Summary and Keywords

Much progress has been made in unraveling the mechanisms that underlie the transition from acute to chronic pain. Traditional beliefs are being replaced by novel, more powerful concepts that consider the mutual interplay of neuronal and non-neuronal cells in the nervous system during the pathogenesis of chronic pain. The new focus is on the role of neuroinflammation for neuroplasticity in nociceptive pathways and for the generation, amplification, and mislocation of pain. The latest insights are reviewed here and provide a basis for understanding the interdependence of chronic pain and its comorbidities. The new concepts will guide the search for future therapies to prevent and reverse chronic pain.

Long-term changes in the properties and functions of nerve cells, including changes in synaptic strength, membrane excitability, and the effects of inhibitory neurotransmitters, can result from a wide variety of conditions. In the nociceptive system, painful stimuli, peripheral inflammation, nerve injuries, the use of or withdrawal from opioids—all can lead to enhanced pain sensitivity, to the generation of pain, and/or to the spread of pain to unaffected sites of the body. Non-neuronal cells, especially microglia and astrocytes, contribute to changes in nociceptive processing. Recent studies revealed not only that glial cells support neuroplasticity but also that their activation can trigger long-term changes in the nociceptive system.

Keywords: nociception, antinociception, central nervous system, neurogenic neuroinflammation, long-term potentiation, immune system, glial cell, principal pain neuron

Introduction

The patient’s pain often does not well reflect the intensity, location, or duration of any detectable trigger for it. Clinically relevant forms of pain occur in the absence of any noxious stimulus, may spread to sites remote from the initial pain trigger, and may outlast the primary cause of pain for considerable periods of time. Neuroinflammation and neuroplasticity in nociceptive pathways contribute to the generation, amplification, and mislocation of pain. Neuroinflammation and neuroplasticity are typical consequences of a wide
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variety of conditions, including inflammation, injury, or trauma of peripheral tissues or the central nervous system, as well as long-term treatment with opioids, or abrupt withdrawal from them. Neuroinflammation and neuroplasticity are also associated with the most prevalent comorbidities of chronic pain such as major depression, sleep and anxiety disorders, diabetes, and obesity and might constitute mechanistic links between these conditions.

Peripheral Mechanisms of Pain Hypersensitivity

In the periphery, nociceptive nerve endings are activated and sensitized in case of trauma, injury, or inflammation. These peripheral mechanisms are not covered here but are reviewed elsewhere (Basbaum, Bautista, Scherrer, & Julius, 2009; Hucho & Levine, 2007). Excitation of nociceptive nerve fibers leads to orthodromic conduction of action potentials to the nerve terminals (synapses) in the spinal cord and in the trigeminal nuclei. Action potentials may also be conducted antidromically in peripheral axonal collaterals. In peptidergic nerve fibers, this leads to the release of glutamate and of neuropeptides such as substance P, calcitonin gene-related peptide, and neuropeptide Y. Adenosine triphosphate (ATP) and trophic factors such as brain-derived neurotrophic factor (BDNF) are also released in peripheral tissues from nerve terminals at or near the site of a noxious stimulus. These substances then bind to receptors on non-neuronal, immune competent cells, including macrophages, dendritic cells, T-cells, mast cells, and also bind to vascular cells. Mast cells respond quickly and vigorously by degranulation leading to the release of pro-inflammatory substances, including cytokines, prostaglandins, serotonin, and histamine. This concerted action of neuronal and non-neuronal cells in peripheral tissues constitutes a form of inflammation that is triggered by neuronal activity and is thus labeled neurogenic inflammation (Chiu, von Hehn, & Woolf, 2012). Some of the pro-inflammatory substances released in the course of a neurogenic inflammation directly excite or sensitize nociceptive nerve endings and thus constitute a peripheral generator or amplifier for pain. Neurogenic inflammation also plays a role in migraine and in neuropathic pain and contributes to a variety of other diseases such as psoriasis, asthma, pancreatitis, and inflammatory bowel disease.

Inflammatory reactions in the central nervous system are distinct from those in peripheral tissues and therefore are generally described by their own technical term, neuroinflammation. This chapter deals with pro-nociceptive effects of neuroinflammation and neuroplasticity in the central nervous system with a focus on the spinal cord dorsal horn, a key station for the modulation of nociception.

What Is So Special About “Neuroinflammation”?

