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Central post-stroke pain: advances in clinical and preclinical research

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ABSTRACT

Central poststroke pain (CPSP) is a medical complication that arises poststroke and significantly impacts the quality of life and social functioning of affected individuals. Despite ongoing research, the exact pathomechanisms of CPSP remain unclear, and practical treatments are still unavailable. Our review aims to systematically analyse current clinical and preclinical studies on CPSP, which is critical for identifying gaps in knowledge and guiding the development of effective therapies. The review will clarify the clinical characteristics, evaluation scales and contemporary therapeutic approaches for CPSP based on clinical investigations. It will particularly emphasise the CPSP model initiated by stroke, shedding light on its underlying mechanisms and evaluating treatments validated in preclinical studies. Furthermore, the review will not only highlight methodological limitations in animal trials but also offer specific recommendations to researchers to improve the quality of future investigations and guide the development of effective therapies. This review is expected to provide valuable insights into the current knowledge regarding CPSP and can serve as a guide for future research and clinical practice. The review will contribute to the scientific understanding of CPSP and help develop effective clinical interventions.

INTRODUCTION

Central poststroke pain (CPSP) manifests as neuropathic pain (NP) during either the acute or chronic stages after a cerebrovascular incident (ischaemic or haemorrhagic) resulting from lesions in the central somatosensory pathway.[1] Following an intracerebral haemorrhage (ICH), the occurrence rate of CPSP changes between 8% and 46%, a variation attributed to the diverse brain regions impacted, with a likelihood that patients experience a thalamic stroke.[2] Additionally, CPSP has been reported in young ischaemic stroke (IS) survivors, with an occurrence rate of 5.9%.[3] Typical symptoms of CPSP include persistent headache, spasticity-related pain, shoulder discomfort and musculoskeletal pain.[4] Spontaneous pain can manifest immediately or appear several years after a stroke.[5]

CPSP is often accompanied by symptoms such as anxiety, depression, fatigue and cognitive dissonance as well as physical dysfunction. These comorbidities intensify both the sensitivity and duration of pain, fostering a cyclical relationship between pain and negative emotions. Consequently, this results in limitations in daily activities and a decline in overall well-being.[6] Currently, CPSP treatment is based on a combination of drug therapy and non-pharmacological interventions to alleviate pain. However, prolonged drug use often leads to various adverse effects, and the efficacy and underlying mechanisms of non-pharmacological treatments remain incompletely understood. In preclinical studies, animal models serve as tools for investigating the pathogenesis of CPSP and identifying novel therapeutic strategies. However, the animal models used for CPSP research lack comprehensive characterisation. Therefore, comparisons of different animal models, behavioural evaluation protocols and potential pathogenesis of CPSP are essential to identify suitable animal models and advance research in this field.

The increasing studies on CPSP highlight the need for a thorough and systematic analysis of existing research to enhance our understanding of CPSP and encourage novel experimental research. This review aims to provide the first comprehensive and systematic description of pain patterns and clinical manifestations among CPSP patients. This review begins with clinical studies and then moves on to animal models replicating clinical aspects, including evaluation metrics and potential pathogenesis. By summarising the features and mechanisms of CPSP from both clinical and preclinical perspectives, we suggest strategies to identify new therapeutic targets for CPSP. Furthermore, we analyse inadequacies in

preclinical research design and data analysis to encourage improvements in experimental methodologies.

SEARCH STRATEGY AND SELECTION CRITERIA

For detailed information on the search strategy and selection criteria, please see online supplemental material 1 and online supplemental material 2.

CLINICAL STUDIES

CPSP is a type of NP that frequently develops following cerebrovascular damage to the somatosensory pathways connecting the cortex to the medulla. Unfortunately, a retrospective study has revealed that around 80% of patients with CPSP are not receiving adequate treatment, which affects their quality of life. Clinicians must remain vigilant, use clinical assessments to identify the development of CPSP and promptly administer appropriate treatment to patients.

Clinical features and lesion site

CPSP is a condition that typically manifests within 3–6 months after a stroke. Its cardinal symptoms comprise pain and somatosensory abnormalities. Despite being overlooked as a stroke complication, CPSP affects 36.5% of patients and diminishes their quality of life.[7 8] CPSP encompasses diverse types of pain, such as persistent pain, spontaneous intermittent pain and nociceptive hypersensitivity. The pain can be severe and persist for 3 months to several decades, although interspersed with remission periods.[9] Spontaneous hyperalgesia can provoke touch-induced pain with normal temperature, although with abnormal sensitivity to pinpricks and heat. Moreover, the affected side of the trunk may experience tearing, burning, freezing or squeezing sensations or pain. Clinicians use two criteria to diagnose the condition: pain that manifests within 6 months after a stroke and imaging evidence of a vascular injury in the susceptible area. For more detailed information, please refer to table 1, which presents data from recent clinical studies.

The incidence rate of CPSP varies between studies and depends on the brain injury site.[10] Recent advances in imaging techniques have helped physicians enhance their understanding of how specific anatomical lesions contribute to CPSP development.[3] In patients with IS, CPSP has been observed in 25%–56.1% of cases.[11 12] The involvement of the spinothalamic tract (STT) and the thalamic ventral posterior nucleus, situated at the thalamus/pulvinar border zone, is a prerequisite for CPSP.[13] The interruption of white matter connections between the thalamus and the cerebral cortex significantly affects the development of CPSP.[14] As described in the literature, the primary haemorrhage locations associated with CPSP include thalamic and brain stem/cerebellum lesions.[15 16] The primary haemorrhage locations associated with CPSP include the thalamus, the thalamic capsular region, the supratentorial extrathalamic area, the lenticulocapsular region, the internal capsule, the external capsule, the pons, the lateral medulla, the putamen, the basal ganglia, the cortex, the occipital lobe, the temporal lobe, the frontal lobe, the parietal white matter and the caudate nucleus.[12 17–21]

CPSP often co-occurs with anxiety, depression and sleep disorders.[3] Regrettably, anxiety and stress can exacerbate pain, creating a challenging cycle characterised by the mutual reinforcement of negative emotions and pain, thus complicating CPSP treatment. A neural feedback loop exists between the anterior cingulate cortex, a centre for nociceptive processing and the ventral tegmental area, an emotional centre.[22] This intricate mechanism plays a role in perpetuating chronic pain and negative emotions,[22] thereby complicating the treatment of CPSP. Notably, the interaction between chronic pain and negative emotions implicates diverse neurofunctional networks, including brain regions like the thalamus and primary motor cortex,[23 24] both play crucial roles in this process.

