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J Pain. Author manuscript; available in PMC 2010 September 1.

Published in final edited form as:
J Pain. 2009 September ; 10(9): 895–926. doi:10.1016/j.jpain.2009.06.012.

Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity

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Abstract

Central sensitization represents an enhancement in the function of neurons and circuits in nociceptive pathways caused by increases in membrane excitability and synaptic efficacy as well as to reduced inhibition and is a manifestation of the remarkable plasticity of the somatosensory nervous system in response to activity, inflammation, and neural injury. The net effect of central sensitization is to recruit previously subthreshold synaptic inputs to nociceptive neurons, generating an increased or augmented action potential output: a state of facilitation, potentiation, augmentation, or amplification. Central sensitization is responsible for many of the temporal, spatial, and threshold changes in pain sensibility in acute and chronic clinical pain settings and exemplifies the fundamental contribution of the central nervous system to the generation of pain hypersensitivity. Because central sensitization results from changes in the properties of neurons in the central nervous system, the pain is no longer coupled, as acute nociceptive pain is, to the presence, intensity, or duration of noxious peripheral stimuli. Instead, central sensitization produces pain hypersensitivity by changing the sensory response elicited by normal inputs, including those that usually evoke innocuous sensations.

Perspective—In this article, we review the major triggers that initiate and maintain central sensitization in healthy individuals in response to nociceptor input and in patients with inflammatory and neuropathic pain, emphasizing the fundamental contribution and multiple mechanisms of synaptic plasticity caused by changes in the density, nature, and properties of ionotropic and metabotropic glutamate receptors.

Keywords

Central sensitization; inflammatory pain; neuropathic pain; scaffolding protein; heterosynaptic facilitation

Acute nociceptive pain is that physiological sensation of hurt that results from the activation of nociceptive pathways by peripheral stimuli of sufficient intensity to lead to or to threaten tissue damage (noxious stimuli).[374] Nociception, the detection of noxious stimuli,[282] is a protective process that helps prevent injury by generating both a reflex withdrawal from the stimulus and as a sensation so unpleasant that it results in complex behavioral strategies to avoid further contact with such stimuli. An additional important phenomenon that further enhances this protective function is the sensitization of the nociceptive system that occurs after repeated or particularly intense noxious stimuli, so that the threshold for its activation falls and responses to subsequent inputs are amplified.[132,376,380] In the absence of ongoing tissue injury,

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Editor's Note: This article is 1 in a series of invited Critical Review articles designed to celebrate *The Journal of Pain*'s 10th year anniversary of publication.

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this state of heightened sensitivity returns over time to the normal baseline, where high-intensity stimuli are again required to initiate nociceptive pain; the phenomenon is long lasting but not permanent. The nociceptor-induced sensitization of the somatosensory system is adaptive in that it makes the system hyperalert in conditions in which a risk of further damage is high, for example, immediately after exposure to an intense or damaging stimulus. This sensitization is the expression of use-dependent synaptic plasticity triggered in the central nervous system (CNS) by the nociceptor input and was the first example of central sensitization, discovered 26 years ago.[369] Since then, we have learned that a number of different forms of functional, chemical, and structural plasticity can sensitize the central nociceptive system to produce pain hypersensitivity under both normal and pathological circumstances, some of which are persistent.

In many clinical syndromes, pain is no longer protective. The pain in these situations arises spontaneously, can be elicited by normally innocuous stimuli (allodynia), is exaggerated and prolonged in response to noxious stimuli (hyperalgesia), and spreads beyond the site of injury (secondary hyperalgesia). Central sensitization has provided a mechanistic explanation for many of the temporal, spatial, and threshold changes in pain sensibility in acute and chronic clinical pain settings and has highlighted the fundamental contribution of changes in the CNS to the generation of abnormal pain sensitivity. Although phenomenologically central sensitization may appear to be comparable to peripheral sensitization, it differs substantially, both in terms of the molecular mechanisms responsible and its manifestation. Peripheral sensitization represents a reduction in threshold and an amplification in the responsiveness of nociceptors that occurs when the peripheral terminals of these high-threshold primary sensory neurons are exposed to inflammatory mediators and damaged tissue[46,105,124,242] and, in consequence, is restricted to the site of tissue injury.[124] Although peripheral sensitization certainly contributes to the sensitization of the nociceptive system and thereby to inflammatory pain hypersensitivity at inflamed sites (primary hyperalgesia), it nevertheless represents a form of pain elicited by activation of nociceptors, albeit one with a lower threshold due to the increased peripheral transduction sensitivity, and generally requires ongoing peripheral pathology for its maintenance. Peripheral sensitization appears to play a major role in altered heat but not mechanical sensitivity, which is a major feature of central sensitization.

Central sensitization, in contrast to peripheral sensitization, co-opts novel inputs to nociceptive pathways including those that do not normally drive them, such as large low-threshold mechanoreceptor myelinated fibers to produce Aβ fiber–mediated pain.[376] It also produces pain hypersensitivity in noninflamed tissue by changing the sensory response elicited by normal inputs and increases pain sensitivity long after the initiating cause may have disappeared and when no peripheral pathology may be present. Because central sensitization results from changes in the properties of neurons in the CNS, the pain is no longer coupled, as acute nociceptive pain is, to the presence, intensity, or duration of particular peripheral stimuli. Instead, central sensitization represents an abnormal state of responsiveness or increased gain of the nociceptive system. The pain is effectively generated as a consequence of changes within the CNS that then alter how it responds to sensory inputs, rather than reflecting the presence of peripheral noxious stimuli. In this respect, central sensitization represents a major functional shift in the somatosensory system from high-threshold nociception to low-threshold pain hypersensitivity. We all experience pain as arising from “out there,” and, in consequence, imagine that it is actually triggered by noxious stimuli where we feel the pain. Central sensitization reveals, however, that this in many cases is a sensory illusion; specific alterations in the CNS can result in painful sensations occurring in the absence of either peripheral pathology or noxious stimuli, and the target for treatment in these situations must be the CNS not the periphery.

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Central sensitization corresponds to an enhancement in the functional status of neurons and circuits in nociceptive pathways throughout the neuraxis caused by increases in membrane excitability, synaptic efficacy, or a reduced inhibition. The net effect is that previously subthreshold synaptic inputs are recruited to generate an increased or augmented action potential output, a state of facilitation, potentiation, or amplification. The reason that these cellular changes alter the system so profoundly is that normally only a small fraction of the synaptic inputs to dorsal horn neurons contribute to their action potential output.[373] Nociceptive-specific neurons, for example, although dominated by large monosynaptic and polysynaptic synaptic potentials from nociceptors in their receptive field, typically also have small-amplitude synaptic inputs from low-threshold afferents and from nociceptor inputs outside their receptive fields, which constitute a subliminal fringe that normally does not drive the output of the cells (Fig 1). Recruiting these subthreshold inputs to the output of a neuron markedly alters its receptive field properties, with profound changes in receptive field threshold, spatial, and temporal properties (Fig 2). This provides an opportunity for rapid functional plasticity that can be revealed experimentally by increasing the excitability of the neuron or by blocking inhibitory transmitters. After administration of GABA or glycine receptor antagonists, for example, Aβ inputs are recruited to neurons in the superficial dorsal horn,[17] and pain-like behavior can be elicited by movement of just a few hairs.[289] The receptive field of somatosensory neurons are, therefore, not fixed or hard wired, but are instead highly malleable. This malleability or plasticity is the substrate for the functional effects of central sensitization, and the means is a change in synaptic efficacy.

When neurons in the dorsal horn spinal cord are subject to central sensitization, they exhibit some or all the following: development of or increases in spontaneous activity, a reduction in the threshold for activation by peripheral stimuli, increased responses to suprathreshold stimulation, and an enlargement of their receptive fields (Fig 2). Several features appear particular to central sensitization: conversion of nociceptive-specific neurons to wide-dynamic neurons that now respond to both innocuous and noxious stimuli, progressive increases in the responses elicited by a standard series of repeated innocuous stimuli (temporal windup), an expansion of the spatial extent of their input, and changes that outlast an initiating trigger.[132,368,369,372,376] These electrophysiological changes correlate remarkably with the development in human experimental subjects after a noxious conditioning input of allodynia (particularly dynamic tactile or brush-evoked allodynia), the temporal summation of repeated low-intensity stimuli from an innocuous sensation to pain, with “afterpain” on cessation of the stimulus, and widespread secondary hyperalgesia. These changes can be elicited in human volunteers by noxious stimulation of the skin (as with topical or intradermal capsaicin or repeated heat stimuli[340]) and in the gastrointestinal tract by exposure to low pH solutions.[272]

Central sensitization contributes to neuropathic[37] and inflammatory pain,[26,274,395] migraine,[35] and irritable bowel syndrome.[253] In these patients, it is involved in producing abnormal responsiveness to noxious and innocuous stimuli and a spread of tenderness beyond lesion sites. Central sensitization may also play a fundamental role in the abnormal and widespread pain sensitivity in patients with fibromyalgia.[6,68,301-303] Given the major role of central sensitization in the generation of clinical pain hypersensitivity, it is essential that we understand the triggers and mechanisms responsible for the induction and maintenance of the switch in the somatosensory system from the physiological state, in which the sensory experiences evoked by low-intensity stimuli (innocuous sensations) and noxious stimuli (pain) are quite distinct and separate, to a dysfunctional hypersensitive system in which this discrimination is lost.

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The Discovery of Central Sensitization

The first evidence for a central component to acute pain hypersensitivity was provided in 1983.[369] Electrophysiological recordings from single biceps femoris α-motoneuron axons were used to measure the output of the nociceptive system, in this case the flexor reflex withdrawal response elicited by noxious stimuli (Fig 3). These recordings revealed, as expected, that under normal conditions there was no spontaneous activity in the motor neurons and that their activation required a noxious mechanical or thermal stimulus to the skin. These neurons had high-threshold nociceptive-specific receptive fields restricted to the toes or hind paw, in keeping with their activation only as part of the flexion withdrawal reflex. After repeated peripheral noxious heat stimuli sufficient to generate mild inflammation of the hind paw, however, an increased excitability of the motor neurons was detected that lasted for several hours and included a reduction in threshold and enlargement of the cutaneous receptive fields. The flexor motor neurons were now no longer nociceptive-specific but could be activated by low-intensity (innocuous) peripheral inputs such as light touch.[369] Three experiments showed that this change in receptive field properties was due to alterations in the CNS and not the periphery. First, electric stimulation of Aβ sensory fibers began to elicit responses in the motor neurons after the conditioning noxious heat stimuli, whereas these inputs elicited no response before. Second, a local anesthetic block of the site of the peripheral injury did not result in collapse of the expanded receptive fields: The change was autonomous once it was triggered by the peripheral input. Finally, the hypersensitivity produced by the noxious heat could be mimicked in extent and duration by a brief 20-second low-frequency electrical stimulation of the sural nerve only at C-fiber strength, which produced changes lasting for tens of minutes. The interpretation of all these data was that noxious heat stimulation, by activating C-fiber nociceptors, had induced a central plasticity of the nociceptive system, which was thereafter capable of responding to stimuli outside of the injury area and to low-threshold afferents that previously did not activate the nociceptive system. This led to the articulation of a more general hypothesis that brief trains of nociceptor C-fiber input could trigger or condition a long-lasting sensitization of the nociceptive system (an effect termed central sensitization) by producing activity-dependent changes in the functional properties of neurons in the dorsal horn of the spinal cord and that this contributed both to postinjury flexor reflex and pain hypersensitivity.

Before the discovery of central sensitization, the receptive field properties of dorsal horn neurons was thought to be fixed by the geometry of their dendrites relative to the central terminals of sensory axons.[33] Although plasticity of the receptive fields of dorsal horn neurons had been shown to occur after peripheral nerve injury, this was thought to be due to a loss of presynaptic inhibition increasing synaptic input from silent or ineffective synapses and not to plasticity in dorsal horn neurons.[71] After the first demonstration of central sensitization in flexor motor neurons, essentially identical changes were soon described in many studies in lamina I and V neurons in the dorsal horn of the spinal cord[55,79,173,176,192,287,365,372] (Fig 3) as well as in spinal nucleus pars caudalis (Sp5c),[36] thalamus[78] (Fig 3), amygdala,[219,220] and anterior cingulate cortex.[364] More recently, functional magnetic resonance imaging, positron emission tomography, and magnetoencephalography have revealed in human subjects that several other brain structures implicated in pain (parabrachial nucleus, periaqueductal gray [PAG], superior colliculus, prefrontal cortex) also exhibit changes compatible with increases in excitability corresponding to central sensitization[187,209,212,244,283] (Fig 3).

