

Stage-Specific Mechanisms of Manual Acupuncture and Electroacupuncture in Inflammatory Pain: A Time-Dependent Review

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Abstract: This narrative review synthesizes preclinical evidence from 54 studies to outline the distinct, stage-dependent mechanisms of manual acupuncture (MA) and electroacupuncture (EA) in inflammatory pain. Following a systematic search, we conducted a detailed thematic analysis of studies using CFA-induced rodent models and organized the findings into three pathological phases: acute (1–3 days), subacute (4–14 days), and chronic (>14 days). The results demonstrate a temporal evolution of therapeutic mechanisms that underscores the necessity of stage-specific intervention strategies for optimizing clinical outcomes. In the acute phase, interventions primarily produce rapid analgesia by engaging immediate descending inhibitory pathways and modulating peripheral ion channels. During the subacute phase, treatments work to counteract central sensitization through immune microenvironment reprogramming and the regulation of synaptic plasticity. For the chronic phase, strategies expand beyond pain relief to alleviate neuropsychiatric comorbidities and promote systemic tissue repair via limbic circuit remodeling. By integrating these findings, this work proposes a time-sensitive mechanistic framework. It underscores the principle of “time-window” optimization for precision acupuncture intervention in inflammatory pain, while also pointing to the critical need for future clinical translation and validation.

Keywords: inflammatory pain, manual acupuncture/electroacupuncture, different pathological stages, mechanisms

Introduction

Inflammation constitutes a fundamental defense mechanism against harmful stimuli, with pain hypersensitivity as one of its hallmark manifestations.¹ However, resolution of inflammation does not necessarily coincide with the remission of pain symptoms. Pain frequently persists beyond resolution, potentially progressing from acute to chronic states.^{2,3} Approximately 27.5% of the global population suffers from chronic pain, with incidence rates varying across regions and countries.⁴ The prolonged persistence and recurrent episodes of pain can severely impact the quality of life.

The pathological evolution of pain follows specific temporal patterns. Within hours, peripheral sensitization emerges, marked by nociceptor activation and reduced local pain thresholds.^{5,6} Within days, activation of spinal pro-inflammatory cells and pathways disrupts normal signal processing in spinal and supraspinal circuits, amplifying nociceptive transmission and establishing central sensitization.^{7–10} Notably, 20–30% of inflammatory arthritis patients exhibit central sensitization.^{7–9} Weeks after onset, structural and functional reorganization of limbic circuits—including the prefrontal cortex, amygdala, and hippocampus—occurs, forming the neural basis for pain-related affective disturbances.^{11,12} These findings underscore the necessity of implementing treatment strategies specific to the therapeutic objectives at each phase of inflammatory pain development.

The World Health Organization recommends manual acupuncture(MA) and electroacupuncture (EA), traditional Chinese therapies with proven analgesic effects,¹³ for 16 inflammation-related conditions among 77 diseases.¹⁴

Currently, numerous animal studies have investigated the mechanisms of MA/EA in treating inflammatory pain, but existing reviews lack a systematic phase-specific mechanistic framework. Most prior syntheses either aggregate findings across disease stages or focus on single pathways, without adequately addressing the dynamic shift in therapeutic targets as the pathology progresses. This limitation obstructs the translation of basic research into clinical practice, as optimal intervention timing and parameters remain undefined.

Complete Freund's adjuvant (CFA)-induced inflammation is the most widely used preclinical model for studying inflammatory pain due to its pathological similarity to human conditions (eg, rheumatoid arthritis), predictable time course of pain progression, and reproducible analgesic responses to MA/EA. Its utility lies in mimicking key features of clinical inflammatory pain, including peripheral sensitization, central sensitization development, and late-stage affective comorbidities, making it ideal for stage-specific mechanistic exploration. However, limitations of the CFA model include its focus on peripheral inflammation and limited representation of clinical comorbidities such as metabolic disorders, which should be considered when interpreting findings.

This review adheres to the narrative synthesis guidelines for evidence-based reviews, systematically categorizing MA/EA interventions based on timing relative to CFA induction. By mapping stage-specific mechanisms, this work aims to: (1) clarify how therapeutic targets evolve with pathological progression; (2) provide graded evidence for clinical intervention optimization; (3) identify critical gaps for future research. The focus on “time-window optimization”—defined as selecting intervention timing, frequency, and duration based on the dominant pathological processes at each stage—aims to enhance treatment precision and efficacy in clinical treatment. Based on this, the review will systematically elucidate the time-dependent mechanisms of MA/EA within three characteristic time windows of the CFA model: the acute phase (1–3 days), the subacute phase (4–14 days), and the chronic phase (>14 days).

Methods

This narrative review was conducted to synthesize preclinical evidence on the stage-specific mechanisms of MA and EA in inflammatory pain. A systematic search was conducted in the PubMed, Web of Science databases and China National Knowledge Infrastructure (CNKI), covering the period from the establishment of the databases until the present day. Key search terms included: “acupuncture”, “electroacupuncture”, “inflammatory pain”, “complete Freund's adjuvant”, “CFA”, “stage”, “phase”, “acute”, “subacute”, “chronic”, “mechanism”, “analgesia”, and their combinations.

Study selection followed a two-step screening process. Initially, a total of 72 records were identified through database searching. After removing duplicates, titles and abstracts were screened against predefined eligibility criteria. Studies were included if they: (1) utilized a CFA-induced inflammatory pain model in rodents; (2) investigated EA or EA interventions; (3) reported mechanistic outcomes related to pain modulation; and (4) specified the intervention timing relative to CFA induction. Exclusion criteria were: (1) non-CFA pain models; (2) clinical studies without mechanistic data; (3) review articles, editorials, or conference abstracts; and (4) publications not in English or Chinese.

Following the initial screening, the full texts of potentially relevant articles were retrieved and thoroughly assessed. This rigorous process resulted in the final inclusion of 54 studies that met all criteria. Data from these studies were systematically extracted, capturing information on study design, animal characteristics, MA/EA parameters (acupoints, frequency, intensity, waveform, duration), precise intervention timeline, outcome measures, and key mechanistic findings.

Given the considerable heterogeneity in experimental protocols, stimulation parameters, and molecular endpoints across the included studies, a quantitative meta-analysis was not feasible. Therefore, a narrative synthesis with thematic analysis was adopted. The extracted findings were categorized and analyzed according to three predefined pathological stages based on the timing of intervention post-CFA: acute (1–3 days), subacute (4–14 days), and chronic (>14 days). This staged framework allowed for a descriptive synthesis of the predominant neurobiological and immunomodulatory mechanisms identified at each phase of inflammatory pain.

Time-Dependent Efficacy and Mechanisms of MA/EA Analgesia

Acute Phase (1-3 Days): Immediate Neural Regulation and Peripheral Target Intervention

In the acute phase of pain (Figure 1 and Table 1), analgesia is the primary goal of MA/EA intervention. Immediate MA/EA after modeling can rapidly regulate nerves and reduce pain, while interventions lasting 24 hours or longer target the peripheral nervous system to achieve sustained analgesia.

Immediate Neural Regulation

Immediate neuromodulation primarily involves the rapid engagement of the descending inhibitory system within hours after model induction. Nociceptive signals reaching supraspinal regions trigger top-down pain control mechanisms from brain areas like the thalamus, hippocampus, amygdala, prefrontal cortex, insular cortex, and anterior cingulate cortex.^{69,70} These pathways predominantly utilize 5-hydroxytryptamine (5-HT), norepinephrine, and dopamine as neurotransmitters,^{71–73} with γ -aminobutyric acid (GABA) and endogenous opioids also contributing substantially.^{74–76} The key targets regulated by acupuncture include μ -opioid receptor (MOR)-expressing neurons in the lumbar spinal cord,^{15,16} Gi/o proteins,¹⁷ and astrocytes within the central nervous system.^{16,18}

Descending inhibitory pathway regulation is a well-validated acute-phase mechanism, with multiple studies converging on key receptor subtypes. Rui-Xin Zhang's team conducted research to identify the specific subtypes responsible for the effects of early EA treatment. Their findings show that intrathecal pretreatment with α 2A-AR or 5-HT1A receptor antagonists blocks the analgesic effect produced by EA both immediately after the model establishment and 2 hours later,

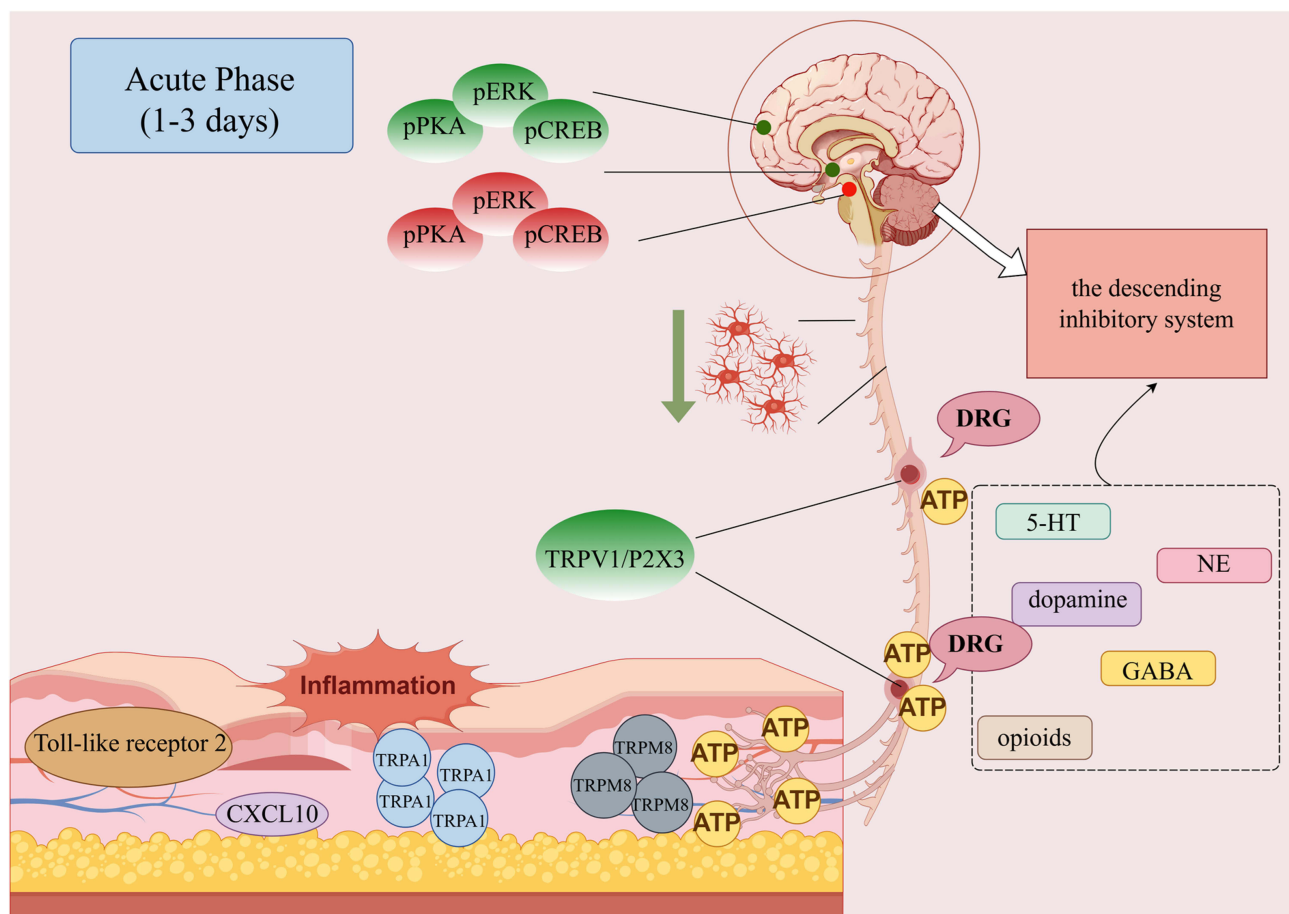


Figure 1 Mechanism of Acupuncture/EA treatment within 1–3 days after modeling. The red gradient background indicates an increase, while the green gradient background indicates a decrease. Created with Figdraw.

