Pain Classics

PAIN®

Gain control mechanisms in the nociceptive system

Rolf-Detlef Treede*

Abstract

The "gate control theory of pain" of 1965 became famous for integrating clinical observations and the understanding of spinal dorsal horn circuitry at that time into a testable model. Although it became rapidly clear that spinal circuitry is much more complex than that proposed by Melzack and Wall, their prediction of the clinical efficacy of transcutaneous electrical nerve stimulation and spinal cord stimulation has left an important clinical legacy also 50 years later. In the meantime, it has been recognized that the sensitivity of the nociceptive system can be decreased or increased and that this "gain control" can occur at peripheral, spinal, and supraspinal levels. The resulting changes in pain sensitivity can be rapidly reversible or persistent, highly localized or widespread. Profiling of spatio-temporal characteristics of altered pain sensitivity (evoked pain to mechanical and/or heat stimuli) allows implications on the mechanisms likely active in a given patient, including peripheral or central sensitization, intraspinal or descending inhibition. This hypothesis generation in the diagnostic process is an essential step towards a mechanism-based treatment of pain. The challenge now is to generate the rational basis of multimodal pain therapy algorithms by including profile-based stratification of patients into studies on efficacy of pharmacological and nonpharmacological treatment modalities. This review outlines the current evidence base for this approach.

Keywords: Gain control mechanisms, Nociceptive system, Sensory gain and loss, Spinal cord, Pain therapy

1. Introduction

Although the 25th anniversary of the gate control theory of pain[23] was a major theme at the World Pain Congress in Adelaide in 1990, its 50th anniversary in the year 2015 has passed almost unnoticed. The model published in *Science* in 1965 by Ronald Melzack and Patrick Wall addressed the convergence of small and large fiber primary afferent inputs to the spinal cord, proposed a specific circuitry in the dorsal horn, and made predictions on how to "close the gate" by large fiber stimulation. Although much detail of the circuitry was not confirmed later on, the model predicted new treatment modalities (transcutaneous electrical nerve stimulation [TENS], spinal cord stimulation) that are still relevant today. This review synthesizes the early observations available in 1965 and modern data into a model that involves prespinal (peripheral) and supraspinal (descending) gain control mechanisms, where the dorsal horn integrates ascending, intraspinal, and descending signals. These mechanisms act together to increase the sensitivity of the nociceptive system to salient stimuli and to decrease its sensitivity to stimuli that are not important. These gain control mechanisms allow the healthy nociceptive system to function as an efficient warning system, whereas lesions or diseases of the warning system may create insensitivity to pain, "false alarms," or both. Test paradigms have been validated to assess some of these mechanisms in humans, mostly at a group level, and these paradigms have been fruitful to study the pathophysiology of chronic pain states. The psychophysical consequences of peripheral and central sensitization, of intraspinal and descending inhibition have been documented in the literature since 1965. Although not conclusive in the strict sense, evidence on which of these gain control mechanisms are likely to act in a given patient can be obtained from clinical findings on spatio-temporal and quality profiles of sensory alterations.

2. Background

In the 19th and 20th century, there was a heated debate (for review, see Ref. 7) whether the presence of noxious stimuli is signaled by specific receptors and neural pathways from the periphery to the brain (labeled-line theory, as proposed by von Frey), or whether pain arises as the consequence of a spatio-temporal pattern of interacting inputs from different sensory fibers (pattern theory, as proposed by Goldscheider). The gate control theory of pain[23] was a pattern theory that took up the earlier concept that large afferent fibres exert an inhibitory action on the more slowly conducting fibres somewhere in the central nervous system (CNS)[12,15,27] and proposed a specific circuitry with the core element that small and large afferents have opposing effects on substantia gelatinosa cells in the spinal cord. This prediction was precise enough that it could be tested by other investigators, who failed to confirm it. A detailed account of the neurophysiological backgrounds of the gate control theory and its successes and failures was recently given in this journal.[24] "Although subsequent experiments and clinical findings have made clear that the model is not correct in detail, the general ideas put forth in the article and the experiments they prompted in both animals and patients have transformed our understanding of pain mechanisms."

