An overview of pathways encoding nociception

S.A. Woller[1], K.A. Eddinger[1], M. Corr[2], T.L. Yaksh[1]

[1]*Department of Anesthesiology, University of California San Diego, La Jolla, CA, USA;*
[2]*Division of Rheumatology, Allergy, and Immunology, University of California San Diego, La Jolla, CA, USA.*

Sarah A. Woller, PhD
Kelly A. Eddinger, BS RVT
Maripat Corr, MD
Tony L. Yaksh, PhD

Please address correspondence to:
Dr Tony L. Yaksh,
9500 Gilman Drive,
MC 0818, La Jolla,
CA 92093, USA.
E-mail: tyaksh@ucsd.edu

Received and accepted on September 1, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 107): S40-S46.

Key words: acute pain, persistent pain, central sensitisation, peripheral sensitisation, inflammation, innate and adaptive immunity

Funding: This review and work described herein was undertaken in part with an NIH grant NS16541, AR-062236, and an Innovative Research grant from the Rheumatology Research Foundation.

Competing interests: none declared.

ABSTRACT

The nervous system detects and interprets a variety of chemical, mechanical, and thermal stimuli. In the face of tissue injury, local inflammatory products perpetuate ongoing activity and sensitisation of the peripheral nerve termini. This ongoing activity evokes a state of robust spinal facilitation mediated by a number of local circuits, the net effect yielding an enhanced message of nociception to higher centres. This messaging typically wanes with the resolution of inflammation or wound healing. However, there are situations in which peripheral and central components of the pain transmission pathway extend and enhance the pain state, leading to a persistent hypersensitivity, e.g., an acute to chronic pain transition. Current work points to the contribution of innate and adaptive immunity in creating these enduring conditions. We briefly describe the underlying biological components of both physiological pain processing and pathological pain processing, as well as the acute to chronic pain transition and the role of innate and adaptive immunity in this transition.

Introduction

Detection of noxious stimuli is essential for survival. Acute, high intensity stimuli are alerting, and warn the organism of impending tissue damage. This acute pain sensation often subsides with the resolution of inflammation. However, there are instances in which pain may extended beyond the period of initial inflammation and tissue repair (1-5). Indeed, individuals with chronic inflammatory conditions can experience intense pain that persists even with remission of the inflammatory signs (6). In these cases, the pain state is pathologic, maladaptive, and debilitating. This uncoupling of pain from other signs of injury and inflammation represents a transition from an "acute to a chronic pain state". In this review, we will briefly outline mechanisms of acute and persistent or chronic pain. In addition, we will consider current thinking regarding the transition from an acute to a chronic pain state, which is thought to involve innate and adaptive immune signalling. A schematic summary of the mechanisms to be discussed are presented in Figure 1. The abbreviations used in the text are presented in the figure legend.

Physiological pain processing initiated by acute stimulation

Under normal conditions, activity in all classes of sensory afferents is largely absent. However, application of a noxious (potentially tissue injuring) stimulus (*e.g.* thermal, mechanical, chemical) will activate ion channels on the peripheral terminal causing depolarisation of the small, first order primary afferent neurons expressing these channels. The action potentials, with a frequency proportional to stimulus intensity, are propagated along the axons of nociceptive Aδ and C fibres, through the dorsal root ganglion (DRG) to the axon terminals in the spinal cord dorsal horn. In response to an intense stimulus, the medium diameter, rapidly conducting Aδ fibres relay well-localised "first" or fast pain, while the small diameter, un-myelinated, slow conducting C fibres convey poorly localised "second" or slow pain. High threshold afferents project into the superficial dorsal horn (referred to as Rexed Laminae I and II), while large, low threshold, mechanically sensitive afferents (Aβ) project into the dorsal horn to terminate in deeper lamina (Lamina III-V) (7).

The second order dorsal horn neurons involved in pain circuitry exist in two broadly characterised populations. Lamina I (marginal) neurons lie in the superficial spinal cord, primarily receive high threshold input, and are "nociceptive specific". Other populations of second order neurons lie more deeply (Lamina V) and send their dendrites dorsally to receive input from low threshold (A fibres) and then high