Table 1 Summary of Research, Intervention Types, Experimental Animals and Key Mechanisms

Pathological Stage	Study Reference	Intervention Type	Animal	Key Mechanisms
Acute (1–3 days)	Zhang et al (2005) ¹⁵	EA (10 Hz, 3 mA)	Rats	Activates spinal MOR-containing neurons to produce analgesia.
	Liao et al (2017) ¹⁶	EA (2 Hz, 1 mA)	Mice	Suppresses Nav1.8 via S100B, TRPV1, opioid, and adenosine pathways, downregulating inflammatory kinases (pPKC α , pERK, pNF- κ B) and glial markers in DRG and spinal cord.
	Liu et al (2005) ¹⁷	EA (10 Hz, 3 mA)	Rats	Depends on spinal PTX-sensitive Gi/o protein-coupled signaling for analgesia.
	Sun et al (2006) ¹⁸	EA (2 Hz/100 Hz, 1–3mA)	Rats	Enhances analgesia by synergistically inhibiting spinal astrocytes cell function.
	Zhang et al (2012) ¹⁹	EA (10 Hz, 3 mA)	Rats	Involves spinal α 2A adrenergic and 5-HT1A receptors to modulate pain transmission.
	Zhang et al (2011) ²⁰	EA (10 Hz, 3 mA)	Rats	Activates spinal 5-HT1A receptors for analgesia.
	Zhang et al (2011) ²¹	EA (10 Hz, 100 Hz, 2 mA)	Rats	Activates μ -opioid receptors in the RVM to disinhibit descending serotonergic analgesia.
	Zhang et al (2004) ²²	EA (10 Hz, 100 Hz, 3 mA)	Rats	Mediates anti-hyperalgesia via spinal μ and δ , but not κ , opioid receptors; combined with sub-threshold morphine enhances analgesia additively (10 Hz) or synergistically (100 Hz).
	Zhang et al (2005) ²³	EA (10 Hz, 100 Hz, 3 mA)	Rats	Synergizes with NMDA receptor antagonism to prolong opioid-mediated analgesia.
	Li et al (2007) ²⁴	EA (10 Hz, 3 mA)	Rats	Activates descending serotonergic and catecholaminergic pathways from the NRM and LC.
	Yen et al (2019) ²⁵	EA (2 Hz, 1 mA)	Mice	Modulates brain TRPV1 and related kinases (PKA, ERK, CREB) in pain-processing centers.
	Liao et al (2017) ²⁶	EA (2 Hz, 1 mA)	Mice	Suppresses Nav1.8 channel in DRG and SCDH via multiple pathways (S100B, TRPV1, opioid, adenosine).
	Liu et al (2021) ²⁷	EA (100 H/2 Hz, 1–2 mA)	Rats	Inhibits interaction between TRPV1 and P2X3 in DRG neurons in a frequency-dependent manner.
	Yao et al (2024) ²⁸	MA	Mice	Activates TRPA1 channels in local acupoint cells (mast cells, macrophages, fibroblasts).
	Pham et al (2024) ²⁹	EA (2 Hz, 2 mA)	Mice	Utilizes TRPM8 to engage the opioid pathway; shifts to cannabinoid system if TRPM8 is blocked.
	Zuo et al (2022) ³⁰	MA	Rats	Mobilizes extracellular ATP at acupoints to initiate analgesic signaling.
	Shen et al (2021) ³¹	MA	Rats	Modulates eATP levels in DRG and sciatic nerve via regulating hydrolytic enzymes (NTPDases).
	Cui et al (2024) ³²	MA	Mice	Depends on adenosine A1R activation for analgesia.
	Hsu et al (2019) ³³	EA (2 Hz, 1 mA)	Mice	Modulates TLR2 signaling in the DRG, spinal cord and thalamus to affect downstream kinases (PI3K/Akt/mTOR, MAPK) and sodium channels.
	Wang et al (2014) ³⁴	EA (100 Hz, 2–3 mA)	Rats	Recruits opioid peptide-containing macrophages via CXCL10/CXCR3 for peripheral analgesia.
Subacute (4–14 days)	Yu et al (2020) ³⁵	EA (2/100 Hz, 2 mA)	Mice	Induces IL-10 production in the hind paws and spinal cord to promote anti-inflammatory resolution (Tregs in the spleen, reduced pro-inflammatory factors).
	Tanaka et al (2023) ³⁶	EA (2/10 Hz, 0.6 mA)	Mice	Activates peripheral FPR2/ALX to increase IL-10 and antioxidant activity.
	Xu et al (2024) ³⁷	MA	Rats	Upregulates adenosine A3R at the acupoint to inhibit NF- κ B signaling.
	Zhang et al (2020) ³⁸	EA (2/100 Hz, 0.5–1.5 mA)	Rats	Increases adenosine at acupoint to suppress substance P and pro-inflammatory cytokine expression in DRG.
	Zhang et al (2023) ³⁹	EA (2/100 Hz, 0.5–1.5 mA)	Rats	Suppresses spinal oxidative stress (reduces ROS/MDA, increases SOD/CAT) and related signaling (p38, ERK, NF- κ B).
	Chen et al (2009) ⁴⁰	EA (2Hz, 100Hz, 1 mA)	Rats	Increases endogenous anandamide to activate peripheral CB2 receptors.
	Zhang et al (2010) ⁴¹	EA (2Hz, 100Hz, 1 mA)	Rats	Upregulates CB2 receptor expression on skin immune and structural cells.
	Su et al (2011) ⁴²	EA (2 Hz, 1 mA)	Rats	Upregulates β -endorphin in inflamed tissue via CB2 receptor-dependent POMC expression.

(Continued)

Table 1 (Continued).

Pathological Stage	Study Reference	Intervention Type	Animal	Key Mechanisms
	Vieira et al (2021) ⁴³	EA (2–10 Hz, 2–3 mA)	Mice	Engages the pro-resolving ANXA1/FPR2/ALX pathway in skin paw, interacting with the opioid system.
	Deng et al (2023) ⁴⁴	EA (100 Hz, 1 mA)	Rats	Activates the immune checkpoint PD-L1/PD-1-SHP-1 pathway to suppress neuroinflammation in DRG.
	Chen et al (2011) ⁴⁵	EA (2 Hz, 1 mA)	Mice	Downregulates ASIC3 expression in DRG.
	Zhang et al (2022) ⁴⁶	EA (2 Hz, 2 mA)	Mice	Inhibits the pro-inflammatory RIP3/NLRP3 pathway in the spinal dorsal horn.
	Wang et al (2016) ⁴⁷	EA (2/100 Hz, 0.5–1.5 mA)	Rats	Restores the expression of the apelin/APJ system in the spinal cord.
	Lin et al (2020) ⁴⁸	EA (2 Hz, 1 mA)	Mice	Modulates TRPV1 signaling in limbic brain regions to ameliorate pain-depression comorbidity.
	Nan et al (2024) ⁴⁹	EA (2–15 Hz, 1 mA)	Mice	Activates AMPK/SIRT1 to promote microglial M2 polarization in the spinal dorsal horn.
	Chen et al (2022) ⁵⁰	EA (2/100 Hz, 1–2 mA)	Mice	Utilizes spinal neuronal GRK2 to regulate microglial activation and neuroinflammation.
	Sun et al (2008) ⁵¹	EA (2/100 Hz, 1–3 mA)	Rats	Suppresses activation of spinal astrocytes and microglia.
	Wang et al (2024) ⁵²	EA (2/60 Hz, 1 mA)	Rats	Suppresses P2Y12R-dependent microglial activation and M1 polarization in the spinal dorsal horn.
	Lee et al (2013) ⁵³	EA (2 Hz, 1 mA)	Rats	Modulates spinal AMPA receptor GluR2 subunit phosphorylation and expression.
	Han et al (2018) ⁵⁴	EA (2–15 Hz, 1 mA)	Mice	Mediates analgesia via ICA69, regulating spinal GluR2 phosphorylation through PICK1.
	Lan et al (2024) ⁵⁵	EA (2Hz, 1 mA)	Mice	By activating AMPK through CB2 receptor-dependent manner, the expression of β -endorphin in skin macrophages is upregulated, thereby enhancing the analgesic effect of μ -opioid receptors.
	Chen et al (2024) ⁵⁶	EA (15 Hz)	Rats	Activates p38 MAPK and Wnt/ β -Catenin pathways in DEG and SCDH to modulate GABAergic signaling and cytokines.
	Zhang et al (2020) ⁵⁷	EA (2 Hz, 3 mA)	Rats	Causes tolerance by downregulating MKP-1 via Let-7b-5p in the hypothalamus, leading to p38 MAPK activation.
	Gu et al (2020) ⁵⁸	EA (2–15 Hz, 1 mA)	Mice	Attenuates pain by inhibiting CaMKII-GluA1 phosphorylation in the ACC.
	Wang et al (2006) ⁵⁹	EA (4/16 Hz, 0.5–1.5 V)	Rats	Modulates NR1 expression in primary sensory neurons.
Chronic (>14 days)	Yang et al (2023) ⁶⁰	EA (2/15 Hz, 1 mA)	Rats	Upregulates hippocampal BDNF/TrkB/CREB signaling to promote synaptic plasticity.
	Yang et al (2023) ⁶¹	EA (2/15 Hz, 1 mA)	Mice	Activates PI3K/Akt pathway to inhibit hippocampal neuronal apoptosis.
	Ma et al (2025) ⁶²	MA	Mice	Improves neuronal morphology and repairs neural coding in the central amygdala.
	Wu et al (2019) ⁶³	EA (2 Hz, 1–2mA)	Rats	Regulates protein expression in the amygdala (eg, GAPDH, GLT-1, PAK6) to ameliorate pain aversion.
	Wu et al (2023) ⁶⁴	EA (100 Hz, 0.5–2 mA)	Rats	Activates the rACC CaMKII to DRN serotonergic neuron circuit to improve anxiety-like behaviors.
	Miao et al (2023) ⁶⁵	MA	Rats	By down-regulating the TGF- β 1/Smads signaling pathway and promoting myocardial metabolic reprogramming, the myocardial damage caused by rheumatoid arthritis can be alleviated.
	Liu et al (2025) ⁶⁶	EA (2/10 Hz, 1 mA)	Rats	Activates Nrf2 to inhibit hippocampal neuronal ferroptosis.
	Jiang et al (2023) ⁶⁷	EA (2 Hz, 6–7 mA)	Rats	Inhibits synovial angiogenesis by suppressing the Notch1 signaling pathway.
	Su et al (2019) ⁶⁸	EA (2 Hz)	Rats	Induces synovial cell apoptosis by activating the p53 signaling pathway.

whereas pretreatment with α 2B-AR, 5-HT2BR, 5-HT3R, or 5-HT2CR antagonists does not produce this effect.^{19,20} Microinjection of a μ -opioid receptor antagonist into the rostral ventromedial medulla (RVM) and the spinal cord blocks the analgesic effects produced by both 10 Hz and 100 Hz EA immediately post-model establishment, unlike a κ -opioid receptor antagonist does not.^{21,22} These findings are mainly the result of the systematic work of the same research team,

demonstrating that $\alpha 2A$ -AR, 5-HT_{1A}AR, and μ -opioid receptors are the key mediators of the immediate analgesic effect induced by EA stimulation. The co-existence of 5-HT_{1A} receptors and the NMDA receptor NR1 subunit in spinal dorsal horn neurons indicates that NMDA receptors may play a role in the regulation of 5-HT-mediated analgesia by EA.²³ EA stimulation, administered immediately post-modeling and followed by a second session of EA two hours later, activates serotonergic and catecholaminergic neurons in the raphe magnus and locus coeruleus of rats that project to the spinal cord. This activation enhances descending inhibition, inhibiting the transmission of nociceptive information and preventing the development of hyperalgesia.²⁴ Immediate EA stimulation after modeling also reduces the expression of Transient receptor potential V1 (TRPV1)-related molecules-including phosphorylated protein kinase A (pPKA), phosphorylated extracellular signal-regulated kinase (pERK), and phosphorylated cAMP response element-binding protein (pCREB)-in the prefrontal cortex (PFC) and hypothalamus. Interestingly, its expression increases in the periventricular gray matter (PAG).²⁵ The PAG is a key hub of the descending pain inhibitory system.^{77,78} The increased expression of TRPV1-related molecule expression here may enhance PAG-mediated suppression of spinal nociceptive transmission, contributing to immediate analgesia by strengthening top-down pain control.

