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Original Article

Research Progress on the Mechanism of Acupuncture Intervention in Migraine Headache Based on PI3K/Akt and NF-Kb Signaling Pathways

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Abstract:
Migraine Headache is clinically characterized primarily by unilateral or bilateral headache, frequently accompanied by symptoms such as nausea, vomiting, photophobia, and phonophobia, significantly impairing patients' quality of life and work efficiency. Acupuncture, as a crucial therapeutic approach in clinical practice, has been widely applied and demonstrates established efficacy. The phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways play pivotal roles in the mechanisms underlying acupuncture treatment for MH. Based on the PI3K/Akt and NF-κB signaling pathways, this review systematically summarizes the research progress on the mechanism of action of acupuncture in treating MH, aiming to provide novel perspectives and approaches for future research and clinical practice.

Keywords: Migraine Headache; Acupuncture; PI3K/Akt; NF-κB; Signaling Pathway

Introduction

Migraine Headache (MH) is a relatively common, globally recognized neurological disorder. Its primary clinical manifestation is recurrent episodes of unilateral or bilateral headache [1]. During the prodromal phase, patients may experience various symptoms, including fatigue, neck pain, sweating, photophobia, or phonophobia [2]. Studies indicate that MH accounts for 88.2% of the total years lived with disability (YLD) attributable to headaches. Furthermore, MH severely impacts patients' daily activity capacity and work efficiency, reaching 38.4% and 39.9%, respectively [3]. Currently, MH ranks among the top ten leading causes of YLD worldwide and has become one of the four most common conditions encountered in emergency departments [4]. The primary pathomechanism of MH involves central sensitization, which is characterized by a sustained enhancement of neuronal excitability in the trigeminal nucleus caudalis (TNC) in response to painful stimuli [5]. Conventional Western pharmacological treatments commonly include calcitonin gene-related peptide (CGRP) receptor antagonists, lasmiditan, and analgesics; for severe attacks, triptans (i.e., 5-HT1B/1D receptor agonists) are frequently used. However, these medications are generally associated with drawbacks such as frequent adverse reactions, inconsistent efficacy, and an inability to effectively slow disease progression [6]. Traditional Chinese Medicine (TCM) acupuncture offers effective relief for MH. Its mechanisms involve regulating neurotransmitter systems, improving vasomotor function, suppressing inflammatory processes, and exhibiting minimal adverse effects [2,3]. From the perspective of

different signaling pathways mediating MH, this article explores the role of acupuncture in modulating MH-related signaling pathways, aiming to provide further insights into its mechanisms of action from the perspective of pathway-based pathogenesis.

1. PI3K/Akt Signaling Pathway

The phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway is a crucial intracellular pathway in mammalian cells. It plays a vital role in regulating numerous physiological processes, including cell growth, differentiation, apoptosis, and metabolism. It is also closely associated with the onset of MH [7]. Activation of the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) can inhibit apoptosis and inflammatory responses by stimulating PI3K and protein kinase A (PKA).

Activation of GLP-1R or its selective agonist liraglutide suppresses the expression of calcitonin gene-related peptide (CGRP) and phosphorylated protein kinase B (p-Akt) in the TNC. Furthermore, the PI3K inhibitor LY294002 effectively prevents nitroglycerin (NTG)-induced hyperalgesia. Additionally, GLP-1R activation significantly reduces the release of inflammatory factors such as the microglial marker ionized calcium-binding adapter molecule 1 (Iba-1), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α), while suppressing NTG-induced changes in the number and morphology of microglia in the trigeminal ganglion. These effects ultimately alleviate hyperalgesia in rat models of MH [8]. Experimental results from Liu et al. [9] demonstrated that, compared to the control group, the expression of PI3K mRNA and p-Akt in the TNC was significantly elevated in the MH model group at 6 to 24 hours post-NTG injection. This indicates abnormal activation of the PI3K/Akt signaling pathway in these rats. These findings suggest that activation of the PI3K/Akt signaling pathway plays a crucial role in the pathogenesis of MH, with its degree of activation closely linked to the occurrence and progression of MH.