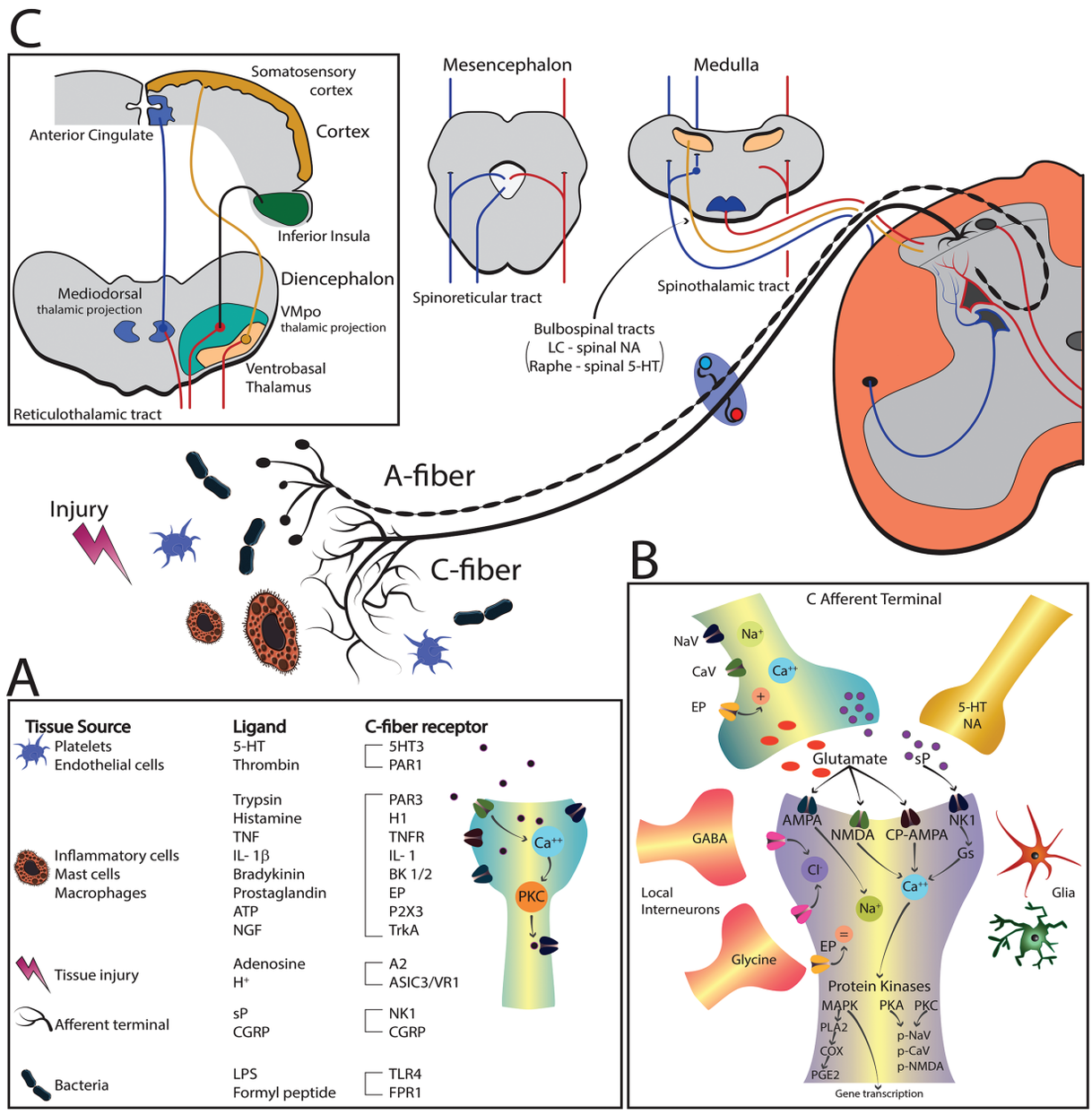

Fig. 1. **A**. Tissue injury, inflammation, or infection lead to local release of pro-inflammatory mediators (inflammatory soup) from resident cells (mast cells, Schwann cells), in migrating cells (macrophages, neutrophils), damaged cells, and blood vessels. These products act on receptors expressed on the afferent C fibre terminal to mediate an ongoing terminal depolarisation and increased intracellular Ca++, which, in turn, activates terminal kinases. Phosphorylation of terminal receptors and channels enhances their responsiveness and results in "terminal sensitisation".

B. Nociceptive afferents synapse onto superficial (Lamina 1) and deep (Lamina V) neurons, and, though activation of afferent terminal CaVs, release glutamate and peptides (substance P) which act on eponymous post-synaptic receptors. In the face of ongoing C fibre input, the second order neuron displays marked increases in excitability resulting from increased intracellular Ca++ that activates a myriad of protein kinases which i) phosphorylate receptors and channels, and ii) activate a variety of excitatory enzyme systems and iii) enhancing gene transcription. Other facilitatory components of dorsal horn function activated by ongoing C fibre input are: i) activation of glia (microglia and astrocytes) which release a constellation of pro-inflammatory molecules, ii) reduced effects of local GABA and glycinergic inhibition and iii) bulbospinal facilitatory input.

C. These events initiate and maintain a hyperexcitable state, sending the processed nociceptive signals to higher brain centres though the contralateral spinothalamic tract to the thalamus, and collateral projections into brainstem nuclei. Supraspinal projections largely follow two major trajectories: those projecting into the lateral (somatosensory) thalamus and thence to the somatosensory cortex and those projecting to more medial regions that then project to areas such as the inferior insula and the anterior cingulate. Other details considered in this figure are presented in the text. Abbreviations: 5-HT, serotonin; A2, adenosine receptor; AMPA, a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ASIC, acid-sensing ion channel; ATP, adenosine triphosphate; BK 1/2, bradykinin receptor; CaV, voltage-gated calcium channel; CGRP, calcitonin gene related peptide; CGRP, calcitonin gene related peptide; COX, cyclooxygenase ; CP-AMPA, calcium permeable AMPA receptor; EP, prostaglandin receptor; FPR1, formyl peptide receptor 1; GABA, gamma-aminobutyric acid; Gs, stimulatory signalling protein.; H1, histamine receptor; IL-1, Interleukin-1; IL-1b, Interleukin-1; LC, locus coeruleus; LPS, lipopolysaccharide; MAPK, mitogen activated protein kinase; NA, noradrenalin; NaV, voltage-gated sodium channel; NGF, nerve growth factor; NK1, neurokinin 1 receptor; NMDA, N-methyl-D-aspartate receptor; P2X3, purinoreceptor 3; PAR, proteinase activated receptor; PGE2, prostaglandin E2; PKA, protein kinase A; PKC, protein kinase C ; PLA2, phospholipase A2; sP, substance P; TLR4, Tropomyosin receptor kinase A; VMPO, ventromedial pars oralis; VR1, vanilloid receptor type 1.

threshold (A∂/C fibre) input, either mono- or poly-synaptically on their distal (superficial) dendrites. This population, referred to as convergent or wide dynamic range (WDR) neurons, shows a graded response over a wide range of A and C fibre mediated inputs. Second order neurons, activated by the acute release of glutamate, acting though glutamate ionophores, such as the AMPA receptor, project to supraspinal sites through crossed ventrolateral tracts. Within the brain, there is not one region responsible for processing all sensory inputs. Rather, projections from the ventrolateral quadrants of the spinal cord ascend following two principal trajectories: i) to the somatosensory thalamus and thence to the somatosensory cortex, and ii) to the medial and ventromedial thalamus, to the limbic forebrain (*e.g.,* anterior cingulate and the inferior insula) (8). The first trajectory appears to encode both location and intensity of the stimulus, while the second provides information to systems associated with emotionality and affect. Hence, acute pain processing is mediated by signals from the periphery through the dorsal horn, relayed through the thalamus to specific central regions for processing, giving rise to the somatosensory and cognitive aspects of pain. For a detailed review, see (9, 10). Typically, these signals cease when the peripheral inciting stimulus subsides.

Persistent pain processing secondary to local injury and inflammation

While acute pain is adaptive, local inflammation and injury frequently result in a pain state initiated by otherwise innocuous or moderately aversive stimuli (allodynia and hyperalgesia, respectively). This change in the input-output function reflects two related events: peripheral and central sensitisation.

