Neuroinflammation and the generation of neuropathic pain

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The inflammatory response

Inflammation is the process by which an organism responds to tissue injury involving both immune cell recruitment and mediator release. It is an attempt to remove the injurious stimulus and initiate healing. The inflammatory response consists of a pro-inflammatory phase in which any pathogens are removed, damaged cells and debris cleared, and the local homeostasis restored. After this, there is a phase of resolution in which there is local tissue repair and the potentially damaging effects of a continued inflammatory response are dissipated.¹ ² Several cell types mediate the immune response with temporally distinct contributions. The immune response is recruited and mediated via the release of a range of chemical mediators, many of which have similar effects. These mediators can be classified into seven subgroups, listed in Table 1 along with some examples from each group.¹

Inflammation is a key biological process and, consequently, its role is not restricted to mounting a response to infection; inflammatory processes play a key role in diverse disease states such as cancer biology and diabetes. It is increasingly recognized that the immune system interacts with the sensory nervous system contributing to persistent pain states.³–⁵ Inflammation is a well-established cause of nociceptive pain whether attributable to autoimmunity (e.g. rheumatoid arthritis) or chemical mediators (e.g. gout). Neuropathic pain is distinct from nociceptive pain, arising as a consequence of a lesion or disease of the somatosensory system.⁶ In certain cases, this lesion may be attributable to an aberrant immune response resulting in excessive neuroinflammation of the peripheral (e.g. Guillain–Barré syndrome) or central (e.g. multiple sclerosis) nervous system. Both of these conditions are associated with a high prevalence of neuropathic pain.⁷ ⁸ In addition, many diverse causes of neuropathic pain (e.g. traumatic neuropathy and spinal cord injury) are in themselves associated with excessive inflammation which may be involved in both the initiation and maintenance of persistent pain.

This review provides an overview of inflammatory mechanisms at differing levels of the sensory neuroaxis shown to play a role in persistent pain states, with a focus on neuropathic pain. Although the inflammatory response is likely to differ depending on the physiological situation, an overview of the stages of an inflammatory response is illustrated in Figure 1.

The inflammatory response to injury within the peripheral nerve trunk

Damage to the peripheral nerve leads to a local inflammatory response which contributes to the generation of...
behavioural hypersensitivity. The first cells to react to damage of the nerve are Schwann cells and resident immune cells such as mast cells and macrophages. An as yet unspecified signal from damaged axons results in activation of the extracellular signal-related (ERK) mitogen-activated protein kinase (MAP) kinase signalling pathway in Schwann cells; this is one of the earliest events triggering the expression of inflammatory mediators and recruiting immune cells to the damaged nerve.9 Myelinating Schwann cells dedifferentiate and begin the process of degrading the myelin sheath at the site of injury, a necessary prerequisite for regeneration.10 Resident mast cells degranulate releasing inflammatory mediators, including histamine, serotonin, nerve growth factor, and leukotrienes, which can sensitize nociceptors and also contribute to the recruitment of neutrophils, the first cells to infiltrate damaged tissue.11–14 Mast cell stabilization with sodium cromoglycate reduces the infiltration of neutrophils to the injured nerve and suppresses the

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<th>Example</th>
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</tr>
<tr>
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<tr>
<td>Cytokines</td>
<td>IL-1β</td>
<td>Schwann cells, mast cells, neutrophils, lymphocytes, macrophages, microglia, and astrocytes15, 117, 118, 125</td>
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<td>Chemokines</td>
<td>MCP-1 (CCL2)</td>
<td>Schwann cells, neutrophils, mast cells, macrophages, microglia, astrocytes, and neurons15, 117, 129–131</td>
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<td>Cathepsin S</td>
<td></td>
<td>Macrophages, microglia135, 139</td>
<td>Indirect nociceptive action via cleavage of membrane-bound fractalkine, which in turn activates microglia and macrophages140</td>
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Trigger of inflammatory response:
- PAMPs
- DAMPs—products of dying cells, e.g. ATP, breakdown products of extracellular matrix

Activation/proliferation of resident cells:
- e.g. mast cells, macrophage, microglia (CNS), astrocytes (CNS)

Immune cell recruitment/migration:
- Neutrophils
- Circulating macrophages
- Helper T cells
- Microglia (CNS)

