People experience the feeling of the missing body part long after it has been removed after amputation are known as phantom limb sensations. These sensations can be painful, sometimes becoming chronic and lasting for several years (or called phantom pain). Medical treatment for these individuals is limited. Recent neurobiological investigations of brain plasticity after amputation have revealed new insights into the changes in the brain that may cause phantom limb sensations and phantom pain. In this article, I review recent progresses of the cortical plasticity in the anterior cingulate cortex (ACC), a critical cortical area for pain sensation, and explore how they are related to abnormal sensory sensations such as phantom pain. An understanding of these alterations may guide future research into medical treatment for these disorders.

**Key words:** anterior cingulate cortex, long-term potentiation, long-term depression, phantom pain, amputation, mice

**INTRODUCTION**

It is well known that adult somatosensory cortex is dynamic and plastic [1-4]. Cortical anatomic connections and functional representations can be modified by experience, and some of these modification can occur within a very short amount of time. At the synaptic level, it has been believed that use-dependent changes in synaptic strength, such as long-term potentiation (LTP) and long-term depression (LTD) may serve as key synaptic mechanisms of cortical plasticity [4-7].

Cortical changes not only occur during development and normal physiological conditions, but also under pathological conditions, such as tissue/nerve injury or the loss of a limb [see 8].

For example, it has been demonstrated that cortical reorganization occurs after limb or digit amputation [9-13]. Most human amputees experience phantom limb sensation or phantom pain [see 14 for review]. However, it is unclear if cortical reorganization directly contributes to phantom sensations and/or phantom pain. Furthermore, the molecular and cellular mechanisms contributing to amputation related cortical reorganization are still largely unknown. In this review, I shall focus on the ACC, a critical forebrain area for pain and cognition, and explore synaptic plastic changes after amputation, under both *in vitro* and *in vivo* conditions.

**ACC AND NOCICEPTION/PAIN**

The ACC forms a large region around the rostrum of the corpus callosum and is involved in emotional and attentive responses to internal and external stimulation [15, 16]. Neuroimaging and electrophysiological studies in humans have shown that
somatosensory stimuli, including those causing pain, activate ACC neurons and other related limbic areas [17-21, see 4 for reviews]. Electrophysiological recordings demonstrate that ACC neurons respond to peripheral nociceptive stimulation in animals [22, 23]. Behavioral experiments in both rats and mice show that lesions of the medial frontal cortex, which includes the ACC, significantly reduces sensitivity to noxious heat applied to the hindpaw in the hot-plate test [24, 25], whereas electrical and chemical stimulation of regions within the ACC facilitates behavioral responses to noxious heat in the tail-flick test [26]. Consistent with these animal studies, the unpleasantness of pain is abolished in patients with frontal lobotomies or cingulotomies [see 4 for review]. As compared with sensory neurons in the spinal cord, ACC neurons show receptive fields receiving input from almost any part of the body surface [see 21 for review]. Furthermore, most ACC neurons are polymodal (e.g., responding to both non-noxious and noxious stimuli). In vivo recording from human patients show that some ACC neurons exhibit bilateral responses to noxious stimuli, although some of them show evidence of restricted receptive fields [19]. In monkeys, it has also been reported that some nociceptive ACC neurons were activated during anticipation of pain [22]. Recently, in adult mice, we performed in vivo whole-cell patch-clamp recordings from pyramidal neurons in adult mice ACC under urethane anesthetized conditions [27]. We found that peripheral noxious pinch stimuli induced evoked spike responses in all three types of ACC neurons, showing that ACC neurons are indeed nociceptive. Moreover, direct electrical stimulation of the ACC in freely moving mice generated fear memory, providing strong evidence that activation of the ACC neurons indeed cause fear or unpleasant feelings in animals [28].

**IMAGING OF PHANTOM PAIN IN THE BRAIN**

Human imaging studies have provided powerful tool for studying cortical involvement in chronic pain including phantom pain, since it is impossible to measure phantom pain in animals directly [see 14, 29 for reviews]. It has been reported that functional and anatomic changes in sensory and motor cortices are related to phantom pain [see 14 for review], although such imaging method may not be useful for detecting plastic change at synaptic level. The precise functional contribution of these cortical changes to phantom pain is still unclear. Stimulation of motor cortex where amputation also triggered long-term plastic changes has been reported to relief phantom pain [see 30 for review]. It is possible that some of these changes may even take place in local inhibitory circuits; and thus activation of these inhibitory circuits can help to reduce pain by indirectly affecting pain related cortical areas such as ACC and insular cortex. Alternatively, they may affect endogenous descending inhibitory systems to produce analgesic effects [4].