Peripheral sensitisation

In the periphery, tissue injury results in a peripheral sensitisation that induces a hyperexcitability of afferent nociceptive neurons (11-14). In the face of tissue injury, there is cell damage, plasma extravasation, activation of local primary afferent terminals, and the movement of inflammatory cells into the injury site all leading to the release of a myriad of active products including amines, lipids, cytokines, and peptide transmitters (15-33). Importantly, the sensory afferent terminal expresses receptors for virtually all of these products. Activation of the terminal receptors leads to depolarisation and increased intracellular calcium. The net effect is terminal depolarisation and the activation of a variety of protein (*e.g.,* protein kinase C) and mitogen activated protein kinases (MAPKs). These kinases phosphorylate transducer proteins (*e.g.,* TRPV1) and ion channels, such as the voltage sensitive sodium channels, leading to their enhanced activation (34-36).

Not all peripheral afferents share the same threshold for transmitting signals. Many C-fibres have little or no spontaneous activity and are activated only by intense physical stimuli and are referred to as "silent nociceptors". In the presence of injury products, these terminals are sensitised such that they become spontaneously active and their activity can be elicited by moderate physical stimuli, analogous to an allodynic state. This functional motif is common to virtually all innervated tissues, (consider diagnoses that end in "-itis").

Central sensitisation

In the dorsal horn, WDR (Lamina V) neurons display a stimulus dependent response to the discrete activation of afferent C-fibres. Repetitive stimulation of C, but not A, fibres at a moderately fast rate results in a progressively facilitated discharge. The exaggerated discharge of WDR neurons evoked by repetitive small afferent stimulation was dubbed "wind up" by Mendell and Wall (37, 38). Intracellular recording in the WDR neuron has indicated that the facilitated state is represented by a progressive and long sustained partial depolarisation of the cell, rendering the membrane increasingly susceptible to subsequent afferent input. This central facilitation represents a complex cascade, including: i) phosphorylation of NMDA (N-methyl-D-aspartate) receptor and removal of the magnesium block, which otherwise prevents the functioning of the NMDA ionophore (39-44); ii) activation of metabotrophic receptors for glutamate and substance P (sP, the NK1 receptor), leading to increased intracellular calcium (45-55); iii) activation of voltage gated calcium channels (Cav 2.2, 3.1, 3.2, 3.3 channels) (56, 57); iv) activation of a variety of kinases leading to the phosphorylation of membrane channels and receptors enhancing their excitability (33, 58-63); v) activation of non-neuronal cells (astrocytes, microglia, T cells) (64-69) leading to the release of a variety of pro-excitatory lipids (prostaglandins) (70, 71), cytokines (Interleukin (IL), IL-8, IL-1β, IL-6, tumour necrosis factor (TNF)) (23,72–75) , chemokines (76-80), matrix metalloproteinases (81-86), and endogenous damage/danger associated membrane signals (DAMPS) (87-90); vi) afferent activation of spinobulbospinal excitatory feedback onto dorsal horn nociceptive neurons (8, 91-94); and vii) reduced activation and efficacy of intrinsic GABA and glycinergic inhibitory regulation of large (Aβ) excitatory input and second order WDR neuron excitability (*e.g.*, by disinhibition) leading to an enhanced response to large afferent input (95). Together, these cascades contribute to the ongoing hyperalgesic and allodynic states initiated by tissue injury and inflammation. Blockade or inhibition of components of the cascade can reduce the hyperpathic phenotype in models of peripheral inflammation and tissue injury. Usually, these states initiated by inflammation and tissue injury abate with resolution of the inflammatory state and wound healing.

Acute to chronic pain transition

As discussed previously, the pain state associated with and originating from prolonged inflammation may persist even when the inflammatory state resolves. This has been demonstrated in a variety of clinical conditions associated with tissue trauma (post-surgical) and chronic inflammation (rheumatic disease such as rheumatoid arthritis). This phenomenon has been experimentally demonstrated in antibody generated murine models of joint inflammation, such as the K/BxN (96-98) and collagen antibody induced arthritis (CAIA)

models (99, 100). In these models, mice develop long lasting, but reversible clinical signs which peak by several days following initiation. At the onset of paw swelling, mice show a decrease in paw withdrawal threshold, indicating development of tactile allodynia. Unexpectedly, this tactile allodynia persists long after resolution of visible swelling and inflammation. Several observations suggest that the pain-like behaviour occurring during active inflammation (inflammatory phase tactile allodynia) is phenotypically distinct from pain-like behaviours persisting after the resolution of inflammation (post-inflammatory phase tactile allodynia). First, tactile allodynia in the inflammatory phase is transiently reversed by anti-inflammatory agents (*e.g.*, non-steroidal anti-inflammatory drugs) and centrally active anti-hyperalgesic agents (*e.g.*, gabapentin) used for the treatment of neuropathic pain, while the post-inflammatory phase tactile allodynia is only affected by the centrally active anti-hyperalgesics (96). Second, mice in the post-inflammatory phase show increased activating transcription factor 3 (ATF3) positive neurons in the DRG, a marker associated with nerve injury and neuropathic pain (96). Finally, in chronic inflammatory models, there is a sprouting of peptidergic and non-peptidergic primary afferents as well as post-ganglionic sympathetic (tyrosine hydroxylase positive) fibres into the inflamed joint and the appearance of growth associated protein (GAP 43), a marker of axonal neurite formation and regeneration (101–104). Together, these observations indicate that there is a transition from an acute inflammation to a post-inflammatory *neuropathic* pain phenotype in these models of arthritis, leading to a persistent pain condition. Additional studies have implicated both the innate and adaptive immune systems as playing distinct roles in governing this transition to chronic pain state.

