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Roles of Inflammation, Neurogenic inflammation, and Neuroinflammation in Pain

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Abstract

Inflammation is the body's response to injury and infection, involving a complex biological response of the somatosensory, immune, autonomic, and vascular systems. Inflammatory mediators such as prostaglandin, pro-inflammatory cytokines, and chemokines induce pain via direct activation of nociceptors, the primary sensory neurons that detect noxious stimuli. Neurogenic inflammation is triggered by nerve activation and results in neuropeptide release and rapid plasma extravasation and edema, contributing to pain conditions such as headache. Neuroinflammation is a localized inflammation in the peripheral nervous system (PNS) and central nervous system (CNS). A characteristic feature of neuroinflammation is the activation of glial cells in dorsal root ganglia, spinal cord, and brain which leads to the production of proinflammatory cytokines and chemokines in the PNS and CNS that drives peripheral sensitization and central sensitization. Here, we discuss the distinct roles of inflammation, neurogenic inflammation, and neuroinflammation in the regulation of different types of pain conditions, with a special focus on neuroinflammation in postoperative pain and opioid-induced hyperalgesia.

Introduction

The biological significance of acute pain is to avoid potential damage and protect wounded tissue. In contrast, chronic pain is maladaptive and has no beneficial biological significance. Chronic pain has long been recognized as a pain state that continues beyond normal healing time, thus lacking the acute warning function of physiological nociception. According to the International Classification of Diseases (ICD), chronic pain is defined as pain that persists or recurs for more than three months and has been further delineated by the IASP Task Force for the Classification of Chronic Pain (2016).

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Chronic pain is a major health concern in the world. It is estimated that chronic pain affects one in three Americans and with an annual cost over $600 billion dollars[1,2]. As shown in Table-1, the incidence of chronic pain in Japan ranges from 13.4% to 47%[3–10]. The largest internet survey of 41,597 Japanese residents by Yubuki et al. (2012) reported a chronic pain (>3 months) incidence of 22.5%[6].

In particular, major surgeries result in high incidence of chronic postsurgical pain (CPSP). The prevalence of CPSP occurs in 20-50% patients after thoracic and breast surgeries (thoracotomies and mastectomies) and up to 80% of patients following amputations, with 5 to 10% patients suffering from severe chronic pain [11–13]. The prevalence of CPSP in Japan at 3 and 6 months is 18% and 12% after lung surgery and 49% and 33% after total knee arthroplasty[14].

Chronic pain is maladaptive and characterized by spontaneous pain (e.g., burning) as well as evoked pain in response to noxious (hyperalgesia) or non-noxious (allodynia) stimuli. It is well understood in the pain research community that neuronal and synaptic plasticity, i.e. neural plasticity in pain coding pathways and circuits results in chronic pain. Neuronal plasticity occurs in primary sensory neurons of dorsal root ganglia (DRG) and trigeminal ganglia (peripheral sensitization) as well as in pain-processing neurons in the spinal cord and brain (central sensitization)[15,16].

Inflammation and pain

A complex interplay between various biological responses of the immune system, the autonomic nervous system, vascular regulation, and the central and peripheral nervous systems in response to the insults of tissue injury, pathogens, and irritants comprises the sensation of pain by the body. Pain can serve a vital protective role for an organism, as is the case with acute inflammation that results in the perception of pain, leading to avoidance of harmful stimulus and encouraging healing of damaged tissue[17]. Inflammatory mediators, produced during inflammation, evokes pain via direct activation and sensitization of nociceptors[18,19]. Nociceptors are a subset of primary afferent neurons, with cell bodies located in the DRG and trigeminal ganglia, that respond to tissue injury, and are made up of both unmyelinated C-fibers and myelinated Aδ-fibers innervating skin, muscle, joint, and visceral organs. These tissue-injury sensitive neurons signal through the activation or sensitization of G-protein coupled receptors (GPCRs), ionotropic receptors, and tyrosine kinase receptors located on nerve terminals and cell bodies. These receptors are directly bound and activated by a variety of inflammatory mediators, including but not restricted to, bradykinin, prostaglandins (e.g., PGE2), H^+, ATP, nerve growth factor (NGF), as well as proinflammatory cytokines and chemokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and CCL2 [17,19–22].

