REVIEW

Role of Sensory Pathway Injury in Central Post-Stroke Pain: A Narrative Review of Its Pathogenetic Mechanism

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Abstract: Central post-stroke pain (CPSP) is a severe chronic neuropathic pain syndrome that is a direct result of cerebrovascular lesions affecting the central somatosensory system. The pathogenesis of this condition remains unclear owing to its extensive clinical manifestations. Nevertheless, clinical and animal experiments have allowed a comprehensive understanding of the mechanisms underlying CPSP occurrence, based on which different theoretical hypotheses have been proposed. We reviewed and collected the literature and on the mechanisms of CPSP by searching the English literature in PubMed and EMBASE databases for the period 2002–2022. Recent studies have reported that CPSP occurrence is mainly due to post-stroke nerve injury and microglial activation, with an inflammatory response leading to central sensitization and de-inhibition. In addition to the primary injury at the stroke site, peripheral nerves, spinal cord, and brain regions outside the stroke site are involved in the occurrence and development of CPSP. In the present study, we reviewed the mechanism of action of CPSP from both clinical studies and basic research based on its sensory pathway. Through this review, we hope to increase the understanding of the mechanism of CPSP.

Keywords: central post-stroke pain, pathogenetic mechanism, spinothalamic tract, thalamus

Introduction

Central neuropathic pain commonly includes pain caused by central post-stroke pain (CPSP), spinal cord injury, and multiple sclerosis.[1] Stroke is one of the most common causes of disability and the second most common cause of death worldwide. The global burden of stroke is increasing as the population ages.[2] CPSP is a known complication during stroke rehabilitation.[3] Stroke patients often suffer from different forms of chronic pain, commonly in the form of CPSP, shoulder pain, painful spasticity.[4] In 1906, Dejerine and Roussy first described a case of severe and persistent lateralized pain after a thalamic stroke; this pain syndrome was later named as the Dejerine–Roussy syndrome.[5] Because central pain also occurs due to vascular lesions in the central nervous system other than the thalamus, the term CPSP is not limited to only thalamic strokes but tends to describe neuropathic pain that occurs after cerebral ischemic or hemorrhagic strokes.[6] At present, there is no stipulated definition for the diverse clinical manifestations of CPSP.[5] The pain can be described as persistent pain such as "burning", "pricking", "freezing", and "squeezing", intermittent pain such as "tearing" or "shooting". CPSP is not easily distinguished from post-stroke peripheral musculoskeletal pain and is easily overlooked in clinical practice, which may delay the recovery process and reduce the quality of life. Moreover, this kind of pain responds poorly to common anti-neuralgic drugs and lasts for a prolonged time; this not only drastically affects the quality of life in the recovery period after stroke, but also has an effect on individuals' psychological health, resulting in anxiety, depression, and sleep disorders.[7] Therefore, in order to develop more effective treatments for CPSP, it is important to review the possible mechanisms of CPSP occurrence.

Treede et al defined neuropathic pain as pain directly caused by an injury or disease affecting the somatosensory nervous system and classified it as peripheral or central neuropathic pain depending on the anatomical location of the lesion or disease.[8] As with other neuropathic pain, the onset and progression of CPSP involves primary or secondary alterations in pain transmission pathways. Nerve fibers and glial cells are closely linked to pain production and development. Nerve fibers conduct pain-related nerve impulses, and glial cells respond to neuronal injury and inflammation through replication. The underlying mechanism of CPSP is closely associated with changes in nerve fibers and glial cells along the conduction pathway.[5] Primary afferent fibers convert painful stimuli into electrical signals; these signals are then transmitted to the dorsal horn of the spinal cord, where they are combined and projected either directly or indirectly to the thalamus via ascending fibers. The pain signals in the thalamus are transmitted to the corresponding cerebral cortex, where the intensity and nature of the pain site are encoded and the emotional response to pain is modulated.[8,9] Ranging from the medulla oblongata to the cerebral cortex, Strokes at any central somatosensory site can contribute to CPSP; pain occurs in the body part corresponding to the injury site of the central nervous system (Figure 1). In this review, we describe the advances in CPSP related to clinical studies and possible molecular targets in animal experiments according to the different pain signaling sites.