Clinical assessment scales

Assessing CPSP can be challenging due to the longitudinal nature required for symptom development and the similarity of symptoms to other chronic pains. Additionally, cognitive impairments resulting from a stroke make self-assessment skills complicated.[5] Physicians can use various scales to detect the severity of stroke and CPSP. The National Institutes of Health Stroke Scale assesses the severity of the stroke. At the same time, questionnaires such as the Pain Detect Questionnaire and Douleur Neuropathique 4 can aid in diagnosing NP by identifying neuropathic symptoms and signs.[21] These questionnaires clarify the frequency of different pain features. Pain questionnaires or Numerical Rating Scales (using numbers 0–10) can be used for pain assessment during the clinical examination of a stroke patient.[5] Quantitative sensory testing semiobjectively evaluates the central sensitivity in the somatosensory pathway in NP, allowing long-term pain tracking and disease development recording. The Visual Analogue Scale assesses spontaneous pain intensity, while the NP symptom inventory evaluates pain intensity with its psychometric properties.[25] The Patient Global Impression of Change scale gauges the degree of general pain improvement.[17] The tactile sensation subscale of the Nottingham Sensory Assessment can be used to evaluate the somatosensory function, with a total score of 20. These scales have been used in various ways in clinical research and trials.

Clinical treatment

CPSP poses several unanswered questions compared with other pain syndromes. Its pathophysiological mechanism remains unclear.[26] Furthermore, there is no established gold-standard drug for CPSP treatment.[26] Clinical research suggests pharmacological and non-pharmacological interventions help manage CPSP.[10] Currently, the primary clinical treatments for CPSP include analgesics, neuromodulation technology and other potential treatments. For more detailed information, please refer to online

Table 1 Patient demographics, clinical characteristics and treatments

Stroke type	Sex	Aged (years)	Lesion site	Type of pain	Treatment	Clinical trials	Reference
Ischaemic (I)	1 male	60	Dorsal thalamic region: pulvinar, sensory nuclei	Pronounced allodynia and burning paresthesia, sharp	Motor cortex stimulation (MCS) in the epidural brain	Visual Analogue Scale (VAS)	50
I	1 female	32	Right posteroinferior, thalamus (T), occipital cortex, parahippocampal	Acute onset of pain and paresthesia	Repetitive transcranial magnetic stimulation (TMS)	Repetitive TMS	70
Haemorrhagic (H)	1 female	57	T	Continuous, tingling and cold sensational	–	Diffusion tensor tractography	71
H, I	8 males 8 females	48–73	T, pons, insula in I, external capsule, lenticulocapsular	Burning, pricking, squeezing, aching, hypoesthesia, allodynia	Repetitive TMS	MCS	12
H, I	17 males 15 females	57.7±8.2	Cortex, T, basal ganglia, brainstem	Light touching painful, cold or thermal painful, slight pressure painful	–	Pain Detect Questionnaire, the Leeds Assessment of Neuropathic Symptoms and Signs, douleur neuropathique questionnaire-4 (DN-4)	21
H, I	12 males 2 females	58.5±8.9	T, pons, lateral medulla, posterior limb of the internal capsule, putamen	Persistent numbness and pain	–	TMS, contact heat evoked potentials, somatosensory evoked potentials, quantitative sensory testing	20
H, I	16 male 21 female	58.9±12.1		–	30 mg duloxetine (once a day)	Use duloxetine	72
H, I	39 patients	59.4±11.9	Cortical, subcortical, brain stem/ cerebellum,	Tactile, mechanical and cold hypoesthesia	–	Short-form McGill pain questionnaire, brief pain inventory, DN-4, neuropathic pain symptoms inventory	7
H, I, H/I	4 males 4 females	37–62	T, basal ganglia, frontal lobe, internal capsule, occipital lobe	–	Peripheral nerve block	Block peripheral nerve	19

Continued

Table 1 Continued

Stroke type	Sex	Aged (years)	Lesion site	Type of pain	Treatment	Clinical trials	Reference
H, I, H/I	6 males 4 females	41–60	T, middle cerebral artery territory, medulla, brainstem, temporal stem, parietal white matter, basal ganglia	–	Bilateral deep brain stimulation (DBS) targeting ventral striatum/anterior limb of the internal capsule	DBS	[18]
H, I, H/I	109 male 54 female	63.4±7.9	T, putamen, pons, medulla	Moderate sensory disturbance, allodynia and hyperpathia	Spinal cord stimulation	VAS, Patient global impression of changes	[17]
H/I	82 patients	≥18	Unilateral brain lesion	–	Flexible-dose placebo (1–2 tablets a day) or (1–2 tablets of 30 mg/day)	Short-form McGill Pain Questionnaire-2, Numerical Rating Scale, Pain Disability Index	[73]
–	17 patients			–	DBS or MCS	DBS, MCS	[74]
	5 males 4 females	57–76	Unilateral thalamic, putaminal, spinal cord	Compressing, lancinating, stinging, burning sensations or twitching	Electrical stimulation the ventral posterolateral nucleus	Stereotactic thalamic ventral posterolateral nucleus stimulation	[75]
–	4 patients			–	DBS of internal capsule	VAS	[76]
–	42 males, 40 females	>50			Use acetaminophen, heat and ice packs	Pain assessment survey	[77]
–	5 patients			–	DBS targeting ventral striatum/ anterior limb of the internal	Functional MRI	[78]
–	1 female	45		Constant burning pain	Transcranial direct current stimulation	VAS, DN-4, Beck Depression Inventory	[79]
–	23 patients			Contralesionally extensive ongoing pain at the lower extremity	Explicit sensory discrimination retraining	VAS	[11]

Continued

Table 1 Continued

Stroke type	Sex	Aged (years)	Lesion site	Type of pain	Treatment	Clinical trials	Reference
	1 male	68	Left hemisphere	Slowly progressive, intense	Directional DBS targeting the thalamic left ventrocaudal nucleus	DBS	[80]
–	5 patients	41–67		Intermittent tingling, burning and lancinating sensations.	Stellate ganglion block	Numerical Rating Scale	[81]
	22 patients	ver 19	M1; C3, C4-Anode, over the contralateral supraorbital region-cathode	–	Transcranial direct current stimulation for 20 min, 5 times weekly, for 2 weeks	Brief pain inventory, Beck Depression Inventory, the patient's quality of life, Euro Quality of Life-5 Dimensions	[82]

DBS, Deep brain stimulation; DN-4, Douleur neuropathique questionnaire-4; H, Hemorrhagic; I, Ischemic; MCS, Motor cortex stimulation; T, thalamus; TMS, transcranial magnetic stimulation; VAS, Visual analogue scale.

supplemental material 3, which presents treatments used in clinical studies.

In summary, CPSP is likely to occur when patients present with pain and somatosensory abnormalities, accompanied by anxiety, depression, sleep disturbance and other brain dysfunctions due to cerebrovascular impairment impacting medulla-to-cortex somatosensory pathways. Since the exact aetiology and pathogenesis of CPSP are unclear, the diagnosis mainly relies on clinical evaluation. Various scales can help doctors evaluate the severity of pain and treatment efficacy. Additionally, based on current research evidences, drugs such as gabapentin have shown curative effects, and neurostimulation therapies are viable options for resistant cases.

