Review

Cortical excitation and chronic pain

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Investigation of the basic mechanisms of chronic pain not only provides insights into how the brain processes and modulates sensory information but also provides the basis for designing novel treatments for currently intractable clinical conditions. Human brain imaging studies have revealed new roles of cortical neuronal networks in chronic pain, including its unpleasant quality, and mouse studies have provided molecular and synaptic mechanisms underlying relevant cortical plasticity. This review paper will critically examine the current literature and propose a cortical network model for chronic pain.

Introduction

Chronic pain is a major health issue all over the world, and is caused by tissue or nerve injury under different disease conditions. In addition to spontaneous pain, there are two common pathological conditions that develop after tissue or nerve injury: allodynia and hyperalgesia. In allodynia, there is a reduction in pain threshold and, consequently, nonnoxious stimuli that normally do not cause pain now induce pain. In hyperalgesia, there is an enhanced response to noxious stimuli. Peripheral and central sensitization are likely to contribute to chronic pain. Integrative research approaches, including the use of human brain imaging and genetically manipulated mice, have consistently suggested that chronic pain is due to long-term plastic changes along sensory pathways. Plastic changes not only take place in peripheral nociceptors and spinal dorsal horn and subcortical areas but also in cortical areas that are involved in the processing of painful information. Thus, treating chronic pain requires understanding of plastic changes in somatosensory pathways. This article will focus on the cortical mechanisms of pain using brain imaging studies, in particular those related to chronic pain mechanisms, and will explore possible synaptic and molecular mechanisms that lead to cortical plasticity in chronic pain using animal models. A cortical network hypothesis is proposed to explain the possible basic mechanisms underlying chronic pain.

A key hypothesis: long-term plasticity in the cortex encoding chronic pain

One key hypothesis I would like to put forward is that peripheral injury triggers plastic changes or long-term potentiation (LTP) in the cortical synapses. Such potentiation or excitation persists for a long period of time, and consequently might generate abnormal neuronal spike activity in the brain without obvious peripheral sensory stimulation. Thus, chronic pain likely employs highly selective synaptic connections and molecular signaling pathways within pain-related cortical areas. Based on this hypothesis, I argue that it is possible to discover novel protein targets that are preferentially involved in chronic pain through basic neurobiological investigations.

Overview of recent progress in imaging studies of pain in the cortex

Brain imaging techniques allow us to investigate cortical regions related to pain, from the feeling of pain to the extent of unpleasantness (see Table 1). It overcomes the limit of animal studies, and has provided detailed information about the cortical areas that respond to painful stimuli. Furthermore, imaging studies allow the correlated analyses to detect the brain areas where activity is correlated with psychological pain reports. Significant progress has been made in the study of acute pain because it can be performed in healthy human subjects with similar background and health history, and testing stimuli are acute and repeatable (Table 1). Among different cortical regions, there are five major cortical areas that are consistently responding to acute pain: anterior cingulate cortex (ACC), insular cortex (IC), primary somatosensory cortex (S1), secondary somatosensory cortex (S2) and prefrontal cortex (PFC) (see Figure 1). The ACC is found to be the most reliable area to be activated by different noxious or painful stimuli [1]. Warm and cold grill stimulation, where warm or cold alone is not sufficient to activate the ACC, activates the ACC along with pain sensation [2]. This report provides direct evidence for the selective involvement of the ACC in pain. In addition to the ACC, the IC is also commonly activated by different painful stimuli [1,3,4]. Neuronal activities in the ACC and IC are believed to be important for pain perception and unpleasantness (but see Ref. [3] for the IC).

Neurons in the ACC and IC are likely to encode multiple forms of pain. Activation of the ACC and IC have been reported to be caused by noxious heat, cold and chemical stimuli [1]. Results from human brain imaging studies suggest that not all pain is processed by a similar brain region(s), and each particular form of pain is coded by several brain areas. For example, both noxious visceral and somatosensory stimuli activated the IC, ACC and S2 [4]; interestingly, only the perigenual cingulate cortex was deactivated by visceral pain [4]. Deactivation of cortical areas, presumably owing to reduction of neuronal activities, is very intriguing. It might suggest that Yin and Yang, excitation (E) and inhibition (I), not only occur at the neuronal level but also at the cortical network level (i.e. one cortical area is activated while an adjacent area is

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Table 1. Recent major human brain imaging and genetically manipulated mouse approaches for the study of cortical pain mechanisms

Experimental approach	Major advantage	Limitation
Human brain imaging	Noninvasive; measurement of hemodynamic responses; image activity of cortical and subcortical structures; performed in conscious subjects; various psychological experiments; ideal for long-term follow-up	Affected by blood flow, volume and others; not correlated with neuronal spike activity; failed to identify activity from excitatory (E) or inhibitory (I) neurons; side effects of various stress, attention, reward and other human factors; limited pharmacological and genetic manipulation
Human magnetoencephalography	Noninvasive, comfort; measurement of population electrical activity; good temporal resolution	Difficult to determine the exact source of change; cannot distinguish between E and I; can be affected by stress, attention and other factors
Human single-neuron recording	Direct measurement of single human neuron responses	Low productivity; difficult or impossible to get appropriate healthy control data; cannot rule out potential side effects of emotional distress
Transgenic mice with forebrain overexpression	Selective enhancement or inhibition of protein in the forebrain neurons without affecting spinal or DRG neurons	Gene overexpression is not physiological; difficult to control or determine the amount of protein expression
Gene knockout mice	100% inhibition of target protein; good for both *in vitro* and *in vivo* behavioral studies	Global gene deletion including the dorsal root ganglion, spinal cord and cortex; potential developmental compensation; changes in other proteins downstream from the targeted protein
Mouse brain electroporation	Regional inhibition or overexpression; without developmental compensation; partial inhibition of protein function; affected neurons can be labeled	Difficult to control the magnitude and duration of expressed protein
In vivo two-photon imaging	Spine, synapse imaging; follow for a long period of time; imaging both neurons and glia	Mostly in anesthetized animals that cortical excitability is affected by anesthetics; only superficial cortical neurons; unclear about physiological significance of spine size changes