Neuroinflammation differs considerably from inflammation in peripheral tissues (Xanthos & Sandkühler, 2014). Neuroinflammation involves innate, parenchymal immune cell types, such as microglia and astrocytes, which are not present in peripheral tissues. On
the other hand, neuroinflammation lacks cell types that dominate peripheral inflammation such as resident dendritic cells. In the central nervous system, their functions are taken over by perivascular macrophages and vascular pericytes. Neuroinflammation is further characterized by the unique properties of the blood-central nervous system barrier leading to vascular responses to inflammation, which are quite distinct from those in peripheral tissues. As compared to peripheral tissues, the reduced permeability of microvessels in the central nervous system for plasma-extravasation and blood cells makes it more difficult to activate complement cascades and to recruit cells of the adaptive immunity into the central nervous system parenchyma (Rochfort & Cummins, 2015). Neuroinflammation is considerably less destructive than inflammation of peripheral tissues, accounting for the lower regenerative capacity of neuronal tissue. Very much like inflammation in the periphery, neuroinflammation can be triggered by infectious microbes, autoimmunity, toxins, and, as recently proposed, also by neuronal activity (see the following section and, for a review, Xanthos & Sandkühler, 2014). Neuroinflammation plays decisive roles in animal pain models of neuropathic, inflammatory, incisional, and central pain. Neuroinflammation is also associated with a number of comorbidities of chronic pain such as diabetes, obesity, sleep and anxiety disorders, and depression (Sandu, Buga, Uzoni, Petcu, & Popa-Wagner, 2015). Recent studies have begun to unravel the complex interplay between neuroinflammation and neuroplasticity, which likely contributes to clinically relevant forms of pain.
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Neurogenic Neuroinflammation

Figure 1. Comparison of two forms of inflammation that are both caused by neuronal activity. The lower part of the figure illustrates a primary afferent, peptidergic nerve fiber, and elements that contribute to neurogenic inflammation in peripheral tissues. Antidromic action potentials conducting toward the peripheral terminals induce neurogenic inflammation. The release of neurotransmitters and neuropeptides from peripheral nerve terminals (black box affects a variety of cell types such as vascular cells (endothelial cells, red), mast cells (purple), macrophages (green), T-cells (orange), and dendritic cells (red). These cells then also release substances (shown in colored boxes) creating the inflammatory milieu. The upper part of the figure illustrates neurogenic neuroinflammation in the central nervous system. Enhanced neuronal activity, arriving at the central terminals of primary afferents, results in neurogenic neuroinflammation due to the release of neurotransmitters, neuropeptides, and ATP (black boxes within the terminal). This then activates microglia (green), astrocytes (blue), 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 and descending neurons). Mast cells on the dura, perivascular macrophages, and CD4+ and CD8+ T cells (orange) may eventually also be recruited to the concerted action. These cells then release a large number of additional substances, some of which are given in colored boxes. Modified from Xanthos and Sandkühler (2014).

The composition of substances that are released at the central terminals of peptidergic sensory nerve fibers is very similar, if not identical, to those substances that are released
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Glutamate, substance P, calcitonin-gene related peptide and neuropeptide Y, ATP, and BDNF are all released peripherally and centrally from primary afferents. Receptors for these substances are found in the central nervous system both on neurons and non-neuronal cells in the spinal cord and in the trigeminal nuclei. For example, receptors for substance P can not only be found on some spinal dorsal horn neurons, but also on microglial cells, astrocytes, and vascular cells, as well as on mast cells and T-cells (for a review, see Xanthos & Sandkühler, 2014). T-cells are, however, relatively sparse in normal central nervous system tissue.

Central Nervous System Mechanisms of Pain Generation and Amplification

Powerful pro-nociceptive mechanisms have been identified along the neuraxis from sensitization of nociceptive nerve endings to neuroplasticity in the spinal cord and in the brain. Short- and long-term modulations of nociceptive processing in the central nervous system are no longer considered to be pure matters of nerves and neuroplasticity. It is now well established that the processing of nociceptive information within the central nervous system involves a finely tuned interplay of different types of neurons and non-neuronal cells, including microglial cells, astrocytes, T-cells, and vascular cells, all of which may contribute to neuroinflammation.