Clinical studies have limitations when exploring new treatments and uncovering potential causes of CPSP. Therefore, it is necessary to conduct preclinical studies using animal experiments. Due to the high incidence of CPSP and the lack of adequate clinical treatments, preclinical studies have become important. Preclinical studies on CPSP have seen a notable rise, offering valuable insights into this condition's mechanisms and impact.

PRECLINICAL STUDIES

Developing appropriate animal models and evaluation criteria is crucial to advance clinical research and identify effective therapies for CPSP. Over the years, researchers have established rodent and primate models of CPSP by inducing a focal stroke to create a lesion toward the thalamic ventral posterolateral nucleus (VPL).[27 28] To monitor pain changes after CPSP induction, researchers evaluate mechanical, cold and thermal pain. They also assess the impact of CPSP by evaluating various behavioural changes in CPSP animals, including anxiety and depression-like behaviours, motor coordination and cognitive functions. The impact of these evaluations and the promising results of various therapeutic interventions tested in CPSP animal models, thanks to the advances in animal models and evaluation criteria, inspire and motivate further research. These advances contribute to furthering our understanding of CPSP and identifying effective therapies. Research on CPSP caused by IS mainly focuses on central sensitisation, neuroinflammation, neuroplasticity, brain dysfunction and neuronal damage (table 2). On the other hand, ICH-induced CPSP research focuses on central sensitisation/disinhibition, neuroinflammation, spinal cord-thalamic tract dysfunction and neurotoxicity (table 3). We will discuss the mechanisms in detail below.

Preclinical models

The CPSP model induced by IS

CPSP can manifest after an IS. Various techniques are employed to establish rodent models of CPSP, including bilateral common carotid artery occlusion, photochemically induced thrombosis and endothelin-1-induced ischaemia in the ventral basal complex (VBC) area. In DDY mice (an outbred rodent strain), a model of cerebral ischaemia is typically induced through temporary occlusion of the bilateral common carotid artery using Sugita standard aneurysm clips for 30 min, resulting in observed hyperalgesia on day 3 via mechanical stimulation testing.[26] Conversely, C57BL/6 mice have been used to develop a long-lasting CPSP mouse model after photochemically induced thrombosis, exhibiting hypersensitivity to electrical stimulation on both paw sides, although without abnormal pain responses in thermal or mechanical nociception tests.[29] Studies using SD rats have demonstrated that ischaemia can be induced by injecting endothelin-1 into the VBC area, targeting the right ventral posterior thalamic nuclei at specific coordinates: anteroposterior: 3.00 mm, mediolateral: −3.00 mm, dorsoventral: 6.00 mm. This injection results in transient ischaemia and cerebral infarction, leading to a reduced thermal pain threshold but no change in the mechanical pain threshold.[30] The absence of increased sensitivity to touch in this model may be due to differences in lesion size, location and mechanisms. These studies indicate that while hypersensitivity is discernible in these three CPSP models induced by IS, there are variations in the induced stimulation, highlighting the intriguing diversity of responses in these models.

The CPSP model induced by thalamic haemorrhage

When simulating pain after thalamic haemorrhage, researchers usually target the right VPL or VBC region. However, the location of these regions in the brain varies between species. For rat CPSP models, the stereotaxic coordinates usually range from anterior to 2.4–3.8 mm, left to 2.8–3.6 mm and ventral to 5.5–6.4 mm.[31 32] Meanwhile, stereotaxic coordinates for establishing the mouse CPSP model are anterior: −0.82 to 2.30 mm; left: −1.30 to 1.95 mm; ventral: −3.01 to 4.25 mm.[33] The stereotaxic location of VPL in non-human primates is determined based on MRI.[28 34] In these models, collagenase VII-s, IV (0.025 U/0.25 µL) or autologous blood (25 µL) is injected into these precise locations to induce CPSP.[27 32] SD rats usually weigh between 200 and 400 g, while CD1 or C57BL/6 mice are typically 7–8 weeks old. Researchers evaluate mechanical, thermal and cold pain to assess the model's success.

Evaluation metrics

Allodynia, hyperalgesia and spontaneous pain manifest in patients with CPSP after a stroke. While the CPSP rodent model can replicate human conditions to a certain extent, direct evaluation of rodent pain sensation is challenging. As a result, indirect assessments using mechanical, cold and heat pain modalities are employed to represent pain manifestations, including allodynia and hyperalgesia, characterised by abnormal pain responses to normal or mildly painful stimuli.

Different protocols exist to detect mechanical, cold and thermal pain in rodents with CPSP. Each pain measurement protocol has pros and cons, and we will

Table 2 The pathophysiological mechanism of CPSP caused by ischaemic stroke in rodents

Experimental animals	Model	Behavioural testing	Mechanism and lesion site	Experimental design	Reference
DDY mice	Bilateral common carotid artery occlusion	Paw-withdrawal mechanical threshold (PWMT) (frequency right pain (FRP), 3 days, n=6)	Orexin-A/orexin 1 receptor signaling injuries lateral hypothalamus to locus coeruleus and rostral ventromedial medulla	B	26
		PWMT (FRP, 3 days, n=6)	N(G),N(G)-Dimethylarginine dimethylaminohydrolase 1↑-nitric oxide synthetase (NOS)↑	B	65
		PWMT (FRP, 3 days, n=6)	The association of spinal glial cells with HMGB1/RAGE/NOS or HMGB1/TLR4/NOS	B	64
		PWMT (FRP, 3 days, n=4)	Decreased pain thresholds: ischaemic neuronal damage	Not clarified	69
		PWMT (FRP, 3 days, n=6)	A decrease in hypothalamic orexin A	B	83
SD rats	Distal middle cerebral artery occlusion	Body asymmetry test (neurological deficits (ND), 3–28 days, n=9), Modified Bederson's score (ND, 3–14 days, n=9), PWL/PWT (no changes)	Cortex	B, randomisation	84
	Endothelin-1	PWL (contralateral pain, 28 days), PWT (no changes), cylinder test (no changes), adhesive removal test (no changes), open field test (no changes), ANY-MAZE test (no changes)	Ventral posterolateral nucleus and ventral posteromedial nucleus	B, randomisation	30
Wistar rats	Left common carotid artery occlusion	Neurological assessment (ND, 1–23 days), current perception threshold (right nociception: 5/250/2000 Hz, 3–15 days; left nociception: 5 Hz, 6–7 days/13–15 days, 250/2000 Hz, 3–15 days)	Hypersensitisation caused by functional changes in nociceptive primary afferent A fibres↑	B	51
C57BL/6J	Photochemically induced thrombosis	Electrical stimulation-induced paw withdrawal (250/2000 Hz bilateral nociception, 4–19 days), PWL (bilateral pain, 3–17 days), PMT (up and down bilateral pain, 4–18 days)	Lysophosphatidic acid receptor 1 and lysophosphatidic acid receptor three signalling; cortex and striatum	B	29

B, Blind; CPSP, central poststroke pain; HMGB1, high-mobility group box-1; ND, neurological deficits; PWL, paw-withdrawal latency; PWT, paw-withdrawal threshold; RAGE, receptor for advanced glycation end products; TLR4, Toll-like receptor 4.