inhibited). Iannetti *et al.* found that gabapentin, a drug commonly used for treating neuropathic pain, reduced chronic pain-related deactivation [5], suggesting deactivation might indeed contribute to chronic pain. The ACC and/or IC can also be triggered by psychological pain and social exclusion, providing further evidence for their importance in the process of pain [6,7]. Furthermore, Singer *et al.* reported that neurons in the IC and ACC were likely to be activated during empathy of pain [8].

Imaging of chronic pain in the brain

Limited information is available on brain activation in chronic pain. Unlike acute pain where stimulation can be easily controlled and healthy subjects are easy to find, chronic pain patients are usually heterogeneous, and many factors affect the evaluation of suffering or pain they report. Despite these difficulties, several reports have investigated some aspect of chronic pain in patients. It has been shown that in neuropathic pain, the physiological discriminative function is downregulated whereas pain-related activity is enhanced [9–12]. In patients with irritable bowel syndrome, rectal distension that induces pronounced pain/urge activation (hyperalgesia) is accompanied by increased activities in the IC and ACC [13].

One unique feature of human subjects is that they allow us to determine brain activities during spontaneous pain in patients. Sustained high levels of spontaneous pain result in increases in activity within the medial PFC (mPFC) including the ACC [14]. Electrophysiological studies using the electroencephalogram (EEG) recording technique found that in neuropathic pain patients there is a spontaneous presence of enhanced activation within high θ (6–9 Hz) and low β frequencies (12–16 Hz) located in the IC, ACC, S1 and S2. These results suggest that frequency-specific ongoing overexcitation might contribute to spontaneous pain reported in patients with chronic pain.

Phantom pain is another form of chronic neuropathic pain caused by amputation. Early animal studies have suggested that cortical plasticity and reorganization might be the cause of phantom pain [15,16]. Recently, it has been reported that phantom pain is indeed correlated with cortical activation (or changes in cortical mapping) [17]. It is likely that the sprouting of nerve terminals into inactivated somatosensory areas and cortical overexcitation in pain areas such as the ACC and IC contribute to phantom pain.

Recent studies in human patients with other forms of chronic pain found opposite structural changes compared to phantom pain. Apkarian *et al.* reported that chronic back pain is associated with decreased prefrontal and thalamic gray matter density [18]. Similarly, Schmidt-Wilcke *et al.* reported that chronic back pain is correlated with decreases of gray matter in the brainstem and somatosensory cortex [19]. Loss of gray matter in patients with fibromyalgia including in the ACC, IC, mPFC and parahippocampal gyri is also found to correlate with chronic pain [20] (but see Ref. [19] for opposite findings in the striatum). It is unclear whether the loss of neurons is limited to local inhibitory neurons. If so, chronic pain could be explained as disinhibition, or the shift in E/I balance in the brain. Furthermore, it remains to be determined whether these structural changes are a consequence of chronic pain or secondary changes due to pain-related mental disorders (such as depression). Draganski *et al.* reported that loss of gray matter correlates well with the duration of amputation, but not the amount of phantom pain [21], suggesting that the loss of neurons might be a

