EDITORIAL

Mast cells and acupuncture analgesia

Amelia Johnson

Johnson A. Mast cells and acupuncture analgesia. Curr. Res.: Integr. Med. 2023;8(3):35-38

ABSTRACT

Mast cells are widely dispersed throughout the body and serve a crucial role in function in the development of numerous illnesses. Recent research has revealed the intimate connection between mast cells and acupoints, and the function of mast cells in acupuncture analgesia has drawn attention The interest of scientists everywhere. Using the search terms mast cells, acupuncture analgesia, and acupoint in CNKI, PubMed, **Web of** Science, and other databases, as well as representative publications from these databases and the released research papers from our team, we summarised the findings**.** Acupoints serve as reaction sites for acupuncture because of the enrichment of mast cells and the close proximity of collagen fibres, microvessels, and nerves; acupuncture can deform collagen fibres and activate TRPV channels on mast cells' membranes to cause mast cells to release bioactive substances and activate nerve receptors to produce analgesia; and system biology models are developed to explain the quantitative process of induction.

Key Words: *Mast cell; Acupuncture analgesia; Acupoint sensitization; Mechanical stimuli*

INTRODUCTION

Mast cells, significant immune cells found throughout the body, are crucial to the development of many diseases. Previously, it was believed that mast cells released cytokines, chemokines, proteases, and biogenic amines after activation, which led to allergic reactions. Mast cells are currently thought to be involved in the regulation of adaptive immunity and protective host immunity, serving as the sentinel of innate immunity . Recent research has revealed the strong connection between mast cells and acupoints. It has been documented that acupuncture-induced mast cell migration, aggregation, and activation. The effectiveness of acupuncture analgesia is acknowledged on a global scale. Numerous diseases' associated pain can be reduced by acupuncture, which involves manually stimulating the skin with small needles [1]. By observing animal behaviours, such as the tail flip and paw withdrawal, the effect can be assessed. In rat models of Adjuvant Arthritis (AA), Zhang et al. found that acupuncture at the zusanli acupoint (ST36) increased Pain Threshold (PT). The acupuncture impact is a multi-step, peripheral to central physiological system dependent process. Acupoints serve as both the stimulation point and the illness reaction point in acupuncture treatments. Mast cells are more abundant in acupoints . According to Zhu's hypothesis, "neuropeptide-mast cell-sensitizer release" is a harmful reaction process that is brought on by the local establishment of "acupoint sensitization pools"[2].

The change of an acupoint from its physiological "resting state" to its pathological "active state" is known as acupoint sensitization. With the introduction of the mechanical signal transduction theory, the humoral theory, and the nerve-humoral theory, the role of mast cells in acupuncture analgesia progressively emerged and became a hot topic. Mast cells can respond to mechanical force signals that affect them through the extracellular matrix, according to the mechanical signal transduction theory. Later, the discovery of mechanically sensitive mast cell channels provided the theoretical underpinnings for foresight. According to the humoral theory, mast cell degranulation is brought on by the active chemicals that are released during mast cell degranulation and diffuse via tissue fluid along the meridian channel. The active substances generated by mast cells may potentially excite nerve endings, enter the brain through an afferent nerve, and then operate on target organs, effectors, or endocrine glands via pituitary or autonomic neurons, according to the nerve-humoral theory. Acupuncture is now known to activate mast cells and trigger their degranulation, which releases biological chemicals and has an analgesic effect [3].

Building a bottom-up model and simulating the calcium and mediator signals in the entire system or network, including mast cell degranulation and mast cell-nerve interactions, are both doable with a thorough grasp of the prior theories . In conclusion, the impact of mast cells on acupuncture analgesia may offer fresh perspectives on how acupuncture therapy works.

Characteristics of Mast Cells and Its Function

Von Recklinghausen made the discovery of mast cells in 1863. Follow

Editorial Office, Current Research : Integrative Medicine , UK

Correspondence: Amelia Jhonson, Editorial Office, Current Research : Integrative Medicine,Uk e-mail: integrativemedicine@emedicalsciences.cm

Received:- 5 May 2023, Manuscript No. pulcrim-23-6400; Editor assigned: 8 May2023, Pre-QC No.- pulcrim-23-6400 (PQ); Reviewed:- 13 May 2023, QC No. pulcrim-23-6400(Q); Revised:-20 May 2023; Manuscript No. - pulcrim-23-6400 (R); Published:-28 May 2023, DOI:10.37532. pulcrim.23.8 (3) 35-38.