Principal Pain Neurons

In the central nervous system, a variety of neurons respond to noxious stimuli and are thus classified as nociceptive neurons. Nociceptive neurons are defined by their excitatory input but not by their function. In fact, the large group of nociceptive neurons serves a multitude of functions, only some of which are related to the perception of pain. For example, nociceptive flexor motor neurons mediate nocifensive reflexes but do not contribute to the perception of pain. Many inhibitory interneurons in the spinal cord are nociceptive. Their functions are largely unknown but include negative feedback during nociception. Thus, a significant proportion of nociceptive neurons actually has anti-nociceptive functions. Some nociceptive spinal dorsal horn neurons project to the brain where they may trigger vegetative responses to noxious stimulus such as increases in heart rate and blood pressure. Other nociceptive spinal dorsal horn neurons project to brain areas that ultimately mediate the perception of pain. The subgroup of nociceptive neurons that contribute to the perception of pain has been termed Principal Pain Neurons (Sandkühler, 2013). Their identity is presently unknown. Good candidates for principal pain neurons in the spinal cord dorsal horn are nociceptive neurons in lamina I that express the neurokinin 1 receptor for substance P and that project to the parabrachial area and/or the midbrain periaqueductal gray. When these neurons are ablated, motor responses to acute noxious stimuli are still intact, but thermal and mechanical hypersensitivity after peripheral inflammation or nerve injury are much reduced (Nichols et al., 1999). The activity of these lamina I neurons and other nociceptive spinal dorsal horn neurons is under power...
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ful control exerted by spinal interneurons and by long, descending tract neurons. Reduced inhibition and enhanced excitation in the spinal cord dorsal horn lead to elevated and prolonged excitation of nociceptive neurons, including neurons with projections to various regions of the brain, such as the ventromedial nucleus of the thalamus, the midbrain periaqueductal gray, and the parabrachial nucleus.

Enhanced Excitation in Nociceptive Pathways

All forms of physiological pain and many forms of chronic pain are triggered by the excitation of nociceptive nerve endings and are thus called nociceptor pain. Normally, the neuronal excitation in response to brief, moderate noxious stimuli is transient and reproducible. This apparently also applies to principal pain neurons, as pain perception in response to these stimuli is also brief and of constant magnitude. In the case of strong and repetitive noxious stimuli, larger quantities and additional signaling molecules are released from the spinal terminals of nociceptive nerve fibers leading to the activation of microglia and astrocytes, in some cases to the degranulation of dural mast cells, to vasodilation, impairment of the blood–spinal cord barrier, and to the recruitment of T-cells to the spinal parenchyma (Xanthos & Sandkühler, 2014). This in turn causes the release of inflammatory mediators in the spinal cord, including chemokines and cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor, neurotrophins such as BDNF, prostaglandins, and nitric oxide (see Figure 1). These substances act as neuromodulators and contribute to a variety of neuroplastic changes in nociceptive pathways, including synaptic long-term potentiation, enhanced neuronal excitability, and impaired inhibition.
Synaptic Long-Term Potentiation

Figure 2. LTP can be induced in vivo and in vitro at spinal synapses of primary afferent C-fibers by various conditioning stimuli, such as direct electrical nerve stimulation at C-fiber intensity at a low (A, LFS, 2 Hz in vitro) or high (B, HFS100 Hz, in vivo) frequency, by natural noxious stimulation with intraplantar injection of transient receptor potential vanilloid type 1 agonist capsaicin (C), or by the abrupt withdrawal from the µ-opioid receptor agonist remifentanil after an intravenous infusion that lasted one hour (black horizontal bar, D). Modified from Sandkühler and Gruber-Schoffnegger (2012).

Long-term potentiation (LTP) between nociceptive nerve fibers and spinal dorsal horn neurons is considered a fundamental mechanism contributing to long-lasting pain amplification (for reviews, see Sandkühler, 2009; Luo, Kuner, & Kuner, 2014; Zhuo, 2014). In spinal cord dorsal horn, LTP can be induced at C-fiber synapses in vivo and in vitro by diverse conditioning stimuli such as natural noxious stimuli, peripheral inflammation, nerve crush, direct electrical nerve stimulation at C-fiber intensity at high (~100 Hz) or low (~2 Hz) frequencies and by the abrupt withdrawal from opioids (see Figure 2 and Sandkühler, 2009). LTP can further be induced by spinal application of agonists at the dopamine D1 receptor, BDNF or ATP (Liu & Zhou, 2015) as well as by cytokines such as IL-1β and tumor necrosis factor (Gruber-Schoffnegger et al., 2013). Most, if not all, of these LTP-inducing stimuli also lead to hyperalgesia in behaving animals (Sandkühler, 2013) and activate glial cells in the spinal cord (Ji, Berta, & Nedergaard, 2013; McMahon & Malcangio, 2009). Glial cell activation has been found to be indispensable both for the induction of LTP at spinal C-fiber synapses (Gruber-Schoffnegger et al., 2013; Zhong et al., 2010; Park et al., 2011) and for many forms of hyperalgesia tested so far (Old, Clark, & Malcangio, 2015). In fact, selective activation of glial cells is not only necessary but can also be sufficient to induce LTP at C-fiber synapses (Kronschläger et al., 2016). This gliogenic LTP may underlie LTP by conditioning stimuli that activate glial cells (Kronschläger et al., 2016). The underlying mechanisms of LTP in nociceptive are currently evolving (see reviews in Sandkühler, 2013; Liu & Zhou, 2015; Luo et al., 2014; Sandkühler, 2009) and involve both pre- (Luo et al., 2012) and postsynaptic signaling (Ikeda, Heinke, Ruscheweyh,
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Neuronal Excitability

