OPINION

Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity

Dimitris N. Xanthos and Jürgen Sandkühler

Abstract | The CNS is endowed with an elaborated response repertoire termed 'neuroinflammation', which enables it to cope with pathogens, toxins, traumata and degeneration. On the basis of recent publications, we deduce that orchestrated actions of immune cells, vascular cells and neurons that constitute neuroinflammation are not only provoked by pathological conditions but can also be induced by increased neuronal activity. We suggest that the technical term 'neurogenic neuroinflammation' should be used for inflammatory reactions in the CNS in response to neuronal activity. We believe that neurogenic neuroinflammation maintains homeostasis to enable the CNS to cope with enhanced metabolic demands and increases the computational power and plasticity of CNS neuronal networks. However, neurogenic neuroinflammation may also become maladaptive and aggravate the outcomes of pain, stress and epilepsy.

The integrity of all body tissues is endangered by microbial pathogens, toxins, traumata and degeneration. In response to such situations, innate and adaptive immune cells, vascular cells and neurons take concerted and finely tuned defence actions to maintain or restore tissue integrity. Initially, innate immune cells, such as macrophages, mast cells and dendritic cells, are activated and respond in a nonspecific manner to exogenous or endogenous danger signals. This leads to tissue reactions that range from mild homeostatic responses (sometimes known as 'para-inflammation') that are close to the basal, non-stressed state to a transition into full-scale inflammation[1]. In the full inflammatory response, the vasculature reacts with vasodilation and extravasation of plasma components and blood cells, establishing three of the four classical signs of inflammation: rubor (redness), calor (warmth) and tumour (swelling). The fourth sign is dolor (pain). The most violent of these reactions are usually seen during an infection or in an inflammatory disease and involve presentation of exogenous or endogenous antigens and activation of the complement system. In peripheral tissues, dendritic cells provide information to cells of the adaptive immune system, leading to vigorous inflammatory responses, such as phagocytosis (and eventually necrosis), the formation of new connective tissue and granulomas. Diverse communication channels link the immune system to the CNS and enable it to support host defence by promoting fever, increased sleep and enhanced pain sensitivity (hyperalgesia)[2]. The spectrum of actions and responses that occur strongly depends upon the type, intensity and duration of the initial trigger signal, the tissue affected and the phase of the reaction. Collectively, this multitude of tissue reactions is termed 'inflammation'.

Inflammatory reactions within the CNS differ substantially from those of other tissues in several ways. First, the CNS parenchyma lacks resident dendritic cells; perivascular macrophages[3] and vascular pericytes[4] take over the functions of mature dendritic cells in the CNS. Second, astrocytes, microglia and — in some regions of the CNS — mast cells are the innate, parenchymal immune cells of the CNS[5–8]. Their activation is actively depressed under non-pathological conditions. Finally, the permeability of microvessels in the CNS for extravasation of large molecules and blood cells is reduced in comparison to the rest of the body by the 'blood–CNS barrier'. Hence, it is much more difficult to activate complement cascades and to recruit cells involved in the adaptive immunity response, such as leucocytes, into the CNS parenchyma. With the notable exception of activated T cells, which readily penetrate the intact blood–CNS barrier, CNS innate immune cells thus do not as efficiently recruit the machinery of the adaptive immune response as do dendritic cells in peripheral tissues[9]. Therefore, resident innate immune cells of the CNS must often deal directly with pathogens and tissue damage, and it is only under severe conditions that inflammatory cells such as infiltrating T cells are involved (see REF. 10 for a review).

The mild inflammatory tissue reactions in the CNS protect neurons — with their low regenerative capacity — from the destructive inflammatory responses that are readily induced in regenerating peripheral tissues. This has led to the introduction of the term 'neuroinflammation' to distinguish inflammatory reactions in the CNS from inflammation in other tissues. From the present literature, it is not always clear which criteria must be met to qualify for the label neuroinflammation. Numerous studies have assessed individual responses such as the production and the release of pro-inflammatory cytokines or disturbances of the blood–brain barrier. For example, it is well established that epileptic seizures lead to the release of cytokines in the affected brain tissue[11,12]. In our opinion, whether the release of a pro-inflammatory cytokine alone is indicative of an inflammatory reaction is debatable. The term 'immune signalling' seems to be more appropriate to describe the isolated release of immune-relevant molecules without any concomitant expression of other signs of neuroinflammation. However, when the respective literature is

reviewed as a whole, it may become clear that under a given experimental condition, the full spectrum of the inflammatory response involving immune cells, vascular cells and neurons takes place; as occurs, for example, in the course of epilepsy[13].

It is often believed that neuroinflammation is induced only by a pathological state, usually in the form of a microbial infection, exposure to toxins or degeneration (FIG. 1) (see REFS 8,10,14 for reviews). However, we feel that neuroinflammation and its mechanisms do not have to be by definition pathological and may encompass immune signalling as long as immune cells, vascular cells and neurons act in concert. This concerted action does not necessarily have to be synergistic at all times: pro- and anti-inflammatory processes may occur simultaneously. FIGURE 1 illustrates the concept of parallel and interacting homeostatic and pathological processes and outcomes.

Many studies demonstrate that, in addition to the classical instigators of inflammation described above, enhanced levels of neuronal activity can trigger inflammatory reactions in peripheral tissues, where it has long been known as 'neurogenic inflammation' (REFS 15–17) (BOX 1; FIG. 2). Here, we discuss emerging evidence suggesting that neuronal activity may also be sufficient to trigger the concerted actions of immune cells, vascular cells and neurons within the CNS in a manner that resembles other forms of neuroinflammation[18–21] (FIG. 3). We thus propose the technical term 'neurogenic neuroinflammation' to describe those inflammatory reactions within the CNS that are triggered by neuronal activity. We suggest that neurogenic neuroinflammation may have beneficial effects such as enabling the nervous system to cope with enhanced metabolic demands, increasing its computational power and promoting regeneration. Neurogenic neuroinflammation may become maladaptive when it persists for longer than necessary or when it spreads to remote sites (FIG. 1), and it may be relevant to conditions as diverse as pain, psychological stress and epileptic seizures.

Neurogenic neuroinflammation

Classical neurogenic inflammation in peripheral tissues is triggered by action-potential-dependent release of substances from the peripheral terminals of peptidergic, sensory nerve fibres and involves vasodilation, plasma extravasation, recruitment of white blood cells and mast cell degranulation (BOX 1; FIG. 2). A number of studies have now shown that similar substances are released from synapses in the CNS in response to neuronal activity; however, few studies have considered this response profile as a whole.

