

Revealing Mast Cell as The Primary Biological Transducers in Acupuncture Effect

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ABSTRACT

Acupuncture has been used for millennia to treat various ailments, yet its biological basis remained elusive until the discovery of the "neuro-immune-endocrine" network. Central to this network is the mast cell (MC). Research indicates that acupoints (meridian points) are characterized by a significantly higher density of mast cells compared to non-acupoint areas. When an acupuncture needle is inserted and manipulated—specifically through lifting, thrusting, or rotation—it creates a mechanical pull on the surrounding connective tissue. This mechanical stress is converted into biochemical signals via a process known as mechanotransduction. Mast cells at the acupoint act as biosensors, detecting this tension through transient receptor potential (TRP) channels. This triggers degranulation, the process by which MCs release a cocktail of bioactive mediators, including histamine, adenosine triphosphate (ATP), tryptase, and cytokines. These mediators subsequently activate local nerve endings (C-fibers) and increase local blood flow, initiating a signaling cascade that reaches the central nervous system to modulate pain and systemic inflammation. This summary explores the specific pathways of MC activation, the chemical nature of their degranulation, and their indispensable role in the "acupuncture effect." In this article, we provide a rigorous scientific framework for the crucial role of mast cell in acupuncture benefits.

Keywords: Mast cell, acupuncture, degranulation, acupoints, mechano-transducer.

INTRODUCTION

Acupuncture is a complementary therapy based on traditional East Asian Medicine, which involves inserting thin needles at specific body locations known as acupoints (meridians) to balance energy (Qi) flow for healing. It is widely used and considered safe, convenient, and cost-effective with minimal side effects. In Western medicine, acupoints are seen as areas that stimulate nerves, muscles, and connective tissue, potentially releasing natural pain killers and promoting well-being by influencing the nervous system. By stimulating acupoints on the skin and muscles, acupuncture triggers morphological changes in the surrounding acupoints, which are thought to initiate acupuncture signals. These changes are believed to play a crucial role in activating various cellular and molecular responses, including local responses.¹⁻³

Recent research has delved into the intricate mechanisms of acupuncture, stressing the importance of stimulating acupoints and the interaction between meridian pathways and molecular processes. Studies have highlighted acupuncture's ability to activate neurons, modulate the immune system, and influence vascular function, all of which contribute considerably to its therapeutic benefits.¹⁻³ Furthermore, imaging methods demonstrated alterations in cerebral blood flow, brain function, and glucose metabolism post-acupuncture.^{4,5}

Acupuncture's effectiveness is still debated, and due to a lack of understanding of the underlying physiological principles, Western medicine has been slow to adopt it. Acupuncture's effectiveness has been questioned due to its delivery technique and subjective character. For decades, scientists have sought to discover the physical foundation of acupoints (meridians). Modern histology has finally provided an explanation for acupoints, it has higher densities of mast cells which are immune cells crucial for acupuncture's effects. In the loose connective tissue, these cells are deliberately placed near blood vessels and nerve endings.^{2,6} Deqi, or the stimulation of "qi" vital energy within meridians, is a key component of the acupuncture response. Acupuncture treatment relies heavily on Deqi to achieve therapeutic success. Acupuncture's sensation of "deqi", such as numbness, heaviness, and tingling, activates nerve fiber (A δ , C, A β) that transmit specific feelings (dull, aching, electric, numb) to the brain. This physiological response is crucial for acupuncture's therapeutic effect, involving distinct nerve pathways and brain regions. The Deqi sensation—that distinctive aching or heaviness—is the macroscopic representation of microscopic cellular activity, notably the wrapping of collagen fibers around the needle and the following signals transmitted to local mast cells.⁷

To comprehend acupuncture, we must look beyond the skin and into the Extracellular Matrix (ECM). Acupoints are not merely random spots on a map; they are biological "hotspots" where the fascia is thinner, nerve terminals are more concentrated, and, most importantly, mast cells (MCs) are much abundant - often three to four times higher than in adjacent non-acupoint tissue (Figure 1).^{2,6} Study conducted on human specimens revealed that acupuncture meridians were a component of the ECM of humans, and that fascia's rich ECM composition contributed significantly to the anatomic substrate of acupuncture meridians.⁸