Only 2 years after publication of the gate control theory, Wall and Sweet[44] reported that stimulation of sensory nerves or roots

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Chair of Neurophysiology, Centre for Biomedicine and Medical Technology Mannheim, Heidelberg University, Mannheim, Germany

**Corresponding author. Address: Chair of Neurophysiology, Centre for Biomedicine and Medical Technology Mannheim, Heidelberg University, Ludolf-Krehl-St 13-17, 68167 Mannheim, Germany. Tel.: +49 621 383 9926; fax: +49 621 383 9921. E-mail address: rolf-detlef.treede@medma.uni-heidelberg.de (R.-D. Treede).*

PAIN 157 (2016) 1199–1204

http://dx.doi.org/10.1097/j.pain.0000000000000499

with parameters adequate for large fiber excitation (100 Hz, 0.1 millisecond pulse width) relieved pain in 8 patients; this technique is now known as TENS and like the other therapy predicted by the gate control theory (spinal cord stimulation) finds its evidence-based applications to the present day.[8,9] Thus, the legacy of the gate control theory is mostly in its application to treatment. In an early critique, Peter Nathan[26] wrote "Ideas need to be fruitful; they do not have to be right."

3. Gain control in the periphery: peripheral sensitization and fatigue

Peripheral nociceptors are readily sensitized to heat by several types of injury, which is known since the first electrophysiological studies on peripheral nociceptors.[5,28] In contrast, peripheral sensitization to mechanical stimuli is much less prominent.[42] Peripheral sensitization is characterized by reduced thresholds, increased suprathreshold responses, and spontaneous activity. After the cloning of the heat sensitive ion channel TRPV1,[6] it became apparent that TRPV1 phosphorylation through multiple pathways makes a major contribution to peripheral sensitization to heat and protons. The activation threshold of TRPV1 to these 2 stimuli can drop below body temperature and tissue pH in inflamed tissue, turning ambient conditions into suprathreshold stimuli.[34] This way, peripheral sensitization contributes to ongoing pain of inflammation.

On repeated stimulation with mild noxious heat pulses, nociceptors exhibit the opposite phenomenon: they lose the phasic part of their response and the number of action potentials generated decreases, because of tachyphylaxis of heat-induced inward currents through TRPV1.[20,39,41] Likewise, nociceptors exhibit adaptation on prolonged constant stimulation that is again mimicked at the molecular level.

Peripheral sensitization and fatigue are mechanisms of gain control at the distal end of the nociceptive system (**Fig. 1**). Fatigue prevails for mild stimuli, whereas sensitization predominates for strong and outright damaging stimuli. This way, the peripheral nociceptor can learn to distinguish between salient and unimportant stimuli (nonassociative learning).

All central nociceptive neurons respond to the synaptic input provided by peripheral nociceptors and not directly to noxious stimuli. Hence, it is important to know the encoding of noxious stimuli (defined as "actually or potentially tissue-damaging events") by nociceptors (defined as "sensory receptors that are capable of transducing and encoding noxious stimuli" www.iasp-pain.org, Ref. 22). Consistent with their warning function, nociceptors already respond to mild noxious stimuli and hence generate afferent input to the spinal cord even when there is no injury nor pain. After peripheral sensitization, they may be spontaneously active and contribute to ongoing pain. Enhanced evoked responses after peripheral sensitization lead to enhanced CNS responses all the way up to the primary somatosensory cortex.[18]