Activation of glial cells also directly impacts neuronal excitability. For example, astrocytes regulate extracellular potassium and glutamate concentrations via Kir4.1 potassium channels and glial specific glutamate transporter 1, respectively. The expression of both of these proteins is reduced by about 80% after crush injury of the spinal cord (Olsen, Campbell, McFerrin, Floyd, & Sontheimer, 2010). The resulting enhanced potassium and glutamate levels facilitate neuronal excitation. Furthermore, non-neuronal cells, including glial cells, may release substances that directly enhance neuronal excitability. This includes glutamate that is released not only from neurons but also from glial cells and that triggers synchronous neuronal excitation (Tian et al., 2005). D-serine is also released by glial cells and enhances neuronal excitability by acting as a co-agonist at the essential glycine binding site of the N-Methyl-D-aspartate (NMDA) receptor. IL-1β likewise enhances NMDA receptor-mediated currents by binding to type 1 IL-1β receptor that is associated with the GluN2B/NR2B subunit of the NMDA receptor complex. Another prototypic pro-inflammatory cytokine, tumor necrosis factor, potentiates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated synaptic currents in the spinal cord by enhancing their membrane insertion (Ferguson et al., 2008).

Impaired Inhibition in Nociceptive Pathways

Proper inhibition is indispensable for all functions of the central nervous system, including nociception. Inhibition in spinal cord dorsal horn and in the brain has essential functions for nociception (see Sandkühler, 2009, 2013; Todd, 2015 for reviews). When the inhibitory control of principal pain neurons becomes insufficient, pain perception will directly be affected in five ways: (1) Tonic inhibition is needed to prevent spontaneous activity to occur in nociceptive dorsal horn neurons. Impaired tonic inhibition can lead to spontaneous pain. (2) Inhibition, including feedforward inhibition, is indispensable for an adequate response magnitude of spinal dorsal horn neurons to noxious stimulation. Hyperalgesia is a potential outcome if this function becomes insufficient. (3) Inhibitory neurons control the spread of excitation from deep dorsal horn, where low-threshold primary afferents terminate, to superficial dorsal horn, where nociceptive nerve fibers terminate. If this function is ineffective, low-threshold sensory input will now also excite otherwise nociceptive specific neurons, resulting in touch-evoked pain (allodynia). (4) Proper levels of inhibition also block the spread of nociceptive excitation beyond somatotopically adequate regions. This inhibition is essential for preventing secondary hyperalgesia and spreading pain. (5) Finally, physiological inhibition raises the threshold for the induction of neuroplasticity in the nociceptive system. Thus, the inhibition is also essential for preventing the transition from acute to chronic pain (see Table 1 for a summary).

Table 1. The five roles of inhibition in nociceptive pathways. (Modified from Sandkühler, 2009, 2013.)
## Modes of Disinhibition

