

Exploring the mechanism of acupuncture and moxibustion in the treatment of cerebral ischemia-reperfusion injury based on network pharmacology

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Abstract. Objective To explore the potential mechanism of acupuncture and moxibustion in the treatment of cerebral ischemia reperfusion injury (CIRI) using network pharmacology. Methods Firstly, the potential targets of acupuncture and moxibustion for CIRI were screened from the GEO database, and then the disease targets of CIRI were screened through data cleaning. Finally, the intersection between the disease targets of acupuncture and moxibustion for CIRI and the disease targets of CIRI were obtained, so as to obtain the key targets of acupuncture and moxibustion for CIRI. The Gene Ontology (GO) and The Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were performed on these key targets. Results A total of 18804 potential CIRI targets, 370 CIRI disease targets and 152 key targets were obtained. GO and KEGG enrichment analysis of the key targets were performed to obtain the most significantly enriched GO entries and key pathways of the targets in cellular components, molecular functions and biological processes. Conclusion Acupuncture and moxibustion may treat CIRI by regulating calcium ion transport, postsynaptic organization and circadian entrainment.

Keywords: Acupuncture, Cerebral ischemia-reperfusion injury, Network pharmacology.

1. Introduction

Stroke is the second leading cause of death worldwide, with ischemic strokes caused by vascular occlusion accounting for 85% of all strokes[1]. Currently, the prompt restoration of blood supply is the fundamental principle in the treatment of this condition. However, a series of cellular, biochemical, and metabolic consequences occur during both ischemia and reperfusion, including the generation of intracellular reactive oxygen species, intracellular calcium overload, glutamate neurotoxicity, inflammation, and apoptosis[2], which not only cause the recanalization of the occluded cerebral blood vessels but also exacerbate the pathological damage to the ischemic tissue and the nervous system, leading to the deterioration of clinical symptoms. This phenomenon is referred to as cerebral ischemia-reperfusion injury (CIRI)[3]. At present, how to reduce the infarct size, alleviate neurological deficits, and improve patient outcomes is an urgent challenge that needs to be addressed in the clinical treatment of CIRI.

Acupuncture and moxibustion is a distinctive therapy in traditional Chinese medicine, which has a variety of functions such as dredging meridians, reconciling Yin and Yang, strengthening the body and eliminating pathogenic factors. It consists of two main components: needle therapy and moxibustion. In the acupuncture method, the needle is inserted into the patient's body at a certain angle, and the acupuncture manipulations such as twisting, lifting and thrusting are used to stimulate specific acupoints in the human body. The moxibustion method involves burning, fumigating, and ironing a certain acupoint on the body surface with a moxibustion stick or herb, and using heat stimulation to unblock the meridians to prevent and treat diseases.

Currently, multiple clinical cases and experiments have demonstrated that acupuncture treatment for CIRI holds excellent prospects. Early acupuncture intervention in the treatment of CIRI can improve the neurological deficits, reduce the volume of cerebral infarction, and effectively alleviate injury symptoms in rats [4]. Electroacupuncture stimulation of Baihui, Yintang and Zusanli acupoints in



cerebral ischemia-reperfusion model rats can promote the expression of brain-derived neurotrophic factor and sigma-1 receptor, and achieve brain protection [5]. Electroacupuncture at Hegu, Chize and other acupoints can significantly alleviate the neurological impairment of CIRI mice and inhibit cell pyroptosis by down-regulating the expression levels of cysteine-aspartic acid specific protease-1 and gasdermin D N protein, which also suggests that electroacupuncture plays a protective role against CIRI [6].

Currently, although there have been reports on the treatment of CIRI with acupuncture, the research primarily focuses on single proteins and channels, lacking investigation into the mechanisms of acupuncture's multi-target and multi-channel interventions on CIRI from the perspectives of cells, mediators, and pathways. This limitation restricts the further development and application of acupuncture in treating CIRI. Network pharmacology, an emerging interdisciplinary discipline, has developed in recent years to study the complex interactions between drugs and biological systems. It emphasizes a systemic and multi-angle understanding of drug mechanisms, which offers a unique advantage for elucidating the key targets and pathways of acupuncture treatment for CIRI. Therefore, this paper analyzes the potential targets of acupuncture treatment for CIRI using network pharmacology techniques, and clarifies the potential mechanisms of treatment. It systematically explores the intervention and influence of acupuncture on the disease network, providing data support for basic research and clinical application.

