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Review

Exploring the spatial effects of acupuncture analgesia

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ABSTRACT

In recent years, researchers have conducted in-depth research on the mechanism of acupuncture analgesia and made many important discoveries. These studies indicate that acupuncture can effectively alleviate pain and improve pain mood. This article summarizes the mechanisms of acupuncture treatment for different types of pain, including peripheral input effects, spinal cord response effects, and brain integration effects. It provides support for the idea that acupuncture analgesia is not a local reaction through a single pathway, but a holistic effect with network connections. However, it is unclear whether the peripheral, spinal cord, and brain levels have equal analgesic effects during the analgesic process, or which level dominates the analgesic effect; The issue of whether the dominant analgesic level is consistent for different types of pain has not been resolved and further experimental research is needed.

Introduction

Pain is a common clinical symptom originating from injurious or potentially injurious stimuli, resulting in unpleasant subjective and emotional experiences that embody complex physiological and psychological interactions. Acupuncture analgesia has a long history as a unique Chinese medicine treatment, which has been documented in traditional medical literature such as the Yellow Emperor's Classic of Internal Medicine. Modern studies have shown that acupuncture can effectively treat a wide range of pain symptoms. The results of literature studies in recent years also show that pain-related acupuncture studies occupy a considerable proportion in the literature(Han and Ho, 2011). It has become one of the key areas of acupuncture research due to its long-lasting and extensive analgesia and rapid onset of action. Pain can be categorized into three types: arthralgia, neuralgia, and visceral pain. Arthralgia is caused by tissue damage or inflammation, accompanied by fever, redness, swelling and dysfunction; neuralgia originates from the damage or abnormal function of the nervous system, usually accompanied by tingling or burning sensation, and may be numbness; visceral pain is related to the damage or dysfunction of internal organs, which is manifested as a deep, dull ache or a feeling of pressure, which is difficult to locate accurately. Researchers have explored the role of acupuncture in pain mechanisms through a variety of animal models, and this paper aims to synthesize these studies to establish a spatial mechanism network of acupuncture analgesia, deepen the understanding of its analgesic effect, and provide ideas for exploring more effective acupuncture analgesic methods and treatment strategies in the future. The animal models involved in this paper are listed below (Table 1).

In this study, we collected the literature on the mechanism of acupuncture for pain treatment from PubMed, SCI-hub and China Knowledge Network (CNN) databases, and filtered the literature related to the topic by searching through a combination of subject terms and free terms and adjusting to different search systems. In the analysis, the focus was on the spatial effects of acupuncture on joint pain-related models. Search subject terms included acupuncture, electro-acupuncture, pain, inflammatory pain, visceral pain, and neuropathic pain. Literature was screened by title or abstract to exclude literature that was clearly inconsistent with the topic and duplicated.

Spatial effects of acupuncture on models related to joint pain

Inflammation is one of the main causes of joint pain. When the body is infected, injured or irritated, an inflammatory response occurs in the joint tissues, leading to the release of inflammatory mediators that

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Table 1
pain model.

Joint pain model	Neuropathic pain model	Visceral pain model
Complete Freund's adjuvant induced arthritis(Wu et al., 2014)	Hronic compressive injury of the sciatic nerve(Yonghui et al., 2022)	Intracolonic injection of acetic acid(Chen et al., 2021)
Capsaicin induced arthritis(Kim et al., 2009)	Postherpetic neuralgia(Li et al., 2019)	Inflammatory bowel disease(Hou et al., 2019)
Carrageenan induced arthritis(Yang et al., 2011)	Diabetes peripheral neuropathy(Fei et al., 2020)	Irritable bowel syndrome(Chen et al., 2023)
Formaldehyde induced arthritis(Yu et al., 2020)	Spinal cord injury(Lee et al., 2013)	Ulcerative colitis(Chen et al., 2021)
Formalin induced arthritis(Liu et al., 2019)	Neuropathic pain induced by chemotherapy drugs (Hong et al., 2018)	Chronic anorectal pain (Yusha et al., 2023)
White rabbit fever model (Wang et al., 2017)	L5-L6 spinal nerve ligation(Sun et al., 2004)	
Knee osteoarthritis(Jingjie et al., 2021)	S3-S4 spinal nerve right caudal superior trunk resection(Hwang et al., 2002)	
Spontaneous osteoarthritis(Wang et al., 2020)	Neuropathic pain in cervical spondylotic radiculopathy(Weidi et al., 2023)	
Collagen induced arthritis(Li et al., 2015)	Thalamic pain(Ma et al., 2022)	

stimulate the nociceptive nerve endings, thus causing pain sensations. Inflammation also leads to edema and compression of local tissues, further aggravating joint pain. Acupuncture can promote local blood circulation, increase the supply of oxygen and nutrients to the tissues around the joints, promote the absorption of inflammation and the removal of metabolic products, thus reducing pain.

Peripheral afferent effect

Pain is usually caused by local tissue injury, which activates peripheral pain receptors and generates pain signals. Acupuncture delivers acupuncture analgesic messages and reduces peripheral pain signaling by stimulating connective tissues, mechanosensitive channels, activating mast cells, and modulating adenosine, cannabinoids, and inflammatory mediators and immune cells, among other pathways.

Connective tissue pathway

Acupuncture acts on acupoints to cause local connective tissue deformation, and Langevin et al. showed(Langevin et al., 2002; Langevin et al., 2007; Langevin et al., 2006) that acupuncture stretches the scaffolding of the lamellar network formed by local connective tissue to form a helix centered on the body of the needle, and at the same time induces cytoskeletal remodeling of connective tissue fibroblasts. Other studies have also confirmed (Li Cheng and Tiehan, 2015) that the acupuncture twisting maneuver changed the skeleton structure of fibroblasts of subcutaneous tissue in the acupuncture point area. The connective tissue changes and fibroblast cytoskeletal remodeling play an important role in acupuncture analgesia. For example, acupuncture of bilateral Yanglingquan (GB34) can significantly activate serine/threonine kinases in fibroblasts that regulate the actin cytoskeleton and mediate the analgesic effect of acupuncture (Park et al., 2024). In addition, acupuncture at the Quchi acupoint reduced serum levels of inflammatory factors in New Zealand white rabbits, but the anti-inflammatory and analgesic effects of acupuncture were reduced after local injection of collagenase at the acupoint(Wang et al., 2017).Yu et al. found that disruption of the collagen fiber structure at the Zusanli(ST36) in rats significantly reduced the analgesic effects of acupuncture (Yu et al., 2008).

Mechanosensitive channels

Mechanosensitive channels are widely distributed in nerve fibers and non-neural cells of human body, including transient receptor potential (TRP) channels, acid-sensing ion channel 3 (ASIC3) and Piezo channels, etc., which are able to sense mechanical stimuli and convert them into biological signals. into biological signals, which play an important role in acupuncture analgesia (Yamamoto et al., 2011).

The study of Wu et al. (2014) showed that acupuncture of Zusanli (ST36) after injection of Complete Freund's Adjuvant (CFA) in the right hindfoot was able to relieve thermal hyperalgesia in rats. Local injection of the transient receptor potential vanilloid subtype 1 (TRPV1) agonist capsaicin at the acupoint reproduced the analgesic effect, suggesting that acupuncture activated the TRPV1 channel to produce analgesia. Yao et al. found (2024) that acupuncture of the Zusanli(ST36) increased the transient receptor anchor protein 1 (Transient Receptor Potential Ankyrin 1,TRPA1) expression and improved right foot pain in mice, and the analgesic effect was significantly reduced in TRPA1 gene-deficient mice. Xu et al. (2016)proposed that ASIC3 receptors on nerve fibers mediate low-intensity electrical stimulation analgesia, and high-intensity electrical stimulation analgesia is dependent on the TRPV1 receptors. Li Yujia et al. (2023) showed that acupuncture increased the expression of Piezo2 in the skin of rats and that the analgesic effect was significantly reduced after specific blockade of Piezo channels in the acupoint area. Therefore, one of the mechanisms by which acupuncture relieves joint pain is the activation of local mechanosensitive channels. Researchers believe that the mechanosensitive channels distributed on nerve fibers and non-neural cells transmit the analgesic information of acupuncture through different pathways: the mechanosensitive channels on the nerve fibers are open, Ca2 + inward flow, which directly prompts the nerve cells to generate action potentials, or make the cells release ATP to act on their own purinergic receptors to generate action potentials, which transmits the information of acupuncture; whereas, mechanosensitive channels on the non-neural cells are open, Ca2 + inward flow, and Ca2 + inward flow, which directly prompts the nerve cells to produce action potentials., Ca2 + inward flow, ATP release to the surrounding interstitium, through the calcium wave transmission to act on the nearby nerve endings, to realize the transmission of acupuncture signal(Baomin et al., 2022).