Methods

We searched the PubMed and EMBASE databases in October 2022 for articles published in English between 2002 and 2022 using the following keywords "Central Post stroke Pain", "CPSP and pathophysiology", "CPSP and pathology", "CPSP and mechanism", "CPSP and rats", "CPSP and mice". Article types included Books and Documents, review, meta-analysis and Original Article. To avoid the possibility that traditional subject terms might not retrieve relevant studies, we did not use subject terms for the search. Further, the references of review articles related to CPSP were manually searched to identify earlier articles that made important contributions to the topic. Duplicate articles, articles that did not clearly define the subject of discussion as CPSP, articles on other types of pain after stroke, articles that did not mention the mechanism or hypothesis of CPSP and other irrelevant articles, such as studies on chronic post-surgical pain (CPSP), were excluded. We identified 182 articles in the literature. Review the full text of these articles. Include articles that provide insightful theories on the mechanisms of CPSP occurrence, and articles that have experiments to support their arguments. Articles that merely repeated arguments and articles with secondary summaries were excluded.
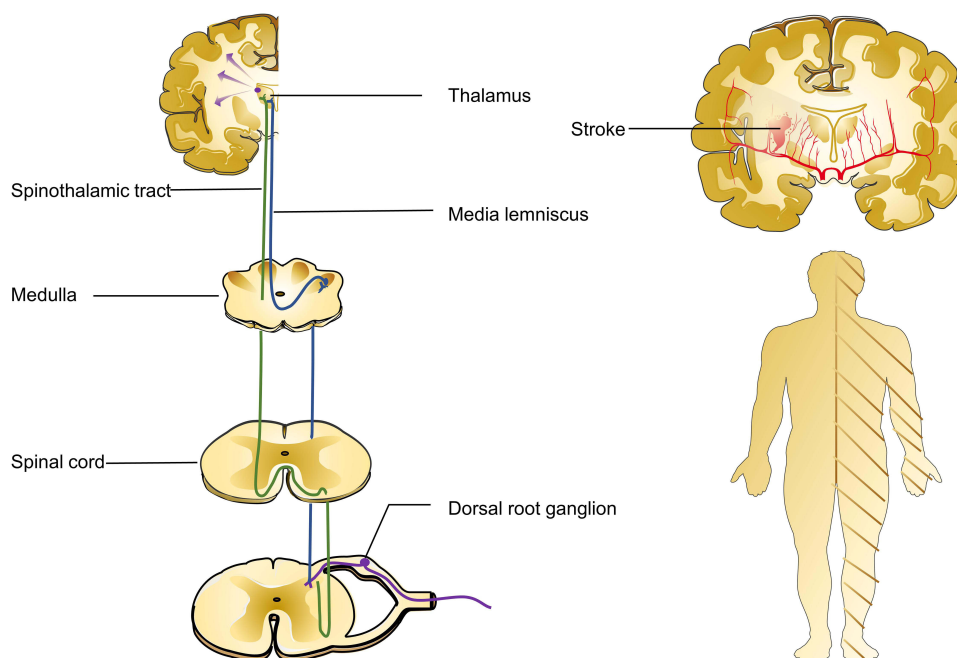
Figure 1 Anatomical schematic diagram of the sensory pathway (left). After stroke, the body corresponds to the possible range of CPSP (right).

Finally, 43 articles met the inclusion and exclusion criteria. We divided the relevant articles into 6 sections according to pain signaling pathways: peripheral nerves, spinal cord, spinal thalamic tract, medial thalamic tract, thalamus, and other brain regions for the review.

