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Disinhibition in pathological pain

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Noxious and tactile stimuli are transmitted into the spinal cord or in the trigeminal nucleus before being delivered to the brain. Inhibitory interneurons are distributed throughout these relay regions and modulate sensory stimuli by inhibiting primary afferent terminals (presynaptic inhibition) and spinal interneurons (postsynaptic inhibition) by releasing γ-aminobutyric acid (GABA) and/or glycine. Regarding pathological pain, the spinal inhibitory interneurons are involved in hyperalgesia, allodynia, spontaneous pain, and referred pain. Disinhibition is the loss of inhibitory power mediated by the inhibitory interneurons, underlying these symptoms. Studies on global GABAergic neurons have shown that dysregulation of intracellular Cl^- concentration, death of inhibitory interneurons, and change of electrophysiological properties are the mechanisms underlying disinhibition. Recent studies exploring the connectivity and function of each specific class of inhibitory interneurons using neurochemical markers will strengthen the basic knowledge of disinhibition in inhibitory interneuron and help develop novel and effective treatments for pathological pain.

Keywords: disinhibition, pathological pain, inhibitory interneuron

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Introduction

Primary sensory neurons transmit peripheral sensory stimuli into the spinal interneurons, called the second-order or relay neurons. The central terminals of sensory neurons within C/Aδ and Aβ fibers mainly terminate in lamina I/II and III/IV of the spinal cord, respectively. The sensory neurons within the C/Aδ and Aβ fibers convey nociceptive and tactile stimuli, respectively. Projection neurons receive inputs from interneurons and project into supraspinal brain regions[1–3]. Interneurons are classified as either excitatory or inhibitory based on the neurotransmitter they release. Inhibitory interneurons use γ-aminobutyric acid (GABA) and/or glycine as a neurotransmitter. Generally, GABAergic neurons also release glycine, and glycinergic neurons that only release glycine are rare. Although the proportion of inhibitory interneurons in the spinal cord is around 30%, they play a crucial role in modulating the transmission of sensory information[1]. As our understanding of the mechanism of pain modulation by inhibitory interneuron remains at a basic level due to their complexity, a deeper understanding of their biological mechanisms is critical for the development of more effective pain management. This review summarizes our current understanding of the basic properties of inhibitory interneurons and their roles in pain transmission. We also discuss the concept and mechanisms of interneuron disinhibition in pathological pain and suggest some promising future research directions.

Basic characteristics of inhibitory interneuron

Inhibitory interneurons can be classified by morphological, electrophysiological, and neurochemical features[4]. There are four morphological types of interneurons (islet, central, radial, and vertical), and inhibitory interneurons are often of the islet cell type. Islet cells form rostrocaudally elongated dendritic trees, but the dorsoventral spreading of dendrites is limited. Therefore, spatial dendritic coverage of inhibitory interneurons tends to be restricted to a specific lamina. When currents are injected into the cell soma, most inhibitory interneurons show a tonic firing pattern. Inhibitory interneurons can be globally stained with GABA, glycine, glutamic acid decarboxylase 65/67 (GAD65/67, which synthesize GABA), and vesicular GABA transporter (VGAT, which loads GABA and glycine into synaptic vesicle) antibodies. In addition, inhibitory interneurons express specific neurochemical markers such as parvalbumin (PV), neuronal nitric oxide synthase (nNOS), galanin, and neuropeptide Y (NPY). Therefore, researchers have been examining the function of inhibitory neurons by genetically manipulating these neurochemical markers.

Laminar location into the spinal cord mainly determines the types of stimuli that inhibitory interneurons receive from primary afferent neurons. Inhibitory interneurons are scattered through all laminas of the spinal cord but each neurochemically defined population of inhibitory interneurons is found in the limited laminar area. For example, PV, nNOS, galanin, and NPY (+) inhibitory interneurons are mainly located in lamina IIi-III, I-III, I-II, and III-IV, respectively[5]. However, the details of the input and output partners of these inhibitory interneurons require more studies.

