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Review Article

Piezo Proteins and their role in Cupping Therapy (*Hijama*); An Interpretation of Novel Mechanism

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Abstract

Piezo proteins are ion channel proteins found in various cells of the human body which detect mechanical forces and convert them into electrical signals that can be interpreted by the nervous system. Recent research has shown that these proteins play an important role in a number of physiological processes, including touch sensation, hearing, proliferation, pain modulation and blood pressure regulation. Further research is ongoing to understand the importance of piezo proteins in human health and disease, that could lead to develop the newer therapies for a wide range of conditions. Some physical therapies including Cupping therapy (CT) (Hijama), a well-known regimental therapy in Greco-Arab (Unani) and Chinese medicine, is reported to treat a variety of diseases like, blood pressure and prevents cardiovascular diseases. It is also effective in treating oral and genital ulceration, musculoskeletal pain, nonspecific low back pain, neck pain, fibromyalgia, headache and migraine. Besides various theories hypothesized to explain mechanism of cupping therapy, the piezo protein gates intruded by this therapy may be the best feasible way to understand the mechanism of action of cupping. This novel hypothetical mechanism could pave the way for more researches in medical field especially in chronic ailments.

Key words: Cupping, Human Health, Pain, Piezo protein, Unani

1. Introduction

Piezo proteins are a type of ion channel proteins that are found in various cells of the human body. These protein receptors are known for their ability to detect mechanical forces, such as pressure or stretch, and convert them into electrical signals that can be interpreted by the nervous system. In recent years, there has been growing interest in the role of piezo proteins in human health and disease, particularly in the field of medicine [1].

A review of the current literature on piezo proteins reveals that these proteins play an important role in a number of physiological processes, for example, piezo sensors in the skin are responsible for our ability to sense pressure and touch, while those in the inner ear help us to detect sound waves [2,3]. Studies have shown that inhibiting piezo proteins may help to lower blood pressure by reducing the stiffness of blood vessels. The importance of piezo channels in human health and disease is becoming increasingly clear. Research in this area could lead to the development of new therapies for a wide range of conditions, from hypertension and chronic pain to hearing loss and sensory disorders. As our understanding of piezo proteins continue to grow, it is likely that we will discover even more ways in which these proteins play a critical role in human biology [1,4].