Effector functions:
- e.g. phagocytosis, degranulation

Pro-inflammatory mediator release:
- e.g. cytokines, chemokines, lipid mediators (see Table 1)

Resolution of inflammation:
- switch to production of pro-resolution mediators, e.g. lipoxins, resolvins, protectins

Resolution of pain
development of thermal and mechanical hypersensitivity, highlighting the importance of the early immune response in the neuropathic pain development.12 Similarly, using an anti-neutrophil antibody to deplete circulating neutrophils at the time of injury has been shown to significantly attenuate subsequent behavioural hypersensitivity.13 Neutrophil infiltration to the site of injury is acute, peaking within the first few hours after injury and declining after 3 days, though levels remain elevated. Neutrophils release mediators capable of sensitizing nociceptors, and recruiting macrophages and T cells to the injury site.15,16 Recruited infiltrating macrophages join the resident macrophages and, along with Schwann cells, take part in the phagocytosis of degenerating axons and myelin sheaths. In addition to this function, they secrete a myriad of pro-inflammatory cytokines/chemokines, and lipid mediators.17 Depletion of the circulating population of macrophages via the administration of liposomes containing clodronate reduces behavioural hypersensitivity after peripheral nerve injury.18 T cells are characterized by the expression of surface molecules and broadly grouped into T-helper cells or cytotoxic T cells. T-helper cells, dependent on their class, release pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-17, and also anti-inflammatory cytokines such as IL-4 and IL-10.19 (For expansion of the abbreviations used in this article, please see the Appendix.)

In addition to the release of inflammatory mediators from infiltrating immune cells, the sensory nerve terminals release neuropeptides such as Substance P and Calcitonin Gene Related Peptide (CGRP) upon antidromic conduction of impulses. These vasoactive peptides enhance the immune response by increasing vascular permeability and also directly interact with immune cells such as Langerhan’s cells and macrophages.20 Additionally, they may feedback and sensitize primary afferent neurons.21

The chemical mediators released by various cells of the peripheral immune response after nerve injury have the undesired effect of sensitizing and stimulating nociceptors. In the short term, this is necessary to alert the individual of damage and promote rest. However, in the case of neuropathic pain, this can promote long-term deleterious plastic changes. Table 1 lists some examples of inflammatory mediators of the immune response shown to have a role in the generation of behavioural hypersensitivity after peripheral nerve injury. The change in the local chemical milieu brought about by the inflammatory response not only has actions on damaged, degenerating neurons, but also on the neighbouring uninjured afferents sharing the same innervation territory. As a result, these ‘spared’ fibres exhibit spontaneous activity, an important driver of neuropathic pain.22,23 The action of these mediators can be direct through binding to receptors on nociceptors, some of which are upregulated after injury.24-26 Indirect actions also occur such as IL-1β indirectly sensitizing nociceptors through enhanced prostaglandin synthesis in addition to directly sensitizing nociceptors via actions on transient receptor potential vanilloid type 1 (TRPV1) and its own IL-1R receptors.27 Inflammatory mediators acting on nociceptor terminals exert their sensitizing effects via multiple second messenger pathways on receptors and ion channels present in the nociceptor, such as transient receptor potential and voltage-gated sodium channels.28 Post-translational modification of these channels results in an alteration of their kinetics and thresholds of activation, resulting in an increase in sensitivity and excitability of the nociceptor terminal. For example, activation of protein kinase C causes increased TRPV1 channel insertion in the plasma membrane, and increased sensitivity to protons, heat, and the endogenous agonist anandamide.29-32 Second messenger activation also results in the activation of transcription factors such as cAMP response element-binding, STAT and ATF-3 which in turn leads to longer-term changes in expression of neurotransmitters, peptides, and ion channel proteins (see Fig. 2).33-41

The inflammatory response also has adaptive functions enabling nerve repair. For example, functional recovery is dependent on IL-1 and TNF-α expression,42 and complete ablation of macrophages results in severely impaired axon regeneration.43 Therefore, analgesic targeting the inflammatory response should aim at reducing excessive inflammation rather than completely switching it off.

