin 1 receptor expressing rat spinal cord neurons in inflammatory pain**. *Mol Pain* 2014, **10**:24.

15. • Prato V, Taberner FJ, Hockley JRF, Callejo G, Arcourt A, Tazir B, Hammer L, Schad P, Heppenstall PA, Smith ES *et al.*: **Functional and molecular characterization of mechanoinsensitive "Silent" nociceptors**. *Cell Rep* 2017, **21**:3102-3115.
Molecular identification of silent nociceptors and discovery that Piezo2 mediated mechanical sensitivity can be unmasked in these neurons by the inflammatory mediator NGF.

16. •• Kim YS, Anderson M, Park K, Zheng Q, Agarwal A, Gong C, Saijilafu, Young L, He S, LaVinka PC *et al.*: **Coupled activation of primary sensory neurons contributes to chronic pain**. *Neuron* 2016, **91**:1085-1096.
Confocal imaging in live mice expressing the genetically encoded calcium indicator GCaMP to monitor activation of several hundred DRG neurons simultaneously demonstrated that DRG neurons, following tissue inflammation, can recruit neighbouring neurons (<1 μm apart), via electrical gap junctions, to facilitate mechanical hyperalgesia.

17. Du X, Hao H, Yang Y, Huang S, Wang C, Gigout S, Ramli R, Li X, Jaworska E, Edwards I *et al.*: **Local GABAergic signaling within sensory ganglia controls peripheral nociceptive transmission**. *J Clin Invest* 2017, **127**:1741-1756.

18. Dickie AC, McCormick B, Lukito V, Wilson KL, Torsney C: **Inflammatory pain reduces C fibre activity-dependent slowing in a sex dependent manner, amplifying nociceptive input to the spinal cord**. *J Neurosci* 2017, **37**:6488-6502.

19. Obreja O, Ringkamp M, Turnquist B, Hirth M, Forsch E, Rukwied R, Petersen M, Schmelz M: **Nerve growth factor selectively decreases activity-dependent conduction slowing in mechano-insensitive C-nociceptors**. *Pain* 2011, **152**:2138-2146.

20. Petersson ME, Obreja O, Lampert A, Carr RW, Schmelz M, Fransen E: **Differential axonal conduction patterns of mechano-sensitive and mechano-insensitive nociceptors - a combined experimental and modelling study**. *PLoS One* 2014, **9**:e103556.

21. Obreja O, Rukwied R, Nagler L, Schmidt M, Schmelz M, Namer B: **Nerve growth factor locally sensitizes nociceptors in human skin**. *Pain* 2018, **159**:416-426.

22. Abrahamsen B, Zhao J, Asante CO, Cendan CM, Marsh S, Martinez-Barbera JP, Nassar MA, Dickenson AH, Wood JN: **The cell and molecular basis of mechanical, cold, and inflammatory pain**. *Science* 2008, **321**:702-705.

23. Daou I, Beaudry H, Ase AR, Wieskopf JS, Ribeiro-da-Silva A, Mogil JS, Seguela P: **Optogenetic silencing of Nav1.8-positive afferents alleviates inflammatory and neuropathic pain**. *eNeuro* 2016, **3**.

24. 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**:9075-9080.

25. Shields SD, Cavanaugh DJ, Lee H, Anderson DJ, Basbaum AI: **Pain behavior in the formalin test persists after ablation of the great majority of C-fiber nociceptors**. *Pain* 2010, **151**:422-429.

26. Urien L, Gaillard S, Lo Re L, Malapert P, Bohic M, Reynders A, Moqrich A: **Genetic ablation of GINIP-expressing primary sensory neurons strongly impairs formalin-evoked pain**. *Sci Rep* 2017, **7**:43493.

27. •• Usoskin D, Furlan A, Islam S, Abdo H, Lonnerberg P, Lou D, Hjerling-Leffler J, Haeggstrom J, Kharchenko O, Kharchenko PV *et al.*: **Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing**. *Nat Neurosci* 2015, **18**:145-153.
Landmark paper that identifies 11 molecularly distinct subsets of primary sensory neurons using single-cell RNA sequencing.

28. Li CL, Li KC, Wu D, Chen Y, Luo H, Zhao JR, Wang SS, Sun MM, Lu YJ, Zhong YQ *et al.*: **Somatosensory neuron types identified by high-coverage single-cell RNA-sequencing and functional heterogeneity**. *Cell Res* 2016, **26**:83-102.

29. Chang W, Kanda H, Ikeda R, Ling J, DeBerry JJ, Gu JG: **Merkel disc is a serotonergic synapse in the epidermis for transmitting tactile signals in mammals**. *Proc Natl Acad Sci U S A* 2016, **113**:E5491-E5500.

