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Electroacupuncture Mechanisms in Managing Preoperative Anxiety and Postoperative Pain Chronification: A Review

Shannah Erasmus[1,*], Zhengyi Lyu[2,*], Jie Zhou[3], Jianqiao Fang[3], Yi Liang[3]

[1]International Education College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China; [2]The Third Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China; [3]Department of Acupuncture, The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yi Liang, Department of Acupuncture, The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, People's Republic of China, Email liangyiwww@126.com

Introduction: Postoperative hyperalgesic priming, exacerbated by preoperative anxiety, complicates pain management and recovery. Electroacupuncture (EA), a technique that combines traditional acupuncture with electrical stimulation applied through needles to enhance therapeutic effect, offers a potential solution by targeting multiple neurobiological pathways.

Objective: This review investigates how EA addresses preoperative anxiety-induced postoperative hyperalgesic priming ie pain chronification, focusing on its mechanisms in three areas: preoperative anxiety, postoperative hyperalgesic priming, and the interaction between EA and these processes.

Methods: A literature search across PubMed, ScienceDirect, and Google Scholar identified relevant studies on EA's effects on neurobiological pathways related to anxiety and pain. The review synthesized findings to understand EA's role in these contexts.

Results: EA alleviates preoperative anxiety by influencing the body's neurochemical and neurophysiological responses. It reduces inflammation, regulates stress hormones, and improves autonomic function. For postoperative pain chronification, EA modulates pain pathways, reduces inflammation, and affects receptor signaling, gene expression, and neurotransmitter systems.

Conclusion: EA offers a promising approach to managing preoperative anxiety and postoperative pain. By addressing both the physiological and neurochemical pathways that contribute to pain and anxiety, EA has the potential to significantly improve clinical outcomes for patients undergoing surgery. Further research is needed to fully understand its mechanisms and optimize its application in clinical settings.

Keywords: preoperative anxiety, chronic postoperative pain, hyperalgesic priming, electroacupuncture mechanisms, analgesic, anxiolytic

Introduction

Surgery triggers complex physiological and psychological responses that impact both the perioperative experience and postoperative outcomes. With over 320 million surgeries performed globally each year, postoperative pain remains a significant challenge.[1] Chronic postsurgical pain, which extends beyond the typical healing period, complicates recovery and management. Chronic postoperative pain affects approximately 10% to 50% of patients following surgery.[2] Those most at risk include individuals undergoing major surgeries, such as thoracic, abdominal, and orthopaedic procedures, with higher rates observed in these cases.[3] Other factors increasing risk include preoperative pain, psychological distress such as anxiety.[4]

Hyperalgesic priming (HP), a phenomenon where prior noxious stimuli enhanced pain sensitivity, provides insights into the transition from acute to chronic pain. HP involves increased pain sensitivity due to changes in both peripheral

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and central pain pathways.(5,6) This includes enhanced excitability of nociceptors, increased synaptic transmission in the spinal cord, molecular alterations, and neuroplastic changes in pain-processing brain regions.[5]

Preoperative anxiety is a key factor that influences this transition. It is associated with increased postsurgical pain and is characterized by stress and physical symptoms like palpitations and disrupted sleep.[6] Preoperative anxiety prevalence ranges from 11% to 80% in adults and 41.7% to 75.44% in children.[7] Recent research links preoperative anxiety with heightened postoperative pain sensitivity.[8–10] This makes exploring interventions to address anxiety-induced hyperalgesic priming crucial for improving patient outcomes.

Electroacupuncture, a traditional Chinese medicine technique combining acupuncture with electrical stimulation, has shown promise in managing both pain and anxiety. Regions involved in stress and anxiety, such as the amygdala and prefrontal cortex have been seen benefited by EA.[11–13] Clinical studies have demonstrated that EA can effectively manage both pain and anxiety. For example, a study by Zhang et al found that EA modulated pain by stimulating endogenous opioid release, reducing inflammation, and inhibiting pain transmission in the spinal cord and brain (Zhang et al, 2014). Similarly, research by Lv et al (2019) showed that EA enhanced the function of descending pain control pathways, further supporting its analgesic effects (Lv et al, 2019).[14–17] In terms of anxiety, a study by Li et al (2023) found that EA decreased anxiety by regulating neurotransmitter levels, such as serotonin and GABA, and by modulating brain regions involved in stress and anxiety, such as the amygdala and prefrontal cortex (Li et al, 2023). Additionally, trials by Amorim et al (2022) highlighted EA's effectiveness in treating anxiety disorders, supporting its potential as a complementary therapy for both pain management and anxiety reduction.[11–13]

While numerous studies have explored the underlying mechanisms of preoperative anxiety and hyperalgesic priming, there remains a lack of comprehensive clinical trials demonstrating the long-term effects of electroacupuncture, despite promising results as a non-invasive alternative to pharmacological treatments, which are often limited by side effects and variable efficacy. Much of the current evidence comes from animal models, and few large-scale clinical trials have been conducted to substantiate these findings in humans. Additionally, the variability in EA protocols, such as stimulation frequency, duration, and electrode placement, can influence outcomes. Therefore, further clinical investigations are required to optimize therapeutic protocols and address these methodological gaps, ultimately exploring the most effective ways to apply EA in clinical practice.

This review aims to bridge that gap by examining the impact of preoperative anxiety on postoperative hyperalgesia and exploring the potential mechanisms through which EA may mitigate these effects. By investigating how EA targets both preoperative anxiety and postoperative hyperalgesic priming, this review encourages further consideration of EA as a promising treatment for managing preoperative anxiety-induced postoperative hyperalgesic priming.