Peripheral Nerve Targets

The peripheral nervous system is another key component of acute-phase intervention. Acupuncture-induced analgesia within 1–3 days post-model establishment is significantly influenced by the modulation of transient receptor potential (TRP) channels. TRP channels are multimodal ion channels that can detect and transduce chemical toxins and physical stimuli.⁷⁹ These channels are widely distributed in various tissues and cell types. The primary receptors in the skin are TRPV1/4, TRPA1, and TRPM3/8.^{79–81} They serve as sensors for diverse painful stimuli including cold, heat, pressure, mechanical stimuli, and chemical irritants, and are important drug-development targets for pain relief in clinical practice.⁸² Furthermore, TRP channels interact with other ion channels (such as P2X₃, Nav1.8), further intensifying the perception of pain.^{83–86} Moreover, the MAPK and Canonical NF- κ B signaling pathways are implicated as well.⁸²

EA significantly lowers TRPV1 expression in the dorsal root ganglion (DRG), subsequently inhibiting Nav1.8.²⁶ Ultimately, it reduces the excitability of neurons and reverses the mechanical and thermal pain sensitivity induced by inflammation. EA at 100Hz and 2Hz frequencies effectively inhibit TRPV1 and P2X₃ co-activation and interaction in the DRG.²⁷ This phenomenon has been observed in various pain models, suggesting that it may be a relatively common regulatory mechanism. In addition, MA activates the TRPA1 ion channel in mast cells, macrophages, and fibroblasts at acupoints, transmitting mechanical signals through collagen fibers, and converting them into bioelectrical signals, prompting these immune cells to release anti-inflammatory and analgesic-related mediators, thereby exerting analgesic effects.²⁸ TRPM8 is crucial for the analgesic effect of EA through opioid-mediated signaling. When TRPM8 is inhibited or knocked out, the endocannabinoid system provides a compensatory mechanism in acupuncture-induced analgesia.²⁹

The purinergic pathway is another important component of the peripheral analgesic mechanism of short-term acupuncture intervention. In 1996, ATP was first confirmed to initiate nociceptive signaling by activating purinergic receptors on sensory nerve endings.⁸⁷ Specifically, ATP hydrolysis releases energy and generates metabolites such as ADP, AMP, and adenosine. ATP and ADP activate P2X ionotropic receptors and P2Y metabotropic receptors,⁸⁸ while adenosine activates G-protein-coupled receptors (A₁, A_{2A}, A_{2B}, and A₃).⁸⁹ These processes influence neural transmission, immune regulation, inflammatory responses, cardiovascular regulation, and cell proliferation and apoptosis. When the levels of adenosine and its receptors on the cell surface are low, osteoarthritis occurs prematurely.^{90,91} Conversely, G-protein-coupled receptor agonists can effectively prevent spontaneous osteoarthritis in mice.^{92–95}

Regulation of ATP hydrolysis is a key mechanism in short-term acupuncture analgesia, with the modulatory effects varying by intervention duration and observation sites. Studies reveal that MA can induce a transient elevation of ATP expression locally at acupoints within minutes and that analgesic effect is abolished by ATP inhibitors.³⁰ However, prolonged MA over two days reduces ATP expression in the dorsal root ganglia (DRG) and peripheral nerves, while reversing disease-induced aberrant expression of NTPDase-2 and NTPDase-3 mRNA.³¹ These temporal dynamics highlight the adaptability of peripheral purinergic signaling to acupuncture stimulation. Furthermore, EA achieves analgesic effects by directly activating adenosine A₁ receptors in the peripheral nervous system.^{26,32} In summary, MA activates local cells at the acupoints through mechanical force, causing the release of eATP. This eATP is then hydrolyzed

by extracellular nucleotidases to produce adenosine, which binds to the A1 receptor to inhibit the transmission of pain signals. The depth of acupuncture, the technique used, and the body's inflammatory state all affect the analgesic effect by regulating the release of eATP. And A1R antagonists such as caffeine directly block this pathway.

Acupuncture also provides peripheral analgesia by modulating key protein pathways, including Toll-like receptor 2 (TLR2) and CXCL10. TLR2 is a pattern recognition receptor that mediates peripheral inflammatory responses by activating NF- κ B signaling and pro-inflammatory cytokine release (eg, IL-1 β , TNF- α) in acute inflammation.³³ EA inhibits TLR2 overexpression in inflamed tissues, thereby suppressing downstream inflammatory cascades and reducing nociceptor sensitization. CXCL10, a pro-inflammatory chemokine, contributes to acute pain by recruiting immune cells and promoting neuronal hyperexcitability. EA downregulates CXCL10 expression in peripheral tissues, which may attenuate immune cell infiltration and reduce chemokine-mediated nociceptor activation, enhancing peripheral analgesia.³⁴

These immediate mechanisms suggest that MA and EA are effective for rapid pain relief following acute inflammation, primarily by modulating both central pain pathways and peripheral nociceptors. The involvement of neurotransmitter systems (eg, 5-HT, norepinephrine) highlights the importance of neuromodulation in acute pain control. The regulation of TRP channels and purine signaling indicates that a dual strategy has been adopted in dealing with the peripheral components of pain.

Subacute Phase (4-14 Days): Immune Regulation and Synaptic Plasticity Modulation

In this phase, the inflammatory response persists, and central sensitization becomes a core pathological feature (Figure 2 and Table 1). The primary goals of MA/EA intervention shift to suppressing excessive immune-inflammatory responses, reversing central sensitization, and initiating regulation of neural network plasticity. Its effects and mechanisms show distinct characteristics from the acute phase, with persistence and cumulative effects benefits becoming apparent.

Immune Regulation

The MA/EA intervention that lasts until the subacute phase demonstrates potent multi-system and multi-target immune regulatory effects. These effects extend beyond local tissues, impacting the immune microenvironment of the dorsal root ganglion (DRG), spinal cord, and upper central spinal cord. MA/EA modulates anti-inflammatory factors and pathways, notably enhancing IL-10 expression in the foot, intervention acupoints, DRG, and spinal cord of experimental animals, while decreasing IL-1 β , NLRP3, and TNF- α levels.^{35–39} This immune pathway is both multi-targeted and multi-pathway. In the foot, the anti-inflammatory effect involves the CB2 receptors activation,^{40–42} and interactions between FPR2/ALX receptors and opioids.^{36,43} Regulation at acupoints involves upregulation of adenosine A3 receptors and inhibition of the NF- κ B pathway, resulting in an anti-inflammatory effect.³⁷ In the DRG, EA primarily decreases substance P secretion by upregulating adenosine A1 receptors,³⁸ activating programmed death ligand-1 (PD-L1), its receptor PD-1, and its downstream Src homology region two domain-containing phosphatase-1 (SHP-1),⁴⁴ while downregulating acid-sensing ion channel 3 (ASIC3).⁴⁵ In the spinal cord, mechanisms include oxidative stress,³⁹ receptor-interacting protein 3 (RIP3), NOD-like receptor family pyrin domain containing 3 (NLRP3),⁴⁶ and the apelin/apelin receptor (APJ).⁴⁷ Additionally, EA can reverse the decreased expression of TRPV1 in the medial prefrontal cortex, hippocampus, and periventricular gray matter of the midbrain, while down-regulating the excessive expression of TRPV1 in the amygdala and reducing the levels of plasma inflammatory mediators.⁴⁸

Central glial cells, particularly microglia and astrocytes, are core targets of EA immune regulation in this phase.^{49–51} During inflammatory pain, the afferent fibers are rapidly activated and exhibit high-frequency discharges, promoting the local release of inflammatory mediators, which activate microglia, and accelerate the activation process of astrocytes. Activated microglia, in turn, release pro-inflammatory mediators, that sensitize nearby nociceptive neurons and astrocytes, triggering astrocyte activation and proliferation.⁹⁶ Activated astrocytes secrete cytokines, chemokines and enzymes that promoting microglial activation and further aggravate the pain.⁹⁷

However, microglia exhibit functional plasticity: beyond the inflammatory M1 type phenotype, they can also transform into an anti-inflammatory M2 type phenotype under specific conditions.⁹⁸ EA exerts key analgesic effects in the subacute phase by finely regulating glial cell activation and phenotypic transformation.^{49,52} EA suppresses CFA-induced

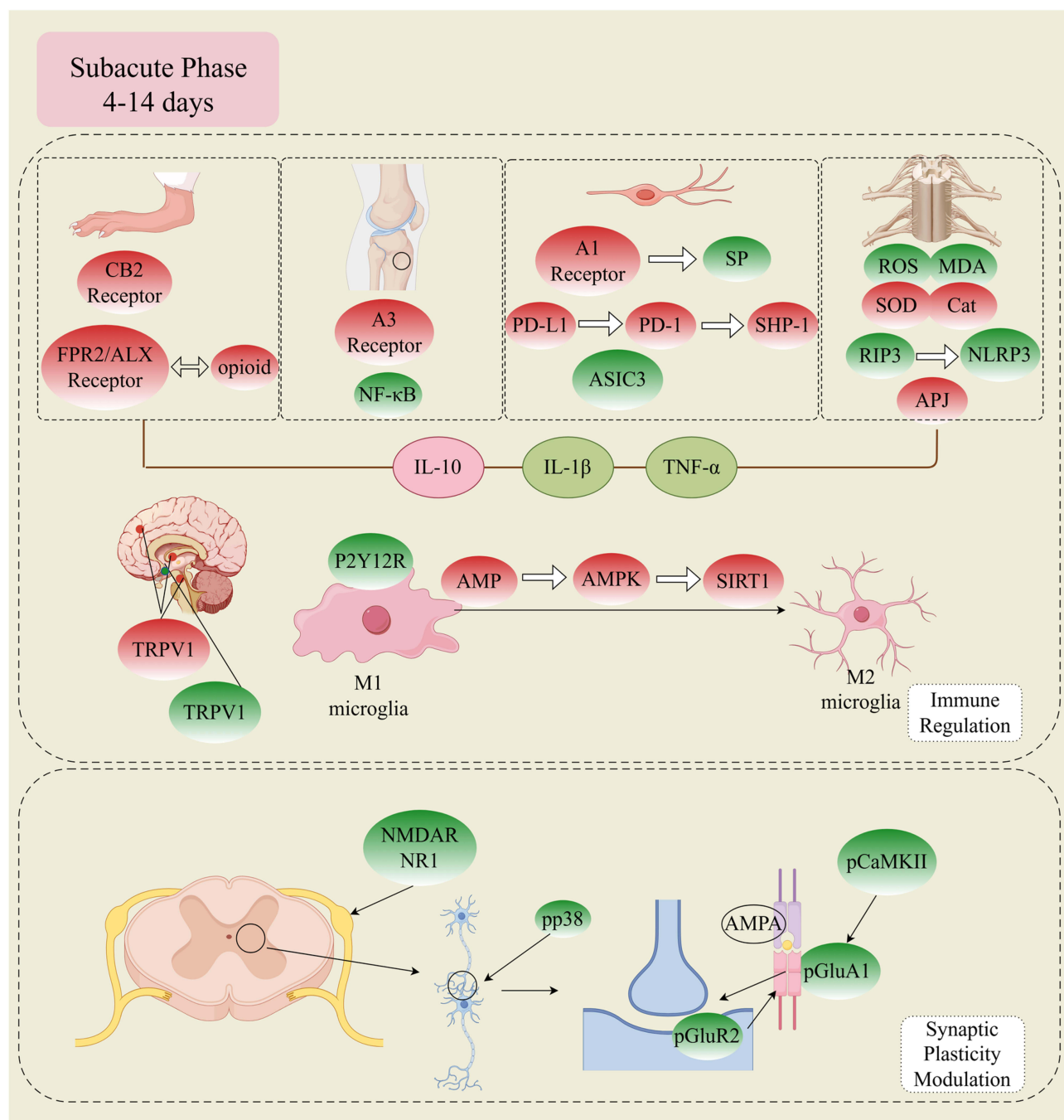


Figure 2 Mechanism of Acupuncture/EA treatment within 4–14 days after modeling. The red gradient background indicates an increase, while the green gradient background indicates a decrease. Created with Figdraw.

