

# The role of NLRP3 inflammasome in stroke and central poststroke pain

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## Abstract

**Background:** NLRP3 inflammasome plays a prominent role in the pathogenesis and progression of many diseases, such as type 2 diabetes mellitus, obesity, atherosclerosis, and Alzheimer's disease. However, little knowledge is known about the role of NLRP3 inflammasome in central post-stroke pain (CPSP).

**Methods:** We selected relevant studies by searching PubMed, Embase, and Medline from inception through February, 2018. We systematically reviewed available publications according to the terms "NLRP3 inflammasome" and "stroke" or "central post-stroke pain" in the title/abstract field.

**Results:** We reviewed the articles and put forward two possible ways for NLRP3 inflammasome in CPSP. One way is that NLRP3 activation causes cerebral cortex injure, decreasing descending projection fiber to thalamus. Such condition may let GABAergic releases reduce, making the ventral basal (VB) neurons excitability increased. Finally, CPSP occur. Another way is that NLRP3 inflammasome leads to thalamic lesion and strengthens inflammatory response of microglia at the same time. Persistent inflammation causes GABAergic alteration in thalamus reticular neurons (TRN) to restrain VB interneurons functions, contributing to CPSP.

**Conclusions:** These possible mechanisms will help become knowledgeable about the occurrence CPSP and provide potential therapy for CPSP.

**Abbreviations:** CPSP = central poststroke pain, NLRP3 = NLR pyrin domain containing 3, NLRs = NOD-like receptors, NO = nitric oxide, PRRs = pattern-recognition receptors, ROS = oxygen species, TNR = thalamus reticular neurons, VB = ventral basal.

**Keywords:** central poststroke pain, NLRP3 inflammasome, stroke

## 1. Introduction

Central poststroke pain (CPSP), which is characterized as a chronic neuropathic pain syndrome, commonly occurs after stroke.<sup>[1]</sup> The prevalence of CPSP varies, from 1% to 14%.<sup>[2,3]</sup>

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It is widely recognized that cerebrovascular accidents (lesion or dysfunction) in the central nervous system (CNS) can result in central neuropathic pain. The neuropathic pain in CPSP has different forms and may develop and vary over time. Pain seems to be severe, persistent, and spontaneous on the hemiplegic side in some cases but not in others. Main feature of spontaneous pain is described as burning or aching. Also, the distribution of CPSP can vary in different patients, ranging from a small area to large areas. In addition, allodynia and dysesthesia are the essential characteristics of CPSP.<sup>[4–6]</sup> Central pain after stroke on the side of lesioned hemisphere may be associated with sensory changes. Over 90% of patients have experienced sensory abnormalities, including thermal or pain sensation.<sup>[7,8]</sup> The stroke involves posterior, lateral, and inferior parts of the sensory thalamus. The impairment of temperature and pain perception is often found in CPSP. And a recent study found that thalamic sensory stroke patients with CPSP differ from those without pain in terms of lesion location.<sup>[9]</sup> Krause et al<sup>[10]</sup> reported 50 patients with CPSP and without pain. They concluded that both patient groups also showed considerable sensory abnormalities involving the ipsilesional side of the body. This result is contrary to clinical manifestation because patients with a unilateral stroke affecting the somatosensory pathway usually describe their sensory syndrome in the same area. The mechanism of sensory alterations in CPSP is unclear. Due to the characteristics and descriptions of CPSP varying between patients, the diagnosis and treatment strategies become quite a frustrating issue.

Pattern-recognition receptors (PRRs) are recognized in the innate immune system. Once activated, the PRRs induce immune responses to eliminate pathogens and repair tissues.<sup>[11]</sup> NOD-like receptors (NLRs) are the family of PRRs. And, the NLR family

can sense the presence of microbial products and danger signals in the cytoplasm, forming multiprotein complexes called inflammasomes. As one of the best-characterized NLRs, NLR pyrin domain containing 3 (NLRP3) possess a critical role in inflammatory response.