We focus here on spinal changes in response to stimulation of peptidergic, nociceptive nerve fibres. These stimuli are of particular interest as they lead to long-term changes in the processing of sensory information in the spinal dorsal horn and are identical to those that trigger neurogenic inflammation in the peripheral tissues (FIG. 2). Effective stimuli in rodent hindpaws include direct electrical nerve stimulation at intensities sufficient to activate C fibres, selective activation of peptidergic primary afferents that express the transient receptor potential V1 (TRPV1) receptor by capsaicin and chemically induced inflammation. As in the periphery (FIG. 2), activation of peptidergic primary afferent C fibres also leads to the spinal release of various mediators, including glutamate, substance P, calcitonin gene-related peptide (CGRP), brain-derived neurotrophic factor (BDNF), fractalkine and ATP (FIG. 3). Receptors for these neurotransmitters and neuropeptides are present in nearby cells of the immune system, vascular cells and higher-order neurons.

Immune responses to neuronal activity. Glial cells can be directly activated by substances that are released from primary afferent nerve fibres upon stimulation. This includes substance P acting on the neurokinin 1 receptor (NK1; also known as substance P receptor), ATP acting on P2X purinoceptor 7 (P2X7) and glutamate acting on metabotropic glutamate receptors (mGluRs) (also see below). Consequently,

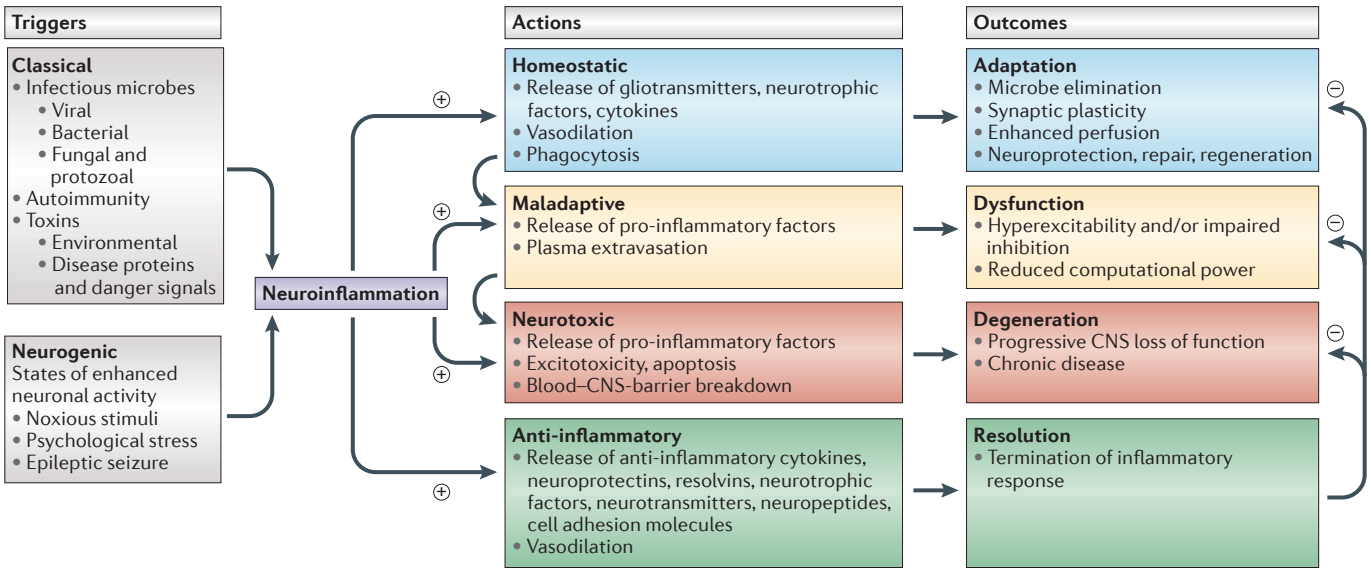

Figure 1 | **Triggers, actions and outcomes of neuroinflammation.** Neuroinflammation can be triggered by 'classical' factors (infection, autoimmunity or toxins) but also by factors that lead to enhanced neuronal activity (including noxious stimuli, psychological stress and epileptic seizures). Immune cells, vascular cells and neurons promote various independent as well as interacting responses (indicated by plus signs). These can be homeostatic, leading to adaptation, or dysfunctional and/or neurotoxic, leading to pathology. Anti-inflammatory mechanisms may be triggered in parallel and serve to terminate neuroinflammation and reduce pathological outcomes (indicated by minus signs). Treatments and interventions may be targeted at various levels to inhibit the triggers and neuroinflammatory processes, or to promote the resolution of inflammation.

Box 1 | **Neurogenic inflammation**

Neurogenic inflammation is a local inflammatory state in peripheral tissues induced by neuronal activity. Upon stimulation, sensory nerve fibres transmit action potentials not only orthodromically to the CNS but also antidromically into inactive branches of the afferent fibre (FIG. 2). Experimentally, various noxious stimuli, such as direct electrical nerve stimulation or activation of transient receptor potential V1 (TRPV1) channels by capsaicin, lead to the excitation of C fibres (unmyelinated, nociceptive nerve fibres) and induce neurogenic inflammation. At the peripheral endings of peptidergic C fibres, neuropeptides such as substance P, calcitonin gene-related peptide (CGRP) and neuropeptide Y are released and trigger inflammatory tissue reactions (FIG. 2). Mast cells are particularly implicated, as they rapidly degranulate and release a large number of substances such as cytokines, prostaglandins, serotonin and histamine. Pro-inflammatory mediators, as well as released glutamate, will sensitize nociceptive nerve endings, leading to pain. Further tissue reactions include vasodilation, plasma extravasation and recruitment of leucocytes to the tissue[15–17,171]. The entire process may be self-amplifying, leading to continuous neuropeptide release. Participation of the CNS is not required for peripheral neurogenic inflammation, although it can clearly amplify it. Neurogenic inflammation has initially been described in the skin but has now also been identified in a wide range of tissues and organs, including peripheral nerves, soft tissue, joints, airway, eye, gums, meninges, pancreas and viscera (see REF. 16 for a comprehensive overview). In the skin, neurogenic inflammation leads to the classical inflammatory signs of rubor (redness), tumour (swelling), calor (warmth) and dolor (pain). Neurogenic inflammation thus resembles other forms of inflammation in many aspects. Neurogenic inflammation may have beneficial effects[168,172] or may amplify disease states such as psoriasis, arthritis, asthma, ocular trauma, periodontitis, migraine, pancreatitis, inflammatory bowel disease, colitis, neuropathic pain, sepsis and cardiovascular disease[16].

