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Mastzellen und Akupunkturanalgesie

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Zugehörige Daten

Datenverfügbarkeitserklärung

Gehe zu:

Abstrakt

Mastzellen sind in verschiedenen Teilen des menschlichen Körpers weit verbreitet und spielen eine wichtige Rolle beim Fortschreiten vieler Krankheiten. Vor kurzem wurde die enge Beziehung zwischen Mastzellen und Akupunkturpunkten aufgeklärt, und die Rolle von Mastzellen in der Akupunkturanalgesie hat die Aufmerksamkeit von Forschern weltweit auf sich gezogen. Unter Verwendung von Mastzellen, Akupunkturanalgesie und Akupunkturpunkt als Schlüsselwörter für die Suche in CNKI, PubMed, Web of Science und anderen Datenbanken, wobei wir die repräsentativen Artikel in diesen Datenbanken mit den veröffentlichten Forschungsarbeiten unserer Gruppe kombinierten, fassten wir zusammen: Die Anreicherung von Mastzellen und die dichte Anordnung von Kollagenfasern, Mikrogefäßen und Nerven bilden die Grundlage für Akupunkturpunkte als Reaktionsorte der Akupunktur; Akupunktur kann die Verformung von Kollagenfasern verursachen und TRPV-Kanäle auf der Mastzellenmembran aktivieren, um Mastzellen zur Freisetzung bioaktiver Substanzen anzuregen und Nervenrezeptoren zu aktivieren, um eine analgetische Wirkung zu erzeugen; Systembiologische Modelle werden aufgebaut, um den quantitativen Prozess der Informationsinitiierung und -übertragung an Akupunkturpunkten zu erklären und darauf hinzuweisen, dass der Akupunktureffekt von der lokalen Mastzelldichte abhängt. In einer Schlussfolgerung wird dieser Review eine wissenschaftliche Erklärung der

Akupunkturanalgesie aus der materiellen Basis von Akupunkturpunkturen, der lokalen Initiation und dem afferenten biologischen Mechanismus geben.

Schlüsselwörter: Mastzelle, Akupunkturanalgesie, Akupunktursensibilisierung, mechanische Reize, TRPV-Kanäle, systembiologisches Modell

Gehe zu:

1. Einleitung

Mastzellen, wichtige Immunzellen, die in verschiedenen Bereichen des menschlichen Körpers verbreitet sind, spielen eine wichtige Rolle beim Fortschreiten vieler Krankheiten. Bisher wurde angenommen, dass Mastzellen allergische Reaktionen hervorrufen, indem sie nach der Aktivierung Zytokine, Chemokine, Proteasen und biogene Amine freisetzen. Derzeit werden Mastzellen auch als mit der schützenden Wirtsimmunität verwandt angesehen, da sie als Wachposten der angeborenen Immunität und als Regulator der adaptiven Immunität fungieren [1,2]. Kürzlich wurde die enge Beziehung zwischen Mastzellen und Akupunkturpunkten aufgeklärt [3]. Die Migration, die Aggregation und die Aktivierung von Mastzellen unter Akupunkturreizen wurden berichtet [3,4,5].

Die Wirksamkeit der Akupunkturanalgesie ist weltweit anerkannt. Akupunktur (eine winzige Nadel in die Haut schlagen und mechanische Stimulationen manuell geben) kann die durch viele Krankheiten verursachten Schmerzen lindern. Der Effekt kann durch Beobachtung des Verhaltens der Tiere bewertet werden, typischerweise durch den Schwanzschlag und den Rückzug der Pfote. Zhang et al. beobachteten eine Erhöhung der Schmerzschwelle (PT) nach Akupunktur am Zusanli-Akupunkturpunkt (ST36) in adjuvanten Arthritis (AA) Rattenmodellen [3]. Der Akupunktureffekt ist ein komplexer Prozess, an dem mehrere physiologische Systeme von der Peripherie bis zur Zentralregion beteiligt sind. Akupunkturpunkt ist der Reaktionspunkt von Krankheiten und auch der Stimulationspunkt der Akupunkturbehandlung. Akupunkturpunkte werden in Mastzellen angereichert [4]. Zhu schlug vor, dass die lokale Bildung von "Akupunktur-Sensibilisierungspools" einen pathologischen Reaktionsprozess der "Neuropeptid-Mastzell-Sensibilisator-Freisetzung" induziert [6]. Die Akupunktursensibilisierung ist der Akupunkturübergang von ihrem physiologischen "Ruhezustand" in den pathologischen "aktiven Zustand". Nach diesem Übergang treten verschiedene Sensibilisierungsphänomene auf, darunter Säuregefühle, Schwellungen, Juckreiz, Taubheit und Schmerzen. Diese Gefühle führen dazu, dass

Menschen unwillkürlich lokale Reize wie Reibung, Kratzen, Kneifen und Hitze suchen. Dieser Prozess initiiert die Homöostaseregulation und aktiviert die Kaskadenreaktion. Durch die Förderung der Homöostase-Regulation heilen Akupunktur und Moxibustion die Krankheit.