4. Gain control in the spinal cord: central sensitization, long-term potentiation, and intraspinal inhibition

Nociceptive neurons in the deep dorsal horn of the spinal cord exhibit a peculiar type of slow temporal summation called wind-up; it refers to an increased response to C-fiber input, when this input arrives at more than 1 impulse every 3 seconds, whereas the response to A-fiber inputs remains unchanged.[30] This illustrates that central processing of nociceptive input is subject to a higher degree of gain control than that of nonnociceptive input. The slow summation called wind-up is a characteristic for wide-dynamic-range neurons that have convergent input of tactile and nociceptive afferents and does not seem to occur in high-threshold or nociceptive-specific (HT) neurons that respond only to stimuli in the noxious range. Both types of neurons fulfil the IASP definition of a nociceptive neuron as "a central or peripheral neuron that is capable of encoding noxious stimuli" (www.iaps-pain.org; Refs. 22,45). Wind-up is believed to partly compensate for peripheral fatigue, but it is too short-lived to contribute to longer lasting phenomena of gain control[47]; in fact, on prolonged low-frequency stimulation, wind-up turns into long-term depression.[17,38]

A longer lasting increase in spinal gain was first described by Woolf[46]: the reflex threshold to punctate mechanical stimuli adjacent to a burn injury in rats was reduced for many hours but reverted to normal within a day. This phenomenon was called central sensitization (**Fig. 1**) and is reminiscent of secondary hyperalgesia, which consists of enhanced mechanical pain sensitivity outside an injury site.[32] In a model of simulated injury (by intradermal capsaicin injection), it was later shown that both wide-dynamic-range and HT neurons increase their response to pinprick, whereas the response of A- and C-fiber nociceptors to the same stimuli in the same model was unchanged.[3,40] This is the only example where both input and output of spinal neurons have been documented within the same model, and hence, the definition of central sensitization is fulfilled "increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input" (www.iasp-pain.org; Ref. 22). Moreover, central sensitization in this model occurs for spinothalamic projection neurons and leads to enhanced pain perception to pinprick stimuli. Because the CNS contains many interneurons that are not part of the pathway to conscious perception,[36] the consequences of central sensitization may be enhanced nonconscious responses (for reflex interneurons) or even reduced pain sensitivity (for inhibitory interneurons).

Central sensitization shares many properties with a molecular mechanism of learning long-term potentiation (LTP). Both are manifestations of use-dependent synaptic plasticity of glutamatergic neurotransmission, which involve a multitude of cellular mechanisms. Central sensitization is induced by peripheral nociceptor input that may be due to an injury to tissue and/or nerves or to other causes.[2] Injury discharges have been simulated by high-frequency electrical C-fiber stimulation, which induces LTP in spinal cord slice preparations and in intact animals.[33,35,36] When the same stimulus protocols are applied to the human skin, mechanical hyperalgesia is induced which lasts for many hours and disappears within a day in most healthy subjects.[29] Central sensitization is often maintained by peripheral input (eg, because of peripheral sensitization or ectopic action potential generators).[2] In vulnerable subjects or on repetitive C-fiber stimulation over many days, LTP may turn into a more permanent form involving altered gene transcription and may thus contribute to some chronic pain states.[31]

Inhibition of spinal nociceptive neurons by tactile afferents according to the gate control theory is exploited by high-frequency low-intensity protocols of TENS (**Table 1**). Peripheral nociceptor input can also reduce synaptic efficacy and leads to long-term depression, when the spinal cord is stimulated at low frequencies such as 1 Hz.[38] When applied to human skin, low-frequency high-intensity electrical stimulation has inhibitory effects on pain perception.[19]