Activation of mast cells and adenosine receptors

Mast cells are immune cells that are mainly distributed in the skin, mucosa and tissue interstitium. Transient receptor potential channels (TRPV1, TRPV2 and TRPV4) are expressed on their cell membrane (Zhang et al., 2012). Activation of TRPV2 allows Ca2 + to enter the cell and induces mast cell degranulation to release bioactive substances, which positively correlates with the analgesic effect of acupuncture (Guanghong et al., 2009). Histamine and other substances released by mast cells can not only cause vasodilation, increase local blood flow, and promote tissue repair, but also act on neighboring nerve cells to transmit acupuncture signals. Yin et al (2017)found that histamine promotes neuronal excitation through the activation of H1 receptors, which is involved in the activation of acupuncture neuroelectric signals.

Activation of mast cells releases ATP, which is enzymatically converted to adenosine (ADO), which acts on adenosine receptor (AR) to produce analgesia(Goldman et al., 2010). Studies have shown that activation of the AR is essential for the anti-injurious effects of adenosine. Electroacupuncture can increase the expression of A2aR in the synovial membrane of mice, inhibit the release of tumor necrosis factor-α (tumor necrosis factor-α,TNF-α), and reduce the pain and swelling of the ankle joint(Li et al., 2015). In rat experiments, electroacupuncture promotes local adenosine release and activates A1R, reducing mechanically sensitive pain. Meanwhile, adenosine also regulates the secretion of substance P (substance P, SP), and the SP-mediated pathway is involved in electroacupuncture analgesia(Zhang et al., 2020). In addition, acupuncture activates adenosine A3 receptors and regulates related signaling pathways to relieve pain(Fei et al., 2021). In conclusion, adenosine and its receptors play a role in acupuncture analgesia.

Huang et al.'s experiments confirmed that needling led to deformation of collagen fibers in connective tissues, and under this mechanical force, TRPV2 channels were activated, inducing degranulation of mast cells, and the concentration of adenosine and histamine in local tissues was increased, which acted on the nearby nerve endings, generating the electrical signals of needling, which were transmitted to the brain through the nerve fibers, and increased the level of β-endorphin in the cerebrospinal fluid, producing analgesia (Huang et al., 2018).

Activation of endogenous cannabinoids and their receptors

Endocannabinoids (EC) are bioactive substances present in the human body that regulate nervous system functions by binding to cannabinoid receptors (CB). Recent studies have shown that the endocannabinoid system plays a significant role in pain regulation, particularly in acupuncture analgesia. CB1 receptors are primarily located in the central nervous system and are closely associated with the transmission of pain signals(Zou and Kumar, 2018); whereas CB2 receptors are mainly distributed in the peripheral nervous system and immune cells, participating in inflammatory responses and immune regulation (Galiègue et al., 1995). Chen et al.(2009)stimulated rats' GB30 and GB34 with electroacupuncture at a frequency of 2/100 Hz to treat hindpaw inflammatory pain. They found that acupuncture could enhance the release of local cannabinoids and activate CB2 receptors, thereby inhibiting pain. Furthermore, electroacupuncture at Huantiao (GB30) and Tanglingquan(GB34) can inhibit the activation of the NLRP3 inflammasome in macrophages in skin tissue through CB2 receptors, thereby increasing the thermal pain threshold of SD rats' plantar soles (Gao et al., 2018). Studies have also revealed that CB2 receptors interact with the endogenous opioid system at the site of inflammation, enhancing the analgesic effect of electroacupuncture. Su et al.(2011) noted that electroacupuncture can activate CB2 receptors, elevate the level of β-endorphin in local skin tissue, and simultaneously increase the proportion of macrophages and T cells expressing β-endorphin.

Inflammatory factors and immune cell pathways

Inflammatory factors and immune cells play a crucial role in acupuncture analgesia. Acupuncture can regulate the expression of inflammatory factors and the activity of immune cells. The most common clinical inflammatory factors include interleukin-1β (IL-1β) and TNF-α, while prostaglandin E2 (PGE2) and SP also participate in the occurrence of inflammatory pain. Studies have shown that acupuncture can reduce the expression of inflammatory factors. After administering 2 Hz electroacupuncture to the Neixiyan and Dubi(ST35) in spontaneous osteoarthritis guinea pigs, the activation of the NLRP3 inflammasome and the protein expression of proinflammatory factors caspase-1 and IL-1β were significantly inhibited, mechanical pain was significantly alleviated, and the analgesic effect could be maintained for at least 7 days(Wang et al., 2020). Fan Jie et al.'s study(Jie et al., 2019) also showed that acupuncture at Zusanli(ST36), Yanglingquan(GB34), and Kunlun(BL60) can reduce the local IL-1 and TNF-α levels in rats. In addition, acupuncture can recruit and activate immune cells, producing anti-inflammatory and analgesic effects. For example, acupuncture at bilateral Zusanli(ST36) can downregulate inflammatory factors in local tissues of rheumatoid arthritis model mice, increase the recruitment of immune cells and local clearance of pathogens, thereby alleviating joint pain (Xu et al., 2018). Shi et al. confirmed that electroacupuncture can increase ICAM-1+/CD11b + immune cells in local inflammatory tissues and inhibit CFA induced pain(Shi et al., 2023). Electroacupuncture at bilateral Zusanli(ST36) and Kunlun(BL60) points promotes T cell proliferation and increases plasma IL-2 levels, relieving left tibial pain in rats (Liang et al., 2018).Studies have also found that acupuncture can significantly increase the concentration of monocyte chemoattractant protein-1 (MCP-1) in rats, enhance immune function, and activate macrophages and CD4 + T cells(Zhang et al., 2020). IL-10 produced by activated immune cells is a key anti-inflammatory factor. Electroacupuncture alleviates CFA-induced arthritic pain by promoting the production of IL-10 in tissues and inhibiting the production of proinflammatory factors, while increasing IL-10 mRNA levels and significantly reducing the expression of IL-1β and TNF-α in the spinal cord of mice(Yu et al., 2020). In a mouse model with inflammation in the right hind paw, bilateral Huantiao(GB30) electroacupuncture promotes the increase of opioid-containing CXCR3 + macrophages, thereby inhibiting pain by activating opioid receptors on sensory neurons through opioid peptides derived from them(Wang et al., 2014). Kuaile et al. found that acupuncture at Kunlun(BL60) on the right hind limb can promote the synthesis and release of local β-endorphin, reduce SP content, alleviate vascular dilation and permeability, and thereby alleviate right lateral ankle pain. The optimal electroacupuncture parameters are 100 Hz, 0.1 mA, and intermittent wave(Le et al., 2008).

Spinal cord response effect

Peripheral pain signals and pinprick signals are transmitted to the spinal cord through nerve fibers, where pinprick signals are initially processed, mainly by inhibiting the activation of neuronal cells and glial cells, and regulating the release of neurotransmitters and opioid peptides, thus inhibiting the transmission of pain signals in the spinal cord.

Inhibition of glial cell activation

Activation of microglia and astrocytes in the dorsal horn of the spinal cord plays an important role in the pain process, and studies have shown that acupuncture can inhibit the activation of these glial cells. Electroacupuncture on the affected side of Huantiao(GB30) and Yanglingquan (GB34) can inhibit the activation of spinal cord glial cells and increase the thermal pain threshold (Mi et al., 2011). In a rat model of right-sided plantar pain, electroacupuncture of Zusanli(ST36) and Yanglingquan (GB34) was able to decrease the expression of c-fos in the spinal cord, inhibit the expression of pain-related factors such as SP, IL-6, and interferon-γ (Interferon-γ,IFN-γ), while increasing the levels of the anti-inflammatory factors IL-4 and IL-10, and reducing pain amplification (Yu et al., 2020; Liu et al., 2019). Hou Yanhong et al. (2020) found that electroacupuncture stimulation of Huantiao(GB30) and Zusanli(ST36) in left hindfoot pain mice reduced microglia activation and intervened in plantar inflammatory pain. A pain model was constructed by injecting CFA into the right hindfoot paw of rats, and electroacupuncture of Zusanli(ST36) and Kunlun(BL60) could inhibit the activation of astrocytes in the dorsal root ganglion and the expression of P2X7 receptor, which further exerted an analgesic effect (You et al., 2020). Shi et al.'s experiments have shown that electroacupuncture can inhibit the activation of spinal glial cells and the production of inflammatory factors, reducing joint and muscle pain caused by surgery (Shi et al., 2017). The experimental results of Wang et al. also reached the same conclusion (Wang et al., 2022).

