

Review Article

Altered synaptic connections and inhibitory network of the primary somatosensory cortex in chronic pain

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ABSTRACT Chronic pain is induced by tissue or nerve damage and is accompanied by pain hypersensitivity (i.e., allodynia and hyperalgesia). Previous studies using *in vivo* two-photon microscopy have shown functional and structural changes in the primary somatosensory (S1) cortex at the cellular and synaptic levels in inflammatory and neuropathic chronic pain. Furthermore, alterations in local cortical circuits were revealed during the development of chronic pain. In this review, we summarize recent findings regarding functional and structural plastic changes of the S1 cortex and alteration of the S1 inhibitory network in chronic pain. Finally, we discuss potential neuromodulators driving modified cortical circuits and suggest further studies to understand the cortical mechanisms that induce pain hypersensitivity.

INTRODUCTION

Prolonged tissue damage or nerve injury can lead to chronic pain, such as inflammatory or neuropathic pain, in which a variety of changes occur throughout the nociceptive pathways, from the periphery to the cortex [1-4]. Many researchers have identified changes in the expression of receptors and channels in the peripheral nervous system and central nervous system in chronic pain models [3]. Additionally, local circuits and/or proportions of cell types have been reported to change in pain-related regions [5-10]. Under chronic pain conditions, hyperexcitability, reorganization, and structural brain changes are observed in the pain matrix brain regions, such as the primary somatosensory (S1) cortex and anterior cingulate cortex [11,12], with modifications in their functional connections [13]. Recently, with advanced two-photon imaging and cell type identification techniques using genetically modified mice, research to elucidate the cortical mechanisms of chronic pain has been actively conducted. Increased activities

in inhibitory and excitatory neurons in the S1 cortex have been reported in chronic pain models [14-16], and plastic structural changes have been observed in the S1 cortex in neuropathic pain models [17-19]. Pain relief following S1 manipulation [15,19] in chronic pain suggests that the S1 cortex is deeply involved in the development and maintenance of chronic pain.

Neural circuits in the S1 cortex consist of pyramidal neurons (PNs) and several subtypes of inhibitory neurons. The activity of PNs is appropriately regulated within a local inhibitory circuit composed of three major subtypes of inhibitory neurons: somatostatin (SOM), parvalbumin (PV), and vasoactive intestinal polypeptide (VIP)-expressing interneurons [20]. SOM and PV inhibitory neurons are known to contribute to the dendritic and perisomatic inhibition of PNs, respectively [21,22]. In contrast, VIP neurons are known to suppress other subtypes of inhibitory neurons [23]. Previous studies have reported alterations in the activities of subtypes of inhibitory neurons in models of chronic pain, suggesting their potential as targets for chronic pain relief



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[15,16]. However, it remains unclear as to which neuromodulators drive such changes in local circuits.

Cholinergic input from the basal forebrain to the S1 cortex is suggested to act on inhibitory neurons to modulate PN activity. Another potential factor is the noradrenergic modulation of the S1 local circuitry. In this article, we review the plastic changes occurring at the neuronal and circuit levels of the S1 cortex in chronic pain models, which were assessed mainly using brain imaging studies. In addition, we discuss the causative neuromodulators that drive local circuit changes in chronic pain and suggest directions for further research to alleviate chronic pain symptoms and understand cortical mechanisms.

NEURAL PLASTIC CHANGES IN THE S1 CORTEX IN CHRONIC PAIN

Brain imaging studies (e.g., functional magnetic resonance imaging [fMRI] or micro-positron emission tomography [micro-PET]) in both humans and animal models have shown increased activation intensity, somatotopic reorganization, and altered cortical thickness of the S1 cortex, as well as modified connectivity patterns in the pain matrix under chronic pain conditions [11,13,24,25]. These findings suggest that the S1 cortex is associated with the development of chronic pain.

