



Central sensitization and LTP: do pain and memory share similar mechanisms?

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Synaptic plasticity is fundamental to many neurobiological functions, including memory and pain. Central sensitization refers to the increased synaptic efficacy established in somatosensory neurons in the dorsal horn of the spinal cord following intense peripheral noxious stimuli, tissue injury or nerve damage. This heightened synaptic transmission leads to a reduction in pain threshold, an amplification of pain responses and a spread of pain sensitivity to non-injured areas. In the cortex, LTP – a long-lasting highly localized increase in synaptic strength – is a synaptic substrate for memory and learning. Analysis of the molecular mechanisms underlying the generation and maintenance of central sensitization and LTP indicates that, although there are differences between the synaptic plasticity contributing to memory and pain, there are also striking similarities.

Synaptic strength is not fixed but rather varies in response to changes in transmitter release from presynaptic terminals or in transmitter responsiveness on the postsynaptic membrane. A synapse can be silent and ineffective at one extreme, or work at maximum capacity at the other. This variation in synaptic function, as well as alterations in synaptic structure, constitute synaptic plasticity, a form of modifiability essential for normal operation of the nervous system. That activity or use can alter synaptic function has been recognized almost since synapses were first identified as the basis for chemical transmission between neurons. Depending on the synapse and the intensity, frequency and duration of activity, both increases (facilitation, potentiation or sensitization) and decreases (habituation, depression or desensitization) in synaptic function can be elicited [1].

At first, synaptic plasticity was thought to reflect primarily either Ca^{2+} accumulation in the presynaptic terminal established during repetitive activation, leading to increased vesicle release, or a depletion of vesicles after prolonged use. It was therefore expected to be both restricted to the activated synapse and relatively transient. However, 30 years ago, Bliss and Lomo revealed the existence of long-lasting changes in the efficacy of synaptic transmission. While recording extracellular synaptic field

potentials in the hippocampus, they showed that these potentials could be potentiated for hours following a brief high-frequency conditioning stimulus: the phenomenon of long-term potentiation (LTP) [2]. Twenty years ago, another form of use-dependent synaptic plasticity was discovered – this time in the spinal cord – that contributed to post-injury pain hypersensitivity: the phenomenon of central sensitization [3,4].

Since these two initial observations, considerable work has been devoted to elucidating the mechanisms underlying both phenomena. It has become clear recently that there are in fact several distinct forms of central sensitization beyond the classical transient activity-dependent form that was first described. These include LTP-like changes, as well as localized and widespread transcription-dependent changes, in spinal cord synaptic transmission. This review examines the different forms of central sensitization in the spinal cord, their contributions to pain, and their similarities and differences with hippocampal LTP.

Why pain, memory and synaptic plasticity?

Living organisms need to be able to sense their immediate environment if they are to withdraw from or avoid potentially hazardous situations. Development in multicellular creatures of the nervous system – a specialized apparatus to effect detection and reaction to external stimuli – together with evolution of specific transduction proteins, has enabled accurate differentiation between innocuous and noxious stimuli. This early warning system was further elaborated by development of the capacity to increase its sensitivity following exposure to an injurious stimulus – that is, nociceptive sensitization. This sensitization enables escape responses to be evoked readily and with a reduced threshold [5], protecting an injured organism from further injury. Nociceptive sensitization is perhaps the neurobiological foundation for the old adage ‘once bitten twice shy’. It can be seen even in simple organisms such as the mollusc *Aplysia*, in which an intense noxious stimulus can produce long-lasting sensitization of the gill-withdrawal reflex, owing to alterations in synaptic efficacy [6]. The persistence of a heightened responsiveness of the nervous system following a brief noxious stimulus has clear parallels with memory, where information needs to

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be stored and retrieved. This review examines the extent to which nociceptive sensitization and memory share common molecular mechanisms.

Pain: peripheral versus central sensitization

In mammals, the early-warning protective pain that occurs in response to noxious stimuli (nociceptive pain) is mediated by specialized high-threshold primary sensory neurons, the nociceptors. Activation of transduction molecules, such as the transient receptor potential ion channel TRPV1, after a heat stimulus ($>42^{\circ}\text{C}$) generates inward currents in the nociceptor peripheral terminal. If these currents exceed a threshold value, they cause action potentials in the nociceptor axon; following conduction and transmission to projection neurons in the spinal cord, and transfer via the thalamus to the cortex, that leads to the sensation of pain [7,8].

Although nociceptive pain is characterized by a high threshold and is typically transient ('ouch' pain), clinical pain associated either with peripheral tissue damage and inflammation (inflammatory pain) or with lesions to the nervous system (neuropathic pain) is characterized by persistent pain hypersensitivity. This includes spontaneous pain (pain experienced in the absence of any obvious peripheral stimulus), hyperalgesia (an increased responsiveness to noxious stimuli) and allodynia (pain in response to normally innocuous stimuli). Two major mechanisms contribute to post-injury pain hypersensitivity: peripheral and central sensitization.