30. Moehring F, Cowie AM, Menzel AD, Weyer AD, Grzybowski M, Arzua T, Geurts AM, Palygin O, Stucky CL: **Keratinocytes mediate innocuous and noxious touch via ATP-P2X4 signaling**. *eLife* 2018, **7**.

31. Moehring F, Halder P, Seal RP, Stucky CL: **Uncovering the cells and circuits of touch in normal and pathological settings**. *Neuron* 2018, **100**:349-360.

32. Latremoliere A, Woolf CJ: **Central sensitization: a generator of pain hypersensitivity by central neural plasticity**. *J Pain* 2009, **10**:895-926.

33. Treede RD, Magerl W: **Multiple mechanisms of secondary hyperalgesia**. *Prog Brain Res* 2000, **129**:331-341.

34. Kuner R: **Spinal excitatory mechanisms of pathological pain**. *Pain* 2015, **156(Suppl. 1)**:S11-S17.

35. Zeilhofer HU, Wildner H, Yevenes GE: **Fast synaptic inhibition in spinal sensory processing and pain control**. *Physiol Rev* 2012, **92**:193-235.

36. Prescott SA: **Synaptic inhibition and disinhibition in the spinal dorsal horn**. *Prog Mol Biol Transl Sci* 2015, **131**:359-383.

37. Ossipov MH, Morimura K, Porreca F: **Descending pain modulation and chronification of pain**. *Curr Opin Support Palliat Care* 2014, **8**:143-151.

38. Chen Q, Heinricher MM: **Descending control mechanisms and chronic pain**. *Curr Rheumatol Rep* 2019, **21**:13.

39. Bannister K, Dickenson AH: **What do monoamines do in pain modulation?** *Curr Opin Support Palliat Care* 2016, **10**:143-148.

40. Ji RR, Berta T, Nedergaard M: **Glia and pain: is chronic pain a gliopathy?** *Pain* 2013, **154(Suppl. 1)**:S10-S28.

41. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W: **Neuroinflammation and central sensitization in chronic and widespread pain**. *Anesthesiology* 2018, **129**:343-366.

42. Torsney C: **Inflammatory pain unmasks heterosynaptic facilitation in lamina I neurokinin 1 receptor-expressing neurons in rat spinal cord**. *J Neurosci* 2011, **31**:5158-5168.

43. 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**:1833-1843.

44. Duan B, Cheng L, Ma Q: **Spinal circuits transmitting mechanical pain and itch**. *Neurosci Bull* 2017, **34**:186-193.

45. Koch SC, Acton D, Goulding M: **Spinal circuits for touch, pain, and itch**. *Annu Rev Physiol* 2018, **80**:189-217.

46. Peirs C, Seal RP: **Neural circuits for pain: recent advances and current views**. *Science* 2016, **354**:578-584.

47. Lu Y, Dong H, Gao Y, Gong Y, Ren Y, Gu N, Zhou S, Xia N, Sun YY, Ji RR *et al.*: **A feed-forward spinal cord glycinergic neural circuit gates mechanical allodynia**. *J Clin Invest* 2013, **123**:4050-4062.

48. Miraucourt LS, Dallel R, Voisin DL: **Glycine inhibitory dysfunction turns touch into pain through PKCgamma interneurons**. *PLoS One* 2007, **2**:e1116.

49. Yasaka T, Tiong SY, Polgar E, Watanabe M, Kumamoto E, Riddell JS, Todd AJ: **A putative relay circuit providing low-threshold mechanoreceptive input to lamina I projection neurons via vertical cells in lamina II of the rat dorsal horn**. *Mol Pain* 2014, **10**:3.

50. •• Duan B, Cheng L, Bourane S, Britz O, Padilla C, Garcia-Campmany L, Krashes M, Knowlton W, Velasquez T, Ren X *et al.*: **Identification of spinal circuits transmitting and gating mechanical pain**. *Cell* 2014, **159**:1417-1432.
Seminal study, using an intersectional genetic strategy to mark and ablate subpopulations of excitatory and inhibitory spinal neurons, revealed that somatostatin excitatory interneurons are within spinal allodynia circuits that are gated by dynorphin inhibitory neurons.

51. •• Peirs C, Williams SP, Zhao X, Walsh CE, Gedeon JY, Cagle NE, Goldring AC, Hioki H, Liu Z, Marell PS *et al.*: **Dorsal horn circuits for persistent mechanical pain**. *Neuron* 2015, **87**:797-812.
Landmark study, using conditional gene deletion and chemogenetics, identified lamina III excitatory neurons that transiently express VGLUT3 during development as 'initiator' neurons within spinal allodynia circuits. These circuits appear to differentially recruit calretinin neurons in inflammatory pain and PKCγ neurons in neuropathic pain.

