

# Study on the Mechanism of Acupuncture and Moxibustion Regulating the Central Nervous System of Osteoarthritis

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**Abstract:** OA is considered a non lethal chronic progressive disease with a particularly complex pathogenesis. Current treatment methods mainly aim to delay the progression of the disease, alleviate pain, and improve bone and joint functional activity. Arthritis pain is the most common cause of OA, which is not only related to pathological changes of bone and joint, but also involves complex neural mechanisms. Clarifying this point has guiding significance for the treatment of osteoarthritis. This article will describe the central nervous mechanism of acupuncture and moxibustion regulating chronic pain in OA.

**Keywords:** Osteoarthritis, Central nervous system mechanisms, Acupuncture and moxibustion analgesia.

## 1. Introduction

Osteoarthritis (OA) occurs in synovial joints, accompanied by bone hyperplasia at the joint edge. It is a bone and joint disease caused by the destruction or loss of articular cartilage, and is one of the common causes of pain and disability in elderly people [1], and it presents a series of special pathological and radiological changes. The main clinical manifestations include joint pain and tenderness, joint stiffness, swelling, limited mobility, and the resulting serious functional impairment. This not only affects the patient's life and work, but also increases psychological burden, affects the patient's emotions, and worsens the development of the disease.

Pain is a special sensation caused by a certain impact on the nociceptor, which is a prominent feature of osteoarthritis and one of the most typical manifestations of osteoarthritis. Joint pain is often the primary issue for patients seeking medical treatment [2], but currently, the clinical diagnosis has not achieved ideal therapeutic effects. The pathogenesis of osteoarthritis is complex, and there is currently no best treatment method to completely curb its progression. Therefore, reducing pain and psychological pressure on patients is the main task of treating osteoarthritis. Pain is the first major indication for acupuncture and moxibustion treatment. "GERAC", "acupuncture and moxibustion in routine nursing research" (ARC) and "acupuncture and moxibustion randomized trial" (ART) show that acupuncture and moxibustion and pseudo acupuncture and moxibustion or minimally invasive acupuncture and moxibustion are equally effective in alleviating chronic pain symptoms [3,4], the treatment of osteoarthritis is also effective. Therefore, the use of acupuncture and moxibustion analgesia is a necessary step in the development of modern medicine.

## 2. Central Nervous System Mechanism

### 2.1 Central Conduction

OA pain is not limited to peripheral pain, but also involves the central nervous system (CNS), which involves the response and morphological changes of the brain and spinal cord to nociceptive stimuli. The generation of pain in OA patients is related to the functional or structural imbalance between the upregulation and downregulation of pain sensation [5,6], which mainly occurs in the spinal cord and brain. The main afferent nerve axons that transmit pain signals are myelinated A delta fibers and unmyelinated C fibers. The nerve cell bodies are located in the dorsal root ganglia (DRG) of the spinal cord, and the primary afferent nerves transmit to or from synaptic neurons. The first synaptic transmission that occurs here transmits pain signals to the hypothalamus, thalamus, brainstem, amygdala, and higher-level somatosensory cortical centers, thereby forming pain perception and recognition. Transmitting signals to the descending nerve fibers of the spinal cord and hypothalamus helps regulate the transmission of pain. At the level above the spinal cord, researchers have used neuroimaging techniques to find that the brain functional structure of KOA patients also undergoes abnormal remodeling processing. For example, studies have shown that the local blood flow of the cortex involved in pain sensation, emotion, cognition, and pain regulation dimensions in KOA patients increases, involving brain regions such as the somatosensory cortex, cingulate gyrus, insula, hippocampus, medial prefrontal lobe, and superior frontal gyrus.

The ascending pathways of pain signals from different parts of the body in the spinal cord can be divided into pain sensation pathways in the trunk and limbs, pain sensation pathways in the head and face, and visceral pain sensation pathways. Pain transmission pathways in the trunk and limbs: spinal ganglia spinal dorsal horn connecting neurons dorsal thalamus; Head and facial pain pathway: trigeminal ganglion - trigeminal sensory nucleus group - dorsal thalamus.