Peripheral sensitization

During tissue injury and inflammation, inflammatory mediators such as prostaglandin E_2 (PGE_2), bradykinin and nerve growth factor (NGF) are released. These chemicals act on G-protein-coupled receptors or tyrosine kinase receptors expressed on nociceptor terminals, activating intracellular signaling pathways that by phosphorylating receptors and ion channels in the nociceptor terminal change their threshold and kinetics. This increases the sensitivity and excitability of the nociceptor terminal – a phenomenon known as peripheral sensitization [8]. For example, PGE_2 and bradykinin cause changes in TRPV1 via activation of cAMP-dependent protein kinase (PKA) and Ca^{2+} /phospholipid-dependent kinase (PKC), such that the receptor can be activated by lower temperatures ($<40^{\circ}\text{C}$) [9]. These inflammatory mediators also cause changes in the sensory-neuron-specific voltage-gated Na^+ channel $\text{Na}_v1.8$, altering its activation kinetics and, hence, terminal-membrane excitability [10]. Peripheral sensitization produces increases in pain sensitivity that are restricted to the site of inflammation. A good example is heat pain sensitivity after sunburn, when a normally warm shower feels burning hot. In addition to post-translational regulation, transcriptional or translational regulation can also contribute to peripheral sensitization. NGF-induced activation of p38 mitogen-activated protein kinase (MAPK) in primary sensory neurons after peripheral inflammation increases the expression and peripheral transport of TRPV1, exacerbating heat hyperalgesia [11].

Central sensitization

The original description of central sensitization referred to an immediate-onset, activity- or use-dependent increase in the excitability of nociceptive neurons (neurons responsive to nociceptor inputs) in the dorsal horn of the spinal cord, as a result of, and outlasting, a short barrage of nociceptor input [3,12,13]. This activity-dependent central sensitization is normally initiated only by nociceptor sensory inflow and is characterized by reductions in threshold and increases in the responsiveness of dorsal horn neurons, as well as by enlargement of their receptive fields [13]. Most input received by dorsal horn neurons is sub-threshold – the synaptic strength is too weak to evoke an action potential output [14]. After induction of activity-dependent central sensitization by a brief (10–20 s) intense nociceptor-conditioning stimulus, however, this normally subliminal input begins to activate dorsal horn neurons as a result of increases in synaptic efficacy [15]. A striking feature of the increase in synaptic efficacy characteristic of activity-dependent central sensitization is that, although it includes those nociceptor central terminal synapses activated by the conditioning stimulus (a form of homosynaptic facilitation), it is also associated with synapses made by low-threshold mechanosensitive $\text{A}\beta$ fibers on dorsal horn neurons [15,16]. Because $\text{A}\beta$ fibers are not activated by the nociceptive conditioning stimuli necessary to induce central sensitization, this is an example of heterosynaptic facilitation (i.e. the synapses activated by the conditioning and test inputs are different). Low-threshold sensory fibers activated by innocuous stimuli such as light touch can now activate normally high-threshold nociceptive neurons, contributing to a reduction in pain threshold (tactile allodynia) that is the consequence of an increased excitability of CNS neurons. Although this pain is referred to the periphery, it arises from within the CNS. This activity-dependent central sensitization manifests within seconds of an appropriate nociceptive conditioning stimulus and can outlast the stimulus for several hours [12]. If the stimulus is maintained, even at low levels, the central sensitization persists. After peripheral nerve injury, for example, ongoing ectopic activity arising from sensory fibers in the injured nerve can elicit prolonged central sensitization [17,18].

Activity-dependent sensitization is extremely robust and has been reported in rodent, cat and primate dorsal horn neurons, including spinothalamic neurons [19–24]. A central sensitization-like phenomenon can also be generated in neurons in other parts of the pain system, such as the rostroventral medulla, anterior cingulate cortex and amygdala [25–27]. Several symptomatic features of headache reflect central sensitization produced in trigeminal nuclei within the brainstem [28,29].

The behavioral consequences of central sensitization can be readily detected in human psychophysical experiments. Intradermal injection of capsaicin, the pungent ingredient in chili peppers that activates the TRPV1 receptor, produces an intense but transient pain owing to activation of TRPV1-expressing nociceptors. This is followed by heightened sensitivity to pinprick outside the region of the capsaicin injection (secondary mechanical hyperalgesia) and to low-threshold mechanosensory (brush)

inputs (secondary mechanical allodynia), due to the induction of central sensitization [24,30–32]. Clinically, central sensitization contributes to pain hypersensitivity in the skin, muscle, joints and viscera [33].

Distinct forms of central sensitization

In addition to the immediate-onset activity-dependent form of central sensitization already described (often referred to as classical central sensitization), several other types of synaptic plasticity occur in the spinal cord in response to noxious stimuli that modify nociceptive transmission by altering synaptic efficacy. These can be considered, therefore, to be components of a more global phenomenon. They include other immediate-onset, transcription-independent phenomena, such as windup and LTP, as well as a late-onset, transcription-dependent, long-lasting facilitation (Figure 1).