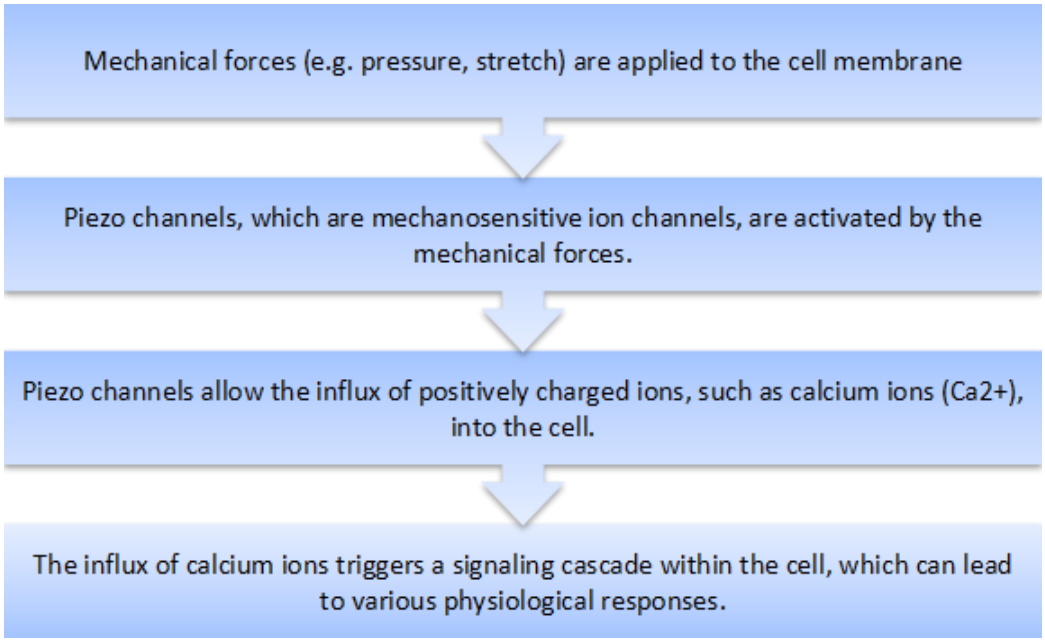
2. Discovery of piezo proteins

Piezo proteins, a family of ion channels that are activated by mechanical force were first discovered in 2010 by a group of researchers at Harvard Medical School, who identified two related proteins, Piezo1 and Piezo2 that play a critical role in the detection and transduction of mechanical stimuli. David Julius and Ardem Patapoutian were honored with Nobel Prize in the year 2021 in Physiology or Medicine for their discovery of these fundamental sensors of temperature and pressure. The Piezo1 and Piezo2 proteins are large transmembrane proteins that act as mechano transducers [5,6].

3. Mechanism of piezo proteins/channels

The Piezo proteins span the cell membrane and form a pore through which ions can pass. When mechanical force is applied to the cell membrane, the Piezo proteins undergo a conformational change that opens the ion channel, allowing ions such as calcium to flow into the cell. This generates an electrical signal that is transmitted to the nervous system, where it is processed and interpreted as mechanical stimulus[7].

Here is a simplified flow chart of the mechanism of piezo channels;



The physiological responses may include changes in cell shape, gene expression, neurotransmitter release, or other cellular functions [8,9]. piezo proteins are involved in the inflection of varied cellular functions such as migration, proliferation, differentiation, and apoptosis as well as in the detection of sensory stimuli such as vibration. Therefore, mechano-transduction is vital for organ development and homeostasis. Both Piezo1 and Piezo2 have a similar homotrimer structure but differ in many aspects. At present, the cryo-electron microscopy structures of mouse Piezo1 and Piezo2 have been obtained [10,11]. However, the structure of human Piezo1 and Piezo2 remains to be resolved. In mouse, Piezo1 is a homotrimer, which is similar to a three-bladed propeller [12] and can be divided into two modules; the peripheral mechano-transduction module and the central ion conduction pore module [12,13]. Piezo1 selectively conducts cations, such as Na+, K+, Ca2+ and Mg2+ preferably Ca2+ while as Piezo2 has the property of non-selective cationic conductance [5]. To be specific, extracellular mechanical stimuli sensed by cells, such as fluid shear stress as well as tension and compression forces, causes the lipid molecules on the cell membrane to change so that tension from the lipid molecules is sufficient to activate the Piezo channels [14]. Furthermore, the peripheral mechano-transduction module of the Piezo channels feels the tension from the lipid molecule and thus opens the central pore module [15]. Because the extracellular CED has a lot of negative charge, the concentration and internal influx of extracellular cations such as Ca2+ leads to the activation of downstream signaling pathways [16,17]. The mechanotransduction has been shown by figure 1 [18].

