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Topical review

Learning and memory in pain pathways

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1. Introduction

The neurons of the central nervous system not only have the capacity to transmit, inhibit and weigh information, but they may also store information for prolonged periods of time (e.g. by use-dependent change in synaptic strength). Synaptic plasticity in hippocampus is an extensively studied cellular model of learning and memory and recent studies suggest that similar mechanisms also apply to pain pathways and may account for some forms of hyperalgesia, allodynia and analgesia. The discovery of synaptic long-term plasticity in nociceptive systems provides a relatively simple and straight forward concept for a number of clinically relevant phenomena. Here, I will briefly summarize key aspects of synaptic plasticity in general. Then I will describe related changes at nociceptive synapses and discuss the potential relevance of these mechanisms for the development, the prevention and the treatment of chronic pain.

2. A synaptic model of learning and memory

Since the early work by Ramón y Cajal and Sherrington, the remarkable capacity of the brain to transform transient experiences into memories has been attributed to long-lasting, activity-dependent changes in synaptic strength. Direct experimental evidence for this was, however, not available until Bliss and Lømo (1973) demonstrated a use-dependent long-term potentiation (LTP) of synaptic strength in hippocampus, an area implicated in learning and memory. Since then the neurobiological mechanisms underlying LTP at glutamatergic synapses, the most common type of excitatory synapses in the nervous system, became one of the most intensively studied topics in modern neuroscience. While synaptic LTP was initially associated only with *cortical* mechanisms of learning it later became clear that LTP is not a unique feature of synapses in hippocampus, but can be induced in numerous areas of the brain and spinal cord. Although the mechanisms of induction and maintenance of LTP may vary between different types of synapses, some principles have emerged that can be found at most glutamatergic synapses throughout the brain. These general properties are summarized below, more detailed descriptions can be found elsewhere (Bliss and Collingridge, 1993; Malenka, 1994; Linden, 1999).

Conditioning electrical stimulation of presynaptic nerve fibers, usually at relatively high frequencies (20–200 Hz for a few seconds) induces an LTP of synaptic strength that involves calcium-dependent *signal transduction* pathways. A transient, but significant increase in postsynaptic $[Ca^{2+}]_i$ is both necessary and sufficient for LTP induction. At most glutamatergic synapses this can be achieved by calcium influx through glutamate-gated channels of the *N*-methyl-D-aspartate receptor (NMDAR) type, but voltage-gated calcium channels, calcium permeable alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (AMPAR) channels or calcium release from intracellular stores (e.g. triggered by activation of group I metabotropic glutamate receptors (mGluRs)) may also be involved. The transient increase in $[Ca^{2+}]_i$ activates calcium-calmodulin-dependent protein kinase II (CaMKII), protein kinase A (PKA) and protein kinase C (PKC) that phosphorylate synaptic phospho-proteins including AMPARs. The GluR1 subunit of the AMPAR is regulated by protein phosphorylation at two sites, at serine 831 by CaMKII / PKC and at serine 845 by PKA. Phosphorylation at either of these sites potentiates AMPAR function through distinct biophysical mechanisms. CaMKII phosphorylation regulates the apparent single channel conductance of the receptor, whereas PKA phosphorylation enhances open channel probability (Lee et al., 2000). In addition, serine/threonine- or tyrosine phosphorylation of the NMDAR channel complex results in enhanced NMDAR-gated currents which contributes to the expression of LTP at some glutamatergic synapses.

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Synapses have been identified that express ionotropic glutamate receptors of the NMDA but not the AMPA type. Because of the voltage-dependent Mg^{2+} block of the NMDAR channel at resting membrane potential, synaptically released glutamate fails to evoke postsynaptic currents at these synapses. Only when the postsynaptic neuron is strongly depolarized will presynaptic activity evoke postsynaptic responses. Stimulation protocols that induce LTP may transform these *silent synapses* into active ones by insertion of functionally active AMPA receptors (Liao et al., 1995). Thus, activity-dependent potentiation of synaptic strength can be attributed to an enhanced number and/or function of postsynaptic AMPARs and NMDARs.