The phenomenon of peripheral sensitization, which is marked by a state of hypersensitivity and hyperexcitability of nociceptors as a result of tissue injury and inflammation, is caused by the activation of a varied collection of ion channels including the transient receptor potential ion channels (i.e. TRPA1, TRPV1, and TRPV4)[23,24], sodium channels (i.e. Nav1.7, Nav1.8, and Nav1.9)[25,26], and mechanosensitive piezo ion channels[27]. Protein kinases including MAP kinases, protein kinase A (PKA), and protein kinase C (PKC) are critical

activating links in the receptor signaling pathways of nociceptors, leading to peripheral sensitization induction and maintenance[28–31]. It has been found that peripheral sensitization is marked by increased TRPV1 activity in response to TNF[32] and increased Nav1.8 activity in response to IL-1β[33], with both of these increased ion channel responses resulting from p38 MAP kinase activation in DRG neurons[34–36]. Continued elevated TRPV1 expression maintains the state of peripheral sensitization and consequently transition from acute to chronic pain[34,37,38]. In addition to inflammatory and neuropathic pain[34,39], activation of p38 MAP kinase in DRG neurons with C- and Aδ-fibers also contributes to pain hypersensitivity after plantar incision[40].

Nociceptor priming or hyperalgesic priming is a unique form of peripheral sensitization[41]. The inflammatory mediator PGE2 normally produces a transient hyperalgesia for hours in naïve animals. However, when preceded by a prior insult (e.g., IL-6 or carrageenan), a peripheral injection of PGE2 results in sustained hyperalgesia for weeks[41]. Interestingly, PGE2 also produces long-lasting hyperalgesia after priming with plantar incision[36]. This sustained post-incisional nociception is mediated by an upregulation of exchange protein directly activated by cyclic adenosine monophosphate (EPAC) in DRG. Of note, treatment with FR167653 [42,43], a selective p38 MAP kinase inhibitor, prior to the incision, prevented the development of nociceptor priming and incision-induced EPAC expression in DRG neurons, presumably nociceptors[36].

Interestingly, nociceptors and immune cells are involved in neuroimmune communication involving a common repertoire of inflammatory mediators including cytokines, chemokines, and TLRs[44,45]. Thus, in the context of inflammation and pain, neuroimmune interactions enable the modulation of both nociceptor and immune response to injury by regulating both resident immune cells as well as recruitment of immune cell populations to the area of local inflammation, primary afferents, and DRG[46]. A particular example is the role of neuronal TLR signaling in regulating macrophage activation in the vicinity of DRG by producing CCL2 chemokine in nociceptors[44,47]. In 2010, Amaya and coworkers first demonstrated that an induction of high mobility group box-1 (HMGB-1), an endogenous ligand of TLR2/4, in DRG neurons occurs after peripheral nerve injury, and this process is critical for the induction of neuropathic pain[48].

It is important to point out that acute inflammation not only induces pain but also promotes the resolution of pain by producing specialized pro-resolving mediators (SPMs), including resolvins (RvD1, RvD2, RvD5, RvE1), protectin or neuroprotectin (PD1/NPD1), and maresin (MaR1) derived from fish oil. SPMs, produced during the resolution phase of inflammation, exhibit potent anti-inflammatory actions in various animal models of inflammation[49,50]. Notably, SPMs are also potent analgesics that inhibit and resolve inflammatory pain and postoperative pain[51,52].

Peripheral inflammation also results in hyperactivity of the central nervous system (CNS), including the spinal cord and brain as well as primary afferent central terminals in the spinal cord and trigeminal nucleus. The CNS exhibits increases in the production and release of neurotransmitters and/or neuromodulators involved in inflammation including glutamate, the neuropeptides substance P and CGRP, as well as the neurotrophic factor BDNF, when

persistently activated by inflammatory input from peripheral nociceptors[39,53]. Persistent nociceptive input in turn results in the development of central sensitization, marked by the hyperactivity and hyperexcitability of neurons in the brain and spinal cord[15,16]. Furthermore, there is particular involvement of postsynaptic glutamate NMDA receptors and insertion of AMPA receptors in the plasma membrane, as well as activation of ERK in postsynaptic neurons[54], to initiate and maintain central sensitization[15,16]. Loss of inhibitory control (e.g., inhibitory synaptic transmission[55]) and inhibitory signal molecules (e.g., β-arrestin-2[56]) is sufficient to drive central sensitization and pain hypersensitivity.