Recently published evidence have shown that NLRP3 inflammasome was associated with many diseases, including atherosclerosis, diabetes, and myocardial/cerebral I/R injuries.<sup>[12–14]</sup> Similarly, NLRP3 inflammasome has been reported to be involved in nervous diseases, such as Alzheimer disease and ischemic stroke.<sup>[15,16]</sup> However, little information is known regarding the relationship between NLRP3 inflammasome and CPSP. This review identifies a new insight of NLRP3 inflammasome and reveals its role in CPSP.

### 1.1. Inflammation response in stroke

Stroke, which is defined as an acute loss of neurological function, is one of the most common causes of death worldwide. Approximately 80% of stroke events are ischemic stroke.<sup>[17]</sup> Systemic inflammation responses are considered as an essential role during and after stroke.<sup>[18]</sup> Traditionally, inflammation is linked to be merely a reaction to tissue damage. Recent study has shown that inflammation mediators contribute to the pathophysiology of stroke caused by arterial occlusion or ischemic stroke.<sup>[19]</sup> Thrombosis and vasculopathy are the possible mechanisms that inflammatory processes affect stroke incidence. Inflammatory respond begins in the early postischemic period. Acute cerebral ischemia elicits brain tissue hypoxia and exerts a potent effect on reactive oxygen species (ROS), leading to activation of many cellular targets, such as platelet, T lymphocytes, macrophages, and endothelial cells.

Oxidative stress, a major cause of tissue damage, is a key initiating event in stroke. Oxidative stress in endothelial cells can not only impact multiple cellular components, including nucleic acids, proteins and lipids, but also stimulate transcription factors directly and activator protein-1 (AP-1) indirectly, thus leading to neuronal and glial damage.<sup>[20,21]</sup> Moreover, Yilmaz and Granger<sup>[22]</sup> reported that oxidative stress could reduce the bioavailability of nitric oxide (NO). The increased production of ROS that induces oxidative stress can damage cellular macromolecules, causing autophagy, apoptosis, and necrosis. Furthermore, the rapid restoration of blood flow increases the level of tissue oxygenation and accounts for a second burst of ROS generation, which leads to reperfusion injury.<sup>[23]</sup> Endres et al<sup>[24]</sup> have found that ischemia/reperfusion injury can induce a robust inflammatory response. The inflammatory response involves peripheral cells such as leucocytes and brain cells such as glial cells and neurons. These cells are activated in the inflammatory process, producing and releasing pro-inflammatory cytokines that result in neuronal and glial cell death. In addition, previous studies have shown that a variety of cytotoxic agents such as tumor necrosis factor (TNF), Interleukin-1 (IL-1), Interleukin-6 (IL-6), nicotinamide adenine dinucleotide phosphate (NADPH), oxidase derived ROS, and matrix metalloproteinases are released to alter the permeability of the blood–brain barrier, exacerbating brain edema, and hemorrhage.<sup>[25,26]</sup> In the perivascular space, perivascular macrophages and mast cells are activated in ischemic reperfusion injury. Vasoactive mediators (histamine, proteases, and TNF) produced by mast cell and proinflammatory cytokines released by activated macrophages modulate the endothelial expression of adhesion molecules.<sup>[27–29]</sup> Also, complement cascade plays important roles in secondary

damage. Inflammatory mediators such as C1, C3a are well correlated with leukocyte recruitment, which contributes to the development of brain lesions and neurological deficits.<sup>[30,31]</sup>

### 1.2. NLRP3 inflammasome in stroke

Inflammation is engaged in immune responses, which have the capability to detect tissue damage and infection. These insults are detected in the onset and progression of stroke by activating a variety of pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs).<sup>[11]</sup> As a class of cytosolic sensors or receptors, the NLRs are key components of the inflammasome. It is well known that inflammasomes are formed as multiprotein complexes through NLRs activation. The inflammasome-forming NLRs consist of many members such as NLRP1, NLRP3, NLRC4, NLRC5, NLRP6, NLRP7, NLRP12, NLRC4, and AIM2.<sup>[32]</sup> Among them, NLRP3 inflammasome is the most extensively studied and is considered to be strongly associated with sterile inflammation.

