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REVIEW

Mechanism of electroacupuncture on inflammatory pain: neural-immune-endocrine interactions

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Abstract

Nociceptive signals are transmitted by peripheral afferents to the central nervous system under pain condition, a process that involves various neurotransmitters and pathways. Electroacupuncture (EA) has been widely used as a pain management technique in clinical practice. Emerging studies have shown that EA can inhibit the induction and transmission of pain signals and, consequently, mediate anti-nociceptive and anti-inflammatory effects by rebalancing the neural-immune-endocrine interactions. This review summarizes the neural-immune-endocrine circuit including peripheral afferent and central efferent, contributing to EA-induced neuroimmune and neuroendocrine modulation in inflammatory pain models. The peripheral afferent circuit includes crosstalk among immune cells, inflammatory cytokines, peripheral nociceptors. In central efferent primarily involves the neuroinflammatory interactions between spinal nociceptive neurons and glial cells. Furthermore, the hypothalamic-pituitary-adrenal axis, sympathetic and vagal nervous may serve as an essential pathway involved in the mechanism of acupuncture-mediated analgesia within the interactions of the central, immune and endocrine systems. Overall, this review focuses on the interactions of neural-immune-endocrine in inflammatory pain, which may be underlying the mechanism of EA-induced anti-inflammatory and antinociceptive effect.

Keywords: Electroacupuncture; Analgesia; Inflammatory pain; Neural-immune-endocrine interactions; Review

INTRODUCTION

Inflammatory pain, which is caused by the activation of peripheral nociceptors in the nervous system by noxious chemicals and mechanical or thermal stimuli, is not only a warning signal for local tissue damage and nerve injury but can also be an indicator of systemic ill-

ness.[1] Physiologically, nociceptive signals that are mediated by central neural circuits lead to the perception of pain. Pain perceived by the brain can have regulatory effects that maintain the homeostasis of the immune, autonomic and endocrine systems. The dysregulation of these bidirectional signaling pathways results in chronic inflammatory pain.[2,3] During this process, peripheral tissue damage induces inflammatory responses by triggering immune cells to release a series of inflammatory mediators. These mediators bind with receptors expressed on nociceptive neurons, causing the neurons to depolarize and generate action potentials, which further transmit the nociceptive signals to the spinal dorsal horn and the brain, contributing to the induction and maintenance of perceived pain.[4] Moreover, peripheral inflammatory mediators, such as inflammatory cytokines, can be activated by vagal and sympathetic nerves, which can aggravate pain and inflammation through cross-talk between the neuroimmune and neuroendocrine systems.[3, 5]

Electroacupuncture (EA), as a complementary and alternative therapy, has been shown to have substantial beneficial effects on pain relieving.[6] Though the mechanisms of action underlying these effects remain to be elucidated, EA may exert a comprehensive modulatory effect on inflammatory pain, affecting the entire nervous system [including the peripheral nervous system (PNS) and the central nervous system (CNS)], the immune system, and the endocrine system. Due to the complexity of pain, a more comprehensive elucidate the mechanisms underlying the EA-mediated regulation of inflammatory pain within the interactions of central, immune and endocrine systems is of great clinical significance. This review summarizes the recent progress towards understanding this process and proposes a mechanism for the multisystem regulatory effects of EA during inflammatory pain.

Anatomical structure of acupuncture points

Acupoints can be sensed and transduced by a variety of stimulation types, such as mechanical stimulation mediated by acupuncture needle, thermal stimulation by moxibustion, electrical stimulation by EA, and radiation by laser beams. The ability of acupoints to transduce stimuli plays an important role in acupuncture-mediated effects on pain.[7,8] According to classical acupuncture theories, disorders of the visceral organs can be manifested at specific points, either on or underneath the skin surface, which is how acupoints have historically been defined.[9] Despite considerable efforts to better understand the anatomy and physiology of acupuncture points and meridians, the definitions and characterizations of these structures remain inconclusive. Early morphology studies analyzed the anatomical structures surrounding acupoints, suggesting that nervous system components, blood vessels, and musculoskeletal tissues represent important constituents of acupoints.[10-12] The anatomical structures surrounding acupuncture points transmit the neuroimmune and neuroinflammation signals induced by stimulation with EA or manual acupuncture.[13] Recent studies have shown that mast cells (MCs), which are important components of the immune system, could be potential effector cells at acupoints.[14,15] EA stimulation at acupoints has been shown to result in MC degranulation and afferent nerve excitation,[16] which is closely related to acupoint sensitization[17] and EA-mediated analgesia.[15] Following acupuncture stimulation, MCs not only initiate a neuroimmune response by releasing inflammatory mediators but also play a crucial role in the cross-talk among the circulatory, nervous and immune networks at acupoints.[16,18] A recent study showed that transcutaneous electrical acupoint stimulation at Binao (LI 14) acupoint induced sensory nerve fibers to express calcitonin gene-related peptide and substance P, which bind with the neurokinin 1 receptor on MCs. This interaction resulted in the degranulation of MCs, releasing 5-hydroxytryptamine (5-HT), and thus producing analgesic effect similar to that of EA.[19] Other studies have also demonstrated that electrical stimulation at the Zusanli (ST 36) acupoint activates the immune system by regulating the production of immune cytokines, such as interferon gamma (IFN-γ), interleukin-2 (IL-2) and interleukin-17 (IL-17), and the differentiation and activation of splenic T cells.[20]