2. Method

2.1. Summary of acupoint selection patterns from literature research

2.1.1. Data sources

The clinical research literatures on acupuncture and moxibustion for CIRI published from January 2010 to February 2024 were selected from China National Knowledge Infrastructure (CNKI), PubMed, VIP and Wan Fang. The search terms "cerebral ischemia-reperfusion injury" "cerebral ischemia injury" "cerebral ischemia-reperfusion" "acupuncture" "electroacupuncture" and "acupuncture" were used alone or in combination to search, and Boolean operators ("not", "and" and "OR") were used to narrow or expand the search results.

2.1.2. Inclusion Criteria

① The type of literature was randomized controlled trial (RCT); ② The sample size of literature was ≥ 30 cases, and the total effective rate was $\geq 80\%$; ③ The prescription of acupuncture and moxibustion is clear and the treatment methods are acupuncture and moxibustion, including moxibustion, electroacupuncture, acupoint injection, etc. ④ The patients were diagnosed and met the definition and clinical manifestations of CIRI.

2.1.3. Exclusion criteria

① Only the latest published article will be retained for duplicate publications; ② Experience, case or systematic reviews that are not classified as clinical trials; ③ Literature without full text or with incomplete content; ④ Using personal experience acupoints or unrecognized acupoints; ⑤ Literature sample size < 30 cases; ⑥ Literature on the treatment of CIRI using a combination of acupuncture and drugs or pure drugs; ⑦ Literature unrelated to CIRI or acupuncture and moxibustion.

2.2. Exploration of potential targets of acupuncture and moxibustion in the treatment of CIRI

In the GEO database (<https://www.ncbi.nlm.nih.gov/>), the key words of "acupuncture and moxibustion cerebral ischemia-reperfusion injury" were used to search, select human species, obtain transcriptome data of patients with CIRI treated by acupuncture and moxibustion, download its

related GSE211253 matrix and platform file, change the file extension to convert the file into Excel table, and sort out and summarize the obtained data. Extract genes with known gene types, and remove data with different trends between the model group and the treatment group by taking the average, subtraction, and product. To prevent errors caused by experimental instruments, data with average values < 100 were removed from the sham surgery group, model group, and treatment group. Subtract the average value of the sham surgery group data from the average value of the model group data and the average value of the treatment group data, and the gene that multiplies the two values by more than 0 is the callback gene after treatment. The callback genes were used T.TEST function, and the data of model group and treatment group were inputted under the assumption of two-tailed distribution and two-sample equal variance to obtain P value. Screen $|\log_2FC| > 1$ and P values < 0.05 genes as acupuncture of potential targets.

2.3. Target mining of CIRI

Utilize the T.TEST function to calculate the P-value by substituting the data of the sham operation group and the model group under the assumption of equal variances and two-tailed distribution. The genes with $|\log_2FC| > 1$ and P value < 0.05 were selected as disease-related targets, and the gene names corresponding to the targets were retrieved and de duplicated.

2.4. Key targets of acupuncture and moxibustion in the treatment of CIRI

Utilize Venny2.1 (<http://bioinfogp.cnb.csic.es/tools/venny/>) to intersect the potential target genes for acupuncture treatment of CIRI (Treat) with the target genes associated with CIRI (Disease), yielding a set of intersection genes. These genes were the key targets for the treatment of CIRI with acupuncture, amounting to 152 genes.

2.5. GO and KEGG enrichment analysis

Input the 152 intersection targets and the eligible \log_2FC values, ensuring the species was set to Homo sapiens. Utilize the SRplot platform (<http://www.bioinformatics.com.cn/>) to conduct GO and KEGG enrichment analyses. Save the enrichment results and generate a bubble plot to represent the biological processes (BP), cellular components (CC), and molecular functions (MF) in which the genes may participate. Proceed with the KEGG enrichment analysis using the same method, create a bar graph and construct a KEGG interaction network.