Der Beitrag von Mastzellen zur Akupunkturanalgesie wurde allmählich aufgedeckt und wurde zu einem Hotspot, mit dem Vorschlag der mechanischen Signaltransduktionstheorie, der humoralen Theorie und der Nervenhumoraltheorie [7]. Die mechanische Signaltransduktion geht davon aus, dass Mastzellen auf mechanische Kraftsignale reagieren und über die extrazelluläre Matrix auf sie einwirken können. Später legte die Entdeckung mechanisch empfindlicher Kanäle an Mastzellen die materielle Grundlage für theoretische Vorausschau [8,9,10]. Die Humoraltheorie bedeutet, dass die durch die Mastzelldegranulation freigesetzten Wirkstoffe entlang des Meridiankanals durch die Gewebeflüssigkeit diffundieren und eine Mastzelldegranulation verursachen. Die Nervenhumortheorie besagt, dass die von Mastzellen freigesetzten Wirkstoffe auch Nervenenden stimulieren, durch den afferenten Nerv in das Zentrum gelangen und dann durch Hypophyse oder autonome Nerven auf Zielorgane, Effektoren oder endokrine Drüsen einwirken können. Heutzutage wird festgestellt, dass Akupunktur Mastzellen aktivieren und ihre Degranulation (Freisetzung biologischer Substanzen) bewirken kann, was eine analgetische Wirkung induziert [11,12,13]. Mit einem umfassenden Verständnis der bisherigen Theorien ist es möglich, ein Bottom-up-Modell aufzubauen und die Kalzium- und Mediatorsignale im gesamten System/Netzwerk zu simulieren, einschließlich Mastzelldegranulation und Mastzell-Nerven-Interaktionen [14,15,16]. Zusammenfassend lässt sich sagen, dass die Wirkung von Mastzellen auf die Akupunkturanalgesie neue Erkenntnisse über den Mechanismus der Akupunkturtherapie bringen kann.

Dieser Artikel konzentriert sich auf die Funktion von Mastzellen in Akupunkturpunkten und überprüft den Mechanismus der Akupunkturanalgesie, indem er die folgenden Themen diskutiert: (1) Mastzelldegranulation und ihre Funktion, (2) die Beziehung zwischen Mastzellen und Akupunktursensibilisierung, (3) die physiologischen Reaktionen von Mastzellen unter mechanischen Stimulationen, (4) die synergistische Wirkung von Mastzellen mit Kollagenfasern und Nerven während der Akupunktur, und (5) das systembiologische Modell zur quantitativen Erklärung der Initiierung und Übertragung von Akupunkturinformationen.

Gehe zu:

2. Eigenschaften von Mastzellen und ihre Funktion

2.1. Herkunft und Verteilung der Mastzellen

Mastzellen wurden 1863 von Recklinghausen entdeckt [17]. Anschließend beschrieb Paul Ehrlich detailliert die histologischen Beobachtungen dieser granulierten Zelle und gab ihr den Namen [18]. Seitdem wurden enorme Fortschritte in der Erforschung der Herkunft, der Verteilung und der Funktion von Mastzellen erzielt.

Mastzellen stammen aus hämatopoetischen Zellen im Knochenmark. Sie wandern in periphere Gewebe und differenzieren sich unter dem Einfluss verschiedener Faktoren wie Monozyten-Chemoattractant-Protein-1 (MCP-1), Stammzellfaktor (SCF), transformierender Wachstumsfaktor Typ-β (TGF-β), Activin (ACT) usw. zu reifen Mastzellen [19]. Weiterhin werden die Adhäsion und die Migration von Mastzellen durch Integrin und Zytoskelett etc. beeinflusst [20,21]. Entsprechend dem umgebenden Gewebe werden Mastzellen in die schleimhautartige Mastzelle (Granula mit reichlich Tryptase) und die Bindegewebs-Mastzelle (Granula, die Tryptase und Chymotrypsin enthalten) eingeteilt [22].

Mastzellen sind weit verbreitet in Bindegewebe und Schleimhautschichten, insbesondere an der Schnittstelle der inneren und äußeren Umgebung wie der Haut [23], dem Verdauungstrakt [24], den Atemwegen [25] und anderen Grenzen, an denen die Interaktion mit der äußeren Umgebung stattfindet. Außerdem finden sich Mastzellen auch in Organen wie Herz, Leber und Lunge [26]. Diese Arbeit konzentriert sich auf Mastzellen an Akupunkturpunkten, die im Bindegewebe der Haut verteilt sind. Mastzellen in der Haut sind oft auf der Intima, Perimysium und Adventitia des Nervenbahnes verstreut; Sie verteilen sich auch um kleine Blutgefäße, Haarfollikel und Schweißdrüsen [5,23]. Darüber hinaus sind Mastzellen eng mit Fibroblasten, vaskulären Endothelzellen, Kardiomyozyten usw. assoziiert. Es wurde auch über ein zelluläres Verhalten der "Transgranulation" berichtet [27].Abbildung 1zeigt den Ursprung und die Verteilung von Mastzellen in der Haut [28]. Mastzellen existieren in einer komplexen stromalen Umgebung und spielen eine wichtige Rolle im Kreislauf-, neurologischen, endokrinen und Immunsystem. Wie ein verbindender Knoten in einem Netzwerk kommunizieren Mastzellen mit diesen physiologischen Systemen und koppeln sie miteinander. Dieser Review zielt darauf ab, den Mechanismus der Beteiligung von Mastzellen an der Akupunkturatangesie im Detail aufzuklären.