The dorsal root ganglia are also subject to an immune response after peripheral nerve injury, similar to that observed in the injured nerve. Neutrophils have been shown to invade the ipsilateral dorsal root ganglion (DRG) after peripheral nerve injury between 7 and 14 days post-surgery (depending on the injury) much later than that observed peripherally, and also at lower levels.44 Peripheral nerve injury also induces significant T-cell infiltration to the ipsilateral DRGs

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**Fig 1** Schematic representing an overview of the stages of the inflammatory response. 1. Infection, tissue injury, or stress can trigger the immune response via activation of receptors responsive to pathogen-associated molecular patterns (e.g. lipopolysaccharide), and danger-associated molecular patterns (e.g. adenosine triphosphate (ATP)) 2. This leads to the activation and proliferation of resident immune cells, including mast cells and macrophages. Activated immune cells release inflammatory mediators, including cytokines (e.g. IL-1β and TNF-α), chemokines (e.g. MCP-1 and fractalkine), purines (e.g. ATP), and lipid mediators (e.g. PGE2 and PGJ2), which mediate the recruitment of circulating immune cells, including neutrophils, macrophages, and T cells. Inflammatory mediator release from these, and resident, cells also induces immune cell effector functions such as phagocytosis, and brings about further inflammatory mediator release. Pro-inflammatory mediators can modulate neuronal excitability and synaptic function for instance in the somatosensory system leading to peripheral and central sensitization. 5. As the course of the inflammatory process progresses, there is a switch in mediator production to pro-resolution mediators such as resolvins. These promote resolution of the inflammatory response, limiting further immune cell infiltration and promoting phagocytosis of infiltrated immune cells and there is evidence that such resolution of inflammation can also reduce pain sensibility.
from ~7 days after injury.13 45 46 Macrophages infiltrate ipsilateral DRGs, forming perineuronal rings around medium to large diameter neurons from ~3 days post-injury, peaking at 7 days, and continuing for several weeks.13 46 As in the nerve, bi-directional signalling between injured sensory neurons and immune cells mediate these interactions. For instance, damaged sensory neurons up-regulate mediators which recruit immune cells.47 Subsequently, infiltrating immune cells secrete numerous inflammatory mediators, sensitizing the neuronal cell bodies and may, in the long-term, bring about plastic changes.

Profound peripheral immune cell infiltration and mediator release within the nerve trunk is well characterized in several animal models of traumatic peripheral nerve injury. In addition, inflammatory processes are observed in diverse models of neuropathic pain, including chemotherapy-induced neuropathy48 49 and EAN as a model of Guillain–Barre syndrome.50 Additionally, pro-inflammatory cytokines have been implicated in the genesis of diabetic neuropathy.51–53 As in animal models of peripheral traumatic nerve injury, an early role for matrix metalloproteinases is evident in neuropathic pain models of diabetic neuropathy, chemotherapy-induced neuropathy, and Guillain–Barré syndrome.48 51 54 In addition to this, several pro-inflammatory mediators have been demonstrated to contribute to behavioural hypersensitivity in these animal models.50 51 55

Similarly, a wide range of painful neuropathies in humans are associated with immune cell recruitment and pro-inflammatory mediator expression.56

The central inflammatory response

Unlike the peripheral nerve and DRG, the spinal cord is protected by the blood–spinal cord barrier, which was thought to prevent the influx of immune cells from the circulation into the spinal cord after nerve injury. However, emerging reports suggest that peripheral nerve injury can result in a disruption of the blood–spinal cord barrier allowing influx of peripheral immune cells, an effect shown to be mediated by monocyte chemoattractant protein-1 (MCP-1, also referred to as CCL2).57 58 This is in line with other reports describing a low-level infiltration of T cells into the dorsal spinal cord after peripheral nerve injury. This likely contributes to the neuropathic pain phenotype as mice deficient in T cells show attenuated behavioural hypersensitivity in response to peripheral nerve injury.59 60 Additionally, there is a profound central inflammatory response involving cell types resident to the central nervous system (CNS) (i.e. microglia and astrocytes). Giall cells constitute some 70% of the total cell population of the brain and spinal cord.61 For many years, it was thought the role of CNS glia was simply one of neurotrophic support and immune protection. However, it is
now well established that glia play an important role in the generation of persistent pain syndromes. Microglia are often considered the resident macrophages of the CNS because of their shared properties with the phagocytic macrophage. Under normal physiological conditions, microglia are thought to act to stabilize the CNS by surveying the local environment for stimuli and changes which may indicate a threat to the physiological homeostasis of the system such as trauma, ischaemia, and infection. After peripheral nerve injury, the microglial phenotype changes markedly to a pro-inflammatory or ‘effector’ phenotype in which they proliferate, become highly motile and phagocytic, express new receptors (e.g. ligand-gated ion channel P2X4), and release pro-inflammatory mediators. The microglial response to several commonly used nerve injury models was recently compared. Consistently, there was an increase in CD11b (OX42/complement receptor 3) immunoreactivity, a commonly used marker of transformation of microglia into an effector phenotype, in the spinal cord 3 days after injury. This was maximal after 7 days, and had begun to decrease by 14 days post-injury. This time course was in agreement with several other studies. Interestingly, increased microglial activation has also been observed in higher brain centres (hypothalamus and periaqueductal gray) after peripheral nerve injury. Because of the challenge of imaging microglia in patients, there is less data on how microglia react in human neuropathic pain states. A positron emission tomography (PET) scan study of patients using a radiolabelled ligand for the peripheral benzodiazepine receptor suggests that microgliosis occurs in the thalamus of amputees with long-standing phantom limb pain. One post-mortem study of a patient with complex regional pain syndrome (CRPS) showed reactive microglia in the spinal cord.