Neurogenic inflammation and pain

Neurogenic inflammation results from nociceptor activation and can be experimentally caused with immediate onset by intradermal administration of capsaicin, which activates TRPV1, or mustard oil, which activates TRPA1[57]. The activated nociceptors, notably C-fibers, release a host of neuropeptides such as substance P, CGRP, and prostanoids. Following the activation of nociceptors, rapid plasma extravasation and edema occurs at a timescale faster than that of immune cell infiltration. Among clinical conditions, neurogenic inflammation has been found to be particularly involved in inflammatory diseases including asthma and psoriasis[18]. Additionally, neurogenic inflammation is a major component of pain caused by migraines as well as complex regional pain syndrome (CRPS) due to bone fracture[58]. Although the ablation of nociceptors can decrease neurogenic inflammation, it must be noted that nociceptors can play a modulatory role that can be beneficial in other scenarios, for example the release of CGRP by nociceptors which has been found to regulate inflammation in bacterial infections[59,60].

The generation of neurogenic inflammation is not only limited to activation of peripheral C-fibers but can also be caused by local inflammation events or even by CNS activation of primary afferents in the case of dorsal root reflex resulting from orthograde or anterograde neuronal activation[61]. The CNS itself can also be subject to neurogenic inflammation following neuroinflammation events in the brain or spinal cord[18,61].

Neuroinflammation and pain

Neuroinflammation is a localized form of inflammation occurring in both the PNS and CNS [17]. Four features of neuroinflammation include increased vascular permeability, leukocyte infiltration, glial cell activation, and increased production of inflammatory mediators such as cytokines and chemokines[17]. In the state of neuroinflammation, the blood brain barrier is subject to an increased level of permeability, exposing the CNS to increased infiltration by peripheral immune cells. Accordingly, neuroinflammation is increasingly being implicated in chronic pain disorders including postsurgical pain following major surgeries such as amputation, thoracotomy, and mastectomy, and postoperative complications such as delirium[18,62].

Although chronic pain is observed as a condition that continues beyond the resolution of observable clinical signs and symptoms of inflammation, neuroinflammation actually maintains a close association with chronic pain states and may be responsible for the mediation and continuation of pain in human patients[63]. Of note, chronic pain is correlated

differently with inflammation and neuroinflammation. Chronic neuroinflammation has been observed in patients of HIV-neuropathy and also in patients with fibromyalgia[63,64]. The involvement of different neuroinflammatory mediators in modulating pain sensitivity in the pain neurocircuitry will be a particularly interesting area of inquiry.

Glial activation and neuroinflammation after surgery and opioid treatment

Peripheral glia (i.e. Schwann cells and satellite glial cells (SGCs) and central glia (i.e. microglia, astrocytes and oligodendrocytes) are activated during neuroinflammation[65,66]. In DRG, nerve injury not only causes neuronal changes leading to peripheral sensitization but also results in activation of SGCs, which contributes to peripheral neuroinflammation and neuropathic pain via SGC-neuron interactions (Fig. 1)[65,67,68]. Notably, opioids produce not only analgesia but also paradoxical hyperalgesia, which could be conveyed by SGCs. Strikingly, a single intraperitoneal injection of morphine is sufficient to activate SGCs[69]. This activation requires the upregulation of matrix metalloprotease-9 (MMP-9) in DRG neurons, which causes IL-1β cleavage and release to activate SGCs[69]. As a result, opioid analgesia is suppressed by MMP-9/IL-1β-mediated SGC activation but enhanced in mice lacking *Mmp9*[69,70]. Plantar incision produced a rapid activation (within one hour) of ERK not only in large-size DRG neurons but also in surrounding SGCs. Blocking the coupling of neuron-SGC with the gap junction blocker carbenoxolone inhibited neuronal ERK activation and postsurgical pain[71], supporting an essential role of neuron-SGC interactions in the initiation of postsurgical pain. It remains to be investigated if MMP-9 and IL-1β are involved in ERK activation in SGCs after plantar incision.

