

Acupuncture for neuropathic pain: focusing on the sympathetic nerve system

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Abstract

Following peripheral nerve injury, the sympathetic nervous system responds to noxious inputs that induce or exacerbate pain. Dorsal root ganglion (DRG) sympathetic sprouting after peripheral nerve injury may induce abnormal firing of neurons. Moreover, the areas of the brain that respond to nociceptive stimuli overlap with those areas activated by the sympathetic nervous system. Acupuncture is a widely used alternative therapy for neuropathic pain. It has been demonstrated that it has positive effects on the regulation of function in the autonomic nervous system. Based on previous studies, there are several possibilities for the regulation of sympathetic nerves by using acupuncture to relieve neuropathic pain. Acupuncture may act on the brain areas of pain and the sympathetic nervous system, decrease sympathetic nerve activity during neuropathic pain, attenuate sympathetic sprouting, and reduce the abnormal firing of neurons. Further studies are required to confirm these hypotheses. This review will help to better understand the potential mechanisms of acupuncture in neuropathic pain.

Keywords: Acupuncture, Neuropathic pain, Potential mechanisms, Sympathetic nerve

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Introduction

Severe peripheral nerve damage may cause chronic pain characterized by spontaneous burning, hyperalgesia, and allodynia^[1]. Since the last century, neuropathic pain has been associated with the sympathetic nervous system and treated with sympathetic blockade^[2–4]. Under physiological conditions, primary afferent nociceptors do not exhibit catecholamine sensitivity; however, under pathological conditions, particularly after trauma, a sympathetic afferent interaction can be established at the peripheral and central levels^[5]. Experimental studies in animals have shown that injured nerves and surrounding uninjured nerves begin to express adrenergic receptors^[6–7]. Local norepinephrine binds to its receptors and activates nociceptors, thereby causing pain^[8–9]. These studies suggest that the

sympathetic nervous system is involved in the maintenance of neuropathic pain.

The fact that sympathetic nerve activation can exacerbate pain in human and animal models has prompted researchers to investigate interactions between the sympathetic and sensory systems in the peripheral nervous system^[10–11]. After peripheral nerve injury, the sympathetic nerve fibers in the dorsal root ganglia (DRG) sprout widely^[6]. When the sympathetic nerves were removed, the sprouting fibers almost entirely disappeared^[12]. Some researchers believe that pathological DRG sympathetic nerve germination is related to the spontaneous activity of primary sensory neurons and may play a key role in the occurrence and development of pain^[13]. Some recent studies have shown that sympathetic nerve block could improve certain pain conditions related to sympathetic nerve sprouting^[14–16]. Understanding the neurophysiological mechanisms by which the sympathetic nervous system invades the peripheral sensory system could promote the progress in pain treatment.

Acupuncture as a non-pharmacological strategy for nerve stimulation, is a valuable therapy for improving neuropathic pain with a low incidence of adverse events^[17–18]. The autonomic nervous system (ANS) is divided into the parasympathetic and sympathetic branches that jointly modulate whole-body physiology. Electroacupuncture at different acupoints has been reported to drive different autonomic pathways^[19–22]. In the normal and hypertensive rats, acupuncture has inhibited sympathetic outflow to the heart and reduced renal sympathetic nerve activity respectively^[23–24]. A literature review was conducted to find all published studies on acupuncture and sympathetically maintained neuropathic pain. We searched PubMed, Web of Science, and Embase for all relevant literature until March 2023. This review summarizes animal experiments and clinical observations to explore the role of the sympathetic

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nervous system in neuropathic pain and raises several possibilities for acupuncture regulation of sympathetic nerves to relieve neuropathic pain.

The mechanism of sympathetic involvement in neuropathic pain

The interaction with sympathetic nerves and primary afferent neurons

In 1986, Roberts^[25] presented a hypothesis concerning the neuronal mechanisms that sympathetically maintained pain. It was proposed that the sensitized wide-dynamic-range (WDR) neurons would continue to respond strongly to mechanical stimulation of A-fiber mechanoreceptors even after healing was complete, leading to allodynia. A-fiber mechanoreceptors were then activated by sympathetic efferent actions in the periphery. This hypothesis emphasized that gentle mechanical stimulation, mediated by A-fibers, could induce sympathetic involvement in pain. Moreover, sustained sensitization or increased gain of WDR neurons was an abnormal neuronal condition required for this hypothesis. However, later evidence showed that nociceptive stimulation of nociceptors within their receptive fields did not lower long-term mechanical thresholds and that selective C-fiber blockade did not reduce sympathetically maintained pain^[26]. Another hypothesis stated that sympathetic activity, resulting in the release of norepinephrine by postganglionic sympathetic terminals, in turn resulted in the activation of α -1 adrenoreceptors, which are expressed on primary afferent nociceptors, and the experience of pain. According to hypothesis, sympathetic-induced tonic activity in nociceptors was required to maintain central sensitization, allowing low-threshold mechanoreceptor input to central neurons, causing pain and allodynia^[26]. After nerve damage, sympathetic stimulation and norepinephrine are excitatory for a subset of skin C-fiber nociceptors, and enhance their responsiveness to tissue-damaging stimulation^[7]. This finding suggests that sympathetic innervation affects pain perception. Nociceptive and non-nociceptive mechanoreceptors are excited by sympathetic activity^[27].