Methodology

In this literature review, a comprehensive search was conducted across various scientific databases, including PubMed, ScienceDirect, and Google Scholar, to identify relevant studies on preoperative anxiety-induced postoperative hyperalgesic priming and the therapeutic role of electroacupuncture. Keywords such as "preoperative anxiety", "chronic postoperative pain", "hyperalgesic priming", "electroacupuncture mechanisms", "analgesic", and "anxiolytic", were used. Inclusion criteria were set to focus on peer-reviewed studies published in English within the last decades, particularly those utilizing animal models, clinical trials, or systematic reviews. Studies were selected based on their relevance to the neurobiological pathways involved in hyperalgesic priming and electroacupuncture's modulation of these mechanisms. Articles were critically assessed for methodological rigor, including study design, sample size, and outcome measures. The findings were synthesized to provide an overview of the current understanding and potential mechanisms of electroacupuncture in addressing preoperative anxiety and postoperative pain sensitivity. See Figure 1. Despite the promising evidence for EA, there are limitations in the current body of research. Much of the evidence comes from animal models, and few large-scale clinical trials have been conducted to substantiate these findings in humans. Additionally, the variability in EA protocols, such as stimulation frequency, duration, and electrode placement, can influence outcomes. Future studies should address these methodological gaps and explore the most effective ways to apply EA in clinical practice.

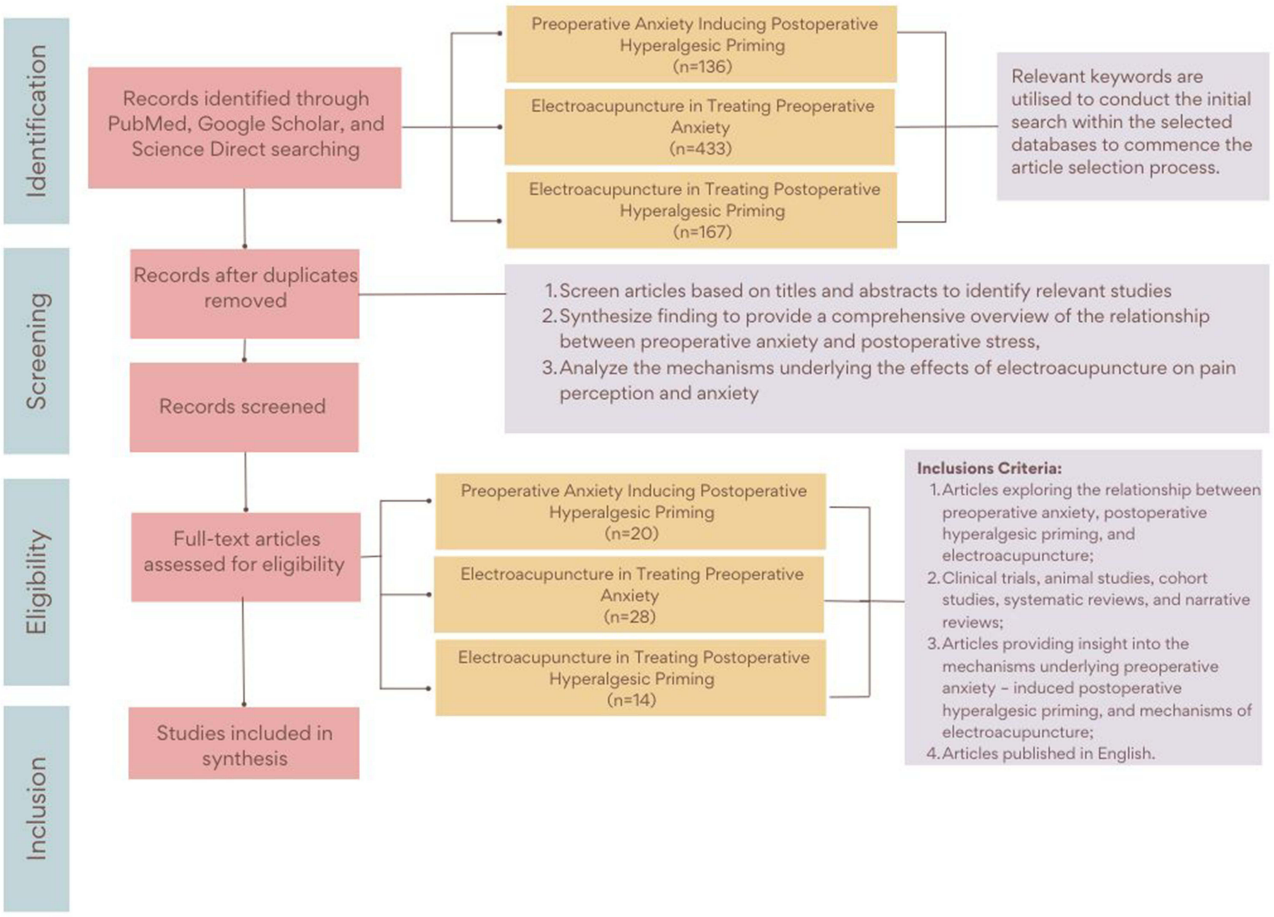

Figure 1 *PRISMA flowchart for article selection in the review.* This figure illustrates the selection process for studies included in the review. The flowchart summarizes the identification, screening, eligibility assessment, and final inclusion of studies based on the established criteria for preoperative anxiety, chronic postoperative pain, and electroacupuncture mechanisms.

Results

Mechanisms and Pathways Possibly Involved in Preoperative Anxiety – Induced Postoperative Hyperalgesic Priming

The relationship between preoperative anxiety and postoperative hyperalgesic priming is complex and not fully understood. Several mechanisms and pathways have been proposed to explain how preoperative anxiety may contribute to the development of this condition:

Neuroinflammatory and Cytokine Signalling Pathways

Blood-Spinal Cord Barrier Disruption and Cytokine Translocation

Preoperative anxiety can profoundly influence the pathophysiology of postoperative pain through its effects on the Blood-Spinal Cord Barrier (BSCB). Elevated preoperative anxiety triggers a heightened stress response, leading to the systemic release of corticosteroids and pro-inflammatory cytokines, notably interleukin-6 (IL-6). These biochemical mediators have been implicated in modulating nociceptive pathways and altering nociceptive sensitivity. Crucially, anxiety-induced stress disrupts the integrity of the BSCB, facilitating the translocation of IL-6 and other pro-inflammatory cytokines into the central nervous system, specifically the spinal cord. This disruption enables the infiltration of inflammatory mediators into neural tissue, priming dorsal horn neurons that are critical in the processing of nociceptive signals. The presence of IL-6 in the spinal cord contributes to the phenomenon of central sensitization, where the nociceptive system becomes hypersensitive to external stimuli. This pathophysiological state results in

allodynia, the perception of pain in response to non-nociceptive stimuli, and hyperalgesia, an exaggerated and prolonged pain response to nociceptive stimuli. Collectively, these alterations in central pain processing mechanisms can significantly exacerbate postoperative pain experiences, underscoring the critical impact of preoperative psychological states on surgical outcomes.[18]