In recent years, using *in vivo* two-photon microscopy imaging, functional and structural changes of the S1 cortex have been reported at the individual cell and synapse levels in rodent chronic pain models. In mice with chronic pain induced by spinal nerve injury, the fraction of active neurons in the S1 cortex significantly increased two days after injury, and the fluorescence of the active neurons was higher than that in sham-operated mice [26]. Previous imaging studies have also reported that the activity of L5 PNs in the S1 cortex was persistently elevated, and L2/3 PNs exhibited higher activity in peripheral nerve-injured mice than in sham mice [15,16]. Cichon *et al.* [15] performed an experiment to inhibit peripheral sensory inputs by local application of the sodium channel blocker tetrodotoxin to the sciatic nerve, and found that inhibition of peripheral inputs did not reduce the elevated somatic Ca^{2+} activity of S1 L5 PNs in nerve-injured mice, unlike in sham mice, suggesting that the hyperactivity of S1 PNs can be due to some major changes in the S1 cortex that are not simply driven by peripheral inputs. In addition, the functional connectivity between S1 L2/3 active neurons was positively increased in response to peripheral stimulation in an inflammatory chronic pain model [27]. Further, Eto *et al.* [28] showed that both spontaneous activity and evoked activity to sensory stimulation of S1 L2/3 neurons increased in the same chronic pain model. The authors also confirmed that evoked activity of inhibitory neurons as well as excitatory neurons in S1 L2/3 was increased upon sensory stimulation under inflammatory chronic pain conditions [28]. Interestingly, even though a GABA_A receptor agonist was applied

to the S1 L2/3 to facilitate overall inhibitory action, pain behavior was transiently alleviated. This result suggests that an overall increase in inhibitory action of S1 L2/3 is insufficient to fundamentally counteract S1 hyperactivity in chronic pain.

Kim and Nabekura [18] demonstrated that remodeling of cortical synapses in the S1 cortex is associated with the development of chronic neuropathic pain induced by peripheral nerve injury. In particular, they showed that the dendritic spine turnover of L5 PNs was markedly increased during the developmental state of chronic pain, and the volume of new spines formed after nerve injury continued to increase. With structural changes in dendritic spines, increased axonal bouton turnover in the S1 cortex was observed in the developmental state of chronic pain [17]. A subsequent study showed that peripheral nerve injury induced upregulation of the metabotropic glutamate receptor 5 signaling in S1 astrocytes, resulting in the release of synaptogenic thrombospondin 1 (TSP-1) from the S1 astrocytes. Overexpression of TSP-1 in the S1 cortex led to increased dendritic spine turnover in S1 pyramidal neurons in chronic pain. Knockdown of TSP-1 expression in the S1 cortex using siRNA reduced spine turnover of S1 PNs and alleviated pain behavior [19]. These findings collectively suggest that structural plastic changes in the S1 cortex are attributed to S1 astrocyte activation in the developmental state of chronic pain.

LOCAL CIRCUIT CHANGES IN THE S1 CORTEX IN CHRONIC PAIN

At the individual cell level, it is well accepted that the spontaneous activity of S1 PNs and their evoked activity in response to peripheral sensory stimulation are increased under chronic pain conditions. In addition, Eto *et al.* [14] reported that both excitatory and inhibitory neurons exhibited increased somatic calcium activity in chronic pain mice, but the hyperactivity of S1 excitatory neurons could not be counteracted by an overall increase in GABAergic neuron activity in the S1 cortex. The mechanisms by which the S1 neuronal circuits, which are composed of excitatory pyramidal neurons and the distinct subtypes of GABAergic interneurons, reorganize to lead to S1 hyperactivity in chronic pain are unknown. A recent study on the medial prefrontal cortex (mPFC) found that nerve injury altered the excitability of distinct subtypes of GABAergic neurons in a sex-specific manner [29]. A chronic pain study performed in the ACC demonstrated that the loss of inhibitory synapses onto excitatory neurons and excitatory synapses onto inhibitory neurons resulted in a disinhibited cortical network [10]. In a model of chronic inflammatory pain, increased synchronization and connectivity among active neurons of the S1 cortex to peripheral sensory stimulation was observed. On the other hand, the correlation between PV-expressing inhibitory neurons decreased without a change in the power of calcium transient and frequency events over the same period [27]. This

means that there is a critical change in the inhibitory network, which may imply that local circuits, including PNs, are modified and that PNs become hyperactive in chronic pain.