### 2.2 Central Sensitization

Central sensitization refers to the amplification of neural signals within the central nervous system (CNS), causing a hypersensitive response to pain. This is due to the sustained increase in excitability and protrusion effects of neurons in the central injury pathway triggered by damaging receptor inputs [7]. Central sensitization includes both spinal and supraspinal levels, mainly in the following aspects: 1. Secondary neurons exhibit high sensitivity to incoming impulses in a state of excitation and increased synaptic efficiency; 2. The suppression effect of the downward correction system has weakened; 3. Brain sensory information processing of plasticity changes. At present, peripheral sensitization, especially central sensitization, is considered as two potential mechanisms of OA pain [8-10]. Same as other chronic musculoskeletal pain disorders [5,7]. Research has shown that central sensitization plays an important role in the generation and maintenance of pain, and the sensitization of neurons in the dorsal horn of the spinal cord mainly occurs in the modulation of pain. The spinal dorsal horn, as a key area in the spinal cord that transmits pain information, is the first stop for pain information transmission and modulation, and also a necessary pathway for its transmission to the central nervous system. In spinal sensitization, pain information is transmitted to the dorsal horn of the spinal cord and processed by neurons before being transmitted to the central sensory pathway, causing pain hypersensitivity and sustained increase. At the same time, neurons in the spinal dorsal horn also exhibit abnormal enhancement, leading to increased sensitivity to pain stimuli and excessive neuronal responses. Clinical studies have found that pain in patients with advanced osteoarthritis is more characterized by spinal sensitization, including widespread pain in the joint area [11], as well as a significant decrease in the pressure pain threshold of the joint and entire lower limb skin and subcutaneous tissue [12]. In spinal cord sensitization, glial cells play an important regulatory role, sensing and responding to pain signal stimuli, and enhancing pain signal transmission and enhancing neuronal excitability by releasing pro-inflammatory cytokines (such as tumor necrosis factor  $\alpha$ , interleukin-1, etc.) and neurotransmitters (such as glutamate, D-aspartate, etc.). Repeated nociceptive stimuli activate nociceptors, inducing central sensitization through the release of excitatory amino acids such as glutamate and TRPV-1 channels. Glial cells play a crucial role in neural regulation, neurotrophic function, and neuroimmunity, and their activation is closely related to pain hypersensitivity and sustained pain. Research has shown that the microglia in the spinal dorsal horn of the OA pain model are in an activated state, which can inhibit the activity of microglia and reduce the painful behavior of OA rats [13]. According to relevant reports, the ATP content in the cerebrospinal fluid of MIA induced OA pain rats is significantly increased, accompanied by high expression of P2X7 receptors (ATP receptors) on microglia in the spinal dorsal horn. The application of P2X7R receptor blockers can significantly increase the mechanical pain threshold in OA rats [14]. The endogenous pain regulatory system (DPMS) in the spinal cord is a key pathway for regulating spinal cord injury information. The descending inhibitory system and descending facilitation system respectively play inhibitory and facilitation roles in harmful impulses transmitted by the spinal cord, playing a key role in pain signal transmission and regulation. The functional changes of descending fibers in the spinal cord structure are triggered by the 5-HT descending

pathway originating from the ventromedial medullary nucleus (RVM), which acts on neurons in the spinal dorsal horn. By acting on different receptors in the spinal dorsal horn, it promotes and inhibits the processing of nociceptive signals in the spinal cord. The neurons in the thalamus, somatosensory cortex, and midbrain gray matter above the spinal cord are involved in pain hypersensitivity, and after nerve injury, changes in the function of the descending facilitation modulation system may be involved in maintaining spinal sensitization. The periaqueductal gray matter area (PAG-RVM) axis plays an important role in central sensitization. Changes in cell membrane excitability, decreased inhibitory conduction, and increased synaptic efficacy contribute to the development of central sensitization. Research has found that the central sensitization components related to the neuropathological characteristics of chronic pain in OA are partially mediated by DPMS. Blocking the descending pain facilitation pathway in the rostral ventromedial nucleus (RVM) of the medulla oblongata can significantly alleviate OA pain [15]. Meanwhile, it was found that the activation of the 5-hydroxytryptamine descending facilitation system in chronic pain OA rats induced by MIA is closely related to the high reactivity of spinal dorsal horn neurons to harmless mechanical stimulation of the rat foot [15]. Chronic pain in OA may lead to structural and functional changes in the brain's neural circuits, including increased neuronal connections and changes in synaptic transmission. The sustained presence of OA pain is closely related to the plasticity changes in pain perception and cognitive regulation related brain regions. According to reports, chronic pain OA patients generally exhibit changes in brain gray matter content, such as a significant decrease in gray matter content in the bilateral orbitofrontal cortex (OFC), right prefrontal cortex (rPFC), central prefrontal cortex, and posterior central cortex of knee OA patients with chronic pain [16]. A study based on resting state functional magnetic resonance imaging (rs fMRI) found that chronic pain in OA involves multiple brain functional connections, including the frontal lobe, parietal lobe, temporal lobe, cerebellum, and limbic system [17,18].