The main inhibitory neurotransmitters in spinal nociceptive pathways are γ-aminobutyric acid (GABA), glycine, and the endogenous opioids enkephalin and dynorphin. Some of these neurotransmitters are co-released from spinal interneurons. In addition, the monoamines 5-hydroxtryptamine and noradrenaline are released from long, descending tract neurons largely originating from the rostral ventromedial medulla or the locus coeruleus, respectively (Todd, 2015; Zeilhofer, Wildner, & Yévenes, 2012). The properties and functions of the inhibitory systems can be impaired at multiple levels, as illustrated in Figure 3. Known mechanisms of altered inhibition include changes in the synthesis, storage, and/or release of inhibitory neurotransmitters, cell death or altered excitability of inhibitory interneurons, altered excitatory drive, or spontaneous activity of inhibitory interneurons. Impaired inhibition can also result from changes that take place in the postsynaptic neuron. For example, altered expression, functions, or trafficking of inhibitory neurotransmitter receptors or downstream signaling can have major impacts on the efficacy of postsynaptic inhibition. Even if all of the above parameters remained the same, inhibition could still be reduced, abolished, or converted into excitation by changes in the driving forces for ions across the postsynaptic plasma membrane, as this may drastically change the ion flux across neurotransmitter receptor channels (Price, Cervero, & De Koninck, 2005).

<table>
<thead>
<tr>
<th>Role of inhibition</th>
<th>Mechanism of action</th>
<th>Desired effect</th>
<th>Pain type upon failure</th>
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<tbody>
<tr>
<td>Muting</td>
<td>Inhibition of nociceptive dorsal horn neurons and interneurons driving those</td>
<td>Silencing principal pain neurons in the absence of noxious stimuli</td>
<td>Spontaneous pain</td>
</tr>
<tr>
<td>Attenuation</td>
<td>Pre- and postsynaptic inhibition of nociceptive spinal dorsal horn neurons</td>
<td>Proper response level of principal pain neurons to noxious stimulation</td>
<td>Hyperalgesia</td>
</tr>
<tr>
<td>Limiting</td>
<td>Inhibition of excitatory interneurons which cross somatotopic borders</td>
<td>Limiting spread of excitation to somatotopically appropriate areas</td>
<td>Radiating pain, Referred pain, Mirror-image pain</td>
</tr>
<tr>
<td>Separating</td>
<td>Inhibition of excitatory interneurons linking Aβ-fiber input to nociceptive specific neurons</td>
<td>Inhibition of excitatory crosstalk between sensory modalities</td>
<td>Allodynia</td>
</tr>
<tr>
<td>Preventing</td>
<td>Reduced Ca(^{2+}) influx into nociceptive spinal dorsal horn neurons</td>
<td>Blocking Ca(^{2+})-dependent signaling pathways engraving memory traces of pain</td>
<td>Chronic pain</td>
</tr>
</tbody>
</table>
Figure 3. Sites (in blue) where inhibitory systems may be impaired. An inhibitory spinal interneuron presynaptically depresses input from nociceptive primary afferents and postsynaptically inhibits a spinal nociceptive neuron, here shown as a principal pain neuron that, by definition, contributes to the sensation of pain when excited. The inhibitory interneuron is activated either by input from sensory afferents (some of which may be nociceptors), by excitatory interneurons, and/or by descending excitatory pathways (not shown). Modified from Sandkühler (2013).

Disinhibition of polysynaptic excitatory pathways from deep to superficial spinal dorsal horn appears to be functionally important for an abnormal crosstalk between low-threshold Aβ-fiber afferents and the nociceptive system (Baba et al., 2003; Schoffnegger, Ruscheweyh, & Sandkühler, 2008). The activation of low-threshold mechanoreceptive primary afferent Aβ-fibers leads to the excitation of low-threshold neurons in deep layers of the spinal cord dorsal horn. Some of these low-threshold dorsal horn neurons also respond to high-intensity, noxious stimuli and are then referred to as “wide-dynamic range” neurons. In contrast, neurons with preferential excitatory input from high-threshold Aδ- and/or C-fibers are located in superficial laminae I and II (Todd, 2010). When GABAergic inhibition in the spinal cord is blocked, the activation of Aβ-fibers now leads to excitation of superficial dorsal horn neurons. The direct excitation of deep dorsal horn neurons by microinjections of glutamate likewise excites superficial dorsal horn neurons, but only when the normal GABAergic inhibition in the dorsal horn is blocked (Schoffnegger et al., 2008). The disinhibition of excitatory, polysynaptic pathways between deep and superficial laminae of the spinal cord dorsal horn may well explain how tactile stimuli evoke withdrawal responses and are perceived as painful in peripheral neuropathy and during an inflammation (Baba et al., 2003; Schoffnegger et al., 2008).
Neuroinflammation and Disinhibition

The inhibitory systems in the spinal dorsal horn interact at multiple levels with mechanisms of neuroinflammation. Receptors for all of the relevant inhibitory neurotransmitters are expressed both by neurons and by non-neuronal cells involved in neuroinflammation. The activity of inhibitory systems in the spinal cord can be sensed by microglia, astrocytes, T-cells, and/or vascular cells. For example, GABA receptors are expressed on microglia, astrocytes, vascular cells, and perhaps mast cells (Haenisch, Huber, Wilhelm, Steffens, & Molderings, 2013). Likewise, monoamines modulate not only the functions of neurons but also those of glial cells, T-cells, and vascular cells.