Inhibition of TRP channels

TRPV1 is widely distributed in the peripheral and central nervous systems, and is a non selective calcium ion channel that can participate in the transmission of pain signals after activation(Premkumar and Sikand, 2008). Acupuncture attenuates the transmission of pain messages by inhibiting the activation of TRP channels. It was found that electroacupuncture of bilateral Zusanli(ST36) decreased the expression of TRPV1 and its downstream signaling molecules in the dorsal root ganglion (DRG) of rats with CFA-induced hind paw pain model, downregulated p38-mitogen-activated protein kinase (MAPK), inhibited the activation of the harmful ion channel Nav1.7 (Liao et al., 2017). Electroacupuncture of either ipsilateral or contralateral Zusanli(ST36) and Shangjuxu(ST37) attenuated TRPV1 and related signaling pathway expression in DRG, inhibited Nav sodium current in neurons, and attenuated mechanical and thermal nociceptive sensitization (Lu et al., 2016). In a plantar inflammation model induced by carrageenan gum or CFA, electroacupuncture to the Zusanli(ST36) effectively reduced the protein levels of TRPV1 and TRPV4 in the DRG, thereby reducing pain (Chen et al., 2012). Fang et al. (2018)showed that 100 Hz electroacupuncture modulated TRPV1 and P2X3 in the DRG better than 2 Hz, and that it was more effective in analgesia.

Combined with the effects of acupuncture on TRP channels, it can be seen that acupuncture exerts different effects on TRP channels in different parts of the body: activation of TRP channels in the periphery causes mast cell excitation to promote the conversion of acupuncture signals, which is conducive to the transmission of analgesic information. In contrast, activation of TRP channels in the spinal cord may exacerbate pain signaling. Therefore, although acupuncture has different effects on TRP channels at different sites, it ultimately exerts analgesic effects.

Inhibition of cell signaling pathways

MAPK is an important class of signaling proteins involved in cellular responses to external stimuli and plays a key role in pain hypersensitivity.The MAPK family consists of four major subfamilies: extracellular signal-regulated kinase (ERK), P38 MAPK, c-Jun amino-terminal kinase/stress-activated protein kinase (JNK/SAPK), and BMK1/ERK5.Inhibition of the MAPK signaling pathway is thought to be a mechanism for achieving analgesia(Obata and Noguchi, 2004). Electroacupuncture can inhibit the activation of p38 MAPK in the spinal cord and alleviate CFA induced joint pain(Fang et al., 2013). Electroacupuncture of bilateral Zusanli(ST36) can reduce inflammatory pain in the left hindfoot of rats by modulating CX3CL1 signaling in the lumbar spinal cord, inhibiting the activation of the p38 MAPK pathway, and decreasing the release of downstream cytokines IL-6, IL-1β, and TNF-α (Li et al., 2019). Studies by Fan Jingjie and Li Yangle et al. showed that electroacupuncture Yanglingquan(GB34) and Dubi(ST35) could activate CB2 receptors in the dorsal horn of the spinal cord, inhibit the MAPK/ERK signaling pathway, and alleviate knee pain (Jingjie et al., 2021; Yangle et al., 2022). In addition, electroacupuncture significantly inhibited ERK1/2 activation and cyclooxygenase-2 (COX-2) expression, increased the pain threshold, and decreased the mRNA and protein levels of Neurokinin1Receptor (NK-1), which further supported that electroacupuncture could alleviate knee pain by blocking ERK1/2-COX-2 signaling pathway in the dorsal horn of rat spinal cord, which further supports that electroacupuncture can produce analgesia by preventing the activation of ERK1/2-COX-2 pathway and ERK1/2-CREB-NK-1 pathway(Fang et al., 2014). Another study showed that electroacupuncture inhibited the spinal astrocyte IL-33/ST2 signaling pathway and the downstream ERK and JNK pathways to reduce formalin-induced joint pain(Han et al., 2015). Experiments of electroacupuncture bilateral Zusanli(ST36) and Kunlun(BL60) for the treatment of inflammatory pain in the left plantar region confirmed that inhibition of the PKC/TRPV1 pathway in the DRG and the dorsal horn of the spinal cord was involved in electroacupuncture intervention for arthritis pain (Liu et al., 2018).

Regulation of neurotransmitters and their receptors

Neurotransmitter release and receptor activation are crucial in pain signaling and central nociceptive formation. The sensory nerve endings in the dorsal horn of the spinal cord release neurotransmitters such as glutamate under stimulation, which not only act on postsynaptic neurons, but also trigger the release of inflammatory mediators from glial cells, and the released inflammatory mediators in turn stimulate the neurons in the presynaptic membrane, causing more neurotransmitters to be released, forming a positive feedback effect and exacerbating the pain (Chenglin and Jolina, 2017). Acupuncture relieves pain by accelerating the degradation of neurotransmitters and inhibiting receptor activation.

Glutamate is one of the main excitatory neurotransmitters mediating pain signaling. Electroacupuncture stimulation of Zusanli(ST36) inhibits the activation of the glutamate receptor GluN1 subunit (Cui et al., 2019) and the phosphorylation of the glutamate receptor subunit GluR2(Lee et al., 2013), thereby reducing pain. Electroacupuncture of bilateral Zusanli(ST36) and Sanyinjiao(SP6) can upregulate the expression of glutamate transporter proteins in spinal astrocytes and promote glutamate degradation, which helps to treat pathological pain (Kim et al., 2012). In addition, the elevated concentration of 5-hydroxytryptamine (5-HT) also helps to enhance the analgesic effect of acupuncture(Han et al., 1979); bilateral Huantiao(GB30) for 10 Hz electroacupuncture can activate spinal 5-HT neurons and inhibit nociceptive hypersensitivity(Zhang et al., 2011).

Activation of opioid peptide receptors

Opioid peptide is an endogenous peptide in the nervous system, which can bind with opioid receptors to exert biological effects such as analgesia and euphoria. Acupuncture can regulate endogenous opioid peptides and their receptors. Electroacupuncture of ipsilateral Houxi (SI3) and Sanyangluo(TE8) significantly reduced capsaicin-induced secondary pain in the left hindfoot. The analgesic effect of electroacupuncture was found to be mediated mainly through μ-opioid and δ-opioid receptors in the spinal cord by intrathecal injection of three opioid receptor antagonists (Kim et al., 2009). In addition, electroacupuncture pretreatment of the contralateral Zusanli(ST36) inhibited carrageenan-induced pain, and the analgesic effect of electroacupuncture was significantly attenuated after intrathecal administration of μ-opioid receptor-selective antagonists (Yang et al., 2011). A study by Yingjun Liu et al. also showed that Mas-related G protein-coupled receptor C was involved in the analgesic effect of electroacupuncture on CFA-induced pain in the right hind paw, and this mechanism may be related to the modulation of the expression of δ-opioid receptor in the DRG of the affected side(Yingjun et al., 2017).

Brain integration effects

After being transmitted in the spinal cord, pain signals continue to be uploaded to the brain for processing and integration, resulting in the pain experience. Acupuncture signals transmitted from the spinal cord to the brain can affect multiple brain nuclei, including the nucleus raphe magnus (NRM), periaqueductal gray (PAG), medulla oblongata, caudate nucleus, and amygdala, to exert analgesic effects. At the same time, the acupuncture signal activates the endogenous downward inhibitory system and inhibits the uploading of pain signals in the spinal cord.

Using fMRI technique, Shen Wei et al. observed the altered brain functional connectivity of analgesic effects in patients with cervical spondylosis and found that the signal input from the thalamus to the anterior cingulate gyrus was reduced and the functional connectivity of the ventral medial prefrontal lobe and the cingulate gyrus was enhanced after acupuncture (Wei et al., 2021). Acupuncture in patients with unilateral frozen shoulder found that acupuncture of Tiaokou(ST38) can play an analgesic role by inhibiting the functional connection between thalamus and cortex, and acupuncture of contralateral Tiaokou(ST38) can play a role by regulating limbic brain areas such as anterior cingulate gyrus and paracentral cingulate gyrus, and the immediate analgesic effect of acupuncture of contralateral Tiaokou(ST38) is better than that of acupuncture of ipsilateral striatum (Shangqing, 2019).

Activation of the dopamine system, endogenous opioid system and 5-HT system has analgesic effects, and acupuncture achieves analgesic effects by activating these systems.

In a model of left ankle inflammation, electroacupuncture at 2/100 Hz was applied to Zusanli(ST36) and Kunlun(BL60) on the affected side, which was shown to increase the gene expression of CB1R and dopamine D1 and D2 receptors in the striatum, which in turn modulated the release of dopamine to alleviate pain through the endogenous cannabinoid system (Shou et al., 2013). In a knee osteoarthritis model, electroacupuncture stimulation of the neixiyan and Dubi(ST35) enhanced the expression of CB1 receptors on gamma-aminobutyric acid (GABA)-ergic neurons in the midbrain, which, in turn, augmented the downstream inhibition of 5-HT related functions in chronic pain(Yuan et al., 2018).

Electroacupuncture with bilateral loop jumps activates μ-opioid receptors in the cephalic anterior cingulate cortex, inhibits spontaneous pain-induced affective responses, and attenuates hind paw pain in rats (Zhang et al., 2012). In addition, electroacupuncture may promote the release of endogenous morphine peptide, eliminate the tense inhibition of 5-HT neurons, and enhance the analgesic effect(Zhang et al., 2011).