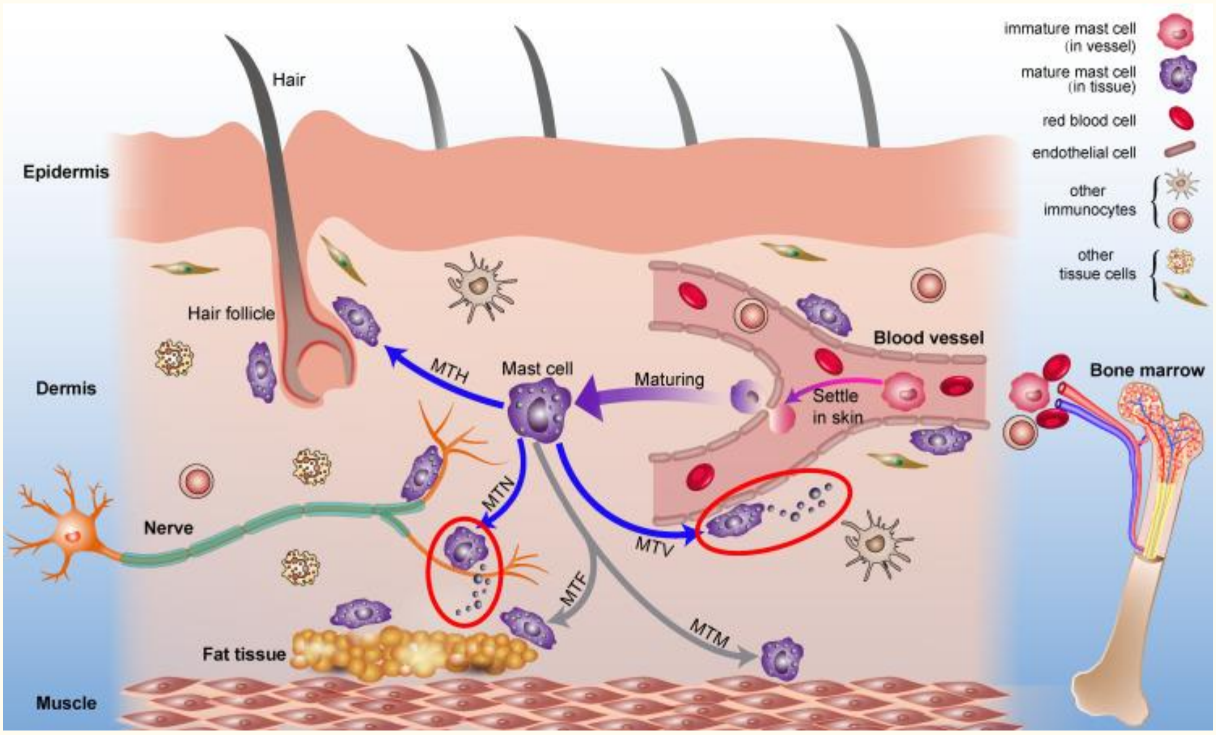

Abbildung 1

Mastzellen in der Haut. Mastzellvorläufer stammen aus dem Knochenmark. Unter bestimmten Bedingungen wandern unreife Mastzellen (rosa gefärbt) in periphere Gewebe und siedeln sich vor allem in der Dermis an. Reife Mastzellen (violett gefärbt) wandern dann zu Gefäßen (MTV), Nerven (MTN), Haarfollikeln (MTH), Muskelgewebe (MTM) und Fettgewebe (MTA). Mastzellen modulieren das Verhalten benachbarter Zellen, indem sie mehrere Mediatoren freisetzen, typischerweise durch Degranulation nach Stimulation (in roten Kreisen markiert), zum Beispiel können Mastzellen, die entlang von Gefäßen verteilt sind, die vaskuläre Permeabilität erhöhen, und Mastzellen, die entlang von Nerven verteilt sind, können aktive Nerven. Adaptiert von [28].

2.2. Mastzelldegranulation und ihre Funktion

Die Funktion von Mastzellen wird hauptsächlich durch den Degranulationsprozess erfüllt. Unter Degranulation wird die Zelle aktiviert und die Zellmembran bricht und setzt reichhaltige Mediatoren frei, darunter Histamin, plättchenaktivierender Faktor (PAF), Interleukine (IL-1, IL-13, IL-4 und IL-5 usw.), Prostaglandin D2 (PGD2), Substanz P, Tryptase, Serotonin, Bradykinin, Heparin, Chemokine usw. [29]. Dank der Verteilung der Mastzellen wirken diese Mediatoren schnell auf die benachbarten Nerven, Blutgefäße und Muskeln und bilden ein neuronal-endokrines Immunnetzwerk. Zum Beispiel bewirkt der Histamin- und Thrombozytenaktivierungsfaktor die Entspannung der Blutgefäße und erhöht die Kapillarpermeabilität, Leukotrien kann eine Kontraktion der glatten Muskulatur und

Vasodilatation verursachen, Interleukine wirken als entzündungsfördernde und entzündliche Zytokine, die Entzündungszellen aktivieren und rekrutieren, einschließlich granulozytärer Leukozyten (Neutrophile, Basophile, Eosinophile) und agranulärer Leukozyten (Monozyten, Lymphozyten) zum Ort der Entzündung, trägt zur Entwicklung von allergischen Erkrankungen wie allergischer Rhinitis bei. Histamin, Substanz P und Serotonin usw. können Nervenaktivitäten regulieren.

Mastzellen sind reich an Rezeptoren und Reaktionen auf eine Vielzahl von Reizen. Dadurch können Mastzellen bei unterschiedlichen Reizen unterschiedlich funktionieren, was je nach spezifischen Bedingungen sowohl positive als auch negative Auswirkungen auf den Körper hat [30,31]. Die Aktivierung im physiologischen Zustand und im Körperreparaturzustand passt die Homöostase der inneren Umgebung an, was für die Gesundheit des Körpers von Vorteil ist, indem es sich gegen die eindringenden Viren und Bakterien wehrt. Eine abnormale Aktivierung in einem pathologischen Zustand verursacht Körperbeschwerden und bedroht die Gesundheit. Das heißt, bei schwachen Reaktionen können Mastzellen lokale pathologische Manifestationen verschlimmern [32,33,34]. Zum Beispiel könnte Interleukin-33 (IL-33), das von Epithelzellen produziert wird, Mastzellen dazu anregen, Histamin zu sezernieren, das der Hauptmediator ist, der das Nasenreiben und Niesen bei Ovalbumin (OVA) induzierter allergischer Rhinitis (AR) stimuliert [35]. Ein weiteres bekanntes Beispiel dafür sind die Berichte, dass Mastzellen durch COVID-19 aktiviert werden und zu Entzündungen und Fibrosen in der Lunge führen. Das Virus bewirkt, dass Mastzellen entzündungsfördernde Moleküle freisetzen und damit zur SARS-CoV-2-Infektion beitragen [36,37]; In anderen Umgebungen, insbesondere bei schwerer Hautüberempfindlichkeit, können Mastzellen den Prozess unterdrücken, teilweise durch die Produktion von Interleukin-10 [38,39]. Mastzellen in der Akupunktursensibilisierung und Akupunkturanalgesie können ihre negativen bzw. positiven Auswirkungen widerspiegeln.