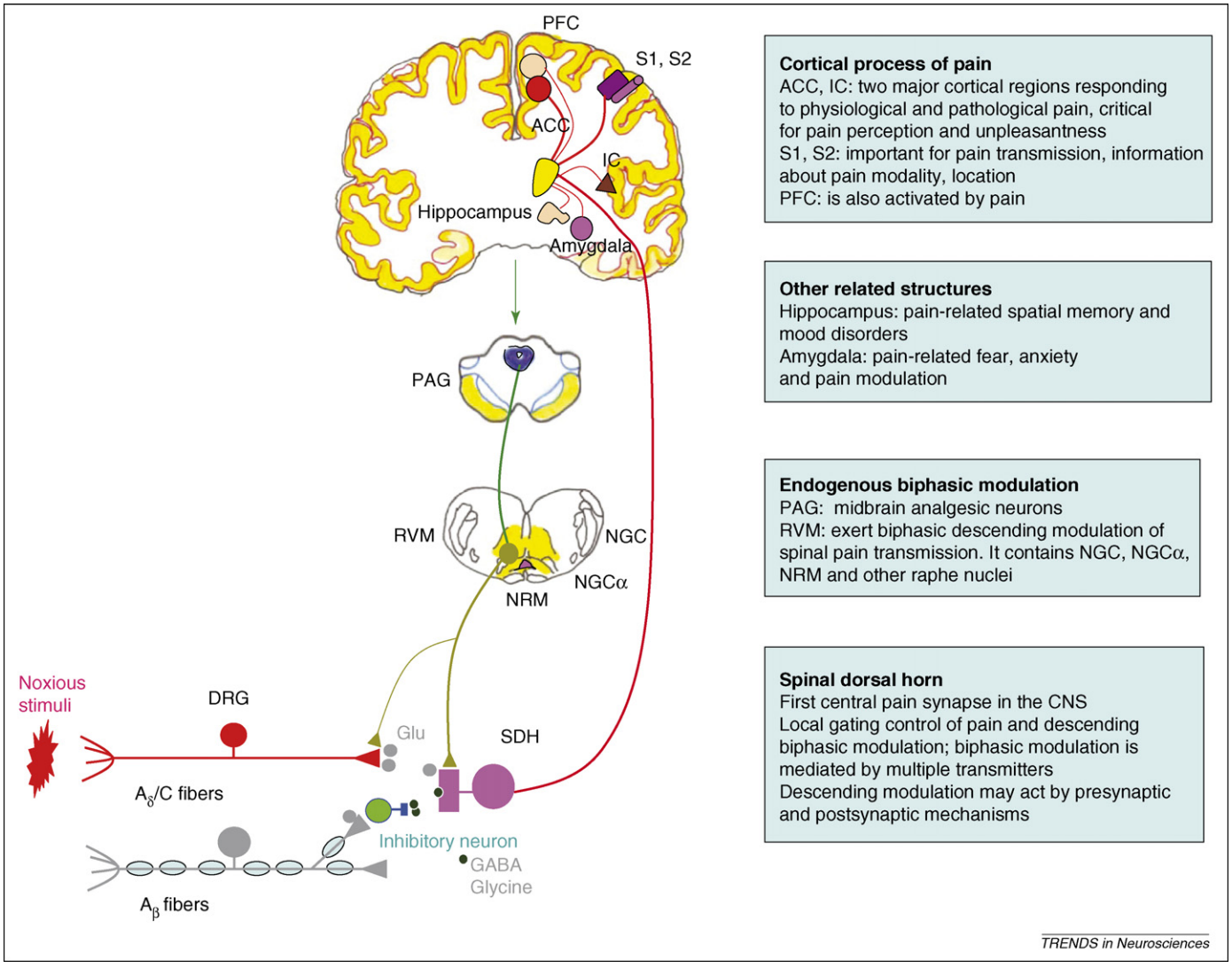

Figure 1. Diagram showing pain transmission and modulation pathways in the central nervous system. Under normal physiological conditions, noxious stimuli activate nociceptive afferent fibers (A_δ and C fibers). Incoming action potentials trigger a release of excitatory transmitter glutamate in the spinal dorsal horn (SDH). In addition, some neuropeptides are also released, including substance P and neurokinin A. Glutamate and neuropeptides activate spinal dorsal horn neurons, including those that send projection terminals to supraspinal structures. Neurons in the thalamus play key roles in relaying these ascending inputs. Five major cortical areas, the ACC, IC, S1, S2 and PFC, are activated, and contribute to different aspects of pain perception, including the unpleasantness of pain. Neurons in the hippocampus are also activated and can contribute to the formation of pain-related spatial memory and mood responses. Activation of the amygdala (as well as the ACC) also contributes to pain-related fear memory and pain modulation. As protective responses to noxious stimuli, endogenous pain modulatory systems are also activated. Descending facilitatory systems can also be activated. Facilitated spinal nociceptive transmission might trigger faster escape responses. In the case of an inescapable situation, the descending inhibitory system can be activated, and neurotransmitters such as 5-HT and norepinephrine will be released from descending projection fibers in the dorsal horn of the spinal cord. They then inhibit dorsal horn synaptic transmission. The midbrain PAG and brainstem RVM are the key components of the endogenous analgesic system. In addition to the descending inhibitory modulation, spinal non-nociceptive fibers can release glutamate as well. Glutamate then acts postsynaptically on spinal dorsal horn inhibitory neurons, causing subsequent release of GABA and glycine from these inhibitory neurons. GABA and glycine bind on projection neurons and reduce pain transmission. Glutamate can also bind to presynaptic KA receptors of inhibitory neurons, and regulates presynaptic modulation of GABA/glycine release. DRG = dorsal root ganglion.

secondary response to injury, rather than the cause of chronic pain. One possibility is that both synaptic elimination and synaptic outgrowth occur within the cortical network and, consequently, the neuronal circuits related to pain are overexcited despite the loss of neurons. Heightened excitation is consistently reported in cortical areas related to pain in patients with phantom pain or other forms of chronic pain. Future studies are needed to explore the potential molecular mechanisms.

From brain imaging studies to the use of animal models

Human brain imaging studies have technical limits. For example, it is difficult to identify the source of neuronal activity, namely *excitatory versus inhibitory neurons*. The activity of the ACC has been reported to be correlated with pain [22] as well as with placebo analgesia/opioid analgesia, two opposite physiological processes. It is impossible to tell whether increased metabolic activity in pain versus analgesia conditions might be a result of changes in the activity of inhibitory versus excitatory neurons. These results can be explained if excitatory neurons are activated during pain, whereas inhibitory neurons are activated during placebo/opioid analgesia. More importantly, recent studies have demonstrated that imaged human brain activities did not correlate with neuronal spike activities in the cortex such as the ACC and IC [23–25]. It is clear that the basic mechanisms of chronic pain cannot be revealed by human imaging studies alone, and the use of animal models is still the key approach of studying chronic pain.