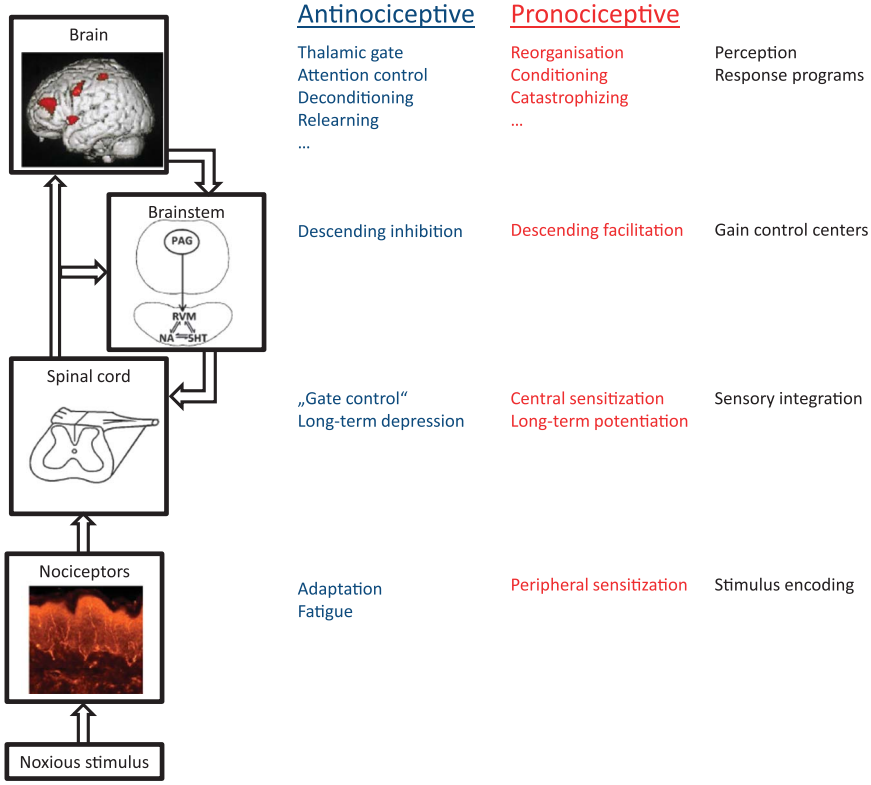

Figure 1. Gain control mechanisms in the nociceptive system. All stages of nociceptive signal processing are subject to continuous adjustments of signaling strength (gain control), from peripheral encoding by nociceptors to perceptual processes and response programming in the brain. The gate control mechanism proposed by Melzack and Wall,[23] describing tactile–nociceptive interactions in the spinal cord is still valid today but is only one of many mechanisms that either reduce (antinociceptive) or enhance (pronociceptive) signal processing in the nociceptive system. Brainstem circuitry plays an important role because it exerts gain control triggered by both ascending and descending signals.[25]

The spinal cord thus performs complex sensory integration processes (**Fig. 1**) through use-dependent plasticity, interactions between large and small fiber inputs, and also descending controls described in the next section.

5. Gain control through brainstem loops: descending inhibition and facilitation

Spinal nociceptive neurons are under both tonic and stimulus-evoked descending inhibitory controls from the brainstem and midbrain.[37] Major descending pathways use norepinephrine or serotonin as transmitters.[25] Lower brainstem and midbrain both receive nociceptive inputs from ascending tracts (**Fig. 1**), and hence, an inhibitory loop through the lower brainstem has been described and was called diffuse noxious inhibitory controls by Besson and coworkers.[21] This loop contributes to pain inhibition by other painful stimuli. One of its characteristics is that the effects are quite widespread,[2] affecting the entire body when only 1 location is stimulated (**Table 1**). A proposed function of this circuitry is to enhance spatial contrast by lateral inhibition, such that only the strongest nociceptive signal reaches the brain for response programming.

Detailed analysis of neuronal properties in the rostral ventral medulla (RVM) revealed that although some neurons are involved in descending inhibition, others facilitate spinal excitability.[16] A prominent descending facilitatory pathway is activated after nerve injury and its transmitter serotonin acts through the 5HT3 receptor.[14] RVM and midbrain periaqueductal grey (PAG) are important centers for setting the gain in the spinal cord (**Fig. 1**), and their circuitry and neuropharmacology are likely to gain more prominence for pain treatment in the future. In humans, experimental paradigms aimed at assessing this bidirectional gain control from the brainstem are called conditioned pain modulation, where usually a tonic painful stimulus is applied to modulate sensitivity to another phasic stimulus.[48]

6. Gain control mechanisms involving higher centers in the brain

The RVM receives descending inputs from the PAG which in turn is controlled by the hypothalamus, amygdala, and parts of the cerebral cortex.[25] This is one of the pathways by which the brain can control its own ascending input. This way, cognitive processes may alter the gain of nociceptive signal processing all the way down to the spinal cord. One example where this has been demonstrated is the placebo effect, where the combination of expectation and conditioning can reduce dorsal horn activation.[10] Because this pathway involves the diffuse descending projections from the brainstem, the resulting effects are expected to be generalized for the entire body. These connections provide potential pathways for cortically programmed cognitive pain control mechanisms that may reach down to the first sensory integration stage of the nociceptive pathways (**Fig. 1**).