Results

Peripheral Sensory Input is Misinterpreted

Recent studies suggest that CPSP is mediated by sensitized central nervous system (CNS) neurons misinterpreting peripheral sensory input, as opposed to being spontaneously produced by damaged CNS cells.[10] Since a long time, the mechanisms of CPSP have been explored by focusing on central nerve injury and believing that peripheral nerves do not play a role. However, Haroutounian et al[10] recently demonstrated the involvement of peripheral nerves in CPSP development. They blocked the peripheral nerves corresponding to the painful areas of patients with CPSP with lidocaine; this resulted in decreased signal transmission from the peripheral nerves to the center. Good analgesic effects were obtained after nerve block, indicating that CPSP depends on afferent input from peripheral pain areas. Further, the findings of a recent case report support those of Haroutounian et al that CPSP does not exclusively originate in the CNS. In the case report, the dorsal root ganglion (DRG) was electrically stimulated to relieve post-stroke lower extremity pain.[11] The DRG consists of a cluster of primary sensory neurons that transmit somatosensory information acquired by the peripheral nerves to sensory centers. Electrical stimulation of the DRG relieved pain by reducing the transmission of injurious stimuli to the spinal cord.[11,12] Peripheral sensory signals are conducted to the spinal cord by three different nerve fibers: A-β fibers, which have the fastest myelinated conduction rate, conduct light touch; A-δ fibers, which have the second fastest myelinated conduction rate, conduct nociceptive stimuli and temperature signals; and C fibers, which have the slowest unmyelinated conduction rate, conduct burning and itching sensations. Animal experiments suggest that A-δfibers play an important role in CPSP. In a rat ischemic stroke model, a transcutaneous sensory nerve detector was to selectively stimulate the three different types of peripheral nerve fibers. The current stimulation thresholds of A-δ fibers were reduced, with the greatest difference in threshold variation.[13,14] However, the role of A-δ peripheral nerve fibers in CPSP development remains unclear.

Secondary Injury to the Spinal Cord

Although there is no direct clinical evidence suggesting secondary injury to the spinal cord in patients with CPSP, animal studies using rats and monkeys have demonstrated that stroke can cause secondary nonischemic injury not only at the infarction site but also in the distal spinal cord.[15,16] Secondary spinal cord injury was mainly characterized by detectable neuronal degeneration and loss in the dorsal horn of the spinal cord and associated neuroinflammatory changes.[16] The inflammatory response in the spinal cord was mainly associated with stromal cell-derived factor 1 (SDF-1), high-mobility group box-1 (HMGB1), and NOS signaling. After a stroke, the glial cells in the spinal cord are activated.[17] Activated microglia, astrocytes, and endothelial cells are the main sources of increased levels of SDF-1α. Elevated SDF-1α mediates monocyte infiltration and the local neuroinflammatory response.[18] Increased expression of spinal HMGB1 and the enzyme protein N(G), N(G)-Dimethylarginine dimethylaminohydrolase 1 (DDAH1), which regulates NOS signaling, in a post-ischemic stroke pain model resulted in bilateral carotid artery occlusion (BCAO).[17,19] HMGB1 is a non-histone nuclear protein that plays a critical role in regulating gene transcription. It can aggravate inflammation and pain via the TLR4 or RAGE signaling pathways.[17] NOS is associated with the development of neuropathic pain. Elevated DDAH1 may be involved in CPSP occurrence by enhancing NO signaling.[19] A proteomic study of the spinal cord and DRG of mice with BCAO revealed that DDAH1 was involved and that its levels were altered, suggesting the role of NOS signaling in the inflammatory response at spinal cord after a stroke.[20] Anterograde, retrograde, and trans-synaptic degeneration may occur after nerve fiber injury.[21] The spinothalamic tract (STT) begins from the dorsal horn of the spinal cord and projects upward to the thalamus. The retrograde degeneration of STT may be involved in secondary injury of the dorsal horn of the spinal cord after CPSP. However, this theory has not yet been proved.

Spinothalamic Tract Injury

STT is generally considered the pain, temperature, and gross tactile conduction pathway of the trunk and extremities.[22] Patients with CPSP often exhibit spontaneous pain and allodynia or dysaesthesia to touch or cold, suggesting STT injury in such patients.[23] Further, clinical use of laser-evoked potentials (LEPs), magnetic resonance imaging, and other detection techniques suggest that partial injury to the STT is necessary for CPSP development (Table 1).