that, Paul Ehrlich named this granules-containing cell and provided a detailed description of the histological observations of it . Since then, the study of the genesis, location, and function of mast cells has advanced dramatically. Hematopoietic cells found in the bone marrow are where mast cells are generated. Under the influence of several stimuli, including Monocyte Chemoattractant Protein-1 (MCP-1), Stem Cell Factor (SCF), Transforming Growth Factor Type- (TGF-), activin (ACT), etc., they migrate into peripheral organs and develop into mature mast cells . Mast cell adhesion and migration are also controlled by cytoskeleton, integrin, and other factors [4]. Mast cells are divided into two types, the connective tissue-type mast cell (granules containing tryptase and chymotrypsin) and the mucosal mast cell (granules having copious tryptase). Mast cells are widely dispersed in connective tissues and mucosal layers, especially at the boundary between the internal and exterior environments, such as the skin, digestive system, airways, and other boundaries where the interaction with the external environment occurs environment takes place. Additionally, mast cells are also present in organs like the heart, liver, and lung. The mast cells at acupoints, which are dispersed throughout the connective tissue of the skin, are the subject of this research. On the intima, perimysium, and adventitia of the nerve tract, as well as around small blood vessels, hair follicles, and sweat glands, mast cells are frequently dispersed in the skin [5].

Mast cell degranulation and its function

The degranulation process primarily fulfils the purpose of mast cells. The cell membrane ruptures during degranulation, activating the cell and releasing a variety of rich mediators, such as histamine, Platelet Activating Factor (PAF), interleukins (IL-1, IL-13, IL-4, and IL-5, etc.), Prostaglandin D2 (PGD2), substance P, tryptase, serotonin, bradykinin, heparin, and others . These mediators will soon operate on the nearby nerves, blood arteries, and muscles as a result of the mast cell dispersion, creating a neuralendocrine-immune network. Leukotriene can cause smooth muscle contraction and vasodilation, histamine and platelet activating factor will relax blood vessels and increase capillary permeability, interleukins work as pro-inflammatory and inflammatory cytokines that activate and recruit inflammatory cells, including granulocytic leukocytes (neutrophils, basophils, and eosinophils) and agranular leukocytes (monocytes, lymphocytes) to the Serotonin, substance P, histamine, and other neurotransmitters can control neuronal activity. Mast cells have many receptors and can react to a variety of stimuli. As a result, mast cells can respond to stimuli differently, which can have both beneficial and negative impacts on the body depending on the circumstances. The body will modify its internal environment's homeostasis as a result of the physiological state's activation and body repair state, which is good for body health because it protects against incoming viruses and germs. In a pathological state, abnormal activation will hurt the body and endanger health. Mast cells can thereby exacerbate local clinical symptoms in the case of inadequate responses.

Mast cells and acupoint sensitization

The conception of acupoint is introduced in Traditional Chinese Medicine (TCM), as effective targets for acupuncture therapy. Acupoints are a series of special points (about360 in human) in the skin. These points may become sensitive to mechanical or thermal stimulus under various pathologies . Yuan et al. found that acupoints were mainly collagen fiber-rich areas such as intermuscular connective tissue, peri-neurovascular connective tissue, and organ portal and peri-neural connective tissue.

In a ground-breaking study of the histomorphology of amputated limbs, Song discovered that the number of mast cells was much higher at acupoints compared to non-acupoints, and that mast cells were identified close to blood arteries and nerve terminals .

Similar findings were made in Crivellato's investigation, which discovered that mast cells were present in large numbers, either diffusely or in groups, in the dermal tissue surrounding acupoints . In the Yang Ming meridian, Zhang et al. discovered "synaptic-like" connections between mast cells and nerve terminals.

Acupuncture points serve as both disease reaction areas and treatment targets. The so-called "acupoint sensitization pool" is made up of numerous compounds that are used in acupoint sensitization. According to He et al., the acupoint sensitization is caused by the elevated expression of local allergic chemicals and nociceptive neuropeptides like substance P, calcitonin gene related peptide (CGRP), histamine, serotonin, and tryptase . Mast cells play a key role in both acupoint sensitization and acupunture by producing these crucial substances**.** Furthermore, He et al. discovered that under normal, pathological, and acupuncture conditions, the concentration of substance P, a peptide related to the calcitonin gene, differs at the same acupoint . Wang et colleagues. discovered substantial variations between the adenosine concentration at acupoints before and after modelling and acupuncture using High-Performance Liquid Chromatography (HPLC). These results suggest that the internal environment or external stimulus can change the molecules present at the acupoints. Therefore, further research into the connection between mast cells and acupoint sensitization is essential to understanding how acupuncture works.