LTP is associative, that is a strong activation of one set of excitatory synapses can facilitate LTP induction at an independent set of adjacent active synapses. This phenomenon is best explained by the necessity to remove the voltage-dependent Mg^{2+} block of NMDAR channels by strong, simultaneous activation of convergent synapses. This is considered a cellular analogy of associative learning and classical conditioning.

Normally LTP is limited to those synapses that were active during conditioning stimulation (*homosynaptic LTP*). Under certain conditions LTP may also involve synapses that converge onto the same postsynaptic neuron but that were not active during conditioning stimulation (*heterosynaptic LTP*). Heterosynaptic plasticity may result from diffusion of Ca^{2+} from active to neighboring inactive synapses or by Ca^{2+}-induced Ca^{2+}-waves that are released from intracellular Ca^{2+}-stores or by action potential back-propagation in the dendritic tree (Magee and Johnston, 1997). While maintenance of the early phase of LTP lasting a few hours involves post-translational changes of synaptic proteins, the late phase lasting days or weeks requires de novo protein synthesis.

Normal synaptic transmission can also be *depressed for long periods* of time (*LTD*) and an established LTP can be de-potentiated by sustained conditioning low frequency stimulation (often 1–2 Hz for 15 min). LTD and de-potentiation require a moderate rise in $[Ca^{2+}]_i$ less than required for induction of LTP. It has been suggested that activation of calcium-dependent protein phosphatases and dephosphorylation of synaptic proteins such as AMPARs are involved. Thus, an important bi-directional regulator of synaptic strength is the phosphorylation state of phospho-proteins in the postsynaptic density. When the postsynaptic membrane is depolarized, brief, burst-like presynaptic activity may lead to a steep rise in Ca^{2+} and thus to LTP. The same presynaptic conditioning stimulus may, however, result in only a small rise in $[Ca^{2+}]_i$ if the postsynaptic neuron is hyperpolarized during conditioning stimulation, leading to LTD rather than to LTP. Prolonged low frequency presynaptic activity results in LTD at normal resting membrane potential and in LTP if the postsynaptic neuron is strongly depolarized. Thus, use-dependent synaptic plasticity provides a rich and versatile computational tool to modify the function of neuronal nets quickly and reversibly. Hippocampal LTP and some forms of learning share pharmacological profiles and become deficient in mice lacking the NMDAR $\alpha 1$ subunit or α-calcium-calmodulin-dependent protein kinase II (CaMKII). An essential piece of evidence for involvement of LTP in learning and memory was provided recently. It was shown that synaptic LTP can be induced in intact animals not only by presynaptic tetanic electrical stimulation, but also when the animals were performing learning tasks or during fear conditioning (McKernan and Shinnick-Gallagher, 1997)

3. Synaptic LTP in pain pathways

Hyperalgesia and allodynia following trauma, inflammation or acute nerve injury are, at least in part, caused by an enhanced sensitivity of nociceptive spinal dorsal horn neurons to sensory stimulation. This phenomenon has been termed *central sensitization* in analogy to peripheral sensitization (i.e. the enhanced sensitivity of nociceptive nerve endings) (see Moore et al., 2000 for a recent review). Central sensitization is triggered by impulses in nociceptive C-fibers. The neural mechanisms that underlie central sensitization are under intensive investigation. Here, I present a concept that explains many pharmacological, physiological and behavioral aspects of central sensitization and injury-induced hyperalgesia: The use-dependent LTP of synaptic strength in fine primary afferent nerve fibers. Repetitive electrical stimulation of fine primary afferents (100–400 pulses given at 2–100 Hz) induces LTP of synaptic strength in Aδ- (Randić et al., 1993) and in C-fibers (Liu and Sandkühler, 1995, 1997) in vitro and in vivo. More importantly, strong natural noxious stimuli such as skin burns, contusions, inflammation and acute nerve injury may also induce synaptic LTP in superficial spinal dorsal horn of deeply anesthetized rats (Sandkühler and Liu, 1998). The conditioning stimuli that induce synaptic LTP in fine primary afferents are similar to those that trigger hyperalgesia. Further, spinal LTP and injury-induced hyperalgesia share signal transduction pathways, time course and pharmacological profile, which makes use-dependent LTP at Aδ- and C-fiber synapses an attractive cellular model of injury-induced central sensitization and hyperalgesia.

