Review Article

Study on the Mechanism of Chinese Medicine in Treating Cervical Spondylosis

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Increasing progress has been made in the research and treatment of cervical spondylosis. Traditional Chinese medicine has been shown to be effective as a complementary alternative therapy for the treatment of cervical spondylosis. However, the intervention mechanism of traditional Chinese medicine in the treatment of cervical spondylosis is still unclear. The aim of this review is to sort out the current knowledge on the mechanisms of traditional Chinese medicine for the treatment of cervical spondylosis, including acupuncture, needle-knife, manipulation, herbal treatments, and commonly used animal models of cervical spondylosis. Finally, the review will discuss the dilemmas faced by traditional Chinese medicine in the treatment of cervical spondylosis, as well as the shortcomings and future directions of traditional Chinese medicine in the treatment of cervical spondylosis.

Key words: Cervical spondylosis, Chinese medicine, non-steroidal anti-inflammatory drugs, apoptosis, protein kinase B

Cervical spondylosis is a common degenerative spinal condition that can cause postural adjustment difficulties and balance perception deficits[1]. According to modern medical research, cervical spondylosis is closely linked to Intervertebral Disc Degeneration (IDD)[2]. IDD is a common age-related phenomenon that typically begins after the age of 45 and progresses continuously. The incidence of cervical spondylosis is gradually increasing due to changes in modern lifestyles and work patterns, affecting more and more young people[3]. For instance, cervical spondylosis affects a significant proportion of high school students, with an incidence rate of up to 48.9 %. This condition can cause symptoms such as pain in the neck, shoulders, and occipital region, as well as activity restrictions, which can significantly reduce the patient's quality of life[4,5]. Early intervention and treatment of cervical spondylosis is crucial in slowing down the course of the disease and improving the quality of life of patients.

Currently, pain and other related symptoms caused by cervical spondylosis are often managed by systemic and topical application of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)[6]. However, long-term use of such drugs may lead to side effects such as dyspepsia, gastritis, gastroduodenal ulcers, and bleeding; therefore, there is an urgent need to develop a more convenient and effective treatment strategy with fewer side effects. Traditional Chinese Medicine (TCM) therapies such as acupuncture, herbal medicine and tuina have been used clinically for >1000 y and are considered effective alternatives for the treatment of a wide range of diseases. The mechanisms of TCM in the treatment of cervical spondylosis are diverse, and although the specific mechanisms of action of different TCM therapies still need to be further clarified, TCM has shown positive results in the treatment of cervical spondylosis in recent years. The aim of this article is to review the mechanism of action of TCM in the treatment of cervical spondylosis, with a view to providing new insights into the treatment and research of this disease.

ANIMAL RESEARCH

Currently, our understanding of the pathogenesis of

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cervical whiplash is limited. Treatment guidelines are currently limited to symptomatic relief due to legal, ethical, and moral constraints that make it difficult to use human tissue for scientific research. Animal models are ethically used in basic research and play an important role in bridging basic experiments with the clinic. Two key animal models for studying cervical disc degeneration are the rat surgical model and the rabbit non-invasive model. Each model has unique advantages and applicable scenarios. The rat surgical model directly simulates cervical degeneration through surgical means, which is highly simulative and controllable. It is particularly suitable for in-depth investigation of the pathological mechanisms of cervical degeneration and evaluation of therapeutic approaches. This model enables precise control over the location and extent of intervention, facilitating detailed pathological and biomechanical assessments. In contrast, the rabbit non-invasive model induces cervical degeneration physically and has the advantage of being simple and non-invasive, making it suitable for large-scale implementation and replication. This model enables the simulation of various stages of cervical degeneration and is appropriate for studying early pathological changes and evaluating non-invasive therapeutic approaches. In summary, the rat surgical model is suitable for in-depth studies of pathological mechanisms and treatment methods, while the rabbit non-invasive model is more appropriate for early studies of cervical spine degeneration and treatment evaluation. The appropriate selection and application of these two models is essential for a comprehensive understanding of the pathological process and treatment strategies for cervical disc degeneration. Table 1[7-22] summarizes the animal studies on the treatment of cervical spondylosis by TCM.

