Pathways of Spinal Pain

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Core Messages

✔ Chronic (persistent) pain has a high prevalence in the general population and is predominately felt as musculoskeletal pain
✔ A temporal classification of pain (i.e. acute, subacute, chronic) is arbitrary and does not reflect the underlying mechanisms of pain
✔ Pain is better differentiated into nociceptive, inflammatory, and neuropathic pain
✔ Neuropathic pain has lost its protective role and is maladaptive
✔ The physiologic processes involved in pain can be differentiated into transduction, conduction, transmission, modulation, projection and perception
✔ Nociceptive signals are modulated by various excitatory and inhibitory mechanisms on their pathways to the brain
✔ Genetic predisposition and biopsychosocial factors have a significant influence on pain perception
✔ Pain pathways can undergo distinct alterations as a result of peripheral tissue damage and neural injuries (neuroplasticity)
✔ The neuroplasticity of the pain pathways can be described in terms of peripheral sensitization, transcriptional changes in the dorsal root ganglion, central sensitization and disinhibition
✔ Persistent pain is not prolonged acute pain but follows distinct alterations in the pain pathways
✔ Neuropathic pain is different from nociceptive pain and results from primary damage or disease of the peripheral or central nervous system
✔ Not all persistent pain is neuropathic. The clinical differentiation of persistent inflammatory and neuropathic pain, however, remains a challenge
✔ Treatment of acute pain should be aggressive, multimodal and preemptive to avoid pain persistence
✔ Adjuvant drugs (e.g. antidepressants, anticonvulsants, anxiolytics) enhance the central effect of analgesics and should be included for an adequate treatment of moderate to severe pain
✔ The scientific evidence for a long-term effectiveness of surgical treatment of persistent spinal pain is lacking

Historical Background

Precartesian Theories

Early civilizations provided a wide variety of explanations for pain and attributed it to factors such as religious influences of gods, the intrusion of magical fluids, the frustration of desires and deficiency or excess in the circulation of Qi [70]. The relief of pain therefore was the task of shamans or priests, who used herbs, rites, and ceremonies to alleviate pain. The early Greeks gave more specific explanations for pain [70]. According to Plato (427 – 347 A.D.), the heart and the liver were the centers of appreciation of all the sensations, and pain arose not only from peripheral sensation but as an emotional response in the soul, which was located in the heart [70]. Hippocrates assumed a wrong mixture of fluids to be the cause of pain. However, Galen of Pergamon (130 – 200 A.D.) made the first observations on the nervous system and the spine but still believed the so-called “fluid doctrine” of Hippocrates (see Chapter 1).
Cartesian Theory

The French philosopher René Descartes (1596 – 1650) presented a dualistic view of the human body and soul, i.e. he assumed a separation of the mind and the body. The body was seen as a machine working according to the laws of nature and the “rational soul” was the “conductor of the orchestra” [70]. With the suggested separation of the soul from the human body, an endless controversy arose about the mind-body relation which has been plaguing and intriguing philosophers and neuroscientists ever since [7]. Descartes also proposed a simple pathway of the transmission of a noxious stimulus to the brain [22]. However, Descartes’ theory was only published after his death in the Traité de l’Homme [7]. Descartes gave a purely mechanical view of the involuntary withdrawal of a foot that comes into contact with a noxious stimulus: “the small rapidly moving particle of fire moves the skin of the affected spot causing a thin thread to be pulled. This opens a small valve in the brain and through it animal spirits are sent down to the muscles which withdraw the foot” [22]. After that it was believed for a long time that there was a one-to-one relationship between the amount of damage and the perceived pain. The theory of Descartes implies that a specific pain pathway carries the message from a pain receptor in the skin to a pain center in the brain. However, it has become apparently clear that pain cannot be alleviated by simply cutting this pathway. On the contrary, a dissection of this pathway can even exacerbate the pain [22].

Gate Control Theory

Major progress in our understanding of pain and its mechanisms followed the introduction of a new theory by Melzack and Wall in 1965 [77]. The authors suggested a gate control system which modulates sensory input from the skin before it evokes pain perception and response. Accordingly, the substantia gelatinosa in the dorsal horn functions as a gate control system that modulates the afferent patterns before they influence the central transmission cells. The afferent pattern in the dorsal column system acts as a central control trigger which activates selective brain processes that influence the modulation properties of the gate control system. The transmission cells activate neural mechanisms which compromise the action system responsible for response and perception [77]. This theory underwent multiple modifications and extensions throughout the following years. Although it has been shown that specific elements of the gate control theory are invalid or too simplistic, the fundamental model remains. Gates in the dorsal horn consisting of interneurons balance the level of sensory fiber activity and are influenced by descending brain signals. This concept explains how pain can be felt with and without tissue damage and how psychological factors can influence pain [84].

Modern Pain Theories

Since the introduction of Melzack and Wall’s theory, most of the research has focused on two general processes that can control the pain gate [19], i.e.:

- the inhibitory mechanism
- the exhibitory mechanism

Inhibitory neuronal circuits control nociceptive transmission in the spinal cord and act as gatekeepers suppressing undesirable inputs [19], while increased excitation can occur as a result of neural plasticity [130]. In the last decade, intriguing progress has been made in dissecting out the molecular and cellular mechanisms
that operate in sensory pathways to generate those neural signals that we ultimately interpreted as pain [9, 18, 55, 112].

**Epidemiology of Chronic Pain**

Epidemiological studies show a prevalence of chronic pain from 24% to 46% in the general population [31, 102]. Elliott et al. [31] showed that about 15% of patients suffer from the worst degree of pain. The most frequently reported forms of pain in this study are back pain and arthritic pain. In a 1-year follow-up study, 79% of patients reporting chronic pain at the baseline investigation still suffered from pain at the end of the study [31]. During this period the average annual incidence was about 8.3%, whereas the recovery rate was about 5.4% [31]. Chronic pain is localized in 90% of patients to the musculoskeletal system.

The incidence of musculoskeletal pain is reported to vary from 21% for shoulder pain up to 85% for low back pain in the industrialized nations [3, 10, 24, 42]. The reported lifetime prevalence of back pain is 84% [15] and that of neck pain 67% [20]. Dorsal (thoracic) pain is much less frequent. The 1-year prevalence of dorsal pain was 17% compared to 64% for neck and 67% for low back pain in a Finnish study [85]. In a primary care setting, most patients improve considerably during the first 4 weeks after seeking treatment. Sixty-six to 75% continue to experience at least mild back pain 1 month after seeking care. At 1 month, approximately 33% report continuing pain of at least moderate intensity, whereas 20–25% report substantial activity limitations. After more than 1 year, approximately 33% of patients report intermittent or persistent pain of at least moderate intensity, 14% continue to report back pain of severe intensity, and 20% report substantial activity limitations [118]. The patient population suffering from chronic back pain has been found to be responsible for an enormous part of the cost of the health care system (intake of analgesics, medical consultations, hospitalizations, requirement for diagnostic and therapeutic procedures) [82] (see also Chapter 6).