Mechanisms of early-onset central sensitization

Windup – reversible synaptic plasticity during a noxious stimulus

Windup is a form of homosynaptic activity-dependent plasticity characterized by a progressive increase in action

potential output from dorsal horn neurons during a train of repeated low-frequency C-fiber or nociceptor stimuli [34]. Unmyelinated C-fiber nociceptor afferents coexpress glutamate and neuropeptide neurotransmitters [substance P and calcitonin-gene-related peptide (CGRP)] [35]. As a consequence, activation of these fibers elicits slow synaptic potentials lasting several-hundred milliseconds [36,37]. Windup results from the summation of these slow synaptic potentials at relatively low afferent input frequencies (<5 Hz). This produces a cumulative depolarization that leads to removal of the voltage-dependent Mg^{2+} channel blockade in NMDA receptors. By increasing glutamate sensitivity, this progressively increases the action potential response to each stimulus in a train of inputs [38]. In addition, afferent inputs can recruit L-type Ca^{2+} channel plateau currents in dorsal horn neurons, contributing to the establishment of a sustained and progressive depolarization over the course of a train of stimuli [39]. A behavioral correlate of windup can be produced by repeated noxious heat or mechanical stimuli, where the pain increases with each successive stimulus even though the stimulus intensity does not change [40,41].

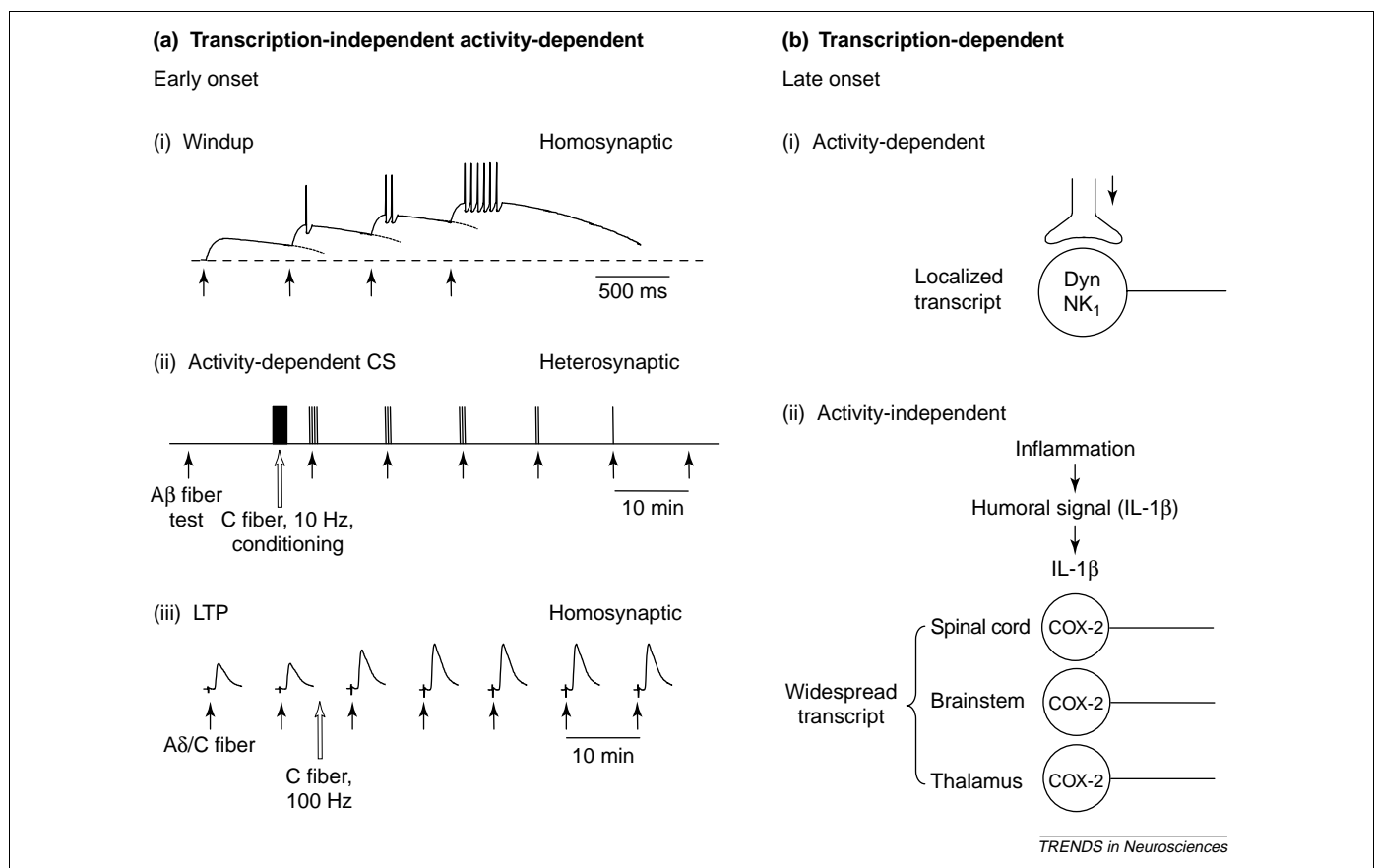


Figure 1. Transcription-independent and transcription-dependent forms of central sensitization. **(a)** There are three forms of immediate-onset transcription-independent central sensitization (CS) in dorsal horn neurons: (i) windup, which is homosynaptic and manifests only during the trains of stimuli that elicit it (arrows); (ii) activity-dependent classical central sensitization that outlasts the initiating stimulus and is predominantly heterosynaptic – low-threshold A β inputs normally elicit no response but begin to do so after the C-fiber conditioning input; and (iii) an LTP-like enhancement of excitatory postsynaptic potentials (EPSPs), the induction phase of which is transcription-independent. This form of central sensitization is largely homosynaptic. **(b)** There are two forms of late-onset transcription-dependent central sensitization: (i) an activity-dependent localized form, which can include late-phase LTP, and (ii) an activity-independent widespread form, both of which take hours to manifest and last for prolonged periods. Two genes upregulated by activity in localized areas of the spinal cord are those encoding dynorphin (Dyn) and the neurokinin 1 (NK $_1$) receptor, while the cytokine interleukin 1 β (IL1 β) produces a widespread induction of cyclooxygenase 2 (COX-2) in many areas of the CNS.