P2Y12R overexpression on spinal dorsal horn microglia, a receptor essential for microglial chemotaxis and activation, thereby reducing M1 polarization and proinflammatory responses.⁵² However, regarding the specific upstream signals that regulate the phenotypic transformation of microglia cells through acupuncture, the results from different studies are not entirely consistent. Another study has shown that EA activates adenosine 5'-adenosine monophosphate (AMP) and adenosine monophosphate-activated protein kinase (AMPK) in the dorsal horn of the spinal cord, leading to the upregulating the silent expression information regulator 1 (SIRT1).⁴⁹ This promotes the microglial polarization towards the M2 phenotype, enhancing their anti-inflammatory and reparative functions and produce sustained analgesia.

Nevertheless, the precise pathways by which acupuncture regulates astrocytes remains insufficiently understood and require further investigation.

Synaptic Plasticity Modulation

During the subacute phase (4–14 days), as central sensitization is established, synaptic connections between spinal cord and supraspinal central neurons undergo adaptive changes in structure and function, known as synaptic plasticity. This plasticity is the key cellular mechanism underlying the formation of pain memory, hyperalgesia and pain-related emotions.⁹⁹ MA/EA intervention during this phase has been proven to effectively regulate this abnormal synaptic plasticity and reverse central sensitization.

Regulating the strength of excitatory synaptic transmission at the spinal level is one of the core pathways through which EA modulates in synaptic plasticity. In CFA-induced chronic inflammatory pain, ionotropic glutamate receptors α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) (primarily GluR1 and GluR2 subunits), are activated on spinal cord neuronal membranes.^{100–102} GluR1 aggregation on the postsynaptic membrane intensifies, whereas alterations in GluR2 subunit phosphorylation influence its internalization and membrane stability. Together, these changes enhanced synaptic transmission efficacy, which is an important manifestation of central sensitization.^{103–105}

EA primarily reduces GluR2 phosphorylation. This altered phosphorylation state directly affects the AMPA receptors endocytosis and membrane expression, leading to the reversal of long-term synaptic transmission between primary afferent fibers and spinal dorsal horn projection neurons or interneurons.¹⁰⁶ Through this mechanism, EA regulates central plasticity and achieving analgesia.^{53,54} In addition to directly targeting ion channels, EA indirectly regulates synaptic plasticity by modulating intracellular signal transduction pathways and neuronal metabolic status. Activation of AMPK is an important mechanism by which EA regulates synaptic plasticity. This view has been supported by multiple studies conducted in different laboratories.^{49,55,56} As a master regulator of cellular energy metabolism, AMPK activation not only promotes M2 polarization of microglia but also inhibits proinflammatory and pro-excitatory signaling in neurons, thereby affecting synaptic protein synthesis and receptor trafficking, and ultimately suppressing abnormal synaptic strengthening.^{107–109}

p38 mitogen-activated protein kinase (p38 MAPK) plays a crucial role in mediating inflammation and stress responses. It is highly activated in spinal cord neurons and glial cells and participates in central sensitization.^{110,111} EA inhibits p38 MAPK phosphorylation and activation, reducing pro-inflammatory factor production and neuronal hyperexcitability, thereby aiding in the restoration of synaptic homeostasis.⁵⁷ The role of the p38 MAPK pathway in inflammatory pain has been widely confirmed,¹¹² and acupuncture's inhibition of this pathway is one of the mechanisms with more supporting evidence. Calcium/calmodulin-dependent protein kinase II (CaMKII) serves as a crucial receptor for calcium signaling in neurons. Activation leads to phosphorylation of the GluA1 subunit of AMPA receptors, facilitating their insertion into the postsynaptic membrane and improving synaptic transmission.¹¹³ Research indicates that EA influences synaptic plasticity by modulating the CaMKII-GluA1 signaling pathway.⁵⁸ NMDAR, particularly the NR1 subunit, is crucial for synaptic plasticity induction.^{108,114} EA may inhibit NMDAR NR1 expression in DRG small neurons, potentially affecting DRG neuron function by modifying stress hormone secretion and the autonomic nervous system.⁵⁹

The immune regulation observed in this phase supports the idea that MA and EA not only alleviate pain but also contribute to the reversal of central sensitization and the restoration of normal neural function. The modulation of synaptic plasticity suggests that these interventions help “reset” the pain pathways that are maladaptive in the subacute phase, providing long-term pain relief and potentially preventing chronic pain development.

Chronic Phase (>14 Days): Comorbidity Treatment and Bodily Function Restoration

When inflammatory pain enters the chronic phase (>14 days), pathological changes are no longer limited to pain itself (Figure 3 and Table 1). The adaptive/dysfunctional remodeling of the limbic system that began in the subacute phase has further intensified and solidified, leading to severe neuropsychiatric comorbidity symptoms (such as anxiety, depression, and cognitive impairment), as well as functional disorders of the affected tissues and organs. The goal of MA/EA intervention in this phase shift strategically from focusing solely on analgesia to comprehensively addressing

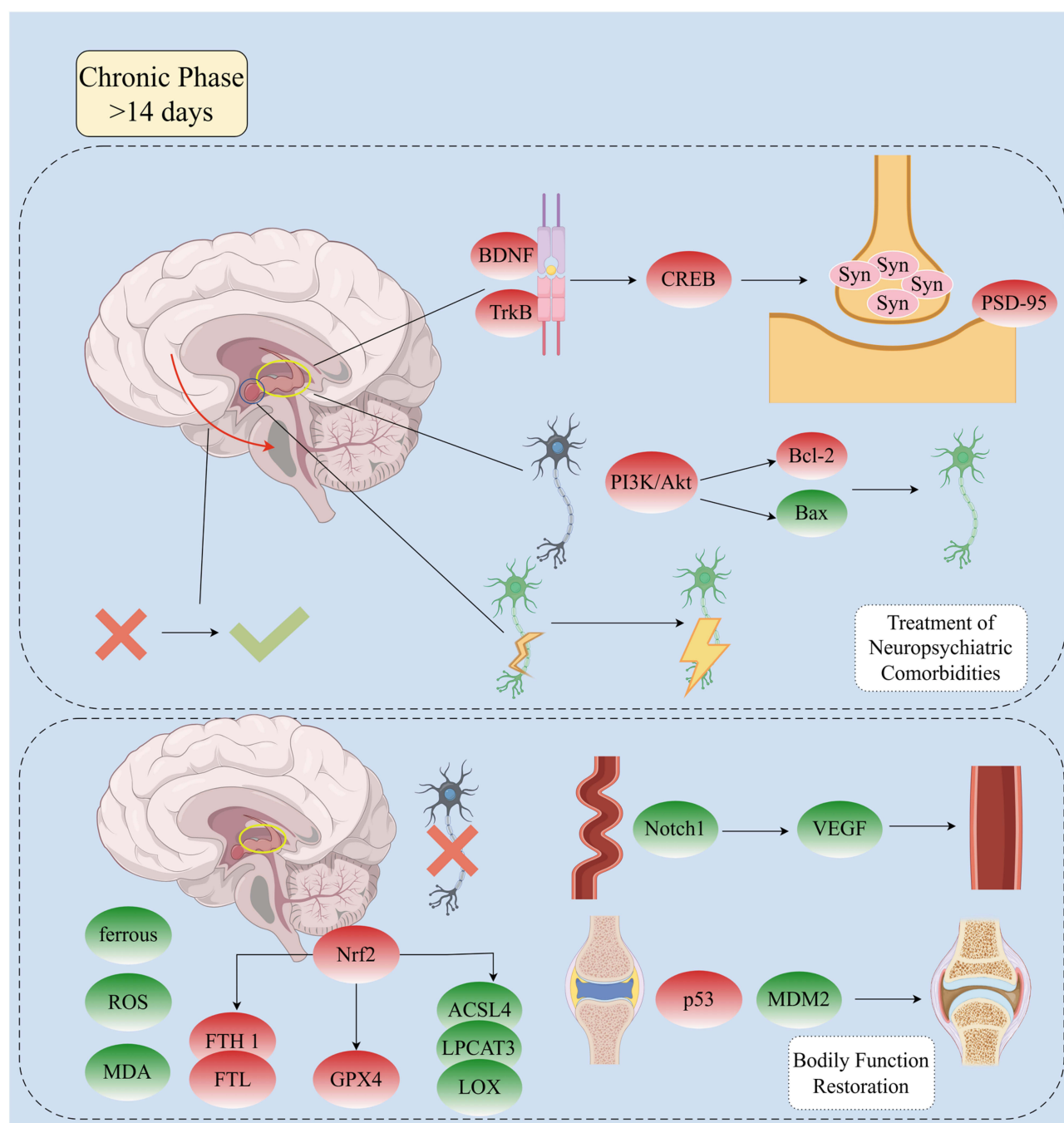


Figure 3 Mechanism of Acupuncture/EA treatment after modeling for more than 14 days. The red gradient background indicates an increase, while the green gradient background indicates a decrease. Created with Figdraw.

neuropsychiatric comorbidities and promoting systemic restoration of damaged bodily functions. Its mechanisms involve neural remodeling in higher brain regions and complex systems biology regulation.

Treatment of Neuropsychiatric Comorbidities

Corresponding to the disease progression, MA and EA interventions are often continued for more than 14 days after the model establishment. These interventions can restore and improve neuronal morphology and function in the limbic system, reshape abnormal neural circuits, alleviating anxiety, depression and cognitive dysfunction associated with pain, and exert broad regulatory effect on neuropsychiatric comorbidities.