Peripheral afferent neuroimmune and neuroendocrine modulation

Peripheral nociceptive afferent fibers include Aδ- and C-fibers, which have peripheral axonal branches at nociceptor terminals. These fibers are found in the dorsal root ganglion (DRG), the trigeminal ganglion, the nodose ganglion of the vagal nerve, and the central axonal branch, all of which form synaptic connections with neurons in the spinal dorsal horn (SDH).[4] The nociceptive signals induced by chemical, mechanical, or thermal stimuli leading to changes in the responsiveness of peripheral nociceptors and peripheral sensitization including hyperalgesia and allodynic.

The neural mechanism underlying acupuncture/EA-mediated analgesia has been addressed previously and includes a wide spectrum of modulating effects mediated by peripheral afferent pathway, transmitters and modulators.[10,21] A large number of studies have explored the distinct roles played by the non-nociceptive large afferent fiber (Aβ-fiber) and the nociceptive small afferent fibers (Aδ- and C-fibers), which are found in the peripheral neural pathways, during EA-induced anti-nociceptive signaling.[22] The transient receptor potential vanilloid receptors 1 (TRPV1) and 4 (TRPV4), and the acid-sensing ion channel 3 (ASIC3) are mechanosensitive channels associated with the release of adenosine triphosphate (ATP) in various local tissues.[23-25] Structurally, they are membrane channel proteins that become permeable to cations, such as sodium and calcium, following mechanical stimulation. ASIC3, which

mediates responses to acidic and mechanical stimuli, is located primarily in the Aβ-fibers that innervate the skin and muscles.[26] TRPV1 belongs to the TRPV subfamily and is highly expressed in nociceptive Aδ- and C-fibers.[27] Previous studies have shown that the ASIC3 and TRPV1 receptors are involved in the peripheral sensations of EA stimulation, based on their distributions and functional properties.[28] The segmental analgesic effects of low-intensity EA are mediated by afferent Aβ-fibers and ASIC3, and the systemic analgesic effects of high-intensity EA are attributed to the activation of Aδ/C-fibers and TRPV1. Other studies have found that TRPV1 is highly expressed at Zusanli (ST 36), which suggests that TRPV1 might act as an acupuncture-responding channel that senses the physical stimulation of acupuncture, conducts the signal to nerve terminals through ATP-induced calcium wave propagation (CWP),[29] and mediates the transduction of EA signals to the CNS. TRPV1 receptors are also expressed in subepidermal connective tissue cells, where they may play a role in the effects of EA on local tissue.[30] TRPV1, as a mechanical sensitive channel, plays an important role in the transmission of the physical stimulation caused by acupuncture or EA to neurological signaling in nervous system. In addition, the activation of TRPV1 receptors upregulates the expression of protein kinases and related downstream molecules, such as protein kinase A (PKA), protein kinase C (PKC), and Phosphoinositide 3-kinase (PI3K)-protein kinase B (PKB/Akt) signaling pathway, during complete Freund's adjuvant (CFA)-induced inflammatory pain. Furthermore, TRPV1 can activate the cellular signaling pathways including the mitogen-activated protein kinase (MAPK) family member p38, extracellular-regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK), and downstream nuclear factor-κB (NF-κB) and cAMP response element binding protein (CREB) during CFA-induced pain. Moreover, nociceptive Nav1.7 and Nav1.8 channels have been shown to be sensitized under pain conduction in both the DRG and SDH. Inflammatory factors, such as glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B), and receptor for advanced glycation end products (RAGE) are also involved in this process.[31] TRPV1 also play a crucial role during EA-mediated analgesia. EA applied to Zusanli (ST 36) can significantly attenuate TRPV1 activation and TRPV1-mediated the above cellular signaling pathways, thus inhibiting the transmission of nociceptive signals.[32,33]