3.1. Signal transduction pathways of LTP at spinal nociceptive synapses

In the spinal dorsal horn, simultaneous activation of multiple receptors – NMDARs, neurokinin receptor1 (NK1R) for substance P and NK2R for neurokinin A and mGluRs – is required for LTP induction, either by tetanic electrical nerve stimulation or by natural noxious stimulation (Randić et al., 1993; Liu and Sandkühler, 1995, 1997). Activation of these receptors during tetanic nerve stimulation leads to a transient and significant increase in $[Ca^{2+}]_i$ in spinal dorsal horn neurons in vitro and noxious stimulation

induces translocation and activation of PKC in these neurons in vivo. In acutely isolated spinal dorsal horn neurons, activation of the α-subunit of CaMKII enhances AMPAR- and NMDAR-gated inward currents and synaptic responses of spinal dorsal horn neurons (Kolaj et al., 1994). Blockade of NMDARs, neurokinin receptors or mGluRs prevents induction of spinal LTP, but not its maintenance or normal synaptic transmission. Correspondingly, blockade of these receptors prevents afferent-induced central sensitization and hyperalgesia following trauma, inflammation or acute nerve injury, but it does not consistently block its maintenance or acute pain (see Moore et al., 2000 for a recent review). Since expression of synaptic LTP may involve enhanced NMDAR-gated postsynaptic inward currents it is not surprising that maintenance of some forms of central sensitization is affected by NMDAR blockade.

3.2. Silent synapses in superficial spinal dorsal horn

In superficial spinal dorsal horn of neonatal rats, silent synapses have been identified that could be transformed into functional ones by serotonin (Li and Zhuo, 1998). In more mature rats no or few silent synapses were found in spinal cord of control rats or in rats with a sciatic nerve injury (Baba et al., 2000). Thus, any role of silent synapses for spinal LTP and neuropathic pain in adult animals remains to be shown.

3.3. Homo- and heterosynaptic plasticity in spinal cord

Conditioning stimulation at Aδ-fiber strength induces LTP at Aδ-fiber synapses (Randić et al., 1993). When stimulation intensity is increased to also recruit C-fibers, LTP at C-fibers synapses is induced (Liu and Sandkühler, 1995, 1997). This is compatible with a homosynaptic form of LTP involving only those synapses that were active during conditioning stimulation. However, prolonged burst-like stimulation of sciatic nerve at Aδ-fiber strength induced LTP at synapses of C-fibers (Liu et al., 1998), suggesting that a heterosynaptic LTP can also be evoked in superficial spinal dorsal horn. Tonic excitation of C-fibers not only leads to an increase in spinal dorsal horn neuron responses to noxious stimuli, but also to an expansion of low threshold mechanoreceptive fields (Hylden et al., 1989). Possibly synaptic transmission in Aβ-fibers was facilitated by conditioning stimulation in C-fibers. Similarly, secondary hyperalgesia surrounding the area of primary injury or outside the area of intra-cutaneous injection of capsaicin in humans may be explained by heterosynaptic LTP (Treede and Magerl, 2000). In a recent psychophysical study, an LTP of pin-prick sensation was elicited in human volunteers following tetanic electrical stimulation of cutaneous peptidergic primary afferents (Klein, Magerl, Sandkühler, Treede, unpublished observations). Up to now, an LTP at synapses of A-fibers by selective stimulation of C-fibers has, however, not been shown. Thus, the underlying neuronal mechanisms remain to be elucidated.

3.4. Time course of spinal synaptic plasticity

The onset and the duration of spinal LTP critically depends upon the type and intensity of conditioning stimulation and the activity of inhibitory controls. Full expression of LTP may take only a few minutes after tetanic nerve stimulation (Randić et al., 1993; Liu and Sandkühler, 1995, 1997) or may require up to an hour after natural noxious stimulation (Sandkühler and Liu, 1998). Potentiation may last for only a few minutes (synaptic short-term potentiation), for example after a single brief tetanus applied to a sensory nerve or following mild natural noxious stimulation. LTP may, however, not be reversible within the recording period of up to 12 h after repetitive tetanic nerve stimulation (Liu and Sandkühler, 1995, 1997). In awake animals hippocampal LTP may last for the whole life span of an animal.