Acupuncture's effects on pain, inflammation, and tissue repair may be explained by its interaction with ECM, the connective tissue network, through the insertion of acupuncture needles. This action produce mechanical forces that stimulate mechanosensitive cells like fibroblasts, activating ion channels and influencing ECM remodelling.⁹ Acupoint sensitization entails transitioning from a resting to an engaged state. Acupuncture responses and their main effects are initiated at the acupoint region.

Mechanical impulses cause mast cell aggregation and degranulation in the subcutaneous tissue, which affects adjacent blood vessels, muscles, and nerve terminals, resulting in the acupuncture effect. Evidence suggests that mast cells play an important role in initiating and reflecting the dynamic features of acupoint sensitization via substance release.⁶ The distribution of mast cells in skin tissue may offer important information on the size, depth, and placement of acupoints. Research has shown that treatments at acupoints with greater frequencies of mast cell degranulation are linked to better results. Furthermore, it has been discovered that administering disodium cromoglycate (DSCG) as a mast cell stabilizer, lessens some of the effects of acupuncture.¹⁰

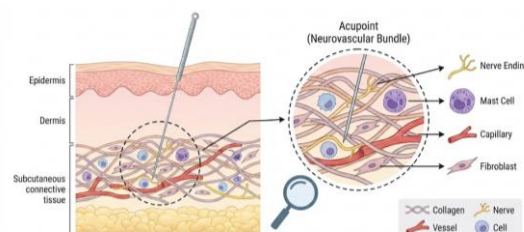


Figure 1. Acupoint structure within connective tissue.

Biological Characteristics of Mast Cell

Mast cells (MCs) are immune cells with cytoplasmic granules containing mediators such as histamine, which are essential for allergic responses, innate immunity, and tissue repair. They are distinguished by their granules (which are positive for toluidine blue staining). It has surface IgE receptors for activation, and varied mediator release (tryptase, chymase, cytokines), which influence inflammation, blood vessel permeability, and interactions with other immune cells. MCs are typically classified into two subsets: one that co-expresses tryptase and chymase (MC-TC) and is found in the skin, peripheral connective tissues, and submucosal regions; the other subset that contains tryptase alone (MC-T) and is primarily found in the mucosal epithelium. Since both MC-Ts and MC-TCs originate from various tissue micro-environments, they show notable transcriptional heterogeneity, with different granule contents and placements, serving as sentinels in connective tissues.^{10,11}

Mast cells are found in abundance in the connective tissues of the skin, particularly around blood vessels and nerves, and their density is significantly higher at classic acupoints compared to non-acupoint areas.^{6,10}

There are some ways of how acupuncture can activate mast cells:^{10,11}

- A. Mechanical activation: needle insertion and manipulation produce mechanical stimuli that activate mechano-sensitive channels in mast cells
- B. Collagen network: the force of acupuncture indirectly activates mast cell via the surrounding collagen networks
- C. Abundant presence: mast cells are abundantly distributed at acupoints, making them suitable for perceiving acupuncture signals. The mast cell releases a number of important mediators upon degranulation:^{6,11}
- D. Histamine: promotes vasodilation, which causes the redness commonly seen at acupoints (the flare response)
- E. Adenosine/ATP: a powerful analgesic, it binds to A1 receptors on local nerve terminals, blocking pain transmission to the brain
- F. Substance P and calcitonin gene related peptide (CGRP): these neuropeptides establish a feedback loop between the neurological and immune system, which boosts the local healing response.

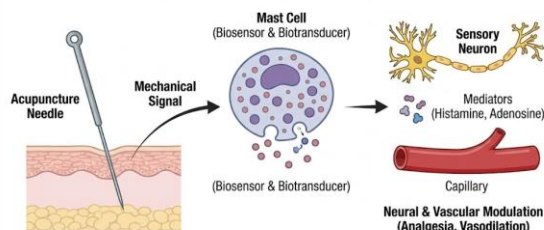


Figure 2. Mast cell activation in acupuncture.