Innate immunity

There is a growing appreciation that components of the evolving pain may reflect a role for innate and adaptive immunity (64, 87, 105-108). The role of microglia (brain resident macrophages) and astrocytes in pain pathophysiology is well appreciated. Recent work has shown that several Toll-like receptors (TLRs), such as TLR4, are robustly expressed on glia and primary afferent neurons (109-111). These receptors are activated by a variety of exogenous pathogen-associated molecular patterns (PAMPs) and endogenous ligands commonly referred to as damage associated molecular patterns (DAMPS) (112, 113). For example, TLR4 may be activated by agents such as high mobility group box 1 (HMGB1), Tenacin C and various lipids to activate downstream signalling, leading to the production of a variety of proalgesic cytokines (64, 87, 88). A specific role of TLR4 in mediating the acute to chronic pain transition in the K/BxN model of arthritis has been described (114). In those studies, TLR4 mutant mice (C3H/HeJ) developed an inflammation commensurate to the wild type control. In contrast, the TLR4 mutants showed a resolution in their pain state with the resolution of inflammation. This work has been confirmed using a TLR4 knockout mouse. Additional work has shown that spinal TLR4 signalling can mediate the acute to chronic pain transition. The intrathecal administration of a TLR4 antagonist (LPS-RS) during the inflammatory phase has no effect on inflammation, but prevents the development of the persistent pain state in a wild type mouse (114). It is important to note, however, that this same treatment in the post-inflammatory phase did *not* affect thresholds, indicating that spinal TLR4 signalling here is specifically mediating the transition from acute to chronic pain.

Adaptive immunity

Current work is beginning to show that elements associated with adaptive or acquired immunity also play a role in persistent pain states. Anomalous chronic pain states have been linked to T-cell activation and the release of cytokines from spinal microglia that enhance neuronal activity (115). Interestingly, recent evidence indicates that microglia are not required for pain hypersensitivity in female mice. Rather, female mice develop hypersensitivity through the activation of T-lymphocytes (116). This sexual dimorphism is only beginning to be investigated, but is a very important subject of current work (117-119). It appears likely that a variety of chronic pain states as diverse as fibromyalgia (120), paraneoplastic syndrome (121), and complex regional pain syndrome (122) may involve autoantibody mediated mechanisms. The role of autoantibodies in the induction of chronic pain states are of significance and may contribute to a pain state by several mechanisms. First, it has been shown that IgG immune complexex may initiate a pain state in the rat through an interaction with Fcγ receptors, which have been identified to have stimulatory effects on DRG neurons (123, 124). Alternatively, autoantibodies may be formed against self-epitopes leading to antibody binding to nerves and DRG, complement fixation, and pain. In fact, autoantibodies against paranodal proteins leading to complement binding have been associated with painful inflammatory demyelinating polyneuropathies (125). Additionally, nerve injury may lead to the generation of autoantibodies to nerve injury products such as myelin basic protein leading to hyperpathia in females (126). Further, plasma taken from human rheumatoid arthritis patients containing autoantibodies against anti-citrullinated protein antibodies (ACPA) can induce pain states independent of inflammation in mice (99, 127). In that study, it was observed that, rather than a direct effect on sensory neurons, ACPA binds CD68+ osteoclasts in the bone marrow and induces CXC-chemokine ligand (CXCL) 1 and 2 expression and release from the joints, which then activates pro-nociceptive receptors on local primary afferents. Importantly, these autoantibodies often appear long before signs of inflammation in rheumatoid arthritis, and this ACPA – osteoclast interaction may contribute to the early arthralgia reported by patients. In other conditions, the targeting of autoantibodies directed at voltage-gated potassium channel complexes leads to neuronal hyperexcitability (128). Overall, there is an emerging and very exciting literature on the role of autoan-

tibodies in generating pain states with chronic inflammatory conditions and after nerve injury indicating, again, a possible mechanistic convergence for the chronic inflammatory with the neuropathic pain phenotype.

Conclusions

Traffic in small afferents leads to a stimulus dependent central processing that is highly aversive. In the face of tissue injury and inflammation, there is the generation of a robust effect on the peripheral terminal that leads to a sensitisation of the peripheral terminal and the generation of ongoing afferent traffic. At the level of the dorsal horn, this input activates second order dorsal horn neurons that encodes the intensity and modality of the stimulus and relays input to higher order centres that give rise to the perceptual experience of pain and drive systems that are associated with complex responses. In the face of injury and inflammation, the persistent afferent input leads to a robust increase in the input/output function and results in modest stimuli being encoded more intensely. Under many circumstances, this input and the attendant pain states will resolve as the injury and inflammation are resolved. Under other circumstances, the chronic inflammatory state leads to major changes in the pain phenotype to resemble that produced by nerve injury. While the mechanisms underlying this transition are not clear, current work points to the importance of resident inflammatory cells in the spinal cord and the pivotal role played by systems commonly associated with innate and adaptive immunity. This immune signalling appears to play a common role in the evolution of a variety of persistent pain phenotypes. Further understanding of neuroimmune interactions will allow for the better treatment or prevention of persistent pain states.