The sympathetic nervous system is the main source of norepinephrine. Sympathetic hyperactivity is characterized by increased circulating norepinephrine levels. Norepinephrine is involved in the intrinsic control of pain. Injecting the adrenergic agonists and phenylephrine into the skin affected by postherpetic neuralgia (PHN) will increase the overall pain and hyperalgesia^[9]. *In situ* hybridization studies of mRNA produced by DRG have shown that the synthesis of α -adrenergic receptors increases after nerve injury^[28]. In the spared nerve injury (SNI) model, functional reinnervation is not possible and the regeneration process gives rise to a tangled neuroma. Clinical and animal experiments have shown that the exacerbated hyperalgesic effect of norepinephrine is not only attenuated by α -2-adrenergic receptor antagonists, but also attenuated by α -1-adrenergic receptor antagonists. This indicates that both α -2 and α -1-adrenergic receptors mediate the peripheral hyperalgesia *via* the sympathetic nervous system^[29–30]. In nerve-injured rats, sympathetic postganglionic activity was enhanced by glutamate receptor activation. Increased activity in the

postganglionic fibers may lead to an increased release of norepinephrine in the postganglionic efferents, which in turn enhances nociceptor activity^[31].

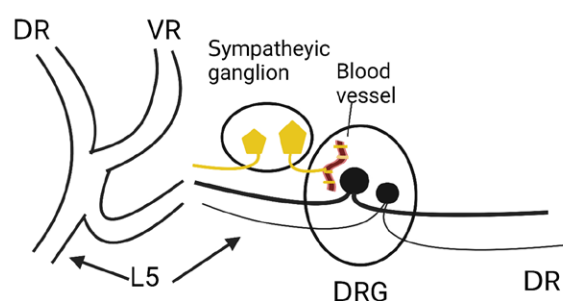
Effect of sympathetic sprouting in neuropathic pain

Light microscopy of the normal DRG revealed that tyrosine hydroxylase (TH)-positive fibers were limited to the perivascular plexuses (Figure 1A). However, in addition to the perivascular plexus, many additional TH-positive fibers were found throughout the ganglion after nerve injury, such as in the interstitial space of the DRG cellular region, sometimes forming several layers of complete wrapping around the DRG neuron (Figure 1B)^[32]. TH-positive fibers were observed in the neuroma at the ligation site at this time point^[33]. Earlier studies have shown that sympathetic stimulation or adrenergic agonists activate neuroma sensory fibers in neuromas that form after a sciatica transection^[34]. The use of lidocaine in the early stages of nerve damage can significantly reduce sympathetic nerve sprouting. Repeated lidocaine treatment has long-term effects on patients with neuropathic pain^[15].

Sympathetic sprouting in several animal neuropathic pain models

Sympathetic nerves sprout into DRG in two ways. One is a lateral branch sprouting from the undamaged perivascular plexus that directly targets the DRG. The other

A Normal Nerve



B Nerve Lesion

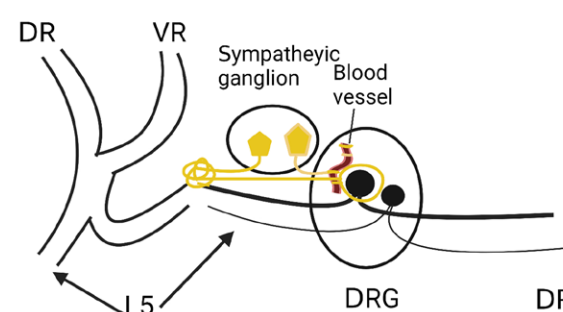


Figure 1. Schematic illustrating the pattern of sympathetic and sensory neurons in uninjured ganglia (A) and peripheral nerve injury (B) in wild-type mice, as well as the proposed underlying mechanism of sympathetic invasion of the DRG (A, B). Normally, sympathetic fibers are only associated with the blood vessel of DRG (A). Sympathetic invasion of the DRG as a result of perivascular axon sprouting or sympathetic regeneration at nerve injury (B). DR: dorsalis radix; DRG: dorsal root ganglion; L5: lumbar 5; VR: ventralis radix.