Activity-Dependent Central Sensitization

The original description of central sensitization referred to an activity- or use-dependent form of functional synaptic plasticity that resulted in pain hypersensitivity after an intense noxious stimulus. This plasticity was triggered by the activity evoked in dorsal horn neurons by input

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from C-nociceptors, as after repeated heat stimuli above 49°C,[369] electrical stimulation of C-fibers (1 Hz for 10 to 20 seconds),[358] and chemical activation of nociceptors by irritant compounds such as allyl isothiocyanate (mustard oil)[372] and formalin, which both act through the TRPA1 channel[135,199] as well as capsaicin, which activates TRPV1 channels.[158] To induce central sensitization, the noxious stimulus must be intense, repeated, and sustained. Input from many fibers is required over tens of seconds; a single stimulus, such as a pinch, is insufficient. Peripheral tissue injury is not necessary, although the degree of noxious stimulation that produces frank tissue injury almost always induces central sensitization, so that the phenomenon is very prominent after post-traumatic or surgical injury. Interestingly, nociceptor afferents innervating muscles or joints produce a longer-lasting central sensitization than those that innervate skin.[358]

Once the phenomenon had been shown to be robust, easily activated, and detected in both preclinical and human subjects, the issue then was what molecular mechanisms were responsible. The first major mechanistic insight was that the induction and maintenance of acute activity-dependent central sensitization was dependent on NMDA receptors,[379] revealing a key involvement of glutamate and its receptors. We now appreciate from 2 decades of investigation by many labs that central sensitization comprises 2 temporal phases, each with specific mechanisms. The early phosphorylation-dependent and transcription-independent phase results mainly from rapid changes in glutamate receptor and ion channel properties.[376] The later, longer-lasting, transcription-dependent phase drives synthesis of the new proteins responsible for the longer-lasting form of central sensitization observed in several pathological conditions.[376] We will review the current understanding of these mechanisms.

Triggers of Activity-Dependent Central Sensitization

Glutamate, the fast transmitter of primary afferent neurons, binds to several receptors on postsynaptic neurons in the dorsal horn of spinal cord, including ionotropic amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), N-methyl-D-Aspartate (NMDA), and Kainate (KA) receptors and several metabotropic (G-protein coupled) glutamate receptor subtypes (mGluR). In the superficial laminae of the dorsal horn, AMPAR and NMDAR are present in virtually every synapse and are arranged in a mosaic-like manner, whereas mGluRs sit at the extremities of the postsynaptic density zone (PSD).[10,11,15,247] At the subunit level, NMDAR is a tetramer that contains 2 low-affinity glycine-binding NR1 subunits and 2 subunits from the 6 different $NR2_{A\text{-}D}$ or $NR3_{A/B}$ subunits.[305] The most common NMDA complexes in the dorsal horn are composed of NR1-$NR2_{A/B}$ subunits.[202,215,243] AMPAR is also a tetramer, and its most abundant subunits in the dorsal horn of the spinal cord are the calcium (Ca^{2+})-permeable subunits GluR1 and GluR3 and the non–Ca^{2+}-permeable GluR2 subunit.[252] In basal conditions, inhibitory interneurons appear to preferentially express GluR1, whereas the excitatory neurons appear to express mostly GluR2.[145,338] The AMPAR complex can also be a GluR1/GluR2 heteromer,[11] in which case the receptor displays mainly GluR2 properties.[233] A subpopulation of lamina I neurons lacking the NK1 receptor and expressing the GluR4 (Ca^{2+}-permeable) subunit has been identified.[248] The mGluR family is composed of 8 receptors that form 3 groups, based on their sequence similarities and their coupling with specific Gα-proteins.[54] Group I mGluRs (mGluR1 and 5) are coupled with Gαq-proteins (whose activation causes an increase of $[Ca^{2+}]_i$), whereas group II (mGluR 2 and 3) and group III (mGluR4, 6, 7 and 8) are coupled with Gαi/o-proteins. All mGluRs except for mGluR6 and 8 are expressed in the spinal cord,[346] whereas only mGluR6 appears not to be expressed by primary afferent neurons.[39] In addition, a lamina-specific pattern of expression has been characterized for mGluR1α (lamina V), mGluR5 (laminas I-II),[10,247] and mGluR2/3 (lamina II inner),[12] suggesting precise and distinct physiological roles for the different subtypes.

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Activation of NMDAR is an essential step in both initiating and maintaining activity-dependent central sensitization as its blockade by noncompetitive (MK801) or competitive (D-CPP) NMDAR antagonists prevent and reverse the hyperexcitability of nociceptive neurons induced by nociceptor conditioning inputs[184,379] and conditional deletion of NR1 abolishes NMDA synaptic inputs and acute activity-dependent central sensitization.[300] NMDAR is both a trigger and effector of central sensitization. Under normal conditions, the NMDAR channel is blocked in a voltage-dependent manner by a magnesium (Mg^{2+}) ion sitting in the receptor pore.[198] Sustained release by nociceptors of glutamate and the neuropeptides substance P and CGRP leads to sufficient membrane depolarization to force Mg^{2+} to leave the NMDAR pore, whereupon glutamate binding to the receptor generates an inward current.[198] Removal of this voltage-dependent block is a major mechanism for rapidly boosting synaptic efficacy and allows entry of Ca^{2+} into the neuron, which then activates numerous intracellular pathways that then contribute to the maintenance of central sensitization. In addition to the critical role of NMDAR in increasing the excitability nociceptive neurons, activation of group I mGluRs by glutamate also appear important for the development of central sensitization. Although these receptors do not participate to basal nociception,[221,392] their activation is necessary for activity-dependent central sensitization mediated by C-fibers.[14,67,165,296,392,393] In contrast, activation of group II-III mGluRs is associated with a reduction of capsaicin-induced central sensitization.[296]

Substance P (SP), which is co-released with glutamate by unmyelinated peptidergic nociceptors, is also involved in the generation of central sensitization.[8,146,183,192,365] Substance P binds to the neurokinin-1 (NK1) G-protein–coupled receptor, which is expressed by spinothalamic, spinoparabrachial, and spino-PAG neurons[101] and causes a long-lasting membrane depolarization,[112] and contributes to the temporal summation of C-fiber–evoked synaptic potentials[80,388,389] as well as to intracellular signaling. Ablation of NK1-positive neurons in the spinal cord leads to a reduction in capsaicin-evoked central sensitization, confirming the importance of projecting neurons expressing the substance P receptor in this phenomenon.[146,192] Calcitonin gene-related peptide (CGRP), also synthesized by small diameter sensory neurons, potentiates the effects of SP[367] and participates in central sensitization through postsynaptic CGRP1 receptors, which activate PKA and PKC.[307,308] CGRP also enhances release of brain-derived neurotrophic factor (BDNF) from trigeminal nociceptors,[34] which may contribute to its involvement in migraine and other primary headaches.[82,103]

BDNF is a neurotrophic factor and synaptic modulator that is synthesized by nociceptor neurons and released into the spinal cord[404] in an activity-dependent manner,[19] where it also has a role in the production of central sensitization.[113,144,330] On binding to its high-affinity trkB receptor, BDNF enhances NMDAR-mediated C-fiber–evoked responses[144] and causes activation of several signaling pathways in spinothalamic track neurons, including ERK[141,245,292] and PKC.[293]

The inflammatory kinin bradykinin is produced in the spinal cord in response to intense peripheral noxious stimuli and acts through its G_q-coupled B2 receptor, which is expressed by dorsal horn neurons[41,359] and boosts synaptic strength by activating PKC, PKA, and ERK.[152] ERK is also activated by a serotoninergic (5-HT) descending input involving the ionotropic 5-HT_3 receptor[143,310,313,396] and possibly the 5-HT_7 G_S-coupled receptor.[29] Fig 4 summarizes the key known synaptic triggers of central sensitization.

Signaling Pathways and Activity-Dependent Central Sensitization

An increase in intracellular Ca^{2+} beyond a certain threshold level appears to be the key trigger for initiating activity-dependent central sensitization. Calcium influx through NMDAR

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appears to be particularly prominent in the induction phase but can also occur through calcium-permeable AMPARs,[159,355] voltage-gated calcium channels,[52,376] as well as from release from intracellular microsomal stores in response to activation of several metabotropic receptors[106,182] (Fig 5, A through C). Why is the calcium-induced activation of intracellular kinases so important? The reason is that ionotropic NMDA and AMPA glutamate receptors can be phosphorylated on several key residues located on their C-terminus,[40,42] and this post-translational modification changes their activity as well as their trafficking to or from the membrane,[40,161] which with similar post-translational changes in other ion channels, produces the functional changes that manifest as central sensitization (Fig 6, A through C). AMPAR subunit GluR1 residue Ser831 is phosphorylated by protein kinase C (PKC) and calcium-calmodulin-dependent protein kinase II (CaM-KII); Ser845 is the phosphorylation target of PKA, and GluR2 has 1 main site for phosphorylation by PKC, on Ser880.[40] For the NR1 subunit of NMDAR, PKC phosphorylates Ser896, whereas PKA has 2 potential phosphorylation sites on Ser890 and Ser897.[168,333] NMDAR conductance properties are modified by phosphorylation of tyrosine residues located on the NR2A and NR2B subunits at 3 potential sites (Tyr1292, 1325, or 1387 for NR2A and Tyr1252, 1336, or 1472 for NR2B), through activation of nonreceptor tyrosine kinases such as Src or Fyn.[42,106,107,268]

Stimulation of AMPAR and group I mGluRs[89,106,118,281] participate with NMDAR in the activation of the intracellular pathways that sustain central sensitization. These include the PLC/PKC pathway, through opening of Ca^{2+} channels on the endoplasmic reticulum,[85,391] the phosphatidylinositol-3-kinase (PI3 K) pathway,[246] and the mitogen-activated protein kinase (MAPK) pathway that involves the extracellular signal-regulated kinases (ERK1 and ERK2), which are 44- and 42-kDa Ser/Thr kinases, respectively, with 90% sequence identity, and the cAMP response element binding protein (CREB).[130,138,141,357,363] One way that ERK and CREB are activated is through an elevation in intracellular Ca^{2+} sufficient to drive a calmodulin-induced stimulation of adenylyl cyclases 1 and 8, whose cAMP production in turn activates PKA and subsequent cascade(s).[363]

The activation of ERK by phosphorylation is regulated by a core signaling module that consists of an apical MAPK kinase kinase (MAP3 K), a MAPK kinase (MEK or MKK), and the downstream ERK. Many different signaling pathways can induce ERK activation in addition to its canonical *ras/raf* pathway, and this can be readily detected immunohistochemically in the dorsal horn within minutes of peripheral noxious stimuli[130] (Fig 7). The presence of phosphorylated ERK reveals the anatomical distribution of those neurons whose intracellular signaling has been activated by the nociceptor input and are presumably undergoing the synaptic changes that constitute central sensitization[120,131,141,152] (Fig 7). In the spinal cord, ERK is only activated in neurons in response to intense peripheral noxious stimulation, effectively identical to those stimuli that induce central sensitization,[130,363] suggesting that ERK phosphorylation is a better marker of the neural plasticity that mediates central sensitization than c-*Fos*, which can be activated by low threshold stimuli that do not induce central sensitization.[126] Because the ERK pathway is composed of successive protein kinases, each of which can be activated by several different signaling pathways,[131] most of the triggers of central sensitization such as NMDAR, group I mGluR, TrkB, NK1, or CGRP1 converge to activate ERK[120,130,131,171] (Fig 8). Once activated, ERK produces translational and post-translational effects that participate in the maintenance of central sensitization in spinal cord neurons.[131,387] The post-translational effects include an increase of NMDAR function through phosphorylation of its NR1 subunit[152,293] (Fig 6, A), recruitment of AMPAR to the membrane[93,254] (Fig 6, B) leading to an increase in AMPAR, and NMDAR currents boosting synaptic efficacy.[152] Furthermore, ERK produces a decrease in K^+ currents through phosphorylation of the residue Ser616 of Kv4.2 channels leading to an increase in membrane excitability[118,119] (Fig 6, A). Transcriptional changes are mediated by activation of CREB as well as other transcription factors, which drives expression of several genes including c-*Fos*,

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NK1, TrkB, and Cox-2[131] (Fig 6, C). Inhibition of ERK activation using inhibitors of MEK reduces behavioral measures of activity-dependent central sensitization.[137,142]

Nitric oxide (NO) synthesized by either neuronal or inducible NO synthases in the dorsal horn[381] also has a role in central sensitization.[381-383] Potential mechanisms for NO actions include the cGMP synthesis cascade, nitrosylation of membrane channels, ADP-ribosylation, and production of reactive species.[64,278] The NO-cGMP pathway involves soluble guanylate cyclase, which is expressed by NK1-positive spinothalamic neurons, as well as inhibitory interneurons.[73] Fig 8 summarizes key intracellular pathways whose activation contributes to the generation of central sensitization.