The rapid onset and variable duration of synaptic plasticity fits well with the temporal profile of hyperalgesia following trauma and inflammation. For example, the brief but strong excitation of a relatively small number of C-fiber nociceptors by an experimental intra-dermal capsaicin injection leads to intense pain for a few minutes and to an immediate primary and secondary hyperalgesia that may last for several hours. The excitation of all C-fibers in a sensory nerve by conditioning electrical nerve stimulation or nerve injury during severe trauma rapidly induces hyperalgesia that may last for days and weeks. The rapid onset of allodynia surrounding an area of injury within a few minutes can not be explained by a phenotypical switch or intraspinal sprouting of Aβ-fibers, but suggests that functional plasticity such as LTP of synaptic strength may be involved. An interesting suggestion is that an injury triggers the potentiation of excitatory synaptic transmission between A-fibers and inhibitory interneurons that make presynaptic contact with primary afferent C-fibers. Activation of these interneurons and release of inhibitory neurotransmitter, probably γ-aminobutyric acid (GABA), then induces a depolarization of C-fiber terminals [i.e. a primary afferent depolarization (PAD)]. When Aβ-fiber-evoked excitation of these spinal interneurons is potentiated, PAD may become sufficiently strong to depolarize C-fibers to threshold for action potential firing. In this case activation of Aβ-fibers would trigger action potentials in C-fibers and, as a consequence, touch-evoked pain (allodynia) (Cervero and Laird, 1996).

3.5. Wind-up and synaptic LTP

Wind-up is a form of short-term plasticity in spinal dorsal horn that can be observed during electrical stimulation of C-fibers at 0.3–3 Hz. In response to the first 10–20 electrical C-fiber stimuli, the action potential firing of some wide-dynamic range (WDR) neurons in deep dorsal horn

increases progressively (i.e. responses are wound-up). Wind-up is typically studied in the absence of central sensitization. Thus, wind-up is a normal feature of the coding properties of some WDR neurons and not an expression of central sensitization. Wind-up is neither necessary nor sufficient for the induction of central sensitization or hyperalgesia (Herrero et al., 2000) leading to the conclusion that "wind-up and central sensitization are not equivalent" (Woolf, 1996). However, wind-up may facilitate induction of LTP at C-fiber synapses, as a progressive postsynaptic depolarization enhances calcium influx into the cell through NMDAR channels and voltage-dependent calcium channels. Because wind-up is rare in neurons of the superficial dorsal horn, this mechanism would apply mainly to C-fiber synapses on deep dorsal horn neurons with dendrites extending into lamina II. In addition, wind-up may be a target of central sensitization. An established LTP at C-fibers synapses might shift the wind-up-frequency function to lower frequencies due to enhanced temporal summation. A leftward shift of perceptual wind-up was indeed found in human volunteers after topical capsaicin application (reviewed in Herrero et al., 2000).

3.6. LTP beyond the first synapse in nociceptive pathways

If this hypothesis is correct and synaptic plasticity at the first synapse of fine primary afferents plays a role in the development and maintenance of hyperalgesia, it should be shown that the effects of this LTP are not being filtered out or compensated at higher levels of the neuraxis. Recently all the characteristics of LTP that were originally described at synapses of primary afferent C-fibers in superficial spinal dorsal horn were confirmed by recording C-fiber-evoked discharges of WDR neurons in deep dorsal horn. This includes the induction mechanisms (Rygh et al., 1999; Svendsen et al., 1999a), the pharmacological profile (Svendsen et al., 1998, 1999b) and sensitivity to descending inhibition (Svendsen et al., 1999a). In their early work, Wall and Woolf (1986) demonstrated that conditioning stimuli to the sciatic nerve at C-fiber strength (1 Hz, 20 s) produced a facilitation of the flexor reflex for at least one hour. Surprisingly, LTP-inducing conditioning electrical stimuli of sciatic nerve evoked a long-lasting increase in hot-plate latencies in animals, which has been interpreted as an override of segmental facilitation by enhanced descending inhibitory control (Svendsen et al., 1999c). A recent psychophysical study in human volunteers suggest, however, that tetanic stimulation of peptidergic primary afferents with parameters similar to those that induce synaptic LTP in spinal cord also leads to LTP of pin-prick sensation (Klein, Magerl, Sandkühler, Treede, unpublished observations). Thus, use-dependent LTP of synaptic strength in fine primary afferents affects nociception downstream to the first synapse and appears to be an important mechanism underlying some forms of hyperalgesia in humans.