Recent imaging studies of the S1 cortex have found that the local inhibitory networks are modified in chronic pain induced by peripheral nerve injury. Cichon *et al.* [15] identified alterations in neuronal calcium activity in three major subtypes (SOM, PV, and VIP neurons) of S1 L2/3 interneurons, along with hyperactivity of L5 and L2/3 PNs in chronic neuropathic pain. The activities of SOM and PV neurons were reduced 1 month after induction of chronic pain, and in particular, the activity of SOM neurons was halved, whereas the activity of VIP neurons dramatically increased under the same conditions. The increase in SOM activity through pharmacogenetic techniques decreased the calcium activities of L5 and L2/3 PNs, and also debilitated allodynia. On the other hand, increasing PV activity was insufficient to alleviate allodynia. Wei *et al.* [16] also confirmed the cell-type-specific changes in the S1 inhibitory circuits that contribute to the development of chronic neuropathic pain. The authors showed that the altered activities of each type of S1 neuron in chronic pain were reversed through electroacupuncture in the periphery, and found that hypersensitivity could be alleviated by CB1R-induced modulation of the activity of VIP neurons [16]. These findings suggest that distinct subtypes of S1 inhibitory neurons in chronic pain shift their activity toward S1 PNs hyperactivity, and that reversing the shifted activity of inhibitory neurons may be a therapeutic strategy to suppress the onset of chronic pain.

POTENTIAL MECHANISMS DRIVING MODIFICATIONS OF LOCAL CIRCUITS IN THE S1 CORTEX IN CHRONIC PAIN

Previous studies on nociceptive pathways have suggested that

alterations in inhibitory transmission are implicated in the development of chronic pain [10,30,31]. Many of the aforementioned studies have shown an impaired S1 inhibitory network in which VIP neuron activity is upregulated and SOM/PV neuron activity is downregulated, which causes enhancement of S1 PN activity in chronic pain. However, it is unknown what drives these changes in the local circuit of the S1 cortex under chronic pain conditions.

In the cortical circuit, the three major subtypes of GABAergic neurons are interconnected, and inhibit each other, and have the following characteristics (Fig. 1A) [23]. VIP neurons inhibit SOM and PV neurons without PN inhibition, and preferentially suppress the firing of SOM neurons. SOM and PV neurons, in turn, inhibit the PNs. SOM neurons strongly inhibit other populations with little inhibition of each other, whereas PV neurons mainly inhibit each other. In the connected relationships, an increase in VIP activity inevitably leads to a decrease in SOM/PV activity and hyperactivity in PNs in chronic pain (Fig. 1B), and reversal of SOM and VIP activities was possibly able to alleviate chronic pain symptoms. Modulation of PV activity did not alleviate allodynia, which may be due to the large difference between SOM synapses onto tuft dendrites of PNs and PV synapses onto the somatic membrane of PNs [21,22]. Therefore, upregulation of SOM activity was effective in chronic pain, but the ultimate solution would be to tune the VIP activity that regulates the firing of other subtypes of inhibitory neurons.

VIP neurons have recently been widely studied for their disinhibitory roles in sharpening cortical functions during sensory processing in multiple areas of the neocortex [32-35]. Activation of VIP neurons in the auditory cortex transiently suppresses SOM and PV neurons that control the input and output of principal neurons [35]. In particular, during an auditory discrimination task, uniform activation of VIP neurons enhanced the gain of a functional subpopulation of principal neurons. Acetylcholine (ACh) has been suggested to influence the disinhibitory action of