**CORTICAL REORGANIZATION AND PHANTOM PAIN**

Cortical reorganization within somatosensory systems following amputation has been reported in both animals and humans [see 31 for review]. For example, the representation of the forepaw in the primary somatosensory cortex of a raccoon that had lost a forearm had been completely reactivated by an expanded representation of the stump. Furthermore, evidence from anatomic, electrophysiological and behavioral approaches consistently indicates that extensive cortical changes occur in the adult brain after amputation [31]. Not only do such changes occur at cortical levels, but long-lasting changes could also occur at subcortical structures, including the thalamus and brainstem nuclei [31, 32]. For example, in the thalamus, it has been reported that neurons that normally respond to stimuli on the missing limb become responsive to touch on the stump of the missing limb [33]. It is proposed that the growth of new connections at both subcortical and cortical levels of the central nervous system, in combination with changes in connectional synaptic strengths at the same levels, mediate most reorganization in the cortex [9, 31]. Furthermore, it has been reported that there is a possible link between cortical reorganization and phantom pain. Flor et al. reported in human studies that the amount of cortical reorganization correlates with the extent of phantom pain [34]. More interestingly, recent studies using animal models of neuropathic pain showed that nerve injury (which can be caused by amputation as well) triggered long-lasting synaptic structural changes within the ACC or related prefrontal cortical areas [35-38].

**DIGIT OR TAIL AMPUTATION AS ANIMAL MODEL FOR STUDYING BRAIN CHANGES**

Due to the difficulty in using animal models for the study of phantom pain, one alternative approaches is to investigate possible synaptic changes in cortical areas that are important for pain perception after amputation or nerve injury. Recent studies using animal studies with distal tail or single digit amputation models revealed that amputation caused prolonged neuronal activation and rapid expression of three immediate early genes in the cortex, including the ACC and hippocampus [39-42]. Interestingly, changes in synaptic plasticity, such as LTP and LTD, have also been reported in both brain slices from amputated animals and recordings in vivo [39, 40, 43, 44]. In vivo intracellular recordings
from anesthetized mice showed that peripheral digit amputation caused long-lasting changes in neuronal excitability. These findings provide strong physiological evidence that synaptic connections in the brain can be altered after amputation. While it is too early to speculate on the behavioral correlates of these synaptic changes, long-term changes in behavioral responses to noxious stimuli had been reported [41].

CORTICAL SYNAPTIC TRANSMISSION

Glutamate is the major fast excitatory transmitter in the ACC [39, 45]. Bath application of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) completely abolishes fast excitatory postsynaptic currents (EPSCs) recorded in the ACC neurons. In addition to the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, postsynaptic glutamate kainate (KA) receptors contribute to fast excitatory synaptic transmission in the ACC. 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 [45].

Gamma-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 [46]. Bath application of picrotoxin completely abolishes spontaneous IPSCs and evoked IPSCs. GABA_A receptors are also found in the ACC neurons, although the role of GABA_B remains to be investigated. 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 [46].

CORTICAL DEPRESSION AND POTENTIATION

LTD and LTP are two major forms of synaptic plasticity in the central synapses. Both LTD and LTP have been reported in ACC synapses. For LTD, at least two forms of LTD have been reported: NMDA receptor-dependent and -independent LTD [47]. ACC LTD induced by presynaptic stimulation with postsynaptic depolarization is NMDA receptor-dependent. However, NMDA receptor-independent LTD has been reported using field potential recordings from adult ACC slices [39, 44]. Thus, it is likely that different induction protocols result in different forms of ACC LTD. Both NMDA receptor NR2A and NR2B contribute to ACC LTD [48 for review]. Paired-pulse facilitation (PPF) is not changed during LTD in the ACC [45], supporting the idea that induction of LTD may depend on postsynaptic mechanisms. Consistently, ACC LTD was abolished in GluR2 knockout mice [47].

While early studies failed to report robust LTP in the ACC neurons using tetanic stimulation, theta burst stimulation (TBS) and other LTP induction protocols induced reliable LTP in ACC synapses of adult animals [see 4, 7 for review]. Genetic, pharmacological and electrophysiological approaches have been used to investigate the basic mechanisms for LTP in the ACC synapses. Different stimulation protocols can be used for inducing LTP in the ACC pyramidal cells. Pairing training protocol (synaptic activity paired with postsynaptic depolarization), the spike-excitatory postsynaptic potential (EPSP) pairing protocol, and TBS protocol all induce LTP in the ACC pyramidal neurons [49]. Unlike the field recordings induced by TBS, LTP induced by the pairing protocol is mainly triggered by the activation of NMDA receptors but not L-type voltage-gated calcium channels (L-VGCCs) [50]. Bath application of NR2A antagonist NVP-AAM077 and NR2B antagonist ifenprodil/Ro 25-6981 almost completely blocked NMDA receptor-mediated EPSCs as well as LTP. By contrast, the NR2A or NR2B antagonist alone only reduced LTP [49]. 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.