Function of inhibitory interneurons

As mentioned in the previous section, inhibitory interneurons inhibit postsynaptic neurons by releasing the inhibitory neurotransmitters GABA and glycine. Hence, their normal function in sensory stimuli processing is to prevent the transmission of sensory information. Pioneering studies used GABA receptor positive and negative modulators to reveal the function of inhibitory interneurons in pain processing. Intrathecal injection of GABA or glycine receptor antagonists in a normal state induces tactile allodynia[6]. Reversely, GABA agonist injection and transplantation of GABAergic precursor neurons have an antinociceptive effect in pathological pain models[7,8]. Regarding nociceptive stimuli processing, four distinct functions of inhibitory interneurons were postulated; 1) attenuating the nociceptive input, 2) muting irrelevant nociception, 3) separating the mechanical stimuli from the nociceptive pathway, and 4) limiting the irrelevant spatial spreading of nociception[1]. If nerve injury or inflammation altered their normal function, the following pathological symptoms developed: hyperalgesia, spontaneous pain, allodynia, and referred pain. After the identification of neurochemical markers of inhibitory interneurons, recent studies explored the distinct functions of specific inhibitory interneurons. For instance, PV and dynorphin (+) interneurons have a gating function that prevents mechanical stimuli through Aβ fibers from entering the nociceptive circuit[9–11]. Therefore, a pathological alteration of these interneurons induces mechanical allodynia. However, detailed functions of the other classes of inhibitory interneurons in pain processing are still not clear.

Pre vs. postsynaptic inhibition

One of the distinct features of inhibitory interneurons is the formation of axo-axonic synapses. Inhibition by inhibitory interneurons can be divided into presynaptic and postsynaptic inhibition. In the case of presynaptic inhibition, the axon of the presynaptic inhibitory interneuron makes a synapse with the central axon terminal of the primary afferent neuron, called axo-axonic synapse. The $GABA_A$ receptor is located on the axonal membrane of primary afferent terminals. The opening of the $GABA_A$ receptor by inhibitory interneuron-released GABA does not induce a chloride ion influx, but rather an efflux because of the high internal Cl^- concentration of primary afferent terminals. The Na-K-Cl cotransporter1 (NKCC1) accumulates chloride ions in the primary afferent terminals. Therefore, the efflux of Cl^- induces primary afferent depolarization (PAD) that shunt action potential propagation from peripheral regions. In the case of postsynaptic inhibition, inhibitory interneurons inhibit both excitatory and inhibitory interneurons in the spinal cord. Potassium–chloride cotransporter 2 (KCC2) usually is highly expressed in interneurons and keeps internal Cl^- levels low. Therefore, inhibitory interneurons-released GABA opens the $GABA_A$ receptor, which induces Cl^- inflow into the cell membrane and results in hyperpolarization.

Disinhibition in pathological states

Dysregulation of chloride ion level

As mentioned in the previous section, the internal Cl^- concentration of primary afferent axon

terminals is maintained higher than in other spinal neurons. However, pathological states such as nerve injuries increase NKCC1 activity, which in turn further increases the internal Cl^- concentrations[12,13]. Hence, if inhibitory interneurons-released GABA binds to $GABA_A$ receptors onto primary afferent terminals, it can induce much higher PAD than in the normal state. In this case, the PAD function can be switched from inhibition to excitation if the PAD is high enough to elicit a synaptic vesicle release[2]. However, some study indicated that this kind of presynaptic disinhibition occurs only within a few days after a nerve injury and it is just a loss of inhibition, not a reversion from inhibition to excitation[13].