Furthermore, under the chronic pain condition, the plasticity of nociceptive neurons in both the PNS and the CNS are also altered, which can result in peripheral and central sensitization.[34] Crosstalk between peripheral nociceptors and immune cells mediates peripheral sensitization. Moreover, the neural, immune, and endocrine systems communicate with each other *via* inflammatory cytokines (Figure 1).[35] Peripheral inflammatory cytokines are potential messengers that mediate the

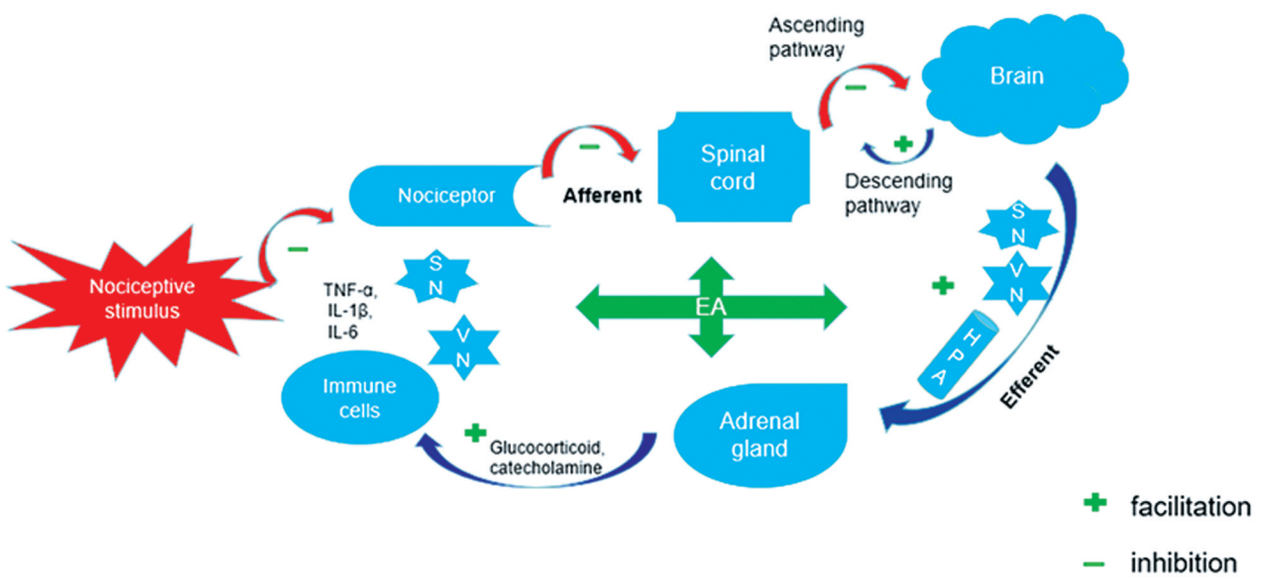

Figure 1 EA-induced neuroimmune and neuroendocrine modulation circuit

This circuit includes peripheral afferent and central efferent pathways. The nociceptive stimulus induced by CFA activates the nociceptor and the vagal and sympathetic terminals in the peripheral afferent pathway. Meanwhile, immune cells form a crosstalk mechanism among the nociceptor, vagal afferent fibers and sympathetic nerve terminal through the release of inflammatory cytokines, such as TNF-α, interleukin-1β, and IL-6. The nociceptive signal is then transmitted to the spinal cord and brain. The modulatory signals received from the neural, immune, endocrine systems are then integrated in the brain, which further conveys secondary neuroimmune and neuroendocrine modulatory signals through the ascending and descending pain control pathway, the VN, SN, and HPA) axis to regulate inflammatory pain. In the central efferent pathway, vagal efferent fibers and sympathetic preganglionic neurons act on the adrenal gland to release glucocorticoids and catecholamines, which further inhibit the release of inflammatory cytokines and eventually mitigate anti-inflammatory pain. EA: electroacupuncture; TNF-α: tumor necrosis factor α; IL-1β: interleukin-1β; IL-6: interleukin-6; VN: vagal nerve; SN: sympathetic nerve; HPA: hypothalamic-pituitary-adrenal.

communication between nociceptors and vagal and sympathetic nerves. Inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), are released by peripheral immune cells to form an "inflammatory soup", and these cytokines bind with ion channel receptors, G protein coupled receptors (GPCRs) and tyrosine kinase receptors (Trk) that are expressed on nociceptive neurons to mediate peripheral sensitization at the cellular and molecular levels.[4,36] However, inflammatory cytokines can also activate the afferent neurons of the vagal nerve and sympathetic nerve endings through a central neural circuit; the efferents of the vagal and sympathetic pre-ganglionic nerves then act on the adrenal gland, immune cells or nociceptive neurons, causing the release of norepinephrine (NE) and acetylcholine (ACh), which inhibit the release of peripheral inflammatory cytokines.[37,38]