**Definition and Classification**

The manifestation of pain is largely variable but we define all sensations that hurt or are unpleasant as pain. The **Taxonomy Committee of the International Association for the Study of Pain** (IASP) [50] has provided a definition, which is widely used today (Table 1).

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<th>Table 1. Definition of pain</th>
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<td>“Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”</td>
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The IASP task force [50] stresses the fact that the inability to communicate verbally does not exclude that an individual is experiencing pain and requires appropriate pain-relieving treatment. Furthermore, the task force highlights that pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Accordingly, pain is that experience we associate with actual or potential tissue damage. It is also always unpleasant and therefore has an emotional experience. However, many people report pain in the absence of tissue damage or any likely pathophysiological cause. This latter pain cannot be differentiated from pain due to tissue damage if...
we consider the subjective report. If these individuals regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain [50].

**Temporal Course**

From a temporal perspective [50, 101], pain can be differentiated as:

- acute pain (<4 weeks)
- subacute pain (4 weeks to 3 months)
- chronic pain (>3–6 months)

**Acute pain** is caused by an adequate stimulation of nociceptive neurons. This pain typically results from soft tissue injury or inflammation and has a protective role by enabling healing and tissue repair [81, 122]. **Subacute pain** is often less intense and follows the acute phase. It is regarded as organic pain from tissue healing and remodeling. It usually lasts up to 12 weeks but usually not longer. In contrast, **chronic pain** has lost its protective role. In retrospect, it is often difficult to identify the noxious stimulus or tissue damage in patients presenting with chronic pain which originally causes the pain. Chronic pain induces biochemical and phenotypic changes in the nervous system that escalate and alter sensory inputs, resulting in physiologic, metabolic and immunologic alterations that threaten homeostasis and contribute to illness and death [81].

**Contemporary Pain Classification**

A timely distinction of pain is given by Clifford Woolf [106, 123], who suggests differentiating (Fig. 1):

- nociceptive pain
- inflammatory pain
- neuropathic pain
- functional pain

**Nociceptive Pain**

Nociceptive pain is a vital physiologic sensation which occurs in situations like trauma or surgery [123]. **Acute nociceptive pain** is elicited by noxious stimulation of normal tissue sufficiently intense to damage tissue. It has the important function of protecting tissue from further damage by, e.g. eliciting withdrawal reflexes.

**Inflammatory Pain**

In the case of tissue damage that occurs despite an intact nociceptive defensive system, the role of the nociceptive system switches from preventing noxious stimulation to promoting healing of the injured tissue. Inflammatory pain is characterized by an increased sensitivity to stimuli, which does not cause pain under normal conditions. This protects the individual from further damage to the injured part until the healing and repair process is completed. Inflammatory pain normally decreases during the healing process. An exception is inflammatory pain states due to surgery or chronic diseases such as rheumatoid arthritis. In these cases, pain management has to be conceptualized that decreases or normalizes pain sensitivity without impairing the warning system of nociceptive pain [59, 61, 106, 123, 125, 126].
Neuropathic Pain

In contrast to nociceptive pain, which is provoked by noxious stimulation of the sensory endings in the tissue, **neuropathic pain** is the result of a direct damage or disease of neurons in the periphery or central nervous system and seems not to have any beneficial effect. Therefore, peripheral neuropathic pain syndromes are differentiated from central pain. Neuropathic pain normally is felt as abnormal, because it is not related primarily to a signal of tissue damage. It often occurs spontaneously in a continuous or episodic form and is associated with other sensory abnormalities. Neuropathic pain often has a burning or electrical character and might be combined with **allodynia and/or hyperalgesia**. This type of pain often shows a chronic course and in most cases is difficult to treat. Neuropathic pain can have a **variety of causes**, e.g. [27, 106, 123, 128, 134]:

- nerve root injury (traumatic, compression syndrome)
- spinal cord injury
- brain lesions
- diabetic polyneuropathy
- AIDS polyneuropathy
- postherpetic

**Figure 1. Classification of pain**

Redrawn from Woolf [123] (with permission from ACP).

**Neuropathic pain** is the result of direct damage or disease of neurons

**Allodynia and hyperalgesia** are found in neuropathic pain
Functional Pain

This form of pain occurs due to an abnormal responsiveness or function of the nervous system. In the clinical examination, no neurological or peripheral abnormalities can be found. The physiological basis of functional pain is an increased sensitivity or hyperresponsiveness of the sensory system that amplifies symptoms. Syndromes which belong to this class of pain are, e.g. [106, 123]:

- fibromyalgia
- irritable bowel syndrome
- non-cardiac chest pain
- tension headache

Pathways of Pain

The physiologic processes [61, 81, 123] involved in pain sensation include (Fig. 2):

- **transduction** of noxious stimuli (thermal, mechanical and chemical) into electrical activity at the peripheral terminal of nociceptor sensory fibers
- **conduction** of the resulting sensory input to the central terminal of nociceptors
- **transmission** and **modulation** of the sensory input from one neuron to another
- **projection** to the brain stem, thalamus and cortex
- **perception** of the sensory input at the somatosensory cortex.
Transduction

Nociception can be defined as the detection of noxious stimuli and the subsequent transfer of encoded information to the brain while pain is a perceptual process that arises in response to such activity [61]. Nociception is mediated by activation of peripheral sensory-nerve terminals located in, e.g. the skin, deep fascias, muscles, and joints. These terminals are called primary sensory neurons or nociceptors. We can differentiate **three types of noxious stimuli** which are targeted by the receptor of nociceptors, i.e.:

- mechanical (pressure and mechanical stress)
- thermal (hot/cold)
- chemical

**Primary sensory neurons** can be excited by noxious heat, intense pressure or irritant chemicals, but not by innocuous stimuli such as warm or light touch [55]. The conversion of a noxious thermal, mechanical, or chemical stimulus into electrical activity in the peripheral terminals of nociceptor sensory fibers is described as **transduction** [123].

**Mechanical stress** resulting from direct pressure, tissue deformation or osmolarity changes can activate nociceptors allowing for the detection of touch, deep pressure, distension of a visceral organ, destruction of bone or swelling [55] (Fig. 3a). These stimuli are mediated by **mechanosensory transducers** such as ion channels of the degenerin family (mammalian degenerin, MDEG) or acid-sensing ion channel 2 (ASIC2) [39, 55]. Mechanical stimulation can release ATP from the cell activating G-protein-coupled ATP receptors (P2Y) or ATP-gated ion channels (P2X) [55, 83]. **Noxious heat** can be detected by the **vanilloid receptor** (TRPV1, formerly also called VR1) and the **vanilloid receptor-like** (TRPV2, formerly called VRL-1) channel, which belong to the larger family of **transient receptor potential** (TRP) channels. The core membrane structure of the receptors resembles that of voltage-gated potassium or cyclic nucleotide-gated channels [55, 83]. The TRPM8 receptor, a distant relative of TRPV1, has been identified as detecting noxious cold [75, 88]. Nociceptors uniquely express two voltage-
gated sodium channels (Nav1.8 and Nav1.9), which could become the target for selective anesthetics blocking only pain but leaving innocuous sensation, motor and autonomic output intact [123].