2.3. Mastzellen und Akupunktursensibilisierung

Das Konzept des Akupunkturpunkturs wird in der Traditionellen Chinesischen Medizin (TCM) als wirksame Ziele für die Akupunkturtherapie eingeführt. Akupunkturpunkte sind eine Reihe von speziellen Punkten (etwa 360 beim Menschen) in der Haut. Diese Punkte können unter verschiedenen Pathologien empfindlich auf mechanische oder thermische Reize reagieren [40]. Yuan et al. fanden heraus, dass Akupunkturpunkte hauptsächlich kollagenfaserreiche Bereiche wie intermuskuläres Bindegewebe, peri-neurovaskuläres Bindegewebe sowie Organportal- und perineurales Bindegewebe waren [41]. Durch

Magnetresonanztomographie (MRT) und Röntgen-Computertomographie (XCT) bemerkten Fei et al. auch die Anreicherung von Bindegewebe in Akupunkturpunkten [42], fanden sie heraus, dass Mastzellen, Blutgefäße, Nervenbahnen und Lymphgefäße zusammen mit dem Bindegewebe als Basis ein sehr komplexes Struktursystem bilden.Abbildung 2zeigt die Verteilung von Kollagenfasern und Mastzellen am Zusanli-Akupunkturpunkt.

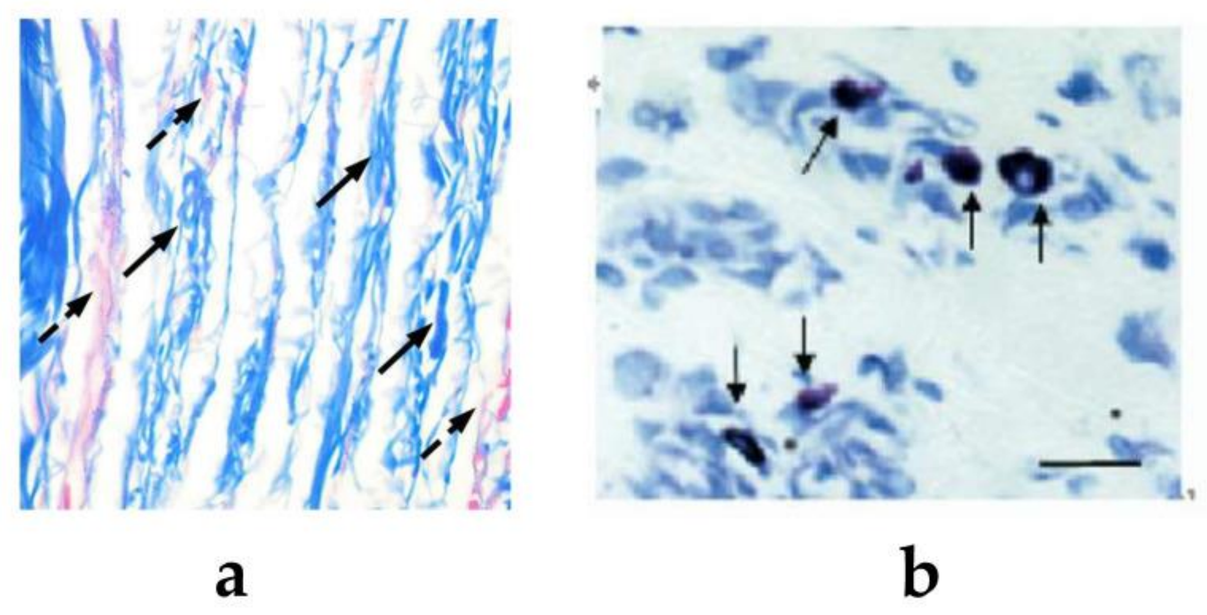

Figure 2

The structure of zusanli acupoint in rats. (**a**) The mallory staining of zusanli acupoint; collagen fibers are in blue, indicated by black solid line arrows. Note that collagen fibers are rich and have a parallel arrangement at the acupoint. Myofibers and blood cells are in red, indicated by black dotted arrows. (**b**) The toluidine blue staining of zusanli acupoint. The scale bar is 10 μm; mast cells are in blue, indicated by solid line arrows. Note that mast cells gather in large numbers at the acupoint [3,43].

In a pioneering histomorphological observation in amputated limbs, Song found that the number of mast cells was significantly larger at acupoints than non-acupoints, she also found that mast cells were located near nerve endings and blood vessels [44,45]. Crivellato's study gave similar results, finding the abundantly presence of mast cells in the dermal tissue of acupoints area, distributed diffusely or in clusters [18]. Zhang et al. found "synaptic-like" connections between mast cells and nerve endings in the Yang Ming meridian [46,47]. In a histomorphological observation of tissues in acupoints, Luo et al. found a composite strip structure of mast cells, blood vessels, and nerves [4]. The close anatomic relation between mast cells, blood vessels, and nerves implies their reciprocity correlation. Figure 3 shows the distribution of mast cells along blood vessels and nerves of zusanli acupoint in rats.