On the other hand, the properties and functions of inhibitory systems in the spinal cord dorsal horn are strongly modulated by mediators of neuroinflammation. For example, BDNF can be released from microglia, astrocytes, and potentially from CD4+ T-cells (Xin et al., 2012), as well as from neurons. BDNF may reduce the inhibition that is mediated by the activation of ionotropic GABA$_A$ or glycine receptors. The inhibitory postsynaptic action of these receptors relies on the proper anion gradient across the plasma membrane of postsynaptic neurons. This gradient much depends on the action of the potassium-chloride co-transporter-2, which is depressed by BDNF (Coull et al., 2005). Thereby inhibition may be diminished or even converted into paradoxical excitation (Coull et al., 2005).

Other Effects Observed

“Central Sensitization”

The literature on pain often uses the phrase “central sensitization” but does not define it well. Some authors use it as an umbrella term for all kinds of central nervous system mechanisms contributing to pain hypersensitivity. This concept was first proposed by Sturge in 1883 and was scientifically elaborated by Hardy and colleagues (1950). Hardy et al. (1950, p. 139) concluded that “the secondary hyperalgesia occurring in undamaged tissue having an unaltered pain threshold but increased pain sensibility is the result of a central excitatory state. It is suggested that this excitability is to be found in a network of internuncial neurons which intercalate the noxious impulses from visceral, deep somatic, and cutaneous tissues.” In 1977, Lynn further elaborated on this concept. The International Association for the Study of Pain (IASP) now defines “central sensitization” as the “increased responsiveness of nociceptive neurons in the central nervous system.” Nociceptive neurons, however, comprise a large and very heterogeneous group of neurons that serve distinct and sometimes opposing functions, as highlighted earlier. Only a subset of nociceptive neurons, termed principal pain neurons (Sandkühler, 2009), is actually involved in the sensation of pain. In fact, an “increased responsiveness of nociceptive neurons” as used by the IASP to define “central sensitization” may cause more intense pain (in case of principal pain neurons), may lead to analgesia (in case of some inhibitory nociceptive neurons), or may simply be unrelated to the sensation of pain (in case of motoneurons). Thus, the phrase “central sensitization” is not suggested for future use as a
technical term in any scientific literature on pain. The IASP also suggests that the term **central sensitization** should normally not be used in any clinical context.

**Wind-Up**

Ongoing discharges in C-fibers at rates around 0.5 and 5 impulses per second may trigger progressively increasing action potential firing in some spinal dorsal horn neurons. This “wind-up” phenomenon is due to temporal summation of excitatory postsynaptic potentials and typically lasts a few seconds only. The discharges then level off or decrease again. The winding up of discharges during the first seconds of an ongoing noxious stimulus may be useful to enforce nocifensive responses. Wind-up is a completely normal aspect of the coding properties of some spinal dorsal horn neurons and per se is neither a form of neuronal plasticity nor a mechanism of hyperalgesia or even chronic pain. Long-lasting changes in wind-up properties can be used as markers—rather than as a mechanism—of plasticity in spinal nociceptive pathways (Herrero, Laird, & Lopez-Garcia, 2000; Sandkühler, 2009).

**Expansion of Receptive Fields (to Low-Threshold Input)**

In the somatosensory system, large receptive fields are generally associated with a low spatial resolution for the respective sensation. In the nociceptive system, injury may lead to enlarged receptive fields of some spinal dorsal horn neurons (McMahon & Wall, 1984; Cook, Woolf, Wall, & McMahon, 1987). The phenomenon of enlarged receptive fields may result from an array of mechanisms, including enhanced excitability, reduced inhibition, or LTP at synapses converging onto the neuron under study or elsewhere in the neuronal circuitry. A potential correlate of enlarged receptive fields has been reported in humans after induction of hyperalgesia with capsaicin. Capsaicin impaired the two-point discrimination ability for non-noxious, tactile stimuli and reduced the ability to detect differences of the roughness of various stimulation surfaces only within the capsaicin-treated area (area of primary hyperalgesia) (Kauppila, Mohammadian, Nielsen, Andersen, & Arendt-Nielsen, 1998). The clinical relevance of this finding is presently unknown.