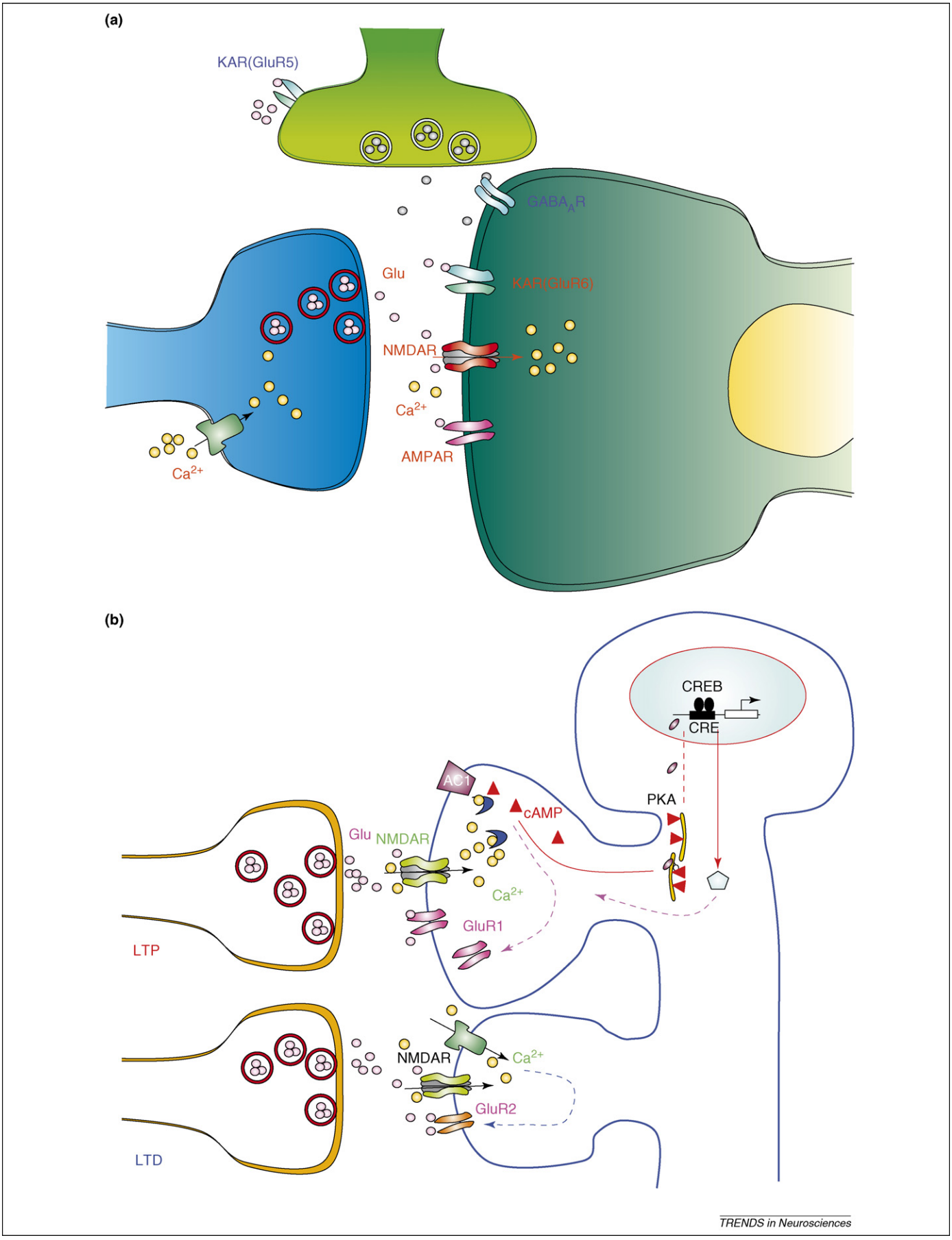

Figure 2. Synaptic transmission and plasticity in the ACC. **(a)** Excitatory and inhibitory synaptic transmission. Action potentials from the thalamic projection fibers trigger release of vesicles containing glutamate. Fast excitatory transmission is mediated by glutamate in the ACC. EPSCs are mediated by AMPA receptors, whereas small

Cortical synaptic transmission

Glutamate (Glu) is the excitatory transmitter

Glutamate is the major fast excitatory transmitter in the ACC [26]. Bath application of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) completely abolishes fast excitatory postsynaptic currents (EPSCs) recorded in ACC neurons [26]. In addition to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, postsynaptic glutamate kainate (KA) receptors contribute to fast excitatory synaptic transmission in the ACC (see Figure 2A). Single-focal stimulation could induce small KA receptor-mediated EPSCs in the presence of a selective AMPA receptor antagonist, GYKI 53655. Genetic deletion of the KA GluR6 and GluR5 subunits completely abolished KA EPSCs and KA-activated currents [27].

GABA mediates inhibitory transmission

γ-Aminobutyric acid (GABA) is the major inhibitory transmitter in the ACC and IC. The inhibitory postsynaptic currents (IPSCs) are mainly mediated by postsynaptic $GABA_A$ receptors [28]. Bath application of picrotoxin completely abolishes spontaneous IPSCs and evoked IPSCs [28]. $GABA_B$ receptors are also found in ACC neurons, although the role of $GABA_B$ remains to be investigated (Figure 2a). There are few studies that investigate the modulation of inhibitory transmission in the ACC. A recent study using KA knockout mice reported that inhibitory transmission in the ACC is under tonic modulation of KA GluR5 receptor [29].