Glucocorticoid-Induced Microglial Activation

Anxiety activates the body's stress response system, leading to the release of glucocorticoids. These hormones play a significant role in sensitizing the microglia within the spinal cord. Once activated, these microglia become more reactive to subsequent stimuli, such as surgical trauma, potentially leading to an exaggerated inflammatory response following surgery. As a result of their activation, microglia release higher levels of proinflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α). These cytokines enhance the transmission of pain signals within the spinal cord, thereby exacerbating postoperative pain. This mechanism underscores the profound impact of preoperative psychological states on the neuroinflammatory pathways that contribute to heightened pain perception post-surgery. Addressing and managing preoperative anxiety could therefore be crucial in moderating the inflammatory response and mitigating postoperative pain.[19]

Cholinergic Anti-Inflammatory Pathway Disruption

Activating the α7 nicotinic acetylcholine receptor (α7 nAChR) on microglia typically has an anti-inflammatory effect, largely by inhibiting the translocation of the transcription factor NFκB p65 to the nucleus, which in turn reduces the expression of pro-inflammatory genes. However, preoperative anxiety and stress complicate this pathway. Anxiety and stress activate the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, both of which can enhance inflammatory processes throughout the body. This systemic increase in inflammation elevates levels of cytokines and other inflammatory mediators. In such conditions, the heightened inflammatory state may potentially overwhelm the α7 nAChR-mediated anti-inflammatory signalling. This results in increased activation of NFκB, further promoting inflammation and consequently, enhancing pain perception. This mechanism highlights the complex interplay between psychological stress, neuroimmune responses, and pain modulation, underscoring the importance of managing anxiety to control inflammation and pain after surgery.[20]

Hypothalamic-Pituitary-Adrenal Axis Modulation

Corticosteroid Response and Pain Modulation

A study found that corticosterone (CORT), a key stress hormone in many animals and the equivalent of cortisol in humans, plays a significant role in pain modulation. Stress-induced increases in corticosterone levels are known to modulate pain pathways, potentially leading to the development of chronic pain states. In the context of surgery, preoperative anxiety can elevate levels of these stress hormones, thereby enhancing pain perception. This enhancement not only increases immediate postoperative pain but also contributes to hyperalgesic priming, wherein the nervous system becomes predisposed to heightened sensitivity to pain. Understanding and managing these hormonal fluctuations induced by anxiety before surgery could be crucial in reducing the risk of prolonged postoperative pain.[21]

Corticotropin-Releasing Factor Signalling in Pain and Inflammation

Corticotropin-Releasing Factor (CRF) plays a pivotal role in the body's stress response system and is closely linked to mechanisms of anxiety. CRF acts through its receptors, CRF1 and CRF2, to modulate both behavioural responses to stress and physiological processes. Preoperative anxiety can enhance CRF activity, which may lead to significant alterations in pain sensitivity and inflammatory responses following surgery. Specifically, CRF1 receptors are implicated in the regulation of pain sensitivity. Preoperative anxiety may prime the system for increased CRF1-mediated responses, potentially resulting in heightened pain perception post-surgery. This receptor is also crucial for resolving inflammation post-surgery. Anxiety, which is known to alter immune responses, could disrupt normal CRF1 receptor function, leading to increased and prolonged postoperative inflammation and associated hyperalgesia.[22]

GABAergic and Serotonergic Modulation Pathways

GABA Receptor Regulation in Central Pain Modulation

Preoperative anxiety plays a critical role in priming the body for postoperative hyperalgesia by engaging molecular pathways such as those mediated by GPR30, a receptor involved in non-genomic signaling mechanisms that influence neuronal function. Activation of GPR30, particularly in the periaqueductal Gray (PAG) region of the brain, leads to significant neurophysiological changes. One such change is the upregulation of GABA_A receptor subunits α4β1δ, which are essential for modulating both synaptic and extra-synaptic transmissions within the central nervous system. This modulation plays a pivotal role in pain perception. Furthermore, GPR30 activation influences the expression of protein kinase A (PKA), a key player in pain modulation pathways. The alteration in PKA levels impacts the descending pain modulation systems. These systems are integral to the management of pain signals transmitted to the brain, with the potential to either amplify or dampen these signals based on the regulatory environment set by preoperative anxiety.[23]

5-Hydroxytryptamine 2B (5-HT2B) Receptor

The 5-Hydroxytryptamine 2B (5-HT2B) receptor, located within the spinal cord, is instrumental in modulating pain at the spinal level. Activation of these receptors plays a crucial role in pain perception and management. Preoperative anxiety can lead to the activation of 5-HT2B receptors, which in turn facilitates the development of hyperalgesia following surgery. This activation suggests a direct link between emotional states prior to surgery and their impact on pain modulation systems within the spinal cord, further emphasizing the complex interaction between psychological stress and pain pathways.[24]

Dysregulation of GABAergic Inhibition and Neuronal Plasticity

Anxiety triggers the release of glucocorticoids, such as cortisol, from the adrenal glands, which are integral to the body's stress response mechanism. These hormones prepare the body to handle threats or challenges by altering various physiological functions, including those in the central nervous system. In the spinal cord, one significant effect of glucocorticoids is the downregulation of GABAergic markers. GABA (gamma-aminobutyric acid), the primary inhibitory neurotransmitter in the nervous system, plays a crucial role in reducing neuronal excitability. The downregulation of GABAergic markers can lead to reduced inhibitory signalling, potentially contributing to altered pain perception. Furthermore, preoperative anxiety impacts the levels of Npas4 in the spinal cord. Npas4 is essential for the development of inhibitory synapses that utilize GABA. Reduced Npas4 levels lead to decreased GABAergic activity, impairing the inhibitory control mechanisms of the nervous system. This impairment is linked to increased pain perception, highlighting how psychological stress not only affects hormonal balance but also directly influences neurochemical pathways critical for pain modulation. Managing these effects of anxiety could thus play a vital role in controlling pain perception and improving postoperative outcomes.[25]