markers of activation are upregulated in spinal microglia and astrocytes within minutes of enhanced neuronal activity. For example, phosphorylated p38 mitogen-activated protein kinase is increased in microglia after stimulation of sensory nerve fibres with formalin in conscious rats[22]. Microglial SRC-family kinases[23] are upregulated after electrical stimulation of C fibres, and connexin dephosphorylation occurs in astrocyte gap junctions after capsaicin or C-fibre stimulation in anaesthetized rats[24]. High-frequency discharges in primary afferent C fibres induce a rise in intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) in spinal astrocytes within seconds, and enhanced expression of immunohistochemical markers of microglia activation in spinal-cord slices within minutes[18]. Electrical nerve stimulation induces morphological changes in microglia and in astrocytes in rat spinal-cord and trigeminal nuclei[19,25]. Hence, glial activation constitutes mainly an innate immune response with a phagocytic macrophage phenotype[26] and probably also involves activation of pattern- and danger-recognition receptors (such as Toll-like receptor 4)[27,28], which are thought to trigger innate immune responses in the CNS[29].

It is becoming increasingly clear that activation of microglia is not an 'all-or-none' process and does not take a linear path with fixed uniform outcomes[6]. Instead, it seems that glial cells are permanently active but remain in a surveillance mode and are even highly motile[30] in the absence of neuronal activity. Glial cells switch to distinct and finely tuned executive phases in response to neuronal activity[6,7]. Thus, in addition to the well-described activation of spinal glial cells in the course of peripheral neuropathies or spinal-cord injuries (see REFS 31,32 for reviews), neuronal activity is also sufficient to activate glial cells in the spinal cord (FIG. 3). However, other peripheral triggers of glial-cell activation in the CNS must not be ignored. For example, cytokines such as tumour necrosis factor-α (TNFα) may be transported in an anterograde direction in sensory nerve fibres from the peripheral tissues to the spinal cord[33], where they could activate glia. Whether glial-cell activation and the release of cytokines alone meet the criteria for being classified as neuroinflammation is debatable. However, as outlined below, neuronal activity also recruits additional components of an inflammatory reaction, and we believe that together these constitute neurogenic neuroinflammation.

Under resting conditions, T cells are present in the CNS parenchyma in relatively low numbers. $CD4^+$ T cells and, to a greater extent, $CD8^+$ T cells are found in the intact spinal-cord parenchyma[34]. Like glial cells, these T cells express a large number of neurotransmitter receptors and can be activated in an antigen-independent fashion by glutamate, substance P, CGRP, somatostatin, BDNF and neuropeptide Y (all of which are released directly from primary afferents in response to neuronal activity)[35,36]. In addition, T cells are activated by serotonin[35] and dopamine[37], substances that are also released in spinal dorsal horn upon afferent stimulation[38,39] (FIG. 3). Furthermore, naive, antigen-inexperienced T cells can be recruited to the CNS by chemoattractant signals produced by activated neurons or glia and by stressed endothelial cells[40].

Mast cells are usually activated by immunoglobulin E (IgE) binding to its receptor FcεRI. However, substances that are released in the spinal cord upon primary afferent stimulation — including substance P, CGRP, nerve growth factor and vasoactive intestinal polypeptide[41] — can also trigger mast-cell degranulation (the release of molecules from secretory vesicles known as granules) (FIG. 3). Activation of TRPV1-expressing primary afferent C fibres by capsaicin, which leads to the spinal release of substance P, enhances the number of degranulated spinal dural mast cells[42].

Neurons thus seem to be powerful triggers of innate and adaptive immune-cell activation in the CNS. However, it is worth noting that neuronal activity may also trigger anti-inflammatory reactions in the CNS, as outlined below.

Vascular responses to neuronal activity. Noxious mechanical stimulation, formalin and capsaicin injections into a rat hindpaw and direct electrical nerve stimulation all increase spinal blood flow[20,43,44]. The coupling between neuronal activity and vascular responses is mediated by the neurovascular unit, which is comprised primarily of neurons, astrocytes and endothelial cells (FIG. 3). Vascular cells constitutively express cytokine receptors such as interleukin-1 (IL-1) receptors[45], purinergic receptors[46], NK1 and CGRP receptors, and soluble guanylyl cyclase (which forms part of the signalling pathway activated by nitric oxide). Many vasoactive substances are released from primary afferents, activated glial cells and vascular cells in the CNS in response to primary afferent activity. For example, spillover beyond the synaptic cleft of substance P and other neurokinins that cause enhanced capillary permeability[47] and of CGRP, an extremely potent vasodilator[48], is known to occur in the spinal cord in response to afferent nerve stimulation[49,50]. ATP is another potent vasodilator[51] in the CNS that is released in an activity-dependent manner in the spinal cord[52,53]. Other potentially vasoactive substances, including prostaglandins from spinal endothelial cells[54] and potassium ions[55], are also released in response to neuronal activity[56] (FIG. 3).