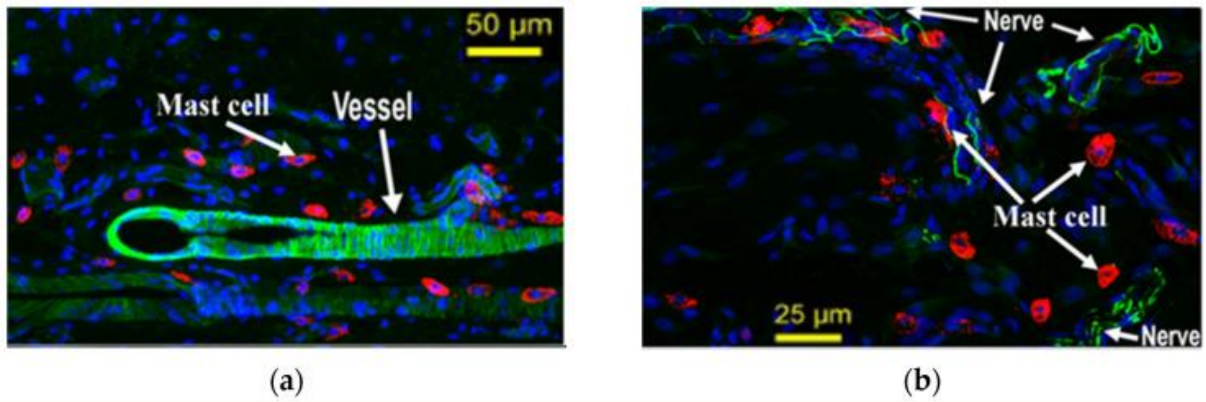

Figure 3

The distribution of mast cells, nerves, and blood vessels at zusanli acupoint in rats after immunofluorescence staining. (**a**) The distribution of mast cells around blood vessels. (**b**) The distribution of mast cells around nerve fibers [28].

Acupoints are reaction sites of disease and targets for acupuncture. Many chemicals are involved in acupoint sensitization, they form the so-called "acupoint sensitization pool". He et al. revealed that the high expression of local allergic substances and nociceptive neuropeptides, such as substance P, calcitonin gene related peptide (CGRP), histamine, serotonin, and tryptase, are responsible for the acupoint sensitization [48]. By releasing these important chemicals, mast cells are closely associated with both the acupoint sensitization and the acupuncture effect [49]. Ding et al. reported that the release of serotonin, histamine, and tryptase during mast cell degranulation regulated the acupoint sensitization [12]. The released substance P may also be involved [50].

Moreover, He et al. found that the concentration of substance P, a calcitonin gene related peptide, at the same acupoint, is different under normal, pathological, and acupuncture conditions [51]. Using high-performance liquid chromatography (HPLC) to measure the adenosine concentration at acupoints, Wang et al. found significant differences before and after modeling and acupuncture [52]. These findings imply a dynamic variation of chemicals at the acupoints, manipulated by the inner environment or the external stimulation. Therefore, a further investigation of the relationship between mast cells and the acupoint sensitization is the key to the mechanism of acupuncture analgesia.

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3. Activation and Mechanical Sensitivity of Mast Cells

3.1. Degranulation of Mast Cells under Mechanical Stimulations

Mast cells are activated by a variety of pathways, such as IgE antibody-antigen complexes, pathogens in the environment, physical stimuli (pressure, heat, electricity, and light), etc. The mechanical sensitivity is one of the main factors for mast cells activation. For example, a mechanical removal of the airway epithelium disrupts the mast cell structure and causes the degranulation, which influences the airway function [25]. Shimbori et al. found that the cyclic mechanical stress induced mast cell degranulation in the rat lung, which contributed to the pulmonary fibrosis [53]. The mechanical sensitivity of mast cells under acupuncture has been widely recognized. Zhang et al. found that the degranulation rate of mast cells increased significantly after the mechanical stimulation of acupuncture [3]. They argued that the released biological mediators would effectively act on the neighboring nerves, blood vessels, and muscles, potentially impacting on the endocrine, the immune, and the neurological systems. In this way, the mechanical stimulation was interpreted into the biological information [54]. Yang et al. found that shear stress induced the calcium changes in rat basophilic leukemia cells (RBL-2H3, a model cell line for mast cells) and led to histamine release [55]. Wang et al. further confirmed the existence of membrane currents during mast cell degranulation under the mechanical stimulation [56]. To conclude, a reasonable assumption is that the acupuncture analgesia effect may begin with the mast cell activation under the mechanical stimulation.

3.2. Mechanosensitive Channels of Mast Cells

Mast cell membranes are enriched with receptors and ion channels, including immunoglobulin E receptor (IgE–FcεRI), Toll-like receptors, immunoglobulin receptor (Ig–FcγRIII), stem cell factor receptors, G protein-coupled receptors, the ATP-sensitive receptors, etc [57]. Nowadays, transient receptor potential vanilloid channels have been reported to be responsible for the mechanical sensitivity of mast cells [8,54,55,58]. Besides, the stretch-activated (SA) chlorine channels also play a role [56]. Transient receptor potential vanilloid channels are reported to exist in HMC-1 (human leukemia cells), RBL-2H3 (rat basophils), and other model cells for the in-vitro study of mast cells. Though not identical, these model cells demonstrate the main characteristics of mast cells.

Members of the transient receptor potential vanilloid family consist of TRPV1 to TRPV6, of which TRPV1 to TRPV4 are sensitive to mechanical or thermal stimulation. Transient receptor potential vanilloid channels are activated to induces a calcium flow into the cell [58]. Zhang et al. convinced the expression of TRPV1, TRPV2, and TRPV4 in HMC-1 cells. They also found that the TRPV2 channel can be activated under mechanical, heat, and laser stimulations. Meanwhile, an increase of histamine release was detected. Moreover, the channel currents (measured by a patch clamp) could be inhibited by the transient receptor potential vanilloid specific inhibitor ruthenium red (RuR) [54]. Stokes et al. convinced the existence of TRPV1, 2 and 6 channels in RBL-2H3 cells. They also detected the current flow through the TRPV2 channel under mechanical and thermal stimulations [8]. Yang et al. also observed the increase of the intracellular calcium concentration and the release of histamine when shear stress was applied to RBL-2H3 cells [55]. They reported a participation of the TRPV4 channel. To conclude, the inflow of calcium seems the key to the mechanical activation of mast cells. The transient receptor potential vanilloid channels, expressed in mast cell membranes, are the main receptors and sensors for mechanical stimulation, such as acupuncture.