Activation and mechanical sensitivity of mast cells

1. Degranulation of Mast Cells under Mechanical Stimulations: A number of factors, including IgE antibody-antigen complexes, environmental infections, physical stimulation (such as pressure, heat, electricity, and light), etc., activate mast cells. One of the key elements in the activation of mast cells is mechanical sensitivity.

   For instance, mechanical ablation of the airway epithelium alters the configuration of the mast cells and results in degranulation, which affects the function of the airways. In the rat lung, Shimbori et al. discovered that cyclic mechanical stress caused mast cell degranulation, which exacerbated pulmonary fibrosis. It is well known that mast cells are mechanically sensitive to acupuncture [6].

   They claimed that the biological mediators would have an impact on the endocrine, immunological, and neurological systems by acting on nearby nerves, blood vessels, and muscles. In this manner, the biological information was translated from the mechanical stimulation. Yang et colleagues discovered that shear stress caused the calcium increases and histamine release in rat basophilic leukaemia cells (RBL-2H3, a model cell line for mast cells). Further evidence of membrane currents during mast cell degranulation in response to mechanical stimulation was provided by Wang et al. In conclusion, it is plausible to

assume that the mast cell activation caused by mechanical stimulation may be the first step in the acupuncture analgesic effect [7].

2. Mechanosensitive channels of mast cell: Immunoglobulin E receptor (IgE-FcRI), Toll-like receptors, immunoglobulin receptor (Ig- FcRIII), stem cell factor receptors, G protein-coupled receptors, the ATP-sensitive receptors, etc. are just a few of the receptors and ion channels that are abundant in mast cell membranes . Nowadays, it has been suggested that transient receptor potential vanilloid channels are to blame for the mechanical sensitivity of mast cells. Additionally, the stretch-activated (SA) chlorine channels contribute. In HMC-1 (human leukaemia cells), RBL-2H3 (rat basophils), and other model cells for the in-vitro research of mast cells, transient receptor potential vanilloid channels are said to exist. These model cells show the primary properties of mast cell, although not being identical. TRPV1 through TRPV6 are members of the transient receptor potential vanilloid family, and TRPV1 to TRPV4 are responsive to mechanical or heat stimuli [7].

   Vanilloid channels with transient receptor potential are opened, causing a passage of calcium into the cell. TRPV1, TRPV2, and TRPV4 were expressed in HMC-1 cells, according to Zhang et al. They also discovered that mechanical, thermal, and laser stimulations can activate the TRPV2 channel. Meanwhile, there was a noticeable increase in histamine release. Moreover, the transient receptor potential vanilloid-specific inhibitor ruthenium red (RuR) may be able to inhibit the channel currents (as determined by a patch clamp) . In RBL-2H3 cells, Stokes et al. were able to demonstrate the presence of TRPV1, 2, and 6 channels. Uncertainty exists regarding the intracellular signalling pathways that lead from the opening of transient receptor potential vanilloid channels to mast cell degranulation. There may be a role for the TRPV2- Protein kinase A (PKA)-Calcium-Inositol triphosphate (IP3) pathway. Furthermore, the cytoskeleton also affects how sensitive to mechanical stimuli mast cells are. Fowlkes et al. discovered that mechanical stretching of 3-dimensionally cultivated RBL-2H3 cells may cause degranulation, but that the degranulation was considerably prevented after inhibiting the RGD-Integrin by echistatin. Uncertainty exists regarding the intracellular signalling pathways that lead from the opening of transient receptor potential vanilloid channels to mast cell degranulation. There may be a role for the TRPV2- Protein kinase A (PKA)-Calcium-Inositol triphosphate (IP3) pathway. Furthermore, the cytoskeleton also affects how sensitive to mechanical stimuli mast cells are. Fowlkes et al. discovered that mechanical stretching of 3-dimensionally cultivated RBL-2H3 cells may cause degranulation, but that the degranulation was considerably prevented after inhibiting the RGD-Integrin by echistatin [8].