With regard to the central glia, which are the focus of the majority of glial studies on pain, the mediators and actions produced by these cells serve major modulatory roles in the processes of synaptic plasticity and central sensitization[18]. Notably, the phenomenon of glial activation has emerged in recent literature as a potent mechanism in chronic pain, and the resulting dysfunction of glia in chronic pain has been referred to as “gliopathy”[65]. Nerve injury results in remarkable microgliosis and astrogliosis in the spinal cord[65,72,73]. Spinal microgliosis was also reported after plantar incision[43]. Multiple receptors, such as ATP receptors (e.g., P2X4, P2X7, P2Y12)[73–75], chemokine receptors (e.g., CX3CR1, CXCR5)[76,77], and Toll-like receptors (e.g., TLR4)[78], along with proteases such as matrix metalloproteases (MMP-9 and MMP-2) and cathepsin S (CatS)[79–81] have been shown to regulate glial activation and neuropathic pain.

In particular, following nerve injury, surgery (e.g. plantar incision), and chronic opioid exposure, p38 MAP kinase is not only activated in DRG neurons during peripheral sensitization but also activated in spinal microglia during central sensitization[43,75,82,83]. Thus, activation of p38 MAP kinase plays an important role in neuropathic pain, postsurgical pain, and opioid tolerance via regulating neuroinflammation[84]. p38 MAP kinase regulates microglial secretion of TNF, IL-1β, and BDNF, all of which are powerful regulators of central sensitization[85,86] (Fig. 2). Interestingly, blockade of both A-fibers and C-fibers together, but not C-fibers alone, can prevent microglial activation in the spinal cord after nerve injury[87]. Consistently, blocking large A-beta fibers but not small C-fibers alleviated mechanical allodynia, a cardinal feature of chronic pain after chemotherapy and

nerve injury[88]. Nerve injury, surgery, and chronic opioid exposure also activate spinal cord astrocytes, and persistent astrocyte activation maintains neuropathic pain via sustained neuroinflammation[65,89]. Mechanistically, astrocyte-produced chemokines such as CCL2 and CXCL1, as well as cytokines (e.g., IL-1β), powerfully regulate central sensitization[90,91] (Fig. 2).

Surgical incisions and resulting nerve injury have been shown to cause increased expression of COX-1 in spinal glial cells which can lead to postsurgical pain and neuropathic pain development following a surgery[92,93]. P2X7 receptors and spinal glial cells also contribute to the development of chronic postsurgical pain induced by incision and retraction of skin and muscle tissue[94]. Furthermore, discrepancies between inflammation in peripheral tissues and central neuroinflammation in acute versus chronic pain support the notion that central neuroinflammation maintains chronic pain states[18,95]. This was suggested from a study of a rat model of complex regional pain syndrome (CRPS), where levels of IL-1β were elevated in peripheral and spinal samples at the acute phase 4-week time point, but at the chronic phase 16-week time point only spinal levels of IL-1β remain elevated. Furthermore, efficacy of anakinra treatment to antagonize IL-1 was delineated along the same peripheral versus central compartments, as peripheral anakinra treatment was effective at inhibiting nociceptive behavior measurements at only the 4-week time point, whereas intrathecal anakinra treatment was able to inhibit nociception at both the 4-week and 16-week time points[96]. Thus neuroinflammation, especially central neuroinflammation, plays an essential role in maintaining chronic pain. Notably, central neuropathic pain after spinal cord injury is associated with peripheral sensitization in DRG neurons[97]. It was recently proposed that central neuroinflammation and central sensitization could maintain chronic pain in part by driving peripheral sensitization via diffusion and retrograde signaling[18].