is regeneration sprouting, in which sympathetic nerve regeneration failed to reach the target site of growth through the damaged areal; therefore, targeted DRG sprout^[12]. The first situation occurs after a peripheral nerve injury. The second occurs with a spinal nerve ligation injury^[35]. Following sciatic nerve transection or spinal nerve lesions, sympathetic axons invade the DRG where they sometimes form pericellular baskets around mostly large-diameter DRG neurons, a possible anatomical substrate for sympathetically maintained pain^[6,10,34,36].

Sympathetic sprouting in the DRG has been studied in various animal models of neuropathic pain^[37–38]. In the spinal nerve ligation (SNL) model, sympathetic nerve fiber density in DRG increased 1 week after surgery^[39], whereas in chronic constriction injury (CCI), DRG sympathetic nerve fiber density increased slightly 20 weeks after surgery^[38]. An increase in TH-positive fibers was observed in the DRG 2 weeks after SNI, and the TH-positive fiber density continued to increase thereafter. However the increase was observed as fibers, but not as basket cells formations around neurons as seen in some other neuropathic pain models. Combined with the results obtained 2 weeks after SNI, the number of sprouting sympathetic fibers in DRG gradually increased at 6 weeks after SNI. Part of the fiber envelops the neuron, and basket-like structures have been observed around DRG neurons at 6 to 8 weeks postoperatively^[40]. The whole-cell patch clamp experiment on DRG of rats at 40 days after SNI found that norepinephrine could increase the excitability of large and medium neurons^[14]. As suggested above, there was a different timing of sprouting after different types of injury: sympathetic invasion of the DRG occurred 2 to 8 weeks to occur following a sciatic nerve injury, while the sympathetic invasion of the DRG occurred within a matter of days following L5 spinal ligation. These reports demonstrated that the SNL model induced earlier and more robust sympathetic sprouting than the CCI and SNI models. These differences may be attributed to different mechanisms underlying sympathetic sprouting into the DRG after distal and proximal nerve injuries, with proximal lesions inducing more pronounced sympathetic sprouting in the DRG than distal lesions^[41]. In addition, sympathetic fiber sprouting in the axonal DRG may have different origins. In SNL rats, most of the fibers originate from the spinal nerve roots or fiber bundles, whereas in rats with partial sciatica, sympathetic fibers often enter the DRG along with the vascular protrusions^[38]. Another obvious cause of this disparity is the difference in the number of injured DRG neurons between the animal models. All neurons in the L5 DRG were injured in the SNL model, whereas only a few were injured in the CCI and SNI models^[41]. Although there are differences in sympathetic nerve sprouting between these neuropathic pain models, sympathetic axons invade the DRG and sympathetically dependent pain develops^[35].

The mechanisms of sympathetic sprouting

Studies suggest that Wallerian degeneration is important for sympathetic sprouting into the DRG^[42]. CCI-induced sympathetic sprouting was undetectable in a mutant strain of mice (Wld^s) in which Wallerian degeneration was impaired compared with that in wild-type mice^[43].

After sciatic nerve injury, Wallerian degeneration occurs in the distal stump and consists of a series of processes, including axonal degeneration, myelin degeneration and disintegration, Schwann cell proliferation, infiltration of macrophages and mast cells, and axonal and myelin debris clearance^[44–45]. These cells produce several growth factors and cytokines, many of which provide an environment favorable for the regrowth of severed axons. Some factors produced in degenerating nerves are some which may act on sympathetic neurons and in some cases induce the sprouting of sympathetic axons^[46]. However, the most studied sprout-inducing factor produced in the degenerating stump is the nerve growth factor (NGF), whose mRNA and protein levels increase following nerve injury. The intact axons left in the degenerating stump transport NGF from the zones of Wallerian degeneration in the nerve stump to the DRG, where it induces sympathetic sprouting^[42,47]. A similar study found that the tyrosine kinase-A (TrkA) mediated the uptake of NGF into spared axons within the degenerating distal stump^[48]. However, sympathetic axons in Wallerian degeneration-deficient Wld^s mice, sprout after SNL to the same extent as in control wild-type mice^[34]. This suggests that Wallerian degeneration does not play a critical role in the sprouting of SNL, which may be caused by the fact that SNL results in the axonal excision of all sensory neurons in the L5 ganglion, leaving none in contact with an NGF-enriched distal stump. Previous research has shown that treatment with NGF antiserum prevents the collateral sprouting of sympathetic axons, but it does not affect sympathetic nerve regeneration^[49]. Therefore, the sprouting of CCI was probably collateral sprouting from uninjured sympathetic axons, and the sprouting of SNL was direct sprouting from injured sympathetic axons.