TABLE 1: THERAPEUTIC MECHANISM OF CHINESE MEDICINE

Animal model	Animals	Methodologies	Intervene	Machine	Bibliographic reference
Non-invasive model for low head position	New Zealand rabbit	The rabbits were positioned in a rabbit fixation box with their necks in a low head flexion position of 45°. Pathological changes in the neck structure were induced after cyclic modeling	Electro-acupuncture combined with gua sha method	Inhibition of the NF-κB/IkB/IKKß pathway suppresses the expression of inflammatory factors, including IL-1ß, IL-6, and TNF-α	[7]
Non-invasive model for low head position	New Zealand rabbit	The rabbits were positioned in a rabbit fixation box with their necks in a low head flexion position of 45°. Pathological changes in the neck structure were induced after cyclic modeling	Needles	The expression of Wnt3α and ß-catenin genes and proteins activates the Wnt/ß-catenin signaling pathway and increases My-HC1 synthesis	[8]
Non-invasive model for low head position	New Zealand rabbit	The rabbits were positioned in a rabbit fixation box with their necks in a low head flexion position of 45°. Pathological changes in the neck structure were induced after cyclic modeling	Herbal	Inhibition of NF-κB signaling pathway to release inflammatory factors such as IL-1, IL-6 and TNF-α	[9]
Invasive neck surgery model	SD rats	A surgical model of the neck was created in rats and anaesthetized to remove specific muscles and ligaments, resulting in pathological changes in the neck structures	Massage	Attenuating the inflammatory response and apoptosis of intervertebral disc cells in rats with cervical spondylosis	[10]
Non-invasive model for low head position	New Zealand rabbit	The rabbits were positioned in a rabbit fixation box with their necks in a low head flexion position of 45°. Pathological changes in the neck structure were induced after cyclic modeling	Needles	Downregulation of Notch1/DLL1 expression levels in muscle	[11]

Invasive neck surgery model	SD rats	A surgical model of the neck was created in rats and anaesthetized to remove specific muscles and ligaments, resulting in pathological changes in the neck structures	Electro-acupuncture	Suppression of TNF-α and IL-6 expression in intervertebral disc chondrocytes by inhibiting the MCP-1/CCR2 signaling pathway	[12]
Non-invasive model for low head position	New Zealand rabbit	The rabbits were positioned in a rabbit fixation box with their necks in a low head flexion position of 45°. Pathological changes in the neck structure were induced after cyclic modeling	Needles	Reduction of autophagy factor Beclin-1, PTEN gene and protein expression levels in cervical muscle of rabbits with cervical spondylosis	[13]
Invasive neck surgery model	SD rats	A surgical model of the neck was created in rats and anaesthetized to remove specific muscles and ligaments, resulting in pathological changes in the neck structures	Herbal	Regulation of MKK3/6-p38MAPK signaling pathway and down-regulation of IL-6 and IL-8 content in chondrocytes within intervertebral discs	[14]
Non-invasive model for low head position	New Zealand rabbit	The rabbits were positioned in a rabbit fixation box with their necks in a low head flexion position of 45°. Pathological changes in the neck structure were induced after cyclic modeling	Herbal	Inflammatory factors such as TNF-α, IL-1, IL-6 and other inflammatory factors released from the NF-κB signaling pathway are inhibited by altering the expression of miR-146a in the tissues of the posterior cervical muscle of model rabbits	[15]
Invasive neck surgery model	New Zealand rabbit	The rabbits were positioned in a rabbit fixation box with their necks in a low head flexion position of 45°. Pathological changes in the neck structure were induced after cyclic modeling	Needles	Regulation of autophagy, apoptosis homeostasis in posterior cervical extensor muscle cells *via* PI3K/Akt signaling pathway	[16]
Non-invasive model for low head position	New Zealand rabbit	The rabbits were positioned in a rabbit fixation box with their necks in a low head flexion position of 45°. Pathological changes in the neck structure were induced after cyclic modeling	Needles	Regulation of cartilage endplate integrin ß1, p-FAK mRNA and protein expression, slowing down disc degeneration and re-establishing the mechanical balance of the cervical spine	[17]
Invasive neck surgery model	SD rats	A surgical model of the neck was created in rats and anaesthetized to remove specific muscles and ligaments, resulting in pathological changes in the neck structures	Herbal	Activation of PPAR-γ pathway, inhibition of NF-κB signaling pathway, reduction of downstream inflammatory factor release	[18]
Invasive neck surgery model	SD rats	A surgical model of the neck was created in rats and anaesthetized to remove specific muscles and ligaments, resulting in pathological changes in the neck structures	Electro-acupuncture	Inhibition of apoptotic cells in the intervertebral disc and increase in the expression level of Axin and ß-catenin proteins	[19]