Other cortical mechanisms of gain control may be localized, for example, when they involve spatial attentional control,[13] or when they are mediated by cortex areas with a clear somatotopic representation of the body, such as primary and

Table 1

Spinal, prespinal, and supraspinal gain control mechanisms and their clinical implications.

Mechanism	Neurons involved	Signaling	Duration	Spatial extent	Clinical manifestation	Implications for treatment
Pronociception						
Peripheral sensitization	Peripheral nociceptors	Inflammatory mediators	Hours to a few days	Strictly confined to site of injury (even part of peripheral RF)	Heat hyperalgesia at injury site, ongoing pain	NSAIDs, …
Wind-up	Spinal WDR neurons	Glutamate, substance P	Seconds	Specific to C-fiber input	Slow temporal summation	?
Central sensitization	Spinal nociceptive neurons and glia	Glutamate, substance P, …	Hours to a few days	Extending beyond injury site (within central RF)	Pinprick hyperalgesia surrounding injury site	Many signaling pathways under study
LTP	Spinal nociceptive neurons and glia, nociceptive afferents	Glutamate, substance P, …, ephrin B	Hours to a few days	Homosynaptic: input specific, heterosynaptic spread to other inputs	Pinprick hyperalgesia at and surrounding site of origin of nociceptive input	Many signaling pathways under study
Descending facilitation	On-cells in RVM, spinal nociceptive neurons, and glia	Serotonin, 5HT3 receptor, …	Hours to a few days	Widespread?	Mechanical hyperalgesia after nerve injury	5HT3 antagonists?
Cortical reorganisation	Primary somatosensory cortex	Glutamate, GABA, …	Minutes to years	Involves neighboring somatotopic representations	Referred sensations, phantom limb pain?	Retraining programs
Antinociception						
Peripheral adaptation and fatigue	Peripheral nociceptors	Intracellular calcium?	Seconds to minutes	Confined to stimulus site	Fatigue of response to mild painful stimuli	Deficient in migraine, cardiac syndrome X and others
Gate control	Spinal nociceptive neurons and tactile afferents	GABA?	Only during conditioning stimulation	Confined to stimulus site	Touch inhibits pain	TENS (high frequency, low intensity)
Long-term depression	Spinal nociceptive neurons, nociceptive afferents	Glutamate, …	Several hours	Confined to stimulus site	Human surrogate models	TENS (low frequency, high intensity)
DNIC	Off-cells in RVM	Norepinephrine, serotonin, …	A few minutes beyond conditioning stimulation	Widespread affects entire body	Pain inhibits pain	Enhanced by SNRI and tricyclic antidepressants, deficient in chronic widespread pain
Cortical pain inhibition through brainstem	Cortex, brainstem, spinal cord	Same as DNIC	?	Predicted to be widespread	Placebo	Cognitive control?
Intracortical pain inhibition	Cortex, thalamus	Glutamate, GABA?	?	Predicted to be according to somatotopic representation	Some psychiatric disorders	Cognitive control?

5HT, serotonin; DNIC, diffuse noxious inhibitory controls; GABA, gamma amino butyric acid; LTP, long-term potentiation; NSAIDs, nonsteroidal antiinflammatory drugs; RF, receptive field; RVM, rostral ventral medulla; TENS, transcutaneous electrical nerve stimulation; WDR, wide dynamic range.

secondary somatosensory cortex or the insula.[4] The thalamus is often considered the gate to the cortex, eg, during wakefulness vs sleep.[43] The transition from wakefulness to sleep leads to a transient functional deafferentation of the cortex, which may share some of its circuitry and neuropharmacology with chronic pain states induced by nerve damage that leads to a more permanent deafferentation.[1] The cortical reorganization observed after amputation[11] is a clinically relevant example of a spatially precise mechanism of gain control in the brain.