Cortical excitation: LTP of excitatory transmission

LTP

Genetic, pharmacological and electrophysiological approaches have been used to investigate the basic mechanisms for LTP in ACC synapses. Different stimulation protocols can be used for inducing LTP in ACC pyramidal cells. Pairing training protocol (synaptic activity paired with postsynaptic depolarization), the spike-excitatory postsynaptic potential (EPSP) pairing protocol, and θ burst stimulation (TBS) protocol all induce LTP in ACC pyramidal neurons [29]. Unlike the field recordings induced by TBS, LTP induced by the pairing protocol is mainly triggered by the activation of N-methyl-D-aspartate (NMDA) receptors but not L-type voltage-gated calcium channels (L-VGCCs) [29]. In ACC pyramidal cells, NMDA receptor-containing NR2A or NR2B subunits contributed to most of the NMDA receptor currents [29,30]. Bath application of NR2A antagonist NVP-AAM077 and NR2B antagonist ifenprodil/Ro compounds almost completely blocked NMDA receptor-mediated EPSCs as well as LTP [29]. By contrast, the NR2A or NR2B antagonist alone only reduced LTP [29].

Activation of NMDA receptors leads to an increase in postsynaptic Ca^{2+} in dendritic spines. Ca^{2+} serves as an important intracellular signal for triggering a series of biochemical events that contribute to the expression of LTP. Ca^{2+} binds to calmodulin (CaM) and leads to activation of calcium-stimulated signaling pathways [29]. Furthermore, postsynaptic injection of BAPTA completely blocked the induction of LTP, indicating the importance of elevated postsynaptic Ca^{2+} concentrations [29]. Work using electroporation of mutant CaM in ACC neurons suggests that calcium binding sites of CaM are critical for the induction of ACC LTP [31]. Ca^{2+}-stimulated, neuron-specific adenylyl cyclase subtype 1 (AC1) is highly expressed in ACC neurons [32], and LTP induced by TBS or pairing stimulation is abolished in AC1 knockout mice [33–35]. Several other signaling proteins or protein kinases are found to be involved in ACC LTP, including Ca^{2+}-calmodulin-dependent protein kinase IV (CaMKIV), early growth response gene 1 (egr1), mitogen-activated protein kinase (MAP kinase) and fragile X mental retardation protein (FMRP) [35,36].

At least four different synaptic mechanisms might contribute to the expression of LTP: (i) presynaptic enhancement of the release of glutamate; (ii) postsynaptic enhancement of glutamate AMPA receptor-mediated responses; (iii) recruitment of previously 'silent' synapses or synaptic trafficking or insertion of AMPA receptors; and (iv) structural changes in synapses. We have recently investigated the roles of GluR1 and GluR2/3 using genetic and pharmacological approaches. We found that the GluR1 subunit C-terminal peptide analog Pep1-TGL blocked the induction of ACC LTP [37,38]. Thus, in the ACC, the interaction between the C terminus of GluR1 and PDZ domain proteins is required for the induction of LTP. Synaptic delivery of the GluR1 subunit from extrasynaptic sites is the key mechanism underlying synaptic plasticity [36], and GluR1–PDZ interactions play a critical role in this type of plasticity. Application of philanthotoxin 433 (PhTx) 5 min after LTP induction reduced synaptic potentiation, whereas PhTx had no effect on basal AMPA receptor-mediated responses [39], suggesting that Ca^{2+}-permeable GluR2-lacking receptors contribute to the maintenance of ACC LTP. Our recent studies found that ACC LTP is absent in GluR1 knockout mice (Zhao *et al.*, unpublished). We also examined the role of GluR2-related peptides in synaptic potentiation in the ACC and found that the GluR2/3–PDZ interaction had no effect on ACC LTP, and the same interfering peptides inhibited ACC LTD [39].

Long-term depression

At least two forms of long-term depression (LTD) have been reported: NMDA receptor-dependent and -independent

percentages of EPSCs are mediated by GluR6-containing KA receptors. In freely moving animals, synaptic responses are also mediated by postsynaptic NMDA receptors. Inhibitory transmission is mediated by postsynaptic $GABA_A$ receptors. GluR5-containing KA receptors located at presynaptic terminals of inhibitory neurons regulate the release of GABA. **(b)**. A model for ACC LTP and LTD. Activation of glutamate NMDA receptors leads to an increase in postsynaptic Ca^{2+} in dendritic spines. Both NMDA NR2B and NR2A subunits are important for NMDA receptor functions in ACC neurons. Ca^{2+} serves as an important intracellular signal for triggering a series of biochemical events that contribute to the expression of LTP. Ca^{2+} binds to CaM and leads to activation of Ca^{2+}-stimulated ACs, mainly AC1 and Ca^{2+}/CaM-dependent protein kinases. The trafficking of postsynaptic GluR1-containing AMPA receptor contributes to enhanced synaptic responses. In addition, activation of AC1 leads to activation of PKA-CREB. For ACC LTD, glutamate and synaptic activity activate postsynaptic neurons, and lead to moderate increases in postsynaptic Ca^{2+}. There is no selective involvement of NMDA subtype NR2A versus NR2B receptor in cingulate LTD. Depending on the induction protocol and recording method, postsynaptic L-VGCCs can contribute to the induction of cingulate LTD. For the expression of LTD, postsynaptic GluR2 AMPA receptor is required. It is likely that the activity of protein phosphatases is needed, as previously reported in other central neurons.