EA inhibits peripheral sensitization by modulating the neural, immune and endocrine systems (Figure 2). At the peripheral level, EA can inhibit the production and release of inflammatory cytokines through various pathways. During inflammation, EA promotes peripheral immune cells to release opioids, cannabinoids (CB) and adenosine (A), which further exert anti-inflammatory effects *via* binding with μ-opioid receptors or CB2, A1 and A2A receptors that are expressed on nociceptive neurons or immune cells, respectively, to inhibit the release of TNF-α, IL-1β, and IL-6.[39-42] In addition to inflammatory cytokines, chemokines also play a role in inflammatory pain. During the early stages of inflammation, the chemokine (C-X-C motif) ligand (CXCL) CXCL2 stimulates opioid release by acting on the chemokine (C-X-C motif) receptor (CXCR) CXCR2 in neutrophils.[43] Studies performed in a rodent model of CFA-induced inflammation have also found that EA applied to acupoint Huantiao (GB 30) upregulates the expression levels of CXCL10 and CXCR3, and then stimulates the release of opioids from macrophages.[44] Macrophages have bidirectional effects on inflammatory responses. The M1 macrophage releases pro-inflammatory cytokines, while the M2 macro-

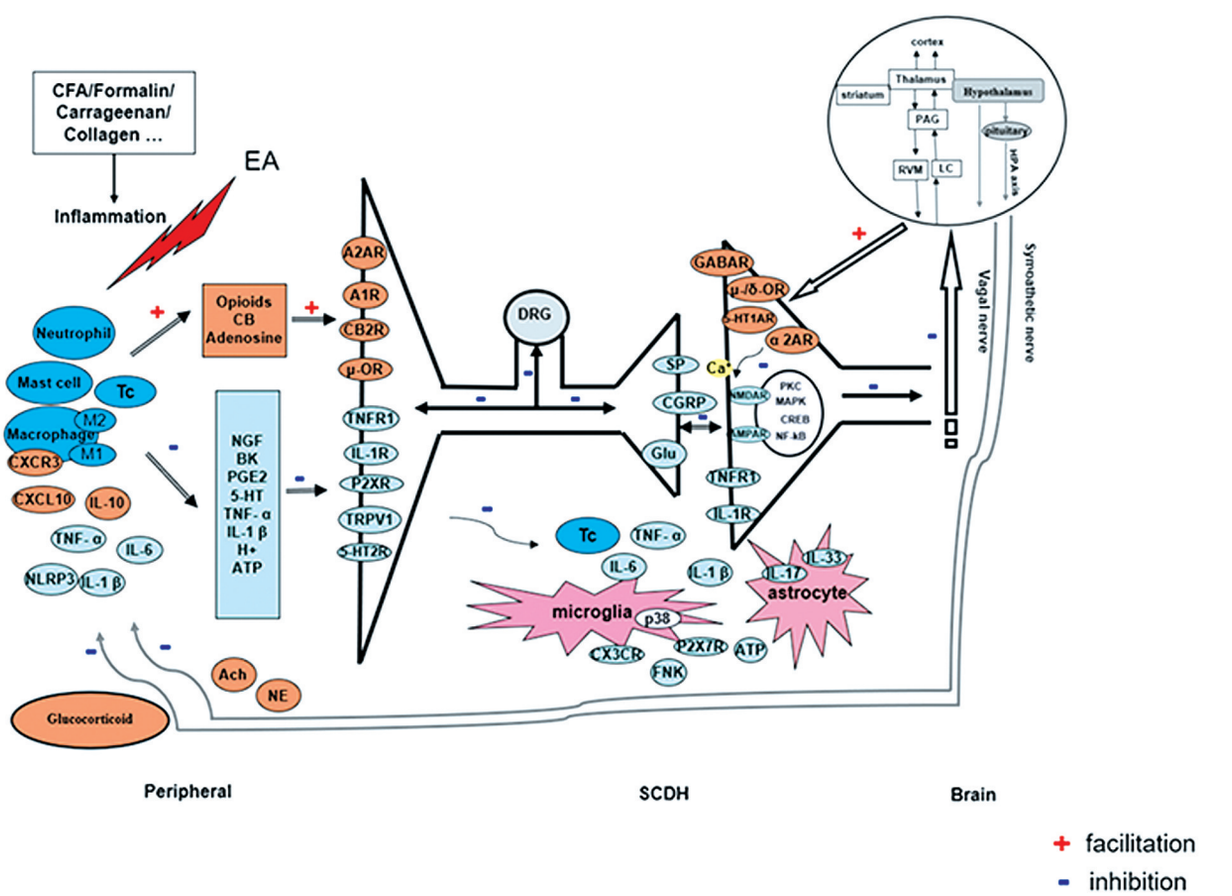

Figure 2 Mechanisms of EA induced-analgesia and anti-inflammatory effects on inflammatory pain, involving interactions among the neural, immune, and endocrine systems, at both peripheral and central levels