The functional status of the central and peripheral segments of the nociceptive pathway is reflected by LEPs, which selectively identify and stimulate thinly myelinated A-δ fibers and unmyelinated C fibers.[24] In studies on central pain after brainstem, thalamic, and cortical stroke, LEPs acting on the painful side were absent, of reduced amplitude, or had delayed latency. These changes in potentials suggest that the afferent nerves of the STT were affected.[25–28] Diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) are magnetic resonance imaging techniques that perform measurements by imaging water diffusion features, thereby allowing us to visualize and estimate nerve tracts.[29] In the clinical application of DTI/DTT to visualize the STT in patients with CPSP, the STT and its thalamocortical pathway were observed from the medulla oblongata to the subcortical white matter.[30,31] Using imaging techniques in clinic settings, partial damage to the STT was observed, with preservation, rather than disruption, of the integrity of the fiber tract more likely leading to CPSP.[32] This is consistent with the concept proposed by Wasner et al that "the partially preserved STT acts as a central pain generator".[33] Processes such as inflammation, which are associated with the

Table 1 Clinical Study of Spinal Thalamic Tract Injury in Central Pain After Stroke

Author Year	Number of Patients	Type of Lesion	Localization of Lesion	Detection Method	Subjects Grouping	Results	Conclusion
Garcia-Larrea, Convers et al, 2002[25]	30	Wallenberg stroke	Brainstem Thalamo-cort	LEP	Unilateral neuropathic central pain VS lateralized pain of non-organic origin	LEPs significantly diminished after stimulation of painful areas	LEPs reflect deafferentation of spinothalamic afferents
Veciana, Valls-Solé et al, 2005[26]	7	Stroke	Lateral medulla	LEP	Affected side VS Non-affected side	LEPs were absent, markedly reduced and delayed	Spinothalamic tract lesions can be demonstrated by abnormal LEP on the affected side
Hong, Bai et al, 2010[68]	30	Intracerebral hemorrhage	Corona radiata and basal ganglia	DTT	CPSP VS Non-CPSP	DTT parameters: TV decreases, FA, MD remain unchanged	CPSP patients STP partially damaged
Hong, Choi et al, 2012[32]	52	Intracerebral hemorrhage	Corona radiata, basal ganglia and thalamus	DTT	STP Preserved VS STP Disrupted	Prevalence of CPSP 47% VS 17%	Partial STP injury is more likely to lead to CPSP than complete injury
Jang, Chang et al, 2017[69]	1	Intracerebral hemorrhage	Corpus Callosum	DTT	3-year VS 1-month postonset	STT had become thinner	Delayed central pain due to STT degeneration
Jang, Lee et al, 2017[70]	5	Cerebral infarction	Corona radiata, Thalamus, Pre- and post-central gyrus	DTT	CPSP VS control DTT	Parameters: TV, FA decreases and MD increases	STT injury may be the cause of CPSP in patients with cerebral infarction
Jang, Kim et al, 2018[71]	1	Intracerebral hemorrhage	Thalamus	DTT	14-month VS 2-week postonset	STT partial tearing and thinning	Late onset CPSP may be attributed to degenerative peripheral neurological changes in STT

Abbreviations: LEP, Laser evoked potentials; DTT, diffusion tensor tractography; TV, tract volume; FA, fractional anisotropy; MD, mean diffusivity; STP, spino-thalamo-cortical pathway; STT, spinothalamic tract.

degeneration of adjacent axons within the STT, may trigger spontaneous activity of the remaining intact neurons.[33] Basic research supports the spontaneous activity of the remaining intact neurons— degenerative damage to the STT causes thalamic hyperexcitability. In Wang and Thompson's study, mice with STT demyelination had central pain symptoms and induced burst discharges in the ventral posterior lateral nucleus of the thalamus.[34]

Medial Lemniscus Injury

The medial lemniscus (ML), in addition to the STT, is an important somatosensory afferent pathway.[35] Peripheral signals are transmitted to the spinal cord, where they enter one of the two upstream pathways based on the functional class of the receptors, with neural activity related to, for example, touch and pressure sensation conducted by the dorsal column pathway and nociception and temperature sensation traveling upstream via the STT. Different sites of medullary infarction separately affect different somatic afferent pathways because the two major afferent pathways, namely, STT and ML, are anatomically separated at the medulla oblongata. While ML is involved in a medial medulla infarct (MMI), STT is involved in a lateral medulla infarct (LMI).[36] The clinical manifestations of LMI and MMI are different, suggesting that the mechanism of CPSP due to ML injury is different from that due to STT injury. Compared with MMI, CPSP due to LMI usually has a late onset, and most patients complain of burning and cold pain, with cold or hot environments acting as aggravating factors. On the other hand, the aggravating factor for patients with MMI tends to be physical activity.[36] Studies have confirmed the inhibitory modulation of the sensory system of the STT by ML; it is hypothesized that ML impairment in patients with MMI causes hypersensitivity of the sensory system through de-inhibition of the STT.[37]