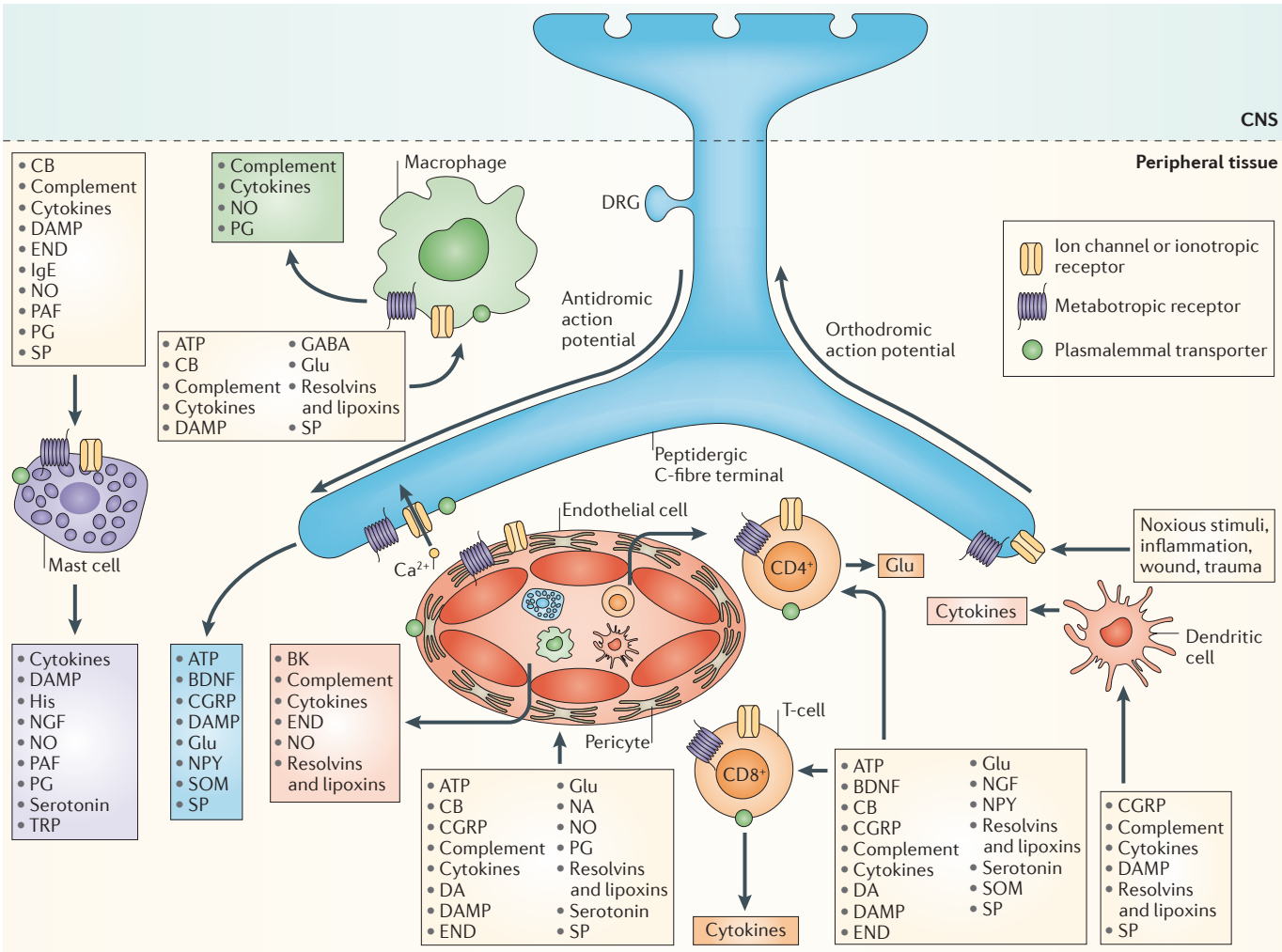

Figure 2 | **Neuronal activity triggers neurogenic inflammation in peripheral tissues.** The figure shows a primary afferent, peptidergic nerve fibre and elements that contribute to neurogenic inflammation at peripheral nerve terminals. Neurogenic inflammation in the periphery is initiated by neuronal activity generated by a wide range of highly specific (such as transient receptor potential V1 (TRPV1) activation) and less-specific stimuli (such as traumatic injury). This results in the generation of orthodromic action potentials that conduct towards the CNS, as well as antidromic action potentials at branch points that conduct towards the peripheral terminals to induce neurogenic inflammation. Neurogenic inflammation results from the release of neurotransmitters and neuropeptides from peripheral nerve terminals (blue box). These rapidly affect various cell types, including vascular cells (endothelial cells), mast cells, macrophages and other immune cells (not shown). T cells and dendritic cells may also be recruited. The different cell types themselves also begin to release substances (shown in coloured boxes), creating the 'inflammatory milieu'. Immune cells, plasma and various mediators can also extravasate into tissue (not shown). Sensory nerve fibres can become sensitized and also lower their threshold for further neurotransmitter and neuropeptide release. Pro- and anti-inflammatory substances and signalling molecules that are released (shown in light yellow boxes) from various sources bind to receptors on the different cells and modulate their function. Signalling from higher-order CNS centres (not shown) may also dampen or aggravate peripheral neurogenic inflammation. BDNF, brain-derived neurotrophic factor; BK, bradykinin; CB, cannabinoid; CD, T-cell surface glycoprotein CD; CGRP, calcitonin gene-related peptide; DA, dopamine; DAMP, danger-associated molecular patterns; DRG, dorsal root ganglia; END, endothelin; Glu, glutamate; His, histamine; IgE, immunoglobulin E; NA, noradrenaline; NGF, nerve growth factor; NO, nitric oxide; NPY, neuropeptide Y; PAF, platelet activating factor; PG, prostaglandin; SOM, somatostatin; SP, substance P; TRP, tryptase.

Although neuronal activity readily enhances regional blood flow in the CNS, the integrity of the blood–CNS barrier is substantially more resistant to change. Formidable neuronal activity is required for such changes to occur. For example, the tight junction protein occludin is altered in spinal endothelial cells and mild IgG extravasation is detected no earlier than 72 hours after hindpaw inflammation with carrageenan[57]. However, a more robust afferent barrage in C fibres, which is triggered by direct sciatic nerve capsaicin application, induces widespread disruption of the blood–spinal-cord barrier 24 hours after stimulation[21].

Vascular cells in the CNS not only respond to pro-inflammatory substances but can also release cytokines and chemokines[58,59], possibly contributing to the inflammatory process.

Contribution of higher-order neurons. Neuronal activity is by definition the primary trigger for neurogenic neuroinflammation. Peptidergic C fibres are, however, not the only logical source for the induction of neurogenic neuroinflammation in the spinal cord. In fact, microglia[60,61] and CNS endothelial cells[61,62] express receptors for a wide range of neurotransmitters, some of which are released from higher-order