In addition, acupuncture is involved in analgesia by modulating signaling molecules and their receptors in the brain; for example, in the hindpaw of CFA-injected mice, the expression of TRPV1-related molecules was increased in the prefrontal cortex and hypothalamus and decreased in the PAG region. Electroacupuncture of bilateral Hegu(LI4) significantly attenuated this phenomenon and achieved analgesia (Yen et al., 2019).

In summary, acupuncture exerts analgesic effects through the three levels of periphery, spinal cord and brain together. These three levels

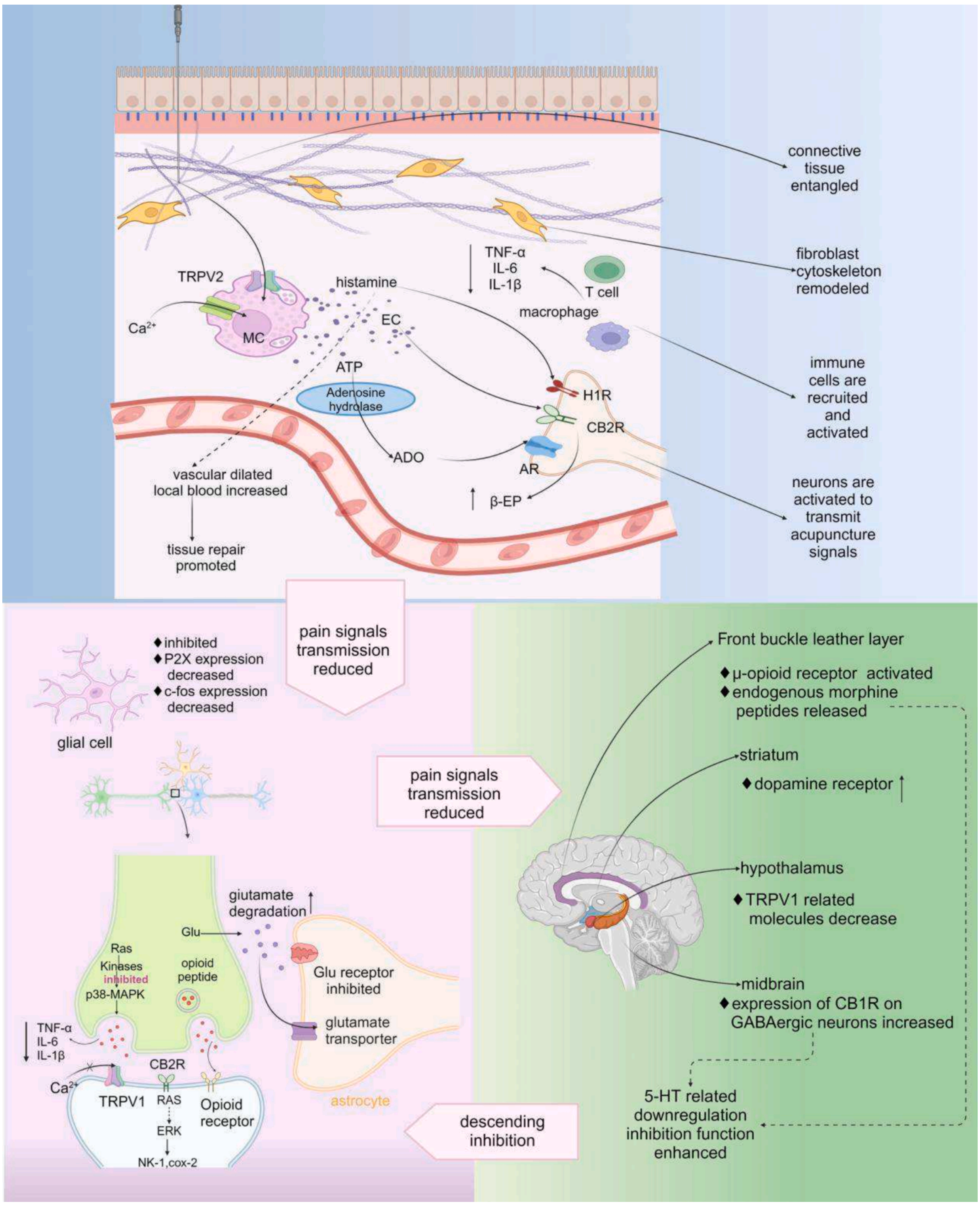

Fig. 1. Mechanism of joint pain analgesia.

interact with each other and are closely linked. Acupuncture induces local connective tissue deformation, activates mechanosensitive channels, degranulates mast cells, and regulates the release of adenosine, cannabinoids, and inflammatory mediators, and also regulates immune cells, thus producing analgesic effects locally. The effect is not only to inhibit the generation of local pain signals, but also to reduce their transmission to the spinal cord. Peripherally transmitted pain signals are reduced, and the resulting abnormal excitation of spinal cord neurons is correspondingly diminished. Acupuncture can also directly inhibit the activation of nerve cells and glial cells, further reducing the generation of pain signals and abnormal excitation of neurons in the spinal cord, and inhibiting the generation and amplification of pain signals in the spinal cord. In addition, acupuncture regulates the release of spinal cord neurotransmitters and opioid peptides, which effectively inhibits the conduction of pain signals to the brain and reduces the pain sensation in the brain. Acupuncture has the same effect on the contralateral side. At the same time, acupuncture activates the opioid peptide system and the downward inhibitory system in the brain to enhance the analgesic function and inhibit the upward transmission of pain signals in the spinal cord. Acupuncture of the contralateral side similarly activates the downward inhibitory system in the brain and reduces analgesia by decreasing abnormal functional connectivity in brain regions. The mechanism of analgesia for joint pain is shown in Fig. 1.

Spatial effects of acupuncture on models related to neuropathic pain

Current studies have explored the analgesic mechanisms of acupuncture in models of arthralgia, but relatively few studies have addressed the peripheral level in models of neuropathic pain, with most studies focusing on the spinal cord and brain levels, confirming the involvement of opioids, glial cells, ion channels, and inflammatory factors.

Spinal cord response effects

Inhibit glial cell activation and regulate immune cells

Acupuncture can relieve neuralgia by regulating abnormally active glial cells and signaling pathways. Electroacupuncture of bilateral Zusanli(ST36) and Kunlun(BL60) significantly inhibited the over-activation of astrocytes and microglia in the spinal cord, thereby increasing the mechanical and thermal pain thresholds of rats and inhibiting the nociceptive sensitization of rats with Complex Regional Pain Syndrome Type I (Qimiao et al., 2019). Acupuncture with Huantiao (GB30) and Yanglingquan(GB34) can inhibit the activation of astrocytes and microglia, and alleviate tetanus induced sciatica (Liang et al., 2010). In another study, acupuncture of Shuigou(GV26) and Yanglingquan (GB34) inhibited the activation of Jun-N-terminal kinase in astrocytes after spinal cord injury and relieved neuropathic pain (Lee et al., 2013).

Electroacupuncture of the Zusanli(ST36) model of neuropathic pain in mice showed inhibition of glial cell activation, decreased levels of TNF − α and IL-1 β in the spinal cord, and increased levels of IgG (Gim et al., 2011). In exploring the mechanism of acupuncture on diabetic peripheral neuropathy, it was shown that acupuncture reduced the expression of P2X4 receptors in spinal microglia and decreased the levels of inflammatory factors TNF-α, IL-1β, and IL-6 (Tang et al., 2020). Electroacupuncture of the Jizhong (GV6) and Zhiyang (GV9) upregulates the proportion of M2 macrophages, reduces the proportion of M1 macrophages and the levels of TNF − α, IL-1 β, and IL-6, and promotes the recovery of spinal cord injury rats (Zhao et al., 2017).

Inhibiting signal transduction pathways

the activation of the p38MAPK signaling pathway promotes the early development of neuropathic pain(Li et al., 2021; Sanna et al., 2015). Electroacupuncture of Zusanli(ST36) and Sanyinjiao(SP6) increased pain threshold in rats with diabetic neuropathic pain, which may be related to the inhibition of p38MAPK expression in the spinal cord (Huan et al., 2016).Electroacupuncture at Zusanli(ST36) can reduce the activation of p38MAPK, thereby delaying the occurrence of neuroinflammation (Yang et al., 2010). Kim et al.'s experiment confirmed that spinal cord TRPV1 activation leads to chronic neuropathic mechanical allodynia (Kim et al., 2012); Other researchers have shown that TRPV1 is crucial for the mechanical hypersensitivity response induced by nerve injury (Kim et al., 2014); and acupuncture can inhibit TRPV1 activation and treat neuropathic pain. Low frequency electroacupuncture may alleviate mechanical allodynia induced by spinal nerve injury by inhibiting the upregulation of TRPV1 in the spinal cord (Jiang et al., 2013). Dou et al. believe that inhibiting TRPV1 and its downstream signaling pathways can reduce peripheral neurogenic inflammatory pain (Dou et al., 2021). In one study, warm acupuncture treatment in Mongolian medicine was shown to block the activity of STAT signaling pathway in microglia in the dorsal horn of the spinal cord and reduce sciatica (Silengge et al., 2023).