It is likely that synaptic strength higher up in nociceptive pathways can also be modulated in a use-dependent manner. The reversible reorganization of cortical maps in patients with phantom limb pain (Flor et al., 1995) are likely caused by transient functional plasticity rather than by slowly reversible morphological changes. If cortical LTP and LTD are cellular substrates of cognitive learning and memory, then behavioral and cognitive therapies of chronic pain should also affect synaptic function in the brain. The activity in descending pathways is not constant but can be modulated, e.g. by the level of vigilance or attention and by stress. Thus, via descending pathways behavioral and cognitive therapies might also affect synaptic transmission in spinal cord and thereby have the capacity to prevent or reverse long-term changes of synaptic strength in pain pathways. This is a possible cellular mechanism of the effectiveness of psychological interventions in those chronic pain syndromes in which synaptic functions are altered.

4. Prevention and reversal of LTP in pain pathways

4.1. Endogenous analgesia and opioids pre-empt induction of LTP at nociceptive synapses

LTP induction requires a steep rise in postsynaptic $[Ca^{2+}]_i$. One can therefore predict that LTP induction is sensitive to pre- and postsynaptic inhibition as this would reduce any synaptically evoked rise in $[Ca^{2+}]_i$. To test this prediction we have used mild conditioning noxious stimuli that were insufficient to induce LTP in animals with descending antinociceptive systems intact. The descending pathways are known to exert a pre- and postsynaptic inhibition on nociceptive spinal dorsal horn neurons. When this inhibition was abolished by spinalization rostral to the recording site, LTP was successfully induced by the same previously ineffective conditioning stimuli (Sandkühler and Liu, 1998). Further, in spinalized but not in intact animals, application of NMDA or substance P directly onto the spinal cord was sufficient to induce LTP at synapses of C-fibers (Liu and Sandkühler, 1998). This suggests that (1) presynaptic activity is not essential for LTP induction and (2) that extrasynaptic spread of neuromodulators in spinal cord can lead to central sensitization in areas remote from the release sites, at least if endogenous antinociception is absent or insufficient. If this also applies to human pain patients one might speculate that in patients who are not well protected by their endogenous antinociceptive systems, even relatively mild injuries may trigger LTP in nociceptive pathways leading to hyperalgesia. These patients should benefit from pre-emptive analgesia. In contrast, in patients with an endogenous analgesia sufficient to block LTP induction, pre-emptive analgesia would not be expected to provide any additional benefits. μ-opioid receptor agonists are currently used for pre-emptive analgesia. However, activation of μ-opioid recep-

tors may enhance NMDAR-gated currents and could therefore facilitate rather than pre-empt the induction of spinal LTP. To test this possibility, we gave the clinically used μ-opioid receptor agonists fentanyl or remifentanyl systemically to adult rats before LTP induction. This reduced C-fiber evoked spinal field potentials to 25% of the pre-drug controls. Conditioning tetanic stimulation of sciatic nerve at C-fiber intensity failed to induce LTP: after washout of short-acting remifentanyl, C-fiber-evoked responses returned to pre-drug baseline (Benrath, Brechtel, Sandkühler, unpublished observations). This indicates that clinically used μ-opioid receptor agonists can effectively prevent induction of LTP. When opioids were applied systemically or directly onto the spinal cord during the maintenance phase of LTP, C-fiber-evoked discharges were temporarily reduced (Rygh et al., 2000) but potentiation was not reversed. The potency of morphine to attenuate potentiated C-fiber-evoked discharges was reduced as compared to control responses (Rygh et al., 2000). These results suggest that clinically used μ-opioid receptor agonists are useful to pre-empt spinal LTP and central sensitization, but fail to normalize (de-potentiate) synaptic strength during the maintenance phase of LTP. A long-lasting analgesia can be achieved, however, by some forms of counter-irritation such as low frequency transcutaneous electrical nerve stimulation (TENS) and (electro-) acupuncture. The potential synaptic mechanisms of these therapeutic interventions are described in the next section.