Table 3 The pathophysiological mechanism of CPSP caused by thalamus haemorrhage in rodents and non-human primates

Animals	Model of CPSP	Behavioural testing	Mechanism and lesion site	Experimental design	Ref
SD rats	Right VPL Collagenase (Coll) IV (0.025U)	PWMT (FBP, 7–28 days, n=8) OFT, novelty-suppressed feeding test, elevated plus maze test, FST	HIF-1α/NLRP3↑	Blind (B), Randomisation (R)	2
		PWMT (FBP, 28 days, n=14)	Endoplasmic reticulum stress/ inflammation interactions/ central sensitisation	B, R	42
		PWMT (FBP, 28 days, n=10), PWTL (no changes)	14,15-EET↓/StAR/ allopregnanolone/δGABA$_A$R signaling-reversed normal thalamic inhibition	B, R	37
		PWMT (FBP, 7–28 days, n=10)	HIF-1α/SDF1/CXCR4 signalling-microglia-astrocytes-neurons interactions.	B, R	35
		PWMT (FBP, 7–28 days, n=8)	Spinal neuronal MCP-1 as a distant trigger for central sensitisation	B, R	53
		PWMT (FBP, 7–28 days, n=7)	Inflammation and apoptosis	B, R	27
		PWMT\PWTL (FBP,7, 14 days, n=5),	Chronic melatonin administrations↓ stimulating complex I and IV activities	B, R	85
	Right VPL 25 µL autologous blood	PWMT (FBP 1–21 days, n=7), PWTL (no changes)	MiR-133b-3p/purinergic P_2X_4 receptors↓ in VPL	Not clarified	32
		PWMT (FBP, 1–21 days, n=8–14), PWTL (no changes)	P_2X_4 receptor↑ in microglia of thalamic perilesional tissues	R	36
	Right VPM/VPL Coll IV (0.125U)	PWMT (FCP, 7–35 days, n=25), PWTL (7–35 days, n=25)	Activation of P_2X_7 receptors on microglia and BDNF and IL1β-glutamate.	Not clarified	43
	Right VBC Coll IV (0.125U)	PWMT (FBP, 7–35 days, n=8), PWTL (FBP, 21–49 days, n=8), Rotarod tests (no changes)	The noxious response in the medial thalamus and the alteration of the oscillation pattern of the thalamocortical pathway	B, R	40
		PWMT/ PWTL (FBP, 7–35 days, n=6–10)	The brain's pain matrix and spinothalamocortical pathway	R	86
	Right VBC and posterior thalamic nucleus Coll IV (0.025U)	PWMT (FBP, 7–21 days, n=6–8)	α2δ–1 subunit↑ in the thalamus and the dorsal horn	R	52
CD1 mice	Right VPL Coll IV (0.07U)	PWMT (FCP, 3 days, n=8), tail suspension test (21–28 days, n=8)	Mediator complex subunit 1/BDNF/ TrkB pathway	B, R	87
	Right VPM and VPL Coll IV (0.01U/10 µL saline)	PWMT (FBP, 1–14 days, n=8), PWTL/cold pain (1–14 days, n=8)	TLR4/NF-κB/ERK1/2 in microglia	B	33
		PWMT/PWTL/cold pain (FCP, 1–28 days, n=10)	The protein–protein collaboration between neuronal nitric oxide synthase and postsynaptic density protein 95 in the thalamus	B	38

Continued

Table 3 Continued

Animals	Model of CPSP	Behavioural testing	Mechanism and lesion site	Experimental design	Ref
C57BL/6J mice	VPM and VPL (right/left) Coll IV (0.075 U)	Bederson score, von Frey test, thermal plate test	Inhibition of Panx1 attenuated proinflammatory factors transcription and neurite disassembly	R	88
Rhesus macaques	VPL (right/left) Coll IV (200 U/mL saline)	PWMT (FCP, 56 days, n=6)	Neuronal morphology alteration, including ipsilateral—PIC/SII synaptic loss	B	28
		PWMT (FCP, 56–84 days, n=4), PWTL (FCP, 28–84 days, n=4)	Microglia-astrocyte interaction-abnormal excitability of surviving neurons	B	39
Japanese monkeys	Left VPL Coll IV (0.8U/site)	PWMT (FCP, 43 days/98–119 days), PWTL (FCP, 98–119 days), cold pain (FCP) (n=2)	Functional connectivity↑ between mediodorsal nucleus of the thalamus and amygdala	B	34
Macaca mulatta	VPL (right/left) Coll IV	PWMT (FCP, 63–273 days, n=5)	Cortical activity↑	B	41

BDNF, brain-derived neurotrophic factor; Coll, collagenase; Contra, hind paw contralateral; CPSP, central poststroke pain; CXCR4, C-X-C chemokine receptor type 4; 14,15-EET, 14,15-Epoxyeicosatrienoic acid; ERK, extracellular signal-regulated kinase; FBP, frequency bilateral pain; FCP, frequency contralateral pain; HIF-1α, hypoxia inducible factor 1α; MCP-1, Monocyte Chemoattractant Protein-1; NLRP3, NOD-like receptor family, pyrin domain containing 3; OFT, Open field test; PIC, posterior insular cortex; PWMT, paw-withdrawal mechanical threshold; PWTL, paw-withdrawal thermal latency; SDF1, stromal cell-derived factor 1; SII, secondary somatosensory cortex; StAR, steroidogenic acute regulatory protein; TLR4, Toll-like receptor 4; TrkB, neurotrophic receptor tyrosine kinase 2; VBC, ventral basal complex; VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus; δGABA$_A$R, δ-subunit gamma-aminobutyric acid A receptor.

analyse them individually to help identify the most suitable option. Furthermore, tests are available to evaluate common complications of CPSP, such as mood disorders and cognitive dysfunction. We will also compare these tests and provide a comprehensive assessment.