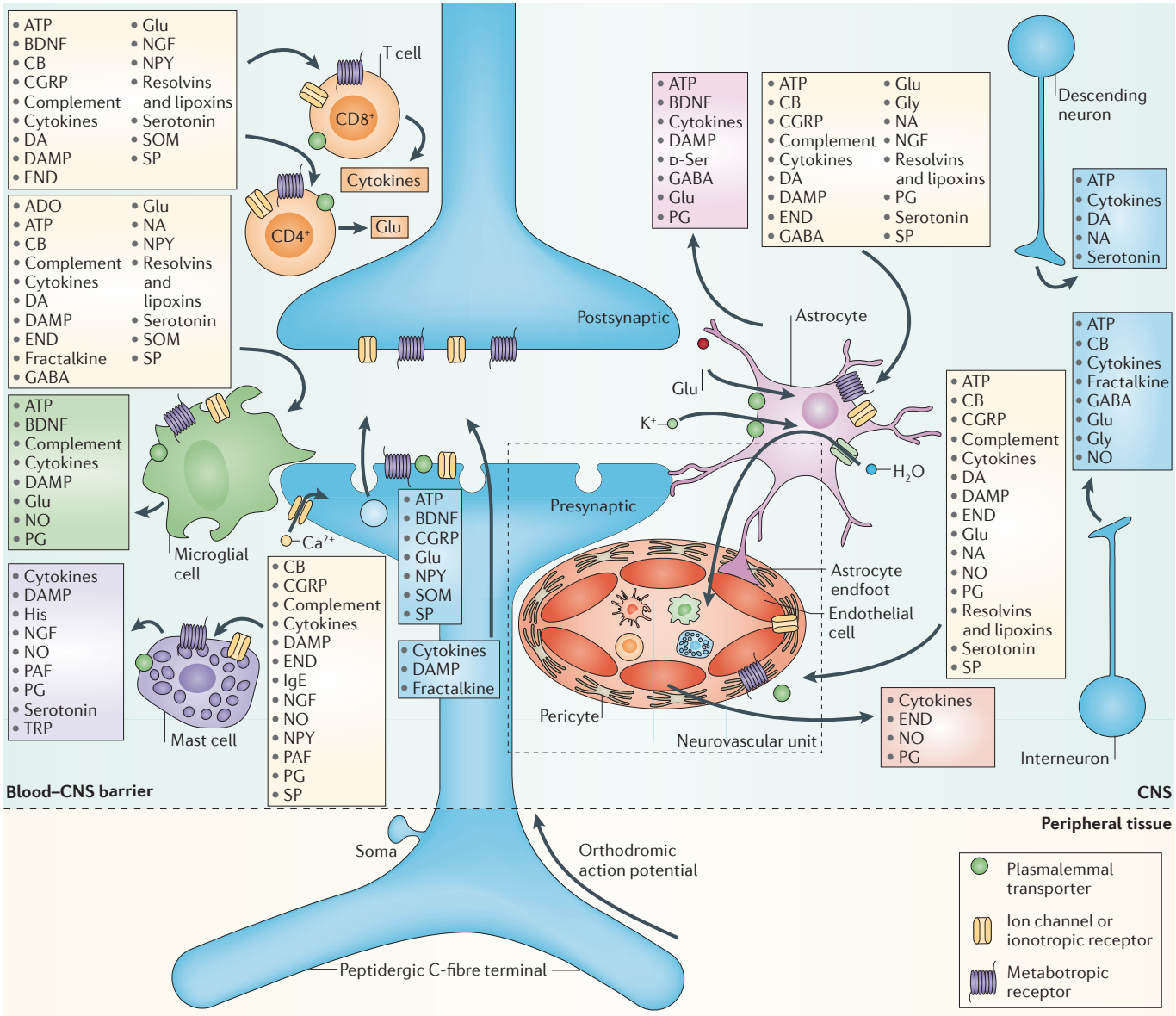

Figure 3 | **Neuronal activity triggers neurogenic neuroinflammation in the CNS.** This figure illustrates neurogenic neuroinflammation at spinal or trigeminal terminals. In the CNS, enhanced neuronal activity coming from peripheral sources will result in neurogenic neuroinflammation owing to vesicular and non-vesicular release of neurotransmitters and neuropeptides from the primary afferent fibre (blue boxes). This will induce concerted and interacting immune responses, vascular responses and higher-order neuronal network responses in the multipartite synapse. This includes, but is not limited to, microglia, astrocytes, the neurovascular unit (composed of endothelial cells, other vascular cells such as pericytes, the presynaptic neuron and the astrocyte endfeet) and second-order neurons within the neuronal network (including interneurons, ascending neurons and descending neurons), all of which are primary players in the response to enhanced C-fibre activity. Mast cells on the dura, perivascular macrophages, and $CD4^+$ and $CD8^+$ T cells may also participate and release substances. With strong neuronal activity, recruitment of peripheral immune cells (including macrophages, T cells and mast cells), and changes at the blood–CNS barrier (for specific substances or involving a regional breakdown) can occur, creating further CNS neuroinflammatory responses. Astrocytes found exclusively in the CNS serve to take up excessive glutamate (Glu) and potassium, thereby providing neuroprotective effects against excitotoxicity. However, they may also participate in neurogenic neuroinflammation to release pro-inflammatory mediators. As in the periphery, both pro- and anti-inflammatory mediators, and signalling molecules and forces can be released from all cell types (key substances shown in boxes of the respective colour of cell type) in the multipartite synaptic region to further affect receptors or channels present on all cell types shown (key substances acting on cells shown in light yellow boxes). Ongoing neurogenic neuroinflammation may serve to amplify neuronal network activity and the resulting long-term potentiation may spread far along the neuraxis, enhancing computational power of the neuronal network. This can serve to elicit appropriate protective responses and behaviours from the organism. In some cases, it may also trigger or aggravate an established pathology. Signalling from higher-order CNS centres (descending neurons) can serve to dampen or aggravate neurogenic neuroinflammation. ADO, adenosine; BDNF, brain-derived neurotrophic factor; CB, cannabinoid; CGRP, calcitonin gene-related peptide; DA, dopamine; DAMP, danger-associated molecular patterns; D-Ser, D-serine; END, endothelin; Gly, glycine; His, histamine; IgE, immunoglobulin E; NA, noradrenaline; NGF, nerve growth factor; NO, nitric oxide; NPY, neuropeptide Y; PAF, platelet activating factor; PG, prostaglandin; SOM, somatostatin; SP, substance P; TRP, tryptase.

neurons but not from primary afferents. Examples are the inhibitory neurotransmitters glycine and GABA, both of which are released from spinal interneurons, and the monoamines noradrenaline, serotonin and dopamine, which are released from descending-tract neurons. These neurotransmitters may modulate the functions of both glial and vascular cells. Monoamines are vasoactive in the CNS[63,64] but they also affect the functions of immune cells (see REF. 65 for a review). In addition, activation of type A GABA receptors leads to the production of oxygen radicals in rodent microglia[66]. Noradrenaline causes retraction of microglial processes through activation of the β2-adrenergic receptor under resting conditions and through activation of the adrenergic α2A receptor under pro-inflammatory conditions in tissue culture and brain slices[67]. Serotonin promotes microglial motility but reduces phagocytic activity[68].

