

Review Article

Mediators, Receptors, and Signalling Pathways in the Anti-Inflammatory and Antihyperalgesic Effects of Acupuncture

John L. McDonald, Allan W. Cripps, and Peter K. Smith

School of Medicine, Griffith Health Institute, Griffith Health, Griffith University, Southport, QLD 4211, Australia

Correspondence should be addressed to John L. McDonald; twindragon@bigpond.com

Received 11 December 2014; Accepted 30 March 2015

Academic Editor: Xianghong Jing

Copyright © 2015 John L. McDonald et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Acupuncture has been used for millennia to treat allergic diseases including both intermittent rhinitis and persistent rhinitis. Besides the research on the efficacy and safety of acupuncture treatment for allergic rhinitis, research has also investigated how acupuncture might modulate immune function to exert anti-inflammatory effects. A proposed model has previously hypothesized that acupuncture might downregulate proinflammatory neuropeptides, proinflammatory cytokines, and neurotrophins, modulating transient receptor potential vallinoid (TRPV1), a G-protein coupled receptor which plays a central role in allergic rhinitis. Recent research has been largely supportive of this model. New advances in research include the discovery of a novel cholinergic anti-inflammatory pathway activated by acupuncture. A chemokine-mediated proliferation of opioid-containing macrophages in inflamed tissues, in response to acupuncture, has also been demonstrated for the first time. Further research on the complex cross talk between receptors during inflammation is also helping to elucidate the mediators and signalling pathways activated by acupuncture.

1. Introduction

In our previous publication, research on the anti-inflammatory effects of acupuncture was reviewed and a model was proposed to guide further research [1]. This review included both demonstrated and proposed effects of acupuncture and drew from both animal and human studies. Anti-inflammatory effects of acupuncture in contexts other than allergic rhinitis were explored for their potential relevance to allergic rhinitis, especially research involving proinflammatory neuropeptides and neurotrophins and modulation of the transient receptor potential vallinoid 1 (TRPV1), a central receptor in allergic inflammatory response.

New research has expanded and clarified the understanding of inflammatory response and how acupuncture might modulate it, and hence a revised model for the anti-inflammatory effects of acupuncture is proposed.

2. The Previously Proposed Model (2013 Model)

Our 2013 model proposed that, in allergic rhinitis, acupuncture downregulated proinflammatory neuropeptides,

substance P (SP), calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP); downregulated neurotrophins, nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF); and downregulated Th2 and proinflammatory cytokines and possibly upregulated Th1 cytokines, thereby shifting Th1/Th2 balance away from Th2 dominance [1]. Acupuncture-induced modulation of TRPV1 (both demonstrated and hypothesised) was also explored.

3. Effects of Acupuncture on Inflammatory Oedema

Inflammatory oedema has been significantly reduced by acupuncture in rodent and murine models of induced hind paw inflammation [2, 3]. This antioedema effect is mediated via the HPA axis as various disruptions of the HPA axis obliterate or significantly attenuate the effect [2, 3]. Many of the pathways, mediators, and receptors involved in acupuncture attenuation of inflammatory hyperalgesia appear to have either no effect or delayed effects on inflammatory oedema [4, 5]. For example, opioid pathways are implicated in acupuncture effects on inflammatory hyperalgesia but have

generally been shown to have no influence on inflammatory oedema as opioid antagonists did not diminish the antioedema effect [4, 6–8]. One study, however, has shown slight reduction in inflammatory oedema which was blocked by opiate antagonists naloxone and natriindole [9].

A single acupuncture treatment was previously reported to produce a significant but short-lived (less than 15 minutes) improvement in the patency of the nasal airway [28]. However, subjective sensations of nasal congestion have consistently been reported to decrease significantly for much longer periods following acupuncture for allergic rhinitis in adults [29–33].

Swelling of the nasal mucosa in allergic rhinitis has been linked to proinflammatory neuropeptides, proinflammatory cytokines, neurotrophins, and chemokines [34].

3.1. Neuropeptides. Downregulation of proinflammatory neuropeptides, SP, and VIP, after EA, has previously been reported in adults with persistent allergic rhinitis [35]. SP was also found to decrease sharply (by 83.2%) 18 to 24 hours after the first manual acupuncture treatment in adults with persistent allergic rhinitis in a study conducted by the authors (unpublished data). Substance P expression was also inhibited in the nasal mucosa of mice with experimentally induced allergic rhinitis following acupuncture (associated with inhibition of signal transducer and activator of transcription 6 (STAT 6), nuclear factor kappa B (NF κ B), and inducible nitric oxide synthase (iNOS)) [36]. While CGRP downregulation after acupuncture has been reported in migraine, menopausal hot flushes, and spinal nerve lesion studies, to date no studies have shown a downregulation of CGRP in allergic rhinitis.

3.2. Cytokines. STAT 6 and NF κ B are transcription factors which play an essential role in Th2 cell differentiation [36]. Inhibition of STAT 6 and NF κ B would therefore suppress Th2 cell differentiation, shifting the Th1/Th2 balance away from Th2 dominance, which characterizes atopy [36]. Significant decreases in STAT 6 and NF κ B, along with the vasodilator iNOS were reported in the mouse study mentioned in the previous paragraph [36]. A recent human study comparing acupuncture with Loratadine for perennial allergic rhinitis reported an increase in mean values for interleukin-10 (IL-10), but the increase was not statistically significant, possibly due the study being underpowered [37]. The same study also found no change in allergen-specific immunoglobulin E (IgE) for house dust mite, total IgE, interleukin-4 (IL-4), or interferon gamma (IFN- γ) [37]. A small number of earlier human studies on the treatment of allergic rhinitis with acupuncture showed that a trend towards Th2 cytokines as being downregulated, but very little evidence of Th1 cytokines is being upregulated [31, 38–40].

3.3. Neurotrophins. Neurotrophins have been shown to be selectively upregulated or downregulated by acupuncture depending on the condition. Recent research on neurotrophins has mainly focused on cerebral ischaemia, spinal cord injury, and depression [13, 41–44]. No research has yet been published on the possible modulation of neurotrophins

by acupuncture in allergic rhinitis. It is hypothesised, however, that the abundance of VIP+ parasympathetic nerves around blood vessels in the lamina propria of the nasal mucosa (which has been observed in allergic rhinitis) may be the result of upregulation of neurotrophins, and this neuronal abundance would contribute to exacerbating inflammatory oedema in the nasal mucosa [45–47].

3.4. Chemokines. Chemokines have received little attention from acupuncture researchers until very recently. A new study has reported that EA upregulated chemokine CXCL10 in a rodent model of complete Freund's adjuvant- (CFA-) induced hind paw inflammation [16]. EA increased the production and release of both IFN- γ and CXCL10 which in turn increased the number of infiltrating opioid peptide-containing CXCR3+ macrophages [16]. This study establishes an important novel link between immune system mediators such as cytokines, chemokines, and macrophages and the nervous system's opioid pathways.