The hippocampus plays a crucial role in learning, memory, and emotional regulation. In chronic pain, it often exhibits neuronal atrophy, synaptic loss and reduced neurogenesis.¹¹⁵ The BDNF/TrkB/CREB pathway is the core pathway of neural plasticity.¹¹⁶ EA can stimulate the brain-derived neurotrophic factor (BDNF) and its high-affinity receptor tropomyosin receptor kinase B (TrkB), activating the downstream transcription factor cAMP response element-binding protein (CREB).⁶⁰ This signaling cascade promotes neuronal survival, dendritic complexity, and the expression of synaptic proteins like postsynaptic density protein-95 (PSD-95) and synaptophysin (Syn), thereby protecting and repairing hippocampal synaptic structures, and improving synaptic function. This mechanism is considered central to improve chronic pain-related memory disorders and depressive-like behaviors.⁶⁰ Furthermore, chronic pain can induce apoptosis of hippocampal neurons.¹¹⁷ EA intervention increases Bcl-2 expression and decreases Bax expression. Activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway significantly decreases apoptosis in hippocampal neurons and enhances their survival.⁶¹ The amygdala is a core hub for processing negative emotions such as fear and anxiety, and its neurons often exhibit hyperexcitability and morphological changes in chronic pain.¹¹⁸ MA/EA alleviates pain-related affective disorders by repairing central amygdala neuronal damage, normalizing aberrant neural encoding, and modulating key proteins such as GAPDH, GLT-1, and PAK6, likely through regulating glutamate excitotoxicity and neurotransmitter imbalances.^{62,63} More importantly, EA can intervene in the abnormal neural circuits connecting different brain regions. In CFA-induced chronic pain model rats, the rACC-CaMKII-DRN-5-HT pathway, consisting of CaMKII α -positive excitatory neurons in the rostral anterior cingulate cortex projecting to serotonin-containing neurons in the dorsal raphe nucleus, is dysfunctional.⁶⁴ This pathway is crucial for anxiety regulation. EA treatment specifically activates the damaged neural pathway, enhancing signal transmission from the rACC to the DRN. This regulation of 5-HT-containing neuron activity in the DRN ultimately improves anxiety-like behaviors in chronic pain model animals.⁶⁴ This provides a mechanism explanation at the circuit level for how EA improves pain-related emotions.

Bodily Function Restoration

Chronic inflammatory pain often leads to structural damage and functional loss of affected tissues, accompanied by systemic metabolic disorders and oxidative stress. Long-term EA intervention facilitates bodily functional repair by targeting multiple pathways, including metabolic reprogramming, antioxidant defense enhancement, inhibition of programmed cell death, and vascular homeostasis reconstruction.

EA inhibits the overactivation of the TGF- β 1/Smads signaling pathway, crucial in fibrosis, inflammation, and tissue remodeling. By modulating this pathway, MA regulates amino acid metabolism, glucose, and fatty acid metabolism, thereby optimizing cellular energy utilization and biosynthesis, enhancing cell survival and function in pathological conditions, and contributing to the maintenance and repair of damaged tissues.⁶⁵

Ferroptosis is a newly identified regulated cell death process characterized by iron-dependent lipid peroxidation. In chronic inflammatory pain, hippocampal neurons exhibit iron metabolism disorders, and antioxidant defense systems such as glutathione peroxidase 4 (GPX4) are impaired, leading to lipid peroxides accumulation and increase susceptibility to ferroptosis. This is one of the underlying chronic pain-related cognitive impairment. EA intervention markedly enhances the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) within the cell nucleus. Activation of the Nrf2 pathway boosts the expression of downstream antioxidant enzymes and iron metabolism-related proteins, thereby enhancing the cells' overall antioxidant capacity. This alleviates intracellular iron overload, reduces free iron with strong oxidizing potential and, inhibit lipid peroxidation. Through these combined effects, EA effectively inhibits ferroptosis in hippocampal neurons and protects neurons from oxidative damage.⁶⁶ The research on acupuncture's ability to inhibit ferroptosis in hippocampal neurons through the Nrf2 pathway is currently relatively preliminary, and its specificity and core role need to be further confirmed.

Tissue remodeling and vascular regulation provide the material basis for functional recovery. In chronic inflammation, pathological angiogenesis is often observed, and the newly formed blood vessels are frequently dysfunctional, leading to tissue hypoxia, insufficient nutrient supply, and persistent infiltration, thereby hindering repair.⁶⁷ Studies have shown that EA can effectively inhibit the abnormal activation of the Notch1 signaling pathway, which plays a key regulatory role in vascular development and pathological angiogenesis.¹¹⁹ By inhibiting Notch1 signaling, EA reduces the production of

pro-angiogenic factors such as vascular endothelial growth factor (VEGF), thereby limiting abnormal blood vessels formation, improving microcirculation and oxygenation, and creating favorable conditions for tissue repair.⁶⁷

In the context of joint inflammation, synovial tissue proliferation and inflammatory infiltration are major contributors in joint destruction.^{120,121} EA can selectively induce apoptosis of excessive proliferating and inflammatory synovial cells by upregulating p53 and its downstream pro-apoptotic proteins. This effectively reducing synovial inflammation infiltration, alleviating joint swelling and structural damage, and ultimately promoting the recovery of joint function.⁶⁸

The ability of acupuncture to modulate neuroplasticity pathways such as “BDNF/TrkB/CREB” highlights its potential to alleviate the neuropsychiatric comorbidities associated with chronic pain, such as anxiety and depression. Moreover, the systemic effects on tissue remodeling suggest that acupuncture might be beneficial not just for pain but for restoring function to damaged tissues, offering a holistic approach to managing chronic inflammatory pain.

Discussion

This paper, for the first time, systematically reviewed the time-dependent intervention mechanism of MA/EA for inflammatory pain based on the evolution pattern of diseases, and revealed the core principle that the pathological process and the intervention mechanism are consistent. The study found that the effects of MA/EA play distinct roles in different pathological processes, with mechanisms showing clear characteristics of “from peripheral to central, from low-level to high-level”.

In the acute phase (1–3 days), where the focus is on rapid analgesia, immediate pain relief is achieved by activating descending inhibitory pathways and regulating peripheral TRP channels and purinergic pathways. During this phase, hyperalgesia mainly results from peripheral sensitization. Acupuncture can activate targets such as μ -opioid receptors and 5-HT_{1A}R to exert rapid inhibition of the nociceptive input, while also inhibiting peripheral pain-causing channels such as TRPV1 and P2X₃, achieving rapid pain relief. In the subacute phase (4–14 days), therapeutic focus shifts to reversing central sensitization, emphasizing immune microenvironment reprogramming and synaptic plasticity modulation. As the disease progresses, spinal glial cell activation and synaptic plasticity changes become key factors in maintaining pain. Acupuncture counteracts central sensitization through AMPK/SIRT1-mediated M2 microglial polarization and GluR2 dephosphorylation, reflecting the therapeutic strategy of preventing further progression. In the chronic phase (>14 days), treatment expands to address neuropsychiatric comorbidities and systemic repair, achieving multidimensional functional recovery by reshaping limbic system neural circuits and regulating metabolic and apoptotic pathways. Since chronic pain is often intertwined with neuropsychiatric comorbidities and tissue damage, acupuncture penetrates into the limbic system to repair hippocampal synapses and regulate systemic metabolic homeostasis, demonstrating the concept of holistic regulation. Acupoints associated with the limbic system include commonly used clinical points such as LI4 (Hegu), PC6 (Neiguan), ST36 (Zusanli), and auricular acupoints, which have been shown to modulate activity in the prefrontal cortex, amygdala, and hippocampus through functional neuroimaging studies.^{122–124} These acupoints are preferred in chronic-phase intervention due to their ability to target both pain and affective comorbidities. The temporal and spatial evolution patterns of these mechanisms demonstrate that MA/EA can produce stage-specific therapeutic effects, depending on the body's state. This further validates that acupuncture has multi-system, multi-level, and multi-target treatment effects, providing a theoretical foundation and new perspectives for understanding its stage-specific adaptability and for optimizing clinical intervention strategies.

Notably, MA and EA exhibit distinct mechanistic preferences across different pain stages. Our analysis reveals complementary roles are based on their differing physical stimuli. MA primarily functions as a peripheral initiator, converting mechanical force into local biological signals to trigger analgesic cascades. In contrast, EA acts as a more potent central and systemic modulator. It directly regulates spinal and supraspinal neurotransmission in the acute phase and exerts broad anti-inflammatory/immunomodulatory effects in the subacute phase. Regarding chronic pain, EA's mechanisms extend to higher-order neural plasticity and limbic circuit remodeling, whereas supporting evidence for MA at this stage is limited. Therefore, MA and EA form a functional complement in the mechanism of pain relief: MA focuses on peripheral initiation, while EA excels in central regulation and systemic integration. This advantage in central regulation is particularly evident in acute rapid pain relief: high-frequency, short-duration EA can most effectively match the explosive transmission of pain signals by rapidly enhancing spinal opioid release, inhibiting key ion channels, and

quickly activating the descending inhibitory pathways in the brainstem, achieving immediate blocking of pain signals. This is in stark contrast to slower-acting, more accumulation-dependent low-frequency stimulation or chronic-phase treatments that target long-term plasticity.

Based on the aforementioned preclinical mechanism evidence, we propose a clinically feasible and stage-appropriate strategy framework that can be verified in the future. This study provides key insights for clinical practice: theoretically, intervention time windows must be individualized. In the acute phase, high-frequency short-term EA should be used to achieve rapid pain relief. In the subacute phase, the treatment duration must be sufficient to accumulate the immune regulatory effect. In the chronic phase, treatment duration should be extended to repair the neuropsychiatric comorbidities. Additionally, precision in target selection is essential: intervention targets should correspond to predominant symptoms at each stage. In the acute phase, acupoints should focus on the nerve trunks distribution, whereas in the chronic phase, the priority should be given to acupoints associated with the limbic system. However, the effectiveness of these specific strategies, the optimal parameters, and their feasibility in real clinical settings still need to be verified through well-designed randomized controlled trials. It is particularly important to note that the “stage-dependent mechanism framework” proposed in this paper, as well as the concepts of “precise acupuncture” and “time window optimization”, are mainly the result of integrating existing preclinical research data and theoretical deductions. Although animal models provide a valuable window for exploring mechanisms under controlled conditions, their findings cannot be directly translated to human disease situations. Currently, there remains a lack of clinical studies that rigorously validate whether these stage-specific intervention strategies are effective in patients and how to implement them optimally. Therefore, the core contribution of this paper lies in systematically reviewing the evidence and proposing a testable hypothesis framework. Future translational research should aim to fill this gap by conducting clinical trials to test these mechanism-based hypotheses and explore specific methods for linking disease staging with acupuncture treatment plans.

Despite constructing a stage-dependent mechanism framework, this study still has limitations. First, inherent evidence heterogeneity—this mainly stems from differences in MA/EA stimulation parameters; inconsistencies in animal strains, CFA injection details, and behavioral assessment methods; and diversity in molecular detection time points and indicators. Therefore, the relative contributions of specific pathways, their causal relationships, and the generalizability of the findings all need further consolidation through standardized, large-scale preclinical studies. Second, this review is confined to CFA-induced models, which carry inherent limitations. The CFA model focuses on peripheral inflammation, inadequately capturing clinical complexities like mixed pain or affective comorbidities. For meaningful clinical translation, the proposed framework requires validation across other pain models and, ultimately, in human studies. Third, the widespread lack of standardized reporting in the included literature hinders a quantitative synthesis of the strength of evidence. Future reviews should, where feasible, employ systematic review and meta-analytic methods to address this gap. Fourth, contextual factors such as placebo and nocebo effects are discussed but not integrated into the mechanistic framework due to limited preclinical data, highlighting the need for more studies combining behavioral pharmacology and neuroimaging to dissect these effects.^{125–128}

Future research should prioritize several directions: (1) identifying optimal acupuncture parameters for each stage through factorial design studies; (2) carrying out clinical trials to validate stage-specific intervention strategies, particularly comparing acupuncture with conventional analgesics and exploring synergistic effects; (3) applying multi-omics technologies to uncover novel stage-specific targets and molecular memory mechanisms of cumulative acupuncture effects; (4) examining contextual effects and their interaction with biological mechanisms to develop comprehensive intervention approaches; (5) promoting standardized reporting guidelines and encouraging independent replication studies to address evidence heterogeneity.