The injection of CFA/Formalin/Carrageenan/Collagen generates peripheral nociceptive signals to further sensitize the peripheral nociceptive afferent fibers. Following its initial integration in the DRG, the nociceptive information is transmitted to the SDH and supraspinal cord through the ascending pathway. Meanwhile, the SDH receives signals that are projected from the descending pain modulatory system in the brain stem (PAG-RVM/LC-SDH pathway). In addition, the VN, SN, and HPA axis are involved in pain processing and induce anti-inflammatory responses. EA: electroacupuncture; CFA: complete Freund's adjuvant; DRG: dorsal root ganglion; SDH: spinal dorsal horn; PAG: periaqueductal grey; RVM: rostral ventromedial medulla; LC: locus coeruleus; VN: vagal nerve; SN: sympathetic nerve; HPA: hypothalamic-pituitary-adrenal.

phage secretes anti-inflammatory cytokines to inhibit inflammatory responses.[45] EA inhibits M1 macrophages, promotes the transformation from M1 to M2 macrophages, and consequently enhances the M2-mediated release of interleukin-10 (IL-10), which alleviates inflammatory pain.[46] The inflammasome NACHT, LRR and PYD domains-containing protein 3 (NLRP3), a member of the NOD-like receptor (NLR) family, is located on macrophages and modulates inflammation and pain by promoting IL-1β maturation.[47] EA can inhibit NLRP3 release by promoting the expression of CB2 and β-endorphin, thereby impeding the maturation of IL-1β and mitigating inflammatory pain.[48] Adenosine exerts anti-inflammatory effects primarily through the activation of A2A receptors in the periphery.[49] EA applied to the acupoints Zusanli (ST 36) and Sanyinjiao (SP 6) increased the levels of A2A receptors, decreased the release of TNF-α, and simultaneously reduced inflammation and hyperalgesia in collagen-induced arthritis model rats.[42,50] EA may also act through MAPK signaling pathways, such as the phosphorylation of ERK and JNK, to regulate the expression levels of TNF-α and IL-1β at both the transcriptional and post-translational levels.[51,52] In addition, EA activates vagal and sympathetic nerves and the HPA axis to inhibit the levels of inflammatory cytokines, which may affect peripheral sensitization.[3,53]

Central efferent neuroimmune and neuroendocrine modulation

The CNS includes the spinal cord and supraspinal structures. The SDH is one of the major tissues that regulate the transfer and processing of nociceptive signals. The lamina Ⅰ, Ⅱ and Ⅴ layers of the SDH, which contain a large proportion of intrinsic neurons, intermediate neurons and projection neurons, primarily receive projections from peripheral nociceptive Aδ- and C-fibers and establish multiple synaptic connections. In addition, under peripheral sensitization conditions, spinal microglia and astrocytes become activated, releasing inflammatory mediators and forming synaptic connections with dorsal horn neurons.[54,55] Nociceptive signals in the SDH are transported to the brain stem, thalamus, and cortex through projection neurons and the ascending pathway (Figure 3). The SDH also receives signals from the descending pathway that can inhibit or facilitate the transduction of nociceptive signals.[56] The change of synaptic plasticity in the SDH, through neuroimmune interactions among spinal nociceptive neurons, glial cells, and T lymphocytes, eventually results in central sensitization.[57,58]

The periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM) are the major brain regions involved in descending pain control. The analgesic effects of EA at the spinal cord level are also mediated by descending inhibitory pathways, which regulate the release of classical neurotransmitters, such as opioids, 5-HT, norepinephrine (NE), and γ-aminobutyric acid