Sprouting and spontaneous neuronal activity may be mutually reinforcing: sympathetic sprouting functionally increases spontaneous activity, and blocking neuronal activity reduces sympathetic sprouting. It has been observed that spontaneous activity occurs after nerve injury, often at the same time or even before sympathetic sprouting. Furthermore, experiments have shown that the manipulation of spontaneous activity can affect sprouting, indicating a potential link between these two processes^[50]. However, this study did not definitively rule out the possibility of an indirect or bidirectional relationship between sympathetic sprouting and spontaneous neuronal. Sympathetic sprouting preferentially targeted Na_v1.6-positive neurons. Local knockdown of Na_v1.6 in DRG markedly reduced sympathetic sprouting into the ligated sensory ganglion. It blocked abnormal spontaneous activity and other measures of hyperexcitability in myelinated neurons in the ligated sensory ganglion and suppressed mechanical pain behaviors induced by SNL^[51]. Another study found that the α -antagonist administered around the DRG could suppress neural plastic changes in the early phase after nerve injury^[52].

Sympathetic sprouting and abnormal firing of neuronal

The sympathetic axons sprout into the DRG, which forms abnormal terminal arborizations or “baskets” surrounding preferentially large -diameter DRG neurons. Large- and medium-diameter DRG neurons often exhibit

high-frequency spontaneous activity following peripheral axonal injury^[14]. Under physiological conditions, pain is conducted by afferent small-diameter unmyelinated C fibers as well as some medium-diameter lightly myelinated A δ , of which cell bodies of these primary afferent neurons are located in the DRG. However, some studies have pointed out that under pathological conditions, fast-conducting myelinated A-fiber ectopic discharge in DRG neurons is a key driver of neuropathic pain^[53–54]. The sympathetic nervous system is directly connected to the somata of DRG neurons, where sympathetic efferent signals are transmitted to secondary afferent neurons through DRG neurons. A previous study observed a correlation between sprouting and spontaneous activity at the level of individual neurons^[50].

Peripherally administered norepinephrine further exacerbates hyperalgesia in rats with spinal nerve injury^[31]. Detection of mRNA revealed the presence of multiple types of α -adrenoceptors in the DRG of primary afferent neurons. These α -adrenoceptors potentially mediate the peripheral actions of norepinephrine, which is locally released from postganglionic sympathetic nerve fibers^[55]. A recent study showed that post-injury sympathetic fibers in the DRG mainly surrounded large neurons, and electrophysiological results indicated that norepinephrine could increase the excitability of large neurons on the injured side. The novel α 2A-adrenergic receptors were involved in the biological effects of sympathetic nerve fiber sprouting within DRG^[14]. In another recent study, researchers employed *in vivo* imaging of DRG neurons and discovered clusters of adjacent DRG neurons firing synchronously following peripheral nerve injury, which correlated directly with nerve injury-induced spontaneous pain. Furthermore, they demonstrated that cluster firing was triggered by the activity of sympathetic nerves that sprout into DRG after injury. Norepinephrine is a key neurotransmitter bound to α 1 receptors that mediates this unique firing^[16].

The same brain areas of the sympathetic nervous system and pain

The cortical areas of the brain that respond to nociceptive stimuli overlap with the areas activated by the sympathetic nervous system. This interaction is primarily mediated by the anterior cingulate cortex (ACC), insular cortex (IC), prefrontal cortex (PFC), and amygdala; fittingly, μ opioid receptors are abundant in these areas^[56]. The IC, ACC, PFC, amygdala, and hypothalamus are the most important parts of the primary fore-brain autonomic area^[57]. Moreover, functional MRI has demonstrated distinct alterations in brain structure and activity that occur with chronic pain; reductions in gray matter volume in the ACC, IC, and PFC; and abnormal activation in the ACC, PFC, and amygdala in response to pain^[58]. The nociceptive stimulus increases in the contralateral spinothalamic pathway, providing a direct connection to the brainstem through the spinoreticular and spinomesencephalic pathways and to the hypothalamus through the spinohypothalamic pathway^[59]. The posterior and lateral hypothalamic areas are involved in autonomic control and pain modulation^[60]. In addition, neurons located in the dorsal horn project to the nucleus