In the case of postsynaptic inhibition, spinal interneurons mainly express KCC2, which pumps chloride ions out of the cytosol. Peripheral nerve injury downregulates KCC2 expression levels via activated microglia-released brain-derived neurotrophic factor (BDNF)[13,14]. The reduction of KCC2 expression has the same effect with enhancement of the NKCC1 expression in primary afferent central terminals, i.e., a high intracellular chloride ion concentration. Therefore, the opening of the $GABA_A$ receptor by GABA can induce a small hyperpolarization or even depolarization[12].

This phenomenon likely fits well with the paradoxical effect of the $GABA_A$ receptor agonist. Although intrathecally injected mucimol or benzodiazepine have an analgesic effect on pathological pain, high doses of these compounds can amplify mechanically induced pain[7,15]. This paradoxical effect of the $GABA_A$ receptor positive modulators can be explained by the fact that disrupting the Cl^- homeostasis induces excitation instead of inhibition. Indeed, when Cl^- homeostasis is rescued with a KCC2 enhancer, a high dose of benzodiazepine has a strong analgesic effect[15].

Inhibitory interneuron death

If the inhibitory interneuron dies, disinhibition can occur. However, there is still controversy regarding this. Some studies reported that nerve injuries temporarily reduce the number of GABA and/or GAD67 (+) cells, which then gradually returns to its original level[16–18]. Moreover, nerve injuries increase the number of TUNEL (+) cells and caspase-3 (+) cells which are markers of cell death and apoptosis, respectively[19,20]. This increase is temporary like the reduction of GABA or GAD67 (+) cells. Blocking cell death ameliorates the nerve injury-induced mechanical allodynia[20]. However, studies that have tried to reproduce the reports on nerve injury-induced inhibitory neuron death have failed to observe a significant loss of inhibitory neurons in the spinal cord after nerve injury. Besides immunofluorescence staining of GABAergic and glycinergic neurons[21,22], ultrastructural analysis of GABAergic neurons using electron microscopy did not show any evidence of loss of inhibitory interneurons after nerve injury[23]. Even studies about the death of inhibitory interneurons using the same nerve injury model yielded different results. Moreover, one study points out that nerve injuries increased caspase-3 expression only in astrocytes, not in neurons, but other studies reported that nerve injury-induced caspase-3 was colocalized with NeuN, mature neuronal marker[19,20,24]. Therefore, it is not clear whether nerve injuries really induce inhibitory neuron death.

This obscure fate of inhibitory interneurons in

a pathological state may be due to the fact that only a specific population of inhibitory interneurons dies. Therefore, investigating whether a pathological state alters a specific subset of the inhibitory interneurons will help to understand the disinhibition mechanisms associated with cell death. Among interneurons, PV (+) interneurons mainly form axo-axonic synapses with Aβ afferent central terminals and give a postsynaptic inhibitory input to PKCγ (+) excitatory interneurons[25]. Although there are disagreements regarding the exact disinhibition mechanisms of PV (+) interneurons induced by nerve injury, no study reports the death of PV (+) interneurons[10,11]. Therefore, future studies about the disinhibition mechanism for other classes of inhibitory interneurons will make clear whether cell death, one of the mechanisms of disinhibition, occurs.

Electrophysiological changes in inhibitory interneurons

Besides inhibitory neuron death, a reduction of GABAergic transmission (at the level of presynaptic release and/or postsynaptic receptor response) can also cause disinhibition. Peripheral nerve injury reduces the excitability of inhibitory interneurons. A chronic constriction injury can reduce the frequency and amplitude of spontaneous/miniature excitatory postsynaptic currents (EPSCs) in tonic firing neurons[26,27]. This reduced excitability induced by peripheral nerve injury also occurs in PV (+) neurons[10]. It seems that one of the reasons for the reduced excitability is the reduction of direct input from primary afferent to inhibitory interneuron[28]. However, in one study, peripheral nerve injury did not cause any electrophysiological change of inhibitory interneurons[29]. Meanwhile, a reduction of GABA contents can contribute to the reduction of presynaptic release, but it is hard to examine because the loss of inhibitory neurons also reduces GABA contents. Although some studies show a reduction of GAD and GABA transporter (GAT-1, which reuptakes GABA) after peripheral nerve injury, these studies also cannot exclude the possibility that neuronal death reduces the levels of these enzymes[19,30]. In contrast, enhancement of GABA contents can be examined regardless of the number of inhibitory interneurons because inhibitory interneurons are nonmitotic cells. Peripheral inflammation increases the number of GABA (+) cells[31]. This result can be interpreted as an increase of GABA production, but given the previous studies showing that peripheral nerve injuries reduced inhibitory interneuron excitability, it is more reasonable to think that inhibitory interneurons accumulate GABA when their activity is reduced.