Thalamic Lesions

The thalamus serves as a relay station for pain transmission, and CPSP is a common complication of thalamic lesions.[38] Clinical studies have found observed that the prevalence of CPSP is related to the stroke site of stroke. For example, the prevalence is 11% regardless of the stroke site; however, it increases to more than 50% when the stroke occurs in the brainstem or thalamus.[38] Certain regions of the thalamus are more closely associated with CPSP development. These mainly include the somatosensory thalamic nucleus, namely, the ventral posterior lateral nucleus (VPL) and ventral posterior medial nucleus; the posterior portion of the ventral medial nucleus (VMpo), which receives a specific type I lamina projection; and the anterior occipital nucleus, which is a major spinothalamic target. Thalamic stroke often involves multiple nuclei, and which nucleus plays a major role in the occurrence of CPSP remains controversial; however, most of these nuclei receive STT projections or are closely related to the STT.[39–41] Wasserman et al[42] successfully established a rat model of post-thalamic hemorrhagic stroke pain by injecting type IV collagenase into the VPL of the thalamus for the first time. Other common animal models for studying CPSP include transient BCAO or middle cerebral artery occlusion resulting in post-ischemic stroke pain.[13,17] The production of CPSP may be associated with direct damage to the thalamus. Mechanical pain and heat-stimulated pain responses were absent in animal models with secondary damage to the thalamus.[43] Models of central pain caused by focal hemorrhage in the thalamus are gradually becoming the cornerstone of studies on CPSP. In such models, pathophysiological changes at the injury site are manifested as changes in glial cells and neurons (Table 2).

At present, microglial proliferation is the main change in glial cells.[44] Microglia are macrophage-like cells present in the central nervous system; they are primarily responsible for eliciting an inflammatory response. The activation and proliferation of microglia are essential for plastic changes that lead to abnormal tactile pain.[46] The P2X-related signaling, SDF1–CXCR4 signaling, and Fgr–NFκB–ERK1/2 signaling pathways are reported to be related to the occurrence and development of CPSP. The surface P2X4 receptors and P2X7 receptors were upregulated in activated microglia.[47,48] The P2X receptor is a purinergic receptor closely related to chronic pain; its upregulation in models with CPSP mediates the release of inflammatory factors such as TNF-α and IL-1β.[49] Activated microglia and astrocytes release the chemokine SDF1, which mediates the positive feedback regulation of glial–glial cells and glial cells–neurons by binding to its receptor CXCR4, which, in turn, leads to the continuous release of inflammatory factors such as TNF-α, IL-1β, and IL-6.[18] In addition, Fgr, a nonreceptor tyrosine kinase of the Src family, expression is increased after thalamic hemorrhage.