The effects of acupuncture on chemokines and chemokine receptors appear to be selective. The upregulation of CXCL10 increased the production and release of CXCR3+ macrophages which contain opioids [16]. Activation of opioid receptors, in turn, will desensitize chemokine receptors thereby inhibiting the production and release of proinflammatory cytokines as well as the chemokines CCL2, CCL3, and CXCL8 [48]. In a rat model of embryo implantation failure, acupuncture increased expression of CCL2, CXCL8, and the subset of uterine natural killer (uNK) cells in the endometrium and reduced embryo implantation failure [49].

4. Complex Cross Talk between Receptors

Chemokine receptors, opioid receptors and TRPV1 receptors have been reported to participate in complex cross talk, not unlike that between neuropeptides, cytokines, and neurotrophins [48]. Chemokine receptors and opioid receptors can inhibit each other by a process known as heterologous desensitization [48]. Adenosine, by activating A2a receptors, can also desensitize chemokine receptors [48] (see Figure 1). Chemokine receptors sensitize TRPV1; hence, any desensitization of chemokine receptors (by adenosine or opioid receptors) would inhibit the sensitization of TRPV1 (via a phospholipase C β /protein kinase C [PLC β /PKC] pathway) [48]. Interactions between cannabinoid receptors and opioid receptors after acupuncture have been reported. Cannabinoid receptor CB2 has been shown to participate in the EA-induced increase of opioid expression in keratinocytes in inflamed skin (in a CFA rat hind paw inflammation model) [12].

Cannabinoid receptor CB1 has been shown to mediate phosphorylation of both STAT3 and glycogen synthase kinase-3 β after acupuncture in rodent cerebral ischaemia studies [50, 51].

Upregulation of CB1 expression after EA also produced upregulation of dopamine receptors D1 and D2 in the striatum (in a CFA rat hind paw inflammation model) [14].

Since acupuncture has already been shown to be capable of activating adenosine and opioid receptors and now has

been shown to selectively modulate chemokines, there are a number of possible pathways via which TRPV1 might be downregulated by acupuncture.

EA has previously been reported to downregulate TRPV1 by inhibiting phosphorylation of PI3K in the dorsal horn of rats (in a carrageenan hind paw inflammation model) [19]. NGF activates the tyrosine kinase A/phosphatidylinositol 3-kinase/phosphatidylinositol phosphate 3/protein kinase Akt (trkA/PI3K/PIP3/Akt) signalling pathway which increases the sensitivity and expression of TRPV1, so blocking this pathway would prevent this sensitization of TRPV1 by NGF [19]. EA also activated p38 mitogen activated protein kinase/activating transcription factor 2/transient receptor potential vallinoid (p38 MAPK/ATF-2/TRPV1) signalling pathway thereby downregulating TRPV1 expression in the dorsal horn of rats; however, cyclooxygenase 2 (COX-2) was found to play no role (in a CFA hind paw inflammation model) [5]. In the same study, hind paw oedema was unchanged until day 14 after CFA injection. However, the reasons for this delayed action are unclear [5].

5. Effects of Acupuncture on Thermal Hyperalgesia and Mechanical Allodynia in Inflammatory and Neuropathic Pain

According to the ancient Roman doctor Celsius, inflammation was characterised by redness, heat, swelling, and pain [52]. In research using animal inflammatory pain models, pain threshold is generally measured as a response to mechanical pressure (allodynia) or to changes in temperature, usually heat (thermal hyperalgesia). In reducing inflammatory hyperalgesia, low frequency EA (typically 1 to 4 Hz) has been consistently reported to be effective (see Table 1). However, there is conflicting data on the effectiveness of high frequency EA (100–150 Hz) with some researchers reporting that 120 Hz EA failed to alleviate thermal hyperalgesia and mechanical allodynia in diabetic neuropathic pain in rats, while 2 Hz EA was effective [22]. Other studies have reported effective attenuation of inflammatory hind paw hyperalgesia in rats using 100 Hz EA [11, 14, 16].

Low frequency EA (2 Hz) effectively relieved mechanical allodynia in a rat spinal nerve ligation model [23]. This improvement in allodynia was associated with a reduction of both TRPV1 and CGRP in the ipsilateral spinal dorsal horn immediately above and below the lesioned level (L5) [23]. Since TRPV1 is capable of producing and releasing both CGRP and SP, the decrease in CGRP may be a direct result of the reduced expression of TRPV1 [53]. Additionally, since CGRP and SP interpromote each other, the CGRP downregulation could be secondary to a downregulation of SP production and release by TRPV1 [54].

EA effects on thermal hyperalgesia were blunted, but not obliterated, in TRPV1 knock-out mice [55]. TRPV1 knock-out mice required a stronger EA stimulation than wild type (C 57 BL/6) mice to achieve an analgesic effect [55]. This suggests that while TRPV1 downregulation contributes to EA effects on thermal hyperalgesia, TRPV1 is not solely responsible, as TRPV1 knock-out did not obliterate the effect. In contrast,

histamine-induced itch is completely extinguished in TRPV1 knock-out mice [56].

Low frequency EA (2 Hz) has also been shown to decrease mechanical hyperalgesia in both CFA and carrageenan-induced CD1 mouse hind paw inflammation, accompanied by a significant downregulation of acid sensing ion channel 3 (ASIC3) overexpression in dorsal root ganglion neurons [17]. In another study, also using CFA and carrageenan-induced mouse hind paw inflammation (this time in ICR mice), 2 Hz EA reduced mechanical and thermal hyperalgesia accompanied with decreased expression of sodium voltage-gated (Nav) channels Nav1.7 and Nav1.8 (but not Nav1.9) in dorsal root ganglion neurons [18].

In another CFA hind paw inflammation study with rats, EA alternating between 2 Hz and 100 Hz alleviated mechanical allodynia and blocked activation of the extracellular-regulated protein kinase 1/2-cyclooxygenase-2 (ERK1/2-COX-2) and extracellular-regulated protein kinase 1/2-cAMP response element binding protein- neurokinin-1 receptor (ERK1/2-CREB-NK-1) pathways, but had no effect on Ets-like kinase 1 (Elk1) (a downstream nuclear substrate of ERK1/2) in the spinal dorsal horn [15]. Since SP is the endogenous ligand for NK-1 receptor, blocking NK-1 would downregulate the proinflammatory effects of SP, as has been previously reported [57].