Conduction

Conduction is the passage of action potentials from the peripheral terminal along axons to the central terminal of nociceptors in the spinal cord [123]. Dorsal root ganglion (DRG) cell bodies give rise to three different fiber types [55, 61]:

- C type fibers
- Aδ fibers
- Aβ fibers

C type fibers are unmyelinated fibers ranging in diameter from 0.4 to 1.2 μm and have a velocity of 0.5 – 2.0 m/s. These fibers present the thermosensitive receptors reacting to temperature (heat/cold), mechanoreceptors of low threshold and specific receptors for algogenic substances [2, 55, 78].

Aδ fibers are lightly myelinated ranging in diameter from 2.0 to 6.0 μm and have a velocity of 12 – 30 m/s. These fibers are classified into two subgroups. Type I presents high-threshold mechanoreceptors and they respond weakly to chemical and thermal stimuli. Type II corresponds mainly to mechanothermal receptors for high temperatures and intense cold [2, 55, 78].

Aβ fibers are myelinated with a diameter of more than 10 μm and a velocity of 30 – 100 m/s. These fibers mediate the sensations of touch and mild pressure, as well as the sensation of joint positions (proprioception) and vibration [2, 55, 78]. Their activation contributes to mechanisms of segmental suppression in the spinal cord.

Activation of C type fibers and Aδ fibers leads to burning sensations and twinges. Under pathological conditions, signs of neuropathic pain, e.g. dysesthesia and paresthesia, can result from activation of Aβ fibers. Pathologic pain sensation can manifest as hyperalgesia mediated by C fibers and Aδ fibers. Under pathologic conditions, activation of low threshold mechanoreceptors (Aβ fibers) can evoke allodynia (touch evoked pain) [2, 55, 78].

Transmission and Modulation

Transmission is the synaptic transfer of sensory input from one neuron to another [123].

The primary sensory neurons terminate in the dorsal horn in a highly organized fashion, innervating both intrinsic dorsal horn interneurons and projection neurons. The dorsal horn is the first site of synaptic transmission (or integration) in the nociceptive pathway and is subject to considerable local and descending modulation [18].

Dorsal Horn Cytoarchitecture

The gray matter of the spinal cord can be divided into ten laminae. Of these, laminae I (marginal layer), II (substantia gelatinosa), III, IV (nucleus propius), V and VI (deep layers) comprise the dorsal horn [78]. The laminae form columns extending along the spinal cord [81, 99]. Within the columns, a large number of second-order excitatory and inhibitory interneurons receive multiple inputs from surrounding columns and send outputs to the brain and to the anterior horn [81]. The neuronal network of the dorsal horn hence serves as a gate controlling propagation of nociceptive signals to higher brain areas [132].
The cytoarchitecture of the dorsal horn is very complex [2, 78, 81, 99, 127]. Simplified, large myelinated low-threshold $\alpha$fferents terminate in laminae III and IV, lightly myelinated high-threshold $\delta$ fibers synapse at laminae I and V, and non-myelinated high-threshold $C$ fibers terminate in lamina II but also terminate with some fibers in laminae I and V [111, 127] (Fig. 4).

Within the dorsal horn three distinct types of neurons can be identified according to the type of afferents and their response pattern to nociceptive input [78]:

- nociceptive-specific (SN) neurons
- multireceptorial or wide-dynamic range (WDR) neurons
- non-nociceptive neurons

**Nociceptive-specific (NS) neurons** are located in the substantia gelatinosa but can also occur in layers (laminae V and VI) under physiologic conditions. They are exclusively activated by high intensity noxious stimuli mediated by $C$ and $\delta$ fibers [78].

**Multireceptorial or wide-dynamic range (WDR) neurons** respond to thermal, mechanical and chemical stimuli via $C$, $\delta$ and $\beta$ fibers. These neurons are found to a lesser degree in the ventral horn (VH). WDR neurons present a considerable convergence from cutaneous, muscle and visceral input. This type of neuron is the major type of neuron that encodes stimulus intensity [26]. Additionally, these neurons participate mainly in the $C$-fiber-mediated processes of sensitization and amplification of prolonged pain [78].

**Non-nociceptive (N-NOC) neurons** are activated by innocuous stimuli such as low intensity mechanical, thermal and proprioceptive stimuli, mediated by $\beta$ and $\beta$ fibers. They are found predominately in laminae II, III and IV [78]. These neurons act indirectly in segmental suppression mechanisms [2]. The different types of neurons are connected via second order excitatory and inhibitory interneurons. These interneurons receive multiple inputs from other columns and send information and impulses to the brain [81]. After modulation and modification of the nociceptive stimulus within the dorsal horn, the information is transmitted to the CNS. Afferents of the spinal cord dorsal horn neurons form so called spinal tracts that transmit nociceptive informations to the CNS.
Plasticity or modifiability of synaptic transfer in the dorsal horn is a key feature of its function and integral to the generation of pain and pain hypersensitivity [18].

The major synapses responsible for transmission are located in the dorsal horn of the spinal cord in lamina I (marginal zone) and lamina II (substantia gelatinsosa). These impulses are conveyed to the thalamus, the main region for the integration of brain input [37]. The transfer of nociceptive stimuli is mediated by direct monosynaptic contact or through multiple excitatory or inhibitory interneurons. Transmission of nociceptive stimulus is inhibited by descending pathways of the brain stem and midbrain and collateral influences within the dorsal horn [37, 106].

Modulation of Sensory Inputs

Transmission of the peripheral nociceptive signals to the brain undergoes various modulatory influences in the dorsal horn by descending pathways [9, 37, 78]. Many neurotransmitters have been identified which mediate this modulation [9, 37] (Table 2).

Modulation can be described as the process in which pain transmission is modified or altered – “gated” – before being transmitted to the CNS. Nociceptive impulses are modulated in two ways, i.e. by:

- excitatory (facilitatory) mechanisms
- inhibitory mechanisms

Inhibitory Mechanisms

Inhibitory mechanisms can originate from local (segmental) inhibitory interneurons or from descending antinociceptive pathways. The majority of local inhibitory neurons in the spinal cord release glycine and/or γ-aminobutyric acid (GABA). The descending inhibition pathways originate at the level of the cortex and thalamus, and descend via the brain stem (periaqueductal gray) and the dorsal columns to terminate at the dorsal horn of the spinal cord. These descending pathways modulate nociceptive transmission through the release of serotonin (5-HT) and/or norepinephrine [37, 78]. Inhibition can be postsynaptic or presynaptic. Postsynaptic inhibition results from a hyperpolarization of the cell membrane and/or from the activation of a shunting conductance, which impairs prop-

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<td>Non-opioid peptides</td>
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<td>- neuropeptide Y</td>
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<td>- calcitonin gene related peptide (CGRP)</td>
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agitation of excitatory postsynaptic potentials along the dendrite of neurons [132]. Presynaptic inhibition occurs at axoaxonic synapses of GABAergic neurons with primary sensory nerve terminals [37].