Classical central sensitization – prolonged synaptic plasticity after a noxious stimulus

Activity in nociceptors, caused either by a synchronized train of repeated inputs (upon electrical stimulation of the nerve sufficient to activate unmyelinated axons or heat stimulation of the skin) or by asynchronous activation of the peripheral terminals of nociceptors (upon an intense noxious stimulus or frank tissue damage) evokes a period of facilitated transmission in dorsal horn neurons. This augments responses in the conditioning nociceptor pathway (homosynaptic potentiation) and recruits novel inputs in non-stimulated afferents (heterosynaptic potentiation) (Figure 1). This activity-dependent form of central sensitization is the consequence of activation of multiple intracellular signaling pathways in dorsal horn neurons by the neurotransmitter glutamate and the neuromodulators substance P, brain-derived neurotrophic factor (BDNF) and ephrin-B ligands (Figure 2). Thus, this central sensitization involves activation of ligand-gated ion channels (NMDA, AMPA and/or kainate receptors), G-protein-coupled metabotropic receptors, the substance-P receptor neurokinin-1 (NK₁) and metabotropic glutamate (mglu) receptors, and tyrosine kinase receptors (trkB and Eph). Two major mechanisms appear to contribute to the resultant increased synaptic efficacy: alterations in ion channel and/or receptor activity owing to post-translational processing, and trafficking of receptors to the membrane [7] (Figure 2).

Activation of several protein kinases leads to the phosphorylation of ionotropic glutamate receptors, increasing synaptic efficacy by altering channel open-time, increasing

bursting, removing the Mg²⁺ channel blockade, and promoting trafficking of receptors to the synaptic membrane [7,42]. Deletion of genes encoding isoforms of adenylyl cyclase, PKA and PKC all impair the development of pain hypersensitivity [43–45]. Noxious stimuli and inflammation induce phosphorylation of NR1, NR2A and NR2B NMDA receptor subunits in dorsal horn neurons [46,47]. A major mediator of NMDA receptor tyrosine phosphorylation appears to be the non-receptor tyrosine kinase Src, which is activated by trkB and EphB receptors and subsequently enhances NMDA receptor currents [48]. The NMDA receptor plays a key role in activity-dependent central sensitization. This has been revealed both pharmacologically and, more recently, by a conditional knockout of the NR1 NMDA receptor subunit, which eliminates both NMDA-sensitive synaptic currents and a behavioral manifestation of central sensitization [49]. It is not yet clear exactly how the different serine/threonine and tyrosine kinases that phosphorylate NMDA and AMPA receptors are activated and controlled in dorsal horn neurons in response to different nociceptor inputs. One major modulator might be the extracellular-signal-regulated kinase ERK (p42/44 MAPK). ERK is activated (phosphorylated) in dorsal horn neurons following nociceptive afferent input, and inhibition of its activation suppresses behavioral manifestations of central sensitization [50]. Docking of Ca²⁺/calmodulin-dependent protein kinase (CaMK)II to the NMDA receptor, and phosphorylation of the GluR1 subunit of the AMPA receptor, might also play a role [51,52].

The balance between mglu and GABA_B receptor activation can switch the intrinsic firing properties of deep