Block of the microglial response with minocycline (second-generation tetracycline) prevents the development of injury-induced behavioural hypersensitivity in rats, as does block of key mediators in the transformation of microglia into an effector phenotype. Therefore, it is clear that microglia are important in the initiation of neuropathic pain. It is less clear as to whether they are essential in maintaining neuropathic pain states. Minocycline is relatively ineffective in reversing established neuropathic pain. However, targeting some of the key microglial signals, such as by block or knockdown of P2X4, can reverse established pain.

Microgliosis has also been observed in other animal models of neuropathic pain, including streptozotocin-induced diabetic neuropathy and bone cancer pain. However, microgliosis is not a universal correlate of neuropathic pain, emphasizing the point that diverse pathophysiological mechanisms operate in the generation of neuropathic pain. The microglial response is generally strongest in surgical models of traumatic nerve injury but is much less, or virtually absent, in some models of chemotherapy-induced neuropathic pain. For example, there is little to no microgliosis observed in anti-retroviral 2,3-dideoxyctidine-induced neuropathy or in the d4T-induced HIV-associated sensory neuropathy (HIV-SN) model of neuropathic pain. In contrast, vincristine has been shown by some groups to induce a microglial response. Even within the realm of diabetic neuropathy, the extent of the microglial reaction depends on the exact model used. In streptozotocin-induced diabetic neuropathy, a small, but significant, increase in IBA1 immunoreactivity is observed. However, in the db/db mouse model of diabetes-induced neuropathy, astrocytic (but not microglial) activation is observed in the spinal cord. There are similar findings in the BioBreeder Worcester rat model of type I diabetes (D.L.H. Bennett and M. Calvo, unpublished observations).

Astrocytes are another type of glia within the CNS with a characteristic ‘star-like’ morphology. Under normal physiological conditions, astrocytes act to ‘mop up’ molecules that are toxic or are in excessively high concentration, maintaining extracellular homeostasis. Additionally, astrocytes are important modulators of synaptic function. Astrocytic activation in animal models of pain occurs several days after the insult and is much longer lasting. After peripheral nerve injury, astrocytes enlarge, and upregulate intermediate filament protein GFAP, vimentin, and the calcium-binding peptide S100. Mice deficient in GFAP do develop pain-like behaviours normally after peripheral nerve injury, although this is shorter-lasting than that observed in wild-type mice. Additionally, the administration of GFAP antisense treatment in rats 6 weeks after peripheral nerve injury reverses established behavioural hypersensitivity. Both these findings point towards a role in maintenance of neuropathic pain for astrocytes.