LTD [40]. ACC LTD induced by presynaptic stimulation with postsynaptic depolarization is NMDA receptor dependent [29,41]. However, NMDA receptor-independent LTD has been reported using field potential recordings from adult ACC slices [42]. Thus, different induction protocols result in different forms of ACC LTD. Unlike ACC LTP, inhibition of NR2A or NR2B is sufficient to block ACC LTD. Furthermore, in the presence of NR2B receptor blockade, strong LTD pairing protocol can rescue LTD. This finding suggests that postsynaptic Ca^{2+} signaling is critical for the induction of LTD [40]. Paired-pulse facilitation (PPF) is not changed during LTD in the ACC [39], further supporting the idea that induction of LTD might depend on postsynaptic mechanisms. Consistently, ACC LTD was abolished in GluR2 knockout mice [39,40]. These findings suggest that GluR1 and GluR2 play different roles in ACC LTP versus LTD (see Figure 2b).

In vivo LTP in excitatory synaptic transmission

In brain slices, cingulate synapses can undergo LTP after experimentally designed training protocols. One key question regarding ACC plasticity is whether or not injury causes long-term changes in synaptic transmission in the ACC in intact animals. To test this, we performed experiments in anesthetized rats. We measured synaptic responses to peripheral electrical shocks by placing a recording electrode in the ACC of anesthetized rats [15]. At high intensities of stimulation, sufficient to activate nociceptive A_δ and C fibers, evoked field EPSPs were recorded in the ACC. Digit amputation at the contralateral hindpaw causes a rapid and long-lasting enhancement (more than 120 min) of sensory responses. Potentiated sensory responses do not require persistent activity from the injured hindpaw [15]. These findings indicate that plastic changes are likely occurring within the ACC synapses. Furthermore, *in vivo* intracellular recordings from anesthetized rats have confirmed similar findings [43].

NMDA NR2B: another key enhancer of chronic pain

Evidence for the involvement of cortical NMDA NR2B receptor in chronic pain first comes from 'Doogie smart' mice [44]. In this transgenic mouse with selective forebrain NMDA NB2B overexpression, electrophysiological and behavioral studies found that NR2B transgenic mice are superperformers in various learning/memory tests with significantly enhanced hippocampal LTP [44]. In the case of tissue injury and inflammation, we found that inflammatory pain and allodynia were significantly enhanced without any significant effect on acute pain [45]. These results provide the first genetic evidence that the kinetics of NMDA receptor currents in forebrain neurons can encode information related to chronic pain.

Because genetic overexpression was used in Doogie mice, it is unclear whether such observation is physiologically relevant. We have recently examined potential changes in NR2B receptors in the cortex of mice with inflammatory pain. We found that NR2B receptor-mediated responses in the ACC are enhanced after peripheral inflammation. The changes in NMDA receptor protein expression are subtype selective, because other NMDA receptor subunits such as NR1 and NR2A did not show any significant change [41]. The increased NR2B receptors are likely to be within synapses, because single-shock focal stimulation-induced NR2B receptor-mediated synaptic currents were enhanced [41]. It is possible that NR2B receptors might also undergo upregulation at extrasynaptic sites. The upregulation of extrasynaptic NR2B receptors might provide a key mechanism to explain the loss of accuracy of acute pain perception in chronic pain patients (see above).

IC: an area to be explored at cellular/molecular levels

The IC has also been reported to play an important role in chronic pain. Most of the data currently available are from brain imaging studies in human patients [1]. In adult rats, local manipulations that enhance GABA function in the IC produced long-lasting analgesic effects in rats, providing a top-down inhibitory modulation of spinal nociception [46]