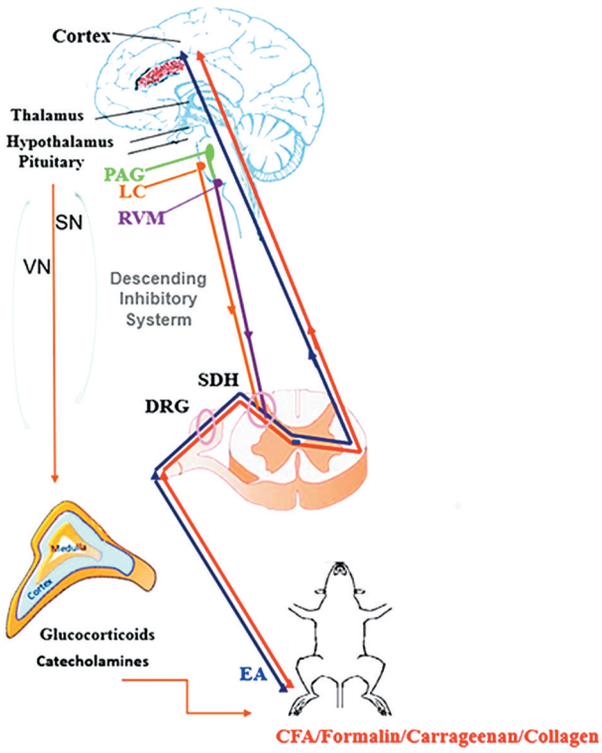

Figure 3 Anti-inflammatory and anti-nociceptive signaling pathway induced by EA through peripheral, spinal, and supraspinal mechanisms during inflammatory pain

EA inhibited a variety of inflammatory mediators (TNF-α, IL-1β, IL-6, NGF, and ATP) and promoted the peripheral release of opioid peptides, cannabinoids and adenosine to suppress peripheral sensitization. In the spinal dorsal horn, EA inhibited the postsynaptic excitation of NMDARs and AMPARs, the MAPK phosphorylation-induced cellular signaling, and the release of glial activation-dependent inflammatory mediators to further attenuate central sensitization. The EA-induced modulation of pain and inflammation at the brain level also involves interactions among the central, immune and endocrine systems. EA modulates the descending pain inhibitory pathway (PAG-RVM/LC-SDH) to induce 5-HT and NE expression in the SDH. In addition, the expression of peripheral inflammatory cytokines was regulated by the HPA axis and the sympathetic and vagal nervous systems, which were associated with EA-induced neuroimmune and neuroendocrine modulations. EA: electroacupuncture; CFA: complete Freund's adjuvant; Tc: T lymphocyte cell; TNF-α: tumor necrosis factor α; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-17: interleukin-17; IL-10: interleukin-10; IL-33: interleukin-33; P2XR: purinergic P2X receptor; TRPV1: transient receptor potential vanilloid 1; CB: cannabinoids; CB2R: cannabinoids 2 receptor; CB1R: cannabinoids1 receptor; u-OR: u-opioid receptor; A1R: adrenergic 1 receptors; A2R: adrenergic 2 receptors; DRG: dorsal root ganglion; SCDH: spinal cord dorsal horn; SP: substance P; CGRP: calcitonin-gene related peptide; 5-HT: 5-hydroxytryptamine; 5-HT1AR: 5-hydroxytryptamine 1A receptors; 5-HT2R: 5-hydroxytryptamine 2 receptors; NE: norepinephrine; μ-/δ-R: μ-/δ-opioid receptors; GABA: γ-aminobutyric acid; $GABA_{A/B}R$: $GABA_{A/B}$ receptors; Glu: glutamate; α2AR: α2 adrenergic receptor; NMDAR: N-methyl-d-aspartate receptor; AMPAR: α amino- 3-hydroxy -5- methyl-4-isoxazole-propionic acid; DA: Dopamine; FNK: fractalkine; GPCRs: G protein-coupled receptors; PKC: protein kinase C; MAPK: mitogen-activated protein kinase; NF-kB: nuclear factor-kB; CREB: cAMP response element binding protein; RVM: rostral ventromedial medulla; LC: locus coeruleus; PAG: periaqueductal grey.