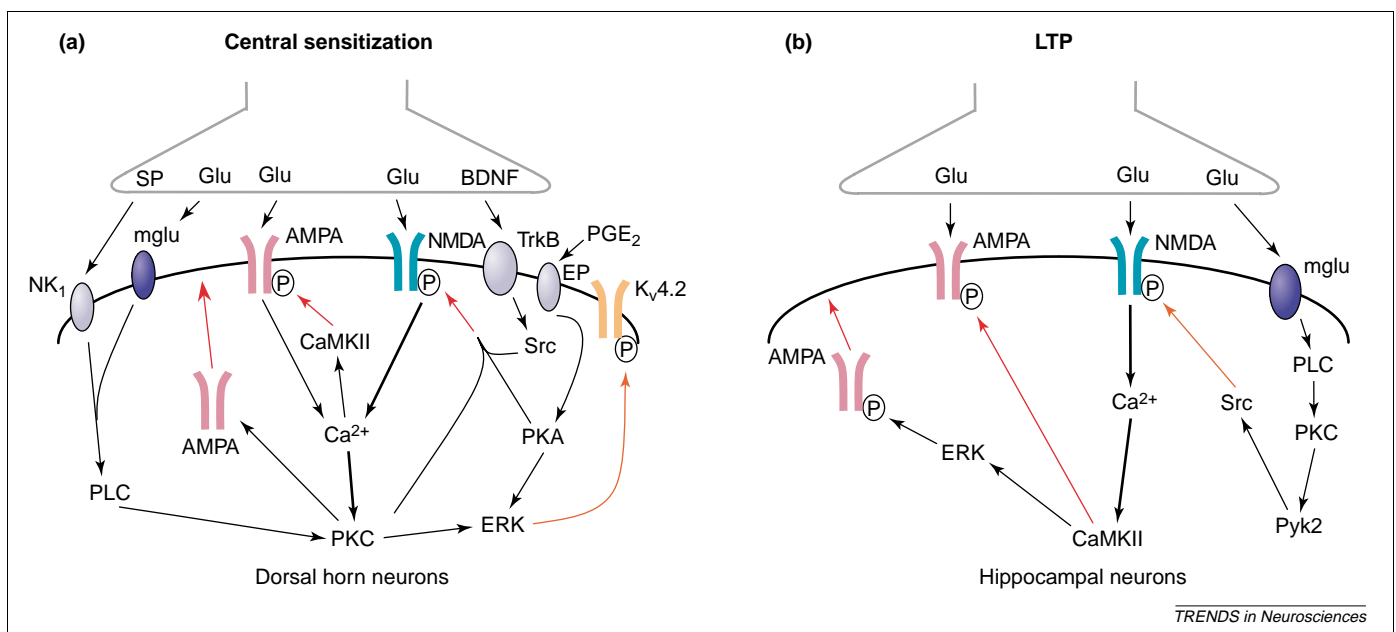


Figure 2. Induction of central sensitization and early-phase LTP. **(a)** Central sensitization in dorsal horn neurons. The central terminals of primary nociceptor afferents release the neurotransmitter glutamate (Glu) and the neuromodulators substance P (SP) and brain-derived neurotrophic factor (BDNF). Glutamate binds to ionotropic AMPA and NMDA receptors and to metabotropic glutamate (mglu) receptors; SP and BDNF bind to the G-protein-coupled neurokinin 1 (NK₁) receptor and to the tyrosine kinase receptor trkB, respectively, on the postsynaptic membrane. An increase of intracellular Ca²⁺ concentration is the major trigger for the activation of serine/threonine protein kinases, including cAMP-dependent protein kinase (PKA), Ca²⁺/phospholipid-dependent protein kinase (PKC) and Ca²⁺/calmodulin-dependent protein kinase II (CaMKII). These kinases, as well as the tyrosine kinase Src, phosphorylate NMDA and AMPA receptors, leading to increased sensitivity. In addition, extracellular-signal-regulated kinase (ERK) downstream of PKA and PKC phosphorylates the Kv4.2 K⁺ channel. PKC induces rapid recruitment of AMPA receptors to the synapse. **(b)** Induction of LTP in hippocampal CA1 neurons. Activation of CaMKII, via NMDA-receptor-induced Ca²⁺ influx, results in phosphorylation of AMPA receptors and trafficking of new AMPA receptors to the synapse, both of which contribute to LTP. The red lines indicate the endpoint of central sensitization or LTP.

dorsal horn neurons from a tonic pattern to a plateau or even to an endogenous bursting pattern through modulation of the inwardly rectifying K^+ channel (Kir3) [53] and this contributes to afferent-induced altered excitability. Dorsal horn neuronal excitability might also be controlled directly through ERK regulation of $K_v4.2$ channels, major contributors to A-type K^+ currents [54]. Finally, PGE_2 produced by cyclooxygenase (COX) in the spinal cord acts on EP seven-pass transmembrane receptors expressed by dorsal horn and primary sensory neurons [55,56] to: (i) facilitate transmitter release from nociceptor central terminals [57], (ii) produce a direct depolarization of dorsal horn neurons [58], and (iii) reduce glycine receptor activity [59]. In non-inflamed animals, the production of PGE_2 in response to nociceptor activity appears to be mediated largely by constitutively expressed COX-1 [55,56]. Although activity-dependent central sensitization is displayed by many cells in both the superficial and deep laminae of the dorsal horn, its impact in terms of pain sensitivity appears to be most important for lamina I spinothalamic or spinoparabrachial projection neurons, particularly those expressing NK_1 [24,60,61].

Dorsal horn LTP

Although LTP has been studied most extensively in the hippocampus and other cortical areas, a similar phenomenon can be elicited in the spinal cord, comprising an activity-dependent, long-lasting homosynaptic facilitation of excitatory postsynaptic potentials in response to brief, high-frequency repeated trains of nociceptor input [62–65]. The biological significance of this is difficult to evaluate fully because C fibers do not normally fire beyond a few spikes at the frequencies required experimentally to produce the LTP (~100 Hz). Nevertheless, dorsal horn AMPA-receptor-mediated excitatory postsynaptic potentials (EPSPs) remain potentiated for tens of minutes following brief repeated trains of high-frequency afferent stimulation. The full duration of this spinal cord LTP is not known. Similar to classical central sensitization, LTP in the dorsal horn seems to occur particularly in NK_1 -expressing spinoparabrachial lamina I neurons. Indeed, induction of LTP in these neurons requires a synergistic interaction between NMDA receptor and NK_1 activation, as well as activation of a low-threshold T-type Ca^{2+} current [61]. The key for induction of the LTP in these dorsal horn neurons seems to be elevation of intracellular Ca^{2+} levels beyond a critical threshold.