Effectors of Activity-Dependent Central Sensitization

AMPAR and NMDAR phosphorylation during central sensitization increases the activity/density of these receptors, leading to postsynaptic hyperexcitability.[32,86-88,134,178,345,394,407,408] The first phase of central sensitization is a fast augmentation of excitatory glutamatergic synapses in the superficial dorsal horn that strengthens nociceptive transmission and recruits non-nociceptive input to the pathway. This is achieved by phosphorylation of numerous receptor and ion channel targets that lead to changes in threshold, channel kinetics, and voltage dependence, as well as a modification in the trafficking of the receptors to the synapse (Fig 6, A and B). On noxious stimulation, PKA phosphorylates GluR1 subunits,[87,88,214] leading to an insertion of these receptors into the synapse[84,93] and thereby an increase in synaptic strength.[20] Phosphorylation of GluR1-containing AMPAR by PKC and CaMKII also increases the excitability of nociceptive neurons.[40,88]

NR1 phosphorylation by PKA[408] or PKC[32,407] participates in the development of hypersensitivity[97,262,345] by increasing the response of NMDARs to glutamate.[44,259] Phosphorylation of the NR2B subunit of NMDAR, mediated through Src activation, increases the opening of the receptor channel[268] and prevents endocytosis of activated receptors by disrupting the binding site of AP-2, a protein involved in clathrin-coated endocytosic vesicle formation.[42] Decoupling Src interaction with NMDAR blocks NR2B phosphorylation and reduces formalin-induced and inflammatory pain without altering basal nociceptive pain.[178]

Activation of PKC contributes to hyperexcitability in nociceptive neurons by several different pathways. First, PKC reduces the Mg^{2+} block of NMDAR and increases the probability of channel opening, facilitating the activated state of NMDAR.[44] Second, activation of PKC decreases inhibitory transmission at the segmental level by reducing GABA and glycine tonic inhibition[174] and the descending inhibition driven from the PAG.[175] Disinhibition, mediated by whatever means, leaves dorsal horn neurons more susceptible to activation by excitatory inputs including non-nociceptive A-fibers, and is 1 of the major mechanisms triggering and maintaining central sensitization.[17,289,341,390] Finally, PKC contributes with PKA to the activation of ERK in a manner that requires their coactivation and is triggered by the central release of bradykinin.[152]

Activation of guanylate cyclase seems to be the major way that NO contributes to the induction of sensitization[275,322,403] through increases in neuronal excitability and a reduction in inhibition,[173,176,275] although an NO-mediated activation of ADP-ribosyltransferase may participate in the maintenance of central sensitization.[403]

Global Features of Activity-Dependent Central Sensitization

The key features of acute activity-dependent central sensitization are that it is induced with a short latency (seconds) by intense, repeated, or sustained nociceptor inputs and typically lasts for tens of minutes to several hours in the absence of further nociceptor input. It generally

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requires activation of NMDA receptors for its induction, and these receptors contribute to its maintenance. Nevertheless, as reviewed above, multiple different triggers can contribute to the establishment of this form of central sensitization: glutamate acting on NMDAR, but also on AMPAR and mGluR, the neuropeptides substance P and CGRP, the kinin bradykinin, as well as BDNF and NO (Fig 4). The reason so many different transmitters, modulators, and their receptors are involved is that it is not their specific action that is important but rather that they are released directly from or induced in response to nociceptor afferent activity, and each can separately or together initiate the activation of those multiple intracellular signaling pathways that lead to the establishment of hyperexcitability in dorsal horn neurons (Figs 6 and 8). In other words, there are many parallel inputs to dorsal horn neurons that can independently or cooperatively initiate central sensitization. Elevation in intracellular calcium, by whatever means, is 1 major trigger, activating multiple calcium-dependent kinases that act on receptors and ion channels to increase synaptic efficacy (Figs 5 and 6). Many central sensitization-inducing inputs also activate ERK, and this MAPK appears to have a pivotal role, contributing to increases in AMPA and NMDA currents as well as reducing potassium currents (Fig 6, A). However, even this kinase may not be essential. Other kinases such as PKC, PKA, and Src can, independent of ERK, also modulate ionotropic receptors to lead to an increase in synaptic efficacy (Fig 6, A).

What has become clear is that there is no single defining molecular mechanism of central sensitization but rather that it is a general phenomenon, one that produces distinct changes in somatosensory processing but nevertheless can be mediated by several different processes that, in response to nociceptor input, can (1) increase membrane excitability, (2) facilitate synaptic strength, or (3) decrease inhibitory influences in dorsal horn neurons. Similarly, the effectors of this plasticity are multiple: changes in the threshold and activation kinetics of NMDA and AMPA receptors and in their trafficking to the membrane, alterations in ion channels to increase inward currents and reduce outward currents, and reductions in the release or activity of GABA and glycine (Fig 9). These changes produce dramatic alterations in function. However, they are usually relatively short-lasting and reversible. Phosphatases will dephosphorylate receptors and ion channels resetting their activity to baseline levels, trafficking to the membrane will reverse by endocytosis, and, with time, the increased gain of the nociceptive neurons will fade, at least in the absence of any further triggering inputs.[186,400-402] Different, transcription-dependent changes are required for longer-lasting effects, and these generally do not occur in response only to nociceptor activity but are the consequence of peripheral inflammation and nerve injury (see below). Activity-dependent central sensitization, even though it increases pain sensitivity, is in most situations an adaptive mechanism. Unlike nociceptive pain, which warns of potential damage in response to noxious stimuli, central sensitization creates a situation in which pain is elicited by innocuous stimuli. This change is protective, because it helps healing by limiting use of an injured body part until the injury is fully repaired. Central sensitization becomes pathological, however, if inflammation persists, as with rheumatoid arthritis, in which no healing occurs, and in situations in which central sensitization becomes autonomous and is maintained in the absence of active peripheral pathology. Central sensitization represents not only a state in which pain can be triggered by less intense inputs but in which the central sensitization itself can be maintained by a lower level or different kind of input. Ongoing activity in C-fibers, even at levels that do not elicit central sensitization in basal conditions, is sufficient to maintain central sensitization once it has been induced for prolonged periods (days).[153] Furthermore, although nociceptor input is required to trigger central sensitization, phenotypic changes in myelinated fibers after inflammation and nerve injury can enable these afferents to acquire the capacity to generate central sensitization (see later).

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Activity-Dependent Central Sensitization and Synaptic Plasticity

That the activity-dependent synaptic plasticity in the dorsal horn responsible for central sensitization is reversible differs from the permanent activity-dependent synaptic change in the cortex that leads to long-term memory, long-term potentiation (LTP), in which the efficacy only of activated synapses is changed. Synaptic changes with some resemblance to cortical LTP do occur in the spinal cord, that is, a form of homosynaptic potentiation. However, the major synaptic alteration underlying activity-dependent central sensitization is heterosynaptic potentiation, in which activity in 1 set of synapses enhances activity in nonactivated synapses, typically by “sensitizing” the entire neuron, something that never occurs with cortical LTP.

Homosynaptic potentiation is a type of use-dependent facilitation of a synapse evoked by activation of that same synapse (Fig 10, A). Classic LTP in the CA1 region of the hippocampus is formally defined as input-specific homosynaptic facilitation[27,164,384] and is dependent on NMDAR activation, Ca^{2+} influx, and activation of Ca^{2+}-dependent intracellular signaling pathways, notably the CaMKII pathway.[164] Although the increased Ca^{2+} is relatively widespread in neurons after tetanic conditioning stimulation of afferents,[128,182,260] only the stimulated synapse is potentiated.[164,260] The development of LTP by 2 independent synapses using asynchronous pairing stimulation has been described in the hippocampus, but, once again, only conditioned synapses are potentiated.[123]

One form of homosynaptic facilitation in spinal cord neurons is windup, in which the action potential discharge elicited by a low-frequency (0.5 to 5 Hz) train of identical C-fiber strength stimuli gets larger on each successive stimulus[200] (Fig 11). Windup is the result of the activation of NK1 and CGRP1 receptors after release of substance P and CGRP from peptidergic nociceptors to produce a cumulative membrane depolarization from the temporal summation of slow synaptic potentials.[290] This then enables activation of NMDAR by removal of the Mg^{2+} block, further boosting the responses in a nonlinear fashion[63,72,331,379] (Fig 11). The stimuli that induce windup (repeated C-fiber stimulation) can lead to central sensitization,[379] and, although windup is often considered to be an aspect of central sensitization, it is instead the reflection of activity-dependent excitability increases in neurons during a nociceptor conditioning paradigm rather than changes that follow such inputs, which is when central sensitization manifests. Windup disappears within tens of seconds of the end of the stimulus train as the membrane potential returns to its normal resting level (Fig 11).

Another form of homosynaptic facilitation occurs in NK1-positive lamina I neurons in the dorsal horn neuron. This has been termed LTP, although, unlike classic hippocampal LTP, this form of homosynaptic facilitation appears not to be persistent, or at least the functional effects on pain sensitivity are not permanent instead lasting, like central sensitization for a few hours, with no evident change equivalent to long-term memory. Perhaps, therefore, to avoid confusion with cortical plasticity, the term LTP should be avoided for homosynaptic potentiation in the spinal cord because the changes in the dorsal horn are long-lasting (hours) rather than long-term (persistent). The original description of this long-lasting homosynaptic potentiation in the dorsal horn referred to an activity-dependent facilitation of excitatory postsynaptic currents in spinoparabrachial neurons in response to high-frequency (tetanic burst; 100 Hz) stimulation of C-fibers.[127,177,271] The physiological relevance of this phenomenon was questionable because C-fibers do not fire at such high frequencies. Conditioning C-fiber stimulation at a low frequency (2 Hz) was subsequently shown also to elicit a long-lasting homosynaptic potentiation in lamina I spino-PAG neurons but not in spinoparabrachial neurons.[128] This low-frequency potentiation is dependent on elevations in Ca^{2+}, which activates PLC, PKC, CaMKII, and NOS.[128] Capsaicin and formalin injection also evoke a homosynaptic long-lasting potentiation, as manifested by an enhancement of C-fiber–evoked synaptic potentials after the capsaicin/formalin evoked conditioning input.[128] Capsaicin is, of course, also a potent

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inducer of activity-dependent central sensitization,[294,340,383] characterized by the production of secondary hyperalgesia and tactile allodynia. However, both of these particular forms of pain hypersensitivity reflect heterosynaptic and not homosynaptic facilitation. Indeed, heterosynaptic facilitation characterizes most major changes in the receptive field properties of neurons and in pain sensitivity, in preclinical models, and human subjects[368,369,376] (Fig 10, B).

Interestingly, healthy human subjects receiving high-frequency stimulation of C-fibers exhibit increased pain in the stimulated region, quite possibly caused by homosynaptic facilitation, but also show evidence of heterosynaptic facilitation, as manifested by dynamic mechanical allodynia in adjacent nonstimulated areas.[149] The combination of the homosynaptic potentiation of conditioning nociceptor inputs and the heterosynaptic facilitation of nonconditioned fibers in the nociceptive pathway constitutes central sensitization.

Heterosynaptic facilitation represents a form of activity-dependent facilitation where activity in 1 set of synapses (the conditioning input) augments subsequent activity in another nonactivated group of synapses (the test input) (Fig 10, B). For homosynaptic potentiation, the test and conditioning inputs are the same; for heterosynaptic facilitation they are different. “LTP”-like phenomena in spinobrachial neurons can only account for the augmentation of the same C-fiber inputs that evoked the facilitation and cannot contribute to either secondary hyperalgesia or tactile allodynia. Repeated nociceptor input, such as that generated by capsaicin, will simultaneously generate both a potentiation of the activated C-fiber synapses (homosynaptic), and, unlike LTP in the hippocampus, also a potentiation of neighboring nonactivated synapses (heterosynaptic). It seems likely, therefore, that long-lasting potentiation in projecting dorsal horn neurons is simply a restricted aspect of the general widespread changes induced in these neurons by nociceptor activity.

Heterosynaptic potentiation appears to dominate the functional sensory manifestations of use-dependent central sensitization. After injection of capsaicin, for example, the thresholds of sensory fibers innervating the area surrounding the injection site are not modified,[23,157,340,365] but pain hypersensitivity in these areas is prominent and depends on centrally mediated heterosynaptic facilitation. The same argument holds for the activation of pain in response to tactile stimulation or Aβ fiber inputs during central sensitization. It is no surprise, then, that spinal “LTP” shares major mechanisms with central sensitization (NMDAR, Ca^{2+}, kinases, and NO) because it is very likely that the phenomenon of central sensitization includes both homosynaptic and heterosynaptic facilitations triggered by the same process; the major difference is that heterosynaptic potentiation results from the spread of signaling from the conditioning synapse to other synapses in the neuron[182,270,371] (Fig 10, B). Homosynaptic changes will contribute with peripheral sensitization to primary hyperalgesia,[128,270] whereas heterosynaptic facilitation alone is responsible for secondary hyperalgesia and allodynia.

Although several different forms of LTP have been characterized in the hippocampus,[188,224,384] “spreading” or heterosynaptic LTP has not been reported, even though release of Ca^{2+} from intracellular stores can cause a spread of long-term depression (LTD) to neighboring, unstimulated synapses.[227] What, then, is responsible for heterosynaptic facilitation in dorsal horn neurons? Two major candidates are the activation of mGluRs and NO. mGluRs are coupled to the Ca^{2+} channels of the endoplasmic reticulum[85] and play an important role in central sensitization.[7] Consequently, the release of intracellular Ca^{2+} in spinal cord neurons on mGluR activation may participate in spreading facilitation from conditioned synapses to neighboring test synapses. NO is also a major effector of spinal cord neuronal plasticity[211,309] and diffuses rapidly from the site of its production to produce multiple effects at a distance via its downstream signaling pathways, and in this way may contribute to the heterosynaptic facilitation characteristic of central sensitization. It is certainly likely that these

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and other "spreading" signals cooperate to produce the widespread synaptic facilitation so characteristic to central sensitization. Scaffolding proteins play a major role in the addressing of specific kinases to the synapse and represent another potential mechanism for widespread synaptic facilitation. A recent study has shown that in the hippocampus, CaMKII activation is restricted to the synaptic bouton of a conditioned synapse, thus only allowing homosynaptic facilitation at that specific site.[164] It is likely in the dorsal horn that CaMKII activation will be much more widespread and indeed the dendrites of dorsal horn neurons lack synaptic boutons.