Mechanical pain

Mechanical pain assessment is a widely used method to evaluate the behaviour of rodents with CPSP. Typically, the assessment lasts between 7 and 28 days. Pain is present bilaterally,[35–37] starting on day 1, peaking between 2 and 7 days, and persisting for 4 weeks.[36 38] There have been reported cases of contralateral pain.[38–40] In primates with CPSP, mechanical and thermal withdrawal tests detected hind limb paralysis on the opposite side of the body within 2–3 days.[39 41] To determine paw withdrawal mechanical threshold (PWMT) in SD rats, researchers often use Von Frey filaments ranging from 2 to 26 g. The threshold is calculated as the average of three minimal forces in consecutive trials, each separated by 5 min.[31 37 40 42–44] In CD1 mice, calibrated von Frey filaments (0.07 and 0.4 g) are employed, and calculating paw withdrawal frequency involves using the formula: response frequency=(number of paw withdrawals/10 trials)×100%.[33 38]

Cold pain

After the induction of CPSP, there is a reduction in the threshold for cold pain in animals.[31] Cold allodynia was assessed by quantifying hind paw withdrawal latency in response to acetone or a cold stimulus.[45] This can be achieved by applying a single drop of cold acetone to the plantar skin of the hind paw of mice without direct skin contact and scoring their response using a 4-point scale as per the established protocol. Alternatively, cold pain evaluation involves placing the animals on a low-temperature (4°C) aluminium plate and recording the duration before lifting their feet. Most studies reported significant changes in cold pain in the contralateral limbs of mice after a stroke.[38]

Thermal pain

Regarding research on thermal pain, please refer to online supplemental material 3 for more information.

Anxiety-like and depression-like behaviour

Please refer to online supplemental material 4 for research on anxiety-like and depression-like behaviour.

Motor coordination and cognitive functions

Please refer to online supplemental material 5 for research on motor coordination and cognitive functions.

Promising strategies that have been tested in an animal model of CPSP

Researchers have explored effective therapies for CPSP in animal models. One such therapy is the stellate ganglion block, which involves enhancing cerebral blood flow and suppressing HIF-1α/NLR pyrin domain containing

3 (NLRP3) inflammatory signalling, effectively reducing anxiety and depression in CPSP rats.[2] New drugs and compounds have also emerged as potential treatments for CPSP. For instance, pretreatment with ZL006 has been found to attenuate haemorrhage-induced thalamic pain.[38] At the same time, exogenous 14,15-EET has demonstrated the ability to alleviate mechanical pain by restoring the normal thalamic inhibition state and exhibiting anti-inflammatory effects.[27 46] Antidepressants and selective serotonin reuptake inhibitors have also shown positive effects on pain associated with depression and comorbid anxiety in CPSP.[47] Regulating genes and proteins have observed positive effects on pain after CPSP. Injection of the tyrosine kinase receptor B -Fc, a brain-derived neurotrophic factor receptor blocker, has been shown to inhibit the nociceptive responses of the medial thalamus.[43] Notably, a remarkable reduction in NP has been observed in rats with knocked-out P_2X_4 receptors.[32]

Moreover, the signal mediated by the CXC factor one chemokine receptor (CXCR4), derived from stromal cells, is responsible for the interaction between glial-glial and glial-neuronal cells. This signal represents a potential new target for CPSP therapy.[35] Additionally, low-frequency electroacupuncture can reduce the haematoma size, inhibit neuronal apoptosis, and alleviate CPSP-induced pain abnormalities. On the one hand, high-frequency electroacupuncture relieves the pain by inhibiting abnormal activation of astrocytes.[44] Furthermore, electroacupuncture can effectively relieve CPSP by inhibiting autophagy in the hippocampus.[35] Lastly, repetitive transcranial magnetic stimulation therapy can restore altered connectivity between the mediodorsal nucleus and the amygdala in primates with CPSP.[34]

Several research studies have been conducted to identify the causes and development of CPSP. These studies have used animal models induced by IS or ICH, including rodents and primates, to help clinicians address the treatment challenges associated with CPSP. Various behavioural tests assessing mechanical pain, thermal pain, cold pain, motor coordination and cognitive functions have helped understand the pathophysiology of CPSP. These studies suggest that CPSP may arise due to central sensitisation theory, neuroinflammation, changes in the spinal cord and thalamic tract function, central imbalance and other factors. The findings from these studies and the effective therapies observed in animal models provide the potential for a breakthrough in the clinical treatment of CPSP.

PROBABLE MECHANISMS OF CPSP

CPSP is a commonly occurring NP syndrome that can develop after a stroke. The condition is characterised by allodynia, hyperpathia and sharp, stabbing or burning pain.[48] These symptoms result from the pain-related network associated with maladaptive plasticity of the central nervous system (CNS).[49] Animal research has indicated that the mechanisms underlying CPSP include central sensitisation theory, neuroinflammation, spinal cord and thalamic tract function changes and central imbalance. A better understanding of the underlying pathophysiological mechanisms of CPSP through research can help physicians identify better treatments for patients.

Central sensitisation theory

Patients suffering from CPSP do not experience pain due to spontaneous generation by their CNS. Instead, neurons' excessive excitation or spontaneous discharge may generate pain in the thalamus or cortex. Additionally, the functional imbalance between the excitatory and inhibitory systems in the pain pathways can contribute to central sensitisation.[1]

After the bilateral carotid artery occlusion, abnormal burst firing activity in the thalamic nucleus was reported.[50] This injury also affects the primary nociceptive afferent neurons Aβ and C. When the primary afferent neurons are stimulated by nociceptive signals, they transmit pain signals to the secondary afferent neurons via the dorsal horn. These signals are then processed by specific brain regions like the cerebral cortex, leading to bilateral hyperalgesia.[51] Additionally, increased inflammatory cytokines within the brain during cerebral ischaemia can cause hyperalgesia through the blood circulation in the hind paw. Please refer to figure 1A for a better understanding.

In models of CPSP with a haematoma in the VPL, increased cortical activity contributes to CPSP.[41] Epoxyeicosatrienoic acids play a role in neuronal survival by reducing perithalamic lesions after CPSP in rats. This reduction leads to a decrease in acute steroidogenic regulatory proteins and the production of neurosteroids, which blocks the activation of extrasynaptic δ-subunit gamma-aminobutyric acid A receptors. The output of neurosteroids blocks the disinhibition of hyperexcitability of medial thalamus relay neurons caused by injury.[37]

During the early stage of CPSP induced by thalamus haemorrhage, in the thalamus and neurons of the lumbar spinal cord dorsal horn (L3–L5), the expression of the voltage-gated Ca^{2+} channel's α2δ–1 subunit is upregulated. This leads to an increase in presynaptic Ca^{2+} flow.[52] ICH can also activate excitatory N-methyl-D-aspartate (NMDA) receptors on the postsynaptic membrane, causing an excessive influx of Ca^{2+} into neurons. This results in an abnormal NO production increase, which activates neuronal nitric oxide synthase (NOS). The influx of Ca^{2+} and NO ultimately leads to neurotoxicity and brain injury[38] or damage to the VPL/ventral posteromedial nucleus/posterior thalamic nucleus system within the dorsal column-medial lemniscus (figure 2A).