In a spinal cord injury neuropathic pain model in rats, manual acupuncture significantly relieved thermal hyperalgesia and mechanical allodynia [24]. These acupuncture analgesic effects were associated with Jun-N-terminal kinase (JNK) inhibition in astrocytes in lamina I-II of the dorsal horn and inhibited phosphorylation of JNK downstream substrate, c-Jun [24]. Acupuncture also inhibited JNK-dependent expression of chemokines monocyte chemotactic protein 1 (MCP-1) (also known as CCL2), macrophage inflammatory protein 1 β (MIP-1 β) (also known as CCL4), and macrophage inflammatory protein 3 α (MIP-3 α) (also known as CCL20) in spinal astrocytes [24]. In a rat CFA hind paw study, EA alleviated mechanical allodynia (alternating between 2 Hz and 100 Hz) but not paw oedema by suppressing the spinal JNK1/2 pathway [4]. In this study, TRPV1 expression in the spinal dorsal horn was unaffected [4].

Further research is needed to investigate whether these modulations of TRPV1, produced by acupuncture in the spinal dorsal horn of rats or mice, can also be found in the trigeminal ganglia or nasal mucosa of humans with allergic rhinitis.

6. A Novel Cholinergic Anti-Inflammatory Pathway

It has been suggested that acupuncture may activate a cholinergic anti-inflammatory pathway involving acetylcholine release from vagus nerves binding to $\alpha 7$ -nicotinic receptors ($\alpha 7$ -nAChRs) on macrophages, thereby inhibiting the release of proinflammatory cytokines [58]. A recent study by Torres-Rosas et al. has demonstrated that there is in fact an anti-inflammatory pathway activated by EA which involves the vagus and sciatic nerves and is mediated by dopamine [59].

TABLE 1: Effects of electroacupuncture and manual acupuncture on inflammatory signalling pathways and receptors.

Author and year Model	EA/acup	Acupuncture points	Effect	Thermal hyperalgesia	Mechanical allodynia	Oedema
Huang et al. 2004 [10]	CFA hind paw FSD rats	EA 100 Hz	(B) ST 36, SP 6	No effect	Reduced	
Huang et al. 2008 [11]	CFA hind paw FSD rats	EA 100 Hz	(B) ST 36, SP 6	Reduced thermal hyperalgesia and increased EA tolerance EA effects abolished by high dose Naloxone suggesting dynorphin mediation	Reduced	
Su et al. 2011 [12]	CFA hind paw MSD rats	EA 2 Hz	(I) GB 30, GB 34	Increased POMC and β -END expression in keratinocytes, macrophages, and T-lymphocytes in inflamed skin via activation of CB2 cannabinoid receptors	Reduced	Reduced
Zhang et al. 2012 [13]	CFA hind paw rats	EA 10 Hz	GB 30	Suppressed spinal IL-17 and p-NR1	Reduced	Reduced
Shou et al. 2013 [14]	CFA hind paw MSD rats	EA 2 Hz EA 100 Hz	ST 36, BL 60	Increased CB1 expression with upregulation of DI and D2 expression in striatum	Reduced	
Fang et al. 2013 [5]	CFA hind paw MSD rats	EA 2/100 Hz alt	(B) ST 36, BL 60	Inhibition of p38/MAPK/ATF-2/TRPV1 pathway producing downregulation of TRPV1 in spinal dorsal horn	Reduced	Reduced only at day 14
Fang et al. 2014 [15]	CFA hind paw MSD rats	EA 2/100 Hz alt	(B) ST 36, BL 60	Inhibited ERK1/2-COX-2 and ERK1/2-CREB-NK-1 pathway Downregulated NK-1 hence inhibiting SP	Reduced	
Wang et al. 2013 [9]	CFA hind paw M Wistar rats	EA 100 Hz	(B) GB 30	EA effects suppressed by opiate antagonists naloxone and natriindole	Reduced	Reduced slightly
Wang et al. 2014 [16]	CFA hind paw M Wistar rats	EA 100 Hz	(B) GB 30	TNF- α and IL-1 β downregulated, IL-13 upregulated, and IL-1 α and IL-4 unchanged IFN- γ up-regulated stimulating CXCL10 increasing CXCR3+ macrophages	Reduced	
Du et al. 2014 [4]	CFA hind paw MSD rats	EA 2/100 Hz alt	(B) ST 36, BL 60	Inhibited JNK1/2 and COX-2 but not TRPV1	Reduced	No effect
Chen et al. 2011 [17]	Carrageenan & CFA hind paw CDI mice	EA 2 Hz	ST 36	Decreased overexpression of ASIC3 in DRG	Reduced	
Huang et al. 2013 [18]	Carrageenan & CFA hind paw F ICR mice	EA 2 Hz	ST 36	Decreased expression of sodium voltage-gated channels Nav 1.7 and Nav 1.8 but not Nav 1.9 in DRG	Reduced	
Kim et al. 2012 [19]	Carrageenan hind paw MSD rats	EA 2/100 Hz alt	(B) ST 36, SP 6	Inhibition of p-PI3K blocked trkA/PI3K/PIP3/Akt pathway	Reduced	
da Silva et al. 2015 [20]	Carrageenan gastrocnemius C57BL/6 mice	Manual acup	SP 6	Increased IL-10 in inflamed muscle Induced a phenotypic switch from M1 to M2 macrophages in inflamed muscle	Reduced	Reduced
Kim et al. 2009 [21]	Capsaicin hind paw MSD rats	EA 2 Hz	(I) SI 3, TE 8 (GB 30, GB 34; BL 40, BL 60; GV 2, GV 6; LI 3, LI 6)	SI 3 & TE 8 effective, but other point combinations were not Secondary (but not primary) hyperalgesia is mediated by MOR and DOR but not KOR or adrenergic receptors	Reduced secondary but not primary hyperalgesia	

TABLE 1: Continued.