3. Results

3.1. The principles of acupoint selection in acupuncture treatment

3.1.1. Acupoint frequency statistics

By summarizing and analyzing the literature on the acupoint selection rules for the treatment of CIRI with acupuncture, it has been found that the clinical acupoint selection for the treatment of CIRI involve a total of 29 acupoints with a total frequency of 2130 times. Acupoints with a frequency of ≥ 50 times were designated as high-frequency acupoints. The acupoints were ranked in descending order of frequency in the acupoint prescriptions and the top 10 were retained. The results are shown in Table 1. The top 5 acupoints with the highest application frequency are Baihui (GV20) with 537 times, Neiguan (PC6) with 376 times, Dazhui (GV14) with 268 times, Zusanli (ST36) with 234 times, and Shuigou (BL67) with 154 times.

Table 1. Statistics on the Frequency of Use for High-Frequency Acupoints in the Treatment of CIRI by Acupuncture (Frequency \geq 50 Times)

Serial Number	Acupoint Name	Frequency
1	Baihui	537
2	Neiguan	376
3	Dazhui	268
4	Zusanli	234
5	Shuigou	154
6	Quchi	142
7	Hegu	81
8	Shenting	78
9	Shenshu	59
10	Sanyinjiao	55

3.1.2. Meridian Frequency Statistics

The selected acupoints for the treatment of CIRI involve a total of 10 meridians, including 8 major meridians and the Ren and Du meridians. The Du meridian has the highest frequency of use and the most selected acupoints, with 6 acupoints and a total frequency of use of 1060 times. Followed by Pericardium Meridian of Hand Jueyin, Stomach Meridian of Foot Yangming and Large Intestine Meridian of Hand Yangming. The results are shown in Table 2.

Table 2. Frequency Statistics of Meridian Selection

Serial Number	Meridian	Frequency	Number of Acupoints Utilized
1	Du meridian	1060	6
2	Pericardium Meridian of Hand Jueyin	376	1
3	Stomach Meridian of Foot Yangming	234	1
4	Large Intestine Meridian of Hand Yangming	223	2
5	Bladder Meridian of Foot Taiyang	61	2
6	Spleen Meridian of Foot Taiyin	60	2
7	Liver Meridian of Foot Jueyin	44	1
8	Ren meridian	25	3
9	Gallbladder Meridian of Foot Shaoyang	24	3
10	Lung Meridian of Hand Taiyin	9	1

3.1.3. Statistics on the Distribution of Acupoints and Specific Acupoints

The 29 acupoints used by acupuncture and moxibustion in the treatment of CIRI were mainly concentrated in the head and neck and limbs, among which the head and neck acupoints were used the most frequently (1050 times). Among the selected acupoints, the most frequently used specific acupoint category was He-sea point, followed by back-shu point and lower he-sea point. Literature analysis suggests that the combination of these acupoints can fully utilize the comprehensive effects of the acupoints on the body, effectively alleviating the symptoms of CIRI patients.

3.2. Targets of Acupuncture Treatment for CIRI

3.2.1. Potential Targets

The GEO database (<https://www.ncbi.nlm.nih.gov/>) was searched with the keyword "acupuncture cerebral ischemia reperfusion injury". A total of 18804 targets with known gene types were extracted, and the Heatmap of the data of disease group, treatment group and sham operation group of each target is shown in Figure 1.