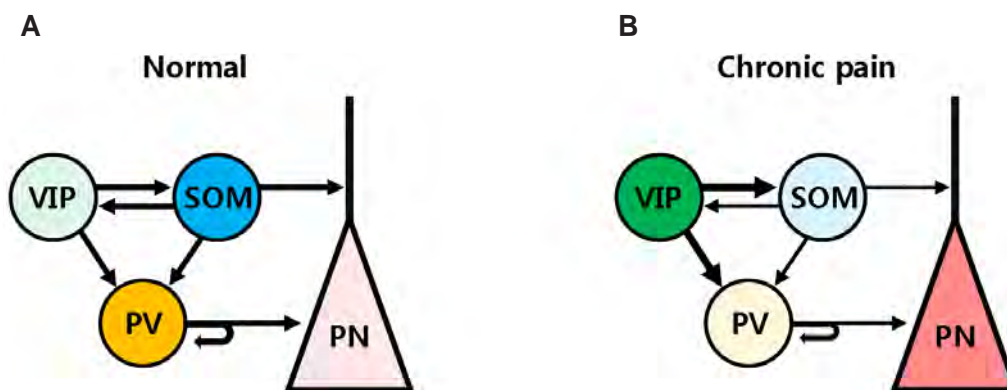


Fig. 1. Local inhibitory circuits are modified in chronic pain. (A) Under normal conditions, pyramidal neurons (PN) are appropriately modulated by mainly somatostatin (SOM) and parvalbumin (PV)-expressing inhibitory neurons. Vasoactive intestinal polypeptide (VIP)-expressing inhibitory neurons primarily inhibit other subtypes of inhibitory neuron, and preferentially suppresses SOM activity. SOM and PV neurons contribute to tuft dendritic and perisomatic inhibition of pyramidal neurons, respectively. (B) Tissue or nerve injury alters local inhibitory circuits towards hyperactivity of pyramidal neurons, leading to chronic pain. Enhanced VIP activity reduces SOM and PV activities and ultimately enhances PN hyperactivity.

VIP. Unlike other cell populations, in the barrel cortex, VIP neurons are depolarized during active whisking [34]. The optogenetic release of ACh selectively depolarized VIP neurons, indicating that VIP neurons selectively receive nicotinic input.

Cholinergic afferents differentially target each subtype of cortical GABAergic neurons, while VIP neurons exhibit a higher expression of nicotinic receptors compared to other subtypes [36]. VIP neurons have also been reported to prominently express non- $\alpha 7$ -subtypes of nicotinic receptors [37]. In addition, it has been suggested that basal forebrain cholinergic afferents to the S1 cortex drive inhibitory neurons, but not PVs, through $\alpha 7$ -subtypes of nicotinic acetylcholine receptor (nAChRs) in L1 and L2/3, thus reducing net inhibitory input to PNs [38,39]. Application of ACh in anesthetized rats enhanced the sensory-evoked discharge of the S1 neurons [40]. However, some neurons responded to tactile stimulation only in the presence of ACh, suggesting that cholinergic modulation by specific subpopulations may exist in the S1 cortex. Although the S1 cortex is known to receive cholinergic inputs from basal forebrain projection neurons, few studies have directly validated the relationship between altered cortical networks in chronic pain and cholinergic modulation. It is necessary to directly prove whether the alteration of VIP activity is attributed to cholinergic input in chronic pain. Moreover, it is necessary to verify whether modified inhibitory circuit and PN hyperactivity through ACh are the result of ACh's direct action on the S1 cortex or due to external factors (e.g., thalamocortical input) (Fig. 2A).

Another potential factor that drives circuit changes in chronic

pain is noradrenergic action on the S1 cortex. The main source of norepinephrine (NE) in the cortex is the locus coeruleus (LC), which contains noradrenergic neurons projecting to multiple areas of the cortex (e.g., S1 cortex, auditory cortex, and prefrontal cortex) [41-43]. LC activity is associated with pain inhibition, and intense pain induces LC activity. Although the LC is known to be involved in pain suppression [44,45], recent findings suggest that it contributes to the development and maintenance of chronic pain after nerve injury. In short-term chronic pain (~14 days), noxious stimulation altered the evoked activity of the contralateral LC, whereas both spontaneous activity and noxious-evoked responses were changed in the contralateral and ipsilateral LC in the long-term state (28 days) after nerve injury [46]. This means that the ascending pathway is bilaterally engaged in the maintenance stage of chronic pain. In another model of chronic neuropathic pain, innocuous tactile stimulation increased neuronal activity in the LC [47]. Selective destruction of LC neurons 2 weeks before nerve injury alleviated allodynia and hyperalgesia after nerve injury. Moreover, 2 weeks after nerve injury, where pain hypersensitivity was fully developed, lidocaine applied directly into the LC reduced pain hypersensitivity. These findings collectively suggest that LC activation induced by nerve injury contributes to the development and maintenance of chronic neuropathic pain. It has also been reported that the expression and sensitivity of alpha 2-adrenoceptor in the LC are enhanced in long-term neuropathic pain [48]. Local administration of alpha 2-adrenoceptor agonists into the LC significantly decreased extracellular norepinephrine