Author and year	Model	EA/acup	Acupuncture points	Effect	Thermal hyperalgesia	Mechanical allodynia	Oedema
Hwang et al. 2011 [22]	Exp. diabetic neuropathic pain MSD rats	EA 2 Hz EA 120 Hz	(B) SP 9 or ST 36	Decreased cleavage of p35 to p25 hence inhibited p35/p25/Cdk5/MAPK and/or p35/p25/Cdk5/NMDA pathways	EA 2 Hz reduced; EA 120 Hz no effect	EA 2 Hz reduced; EA 120 Hz no effect	
Jiang et al. 2013 [23]	SNL MSD rats	EA 2 Hz	(I) ST 36, BL 60	Downregulated TRPV1 in spinal dorsal horn and reduced CGRP		Reduced	
Lee et al. 2013 [24]	SCI MSD rats	Manual acup	GV 26, (B) GB 34	Inhibited JNK/p-c-Jun in spinal astrocytes Decreased chemokines MCP-1, MIP-1 β , and MIP-3 α	Reduced	Reduced	
Yu et al. 2013 [25]	CCI SD rats	EA 2 Hz EA 15 Hz	ST 36, GB 34	EA reduced ERK1/2 phosphorylation and P2X3 expression in spinal cord	Reduced EA 2 Hz > 15 Hz	Reduced EA 2 Hz > 15 Hz	
Hsu et al. 2014 [26]	CCI MSD rats	EA 2 Hz EA 15 Hz	(R) ST 36, ST 37	EA increased cerebral TRPV4 but not TRPV1 No change in spinal TRPV4 or TRPV1	Reduced	Reduced	
Wang et al. 2009 [27]	Surgical trauma MSD rats	EA 2/60 Hz alt	(B) ST 36, Lanwei (M-LE-13)	Suppressed lymphocyte proliferation Reduced splenic T cells production of Th1 cytokines (IL-2 and IFN- γ) increased Th2 cytokines (IL-4, IL-10) Suppressed activity of ERK1/2, p38, NF- κ B, and AP-1	Reduced	Reduced	

EA: electroacupuncture, acup: acupuncture, CFA hind paw: model of inflammation induced by injection of complete Freund's adjuvant into rats' hind paws, FSD rats: female Sprague Dawley rats, MSD: male Sprague Dawley rats, alt: alternating, (B): bilateral, (I): ipsilateral, CB: cannabinoid receptor, TRPV: transient receptor potential vanilloid, proopiomelanocortin, β -END: beta endorphin, p-NRI: phosphorylation of NRI, SP: substance P, CGRP: calcitonin gene-related peptide, NK-1: neurokinin 1 receptor, DRG: dorsal root ganglion, MAPK: mitogen activated protein kinase, ATF-2: activating transcription factor 2, ERK: extracellular-regulated protein kinase, CREB: cAMP response element binding protein, NK-1: neurokinin 1 receptor, JNK: c-jun N terminal kinase, ASIC3: acid sensing ion channel 3, Nav: sodium voltage-gated channels, trkA: tyrosine kinase A, P13K/PIP3: phosphatidylinositol 3 kinase/phosphatidylinositol phosphate 3 pathway, MOR: mu opioid receptor, DOR: delta opioid receptor, KOR: kappa opioid receptor, AP-1: activator protein 1, Cdk5: cyclin-dependent kinase 5, and NMDA: N-methyl-D-aspartate.

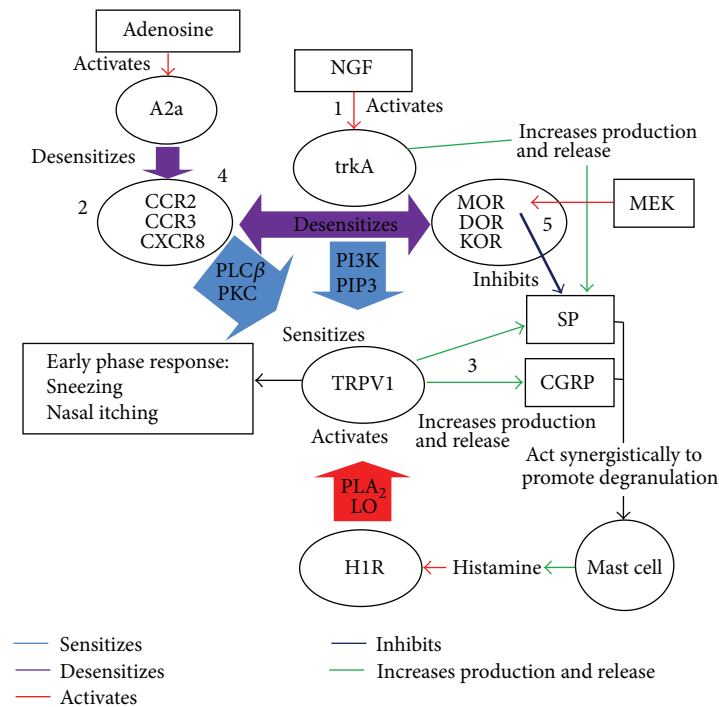


FIGURE 1: Proposed model for the complex cross talk between various receptors and mediators in early phase response in allergic rhinitis. 1: nerve growth factor (NGF) activates tyrosine kinase A (TrkA) receptor which in turn increases production and release of substance P (SP). Activation of TrkA receptor also initiates signalling via the PI3K/PIP3 pathway to increase expression and sensitivity of transient receptor potential vallinoid (TRPV1) receptor. 2: chemokine receptors (CCR2, CCR3, and CXCR8) sensitize TRPV1 receptor via a PLC β /PKC pathway. 3: TRPV1 receptor increases production and release of proinflammatory neuropeptides SP and CGRP which act synergistically to promote degranulation of primed mast cells. Histamine released by mast cells activates histamine 1 receptor (H1R) producing signalling via the phospholipase A₂/lipoxygenase pathway to activate TRPV1, triggering early phase allergic inflammatory response. 4: chemokine receptors are heterologously desensitized by both adenosine (A2a) receptors and opioid receptors (MOR, DOR, and KOR). 5: Substance P is inhibited by met-enkephalin via Mu opioid receptors (MOR). A2a: adenosine 2a receptor, CCR2, CCR3: CC chemokine receptors 2 & 3, CXCR8: CXC chemokine receptor 8, PLC β : phospholipase C β , PKC: protein kinase C, NGF: nerve growth factor, TRPV1: transient receptor potential vallinoid 1, TrkA: tyrosine kinase A receptor, H1R: histamine 1 receptor, SP: substance P, CGRP: calcitonin gene-related peptide, PI3K/PIP3: phosphatidylinositol 3 kinase/phosphatidylinositol phosphate 3 pathway, PLA₂/LO: phospholipase A₂/lipoxygenase pathway, MOR: Mu opioid receptor, DOR: delta opioid receptor, KOR: kappa opioid receptor, and MEK: met-enkephalin.

However, this study also found that $\alpha 7$ -nAChRs were not involved in this anti-inflammatory pathway [59]. In a mouse model of induced sepsis, EA rescued mice from polymicrobial peritonitis and controlled systemic inflammation [59]. EA stimulation of the sciatic nerve induced release of DOPA decarboxylase from the vagus nerve leading to dopamine production in the adrenal medulla [59]. Of the dopamine receptor family, D1 receptors were shown to be essential to EA anti-inflammatory effects, but D2 receptors appeared to have little involvement [59]. Vagal stimulation was also associated with reduced serum levels of the cytokines tumour necrosis factor (TNF), MCP-1/CCL2, IL-6, and IFN- γ [59]. TRPV1 agonist, capsaicin, abolished the anti-inflammatory effects of EA [59]. This underlines the importance of TRPV1 role in the anti-inflammatory effects of acupuncture.