References

1. KEHLET H, JENSEN T S, WOOLF CJ: Persistent postsurgical pain: risk factors and prevention. *The Lancet* 2006; 367: 1618-25.
2. CHAPMAN CR, VIERCK CJ: The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. *J Pain* 2017; 18: 359.e1-359.e38.
3. WOODEN SR: Chronic postsurgical pain. *Annu Rev Nurs Res* 2017; 35: 91-115.
4. BJØRNNES AK, PARRY M, LIE I *et al*.: Pain experiences of men and women after cardiac surgery. *J Clin Nurs* 2016; 25: 3058-68.
5. MALLICK-SEARLE T, SNODGRASS B, BRANT JM: Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. *J Multidiscip Healthc* 2016; 9: 447-54.
6. SOKKA T, KAUTIAINEN H, TOLOZA S *et al*.: QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. *Ann Rheum Dis* 2007; 66: 1491-6.
7. BASBAUM AI, BAUTISTA DM, SCHERRER G, JULIUS D: Cellular and molecular mechanisms of pain. *Cell* 2009; 139: 267-84.
8. OSSIPOV MH, DUSSOR GO, PORRECA F: Central modulation of pain. *J Clin Invest* 2010; 120: 3779-87.
9. RALSTON HJ: Pain and the primate thalamus. *Prog Brain Res* 2005; 149: 1-10.
10. WILLIS WD: The somatosensory system, with emphasis on structures important for pain. *Brain Res Rev* 2007; 55: 297-313.
11. GUENTHER S, REEH P W, KRESS M: Rises in [Ca2+]i mediate capsaicin- and proton-induced heat sensitization of rat primary nociceptive neurons. *Eur J Neurosci* 1999; 11: 3143-50.
12. PETHÖ G, DEROW A, REEH PW: Bradykinin-induced nociceptor sensitization to heat is mediated by cyclooxygenase products in isolated rat skin. *Eur J Neurosci* 2001; 14: 210-8.
13. HUCHO T, LEVINE JD: Signaling pathways in sensitization: toward a nociceptor cell biology. *Neuron* 2007; 55: 365-76.
14. CHEN X, TANNER K, LEVINE JD: Mechanical sensitization of cutaneous C-fiber nociceptors by prostaglandin E2 in the rat. *Neurosci Lett* 1999; 267: 105-8.
15. KIM CF, MOALEM-TAYLOR G: Detailed characterization of neuro-immune responses following neuropathic injury in mice. *Brain Res* 2011; 1405: 95-108.
16. ELLIS A, BENNETT DLH: Neuroinflammation and the generation of neuropathic pain. *Br J Anaesth* 2013; 111: 26-37.
17. SCAFFIDI P, MISTELI T, BIANCHI ME: Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. *Nature* 2002; 418: 191-5.
18. LUO L, ZHANG S, WANG Y *et al*.: Proinflammatory role of neutrophil extracellular traps in abdominal sepsis. *Am J Physiol Lung Cell Mol Physiol* 2014; 307: L586-96.
19. GREGUS AM, DOOLEN S, DUMLAO DS *et al*.: Spinal 12-lipoxygenase-derived hepoxilin A3 contributes to inflammatory hyperalgesia via activation of TRPV1 and TRPA1 receptors. *Proc Natl Acad Sci USA* 2012; 109: 6721-6.
20. SISIGNANO M, PARK C-K, ANGIONI C *et al*.: 5,6-EET is released upon neuronal activity and induces mechanical pain hypersensitivity via TRPA1 on central afferent terminals. *J Neurosci* 2012; 32: 6364-72.
21. BOYCE VS, MENDELL LM: Neurotrophins and spinal circuit function. *Front Neural Circuits* 2014; 8: 59.
22. NIU X, CHEN G: Clinical biomarkers and pathogenic-related cytokines in rheumatoid arthritis. *J Immunol Res* 2014; 2014: 698192.
23. MILLER RE, MILLER RJ, MALFAIT A-M: Osteoarthritis joint pain: the cytokine connection. *Cytokine* 2014; 70: 185-93.
24. BARCLAY J, PATEL S, DORN G *et al*.: Functional downregulation of P2X3 receptor subunit in rat sensory neurons reveals a significant role in chronic neuropathic and inflammatory pain. *J Neurosci* 2002; 22: 8139-47.
25. BIBER K, BODDEKE E: Neuronal CC chemokines: the distinct roles of CCL21 and CCL2 in neuropathic pain. *Front Cell Neurosci* 2014; 8: 210.
26. LI D, REN Y, XU X *et al*.: Sensitization of primary afferent nociceptors induced by intradermal capsaicin involves the peripheral release of calcitonin gene-related Peptide driven by dorsal root reflexes. *J Pain* 2008; 9:1155-68.
27. CHIU IM, HEESTERS BA, GHASEMLOU N *et al*.: Bacteria activate sensory neurons that modulate pain and inflammation. *Nature* 2013; 501: 52-7.
28. JÄNIG W, LEVINE JD, MICHAELIS M: Interactions of sympathetic and primary afferent neurons following nerve injury and tissue trauma. *Prog Brain Res* 1996; 113: 161-84.
29. KELLY S, DUNHAM JP, DONALDSON LF: Sensory nerves have altered function contralateral to a monoarthritis and may contribute to the symmetrical spread of inflammation. *Eur J Neurosci* 2007; 26: 935-42.
30. LI KW, KIM DS, ZAUCKE F, LUO ZD: Trigeminal nerve injury-induced thrombospondin-4 up-regulation contributes to orofacial neuropathic pain states in a rat model. *Eur J Pain* 2014; 18: 489-95.
31. DRUMMOND PD: Sensory-autonomic interactions in health and disease. *Handb Clin Neurol* 2013; 117: 309-19.
32. FANG L, WU J, LIN Q, WILLIS WD: Calcium-calmodulin-dependent protein kinase II contributes to spinal cord central sensitization. *J Neurosci* 2002; 22: 4196-204.
33. PEZET S, MARCHAND F, MELLO RD *et al*.: Phosphatidylinositol 3-kinase is a key mediator of central sensitization in painful inflammatory conditions. *J Neurosci* 2008; 28: 4261-70.
34. BAGAL SK, CHAPMAN ML, MARRON BE *et al*.: Recent progress in sodium channel modulators for pain. *Bioorg Med Chem Lett* 2014; 24: 3690-9.
35. DELMAS P, HAO J, RODAT-DESPOIX L: Molecular mechanisms of mechanotransduction in mammalian sensory neurons. *Nat Rev Neurosci* 2011; 12: 139-53.
36. HOEIJMAKERS JG, FABER CG, LAURIA G, MERKIES IS, WAXMAN SG: Small-fibre neuropathies--advances in diagnosis, pathophysiology and management. *Nat Rev Neurol* 2012; 8: 369-79.
37. MENDELL LM, WALL PD: Responses of single dorsal cord cells to peripheral cutaneous unmyelinated fibres. *Nature* 1965; 206: 97-9.
38. MENDELL LM: Physiological properties of unmyelinated fiber projection to the spinal cord. *Exp Neurol* 1966; 16: 316-32.
39. PAOLETTI P: Molecular basis of NMDA receptor functional diversity. *Eur J Neurosci* 2011; 33: 1351-65.