TCM posits that the " Liver governs the smooth flow of qi " (gan zhu shu xie). If the liver fails to disperse qi, qi movement becomes stagnant. This stagnation can transform into fire (huo). As pathogenic fire tends to flame upward (huo yue yan shang), it may disturb the clear orifices (qing qiao), leading to distending head and eye pain, thereby predisposing to MH. MH typically manifests in the temporal region of the head, which corresponds to the Liver meridian of Foot-Jueyin (LR) and the Gallbladder meridian of Foot-Shaoyang(GB). Shuaigu (GB8), located in the temporal region, belongs to GB. As GB and LR are interiorly-exteriorly related, acupuncture at GB8 can both dredge the meridian qi and blood in the head to improve temporal circulation, and subdue rise of liver yang (gan yang shang kang). Yanglingquan (GB34), situated on the lateral aspect of the lower leg, is the He-Sea point of GB (He-Sea points treat internal fu organs). According to the principle "where the meridian passes, it can treat," acupuncture at GB34 also dredges GB qi and blood, regulating meridian blockages in the head, and help prevent MH triggered by ascending wind-yang (feng yang). Zheng et al. [10] selected these two acupoints. Using disposable sterile needle acupuncture (0.18 × 13 mm), they performed shallow insertion at GB8 and perpendicular insertion at GB34 to a depth of approximately 5mm. Acupuncture were retained for 20 minutes and stimulated (via lifting, thrusting, and twisting) once every 5 minutes. Treatment lasted 9 days. Compared to the control group, the experimental group showed significantly reduced levels of IL-1β and TNF-α, and a relative increase in TGF-β levels in both serum and the TNC, suggesting an anti-inflammatory effect. Shao et al. [11] demonstrated that acupuncture based on the "Liver-Soothing and Spirit-Regulating" (Shu gan Tiao shen) method, by regulating the PI3K/Akt pathway, can improve immune responses and inflammatory reactions. It modulates various cytokines and inflammatory factors, including interleukins, attenuates neurovascular inflammation, thereby exerting protective effects on cerebral blood vessels and nerves, and ultimately alleviates MH symptoms. Zhao et al. [12] found that acupuncture can activate the PI3K/Akt pathway mediated by α7 nicotinic acetylcholine receptors (α7nAChRs). This suppresses the expression of pro-inflammatory factors such as IL-1β and TNF-α in serum, alleviates peripheral inflammatory responses, and ultimately relieves hyperalgesia in rat models of MH.

2. NF-κB Signaling Pathway

The nuclear factor kappa-light-chain-enhancer of

activated B cells (NF-κB) signaling pathway is a critical signal transduction system within cells, regulating gene expression and plays a central role in diverse biological processes such as inflammatory responses, immune reactions, cell differentiation, proliferation, and survival. As a convergence point for numerous signaling pathways, this pathway is regarded as a potential and ideal therapeutic target for MH. NF-κB is a pleiotropic transcription factor within eukaryotic cells capable of rapidly responding to extracellular signals. In the presence of stimulatory factors such as inflammatory cytokines or growth factors, the IκB kinase (IKK) complex is activated. This activation mediates the phosphorylation of the inhibitor of kappa B (IκB). The phosphorylated IκB subsequently undergoes ubiquitination and degradation. This degradation leads to the dissociation of the NF-κB dimer, its translocation into the nucleus, and its activation. The activated NF-κB then promotes the transcription of its target genes and the release of associated cytokines, participating in the regulation of various physiological and pathological processes within the nervous system [13,14].

As a pivotal hub for inflammatory signaling, NF-κB participates in the expression and regulation of multiple pro-inflammatory mediators, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). It can activate early inflammatory signaling pathways, trigger neurogenic inflammation and trigeminal sensitization, ultimately leading to the onset of MH [15]. For instance, studies indicate that following nitroglycerin (NTG)-induced transcriptional events, Citrus aurantium (Zhi shi) can alleviate MH by inhibiting the NF-κB pathway [16]. Furthermore, research by Guo et al. [17] revealed significantly elevated plasma levels of NF-κB and IL-6 in MH patients compared to healthy controls. This elevation suggests that NF-κB and IL-6 may collaboratively initiate an inflammatory cascade during MH attacks, indicating their close association with the pathogenesis of MH.