Table 2 Molecular Mechanism Studies of CPSP

Author Year	Animal	Model	Molecules Cells	Mechanism
Infantino et al, 2022[58]	CD1 mice	TH	MED1/BDNF/TrkB microglia	Activation of microglia around thalamic injury and and depression-related molecules were expressed in hippocampus
Lu et al, 2021[47]	Sprague-Dawley rats	TH	P2X4R/TNF-a/ TNFR1/GABAaR microglia	Elevated TNF-a levels around thalamic injury, surface GABAaR endocytosis
Fu, Du et al, 2021[50]	CD1 mice, C57BL/6J mice	TH	FTO/TLR4 neurons	FTO participates in the occurrence of CPSP by stabilizing the up-regulation of TLR4 in thalamic neurons
Hiraga, Itokazu et al, 2020[44]	C57BL/6J mice	TH	_microglia	The microglia in the damaged thalamus and ipsilateral primary sensory cortex were activated, and lesion-induced neural network reorganization occurred
Huang, Fu et al, 2020[72]	CD1 male mice	TH	Fgr/NF-KB, ERK/ TNF-α microglia	The increase of Fgr in the damaged part of thalamus mediates the up-regulation of inflammatory factor TNF-αand participates in the production and maintenance of CPSP
Chen et al, 2019[55]	Sprague-Dawley rats	TH	AP/δGABAaR neurons[45]	Reduced concentration of AP in the VPL and downregulation of δGABAAR expression in the medial thalamus
Cai et al, 2018[56]	CD1 mice	TH	PSD-95 /nNOS neurons	Protein-protein interactions between PSD-95 and thalamic nNOS mediate CPSP production
Yang et al, 2017[18]	Sprague-Dawley rats	TH	SDF1/CXCR4 astrocytes/ microglia	SDF1 binds to CXCR4 around thalamic injury and mediates microglial-astrocyte neuronal interactions and release of pro-inflammatory mediators
Shih, Kuan et al, 2017[73]	Sprague Dawley rats	TH	P2X4R/BDNF microglia	P2X4R leads to phosphorylation of p38 mitogen-activated protein kinase, allowing BDNF release leading to CPSP
Y. Yang et al, 2016[53]	Sprague–Dawley rats	TH	a2d-1 subunit neurons	Upregulation of a2d-1 on thalamic and spinal cord neurons early in CPSP
Kuan, Shih et al, 2015[48]	Sprague–Dawley rats	TH	P2X7R/ IL-1β microglia	P2X7R promotes downstream secretion of IL-1β and contributes to hyperexcitability of neurons, leading to CPSP

Abbreviations: TH, Thalamic hemorrhage; MED1, Mediator Complex Subunit 1; BDNF, Brain Derived Neurotrophic Factor; TrkB, tropomyosin receptor kinase B; P2X4R, P2X4 receptors; TNF, tumor necrosis factor; (δ)GABAaR, (δ-subunit) gamma-aminobutyric acid A receptors; ERK, extracellular regulated protein kinases; FTO, fat-mass and obesity-associated protein; TLR4, Toll-like receptor 4; AP, allopregnanolone; PSD-95, postsynaptic density protein 95; nNOS, neuronal nitric oxide synthase; SDF1, stromal cell-derived factor 1; CXCR4, Chemokine receptors 4; P2X7R, P2X7 receptors; IL-1β, interleukin-1β.

This increase in expression may trigger TNF-α production in the microglia via the NF-KB and ERK1/2 signaling pathways, promoting the induction and maintenance of pain hypersensitivity responses.[72]

Thalamic neuronal damage is manifested by changes in its receptors and functions. Changes are mainly induced in the neuronal receptors TLR4, GABAaR, and a2d-1 subunit. Fu et al observed that fat-mass and obesity-associated protein (FTO) was elevated in the nuclei of ipsilateral thalamic neurons after thalamic hemorrhage. FTO, an m6A demethylase, plays a regulatory role at the gene level. An increase in FTO may lead to loss of the m6A site in Tlr4 mRNA; this results in the upregulation of TLR4 in the thalamus.[50] TLR4 activation results in the release of proinflammatory cytokines, which, in turn, promotes the development of cerebral hemorrhage and causes pain. In the murine thalamus, GABAaR is mostly expressed at the synapses and extrasynapses of GABAergic neurons in the reticular nucleus. It is involved in GABA inhibitory postsynaptic potentials that mediate inhibitory activity in the thalamus.[51,52] The a2d-1 subunit is a calcium channel subunit expressed on thalamic neurons. It acts as a target for the action of gabapentin.[53,54] Extrasynaptic GABAaR expression was downregulated in CPSP but a2d-1 subunit expression was upregulated; this may be related to abnormal electrical activity in the thalamus in patients with CPSP.[47,53,55] Blocking the protein–protein

reaction of postsynaptic density protein 95 (PSD-95) and neuronal nitric oxide synthase (nNOS) before thalamic hemorrhage can alleviate the hemorrhage-induced thalamic pain. As a result, protein–protein interaction between PSD-95 and nNOS in thalamic neurons may be induce CPSP. Relief from CPSP may be achieved by blocking the over-activation of the NMDA receptor by PSD-95.[56] Some clinical drugs can partially relieve CPSP, including the calcium channel blocker gabapentin, pregabalin, GABA$_A$ agonist thiopental (intravenous injection at a sub-anesthetic dose), and lamotrigine, which can reduce glutamate release by blocking sodium channels in the presynaptic membrane.[57] These drug actions provide support and guidance for studying the mechanism of CPSP.