Regulation of receptors on neurons and glial cells

Purinergic receptors P2X are an important class of non-selective cation channels involved in pain signaling. Electroacupuncture has been found to reduce diabetic peripheral neuralgia by inhibiting the upregulation of P2X3 receptors in DRG(Fei et al., 2020; Zhou et al., 2018). Electroacupuncture of bilateral Zusanli(ST36) and Kunlun(BL60) reduced the expression of P2X4 and P2X7, which attenuated thermal hyperalgesia caused by diabetic peripheral neuralgia (Hu et al., 2023). Electroacupuncture at Zusanli(ST36) and Yanglingquan(GB34) on the contralateral side can downregulate the expression of spinal cord P2X3 receptor protein and alleviate pain in rats with sciatic nerve compression injury (Wenzhan et al., 2013).

Endogenous cannabinoid receptors are a class of G-protein-coupled receptors, and binding to endogenous cannabinoids modulates neurotransmitter release and influences synaptic plasticity, which is involved in the pain process. In the paclitaxel-induced neuropathic pain model, electroacupuncture of bilateral Huantiao(GB30) significantly increased the mechanical pain threshold, enhanced the expression of CB2 receptors in sciatic nerve tissues, and reduced the release of the inflammatory factor IL-1β, an effect that was not observed in CB2 knockout mice (Hong et al., 2018).

Activation of the endogenous opioid peptide system

Activation of the opioid peptide system is essential for the treatment of neuropathic pain. Electroacupuncture of Yanglingquan(GB34) and Huantiao(GB30) reduced primary afferent nerve germination in post-herpetic neuralgia (PHN) rats, possibly through activation of μ-opioid receptors with decreased expression of Netrin-1 and its receptors in the spinal cord (Li et al., 2019). In the sciatic nerve chronic compression injury model, observations after electroacupuncture of bilateral Zusanli (ST36) and Yanglingquan(GB34) showed that the thermal pain threshold of the model rats was elevated, the cytosol of spinal microglia was reduced, and the expression of Toll-like receptor 4 was decreased, and after the use of the κ-opioid receptor inhibitor, the latency of foot-shrinking response was shortened, and the Toll-like receptor 4 was significantly elevated, suggesting that the analgesic mechanism of electroacupuncture may be related to the enhancement of κ opioid receptor expression and inhibition of Toll-like receptor 4 induced analgesic signaling(Yonghui et al., 2022). In the L5-L6 spinal neuralgia model, after electroacupuncture to bilateral Zusanli(ST36) and jiaji acupoints, the cold plate test showed a reduction in neuropathic pain and naloxone similarly blocked this analgesic effect, supporting the involvement of μ-opioid receptors in the analgesic process. In addition, electroacupuncture showed a cumulative effect with no tolerance (Sun et al., 2004). In rats with L5/L6 spinal nerve ligation, unilateral Zusanli (ST36) and Sanyinjiao(SP6) needling had similar effects to gabapentin, both reducing mechanical hypersensitivity, and naloxone blocked this effect, suggesting that needling analgesia is dependent on the opioid system (Cidral-Filho et al., 2011). In a model of neuralgia established after resection of the right superior caudal trunk between the S3-S4 spinal nerves, an analgesic effect appeared in 2 Hz electroacupuncture of Houxi(SI3), but naloxone pretreatment blocked this effect, suggesting that the analgesic effect of low-frequency electroacupuncture is mediated through the endogenous opioid system (Hwang et al., 2002).

Other effects

Acupuncture reduces neuropathic pain through mechanisms such as reducing the release of inflammatory factors, improving neuronal plasticity and inhibiting autophagy or iron death. For example, acupuncture at C6 and C7 jiaji acupoints can inhibit the expression of CX3CL1 and SP in the dorsal horn of the spinal cord of rats with a model of neurogenic cervical spondylosis, reduce inflammatory responses and impede central sensitization(Weidi et al., 2023). Electroacupuncture reduced the expression of TNF-α, IL-1β and Caspase-1 in the spinal cord of PHN model(Zhigang et al., 2023). Liao Wenyan et al. found that Zhuang acupuncture improved neuropathic pain, inhibited IKKβ/NF-kB pathway in the dorsal horn of the spinal cord, and reduced the release of inflammatory factors(Wenyan et al., 2023).

Electroacupuncture of Huantiao(GB30) and Yanglingquan(GB34) could increase the expression of miR-223-3p, inhibit neuronal autophagy, and improve the mechanical pain threshold of PHN rats (Zou et al., 2021).Electroacupuncture of Zusanli(ST36) and Baihui(GV20) may prevent neuropathic pain by inhibiting neuronal iron death (Xue et al., 2024). In rats with resin toxin-induced PHN, electroacupuncture to Huantiao(GB30) and Yanglingquan(GB34) reduced the expression of vascular endothelial growth factor in the dorsal horn of the spinal cord and relieved abnormal mechanical pain, and 2 Hz was better than 15 Hz or 100 Hz(Wu et al., 2018). In addition, Qu Si-Ying et al. showed that electroacupuncture of bilateral Zusanli(ST36) and Kunlun(BL60) inhibited the expression of brain-derived neurotrophic factor in microglial cells in the dorsal horn of the spinal cord, which improved diabetic neuralgia (Siying et al., 2020). 2 Hz electroacupuncture improved neuronal plasticity and inhibited neuropathic pain caused by ligature of the L5 spinal nerve by up-regulating the A2AR/cAMP/PKA signaling pathway(Wu et al., 2021).

Brain integration effects

Acupuncture affects the activity of multiple nuclei and neurons in the brain, as well as regulates signaling pathways and receptors in the brain to relieve neuropathic pain. Repetitive electroacupuncture upregulates multiple receptors and protein expression in the rat amygdala and modulates chronic pain perception. Duanmu Chenglin et al. showed that repetitive electroacupuncture to bilateral Zusanli(ST36) and Yanglingquan(GB34) improved the plasticity of synaptic structure of amygdala nerve cells in a rat model of chronic sciatica, thus exerting analgesic effects (Chenglin et al., 2017; Chenglin et al., 2017). Electroacupuncture may also improve the nociceptive behavior of neuralgia rats by regulating the expression of inflammation-related proteins in the hippocampus (Changyue et al., 2023). Electroacupuncture at bilateral Zusanli(ST36) and Yanglingquan(GB34) reversed the changes in ERK and p38MAPK in the hippocampus caused by chronic compression injury (Wang et al., 2015). Electroacupuncture treatment attenuates central post-stroke pain by inhibiting cerebral neuronal apoptosis and abnormal astrocyte activation (Tian et al., 2016). Electroacupuncture Yanglingquan(GB34) and Huantiao(GB30) effectively alleviated pain hypersensitivity in mice in a sciatic nerve chronic compression injury model. Electroacupuncture exerts anti-injury sensory effects by increasing CB1 receptors to inhibit GABAergic neurons in the ventrolateral periaqueductal gray (vlPAG) and excites glutamatergic neurons (Zhu et al., 2019), and the released glutamate stimulates the PAG to activate the downward inhibitory system and inhibit spinal cord injury sensory transmission (Zhuomin, 1993). Acupuncture can inhibit thalamic P2X7 receptor expression (Ting, 2020), and reduced P2X7 receptor expression may alleviate post-stroke thalamic pain (Huang et al., 2024; Kuan et al., 2018). Inhibition of thalamic adenylate cyclase isoform 1 as well as increased expression of the cAMP signaling pathway is one of the pathways of electroacupuncture for thalamic pain (Ma et al., 2022). Li Ji et al. found that electroacupuncture at Yanglingquan (GB34) and Xuanzhong(GB39) on the affected or contralateral side can relieve pain in patients with sciatica, but the signals in the PAG area, bilateral caudate nucleus, contralateral lentiform nucleus, and contralateral hippocampus on the affected side were significantly increased, while the signals in the bilateral amygdala and visual cortex on the contralateral side were altered (Ji et al., 2007). Liu et al. experimentally found that the otherwise abnormal default mode network of the brain in sciatica patients normalized after acupuncture and that downward inhibition of the brain was enhanced (Liu et al., 2020).

It is thus clear that the main effects of acupuncture on neuropathic pain are concentrated at the spinal cord and brain levels. At the spinal cord level, acupuncture inhibits excessive activation of glial cells, regulates receptors on nerve cells, and regulates immune cell balance, reducing the release of inflammatory factors, lowering the production of pain signals, and reducing abnormal neural excitation. Acupuncture of the contralateral side likewise reduces abnormal nerve excitation. At the same time, acupuncture inhibits pain signaling pathways in the spinal cord and reduces the transmission of pain signals to the brain. Activation of the spinal opioid peptide system also produces analgesic effects. The production and transmission of abnormal pain signals in the spinal cord is inhibited, the transmission of pain signals to the brain is reduced, and pain perception in the brain is diminished. In addition, acupuncture further modulates brain perception of pain by affecting multiple nuclei and neuronal activity in the brain, as well as modulating receptors and signaling pathways in the brain. The downward inhibitory system in the brain is also activated by acupuncture to inhibit the upward transmission of pain signals in the spinal cord. Although the effects of acupuncture ipsilateral versus acupuncture contralateral to the brain region were inconsistent, overall both enhanced downward inhibition of the brain. The mechanism of analgesia for neuropathic pain is shown in Fig. 2.