Mechanisms of late-onset transcription-dependent central sensitization

It is just beginning to be appreciated that nociceptor activity and/or peripheral tissue inflammation produces long-term changes in synaptic efficacy in the dorsal horn. Whether there is late-phase LTP in the spinal cord is not yet known. However, like consolidation of memory in the cortex, late-onset plasticity in the dorsal horn involves activation of transcription factors and alterations in transcription. Such changes take several hours to manifest, last for prolonged periods, and can be elicited either by activity [66] or by humoral signals [67]. In the case of activity, changes in synaptic efficacy are restricted to areas

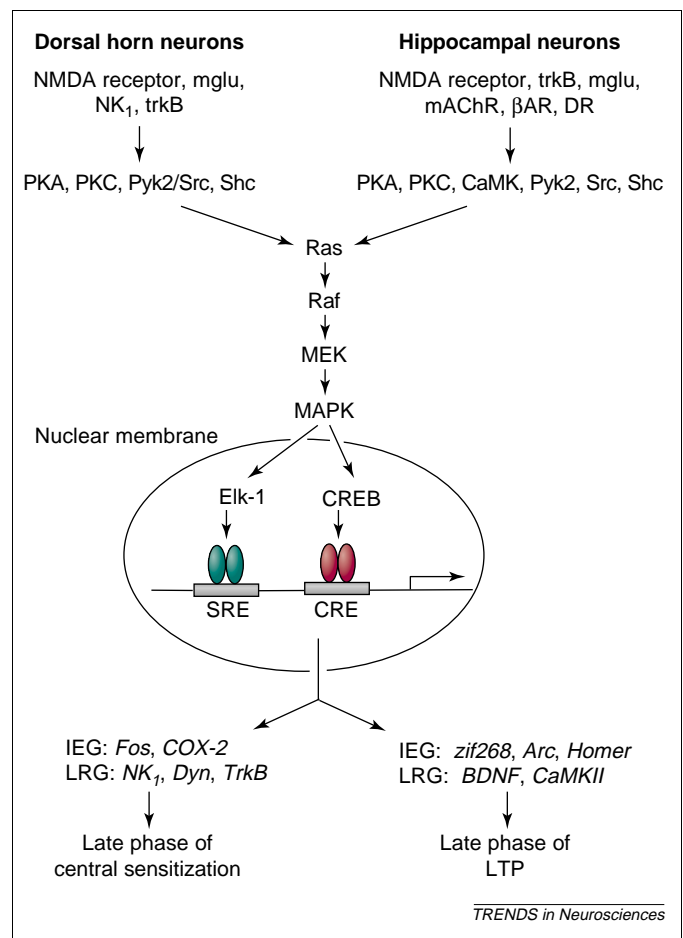


Figure 3. Maintenance (late phase) of LTP and central sensitization. The mitogen-activated protein kinase (MAPK) cascade is activated in both hippocampal and dorsal horn neurons. The receptors and signaling pathways in dorsal horn and hippocampal neurons are indicated. Activated extracellular signal-regulated kinase (ERK; a MAPK) is translocated to the nucleus and activates the transcription factors cAMP-response-element-binding protein (CREB) and Elk-1, causing them to bind to cAMP-response elements (CRE) or serum-response elements (SRE) on gene promoter regions, respectively. This triggers transcription of immediate-early genes (IEG) and late-response genes (LRG). Abbreviations: β AR, β adrenoceptor; CaMK, Ca^{2+} /calmodulin-dependent protein kinase; DR, dopamine receptor; Dyn, dynorphin; mAChR, muscarinic ACh receptor; MEK, MAPK kinase; mglu, metabotropic glutamate receptor; NK_1 , neurokinin 1; PKA, cAMP-dependent protein kinase; PKC, Ca^{2+} /phospholipid-dependent protein kinase; trkB, tropomyosin-related kinase B.

that receive sensory innervation from the inflamed area; in humoral responses, such changes are widespread.

Intense nociceptor activity results in NMDA, mglu, NK_1 and trkB receptor activation in dorsal horn neurons as a result of the release of glutamate, substance P and BDNF. This, in turn, activates PKA, PKC and ERK. ERK can enter the nucleus and leads to cAMP-response-element-binding protein (CREB) phosphorylation at Ser133 [42,68,69] (Figure 3). Noxious stimulation and inflammation [70] also increase expression of the immediate-early genes encoding c-fos and COX-2 [67,71] and the late-response genes encoding prodynorphin, NK_1 and trkB in the dorsal horn [66,72–75]. All these genes contain cAMP-response element (CRE) sites in their promoter regions [76], and the ERK–CREB pathway might mediate induction of these CRE-containing genes [66,77]. Blocking ERK activation reverses these transcriptional changes and the development of a late-onset component of

post-inflammatory pain hypersensitivity [66]. These activity-dependent transcriptional changes in spinal cord neurons are accompanied by transcriptional changes in primary sensory neurons. Following peripheral inflammation, there is an elevation in levels of BDNF and substance P, which are ligands for trkB and NK₁, respectively [74,78]; following peripheral nerve injury, there are changes in expression of hundreds of genes that alter primary afferent excitability and transmission properties [79]. Finally, following both peripheral inflammation and nerve injury, there is a phenotypic switch in some dorsal root ganglion neurons. For example, large dorsal root ganglion neurons begin to express substance P and BDNF [74,80]. As a consequence, these non-nociceptor afferents gain the capacity to induce central sensitization, and repeated light-touch can induce a progressive tactile pain hypersensitivity that lasts for many hours [81,82].