Central Sensitization in Pathological Settings

In addition to its role in rapidly and reversibly sensitizing the nociceptive system by activity-dependent changes in synaptic strength and excitability, central sensitization also contributes to the longer-lasting and sometimes persistent pain hypersensitivity present in pathological situations involving inflammation and damage to the nervous system. The molecular and cellular mechanisms involved include some that are also responsible for activity-dependent central sensitization and others that are unique to either inflammation or nerve injury. NMDAR,[47,193,255,280,315] AMPAR,[180,239] group I mGluR,[7,65,75,92,102,118,221,288,392,405] group II-III mGluR,[45,104,194,207,286,398] BDNF,[144,179,190,230] SP and CGRP,[2,4,163] NO,[50,316] and bradykinin[241] have all been shown to contribute both to the development of central sensitization and to pain hypersensitivity in inflammatory and neuropathic pain models.

Inflammatory Pain

Peripheral inflammation induces a phenotypic switch in primary sensory neurons that comprises a change in their neurochemical character and properties due to alterations in transcription and translation. We will only discuss here those changes that relate specifically to central sensitization by virtue of changes in the synaptic input produced by the afferents and will not review the major changes that also alter peripheral transduction sensitivity and membrane excitability (peripheral sensitization), although of course, anything that increases nociceptor afferent input will also indirectly lead to increased central sensitization. Large DRG neurons begin, unlike in their naive condition, to express SP and BDNF when their peripheral terminals are exposed to inflammatory signals and nerve growth factor (NGF).[191,223] Consequently, activation of the myelinated fibers by low-intensity innocuous stimuli now releases these neuropeptides in the spinal cord, and conditioning stimulation of the afferents acquires the capacity to generate central sensitization, something they normally cannot do[185,190,223] (Fig 12). After peripheral inflammation, Aβ-mediated synaptic input to superficial dorsal horn neurons is substantially increased from the very low levels found in noninflamed animals.[16] TrkA-expressing nociceptors, instead of a phenotypic switch, begin to express higher levels of neuropeptides and other NGF-dependent proteins as a result of exposure to the increased NGF produced by inflammation.[370,375]

A critical central pathway for the generation of inflammatory pain hypersensitivity involves induction of cyclooxygenase-2 (Cox-2) in dorsal horn neurons, to drive production of prostaglandin E2 (PGE2).[269,349] PGE2 binds to its EP2 GPCR on dorsal horn neurons to potentiate AM-PAR and NMDAR currents,[152] activate nonselective cation channels,[18] and reduce in inhibitory glycinergic neurotransmission by blocking glycinergic receptors with α3 subunits[9,111,152,213] (Fig 12). PGE2 also acts on EP4 receptors on presynaptic terminals to increase transmitter release.[350] The importance of the central neuronal induction of COX-2 to inflammatory hyperalgesia is revealed by conditional deletion of COX-2 only in neurons, which results in the retention of peripheral inflammation and heat hyperalgesia but an almost complete loss of mechanical pain hypersensitivity.[350]

Under normal conditions, microglia are the only immunocompetent cells of the nervous system[66,362] and constantly probe or survey the CNS parenchyma to maintain homeostasis.

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[62,225] After peripheral inflammation, some spinal cord microglial cells change their shape, function, and chemical expression.[115,258,311,312] In particular, p38 MAPK is activated[311,312] and leads to the synthesis and release of pro-inflammatory cytokines,[115,258] among which, IL-1β and TNF-α contribute to the development of central sensitization by enhancing excitatory and reducing inhibitory currents and by activating induction of COX-2[142,269] (Fig 12).

Neurons in the superficial lamina of the dorsal horn usually display a GluR2 AMPAR phenotype (ie, are Ca^{2+}-impermeable)[252]; however, peripheral inflammation triggers a shift from GluR2/3 to GluR1-containing AMPARs at the membrane[159,238,355] (see "PSD Proteins and AMPAR Recycling and Subunit Switch," below). Under these conditions, activation of AMPAR elicits entry of Ca^{2+}, which can then participate in the activation of the signaling pathways that drive central sensitization. Ca^{2+}-permeable AMPARs appear to be a major source of the $[Ca^{2+}]_i$ increase in inflammatory pain, generating as much Ca^{2+} influx as with NMDAR activation.[182] The functional state of NMDAR is also modified in response to peripheral inflammation, with phosphorylation of NR2B subunits by Src resulting in increased activity of the receptors[106,107,178] and in their maintenance at the synapse.[42] Finally, peripheral inflammation also promotes group I mGluR insertion into the membrane (mGluR5) and closer to the synapse (mGluR1), thereby further clustering these receptors at the synapse.[247]

Neuropathic Pain

After peripheral nerve injury, damaged and nondamaged A- and C-fibers begin to generate spontaneous action potentials. Because these do not arise from the peripheral terminal, it is a form of ectopic input.[70,74] Such input in C-fibers can initiate and then maintain activity-dependent central sensitization in the dorsal horn.[154] However, because of chemical and structural changes in A fibers,[56,229,386] input in these afferents can also begin to drive central sensitization.[69] Injured, and to a much lesser extent, noninjured sensory neurons in the dorsal root ganglion exhibit a massive change in transcription that alter their membrane properties, growth, and transmitter function.[56,231,232,386] These changes are much greater than those that occur in response to peripheral inflammation, where only a few tens of transcripts are altered in the DRG[195] and involve altered expression of about 1000 transcripts, including ion channels, receptors, transmitters, and the molecular machinery necessary for axon regeneration.[56,261] Among the many changes, large fibers begin to express new transmitters and neuromodulators including substance P and BDNF and the synthetic enzymes for tetrahydrobiopterin, an essential cofactor for NOS. Stimulation of non-nociceptive fibers now triggers release of factors that can drive central sensitization.[24,56,91,229,327,386]

Structural changes also contribute to altered synaptic function. Peripheral nerve injury leads to a transganglionic degeneration of C-fiber terminals in lamina II.[13,136] This loss of presynaptic input, together with the triggering of increases in the intrinsic axonal growth capacity as part of the regenerative response of the injured neurons, provides an opportunity and the molecular means for myelinated A-β fibers to sprout from laminae III-IV into laminae I-II and make contact with nociceptive-specific neurons.[166,191,285,377,378] The original experiments describing the sprouting phenomenon were conducted using cholera toxin B subunit as a selective tracer for A-fibers as well as single axonal label with HRP. The selectivity of this toxin after peripheral nerve injury is somewhat controversial.[125,339] Nevertheless, immunostaining for c-*Fos* activation and electrophysio-logical recordings have clearly established that peripheral nerve injury causes large myelinated fibers to begin to drive nociceptive neurons in superficial lamina.[24,151,235,366]

A reduction in the synthesis, release, or activity of inhibitory transmitters leads to a state of disinhibition, whose net functional effects are very similar to that produced by increases in synaptic strength of excitatory synapses and in membrane excitability.[289,341,390] In

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neuropathic pain states, there is substantial disinhibition in the superficial dorsal horn with loss of GABAergic and a reduction in glycinergic inhibitory currents[210] that can be attributed, at least in part, to apoptosis of inhibitory interneurons.[277] This neuronal death appears to be the result of an NMDAR-induced excitotoxicity that develops over time rather than to the large amount of glutamate released centrally at the time of nerve injury.[277] One laboratory failed to find significant loss of neurons or of GA-BAergic content in the dorsal horn of neuropathic pain animal models.[249-251] The reasons for this discrepancy are not clear but may reflect technical differences in how the studies were performed. Interestingly, the reduction in glycinergic neurotransmission caused by the activation of EP2 receptors after peripheral inflammation does not appear to operate after nerve injury, further indicating that some inflammatory and neuropathic pain mechanisms differ.[117]

Another mechanism contributing to the reduction in segmental inhibition in a subpopulation of lamina I neurons in the spinal cord after nerve injury is dependent on BDNF effects on an anion transporter, changing anion gradients across neuronal membrane to alter the inhibitory efficacy of GABA. Under normal conditions, the intracellular concentrations of Cl^- are maintained by the opposed effects of Cl^--cotransporter K^+-Cl^- exporter 2 channels (KCC2) and Na^+-K^+-Cl^- exporter 1 channels (NKCC1). KCC2 drives Cl^- ions out of the cells (along with K^+) and NKCC1 is responsible for an influx of K^+, Na^+, and Cl^- into the cells. The net effect of these 2 co-transporters is a steady-state Cl^- concentration gradient in which opening of Cl^- channels (such as $GABA_A$ receptors) causes entry of Cl^- into the neuron and hyperpolarizes the neurons. After peripheral nerve injury, BDNF released by activated microglial cells results in a reduction of KCC2 expression in a subset of neurons in the superficial lamina of the dorsal horn.[57,58,203] Consequently, activation of $GABA_A$ receptors by GABA result in a diminution or absence of Cl^- entry into the cell and thus a disinhibition of these nociceptive neurons[57,58,179,203] (Fig 12). As after peripheral inflammation, there is also an increase in descending excitatory controls from the RVM in the brainstem after peripheral nerve injury, as well as a reduction of descending inhibitory controls.[60,95,351,356]

Peripheral nerve injury causes a massive activation of, and change in, glial cells in the spinal cord as well as infiltration of peripheral immune-competent cells, notably macrophages and T-cells.[38,317,360] The extent and duration of the changes in microglia and astrocytes is much greater than in response to peripheral inflammation. Activated microglia produce and release trophic factors, neurotransmitters, cytokines, and reactive oxygen species[263,361] and appear to play an essential step in the development of pain after nerve injury by triggering central sensitization through their interaction with neurons.[133,160,162,201,206,256,257,352] Numerous signals trigger microglial activation and recruitment, including ATP and NO,[62,81,225] cytokines, and chemokines, some of which are released by injured sensory neurons and others by microglial cells themselves or by astrocytes and T-cells.[1,3,66,76,204,348,361,362] Release of cytokines by microglia increases neuronal excitability through activation of ERK and CREB.[131,142] Activated microglia also release BDNF and NO,[58,116] promoting segmental disinhibition.[57] Finally, microglia can also provoke neuronal death by producing ROS, pro-apoptotic cytokines such as TNF,[121] and by a diminished glutamate uptake.[48,326,332] T-cells produce specific cytokines such as IFN-γ, which reduce GABAergic currents in the dorsal horn[354] through activation of IFN-γ receptors[353] and also activate and recruit microglia. Astrocytes also become activated after peripheral nerve injury,[98,131,205] with a slower onset and more prolonged time course than microglia, and may play more of a role in the maintenance of neuropathic pain hypersensitivity than microglia.[94,399,406] What seems clear is that multiple different mechanisms operate after nerve injury to increase excitability and reduce inhibition.

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Scaffolding Proteins, Synaptic Plasticity, and Central Sensitization During Inflammation and After Nerve Injury

The proteins that make up the PSD can drive a major functional reorganization of synapses, modifying post-synaptic efficacy by altering receptor density at the membrane and producing switches from Ca^{2+}-impermeable to Ca^{2+}-permeable AMPARs (Fig 13). The PSD is not simply a structural landmark of the synapse but contains elements essential both for the formation of the synapse and for changes in its properties. Absence of scaffolding proteins or specific disruption of their binding sites results in a dramatic reduction in synaptic plasticity because the proteins contribute both to transcriptional and post-translational events. They initiate signaling cascades that lead to the activation of transcription factors, traffic newly synthesized receptors to the PSD, and "address" kinases and phosphatases to specific receptors in a stimulus-dependent manner. Although the involvement of the PSD in synaptic plasticity in the cortex is much better established than in the spinal cord, there is increasing evidence for a major role for the PSD in changing synaptic efficacy in response to peripheral inflammation and nerve injury.