Spatial effects of acupuncture on visceral pain-related models

There is growing evidence that acupuncture is effective in reducing visceral pain, and researchers have actively explored its mechanism of action.

Peripheral afferent effects

Modulation of expression and activity of multiple receptors

The effect of acupuncture on multiple receptors such as adenosine and cannabinoids plays an important role in the treatment of visceral pain. Experimenting with trinitrobenzene sulfonic acid-induced inflammatory bowel disease (IBD) mice, Hou et al(2019) found that electroacupuncture stimulation of bilateral BL25 in mice increased the expression of adenosine A1, A2a, and A3 receptors in colonic tissues, while decreasing the expression of adenosine A2b receptor, and reducing the levels of SP and IL-1β. The application of receptor antagonists showed that the analgesic effect of electroacupuncture was significantly diminished after inhibition of adenosine A1, A2a, or A3 receptors, whereas the adenosine A2b antagonist, although it did not significantly affect the mechanical pain threshold, still inhibited the expression of SP and IL-1β. This suggests that electroacupuncture inhibits inflammatory factors by modulating peripheral adenosine receptors, thereby reducing pain. In addition, electroacupuncture stimulation of Dachangshu(BL25) for 7 consecutive days also improved IBD-associated visceral hypersensitivity by activating CB2 receptors and inhibiting macrophage activation and IL-1β expression (Zhang et al., 2022). Electroacupuncture ST36 reduces chronic visceral hypersensitivity in rats when it reduces colonic 5-HT3 receptor levels(Chu et al.,

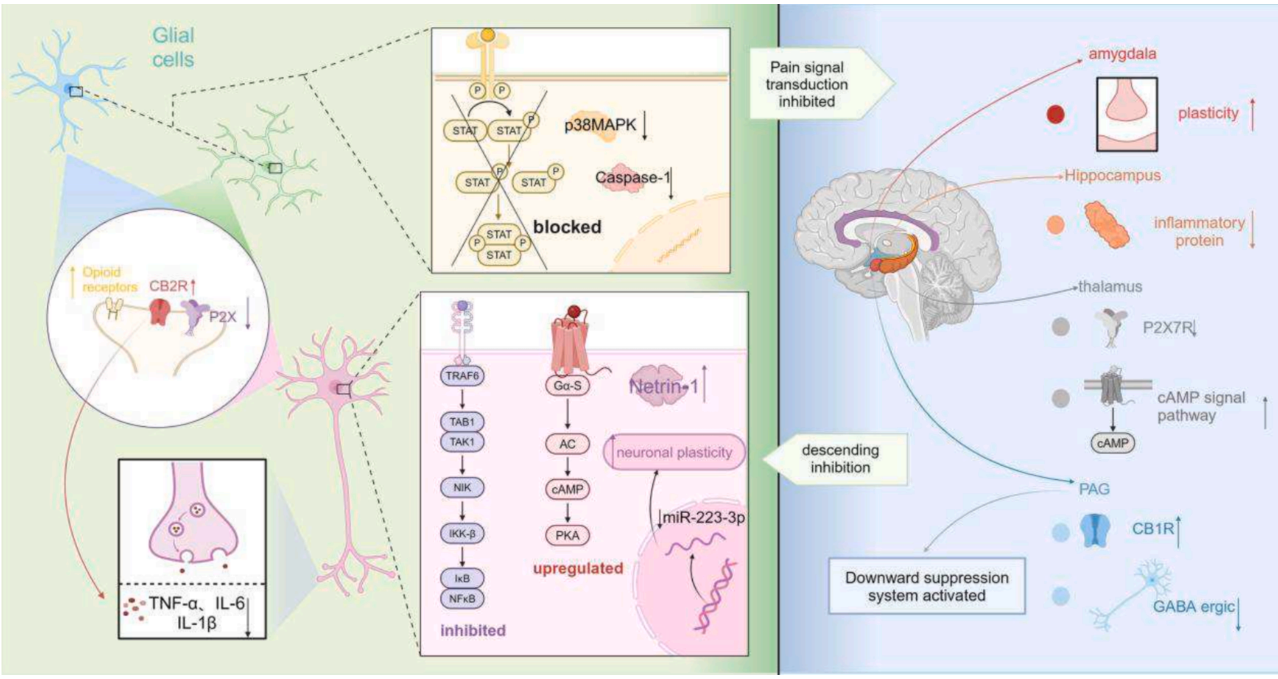

Fig. 2. Mechanism of neuropathic pain analgesia.

2011).

Inhibition of signaling channels

Werend Boesmans et al. proposed that TRP channels play an important role in controlling visceral sensation and are associated with visceral hypersensitivity and pain(Boesmans et al., 2011). Chen et al (2021) pointed out that the PI3K/Akt pathway passed by acupuncture Shangjuxu(ST37) down-regulated TRPV1, TNF-α, IL-1β and IL-6 expression in the colon and improved acute visceral pain. Electroacupuncture Zusanli(ST36) similarly decreased TRPV1 channel expression in the intestine and attenuated visceral nociceptive hypersensitivity induced by dextrose sodium sulfate (Chen et al., 2021). In a chronic visceral pain model of irritable bowel syndrome (IBS), electroacupuncture Shangjuxu(ST37) demonstrated an analgesic effect, which may be related to the modulation of the NGF/PI3K/TRPV1 signaling pathway (Chen et al., 2023). In addition, Tian et al. found that electroacupuncture Zusanli(ST36) down-regulated colonic TNF-α mRNA levels in ulcerative colitis mice, thereby alleviating ulcerative colitis pain (Tian et al., 2003). Electroacupuncture at Zusanli (ST36) and Shangjuxu (ST37) reduced intestinal hypersensitivity by decreasing the expression of TRPV1 and decreasing the phosphorylation of ERK1/2 in intestinal tissue(Wang et al., 2012).

Regulating immune balance

The Th17 cells in the intestinal tissue of IBD patients are higher than those in healthy individuals, while the Treg cells are lower(Geng and Xue, 2016). Electroacupuncture with Guanyuan (RN4) and Zusanli (ST36) can increase CD4 + CD25 + Foxp3 + Treg cells, decrease CD3 + CD8 + IL-17 + Th17 cells, regulate the balance of Th17/Treg axis, and improve ulcerative colitis(Sun et al., 2017). Wang et al.'s (2016)experiment also confirmed that electroacupuncture reversed the increase in Th17/CD8 + T cell ratio and the decrease in Treg/CD4 + T cell ratio in rats with ulcerative colitis. Acupuncture can also affect the Th1/Th2 immune balance. Electroacupuncture at Tian Shu (ST25) and Qi Hai (CV6) can reduce the proportion of CD4 + IFN-γ+/CD4 + IL-4 + cells and the levels of IFN-γ and IL-12 in the colon tissue of ulcerative colitis rats, and increase the levels of IL-4 and IL-10. Chen et al. pointed out that electroacupuncture can regulate the Th1/Th2 balance (Chen, 2016). Electroacupuncture at Zusanli(ST36) promotes macrophage polarization towards M2 direction and improves acute colitis in rats (Song et al., 2019).

Spinal cord response effects

Acupuncture effectively relieves visceral pain by inhibiting neuronal and glial cell activity, modulating signaling channels, modulating P2X receptors and activating the opioid peptide system. Zeng Yusha's study showed that electroacupuncture bilaterally at the Baliao point inhibited glial cell activation and decreased the levels of IL-1β, TNF-α, and IL-6 in the spinal cord(Yusha et al., 2023). Qi et al. found that electroacupuncture bilaterally at Zusanli(ST36) and Shangjuxu(ST37) significantly decreased the expression of the c-fos protein in the dorsal horn of the spinal cord in the model of IBS, and hypothesized that abnormal excitability of neurons in the spinal cord is associated with visceral nociceptive sensitization, which electroacupuncture has an inhibitory effect (Qi and Li, 2012).Xu et al. showed that electroacupuncture at jiaji acupoint may exert analgesic effects by inhibiting the p38MAPK signaling pathway in the dorsal horn of the spinal cord(Xu et al., 2010).

In the IBS model, acupuncture of Tianshu(ST25) and Dachangshu (BL25) was effective in reducing abdominal pain, which was mainly realized by inhibiting P2X4 expression in DRG and inflammation of spinal microglia (Tang et al., 2022). Electroacupuncture of bilateral Shangjuxu(ST37) and Tianshu(ST25) was similarly able to down-regulate spinal P2X3 receptor expression and attenuate visceral pain sensitivity (Weng et al., 2015). The opioid peptide system plays an important role in the regulation of visceral pain, and electroacupuncture of bilateral Zusanli(ST36) attenuated nociceptive responses in rats with chronic visceral pain, and enkephalin injections achieved a similar effect, which was reversed by naloxone (Xu et al., 2009).