Our research aims to provide a clear framework for guiding future mechanistic studies. Researchers can select disease stages for intervention based on objectives, focusing on specific targets and pathways. Clinicians, in turn, should tailor treatment courses based on the patient’s disease stage and main symptoms to maximize therapeutic effects.

Conclusion

In summary, building on the principle of disease stage progression, this study systematically elucidates the time-dependent intervention mechanisms of MA/EA on inflammatory pain. It demonstrates that MA/EA exerts different effects across distinct pathological stages, with mechanisms characterized by a progression “from peripheral to central, from low-level to high-level”, as well as consistency between pathological progression and intervention mechanisms. This mechanistic framework, which is derived from preclinical research, not only offers crucial insights for future clinical practice, such as the potential significance of individualized determination of intervention time windows and precise target selection. These help to refine intervention strategies and improve therapeutic effects, but also identifies urgent directions for future research, including cross-stage mechanism interaction networks, clinical validation, and multi-omics integration. However, to translate it into routine clinical practice, it is necessary to overcome the gap in transformation from animal models to human patients. As these issues are gradually addressed, the theoretical system of acupuncture for inflammatory pain treatment will be further improved, laying a solid foundation for its wider application and precise implementation in clinical practice.

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Author Contributions

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

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. *Nat Rev Drug Discov*. 2014;13(7):533–548. doi:10.1038/nrd4334
2. Zhu Y, Jiang Y, Lu X, et al. Curcumin relieves CFA-induced inflammatory pain by inhibiting the AP-1/c-Jun-CCL2-CCR2 pathway in the spinal dorsal horn. *Mol Pain*. 2025;21:17448069251323668. doi:10.1177/17448069251323668
3. van der Vlist M, Raoof R, Willemen H, et al. Macrophages transfer mitochondria to sensory neurons to resolve inflammatory pain. *Neuron*. 2022;110(4):613–626.e9. doi:10.1016/j.neuron.2021.11.020
4. Zimmer Z, Fraser K, Grol-Prokopczyk H, Zajacova A. A global study of pain prevalence across 52 countries: examining the role of country-level contextual factors. *Pain*. 2022;163(9):1740–1750. doi:10.1097/j.pain.0000000000002557
5. Julius D. TRP channels and pain. *Annu Rev Cell Dev Biol*. 2013;29:355–384.
6. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell*. 2009;139(2):267–284. doi:10.1016/j.cell.2009.09.028
7. Lau BK, Vaughan CW. Descending modulation of pain: the GABA disinhibition hypothesis of analgesia. *Curr Opin Neurobiol*. 2014;29:159–164. doi:10.1016/j.conb.2014.07.010
8. Sarzi-Putini P, Pellegrino G, Giorgi V, et al. “Inflammatory or non-inflammatory pain in inflammatory arthritis - How to differentiate it? *Best Pract Res Clin Rheumatol*. 2024;38(1):101970. doi:10.1016/j.berh.2024.101970
9. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 Suppl):S2–S15. doi:10.1016/j.pain.2010.09.030
10. Ji -R-R, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiology*. 2018;129(2):343–366. doi:10.1097/ALN.0000000000002130
11. Ren W-J, Liu Y, Zhou L-J, et al. Peripheral nerve injury leads to working memory deficits and dysfunction of the hippocampus by upregulation of TNF- α in rodents. *Neuropsychopharmacology*. 2011;36(5):979–992. doi:10.1038/npp.2010.236

12. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci.* 2013;14(7):502–511. doi:10.1038/nrn3516
13. Zhang R, Lao L, Ren K, Berman BM. Mechanisms of acupuncture-electroacupuncture on persistent pain. *Anesthesiology.* 2014;120(2):482–503. doi:10.1097/ALN.0000000000000101
14. Zhang Q, Zhou M, Huo M, et al. Mechanisms of acupuncture-electroacupuncture on inflammatory pain. *Mol Pain.* 2023;19:17448069231202882. doi:10.1177/17448069231202882
15. Zhang R-X, Wang L, Liu B, et al. Mu opioid receptor-containing neurons mediate electroacupuncture-produced anti-hyperalgesia in rats with hind paw inflammation. *Brain Res.* 2005;1048(1–2):235–240. doi:10.1016/j.brainres.2005.05.008
16. Liao H-Y, Hsieh C-L, Huang C-P, Lin Y-W. Electroacupuncture attenuates induction of inflammatory pain by regulating opioid and adenosine pathways in mice. *Scient Rep.* 2017;7(1). doi:10.1038/s41598-017-16031-y
17. Liu B, Zhang R-X, Wang L, et al. Effects of pertussis toxin on electroacupuncture-produced anti-hyperalgesia in inflamed rats. *Brain Res.* 2005;1044(1):87–92. doi:10.1016/j.brainres.2005.03.006
18. Sun S, Chen W-L, Wang P-F, Zhao Z-Q, Zhang Y-Q. Disruption of glial function enhances electroacupuncture analgesia in arthritic rats. *Exp Neurol.* 2006;198(2):294–302. doi:10.1016/j.expneurol.2005.11.011
19. Zhang Y, Zhang RX, Zhang M, et al. Electroacupuncture inhibition of hyperalgesia in an inflammatory pain rat model: involvement of distinct spinal serotonin and norepinephrine receptor subtypes. *Brit J Anaesthesia.* 2012;109(2):245–252. doi:10.1093/bja/aes136
20. Zhang Y, Li A, Xin J, et al. Involvement of spinal serotonin receptors in electroacupuncture anti-hyperalgesia in an inflammatory pain rat model. *Neurochem Res.* 2011;36(10):1785–1792. doi:10.1007/s11064-011-0495-1
21. Zhang Y, Li A, Lao L, et al. Rostral ventromedial medulla μ , but not κ , opioid receptors are involved in electroacupuncture anti-hyperalgesia in an inflammatory pain rat model. *Brain Res.* 2011;1395:38–45. doi:10.1016/j.brainres.2011.04.037
22. Zhang R-X, Lao L, Wang L, et al. Involvement of opioid receptors in electroacupuncture-produced anti-hyperalgesia in rats with peripheral inflammation. *Brain Res.* 2004;1020(1–2):12–17. doi:10.1016/j.brainres.2004.05.067
23. Zhang R, Wang L, Wang X, Ren K, Berman B, Lao L. Electroacupuncture combined with MK-801 prolongs anti-hyperalgesia in rats with peripheral inflammation. *Pharmacol Biochem Behav.* 2005;81(1):146–151. doi:10.1016/j.pbb.2005.03.002
24. Li A, Wang Y, Xin J, et al. Electroacupuncture suppresses hyperalgesia and spinal Fos expression by activating the descending inhibitory system. *Brain Res.* 2007;1186:171–179. doi:10.1016/j.brainres.2007.10.022
25. Yen C-M, Wu T-C, Hsieh C-L, Huang Y-W, Lin Y-W. Distal electroacupuncture at the LI4 acupoint reduces CFA-induced inflammatory pain via the brain TRPV1 signaling pathway. *Int J Mol Sci.* 2019;20(18):4471. doi:10.3390/ijms20184471
26. Liao H-Y, Hsieh C-L, Huang C-P, Lin Y-W. Electroacupuncture attenuates CFA-induced inflammatory pain by suppressing Nav1.8 through S100B, TRPV1, opioid, and adenosine pathways in mice. *Scient Rep.* 2017;7(1):42531. doi:10.1038/srep42531
27. Liu Y, Du J, Fang J, et al. Electroacupuncture inhibits the interaction between peripheral TRPV1 and P2X3 in rats with different pathological pain. *Physiol Res.* 2021;70(4):635–647. doi:10.33549/physiolres.934649
28. Yao K, Chen Z, Li Y, et al. TRPA1 ion channel mediates the analgesic effects of acupuncture at the ST36 acupoint in mice suffering from arthritis. *J Inflamm Res.* 2024;17:1823–1837. doi:10.2147/JIR.S455699
29. Pham D-T, Hsu R-M, Sun M-F, Huang -C-C, Chen Y-H, Lin J-G. TRPM8's role in the shift between opioid and cannabinoid pathways in electroacupuncture for inflammatory pain in mice. *Int J Mol Sci.* 2024;25(23):13000. doi:10.3390/ijms252313000
30. Zuo W-M, Li Y-J, Cui K-Y, et al. The real-time detection of acupuncture-induced extracellular ATP mobilization in acupoints and exploration of its role in acupuncture analgesia. *Purinergic Signalling.* 2022;19(1):69–85. doi:10.1007/s11302-021-09833-3
31. Shen D, Zheng Y-W, Shen D, Zhang X-Y, Wang L-N. Acupuncture modulates extracellular ATP levels in peripheral sensory nervous system during analgesia of ankle arthritis in rats. *Purinergic Signalling.* 2021;17(3):411–424. doi:10.1007/s11302-021-09777-8
32. Cui X, Wei W, Zhang Z, et al. Caffeine impaired acupuncture analgesia in inflammatory pain by blocking adenosine A1 receptor. *J Pain.* 2024;25(4):1024–1038. doi:10.1016/j.jpain.2023.10.025
33. Hsu H-C, Hsieh C-L, Wu S-Y, Lin Y-W. Toll-like receptor 2 plays an essential role in electroacupuncture analgesia in a mouse model of inflammatory pain. *Acupuncture Med.* 2019;37(6):356–364. doi:10.1136/acupmed-2017-011469
34. Wang Y, Gehring R, Mousa SA, Hackel D, Brack A, Rittner HL. CXCL10 controls inflammatory pain via opioid peptide-containing macrophages in electroacupuncture. *PLoS One.* 2014;9(4):e94696. doi:10.1371/journal.pone.0094696
35. M-I Y, R-d W, Zhang T, et al. Electroacupuncture relieves pain and attenuates inflammation progression through inducing IL-10 production in CFA-induced mice. *Inflammation.* 2020;43(4):1233–1245. doi:10.1007/s10753-020-01203-2
36. Tanaka F, Mazzardo G, Salm DC, et al. Peripheral activation of formyl peptide receptor 2/ALX by electroacupuncture alleviates inflammatory pain by increasing interleukin-10 levels and catalase activity in mice. *Neuroscience.* 2023;529:1–15. doi:10.1016/j.neuroscience.2023.08.004
37. Xu J-P, Ouyang Q-W, Shao M-J, et al. Manual acupuncture ameliorates inflammatory pain by upregulating adenosine A3 receptor in complete Freund's adjuvant-induced arthritis rats. *Int Immunopharmacol.* 2024;133:112095. doi:10.1016/j.intimp.2024.112095
38. Zhang R, Zhu B, Wang L, et al. Electroacupuncture alleviates inflammatory pain via adenosine suppression and its mediated substance P expression. *Arquivos de Neuro-Psiquiatria.* 2020;78(10):617–623. doi:10.1590/0004-282x20200078
39. Zhang R, Zhu B, Zhao J, Wang L, Zhao L. Electroacupuncture stimulation alleviates inflammatory pain in male rats by suppressing oxidative stress. *Physiol Res.* 2023;72(5):657–667. doi:10.33549/physiolres.934965
40. Chen L, Zhang J, Li F, et al. Endogenous anandamide and cannabinoid receptor-2 contribute to electroacupuncture analgesia in rats. *J Pain.* 2009;10(7):732–739. doi:10.1016/j.jpain.2008.12.012
41. Zhang J, Chen L, Su T, et al. Electroacupuncture increases CB2 receptor expression on keratinocytes and infiltrating inflammatory cells in inflamed skin tissues of rats. *J Pain.* 2010;11(12):1250–1258. doi:10.1016/j.jpain.2010.02.013
42. Su T-F, Zhang L-H, Peng M, et al. Cannabinoid CB2 receptors contribute to upregulation of β -endorphin in inflamed skin tissues by electroacupuncture. *Mol Pain.* 2011;7:7. doi:10.1186/1744-8069-7-7
43. Vieira C, Salm DC, Horewicz VV, et al. Electroacupuncture decreases inflammatory pain through a pro-resolving mechanism involving the peripheral annexin A1-formyl peptide receptor 2/ALX-opioid receptor pathway. *Pflugers Arch.* 2021;473(4):683–695. doi:10.1007/s00424-020-02502-1