The Mechano-Transduction Pathway

The needle-tissue interaction is the first step in acupuncture healing process. The needle acts as a mechanical anchor when it is raised, shoved, or rotated. "Needle grasp" is the consequences of the collagen and elastin fibers in the fascia wrapping around the needle shaft. These wrappings create a tangible tether that pulls on the local mast cells' membranes. These mast cells serve as 'quiet' sentinels when they are in good health. However, the needle's mechanical damage causes a physical tug on the cell's cytoskeleton. The mechanical stress causes specific gates on the mast cell membrane (including transient receptor potential channels – TRP, and Piezoelectric channels) to open, allowing ions to enter and signal the cell to release its chemical contents (Figure 3).¹² An influx of calcium (Ca^{2+}) triggered the opening of the channels, allowing the exocytosis or degranulation process to occur.^{9,10} These process will trigger nerve responses, modulate pain pathways and produce local or systemic anti-inflammatory and analgesic effects. The key player in this pathway involves:

- A. Fibroblasts: play as central mediators, sensing mechanical stress and releasing signal molecules.
- B. Extracellular matrix: acts as mechanical transducer, transmitting forces.
- C. Mast cells: release their chemical cargo – ATP/adenosine upon mechanical stimulation.
- D. Ruffini corpuscles: slow-adapting mechano-receptors activated by needle manipulation.¹³

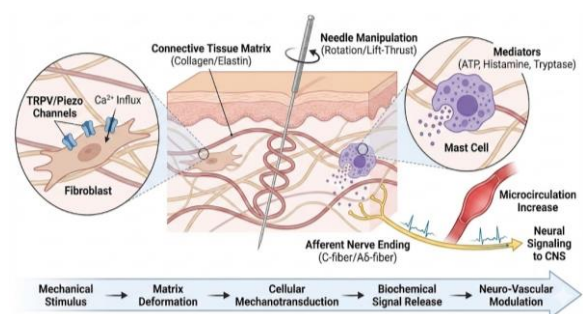


Figure 3. Manipulation of acupuncture needle acts as mechano-transducer in connective tissue.

Studies Related to the Crucial Roles of Mast Cell in Acupuncture Effects

Table 1. Some studies in Mast Cells and Acupuncture Effects.

Authors & Year	Subject	Results	Methods	Conclusion
Oh et al., 2024 ¹⁴	C57BL/6 J mice – Parkinson (PD) model	Acupuncture significantly increased the quantity and activity of mast cells (MCs) in peripheral tissues. However, cromolyn, an MC stabilizer, greatly inhibited the augmentation of MC activity, while lidocaine had no effect.	Toluidine blue staining - investigate the MC degranulation in skin sample	The critical involvement of peripheral MCs and their activation at the GB34 acupoint in mediating acupuncture's therapeutic effects in a Parkinson's disease mice model.
Bing-Rong Li et al., 2023 ¹⁵	acute ankle arthritis rats	Needling increased 5-HT build up at the Zusanli acupoint and increased the analgesic effect, which was reduced by sodium cromolyn	Toluidine blue staining	MC-associated 5-HT release at acupoints contributes to acupuncture analgesia, through modulation of ATP secretion via 5-HT receptors
Yan Chen, et al., 2021 ¹⁶	DSS-treated post-inflammation rats	Mast cell expression and activation were dramatically reduced after two weeks of electroacupuncture (EA) treatment, as was the expression of colonic NGF/TrkA and TRPV1 in both the colon and the dorsal root ganglion.	Collagen was stained with Masson's trichrome, and mast cell degranulation was assessed using toluidine blue.	DSS-treated post-inflammation rats, EA at ST36 has no effect on reduced rectal compliance but does alleviate visceral discomfort via the mast cell-triggered NGF/TrkA/TRPV1 afferent pathway.
Xiang Cui et al., 2018 ¹⁷	WsRC-Ws/Ws rats	Compared to wild-type rats, mutant animals have less MCs in their ST36 skin. The light, mild, and heavy osteoarthritis groups had more degranulated and extensively degranulated MCs at acupoints GB34 and EX-LE2 compared to the normal control and were positively linked with illness severity.	MCs in skin of ST36 - Immunofluorescence	MCs have an effect on the basic pain threshold but not the thermal one.
Ning Ding et al., 2018 ¹⁸	Rat model of knee osteoarthritis		Toluidine blue and immunofluorescence	Acupoint sensitization increases MC recruitment and degranulation levels on an acupoint-specific and disease severity-dependent basis through the release of tryptase, 5-HT, and HA during MC degranulation.
Meng Huang et al., 2018 ¹²	TRPV2 knockout male mice	TRPV2 KO male mice showed lower activation of mast cells at stimulated acupoints, which suppressed acupuncture-induced analgesia.	Toluidine blue (TB) was used to stain the mast cells	Acupuncture activates TRPV2 channels in mast cells, which converts mechanical inputs into acupuncture signals by activating either H1 or A1 receptors, causing the acupuncture effect.
Dimitrov et al., 2017 ¹⁹	Rat	Serotonin positive degranulation MC	Immunohistochemistry of Serotonin	Insertion of acupuncture needle into the rat skin produced an evident of needle tract, tissue displacement, and the degranulation of 5-HT immuno-positive MCs.