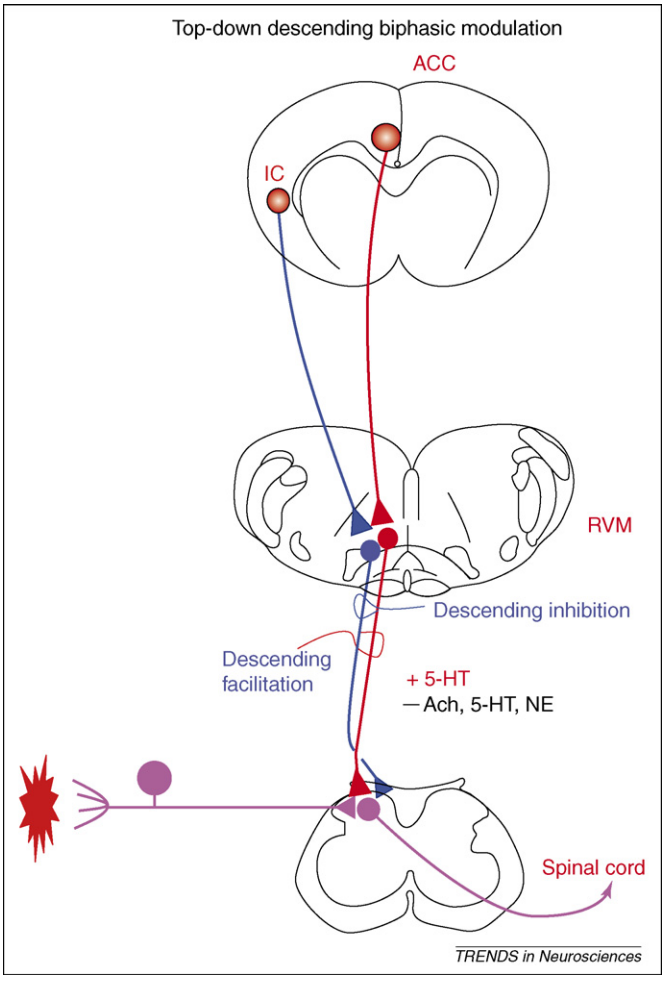

Figure 3. Top-down ACC RVM-generated descending facilitation. A model showing supraspinal control of RVM-generated descending facilitation of spinal nociception by ACC neurons. Neurons in the RVM project to the spinal dorsal horn (fibers travel at the ventrolateral funiculi [VLF] and ventral funiculi [VF]) and modulate sensory synaptic transmission in the spinal cord. 5-HT is the major transmitter for mediating this facilitatory effect. Stimulation of neurons in the ACC also activates descending facilitation, and activity within the RVM is required for mediating descending facilitation from the ACC to the spinal dorsal horn. Unlike the ACC, there is a recent report of descending inhibition from the IC. It is possible that IC might control RVM-generated descending inhibition of spinal nociceptive transmission. Unlike the facilitatory effect, inhibitory modulation (traveling through the dorsolateral funiculi [DLF]) is likely mediated by spinal multiple transmitters, including 5-HT, acetylcholine (Ach) and NE in the spinal cord.

Table 2. Potential cortical mechanisms for chronic pain

Proposed model	Synaptic effect
Plasticity of synaptic transmission	Enhanced existing AMPA responses
LTP	GluR1-mediated LTP
Loss of LTD	Enhanced glutamate release
	Failure to depotentiate enhanced responses
Structural reorganization	Growth of new intra- and intercortical connections
Cortical reorganization	Loss of neurons as a result of cell death; many of them might be inhibitory neurons
Neuronal cell death	
Altered descending modulation	Enhanced facilitatory influences from the ACC and RVM
Enhanced descending facilitation	

(see Figure 3). Further studies are clearly needed for detailed synaptic and molecular studies of IC neurons and circuits. LTP in the IC has been reported in *in vitro* brain slice preparations [34] and *in vivo* in freely moving rats [47]. TBS produces LTP in the IC of adult mice and CaMKIV is required for the induction [34].

Cortical disinhibition: loss of inhibitory modulation

In addition to LTP, ACC LTD has been reported to be altered after injury. In ACC neurons, low-frequency stimulation that induced LTD in normal brain slices failed to induce any LTD after amputation, providing a possible disinhibitory mechanism for chronic pain in the cortex [42].

Box 1. Cellular and synaptic mechanisms for chronic pain in the cortex

In early phase (I), excitatory synaptic transmission might undergo rapid potentiation such as LTP, which can last for hours to days (see Table 2). Changes in presynaptic releases and postsynaptic receptor modifications are the likely key mechanisms for early changes. Possible changes in local inhibitory transmission can occur as well (Figure I). In late phase (II), translational events become involved. These include synthesis of key synaptic signaling proteins such as NMDA NR2B receptor, novel signaling messengers as well as other proteins that are required for prolonged structural changes. Trophic factors and other growth-related molecules might be involved in cortical reorganization. Some of these signaling proteins and receptors might even form positive feedback loops and induce prolonged excitation of cortical circuits (Figure I). In enduring phase (III), reorganization of the cortical networks happens, which can take years to occur, resulting in the formation of new structural connections within the cortex as well as between cortical areas. Such plastic changes might not be limited to pain-related areas. Potential neuronal cell loss (including inhibitory neurons) might occur among certain populations of cells. The three proposed phases are mutually exclusive; early phase will likely interfere or set up events that are critical for the next phase (Figure I).

