Definition

This is a long-lasting increase in synaptic efficacy resulting from repetitive activation of the synapse. This process was first described in hippocampus, whereby high-frequency stimulation of afferent pathways leads to a potentiated post-synaptic response that can last for hours to days. It is a form of activity-dependent plasticity. LTP may increase the efficiency of pain transmission for weeks to months or longer.

- ► Alternative Medicine in Neuropathic Pain
- ► Opioids in the Spinal Cord and Central Sensitization
- ► Spinothalamic Tract Neurons, Role of Nitric Oxide

Long-Term Potentiation and Long-Term Depression in the Spinal Cord

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Synonyms

Long-Term Potentiation in the Spinal Cord; Long-Term Depression in the Spinal Cord

Definition

Hyperalgesia may result from an acute noxious event such as trauma, inflammation or nerve injury and may persist long after the primary cause for pain has disappeared. Altered processing of sensory information in the central nervous system may contribute to these forms of hyperalgesia. The long-term potentiation of synaptic strength in nociceptive pathways is a cellular model of pain amplification.

Long-term potentiation (LTP) and long-term depression (LTD) of synaptic strength are long-lasting changes in synaptic efficiency irrespective of the type and the location of chemical synapse. Activity dependent forms outlast conditioning pre- and/or post-synaptic stimulation by at least 30 min. Shorter lasting forms of synaptic plasticity are short-term potentiation or depression, post-tetanic potentiation and paired-pulse facilitation or depression. LTP and LTD may be induced and maintained by pre- and/or by post-synaptic mechanisms such as changes in transmitter release or receptor sensitivity or density. LTP and LTD are divided into at least two phases; the early phase up to 6 h is caused solely by posttranslational changes. In contrast, maintenance of the late stage (more than 6 h after conditioning) requires *de novo* protein synthesis. The signal transduction pathways involved depend upon the induction protocol, type of synapse, types of pre- and post-synaptic neurons, direction of synaptic plasticity and developmental stage. While synaptic plasticity cannot be studied by recording action potential firing or polysynaptic or behavioural responses, evaluation of these parameters is indispensable to show that synaptic plasticity is relevant to information processing downstream in the transmission path.

Characteristics

Synaptic Models for Learning and Memory in Pain Pathways

LTP and LTD were first described for synapses in the hippocampus and are now considered the major cellular models for learning and memory. The final proof is, however, still lacking, mainly since the neuronal elements and their activity patterns involved in cognitive or motor learning are largely unknown (Barnes 1995). Fortunately, in the nociceptive system our knowledge is considerably more advanced: The primary afferent nerve fibres as well as their activity patterns that lead to pain are known. Recently, 2nd order neurons in superficial spinal dorsal horn were identified that mediate hyperalgesia and allodynia. In particular, neurons in lamina I that express the NK1 receptor for substance P are essential for full expression of hyperalgesia in various animal model of inflammation and neuropathy (Nichols et al. 1999). These neurons are all nociceptive specific, most project to the parabrachial area and/or periaqueducatal grey and receive input from primary afferent, peptidergic C-fibres.

Conditioning stimulation of primary afferent C-fibres leads to LTP at C-fibre synapses with these lamina I projection neurons, but not other lamina I neurons (Ikeda et al. 2003). Several independent and convergent lines of evidence suggest that synaptic LTP in superficial spinal dorsal horn is a cellular mechanism of afferent induced hyperalgesia (reviewed in (Sandkühler 2000a; Willis 2002; Moore et al. 2000), see also additional original work cited in the text):

a) Protocols that Induce LTP also Cause Hyperalgesia in Animals and Humans

   1. Continuous electrical stimulation of C-fibres at low frequencies (1–5 Hz for 2 or 3 min) or high frequency burst-like stimulation (three to five 100 Hz bursts of 1 sec duration) induce LTP in various spinal cord-dorsal root slice preparations under different recording conditions (Ikeda et al. 2000; Ikeda et al. 2003; Randic et al. 1993) and in intact animal models (Liu and Sandkühler 1997) (Fig. 1). LTP at the first nociceptive synapse apparently affects downstream events in nociceptive pathways. Action potential firing in deep dorsal horn, wide dynamic range neurons (Svendsen et al. 1999) and pain rating in human volunteers (Klein et al. 2004) are also potentiated by similar conditioning stimuli (Fig. 1).
   2. Natural patterns of afferent barrage during noxious stimuli (subcutaneous injections of capsaicin

or formalin) in intact (i.e. not spinalised) animals also induce LTP in spinal cord and hyperalgesia in behaving animals.