**How do microglia and astrocytes enhance excitability within the dorsal horn of the spinal cord?**

In neuropathic pain states, the final common pathological outcome is enhanced excitatory transmission within the dorsal horn leading to pain. We now recognize that this enhanced excitability occurs via a complex four-way communication between primary afferent terminals, dorsal horn neurons, astrocytes, and microglia (and may also involve additional cell types such as B-lymphocytes). Microglia and astrocytes contribute to the release of multiple inflammatory mediators, neuromodulators, and growth factors. This is not simply a passive process triggered by degeneration of axon terminals; it is an active process initiated by injury signals released from damaged neurons. For example, the cytokine TNF-α enhances the amplitude of glutamate-induced excitatory currents, while IL-1β not only enhances excitatory synaptic transmission, but also reduces inhibitory transmission. Released Cathepsin S cleaves neuronal fractalkine with the resultant soluble fractalkine stimulating, and further activating, microglia in a positive feedback loop. Brain-derived neurotrophic factor (BDNF) released from microglia alters the expression of a key transporter, KCC2, which regulates the anion gradient across neuronal membranes. As a result, there is an anion gradient shift such that the hyperpolarizing effects of GABA are reduced, resulting in disinhibition (see...
Recently, morphine treatment has been shown to increase expression of the ligand-gated ion channel P2X4 in microglia, release of BDNF and development of hyperalgesia. Therefore, not only are microglia important in gating the development of neuropathic pain, they also contribute to some of the unwanted side-effects of opioid treatment. Finally, transmission at the level of the dorsal horn is under strong descending control from the brainstem [the rostral ventromedial medulla (RVM) is an important locus for this modulation]. This may have facilitatory and inhibitory components. It has been demonstrated that there is a microglial and astrocytic reaction within the RVM, which contributes to descending facilitation and enhanced pain related hypersensitivity after nerve injury.

As previously mentioned, an inflammatory response should also consist of a resolution phase. It is now accepted that this is an active phase of the inflammatory response, mediated by pro-resolution molecules. Lipoxins (derived from arachidonic acid), and resolvins and protectin (derived from ω-3 essential polyunsaturated fatty acids) have recently been identified as pro-resolution molecules. Anti-inflammatory actions of these molecules include the promotion of phagocytosis of dead cells by macrophages, cessation of production of chemoattractants and departure of inflammatory cells from the site of inflammation via the lymphatics. The role of pro-inflammatory molecules in pain has begun to generate interest. Intrathecal pretreatment with Resolvin E1 has been shown to attenuate the development of peripheral nerve injury-induced hyperalgesia by preventing the microglial inflammatory response. Additionally, intrathecal application of Lipoxin A4 prevented development of behavioural hypersensitivity after chronic compression of DRG and prevented the spinal upregulation of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. Thus, a pharmacological approach aimed at enhancing the pro-resolution phase of inflammation may prove beneficial in the treatment of neuropathic pain.

**Targeting excessive inflammation as a therapy for neuropathic pain**

There is now strong evidence from preclinical studies, and more restricted evidence using patient samples, that injury...
to the nervous system can lead to a maladaptive inflammatory response contributing to the generation of persistent pain. There remain a number of hurdles to translating this knowledge into patient benefit. There are challenges in the design of appropriate clinical trials (which have so far been relatively under-powered). Interventions in animal models are most efficacious at the time of injury, whereas delayed treatment is a more likely clinical scenario. Only a subset of patients develop neuropathic pain after a lesion and we do not yet have powerful predictive models. We increasingly realize there are multiple pathophysiological mechanisms leading to persistent pain after nerve injury. It would be of great benefit to use either clinical or molecular biomarkers to individualize treatment (e.g. targeting excessive inflammation only in those patients where there is evidence of an ongoing inflammatory response). Some agents which modulate inflammation are already in use in selected groups of neuropathic pain patients, although trial evidence is often lacking. Corticosteroids suppress pro-inflammatory cytokine expression and cell-mediated immunity. They are administered by several routes (including oral, perineural, epidural, or even intrathecal) for the treatment of several neuropathic pain conditions, such as post-herpetic neuralgia, CRPS, and radicular back pain. However, definitive evidence for their efficacy is absent because of the scarcity of placebo-controlled studies and, in some cases, trials have shown detrimental effects.

Another approach is to target individual cytokines. Although small case series in which anti-TNF-α drugs have been used have been encouraging, randomized controlled trials using systemic or subcutaneous anti-TNF-α therapy have shown no efficacy. One potential difficulty is the significant redundancy in the action of cytokines. Furthermore, as with corticosteroid suppression of the immune system, if these agents are given systemically they may be associated with a significantly increased risk of infection. One approach which could use a broad anti-inflammatory action would be the use of pro-resolution agents such as the resolvins.