7. Adenosine

Adenosine triphosphate (ATP) released locally at acupuncture points, in response to needle stimulation is metabolized

into adenosine, which activates adenosine A1 receptors, creating an analgesic effect in inflammatory pain [60, 61]. Adenosine, via A2a receptors, has also been shown to desensitize chemokine receptors, hence blocking the capacity of chemokine receptors to both sensitize TRPV1 receptors via a PLC β /PKC pathway and to desensitize opioid receptors [48]. Adenosine has previously been reported to inhibit TRPV1 activation, and this action may be mediated via the PLC β /PKC pathway [62]. In addition, adenosine, via A3 receptor activation has recently been shown to be effective in relieving persistent neuropathic pain [63]. Further investigation is needed to determine whether or not adenosine modulates TRPV1 (and possibly opioid receptors) in the nasal mucosa or trigeminal ganglia.

8. A Revised Model for the Effects of Acupuncture in Allergic Rhinitis

The central importance of TRPV1 in allergic rhinitis raises the question of how acupuncture might modulate TRPV1

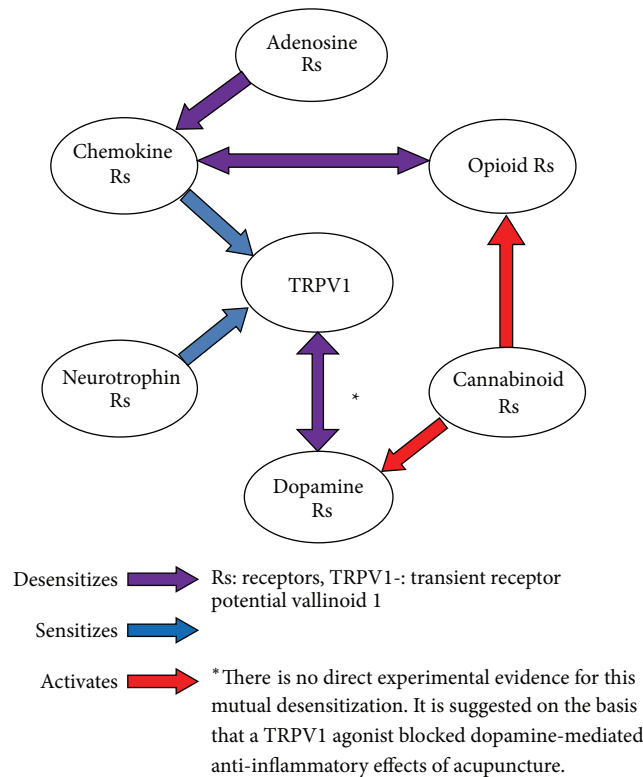


FIGURE 2: Receptor interactions potentially involved in the anti-inflammatory effects of acupuncture.

either directly or indirectly. In our previous proposed model, it was suggested that acupuncture might modulate TRPV1 by blocking neurotrophic sensitization (by blocking phosphorylation of PI3K, as seen in EA for neuropathic pain), by downregulating SP and CGRP (with consequent suppression of degranulation of primed mast cells) and possibly through some pathway associated with adenosine. It now appears that this adenosine-induced downregulation of TRPV1 may occur through desensitization of chemokines receptors (which sensitize TRPV1 via a PLC β /PKC pathway) [48] (see Figure 1).

Downregulation of SP by met-enkephalin has previously been reported [64, 65]. New research showing that acupuncture can stimulate production of CXCR3+ macrophages (which contain met-enkephalin) clarifies the source of the opioid stimulation. Opioid receptor desensitization of chemokine receptors, with consequent inhibition of both cytokine production and sensitization of TRPV1, provides another pathway via which acupuncture-induced opioid stimulation could generate anti-inflammatory effects.

TRPV1 interactions with both cannabinoid and dopamine receptors have also now been demonstrated in murine and rodent studies of inflammatory hyperalgesia (see Table 1). Further studies are needed to determine whether these effects of acupuncture in the spinal dorsal root ganglia during inflammatory hyperalgesia are relevant to the trigeminal ganglia in allergic rhinitis.

Recent research into the effects of acupuncture on signalling pathways and receptors in inflammatory pain has focused mainly on mechanical allodynia and thermal hyperalgesia, but little new work has been done on inflammatory

oedema. Since TRPV1 appears to play a central role in inflammatory oedema, it is possible that signalling pathways activated by acupuncture which are independent of TRPV1 may be associated with reduction of thermal and mechanical hyperalgesia but not inflammatory oedema [66]. Since nasal swelling is more significant clinically in allergic rhinitis than hyperalgesia, signalling pathways identified in hyperalgesia studies which do not involve TRPV1 may be less relevant to acupuncture's effects on allergic rhinitis.

The effects of acupuncture on chemokines and chemokine receptors appear to be selective. While desensitization of chemokine receptors by adenosine and by interaction with opioid receptors may reduce sensitivity of TRPV1, it is also clear that acupuncture can increase chemokines such as CXCL10, CCL2, and CXCL8.

Interactions between receptor types are now being reported with an increasing frequency. Acupuncture has been shown to influence the interactions between opioid receptors and chemokine receptors, as well as cannabinoid receptors (see Figure 2). Interactions between cannabinoid receptors and dopamine receptors have also been shown to be modulated by acupuncture [14].

9. Conclusion

Our 2013 model proposed that acupuncture downregulates proinflammatory neuropeptides and neurotrophins, alters Th1/Th2 cytokine balance, and modulates TRPV1.

Acupuncture has already been shown to downregulate SP and VIP in allergic rhinitis and may also downregulate

CGRP. This reduction in SP and VIP has been associated with improvements in clinical signs and symptoms.

Acupuncture may downregulate neurotrophins NGF and BDNF in allergic rhinitis, but evidence is currently lacking.

Acupuncture has been shown to alter Th1/Th2 cytokine balance away from Th2 dominance in a variety of clinical contexts including allergic rhinitis; however, more robust evidence is still needed. The role of transcription factors involved in Th2 differentiation (such as STAT 6 and NFκB) merits further investigation.

While numerous new signalling pathways have been identified in the anti-inflammatory actions of acupuncture in animal model studies on induced hind paw inflammation, spinal cord injury, and chronic constriction injury, it is unclear how much relevance these studies might have to allergic rhinitis (see Table 1). Frequently, the main outcome measures for these studies have been measures of inflammatory pain, thermal and mechanical hyperalgesia, as opposed to inflammatory oedema, which would be more likely to be relevant to allergic rhinitis.