In summary, the available evidence suggests that neuronal activity in primary afferent nerve fibres or higher-order neurons is sufficient to activate innate and adaptive immune cells, vascular cells and neurons in the spinal cord. It thus resembles other triggers of neuroinflammation in the CNS[8,10], and we therefore suggest that the term neurogenic neuroinflammation should be used to describe this phenomenon.

The multipartite synapse

All the elements of neurogenic neuroinflammation described above interact in a complex manner, the details of which have only become better understood in recent years. For example, neurons and microglia interact bidirectionally, and the dialogue between these cells involves fractalkine (also known as CX3CL1), a transmembrane chemokine that is expressed by neurons and acts through a receptor (CX3CR1) that is exclusively present on microglia[69,70]. Fractalkine is biologically active both as a membrane-bound adhesion molecule and in its soluble form. For the soluble form of fractalkine to bind CX3CR1, its extracellular domain must be cleaved by cathepsin S, which is released from activated microglia. Activity in primary afferent nerve fibres can activate spinal microglia, as described above, which in turn releases cathepsin S. This liberates soluble fractalkine from neurons, which boosts microglia activation and is proposed to cause hyperalgesia (see REFS 71,72 for reviews).

In addition, astrocytes, T cells, and the extracellular matrix have profound effects on synaptic transmission. This has led to the concepts of tri-, tetra- and pentapartite synapses[73–75]. The list of relevant synaptic partners is likely to increase as we broaden our knowledge of the mechanisms of neurogenic neuroinflammation. Eventually, this growth in knowledge will culminate in the concept of a 'multipartite synapse'. The actual number of critical cellular and extracellular elements modulating the transmission at multipartite synapses will depend upon the context and is likely to differ between CNS regions.

Overlapping signalling pathways. The various intracellular signalling pathways that contribute to neurogenic neuroinflammation exist in more than one type of cell in the multipartite synapse. Pharmacologically modulating these signalling pathways systemically or regionally (but not cell specifically) may therefore result in complex synergistic and/or antagonist interactions. For example, the binding of substance P to NK1 receptors in spinal neurons after stimulation of C fibres activates the phospholipase C and inositol triphosphate ($InsP_3$) signalling pathway, leading to increased $[Ca^{2+}]_i$ and synaptic long-term potentiation (LTP)[76]. Activation of NK1 receptors on astrocytes can also lead to increases in $[Ca^{2+}]_i$ levels[77] and NK1 receptor antagonists can reverse spinal astrocyte activation[78]. Activation of microglial NK1 receptors leads to the activation of the pro-inflammatory nuclear factor-κB pathway[79]. NK1 receptor activation in endothelial cells, as in neurons, also leads to phospholipase C activation, $InsP_3$ accumulation, and $[Ca^{2+}]_i$ rises[80]. Thus, substance P exerts synergistic pro-inflammatory actions on various cell types of the multipartite synapse through NK1 receptors.

Release of cytokines may likewise have synergistic effects. For example, after peripheral nerve stimulation[56], activation of TNFα and IL-1 receptors present on superficial dorsal horn neurons, glial cells[18] and endothelial cells[81], can induce prostaglandin release through cyclooxygenase 1 (COX1; also known as PTGS1) and COX2 (also known as PTGS2) activation in these cell types[81–83]. This can then drive further primary afferent glutamate, substance P and CGRP release[56].

By contrast, the actions of glutamate on cellular signalling are considerably more mixed. An example of this is provided by group I mGluRs, which are expressed on a wide variety of cell types[84], including neurons, astrocytes, microglia, T cells and endothelial cells. Activation of group I mGluRs (and particularly mGluR5) leads to a rise in $InsP_3$ levels and $[Ca^{2+}]_i$ in neurons, microglia and astrocytes, resulting in glial-cell activation[85] and LTP[86]. However, mGluR5 activation in spinal microglia inhibits the release of inflammatory mediators (cytokines or free radicals) both *in vitro*[87] and *in vivo*[88] and a specific group I mGluR agonist induces long-term depression at spinal Aδ-fibre synapses[89]. Evidence from experiments using *in vitro* oxidative stress and excitotoxicity protocols also suggests anti-inflammatory roles for mGluR1 activation[90], and specific stimulation of group I mGluRs in astrocytes leads to increased glutamate and potassium uptake[91]. In addition, vascular cells in the CNS express mGluRs[92] and it has been suggested that activation of group I mGluRs can increase vascular permeability[93], although these effects remain to be investigated further. Hence, the downstream effects of activity-dependent glutamate release are likely to result in both pro- and anti-inflammatory actions.

Therapeutic resolution

Most inflammatory conditions are of limited duration. Resolution of inflammation is an active process that involves the actions of anti-inflammatory mediators such as IL-10 (REF. 94), neuroprotectin D1 (REF. 95), resolvins[96], neurotrophic factors, and TNFα and fractalkine (under some conditions)[97], produced by immune, vascular and/or neuronal cells (FIG. 1). Anti-inflammatory actions have been described for dopamine acting on astrocytic dopamine D2 receptors[68] (see REF. 65 for a review), and for somatostatin[98], neuropeptide Y[99] and adenosine acting on adenosine A_{2A} receptors on microglia[100].

Other anti-inflammatory responses to neuronal activity involve major histocompatibility complex (MHC) molecules. Upon exposure to interferon-γ, neurons can express MHC molecules at their surface to interact with $CD8^+$ cytotoxic T cells[101]. Neuronal activity dampens the neuronal[101] and glial[102] expression of MHC molecules in part by increasing the release of nerve-growth factor and BDNF[102]. Consequently, silencing neuronal activity by blocking some voltage-gated sodium channels with tetrodotoxin (TTX) induces upregulation of MHC molecules in microglia *in vivo*[103,104] and activates glial cells[30]. This finding cannot be explained by the expression of TTX-sensitive sodium channels on glial cells, as blockade of glial TTX-sensitive sodium channels reduces rather than increases cytokine release from glia[105]. The loss of physiologic neuronal and synaptic activity may also underlie activation of microglia after deafferentation[106]. This is

consistent with one of the known important roles of activated microglia, which is to maintain functional neuronal circuits by eliminating inactive synapses[107,108].

Neuronal activity may also exert inhibitory influences on parenchymal microglia through contact-dependent inhibition involving adhesion molecule–receptor pairs (such as CD200–CD200 receptor, CD22–CD45 or HSP60–TREM2 (coupled to DAP12)), soluble adhesion molecules (such as intercellular adhesion molecule 5 or extracellular fractalkine), neuron-derived IgG[109] or anti-inflammatory cytokines[110,111].