tractus solitarius (NTS) and parabrachial nuclei (PBN), which are involved in pain perception and autonomic nerve regulation^[61]. The descending system regulates pain and creates a regulatory effect by contributing aminergic neurotransmitters^[56]. The hypothalamus, amygdala, and periaqueductal gray (PAG) regulate the tonic effect from the brain to the spinal cord level in the descending pain control pathway^[59]. The PAG receives afferents from the central and peripheral nervous systems and modulates the descending pain pathway. The lateral and dorsolateral PAG initiate fight responses associated with tachycardia and hypertension. It mediates sympathoexcitatory responses that activate sympathetic preganglionic neurons that control cardiovascular effectors^[62].

The inflammatory effects of sympathetic innervation

In immune organs, sympathetic innervation is often anti-inflammatory; however, the local effects in other tissues may be proinflammatory^[22,63]. Following peripheral nerve injury, sterile inflammation develops in the sympathetic nervous system and DRG with axons that project into the damaged nerve trunk. Macrophages and T-lymphocytes invade these ganglia where they are believed to release cytokines that lead to hyperexcitability and ectopic discharge, possibly contributing to neuropathic pain^[64–65]. In rats with sciatic nerve injury, the removal of relevant lumbar sympathetic activity caused less DRG inflammation than sham sympathectomy^[65]. In both models of nerve injury and inflammation, such as the SNL, SNI, and peripheral foot inflammation models, microsympathetic resection, which cut the gray rami containing sympathetic postganglionic axons where they enter the L4 and L5 spinal nerves, reduces the density of macrophages in the sensory ganglia and peripheral nerves and suppresses mechanical hypersensitivity^[29,66]. A study on the effects of microsympathetic resection on the cytokine profile in the locally inflamed DRG showed that microsympathetic resection reduced type 1 inflammatory cytokines and increased type 2 cytokines, countering the effects of DRG inflammation^[66]. In the L5 spinal nerve ligation model and L5 DRG local inflammation model, neuroinflammation of the lumbar sympathetic ganglia (SG) and moderate neuronal excitability were observed. Surprisingly, inflammation and electrophysiological changes in the SG of the SNL model were more severe than those in the local inflammation model. Except for the macrophage response in SG, the increase in T-cell response, the satellite glial response, and neuronal excitability were greater after L5 spinal nerve ligation^[67]. It was concluded that sympathetic nerve fibers in the gray branch of L4/L5 were proinflammatory. Immune cells in this situation downregulated the expression of β 2-adrenergic receptors and upregulated the expression of α 1-adrenergic receptors^[68]. Nerve lesion activates immune cells. While β 2 receptors are downregulated, α 1 receptors are upregulated on immune cells. Activation of α 1-receptors induces the release of proinflammatory cytokines, which in turn activate nociceptors. After nerve lesions, the expression of functional adrenoceptors, which were physiologically absent in peripheral nociceptors, was activated. Activation of the sympathetic nerves induce the release of norepinephrine, which might then directly activate α 1 and

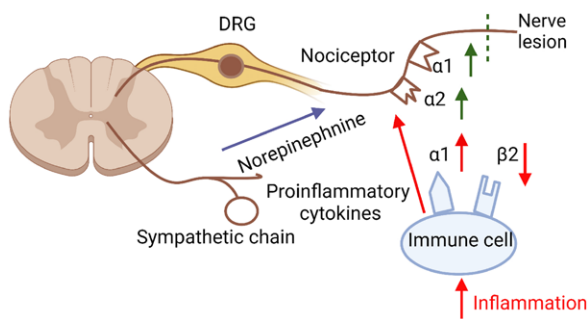


Figure 2. Nerve lesion activates immune cells. Activation of $\alpha 1$ -receptors on immune cells induces the release of proinflammatory cytokines, which subsequently activate nociceptors. Conversely, $\beta 2$ receptors are downregulated on immune cells. Following nerve lesions, there is an increase in the expression of adrenoceptors $\alpha 1$ and $\alpha 2$, which are not normally found on peripheral nociceptors. The activation of sympathetic nerves leads to the release of norepinephrine, which can directly activate the $\alpha 1$ and $\alpha 2$ receptors on these afferent fibers. In the diagram, the red arrow represents the immune response, the green arrow represents the activation of adrenoceptors $\alpha 1$ and $\alpha 2$, and the grey arrow represents the release of norepinephrine. DRG: dorsal root ganglion.

$\alpha 2$ receptors on these afferent fibers (Figure 2)^[69]. This further confirms that sympathetic nerves affect pain through immune functions.