The expression level or activity of the $GABA_A$ receptor can affect disinhibition in the pathological state. Although the pathological state does not change the number of inhibitory synapses[23], peripheral nerve injuries reduce the expression level of $GABA_A$ receptors in primary afferent terminals[13,32]. However, it seems that these results are not compatible with the disinhibition mechanism via dysregulation of Cl^- ion because, in primary afferent terminals, more $GABA_A$ receptors can guarantee more powerful disinhibition through a strong PAD. Therefore, further studies are required.

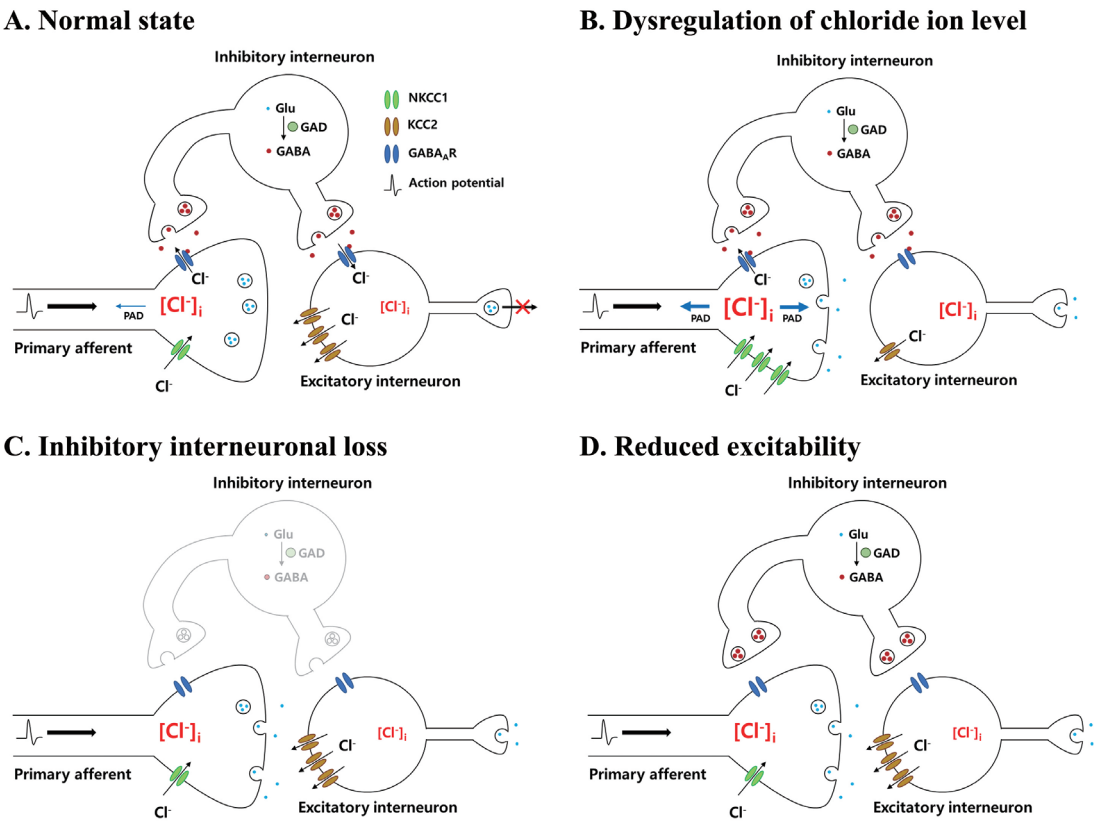

Figure 1. Diagrams illustrating disinhibition mechanism of inhibitory interneuron in pathological pain state. (A) Normal state. Inhibitory interneuron inhibits primary afferent terminal and interneuron by releasing γ-aminobutyric acid (GABA). Primary afferent terminal maintains high internal chloride ion level by Na-K-Cl cotransporter1 (NKCC1). The binding of GABA on $GABA_A$ receptor induces outward flow of chloride ion, which generates primary afferent depolarization (PAD). Thus, propagation of action potential is inhibited by PAD. In case of postsynaptic interneuron, GABA induces inward flow of chloride ion, which induces hyperpolarization. (B) Dysregulation of chloride ion level. Pathological state further enhances internal chloride ion level into primary afferent terminal and interneuron. This increased internal chloride ion level weakens inhibitory power through the $GABA_A$ receptor, and can even induce synaptic vesicle release by depolarization. (C) Inhibitory interneuronal loss. Pathological state induces death of inhibitory interneuron. (D) Reduced excitability. Pathological state lowers excitability of inhibitory interneuron, which leads to reduction of GABA release.