Another novel prospect is the inhibition of microglial function. Clinical trials of minocycline are underway (NCT0131 4482) for the prevention of postoperative intercostal pain, an ideal condition in which to test this agent. Propentofylline reduces the production of free radicals and activation of microglia. A randomized controlled trial of this agent did not find efficacy in the treatment of post-herpetic neuralgia. One reason the authors gave for this was that there may be intrinsic differences between rodent microglia (in which the agent was validated) and human microglia—a cautionary note for the future. Further approaches would be to target key ligand-gated ion channels expressed in microglia (e.g. P2X4 and P2X7) or downstream signalling pathways that drive microglia towards an effector state (e.g. p38 MAP Kinase). In a small double-blind crossover trial, the p38 mitogen-activated protein kinase inhibitor SB-681323 significantly reduced the daily pain score in patients with neuropathic pain.

In summary, there are increasing opportunities to intervene and reduce excessive neuroinflammation; the challenge will be to develop means to identify patients who are at risk of developing persistent pain (as treatment is most likely to be effective when delivered early) and, in those patients with established pain, to identify the process of ongoing inflammation in order to appropriately individualize treatment.

Conclusions

We are now confident that neuropathic pain states can be associated with a profound inflammatory response which is not just a bystander phenomenon but, in some cases, drives the development and persistence of neuropathic pain. Multiple mechanisms by which inflammatory mediators such as cytokines/chemokines or lipids result in pain have now been described through increasing primary afferent excitability or facilitating synaptic transmission within the dorsal horn of the spinal cord. The degree of the inflammatory response varies greatly depending on the underlying aetiology of neuropathic pain: it is much more marked in traumatic neuropathy compared with chemotherapy-induced neuropathy. In appropriately selected patient cohorts, the inflammatory response provides a therapeutic opportunity. Despite a wealth of preclinical evidence that inflammation contributes to neuropathic pain, there is a lack of high quality clinical evidence, although a number of trials are ongoing. Challenges include the high degree of redundancy within inflammatory pathways and the risk of immunosuppression. One interesting concept may be to drive inflammation towards a pro-resolution phase.

Declaration of interest

A.E. has no conflict of interest to declare. D.L.H.B. is a member of the Innovative Medicines Initiative European collaboration, whose industry members are AstraZeneca, Pfizer, Esteve, UCB, Sanofi-Aventis, Grunenthal, Eli Lilly, Neuroscience Technologies, and Boehringer Ingelheim. D.L.H.B. has also received consultancy fees from Pfizer, Astellas, and Acorda. This article has not been influenced by and will have no impact on the business or financial interests of these companies.

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**Appendix**

**Expansion of abbreviations**

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ERK MAP kinase</td>
<td>Extracellular signal-related mitogen-activated protein kinase</td>
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<tr>
<td>NGF</td>
<td>Nerve growth factor</td>
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<tr>
<td>IL</td>
<td>Interleukin (eg IL-1β)</td>
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<tr>
<td>TNF-α</td>
<td>Tumor necrosis factor-alpha</td>
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<tr>
<td>CGRP</td>
<td>Calcitonin gene-related peptide</td>
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<tr>
<td>TRPV1</td>
<td>Transient receptor potential cation channel subfamily V member 1 (previously vanilloid receptor 1)</td>
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<tr>
<td>PKC</td>
<td>Protein kinase C</td>
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<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
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<tr>
<td>CREB</td>
<td>cAMP response element-binding protein</td>
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<tr>
<td>STAT</td>
<td>Signal transducer and activator of transcription</td>
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<tr>
<td>ATF-3</td>
<td>Activating transcription factor-3</td>
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<tr>
<td>DRG</td>
<td>Dorsal root ganglion</td>
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<tr>
<td>EAN</td>
<td>Experimental autoimmune neuritis</td>
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<tr>
<td>MCP-1</td>
<td>Monocyte chemoattractant protein, also known as CCL2 (Chemokine C-C motif ligand 2)</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<td>CD11b</td>
<td>Cluster of differentiation molecule 11b</td>
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<td>GFAP</td>
<td>Gial fibrillary acidic protein</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-derived neurotrophic factor</td>
</tr>
<tr>
<td>KCC2</td>
<td>Potassium chloride co-transporter 2</td>
</tr>
<tr>
<td>RVM</td>
<td>Rostral ventromedial medulla</td>
</tr>
</tbody>
</table>

*Handling editors: L. Colvin and D. J. Rowbotham*