Although widely being reported, the activation mechanism of NLRP3 is still unclear. Structurally, the NLR proteins comprise 3 major domains: a C-terminal leucine-rich repeat (LRR) domain, a central nucleotide binding (NACHT) domain, and an N-terminal pyrin domain (PYD).<sup>[33]</sup> The LRRs domain is considered to be associated with putative ligand and mediates autoinhibition, and the NACHT domain is involved in self-oligomerization and inflammasome assembly.<sup>[34,35]</sup> NLRP3 can be activated by a number of danger signals such as danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). Once receiving an activating signal, NLRP3 forms an inflammasome, which is composed of NLRP3, the adaptor protein ASC (apoptosis-associated Speck-like protein containing a Caspase activation and recruitment domain (CARD)), and the inflammatory caspase-1. Latz et al<sup>[36]</sup> have shown that the LRRs have a regulatory function and hinder oligomerization of NLRP3 under healthy cellular conditions. Once activated, NLRP3 oligomerizes through homotypic interactions between NACHT domains. The ASC proteins that assemble into fiber-like structures interact with PYD of NLRP3, recruiting procaspase-1, thus resulting in the activated caspase-1 significantly amplified.<sup>[37–39]</sup>

Generally, studies have identified 3 potential stimulus of NLRP3 receptor activation: a decrease in the intracellular K<sup>+</sup> concentration, mitochondrial ROS, and disruption of the lysosomal membrane.<sup>[40,41]</sup> NLRP3 receptor may be activated by extracellular ATP and pore-forming toxins, which cause a nonselective conductance of K<sup>+</sup> across the cell membrane and the alteration of intracellular ionic contents. One study has demonstrated that because of autocrine and paracrine P2X7 activation by secreted ATP, a decrease in K<sup>+</sup> levels (<90 mM) in the cytoplasm can activate NLRP3 inflammasome.<sup>[42]</sup>

Another persuasive model shows that NLRP3 inflammasome activation was associated with mitochondrial dysfunction.<sup>[43]</sup> A study demonstrated that the cytosolic increase of oxidized mitochondrial DNA was caused by NLRP3-triggering agents, which can induce mitochondrial dysfunction and cell death.<sup>[44]</sup> Furthermore, ROS may be connected with Thioredoxin-interacting protein (TXNIP) that translocates to mitochondria along with NLRP3 during inflammasome activation. NLRP3 agonist can oxidize the production of ROS, resulting in TXNIP to dissociate from thioredoxin. Also, Huang et al<sup>[45]</sup> reported that voltage-dependent anion channel (VDAC) knockdown not only

suppress NLRP3 inflammasome activation but also prevented the generation of mitochondrial ROS in response to NLRP3 agonists.

Lysosomal disruption is also a well-established mechanism of NLRP3 inflammasome activation. NLRP3 inflammasome was activated by different PAMPs and DAMPs that are dependent on lysosomal destabilization. It has been shown that cathepsin B or a propeptide modified by cathepsin B is required for NLRP3 inflammasome activation.<sup>[44]</sup> Also, Kawaguchi et al<sup>[46]</sup> demonstrated that lysosomal disruption plays an important role in the myocardial fibrosis process. Particulate phagocytosis results in lysosomal rupture and the release of lysosomal hydrolases, influencing inflammatory responses and myocardial ischemia-reperfusion injury.

Indeed, all these mechanisms of NLRP3 inflammasome activation are still elusive. There are many additional mechanisms, including mitochondrial Ca<sup>2+</sup> uptake, NO downregulation, NLRP3 activation, and endoplasmic reticulum stress.<sup>[47-49]</sup> Therefore, further studies are urgently needed.

### 1.3. Stroke and CPSP

CPSP occurs after a cerebrovascular accident, especially stroke. But the correlation between stroke and CPSP is extremely complex. One of the potential explanations for pain was associated with thalamus. Previous study has identified that there were some pathological changes in cell activity that were documented by electrophysiological records in CPSP of thalamic regions.<sup>[50]</sup> They found that ventral/dorsal thalamic nucleus (VPL) neurons showed a regular 10Hz action potential in non-CPSP patients, while explosive and high frequency of action potential was observed in patients with CPSP. Similarly, abnormal signals activation in thalamus was recorded in CPSP patients. Explosive signals were detected in ventral posterior nucleus of thalamus when the patients were treated with intracranial electrode.<sup>[51]</sup> In contrast, not all the CPAP patients have signs of lesions in the thalamus. Bogousslavsky et al<sup>[52]</sup> found that only 3 of 18 patients with inferolateral thalamic lesions developed CPSP.