Conclusions

Until now, studies on inhibitory interneurons in pathological pain have explored their general function and global change. Many recent studies have used transgenic mice to isolate each class of inhibitory interneurons. Functional studies have combined transgenic mice expressing Cre recombinase in specific inhibitory interneuronal class with optogenetic and chemogenetic methods. However, information about the inputs and the outputs of the inhibitory interneurons of a particular class is still lacking. Therefore, studies on the connectivity of each class of inhibitory interneurons should be combined with functional studies. In understanding inhibitory interneurons, this

approach will provide accurate information on the mechanisms by which they play a role in pain transmission. Moreover, discovering the mechanisms of injury-related disinhibition specific to each class of inhibitory interneuron will greatly help the development of future treatments for pathological pain.

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한글초록

병리적 통증에서의 탈억제 기전: 종설

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유해 및 촉각 자극은 척수 또는 삼차신경핵을 거쳐서 뇌로 전달된다. 억제사이신경세포 (inhibitory interneuron)는 척수 또는 삼차신경핵 같은 중계 지역에 고루 걸쳐서 분포하며, 가바 (γ-aminobutyric acid, GABA) 또는 글라이신 (glycine)을 분비하여 일차 구심성 말단과 척수 사이신경세포를 억제함으로써 감각 자극의 전도를 조절한다. 병리적 통증과 관련하여 억제사이신경세포는 통각과민, 무해자극통증, 자발통증, 연관통증의 발생에 관여한다. 탈억제는 억제사이신경세포에 의해 매개되는 억제력의 손실을 의미하여, 이러한 증상들의 기저에 관여하고 있다. 그동안의 억세사이신경세포에 대한 연구를 통해 세포내 염소이온 농도 조절곤란, 억제사이신경세포의 사멸, 억제사이신경세포의 전기생리학적 변화 등이 탈억제의 기작으로 밝혀졌다. 최근의 연구들은 전체 억제사이신경세포를 대상으로 한 연구보다는 억제사이신경세포들에서 특이적으로 발현되는 신경화학적 표지를 이용하여 개별 종류의 억제사이신경세포들의 연결성과 기능에 대해 연구하고 있는 추세이다. 이러한 연구의 흐름은 병리적 통증에서 나타나는 억제사이신경세포의 탈억제 현상에 대한 이해를 넓혀주고, 차후 병리적 통증 치료에 기반을 마련해 줄 것이다.

주제어: 탈억제, 병리적 통증, 억제사이신경세포