The pathogenesis of CPSP could be closely associated with the glial activation and neuronal hyperexcitability that occur in response to thalamic haemorrhage in rats. Specifically, spinal monocyte chemoattractant protein-1 is released, which results in the effects above.[53] At present, the treatment of CPSP involves the use of drugs that decrease neuronal excitability,[37] indirectly supporting the central axis sensitisation mechanism. However, relative

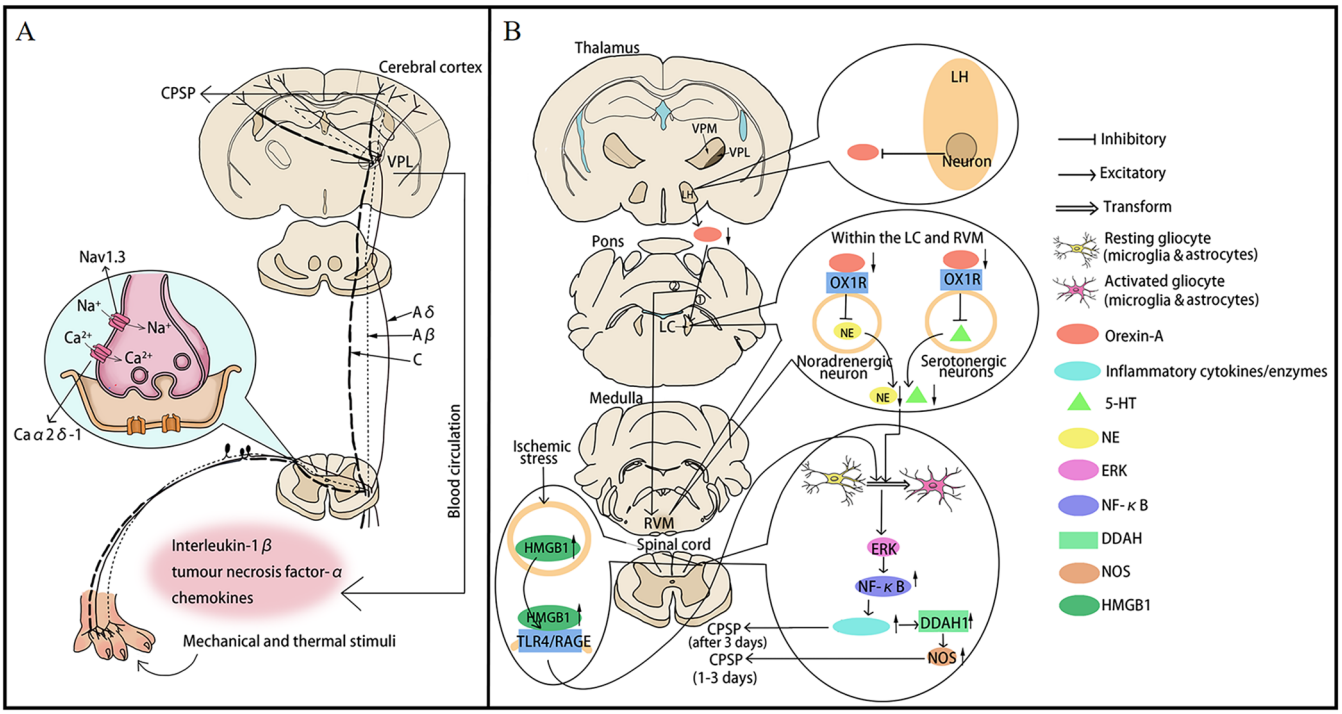

Figure 1 The pathophysiological mechanism of CPSP caused by ischaemic stroke. (A) Central sensitisation: It is a phenomenon that may give rise to hypersensitivity, resulting from functional changes in Aβ, Aδ and C fibres. These nerve fibres express specific calcium and voltage-gated sodium channels, such as Caα2δ–1 and Nav1.3, facilitating signal transmission to the thalamus-cerebral cortex. Furthermore, hyperalgesia can occur as a result of inflammatory cytokines. (B) Neuroinflammation: It is a biological process that involves glial cells and signalling pathways, such as HMGB1/TLR4/NOS and HMGB1/RAGE/NOS, which all play a crucial role in the induction of CPSP. A decrease in Orexin A expression also influences the occurrence of CPSP, which reduces the binding of Orexin A and OX1R and a corresponding reduction in the production and release of NE and 5-HT, both essential for CPSP. Microglial activation can also contribute to mechanical allodynia by upregulating DDAH1 and increasing NOS. Furthermore, ischaemic stroke can damage neurons, contributing to the induction of CPSP. CPSP, Central poststroke pain; DDAH1, $N^{(G)}$, $N^{(G)}$-Dimethylarginine dimethylaminohydrolase 1; ERK, extracellular signal-regulated kinase; 5-HT, 5-hydroxytryptamine; HMGB1, high-mobility group box-1; NE, norepinephrine; NF-κB, nuclear factor kappa-B; NOS, nitric oxide synthase; LC, locus coeruleus; LH, lateral hypothalamus; RAGE, receptor for the advanced glycation end products; RVM, rostral ventromedial medulla; TLR4, Toll-like receptor 4; OX1R, orexin one receptor; VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus.

blockers in these pathways should be developed to relieve symptoms in preclinical and clinical trials. Such drugs would be instrumental in targeting the underlying mechanisms of CPSP, thereby providing significant therapeutic benefits to patients.

Neuroinflammation

Neuroinflammation is considered a significant factor in developing chronic pain.[40] Apoptosis and inflammation in the VPL also contribute to CPSP.[27] Moreover, neuroinflammation can interact with endoplasmic reticulum stress, leading to central sensitisation.[42] A review suggests that factors, for instance, inflammasome with the NLR pyrin domain-containing 3 (NLRP3),[54] an increased microglial inflammatory response, alteration of GABAergic pathways in thalamic reticular neurons and inhibition of ventral basal interneurons may contribute to CPSP.[55] For detailed research on neuroinflammation, please see online supplemental material 6.

It is essential to recognise that neuroinflammation is a complex process that involves activating various immune cells[56] and the secretion of proinflammatory cytokines.[57–59] The resulting inflammation reaction can profoundly impact the CNS, leading to hyperexcitability and hyperalgesia.[60–62] Given the significant contribution of neuroinflammation to CPSP pathogenesis, it is imperative to develop effective strategies to mitigate this response. Enhancing researchers' comprehension of neuroinflammation's basic mechanisms and its impact on CPSP will undoubtedly lead to the development of novel therapeutic interventions and improve the stroke survivors' quality of life

Changes in the spinal cord and thalamic tract function

The STT is a group of nerve fibres responsible for transmitting pain, temperature, touch and pressure sensations from the trunk and limbs to the thalamus. The continuous activation of the STT can result in central pain, also