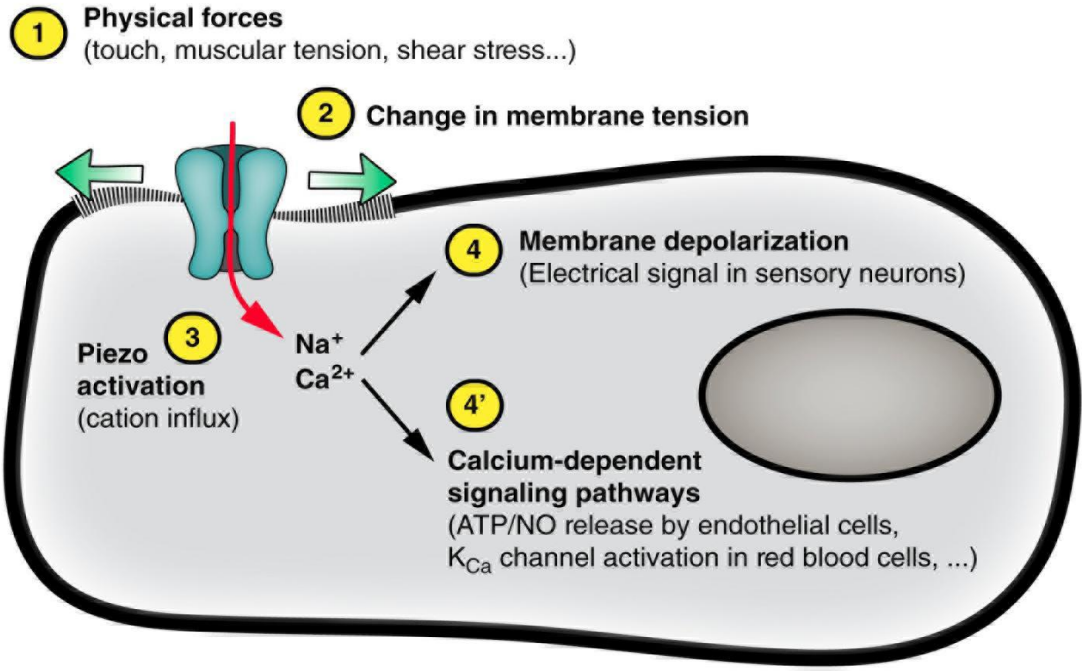


Figure1: Mechanotransduction by piezo channels [18]

4. Role of piezoproteins in medicine and different treatment interventions

In medicine, the study of piezo proteins has become increasingly important in understanding a variety of health conditions. Researchers have found that dysfunction or damage to piezoproteins in the skin may contribute to neuropathic pain and other sensory disorders. The Piezo channels play vital roles in numerous physiological and pathological processes by functioning as cellular mechanotransducers [19,20,21,22,23]. Piezo1 has recently been discovered to be important for vascular mechanotransduction like blood pressure regulation [24], urinary osmolarity [23], cartilage mechanotransduction [25], dorsal root ganglion neuron physiology [26], peripheral trigeminal nociception [27], and other physio pathological conditions. Piezo2 mainly functions in somatosensory neuron physiology, airway stretch, and lung inflation [3,28]. More recently, the Piezo channels have shown key roles in mediating the mechanotransduction in bone cells, bone development and bone disease [29,30]. They are involved in regulating movement play a role in muscles and joints and contribute in conditions such as arthritis and other musculoskeletal disorders. Osteoclast differentiation is regulated by the expression of bone matrix proteins (collagen type II and IX), but these collagens are controlled by Piezo1 in osteoblasts via regulating nuclear translocation of YAP1[1] [31]. The Piezo1-YAP1-collagen pathway suggests that Piezo1 indirectly regulates bone resorption activity in osteoclasts, thus affecting bone metabolism. Interestingly, Zhou et al. pointed out that while Piezo2 is dispensable for bone development, it shares redundant functions with Piezo1 in vivo [32]. Deficiency of Piezo1 and Piezo2 in osteoblasts results in more severe bone loss in mice than deficiency of Piezo1 [32]. Thus targeting mechanosensitive ion channels, such as Piezo channels and TRPV4[2], is the direction of future research for OA treatment [33]. Mechanical force when applied to the skin, muscles, or joints, activates piezoproteins, which then send signals to the brain that can block or reduce pain signals. For example, deep pressure massage or acupressure may help relieve pain by stimulating piezoproteins in the muscles and skin. Likewise, some types of physical therapy or chiropractic treatments may also target piezoproteins to ameliorate pain and improve range of movement. However, piezoreceptor stimulation for pain relief can vary depending on the individual and the underlying cause of the pain.

Piezoproteins are being studied for their role in prosthetics and sensory replacement devices. By mimicking the signals sent by piezoproteins, researchers may be able to create more realistic and responsive prosthetic limbs that allow amputees to better control their movements and sense touch. Piezoproteins have also been found to play some role in bone and cartilage growth. When mechanical force is applied to bone or cartilage, piezoproteins located in the cells of these tissues get activated. The activation of these piezoproteins can trigger a signaling cascade that leads to the production of growth factors, which then stimulate bone and cartilage growth. Similarly, mechanical stimulation of cartilage cells can enhance the production of extracellular matrix molecules and proteoglycans, which are important for cartilage growth and maintenance. Furthermore, piezoproteins may play a role in bone remodeling and repair. When bones are subjected to mechanical stress or damage, piezoproteins can trigger a signaling cascade that leads to the activation of bone-resorbing cells called osteoclasts and bone-forming cells called osteoblasts. This process helps to maintain bone strength and repair damage [33].