Possible mechanisms for the regulation of sympathetic nerves by acupuncture to relieve neuropathic pain

Acupuncture as an alternative therapy has been widely used for the treatment of neuropathic pain such as peripheral neuropathic pain, prosopalgia, and postherpetic neuralgia^[70–72]. Acupuncture has a benign effect on the ANS regulating function^[20,73–74]. In rats with hypertension, heart failure, or pain, acupuncture tends to suppress sympathetic nerves. However, the potential mechanisms of acupuncture for neuropathic pain, based on pathological pain mediated by sympathetic nerves, remain unclear. In the following sections, we analyze several possible mechanisms to explore them.

Acupuncture may decrease sympathetic nerve activity during neuropathic pain

Early studies have shown that acupuncture inhibits sympathetic activity, and that such inhibition plays a favorable role in acupuncture analgesia^[75]. EA increased pain thresholds in rats and decreased serum norepinephrine levels^[76]. Several studies have revealed the crucial role of acupuncture in controlling excessive sympathetic excitation during pain and other diseases. Acupuncture has a beneficial effect on the ANS in patients with migraine, with better clinical outcomes. It manifests mainly as a reduction in the low-frequency power of heart-rate variability due to a reduction in sympathetic nerve activity^[77]. Short-term low-frequency EA of the ST36 acupoint had inhibitory effects on the cardiovascular system by decreasing sympathetic nerve activity^[78]. In patients with hypertension, EA inhibited cardiovascular sympathoexcitatory neurons by inhibiting the activity of premotor sympathetic neurons in the rostral ventrolateral medulla (RVLM)^[79]. In addition, EA significantly decreased renal

sympathetic nerve activity, inhibited cardiac sympathetic afferent reflexes, and lowered blood pressure in rats with chronic heart failure^[80]. Thus, we speculate that acupuncture may inhibit abnormal activation of the sympathetic nervous system in patients with neuropathic pain, which may have a positive effect on pain relief.

Acupuncture may attenuate sympathetic sprouting

EA at ST36 relieved colitis-induced hyperalgesia *via* inhibiting sympathetic sprouting into the DRG and surface neurogenic inflammation^[81]. Both EA and guanethidine attenuated visceral and referred hind paw hyperalgesia by inhibiting the overexpression of TH-positive neurons and fibers in the sixth lumbar (L6) DRG^[82]. Acupuncture treatment postponing Wallerian degeneration effectively protected the neurons and facilitated recovery^[83]. NGF is a powerful and selective endogenous neurotrophin for sympathetic and sensory neurons^[84]. This process has been shown to contribute to sympathetic sprouting^[85]. Acupuncture may reduce sprouting by interfering with neurotrophin expression. Pharmacological and molecular studies have shown that the hyperalgesic actions of NGF may be, in part, a consequence of an increase in the sensitivity of TrkA-expressing peripheral terminals of nociceptors^[86–87]. In addition, TrkA mediates the uptake of NGF into spared axons within the degenerating distal stump, which induces sympathetic nerve sprouting. In rats with diabetic neuropathic pain, thermal hyperalgesia was corrected by EA, and the parallel increase in NGF and TrkA in the spinal cord was counteracted by EA^[88]. EA effectively modulates NGF signaling, which not only affects sensory function but also has a neuroprotective value for sensory neurons^[89]. Acupuncture stimulation suppressed NGF overexpression in the diseased state, indirectly demonstrating that EA inhibited hyperactivity in the sympathetic nervous system^[90]. Therefore, we hypothesized that EA might inhibit NGF and sympathetic nerve sprouting, which would promote the analgesic effect of EA.

Acupuncture may reduce the abnormal firing of neurons

As mentioned above, WDR neurons continue to sensitize for a period of time after peripheral nerve injury, so that even after healing is complete, they continue to respond strongly to mechanical stimulation of A-fiber mechanoreceptors, resulting in allodynia or ectopic pain. However, the spontaneous firing of WDR neurons is inhibited and pain relief is offered by EA^[91–92]. EA with a fast onset might rapidly reduce C-fiber-evoked WDR neuronal discharges within 60 seconds^[93]. Peripheral stimulation activates multiple types of primary afferent nerves (PANs). Huo et al^[94], suggested that the analgesic acupuncture signal from the peripheral to the central nervous system appeared to be mediated primarily by the large-diameter myelinated A β - and A δ -fibers of PANs, which was the same neuron type as the sympathetic sprouting wrapped neuron. If acupuncture stimulates abnormally excited, large-diameter neurons, it affects the transmission of pain signals, which may reduce hyperalgesia. Future studies will need to use techniques such as *in vivo* electrophysiology or neuronal calcium