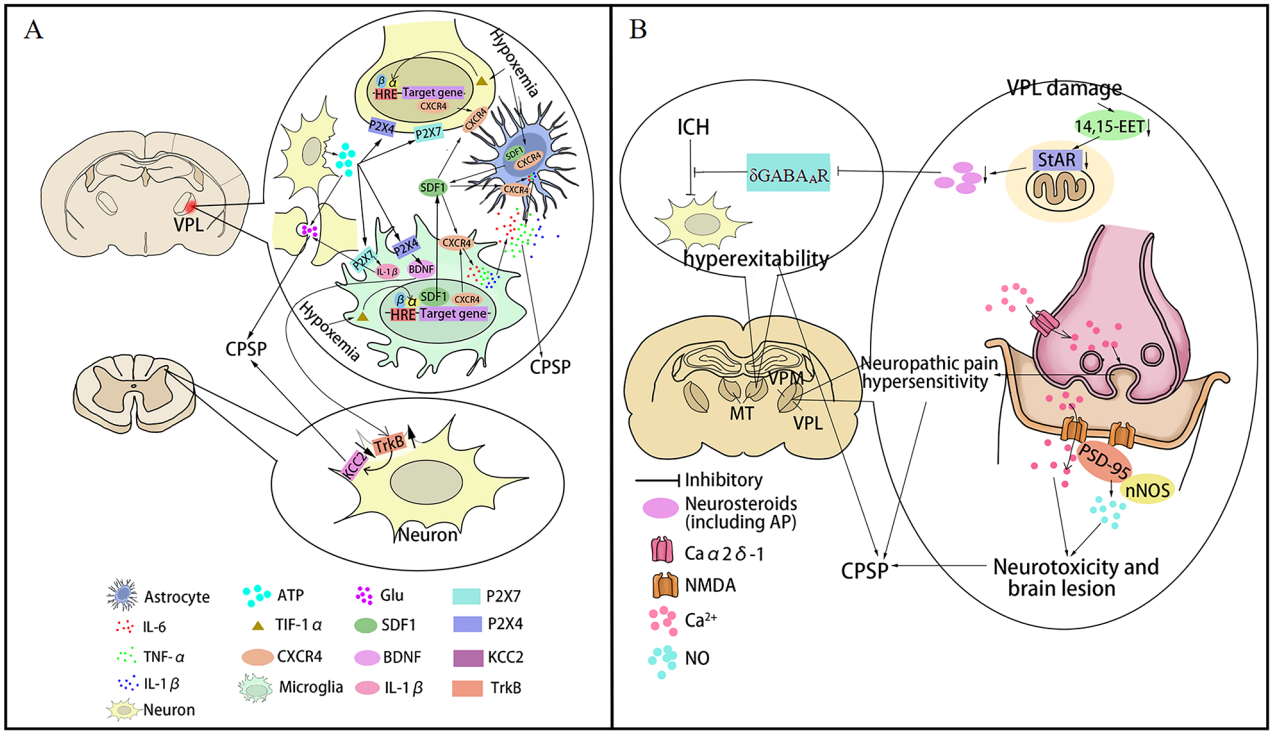

Figure 2 The pathophysiological mechanism of CPSP resulting from thalamic haemorrhage. (A) Neuroinflammation: When cells in the thalamus get damaged, ATP is released outside the cell, which triggers the activation of P_2X_7 receptors in microglia. This process leads to an increase in the levels of BDNF and IL-1β, as well as glutamate signalling. As a result, more neurons start firing frequently along the thalamocingulate pathway, causing abnormal excitability of the surviving neurons in VPL. Additionally, the interactions between microglia, astrocytes and neurons contribute to the development of CPSP through HIF-1α/SDF1/CXCR4 signalling and astrocyte-related mediators, which increases the transmission of pain-related signals. (B) Central sensitisation: It is a phenomenon where the normal inhibitory function of the thalamus is reversed due to reduced levels of 14,15-EET after a thalamic haemorrhage in VPL. This process is mediated by the StAR/AP/δGABAAR signalling, resulting in altered pain perception through Ca^{2+} influx into thalamic neurons. This process is facilitated by the activation and production of NO by the NMDA receptor, along with the presence of PSD-95/nNOS/NMDA subunits. Furthermore, overexpression of the α2δ–1 subunit increases Ca^{2+} influx and neurotransmitter release. Damage to the medial lemniscus system or partial damage to the spinothalamic tract can lead to neuropathic pain or bilateral mechanical hypersensitivity through central sensitisation/inhibition.AP, allopregnanolone; BDNF, brain-derived neurotrophic factor; CXCR4, C-X-C chemokine receptor type 4; CPSP, Central poststroke pain; HIF-1α, hypoxia-inducible factor 1α; KCC2, potassium/chloride cotransporter 2; IL-1β, interleukin-1β; MT, middle temporal area; SDF1, stromal cell-derived factor 1; StAR, acute regulatory protein steroidogenic; Po, posterior thalamic nucleus; PSD-95, postsynaptic density protein 95; TIF1, Transcriptional intermediary factor 1; TrkB, tyrosine kinase receptor B; 14,15-EET, 14,15-epoxyeicosatrienoic acids; δGABA$_A$R, δ-subunit gamma-aminobutyric acid A receptor; nNOS, neuronal nitric oxide synthase; NO, Nitric oxide; VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus.

known as CPSP.[1] CPSP implies dysfunction of the pain matrix of the brain and the thalamocortical pathway of the spinal cord and damage to the VBC in the spinal thalamocortical pathway can result in mechanical and thermal hyperalgesia,[56] contributing to the development of CPSP. Activating the NLRP3 inflammasome in the cerebral cortex can cause CPSP by decreasing descending projection fibres to the thalamus, reducing GABAergic release and increasing ventral basal neuron excitability.[55] Sensory input from the afflicted region is vital in perpetuating spontaneous and elicited pain in CPSP.[19] Peripheral nerve blocks in the painful area have been found to halt ongoing pain in CPSP, indicating that it results from maladaptive changes that cause CNS neurons to become sensitised to input from peripheral nerves. Retrograde axonal degeneration within the STT projecting system, triggered by thalamic haemorrhage, underlies subsidiary neuroinflammation and neuronal loss in the spinal dorsal horn.[63]

The other potential mechanisms

According to the proposed dynamic reverberation theory, an imbalance in the oscillatory pattern of a sensory corticothalamocortical reverberatory loop can result in central pain.[38] The STT and the thalamic cingulate gyrus pathways regulate CPSP. Please refer to online supplemental material 7 for the latest findings.

DISCUSSION AND FUTURE PERSPECTIVES

CPSP is a painful condition that occurs following primary brain injury after a stroke. It is characterised by various

anatomical, neurochemical and neurophysiological alterations to the CNS, including nerve excitability, neurotoxicity, nerve conduction pathways and neuroinflammation.[51] This debilitating complication often leads to somatosensory abnormalities and pain experienced by patients, impairing their quality of life.[8] Over the years, comprehensive researchs have been conducted, including clinical and preclinical studies, to advance the understanding of CPSP. These studies have focused on epidemiology, treatments, animal models and underlying mechanisms.