44. Deng D, Xu F, Ma L, et al. Electroacupuncture alleviates CFA-induced inflammatory pain via PD-L1/PD-1-SHP-1 pathway. *Mol Neurobiol.* 2023;60(5):2922–2936. doi:10.1007/s12035-023-03233-x
45. Chen WH, Hsieh CL, Huang CP, et al. Acid-sensing ion channel 3 mediates peripheral anti-hyperalgesia effects of acupuncture in mice inflammatory pain. *J Biomed Sci.* 2011;18(1):82. doi:10.1186/1423-0127-18-82
46. Zhang Y, Wang Y, Zhao W, et al. Role of spinal RIP3 in inflammatory pain and electroacupuncture-mediated analgesic effect in mice. *Life Sci.* 2022;306:120839. doi:10.1016/j.lfs.2022.120839
47. Wang K, Ju Z, Yong Y, Chen T, Song J, Zhou J. The effects of electroacupuncture on the Apelin/APJ system in the spinal cord of rats with inflammatory pain. *Anesthesia Analgesia.* 2016;123(6):1603–1610. doi:10.1213/ANE.0000000000001535
48. Lin Y-W, Chou AIW, Su H, Su K-P. Transient receptor potential V1 (TRPV1) modulates the therapeutic effects for comorbidity of pain and depression: the common molecular implication for electroacupuncture and omega-3 polyunsaturated fatty acids. *Brain Behav Immun.* 2020;89:604–614. doi:10.1016/j.bbi.2020.06.033
49. Nan F-B, Gu Y-X, Wang J-L, Chen S-D. Electroacupuncture promotes macrophage/microglial M2 polarization and suppresses inflammatory pain through AMPK. *NeuroReport.* 2024;35(6):343–351. doi:10.1097/WNR.0000000000002005
50. Chen Y, Zhou Y, Li X-C, et al. Neuronal GRK2 regulates microglial activation and contributes to electroacupuncture analgesia on inflammatory pain in mice. *Biol Res.* 2022;55(1):5. doi:10.1186/s40659-022-00374-6
51. Sun S, Cao H, Han M, Li TT, Zhao ZQ, Zhang YQ. Evidence for suppression of electroacupuncture on spinal glial activation and behavioral hypersensitivity in a rat model of monoarthritis. *Brain Res Bull.* 2008;75(1):83–93. doi:10.1016/j.brainresbull.2007.07.027
52. Wang J, Song W, Zhang Y, et al. Electroacupuncture alleviates pain by suppressing P2Y12R-dependent microglial activation in monoarthritic rats. *Neurochem Res.* 2024;49(5):1268–1277. doi:10.1007/s11064-024-04114-y
53. Lee Y-S, Lee J-H, Lee I-S, Choi B-T. Effects of electroacupuncture on spinal α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor in rats injected with complete Freund's adjuvant. *Mol Med Rep.* 2013;8(4):1130–1134. doi:10.3892/mmr.2013.1633
54. Han K, Zhang A, Mo Y, et al. Islet-cell autoantigen 69 mediates the antihyperalgesic effects of electroacupuncture on inflammatory pain by regulating spinal glutamate receptor subunit 2 phosphorylation through protein interacting with C-kinase 1 in mice. *Pain.* 2018;160(3):712–723. doi:10.1097/j.pain.0000000000001450
55. Lan Y, Jing X, Zhou Z, et al. Electroacupuncture ameliorates inflammatory pain through CB2 receptor-dependent activation of the AMPK signaling pathway. *Chin Med.* 2024;19(1):176. doi:10.1186/s13020-024-01048-z
56. Chen R, Li M, Ding M. Optogenetic stimulation of the “Zusanli” acupoint alleviates inflammatory pain through active Wnt/ β -Catenin and MAPK signaling pathway in rats. *Heliyon.* 2024;10(21):e39992. doi:10.1016/j.heliyon.2024.e39992
57. Zhang Q, Abouelfetouh MM, Chen S, Li M, Ding M, Ding Y. MicroRNA Let-7b-5p induces electroacupuncture tolerance by downregulating the MKP-1 gene in rats subjected to CFA-induced inflammatory nociception. *J Mol Neurosci.* 2020;70(8):1198–1207. doi:10.1007/s12031-020-01527-6
58. Gu Y, Chen S, Mo Y, et al. Electroacupuncture attenuates CFA-induced inflammatory pain by regulating CaMKII. *Neural Plast.* 2020;2020:1–12. doi:10.1155/2020/8861994
59. Wang L, Zhang Y, Dai J, Yang J, Gang S. Electroacupuncture (EA) modulates the expression of NMDA receptors in primary sensory neurons in relation to hyperalgesia in rats. *Brain Res.* 2006;1120(1):46–53. doi:10.1016/j.brainres.2006.08.077
60. Yang P, Chen H, Wang T, et al. Electroacupuncture promotes synaptic plasticity in rats with chronic inflammatory pain-related depression by upregulating BDNF/TrkB/CREB signaling pathway. *Brain Behav.* 2023;13(12):e3310. doi:10.1002/brb3.3310
61. Yang P, Chen H, Wang T, et al. Electroacupuncture attenuates chronic inflammatory pain and depression comorbidity by inhibiting hippocampal neuronal apoptosis via the PI3K/Akt signaling pathway. *Neurosci Lett.* 2023;812: 137411.
62. Ma C, Zhang R-Z, Lu H-Y, Dou -T-T, Li L, Yan X-K. The effect of acupuncture on the morphology and neural coding damage of the central amygdala in mice with chronic inflammatory pain and depression. *J Inflamm Res.* 2025;18:3255–3268. doi:10.2147/JIR.S501170
63. Wu Y, Jiang Y, Shao X, et al. Proteomics analysis of the amygdala in rats with CFA-induced pain aversion with electroacupuncture stimulation. *J Pain Res.* 2019;12:3067–3078. doi:10.2147/JPR.S211826
64. Wu Z, Shen Z, Xu Y, et al. A neural circuit associated with anxiety-like behaviors induced by chronic inflammatory pain and the anxiolytic effects of electroacupuncture. *CNS Neurosc Therapeut.* 2023;30(4):e14520. doi:10.1111/cns.14520
65. Miao W, Yan Z, Hui Z, Hongfang Z. Moxibustion enables protective effects on rheumatoid arthritis-induced myocardial injury transforming growth factor β 1 signaling and metabolic reprogramming. *J Tradit Chin Med.* 2023;43(6):1190–1199. doi:10.19852/j.cnki.jtcm.20230802.005
66. Liu G, Shi D, Liu D, Wang Z, Fu W. Electroacupuncture ameliorates chronic inflammatory pain and depression comorbidity by inhibiting Nrf2-mediated ferroptosis in hippocampal neurons. *Neurochem Res.* 2025;50(3):149. doi:10.1007/s11064-025-04401-2
67. Jianzhen J, Xin Z, Zhenguo L, et al. Efficacy of electroacupuncture stimulating Zusanli (ST36) and Xuanzhong (GB39) on synovial angiogenesis in rats with adjuvant arthritis. *J Tradit Chin Med.* 2023;43(5):955–962. doi:10.19852/j.cnki.jtcm.20221111.002
68. Su C, Chen Y, Chen Y, et al. Effect of electroacupuncture at the ST36 and GB39 acupoints on apoptosis by regulating the p53 signaling pathway in adjuvant arthritis rats. *Mol Med Rep.* 2019;20(5):4101–4110. doi:10.3892/mmr.2019.10674
69. Bannister K, Dickenson AH. The plasticity of descending controls in pain: translational probing. *J Physiol.* 2017;595(13):4159–4166. doi:10.1113/JP274165
70. Kwon M, Altin M, Duenas H, Alev L. The role of descending inhibitory pathways on chronic pain modulation and clinical implications. *Pain Pract.* 2014;14(7):656–667. doi:10.1111/papr.12145
71. Stamford JA. Descending control of pain. *Br J Anaesth.* 1995;75(2):217–227. doi:10.1093/bja/75.2.217
72. Zhao ZQ, Chiechio S, Sun YG, et al. Mice lacking central serotonergic neurons show enhanced inflammatory pain and an impaired analgesic response to antidepressant drugs. *J Neurosci.* 2007;27(22):6045–6053. doi:10.1523/JNEUROSCI.1623-07.2007
73. Pertovaara A. Noradrenergic pain modulation. *Prog Neurobiol.* 2006;80(2):53–83. doi:10.1016/j.pneurobio.2006.08.001
74. Willer JC, Le Bars D, De Broucker T. Diffuse noxious inhibitory controls in man: involvement of an opioidergic link. *Eur J Pharmacol.* 1990;182(2):347–355. doi:10.1016/0014-2999(90)90293-F
75. Le Bars D, Chitour D, Kraus E, Dickenson AH, Besson JM. Effect of naloxone upon diffuse noxious inhibitory controls (DNIC) in the rat. *Brain Res.* 1981;204(2):387–402. doi:10.1016/0006-8993(81)90597-7