imaging to verify the effects of acupuncture on these neurons. The transient receptor potential vallinoid 1 (TRPV1) channel, a nonselective cation channel mainly expressed in nociceptive primary sensory neurons, is activated by various ligands to cause intracellular Ca^{2+} elevation, trigger action potentials, and transmit nociceptive signals^[95]. EA reduced TRPV1 channel overexpression and functional activity in DRG neurons in rats with chemotherapy-induced peripheral neuropathy^[96]. It demonstrates that EA alleviates neuropathic pain *via* mechanisms that possibly inhibit TRPV1 upregulation and neuronal firing in DRG. Therefore, acupuncture may indirectly affect sympathetic excitability and sprouting by reducing abnormal firing of neurons *via* both peripheral and central mechanisms.

Acupuncture acts on the brain areas of pain and the sympathetic nervous system

There is a strong connection between pain processing and the central autonomic nervous network. Many of these regions are pain-regulatory circuits that regulate nociceptive processing and pain by projecting to the spinal cord and trigeminal ganglia. In turn, pain-related regions, including the IC, ACC, PAG, and PBN through their connections to the hypothalamus and brainstem, finally generate sympathetic responses^[97]. Manual acupuncture on bilateral GB30, which downregulates extracellular signal-regulated kinase activation in ACC neurons, can relieve pain and pain-related anxiety. According to a systematic review of resting-state fMRI, genuine acupuncture resulted in significantly enhanced connectivity between the PAG, ACC, left posterior cingulate cortex, and right anterior insula, compared with sham acupuncture^[98]. Some studies had shown that acupuncture could adjust the hypothalamus, the NTS, and RVLM brain areas^[99–101]. NTS neurons integrate a large amount of sensory information with inputs from other brainstem and higher autonomic nuclei and regulate autonomic nerves. EA could regulate NTS-related neurons through a polysynaptic crosstalk mechanism that mediates analgesia in rats^[102]. Moreover, one study elucidated that the central mechanism of acupuncture regulating the cardiovascular reflex involved the NTS and RVLM in rats with pain^[101]. The RVLM is a key control center for sympathetic nervous output^[103]. Limbic systems such as the IC and ACC are essential for the regulation of painful emotions. These autonomic cortical regions form a complex pain regulatory network with autonomic nuclei related to descending inhibition systems, such as the PAG, NTS, RVLM, and dorsal reticular nucleus, to participate in acupuncture analgesia and alleviate pain-related emotions^[104]. Several studies have shown that EA can reduce sympathoexcitatory responses, in part, through its effect on multiple brain regions, such as the arcuate nucleus in the hypothalamus, PAG, and RVLM and raphe nuclei in the brainstem, among others^[105–107]. However, it is unclear whether acupuncture or EA alleviate pain by regulating the sympathetic nervous system *via* these nuclei, and further research needs to be conducted in the future.

Discussion

Treatment and clinical management of neuropathic pain are among the most vexing challenges currently faced by primary care providers^[108]. Integrative treatments such as acupuncture are increasingly used in pain clinics and are gaining acceptance among the US public and academic communities^[109]. In recent years, preclinical investigations of the mechanisms of acupuncture in neuropathic pain have increased. Modulation of sensory input occurs in primary afferent neurons and the spinal dorsal horn during acupuncture. Acupuncture may inhibit neuronal activity caused by neuropathic pain by reducing pain-related ion channel and protein kinase activation. In addition, EA reduced the release of inflammatory factors such as tumor necrosis factor α and interleukin-1 β , suppressing the neuronal excitability and inflammatory response^[71]. Acupuncture as a non-pharmacological treatment has the potential to activate the descending pain control system by increasing the levels of spinal or brain 5-hydroxytryptamine, and opioid peptides^[110]. The types of endogenous opioid peptides is shown to be influenced by EA frequency. The 2- and 100-Hz EA reduced mechanical nociceptive hypersensitivity separately through activation of μ -, δ -opioid receptors, and kappa-opioid receptors^[111].

The relationship between neuropathic pain and the sympathetic nervous system has gradually been confirmed^[16,112–113]. Sympathetic excitation or abnormal sprouting of sympathetic fibers may be involved in pain transmission; therefore, sympathetic blockade is recommended. While many reports have focused on the autonomic nervous regulation of acupuncture^[20,22,114–116], there is little evidence for the regulation of sympathetic nerves by acupuncture in the presence of pain. In this paper, we summarized the mechanisms of sympathetically maintained pain, including the interaction between sympathetic nerves and primary afferent neurons, the effect of sympathetic sprouting on neuropathic pain, and the overlap of brain areas responding to nociceptive stimuli with areas activated by the sympathetic nervous system. Acupuncture can directly and indirectly regulate these mechanisms. Therefore, it may alleviate neuropathic pain by altering the sympathetic nerve activity.