7. Clinical implications of gain control mechanisms

Table 1 summarizes the prespinal, intraspinal, and supraspinal pronociceptive and antinociceptive mechanisms of gain control in the nociceptive system. Each of these mechanisms involves multiple signaling pathways that are mentioned only incompletely in the table and that overlap considerably across mechanisms. The next 3 columns list temporal and spatial characteristics of the various types of gain control and their known clinical manifestations in humans. Although not conclusive in the strict sense, clinical findings on spatio-temporal and quality profiles of altered pain sensitivity are useful for tentative clinical implications on the mechanisms likely active in a given patient (hypothesis generation in the diagnostic process). More detailed assessment of pain mechanisms in individual patients will be essential for the development of mechanism-based treatment of pain.

(1) Ongoing pain with hyperalgesia to heat that is restricted to a region of tissue damage are suggestive of peripheral sensitization: peripheral sensitization is induced by injury and leads to pronounced hypersensitivity of nociceptors to heat and low pH, which may lead to ongoing pain when tissue temperature and pH become suprathreshold stimuli. It lasts for up to a day and is strictly limited to the site of the injury: peripheral sensitization and fatigue are highly localized to the stimulated nociceptors and even to the stimulated part of the receptive field.

(2) Hyperalgesia to punctate stimuli (v. Frey or pinpricks) and dynamic mechanical allodynia that extend somewhat beyond the region of tissue damage or occur without any such damage are suggestive of central sensitization: central sensitization is induced by intense or prolonged nociceptor input and leads to

pronounced mechanical hypersensitivity (to pinpricks and light touch). It lasts for up to a day and may spread to adjacent skin (secondary hyperalgesia) within the limits of the central receptive fields and subthreshold central connections.

(3) Pain inhibition by large fiber activation that is confined to the stimulated body part and occurs only during the stimulation is consistent with the gate control theory.

(4) Pain inhibition that is confined to the stimulated body part but outlasts the stimulation considerably and requires stimulus intensities that recruit A-delta fibers is consistent with long-term depression: LTD leads to strictly localized effects but can act for several hours.

(5) Whole-body hyperalgesia and widespread pain are suggestive of deficits in descending inhibition or activation of descending facilitation: modulatory pathways through the lower brainstem inhibit or facilitate nociceptive processing for the entire body. These widespread effects have a short duration: diffuse noxious inhibitory control outlasts the conditioning stimulus by a few minutes only.

(6) At present no clear guidance can be given as to when cortical pain inhibition is the likely mechanism. Imaging findings are often inconclusive because peripheral and central sensitization will be reflected in stronger activation of the brain due to the enhanced ascending input.[2] Effects of cortical gain control may be widespread, when the brainstem centers are involved, or localized, when the thalamic gate or intracortical circuitry is engaged.

8. Conclusions and outlook

This review outlined, how modern concepts of gain control integrate plasticity of nociceptive signal processing in the peripheral and central nervous system, the interactions of various types of nociceptive and nonnociceptive inputs at the level of the spinal cord, the contributions of supraspinal networks, and how these mechanisms of gain control in the nociceptive system relate to clinically observable phenomena of sensory gain and loss.

Gain control starts in the periphery, where habituation is prominent to potentially tissue-damaging stimuli, while sensitization dominates for the salient actually tissue-damaging noxious stimuli. The peripheral input enhances or reduces spinal signal processing through central sensitization and LTP, or long-term depression and the classical tactile gate control. The spinal cord is also the target of descending controls from the brainstem that can have both inhibitory and facilitatory actions. Through PAG and brainstem, the brain can control the gain of its own ascending input at the level of the spinal cord. In addition, there is a thalamic gate controlling access to the cortex and a multitude of intracortical gain control mechanisms that may be the basis of many cognitive and behavioral treatment approaches.