Apart from triggering activity-dependent transcriptional changes in dorsal horn neurons, inflammation also generates a humoral cytokine signal that, following systemic spread in the bloodstream, acts on endothelial cells of the cerebrovascular system to produce the cytokine interleukin-1 β (IL-1 β), which enters the cerebrospinal fluid [83]. A further source of IL-1 β and other cytokines in the CNS is recruitment and activation of microglia [84]. Activated microglia in the dorsal horn seem to have a particular role in inducing neuropathic pain [85], including one that involves p38 MAPK [86,87]. IL-1 β acts on receptors expressed on many neurons in the spinal cord and leads to a widespread transcription of COX-2 in neurons [67] (Figures 1,3). The resultant prostaglandin production augments neuronal excitability in somatosensory pathways. Inhibition of centrally induced COX-2 is a major contributor to the analgesic action of COX-2 inhibitors on post-traumatic and inflammatory pain.

Similarities and differences between mechanisms of central sensitization and hippocampal LTP

Resemblance between the early phase of CA1 hippocampal LTP and activity-dependent classical central sensitization

The postsynaptic mechanisms responsible for the induction and expression of the early phase of CA1 hippocampal LTP [88,89] are compared here with known or proposed mechanisms of classical central sensitization. In general, however, considerably less is known about the precise cellular mechanisms of central sensitization than about hippocampal LTP.

Hippocampal LTP displays several basic properties relevant to its role in memory consolidation. LTP is input-specific, meaning that synaptic strength is selectively enhanced in those inputs subjected to repetitive activation (i.e. homosynaptic inputs). Other synapses onto the same postsynaptic cell will not be strengthened unless they too are active during the period of repetitive activation – the property of associativity. A minimum number of synapses must be activated to induce LTP. This is related to the need for sufficient postsynaptic depolarization, which can be accomplished by co-activating a large number of synapses – the property of cooperativity. Each of these characteristics points to a crucial role for NMDA receptors in LTP

induction because NMDA receptors require both glutamate and adequate depolarization of the postsynaptic cell for activation. Indeed, it has been well established that NMDA receptors are essential for the initiation of LTP, in the same way that they are indispensable for activity-dependent central sensitization. As in the dorsal horn, Src enhances hippocampal NMDA currents through phosphorylation of NR2A or NR2B NMDA receptor subunits [90,91].

Activation of the NMDA receptor and opening of its associated ion channel permits Ca²⁺ influx which, if sufficiently robust, leads to autophosphorylation of hippocampal CaMKII on Thr286 [92]. CaMKII can then move into the postsynaptic density, where it binds the NR2B subunit of the NMDA receptor and transforms into a persistently active state. In this state, it continues to be active even in the absence of Ca²⁺ and calmodulin, and is no longer a substrate for inactivation by phosphatase 1 (PP1) [93]. Phosphorylated CaMKII also associates with NR2 subunits in the dorsal horn [52] suggesting that a similar mechanism might also exist here (Figure 2).

Once docked to NMDA receptors at the synapse, CaMKII phosphorylates GluR1 AMPA receptor subunits on Ser831, enhancing the single-channel conductance of synaptic AMPA receptors [94]. In addition, CaMKII also induces rapid trafficking and incorporation of GluR1-containing AMPA receptors into hippocampal synapses via Ras and the subsequent activation of either the ERK or phosphatidylinositol 3-kinase pathways [95,96]. PKA-mediated phosphorylation of GluR1 at Thr845 is essential for delivery of GluR1-containing AMPA receptors to hippocampal synapses but, unlike that by CaMKII, phosphorylation by PKA alone is not sufficient for trafficking of new receptors [88]. Trafficking and insertion of GluR1-containing AMPA receptors has not yet been shown to contribute to central sensitization. However, following PKC activation, GluR2- and/or GluR3-containing AMPA receptors can be recruited to dorsal horn synapses, leading to synaptic strengthening [97]. Certain forms of LTP in the hippocampus involve signaling by Rap1, which couples cAMP to ERK and leads to phosphorylation of the A-type K⁺ channel K_v4.2 [98]. ERK also modulates A-type K⁺ currents in dorsal horn neurons [54] and contributes to central sensitization [70].

To function as a mechanism of information storage, LTP must be counterbalanced by mechanisms of depotentiation and long-term depression (LTD). In the hippocampus, these processes are mediated by protein phosphatases (e.g. PP1 and calcineurin), which induce AMPA receptor internalization [88]. Bidirectional modifiability of synaptic strength has also been demonstrated in the dorsal horn [65].

In summary, central sensitization and the early phase of hippocampal LTP share two general mechanisms: (i) phosphorylation of synaptic receptors and (ii) insertion of new AMPA receptors into the postsynaptic membrane. However, there is an important mechanistic distinction between the two phenomena. Hippocampal LTP reflects only synaptic strengthening, whereas central sensitization might also reflect other cellular mechanisms, such as