Invasive neck surgery model	SD rats	A surgical model of the neck was created in rats and anaesthetized to remove specific muscles and ligaments, resulting in pathological changes in the neck structures	Electro-acupuncture	Up-regulation of Wnt1 and GSK-3 proteins inhibits apoptosis of intervertebral disc fibrous annulus cells in rats with cervical spondylosis model	[20]
Invasive neck surgery model	SD rats	A surgical model of the neck was created in rats and anaesthetized to remove specific muscles and ligaments, resulting in pathological changes in the neck structures	Electro-acupuncture	Activation of PI3K/Akt pathway and inhibition of chondrocyte apoptosis in intervertebral discs	[21]
Invasive neck surgery model	SD rats	A surgical model of the neck was created in rats and anaesthetized to remove specific muscles and ligaments, resulting in pathological changes in the neck structures	Herbal	Inhibition of inflammatory response and ECM degeneration through the MAPK pathway in a rat model of degenerative cervical intervertebral discs	[22]

Note: (DLL1): Delta-like protein 1

Due to the complex pathogenesis of cervical spondylosis and subjective symptoms such as restricted movement, current animal models are insufficient to fully describe the complete mechanism of this condition. In the future, it is important to consider not only the simulation and controllability of the model but also the complexity of the mechanism itself. This will allow us to fully incorporate the advantages of existing models and reduce their disadvantages. By doing so, we can establish a more comprehensive model that accurately simulates the multiple pathogenic mechanisms of cervical spondylosis. This will help us explore the therapeutic mechanism of Chinese medicine in a more in-depth manner.

MECHANISMS OF CHINESE MEDICINE IN THE TREATMENT OF CERVICAL SPONDYLOSIS

IDD is a complex process involving multiple factors such as changes in Extracellular Matrix (ECM) content, cellular aging and apoptosis, and cytokines. During this process, we observe a series of pathological changes such as increased degradation of the ECM and decreased synthesis of the matrix, decreased number of active cells, destruction of the disc's tissue structure, and functional damage[23]. In response to these key aspects, Chinese medicine has made significant progress in the treatment of cervical spondylosis in recent years, which can effectively relieve symptoms and restore the physiological function of neck structures. In view of the available research evidence, this article reviews the mechanisms of TCM in the treatment of cervical spondylosis as follows:

Regulation of inflammatory factor secretion:

The pathological progression of cervical spondylosis can be driven by a cycle of tissue damage and repair triggered by chronic inflammation, which in turn leads to tissue structural and functional dysfunction. In the process, a vicious cycle between degenerative disc changes and neck muscle imbalances accelerates disease progression. Abnormal activity of key inflammatory factors such as Tumor Necrosis Factor-Alpha (TNF-α), Interleukin-1Beta (IL-1β), Prostaglandin E2 (PGE2), and IL-6, etc., within the intervertebral discs and muscles, not only exacerbates the local inflammatory response, but also leads to the development of the disease. That not only exacerbate the local inflammatory response but also drive the disease process[24]. Therefore, the treatment of cervical spondylosis needs to focus on the regulation of these inflammatory factors to achieve effective treatment by alleviating the vicious cycle of disc degeneration and muscle imbalance.