However, the present study shows that CPSP occurs after brain lesions including not only thalamus but also medulla and cerebral cortex.<sup>[53]</sup> Almost 90% of the CPSP was caused by brain tissue injury, especially cerebral ischemia.<sup>[54]</sup> The researchers found that thalamic ischemia could lead to different levels of CPSP after 3 months in the stroke patients. Equally, 1 randomized controlled trial revealed that CPSP accounted for the majority of neuropathic pain that occurred after cortical injury, resulting in chronic pain.<sup>[55]</sup> Animal studies have also identified that cerebral ischemia injury caused pain (thermal hyperalgesia and mechanical allodynia) in the bilateral hind limbs of mouse.

In addition, it is widely recognized that there is a close relationship between cerebral cortex and thalamus. The cerebral cortex can modulate the activity of neurons in the thalamus. Once damaging, cerebral cortex can disinherit medial thalamus activity and cause excessive activation of nerve cell, leading to pain. Studies have found that hyperalgesia or allodynia can occur when the injury is at any level of the spinothalamic and thalamocortical pathway. The brain pathways, including spinothalamic pathway, thalamocortical pathway, and medial lemniscus pathway, are considered to play a significant role in the pathogenesis of CPSP. The injury of spinothalamic pathway is thought to be a required event for CPSP. In addition, the central sensitization in thalamic neurons is closely related to hyperalgesia in the painless region of CPSP.<sup>[56]</sup> It is known that the projection fibers in thalamic-cortical pathway are much more than that of in

thalamus. Afferent fibers in the thalamocortical pathway are involved in the process that thalamic neurons regulate sensory information. And the regulation (enhancement/suppression) event depends on the connection between afferent fibers in the thalamocortical pathway and thalamic neurons.<sup>[57]</sup>

There are 2 types of cells involved in hyperalgesia caused by central sensitization in the thalamus. One is the thalamus reticular neurons (TRNs), which receive projection fibers from the cerebral cortex. TRN neurons are GABAergic (gamma-aminobutyric acid, GABA) interneurons.<sup>[58]</sup> Another is ventral basal (VB) neurons, which locate in the basal part of the thalamus. One study found that GABAergic interneurons in TRN expressed signals that impacted VB neurons functions. Electrical stimulation in the region of cerebral cortex can increase GABA neuron excitability, which in turn significantly suppresses the functional activity of VB neurons. Once TRN neurons are uncontrolled by the afferent innervations in cortical neurons, an explosive discharge takes place, leading to cell membrane hyperpolarization. Then, GABA interneurons are inhibited, but the inhibition effect of VB neurons in the thalamus is resolved, which enhances its excitability.<sup>[59,60]</sup>

All in all, acute cerebral ischemia can result in the injury of thalamocortical pathway, which causes the GABA interneuron changes in TRN and strengthens VB neurons excitability, thus leading to CPSP.

### 1.4. Current theories in CPSP

Current theories on the cause of CPSP remain controversial, and they are mainly focused on disinhibition theories, central sensitization, and alterations in spinothalamic tract function. One previous study has found a disinhibition effect between lateral and medial thalamus.<sup>[61]</sup> A lesion in the lateral thalamus may lead to a lack of restraint of medial thalamus activity. This theory emphasized on the balance between systems of facilitation and inhibition. Once the injury in the lateral thalamus disrupted inhibitory pathways, central pain occurred. However, Craig and Bushnell<sup>[62]</sup> found that this mechanistic was incomplete, and stated that the loss of normal inhibition of the thermal (cold) system of nociceptive neurons produces an imbalance between lateral spinothalamic tracts. This could explain burning pain and cold allodynia in CPSP. In fact, several authors questioned the inadequate explanation of symptoms with regard to pain sensitivity deficit and less affected touch sensitivity.<sup>[63,64]</sup> Therefore, central sensitization was proposed and it was mainly based on evidence of the efficacy in treating CPSP. Studies have found that many drugs, such as N-methyl d-aspartate (NMDA) antagonists and GABA agonists, are available for the pain relief in CPSP.<sup>[53,65]</sup> An increased neuronal excitability was thought to be associated with brain lesion that can lead to the loss of inhibition or increased facilitation. This change may result in hyperexcitability in the thalamus or cortex. Another possible mechanistic clue lies in the injury of the spinothalamic tract. According to a previous study, CPSP exhibited pain and temperature sensitivity deficit though a lesion of spinothalamic tract. In addition, the occurrence of CPSP may be related to brain metabolism. Kim et al<sup>[66]</sup> reported that changes in brain glucose metabolism in patients with CPSP following thalamic Intracerebral Hemorrhage (ICH) encompassed various regions that were associated with cognitive functioning and nociception. Guo et al<sup>[67]</sup> found that ketogenic diets may suppress endoplasmic reticulum stress and protect mitochondrial integrity by suppressing the mitochondrial translocation of Drp1 to inhibit NLRP3