Clinical significance and future perspectives

As detailed in the preceding sections, there are different types of inflammation, namely classic inflammation (referred to as “inflammation” in this review), neurogenic inflammation, and neuroinflammation. Although all three types of inflammation play active roles in pain and anti-inflammatory drugs are partially effective in treating acute pain and pain, it is important to make distinctions among different types of inflammation from a therapeutic perspective. For example, inhibiting neurogenic inflammation with nerve block such as by Botox (Botulinum neurotoxin A) or anti-CGRP antibody show great efficacy in reducing bacterial infection, inflammatory pain, and headache[57,98–100]. Given the important role of central neuroinflammation in maintaining chronic pain, delivery of anti-inflammatory drugs to the CNS is critical. Thus, intrathecal but not peripheral administration of anakinra, an FDA-approved anti-IL-1β treatment, can alleviate CPSP in rodents in the late phase (16-weeks) after bone fracture[96].

Neuroinflammation resulting from neuro-glial and neuro-immune interactions not only serves as a driving force for chronic pain, but is also implicated in other neurological and psychiatric diseases such as Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, autism, major depression, and schizophrenia[17], as well as in cognitive deficits after major surgeries[62]. Chronic pain is commonly associated with depression, anxiety, sleep disorders,

and cognitive decline, which are clinical sequelae of particular concern to the growing aging population which has increasingly high prevalence of chronic pain. Neuroinflammation and astrocyte reactivity is also associated with chronic pain in postmortem human spinal cord samples[63]. Glial activation can further be detected in patients with chronic low back pain using positron emission tomography (PET) imaging[101]. Thus, targeting excessive neuroinflammation will be a promising approach to alleviate chronic pain and control the progression of neurological and psychiatric diseases. Notably, there is ongoing opioid crisis in the United States with hundreds of Americans dying from opioid overdoses every day[102]. Therefore, the development of effective non-opioid treatments for the prevention and resolution of neuroinflammation and postoperative pain is of utmost urgency. Finally, it is worthy to mention that non-pharmacological alternative treatments, such as cellular therapy with bone marrow stem cells show promising long-term pain relief via powerful control of neuroinflammation[103–105]. Autologous conditioned serum and platelet-rich plasma contain high levels of anti-inflammatory cytokines and produce relief in patients with knee osteoarthritis [106–108]. Neuromodulation via spinal cord stimulation and electroacupuncture also demonstrate the ability to control neuroinflammation for pain relief[18,109,110]. Further studies are warranted in the future to investigate how these alternative strategies control CPSP and neuroinflammation after surgery.