**Sprouting of Low-Threshold Myelinated Afferents**

Low-threshold mechanosensitive Aß-fiber afferents terminate in laminae II inner, III, and IV. It has been proposed that after nerve injury low-threshold mechanosensitive Aß-fibers would extensively sprout into more superficial laminae I and II outer and make synaptic contact with nociceptive specific neurons. This would then lead to Aß-fiber-mediated allodynia (Woolf, Shortland, & Coggeshall, 1992). Nerve injury does, however, change the phenotype of C-fibers, so that the marker used to label Aß-fibers (the B unit of the choleratoxin) now also labels C-fibers. This phenotypic switch in C-fibers, rather than sprouting of Aß-fibers, largely explains that the label was found extensively in superficial layers after nerve injury (Bao et al., 2002; Hughes, Scott, Todd, & Riddell, 2003). Labeling of individual Aß-fiber afferents suggested, however, that sprouting of Aß-fibers into superficial lamina does occur but to a rather minor extent. Opening of preexisting polysynaptic pathways between deep and superficial spinal dorsal horn neuron appears, as outlined earlier,
to be functionally more important than sprouting of Aβ-fibers (Baba, Doubell, & Woolf, 1999; Schoffnegger et al., 2008).

**New Therapeutic Targets**

The new insights into the roles of neuroinflammation and neuroplasticity in pain have paved novel paths for the prevention (preemptive strategies) and treatment (confinement strategies) of chronic pain conditions. Neuroinflammation and neuroplasticity are probably involved in all forms of clinically relevant pain and can be targeted by an array of strategies. Preemptive strategies aim at changing the expected course of neuroinflammation and neuroplasticity in pain. These strategies are typically attempted in situations that are known to often cause chronic pain such as herpes zoster neuralgia, some forms of chemotherapy, and surgeries. Any preemptive strategy needs to be implemented in time and for sufficiently long periods of time to effectively interfere with the anticipated pathomechanisms of chronic pain. In contrast, confinement strategies are employed while the pain etiopathology is in full course, sometimes for month or years. They aim at limiting the intensity, frequency, spread, and/or duration of existing chronic pain.

**Targeting Neuroinflammation**

**Preemptive Strategies for Neuroinflammation**

Recent studies have addressed the question of whether preemptive tackling of neuroinflammation has any beneficial effects on the incidence of neurodegenerative or neurovascular diseases, traumatic head or spinal cord injuries, or infections. Epidemiologic studies revealed mixed effects of preemptively depressing neuroinflammation on the risk of developing Alzheimer’s disease (Heneka et al., 2015), Parkinson’s disease (Leith, Wilson, You, Lumb, & Donaldson, 2014), other neurodegenerative diseases, or cardiovascular diseases (Awan & Genest, 2015). Neurogenic neuroinflammation directly results from enhanced neuronal activity (Xanthos & Sandkühler, 2014). It can thus be tackled by blocking or normalizing the underlying neuronal activity, very similar to preventing neurogenic neuroplasticity (as discussed in the next paragraphs). In the context of nociception, only few studies have addressed the potential effects of preemptive depression of neuroinflammation. Pretreatment with preferential cyclooxygenase-1 or -2 inhibitors before swim-stress in rats reduces both the increase in spinal prostaglandin E2 levels and thermal hypersensitivity. This suggests that preempting spinal neuroinflammation can prevent some forms of hyperalgesia (Guevara, Fernandez, Cardenas, & Suarez-Roca, 2015).