4.2. Synaptic effects of TENS and acupuncture

In spinal cord, synaptic strength between primary afferent Aδ- or C-fibers and spinal dorsal horn neurons can not only be potentiated, but can also be depressed for long periods of time by conditioning afferent stimulation (Randić et al., 1993; Sandkühler et al., 1997; Chen and Sandkühler, 2000). A homosynaptic depression is induced at Aδ-fiber synapses when dorsal roots are stimulated in vitro at 1 Hz for 30 min. This inhibition is independent of activation of $GABA_A$ or glycine receptors, but requires activation of NMDARs (Sandkühler et al., 1997) and mGluRs (Chen et al., 2000; Chen and Sandkühler, 2000). A putatively heterosynaptic depression of synaptic strength in C-fibers can be achieved by repetitive burst-like stimulation of Aδ-fibers in adult rats in vivo (Liu et al., 1998). The selective stimulation of Aα/β-fibers afferents failed to modify synaptic strength in Aδ- or C-fibers in vitro and in vivo (Sandkühler et al., 1997; Liu et al., 1998). Similar results were recently found by optical recording of C-fiber-evoked activity in lamina II of young rat spinal cord slices (Ikeda et al., 1999, 2000). The afferent-induced long-lasting antinociception requires activation of Aδ-fibers and is independent of GABAergic and glycinergic inhibition. This is different to the antinociception during stimulation of sensory nerves at Aα/β-fiber intensity which is short-lived and involves GABAergic interneurons. Thus, two fundamentally different forms of spinal analgesia can be evoked by transcutaneous electrical nerve stimulation (TENS) and (electro-) acupuncture: The analgesia during TENS at low Aα/β-fiber intensity causing paresthesia but no pain is best explained by the gate-control theory (Melzack and Wall, 1965). The long-lasting analgesia following TENS at a higher (mildly painful) Aδ-fiber intensity or electro-acupuncture is best explained by an LTD of synaptic strength in Aδ and C-fibers (Sandkühler, 2000).

The direction of synaptic plasticity critically depends upon the postsynaptic membrane potential during conditioning stimulation. Depolarization favors induction of LTP while hyperpolarization favors induction of LTD in spinal dorsal horn neurons (Randić et al., 1993). Repetitive burst-like stimulation of Aδ-fibers induced LTD in intact animals. In spinalized animals (i.e. with tonic descending inhibitory pathways interrupted), the same stimulation protocol now induced an LTP rather than an LTD (Liu et al., 1998). In addition to tonic inhibitory descending pathways, descending systems exist that facilitate spinal nociception and induction of hyperalgesia (Urban et al., 1996). The variable and typically unknown balance between the activity in inhibitory and facilitating systems during therapeutic counter-stimulation may explain the clinical observation that identical stimulation protocols may produce strong and lasting analgesia in some patients, but may initially aggravate pain or be ineffective in others. Based on these synaptic mechanisms, I have recently suggested to use a novel form of *sequential TENS* (or electro-acupuncture) to improve efficacy of counter-stimulation (Sandkühler, 2000).

In conclusion, LTP at synapses of fine primary afferents in superficial spinal dorsal horn has striking similarities with phenomena of central sensitization and constitutes an attractive cellular model of injury-induced hyperalgesia. This includes the possibility that slow-onset changes of gene expression (Dubner and Ruda, 1992; Neumann et al., 1996; Woolf and Costigan, 1999) and/or structural reorganization in spinal dorsal horn (Woolf and Doubell, 1994) contribute to late phases of hyperalgesia as late stages of synaptic LTP may require de novo protein synthesis for maintenance (Bliss and Collingridge, 1993; Malenka, 1994; Linden, 1999). The fact that late, durable stages of synaptic plasticity may be less responsive to treatment provides a rational for the early and effective therapy of acute pain states.

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