The PSD consists of cytoskeletal proteins, signaling molecules, membrane receptors, and scaffolding proteins.[234] Scaffolding proteins are families of proteins characterized by their ability to interact with numerous partners, and these proteins form the dense molecular structure of the postsynaptic component of the synapse. A particularly abundant component of the PSD are proteins containing a specific peptidergic domain called PDZ, which is named after the protein in which the sequence was first identified (postsynaptic density protein 95 [PSD-95]/ discs large/zonula occludens 1). This family of proteins includes, among hundreds of members, the 4 membrane-associated guanylate kinases (MAGUK): PSD-95, PSD-93, synapse associated protein (SAP)-97, SAP-102. The MAGUKs represent the most abundant scaffolding protein family in the PSD[234] and are characterized by 3 PDZ domains, an Src homology region (SH3) domain, and a guanylate kinase-like (GK) domain,[148] making them central elements of the synapse scaffold. The prime binding protein for the MAGUK family is the NMDAR subunit NR2,[155] but it also binds to the transmembrane AMPAR regulatory proteins (TARPs),[43] nonreceptor tyrosine kinases,[329] nNOS,[30,31] GKAP,[217] and AKAP79/150.[53] MAGUKs can be seen as the functional scaffold of the PSD and are essential for the structural integrity of synapses but also modulate the insertion of glutamate receptors into the synapse and physically bring together key enzymes to the PSD.[59,148,167,197,265] Knock-down of PSD-95 and PSD-93, as well as targeted mutagenesis of the residues required for their protein:protein interaction, both prevent and reduce central sensitization in normal conditions[321] as well as in inflammatory[319,323,397] and neuropathic pain models[99,320,323,397] but do not alter nociception or locomotor functions.[319-321,323]

Another member of the PDZ family, stargazin, is a 4-transmembrane domain protein whose putative secondary structure is close to the Ca^{2+}-channel γ subunit, and was named γ2.[170] Stargazin however, does not play an important role in neuronal Ca^{2+} channels[170] but is instead highly concentrated in the PSD and co-immunoprecipitates with GluR1, 2, and 4.[43,335] The protein is a major AMPAR partner, along with the 4 other isoforms, γ3, γ4, γ7, and γ8,[140,335] which form the TARP subgroup.[335] Stargazin traffics AMPAR from the endoplasmic reticulum to the extrasynaptic membrane.[43,334] Once stargazin and AMPAR are addressed to the extrasynaptic membrane, their recruitment to the synapse requires interaction of the C-terminus segment of stargazin with PSD-95.[21,276] Activity-dependent phosphorylation of stargazin by PKC and CaMKII[342] produces a massive insertion of AMPAR into the membrane,[337] whereas stargazin's dephosphorylation by PP1 or PP2B reduces the number of AMPAR at the synapse.[337] In addition, via the interaction between stargazin's ectodomain and the glutamate binding region of AMPAR, stargazin modulates the activity of AMPAR by slowing channel deactivation and desensitization and increasing the affinity of the receptors for

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glutamate,[49,334,336] thereby potentiating synaptic strength. Disruption of stargazin in the spinal cord inhibits the second phase of formalin-induced pain and reduces the heat hyperalgesia caused by intraplantar CFA injection.[318] Recently, cornichon homolog 2 (CNIH-2) and cornichon homolog 3 (CNIH-3) have been found to be novel partner proteins for AMPAR in the CNS.[279] Cornichon proteins bind to GluR1-4 AM-PAR and, as for stargazin, they promote AMPAR surface expression and slow their deactivation kinetics.[279] Because their expression in the CNS is estimated to be in 70% of neurons, and because cornichon and stargazin appear to be mutually exclusive,[279] the determination of their presence in spinal cord neurons and their role in central sensitization is something that needs to be investigated.

EphrinB-ephBR receptor interactions participate in NMDAR clustering at the PSD.[90] EphBRs are receptor tyrosine kinases expressed by postsynaptic neurons, whereas EphrinB is anchored to the presynaptic membrane.[156] The kinase activity of EphBR is not required for the initial clustering of NMDAR at the synapse but is essential for their maintenance.[61] Stimulation of EphBR potentiates NMDAR-induced Ca^{2+} influx and the phosphorylation of CREB through the activation of the nonreceptor tyrosine kinase src[314] and recruits CaM-KII to the synapse[236] to increase NMDAR activity.[314] Activation of EphBR in the spinal cord induces thermal hyperalgesia (but not allodynia),[22,299] without modifying nociception.[22] Inhibition of EphRB prevents or reverses inflammatory[22,291] and neuropathic[150,299] pain and prevents establishment of NMDAR-induced spinal cord "LTP."[299] More specifically, targeted disruption of the coupling between EphRB-activated Src and NR2B also prevents the development of central sensitization without altering basal nociceptive transmission.[178] In addition, sustained nociceptive activity leads to an upregulation and reorganization of presynaptic EphB increasing EphB-EphRB interaction.[22,298,299]

The nonreceptor tyrosine kinase family also includes Fyn, which phosphorylates NR2 subunits[268] and binds to PSD-93 to phosphorylate $NR2_{A/B}$[273] and could play a role in the maintenance of neuropathic pain.[5]

NMDA receptors are structurally connected with group I metabotropic glutamate receptors through a complex composed of PSD-95, GKAP, Shank1, and Homer1b/c. GKAP binds to the GK domain of PSD-95[147,217] and recruits Shank1 to the PSD via their PDZ domain.[216,264] Shank1 then binds to the EVH1 domain of homer1b/c.[343] Homer1b/c proteins have a coiled-coil structure in their C-terminus region that enables them to form homotetramers or heterotetramers.[284] This assembly of Homers leaves 3 available EVH1 domains that can bind several other targets such as group I mGluRs (but not group 2 or 3 mGluRs),[28] inositol triphosphate receptors (IP3R), or the actin cytoskeleton.[284,344] The interaction between Homer1b and IP3R and between Shank1 and Homer1b/c controls local Ca^{2+} release from the endoplasmic reticulum upon mGluRs activation.[266,267] Homer1a, a short isoform of Homer1b/c that lacks the coiled-coil structure, is an immediate early gene activated on neuronal activity and participates in remodeling synapses in an activity-dependent manner.[129] Homer1a is upregulated in dorsal horn neurons after the subcutaneous injection of formalin or CFA[324] as well as transiently after peripheral nerve injury.[208] Factors responsible for Homer1a activation include NMDAR, ERK1/2 and Src.[208,324] Knock-down of Homer1a increases pain-like behaviors specific to central sensitization and not those associated with peripheral sensitization,[324] whereas overexpression reduced inflammatory pain-like behavior without altering basal nociception.[324] Homer1a probably causes a disruption of the clustering properties of Homer1b/c protein and of Ca^{2+} release on NMDAR or mGluR activation.[324] In contrast, homer1b activation leads to an increase of AMPAR activity after the stimulation of mGluR, whereas activation of Homer1a inhibits this.[347] In addition, Homer1b/c proteins could play an important role in clustering group 1 mGluRs at the synapse after CFA injection,[247] an effect that is reduced by Homer1a overexpression.[385] Homer proteins are, therefore, convergent factors that potentially link major glutamate receptors with Ca^{2+} stores in neurons, and the balance between

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Homer1b/c and Homer1a may play an important role in the development and maintenance of central sensitization.

PSD Proteins and AMPAR Recycling and Subunit Switch

Stargazin may be important in creating the switch from GluR2- to GluR1-containing AMPAR in response to peripheral inflammation[159,355] by specifically addressing GluR1-containing AMPARs to the synapse and then strengthening their activity via its ectodomain.[334] Peripheral inflammation leads via PKA to a phosphorylation of Ser831 and Ser845 on GluR1 in the spinal cord,[180] which, in association with CaMKII activation, promotes a transfer of GluR1-containing AMPARs to the membrane,[84] where they are maintained by synaptic activity.[189]

GluR2-containing AMPARs are associated with high affinity to GRIP-1, which clusters the receptors at the synapse,[77,114] whereas PICK-1 is a critical element for activity-dependent endocytosis of the receptor.[51,96,226] NMDAR activation leads to a PKC-mediated phosphorylation of GluR2 at Ser880,[172,238] which decreases GluR2's affinity for GRIP-1, whereas the increase in intracellular Ca^{2+} recruits PICK-1 to the synapse,[51,108,238] where it reduces the clustering of GluR2-containing AM-PAR[51,172,196,238,304,328] (Fig 14). On endocytosis, vesicles can either be inserted back into the synapse under the action of NSF,[122,226,228,297] which disrupts the [GluR2-PICK-1] complex,[109] or be maintained out of the synapse through PICK-1.[172] During inflammation, NSF expression is reduced in the spinal cord,[139] thereby preventing GluR2-containing AMPAR reinsertion into the synapse.

The net effect of these complex changes is an increase in GluR1 and a decrease in GluR2 containing AMPAR at the synapse (Fig 14). Once inserted into the synapse, GluR1-containing AMPAR remain there for as long as there is glutamate release,[83,189] and their activation is potentially increased by stargazin's ectodomain, thereby further promoting the Ca^{2+}-dependent pathways required for maintenance of central sensitization. In addition, the phosphorylation of stargazin's C-terminus domain by PKC and CaMKII[342] increases its affinity for PSD-95, thereby re-enforcing the clustering of AMPAR with NMDAR at the synapse.[276]

After peripheral nerve injury, GluR2 and GRIP-1 are up-regulated in dorsal horn neurons,[100,110] whereas PICK-1 expression is not modified and NSF is downregulated.[100] Peptides that disrupt the binding of GRIP-1 or NSF with GluR2 partially decrease neuropathic pain-like behaviors.[100] PICK-1 is also required for $G_{i/o}$-coupled mGluR7 trafficking to the membrane.[306] Activation of mGluR7 can block P/Q-type Ca^{2+} channels[240] and reduces the pain caused by injection of capsaicin[218] or peripheral nerve injury.[237] The upregulation of GRIP-1 but not of PICK-1 in neuropathic pain models would promote AM-PAR maintenance at the synapse but not that of mGluR7, resulting in increased excitability in these cells.

Finally, the A kinase-anchoring protein 79/150 (AKAP79/150) binds to PSD-95[53] and is a scaffold for protein kinases and phosphatases,[53,169] specifically trafficking enzymes within the PSD to increase (kinases) or reduce (phosphatases) synaptic transmission. When AKAP79/150 recruits PKA[181,295] or PKC[325] in the PSD, it promotes insertion of new AMPAR to the membrane (via PKA) as well as increasing their activity (via PKC). In contrast, recruitment of PP2B[25,169] triggers AMPAR endocytosis.[25] AKAP79/150 may function therefore as a "master switch" of central sensitization by promoting phosphorylation or dephosphorylation of stargazin and AMPAR.

Conclusion

Before central sensitization was discovered, there were 2 major models of pain. The first was that it was a labeled-line system, in which specific "pain pathways" were activated only by particular peripheral "pain stimuli" and that the amplitude and duration of pain was determined

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solely by the intensity and timing of these inputs. The second model evoked “gate controls” in the CNS, which, by opening or closing, enabled or prevented pain. Neither model envisaged, however, that pain may arise as a result of changes in the properties of neurons in the CNS: central sensitization. We now appreciate that there are indeed specific nociceptive pathways and that these are subject to complex facilitating and inhibitory controls; both models were in part correct. We also know though, that changes in the functional properties of the neurons in these pathways are sufficient to reduce pain threshold, increase the magnitude and duration of responses to noxious input, and permit normally innocuous inputs to generate pain sensations. Pain is not then simply a reflection of peripheral inputs or pathology but is also a dynamic reflection of central neuronal plasticity. The plasticity profoundly alters sensitivity to an extent that it is a -major contributor to many clinical pain syndromes and represents a major target for therapeutic intervention. The past 26 years have seen enormous advances both in our appreciation of the nature and manifestations of central sensitization and in its underlying molecular mechanisms. We have great insight into what triggers can induce central sensitization, through which signaling pathways and by means of which effectors. The complexity is daunting because the essence of central sensitization is a constantly changing mosaic of alterations in membrane excitability, reductions in inhibitory transmission, and increases in synaptic efficacy, mediated by many converging and diverging molecular players on a background of phenotypic switches and structural alterations. Nevertheless, enormous progress has been made in dissecting out where, when, and how the plasticity occurs, although clearly, more is still waiting to be learned.

Acknowledgments

Supported by the National Institutes of Health and the Fondation pour la Recherche Médicale.

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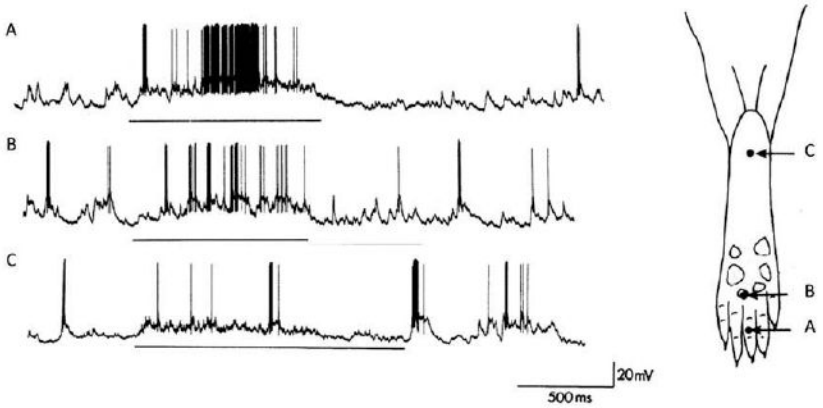

Figure 1.

Subthreshold synaptic inputs. The substrate for receptive field plasticity. Intracellular in vivo recordings from a nociceptive-specific rat dorsal horn neuron revealing subthreshold synaptic inputs. The output of somatosensory neurons is determined by those peripheral sensory inputs that produce sufficiently large-amplitude monosynaptic and polysynaptic potentials to evoke an action potential discharge **(A** and **B)**. This constitutes the receptive field or firing zone of the neuron. However, stimuli outside the receptive field can evoke synaptic inputs that are too small normally to produce action potential outputs **(C)**, and this constitutes a subliminal fringe or low-probability firing fringe, which can be recruited if synaptic efficacy is increased, to expand and change the receptive field. In this particular neuron, a standard pinch stimulus applied to points A, B, and C evoked only action potentials at points A and B but clear subthreshold synaptic inputs at C. Modified from [Reference 365].