(GABA), and their corresponding receptors (Figure 2).[10,21] Studies have demonstrated that CB1 receptors are expressed on both GABAergic and glutamatergic neurons in the PAG, which has different effects on ascending and descending pain modulation.[59] EA can upregulate CB1 expression in GABAergic neurons, inhibiting GABA release from PAG neurons, and subsequently disinhibiting the release of 5-HT in the RVM, which promotes the inhibition of chronic pain by descending inhibitory pathways.[60] Glial activation is recruited during EA-mediated neuroimmune modulation in the CNS. EA inhibits glial activation and reduces the levels of inflammatory cytokines and other inflammatory mediators released by microglia and astrocytes, which suppresses central sensitization (Figure 2).[61] Inflammation promotes ATP release and binding with the P2X7 receptors on glial cells, which further activates the chemokine fractalkine (FTK). FTK binds with the receptor CX3CR to induce p38 phosphorylation, causing glial activation and the release of TNF-α, brain-derived neurotrophic factor and other inflammatory mediators, which modulate central sensitization.[62] EA can inhibit the ATP-FTK-p38 signaling pathway and suppress glial cell activation, thereby reducing the expression levels of TNF-α and IL-1β.[63] Excitatory glutamatergic neurons, which primarily express α-amino-3- hydroxy- 5- methyl- 4- isoxazole-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors (NMDARs), promote the transmission of nociceptive signals to the spinal cord and mediate central sensitization. The NMDAR subtype NR1 plays a major role during the regulation of NMDAR excitability,[64,65] and the phosphorylation of NR1 promotes the central sensitization. Inflammatory cytokines released by glial cells, such as IL-1β and interleukin-17 (IL-17), also promote the NR1 phosphorylation.[66,67] EA inhibits the IL-1β- and IL-17-induced NR1 phosphorylation in glial cells, alleviating CFA-induced inflammatory pain.[68] Moreover, EA also regulates the production and release of TNF-α, IL-1β, neurokinin-1, and cyclooxygenase-2 at the transcriptional and post-translation levels through spinal cell signaling pathways, such as the PKA, PKC, and downstream NF-κB, and CREB pathways, which eventually inhibit central sensitization.[69-73]

At the supraspinal cord level, the brain stem, hypothalamus, thalamus, limbic system, cortex, and other important brain regions are integrated to manage pain information, including pain related sensory components, anxiety, depression and other affective components, which involves the comprehensive regulation of the nervous, immune and endocrine systems in the brain (Figure 2). On the one hand, EA regulates pain sensations and pain aversion through pain-related brain regions in the CNS.[74-77] On the other hand, the central efferents of the hypothalamic-pituitary-adrenal (HPA) axis, and the sympathetic and the vagal nervous systems regulate the expression of peripheral inflammatory cytokines (Figure 1).[78-80] The adrenal gland is closely associated with the process of EA-mediated neuroimmune and neuroendocrine modulation. The primary glucocorticoid released from the adrenal cortex is cortisol in humans and corticosterone in rodents. The adrenal medulla releases catecholamines, including epinephrine, NE and dopamine (DA). Peripheral nociceptive stimuli are transmitted through the spinal cord to the paraventricular nucleus in the hypothalamus, which further activates the HPA axis to release glucocorticoids and inhibit inflammatory responses.[3,81] Previous studies have demonstrated that EA stimulated the activation of the HPA axis to release glucocorticoids and increased the levels of peripheral serum corticosterone, while inhibiting the expression of inflammatory cytokines, thus alleviating inflammatory pain induced by CFA.[82,83] The neuroimmune and neuroendocrine modulation induced by vagal and sympathetic nerves is primarily mediated by the release of ACh and NE. The vagal nerve acts on the adrenal gland to release ACh through the afferent nucleus tractus solitarius and the efferent dorsal motor nucleus. ACh then binds to α7 nicotinic cholinergic receptors expressed on macrophages to inhibit the release of TNF-α.[84,85] Sympathetic preganglionic neurons may stimulate the adrenal gland to release ACh, while postganglionic neurons directly release NE, independent of the adrenal gland, *via* α2-/β-adrenergic receptors in T lymphocytes, which further inhibits inflammation. In addition, the postganglionic neurons of the vagal nerve also inhibit the production of inflammatory cytokines in the spleen by activating the sympathetic adrenergic splenic nerve *via* a7nAChRs at the celiac ganglion. NE from the splenic nerve activates T lymphocytes to inhibit cytokine production in splenic macrophages.[3,5,86] The application of different EA frequencies results in the selective activation of sympathetic preganglionic and postganglionic neurons, which results in different neuroimmune and neuroendocrine modulatory effects.[80] The vagal nerve plays a role in EA-induced neuroimmune and neuroendocrine modulation.[78,79] A previous study also suggested that EA application stimulated the vagal nerve caused the adrenal gland to release DA, and decreased TNF-α levels in the serum and spleen.[79] Furthermore, vagotomy, adrenalectomy and splenectomy can affect the neuroimmune and neuroendocrine modulation induced by EA.[78,79,83] Although the vagal nerve mediates the anti-inflammatory effects of EA, the role of the vagal nerve during pain perception remains poorly understood.