In summary, as 50 years ago, the spinal cord dorsal horn remains a major site of sensory integration of the nociceptive system, and the brainstem still is a prominent center for setting the gain controls of the nociceptive system. However, in the meantime, it has been recognized that at the peripheral end of the nociceptive system, functional and structural plasticity modulate the gain for nociceptive input to the spinal cord. And at the rostral end of the nociceptive system, we are at the verge of delineating the intracortical and descending mechanisms of gain control, which may be the neurobiological basis of many components of multimodal pain therapy.

Conflict of interest statement

The author has no conflict of interest to declare.

Acknowledgements

The author is grateful to the British Pain Society for their invitation to give the 2014 Patrick D. Wall lecture.

Article history:
Received 30 November 2015
Received in revised form 14 January 2016
Accepted 19 January 2016
Available online 25 January 2016

References

[1] Anderson WS, O'Hara S, Lawson HC, Treede RD, Lenz FA. Plasticity of pain-related neuronal activity in the human thalamus. Prog Brain Res 2006;157:353–64.
[2] Baron R, Hans G, Dickenson AH. Peripheral input and its importance for central sensitization. Ann Neurol 2013;74:630–6.
[3] Baumann TK, Simone DA, Shain CN, LaMotte RH. Neurogenic hyperalgesia: the search for the primary cutaneous afferent fibers that contribute to capsaicin-induced pain and hyperalgesia. J Neurophysiol 1991;66:212–27.
[4] Baumgartner U, Iannetti GD, Zambreanu L, Stoeter P, Treede RD, Tracey I. Multiple somatotopic representations of heat and mechanical pain in the operculo-insular cortex: a high-resolution fMRI study. J Neurophysiol 2010;104:2863–72.
[5] Bessou P, Perl ER. Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. J Neurophysiol 1969;32:1025–43.
[6] Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997;389:816–24.
[7] Dallenbach KM. Pain: history and present status. Am J Psychol 1939;52: 331–47.
[8] de Vos CC, Meier K, Zaalberg PB, Nijhuis HJ, Duyvendak W, Vesper J, Enggaard TP, Lenders MW. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. PAIN 2014;155:2426–31.
[9] Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, Levy RM, Backonja M, Baron R, Harke H, Loeser JD, Treede RD, Turk DC, Wells CD. Interventional management of neuropathic pain: NeuPSIG recommendations. PAIN 2013;154:2249–61.
[10] Eippert F, Finsterbusch J, Bingel U, Büchel C. Direct evidence for spinal cord involvement in placebo analgesia. Science 2009;326:404.
[11] Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 1995;375:482–4.
[12] Foerster O. Die Leitungsbahnen des Schmerzgefühls. Vienna: Urban und Schwarzenberg, 1927.
[13] García-Larrea L, Lukaszewicz AC, Mauguière F. Somatosensory responses during selective spatial attention: the N120-to-N140 transition. Psychophysiology 1995;32:526–37.
[14] Guo W, Miyoshi K, Dubner R, Gu M, Li M, Liu J, Yang J, Zou S, Ren K, Noguchi K, Wei F. Spinal 5-HT3 receptors mediate descending facilitation and contribute to behavioral hypersensitivity via a reciprocal neuron-glial signaling cascade. Mol Pain 2014;10:35.
[15] Head H. Studies in neurology. London: Oxford Medical Publications, 1920. p. 653.
[16] Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: specificity, recruitment and plasticity. Brain Res Rev 2009; 60:214–25.
[17] Herrero JF, Laird JMA, López-Garcia JA. Wind-up of spinal cord neurones and pain sensation: much ado about something? Prog Neurobiol 2000;61:169–203.
[18] Kenshalo DR, Isensee O. Responses of primate SI cortical neurons to noxious stimuli. J Neurophysiol 1983;50:1479–96.
[19] Klein T, Magerl W, Hopf HC, Sandkühler J, Treede RD. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. J Neurosci 2004;24:964–71.
[20] LaMotte RH, Campbell JN. Comparison of responses of warm and nociceptive C-fiber afferents in monkey with human judgments of thermal pain. J Neurophysiol 1978;41:509–28.
[21] Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. PAIN 1979;6:283–304.
[22] Loeser JD, Treede RD. The kyoto protocol of IASP basic pain terminology. PAIN 2008;137:473–7.