Genetic Influence and Pro-Inflammatory Activation on Pain Pathways

Genomic and Epigenomic Modifications in Pain Sensitivity

The release of stress hormones such as cortisol in response to anxiety can directly alter pain perception pathways. This effect can be further influenced by genetic and epigenetic factors such as differential DNA methylation in pain-related pathways or altered expression of genes associated with pain sensitivity, such as CACNG2 and P2RX7. These genetic predispositions can modify the body's response to psychological stress, increasing the susceptibility to chronic post-surgical pain. Furthermore, genetic predispositions that affect neurotransmitter pathways, including those involving dopamine or GABA, may interact with the heightened emotional state before surgery to amplify pain signalling pathways. This interaction suggests a complex interplay between preoperative psychological states and genetic factors that predispose individuals to enhanced pain perception. Additionally, preoperative anxiety may induce epigenetic changes that affect gene expression related to pain sensitivity and inflammation. Processes such as DNA methylation and alterations in miRNA expression can be responsive to psychological stressors, potentially priming the nervous system towards a hyperalgesic state following surgery.[26,27]

Pro-Inflammatory Mediator Activation

The pathways involving pain mediators such as prostaglandin E2 (PGE2), EP4 receptors, and TRPV1 channels are critical in the development of prolonged pain sensitization, particularly under conditions of stress or anxiety. PGE2 is a key inflammatory mediator that enhances pain sensitivity by interacting with EP4 receptors, which are part of the prostaglandin receptor family involved in pain and inflammatory processes. TRPV1 channels, known for their role in detecting and regulating body temperature as well as pain, also play a crucial role in this context. Preoperative anxiety can amplify the activity of these mediators, potentially leading to an enhanced and prolonged postoperative pain response. The heightened activity of PGE2, EP4 receptors, and TRPV1 channels under the influence of preoperative anxiety may intensify pain signaling pathways, thus exacerbating pain perception and contributing to a hyperalgesic state. Managing these mediators through appropriate interventions could therefore be key in mitigating postoperative pain exacerbated by preoperative anxiety.[21]

Signal Transduction and Pain Sensitization

Protein Kinase C-Epsilon (PKCε) Mediated Pain Pathways

Protein kinase type C-epsilon (PKCε) is a crucial enzyme found in sensory neurons of the peripheral nervous system (PNS), where it plays a significant role in controlling the onset and chronification of pain.[28] PKCε is integral to the process of hyperalgesic priming, a phenomenon characterized by the sensitization of nociceptive pathways. This sensitization occurs when an initial painful or pro-inflammatory stimulus leads to a prolonged or enhanced response to subsequent stimuli, mediated by biochemical changes in pain signalling pathways, including those involving PKCε. Hyperalgesic priming reflects a lasting readiness of the nociceptive system to respond to new painful stimuli and involves a kind of molecular memory in the primary afferent nociceptors, with PKCε playing a key role. Beyond its role in pain modulation, PKCε also influences the function of immune cells, which are responsive to stress and emotional states. Anxiety can alter the behaviour of these immune cells through changes in PKCε activity, potentially affecting inflammation and the body's overall stress response. Addressing the modulation of PKCε activity could thus be crucial for managing pain and immune responses in patients experiencing preoperative anxiety.[29,30]

AMPA Receptor Phosphorylation and Central Pain Processing

The anterior cingulate cortex (ACC) plays a crucial role in both pain perception and emotional processing, including anxiety. Emotional states are known to influence pain perception; thus, heightened anxiety before surgery could increase baseline activity within the ACC, setting the stage for enhanced pain sensitivity. Within the ACC, GluR1 is a subunit of AMPA receptors, which are essential for synaptic transmission in the central nervous system and are involved in the development of pain and hyperalgesia. Phosphorylation of GluR1 at Ser845 is a key biochemical change associated with hyperalgesia. Preoperative anxiety may influence this phosphorylation process, priming the pain pathways for heightened responsiveness. This modification increases the sensitivity of neurons in the ACC to pain signals, potentially leading to an intensified pain experience post-surgery.[31]

Glucocorticoid-Serum/Glucocorticoid Regulated Kinase (SGK1)-ATP Pathway Activation

Preoperative anxiety can lead to an increase in glucocorticoids such as corticosterone. This elevation in glucocorticoids activates a specific signaling pathway in spinal astrocytes: the GCs-SGK1-ATP pathway. Activation of this pathway stimulates the expression of serum/glucocorticoid-regulated kinase 1 (SGK1) within the astrocytes. SGK1 plays a pivotal role because it promotes the release of adenosine triphosphate (ATP) from astrocytes. This released ATP interacts with purinergic receptors on nearby neurons, which amplifies pain signaling pathways. The elevated levels of ATP are associated with increased pain sensitivity, thus contributing to the development of hyperalgesia. As a result, preoperative anxiety not only primes the GCs-SGK1-ATP pathway but also sets the stage for heightened and prolonged pain post-surgery.[32]

Cholecystokinin 2 (CCK2) Receptor

The Cholecystokinin 2 (CCK2) receptor, situated in the rostral ventromedial medulla (RVM), plays a pivotal role in the

modulation of pain. This receptor is integral in receiving and transmitting nerve impulses that can significantly amplify pain signals. Anxiety, particularly preoperative anxiety, can activate these CCK2 receptors. This activation primes the pain pathways, setting the stage for a hyperalgesic state post-surgery.[24]

Proposed Mechanisms of Electroacupuncture Treating Anxiety

Research indicates that the mechanisms by which electroacupuncture alleviates preoperative anxiety are intricate and involves multiple neurobiological process. EA is thought to influence various neurophysiological and biochemical pathways, including the modulation of neurotransmitter systems, alterations in neuroendocrine responses, and adjustments in brain activity patterns. These proposed processes collectively contribute to its efficacy in reducing preoperative anxiety:

Neurophysiological Effects

Electroacupuncture has shown significant neurophysiological effects that contribute to its ability to reduce anxiety. One key mechanism is its ability to reduce Fos-immunoreactivity in various brain regions such as the prefrontal cortex, amygdala, hypothalamic nuclei, and hippocampus. These areas are crucial in regulating stress and anxiety responses. By reducing activity in these regions, EA helps alleviate anxiety-related symptoms. Furthermore, EA modulates specific neural circuits, including the rACC-DRN circuit, the rACC-thalamus circuitry, and PV interneurons in the anterior cingulate cortex (ACC). This modulation of neural pathways is associated with anxiety reduction as it influences emotional processing and stress regulation. Additionally, EA has been found to enhance synaptic plasticity in the CA1 region of the hippocampus by increasing dendritic spine density and normalizing synaptic structures. This improvement in synaptic function supports better cognitive and emotional stability, further contributing to the treatment of anxiety.[33,34]

Neurochemical Balance

EA plays a vital role in promoting neurochemical balance, which is crucial in managing anxiety. One of its primary effects is the activation of serotonin production, a neurotransmitter known for its role in mood regulation. By increasing serotonin levels, EA helps stabilize emotional states, enhancing the overall ability to cope with anxiety. Beyond serotonin, EA also modulates other critical neurotransmitters, including GABA, dopamine, and endorphins, which collectively promote relaxation and alleviate stress. GABA, an inhibitory neurotransmitter, helps calm neuronal activity, while dopamine and endorphins contribute to feelings of pleasure and well-being. Furthermore, EA affects the cannabinoid system, specifically by modulating CB1R expression. This modulation leads to increased GABA release, which helps maintain balanced neurotransmission and further reduces anxiety symptoms. Through these neurochemical mechanisms, EA provides a comprehensive approach to reducing anxiety.[35–37]

Anti-Inflammatory Effects

Electroacupuncture exerts significant anti-inflammatory effects that contribute to its therapeutic potential in treating anxiety. One of the key mechanisms is the reduction of pro-inflammatory cytokines. By decreasing the expression of these cytokines and inhibiting inflammation-related pathways such as the TLR4/NF-κB signaling pathway, EA effectively lowers systemic inflammation. This reduction in inflammation is crucial, as chronic inflammation is often linked to anxiety and other mood disorders. Additionally, EA reduces neuroinflammation, which is particularly important in managing anxiety-related symptoms. EA specifically targets neuroinflammatory markers, including components of the NLRP3 inflammasome and pro-inflammatory cytokines in the hippocampus, a brain region associated with mood regulation. By decreasing neuroinflammation in the hippocampus, EA helps restore a healthier brain environment, further alleviating anxiety.[38,39]

Autonomic Nervous System Regulation

EA plays a crucial role in regulating the autonomic nervous system, which directly impacts anxiety levels. One of the primary effects of EA is its ability to enhance parasympathetic activity, particularly through increased vagal stimulation. The parasympathetic nervous system is responsible for the body's "rest and digest" responses, promoting relaxation and reducing stress. Simultaneously, EA reduces sympathetic activity, which is associated with the body's "fight or flight"

responses often heightened during anxiety. By restoring balance between these two branches of the autonomic nervous system, EA helps alleviate anxiety symptoms, allowing for better emotional regulation and a calmer physiological state.[28]

HPA Axis Modulation

Electroacupuncture plays a significant role in modulating the hypothalamic-pituitary-adrenal (HPA) axis, which is a central stress response system closely linked to anxiety. EA reduces the levels of key stress hormones, including cortisol, corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and corticosterone (CORT). These hormones are typically elevated in response to stress and are known to contribute to heightened anxiety levels. By reducing the secretion of these stress-related hormones, EA exerts a calming effect on the HPA axis, helping to regulate the body's stress response and mitigate anxiety symptoms. This hormonal balance is crucial for emotional stability and stress management.[13,33,37,38,40]

Gut-Brain Axis Modulation

EA has been found to positively influence the gut-brain axis, an essential pathway in mental health regulation. One of the key ways EA achieves this is by modulating the composition of the gut microbiota. Specifically, EA increases the abundance of beneficial bacterial strains such as Ruminococcaceae, Phascolarctobacterium, and Akkermansiaceae. These bacteria are known for their role in promoting a healthy gut environment, which can have far-reaching effects on brain function and emotional well-being. The gut-brain axis is a bidirectional communication system that links the gastrointestinal system with the central nervous system, playing a critical role in mental health. By fostering a healthier gut microbiome, EA can reduce anxiety by improving gut health, thereby influencing brain function and behavior in a positive manner.[38]

Neurogenesis and Neuroprotection

Electroacupuncture has demonstrated the ability to promote neurogenesis and provide neuroprotective effects, which are beneficial in alleviating anxiety. One of the critical mechanisms through which EA achieves this is by promoting the proliferation of neural progenitors in the hippocampus, a region of the brain essential for learning, memory, and emotional regulation. By encouraging the growth of these neural progenitor cells, EA supports brain plasticity and cognitive resilience. Additionally, EA inhibits apoptosis (programmed cell death), which protects existing neurons from damage. This combination of promoting new neural growth and protecting current neural structures contributes to the reduction of anxiety-like behaviors, enhancing both brain function and emotional stability.[41]

NPS/NPSR System Modulation

EA also modulates the Neuropeptide S (NPS) and Neuropeptide S Receptor (NPSR) system, which plays a key role in anxiety regulation. EA increases the expression of both NPS and NPSR in the anterior cingulate cortex (ACC), a brain region involved in emotional processing and pain regulation. The NPS/NPSR system has anxiolytic (anxiety-reducing) and analgesic effects, meaning that higher levels of NPS and NPSR expression help reduce anxiety and alleviate pain. By enhancing the activity of this system, EA offers a targeted mechanism for decreasing anxiety, contributing to its therapeutic effects in anxiety management.[42]

Proposed Mechanism of EA in Treating Postoperative Hyperalgesic Priming

Postoperative hyperalgesic priming, marked by increased pain sensitivity following surgery, can be exacerbated by preoperative anxiety and complicates recovery. Electroacupuncture offers a promising approach to mitigate this condition by influencing neurophysiological and biochemical pathways. These mechanisms explore how electroacupuncture may affects postoperative hyperalgesic priming:

Neuroinflammation Modulation

Electroacupuncture modulates several neuroinflammatory pathways, which plays a critical role in alleviating pain hypersensitivity. One prominent mechanism involves the STING/IFN-1 pathway. EA helps inhibit neuroinflammation and restore normal EEG rhythms, which contributes to a reduction in pain hypersensitivity.[43] Furthermore, EA affects inflammatory pathways by reducing levels of pro-inflammatory markers such as tumor necrosis factor-alpha (TNF-α) and

p38 mitogen-activated protein kinase (p38 MAPK). This reduction contributes to its analgesic effects by decreasing central sensitization.[44,45] Additionally, EA plays a role in mitigating spinal glial cell activation and lowering inflammatory cytokine production, which are key processes in the development of hyperalgesia.[46,47]

Pain Pathway Modulation

EA influences pain pathways through various mechanisms, including frequency-specific effects and modulation of pain-related biomarkers. Different frequencies of EA affect pain sensitivity and receptor priming differently: 100 hz EA is particularly effective in preventing the priming of pain receptors, while 2 hz EA is more effective in controlling pain once it has developed.[48] EA also impacts pain-related biomarkers by enhancing inhibitory neurotransmission through receptors such as GABA_Aα2R and GABA_BR1, and by decreasing overall pain signaling.[47] Additionally, EA modulates mechanical pain by affecting the p38 MAPK pathway, which is crucial in the development of mechanical allodynia.[49]

Receptor and Signalling Pathways

EA regulates various receptors and signaling pathways involved in pain and inflammation modulation. For instance, EA upregulates cannabinoid receptor type 1 (CB1) in the spinal cord, which plays a crucial role in reducing hyperalgesia by modulating pain signaling and inhibiting central sensitization.[50] EA also affects ATP levels and purinergic receptors, such as P2X7, which are integral to pain signaling and inflammatory processes.[44,45] Furthermore, EA modulates the interleukin-33 (IL-33)/ST2 pathway, which is involved in inflammatory responses and contributes to the reduction of chronic pain development.[51]

Gene Expression and Cellular Processes

EA influences gene expression in key pain-related regions, including the periaqueductal gray and dorsal horn. This modulation affects pain processing and nociceptive signal transduction. Additionally, EA impacts several biological processes related to immunity, stress response, and neural functions that are associated with pain processing and neurogenesis.[52]

GABAergic Modulation

EA enhances GABAergic neurotransmission by increasing the expression of GABA_Aα2R and GABA_BR1 receptors. This augmentation of inhibitory neurotransmission contributes to a reduction in pain sensitivity and improved pain management.[47]

Systemic Effects

The analgesic effects of EA are also linked to the endogenous opioid system. Studies have shown that pain relief from EA is diminished when opioid antagonists are administered, suggesting that the analgesic effects of EA are mediated through the release of endogenous opioids.[48]

Critical Perspectives

Evidence on the efficacy of electroacupuncture (EA) in treating preoperative anxiety and postoperative chronic pain is somewhat conflicting, reflecting the complexity of these conditions and the variability in study designs. While numerous studies have explored the underlying mechanisms of preoperative anxiety and hyperalgesic priming, there remains a lack of comprehensive clinical trials demonstrating the long-term effects of EA, despite its promising potential as a non-invasive alternative to pharmacological treatments, which are often limited by side effects and variable efficacy. Some research highlights EA's benefits, demonstrating its capacity to modulate the hypothalamic-pituitary-adrenal axis, reduce pro-inflammatory cytokines, and regulate neurotransmitter systems, collectively alleviating anxiety and pain. However, much of this evidence comes from animal models, with few large-scale clinical trials substantiating these findings in humans. Additionally, the variability in EA protocols—such as stimulation frequency, duration, and electrode placement—can significantly influence outcomes, contributing to inconsistent results in existing studies. These disparities underscore the need for standardized methodologies, larger-scale trials, and further investigations to optimize therapeutic protocols and address methodological gaps, ultimately clarifying EA's role in managing these interconnected conditions.

Conclusion

Electroacupuncture demonstrates significant potential as a transformative approach to managing preoperative anxiety and postoperative pain. By targeting the neuroinflammatory, neuroimmune, and hormonal disruptions that underlie hyperalgesic priming, EA effectively modulates pain sensitivity and anxiety through well-established mechanisms, including neurotransmitter regulation and endogenous opioid activation. While further research is necessary to fully elucidate its mechanisms and optimize protocols, the evidence underscores EA's clinical relevance as a complementary therapy capable of improving patient outcomes and advancing pain management strategies. Further research, particularly large-scale clinical trials, is needed to optimize EA protocols and establish its clinical efficacy. This review calls for a deeper exploration of EA's potential to transform postoperative pain management and patient recovery.

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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

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References

1. Mulugeta H, Ayana M, Sintayehu M, Dessie G, Zewdu T. Preoperative anxiety and associated factors among adult surgical patients in Debre Markos and Felege Hiwot referral hospitals, Northwest Ethiopia. *BMC Anesthesiol*. 2018;18(1). doi:10.1186/s12871-018-0619-0
2. Fuller AM, Bharde S, Sikandar S. The mechanisms and management of persistent postsurgical pain. *Front Pain Res*. 2023;4. doi:10.3389/fpain.2023.1154597
3. Rosenberger DC, Pogatzki-Zahn EM. Chronic post-surgical pain – update on incidence, risk factors and preventive treatment options. *BJA Educ*. 2022;22(5):190–196. doi:10.1016/j.bjae.2021.11.008
4. Koneti KK, Rajasekar N. Chronic pain management after surgery. *Surgery*. 2022;40(6):386–390. doi:10.1016/j.mpsur.2022.03.010
5. Chapman CR, Vierck CJ. The Transition of Acute Postoperative Pain to Chronic Pain: an Integrative Overview of Research on Mechanisms. *J Pain*. 2017;18(4):359.e1–359.e38. doi:10.1016/j.jpain.2016.11.004
6. Gu X, Zhang Y, Wei W, Zhu J. Clinical Medicine Effects of Preoperative Anxiety on Postoperative Outcomes and Sleep Quality in Patients Undergoing Laparoscopic Gynecological Surgery. *J Clin Med*. 2023;12(5):1835. doi:10.3390/jcm12051835
7. Ni K, Zhu J, Ma Z. Preoperative anxiety and postoperative adverse events: a narrative overview. *Anesthesiol Perioperative Sci*. 2023;1(3):1. doi:10.1007/s44254-023-00019-1
8. Tadesse M, Ahmed S, Regassa T, et al. Effect of preoperative anxiety on postoperative pain on patients undergoing elective surgery: prospective cohort study. *Ann Med Surg*. 2022;73. doi:10.1016/j.amsu.2021.103190
9. Baagil H, Baagil H, Gerbershagen MU. Preoperative Anxiety Impact on Anesthetic and Analgesic Use. *Medicina*. 2023;59(12):2069. doi:10.3390/medicina59122069
10. Liu Q, Li L, Wei J, Xie Y. Correlation and influencing factors of preoperative anxiety, postoperative pain, and delirium in elderly patients undergoing gastrointestinal cancer surgery. *BMC Anesthesiol*. 2023;23(1). doi:10.1186/s12871-023-02036-w
11. Li X, Zhu Y, Sun H, et al. Electroacupuncture Inhibits Pain Memory and Related Anxiety-Like Behaviors by Blockading the GABAB Receptor Function in the Midcingulate Cortex. *Mol Neurobiol*. 2023;60(11):6613–6626. doi:10.1007/s12035-023-03467-9
12. Amorim D, Amado J, Brito I, et al. Acupuncture and electroacupuncture for anxiety disorders: a systematic review of the clinical research. *Complement Ther Clin Pract*. 2018;31:31–37. doi:10.1016/j.ctcp.2018.01.008
13. Amorim D, Brito I, Caseiro A, et al. Electroacupuncture and acupuncture in the treatment of anxiety - A double blinded randomized parallel clinical trial. *Complement Ther Clin Pract*. 2022;46:101541. doi:10.1016/j.ctcp.2022.101541