Ca^{2+}-stimulated, neuron-specific adenyl cyclase subtype 1 (AC1) is highly expressed in the ACC neurons, and LTP induced by TBS or pairing stimulation are abolished in AC1 knockout mice [50]. The importance of AC1 activity in the ACC LTP has been further confirmed by the use of a selective AC1 inhibitor [51]. 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) [4]. We have recently investigated the roles of GluR1 and GluR2/3 using genetic and pharmacological approaches. We found that GluR1 subunit C-terminal peptide analog, Pep1-TGL, blocked the induction of ACC LTP. 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 and GluR1-PDZ interactions play a critical role in this type of plasticity. Application of Phanlantoxin-433 (PhTx) 5 min after LTP induction reduced synaptic potentiation, while PhTx had no effect on basal AMPA receptor-mediated responses, suggesting that Ca^{2+}-permeable GluR2-lacking receptors

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Contribute to the maintenance of ACC LTP. ACC LTP is absent in GluR1 knockout mice [52]. 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. Recent studies found that PKMζ (PKM) activity is critical for maintaining synaptic potentiation in the ACC [38].

CORTICAL NETWORK PLASTICITY

To explore plastic changes within cortical circuit, we recently used a 64-channel multi-electrode dish (MED64) system, a two-dimensional electric activity monitoring device, to characterize LTD in adult mouse ACC. The MED64 system allows us to detect the field excitatory postsynaptic potentials (fEPSP) at multiple sites in mouse ACC, which is difficult to achieve with conventional field recording systems. Within the ACC, we observed spatial distribution of excitatory synaptic transmission when stimulating deep layer V [44]. This was the only area we could detect more than 20 channels with inward responses. Stimulating other areas, such as layer I or II/III, induced at most 10 channels of inward responses. We found, however, that not every activated channel underwent LTD; the channels that are within a 300 µm radius of the stimulation site being the most likely to exhibit this form of synaptic plasticity [44]. It is believed that such multiple channel recording system will provide new information about cortical LTP and LTD at both synaptic and circuit levels in near future.

LOSS OF LTD AFTER AMPUTATION

One major hypothesis for central plastic changes after peripheral injury is enhanced central synaptic transmission and neuronal excitability. There are at least two possible mechanisms to achieve this at synaptic level; enhanced synaptic transmission, and the loss of the ability to undergo LTD. Indeed, our previous work found that amputation of a third hindpaw digit in an adult rat induced rapid expression of immediate early genes in the ACC bilaterally and caused a loss of LTD that persisted for at least 2 weeks [39]. Similar to previous studies in rats, we also found that a loss of LTD in mouse ACC after distal tail amputation [44]. Similarly, LTD induced by the pharmacological activation of mGluR1 was also lost following amputation. Biochemical data showed that the surface level of mGluR1 was not changed after amputation compared to the sham group, suggesting that amputation triggered loss of LTD is not due to reduction of postsynaptic membrane levels of mGluR1. The modification is thus likely to be downstream of the mGluRs. Future studies are clearly needed for revealing the exact signaling pathways.

CORTICAL NETWORKS IN PHANTOM PAIN

Most of recent work at molecular and cellular levels focused on synaptic changes after nerve injury or amputation [4, 7]. It is well known that pain-related cortical neurons are highly wired with other cortical regions as well as subcortical areas [see 21 for review]. Future studies are clearly needed to understand synaptic changes within these cortical-cortical and cortical-subcortical connections. For example, a recent study showed that in neuropathic pain conditions (Note: the injury to peripheral nerve happen in most cases of limb amputation) can trigger facilitated synaptic transmission between somatosensory cortex and ACC [53], in addition to well-known plastic changes within the ACC [see 4, 7]. Furthermore, our recent study found that cortical-spinal projection neurons in the ACC undergoing potentiation after nerve injury (Chen et al., unpublished data). It is thus likely that amputation may trigger wide-spreading plastic changes in sensory
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OPIOID ANALGESIA AND AMPUTATION

Opioids have been commonly used for the treatment of phantom pain. It produces some analgesic effects in subpopulation of patients, while other patients did not respond to the treatment as those often reported in neuropathic pain [for example see 54 for review]. Few studies have been reported using animal models. To test possible changes in opioid produced analgesic effects, we used distal tail amputation mouse model for studying this. Amputation of a segment of the tail produced long-lasting changes in nociception and morphine-induced antinociception. Plastic changes in nociceptive transmission may occur at the spinal cord as well as supraspinal structures after tail amputation [55]. Acute hyperalgesia is detected at the remaining part of the tail as well as hindpaw. Morphine induced facilitation of the HP response at a low dose and a greater dose of morphine is required to produce complete inhibition of the HP response. Since these effects happen at five weeks after the surgery, tail amputation may serve as a mouse model for studying long-term plastic changes in morphine produced analgesia after amputation.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, integrative physiological studies in genetically manipulated mice, have generated new and novel information regarding the basic mechanisms of chronic pain including phantom pain, particularly at the cortical levels. It is clear that nerve injuries or amputations trigger a series of plastic changes in pain-related cortical areas including the ACC. Loss of LTD as well as potentiation of synaptic transmission within the ACC and between cortical areas contributes to enhanced excitability of pain-processing and feeling cortical neurons (see Figure 1). Some of these cortical changes may not require persistent peripheral sensory inputs; thus will not respond to any medical treatment that targeted at lower subcortical levels. In addition to contribution to pain or phantom pain, such cortical plastic changes may 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 for patients including those with phantom pain.

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