The intracellular signaling pathways from transient receptor potential vanilloid channels opening to mast cell degranulation remain unclear. The TRPV2- Protein kinase A (PKA)-Calcium-Inositol triphosphate (IP3) pathway may be involved [8,16]. Moreover, the cytoskeleton also plays a role in the mechanical sensitivity of mast cells. Fowlkes et al. found that a mechanical stretching of 3-dimensional cultured RBL-2H3 cells could induce degranulation, but after blocking the RGD-Integrin by Echistatin, the degranulation was significantly inhibited [59]. Stretch-activated chlorine channels are also associated with mast cell degranulation. Wang et al. found that osmotic stress activated stretch-activated chlorine channels in HMC-1 cells, generated membrane currents, and caused cell degranulation. The degranulation could be inhibited by DIDS (a chloride channel blocker) [56]. They presumed that the activation of stretch-activated chlorine channels induced the chlorine influx and caused cell hyperpolarization, then the increased cross-membrane potential drove the calcium inflow and consequently induced the cell degranulation.

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4. Mast Cells and Acupuncture Analgesia

4.1. Mast Cells in Acupuncture Analgesia

Zhang et al. found the increase of pain threshold after acupuncture at zusanli acupoint in adjuvant arthritis rat models depended on mast cell degranulation in the neighboring tissue. After reducing the mast cell degranulation with disodium cromolyn (DSCG, mast cell membrane stabilizer), the analgesic effect of acupuncture was inhabited [3]. Cui et al. found that the analgesic effect was closely related with the intensity of mechanical stimulation, and mast cell deficiency in rat attenuated the analgesic effect of acupuncture [60]. Therefore, they concluded that mast cells were essential in acupuncture analgesia. As discussed previously, the TRPV2 channel on mast cells also affects the analgesic effect of acupuncture. Huang et al. observed a great reduction in mast cell degranulation rate at zusanli acupoint in the TRPV2 gene knockout mice (comparing with wild-type animals), as well as a suppression of acupuncture analgesic effect [61].

Mast cells release multiple kinds of biological substances, some of which may be involved in acupuncture analgesia [5]. Huang et al. found that both histamine injection and acupuncture at zusanli acupoint in adjuvant arthritis rats increased the pain threshold, and also promoted the mast cell degranulation. The pretreatment with clemastine (histamine H1 receptor antagonist) could suppress the analgesic effect of acupuncture and decrease the mast cell degranulation rate induced by histamine, while the degranulation rate induced by acupuncture was not affected. Moreover, the pretreatment with disodium cromolyn reduced the mast cell degranulation in both conditions, but the analgesic effect remained in the histamine injection group. These experiments indicated a key role of histamine in the activation of mast cells and the fulfillment of acupuncture analgesia, with a positive feedback effect [62]. Through microdialysis sampling and high-performance liquid chromatography detection of acupoint tissues, Goldman et al. reported an increase in ATP, ADP, AMP, and adenosine induced by acupuncture. Adenosine could induce the anti-nociceptive effect by activating the adenosine A1 receptor. The anti-nociceptive effect could also be reproduced with a direct injection of an agonist to the receptor. Acupuncture treatment fails to suppress pain in the mice lacking adenosine A1 receptors. These observations indicate that adenosine mediates acupuncture analgesia effects [63].

4.2. Function of Mast Cells and Collagen at Acupoint

The clinical criterion for achieving acupuncture effect is the acquisition of sensations (a concept called De Qi in Chinese), which is a feeling, including tingling, numbness, and heaviness, elicited by acupuncture. Acupuncturists feel the needle sink tightly, like a fish swallowing a hook [64]. Researchers are attempting to reveal the biophysical basis of this subjective, vague, and incomprehensible concept. Liu et al. performed a biopsy on a patient with the meridian pathology, and they assumed that De Qi is related with the tubular structure formed by the interconnected collagen fibers [65]. The bundles of collagen fibers arrange in parallel at the zusanli acupoint, having a high transmittance of 9–20 um infrared rays [42]. Based on magnetic resonance imaging and X-ray computed tomography observations of the acupoint, Langevin et al. concluded that De Qi is a manifestation of the mechanical coupling between the subcutaneous collagen fibers and the needle body [66]. Collagen fibers are intertwined and interlaced, forming a three-dimensional network in the connective tissue. In the De Qi state, the mechanical stimulation of the needle (lifting, thrusting, and rotation) effectively causes tissue deformation, and the signal is easily transferred to the mast cell, inducing its degranulation. This hypothesis is supported by animal experiments. Yu et al. destroyed the collagen at zusanli acupoint in rats by collagenase, and they found that acupuncture could not cause mast cell degranulation effectively, thus the analgesic effect was significantly weakened. Moreover, the lifting and twisting force of the needle body on the acupoint was dramatically reduced [43]. Therefore, effective coupling of the needle body to the collagen at the acupoint is the key to De Qi during acupuncture.

4.3. Mast Cell-Nerve Cell Interaction at Acupoint

Nerves play an essential role in the acupuncture process. The acupuncture analgesic effect is significantly attenuated by either blocking the peripheral nerves at acupoints, or blocking the nerve pathways, or damaging part of the central nervous system. Zhu et al. suggested that the nerve excitation at acupoints was necessary for acupuncture effect [67]. Sa et al. observed discharges of the peripheral nerve tracts when stimulating the zusanli acupoint in rats. The injection of disodium cromolyn (blocking mast cell degranulation) at the acupoint weakened the discharges [68]. This experiment verified the mast cell participation in the changing of neural electrical signals during acupuncture. The changing of neural electrical signals could also be detected at the dorsal root of the spinal cord [69], indicating the existence of an afferent signal pathway. Yin et al. further proved that the histamine released by mast cell degranulation participated in the activation process of acupuncture neuroelectric signals [70].