The vagus nerve, a key component of the ANS, has somatic analgesic potential. ANS imbalance with an increase in sympathetic activity is usually accompanied by a decrease in vagus nerve activity^[117]. In a rat model of vincristine-induced pain, decreased vagal activity aggravates the severity and time course of painful polyneuropathy^[118]. Stimulation of the auricular branch of the vagus nerve produced an antinociceptive effect in rat models of acute pain^[119]. Zhang et al^[29,66] showed that sympathectomy reduced the macrophage density in the sensory ganglia and peripheral nerves, suppressing the inflammatory response in SNI and SNL models. Acupuncture modulates the immune system to relieve inflammation-induced pain by stimulating the ANS^[120–121]. According to traditional Chinese medicine, “acupuncture is believed to restore the balance between *yin* and *yang*.” This interaction might be similar to the way that acupuncture modulates the imbalance between parasympathetic and sympathetic activities^[110]. The parasympathetic and

sympathetic nervous systems antagonize each other; therefore, parasympathetic activation may inhibit sympathetic activity^[122].

When acupuncture was applied to an abdominal location, it increased the activity of efferent fibers in gastric sympathetic nerves, which inhibited gastric motility^[123]. A 3.0 mA EA stimulation at the abdominal ST25 acupoint or hind limb ST36 acupoint was able to drive the spinal-sympathetic axis, producing anti-inflammatory effects when EA stimulation was applied before lipopolysaccharide exposure^[22]. During EA of 2.0 mA, both vagus and sympathetic nerve discharges increased in normal rats, with a much higher frequency of vagus nerve discharge than sympathetic discharge^[124]. However, low-intensity electrical vagal stimulation that activated vagal afferent Aδ fibers reduced visceral pain more than high-intensity electrical vagal stimulation of C fibers^[125]. Moreover, acupuncture could reduce sympathetic hyperactivity in patients with hypertension and arrhythmias^[79–80]. Therefore, activation or inhibition of the sympathetic nervous system by acupuncture may depend on the acupoint, stimulation intensity, and disease state^[126].

Anatomically, the brain structure that regulates the ANS consists of autonomic centers in the brainstem as well as supratentorial brain regions involved in autonomic regulation, such as the subgenual and dorsal parts of the anterior cingulate, insula, amygdala, and hypothalamus^[127]. The hypothalamus is the higher-order center of the ANS. As the site of autonomic regulation, the hypothalamus has been shown to be involved in the pathway of EA-attenuating sympathetic activity^[128]. The RVLM, which is an important part of the sympathetic efferent limb of cardiovascular reflex activity, mediates the central control of autonomic function^[129]. Injection of L-glutamate into the NTS in awake rats produced pressor responses and bradycardia similar to peripheral chemoreceptor activation, which might have been induced via the NTS-RVLM pathway^[130]. Two Hz EA stimulated at ST 36 significantly increased the number of excited NTS neurons and spike frequency^[131]. In summary, most current studies on the regulation of the ANS by acupuncture focus on the peripheral, RVLM, NTS, and other downstream central nuclei. Acupuncture acts as a somatosensory afferent to regulate higher pain centers such as ACC and IC, which are higher centers of autonomic nervous regulation. Therefore, acupuncture may further regulate sympathetic nerves by regulating the hypothalamus, NTS, RVLM, and other downstream central nuclei through higher central nuclei such as ACC and IC; however, this needs further experimental verification.

Conclusions

The sympathetic nervous system and pain interact at various levels of the neuraxis. For physicians to manage neuropathic pain, it is crucial to consider these factors, especially in patients with sympathetic symptoms. Acupuncture is increasingly being used as an integrative or complementary therapy for pain management. Various lines of evidence have shown that acupuncture alleviates the diseases and symptoms associated with autonomic disorders. Both laboratory and clinical findings suggest the need for further investigation into the

role of the sympathetic nervous system in acupuncture techniques and specific acupoints for the management of neuropathic pain.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Xin Ma wrote the original draft. Hongping Li and Cunzhi Liu edited the manuscript. Wen Chen and Yiming Fu draw the manuscript. All authors read and approved the final manuscript.

Ethical approval of studies and informed consent

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Data availability

All data generated or analyzed during this study are included in this published article.

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