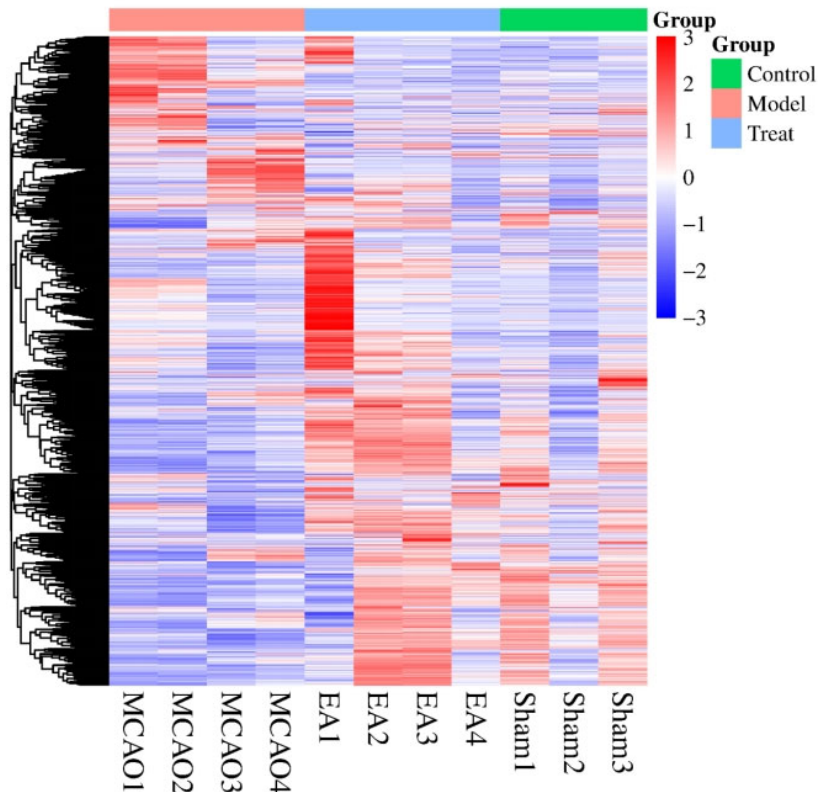


Figure 1. Heatmap of acupuncture treatment for CIRI targets in Control, Disease, and Treatment groups

(Middle Cerebral Artery Occlusion, MCAO 1-4: Disease Groups 1-4; Electroacupuncture, EA1-4: Treatment Groups 1-4; Sham Operation Group, Sham1-3: Control Groups 1-3)

Utilizing the T.TEST function, the p-value values for the callback genes were determined under the conditions of a two-tailed distribution and the assumption of equal variances between two samples. Take \log_2FC as the abscissa and $(-\log_{10}(pvalue))$ as the ordinate to obtain the volcano map of callback genes, as shown in Figure 2.

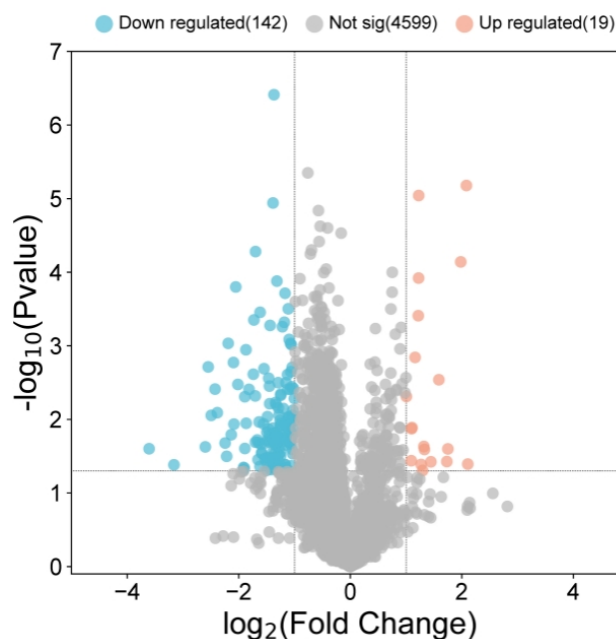


Figure 2. Volcano diagram of CIRI callback genes for acupuncture treatment

(Down regulated: significantly down-regulated genes; Not sig: genes that do not change significantly before and after treatment; Up regulated: genes that are significantly up-regulated)

3.2.2. Key Targets

Under the condition of $|\log_2FC| > 1$ and $P \text{ value} < 0.05$, the disease targets of CIRI and the potential targets of acupuncture and moxibustion treatment of CIRI were analyzed through data screening, and 152 key targets of acupuncture and moxibustion treatment of CIRI were obtained, as shown in Figure 3.