IL-6 is a cytokine that has various biological functions and plays a crucial role in inflammatory responses and immune regulation[25]. In the development of cervical spondylosis, IL-6 exacerbates the inflammatory state of the intervertebral discs and neck muscles through multiple mechanisms. Firstly, IL-6 promotes the activation and proliferation of inflammatory cells, leading to their accumulation in the damaged area. Subsequently, activated inflammatory cells release additional inflammatory mediators, which worsen the local inflammatory response. Furthermore, IL-6 affects the expression

and synthesis of Matrix Metalloproteinases (MMPs), a group of enzymes that can degrade the ECM. Over-activation of MMPs leads to the destruction of the ECM, which exacerbates the structural damage to the discs and neck muscles. Destruction exacerbates the inflammatory response and impairs tissue function and repair[26]. Studies indicate that Wu Fu Drink, a TCM, may inhibit IL-6 expression and reduce MMP-3 expression, slowing down matrix degradation in intervertebral discs. According to[27], this action is expected to slow down the degeneration of intervertebral discs, thereby slowing down the process of IDD. Research has found that paralytic granules, a TCM item, can effectively alleviate inflammatory injury in the posterior cervical muscle of rats. The mechanism of action may be related to the activation of the Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) pathway and inhibition of the Nuclear Factor Kappa B (NF-κB) pathway, which in turn reduces the release of the inflammatory factor IL-6[18]. This finding provides a new therapeutic target for the treatment of damage to the power balance system in whiplash.

IL-1β, as a key member of the IL-1 family, plays an integral role in a variety of physiological and pathological responses in the body. Especially in skeletal muscle tissues, IL-1β is considered to be one of the most prominent inflammatory mediators[28]. By stimulating the release of other cytokines, it not only promotes and maintains the continuation of the inflammatory response, but also exacerbates muscle tissue damage in the context of chronic disease. In studies of degenerative disc disease, IL-1β stimulates the production of several pro-inflammatory mediators (e.g. cytokines, chemokines, and MMPs), as well as inducing cellular senescence and accelerating ECM degradation[29], a finding that positions it as a key mediator in the development of IDD. Further studies have shown a strong association between increased IL-1β and the onset of neck disease symptoms, emphasizing its central role in this disease mechanism. It has been shown that chiropractic manipulation reduces the inflammatory response of intervertebral disc cells and improves the progression of IDD in rats with cervical spondylosis[10], and its mechanism of action may be related to the inhibition of the IκB Kinase (IKK)/ NF-κB pathway. Studies have shown that in a rabbit model of cervical spondylosis[15], different doses of *Paeonia lactiflora* and *Glycyrrhiza glabra* soup can effectively inhibit the NF-κB signaling pathway and reduce the expression of IL-1β inflammatory factors and microRNAs, which in turn alleviates the inflammatory neck injury caused by cervical spondylosis.

TNF-α is a crucial inflammatory factor in disc degeneration, with significantly higher levels in degenerated discs compared to normal discs[30]. It promotes degeneration by inducing the production and release of other inflammatory factors, increasing endothelial cell permeability, activating MMPs activity and gene expression, and inhibiting collagen and proteoglycan synthesis. Furthermore, TNF-α is strongly associated with muscle damage and pain levels. It can also impede the expression and activity of growth hormone and insulin-like growth factor, which hinders myoblast genesis and results in abnormal muscle damage[31]. The given effects demonstrate the significant role of TNF-α in IDD and muscle injury, indicating its potential as a therapeutic target. Chen *et al.*[32] applied tretinoin to a rat model of IDD and observed a reduction in the expression of TNF-α and MMP, which resulted in a slower degeneration of intervertebral discs in rats. According to[7], electroacupuncture combined with gua sha therapy may improve the pathological injury of neck muscles by down-regulating the expression of factors related to the NF-kB/IkB/IKKβ signaling pathway, which in turn reduces the expression of TNF-α inflammatory factors.

PGE2 plays a crucial role in the inflammatory process. It regulates pain sensation and inflammatory response, and also directly affects the inflammatory state of intervertebral discs and muscles[33]. PGE2 is released in inflammatory tissues during disc degeneration. It promotes the degeneration process and increases tissue sensitivity to pain-causing factors, contributing to the pain symptoms of cervical spondylosis[34]. The mechanism of action indicates that PGE2 has a dual function in regulating the inflammatory state of intervertebral discs and muscles, as well as in the formation of pain sensation in cervical spondylosis. Therefore, it is an important target for clinical diagnosis and treatment of this condition[35]. According to a study[36], needle knife intervention can significantly reduce the inflammatory expression of PGE2 in the muscle, which in turn improves neck muscle imbalance and slows down the process of disc degeneration. Additionally, the intervention can also reduce the expression level of PGE2 within the

intervertebral disc, effectively alleviating symptoms associated with the neck. This result indicates that the needle knife intervention plays a significant role in regulating the inflammatory state of the neck and relieving the symptoms of cervical spondylosis.