Recent research has also shown that acupuncture can modulate chemokines and that interactions between chemokine and opioid receptors may have relevance to reducing the expression and sensitivity of TRPV1. Further research on the effects of acupuncture on chemokines is needed.

A novel cholinergic anti-inflammatory pathway involving vagal stimulation and dopamine mediation has now been demonstrated [59]. This pathway is neither parasympathetic nor sympathetic but involves both. In acupuncture analgesia research, dopamine receptors have been shown to act in a selective manner. D1 receptors in the brain inhibited acupuncture analgesia, while D2 receptors in the spine enhanced analgesic effects [27]. Torres-Rosas et al. demonstrated that D1 receptors appeared to play a significant role in the anti-inflammatory effects of acupuncture while D2 receptors did not [59]. The role of dopamine receptors and their interactions with cannabinoid receptors, and possibly TRPV1, in the anti-inflammatory effects of acupuncture have only just begun to be explored. Further exploration of receptor interactions and their possible involvement in acupuncture effects would be valuable.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- [1] J. L. McDonald, A. W. Cripps, P. K. Smith, C. A. Smith, C. C. Xue, and B. Golianu, "The anti-inflammatory effects of acupuncture and their relevance to allergic rhinitis: a narrative review and proposed model," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 591796, 12 pages, 2013.
- [2] A. Li, L. Lao, Y. Wang et al., "Electroacupuncture activates corticotrophin-releasing hormone-containing neurons in the paraventricular nucleus of the hypothalamus to alleviate edema in a rat model of inflammation," *BMC Complementary and Alternative Medicine*, vol. 8, article 20, 2008.
- [3] A. Li, R.-X. Zhang, Y. Wang et al., "Corticosterone mediates electroacupuncture-produced anti-edema in a rat model of inflammation," *BMC Complementary and Alternative Medicine*, vol. 7, article 27, 2007.
- [4] J.-Y. Du, J.-Q. Fang, Y. Liang, and J.-F. Fang, "Electroacupuncture attenuates mechanical allodynia by suppressing the spinal JNK1/2 pathway in a rat model of inflammatory pain," *Brain Research Bulletin*, vol. 108, pp. 27–36, 2014.
- [5] J.-Q. Fang, J.-Y. Du, Y. Liang, and J.-F. Fang, "Intervention of electroacupuncture on spinal p38 MAPK/ATF-2/VR-1 pathway in treating inflammatory pain induced by CFA in rats," *Molecular Pain*, vol. 9, no. 1, article 13, 2013.
- [6] H.-W. Kim, D.-H. Roh, S.-Y. Yoon et al., "The anti-inflammatory effects of low- and high-frequency electroacupuncture are mediated by peripheral opioids in a mouse air pouch inflammation model," *Journal of Alternative and Complementary Medicine*, vol. 12, no. 1, pp. 39–44, 2006.
- [7] R. Sekido, K. Ishimaru, and M. Sakita, "Differences of electroacupuncture-induced analgesic effect in normal and inflammatory conditions in rats," *American Journal of Chinese Medicine*, vol. 31, no. 6, pp. 955–965, 2003.
- [8] S. P. Zhang, J. S. Zhang, K. K. L. Yung, and H. Q. Zhang, "Non-opioid-dependent anti-inflammatory effects of low frequency electroacupuncture," *Brain Research Bulletin*, vol. 62, no. 4, pp. 327–334, 2004.
- [9] Y. Wang, D. Hackel, F. Peng, and H. L. Rittner, "Long-term antinociception by electroacupuncture is mediated via peripheral opioid receptors in free-moving rats with inflammatory hyperalgesia," *European Journal of Pain*, vol. 17, no. 10, pp. 1447–1457, 2013.
- [10] C. Huang, Z.-P. Hu, H. Long, Y.-S. Shi, J.-S. Han, and Y. Wan, "Attenuation of mechanical but not thermal hyperalgesia by electroacupuncture with the involvement of opioids in rat model of chronic inflammatory pain," *Brain Research Bulletin*, vol. 63, no. 2, pp. 99–103, 2004.
- [11] C. Huang, Z.-Q. Huang, Z.-P. Hu et al., "Electroacupuncture effects in a rat model of complete Freund's adjuvant-induced inflammatory pain: antinociceptive effects enhanced and tolerance development accelerated," *Neurochemical Research*, vol. 33, no. 10, pp. 2107–2111, 2008.
- [12] T. F. Su, L. H. Zhang, M. Peng et al., "Cannabinoid CB2 receptors contribute to upregulation of beta-endorphin in inflamed skin tissues by electroacupuncture," *Molecular Pain*, vol. 7, article 98, 2011.
- [13] X.-F. Zhang, Y. Zou, Y. Zhao, T.-H. Wang, and W. Zhang, "Effects of electroacupuncture of 'governor vessel' acupoints on changes of BDNF in the cortical motor area of mice with spinal cord transection," *Journal of Sichuan University*, vol. 43, no. 2, pp. 250–253, 2012.
- [14] Y. Shou, Y. Yang, M.-S. Xu, Y.-Q. Zhao, L.-B. Ge, and B.-M. Zhang, "Electroacupuncture inhibition of hyperalgesia in rats with adjuvant arthritis: involvement of cannabinoid receptor 1 and dopamine receptor subtypes in striatum," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 393460, 10 pages, 2013.
- [15] J. Q. Fang, J. F. Fang, Y. Liang, and J. Y. Du, "Electroacupuncture mediates extracellular signal-regulated kinase 1/2 pathways in the spinal cord of rats with inflammatory pain," *BMC Complementary & Alternative Medicine*, vol. 14, no. 1, article 285, 2014.