14. 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
15. Lv Q, Wu F, Gan X, et al. The Involvement of Descending Pain Inhibitory System in Electroacupuncture-Induced Analgesia. *Front Integr Neurosci*. 2019;13. doi:10.3389/fnint.2019.00038
16. Zhou M, Zhang Q, Huo M, et al. The mechanistic basis for the effects of electroacupuncture on neuropathic pain within the central nervous system. *Biomed Pharmacother*. 2023;161:114516. doi:10.1016/j.biopha.2023.114516
17. Chen P, Xu H, Zhang R, Song TIANX. Dose-effect relationship between electroacupuncture with different parameters and the regulation of endogenous opioid peptide system. *World J Acupuncture*. 2023. doi:10.1016/j.wjam.2023.06.003
18. Zhu J, Hou B, Rong H, et al. Blocking brown adipocyte β3-adrenoceptor attenuates blood-spinal cord barrier impairment and chronic postsurgical pain in a rat model of preoperative stress. *Int Immunopharmacol*. 2024;128:111530. doi:10.1016/j.intimp.2024.111530
19. Sun R, Zhao Z, Feng J, et al. Glucocorticoid-Potentiated Spinal Microglia Activation Contributes to Preoperative Anxiety-Induced Postoperative Hyperalgesia. *Mol Neurobiol*. 2017;54(6):4316–4328. doi:10.1007/s12035-016-9976-1
20. Sun R, Liu Y, Hou B, et al. Perioperative activation of spinal α7 nAChR promotes recovery from preoperative stress-induced prolongation of postsurgical pain. *Brain Behav Immun*. 2019;79:294–308. doi:10.1016/j.bbi.2019.02.017
21. Ma W, Li L, Xing S. PGE2/EP4 receptor and TRPV1 channel are involved in repeated restraint stress-induced prolongation of sensitization pain evoked by subsequent PGE2 challenge. *Brain Res*. 2019;1721:146335. doi:10.1016/j.brainres.2019.146335
22. Romero A, García-Carmona JA, Laorden ML, Puig MM. Role of CRF1 receptor in post-incisional plasma extravasation and nociceptive responses in mice. *Toxicol Appl Pharmacol*. 2017;332:121–128. doi:10.1016/j.taap.2017.04.021
23. Jiang M, Sun Y, Lei Y, et al. GPR30 receptor promotes preoperative anxiety-induced postoperative hyperalgesia by up-regulating GABAA-α4β1δ subunits in periaqueductal gray in female rats. *BMC Anesthesiol*. 2020;20(1):93. doi:10.1186/s12871-020-01017-7
24. Jiang M, Bo J, Lei Y, et al. Anxiety-induced hyperalgesia in female rats is mediated by cholecystokinin 2 receptor in rostral ventromedial medulla and spinal 5-hydroxytryptamine 2B receptor. *J Pain Res*. 2019;12:2009–2026. doi:10.2147/JPR.S187715
25. Wu H, Huang Y, Tian X, et al. Preoperative anxiety-induced glucocorticoid signaling reduces GABAergic markers in spinal cord and promotes postoperative hyperalgesia by affecting neuronal PAS domain protein 4. *Mol Pain*. 2019;15. doi:10.1177/1744806919850383
26. Dourson AJ, Willits A, Raut NGR, et al. Genetic and epigenetic mechanisms influencing acute to chronic postsurgical pain transitions in pediatrics: preclinical to clinical evidence. *Canad J Pain*. 2022;6(2):85–107. doi:10.1080/24740527.2021.2021799
27. James SK. Chronic postsurgical pain: is there a possible genetic link? *Br J Pain*. 2017;11(4):178–185. doi:10.1177/2049463717723222
28. Fereidoni M, Li S, Boscia F, Magnaghi V. Protein kinase C epsilon activation regulates proliferation, migration, and epithelial to mesenchymal-like transition in rat Schwann cells. *Front Cell Neurosci*. 2023;17:1237479.
29. Shipton EA. The transition of acute postoperative pain to chronic pain: part 1 – risk factors for the development of postoperative acute persistent pain. *Trends Anaesth Crit Care*. 2014;4(2–3):67–70. doi:10.1016/j.tacc.2014.04.001
30. Shipton EA. The Transition of Acute Postoperative Pain to Acute Persistent Pain to Chronic Pain: assessing and Managing the Risks. In: *Perioperative Medicine – Current Controversies*. Cham: Springer International Publishing; 2016:421–452.
31. Zeng J, Li S, Zhang C, Huang G, Yu C. The Mechanism of Hyperalgesia and Anxiety Induced by Remifentanil: phosphorylation of GluR1 Receptors in the Anterior Cingulate Cortex. *J Mol Neurosci*. 2018;65(1):93–101. doi:10.1007/s12031-018-1072-8
32. Zhang Z, Wu H, Liu Y, Gu X, Zhang W, Ma Z. The GCs-SGK1-ATP Signaling Pathway in Spinal Astrocytes Underlied Presurgical Anxiety-Induced Postsurgical Hyperalgesia. *Anesth Analg*. 2019;129(4):1163–1169. doi:10.1213/ANE.0000000000003682
33. Bassetto RM, Wscieklica T, Pouza KCP, et al. Effects of electroacupuncture on stress and anxiety-related responses in rats. *An Acad Bras Cienc*. 2017;89(2):1003–1012. doi:10.1590/0001-3765201720160531
34. 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 Neurosci Ther*. 2023;30:e14520.
35. Jia YZ, Li HT, Zhang GM, et al. Electroacupuncture alleviates orofacial allodynia and anxiety-like behaviors by regulating synaptic plasticity of the CA1 hippocampal region in a mouse model of trigeminal neuralgia. *Front Mol Neurosci*. 2022;15. doi:10.3389/fnmol.2022.979483
36. Hu XF, Zhang H, Yu LL, et al. Electroacupuncture Reduces Anxiety Associated With Inflammatory Bowel Disease By Acting on Cannabinoid CB1 Receptors in the Ventral Hippocampus in Mice. *Front Pharmacol*. 2022;13:919553.
37. Wei D, Zhao N, Xie L, et al. Electroacupuncture and Moxibustion Improved Anxiety Behavior in DSS-Induced Colitis Mice. *Gastroenterol Res Pract*. 2019;2019:1–12.
38. Zhou F, Jiang H, Kong N, et al. Electroacupuncture Attenuated Anxiety and Depression-Like Behavior via Inhibition of Hippocampal Inflammatory Response and Metabolic Disorders in TNBS-Induced IBD Rats. *Oxid Med Cell Longev*. 2022;2020:1–19.
39. Yue N, Li B, Yang L, et al. Electro-Acupuncture Alleviates Chronic Unpredictable Stress-Induced Depressive- and Anxiety-Like Behavior and Hippocampal Neuroinflammation in Rat Model of Depression. *Front Mol Neurosci*. 2018;11. doi:10.3389/fnmol.2018.00149
40. Zhu J, Wang C, Wang Y, et al. Electroacupuncture alleviates anxiety and modulates amygdala CRH/CRHR1 signaling in single prolonged stress mice. *Acupunct Med*. 2022;40(4):369–378. doi:10.1177/09645284211056352
41. Yang L, Yue N, Zhu X, et al. Electroacupuncture Promotes Proliferation of Amplifying Neural Progenitors and Preserves Quiescent Neural Progenitors from Apoptosis to Alleviate Depressive-Like and Anxiety-Like Behaviours. *Evid Based Complement Alternat Med*. 2014;2014 (1):1–13. doi:10.1155/2014/872568
42. Du J, Fang J, Xu Z, et al. Electroacupuncture suppresses the pain and pain-related anxiety of chronic inflammation in rats by increasing the expression of the NPS/NPSR system in the ACC. *Brain Res*. 2020;1733:146719. doi:10.1016/j.brainres.2020.146719
43. Yuan DY, Xu F, feng WY, et al. Electroacupuncture alleviates postoperative pain through inhibiting neuroinflammation via stimulator of interferon genes/type-1 interferon pathway. *J Integr Med*. 2023;21(5):496–508. doi:10.1016/j.joim.2023.07.001
44. Jin Y, Zhou J, Xu F, et al. Electroacupuncture alleviates the transition from acute to chronic pain through the p38 MAPK/TNF-α signalling pathway in the spinal dorsal horn. *Acupunct Med*. 2021;39(6):708–715. doi:10.1177/09645284211020766
45. Gao YH, Li CW, Wang JY, et al. Effect of electroacupuncture on the cervicospinal P2X7 receptor/fractalkine/CX3CR1 signaling pathway in a rat neck-incision pain model. *Purinergic Sig*. 2017;13(2):215–225. doi:10.1007/s11302-016-9552-1
46. Shi C, Liu Y, Zhang W, et al. Intraoperative electroacupuncture relieves remifentanil-induced postoperative hyperalgesia via inhibiting spinal glial activation in rats. *Mol Pain*. 2017;13:174480691772563. doi:10.1177/1744806917725636