40. LATREMOLIERE A, WOOLF CJ: Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009; 10: 895-926.
41. VIKMAN KS, RYCROFT BK, CHRISTIE MJ: Switch to Ca2+-permeable AMPA and reduced NR2B NMDA receptor-mediated neurotransmission at dorsal horn nociceptive synapses during inflammatory pain in the rat. *J Physiol* (Lond) 2008; 586: 515-27.
42. KOPACH O, KAO S-C, PETRALIA RS *et al*.: Inflammation alters trafficking of extrasynaptic AMPA receptors in tonically firing lamina II neurons of the rat spinal dorsal horn. *Pain* 2011; 152: 912-23.
43. STUDNIARCZYK D, COOMBS I, CULL-CANDY SG, FARRANT M: TARP γ-7 selectively enhances synaptic expression of calcium-permeable AMPARs. *Nat Neurosci* 2013; 16: 1266-74.
44. MAYER ML, WESTBROOK GL, GUTHRIE PB: Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. Nature 1984; 309: 261-3.
45. BIBER K, LAURIE DJ, BERTHELE A *et al*.: Expression and signaling of group I metabotropic glutamate receptors in astrocytes and microglia. J Neurochem 1999; 72: 1671-80.
46. PETRENKO AB, YAMAKURA T, BABA H, SHIMOJI K: The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg* 2003; 97: 1108-16.
47. COLLINS S, SIGTERMANS MJ, DAHAN A, ZUURMOND WWA, PEREZ RSGM: NMDA receptor antagonists for the treatment of neuropathic pain. *Pain Med* 2010; 11: 1726-42.
48. SHEFFLER DJ, GREGORY KJ, ROOK JM, CONN PJ: Allosteric modulation of metabotropic glutamate receptors. *Adv Pharmacol* 2011; 62: 37-77.
49. SOLIMAN AC, YU JSC, CODERRE TJ: mGlu and NMDA receptor contributions to capsaicin-induced thermal and mechanical hypersensitivity. *Neuropharmacology* 2005; 48: 325-32.
50. YOUNG MR, FLEETWOOD-WALKER SM, DICKINSON T *et al*.: Behavioural and electrophysiological evidence supporting a role for group I metabotropic glutamate receptors in the mediation of nociceptive inputs to the rat spinal cord. *Brain Res* 1997; 777: 161-9.
51. YOUNG MR, FLEETWOOD-WALKER SM, MITCHELL R, MUNRO FE: Evidence for a role of metabotropic glutamate receptors in sustained nociceptive inputs to rat dorsal horn neurons. *Neuropharmacology* 1994; 33: 141-4.
52. AFRAH AW, FISKÅ A, GJERSTAD J *et al*.: Spinal substance P release in vivo during the induction of long-term potentiation in dorsal horn neurons. *Pain* 2002; 96: 49-55.
53. KHASABOV SG, ROGERS SD, GHILARDI JR *et al*.: Spinal neurons that possess the substance P receptor are required for the development of central sensitization. *J Neurosci* 2002; 22: 9086-98.
54. MANTYH PW, ROGERS SD, HONORE P *et al*.: Inhibition of hyperalgesia by ablation of lamina I spinal neurons expressing the substance P receptor. *Science* 1997; 278: 275-9.
55. MA QP, WOOLF CJ: Involvement of neurokinin receptors in the induction but not the maintenance of mechanical allodynia in rat flexor motoneurones. *J Physiol* (Lond) 1995; 486: 769-77.
56. CODERRE TJ, MELZACK R: The role of NMDA receptor-operated calcium channels in persistent nociception after formalin-induced tissue injury. *J Neurosci* 1992; 12: 3671-5.
57. WOOLF CJ, SALTER MW: Neuronal plasticity: increasing the gain in pain. *Science* 2000; 288: 1765-9.
58. FAGNI L, CHAVIS P, ANGO F, BOCKAERT J: Complex interactions between mGluRs, intracellular Ca2+ stores and ion channels in neurons. *Trends Neurosci* 2000; 23: 80-8.
59. YASHPAL K, FISHER K, CHABOT J G, CODERRE TJ: Differential effects of NMDA and group I mGluR antagonists on both nociception and spinal cord protein kinase C translocation in the formalin test and a model of neuropathic pain in rats. *Pain* 2001; 94: 17-29.
60. KARIM F, WANG CC, GEREAU RW: Metabotropic glutamate receptor subtypes 1 and 5 are activators of extracellular signal-regulated kinase signaling required for inflammatory pain in mice. *J Neurosci* 2001; 21: 3771-9.
61. JI RR, BABA H, BRENNER GJ, WOOLF CJ: Nociceptive-specific activation of ERK in spinal neurons contributes to pain hypersensitivity. *Nat Neurosci* 1999; 2: 1114-9.
62. KAWASAKI Y, KOHNO T, ZHUANG Z-Y *et al*.: Ionotropic and metabotropic receptors, protein kinase A, protein kinase C, and Src contribute to C-fiber-induced ERK activation and cAMP response element-binding protein phosphorylation in dorsal horn neurons, leading to central sensitization. *J Neurosci* 2004; 24: 8310-21.