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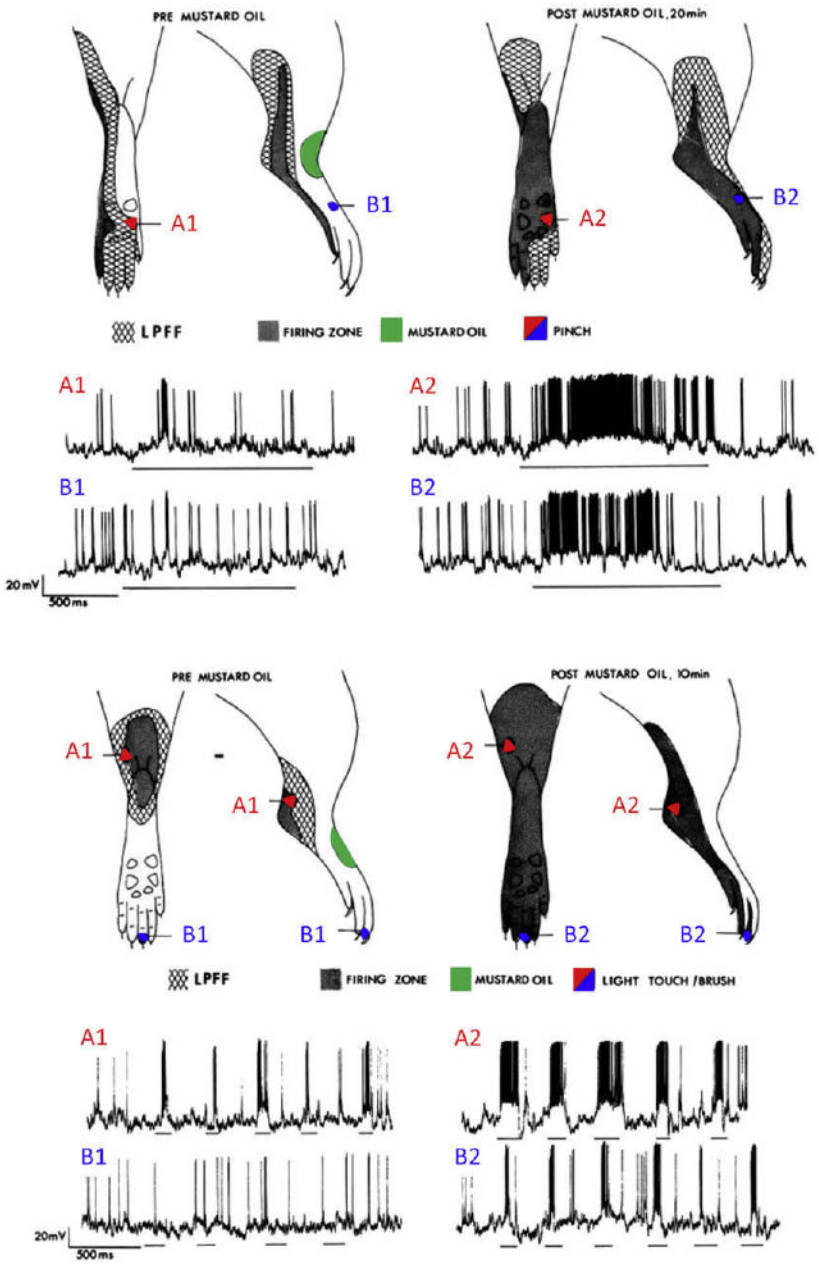

Figure 2.

Expansion of receptor fields during central sensitization. Recruiting subthreshold synaptic inputs to the output of a nociceptive-specific neuron can markedly alter its receptive field properties, producing changes in receptive field threshold and spatial extent. When neurons in the dorsal horn spinal cord are subject to activity-dependent central sensitization, they exhibit some or all the following: development of or increases in spontaneous activity, a reduction in threshold for activation by peripheral stimuli, increased responses to suprathreshold stimulation, and enlargement of their receptive fields. The examples in this figure of intracellular recordings of rat dorsal horn neurons show the cutaneous receptive fields before central sensitization (pre mustard oil) and after the induction of central sensitization (post mustard oil) and indicate how subthreshold nociceptive (pinch, top) and low-threshold (brush, bottom) inputs in the low-probability firing fringe (LPFF) are recruited by central sensitization.

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Central sensitization was produced by topical application of mustard oil, which generates a brief burst of activity in TRPA1-expressing nociceptors and resulted in the neural equivalent of secondary hyperalgesia (top) and tactile allodynia (bottom). Note that the mustard oil (conditioning input) was applied to a different area (in red) from the test pinch or brush inputs (in blue), so that the changes observed are due to hetero-synaptic facilitation. Modified from Reference 364.

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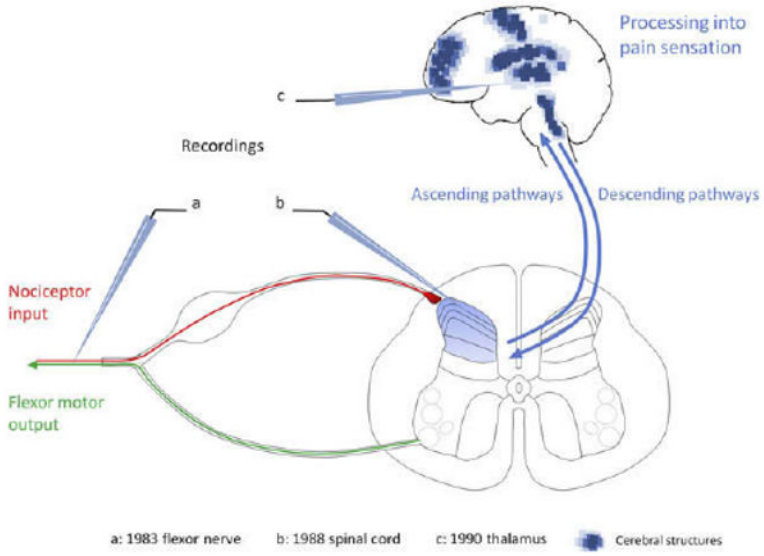

Figure 3.

Schematic representation of the structures exhibiting central sensitization. The first evidence for central sensitization was generated in 1983 by revealing injury-induced changes in the cutaneous receptive field properties of flexor motor neurons as an integrated measure of the functional plasticity in the spinal cord. A conditioning noxious stimulus resulted in long-lasting reductions in the threshold and an expansion of the receptive field of the motor neurons that was shown to be centrally generated. Essentially identical changes were then described in lamina I and V neurons in the dorsal horn of the spinal cord (b) as well as in spinal nucleus pars caudalis (Sp5c), thalamus (c), amygdala, and anterior cingulate cortex. Imaging techniques have revealed several brain structures in human subjects that exhibit changes compatible with central sensitization (blue dots).

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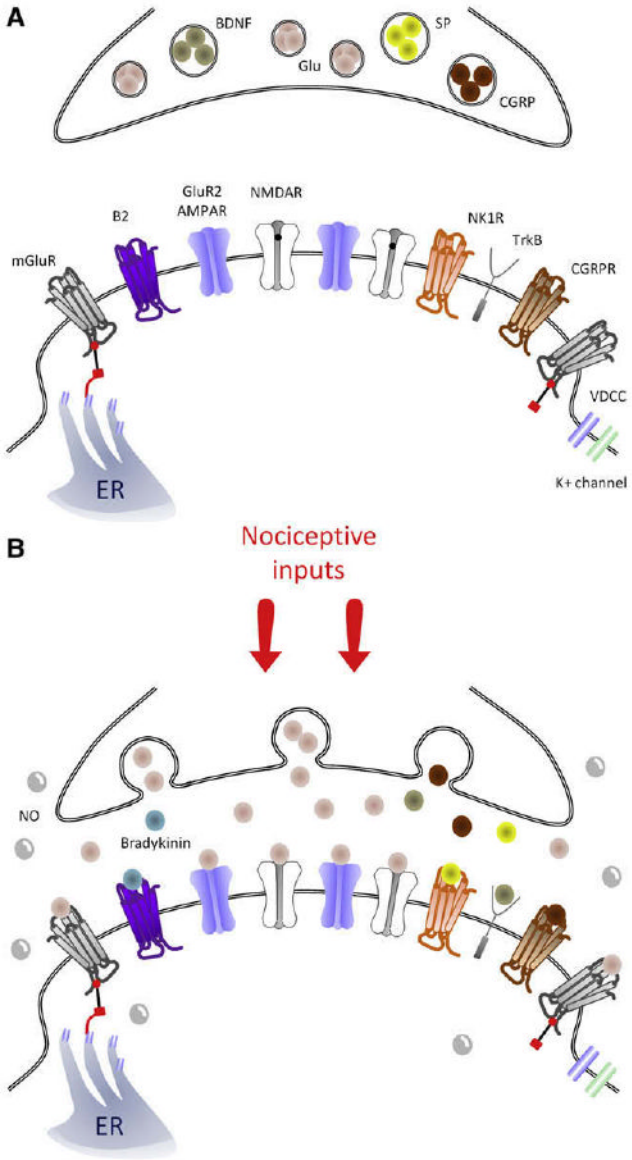

Figure 4.

Central sensitization triggers: Schematic representation of key synaptic triggers of central sensitization. **(A)**, Model of the synapse between the central terminal of a nociceptor and a lamina I neuron under control, basal conditions. mGluR receptors sit at the extremities of the synapse and are linked to the endoplasmic reticulum (ER). Note that NMDAR channels are blocked by Mg^{2+} in the pore (black dot). After a barrage of activity in the nociceptor **(B)**, the primary afferent presynaptic terminal releases glutamate that binds to AMPAR, NMDAR (now without Mg^{2+}), and mGluR, as well as substance P, CGRP, and BDNF, which bind to NK1, CGRP1, and TrkB receptors, respectively. B2 receptors are also activated by spinally produced bradykinin. NO is produced by several cell types in the spinal cord and can act presynaptically and postsynaptically.

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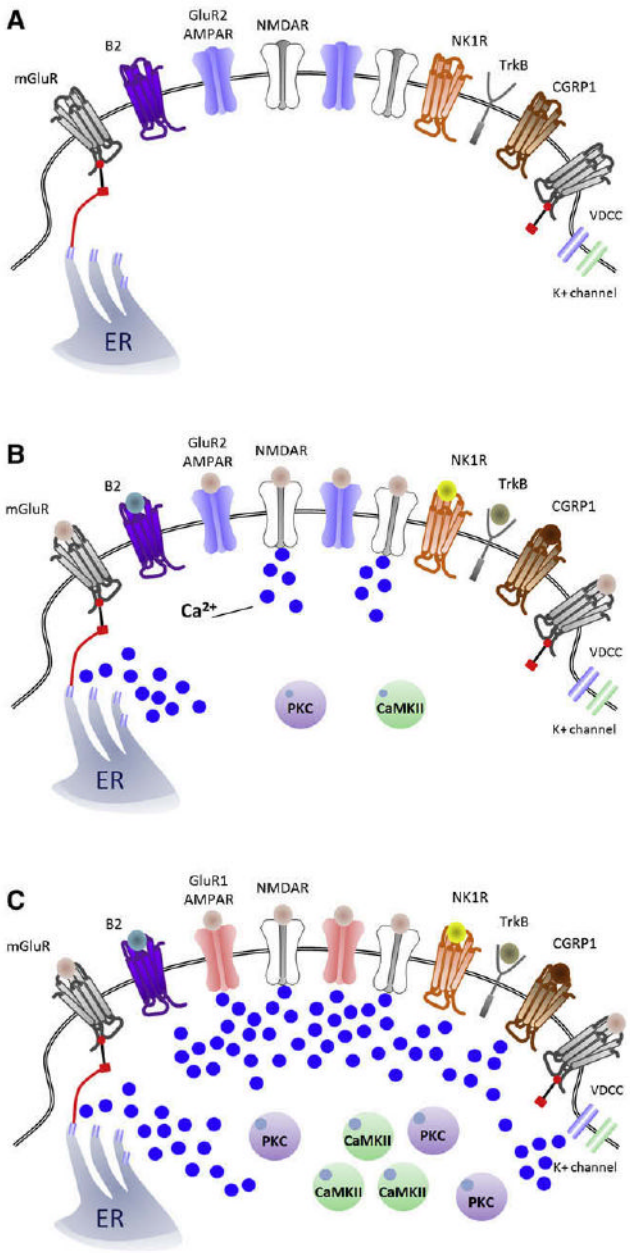

Figure 5.

Sources of Ca^{2+} in the synapse of nociceptive neurons for inducing central sensitization. **(A)**, Model of a nociceptor–dorsal horn neuron synapse under control, nonactivated conditions. After nociceptor input **(B)**, activation of NMDAR and mGluR result in a rapid increase of $[Ca^{2+}]i$ that activates PKC and CaMKII, 2 major effectors of central sensitization. **(C)**, Representation of a synapse during peripheral inflammation-induced central sensitization, where there is a shift from GluR2/3 to GluR1-containing AMPARs that enables, along with voltage-dependent calcium channels and NMDAR, entry of Ca^{2+} and which, together with activation of the G-coupled MGluR, NK1, B2, and CGRP1 receptors, which release intracellular Ca^{2+} stores, recruits PKC and CaMKII, strengthening the excitatory synapse.