Mast cell-nerve cell spatial contacts has been verified both in vitro and in vivo [71]. The functional associations between mast cells and nerves have been proven at both the anatomic and the molecular levels [72,73,74]. The interaction between nerve cells and mast cells is mutual. Immune activation of mast cells by the injection of antigen into sensitized animals causes the release of histamine to excite neurons, which can be inhibited by histamine H2 receptor blockers [75]. The stimulated nerve cells will also affect the activity of mast cells. Studies have found that stimulating the enteric nerve in rats caused histamine release, and reduced mast cell degranulation [76]. Prolonged electrical stimulation of sensory nerves can lead to degranulation of mast cells and an increase of the vascular permeability in the rat [77].

To conclude, mast cells and nerves interact with each other. The mediators released by mast cells induce neuroelectric activities (both locally and centrally), and the transmitters released from sympathetic neurons manipulate mast cell activation in turn, forming a feedback network. One possible advantage of the network, although remaining mysterious, is the capability to link different parts of the body together and cause collaborative responses.

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5. Mathematical Model of Mast Cell Involvement in Acupuncture Analgesia

The acupoint response to mechanical stimulation includes local mast cell degranulation and the cascade reaction of biological transmitters. The acupuncture is a complex and multi-scale process, involving biochemical and biophysical factors. Mathematical modeling provides an effective method to help systematically understand and quantitatively analyze the process. In this review, we will give a very brief introduction to those models. One of the important advantages of these models is the convenience to giving deductive but reasonable quantitative results that are not possible to measure with current techniques. Yannick et al. analyzed the effect of mast cells density on acupuncture by numerical simulation [78]. Shi et al. established a mathematical model to simulate the intracellular calcium signal and degranulation of a mast cell [79]. Yao et al. proposed a series of mathematical models that demonstrated the biophysical and biochemical processes during acupuncture. The calcium rise in a mast cell was described using differential equations based on behaviors of the ion channels [16], and the calcium signal propagation in mast cells network was investigated [14]. Numerical simulation results showed that the acupuncture effect is not only dependent on the mast cells at the acupoints, but is also influenced by the local mast cell density. The chain reactions of mast cell degranulation and neuroreceptor activation are not elicited where mast cell density is low. The vast majority of acupoints in the human body are enriched in mast cells, so acupuncture at these acupoints is easier in order to produce acupuncture effects. Furthermore, the mast cell and nerve interaction was also modeled mathematically [14,15,16].

The second advantage of mathematical models is the ability to synthesize the complex, multiscale process with a framework of combined abstract blocks (or stages). The dynamic process of the mast cell activation is illustrated in Figure 4 [14,15]. In the first stage, mechanical stimulations activate the mechanical sensitive ion channels on mast cells membrane and allow calcium entry; the intracellular calcium increase activates protein kinase C (PKC) and increases the sensitivity of secretory granules to calcium, thus driving exocytosis and mediators release. In the second stage, the released mediators trigger cellular responses through the G-protein linked receptors. These receptors bind to phospholipase C (PLC), and phospholipase C catalyzes the hydrolysis of phosphatidylinosital biphosphate (PIP2) and the release of inositol triphosphate. Inositol triphosphate acts on receptors (IP3R) of the endoplasmic reticulum (ER) and leads the stored calcium release; the depletion of calcium in endoplasmic reticulum triggers calcium entry through calcium release-activated calcium (CRAC) channels. In the third stage, mediators diffuse or flow in extracellular space (ECS) and activate other mast cells. Mediators can also bind to receptors of adjacent nerve terminals (sensory neuron) and trigger action potentials, which induce passive electrical flow from primary sensory neurons to spinal cord neurons.