**Excitatory Mechanisms**

The excitatory transmitter glutamate is released by primary afferent fibers and plays a pivotal role in the spinal mechanisms of nociceptive transmission [9]. Synaptically released glutamate acts on kainate and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, being responsible for a fast synaptic transmission at the first synapse in the dorsal horn (Fig. 3b). Transient and non-injurious noxious stimuli result in stable AMPA receptor-mediated synaptic signals which are finally perceived as a transient localized pain [123]. Glutamate can also act on N-methyl-D-aspartate (NMDA) receptors, but this receptor is blocked under resting conditions by extracellular magnesium ions [81]. Depolarization of the postsynaptic neuron, e.g., through intense AMPA receptor activation, removes this magnesium block. In addition, activators of protein kinase C can reduce the sensitivity of NMDA receptors to magnesium, possibly contributing to spinal hypersensitivity and amplification of peripheral inputs. The activation of the NMDA receptors also leads to an entry of calcium, which is a key event in the generation of long lasting potentiation of synaptic transmission (LTP). In addition, calcium activates various enzymes such as nitric oxide (NO) synthase and phospholipases [9], which can also augment pain sensitivity.

Closely timed repeated stimulation of C fibers results in an increased response even though the amplitude of the input signal remains unchanged. This activity-dependent phenomenon known as wind-up is responsible for the increasing pain experienced in response to closely repeated stimulation of the skin by noxious heat [72, 123].

**Pain Projection**

Subsequent to pain transmission and modulation within the dorsal horn, nociceptive information is projected to the supraspinal structures via afferent bundles (Fig. 5). These bundles can be differentiated into several tracts with special functions [2]:

- **spinothalamic tract** involved in sensory-discriminative components and motivational-affective aspects of pain as well as the affective components of painful experience
- **spinoreticular tract** involved in the motivational-affective aspects and neurovegetative responses to pain
- **spinomesencephalic tract** involved in somatosensory processing, activation of descending analgesia, inducing aversive behaviors in response to nociceptive stimuli as well as autonomic, cardiovascular, motivational and affective responses
- **spinoparabramial tract** involved in autonomic, motivational, affective regulation and in the neuroendocrine responses to pain
- **spinohypothalamic tract** involved in neuroendocrine autonomic, motivational, affective and alert responses of somatic and visceral pain
- **spinocephalic tract** involved in the sensory-discriminative components and motivational-affective and autonomic responses of pain, and plays a role in sensory integration and modulation of afferent inputs
- **postsynaptic pathways** of spinal column involved in the sensory-discriminative components and motivational-affective aspects of pain
Pain Perception

The spinal projection pathways project to the reticular formation of the brain stem and surrounding nuclei before converging in the thalamus, the main structure for reception, integration and nociceptive transfer of nociceptive stimuli before transmission to the somatosensory cortex. However, only a small proportion of all the sensory input from the spinal cord arrives at the thalamus because of local processing, modulation, and controlling [123]. The somatosensory cortex in turn projects to adjoining cortical association areas, predominately the limbic system. The **limbic system** includes [81]:

- cingulate gyrus (behavior and emotion)
- amygdala (conditioned fear and anxiety)
- hippocampus (memory)
- hypothalamus (sympathetic autonomic activity)
pathways. Peripheral tissue damage or nerve injury can result in a pathological state in which there is a reduction in pain threshold (allodynia), an increased response to noxious stimuli (hyperalgesia), an increase in the duration of response to brief stimulation (persistent pain) and a spread of pain and hyperalgesia to uninjured tissue (referred pain and secondary hyperalgesia) [17]. These alterations in the pain pathways are usually referred to as neuroplasticity. Neuroplasticity

Peripheral Sensitization

Tissue damage results in the release of inflammatory mediators including ions (H\(^+\), K\(^+\)), bradykinin, histamine, 5-hydroxytryptamine (5-HT), ATP and nitric oxide (NO). The tissue injury activates the arachidonic acid pathway, which results in the production of prostanoids and leukotrienes [60]. Inflammatory mediators are also released from attracted cells such as mast cells, fibroblasts, neutrophils and platelets [55]. Tissue damage and inflammation leads to low pH, which enhances painful sensations by sensitizing and activating the vanilloid receptor 1 (TRPV1) [49]. Inflammatory mediators, e.g. prostaglandin E\(_2\), bradykinin, histamine, 5-HT, ATP, nitric oxide (NO), and ions, all play a role in the development of peripheral sensitization.

**Figure 6. Neuroplasticity of the nociceptor**

a **Peripheral sensitization** (NGF nerve growth factor, BK bradykinin, TRPV1 transient receptor potential vanilloid 1 channel, EP prostaglandin E receptor, PK protein kinases, AA arachidonic acid, PGE\(_2\) prostaglandin, TrkA tyrosine kinase A receptor, Cox2 cyclooxygenase 2). b **Transcriptional change in the DRG** (PKA protein kinase A, CamKIV camkinase IV, JNK jun kinase, ERK extracellular signal-regulated kinase). Redrawn from Woolf [123] (with permission from ACP).
kinin and nerve growth factor (NGF) [108], activate intracellular protein kinases A and C in the peripheral terminal that phosphorylate TRPV1 and tetrodotoxin-resistant (TTXr) sodium channels (Na\textsubscript{v}1.8, Na\textsubscript{v}1.9) to increase excitability [123, 125, 130]. These mechanisms (Fig. 6a) contribute to the sensitization of the peripheral terminal leading to pain hypersensitivity [130].

**Transcriptional DRG Changes**

In damaged tissue, nerve growth factor (NGF) and inflammatory mediators are expressed and transported from the periphery to the cell body of peripheral neurons [123]. Within the DRG, signal transduction cascades are activated involving protein kinase, CaM kinase IV, extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK) p38, and jun kinase [52, 53, 71, 86, 123]. These cascades control the transcription factors that modulate gene expression, leading to changes in the levels of receptors, ion channels, and other structural proteins [86, 123] (Fig. 6b).

**Central Sensitization**

Central sensitization is the form of synaptic plasticity that amplifies and facilitates the synaptic transfer from the nociceptor central terminal to dorsal horn neurons [59, 123]. During nociception the release of glutamate predominately acts on kainate and AMPA receptors within the dorsal horn. The intense stimulation of nociceptors (e.g. by spinal injuries) releases transmitters [brain-derived neurotrophic factor (BDNF), substance P, glutamate], which act on multiple dorsal horn receptors, e.g. AMPA, NMDA, NK1 and TrkB [64, 125, 135]. In this early phase (Fig. 7a) of central sensitization, intracellular kinases are also activated which phosphorylate receptor ion channels. This effect also increases the responsiveness to glutamate by removal of the Mg\textsuperscript{2+} block of the NMDA channel leading to spinal hypersensitivity and amplification of peripheral inputs [110, 123, 124, 131].