b) Time Courses for LTP and Hyperalgesia are similar

3. LTPand hyperalgesia are induced within minutes after conditioning stimulation, excluding any time consuming processes such as sprouting of nerve fibres. LTP and hyperalgesia may outlast the conditioning stimulation by hours.
4. LTP and hyperalgesia may spontaneously reverse within hours or days or may persist for longer periods depending upon induction protocols and the context of conditioning.

c) Shared Pharmacology and Signal Transduction Pathways for LTP and Hyperalgesia

5. Co-activation of NMDA-, group I mGlu- and NK^{1}-receptors is required.
6. Activation of voltage-gated calcium channels is required.
7. Ca^{2+}-dependent signal transduction pathways are involved.
8. Activation of protein kinase C, calcium-calmodulin-dependent protein kinase II and nitric oxide synthase (in some cases) is necessary.

d) LTP and Hyperalgesia Can Be Prevented by the Same Means

9. Activity in descending inhibitory pathways raises the threshold for induction of both LTP and hyperalgesia.
10. Opioids can pre-empt induction of LTP (Benrath et al. 2004) and hyperalgesia (Katz et al. 2003).

Not all details of signal transduction pathways that have been explored in one model have also been investigated in the other. All presently known cellular key elements are, however, shared by spinal LTP and afferent induced, centrally expressed hyperalgesia. This strongly suggests that LTP at synapses of primary afferent C-fibres is a cellular mechanism of hyperalgesia. However, until now LTP has only been found at synapses of primary afferent C-fibres, but not at synapses of Aβ- or Aδ-fibres. Thus, neither Aδ-fibre mediated hyperalgesia, nor Aβ-fibre induced allodynia can presently be explained by synaptic LTP in superficial spinal dorsal horn.

Synaptic Long-Term Depression in Pain Pathways

Conditioning stimulation of primary afferent Aδ-fibres but not Aβ-fibres at low frequencies (1 Hz for 15 min) induces a homosynaptic LTD at Aδ-fibres synapses *in vitro* (Sandkühler et al. 1997; Chen and Sandkühler 2000; Randic et al. 1993) and a heterosynaptic LTD at synapses of C-fibres in intact animals (Liu et al. 1998). Similar stimulation parameters lead to long-term depression of primary afferent induced EPSCs in deep dorsal horn neurons (Garraway and Hochman 2001), of the jaw-opening reflex in mice (Ellrich 2004) and of human nociceptive skin senses (Nilsson et al. 2003; Klein et al. 2004). High intensity, low frequency forms of transcutaneous electrical nerve stimulation (TENS) can alleviate clinical pain in some human pain patients. (Electro-) Acupuncture, which leads to the "d Q" sensation, probably also induces a low frequency afferent barrage in Aδ-fibres. When effective, pain relief outlasts the duration of these forms of TENS and acupuncture for hours or days. This is compatible with synaptic LTD in pain pathways if counterirritation is applied closely to the painful area. In contrast, TENS given at high frequencies, but at low (Aβ-fibre) intensity, does not lead to long-lasting analgesia and cannot be explained by synaptic LTD in pain pathways. This low intensity-high frequency form of TENS most probably involves excitation of spinal inhibitory interneurons as described in the "gate-control" theory (reviewed in Sandkühler 2000b). In conclusion convergent evidence suggest that long-term potentiation at or near the first central synapse in pain pathways is relevant to some forms of hyperalgesia (synaptic long-term potentiation) and can also be used therapeutically to treat and perhaps prevent chronic pain states (synaptic long-term depression).