**Confinement Strategies for Neuroinflammation**

Recent studies have identified a number of targets that limit or reverse neuroinflammation in animal models of chronic pain. Minocycline, a semisynthetic tetracycline, not only exerts antibiotic properties but also inhibits the release of pro-inflammatory cytokines from activated microglia. A large number of animal studies suggest that minocycline is beneficial for various forms of neuropathic, traumatic, and inflammatory pain (for a review, see Bastos, de Oliveira, Watkins, Moraes, & Coelho, 2012). Minocycline has been a
clinically approved drug for over 30 years, and thus in principle it is also available for off-label use in human pain patients. The potential usefulness of other approved drugs that interfere with neuroinflammation may well be worth testing in patients with chronic pain. Examples are drugs that act on the progesterone receptor. In spinal cord injured rats, progesterone reduces overexpression of the mRNAs of interleukin 1β and interleukin 6, tumor necrosis factor, inducible nitric oxide synthase and cyclooxygenase 2, and thus neuroinflammation (Labombarda et al., 2015). There are also more experimental approaches to block neuroinflammation. For example, resolvins are anti-inflammatory lipid mediators generated during the resolution phase of an inflammation. Resolvins E1 and D1 can effectively dampen neuroinflammation and postoperative pain (Xu et al., 2010; Ji, Xu, Strichartz, & Serhan, 2011). Another example is the intrathecal injection of bone marrow stromal cells. This alleviates mechanical and thermal hypersensitivity in rats with a chronic constriction injury by secreting transforming growth factor-β1 into the cerebrospinal fluid (Chen, Park, Xie, & Ji, 2015). Transforming growth factor-β1 is an anti-inflammatory cytokine that potently inhibits the activation and proliferation of microglia and astrocytes. It thereby reduces the expression of proinflammatory cytokines under various conditions, including neuropathic pain (Echevery et al., 2009; Chen et al., 2013). CD200 is a membrane glycoprotein of the immunoglobulin superfamily with immune suppression effects via its receptor CD200R that dampen microglia activation. Intrathecal application of CD200 fusion protein reduces mechanical and thermal hypersensitivity in animals with a neuropathy (Bennett, 1994). Finally, i.t. injections of curcumin, an anti-inflammatory component of turmeric, reduces the activation of glial cells and the production of inflammatory mediators, including interleukin-1β, monocyte chemoattractant protein-1, and monocyte inflammatory protein-1 in the spinal cord after inflammation of a hindpaw. This treatment also reverses hyperalgesia in arthritic rats (Chen et al., 2015).

Targeting Neuroplasticity

Preemptive Strategies for Neuroplasticity

In principle, neuronal plasticity that is triggered by neuronal activity (i.e., neurogenic neuroplasticity) can be prevented by any means that reduces or abolishes the causative activity. In case of nociceptor-driven neuroplasticity, local anaesthetic infiltrations of injured tissues, sensory nerves, plexuses, or spinal cord appear straightforward for preventing neuroplasticity. Their usefulness is, however, limited by incomplete blocks and by their notoriously short duration of action. The release of neuromediators from the central terminals of nociceptive nerve fibers can be inhibited presynaptically, for example, with agonists acting at µ-opioid receptors (Terman, Eastman, & Chavkin, 2001) or α2-adrenergic receptors (Ge et al., 2006), thereby blocking the induction of activity-dependent plasticity in nociceptive pathways. Enhancing endogenous antinociceptive and/or reducing pro-nociceptive systems can likewise prevent or reduce the development of neurogenic neuroplasticity (You et al., 2016; Drake, Hulse, Lumb, & Donaldson, 2014). Long-term potentiation at C-fiber synapses and hyperalgesia can further be blocked by preventing postsynaptic rise in Ca2+, for example, by NMDA receptor antagonists (Ikeda et al., 2003, 2006) or ryanodine receptors (Cheng, Lu, Zhang, & Zhao, 2010; Ohsawa & Kamei, 1999).
Deep surgical anaesthesia under the volatile anaesthetics isoflurane or sevoflurane is, however, insufficient to prevent LTP induction at C-fiber synapses (Benrath, Brechtel, Martin, & Sandkühler, 2004; Ikeda et al., 2006). Interestingly, the anaesthetic noble gas Xenon is highly effective in preventing LTP induction (Benrath, Kempf, Georgieff, & Sandkühler, 2007), probably because of its NMDA receptor blocking effect. Up to now the translation of these findings into clinical practice has largely failed. The reasons for this failure are presently unknown.

Confinement Strategies for Neuroplasticity

Synaptic LTP is long-lasting but not necessarily permanent. Many forms of LTP vanish over time periods of hours or days, whereas some may persist for longer. From a therapeutic point of view, reversal of LTP can be important in cases where LTP contributes to pain amplification or chronicity. LTP at C-fiber synapses has been reversed by conditions such as stimulation at Aδ-fiber intensity (Liu, Morton, Azkue, Zimmermann, & Sandkühler, 1998), by a brief, systemic application of a very high dose of a µ-opioid receptor agonist (Drdla-Schutting, Benrath, Wunderbaldinger, & Sandkühler, 2012) or by diazepam (Hu et al., 2006); for a review, see Sandkühler and Lee (2013).

References


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