63. WALKER SM, MEREDITH-MIDDLETON J, LICKISS T, MOSS A, FITZGERALD M: Primary and secondary hyperalgesia can be differentiated by postnatal age and ERK activation in the spinal dorsal horn of the rat pup. *Pain* 2007; 128: 157-68.
64. GRACE PM, HUTCHINSON MR, MAIER SF, WATKINS LR: Pathological pain and the neuroimmune interface. *Nat Rev Immunol* 2014; 14:217–231.
65. JI R-R, BERTA T, NEDERGAARD M: Glia and pain: is chronic pain a gliopathy? *Pain* 2013; 154 (Suppl. 1): S10-28.
66. YDENS E, LORNET G, SMITS V *et al*.: The neuroinflammatory role of Schwann cells in disease. *Neurobiol Dis* 2013; 55: 95-103.
67. BLUM E, PROCACCI P, CONTE V, HANANI M: Systemic inflammation alters satellite glial cell function and structure. A possible contribution to pain. *Neuroscience* 2014; 274: 209-17.
68. BARRAGÁN-IGLESIAS P, PINEDA-FARIAS JB, CERVANTES-DURÁN C *et al*.: Role of spinal P2Y6 and P2Y11 receptors in neuropathic pain in rats: possible involvement of glial cells. *Mol Pain* 2014; 10: 29.
69. TSUDA M, MASUDA T, TOZAKI-SAITOH H, INOUE K: P2X4 receptors and neuropathic pain. *Front Cell Neurosci* 2013; 7: 191.
70. SVENSSON CI, LUCAS KK, HUA XY *et al*.: Spinal phospholipase A2 in inflammatory hyperalgesia: role of the small, secretory phospholipase A2. *Neuroscience* 2005; 133: 543-53.
71. MATSUI T, SVENSSON CI, HIRATA Y *et al*.: Release of prostaglandin E(2) and nitric oxide from spinal microglia is dependent on activation of p38 mitogen-activated protein kinase. *Anesth Analg* 2010; 111: 554-60.
72. CABAL-HIERRO L, LAZO PS: Signal transduction by tumor necrosis factor receptors. *Cell Signal* 2012; 24: 1297-305.
73. KO JS, EDDINGER KA, ANGERT M *et al*.: Spinal activity of interleukin 6 mediates myelin basic protein-induced allodynia. *Brain Behav Immun* 2016; 56: 378-89.
74. BAS DB, ABDELMOATY S, SANDOR K *et al*.: Spinal release of tumour necrosis factor activates c-Jun N-terminal kinase and mediates inflammation-induced hypersensitivity. *Eur J Pain* 2015; 19: 260-70.
75. SHUBAYEV VI, KATO K, MYERS RR: Cytokines in Pain. *In*: KRUGER L, LIGHT AR (Eds.): *Translational pain research: from mouse to man*. Boca Raton, FL, CRC Press/ Taylor & Francis; 2010.
76. MILLER RE, TRAN PB, DAS R *et al*.: CCR2 chemokine receptor signaling mediates pain in experimental osteoarthritis. *Proc Natl Acad Sci USA* 2012; 109: 20602-7.
77. WHITE FA, FELDMAN P, MILLER RJ: Chemokine signaling and the management of neuropathic pain. *Mol Interv* 2009; 9: 188-95.
78. HULSEBOSCH CE, HAINS BC, CROWN ED, CARLTON SM: Mechanisms of chronic central neuropathic pain after spinal cord injury. *Brain Res Rev* 2009; 60: 202-13.
79. VAN STEENWINCKEL J, REAUX-LE GOAZIGO A, POMMIER B *et al*.: CCL2 released from neuronal synaptic vesicles in the spinal cord is a major mediator of local inflammation and pain after peripheral nerve injury. *J Neurosci* 2011; 31: 5865-75.
80. CLARK A K, MALCANGIO M: Fractalkine/ CX3CR1 signaling during neuropathic pain. *Front Cell Neurosci* 2014; 8: 121.
81. MALEK MAHDAVI A, MAHDAVI R, KOLAHI S: Effects of l-carnitine supplementation on serum inflammatory factors and matrix metalloproteinase enzymes in females with knee osteoarthritis: a randomized, double-blind, placebo-controlled pilot study. *J Am Coll Nutr* 2016; 35: 597-603.
82. NISHIHARA T, REMACLE AG, ANGERT M *et al*.: Matrix metalloproteinase-14 both sheds cell surface neuronal glial antigen 2 (NG2) proteoglycan on macrophages and governs the response to peripheral nerve injury. *J Biol Chem* 2015; 290: 3693-707.
83. HONG S, REMACLE AG, SHIRYAEV SA *et al*.: Reciprocal relationship between membrane type 1 matrix metalloproteinase and the algesic peptides of myelin basic protein contributes to chronic neuropathic pain. *Brain Behav Immun* 2017; 60: 282-92.
84. REMACLE AG, KUMAR S, MOTAMEDCHABOKI K *et al*.: Matrix metalloproteinase (MMP) proteolysis of the extracellular loop of voltage-gated sodium channels and potential alterations in pain signaling. *J Biol Chem* 2015; 290: 22939-44.