- [16] Y. Wang, R. Gehringer, S. A. Mousa, D. Hackel, A. Brack, and H. L. Rittner, "CXCL10 controls inflammatory pain via opioid peptide-containing macrophages in electroacupuncture," *PLoS ONE*, vol. 9, no. 4, Article ID e94696, 2014.
- [17] W.-H. Chen, C.-L. Hsieh, C.-P. Huang et al., "Acid-sensing ion channel 3 mediates peripheral anti-hyperalgesia effects of acupuncture in mice inflammatory pain," *Journal of Biomedical Science*, vol. 18, no. 1, article 82, 2011.
- [18] C.-P. Huang, H.-N. Chen, H.-L. Su et al., "Electroacupuncture reduces carrageenan- and CFA-induced inflammatory pain accompanied by changing the expression of Nav1.7 and Nav1.8, rather than Nav1.9, in mice dorsal root ganglia," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 312184, 8 pages, 2013.
- [19] H. N. Kim, Y. R. Kim, J. Y. Jang, H. K. Shin, and B. T. Choi, "Electroacupuncture inhibits phosphorylation of spinal phosphatidylinositol 3-kinase/Akt in a carrageenan-induced inflammatory rat model," *Brain Research Bulletin*, vol. 87, no. 2-3, pp. 199–204, 2012.
- [20] M. D. da Silva, F. Bobinski, K. L. Sato, S. J. Kolker, K. A. Sluka, and A. R. Santos, "IL-10 cytokine released from M2 macrophages is crucial for analgesic and anti-inflammatory effects of acupuncture in a model of inflammatory muscle pain," *Molecular Neurobiology*, vol. 51, no. 1, pp. 19–31, 2015.
- [21] H. Y. Kim, J. Wang, I. Lee, H. K. Kim, K. Chung, and J. M. Chung, "Electroacupuncture suppresses capsaicin-induced secondary hyperalgesia through an endogenous spinal opioid mechanism," *Pain*, vol. 145, no. 3, pp. 332–340, 2009.
- [22] H. S. Hwang, E. J. Yang, S. M. Lee, S. C. Lee, and S. Choi, "Antiallodynic effects of electroacupuncture combined with MK-801 treatment through the regulation of p35/p25 in experimental diabetic neuropathy," *Experimental Neurobiology*, vol. 20, no. 3, pp. 144–152, 2011.
- [23] Y.-L. Jiang, X.-H. Yin, Y.-F. Shen, X.-F. He, and J.-Q. Fang, "Low frequency electroacupuncture alleviated spinal nerve ligation induced mechanical allodynia by inhibiting TRPV1 upregulation in ipsilateral undamaged dorsal root ganglia in rats," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 170910, 9 pages, 2013.
- [24] J. Y. Lee, D. C. Choi, T. H. Oh, and T. Y. Yune, "Analgesic effect of acupuncture is mediated via inhibition of JNK activation in astrocytes after spinal cord injury," *PLoS ONE*, vol. 8, no. 9, Article ID e73948, 2013.
- [25] J. Yu, C. Zhao, and X. Luo, "The effects of electroacupuncture on the extracellular signal-regulated kinase 1/2/P2X3 signal pathway in the spinal cord of rats with chronic constriction injury," *Anesthesia & Analgesia*, vol. 116, no. 1, pp. 239–246, 2013.
- [26] H.-C. Hsu, N.-Y. Tang, Y.-W. Lin, T.-C. Li, H.-J. Liu, and C.-L. Hsieh, "Effect of electroacupuncture on rats with chronic constriction injury-induced neuropathic pain," *The Scientific World Journal*, vol. 2014, Article ID 129875, 9 pages, 2014.
- [27] H.-C. Wang, C.-T. Zuo, and Y.-H. Guan, "Research on receptors related to acupuncture analgesia and positron emission tomography radioligands: a review," *Journal of Chinese Integrative Medicine*, vol. 7, no. 6, pp. 575–581, 2009.
- [28] Y. C. Park, J. H. Jo, K. E. Hong, W. C. Kang, and S. M. Choi, "Effect of acupuncture on nasal obstruction in patients with persistent allergic rhinitis: a randomized, controlled trial," *The Journal of Korean Acupuncture & Moxibustion Society*, vol. 22, pp. 229–239, 2005.
- [29] B. Brinkhaus, M. Ortiz, C. M. Witt et al., "Acupuncture in patients with seasonal allergic rhinitis: a randomized trial," *Annals of Internal Medicine*, vol. 158, no. 4, pp. 225–234, 2013.
- [30] S. M. Choi, J. E. Park, S.-S. Li et al., "A multicenter, randomized, controlled trial testing the effects of acupuncture on allergic rhinitis," *Allergy*, vol. 68, no. 3, pp. 365–374, 2013.
- [31] Y. Q. Rao and N. Y. Han, "Therapeutic effect of acupuncture on allergic rhinitis and its effects on immunologic function," *Zhongguo Zhen Jiu*, vol. 26, pp. 557–560, 2006.
- [32] C. C. Xue, X. An, T. P. Cheung et al., "Acupuncture for persistent allergic rhinitis: a randomised, sham-controlled trial," *Medical Journal of Australia*, vol. 187, no. 6, pp. 337–341, 2007.
- [33] C. C. Xue, R. English, J. J. Zhang, C. da Costa, and C. G. Li, "Effect of acupuncture in the treatment of seasonal allergic rhinitis: a randomized controlled clinical trial," *The American Journal of Chinese Medicine*, vol. 30, no. 1, pp. 1–11, 2002.
- [34] S. Sarin, B. Udem, A. Sanico, and A. Togias, "The role of the nervous system in rhinitis," *The Journal of Allergy and Clinical Immunology*, vol. 118, no. 5, pp. 999–1014, 2006.
- [35] Y.-M. Li, L.-X. Zhuang, X.-S. Lai, and G.-H. Jiang, "Effects of electroacupuncture on plasma vasoactive intestinal peptide and substance P in perennial allergic rhinitis patients," *Zhen Ci Yan Jiu*, vol. 32, no. 2, pp. 136–138, 2007.
- [36] D. Jung, S. Lee, and S. Hong, "Effects of acupuncture and moxibustion in a mouse model of allergic rhinitis," *Otolaryngology—Head and Neck Surgery*, vol. 146, no. 1, pp. 19–25, 2012.
- [37] B. Hauswald, C. Dill, J. Boxberger, E. Kuhlisch, T. Zahnert, and Y. M. Yarin, "The effectiveness of acupuncture compared to loratadine in patients allergic to house dust mites," *Journal of Allergy*, vol. 2014, Article ID 654632, 7 pages, 2014.
- [38] F. B. Petti, A. Liguori, and F. Ippoliti, "Study on cytokines IL-2, IL-6, IL-10 in patients of chronic allergic rhinitis treated with acupuncture," *Journal of Traditional Chinese Medicine*, vol. 22, no. 2, pp. 104–111, 2002.
- [39] H.-S. Shiue, Y.-S. Lee, C.-N. Tsai, Y.-M. Hsueh, J.-R. Sheu, and H.-H. Chang, "DNA microarray analysis of the effect on inflammation in patients treated with acupuncture for allergic rhinitis," *Journal of Alternative and Complementary Medicine*, vol. 14, no. 6, pp. 689–698, 2008.
- [40] M.-F. Zheng, C. Lin, L.-P. Zheng, and F.-R. He, "Effects of acupuncture-moxibustion on monocyte Th1/Th2 cytokine in peripheral blood of patients with perennial allergic rhinitis," *Journal of Acupuncture and Tuina Science*, vol. 8, no. 2, pp. 85–88, 2010.
- [41] Y. R. Kim, H. N. Kim, S. M. Ahn, Y. H. Choi, H. K. Shin, and B. T. Choi, "Electroacupuncture promotes post-stroke functional recovery via enhancing endogenous neurogenesis in mouse focal cerebral ischemia," *PLoS ONE*, vol. 9, no. 2, Article ID e90000, 2014.
- [42] J. Liang, J. Lu, S. F. Cui, J. R. Wang, and Y. Tu, "Effect of acupuncture on expression of brain-derived neurotrophic factor gene and protein in frontal cortex and hippocampus of depression rats," *Zhen Ci Yan Jiu*, vol. 37, no. 1, pp. 20–24, 2012.
- [43] D. Lin, I. D. L. Pena, L. Lin, S.-F. Zhou, C. V. Borlongan, and C. Cao, "The neuroprotective role of acupuncture and activation of the BDNF signaling pathway," *International Journal of Molecular Sciences*, vol. 15, no. 2, pp. 3234–3252, 2014.
- [44] H. Sun, H. Zhao, C. Ma et al., "Effects of electroacupuncture on depression and the production of glial cell line-derived neurotrophic factor compared with fluoxetine: a randomized controlled pilot study," *Journal of Alternative and Complementary Medicine*, vol. 19, no. 9, pp. 733–739, 2013.