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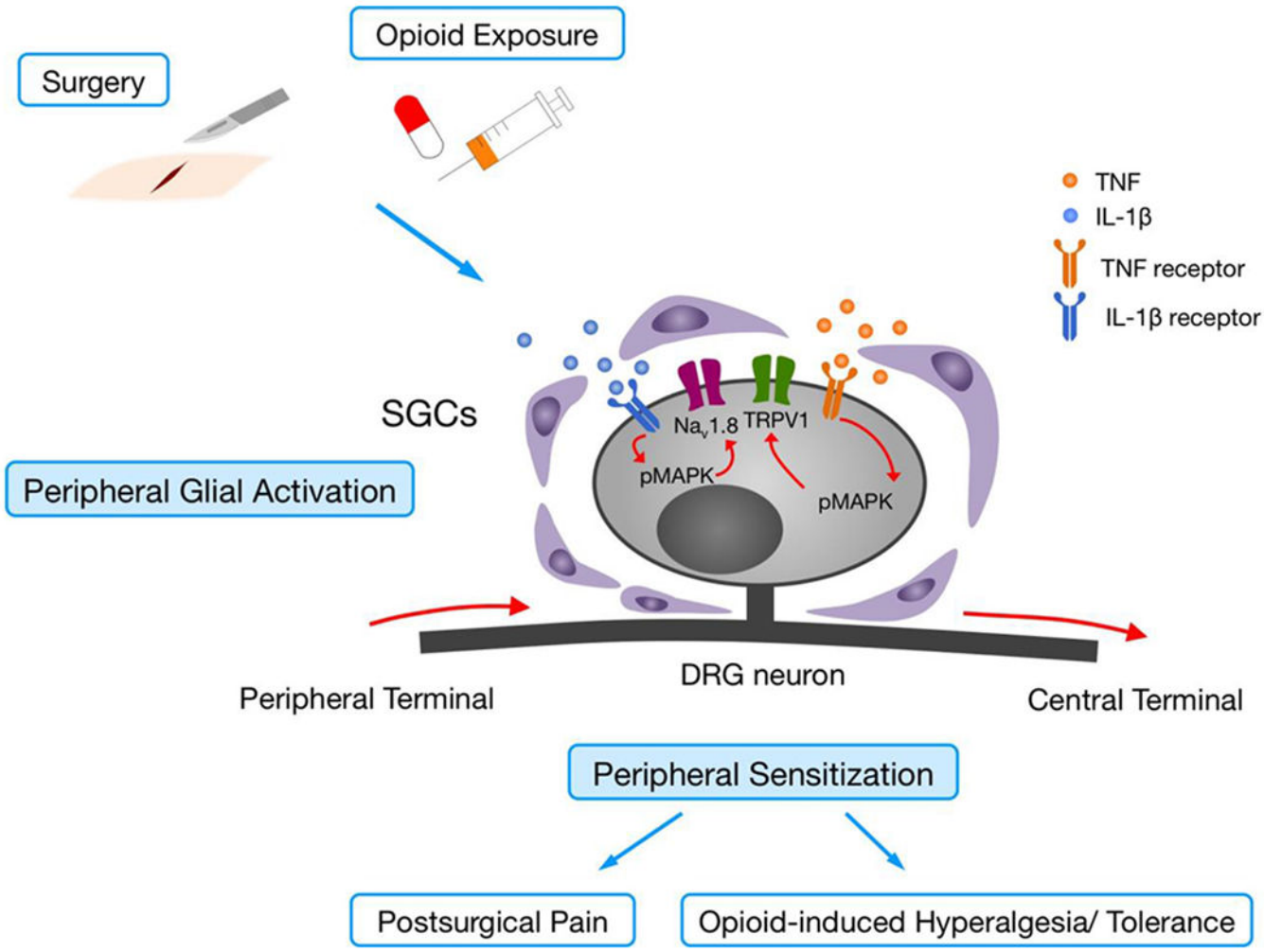

Figure 1.

Schematic illustration of peripheral sensitization induced by peripheral glial activation and neuroinflammation in dorsal root ganglia (DRG) following surgeries and opioid exposure. Activation of peripheral glia (i.e. SGCs: satellite glial cells) by surgery and/or opioid treatment results in secretion of glial mediators such as TNF and IL-1β, leading to peripheral sensitization, postsurgical pain, and opioid-induced hyperalgesia and tolerance.