MH, known in TCM as “Shoufeng” (首风，Head Wind) or “Pian zheng Tou tong” (偏正头痛, Unilateral/Bilateral Headache) , is considered a disorder located in the brain. *Compendium of Acupuncture and Moxibustion* records that Fengchi (GB20) "treats aversion to cold with fever, absence of sweating in febrile diseases or warm diseases, dizziness and visual disturbance, and migraine headache." indicating that the GB20 as a key acupoint for MH treatment since. Wai guan (SJ5), the Luo-Connecting point of the Sanjiao Meridian of Hand-Shaoyang, connects with the Yang Link Vessel (Yang wei Mai). It functions to regulate qi, activate blood, and relieve pain. He et al. [18] used electroacupuncture(EA) as an intervention in a rat model of migraine induced by intracranial injection of inflammatory soup through an implanted catheter. EA intervention was applied at GB20, GB34, and SJ5. EA parameters were set to a dense-disperse wave (5 Hz/30 Hz) at 0.5 mA intensity, administered once daily for 25 minutes. Results demonstrated that, compared to the control group, the EA group effectively suppressed neurogenic inflammation and alleviated symptoms in the acute MH rat model. This effect was achieved by upregulating the expression of peroxisome proliferator-activated receptor gamma (PPARγ) and downregulating NF-κB expression. Song et al. [19] induced a rat model via subcutaneous NTG injection. Acupuncture intervention was applied at bilateral He gu (LI4) and Tai chong (LR3) over 28 days. Results showed that, compared with baseline, the experimental group exhibited reductions in: CGRP, Visual Analog Scale (VAS) scores, symptom duration, attack frequency, NF-κB levels, blood flow velocity in the anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), and vertebral artery (VA), and TNF-α levels. Conversely, β-endorphin (β-EP) and serotonin (5-HT) levels significantly increased post-treatment. The results indicated that modulating the NF-κB signaling pathway can effectively regulate cerebral arterial blood flow velocity, ultimately improving MH symptoms. Ma et al. [20] found that acupuncture significantly reduced serum levels of IL-1β, interleukin-4 (IL-4), IL-6, and TNF-α in rats. It concurrently decreased protein expression levels of the nuclear factor kappa-B p65 subunit (NF-κB p65) and cyclooxygenase-2 (COX-2) in skin tissue while upregulating IκB expression. These results collectively suggested that acupuncture likely inhibits the amplification of the inflammatory cascade by regulating the NF-κB signaling pathway. Given the multifactorial complexity of MH and its pathogenic mechanisms, future research needs to delve

deeper into exploring novel molecular targets that regulate NF-κB signal transduction. Additionally, detecting potential biomarkers during the early stages of MH onset will be crucial for gaining deeper insights into its pathogenesis and laying the foundation for developing targeted therapies.

3. Discussion

In summary, the PI3K/Akt and NF-κB signaling pathways exhibit a close relationship with MH. Regarding the PI3K/Akt Signaling Pathway: 1. Anti-inflammatory Effects: Acupuncture significantly upregulates the expression of PI3K and Akt proteins. This subsequently inhibits the release of inflammatory factors, reduces neurogenic inflammation, and thereby alleviates MH symptoms. 2. Pain Modulation: Acupuncture modulates the PI3K/Akt signaling pathway, influencing the expression of neurotransmitters and related receptors, which improves pain perception function in MH patients. Regarding the NF-κB Signaling Pathway: 1. Vasoactive Regulation: Activation of the NF-κB signaling pathway promotes the release of CGRP. Acupuncture inhibits this pathway, lowering CGRP levels, thereby reducing vasodilation and plasma extravasation, and ultimately mitigating MH symptom attacks. 2. Inflammation Regulation: Activation of the NF-κB signaling pathway drives the substantial production of pro-inflammatory factors such as IL-1β and IL-6. Acupuncture attenuates the inflammatory response by inhibiting its activation. 3. Hemodynamic Optimization: Acupuncture also optimizes hemodynamic parameters by modulating the NF-κB signaling pathway. This regulates cerebral blood flow velocity and enhances cerebral tissue perfusion, further alleviating MH symptoms.

Currently, clinical practice frequently employs acupuncture at points such as GB20, GB34, and LI4 for MH treatment. However, research gaps remain: Firstly, Limited Research on Acupoint Specificity: The differential regulatory effects of distinct acupoints on MH-related signaling pathways have not been systematically elucidated. There is a pressing need to explore the targeted associations between specific acupoints and signaling pathways in depth. Secondly, Unclear Dose-Response and Time-Effect Relationships: Quantitative models urgently need to be established to define the relationships between acupuncture stimulation parameters (intensity, frequency, treatment course duration) and the responses within MH signaling pathways. As research into the PI3K/Akt and NF-κB signaling pathways deepens, it is anticipated that these findings will provide novel targets and therapeutic strategies for the clinical diagnosis and treatment of MH. This progress will facilitate the transition of acupuncture therapy from an empirically based practice to a mechanism-guided approach.

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