- [45] S. Y. Fang and C. L. Shen, "Neuropeptide innervation and neuroendocrine cells in allergic rhinitis and chronic hypertrophic rhinitis," *Clinical and Experimental Allergy*, vol. 28, no. 2, pp. 228–232, 1998.
- [46] J. M. Figueroa, E. Mansilla, and A. M. Suburo, "Innervation of nasal turbinate blood vessels in rhinitic and nonrhinitic children," *American Journal of Respiratory and Critical Care Medicine*, vol. 157, no. 6, pp. 1959–1966, 1998.
- [47] A. Fischer, A. Wussow, A. Cryer et al., "Neuronal plasticity in persistent perennial allergic rhinitis," *Journal of Occupational and Environmental Medicine*, vol. 47, no. 1, pp. 20–25, 2005.
- [48] N. Zhang and J. J. Oppenheim, "Crosstalk between chemokines and neuronal receptors bridges immune and nervous systems," *Journal of Leukocyte Biology*, vol. 78, no. 6, pp. 1210–1214, 2005.
- [49] W. Gao, X. Tang, Z. Chen et al., "Effects of acupuncture on CCL2 and CXCL8 expression and the subset of uNK cells in rats with embryo implantation failure," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 678390, 12 pages, 2013.
- [50] H. Wei, X. Yao, L. Yang et al., "Glycogen synthase kinase-3 β is involved in electroacupuncture pretreatment via the cannabinoid CB1 receptor in ischemic stroke," *Molecular Neurobiology*, vol. 49, no. 1, pp. 326–336, 2014.
- [51] H. Zhou, Z. Zhang, H. Wei et al., "Activation of STAT3 is involved in neuroprotection by electroacupuncture pretreatment via cannabinoid CB1 receptors in rats," *Brain Research*, vol. 1529, pp. 154–164, 2013.
- [52] M. Rocha e Silva, "A brief survey of the history of inflammation. 1978," *Agents and Actions*, vol. 43, no. 3–4, pp. 86–90, 1994.
- [53] Q. T. Dinh, D. A. Groneberg, C. Peiser et al., "Substance P expression in TRPV1 and trkA-positive dorsal root ganglion neurons innervating the mouse lung," *Respiratory Physiology and Neurobiology*, vol. 144, no. 1, pp. 15–24, 2004.
- [54] J. J. Brokaw and G. W. White, "Calcitonin gene-related peptide potentiates substance P-induced plasma extravasation in the rat trachea," *Lung*, vol. 170, no. 2, pp. 85–93, 1992.
- [55] J.-J. Xin, Y.-S. Su, Z.-K. Yang et al., "Effects of electroacupuncture and regional thermal stimulation at 'Zusanli' (ST 36) on pain thresholds of TRPV 1 knock-out mice," *Acupuncture Research*, vol. 37, no. 6, pp. 431–439, 2012.
- [56] W.-S. Shim, M.-H. Tak, M.-H. Lee et al., "TRPV1 mediates histamine-induced itching via the activation of phospholipase A₂ and 12-lipoxygenase," *The Journal of Neuroscience*, vol. 27, no. 9, pp. 2331–2337, 2007.
- [57] R.-X. Zhang, B. Liu, J.-T. Qiao et al., "Electroacupuncture suppresses spinal expression of neurokinin-1 receptors induced by persistent inflammation in rats," *Neuroscience Letters*, vol. 384, no. 3, pp. 339–343, 2005.
- [58] K. J. Tracey, "Physiology and immunology of the cholinergic antiinflammatory pathway," *The Journal of Clinical Investigation*, vol. 117, no. 2, pp. 289–296, 2007.
- [59] R. Torres-Rosas, G. Yehia, G. Peña et al., "Dopamine mediates vagal modulation of the immune system by electroacupuncture," *Nature Medicine*, vol. 20, no. 3, pp. 291–295, 2014.
- [60] N. Goldman, M. Chen, T. Fujita et al., "Adenosine A1 receptors mediate local anti-nociceptive effects of acupuncture," *Nature Neuroscience*, vol. 13, no. 7, pp. 883–888, 2010.
- [61] T. Takano, X. Chen, F. Luo et al., "Traditional acupuncture triggers a local increase in adenosine in human subjects," *Journal of Pain*, vol. 13, no. 12, pp. 1215–1223, 2012.
- [62] M. Tominaga and T. Tominaga, "Structure and function of TRPV1," *Pflügers Archiv*, vol. 451, no. 1, pp. 143–150, 2005.
- [63] J. W. Little, A. Ford, A. M. Symons-Liguori et al., "Endogenous adenosine A₃ receptor activation selectively alleviates persistent pain states," *Brain*, vol. 138, no. 1, pp. 28–35, 2015.
- [64] M. K. Ai, X. M. Guan, C. G. Zhu, and L. L. Vacca, "The influence of electroacupuncture and morphine on Substance P (SP) Enkephalin (ENK) and Acetylcholine Esterase (AChE) in the spinal cord of rats," *Zhen Ci Yan Jiu*, vol. 11, pp. 96–105, 1986.
- [65] I. Kondo, J. C. G. Marvizon, B. B. Song et al., "Inhibition by spinal μ - and δ -opioid agonists of afferent-evoked substance P release," *The Journal of Neuroscience*, vol. 25, no. 14, pp. 3651–3660, 2005.
- [66] J. Keeble, F. Russell, B. Curtis, A. Starr, E. Pinter, and S. D. Brain, "Involvement of transient receptor potential vanilloid 1 in the vascular and hyperalgesic components of joint inflammation," *Arthritis & Rheumatism*, vol. 52, no. 10, pp. 3248–3256, 2005.