**Figure 7. Central sensitization**

- **Acute phase** (AMPA \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, NMDA \(N\)-methyl-D-aspartate, EP prostaglandin E receptor, NK1 neurokinin 1 receptor, TrkA tyrosine kinase B receptor, PK protein kinases).  
  - **Late phase** (EP prostaglandin E receptor, AA arachidonic acid, PGE\textsubscript{2} prostaglandin, \(\text{IL-1}\beta\) interleukin-1\(\beta\), Cox2 cyclooxygenase 2). 

Redrawn from Woolf [123] (with permission from ACP).
Prostaglandins not only sensitize the nociceptive system at the level of the primary nociceptor but also centrally at the level of the dorsal horn [133]. In the late phase (Fig. 7b) of central sensitization, PGE$_2$ is produced by COX-2 in the dorsal horn, which is induced by proinflammatory cytokines such as interleukin-1β [103, 123, 133]. This expression of PGE$_2$ appears to be a key factor responsible for central pain sensitization [1, 98]. These mechanisms of central sensitization are responsible for the well known clinical symptoms such as *alldynia, hyperalgesia*, and *secondary hyperalgesia*.

Disinhibition

Afferent nociceptive signals from the periphery to the brain are modulated by a well balanced interplay of excitatory and inhibitory neurons [123]. The loss of inhibition, i.e. **disinhibition of dorsal horn neurons**, is a key element in persistent inflammatory and neuropathic pain [132]. Inhibitory mechanisms within the spinal cord are mediated by the neurotransmitters glycine and GABA. The expression of PGE$_2$ during inflammation leads to a protein kinase A-dependent phosphorylation which inhibits the glycine receptors. Dorsal horn neurons are relieved from the glycinergic neurotransmission [1, 46]. Furthermore, partial nerve injury has been shown to decrease dorsal horn levels of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD) and induce neuronal apoptosis. Both of these mechanisms could reduce presynaptic GABA levels and promote a functional loss of GABAergic transmission in the superficial dorsal horn [79]. However, significant loss of GABAergic or glycinergic neurons is not necessary for the development of thermal hyperalgesia in the chronic constriction injury (CCI) model of neuropathic pain [92].

Additional mechanisms involved in the neuroplasticity leading to pathologic pain processing include **spinal cord glial changes** and **medullary descending facilitation**. Similar to immune cells responding to viruses and bacteria, spinal cord glia (microglia and astrocytes) can amplify pain by expressing proinflammatory cytokines [119]. These spinal cord glia also become activated by certain sensory signals arriving from the periphery, e.g. as a result of a nerve root injury [54, 119]. **Nerve root injury** and inflammation can result in persistent input of pain signals and lead to sustained activation of descending modulatory pathways that facilitate pain transmission [93, 123].

**Endogenous and Environmental Influences on Pain Perception**

There is an increasing plethora of studies indicating a strong influence of endogenous and environmental factors on pain perception and processing (see Chapters 6, 7). It is common knowledge that the identical noxious stimulus does not lead to an equal pain perception neither on the intraindividual nor on the interindividual level. Similarly, it is well known that not every patient with severe injury to the nervous system develops chronic/neuropathic pain [87]. With the advance of molecular biological techniques, research has focused on exploring the **genetic predisposition** for these interindividual differences. The genetic predisposition for disc degeneration but not necessarily pain has been established in several studies [6]. Tegeder et al. [112] recently reported that a haplotype of the GTP cyclohydrolase gene was significantly associated with less pain following discectomy for persistent radicular leg pain. GTP cyclohydrolase (GCH1) is the responsible enzyme for tetrahydrobiopterin (BH$_4$) synthesis. BH$_4$ is an essential cofactor for catecholamine, serotonin and nitric oxide production and thus a key modulator of peripheral neuropathic and inflammatory pain. Healthy individu-
als homozygous for this haplotype exhibited reduced experimental pain sensitivity, and forskolin-stimulated immortalized leukocytes from haplotype carriers upregulated GCH1 less than did normal controls [112]. Considering the complexity of persistent pain, it appears very likely that many genes are involved and we are only at the beginning of unraveling the molecular background of individual differences in pain perception.

Additionally to biological mechanisms, there are several established predisposing biopsychosocial risk factors for the development of persistent pain:

- gender [34, 100]
- age [38]
- ethnicity [28, 47]
- affective-emotional behavioral pattern [16, 69]
- psychosocial factors [11, 58, 115]
- previous pain states [94, 109, 113]
- personality traits [69, 90]

Although various studies show that gender, age, ethnicity, personality traits, etc., play a role in pain perception and pain processing, there is no evidence for a specific pain-prone personality that reliably predicts the development of a persistent pain syndrome [69, 91].

### Clinical Assessment of Pain

Nociceptive pain is an important warning sign to prevent the individual from injury, whereas neuropathic pain has lost this role and presents as a disease by itself. Nociceptive spinal pain occurs due to circumscribed actual or impending tissue damage. Patients suffering from nociceptive spinal pain present specific clinical signs corresponding to the affected tissue. In contrast to nociceptive spinal pain, neuropathic spinal pain occurs as consequence of a direct injury or affection of the nervous system. Severe nerve root and spinal cord injuries are the most common causes of the neuropathic form of spinal pain. Clinical experience and rather discouraging research mainly related to the treatment of chronic pain has demonstrated that a strategy directed at examining, classifying and treating pain on the basis of anatomy or underlying disease is of limited help [51]. Clifford Woolf has first advocated that a mechanism-based approach to pain is more reasonable and has direct implications on present and future pain treatment [129].

### Differentiating Inflammatory and Neuropathic Pain

While the diagnosis and assessment of nociceptive and acute inflammatory pain is straightforward, the clinical differentiation of persistent inflammatory and neuropathic pain often remains a diagnostic challenge for several reasons [51]:

- lack of a single diagnostic test which can confirm/reject the putative diagnosis
- perception of neuropathic pain is purely subjective
- various diseases (e.g. low back pain) exhibit a variable degree of neuropathic component
- pain is not static but changes in a dynamic way
- signs and symptoms may change during the course of the disease
- lack of a commonly agreed definition of neuropathic pain

Not all persistent pain is neuropathic. It is most important to stress that not all persistent pain is neuropathic. This diagnosis should only be made in the presence of positive findings [40]. However, the
According to Rasmussen et al. [97]

| Table 3. Criteria for classifying neuropathic pain |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Definite**                                    | **Possible**                                    | **Unlikely**                                    |
| Pain located in a neuroanatomical area and      | Pain located in a neuroanatomical area and      | Pain fulfilling at least the                    |
| fulfilling at least two of the following:       | fulfilling at least two of the following:       | following:                                     |
| • decreased sensibility in all/part of the      | • decreased sensibility in all/part of the      | • pain located in a non-neuroanatomical area    |
|   painful area                                  |   painful area                                  | • presence of former disease known to cause     |
| • present or former disease known to            |   unknown etiology                               |   nociceptive pain                              |
|   cause nerve lesion relevant for the pain      | • present or former disease known to cause      | • no sensory loss                               |
| • nerve lesion confirmed by neurophysiology,    |   either nociceptive or neuropathic pain         |                                                 |
|   surgery or neuroimaging                       |   radiation pain or paroxysms                   |                                                 |
|                                                 |                                                 |                                                 |
| **Pain fulfilling at least the**                |                                                 |                                                 |
| **following:**                                  |                                                 |                                                 |
| • pain located in a non-neuroanatomical area    |                                                 |                                                 |
| • presence of former disease known to cause     |                                                 |                                                 |
|   nociceptive pain                              |                                                 |                                                 |
| • no sensory loss                               |                                                 |                                                 |

