Electroacupuncture: Mechanisms of Action and Clinical Applications in Pain and Neuroinflammatory Disorders

Abstract

Electroacupuncture (EA) is a modern adaptation of traditional acupuncture that delivers controlled electrical stimulation through inserted needles, producing frequency- and intensity-dependent physiological effects. Over the past three decades, mechanistic research has clarified how EA modulates peripheral nerve signaling, central pain-processing circuits, endogenous opioid systems, neuroimmune pathways, and synaptic plasticity. Concurrently, randomized clinical trials and meta-analyses have demonstrated therapeutic efficacy in chronic musculoskeletal pain, neuropathic pain, post-stroke complications, cancer-related symptoms, and selected gastrointestinal disorders. This review synthesizes current mechanistic and clinical evidence, emphasizing frequency-specific neurochemical release, microglial regulation, inflammatory signaling modulation, and predictors of treatment response. Understanding these mechanisms supports rational parameter selection and integration of EA into multidisciplinary pain and rehabilitation strategies.

Introduction

Electroacupuncture (EA) combines traditional needle insertion with electrical stimulation, allowing precise control over stimulation frequency, intensity, and waveform. Unlike manual acupuncture, EA produces reproducible afferent activation patterns and frequency-dependent neurochemical effects. Increasing experimental and clinical evidence demonstrates that EA produces therapeutic outcomes through coordinated peripheral, spinal, supraspinal, neuroimmune, and molecular mechanisms .

This paper reviews (1) peripheral and central neurophysiological mechanisms, (2) molecular and neuroimmune pathways, (3) frequency-dependent neurochemical specificity, (4) clinical efficacy across conditions, and (5) parameter optimization for clinical implementation.

Peripheral Mechanisms: Afferent Fiber Recruitment

EA initiates its effects at the acupoint microenvironment through activation of specific afferent fibers. Experimental data demonstrate that EA preferentially stimulates Aβ and Aδ fibers, whereas manual acupuncture recruits both A and C fibers (Fan et al., 2023). The

stimulation threshold determines fiber recruitment: A-fiber threshold stimulation at the muscle layer produces analgesia, while C-fiber threshold intensity is required at the cutaneous level .

Ascending signals travel primarily via the spinal ventrolateral funiculus toward supraspinal pain-processing centers (Zhao, 2008). This afferent specificity provides a neurophysiological basis for frequency- and intensity-dependent therapeutic effects.

Central Nervous System Modulation

EA activates and modulates a distributed pain-regulatory network including:

- Periaqueductal gray (PAG)
- Nucleus raphe magnus (NRM)
- Locus coeruleus
- Arcuate nucleus
- Limbic and autonomic structures

These structures form the descending inhibitory Arc–PAG–NRM–spinal dorsal horn pathway, which plays a central role in EA-induced analgesia (Zhao, 2008). Functional neuroimaging studies confirm that human brain activation patterns correspond to findings in animal models .

EA also modulates neural oscillations and functional connectivity, restoring abnormal brain electrical activity patterns and promoting network reorganization in neurological rehabilitation (Wu et al., 2023).

Endogenous Opioid System and Frequency Specificity

One of the most robust mechanistic findings in EA research is frequency-dependent endogenous opioid release:

- **2 Hz stimulation** → enkephalins and β-endorphin
- **100 Hz stimulation** → dynorphins

(Ulett et al., 1998; Zhao, 2008)

Low-frequency EA (2 Hz) activates spinal microglial IL-10 signaling, leading to β-endorphin upregulation and μ-opioid receptor–mediated analgesia (Ali et al., 2020). μ- and δ-opioid receptors within the Arc–PAG–NRM–spinal pathway are particularly critical for analgesic effects .

Clinically, low-frequency stimulation (2–10 Hz) demonstrates superior efficacy for inflammatory and neuropathic pain, whereas higher frequencies selectively recruit alternative opioid pathways .

Neurotransmitter Modulation

Beyond opioids, EA engages multiple neurotransmitter systems:

- **Serotonergic and noradrenergic systems** reduce spinal NMDA receptor (GluN1) phosphorylation (Zhang et al., 2014).
- **Glutamate reduction** and increased **GABA and GAD67 expression** restore excitatory–inhibitory balance.
- Activation of **5-HT1A, 5-HT3, α2-adrenergic, M1 muscarinic, GABAA, and GABAB receptors** has been demonstrated in neuropathic models .