[23] Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150: 971–9.
[24] Mendell LM. Constructing and deconstructing the gate control theory of pain. PAIN 2014;155:210–16.
[25] Millan MJ. Descending control of pain. Prog Neurobiol 2002;66:355–474.
[26] Nathan PW. The gate-control theory of pain. A critical review. Brain 1976; 99:123–58.
[27] Noordenbos W. Pain. Amsterdam: Elsevier, 1959. p. 34–42.
[28] Perl ER. Sensitization of nociceptors and its relation to sensation. In: Advances in pain research and therapy, Vol. 1. New York: Raven Press, 1976. p. 17–28.
[29] Pfau DB, Klein T, Putzer D, Pogatzki-Zahn EM, Treede RD, Magerl W. Analysis of hyperalgesia time courses in humans after painful electrical high-frequency stimulation identifies a possible transition from early to late LTP-like pain plasticity. PAIN 2011;152:1532–9.
[30] Price DD, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. PAIN 1977;3:57–68.
[31] Price TJ, Inyang KE. Commonalities between pain and memory mechanisms and their meaning for understanding chronic pain. Prog Mol Biol Transl Sci 2015;131:409–34.
[32] Raja SN, Campbell JN, Meyer RA. Evidence for different mechanisms of primary and secondary hyperalgesia following heat injury to the glabrous skin. Brain 1984;107:1179–88.
[33] Randic M, Jiang MC, Cerne R. Long-term potentiation and long-term depression of primary afferent neurotransmission in the rat spinal cord. J Neurosci 1993;13:5228–41.
[34] Reeh PW, Petho G. Nociceptor excitation by thermal sensitization—a hypothesis. Prog Brain Res 2000;129:39–50.
[35] Ruscheweyh R, Wilder-Smith O, Drdla R, Liu XG, Sandkühler J. Long-term potentiation in spinal nociceptive pathways as a novel target for pain therapy. Mol Pain 2011;7:20.
[36] Sandkühler J. Models and mechanisms of hyperalgesia and allodynia. Physiol Rev 2009;89:707–58.
[37] Sandkühler J, Fu QG, Zimmermann M. Spinal pathways mediating tonic or stimulation-produced descending inhibition from the periaqueductal gray of nucleus raphe magnus are separate in the cat. J Neurophysiol 1987;58:327–41.
[38] Sandkühler J, Chen JG, Cheng G, Randic M. Low-frequency stimulation of afferent Adelta-fibers induces long-term depression at primary afferent synapses with substantia gelatinosa neurons in the rat. J Neurosci 1997; 17:6483–91.
[39] Schwarz S, Greffrath W, Büsselberg D, Treede RD. Inactivation and tachyphylaxis of heat-evoked inward currents in nociceptive primary sensory neurones of rats. J Physiol 2000;528:539–49.
[40] Simone DA, Sorkin LS, Oh U, Chung JM, Owens C, LaMotte RH, Willis WD. Neurogenic hyperalgesia: central neural correlates in responses of spinothalamic tract neurons. J Neurophysiol 1991;66:228–46.
[41] Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 1998;21: 531–43.
[42] Treede RD, Meyer RA, Raja SN, Campbell JN. Peripheral and central mechanisms of cutaneous hyperalgesia. Prog Neurobiol 1992;38: 397–421.
[43] Tsoukatos J, Kiss ZHT, Davis KD, Tasker RR, Dostrovsky JO. Patterns of neuronal firing in the human lateral thalamus during sleep and wakefulness. Exp Brain Res 1997;113:273–82.
[44] Wall PD, Sweet WH. Temporary abolition of pain in man. Science 1967; 155:108–9.
[45] Willis WD. The pain system. Basel: Karger, 1985.
[46] Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306:686–8.
[47] Woolf CJ. Windup and central sensitization are not equivalent. PAIN 1996;66:105–8.
[48] Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. Curr Opin Anaesthesiol 2010;23:611–15.