According to Jensen and Baron [51]

The **diagnostic work-up** of patients with neuropathic pain should include:

- medical history
- sophisticated quantitative sensory testing
- neurophysiological studies
- imaging studies
- pharmacological tests

**Medical History**

A thorough history and physical examination (see Chapter 8) including a detailed neurologic assessment (see Chapter 11) is the prerequisite for a mechanism based diagnosis and effective pain treatment. A detailed history of persistent pain should include the following aspects:

- beginning
- localization
- intensity
- quality
- temporal pattern
- pain aggravating and relieving factors
- autonomic changes
- confounding biopsychosocial risk factors

A **pain drawing** can be used to graphically document the pain distribution [73, 96]. The graphic depiction of the subjective pain perception often instantaneously shows a non-anatomic distribution which argues against neuropathic pain. However, the general discriminative power of the pain drawing to assess psychological disturbance is limited [44]. Pain can further be differentiated according to its character. Melzack [76] has developed a questionnaire which distinguishes sensory and affective pain descriptors, which can be helpful in the assessment of the pain character (see Chapter 8). The history sometimes allows a differentiation of nociceptive and neuropathic pain (Table 4).

Table 4. Differentiating nociceptive and neuropathic pain

<table>
<thead>
<tr>
<th>Nociceptive pain</th>
<th>Neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• sharp, aching or throbbing quality</td>
<td>• burning, tingling, numbness, shooting, stabbing quality, or electric-like sensation</td>
</tr>
<tr>
<td>• well localized</td>
<td>• spontaneous or evoked</td>
</tr>
<tr>
<td>• transient</td>
<td>• persistent or paroxysmal pain</td>
</tr>
<tr>
<td>• good response to analgesic treatment</td>
<td>• resistance to non-steroidal anti-inflammatory drugs and limited or no response to opioids</td>
</tr>
</tbody>
</table>

The diagnosis of neuropathic pain requires a thorough work-up

A pain drawing can be helpful in differentiating anatomic and non-anatomic pain distribution
Clinical Examination

The examination should include the assessment of negative and positive sensory symptoms and signs (Table 5). Currently there is no consensus about what, where and how to measure and what to compare with [51]. Although the mirror side can serve as an internal control, the assessment can be influenced by contralateral segmental changes [51].

Screening tools and questionnaires (e.g. LANSS, NPQ, DN4, painDETECT) have been developed and are recommended to supplement the assessment for neuropathic pain [8].

Neurophysiological Studies

Recent advances in neurophysiology have become a valuable diagnostic tool in identifying the extent of neurologic disturbance in neuropathic pain [25, 63].

Imaging Modalities

The primary objective of imaging studies in the evaluation of neuropathic pain is to identify a structural abnormality or damage to neural tissue, which is a prerequisite in making a definite diagnosis. However, imaging studies can go beyond a pure anatomical appraisal. Functional imaging such as positron emission tomography (PET), magnetic resonance spectroscopy and functional MRI (fMRI) allow the identification of local cerebral blood flow changes which reflect local synaptic activity, thereby revealing the cortical representation of pain [12, 13, 43, 68, 95, 107].

Pharmacological Testing

Pharmacological tests in a controlled manner with either different drugs or different administration forms of the same substance allow for an examination of the location of the pain generator and the molecular mechanisms involved in pain [40, 51].

Table 5. Clinical testing

<table>
<thead>
<tr>
<th>Negative sensory symptoms/signs</th>
<th>Bedside examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td></td>
</tr>
<tr>
<td>- paresthesia</td>
<td>touch skin with cotton wool</td>
</tr>
<tr>
<td>- dysesthesia</td>
<td>prick skin with a pin single stimulus</td>
</tr>
<tr>
<td>- paroxysms</td>
<td>thermal response to cold, 20° and 45°</td>
</tr>
<tr>
<td>- superficial burning pain</td>
<td>tuning fork on malleoli/interphalangeal joints</td>
</tr>
<tr>
<td>- deep pain</td>
<td></td>
</tr>
<tr>
<td>Evoked</td>
<td></td>
</tr>
<tr>
<td>- touch evoked hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>- static hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>- punctuate repetitive hyperalgesia (wind-up)</td>
<td></td>
</tr>
<tr>
<td>- alluresation</td>
<td></td>
</tr>
<tr>
<td>- cold hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>- heat hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>- chemical hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>- sympathetic maintained pain</td>
<td></td>
</tr>
</tbody>
</table>

According to Jensen and Baron [51]
**General Concepts of Pain Treatment**

**Pharmacological Treatment**

A systemic pharmacological treatment remains the cornerstone of the management of acute or persistent pain [67]. The three-step pain relief ladder developed by the WHO [120] originally for the treatment of cancer pain in 1986 also applies for other pain disorders such as spinal pain. The pain relief ladder (Fig. 8) suggests starting with a weak analgesic and stepwise increasing the potency of the medication until pain relief is felt [29]. In cases of severe pain, it may be necessary to immediately start with step 3 opiate analgesics (stratified therapy) [57]. There is increasing evidence that acute painful experiences can lead to longer-term painful consequences, even when tissue healing has occurred [41]. The increasing understanding of the neurobiology of pain has prompted an aggressive, multimodal, preemptive approach to the treatment of acute pain to prevent pain persistence [30, 41].

**Drug Types**

A detailed discussion of the various drug types and their application is far beyond the scope of this chapter and the reader is referred to the literature [4, 5, 30, 56, 62, 66, 105].

**Non-opioid Analgesics**

Although paracetamol (acetaminophen) has been known for a century, the exact mechanisms of its antinociceptive effect are still controversial. Paracetamol

---

![Figure 8. Pain relief ladder](image-url)
Paracetamol and tramadol are the most frequently used non-opioid analgesics. Paracetamol appears to cause a weak peripheral cyclooxygenase (COX) inhibition but also inhibits COX centrally [66]. The analgesic effect of paracetamol is thought to be related to an increasing pain threshold by means of central prostaglandin inhibition [30]. Tramadol is a synthetic analog of codeine. It has a central acting analgesic effect and inhibits norepinephrine and serotonin uptake [30].

NMDA antagonists are potent analgesics which interfere with the transmission in primary afferent pain pathways at the NMDA receptor. The prototype of NMDA antagonists is ketamine, which is effective in neuropathic and other chronic pain conditions.