52. Christensen AJ, Iyer SM, Francois A, Vyas S, Ramakrishnan C, Vesuna S, Deisseroth K, Scherrer G, Delp SL: **In vivo interrogation of spinal mechanosensory circuits**. *Cell Rep* 2016, **17**:1699-1710.

53. 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**:1137-1153.

54. Wang X, Zhang J, Eberhart D, Urban R, Meda K, Solorzano C, Yamanaka H, Rice D, Basbaum AI: **Excitatory superficial dorsal horn interneurons are functionally heterogeneous and required for the full behavioral expression of pain and itch**. *Neuron* 2013, **78**:312-324.

55. Petitjean H, Pawlowski SA, Fraine SL, Sharif B, Hamad D, Fatima T, Berg J, Brown CM, Jan LY, Ribeiro-da-Silva A *et al.*: **Dorsal horn parvalbumin neurons are gate-keepers of touch-evoked pain after nerve injury**. *Cell Rep* 2015, **13**:1246-1257.

56. • Cheng L, Duan B, Huang T, Zhang Y, Chen Y, Britz O, Garcia-Campmany L, Ren X, Vong L, Lowell BB *et al.*: **Identification of spinal circuits involved in touch-evoked dynamic mechanical pain**. *Nat Neurosci* 2017, **20**:804-814.
Genetic neuronal ablation approaches identified morphine resistant polysynaptic circuits, involving excitatory spinal neurons defined by co-expression of VGLUT3 and Lbx1, required for dynamic not punctate mechanical allodynia.

57. •• Liu Y, Latremoliere A, Li X, Zhang Z, Chen M, Wang X, Fang C, Zhu J, Alexandre C, Gao Z *et al.*: **Touch and tactile neuropathic pain sensitivity are set by corticospinal projections**. *Nature* 2018, **561**:547-550.
Seminal study that identifies a touch driven feed-forward spinal-cortical-spinal sensitization loop important for the recruitment of spinal allodynia circuits following nerve injury. These circuits are also likely to be engaged following tissue injury given that transection of the corticospinal tract similarly reduced neuropathic and inflammatory mechanical allodynia.

58. •• Haring M, Zeisel A, Hochgerner H, Rinwa P, Jakobsson JET, Lonnerberg P, La Manno G, Sharma N, Borgius L, Kiehn O *et al.*: **Neuronal atlas of the dorsal horn defines its architecture and links sensory input to transcriptional cell types**. *Nat Neurosci* 2018, **21**:869-880.
Seminal paper that identifies 15 inhibitory and 15 excitatory molecularly distinct subsets of dorsal horn neurons using single-cell RNA sequencing.

59. Sathyamurthy A, Johnson KR, Matson KJE, Dobrott CI, Li L, Ryba AR, Bergman TB, Kelly MC, Kelley MW, Levine AJ: **Massively parallel single nucleus transcriptional profiling defines spinal cord neurons and their activity during behavior**. *Cell Rep* 2018, **22**:2216-2225.

60. Murthy SE, Loud MC, Daou I, Marshall KL, Schwaller F, Kuhnemund J, Francisco AG, Keenan WT, Dubin AE, Lewin GR *et al.*: **The mechanosensitive ion channel Piezo2 mediates sensitivity to mechanical pain in mice**. *Sci Transl Med* 2018, **10**.

61. • Szczot M, Liljencrantz J, Ghitani N, Barik A, Lam R, Thompson JH, Bharucha-Goebel D, Saade D, Necaise A, Donkervoort S *et al.*: **PIEZO2 mediates injury-induced tactile pain in mice and humans**. *Sci Transl Med* 2018, **10**.
Demonstrates that humans with loss of function mutations in PIEZO2 do not develop capsaicin-induced mechanical allodynia. This finding alongside evidence that Piezo2 is essential for detection of light touch mechanical stimuli, in the presence or absence of inflammation convincingly shows that low threshold mechanoreceptors expressing PIEZO2 activate spinal allodynia circuitry.

62. Scherrer G, Imamachi N, Cao YQ, Contet C, Mennicken F, O'Donnell D, Kieffer BL, Basbaum AI: **Dissociation of the opioid receptor mechanisms that control mechanical and heat pain**. *Cell* 2009, **137**:1148-1159.

63. Dhandapani R, Arokiaraj CM, Taberner FJ, Pacifico P, Raja S, Nocchi L, Portulano C, Franciosa F, Maffei M, Hussain AF *et al.*: **Control of mechanical pain hypersensitivity in mice through ligand-targeted photoablation of TrkB-positive sensory neurons**. *Nat Commun* 2018, **9**:1640.