Some cytokines exert both pro- and anti-inflammatory actions, depending upon the context and the CNS region. For example, soluble fractalkine has pro-inflammatory and pronociceptive actions in the spinal dorsal horn (see REFS 71,72 for reviews). Conversely, both soluble and membrane-bound forms of fractalkine attenuate lipopolysaccharide-induced activation of microglia in primary cortical glial–neuronal co-cultures[112] and reduce microglial neurotoxicity *in vivo* in a murine Parkinson's disease model[70]. Furthermore, fractalkine-stimulated microglia exert neuroprotective effects *in vitro* through adenosine production[113] (see REF. 5 for a review). Similarly the cytokine TNFα (usually assumed to be pro-inflammatory) may have a physiological and neuroprotective role when present at the low tissue concentrations that are sufficient for the activation of TNF receptor 2. Only at higher concentrations, which are required for TNF receptor 1 activation, does TNFα become a neurotoxic signal (see REF. 114 for a review).

Thus, the available evidence suggests that moderate levels of neuronal activity exert anti-inflammatory reactions. It may therefore be speculated that the therapeutic use of electrical nerve stimulation such as transcutaneous electrical nerve stimulation, electroacupuncture[115,116] or transcranial direct-current stimulation[117] may exert beneficial effects in part by modulating neuroinflammation and promoting neuroprotective and regenerative mechanisms in the CNS.

The emerging roles of neuroinflammation in CNS functions (and dysfunctions) likewise call for a fresh look at old drugs. It is likely that some drugs may exploit their full therapeutic potential by modulating neuroinflammation rather than by their traditionally ascribed modes of action only. Examples include COX inhibitors (which have antinociceptive effects in both the periphery and the spinal cord[118]), antipsychotics[119], antidepressants that reduce neuroinflammation[120], and antiepileptic drugs that depress nuclear factor-κB pathways[121]. Similarly, cannabinoids act on cannabinoid 1 and 2 receptors on neuronal, immune and endothelial cells of the CNS, the effects of which may collaborate to reduce neuroinflammation[122,123]. Conversely, opioids activate innate immune cells in the CNS, which contributes to opioid tolerance[124], opioid withdrawal LTP[125] and paradoxical opioid-induced hyperalgesia[126].

Interestingly, anti-inflammatory dietary elements such as omega-3 polyunsaturated fatty acids, neuroprotectin 1 or resolvins can reduce neuroinflammation in the brain[127] and spinal cord[128], block LTP at spinal C-fibre synapses[95] and reduce pain-related behaviour[128] (see REF. 96 for review).

Friend or foe?

Evidence suggests that neurogenic neuroinflammation has roles in tissue metabolism, synaptic plasticity, modulation of neuronal excitability, glutamate excitotoxicity, and degeneration and regeneration. Neurogenic neuroinflammation may be beneficial and/or detrimental: the prevailing effect depends on the context and the phase of the responses (FIG. 1). It is therefore possible that broad anti-inflammatory interventions may not only reduce the unwanted effects of neuroinflammation but may also impede its beneficial components.

Effects in stressed tissue. Enhanced neuronal activity, such as that occurring during encoding of a noxious stimulus or during psychological stress, increases the metabolic demands of the neuronal tissue. Neurogenic neuroinflammation, which increases regional blood flow in the CNS can therefore provide the appropriate oxygen supply and transport capacity for metabolites. Beyond this, neurogenic neuroinflammation has a number of additional effects.

Enhanced activity at glutamatergic synapses may result in excessive extracellular glutamate concentrations that can become highly toxic to neurons[129]. Astrocytes express glutamate transporters that remove glutamate from the extracellular space and that are upregulated by neuronal activation[130] and group I mGluR signalling[91]. Hence, activated astrocytes can potentially avoid or reduce glutamate excitotoxicity.

Neuroplasticity allows the nervous system to adapt to changing conditions. Usually, this involves direct interactions between neurons. A prominent example of such an interaction is the induction of LTP at glutamatergic synapses[131], including C-fibre synapses in the spinal dorsal horn *in vitro*[132] and *in vivo*[133] (see REF. 134 for a review). Recent studies have revealed that mediators of neurogenic neuroinflammation such as BDNF, ATP, TNFα and IL-1β are also all essential for LTP induction in spinal-cord dorsal horn (see REFS 134,135 for reviews).

Neurogenic neuroinflammation also affects synaptic inhibition in the spinal cord, which has five essential effects on nociception: it prevents hyperalgesia, radiating pain, allodynia and spontaneous pain, and reduces the risk of pain chronicity[134]. However, the release of BDNF from central terminals of afferent nerve fibres[136], or from spinal glial cells (in peripheral neuropathy)[137] results in impaired inhibition of nociception[137,138] (see REF. 139 for a review). Both LTP and reduced inhibition can be adaptive if the resulting hyperalgesia enables better protection of injured tissues. However, they can also become maladaptive when they persist after healing of the tissue or spread to somatotopically inappropriate (uninjured) sites.

Transitions to pathology. As with other forms of inflammation, neurogenic neuroinflammation can become pathological (FIG. 1). During normal neuronal activity, such as that occurring in response to a touch or brief pinch, glial cells and the vasculature perform housekeeping functions. With enhanced levels of activity (such as that following a minor injury), glial and vascular cells become activated in order to cope with enhanced metabolic demands. Synaptic spillover of neurotransmitters and accumulation of toxic metabolites or nitrogen and free oxygen radicals[140,141] can occur. Vasodilation will be engaged without any detectable extravasation. LTP will be induced at C-fibre synapses, resulting in hyperalgesia that initially fulfils the homeostatic functions described above. With more persistent activity in peptidergic C fibres (in the case of a chronic inflammation or wound and in some forms of peripheral neuropathy), a transition to maladaptive forms of neuroinflammation starts with changes in the blood–CNS barrier, leading to the presence of novel pro- and/or anti-inflammatory mediators or cells. Neuroinflammation may reach neighbouring areas beyond the termination zones of activated primary afferents. Finally, a 'breakdown' of the blood–CNS barrier results in the excessive extravasation of large molecules and recruitment of immune cells into the CNS parenchyma, which can damage the neuronal network. Higher-order neurons, including descending-tract neurons, may

amplify neurogenic neuroinflammation in the spinal cord and maintain immune-cell activation, as well as releasing and promoting the release of further pro-inflammatory substances. Glial cells may no longer reduce glutamate excitotoxicity by uptake mechanisms but may now release excessive amounts of glutamate (at least when challenged *in vitro*), causing excitotoxicity[142] and hyperalgesia in non-injured tissues.