Non-steroidal Anti-inflammatory Drugs

The primary mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) is blocking cyclooxygenase (COX), which catalyzes the biotransformation of arachidonic acid to prostaglandins [62]. In most tissues, COX-1 is constitutively expressed, while COX-2 is induced in many cell types as a result of inflammation [62]. The products of COX-1 and COX-2, particularly prostaglandin E₂ and I₂, induce inflammatory alterations and act directly on sensory nerve endings [104]. Non-selective COX inhibitors (e.g. aspirin, ibuprofen, naproxen, diclofenac, piroxicam) inhibit both isoforms of COX. The inhibition of COX-1 has the disadvantage that it also prevents the synthesis of PGs that act to protect the tissue [66]. Subsequent to the discovery of COX isoenzymes, selective COX-2 inhibitors have been developed. However, selective COX-2 inhibitors (e.g. celecoxib, rofecoxib, valdecoxib) have recently been scrutinized because of the report of potential serious side effects [21, 48, 74].

Opioids

Opioids include all the endogenous and exogenous compounds that possess morphine-like analgesic properties [30]. Among the most commonly used opioids are morphine, hydromorphone, methadone, oxycodone, oxymorphone and fentanyl. These drugs remain the mainstay for the treatment of severe acute pain. Controversy exists about their effectiveness and safety with long-term use. A recent systematic review indicates that the short-term use of opioids is good in both neuropathic and musculoskeletal pain [56]. However, conclusions on tolerance and addiction were not possible because of the small numbers of patients with long-term opioid medication, not allowing conclusions to be drawn regarding the treatment of chronic pain [56].

Adjuvants

The WHO has recommended adding adjuvant drugs to relieve pain associated fears and anxiety [120] and enhance the central effect on pain relief. Several categories of adjuvant medications can be differentiated:

- antidepressants
- anticonvulsants
- anxiolytics
- muscle relaxants
- sleep-promoting medications

Tricyclic antidepressants (e.g. amitriptyline, desipramine, nortriptyline) have a long history of use in neuropathic pain syndrome and act primarily by enhancing adrenergic α₂-adrenoreceptor stimulation. Some also possess NMDA receptor-
blocking activity [66]. The rationale for their use in chronic low-back pain (LBP) is based on the frequent coexistence of pain and depression, their sedating effect (improving sleep) and supposed analgesic effect in lower doses [116]. However, there is contradictory evidence that antidepressants are effective for low back pain in the short to intermediate term [80, 116]. Anticonvulsants are extremely useful for neuropathic pain [89]. The effectiveness of the anticonvulsant drugs in the treatment of neuropathic and central pain states lies in their action as non-selective Na⁺-channel-blocking agents [66]. Until recently, the first generation of anticonvulsants (e.g. phenytoin, carbamazepine and valproic acid) were used to treat neuropathic pain [36]. However, the newer antiepileptic agents including gabapentin and pregabalin are rapidly becoming the initial medications of choice to treat neuropathic pain [89]. Selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine) are frequently used for the treatment of anxiety disorders. However, the therapeutic effects are not seen immediately because of a slow onset of action (2–4 weeks). Benzodiazepines are used to treat acute anxiety states and serve as a pre-medicament before a surgical intervention to reduce stress and muscle spasm [89]. Muscle relaxants have a central action on the nervous system rather than a direct peripheral effect on muscle spasm. Benzodiazepines (e.g. diazepam) are sedative and exhibit an addictive potential as well as a withdrawal syndrome [89]. Baclofen centrally facilitates GABA₉ receptor-mediated transmission while tizanidine is a centrally acting α₂-adrenergic agonist and reduces the release of excitatory neurotransmitters and inhibits spinal reflexes [89]. There is strong evidence that oral non-benzodiazepines are more effective than placebo for patients with acute LBP on short-term pain relief, global efficacy and improvement of physical outcomes. However, there is only moderate evidence for the short-term effectiveness in chronic LBP [116]. Sleep-promoting medications are helpful as adjuvant medication because of the high correlation of insomnia, depression and pain [121]. Appropriate pain treatment therefore also improves insomnia. Traditionally, antidepressants have been used because of their sedative effect. Benzodiazepines should only be used for short-term management of insomnia because of the well known side effects such as oversedation (“morning hangover”), addiction, dependence and withdrawal syndrome. Newer omega-1 receptor agonists (e.g. zolpidem, zaleplon) minimize morning hangover and withdrawal symptoms and have a shorter half-life [89].

Non-pharmacological Treatment of Spinal Pain

It is well established that bed rest of more than 3 days for acute back pain is ill-advised [45, 116]. There is conflicting evidence on the effectiveness of back schools for patients with chronic LBP. While there also is conflicting evidence for the effect of exercise therapy for acute LBP, exercise is at least as (in-)effective as other conservative interventions for chronic LBP [116]. Spinal manipulation is not more effective in the short and long term compared with other conventionally advocated therapies such as general practice care, physical or exercise therapy, and back school [116].

Biopsychosocial Interventions

Since Melzack and Wall’s introduction on the gate control theory [77], our understanding of how psychosocial factors can modulate the pain signal has substantially increased. Furthermore, our understanding of pain has been shaped by another landmark paper. In the late 1970s, Engel [32] realized that the dominant biomedical model left no room within its framework for the social, psychological, and behavioral dimensions of illness. He therefore proposed a biopsychosocial
model which included physiologic as well as psychological and social factors, allowing for a more comprehensive understanding of pain. These two theoretical advances resulted in the development of various new treatment approaches, e.g. behavioral [33] and cognitive-behavioral treatments [114] that went beyond the biomedical dimension [84]. The rationale for this approach is that of altering the range of physical, psychological and social components of pain [84].

In persistent pain disorders, the actual tissue damage has almost always disappeared and rest is no longer required to promote healing. Therefore the advice to stay as active as possible is the most important advice which should be given to patients. There is evidence that this advice improves pain and function at least in the short term [116]. Fordyce and coworkers [35, 65] also indicated that pain does not hurt so much if you have something to do.

Although cognitive-respondent treatment and intensive multidisciplinary treatment have been shown to be effective for short-term improvement of pain and function in chronic LBP, there is still no evidence that any of these interventions provides long-term effects on low back pain and function [116].

Surgical Treatment

The surgical treatment of chronic spinal pain continues to be very controversial [23]. So far, convincing evidence for the mid- and long-term superiority of spinal fusion over cognitive behavioral treatment and exercise is still lacking. Similarly, surgery for persistent non-specific pain is not evidence-based there is a lack of other invasive interventions (e.g. spinal injection, spinal cord stimulation, intrathecal pumps) to treat chronic low back pain other than disc herniation, spinal stenosis and spondylolisthesis [14, 117].

Recapitulation

**Epidemiology.** The incidence of chronic pain ranges from 24% to 46% in the general population. In 90% of chronic pain patients the pain is located in the musculoskeletal system. The natural history of chronic pain is poor due to a strong risk of pain persistence often regardless of treatment.

**Classification.** Pain may be differentiated into acute pain (1–4 weeks) caused by an adequate stimulation of nociceptive neurons. Chronic pain (>6 months) can occur spontaneously or can be provoked by a normally non-noxious stimulus. However, the temporal classification of pain does not reflect the underlying pain mechanism. A mechanism-based classification of pain is more reasonable. A contemporary definition of pain differentiates adaptive (nociceptive and inflammatory) pain protecting the individual from further damage and maladaptive (neuropathic and functional) pain that has lost this protective function and can be considered as a disease by itself.