These findings suggest EA modulates central sensitization by correcting excitatory neurotransmission dysregulation.

Neuroimmune and Anti-Inflammatory Mechanisms

Neuroinflammation plays a pivotal role in chronic pain and neurodegeneration. EA exerts anti-inflammatory effects by:

- Suppressing **TLR4/NF-κB signaling**
- Inhibiting **NLRP3 inflammasome activation**
- Promoting **JAK2/STAT3 and PI3K/Akt signaling**
- Inducing macrophage and microglial M2 polarization via **AMPK–SIRT1 pathways**

This reduces pro-inflammatory cytokines (IL-6, TNF-α) and modulates blood–brain barrier permeability (Nan et al., 2024; Quiroz-González et al., 2025).

Low-frequency EA specifically activates spinal microglial IL-10 pathways, further linking immune modulation to endogenous opioid release (Ali et al., 2020).

Neuroprotection and Synaptic Plasticity

EA enhances neuroprotection and synaptic remodeling by:

- Upregulating **brain-derived neurotrophic factor (BDNF)** and **TrkB**
- Reducing oxidative stress via increased **glutathione, SLC7A11, and GPX4 expression**

These mechanisms support its use in post-stroke spasticity, neurodegeneration, and neuropathic conditions. Synergistic benefits have been observed when EA is combined with pharmacologic agents such as L-DOPA, donepezil, and minocycline .

Clinical Evidence

Chronic Musculoskeletal Pain

The PEACE randomized trial demonstrated clinically meaningful pain reduction (−1.9 BPI points) in cancer survivors receiving EA (Mao et al., 2021). Meta-analyses support efficacy in knee osteoarthritis (Chen et al., 2017) and acute gouty arthritis (Ni et al., 2023).

Neuropathic Pain

Low-frequency EA (2–10 Hz) is superior to 100 Hz for neuropathic pain suppression (Zhou et al., 2023). Combined-acupoint protocols (e.g., ST36 + GB30) activate both opioid and endocannabinoid systems, enhancing analgesia (Jiang et al., 2022).

Post-Stroke Complications

High-certainty evidence supports acupuncture use in selected stroke-related conditions (Allen et al., 2022). EA significantly improves post-stroke depression (Hu et al., 2025) and spasticity through glutamate/GABA modulation and BDNF pathways (You et al., 2025).

Gastrointestinal Disorders

EA improves functional dyspepsia with efficacy comparable to pharmacologic therapy and superior safety (Mao et al., 2020). Electrical acupoint stimulation reduces postoperative nausea and vomiting (Lu et al., 2023).

Treatment Parameters

Duration and Frequency

- Minimum 5 weeks for maximal chronic pain benefit (Li et al., 2020).
- ≥2 sessions per week improves outcomes (Chen et al., 2019).
- Typical session duration: 30 minutes.

Intensity

Strong stimulation (>2 mA) produces superior analgesia compared with weak stimulation (<0.5 mA) in knee osteoarthritis (Lv et al., 2019).

Acupoint Selection

Common points for musculoskeletal pain include:

- Knee OA: ST35, ST34, SP10, GB34, SP9
- Low back pain: BL23, GV3, BL25, BL40
- Neuropathic pain: ST36 + GB30

Distal regulatory points such as ST36, LI4, and LR3 are frequently incorporated (Lee et al., 2020).

Predictors of Treatment Response

Baseline pain severity is the most consistent predictor of response (Witt et al., 2019). Temporal summation predicts fibromyalgia response (Murphy et al., 2024). Neuroimaging biomarkers including striatal volume and default mode network connectivity predict treatment response with high accuracy (Wang et al., 2023).

Safety

EA is well tolerated with low incidence of serious adverse events across clinical trials (Allen et al., 2022). It may reduce opioid requirements in postoperative settings (Park et al., 2021).

Conclusion

Electroacupuncture produces therapeutic effects through coordinated peripheral nerve activation, descending inhibitory circuit engagement, frequency-specific endogenous

opioid release, neurotransmitter modulation, neuroimmune regulation, and neuroplastic remodeling. Its frequency-dependent specificity provides a mechanistic basis for individualized parameter selection.

High-quality clinical evidence supports EA for chronic musculoskeletal pain, neuropathic pain, post-stroke complications, cancer-related symptoms, and select gastrointestinal disorders. Given its favorable safety profile and multimodal mechanisms, EA represents a biologically plausible and clinically effective adjunct in integrative pain and rehabilitation medicine.

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