In summary, it is evident that the administration of TCM and other treatments such as chiropractic and needle-knife interventions can slow down the progression of cervical spondylosis by modulating inflammatory factors and reducing disc degeneration and neck muscle damage. These findings suggest new strategies for the treatment of cervical spondylosis and highlight the significance of targeting inflammation modulation.

Inhibition of apoptosis:

Biomechanical factors, particularly long-term unbalanced flexion stress, play a crucial role in the degeneration of cervical intervertebral discs by inhibiting apoptosis. Stress can have negative effects on the intervertebral disc, including disturbances to stress distribution, internal pressure, and nutrient metabolism. Additionally, stress can cause injuries to the cervical muscle groups, such as spasm and ischemia, which can disrupt the dynamic balance of the neck. These injuries can aggravate the degeneration of the intervertebral discs and accelerate the development of cervical spondylosis[37].

It has been found by scholars that apoptosis of cervical muscle cells is a significant factor in the development of cervical spondylosis. The cervical muscles, intervertebral discs, and cervical segmental spinal cord neuronal cells are all subject to increased apoptosis, which is consistent with the degree of lesion strain[38]. Chondrocyte apoptosis in excess reduces the number of activated chondrocytes in the intervertebral disc. This affects their ability to synthesize or degrade ECM, leading to metabolite accumulation and insufficient nutrient supply. Consequently, IDD is triggered[39]. This passage describes how biomechanical and cell biological changes interact to exacerbate disc degeneration and promote the development of cervical spondylosis through apoptosis of cervical myocytes and intervertebral disc cells. Research has demonstrated that needle knife treatment can regulate the balance of apoptosis in posterior cervical extensor muscle cells through the Phosphatidylinositol-3-Kinase (PI3K)/Protein Kinase B (Akt) signaling pathway[16], which may be a potential target for needle knife repair of strained cervical muscles caused by cervical spondylosis. Research has demonstrated that needle knife intervention can effectively decrease the apoptosis rate of cervical nucleus pulposus cells in rabbits with cervical spondylosis[40], thereby aiding in the alleviation of IDD.

Therefore, it can be concluded that therapeutic means in TCM can effectively inhibit abnormal cell apoptosis in cervical muscles and intervertebral discs. This has a significant effect on repairing damaged cervical muscles and slowing down the pathological progression of cervical spondylosis.

Regulation of autophagy:

Autophagy is a mechanism present in all eukaryotic cells. Its central role is to synthesize essential parts by degrading intracellular components and recycling macromolecules during cell starvation[41]. Autophagy has gained much attention in the study of IDD, particularly under low-nutrient, low-pH, and low-oxygen conditions, where it is considered a key cell survival mechanism[42]. Although the role of autophagy in IDD is still debated, recent studies suggest that activating autophagy can have a protective effect[43]. This can reduce apoptosis, decrease ECM depletion, and inhibit inflammation and calcification of cartilage endplates[44]. In addition, autophagy and apoptosis occur simultaneously during skeletal muscle injury and repair, demonstrating the presence and importance of autophagy in various degenerative diseases and in the metabolic breakdown and remodeling of skeletal muscle. Autophagy also plays a role in the remodeling of skeletal muscle cells by participating in the process of cellular dedifferentiation, neo-division, and proliferation. This highlights the importance of autophagy in skeletal muscle repair[45].

A study conducted on a rabbit model of cervical spondylosis found that excessive activation of autophagy in cervical myocytes can cause damage to the organism[13]. However, the needle-knife treatment prevented autophagy-induced cell death by reducing the expression levels of autophagy-related proteins beclin-1 and PTEN. This promoted muscle repair and slowed down the pathological process of cervical spondylosis. Furthermore, the application of herbal hot compress treatment can improve the autophagy function of intervertebral disc cells and decrease cell apoptosis by upregulating the expression of beclin-1, Light Chain 3 (LC3), and B-Cell Lymphoma 2 (Bcl-2) and messenger Ribonucleic Acid (mRNA). This, in turn, mitigates disc degeneration and alleviates

symptoms such as discomfort in the cervical spine. The study shows potential for further research into the prevention and treatment of cervical spondylosis[46].