Brain integration effects

γ-GABAergic neurons are inhibitory neurons that can play a role in the analgesic process. The study of Xinyue Wang et al. showed that electroacupuncture of bilateral Zusanli(ST36) activated GABAergic neurons in the PAG, which in turn alleviated visceral pain in IBS mice

(Xinyue et al., 2023).The activation of the PAG also stimulated the downward inhibitory system and inhibited the uploading of pain signals from the spinal cord. Electroacupuncture also inhibits the expression of P2X3 receptors in the anterior cingulate cortex and prefrontal cortex of IBS rats, thereby relieving pain(Weng et al., 2015). Acupuncture also achieves analgesic effect on visceral pain mice by increasing β-endorphin in the hypothalamus(Yu et al., 2008).Electroacupuncture in Zusanli (ST36) was more effective than 2 Hz at 100 Hz in relieving gastric pain, probably due to the fact that electroacupuncture promotes the synthesis and release of β-endorphin in the hypothalamus(Lin et al., 2009).

When glutamate is released in excess, it produces excitotoxicity, leading to a variety of disorders including pathological pain(Mahmoud et al., 2019). Excitatory amino acid transport proteins are the main transport mechanism for the removal of extracellular glutamate in the central nervous system(O'Donovan et al., 2017). Stimulation of bilateral Zusanli(ST36) and Shangjuxu(ST37) using 5 Hz electroacupuncture can alleviate IBD-induced visceral pain by modulating the glutamatergic system in the prefrontal cortex, and electroacupuncture can clear extracellular glutamate and alleviate visceral pain through inhibition of glutamate receptors and enhancement of excitatory amino acid transport proteins expression(Jiang et al., 2023).

Su Chengguo et al. found that after acupuncture activated the nociceptive modulation system in the brain, such as the brainstem, the nucleus accumbens, and the thalamus, thus achieving the analgesic effect. At the same time, the limbic system, which is related to the cognition of pain sensation, was activated. Therefore, it is believed that the analgesic effect of acupuncture may be realized through the interaction of multiple functional brain regions(Chengguo et al., 2016).

Peripheral modulation of visceral pain by acupuncture reduces the production of visceral pain signals mainly by affecting the expression and activity of various receptors such as adenosine and cannabinoids, modulating immune homeostasis, and reduces the transmission of pain signals to the spinal cord by inhibiting signalling channels. This process reduces the transmission of pain signals to the spinal cord, resulting in a decrease in the abnormal excitation of spinal cord nerve cells. Acupuncture also directly inhibits the over-activation of neurons and glial cells, which further inhibits the generation of abnormal excitatory signals in the spinal cord. By modulating signaling channels, acupuncture reduces the transmission of abnormal neural excitation to the brain, and therefore pain perception in the brain is subsequently diminished. In addition, acupuncture activates the glutamate system in the brain, removing excess glutamate and relieving pain. At the same time, acupuncture also activates the downward inhibitory system in the brain to inhibit pain signals transmitted upward from the spinal cord, and activates the opioid peptide system in the brain to relieve visceral pain. The mechanism of analgesia for visceral pain is shown in Fig. 3.

Pain emotions

As research continues, it is recognized that pain not only causes physical discomfort, but also elicits negative emotions, which in turn exacerbate the pain experience. Pain relief produces a sense of pleasure that activates the brain's reward system and improves pain-related emotions. Inhibition of glutamate and its receptors has a large role in improving pain mood. Electroacupuncture Huantiao(GB30) may achieve relief of CFA-induced pain mood by activating μ-opioid receptors in the anterior cingulate cortex and down-regulating the levels of N-methyl-D-aspartate receptor subunits 2A and 2B (Xia et al., 2022). Electroacupuncture of bilateral Dachangshu(BL25) reduces glutamate release and inhibits anxiety circuits associated with the ventral hippocampus (Hu et al., 2022). Acupuncture also improves pain-induced moods such as anxiety and depression through various other pathways. Liu Wenhao et al(2024) observed that acupuncture on Zusanli (ST36) and Sanyinjiao(SP6) significantly alleviated cancer pain and its induced depression-like mood, and the mechanism may be related to the alleviation of neuroinflammation and the recovery of abnormal activity of specific neurons in the amygdala of model animals. Du et al (2020) demonstrated that electroacupuncture inhibited pain and pain-related anxiety-like behaviors associated with chronic inflammation in rats by increasing the expression of the neuropeptide S/Neuropeptide S receptor system in the anterior cingulate cortex. Electroacupuncture of Zusanli(ST36) on a rat model of pain memory established by cross-injection of carrageenan gum, the results of which demonstrated that inhibition of GABAB receptors in the middle cingulate cortex plays a key role in electroacupuncture in blocking pain memory and related anxiety-like behaviors (Li et al., 2023). Electroacupuncture modulates synaptic plasticity through the BDNF/TrKB/CREB signaling pathway and improves pain and depressive behaviors in chronic inflammatory pain rats (Yang et al., 2023). Ma Qiufu et al. found that excessive activity in the anterior cingulate cortex and amygdala is closely related to anxiety and depression like behavior (Huang et al., 2019). Acupuncture can have an impact on these areas.

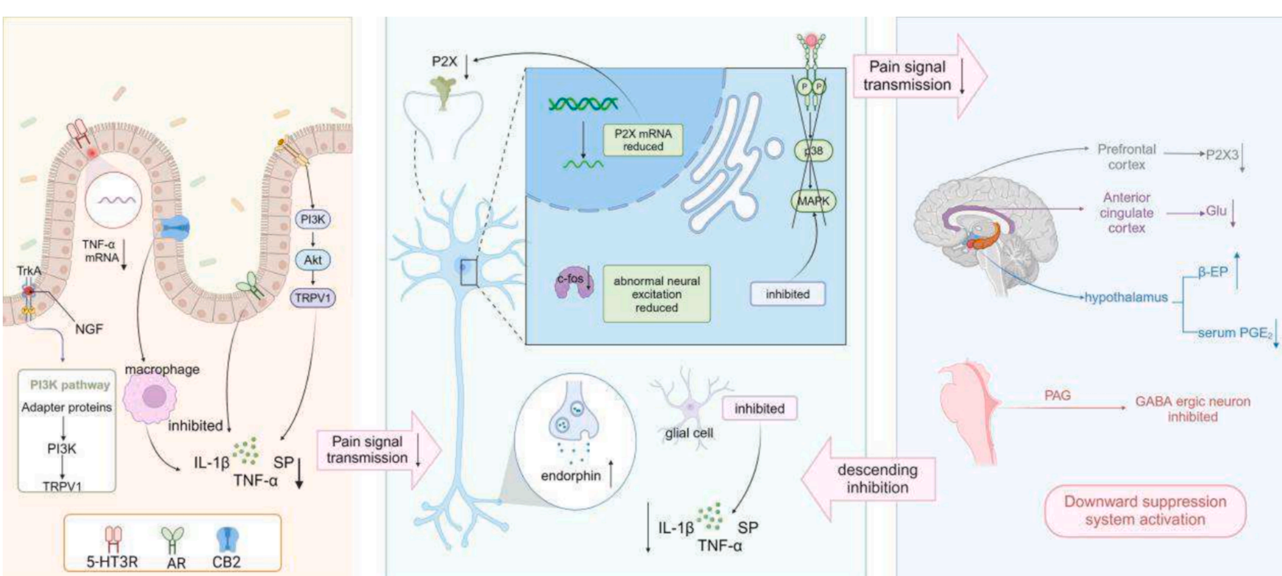

Fig. 3. Mechanism of visceral pain analgesia.

Conclusions

The analgesic effect of acupuncture is realized through a complex network loop involving multiple links and mechanisms. Academician Zhang Xiangtong pointed out that this effect originates from the integration of neural information at pain sites and acupoints, which interact at various levels of the central nervous system(Xiangtong, 1978). Professor Zhao Zhiqi also believes that acupuncture analgesia is essentially the manifestation of a comprehensive process at different levels of the central nervous system between incoming impulses from the pain area and impulses from acupoints(Zhao, 2008). First, nociceptive information is processed at the level of the spinal cord, where part of the information acts directly on the anterior horn cells, and the other part can be processed within the spinal cord or continue to be transmitted upward after spinal cord integration. Next, at the level of the brainstem, pain signals and pinprick signals are transmitted to the medulla oblongata via the lateral thalamic tracts of the spinal cord, which interact to inhibit pain signals. Finally, the thalamus and cerebral cortex integrate the two nerve impulses, with the central nucleus of the thalamus playing an important role in the integration of information and the cerebral cortex modulating the pain signal through a downward inhibitory system.