inflammasome. Overall, a simple theory is difficult to explain the development of CPSP.

### 1.5. NLRP3 inflammasome activity in CPSP

Although the role of NLRP3 inflammasome in stroke is well-reviewed elsewhere,<sup>[68,69]</sup> whether NLRP3 inflammasome has a correlation with CPSP is uncertain. CPSP is considered as a group of chronic pain disorders, which are called central neuropathic pain due to pain often occurring after stroke.<sup>[70]</sup> Ischemia/reperfusion injury (I/R), which leads to necrotic and apoptotic cell death, is a complex cascade of events that occur in stroke. Postischemic inflammation and immune responses are major mediators in I/R injury. Indeed, the NLRP3 inflammasome has been demonstrated to be activated by exogenous microbial stimuli, endogenous danger signals, asbestos, and silica.<sup>[71-73]</sup> More specifically, cells that undergo necrotic can release IL-1 $\beta$  and IL-18, leading to sterile inflammation response.<sup>[74]</sup> NLRP3 inflammasome has been found to be expressed and thought as an initial sensor for danger signal(s) in I/R injury. The main process causing brain damage is associated with neutrophil infiltration, ROS accumulation, and inflammatory responses to necrotic cell death.<sup>[75]</sup> Nagasaka et al<sup>[76]</sup> found that microglial activation may play a key role in CPSP. They developed and characterized a macaque model of CPSP. The results revealed that the long-lasting glial activation revealed may be characteristic of primate brains following injury. However, this study did not demonstrate a causal relationship between microglial activation and the development of CPSP. Another study have also shown that the activation of microglial cells, via a TLR2 $\rightarrow$ Sphk1 $\rightarrow$ pro-inflammatory cytokine (IL-1 $\beta$ , TNF- $\alpha$ , IL-17, and IL-23) pathway, may participate in I/R injury.<sup>[77]</sup> Also, high expression of NLRP3, ASC, and caspase-1 is found in microglia and macrophages due to the large amount of immune cells in brain. One study used C57BL/6J mice to induce ischemic stroke. They found that levels of NLRP1 and NLRP3 inflammasome proteins, IL-1 $\beta$ , and IL-18 were elevated in primary cortical neurons and ipsilateral brain tissues of cerebral I/R mice.<sup>[78]</sup> Similarly, another study concluded that intracerebral hemorrhage could activate the NLRP3 inflammasome and inflammation, but NLRP3 RNAi could attenuate inflammation and brain injury.<sup>[79]</sup>

### 1.6. Possible mechanisms of NLRP3 inflammasome in CPSP

As discussed above, the molecular mechanisms of NLRP3 inflammasome in CPSP possibly lie in the following aspects. First, acute or chronic stimulation caused by either cellular damage (DAMPs stimulation) or invading organisms (PAMPs stimulation) is injurious and responsible for the pathology of stroke. Brain tissue injury can cause systemic inflammatory disorders. These can activate many cellular targets, including monocytes, macrophages, platelets, endothelial cells, glial cells, endothelial cells, and neurons, which can increase the production of cytokines and chemokines levels.<sup>[80]</sup> Studies on both humans and experimental animals have demonstrated that interleukin 1 $\beta$ , 4, TNF, and lymphocytes have been implicated in ischemic insult.<sup>[81,82]</sup> At the same time, NLRP3 is activated by various danger signals after stroke.