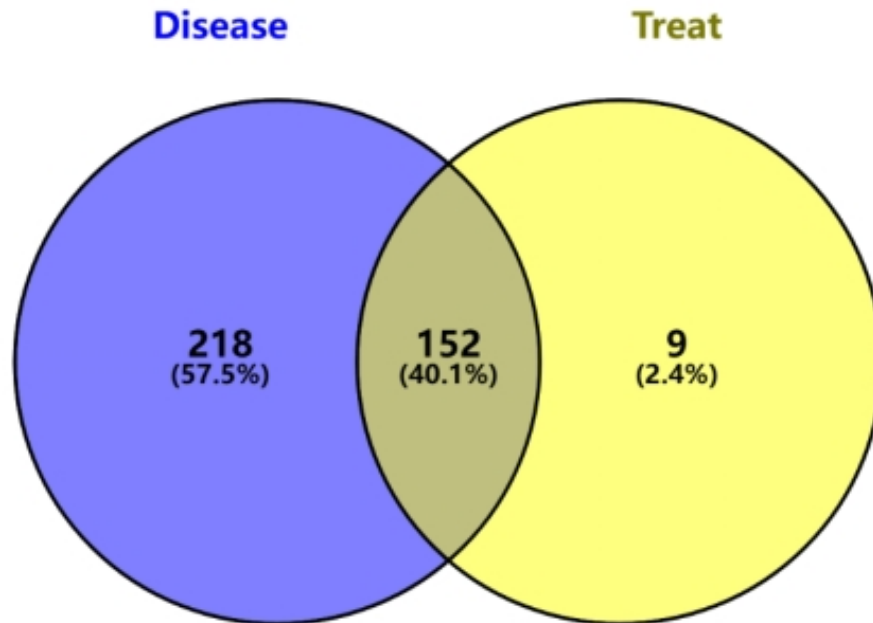


Figure 3. Venn diagram of CIRI targets and potential acupuncture treatment targets for CIRI

3.3. The potential therapeutic mechanisms of acupuncture treatment for CIRI

3.3.1. GO analysis

GO analysis of the key targets of acupuncture and moxibustion in the treatment of CIRI was carried out through the SRplot platform, and the top 10 GO entries with the most significant enrichment in BP, CC and MF of the targets could be obtained, as shown in Figure 4. Among these, the top 10 most significantly enriched GO terms of BP are: regulation of cation transmembrane transport, regulation of ion transmembrane transport, regulation of metal ion transport, postsynapse organization, protein localization to cell periphery, regulation of transmembrane transporter activity, calcium ion transport, regulation of transporter activity, regulation of postsynapse organization, and calcium ion transmembrane transport. The top 10 most significantly enriched GO terms of CC are: cation channel complex, synaptic membrane, postsynaptic membrane, ion channel complex, integral component of postsynaptic membrane, neuron to neuron synapse, postsynaptic specialization, intrinsic component of postsynaptic membrane, transmembrane transporter complex, and postsynaptic density. The top 10 most significantly enriched GO terms of MF are: channel regulator activity, structural constituent of cytoskeleton, Arp2/3 complex binding, ion channel regulator activity, actin binding, sodium channel regulator activity, Rho GTPase binding, GTPase activator activity, nucleoside-triphosphatase regulator activity, and phospholipase binding.

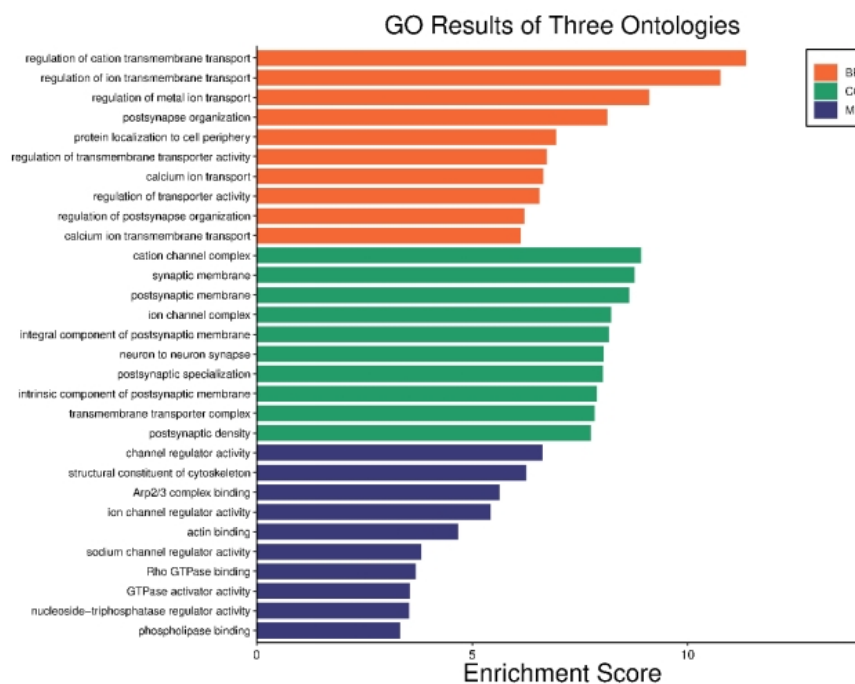


Figure 4. Top 10 most significantly enriched GO terms of BP,CC and MF in the GO analysis of key targets for acupuncture treatment of CIRI