Acupuncture does not regulate pain at one level, but rather produces a comprehensive modulation of pain from a spatial whole formed by the periphery, spinal cord and brain, which are interrelated, closely coordinated and work together to effect pain at the same time. Acupuncture can also change the perception and experience of pain, improve the pain mood and relieve pain. In conclusion, acupuncture analgesia is a complex and dynamic process covering from the periphery to the center, and the various links are coordinated with each other and do not exist in isolation.

In the acupuncture analgesic response, the periphery is the initial link. Local cells, released active substances, and peripheral nerves and receptors are involved. Mast cells are activated by needling through mechanosensitive channels, and degranulation produces biological effects that translate needling signals into biological signals. Immune cells are recruited under the action of acupuncture and the release of inflammatory factors is inhibited. Acupuncture also regulates the Th1/Th2, Th17/Treg and M1/M2 balance and improves the activity of immune cells in order to maintain immune homeostasis and produce anti-inflammatory and analgesic effects (Liu et al., 2024; Wang et al., 2021). Adenosine and cannabinoid receptors in nerve endings are similarly involved in analgesia. Acupuncture inhibits the production and transmission of pain signals in the periphery through these multiple pathways.

At the spinal cord level, there is a reduction in the transmission of pain signals from the periphery and a reduction in the resulting nerve hyperexcitability within the spinal cord. Acupuncture also directly inhibits spinal cord nerve hyperexcitability and reduces the production of spinal cord pain signals. Microglia are a class of immune cells in the central nervous system that are macrophages, and acupuncture may reduce neuroinflammatory production by regulating microglial function and thus immune balance. Relevant receptors and channels in the spinal cord are inhibited, reducing intracellular signaling and inhibiting the transmission of pain information to the brain. In addition, acupuncture accelerates the degradation of damaging neurotransmitters and relieves nociceptive hypersensitivity, while activating the opioid peptide system to enhance analgesia.

In the brain, pain signals perceived in the brain decrease with the reduction of pain signals transmitted upward from the spinal cord. Acupuncture modulates GABAergic neurons, inhibits pain signal production and modulates the release of other neurotransmitters, which in turn activates the downward inhibitory system and inhibits the transmission of pain signals from the spinal cord to the brain. Thus, acupuncture forms a complex analgesic network through the peripheral, spinal cord and brain levels. In contrast, studies on the improvement of pain mood and the role of the brain in acupuncture analgesia are still insufficient, and techniques such as optogenetics can be introduced in the future to further clarify the mechanism of acupuncture analgesia.

Shortcomings and prospects

Acupuncture analgesia is widely used in clinical practice, especially in the treatment of arthralgia and neuralgia, visceral pain. Compared with drug analgesia, acupuncture has less adverse effects and its analgesic effect can still last for a period of time after stopping the needle. In addition, the combination of acupuncture and analgesics can reduce drug dosage and enhance analgesic effects, such as the combination of morphine and electroacupuncture improved analgesia and reduced tolerance(Sima et al., 2016), electroacupuncture enhanced the analgesic effect of low-dose celecoxib(Mi et al., 2008), and acupuncture enhanced the effect of etoricoxib in the treatment of knee osteoarthritis (Mavrommatis et al., 2012). Despite the advantages of a wide range of indications and small adverse effects, acupuncture analgesia still has certain shortcomings, such as the inability to achieve complete analgesia, large individual differences, and possible tolerance problems. Professor Zhao Zhiqi pointed out that the analgesic effect of acupuncture and moxibustion alone without auxiliary drugs is not ideal in most cases (Zhao, 2008). Moreover analgesic effect of acupuncture only occurs after the feeling of “de qi” (Zhao, 2008), resulting in significant individual differences.

Although the academic research on acupuncture analgesia has achieved results, no consensus has been reached on the selection of acupoints, stimulation parameters, treatment frequency and methods.

In the selection of acupoints, the selection of acupoints has a significant effect on the analgesic effect, but at present, most of them are mainly localized acupoints or acupoints according to the ganglion segment, and Zusanli(ST36) is often chosen as the analgesic acupoint. It is recorded in the ancient books of Chinese medicine that “Shu acupoints are used to treat body and joint pains”, and later physicians summarized that “Xi acupoints of the Yang meridian are often used to treat pains”, and Shu acupoints and Xi acupoints are also widely used in the process of clinical acupuncture for analgesia, but the research of their analgesic effects is relatively in a blank stage, and further explorations are needed (Cailing et al., 2015). Regarding the issue of stimulation parameters, Professor Han Jisheng’s research has shown that electroacupuncture at different frequencies has different effects on the types of central opioid peptide release and analgesic effects(Han, 2003); 2 Hz electroacupuncture stimulates the release of β-endorphins in the brain, while 100 Hz electroacupuncture stimulates the release of dynorphin in the spinal cord (Han and Terenius, 1982). However, there is no significant difference in analgesic effect between electroacupuncture with different frequencies Peripheral stimuli of different frequencies generate distinct neurophysiological responses by activating different types of primary afferent fibers (Huo et al., 2020). The research by Ma Qiufu et al. shows that electroacupuncture of different intensities can drive different autonomic nervous pathways and treat specific areas. For example, low-intensity electroacupuncture can selectively activate the vagus nerve adrenal axis, while high-intensity electroacupuncture can activate nerve reflexes independent of PROKR2ADV neurons to exert anti-inflammatory and analgesic effects (Liu et al., 2021); Low intensity electroacupuncture can exert anti-inflammatory and analgesic effects in non splenic tissues, while high-intensity electroacupuncture can inhibit inflammation in the spleen and other parts (Liu et al., 2020). Regarding the frequency and number of treatments, researchers are divided, with some advocating daily needling and others advocating every other day administration, and the number of treatments ranging from one to dozens. This suggests that there is a lack of consensus on stimulation parameters and treatment frequency, and more quantitative studies are needed to improve the relevance and effectiveness of treatment.

Studies of acupuncture methods have shown that different acupuncture methods are effective, such as fire acupuncture relieving pain in advanced cancer patients(Gao and Zhang, 2020), and auricular acupuncture reducing pain in chemotherapy patients(Ruela et al., 2018), The analgesic effect of acupunturing the contralateral side on patients after knee arthroplasty is similar to that of acupunturing the affected side (Hai, 2020), Fang Jianqiao et al. also confirmed that ipsilateral and contralateral electroacupuncture had similar analgesic effects (Fang Jianqiao, 1994); but the comparison and combination of various methods are still insufficient, and special methods such as warm acupuncture and moxibustion and bloodletting by stabbing have not been given sufficient attention. The comprehensive use of science and technology to explore the relationship between acupuncture points, methods, and quantitative and temporal effects will have important guiding significance to the clinic and help optimize the therapeutic effect.

Currently, most studies have been conducted on male SD rats, and females have been less frequently included, but researchers have suggested that pain and treatment effects are related to gender, and studies need to be conducted to confirm the effect of gender on the analgesic effect of acupuncture(Mogil, 2020). In addition, the long-term efficacy and recurrence rates of acupuncture analgesia are still understudied, and further studies are needed to explore the long-term maintenance effects and recurrence.

In addition, acupuncture can regulate and provide analgesia for different types of pain from the spatial network formed at three levels: peripheral, spinal cord and brain. However, it is not clear whether the three levels of periphery, spinal cord and brain have equal analgesic effect or which level dominates the analgesic effect in the process of analgesia, and whether the dominant analgesic level is the same in different types of pain is not yet solved, and further experimental studies are still needed. For the same category of pain, the analgesic effect of acupuncture shows significant variability depending on the anatomical site. For example, in neuralgia, when the peripheral nerve is injured, acupuncture can relieve pain by regulating local blood flow, reducing the release of inflammatory mediators, inhibiting abnormal discharges, and so on, and the effect is usually more direct; when the central nervous system is injured, acupuncture can inhibit pain signaling by activating the downward inhibitory pathway, regulating brain function, and affecting the emotion and cognition of pain, and the effect is more extensive but with a large individual variance. It can be seen that this variability mainly stems from the differences in the neuroanatomy, local microenvironment, pain transmission pathways and central nervous system integration in different sites, and further research on these differences can help to optimize the treatment plan and improve the therapeutic efficacy.

Acupuncture analgesia has good application prospects as an effective Chinese medicine treatment. However, the lack of scientific elaboration of its mechanism of action has limited its development and application in modern medicine. In the future, with the deepening of clinical and mechanism studies, we are expected to better understand the mechanism of acupuncture analgesia, formulate the optimal acupuncture prescription, and provide a stronger scientific basis for clinical treatment.

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CRediT authorship contribution statement

Zihe Wang: Writing – original draft. **Peng Qin:** Writing – original draft. **Yuyan Chen:** Writing – review & editing. **Yupei Cheng:** Writing – review & editing. **Longxiao Liu:** Writing – review & editing. **Yuxing Zhang:** Writing – review & editing. **Bangqi Wu:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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