47. Qiao LN, Yang YS, Liu JL, et al. Contribution of GABAergic modulation in DRGs to electroacupuncture analgesia in incisional neck pain rats. *J Pain Res*. 2019;12:405–416. doi:10.2147/JPR.S180165
48. Silva ML, Silva JRT, Prado WA. 100-Hz Electroacupuncture but not 2-Hz Electroacupuncture is Preemptive Against Postincision Pain in Rats. *J Acupunct Meridian Stud*. 2016;9(4):200–206. doi:10.1016/j.jams.2016.04.006
49. Hsu SF, Zeng YJ, Tsai SY, et al. Spinal p38 activity and analgesic effect after low- and high-intensity electroacupuncture stimulation in a plantar incision rat model. *Life Sci*. 2015;128:15–23. doi:10.1016/j.lfs.2015.01.035
50. Wang J, Zhang J, Gao Y, Chen Y, Duanmu C, Liu J. Electroacupuncture Alleviates Hyperalgesia by Regulating CB1 Receptor of Spinal Cord in Incisional Neck Pain Rats. *Evid Based Complement Alternat Med*. 2021;2021:1–12.
51. Jin Y, Zhou J, Fang Y, et al. Electroacupuncture prevents the development or establishment of chronic pain via IL-33/ST2 signaling in hyperalgesic priming model rats. *Neurosci Lett*. 2024;820:137611. doi:10.1016/j.neulet.2023.137611
52. Wang K, Xiang XH, Qiao N, et al. Genomewide Analysis of Rat Periaqueductal Gray-Dorsal Horn Reveals Time-, Region- and Frequency-Specific mRNA Expression Changes in Response to Electroacupuncture Stimulation. *Sci Rep*. 2014;4(1):6713. doi:10.1038/srep06713