DISCUSSION

Mast cells are one of the important cell in immune system. Studies have shown that mast cell is crucial in creating the acupuncture effect for healing. Biologically it has specific mechano-sensitive membrane channels that activated by acupuncture needle stimulation resulting in bursting their chemicals cargo that play significant physiological roles in local environment.¹⁰ The knock-out or inhibition studies show that mast cells are required for acupuncture to be effective. When mast cells

are stabilized (preventing from degranulating) or chemically reduced at an acupoint, the analgesic and anti-inflammatory benefits of acupuncture are almost completely eliminated.^{11,12,14} This shows that mast cells are more than merely participants in the acupuncture response, which serve as gate-keepers. Furthermore, the recruitment of mast cells to the acupoint following acupuncture stimulation suggests that the body 'primes' these locations for continued healing.

Furthermore, the role of mast cells contributes to the "Acupuncture Non-Responder" phenomena. Studies showed that people with low mast cell counts or who take mast-cell-stabilizing medicines considerably less pain reduction with acupuncture.²⁰ This implies that the "Qi" or vitality of an acupoint is proportional to its mast cell reactivity. Another interesting feature is the feedback loop. Mast cells degranulate and release cytokines, which travel through the blood to the hypothalamus and pituitary gland. This causes the release of endogenous opioids (endorphins), which alleviate systemic pain. Concurrently, these substances instruct the brain to reduce systemic inflammation. As a result, a local mechanical event might successfully "re-program" the immune system's inflammatory state in the entire body.^{10,11,21}

Acupuncture not only stimulates mast cells, but also regulates the mediators they generate. Acupuncture stimulates mast cells to release mediators such as histamine, serotonin, and adenosine, all of which play important roles in pain transmission and inflammation.²¹ These chemical substances not only reduce pain, but also improve local blood flow and immunological responses by interacting with brain receptors, resulting in decreased pain and inflammation.^{10,11} Furthermore, acupuncture can restrict the production of inflammatory mediators by controlling mast cell degranulation, relieving pain and discomfort caused by chronic inflammation. Acupuncture can also help prevent excessive mast cell degranulation, which reduces the release of inflammatory mediators that cause the symptoms in allergic condition.^{3,10,21}

In conclusion, the mast cell bridges the gap between mechanical needle manipulation and biological repair. The acupuncture effect is a complex type of mechano-transduction in which a physical needle causes a chemical degranulation event through mast cell activation. Recognizing the mast cell as a key actor enables us to standardize acupuncture approaches and create new integrative therapies targeted these diverse bio-sensors.

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