Extracellular ATP, which is a canonical danger signal for activation of the NLRP3 inflammasome can impact the function of Na<sup>+</sup>/K<sup>+</sup>-ATPase pumps. The decreased production of cytosolic ATP can reduce the ratio of ATP to AMP, which may elicit the

cytosolic cation changes. The increased Na<sup>+</sup> influx promote an osmotic movement of water through aquaporins into the intracellular environment, leading to K<sup>+</sup> efflux.<sup>[83]</sup> In addition, sterile inflammation response in the progress of stroke can induce the infiltration and activation of macrophages, neutrophils, lymphocytes, vascular smooth muscle cell, thus resulting in cell death. One study has reported that necrotic cells can induce the damage of mitochondria, which is one of the main intracellular organelles contributing the ROS.<sup>[84]</sup> Zhou et al<sup>[85]</sup> reported that NLRP3 inflammasome could be activated by the thioredoxin-interacting protein (TXNIP), which was a ROS-sensitive regulator. ROS is demonstrated to be associated with perturbation of the electron transport chain in the mitochondria. Moreover, mitochondrial ROS has a close relationship with K<sup>+</sup> efflux. A study found that the anthracycline doxorubicin causing systemic inflammation could be controlled by cotreatment with ROS inhibitors and high levels of extracellular K<sup>+</sup>.<sup>[86]</sup> Similarly, during the process of cerebral injury, an increase in K<sup>+</sup> efflux links with ROS with the production of oxidized mitochondrial DNA. Both increased K<sup>+</sup> level and oxidized mitochondrial DNA can induce NLRP3 activation to release IL-1 $\beta$  and IL-18. Recent data suggest that disruption of the lysosomal membrane is mediated by cellular autophagy.<sup>[87]</sup> The activation of NLRP3 inflammasome can be restrained by proton pump inhibitors and blockade of cathepsins. Pyroptosis, which is found in monocytes, macrophages, and dendritic cells, can mediate caspase-1 activation, leading to lysosomal exocytosis and lysosomal protein secretion.<sup>[88]</sup> And, autophagy can eliminate the damaged mitochondria. In addition, lysosomal protease cathepsin B is required for IL-1 $\beta$  release in NLRP3 inflammasome activation process.<sup>[89]</sup> Another possible mechanism of NLRP3 inflammasome following stroke is endoplasmic reticulum stress. A study concluded that endoplasmic reticulum stress can cause endothelial dysfunction through initiation of oxidative stress, inflammation, and endothelium apoptosis. However, this mechanism has been reported to be related to cardiovascular diseases.<sup>[90]</sup> Whether endoplasmic reticulum stress is connected with stroke is unknown.

Second, thalamus is regarded to play a critical role in CPSP. According to 1 study, CPSP is caused by a lesion of thalamus, which is thought to be as abnormal processing of ascending input or pain generator.<sup>[49]</sup> Head and Holmes<sup>[61]</sup> stated that injury to the lateral thalamus frees the medial thalamus from its control. CPSP results from impairment of the normal inhibition of pain from cold signals owing to a lesion. Jang et al<sup>[91]</sup> investigated injury of the spinothalamic tract in 5 patients with CPSP following cerebral infarction. The study using diffusion tensor tractography has revealed that injury of the spinothalamic tract might be the pathogenetic etiology of CPSP in patients with cerebral infarction. A recent study reported that brain-derived neurotrophic factor expression was enhanced in the medial thalamus, whereas the expression of GABAA channels and the cotransporter KCC2 decreased in the same area after CPSP.<sup>[92]</sup> NLRP3 inflammasome is activated to mediate inflammatory responses, which may result in cellular damage in cerebral cortex. Once pallium is injured, the descending projection fiber may decrease. This can cause the changes of TRN neurons excitability. Then, GABAergic release reduces due to the lower excitability of TRN neurons, resulting in the loss of inhibition in VB interneurons.