Other Brain Regions Involved

The hippocampus may be involved in the manifestation of depression in CPSP. Some patients with CPSP experience secondary depression, possibly leading to suicidal tendencies in severe cases.[7] Infantino et al[58] studied eight paraffin-embedded cadaveric specimens different regions of the brain after hemorrhagic events and found that mediator complex subunit 1 (MED1) was overexpressed in the brain samples of subjects who succumbed to hemorrhagic stroke compared with the brain samples of healthy subjects. MED1, a transcriptional regulator of the microRNA miR-191, negatively regulates the expression of brain-derived neuropathic factor (BDNF), which is related to depression.[59] They subsequently observed decreased BDNF expression in the hippocampus and depressive behavior in an animal model of CPSP.[58]

The insular and somatosensory cortices are associated with the pain manifestations of CPSP and may be involved in the development of burning and thermal pain. A widespread decrease in cortical gray matter volume was observed in patients with CPSP, including in the insular and somatosensory cortices.[60] The insular cortex is involved in the cold sensory conduction pathway (spinal cord–VMpo–insula). Craig et al[61] suggested that the burning pain observed in patients with CPSP is caused by damage to the central nervous system, thereby affecting the cold sensory transmission pathway; this results in deinhibition of the class C injurious fiber transmission pathway. The somatosensory cortex contains the primary (S1) and secondary (S2) somatosensory cortices. Nagasaka et al[62] observed an increase in the activities of the posterior insular cortex and S2 using functional magnetic resonance imaging in a macaques model with CPSP caused by thalamic hemorrhage. Inhibition of the activities of the insular cortex and S2 with drugs resulted in the disappearance of mechanical ectopic pain and thermal pain in the CPSP model.[62] This suggests that analgesic effects in CPSP can be achieved by modulating the insular and somatosensory cortices. Further, the insular and somatosensory cortices may be involved in CPSP occurrence via structural changes and recombination of the conduction pathways. Further, the insular and somatosensory cortices may be involved in CPSP occurrence via structural changes and recombination of the conduction pathways. Similar to the CPSP model, Kadono et al[63] used DTI and observed that the connectivity of the white matter structure between the VPL and S1/S2 regions decreased after CPSP. In a mouse model with CPSP, the nerve fiber projections from the thalamus to the S1 region were reorganized.[44]

The anterior cingulate cortex (ACC) and amygdala are said to be associated with CPSP. In general, ACC may be involved in the emotional response to pain. In normal volunteers, painful stimulation was observed in the ACC with increased cerebral blood flow; this correlated with the unpleasant sensations described by the subjects.[8,64] In patients with CPSP with thalamic VPL infarction and adjacent posterior limb of the internal capsule infarction, functional magnetic resonance imaging revealed specific signal changes in the ACC, further suggesting the involvement of the ACC in CPSP development.[65] Kadono et al[63] observed enhanced functional connectivity between the mediodorsal nucleus (MD) of the thalamus and the amygdala in a macaques model with CPSP. This increased connectivity was reduced to baseline levels after analgesic treatment with repetitive transcranial magnetic stimulation. This suggests that the abnormally enhanced functional connectivity between the MD and the amygdala causes CPSP.[63] Lu et al compared the [^{14}C]IAP brain imaging results of normal and CPSP rats and found that rats with CPSP exhibited strong activation of the thalamus–cingulate and medial prefrontal cortex–amygdala pathways.[66]