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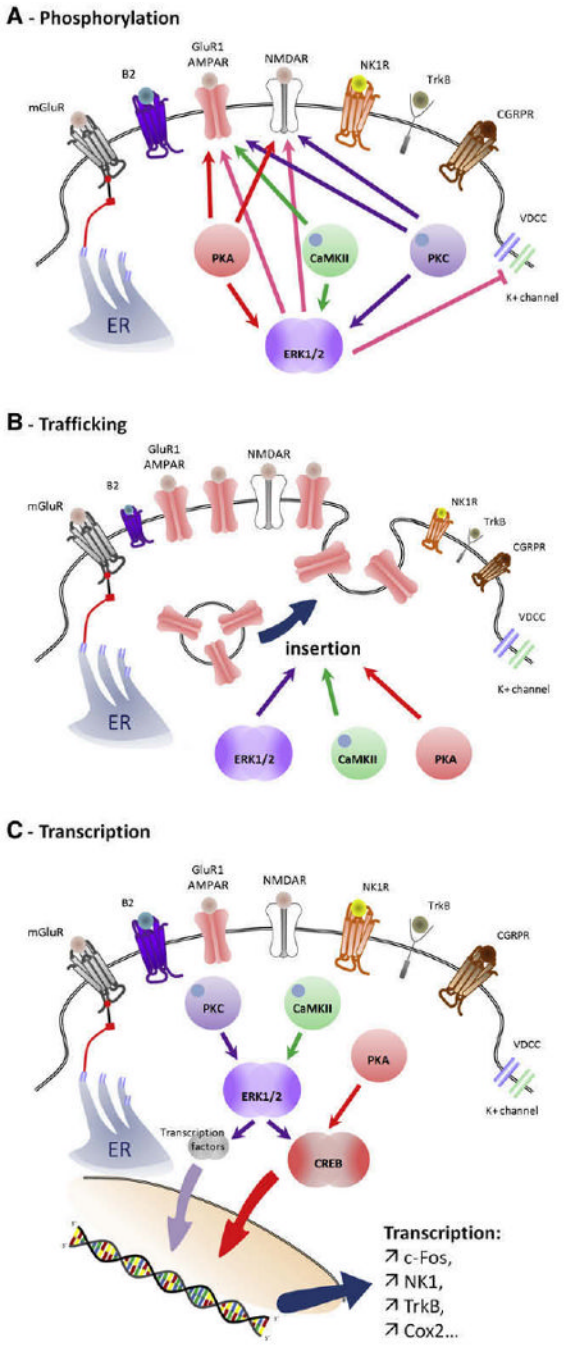

Figure 6.

Contribution of PKC, CaMKII, PKA, and ERK activation to central sensitization. **(A)**, Phosphorylation by PKC, CaM-KII, PKA, and ERK cause changes in the threshold and activation kinetics of NMDA and AMPA receptors, boosting synaptic efficacy. ERK also produces a decrease in K^+ currents through phosphorylation of Kv4.2 channels, increasing membrane excitability. **(B)**, PKA, CaMKII, and ERK promote recruitment of GluR1-containing AMPAR to the membrane from vesicles stored under the synapse. **(C)**, Transcriptional changes mediated by activation of CREB and other transcription factors driving expression of genes including c-*Fos*, NK1, TrkB, and Cox-2, to produce a long-lasting strengthening of the synapse.

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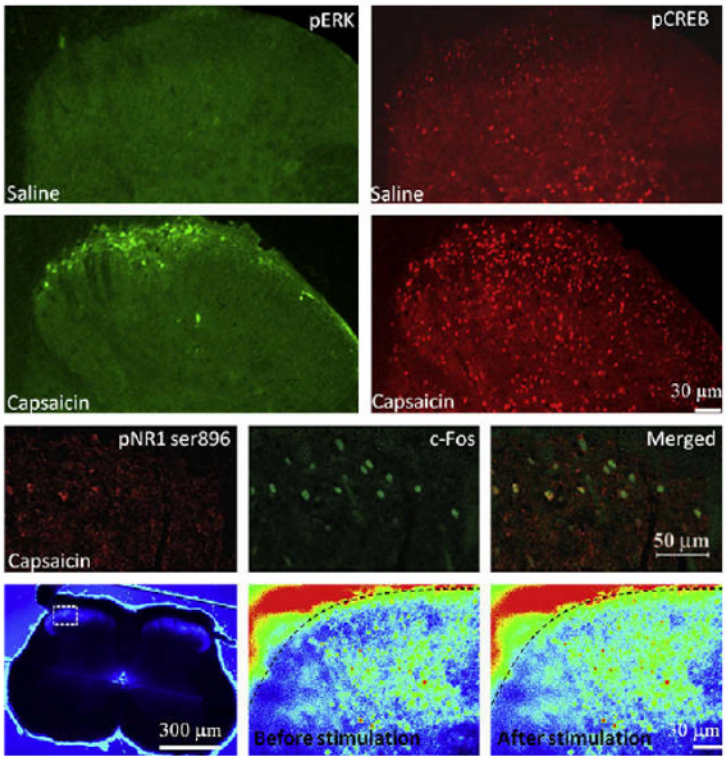

Figure 7.

Key effectors of central sensitization in the dorsal horn. Subcutaneous injection of capsaicin, a potent inducer of central sensitization, causes rapid activation of ERK and CREB (upper panels) as well as a PKC-induced phosphorylation of the NR1 subunit of NMDAR in c-*Fos*–positive neurons of the superficial laminas of the spinal cord (middle panels). ERK activation participates in transcriptional and post-translational changes, CREB activation promotes transcription of several genes involved in central sensitization. NR1 phosphorylation by PKC increases NMDAR activity. ERK and PKC are activated through the increase of intracellular calcium that occurs during stimulation of nociceptive fibers (lower panels). Signals are shown in pseudocolor from blue (weak intensity) to red (strong intensity). ERK and CREB staining are from [Reference 141]; NR1 phosphorylation staining from [Reference 32], and calcium imaging from [Reference 179].

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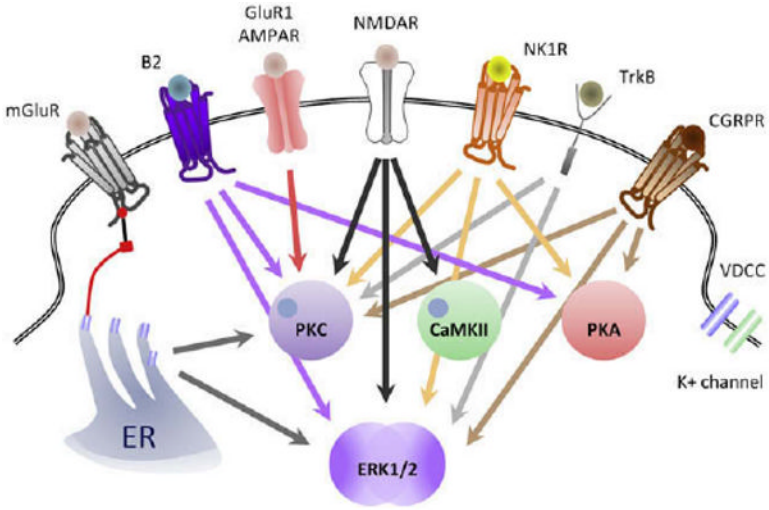

Figure 8.

Key intracellular pathways contributing to the generation of central sensitization. NMDAR activation causes activation of PKC, CaMKII, and ERK (black arrows); GluR1-containing AMPAR activate PKC (red arrow); NK1 and CGRP1 receptors activate PKC, PKA, and ERK (orange and brown arrows, respectively); TrkB s activates of PKC and ERK (purple arrows); and mGluR, via release of Ca^{2+} from microsomal stores, activates PKC and ERK (gray arrows). Note that most of the triggers of central sensitization: Activation of NMDAR, mGluR, TrkB, NK1, CGRP1, or B2 converge to activate ERK.

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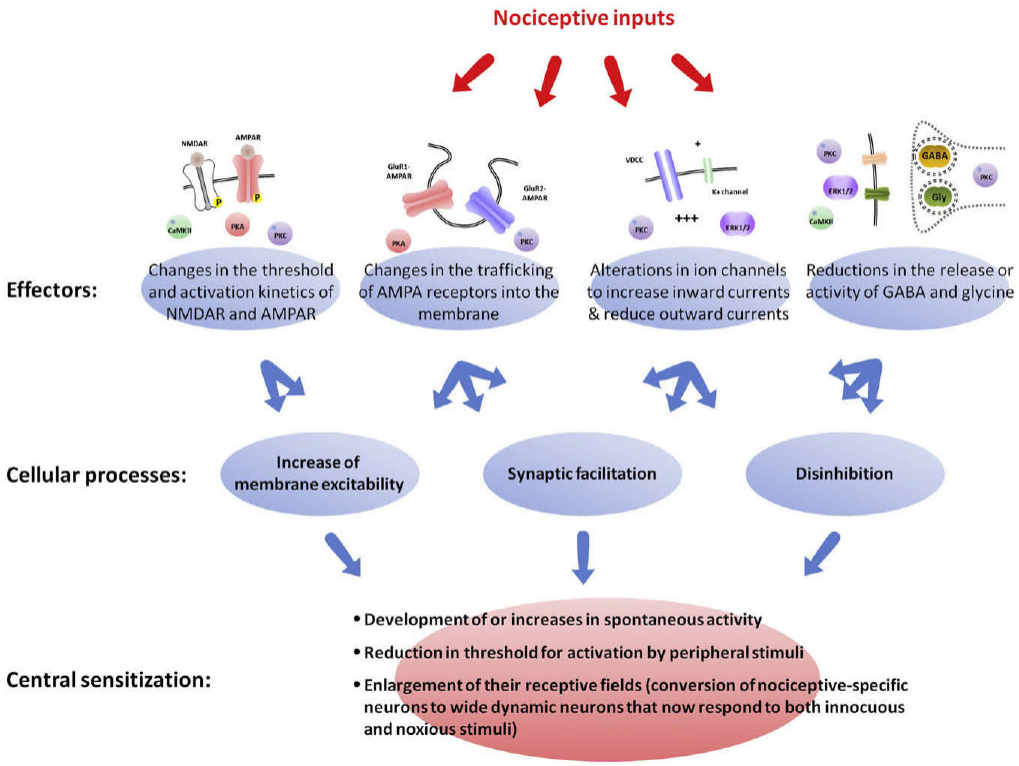

Figure 9.

Multiple cellular processes lead to central sensitization. Central sensitization is not defined by activation of a single molecular pathway but rather represents the altered functional status of nociceptive neurons. During central sensitization, these neurons display 1 or all of the following: i, development of or an increase in spontaneous activity; ii, reduction in threshold for activation; and iii, enlargement of nociceptive neuron receptive fields. These characteristics can be produced by several different cellular processes including increases in membrane excitability, a facilitation of synaptic strength, and decreases in inhibitory transmission (disinhibition). Similarly, these mechanisms can be driven by different molecular effectors including PKA, PKC, CaMKII, and ERK1/2. These kinases participate in changes in the threshold and activation kinetics of NMDA and AMPA receptors and in their trafficking to the membrane, cause alterations in ion channels that increase inward currents and reduce outward currents, and reduce the release or activity of GABA and glycine.

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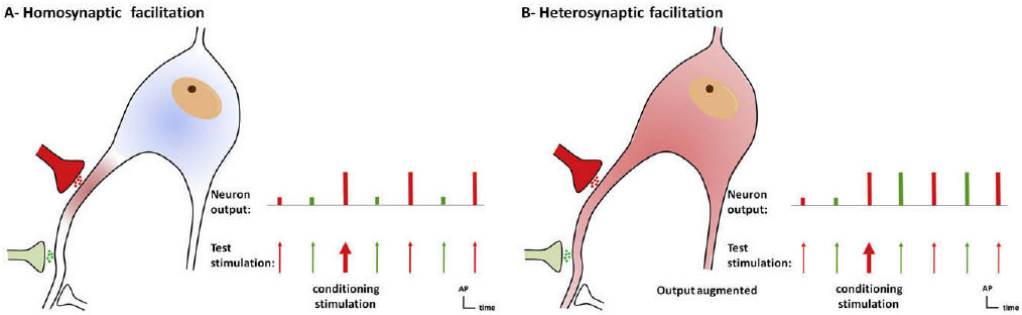

Figure 10.

Homo synaptic and heterosynaptic facilitation. **(A)**, Homosynaptic potentiation is a form of use-dependent facilitation of a synapse evoked by activation of that same synapse (in red). A nonconditioned synapse (green) is not potentiated. This type of potentiation is commonly called long-term potentiation (LTP). LTP-like homosynaptic potentiation can contribute to primary hyperalgesia. **(B)**, Heterosynaptic facilitation represents a form of activity-dependent facilitation in which activity in 1 set of synapses (conditioning input, red) augments subsequent activity in other, nonactivated groups of synapses (test input, green). Heterosynaptic potentiation is responsible for the major sensory manifestations of use-dependent central sensitization: pain in response to low-threshold afferents (allodynia) and spread of pain sensitivity to noninjured areas (secondary hyperalgesia).