76. Huang J, Gadotti VM, Chen L, et al. A neuronal circuit for activating descending modulation of neuropathic pain. *Nat Neurosci.* 2019;22(10):1659–1668. doi:10.1038/s41593-019-0481-5
77. Lin HC, Park HJ, Liao HY, Chuang KT, Lin YW. Accurate chemogenetics determines electroacupuncture analgesia through increased CB1 to suppress the TRPV1 Pathway in a mouse model of fibromyalgia. *Life.* 2025;15(5):819.
78. Madasu MK, Okine BN, Olango WM, et al. Genotype-dependent responsivity to inflammatory pain: a role for TRPV1 in the periaqueductal grey. *Pharmacol Res.* 2016;113(Pt A):44–54. doi:10.1016/j.phrs.2016.08.011
79. Chen Y, Mu J, Zhu M, Mukherjee A, Zhang H. Transient receptor potential channels and inflammatory bowel disease. *Front Immunol.* 2020;11:180. doi:10.3389/fimmu.2020.00180
80. Muller C, Morales P, Reggio PH. Cannabinoid ligands targeting TRP channels. *Front Mol Neurosci.* 2018;11:487. doi:10.3389/fnmol.2018.00487
81. Chen M, Li X. Role of TRPV4 channel in vasodilation and neovascularization. *Microcirculation.* 2021;28(6):e12703. doi:10.1111/micc.12703
82. Zhang M, Ma Y, Ye X, Zhang N, Pan L, Wang B. TRP (transient receptor potential) ion channel family: structures, biological functions and therapeutic interventions for diseases. *Signal Transduct Target Ther.* 2023;8(1):261. doi:10.1038/s41392-023-01464-x
83. Chaban VV. Visceral sensory neurons that innervate both uterus and colon express nociceptive TRPV1 and P2X3 receptors in rats. *Ethn Dis.* 2008;18(2 Suppl 2):S2–20–4.
84. Piper AS, Docherty RJ. One-way cross-desensitization between P2X purinoceptors and vanilloid receptors in adult rat dorsal root ganglion neurones. *J Physiol.* 2000;523 Pt 3(Pt 3):685–696. doi:10.1111/j.1469-7793.2000.t01-1-00685.x
85. Yu J, Du J, Fang J, et al. The interaction between P2X3 and TRPV1 in the dorsal root ganglia of adult rats with different pathological pains. *Mol Pain.* 2021;17:17448069211011315. doi:10.1177/17448069211011315
86. Riol-Blanco L, Ordoñas-Montanes J, Perro M, et al. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. *Nature.* 2014;510(7503):157–161. doi:10.1038/nature13199
87. Burnstock G. A unifying purinergic hypothesis for the initiation of pain. *Lancet.* 1996;347(9015):1604–1605. doi:10.1016/S0140-6736(96)91082-X
88. Muñoz MF, Griffith TN, Contreras JE. Mechanisms of ATP release in pain: role of pannexin and connexin channels. *Purinergic Signal.* 2021;17(4):549–561. doi:10.1007/s11302-021-09822-6
89. Borea PA, Gessi S, Merighi S, Vincenzi F, Varani K. Pharmacology of adenosine receptors: the state of the art. *Physiol Rev.* 2018;98(3):1591–1625. doi:10.1152/physrev.00049.2017
90. Ichikawa N, Taniguchi A, Kaneko H, et al. Arterial calcification due to deficiency of CD73 (ACDC) as one of rheumatic diseases associated with periarticular calcification. *J Clin Rheumatol.* 2015;21(4):216–220. doi:10.1097/RHU.0000000000000245
91. Shkhyan R, Lee S, Gullo F, et al. Genetic ablation of adenosine receptor A3 results in articular cartilage degeneration. *J Mol Med (Berl).* 2018;96(10):1049–1060. doi:10.1007/s00109-018-1680-3
92. Corciulo C, Castro CM, Coughlin T, et al. Intraarticular injection of liposomal adenosine reduces cartilage damage in established murine and rat models of osteoarthritis. *Sci Rep.* 2020;10(1):13477. doi:10.1038/s41598-020-68302-w
93. Cronstein BN, Angle SR. Purines and adenosine receptors in osteoarthritis. *Biomolecules.* 2023;13(12):1760. doi:10.3390/biom13121760
94. Bar-Yehuda S, Rath-Wolfson L, Del Valle L, et al. Induction of an antiinflammatory effect and prevention of cartilage damage in rat knee osteoarthritis by CF101 treatment. *Arthritis Rheum.* 2009;60(10):3061–3071. doi:10.1002/art.24817
95. Liu L, Bai H, Jiao G, et al. CF101 alleviates OA progression and inhibits the inflammatory process via the AMP/ATP/AMPK/mTOR axis. *Bone.* 2022;155:116264. doi:10.1016/j.bone.2021.116264
96. Donnelly CR, Andriessen AS, Chen G, et al. Central nervous system targets: glial cell mechanisms in chronic pain. *Neurotherapeutics.* 2020;17(3):846–860. doi:10.1007/s13311-020-00905-7
97. Lu HJ, Gao YJ. Astrocytes in chronic pain: cellular and molecular mechanisms. *Neurosci Bull.* 2023;39(3):425–439. doi:10.1007/s12264-022-00961-3
98. Fiore NT, Debs SR, Hayes JP, Duffy SS, Moalem-Taylor G. Pain-resolving immune mechanisms in neuropathic pain. *Nat Rev Neurol.* 2023;19(4):199–220. doi:10.1038/s41582-023-00777-3
99. Mohammadi AH, Seyedmoalemi S, Moghanlou M, et al. MicroRNAs and synaptic plasticity: from their molecular roles to response to therapy. *Mol Neurobiol.* 2022;59(8):5084–5102. doi:10.1007/s12035-022-02907-2
100. Collingridge GL, Isaac JT, Wang YT. Receptor trafficking and synaptic plasticity. *Nat Rev Neurosci.* 2004;5(12):952–962. doi:10.1038/nrn1556
101. Park JS, Yaster M, Guan X, et al. Role of spinal cord alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors in complete Freund's adjuvant-induced inflammatory pain. *Mol Pain.* 2008;4:67. doi:10.1186/1744-8069-4-67
102. Atianjoh FE, Yaster M, Zhao X, et al. Spinal cord protein interacting with C kinase 1 is required for the maintenance of complete Freund's adjuvant-induced inflammatory pain but not for incision-induced post-operative pain. *Pain.* 2010;151(1):226–234. doi:10.1016/j.pain.2010.07.017
103. Burnashev N, Khodorova A, Jonas P, et al. Calcium-permeable AMPA-kainate receptors in fusiform cerebellar glial cells. *Science.* 1992;256(5063):1566–1570. doi:10.1126/science.1317970
104. Zhou QQ, Imbe H, Zou S, Dubner R, Ren K. Selective upregulation of the flip-flop splice variants of AMPA receptor subunits in the rat spinal cord after hindpaw inflammation. *Brain Res Mol Brain Res.* 2001;88(1–2):186–193. doi:10.1016/S0169-328X(01)00041-9
105. Park JS, Voitenko N, Petralia RS, et al. Persistent inflammation induces GluR2 internalization via NMDA receptor-triggered PKC activation in dorsal horn neurons. *J Neurosci.* 2009;29(10):3206–3219. doi:10.1523/JNEUROSCI.4514-08.2009
106. Chen J, Sandkühler J. Induction of homosynaptic long-term depression at spinal synapses of sensory alpha-delta-fibers requires activation of metabotropic glutamate receptors. *Neuroscience.* 2000;98(1):141–148. doi:10.1016/S0306-4522(00)00080-4
107. Li W, Zhu W, Chen J, Ali T, Li S. SARM1 deficiency induced depressive-like behavior via AMPKa/p-eEF2 axis to synapse dysfunction. *Neuropharmacology.* 2025;262:110206. doi:10.1016/j.neuropharm.2024.110206
108. Chu MC, Wu HF, Lee CW, et al. Soluble epoxide hydrolase deletion rescues behavioral and synaptic deficits by AMPK-mTOR pathway in autism animals. *Prog Neuropsychopharmacol Biol Psychiatry.* 2025;136:111190. doi:10.1016/j.pnpbp.2024.111190
109. Wang M, Jin B, Jo J. Acute restraint stress induces long-lasting synaptic enhancement by inhibiting AMPK activation in AD model mice. *CNS Neurosci Ther.* 2025;31(3):e70335. doi:10.1111/cns.70335

110. Agostini S, Eutamene H, Cartier C, et al. Evidence of central and peripheral sensitization in a rat model of narcotic bowel-like syndrome. *Gastroenterology*. 2010;139(2):553–63, 563.e1–5. doi:10.1053/j.gastro.2010.03.046
111. Cao Y, Li K, Fu KY, Xie QF, Chiang CY, Sessle BJ. Central sensitization and MAPKs are involved in occlusal interference-induced facial pain in rats. *J Pain*. 2013;14(8):793–807. doi:10.1016/j.jpain.2013.02.005
112. Zhao L, Tao X, Wan C, et al. Astaxanthin alleviates inflammatory pain by regulating the p38 mitogen-activated protein kinase and nuclear factor-erythroid factor 2-related factor/heme oxygenase-1 pathways in mice. *Food Funct*. 2021;12(24):12381–12394. doi:10.1039/D1FO02326H
113. Yasuda R, Hayashi Y, Hell JW. CaMKII: a central molecular organizer of synaptic plasticity, learning and memory. *Nat Rev Neurosci*. 2022;23(11):666–682. doi:10.1038/s41583-022-00624-2
114. Feng X, Chen X, Zaeem M, et al. Sesamol attenuates neuroinflammation by regulating the AMPK/SIRT1/NF- κ B Signaling pathway after spinal cord injury in mice. *Oxid Med Cell Longev*. 2022;2022:8010670. doi:10.1155/2022/8010670
115. Vasic V, Schmidt MHH. Resilience and vulnerability to pain and inflammation in the hippocampus. *Int J Mol Sci*. 2017;18(4):739. doi:10.3390/ijms18040739
116. Ye Z, Wang J, Fang F, et al. Zhi-Zi-Hou-Po decoction alleviates depressive-like behavior and promotes hippocampal neurogenesis in chronic unpredictable mild stress induced mice via activating the BDNF/TrkB/CREB pathway. *J Ethnopharmacol*. 2024;319(Pt 3):117355. doi:10.1016/j.jep.2023.117355
117. Zhang H, Li N, Li Z, Yu Y, Li Y, Zhang L. The involvement of caspases in neuroinflammation and neuronal apoptosis in chronic pain and potential therapeutic targets. *Front Pharmacol*. 2022;13:898574. doi:10.3389/fphar.2022.898574
118. Lee B, Kwon JT, Jeong Y, et al. Inflammatory and anti-inflammatory cytokines bidirectionally modulate amygdala circuits regulating anxiety. *Cell*. 2025;188(8):2190–2202.e15. doi:10.1016/j.cell.2025.03.005
119. Gao W, Sweeney C, Walsh C, et al. Notch signalling pathways mediate synovial angiogenesis in response to vascular endothelial growth factor and angiopoietin 2. *Ann Rheum Dis*. 2013;72(6):1080–1088. doi:10.1136/annrheumdis-2012-201978
120. Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. *Arthritis Res Ther*. 2017;19(1):18. doi:10.1186/s13075-017-1229-9
121. Sanchez-Lopez E, Coras R, Torres A, Lane NE, Guma M. Synovial inflammation in osteoarthritis progression. *Nat Rev Rheumatol*. 2022;18(5):258–275. doi:10.1038/s41584-022-00749-9
122. Ho SC, Chiu JH, Yeh TC, et al. Quantification of electroacupuncture-induced neural activity by analysis of functional neural imaging with monocrystalline iron oxide nanocolloid enhancement. *Am J Chin Med*. 2008;36(3):493–504. doi:10.1142/S0192415X0800593X
123. Peng L, Mu K, Liu A, et al. Transauricular vagus nerve stimulation at auricular acupoints Kindey (CO10), Yidan (CO11), Liver (CO12) and Shenmen (TF4) can induce auditory and limbic cortices activation measured by fMRI. *Hear Res*. 2018;359:1–12. doi:10.1016/j.heares.2017.12.003
124. Hui KK, Liu J, Marina O, et al. The integrated response of the human cerebro-cerebellar and limbic systems to acupuncture stimulation at ST 36 as evidenced by fMRI. *Neuroimage*. 2005;27(3):479–496. doi:10.1016/j.neuroimage.2005.04.037
125. Mamud-Meroni L, Tarcaya GE, Carrasco-Uribarren A, Rossetini G, Flores-Cortes M, Ceballos-Laita L. “the dark side of musculoskeletal care”: why do ineffective techniques seem to work? A comprehensive review of complementary and alternative therapies. *Biomedicines*. 2025;13(2). doi:10.3390/biomedicines13020392
126. Ezzatvar Y, Dueñas L, Balasch-Bernat M, Lluch-Girbés E, Rossetini G. Which portion of physiotherapy treatments’ effect is not attributable to the specific effects in people with musculoskeletal pain? A meta-analysis of randomized placebo-controlled trials. *J Orthop Sports Phys Ther*. 2024;54(6):391–399. doi:10.2519/jospt.2024.12126
127. Palese A, Rossetini G, Colloca L, Testa M. The impact of contextual factors on nursing outcomes and the role of placebo/nocebo effects: a discussion paper. *Pain Rep*. 2019;4(3):e716. doi:10.1097/PR9.0000000000000716
128. Rossetini G, Campaci F, Bialosky J, Huysmans E, Vase L, Carlino E. The biology of placebo and nocebo effects on experimental and chronic pain: state of the art. *J Clin Med*. 2023;12(12):4113. doi:10.3390/jcm12124113

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