3.3.2. KEGG enrichment analysis

KEGG enrichment was performed on the key targets of CIRI treated with acupuncture and moxibustion, and the top 10 signaling pathways were selected according to the P value from small to large to draw the bubble diagram, as shown in Figure 5. The ordinate represents the name of the pathway, the number of enriched genes in the pathway increases gradually from small to large, and the color of the bubble from blue to red indicates the degree of enrichment is more and more significant, which means that the pathway is more correlated with the disease and may be a key pathway. The results showed that the core pathways included Aldosterone synthesis and secretion, Adrenergic signaling in cardiomyocytes, Long-term potentiation, and Bacterial invasion of epithelial cells, Calcium signaling pathway, etc.

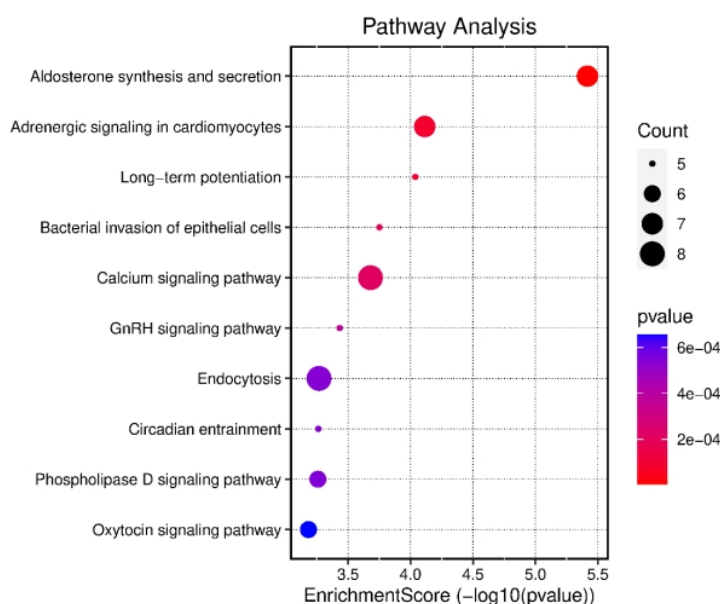


Figure 5. Top 10 most significantly enriched KEGG pathways identified by KEGG enrichment analysis

4. Discussion

CIRI belongs to the category of "stroke" in the theory of traditional Chinese medicine [7]. Qi and blood deficiency or Yin deficiency of liver and kidney are the causes of the disease, and wind, fire, phlegm and blood stasis are the symptoms of the disease [8]. Sudden dizziness, hemiplegia, and mouth and eyes deviation are the main manifestations. The treatment follows the principle of "treating the symptoms and the root cause according to their urgency". In acute stages, the focus is on eliminating the pathogenic factors. During the recovery and sequelae phases, the treatment involves supporting the body's vital energy and eliminating pathogenic factors, while also considering both the symptoms and the root cause.

The analysis of this study reveals that the meridians most frequently used and with the highest number of selected acupoints for the treatment of CIRI are the Du Meridian. The Du Meridian, one of the eight extraordinary channels in the human body, governs all the Yang channels and has a regulatory function on the Qi and blood of these channels. The six Yang channels converge at the Dazhui acupoint, hence it is referred to as the "Sea of Yang." The Nanjing, chapter 28, records, "The Du Meridian originates from the lower extreme point and runs through the spine, ascending to the Fengfu acupoint and entering the brain." Additionally, the Ling Shu, chapter 12, states, "A branch of the Du Meridian is called Changqiang, which wraps around the spine and ascends to the neck, dispersing upwards towards the head." Studies indicate that the stimulation of acupoints such as Dazhui, Baihui, and Shuigou on the Du Meridian can promote the repair of neurons, induce angiogenesis, and thereby alleviate CIRI to some extent [9]. It is evident that the Du Meridian is not only closely related to the brain structurally, but also plays a significant role in the normal functioning of the brain.