85. CHATTOPADHYAY S, MYERS RR, JANES J, SHUBAYEV V: Cytokine regulation of MMP-9 in peripheral glia: implications for pathological processes and pain in injured nerve. *Brain Behav Immun* 2007; 21: 561-8.
86. MIRANPURI GS, SCHOMBERG DT, ALRFAEI B *et al*.: Role of matrix metalloproteinases 2 in spinal cord injury-induced neuropathic pain. *Ann Neurosci* 2016; 23: 25-32.
87. KATO J, SVENSSON CI: Role of extracellular damage-associated molecular pattern molecules (DAMPs) as mediators of persistent pain. *Prog Mol Biol Transl Sci* 2015; 131: 251-79.
88. AGALAVE NM, LARSSON M, ABDELMOATY S *et al*.: Spinal HMGB1 induces TLR4-mediated long-lasting hypersensitivity and glial activation and regulates pain-like behavior in experimental arthritis. *Pain* 2014; 155: 1802-13.
89. HUTCHINSON MR, RAMOS KM, LORAM LC *et al*.: Evidence for a role of heat shock protein-90 in toll like receptor 4 mediated pain enhancement in rats. *Neuroscience* 2009; 164: 1821-32.
90. FELDMAN P, DUE MR, RIPSCH MS, KHANNA R, WHITE FA: The persistent release of HMGB1 contributes to tactile hyperalgesia in a rodent model of neuropathic pain. *J Neuroinflammation* 2012; 9: 180.
91. PERTOVAARA A: The noradrenergic pain regulation system: a potential target for pain therapy. *Eur J Pharmacol* 2013; 716: 2-7.
92. TYCE GM, YAKSH TL: Monoamine release from cat spinal cord by somatic stimuli: an intrinsic modulatory system. *J Physiol* (Lond) 1981; 314: 513-29.
93. YAKSH TL: Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. *Pharmacol Biochem Behav* 1985; 22: 845-58.
94. SUZUKI R, RYGH LJ, DICKENSON AH: Bad news from the brain: descending 5-HT pathways that control spinal pain processing. *Trends Pharmacol Sci* 2004; 25: 613-7.
95. BABA H, JI R-R, KOHNO T *et al*.: Removal of GABAergic inhibition facilitates polysynaptic A fiber-mediated excitatory transmission to the superficial spinal dorsal horn. *Mol Cell Neurosci* 2003; 24: 818-30.
96. CHRISTIANSON CA, CORR M, FIRESTEIN GS *et al*.: Characterization of the acute and persistent pain state present in K/BxN serum transfer arthritis. *Pain* 2010; 151: 394-403.
97. CHRISTIANSON CA, CORR M, YAKSH TL, SVENSSON CI: K/BxN serum transfer arthritis as a model of inflammatory joint pain. *Methods Mol Biol* 2012; 851: 249-60.
98. BAS DB, SU J, WIGERBLAD G, SVENSSON CI: Pain in rheumatoid arthritis: models and mechanisms. *Pain Manag* 2016; 6: 265-84.
99. BAS DB, SU J, SANDOR K *et al*.: Collagen antibody-induced arthritis evokes persistent pain with spinal glial involvement and transient prostaglandin dependency. *Arthritis Rheum* 2012; 64: 3886-96.
100. SU J, GAO T, SHI T *et al*.: Phenotypic changes in dorsal root ganglion and spinal cord in the collagen antibody-induced arthritis mouse model. *J Comp Neurol* 2015; 523: 1505-28.
101. GHILARDI JR, FREEMAN KT, JIMENEZ-ANDRADE JM *et al*.: Neuroplasticity of sensory and sympathetic nerve fibers in a mouse model of a painful arthritic joint. *Arthritis Rheum* 2012; 64: 2223-32.
102. CHUNG K, CHUNG JM: Sympathetic sprouting in the dorsal root ganglion after spinal nerve ligation: evidence of regenerative collateral sprouting. *Brain Res* 2001; 895: 204-12.
103. JIMENEZ-ANDRADE JM, MANTYH PW: Sensory and sympathetic nerve fibers undergo sprouting and neuroma formation in the painful arthritic joint of geriatric mice. *Arthritis Res Ther* 2012; 14: R101.
104. BENOWITZ LI, ROUTTENBERG A: GAP-43: an intrinsic determinant of neuronal development and plasticity. *Trends Neurosci* 1997; 20: 84-91.
105. CARNIGLIA L, RAMÍREZ D, DURAND D *et al*.: Neuropeptides and microglial activation in inflammation, pain, and neurodegenerative diseases. *Mediators Inflamm* 2017; 2017: 5048616.
106. GIERUT A, PERLMAN H, POPE RM: Innate immunity and rheumatoid arthritis. *Rheum Dis Clin North Am* 2010; 36: 271-96.
107. JI R-R, CHAMESSIAN A, ZHANG Y-Q: Pain regulation by non-neuronal cells and inflammation. *Science* 2016; 354: 572-7.
108. WILLEMEN HLDM, EIJKELKAMP N, GARZA CARBAJAL A *et al*.: Monocytes/Macrophages control resolution of transient inflammatory pain. *J Pain* 2014; 15: 496-506.
109. HELLEY MP, ABATE W, JACKSON SK, BENNETT JH, THOMPSON SWN: The expression of Toll-like receptor 4, 7 and co-receptors in neurochemical sub-populations of rat trigeminal ganglion sensory neurons. *Neuroscience* 2015; 310: 686-98.
110. BSIBSI M, RAVID R, GVERIC D, VAN NOORT JM: Broad expression of Toll-like receptors in the human central nervous system. *J Neuropathol Exp Neurol* 2002; 61: 1013-21.
111. JACK CS, ARBOUR N, MANUSOW J *et al*.: TLR signaling tailors innate immune responses in human microglia and astrocytes. *J Immunol* 2005; 175: 4320-30.
112. TAKEDA K, AKIRA S: Toll-like receptors. *Curr Protoc Immunol* 2015; 109: 14.12.1-10.
113. UEMATSU S, AKIRA S: Toll-Like receptors (TLRs) and their ligands. *Handb Exp Pharmacol* 2008; 183: 1-20.
114. CHRISTIANSON CA, DUMLAO DS, STOKES JA *et al*.: Spinal TLR4 mediates the transition to a persistent mechanical hypersensitivity after the resolution of inflammation in serum-transferred arthritis. *Pain* 2011; 152: 2881-91.
115. MIFFLIN KA, KERR BJ: Pain in autoimmune disorders. *J Neurosci Res* 2017; 95: 1282-94.
116. SORGE RE, MAPPLEBECK JCS, ROSEN S *et al*.: Different immune cells mediate mechanical pain hypersensitivity in male and female mice. *Nat Neurosci* 2015; 18: 1081-3.
117. MAPPLEBECK JCS, BEGGS S, SALTER MW: Sex differences in pain: a tale of two immune cells. *Pain* 2016; 157 (Suppl. 1): S2-6.
118. DOYLE HH, MURPHY AZ: Sex differences in innate immunity and its impact on opioid pharmacology. *J Neurosci Res* 2017; 95: 487-99.
119. SORGE RE, TOTSCH SK: Sex differences in pain. *J Neurosci Res* 2017; 95: 1271-81.
120. GIACOMELLI C, TALARICO R, BOMBARDIERI S, BAZZICHI L: The interaction between autoimmune diseases and fibromyalgia: risk, disease course and management. *Expert Rev Clin Immunol* 2013; 9: 1069-76.
121. JARIUS S, RINGELSTEIN M, HAAS J *et al*.: Inositol 1,4,5-trisphosphate receptor type 1 autoantibodies in paraneoplastic and non-paraneoplastic peripheral neuropathy. *J Neuroinflammation* 2016; 13: 278.
122. KOHR D, TSCHERNATSCH M, SCHMITZ K *et al*.: Autoantibodies in complex regional pain syndrome bind to a differentiation-dependent neuronal surface autoantigen. *Pain* 2009; 143: 246-51.
123. JIANG H, SHEN X, CHEN Z *et al*.: Nociceptive neuronal Fc-gamma receptor I is involved in IgG immune complex induced pain in the rat. *Brain Behav Immun* 2017; 62: 351-61.
124. QU L, ZHANG P, LAMOTTE RH, MA C: Neuronal Fc-gamma receptor I mediated excitatory effects of IgG immune complex on rat dorsal root ganglion neurons. *Brain Behav Immun* 2011; 25: 1399-407.
125. DOPPLER K, APPELTSHAUSER L, VILLMANN C *et al*.: Auto-antibodies to contactin-associated protein 1 (Caspr) in two patients with painful inflammatory neuropathy. *Brain* 2016; 139: 2617-30.
126. SHUBAYEV VI, STRONGIN AY, YAKSH TL: Role of myelin auto-antigens in pain: a female connection. *Neural Regen Res* 2016; 11: 890-1.
127. WIGERBLAD G, BAS DB, FERNADES-CERQUEIRA C *et al*.: Autoantibodies to citrullinated proteins induce joint pain independent of inflammation via a chemokine-dependent mechanism. *Ann Rheum Dis* 2016; 75: 730-8.
128. KLEIN CJ, LENNON VA, ASTON PA, MCKEON A, PITTOCK SJ: Chronic pain as a manifestation of potassium channel-complex autoimmunity. *Neurology* 2012; 79: 1136-44.