Mast cells and acupuncture analgesia

During the acupuncture procedure, nerves are crucial. When the peripheral nerves at acupoints, the nerve pathways, or a portion of the central nervous system are damaged, the analgesic impact of acupuncture is dramatically reduced. According to Zhu et al., the acupuncture effect required nerve activation at acupoints .Sa et al. noted peripheral nerve tract discharges in rats after stimulating the zusanli acupoint. Disodium cromolyn, which prevents mast cell degranulation, was injected into the acupoint to lessen the discharges. This study established the role of mast cells in the alteration of brain electrical signals during acupuncture. The presence of an afferent signal pathway was confirmed by the detection of altered neural electrical signals at the dorsal root of the spinal cord. Further evidence was provided by Yin et al. that the mast cell degranulation-induced release of histamine was involved in the activation of acupuncture neuroelectric signals. Spatial connections between mast cells and nerve cells have been demonstrated both in vitro and in vivo . .At both the anatomical and molecular levels, the functional relationships between mast cells and nerves have been demonstrated. Mast cells and nerve cells communicate with one another. The activity of mast cells will also be impacted by the activated nerve cells. Histamine was released when the rat enteric nerve was stimulated, and mast cell degranulation was decreased. In the rat, prolonged electrical stimulation of sensory nerves can cause mast cells to degranulate and increase vascular permeability.

Mathematical model of mast cell involvement in acupuncture analgesia

Local mast cell degranulation and a cascade of biological signals are two components of the acupoint's reaction to mechanical stimulation. Acupuncture is a multi-scale, intricate procedure that involves both biochemical and biophysical elements. An efficient way to aid in the process' methodical understanding and quantitative analysis is through mathematical modelling. We will provide a very basic introduction to those models in this review.

These models' ease in providing deductive but realistic quantitative answers that are impossible to measure with present methods is one of its key benefits. By using numerical simulation, Yannick et al. examined the influence of mast cell density on acupuncture [9] .

To replicate the intracellular calcium signal and mast cell degranulation, Shi et al. developed a mathematical model. A series of mathematical models that Yao et al. proposed illustrated the biophysical and biochemical procedures involved in acupuncture. Using differential equations based on ion channel behaviours, the calcium rise in a mast cell was characterised , and calcium signal propagation in the network of mast cells was examined .

The findings of a numerical simulation demonstrated that the local mast cell density has an impact on the acupuncture effect in addition to the mast cells at the acupoints. Where mast cell density is low, the cascades of mast cell degranulation and neuroreceptor activation are not triggered. The majority of acupoints on the human body are rich in mast cells, making it simpler to produce acupuncture effects when these acupoints are treated with acupuncture. Additionally, a mathematical model of the relationship between mast cells and nerves was developed.

The second benefit of mathematical models is their capacity to synthesise the intricate, multiscale process using a structure of combined abstract blocks (or phases). The first stage of the process involves mechanical stimulations that open mechanically sensitive ion channels on the membrane of mast cells, allowing calcium to enter; the increased intracellular calcium then activates protein kinase C (PKC) and increases the sensitivity of secretory granules to calcium, driving exocytosis and the release of mediators. Through the G-protein-linked

receptors, the released mediators cause cellular responses in the second stage [10].

These receptors attach to Phospholipase C (PLC), which catalyses the release of inositol triphosphate and the breakdown of Phosphatidylinositol Biphosphate (PIP2). When the Endoplasmic Reticulum (ER) is depleted of calcium, calcium enters the cell through Calcium Release-Activated Calcium (CRAC) channels. Inositol triphosphate acts on the ER's IP3R receptors to lead the release of stored calcium. The Extracellular Space (ECS) is where mediators diffuse or flow in the third stage, activating more mast cells.

CONCLUSION AND DISCUSSION

There are many uses for acupuncture analgesia, which is a widely used and approved kind of treatment in Traditional Chinese Medicine. However, its modern development and use in conventional medicine have been hampered by the lack of scientific elucidation of the underlying mechanism. The information on mast cells and acupuncture analgesia was reviewed in this article since it is crucial to understanding how acupuncture works. These studies conducted over the past few decades have helped advance our understanding of how acupuncture works on all levels, from the anatomical, cellular, and molecular foundations of acupoints and acupuncture to the initiation, transformation, and transmission of acupuncture signals. Without a doubt, mast cells play a crucial function.

In a larger sense, acupuncture encompasses physical therapies like acupuncture, electroacupuncture, and moxibustion. The sole subject of this review is acupuncture. We hypothesise that the therapeutic mechanism of moxibustion is similar to that of acupuncture: activate mast cells by heat or mechanism stimulation, which results in an analgesic effect. This is because the primary mechanical sensitive channel TRPV2 may also be activated by heat stimulation This theory is supported by certain moxibustion research. Electroacupuncture's method is intricate; electrical stimulation can activate both mast cells and nerve cells.

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