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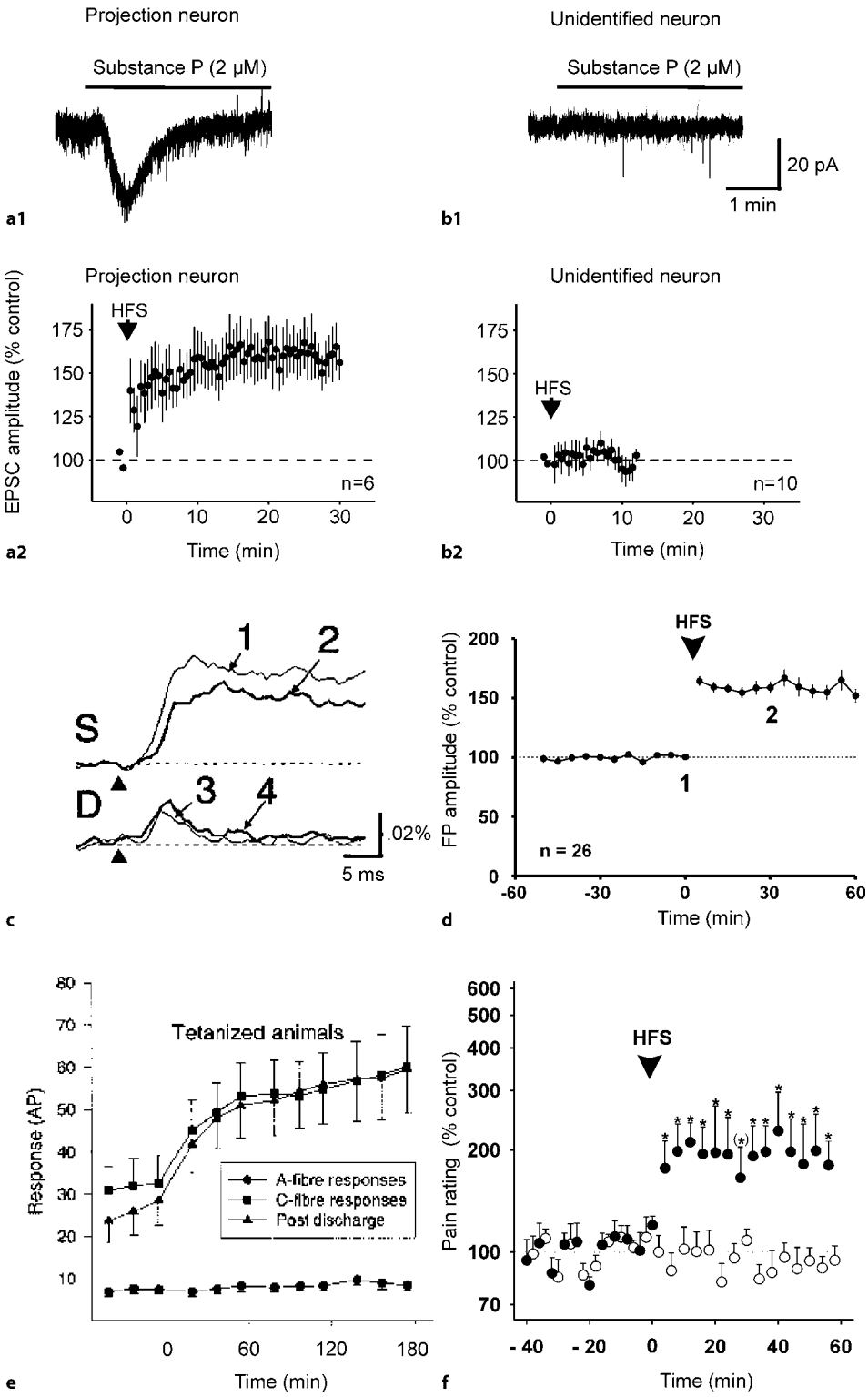
Projection neuron
Substance P (2 μM)
a1
Unidentified neuron
Substance P (2 μM)
20 pA
1 min
b1
EPSC amplitude (% control)
Projection neuron
HFS
175
150
125
100
n=6
0
10
20
30
Time (min)
a2
Unidentified neuron
HFS
175
150
125
100
n=10
0
10
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Time (min)
b2
1
2
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FP amplitude (% control)
HFS
200
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n = 26
-60
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60
Time (min)
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Response (AP)
Tetanized animals
A-fibre responses
C-fibre responses
Post discharge
80
70
60
50
40
30
20
10
0
60
120
180
Time (min)
e
Pain rating (% control)
HFS
600
500
400
300
200
100
70
- 40
- 20
0
20
40
60
Time (min)
f