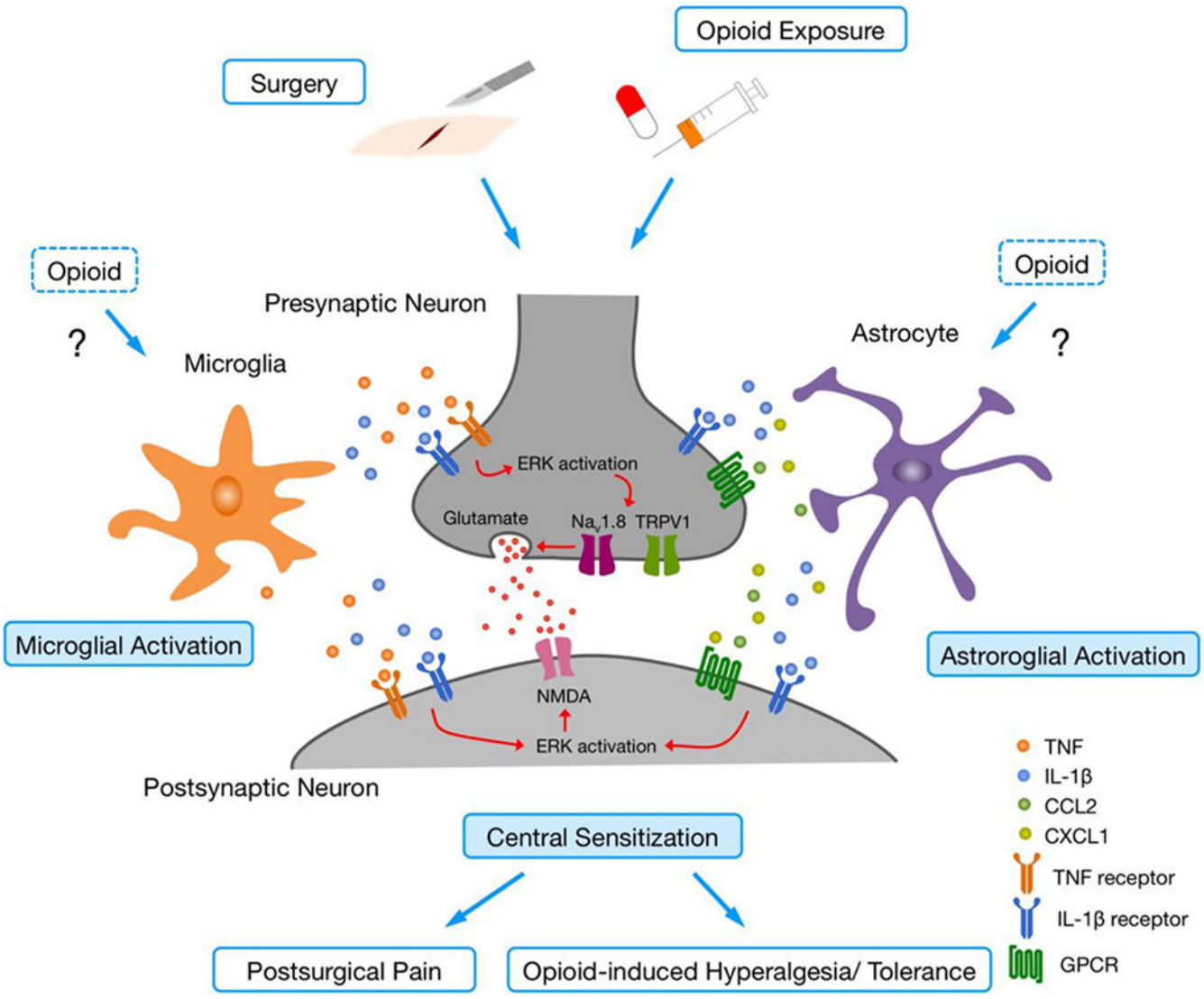

Figure 2.

Schematic illustration of central sensitization induced by glial activation and neuroinflammation in the spinal cord following surgery and/or opioid exposure. Activation of central glia (microglia and astrocytes) in the spinal cord by surgery and/or opioids treatment results in secretion of glial mediators including TNF, IL-1β, CCL2, CXCL1, and BDNF. These factors can act as neuromodulators to induce central sensitization via the modulation of excitatory and inhibitory synaptic transmission. Central sensitization is a driving force of postsurgical pain as well as opioid-induced hyperalgesia and tolerance.

Table 1:

Chronic pain prevalence in Japan

1st author	Year	Survey method	Age (years)	Participants (Response rate)	Duration of Pain (months)	Prevalence
Hattori (3)	2004	Internet	≥18	18,300 (72.2%)	6	13.4%
Matsudaira (4)	2011	Internet	20 - 80	20,044 (20.1%)	3	22.9%
Nakamura (5)	2011	Postal	≥18	11,507 (60%)	6	15.4%
Yabuki (6)	2012	Internet	≥20	41,597 (unknown)	3	22.5%
Ogawa (7)	2012	Internet	20 - 69	20,000 (unknown)	3	26.4%
Shibata (8)	2014	Interview	≥40	927 (46%)	6	47%
Inoue (9)	2015	Postal	≥20	2,628 (43.8%)	6	39.3%
Inoue (10)	2017	Postal	≥20	5,437 (54.4%)	6	16.6%