In recent era, piezoproteins have emerged as potential therapeutic targets for the management of chronic pain, as they have been shown to play a key role in pain signaling pathways. Murthy et al. and Szczot et al. discovered that PIEZO2 ion channels expressed in sensory neurons are required for the development of mechanical allodynia in mice and humans. They suggest that local inhibition of PIEZO2 ion channels might be effective for treating mechanical allodynia. Piezo2 has been seen to act a key player in touch sensation and demonstrates its role in mechanical pain signaling [34].

5. Cupping Therapy (CT)/ Hijama

CT can generally be described as a technique that uses cups placed over the skin to create negative pressure through suction. It dates back to ancient times and was used around the world. In 400 BC, Herodotus listed wet and dry cupping as a treatment for multiple ailments, including indigestion, lack of appetite, and headaches. Hippocrates advocated cupping for gynecological complaints, back and extremity illnesses, pharyngitis, lung diseases, and ear ailments. CT was mentioned in the famous Papyrus Ebers in Ancient Egypt (1550 BC). In the Middle East, cupping was advocated by prominent physicians like Abu Bakr Al-Razi (AD 854-925), Ibn Sina (AD 980-1037), and Al-Zahrawi (AD 936-1036). Cupping was recorded as a medical treatment in the Mawangdui Silk texts in China (sealed in 168 BC). CT was used in ancient Europe as well. In the first century AD, Celsus advised CT for extracting poison from bites and for abscesses. In the 2nd century AD, Aretaeus treated prolapse of the uterus, cholera, epilepsy, and ileus with wet cupping. Galen was an advocate for CT and detailed a variety of materials that could be used for cups like horns, glass, and brass [35].

There are two types of cupping methods, dry and wet cupping. Dry cupping is noninvasive with no bloodletting but, wet cupping is invasive and includes bloodletting [35].

5.1. A brief description of CT technique

Cupping is application of cups to induce vacume and hence negative pressure to stimulate muscles and is particularly helpful in the treatment of aches and pains associated with various diseases. Cupping therapy possesses the potential to enhance the quality of life [36]. Each cupping session takes about 20 minutes and could be conducted in five steps. The first step includes primary suction. in which the therapist allocates specific points or areas for cupping and disinfects the area. A cup with a suitable size is placed on the selected site and the therapist suck the air inside the cup by fire flame, electrical or manual suction. Then the cup is applied to the skin and left for a period of three to 5 min. The second step is about scarification with superficial incisions made on the skin using Surgical Scalpel Blade No. 15 to 21, or puncturing with a needle, auto-lancing device or a plum-blossom needle [37]. The third step is about suction and bloodletting. The cup is placed back on the skin using the similar procedure described above for three to 5 min. The fourth step includes the removal of the cup, followed by the fifth step which includes dressing the area after cleaning and disinfecting with FDA approved skin disinfectant. Furthermore, suitable sizes of adhesive strips are then applied to the scarified area, which remain there for 48 h [38]. It is wise to know that the scarification and bloodletting are the two main techniques of wet CT.