Table 1. Molecules involved in LTP in hippocampal neurons and central sensitization in dorsal horn neurons^{a,b}

| Molecule | LTP | CS | Molecule | LTP | CS |
|--|-----|----|---|-----|----|
| Glutamate receptor subunits | | | Protein kinases and phosphatases | | |
| NR1 (NMDA-receptor subunit) | ↑ | ↑ | PKA, Cβ1 subunit | ↑ | ? |
| NR2A (NMDA-receptor subunit) | ↑ | ↑ | PKA, R1β subunit | ↑ | ↑ |
| GluR1 (AMPA-receptor subunit) | ↑ | ↑ | PKC, γ subunit | ↑ | ↑ |
| mglu ₁ | ↑ | ↑ | PKG | ↑ | ↑ |
| mglu ₅ | ↑ | ↑ | CaMKII | ↑ | ↑ |
| Other neurotransmitter and neuromodulator receptors | | | CaMKIV | ↑ | ? |
| NK ₁ (receptor for substance P) | ? | ↑ | ERK1 and ERK2 | ↑ | ↑ |
| μ opioid receptor | ↑ | ↓ | p38 MAPK | ↓ | ↑ |
| δ opioid receptor | ↑ | ↓ | Src | ↑ | ↑ |
| κ opioid receptor | → | ↓ | Pyk2 | ↑ | ? |
| CB ₁ (receptor for cannabinoids) | ↓ | ↓ | Protein phosphatase I | ↓ | ? |
| GABA _A receptor | ↓ | ↓ | Calcineurin | ↓ | ? |
| GABA _B receptor | ↓ | ↓ | STEP | ↓ | ? |
| EP receptor (receptor for PGE ₂) | ↑ | ↑ | Transcription factors and IEGs | | |
| TrkB (receptor for BDNF) | ↑ | ↑ | CREB | ↑ | ↑ |
| IL-1 receptor | ↓ | ↑ | Zif268 | ↑ | ? |
| Intracellular messengers | | | Arc | ↑ | ? |
| Carbon monoxide | ↑ | ↑ | Homer | ↑ | ? |
| Nitric oxide | ↑ | ↑ | | | |
| NNOS | ↑ | ↑ | | | |
| iNOS | ↑ | ↑ | | | |
| COX-1 | → | ↑ | | | |
| COX-2 | ↑ | ↑ | | | |

^aAbbreviations: CaMK, Ca²⁺/calmodulin-dependent protein kinase; COX, cyclooxygenase; CREB, cAMP-response-element-binding protein; CS, central sensitization; ERK, extracellular signal-regulated kinase; IEGs, immediate-early genes; IL, interleukin; iNOS, inducible NOS; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; mglu, metabotropic glutamate receptor; NK₁, neurokinin-1; nNOS, neuronal NOS; NOS, nitric oxide synthase; PGE₂, prostaglandin E₂; PKA, cAMP-dependent protein kinase; PKC, Ca²⁺/phospholipid-dependent protein kinase; PKG, cGMP-dependent protein kinase; TrkB, tropomyosin-related kinase B; STEP, striatum-enriched protein phosphatase.

^bSymbols: ↑, increase; ↓, decrease; →, no change; ?, unknown.

changes in intrinsic membrane properties and/or neuronal networks (e.g. disinhibition).

Resemblance between the late phase of LTP and transcription-dependent central sensitization

The late phase of hippocampal LTP requires CREB-mediated synthesis of mRNA and protein [99]. This process is initiated by NMDA receptors, mglu receptors, muscarinic receptors, β-adrenoceptors and/or dopamine receptors, and the subsequent activation of PKA, PKC and/or CaMK signaling cascades [68,100] (Figure 3). These cascades converge on ERK activation, resulting in phosphorylation of CREB at Ser133 [101] and CREB binding to CRE [76]. In the hippocampus, this leads to the transcription of immediate-early genes with CRE promoters [76], including those encoding zif268, Arc and Homer, and the late-response genes encoding BDNF and CaMKII. CREB activation in the dorsal horn follows a similar pathway but leads to transcription of the immediate-early gene encoding COX-2 and the late-responsive genes encoding NK₁, prodynorphin and trkB [66].

Central sensitization and clinical pain

Central sensitization plays a major role in the generation of acute post-operative and post-traumatic pain [102,103], migraine and neuropathic pain [104–108]. Some clinical conditions, such as tension-type headache and fibromyalgia, appear not to be a reaction to a peripheral pathology but instead an expression of the presence of central sensitization [104,109]. Why central sensitization

manifests – apparently spontaneously – in these patients remains to be established.

Multiple molecules mediating LTP and central sensitization

More than 100 molecules have been implicated as mediators or modulators of hippocampal LTP [110]. Many of these are also involved in spinal central sensitization and the subsequent generation of pain hypersensitivity (Table 1). The similarities between these two forms of synaptic plasticity are striking, particularly post-translational regulation of AMPA and NMDA receptors, trafficking of AMPA receptors, and activation of the ERK–CREB pathway. However, there are also differences. For example, NK₁ and COX-2 play roles in central sensitization but not in hippocampal LTP.

Concluding remarks

The prolonged sensitization of pain transmission neurons after peripheral injury, by producing pain hypersensitivity and thereby promoting repair, is an adaptive response. This is usually followed by return to a normal high-threshold for activation of pain when healing is complete, unless the nervous system is damaged. Targeting the mechanisms responsible for the induction and maintenance of central sensitization is a major component of analgesic therapy that is made difficult by the need to avoid interrupting memory formation and cortical function. NMDA receptor antagonists such as ketamine are effective in reducing pain hypersensitivity but at an unacceptable

price of psychotomimetic effects and amnesia. Thus, optimal analgesia requires not only efficacy but also specificity. To achieve this, we need to search for the differences as well as the similarities between central sensitization and cortical LTP.

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