Role in pain, stress and epilepsy

Neurogenic neuroinflammation is likely to have a role in a wide variety of conditions in the normal and diseased CNS, including inflammatory and injury-related pain, psychological stress and epilepsy. It may also affect other functions and conditions such as neuropathic pain[31], migraine[143], sleep[144], learning and memory formation[145], mood disorders[146] and autism[147].

Neurogenic neuroinflammation in pain. Neurogenic neuroinflammation boosts nociception, as outlined above. Astrocyte signalling through gap junctions and the diffusion of pro-inflammatory mediators through spinal cord tissue may lead to spreading of neurogenic neuroinflammation beyond the spinal projection zones of activated C fibres. This may then contribute to hyperalgesia in uninjured sites (secondary hyperalgesia), mirror-image pain (pain at corresponding contralateral sites) and widespread pain[134,148].

Some forms of neuropathy lead to ectopic discharges in small afferent nerve fibres, including C fibres[149,150]. It is therefore possible to speculate that some types of neuropathic pain involve neurogenic neuroinflammation in the spinal cord. Indeed, most animal models of peripheral neuropathy are characterized by the activation of spinal glial cells (see REFS 31,32 for reviews) and by the impairment of the blood–spinal-cord barrier[151], including the recruitment of T cells[152].

Neurogenic neuroinflammation in stress. It is now becoming increasingly clear that psychological stress involves not only neurohormonal responses[153] but also components of neuroinflammation. For example, in rats, acute stress as a result of immobilization activates mast cells and leads to plasma extravasation in the diencephalon[154]. Inescapable footshock also causes upregulation of the microglia activation marker MHCII and downregulation of the neuronal cell adhesion molecule CD200, which normally holds microglia in a non-activated state[155].

Repetitive sessions of experimental restraint in rats induce chronic stress and lead to an increase in allograft inflammatory factor 1 IBA1 (also known as AIF1), a microglia marker, in a number of stress-related brain nuclei[156]. Repeated defeat stress also increases the number of mast cells in the brain[157]. Chronic stress as a result of social dominance paradigms leads to higher levels of inducible nitric oxide synthase and *COX2* gene expression in the rat spinal cord and to a lowered pain threshold over a similar time course[158]. Chronic unpredictable stress and methamphetamine further disrupt the integrity of the blood–CNS barrier[159]. Interestingly, chronic stress may also increase gastrointestinal permeability with bacterial lipopolysaccharide translocation leading to the release of inflammatory mediators in the CNS[160]. Thus, neuronal activity patterns that encode psychological stress responses and peripheral immune responses may act synergistically to trigger neuroinflammation in the brain.

Neurogenic neuroinflammation in epilepsy. Experimental induction of epileptic seizures by kainic-acid injections into rodent cortical areas of the brain[11] or electrical stimulation in the CA3 region of the hippocampus[161] leads to mRNA upregulation of several cytokines (such as TNFα, IL-1β and IL-6) and class I MHC[162] in brain areas within hours of stimulation. Similarly, a single epileptic seizure in human patients raises serum levels of IL-1 receptor and IL-6 (REF. 163). Surgical removal of the epileptic focus by anterior temporal lobectomy not only prevents any further epileptic seizures in these patients but also markedly reduces circulating levels of TNFα and IL-1β[164]. Even brief epileptic seizures lead to perturbations of the blood–CNS barrier, with considerable extravasation of plasma proteins and recruitment of white blood cells into the brain parenchyma[165]. Simultaneously, regenerative processes are triggered, and these are also thought to involve class I MHC[162,166]. Taken together, the available data suggest that neuronal activity during epileptic seizures not only activates glial cells and leads to the release of pro-inflammatory cytokines but also engages several additional parameters of neurogenic neuroinflammation. Together, this further enhances the frequency and severity of epileptic seizures[27,167,168] (also see REFS 13,169 for reviews).

Summary and outlook

It is possible that after a transient glial-cell response, microglia may not return to their normal resting mode even if classical morphological or immunohistochemical markers would suggest so. Instead, it has been proposed that microglia may still bear long-lasting (that is, plastic) changes that may alter their future responses to similar and/or different challenges[6], indicating that not only neurons and T cells express memory functions (see REF. 170 for a review). Furthermore, it is likely that neurogenic neuroinflammation and other forms of inflammation in the CNS interact, possibly leading to priming of CNS inflammatory reactions by conditions such as pain, psychological stress or epilepsy. This would be similar to the proposed impact of systemic infection on the progression of neurodegenerative disease[121].

An increasing body of literature shows that neuronal activity leads to the activation of glial cells and to the release of cytokines and chemokines in the CNS. However, whether these responses alone fulfil the criteria for 'inflammation' has been a matter for debate. The evidence described here demonstrates that these reactions are not evoked in isolation but that neuronal activity triggers finely orchestrated response patterns in CNS areas that involve innate and adaptive immune cells, vascular cells and neurons. Although it may still be debatable whether the earliest and mildest responses deserve the label 'neuroinflammation', stronger and longer-lasting neuronal activity clearly leads to classical inflammatory signs, including plasma extravasation and activation of immune cells. Homeostatic and maladaptive reactions may be active simultaneously with anti-inflammatory responses. In some cases, it may not be possible to decide to which category a given response should be assigned. It therefore seems that no unequivocal criteria would draw an objective line between homeostatic, physiological para-inflammation on one hand and pathological neuroinflammation on the other. Furthermore, evidence suggests that classical neuroinflammation also has a homeostatic function. We therefore propose that neurogenic neuroinflammation comprises all of the responses outlined in FIG. 1.

In summary, the elaborated inflammatory response repertoire of CNS tissue may not only be used to deal with infectious, toxic or degenerative processes but also to cope with the demands of increased levels of neuronal activity and to enhance the computational power of neuronal networks in the CNS. However, neurogenic neuroinflammation may become maladaptive and aggravate clinical conditions such as pain, stress and epilepsy.

Dimitris N. Xanthos and Jürgen Sandkühler are at the Department of Neurophysiology, Center for Brain Research, Medical University of Vienna, Spitalgasse 4, A-1090 Vienna, Austria.
Correspondence to J.S.
e-mail: juergen.sandkuehler@meduniwien.ac.at

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Competing interests statement
The authors declare no competing interests.