5.2. CT outcomes in certain medical conditions

CT is reported to treat a variety of diseases due to the effects of multiple types of stimulation [39]. Cao and associates (2010)

[1] YAP1- Yes-associated protein 1
[2] TRPV4- Transient receptor potential vanilloid 4

suggested that CT appears to be effective for various medical conditions, in particular herpes zoster and associated pain and acne, facial paralysis, and cervical spondylosis [40]. CT is often used for lowering blood pressure and prevents the development of cardio vascular diseases CVDs in healthy people [41]. Wet cupping in conjunction with conventional treatment is reported to effectively treat oral and genital ulceration in patient with Behçet's disease [42]. There is growing evidence that wet cupping is effective in musculoskeletal pain [43], nonspecific low back pain [44], neck pain [45], fibromyalgia [46] and other painful conditions [36]. Michalsen et al. (2009) concluded that CT may be effective in alleviating the pain and other symptoms of Carpal Tunnel Syndrome [47]. CT is also found to be effective in headache and migraine [48]. CT is effective for reducing systolic blood pressure in hypertensive patients for up to 4 weeks without any serious side effects [49]. Evidently, CT is effective in the treatment of cellulitis [50]. CT has been used with various level of evidence (I to V) in many conditions such as cough, asthma, acne, common cold, urticaria, facial paralysis, cervical spondylosis, soft tissue injury, arthritis and neuro-dermatitis [37,51,52,53].

5.3. Mechanism of CT/*Hijama*

Cupping/*Hijama* is believed to work through several mechanisms in managing pain which are [53];

i) Increased blood flow: Cupping creates suction on the skin, which increases blood flow to the affected area. This increased blood flow can help to reduce inflammation and promote healing of the affected tissues, which can in turn reduce pain.

ii) Stimulating the nervous system: Cupping can stimulate the nervous system, which can help to reduce pain. This stimulation can occur through the activation of the parasympathetic nervous system, which can help to reduce stress and tension in the body, as well as through the release of endorphins, which are natural pain-relieving chemicals produced by the body.

iii) Myofascial release: Cupping can also help to release tightness in the muscles and connective tissue, which can contribute to pain. This is thought to occur through the stretching of the tissues and the release of adhesions or scar tissue.

iv) Acupressure points: Cupping is often used in conjunction with traditional Chinese medicine, which emphasizes the use of specific acupressure points to treat pain and other conditions. By targeting these specific points, cupping can help to stimulate the body's natural healing processes and reduce pain.

Many theories have been suggested to explain numerous effects of CT and its mechanisms of action [54]. Several researchers proposed biological and mechanical processes associated with the cupping session. The specific mechanism in which cupping exerts its therapeutic effect has not been identified. However, a number of theories have been proposed such as "Pain-Gate Theory" (PGT), [55] "Diffuse Noxious Inhibitory Controls" (DNICs),[56] and "Reflex Zone Theory" (ZRT) [57]. For wet cupping Taibah theory suggests wet cupping mimics an artificial kidney. Where an in vivo kidney filters hydrophobic materials through the glomeruli via normal pressure filtration, wet cupping filters both hydrophilic and hydrophobic material through high-pressure filtration. Wet cupping can help relieve pain or improve overall health, such as reducing inflammation or promoting blood flow.

5.4. Role of piezo proteins in CT

While the exact mechanism of cupping in managing pain is not fully understood, it is thought to work through a combination of increased blood flow, stimulation of the nervous system, myofascial release, and targeting of specific acupressure points. Increased blood flow may help to promote the release of natural pain-relieving compounds in the body, such as endorphins.

As mentioned earlier Piezo proteins are a type of sensory receptors found in the skin, vessels, bones etc that respond to mechanical pressure and vibrations [1]. These have shown key roles in proprioception, pain inflection, vascular changes and blood pressure regulation, mediating the mechanotransduction in bone cells, bone development and bone disease [29,30]. The multi tissue effect by piezo proteins can be simply understood by figure 2 [58]. During CT/ hijama, suction cups are applied to the skin, near joints or areas of somatic pains, creating a negative pressure. Negative pressure can stimulate angiogenesis, improves blood circulation, promote granulation tissue growth and accelerate the tissue wound healing. Likewise intermittent negative pressure can promote the regeneration of bone possibly by enhancing the expression of vascular endothelial growth factor (VEGF) and bone morphogenetic protein (BMP)-2 [52,59]. obviously the applied pressure by CT might have involved the piezo proteins for its action. Furthermore, the role of CT and newly discovered piezo proteins in modulating pains, bone development and lowering blood pressure suggests a close link between the two. Hence the piezo protein guided effect of CT is one of the most appropriate mechanisms that could be hypothesized in the current era. However, more comprehensive research is needed to fully understand this newly hypothesized 'piezo protein theory of Cupping Therapy'.