**Pain pathways.** The physiologic processes involved in pain can be differentiated into transduction, conduction, transmission, modulation, projection and perception. **Transduction** is the conversion of noxious stimuli (thermal, mechanical and chemical) into electrical activity at the peripheral terminal of nociceptor sensory fibers. The DRG cell bodies give rise to three different fiber types (Aβ, Aδ and C fibers) responsible for nociception. The resulting sensory input to the central terminal of nociceptors is described as **conduction.** Transmission is the synaptic transfer and modulation of sensory input from one neuron to another. The peripheral nociceptive signals to the brain undergo various modulations by excitatory (facilitatory) and inhibitory mechanisms in the dorsal horn of the spinal cord. This modulation provides a framework to explain how pain can be felt even without tissue damage and how psychosocial factors can influence pain. After pain transmission and modulation, nociceptive information is transferred to the supraspinal structures via afferent bundles, which is known as **projection.** The spinal pathways project to the reticular formation of the brain stem before converging in the thalamus, the main structure for reception, integration and nociceptive transfer of noci-
ceptive stimuli before transmission to the somatosensory cortex (perception).

**Neuroplasticity.** Alterations in the physiological function of pain pathways as a result of tissue damage or neural injury are referred to as neuroplasticity. Injured tissue can release inflammatory mediators which activate and sensitize receptor channels in the peripheral terminal of the nociceptor. High-threshold and silent nociceptors are activated by a decrease in their threshold and show an increase in the responsiveness (peripheral sensitization). Tissue damage may also result in transcriptional changes in the dorsal root ganglion. Similarly, pain transmission is facilitated and inhibitory influences are attenuated by distinct neurobiological alterations of the receptor channels in the dorsal horn (central sensitization). Afferent nociceptive signals from the periphery to the brain are modulated by a well balanced interplay of excitatory and inhibitory neurons which can be disturbed as a result of an injury. **Disinhibition** is the disturbance of this balance with relief from inhibitory neuronal mechanisms. **Genetic predisposition** and **biopsychosocial factors** have a significant influence on the modulation of the afferent sensory input.

**Clinical assessment.** The clinical assessment of pain encompasses a detailed medical history, sophisticated quantitative sensory testing, neurophysiological studies, imaging studies, and pharmacological tests. The clinical differentiation of persistent inflammatory pain and neuropathic pain remains difficult because of the lack of an objective test for neuropathic pain (the missing gold standard). It is important to note that not all persistent pain is neuropathic. The diagnosis of neuropathic pain should be based on the presence of negative and positive sensory symptoms and signs.

**General treatment concepts.** The pharmacological treatment of acute pain must be aggressive, multi-modal and preemptive to reduce the likelihood of pain persistence. The **WHO three-step pain relief ladder** indicates one should start with a weak analgesic and stepwise increase the potency of the medication until pain relief is felt. Analgesics can be differentiated into **non-opioid analgesics** (e.g. paracetamol, tramadol, ketamine), **NSAIDs**, and **opioids**. Opioids include all the endogenous and exogenous compounds that possess morphine-like analgesic properties. **Adjuvant drugs** (e.g. antidepressants, anticonvulsants, anxiolytics) are useful adjunct medications because they enhance the central effect of analgesics and target associated depression, fear or anxiety. **Non-pharmacological treatments** of chronic back pain such as back school, exercise therapy, or spinal manipulation have not passed the test of mid- and long-term clinical effectiveness. **Cognitive-behavioral treatment** is effective in chronic LBP only in the short term. Surgical treatment of chronic pain syndromes particularly chronic LBP has not been proven to be effective in the long term.

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**Key Articles**

This paper introduced the gate control theory and substantially contributed to our increasing understanding of the pain signal.

The previous dominant model of disease in the late 1970s was biomedical, and it left no room within its framework for the social, psychological, and behavioral dimensions of illness. Therefore, Engel proposed a biopsychosocial model that closed the gap between the mind and the body.

This landmark paper introduces the phenomenon of central sensitization demonstrating that the long-term consequences of noxious stimuli result from central as well as from peripheral changes.

Review Articles (recommended for further reading)

### Appendix: IASP Pain Terminology (www.iasp-pain.org)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>allodynia</td>
<td>pain due to a stimulus that does not normally provoke pain</td>
</tr>
<tr>
<td>analgesia</td>
<td>absence of pain in response to stimulation that would normally be painful</td>
</tr>
<tr>
<td>anesthesia dolorosa</td>
<td>pain in an area or region that is anesthetic</td>
</tr>
<tr>
<td>causalgia</td>
<td>a syndrome of sustained burning pain, allodynia, and hyperpathia after a traumatic nerve lesion, often combined with vasomotor and sudomotor dysfunction and later trophic changes</td>
</tr>
<tr>
<td>dysesthesia</td>
<td>an unpleasant abnormal sensation, whether spontaneous or evoked</td>
</tr>
<tr>
<td>hyperalgesia</td>
<td>an increased response to a stimulus that is normally painful</td>
</tr>
<tr>
<td>hyperesthesia</td>
<td>increased sensitivity to stimulation, excluding special senses</td>
</tr>
<tr>
<td>hyperpathia</td>
<td>a painful syndrome, characterized by increased reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold</td>
</tr>
<tr>
<td>hypoalgesia</td>
<td>diminished sensitivity to noxious stimulation</td>
</tr>
<tr>
<td>hypoesthesias</td>
<td>diminished sensitivity to stimulation, excluding special senses</td>
</tr>
<tr>
<td>neuralgia</td>
<td>pain in distribution of nerve or nerves</td>
</tr>
<tr>
<td>neuritis</td>
<td>inflammation of a nerve or nerves</td>
</tr>
<tr>
<td>neurogenic pain</td>
<td>pain initiated by a primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system</td>
</tr>
<tr>
<td>neuropathic pain</td>
<td>any pain syndrome in which the predominating mechanism is a site of aberrant somatosensory processing in the peripheral or central nervous system</td>
</tr>
<tr>
<td>neuropathy</td>
<td>a disturbance of function or pathologic change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if symmetrical and bilateral, polyneuropathy</td>
</tr>
<tr>
<td>nociceptor</td>
<td>a receptor preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged</td>
</tr>
<tr>
<td>noxious stimulus</td>
<td>a noxious stimulus is one that is potentially or actually damaging to body tissue</td>
</tr>
<tr>
<td>pain</td>
<td>an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage</td>
</tr>
<tr>
<td>pain threshold</td>
<td>the least experience of pain that a subject can recognize</td>
</tr>
<tr>
<td>pain tolerance level</td>
<td>the greatest level of pain that a subject is prepared to tolerate</td>
</tr>
<tr>
<td>paresthesia</td>
<td>an abnormal sensation, whether spontaneous or evoked</td>
</tr>
</tbody>
</table>

### References


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