Comprehensive analyses indicate that autophagy plays a crucial role in the development and therapeutic strategy of IDD. TCM therapeutic approaches effectively activate the autophagy pathway, promoting the repair of cervical muscles and demonstrating a significant role in preventing abnormal disc degeneration. However, the precise regulation of autophagy flux in cervical spondylosis remains an important focus for future research. In-depth exploration of the detailed changes in the autophagy process may aid in better understanding its mechanism of action in treating cervical spondylosis.

Improvement of cervical muscle fibrosis:

Long-term strain and degenerative changes in the neck can lead to the development of chronic inflammation. This, in turn, causes fibrosis of the neck muscles, which is the pathological basis for the mechanical imbalance in the neck[47]. After injury, fibroblasts and other stromal cells recruit myofibrils, the basic unit of skeletal muscle structure, to the site of injury and begin to deposit collagen (type I, etc.)[48]. Although skeletal muscle has a high regenerative capacity, excessive collagen deposition can lead to muscle fibrosis, which can impair skeletal muscle's ability to regenerate. The process involves the conversion of fibrotic effector cells, including resident and circulating fibrotic progenitor cells, into myofibroblasts, which is promoted by Transforming Growth Factor-Beta (TGF-β) signaling. TGF-β signaling becomes particularly active 3 d-5 d after injury and may persist for days to weeks as multiple cell populations, including fibrotic effector cells, are recruited to the site of injury[49]. Therefore, inhibiting TGF-β signaling could delay the fibrotic response and promote the proliferation and recovery of functional myogenic fibers. This provides a potential strategy for treating mechanical homeostasis disorders in the neck.

Previous research has demonstrated that needle knife treatment can effectively down-regulate the expression of type I collagen in neck muscle tissues, thereby improving neck musculature fibrosis[50]. Modulating the Notch2/TGF-β1 signaling pathway can achieve this effect. Needle knife therapy not only directly affects the degree of fibrosis in the muscle tissue but also promotes the restoration of neck muscle health and function through specific molecular mechanisms, such as the regulation of the Notch2/TGF-β1 signaling pathway. This provides a scientific basis for the role of needle knife therapy in improving fibrosis in the neck muscle groups.

Comprehensive analyses suggest that prolonged neck strain may result in muscle fibrosis, which can affect the mechanical balance of the neck. TCM therapies, such as needle knife therapy, have been demonstrated to be effective in improving fibrosis in the neck muscle groups, thereby promoting muscle health and recovery. This presents a novel approach to treating neck mechanical balance disorders. However, further research and exploration are required to fully understand the mechanisms of action of TCM therapies and their potential applications.

CONCLUSION

In this paper, we have reviewed the potential mechanisms of Chinese medicine in the treatment of cervical spondylosis and provided an overview of current research progress. Considering the specific pathological characteristics of cervical spondylosis, and based on the hypothesis of an imbalance of dynamic and static forces in the neck, it is believed that the key mechanisms of TCM in treating cervical spondylosis may include improving autophagy and apoptosis, alleviating inflammation, and repairing cervical muscle fibrosis. With its unique therapeutic concepts, easy-to-use methods, low cost, and minimal side effects, TCM has shown great potential as an effective treatment for cervical spondylosis.

However, the use of TCM to treat cervical spondylosis faces challenges due to its complex mechanism of action, which involves multiple targets and pathways. The specific mechanism of TCM in treating cervical spondylosis is not yet fully understood. Therefore, there is an urgent need for an in-depth investigation into the mechanism of action of TCM in treating cervical spondylosis. This investigation should involve interdisciplinary collaboration, the use of large sample sizes, and multi-omics techniques. Such in-depth studies will help to improve the scientific basis of TCM in the treatment of cervical spondylosis and further promote its application and development in clinical practice.

Conflict of interests:

The authors declared no conflict of interests.

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