This suppression condition may in turn lead to the VB neurons excitability, which increased significantly, thus causing CPSP. In 2004, a double-blind, placebo-controlled, crossover study found

that propofol, a GABA<sub>A</sub> agonist, alleviated central pain. They also concluded the key role of GABA modulation in central pain.<sup>[93]</sup> Moreover, several studies have reported that motor cortex stimulation (MCS) modulated various structures and neuronal pathways and provided satisfactory long-lasting pain control in CPSP.<sup>[94–96]</sup> However, other studies had different voices. Studies concluded that MCS does not consistently alleviate CPSP in the long-term follow-up. Another therapy for CPSP is deep brain stimulation (DBS), whose main targets are the specific thalamic nuclei and the periventricular grey area. Disappointingly, the efficacy rates of such therapy ranged from 25% to 70%.<sup>[97,98]</sup> All these conclusions indicate that the mechanism discussed above is not enough to explain the pain in CPSP.

So, we present another hypothesis that NLRP3 inflammasome induced inflammatory reaction plays an important role in thalamic lesion. The parenchymal microglial cells mainly distribute in hippocampus, basal nucleus, and thalamus. Microglia, equivalent to macrophages in the brain and spinal cord, are one type of glial cells and are the first and most important line of defense in the CNS. The activation of microglia can mediate an inflammatory reaction in the brain. Meanwhile, NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response. When activated, NLRP3 inflammasome can induce caspase-1 activation, mediate the processing, and release of the leaderless cytokine IL-1b. One study found that upon activation of caspase-1, oligomeric NLRP3 inflammasome particles could be released from macrophages.<sup>[99]</sup> We suppose that on the one hand, the activation of NLRP3 inflammasome itself can induce thalamic lesion, while on the other hand, NLRP3 inflammasome may enhance the function of microglia in inflammatory reaction. Furthermore, persistent inflammation is associated with diffuse GABAergic alteration in neurons. Rossi et al<sup>[100]</sup> found that cerebrospinal fluid (CSF) from multiple sclerosis patients with enhanced brain lesions on magnetic resonance imaging inhibited GABA transmission in mouse brain slices. Avramescu et al<sup>[101]</sup> found that inflammation increases the number of  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptors expressed on the surface of neurons. Also, Zhu et al<sup>[102]</sup> reported that the primary afferent is thought to be one site of the inflammation-induced shifts in GABA<sub>A</sub> signaling. This GABA<sub>A</sub> signaling is mainly caused by a Na<sup>+</sup>-K<sup>+</sup>-Cl<sup>-</sup>-cotransporter (NKCC1)-dependent depolarization of the GABA<sub>A</sub> current equilibrium potential (EGABA). More importantly, Sun et al<sup>[103]</sup> found that GABAergic neurons in TRN lead to inhibitory connections with other thalamic nuclei. Synaptic GABA<sub>A</sub> receptor activation triggers postsynaptic depolarizations in mouse TRN neurons.

## 2. Conclusion

There may be 2 ways for the role of NLRP3 inflammasome in CPSP. One way is that NLRP3 activation causes cerebral cortex injury, decreasing descending projection fiber to thalamus. Such condition may let GABAergic releases reduce, making the VB neurons excitability to increase. Finally, CPSP occurs. Another way is that NLRP3 inflammasome leads to thalamic lesion and strengthens inflammatory response of microglia at the same time. Persistent inflammation causes GABAergic alteration in TRN to restrain VB interneurons functions, contributing to CPSP. Although management of CPSP is difficult and limited, targeting inhibition of NLRP3 activation may be a promising therapeutic approach for CPSP. Ismael et al<sup>[104]</sup> have shown that inhibition of NLRP3-inflammasome with MCC950 may be therapeutic

potential in ischemic stroke models. Blocking the NLRP3 inflammasome pathway may be benefit for pain relief in various pain-related diseases. Targeting NLRP3 inflammasome to treat inflammatory pain and neuropathic pain is becoming increasingly evident in rats, mice, and even humans. This could establish the basis for more systematic and controlled clinical trials in humans. Therefore, further studies about the role of NLRP3 inflammasome in CPSP are highly desirable and anxiously awaited.

## Author contributions

**Data curation:** Shao-jun Li.  
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