In this study, 161 targets of acupuncture and moxibustion for CIRI were mapped to 370 CIRI-related target genes, and the key targets of acupuncture and moxibustion for CIRI were obtained. From GO and KEGG enrichment analysis, it was found that these core targets were mainly concentrated in cation channel complex, calcium ion transport, postsynaptic density and other cellular components and pathophysiological processes, while the pathways primarily involved include Long-term potentiation and Circadian entrainment.

Calcium ion transport plays a crucial role in mediating CIRI. Studies have demonstrated that CIRI activates the transient receptor potential melastain 2 (TRPM2) channel, which is involved in the disruption of the blood-brain barrier during the CIRI process [10]. TRPM2 is a tetrameric non-selective cation channel that mediates calcium influx and regulates the injury process following cerebral ischemia and reperfusion [11]. Experimental data from LONG M et al. [12] show that electroacupuncture preconditioning significantly reduces infarct volume in MCAO rats by increasing the levels of the anti-apoptotic protein Bcl-2, inhibiting the transcriptional activity of NF- κ B (p65), and reducing TRPV1 expression, given that the Bcl-2 family may inhibit apoptosis by suppressing calcium transmembrane flux [13]. Moreover, studies have shown that TRPV1 channel is a calcium channel expressed in the central nervous system and can participate in the apoptosis process by regulating calcium ion flow, suggesting that the down-regulation of TRPV1 expression in neurons induced by electroacupuncture preconditioning can protect MCAO rats from CIRI by inhibiting the NF- κ B pathway and playing an anti-apoptotic role [14].

CIRI can induce structural plasticity changes in neurons, which are primarily manifested as alterations in the neuronal structure itself and in synaptic structures [15]. The postsynaptic density (PSD) is a specialized structure on the intracellular side of the chemical synaptic postsynaptic membrane, serving as an essential foundation for neural information transmission. It is a significant indicator of synaptic plasticity changes in the brain after CIRI. When CIRI occurs, damage-induced information activates the plasticity of the damaged neurons and their corresponding synapses, leading to compensatory formation of new synapses and neural circuits, causing PSD changes. NIE Huiang [16] et al. have experimentally confirmed that electroacupuncture stimulation at the Baihui acupoint in MCAO model rats can upregulate the expression of PSD proteins after ischemia, promoting synaptic information transmission and neural remodeling after injury. Additional studies have found that the

PSD thickness in the hippocampal CA1 region of rat models of cerebral ischemia and reperfusion is significantly reduced, the synaptic gap width is significantly increased, and spatial learning and memory function is impaired. Electroacupuncture can reverse these phenomena [17], suggesting that electroacupuncture can improve synaptic plasticity in the hippocampal neurons of CIRI rats by enhancing PSD thickness and reducing the width of the synaptic gap, thereby mitigating the degree of brain injury.

CIRI is closely related to the circadian rhythm. The circadian rhythm is an internal time-regulating mechanism in organisms that influences a variety of physiological and pathological processes. The study showed that there were significant differences in the symptoms of nerve injury and the degree of brain tissue lesions in the rat CIRI model prepared at different time points. After 24 h of modeling, the rats in each group had obvious symptoms of nerve injury, but the symptoms of nerve injury in the 18:00 and 24:00 groups were lighter than those in the 6:00 and 12:00 groups, while the symptoms of nerve injury in the 24:00 group were significantly lighter than those in the 6:00 group. It shows that circadian rhythm has a significant effect on CIRI in rats [18].

5. Summary

Acupuncture and moxibustion in the treatment of CIRI is a complex mechanism involving multi-targets, multi-pathways, which encompasses factors such as ion transport, synaptic structure changes and other factors. This article first summarizes the meridian and point selection rules for acupuncture treatment of CIRI through literature review. By mining the GEO database, it obtains known targets for acupuncture treatment of CIRI and, through data screening and processing, identifies potential targets. Subsequently, these potential therapeutic targets are intersected with disease targets for CIRI to obtain key targets for acupuncture treatment. Through GO and KEGG enrichment analysis, it elucidates that acupuncture and moxibustion may treat CIRI by regulating mechanisms such as calcium ion transport, postsynaptic tissue, and circadian entrainment. This provides a reference for further research validation.

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