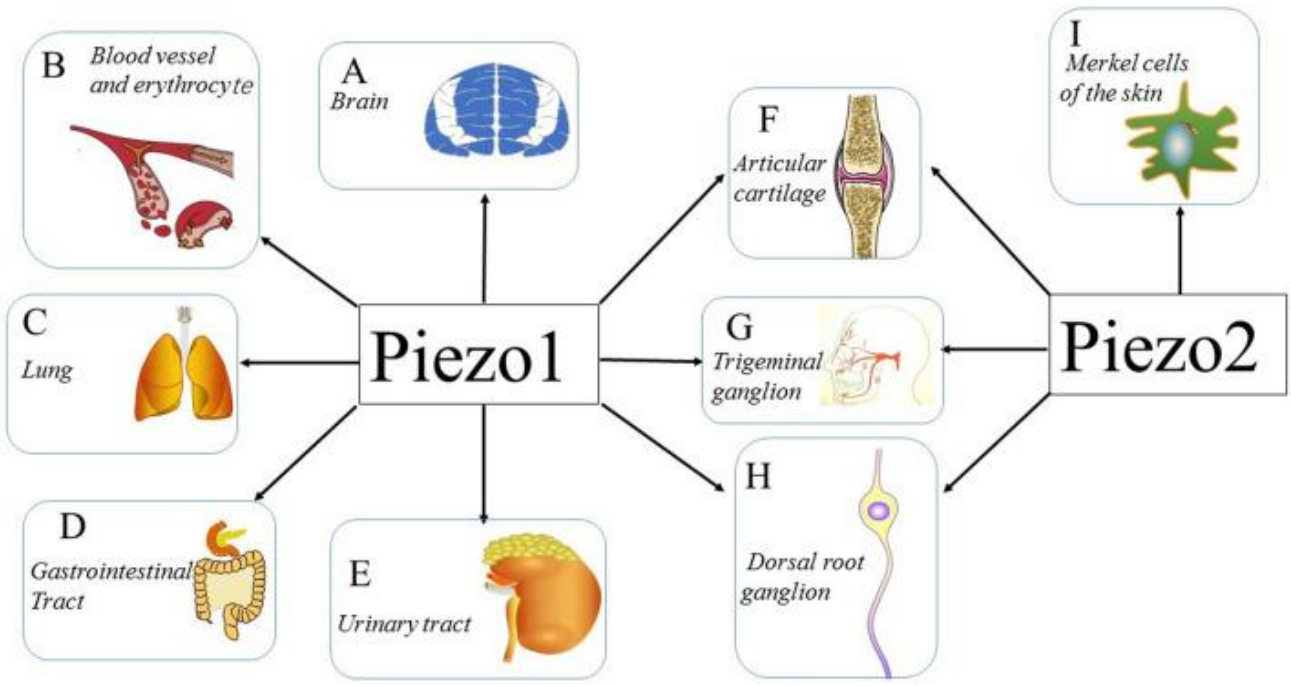


Figure 2: piezo 1 and piezo 2 expression and function in multiple tissues and cells.

6. Conclusion

Mechanical force applied to the cell membrane results a conformational change in the Piezo proteins that opens the ion gate. This stimulation of piezo proteins is responsible for developing and relieving pains, growth of bones and cartilages, influences vascular changes and regulates blood pressure and so on. CT, an age-old treatment therapy used in Greco-Arab and Chinese medicine, creates a negative pressure which may stimulate piezo channels and produce its astounding effects through this pathway. This proposition opens a gateway for novel researches beneficial in health of mankind both for its maintenance and cure.

Conflict of Interest

The authors declare to have no conflict of interest.

Authors' contribution

All the four authors participated finely in collecting the data, its analysis and interpretation. The corresponding author has a major contribution in writing the manuscript, collecting, analyzing and interpreting the data. All authors read and agreed for the manuscript.

Abbreviations

CT- Cupping Therapy

OA- Osteoarthritis

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