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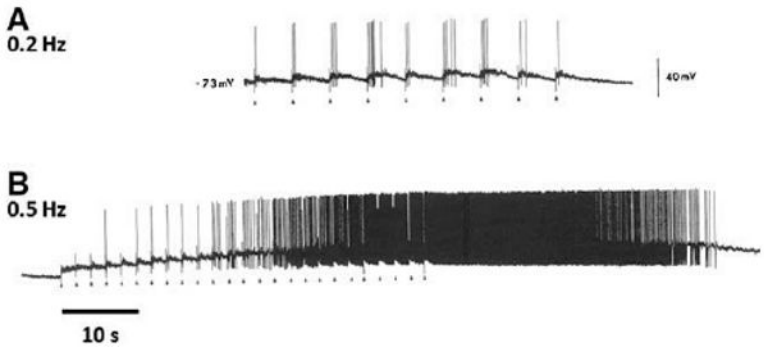

Figure 11.

Action potential windup. Windup is the consequence of a cumulative membrane depolarization resulting from the temporal summation of slow synaptic potentials. Under normal conditions, low-frequency stimulations of C-fibers (0.2 Hz) cause steady neuronal discharges **(A)** as the membrane potential has sufficient time to return to resting potential between stimuli. At a frequency of 0.5 Hz or higher, activation of NK1 and CGRP1 receptors by release of substance P and CGRP from peptidergic nociceptors produces a cumulative increase in membrane depolarization. This then enables activation of NMDAR by removal of the voltage-dependent Mg^{2+} block, further boosting the responses in a non-linear fashion **(B)**. Windup disappears within tens of seconds of the end of the stimulus train as the membrane potential returns to its normal resting level **(B)**. Modified from [Reference 323].

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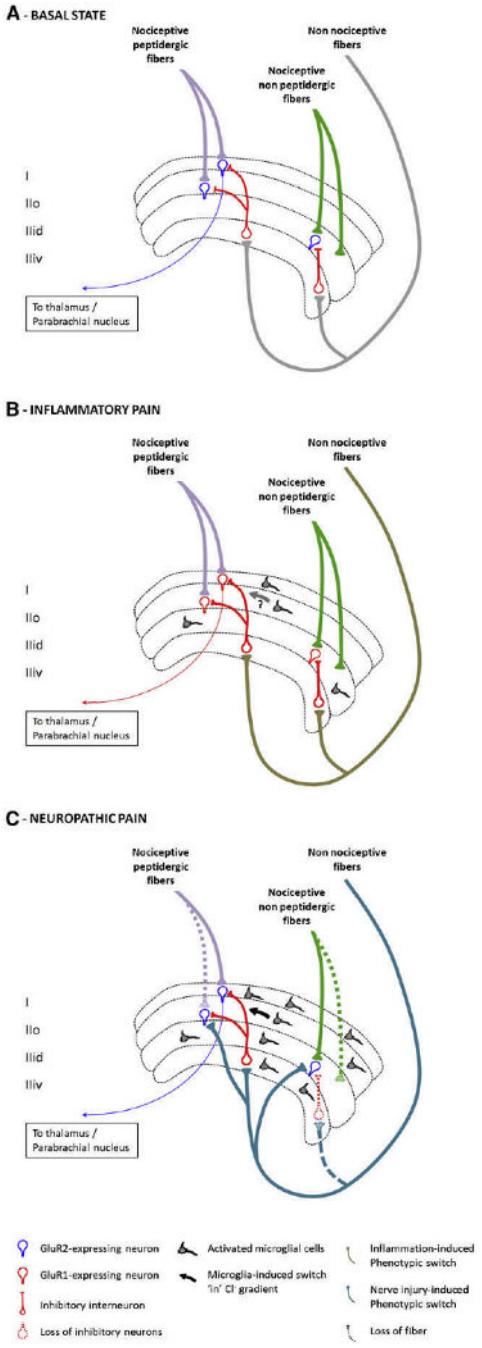

Figure 12.

Central sensitization in pathological settings. **A**, Representation of the superficial lamina of the dorsal horn of the spinal cord. Nociceptive peptidergic fibers contact lamina I and II outer (I and IIo) neurons that express GluR2-containing AMPAR (in blue). Some of these neurons project to the thalamus, parabrachial nucleus, and PAG. Nociceptive nonpeptidergic fibers contact neurons in dorsal lamina II inner (IIid), which also express GluR2-containing AMPAR. Non-nociceptive large fibers contact deeper laminae but also send collaterals to inhibitory interneurons in the ventral part of lamina II (IIiv).[222] **B**, Alterations in the superficial lamina in inflammatory pain. Because large DRG neurons begin to express SP and BDNF, stimulation of these afferents acquires the capacity to generate central sensitization. Neurons now express

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GluR1-containing AMPAR at their synapse (in red), resulting in an increase of Ca^{2+} influx on their activation. Some spinal cord microglial cells are activated and release factors that contribute to the development of central sensitization by enhancing excitatory and reducing inhibitory currents. **C**, Representation of superficial lamina in neuropathic pain states. After peripheral nerve injury, there is a loss of C-fiber central terminals and the sprouting of myelinated A-β fibers from deep to superficial lamina. Injured sensory neurons in the dorsal root ganglion exhibit a change in transcription that alters their membrane properties, growth, and transmission. Large fibers begin to express substance P, BDNF, and the synthetic enzymes for tetrahydrobiopterin, an essential cofactor for NOS and can drive central sensitization. Recruitment and activation of microglial cells is an essential step in the development of pain after nerve injury and to trigger central sensitization by releasing proinflammatory cytokines that increase neuronal excitability and BDNF that induces a switch in Cl^- gradients, resulting in a loss of inhibition. Loss of inhibition is also caused by excitotoxic apoptosis of inhibitory interneurons.

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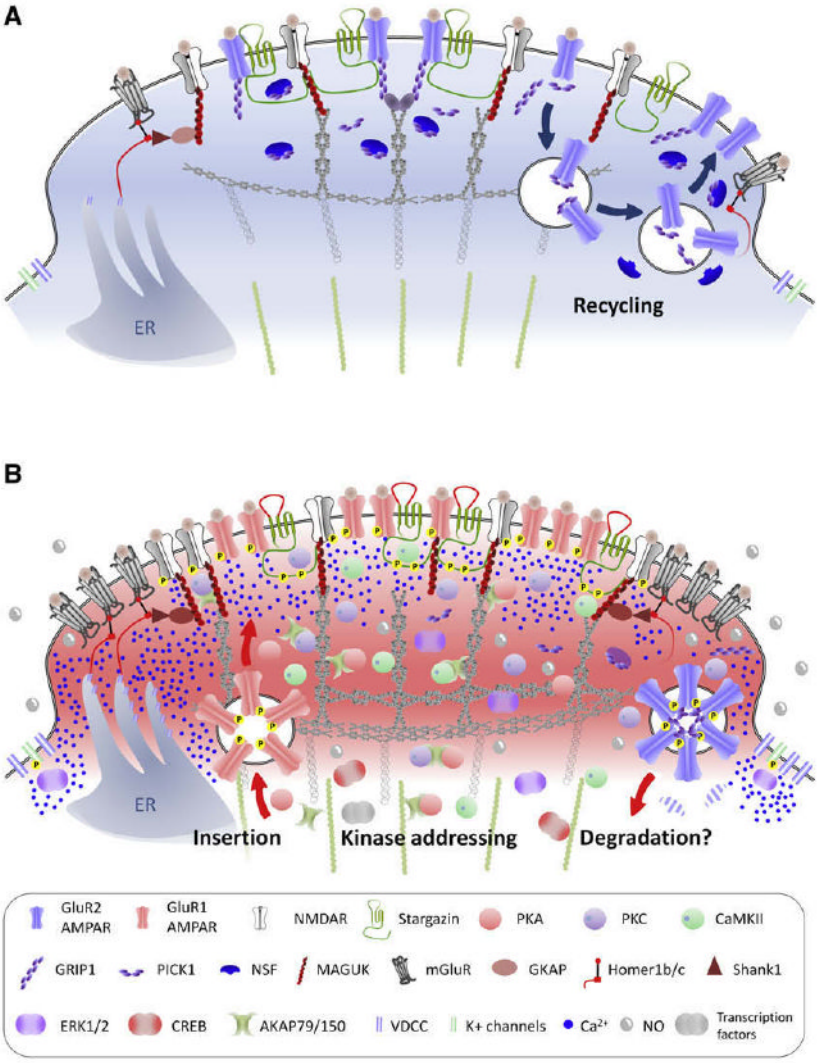

Figure 13.

Role of scaffolding proteins in central sensitization. Representation of the post synaptic density (PSD) region of a synapse of a nociceptive neuron in the superficial lamina of the spinal cord under basal conditions **(A)** and during inflammatory pain **(B)**. The proteins that make up the PSD can drive a major functional reorganization of synapses, modifying postsynaptic efficacy by altering receptor density at the membrane and producing switches from Ca^{2+}-impermeable to Ca^{2+}-permeable AMPARs. In addition, scaffolding proteins mediate the "addressing" of kinases to the receptors, thereby increasing their activity. Under normal conditions **(A)**, neurons mostly express GluR2-containing AMPAR that are anchored to the PSD via GRIP-1. NMDAR are recycled in an activity-dependent manner via PICK-1 and NSF. During inflammation **(B)**, there is an endocytosis of GluR2-containing AMPAR (initiated by PKC phosphorylation of GluR2) along with a loss of NSF that prevents their reinsertion into the synapse. GluR1-containing AMPAR are expressed at the membrane, where their activity is increased by phosphorylation with PKA as well as by the ectodomain of stargazin, whose C-terminus segment is phosphorylated by PKC and CaMKII. MAGUK can participate to increase glutamate receptors density at the synapse, and phosphorylated stargazin promotes AMPAR and NMDAR clustering. Scaffolding proteins such as AKAP79/150 and the MAGUKs also "address" kinases to specific synaptic position at the right time to phosphorylate AMPAR and

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NMDAR subunits, thereby increasing their activity. The Homer-Shank1-GKAP-MAGUK complex couples mGluR and NMDAR to intrasomal Ca^{2+} stores, so that activation of glutamate receptors leads to high levels of Ca^{2+} in the PSD that activate PKC and CaMKII, also recruited to the PSD by scaffolding proteins. PKC, CaMKII, and other kinases converge to activate ERK, which reduce K^{+} channels activity and promote transcriptional activity.

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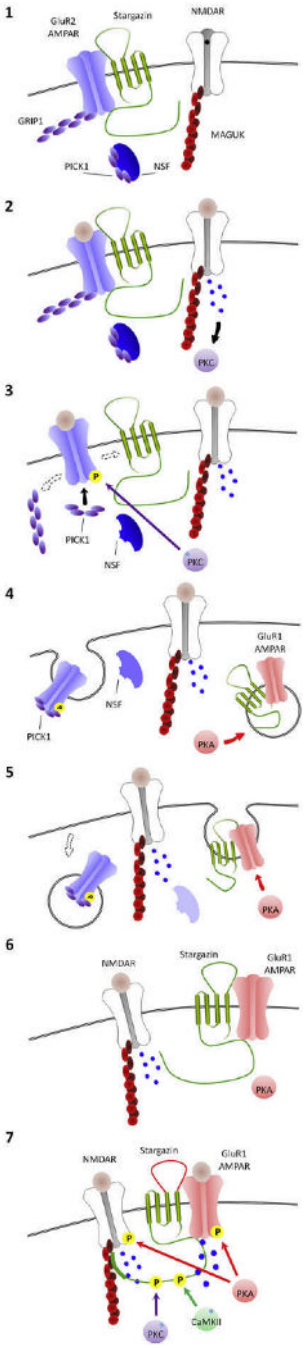

Figure 14.

Synaptic scaffolding proteins and the switch to GluR1-containing AMPAR after peripheral inflammation. Under basal conditions, GluR2-containing AMPARs are associated in the synapse with stargazin and GRIP-1. The C-terminus of stargazin binds to PSD-95 (1). Peripheral inflammation leads to glutamate release from nociceptors and AMPA and NMDA receptor activation. NMDAR activation leads to a Ca^{2+} influx that activates PKC (2). Activated PKC phosphorylates GluR2-containing AMPARs at ser880, which leads to a loss of affinity for stargazin and GRIP-1, allowing PICK-1 to bind to the receptor (3). The GluR2-containing AMPAR and PICK-1 complex undergo endocytosis, whereas NSF is downregulated, preventing reinsertion of GluR2-containing AMPAR into the synapse. Meanwhile, peripheral

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inflammation also leads to activation of PKA that promotes GluR1-containing AMPAR to be inserted into the membrane (4). Because GluR2-containing AMPARs are internalized and the Ca^{2+}-permeable GluR1-containing AMPAR are inserted into the membrane, there is a switch from GluR2- to GluR1-containing AMPAR (5 and 6). Increased $[Ca^{2+}]i$ causes an activation of PKC and CaMKII, which phosphorylate the C-terminus of stargazin, increasing its affinity for PSD-95 (CaMKII) and modifying its ectodomain (PKC), which causes increased GluR1 affinity for glutamate and single-channel conductance and a higher channel opening probability, further increasing Ca^{2+} influx (7).