Discussion

Although the clinical incidence of CPSP is not high (1–12%), it is an intractable pain syndrome.[5] Current clinical studies have majorly focused on describing the disease characteristics and treatment effects of CPSP; however, there is

insufficient evidence on the relationship between CPSP pain mechanisms and clinical manifestations and treatment response. DTT, a new imaging technique, allows visualization of the changes in fiber bundles and provides the basis of CPSP pathology. Most basic research on CPSP has focused on primary thalamic injury. Neuronal injury and activation of the microglia underlie thalamic changes after CNS injury. The disinhibition theory and central sensitization can explain the generation and maintenance of CPSP at a macroscopic level. The disinhibition theory, proposed by Head and Holmes in 1911, explains the imbalance between systems of facilitation and inhibition.[67] CNS transmission is controlled by an intricate balance between the facilitation and inhibitory systems; disruption of this balance may be a potential mechanism for the generation of central pain. In addition, CNS lesions cause neurochemical, excitotoxic, and inflammatory changes that can increase neuronal excitability and lead to central sensitization; this, in turn, can develop into chronic pain.[5] Few studies on secondary damage outside the primary CPSP injury site, particularly in the distal peripheral nerves and spinal cord, is supported only by individual clinical treatment responses and animal experiments. Hiraga et al[44] did not observe glial cell activation at the spinal cord level in a thalamic hemorrhagic post-stroke pain model; the inflammatory response at the spinal cord level may correlate with stroke severity. Changes in the brain regions after CPSP mainly involve alterations and remodeling of the conduction pathways; pain transmission has complex connections in various brain regions, and changes and connections in various brain regions after CPSP remain to be explored.

Our study has the following limitations. First, as a narrative review, we attempted to describe more fully the theories or hypotheses of the mechanisms of occurrence of CPSP and did not attempt to assess the risk of bias for the included literature. Therefore, we listed multiple possible hypotheses for the development of CPSP without specifying the priority or preference of the hypotheses. These pathophysiological processes may be co-existing and they promote the formation and development of CPSP. Second, there is less high-quality evidence in the currently searched literature describing the occurrence and development of CPSP. Haroutouian et al[10] innovatively proposed the involvement of peripheral sensory afferents in the occurrence of CPSP, but based on a small sample (8 subjects), open-label, and self-controlled clinical study. Compared with LEP, the new imaging technique DTT presents fiber bundle changes more visually and provides a pathological basis for CPSP. However, DTT has not been used in large-scale studies with strict enrollment on CPSP, and most studies are case reports (Table 1). Hong et al[32] applied DTT several times in patients with CPSP. The trial with the largest number of recruited subjects was enrolled 52 stroke patients and found a higher incidence of CPSP in patients with STP preserved compared to STP disrupted. The mechanisms behind this clinical phenomenon need to be explored more. Liampas et al[38] performed a systematic analysis of 23 papers involving stroke sites and found that the most common site of stroke in patients with CPSP is the thalamus. The molecular mechanisms underlying the occurrence of CPSP after thalamic stroke have been studied to some extent in animal experiments, but the studies are still few and the key targets and effective treatments have not been proposed (Table 2). In other brain regions, larger studies have been conducted on cortical structural reorganization and plasticity. Krause et al[60] recruited 45 subjects to analyze GMV in patients with sensory stroke with and without CPSP and found a distinct pattern of extensive structural plasticity accompanying CPSP. However, the molecular mechanisms behind this remain unclear. In conclusion, further clinical studies involving a large number of subjects and more in-depth basic research are warranted.

Conclusion

There has been an increase in the number of patients with stroke.[74] It is particularly important to explore the mechanism underlying the occurrence of CPSP as a serious complication after stroke. Based on clinical and basic research, there are four main hypotheses for the mechanism of CPSP occurrence. First, the misinterpretation of peripheral afferent sensation by sensitized neurons in the brain. Second, after injury of the afferent pathway, spontaneous activity is enhanced or other pathways are induced to be enhanced, resulting in high excitability of the thalamus. Third, neuronal damage and microglial activation leading to central sensitization or deinhibition occur after thalamic injury. Fourth, some brain regions are damaged, resulting in damage of the pain sensation system. Anti-inflammatory treatment, treatment of distal secondary injury, and functional rebalancing among brain regions may be the main treatment strategies for CPSP.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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