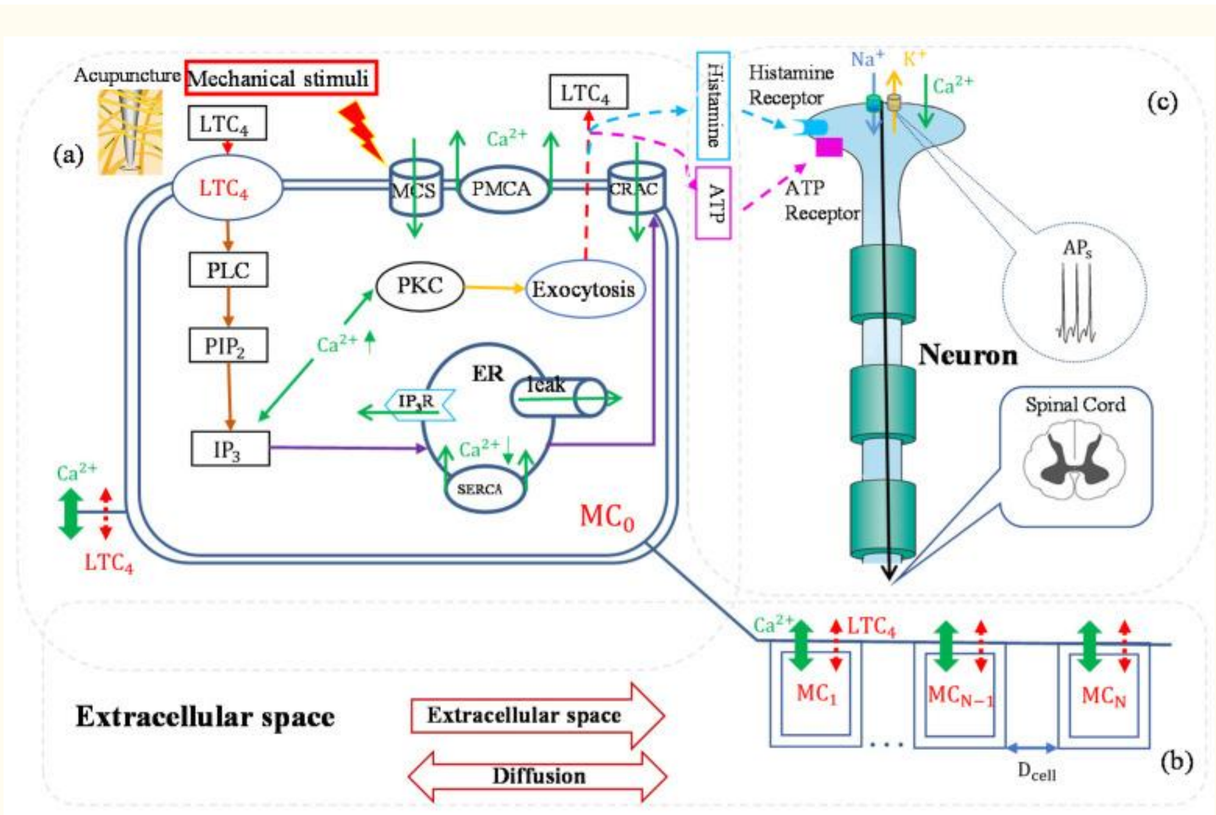

Figure 4

The bio-mathematical model of acupuncture effect by the synergistic action mechanism of interstitial substances. The kinetic models describe the biochemical response of individual cell to stimulation. The conductance models describe the transmission of electrical signals in continuous nerve fibers. The mast cells network models describe the information response between mast cells. (**a**) The representation of single mast cell. (**b**) The representation of mast cells network. (**c**) The representation of nerve cells. Unidirectional arrows represent substance transport directions, the green solid line bidirectional arrows represent calcium, and the red dash line bidirectional arrows represent mediators such as leukotriene c-4 (LTC_4) and histamine, etc. MC_0 is the mast cell activated by mechanical stimuli; the steps leading from mechanical sensitivity channel (MSC) activation to calcium release from the calcium store (Endoplasmic Reticulum) into the cytosol and mediators release into extracellular space by exocytosis described in MC_0. A lane of model mast cells (MC_1 means the first mast cell from MC_0 in the flow direction; MC_{-1} means the first mast cell from MC_0 in the contra-flow direction; MC_N means the N*th* mast cell from MC_0 in the flow direction; and MC_{-N} means the N*th* mast cell from MC_0 in the contra-flow direction) are separated by D_{cell}. Each cell exchanges biological messengers through cell membrane with extracellular space. Extracellular space is regarded as continuous, and diffusion and convection are included. Adapted from [14].

Table 1 shows the response results of mast cells and nerves. Nerve cells at D_{ist} (distance from mast cell) of 200 μm, 400 μm, 600 μm, and 800 μm can be activated by mediators released from the stimulated mast cell. The response time of membrane potential (E_m) activation of the nerve cell increases with distance, causing this signal intensity to decrease. However, when the D_{ist} is 1×10^{-4} m, the nerve cells are no longer activated, in other words, when the distance between the mast cell and the nerve cell is too large, there is no acupuncture analgesia effect.

Table 1

Response time of E_m and $[Ca^{2+}]_i$ (calcium concentration) peak of different D_{ist}s [15].

D_{ist}	Response Time of E_m	$[Ca^{2+}]_i$ Peak (μM)
2×10^{-5} m	22 s	0.33
4×10^{-5} m	24 s	0.31
6×10^{-5} m	27 s	0.29
8×10^{-5} m	33.1 s	0.27
1×10^{-4} m	No	0.24

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6. Conclusions and Discussion

Acupuncture analgesia is an internationally accepted effective treatment in Traditional Chinese Medicine and has a wide range of applications. However, the lack of scientific elucidation of the background mechanism has hindered its modern development, as well as its application in mainstream medicine. In this paper, we reviewed the literature on mast cells and acupuncture analgesia, which is a major concern in revealing the acupuncture mechanism. These research efforts in the past decades have contributed to a scientific explanation of acupuncture effect in all aspects: from the material basis of acupoints and acupuncture (in anatomical, cellular, and molecular levels), to the initiation, transformation, and propagation of acupuncture signals. Mast cells play a key role—without doubt.

Acupuncture in a broader context includes mechanical (acupuncture), electrical (electroacupuncture), and heat (moxibustion) treatments. This review only focuses on acupuncture. Because the main mechanical sensitive channel TRPV2 can also be activated by heat stimulation [57], we suppose that the therapeutic mechanism of moxibustion is similar to that of acupuncture: activate mast cells by heat or mechanism stimulation, which leads to an analgesia effect. Some works on moxibustion support this hypothesis [80]. The mechanism of electroacupuncture is complex; electrical stimulation may activate both mast cells and nerve cells. Acupuncture mainly activates the local mast cell, while electroacupuncture not only caused degranulation of mast cells at the zusanli acupoint, but also in the abdominal cavity on the same meridian [81]. On one hand, the effect of electroacupuncture on mast cells and mast cell-mediated analgesia is not as good as that of acupuncture. On the other hand, unlike what was observed in acupuncture, the analgesia effect of electroacupuncture cannot be totally blocked by the mast cell membrane stabilizer (disodium cromolyn) [82]. It reminds us that there is another mechanism involved in electroacupuncture analgesia besides mast cell activation.

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Author Contributions

Conceptualization, W.Y.; methodology, Y.L. (Yingchen Li), Y.Y., and W.Y.; formal analysis, Y.L. (Yingchen Li), Y.Y.; resources, Y.L. (Yingchen Li), Y.Y., and Y.L. (Yuhang Liu); validation, Y.L. (Yingchen Li), Y.Y., and W.Y.; writing—original draft preparation, Y.L. (Yingchen Li), Y.Y., and W.Y.; writing—review and editing, Y.Y., W.Y., Y.L. (Yingchen Li), and Y.L. (Yuhang Liu), supervision, W.Y.; project administration, W.Y.; funding acquisition, W.Y. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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