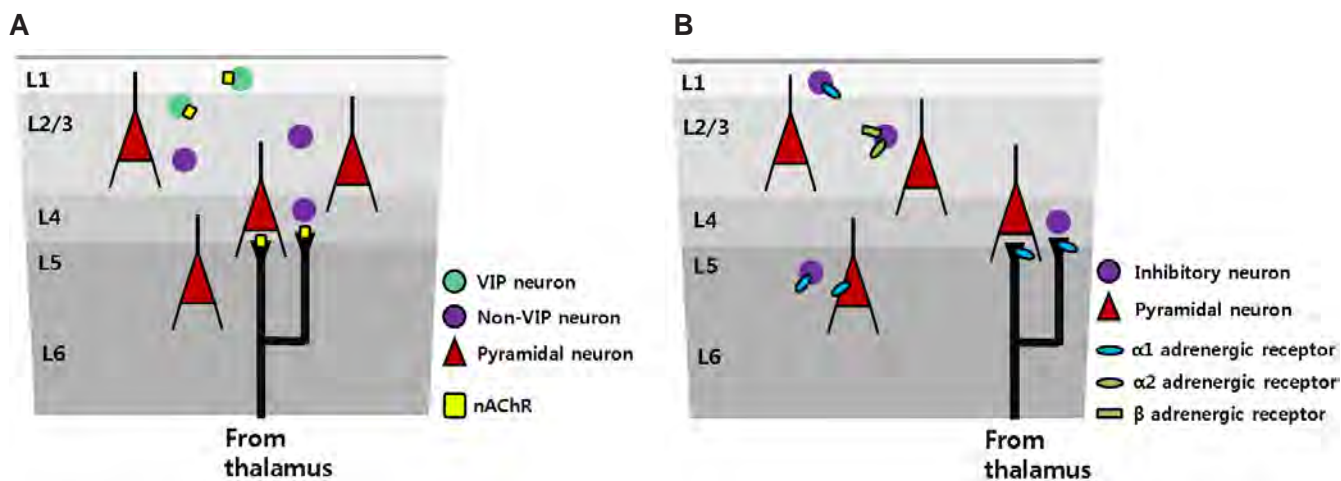


Fig. 2. Potential local circuit plasticity evoked by cholinergic and noradrenergic inputs in chronic pain. (A) Acetylcholine is the one of the potential neuromodulators that drives circuit changes in chronic pain. Cholinergic input from basal forebrain projection neurons can differentially target each subtype of cortical GABAergic neurons. Vasoactive intestinal polypeptide (VIP) neurons are mainly located in L1 and L2/3, and, in particular, exhibit a higher expression of nicotinic receptors compared to other subtypes. In chronic pain, VIPs expressing nicotinic acetylcholine receptors (nAChR) can be driven by cholinergic inputs and reduce the net inhibitory effects on pyramidal neurons. Along with the action on nAChRs in VIP neurons, the activation of presynaptic nAChRs in thalamocortical neurons may modulate thalamocortical transmission in layer 4 of the S1 cortex in chronic pain. (B) Another potential factor is noradrenergic action of the S1 cortex during chronic pain conditions. Noradrenergic inputs projected from the locus coeruleus may exert layer-specific modulation by the action of different types of adrenergic receptors in the S1 cortex. Norepinephrine (NE) regulates the excitability of L1 and L2/3 excitatory neurons via presynaptic alpha-1 and alpha-2/beta-adrenergic receptors, respectively, on inhibitory neurons. In addition, NE modulates the synaptic responsiveness of L5 pyramidal neurons via alpha-1 receptors. NE may also act on presynaptic thalamocortical neurons, resulting in local circuit plasticity.

concentration in the mPFC but not LC, suggesting that NE release of noradrenergic projections on the mPFC is reduced through the action of alpha 2-adrenoceptors in the LC.