DISCUSSION

The mechanism underlying EA-mediated pain reduction is multifaceted, ranging from the activation of single systems to multisystem connections. The nervous, immune, and endocrine systems are fundamental to the autoregulation of the body, and these systems are all involved in the EA-mediated analgesia.[3] This article

describes the anti-inflammatory and anti-nociceptive response induced by EA application, with a particular focus on the role played by neural-immune-endocrine interactions during this process. During inflammation, peripheral inflammatory cytokines sensitize nociceptive neurons to transmit nociceptive signals to the spinal cord and supraspinal cord. Meanwhile, through the HPA axis and the sympathetic and vagal nervous systems, nociceptive signals can stimulate the release of NE and ACh from the adrenal gland, inhibiting the expression of inflammatory cytokines and forming a neuroimmune and neuroendocrine modulatory circuit (Figure 1). This circuit includes interactions among peripheral afferents and central efferents that are induced by the application of EA and mediates the modulation of the neuroimmune and neuroendocrine systems during inflammatory pain. The immune cells and cytokines sensitize the nociceptive neurons, which in turn activate the immune response. Furthermore, the HPA axis and sympathetic and vagal nerves inhibit inflammation through interactions with immune cells and nociceptive neurons, forming a feedback loop.[3,5,36,87] The peripheral afferent circuit includes crosstalk among immune cells, inflammatory cytokines, peripheral nociceptive neurons, the HPA axis, and sympathetic and vagal nerves. In central efferent pathways, changes in the synaptic plasticity of spinal nociceptive neurons and glial cells can lead to neuroimmune interactions. Furthermore, nociceptive signals in the neural, immune and endocrine systems are integrated in corresponding functional brain areas, further modulating the interactions of neuroimmune and neuroendocrine under pain condition. The anti-inflammatory and anti-nociceptive signaling pathways are regulated by EA at the peripheral, spinal, and supraspinal levels in inflammatory pain models, and the mechanisms of EA-induced analgesia are associated with the inhibition of peripheral and central sensitization (Figure 2).[21] Peripherally, EA inhibits the release of pain-related inflammatory mediators during inflammatory responses caused by tissue injury, the expression of pro-nociceptive receptors in peripheral neurons, and the phosphorylation of cellular signaling pathways, all of which desensitize peripheral pain perception. Furthermore, EA also promotes the release of peripheral opioid peptides, cannabinoids and adenosine to inhibit peripheral inflammatory pain. Centrally, EA inhibits the activation of spinal cord excitatory neurons, including NMDAR and AMPAR-mediated postsynaptic excitation, the activation of MAPK phosphorylation-induced cellular signaling pathways, the activation of glial cells, and the release of inflammatory mediators, such as inflammatory cytokines, chemokines, and ATP, thereby inhibiting central sensitization.[10, 21] In addition, EA enhances descending inhibitory pathways to prohibit the transmission of pain. At the brain level, EA modulates pain and inflammation through interactions with the central nervous, immune and endocrine systems. Furthermore, the peripheral inflammatory cytokine-dependent anti-inflammatory response, mediated by the HPA axis and the sympathetic and vagal nervous systems, is also involved during EA-mediated analgesia (Figure 3).[3] Consequently, the multiple modulatory effects of EA on inflammatory pain may be associated with neural-immune-endocrine interactions.

However, further studies on the EA-induced neuroimmune and neuroendocrine modulation of inflammatory pain are required because the neuroimmune and neuroendocrine modulation mediated by EA is not the simple addition of EA-induced analgesia to anti-inflammatory effects; instead, this modulation represents an integrated effect that requires interactions among the nervous, immune and endocrine systems. This article focused on the inflammatory cytokines that are involved in the interactions among nociceptive neurons, vagal afferent nerves and sympathetic nerve terminals. Previous studies showed that crosstalk between sympathetic nerve terminals and peripheral nociceptors involves bradykinin, prostaglandin E2, nerve growth factor, and adrenaline, in addition to adenosine receptors, which causes the sensitization of nociceptive neurons.[88-90] The vagal afferent nerve may have similar properties to nociceptive neurons, including discriminative responsiveness to potentially noxious physical and chemical stimuli, peripheral sensitization and the capacity to induce central sensitization.[91,92] Future studies are necessary to explore other inflammatory mediators involved in nociceptor- and sympathetic/vagal nerve-mediated neuroimmune and neuroendocrine modulation to further clarify their roles during the potentiation of inflammatory pain. In addition, although there are several studies investigating the mechanism through which EA acts on inflammatory pain in the nervous system, mechanistic perspectives on the EA-induced neuroimmune and neuroendocrine modulation of inflammatory pain involving the HPA axis and the sympathetic/vagal nervous systems are still lacking. The elucidation of the mechanisms that underly the effects of EA on inflammatory pain from multiple perspectives may further contribute to the clinical practice of pain management, and studying EA-mediated neuroimmune and neuroendocrine modulation is important for inflammatory pain control.

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