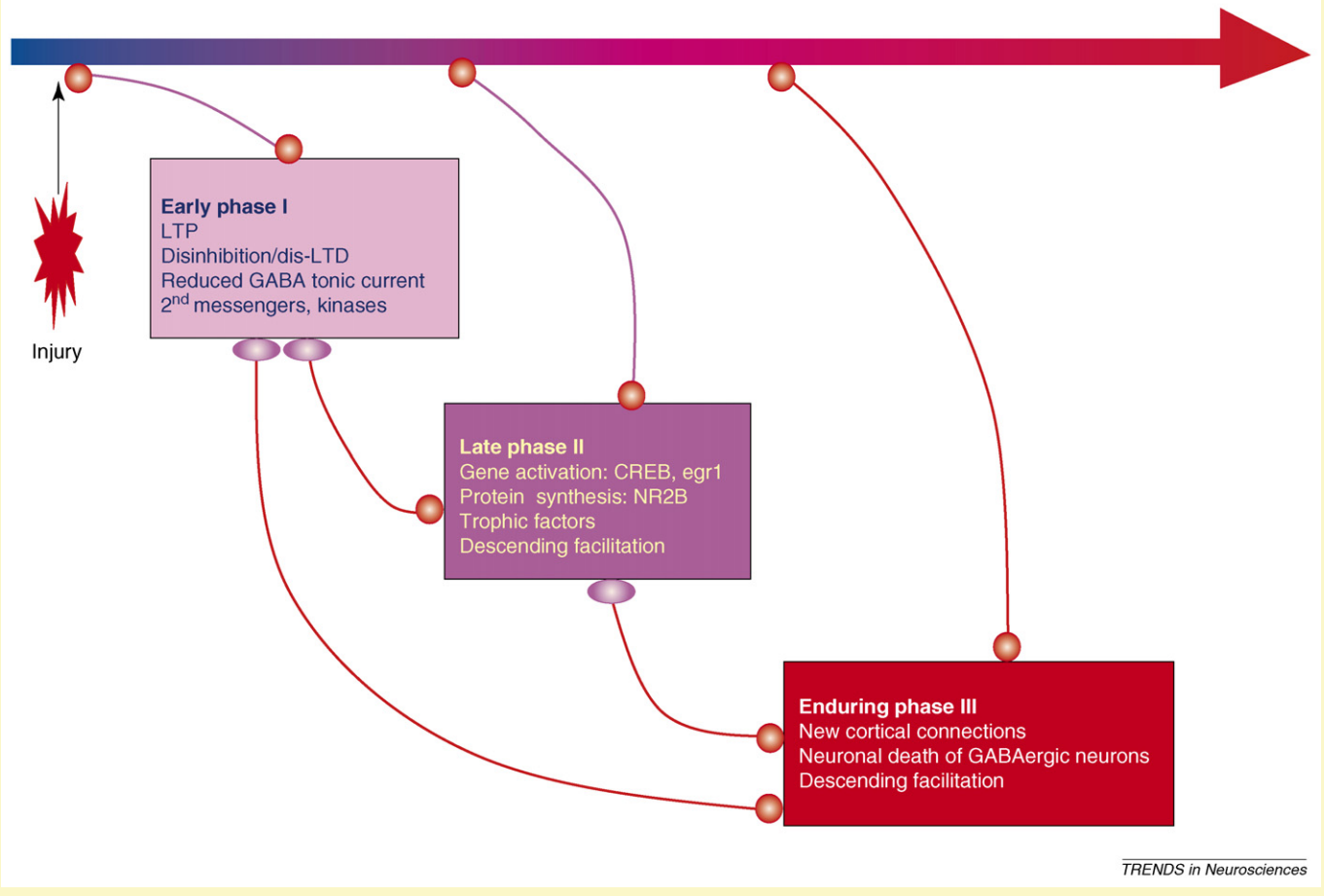

Figure I. Cortical plasticity and reorganization in chronic pain.

Loss of ability to undergo LTD might allow cortical synapses to stay in excitation for a long period of time. In human imaging studies, most of the reports focused on 'hot' spots, the areas where neuronal activities are thought to be increased. A few studies have reported that in 'cold' areas, neuronal activities can be inhibited. Deactivation also occurs in some cortical areas during acute pain. Dunckley *et al.* have found deactivation of the ACC and activation of the IC by visceral colorectal distention in healthy humans [4].

Proposed cortical network model for chronic pain

Based on recent findings including those described above, it is likely that chronic pain is mediated by multiple cellular and molecular mechanisms. There is no single mechanism that explains chronic pain at the level of the spinal cord or cortex. Table 2 lists several possible cortical mechanisms that might contribute to chronic pain. To assist future investigations of chronic pain, I propose a cortical model for chronic pain. This model contains at least three different phases (I–III): early phase (I), late phase (II) and enduring phase (III) (see Box 1).

It is well known that spinal nociceptive transmission is under biphasic modulation from supraspinal structures [42,48–50]. Because direct projections from the cortex to the spinal cord are not common, it is likely that many of these descending cortical influences are relayed by brainstem neurons and other subcortical neurons. Descending facilitation from the rostroventral medulla (RVM) has been well characterized. Here an additional top-down facilitatory mechanism is added to the model to link the cortical activity to the spinal dorsal horn gating control (see Figure 3). Unlike normal inhibitory control, in chronic pain conditions, descending modulatory influences from supraspinal structures are switched from inhibitory to facilitatory. Using a spinal nociceptive reflex, we showed that ACC stimulation-induced facilitation is reversibly blocked by inhibition of glutamate-mediated synapse transmission in the RVM [51] (see Figure 3). Contribution of brainstem-induced descending facilitation to chronic pain has been investigated. Lesions of the ACC in patients, pharmacological inhibition of NMDA receptor/cAMP pathways in the ACC, inhibition of descending facilitation by lesions of the RVM, or spinal blockade of serotonin (5-HT) subtype receptors has been shown to be analgesic or antinociceptive in chronic pain conditions in both human and animal studies [42,52], providing key basic and clinical evidence for the current model.

Conclusions and future directions

In conclusion, two major areas of research activities, human brain imaging and integrative physiological studies in genetically manipulated mice, have generated new and novel information regarding the basic mechanisms of chronic pain, particularly at the cortical levels. It is clear that injuries trigger a series of plastic changes in pain-related cortical areas, including the ACC. Chronic pain also triggers a series of brain disorders such as emotional fear, anxiety, mood depression and impairment of cognitive functions. Future studies designed to understand the relationship between pain and mood disorders, and identify novel molecular targets contributing to these events, will help us to find better pain medicine.

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