◄ **Long-Term Potentiation and Long-Term Depression in the Spinal Cord, Figure 1,** Long-term potentiation (LTP) of synaptic strength in nociceptive pathways can be demonstrated under a wide range of experimental conditions *in vitro* (a-c) and *in vivo* (d-f) including human subjects (f). (a) In a rat spinal cord-dorsal root slice preparation, conditioning stimulation of dorsal root at C-fibre strength induces LTP at synapses of primary afferent C-fibres with lamina I projection neurons that express NK1 receptors for substance P. A1 illustrates an inward current elicited by bath application of substance P in the presence of tetrodotoxin. A2 shows the mean time course of peaks of monosynaptically, C-fibre-evoked postsynaptic currents before and after conditioning stimulation at time zero. (b) The same conditioning stimulation failed to induce LTP in unidentified neurons of lamina I that did not respond to substance P. Modified from Ikeda et al. 2003. (c) LTP can also be demonstrated by optical recording of C-fibre-evoked responses in superficial spinal dorsal horn in a spinal cord slice preparation. Superimposed time courses of optical responses immediately before (thin lines) and 75 min after (bold lines) high-frequency stimulation at two different locations in the dorsal horn, lamina II "S" and deeper dorsal horn "D". These responses are spatial averages recorded in all pixels present in the area ($\approx$ 60 pixels). Modified from Ikeda et al. 2000. (d) C-fibre-evoked field potentials recorded in superficial spinal dorsal horn of intact, deeply anaesthetized rats are potentiated throughout the recording period of up to 17 h by conditioning high-frequency stimulation of sciatic nerve at C-fibre strength (modified from Benrath et al. 2004). (e) C-fibre but not A-fibre-evoked firing responses of deep dorsal horn neurons and post discharge in spinalised rats are potentiated by a tetanic sciatic nerve stimulation at time zero (mean $\pm$ S.E.M. $n = 8$), modified from Svendsen et al. 1999. (f) Heterotopic effects of conditioning high frequency electrical stimulation of peptidergic cutaneous nerve fibres on pin prick-evoked pain. Conditioning HFS induced a significant enhancement of pin prick-evoked pain adjacent to the conditioning electrode (•) but not adjacent to the control electrode (○). This secondary hyperalgesia occurred after conditioning stimulus intensities of $10\times$ the detection threshold. Mean $\pm$ S.E.M. values across eight subjects are shown. Modified from Klein et al. 2004.

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Long-Term Potentiation in the Spinal Cord

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Loss of Consciousness Associated with Fentanyl

Definition

Loss of consciousness associated with fentanyl occurs at mean serum concentrations of 34 ng/ml.

► Postoperative Pain, Fentanyl

Loss of Olfactory Function

Definition

Also called dysosmia; anosmia describes the total loss of the sense of smell, and hyposmia describes a partial loss of olfactory function.

► Nociception in Nose and Oral Mucosa

Low Back Pain

Definition

Low back pain affects almost everyone at some point in their lives. It can be acute or chronic in nature and is a primary cause of functional disability in the working population. Multiple causes exist for low back pain including degeneration of the lumbar spine and associated intervertebral discs; intervertebral disc herniation; strain of associated muscles, ligaments, and tendons; and referral from other organs and tissues.

► Chronic Low Back Pain, Definitions and Diagnosis
► Evoked and Movement-Related Neuropathic Pain
► Low Back Pain, Epidemiology
► Low Back Pain Patients, Imaging

Low Back Pain, Epidemiology

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Synonyms

Pervasiveness of low back pain; Prevalence of low back pain; Incidence of Low Back Pain; Frequency of Low Back Pain; Factors Associated with Low Back Pain