NE axons project onto the S1 cortex, but the action of NE on the S1 cortex is not well understood. Some of the S1 neurons were activated by NE or alpha-1 agonists, but some showed reduced responses to NE or beta-agonists [49,50]. In the S1 barrel cortex, NE and alpha-1 agonists increased or decreased the synaptic responsiveness of L5 PNs to differentially defined classes of L5 neurons. A recent study showed that NE axons projecting into the S1 barrel cortex responded reliably to whisker stimulation. After associative auditory fear conditioning, NE axons showed an increase in calcium activity only for CS⁺, indicating experience-dependent plasticity. In addition, a nonlinear relationship exists between the NE axons and local dendrites in the S1 cortex [51]. These results imply that NE can sufficiently modulate the S1 local circuitry under physiological and pathological conditions. A previous study in the auditory cortex suggested layer-specific noradrenergic modulation by the action of different receptor types [52]. NE decreased the amplitude of evoked inhibitory postsynaptic currents (eIPSCs) of L1 excitatory neurons via alpha-1 adrenergic receptors, as well as increased the amplitude of eIPSCs of L2/3 excitatory neurons via alpha-2 and beta-adrenergic receptors. This NE-induced modulation was shown to be a presynaptic contribution. It is necessary to verify that NE projections directly affect S1 circuitry and ultimately lead to PN hyperactivity (Fig. 2B).

CONCLUSIONS AND PERSPECTIVES

In vivo two-photon imaging studies have revealed functional and structural plastic changes in the S1 cortex at the individual cell and synaptic levels in rodent models of chronic pain. Both spontaneous and sensory-evoked activities are elevated in the L2/3 and L5 neurons of the S1 cortex in inflammatory and neuropathic chronic pain. S1 synaptic remodeling associated with S1 astrocyte reactivation also occurs during the development of neuropathic pain. As mainly reviewed in this paper, the S1 local inhibitory circuit was modified for S1 hyperexcitability in chronic pain. Unsolved questions remain as to which neuromodulator drives such changes in the S1 cortex in chronic pain. ACh and NE can induce S1 PN hyperactivity by modifying the inhibitory network or by acting directly on the PNs. It is necessary to confirm whether cholinergic or noradrenergic modulation directly acts on the S1 cortex.

Finally, the cortical mechanism by which hypersensitivity occurs needs to be clarified. Individual neurons in the S1 cortex have intrinsic response properties that specifically respond to sensory stimulation [53,54]. The aforementioned changes in the S1 cortex may also be related to alterations in the response properties of S1 neurons, such as changes in response intensity or response preference to painful and non-painful stimuli un-

der chronic pain conditions. What is the relationship between alterations in response properties in a specific cell population of S1 and pain hypersensitivity in chronic pain? Chronic pain is characterized by allodynia and hyperalgesia, which impair the quality of life and lead to hyperexcitability of the S1 cortex [4]. It is unknown whether the hypersensitivity is due to the altered activity of nociceptive neurons or if other populations are newly recruited in chronic pain. In our previous study [55], we classified the cell types of S1 individual neurons according to their response patterns to painful and non-painful stimuli. Although excitatory and inhibitory neurons were not distinguished in the study, we were able to identify pain-intensity coding neurons, innocuous preferred neurons, and noxious preferred neurons. Alterations in the response properties of each cell population to sensory stimulation before and after the onset of chronic pain may be associated with behavioral hypersensitivity. To understand the cortical mechanisms of allodynia and hyperalgesia, it would be meaningful to perform experiments by regulating the activity of each cell population that shows changes in response properties.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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