The incidence rate of CPSP varies significantly across different studies and lesion sites.[10] In clinical settings, pain management interventions such as the use of analgesics (eg, gabapentin, NMDA inhibitors, lamotrigine), neuromodulation technology (motor cortex stimulation, transcranial magnetic stimulation, deep brain stimulation) and other treatments, like acupuncture and mirror therapy, have been applied. Preclinical models have also been used to understand the underlying mechanisms of CPSP induction. These models include IS and ICH, which have been used to explore various potential mechanisms of CPSP, including central sensitisation theory, neuroinflammation, spinal cord and thalamic tract function alterations, central imbalance and other modifications.

In IS models, alterations in the functioning of Aβ, Aδ and C fibres can lead to hypersensitisation, which in turn causes mechanical changes that activate Caα2δ–1 or Nav1.3. These changes then transmit pain signals to the thalamus, subsequently sending them to the cerebral cortex. CPSP can be triggered by neuroinflammation, often activated by pathways such as toll-like receptor 4/NOS or box-1 high-mobility group/receptor for advanced glycation end products/NOS signalling due to activated glial cells and box-1 high-mobility group.[64] The binding of orexin-A and orexin 1 receptors can reduce norepinephrine and 5-hydroxytryptamine signalling, thereby decreasing microglial activation.[26] Additionally, increased NOS activity and upregulated enzymes–N(G), N(G)-dimethylarginine dimethylaminohydrolase-1 can contribute to mechanical allodynia.[65]

The central sensitisation theory in models of ICH posits that injury to the VPL nucleus decreases in 14,15-EET.[37] Acute steroidogenic regulatory proteins modulate allopregnanolone, influencing extrasynaptic δ-subunit gamma-aminobutyric acid A receptors and reversing normal thalamic inhibition signalling.[37] The interaction between PSD-95/neuronal NOS and NMDA subunits triggers NMDA receptor activation, producing NO and the influx of Ca^{2+} into thalamic neurons, ultimately influencing pain sensation.[38] Neuroinflammation occurs due to damage to the thalamic cell, which releases ATP into the extracellular space. This activates the P_2X_7 receptors in microglia, releasing brain-derived neurotrophic factor and interleukin-1β, further enhancing glutamate signalling.[43] Neuron bursting occurs due to interactions between microglia, astrocytes and neurons initiated by hypoxia-inducible factor 1α/stromal cell-derived factor 1/CXCR4 signalling.[35]

CPSP pathogenesis may include central sensitisati on, neuroinflammation and other contributory factors. Various models postulate the following underlying mechanisms: alterations in the function of the spinal cord and thalamic tract, NLRP3 activation leading to injury of the cerebral cortex, resulting in a decline in descending projection fibres to the thalamus. This decrease leads to reduced GABAergic releases and an increase in the excitability of ventral neurons. Furthermore, an imbalance occurs integrating the lateral spinal thalamic system, which comprises the lateral thalamic nucleus and the insular lobe, and the medial thalamic system, which includes the anterior cingulate gyrus. Further investigation into these mechanisms and developing effective treatments using animal models could lead to significant advancements in clinical practice.

Table 3 shows the occurrence of mechanical pain on both sides in previous studies. It is worth noting that in the studies where bilateral pain was present, the threshold for pain in the hind paw on the opposite side was lower. This difference could be due to the animal model, injury progression or location. Genotype, microglial state or oestrogen can also affect pain research outcomes. It is essential to mention that all the experimental animals used in the studies were male. Still, there are significant differences between males and females regarding pain perception. Therefore, it is essential to consider sex as a biological variable in preclinical research.[35 42 66]

Studies have not established the examination of neural circuits in animal models of CPSP. However, the thalamus has played a role in investigating neural circuits in pain. Specifically, a projection from glutamatergic neurons in the posterior thalamic nucleus to glutamatergic neurons in the primary somatosensory cortex is responsible for allodynia induced by tissue injury. In contrast, the parafascicular thalamic nucleus mediates allodynia in a depression-like state.[23] These circuits could also be related to CPSP.

To gain a deeper understanding of CPSP, research methods related to neural loops, such as optogenetics and chemogenetics, should be employed in future CPSP studies. Optogenetics, for instance, involves targeting the expression of opsins in specific cell types using viral vectors. The light of particular wavelengths is then used to modulate neuronal excitability.[67] On the other hand, chemogenetic technology employs viral vectors to deliver designer receptors activated exclusively by designer drugs, which are activated by clozapine N-oxide.[68] Optometry and chemotherapy focus on experimental interventions performed with genetic, anatomical and temporal precision.

The use of optogenetics and chemogenetics in CPSP research represents a novel and exciting approach to exploring the neural circuits involved in pain processing. These cutting-edge research methods have the potential to significantly advance our understanding of CPSP,

thereby paving the way for innovative therapeutic interventions for this challenging condition.

Considering specific issues identified in prior studies, we would like to present five points regarding suggested prospectives for future research:

1. To diagnose CPSP, physicians use a patient's history, symptoms, signs and lesion location, which require comprehensive clinical assessment scales and specific guidelines. Unfortunately, there is a lack of effective treatment for CPSP, and there is a pressing need to develop drugs and novel non-pharmacological therapies for clinical trials based on the elucidated pathomechanism of CPSP.
2. Emerging pain research methods such as optogenetics, chemogenetics and neurocircuitry present promising avenues for future investigation, but they have not yet been applied in CPSP research.
3. Animal models frequently assess mechanical pain, yet establishing an objective measurement protocol remains elusive. Consideration should be given to exploring bilateral hind paw measurements as an alternative to unilateral focus. Although hypersensitivity is observable across CPSP models, variations in the induced stimulation exist. Notably, comprehensive studies on allodynia and spontaneous pain responses are lacking in the literature. Furthermore, employing well-trained researchers is imperative to minimise observer bias in results.
4. Stimulation hypersensitivity tests may yield similar reactions in decerebrated animals. To enhance the credibility of the findings, it is suggested that tests incorporate effective supraliminal inhibition.
5. Blinding or randomisation principles are commonly employed in preclinical studies to bolster the credibility of experimental results. However, researchers must elucidate the application of these principles during the experiments.[27 28 32 34 36 41 43 69] Therefore, rigorously designed preclinical research must be conducted to enhance understanding of the pathomechanism of CPSP.

CONCLUSIONS

The study of CPSP has been subject to continuous research, which has led to progress in understanding its pathogenesis, diagnosis and treatment. A comprehensive analysis of behavioural changes, pathogenic mechanisms and drug interventions in patients and animals has identified therapeutic targets for CPSP, along with the effectiveness of several drugs. These findings provide a foundation for future CPSP treatments, which could involve a combination of pharmacological and non-pharmacological interventions to achieve optimal results. Such an approach could lead to enhanced efficacy and a more comprehensive treatment of CPSP, thereby improving the quality of life for those impacted by this condition.

In conclusion, CPSP requires a thorough comprehension of its underlying mechanisms to facilitate effective pain management. The latest advances in clinical and preclinical research have provided valuable information, including epidemiology, treatment, animal models and mechanisms. These insights offer the potential for more effective pain management strategies for patients, significantly improving their quality of life.

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