64. Peng C, Li L, Zhang MD, Bengtsson Gonzales C, Parisien M, Belfer I, Usoskin D, Abdo H, Furlan A, Haring M *et al.*: **miR-183 cluster scales mechanical pain sensitivity by regulating basal and neuropathic pain genes**. *Science* 2017, **356**:1168-1171.

65. 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**:1326-1331.

66. Wetzel C, Pifferi S, Picci C, Gok C, Hoffmann D, Bali KK, Lampe A, Lapatsina L, Fleischer R, Smith ES *et al.*: **Small-molecule inhibition of STOML3 oligomerization reverses pathological mechanical hypersensitivity**. *Nat Neurosci* 2017, **20**:209-218.

67. Todd AJ: **Neuronal circuitry for pain processing in the dorsal horn**. *Nat Rev Neurosci* 2010, **11**:823-836.

68. Chen Q, Roeder Z, Li MH, Zhang Y, Ingram SL, Heinricher MM: **Optogenetic evidence for a direct circuit linking nociceptive transmission through the parabrachial complex with pain-modulating neurons of the rostral ventromedial medulla (RVM)**. *eNeuro* 2017, **4**.

69. Roeder Z, Chen Q, Davis S, Carlson JD, Tupone D, Heinricher MM: **Parabrachial complex links pain transmission to descending pain modulation**. *Pain* 2016, **157**:2697-2708.

70. Kim W, Kim SK, Nabekura J: **Functional and structural plasticity in the primary somatosensory cortex associated with chronic pain**. *J Neurochem* 2017, **141**:499-506.

71. Zhuo M: **Long-term cortical synaptic changes contribute to chronic pain and emotional disorders**. *Neurosci Lett* 2019, **702**:66-70.

72. Thompson JM, Neugebauer V: **Cortico-limbic pain mechanisms**. *Neurosci Lett* 2019, **702**:15-23.

73. Geranton SM, Fratto V, Tochiki KK, Hunt SP: **Descending serotonergic controls regulate inflammation-induced mechanical sensitivity and methyl-CpG-binding protein 2 phosphorylation in the rat superficial dorsal horn**. *Mol Pain* 2008, **4**:35.

74. Wei F, Dubner R, Zou S, Ren K, Bai G, Wei D, Guo W: **Molecular depletion of descending serotonin unmasks its novel facilitatory role in the development of persistent pain**. *J Neurosci* 2010, **30**:8624-8636.

75. Llorca-Torralba M, Borges G, Neto F, Mico JA, Berrocoso E: **Noradrenergic locus coeruleus pathways in pain modulation**. *Neuroscience* 2016, **338**:93-113.

76. Kim JY, Tillu DV, Quinn TL, Mejia GL, Shy A, Asiedu MN, Murad E, Schumann AP, Totsch SK, Sorge RE *et al.*: **Spinal dopaminergic projections control the transition to pathological pain plasticity via a D1/D5-mediated mechanism**. *J Neurosci* 2015, **35**:6307-6317.

77. •• Tan LL, Oswald MJ, Heinl C, Retana Romero OA, Kaushalya SK, Monyer H, Kuner R: **Gamma oscillations in somatosensory cortex recruit prefrontal and descending serotonergic pathways in aversion and nociception**. *Nat Commun* 2019, **10**:983.
Landmark study employing chronic microelectrode recording in awake freely moving mice to elucidate the significance of S1 cortical gamma oscillations for nociceptive circuits and behaviour. Optogenetic induction of oscillatory activity combined with functional mapping, anatomical tracing and behavioural pharmacology reveals that S1 cortical gamma oscillations facilitate mechanical allodynia via RVM descending serotonergic systems.

78. Eliava M, Melchior M, Knobloch-Bollmann HS, Wahis J, da Silva Gouveia M, Tang Y, Ciobanu AC, Triana Del Rio R, Roth LC, Althammer F *et al.*: **A new population of parvocellular oxytocin neurons controlling magnocellular neuron activity and inflammatory pain processing**. *Neuron* 2016, **89**:1291-1304.

79. Zhang Y, Liu S, Zhang YQ, Goulding M, Wang YQ, Ma Q: **Timing mechanisms underlying gate control by feedforward inhibition**. *Neuron* 2018, **99**:941-955 e944.

80. Li J, Baccei ML: **Neonatal tissue damage promotes spike timing-dependent synaptic long-term potentiation in adult spinal projection neurons**. *J Neurosci* 2016, **36**:5405-5416.

81. Denk F, McMahon SB, Tracey I: **Pain vulnerability: a neurobiological perspective**. *Nat Neurosci* 2014, **17**:192-200.