### 3. The Mechanism of Acupuncture Analgesia

Acupuncture and moxibustion has a good analgesic effect. At all levels of the central nervous system, there are organizational structures related to analgesia. Together, they form a "pain modulation system". Their activities can also inhibit or modulate the transmission of pain impulses in the central nervous system. Acupuncture effects mainly affect the central nervous system to improve endogenous analgesia (downward inhibition) mechanism. Experimental studies have shown that the endogenous pain modulation system mainly functions in the hypothalamus, amygdala, and head end cingulate gyrus (rACC) through the descending pain modulation loop of the periaqueductal gray (PAG) in the midbrain. Fibers emitted from the PAG project downwards to the spinal cord or dorsal horn of the medulla through the nucleus raphe magnus (NRM) and reticular giant cell nucleus neurons in the ventromedial medulla (RVM), directly or indirectly regulating the transmission of pain information [19]. The afferent nerves transmit acupuncture signal information into the spinal cord, and under the interaction of the central pain modulation system and pain stimulation, inhibit the expression of pain signals, thereby achieving analgesic effects.

According to neuroimaging studies conducted by relevant researchers on acupuncture treatment of chronic pain, it has been found that acupuncture treatment mainly exerts analgesic effects by benign adjustment of brain functions such as pain cognitive control network, descending pain regulation pathway, reward circuit, etc [20,21]. There is an experimental study comparing the effects of acupuncture at true acupoints and acupuncture at false acupoints on the brain function and structure of KOA patients. The results show that acupuncture at true acupoints can protect the rate of decline in the thickness of the posterior medial PFC cortex in KOA patients relative to acupuncture at false acupoints; Can enhance the resting state functional connectivity (rs-FC) of posterior PFC, anterior cingulate gyrus (pgACC), periaqueductal gray (PAC) in KOA patients, as well as the rs FC of medial PFC and posterior medial PFC [22]; rs-FC acupuncture at the true acupoint can specifically improve the rs-F of the right frontal and temporal lobe network, executive control network, pgACC, and medial PFC in KOA patients [23,24]; And it can also specifically adjust the rs-FC of PAG, medial PFC, and parahippocampal gyrus [24]; Meanwhile, with KOA as the subject, Jian Kong's research team also found that high expectation acupuncture was more effective in activating the functional connectivity between the nucleus accumbens, medial prefrontal lobe, and anterior cingulate gyrus of the beak compared to standard acupuncture.

Numerous studies have shown that acupuncture analgesia (AA) induces neuronal mechanisms in the central nervous system (CNS) [25], including the descending inhibitory pathway (hypothalamus PAG raphe nucleus spinal cord). In the spinal cord, acupuncture signals inhibit pain transmission through the "gate control theory" mechanism, and the descending activity of the central nervous system can modulate gate activity [26]; and ascend along the ventrolateral cord, reaching the brainstem, diencephalon, and brain, respectively, to excite some of the structures belonging to the pain modulation system in these areas, causing inhibitory impulses to rise or fall, affecting the pain modulation system, and inhibiting the transmission of pain signals. The hypothalamus is the central nervous system (CNS) and may play a crucial role in the pathogenesis of AA [27]. Acupuncture at the true acupoint can more effectively mobilize the functional connections between the posterior medial prefrontal lobe and the anterior cingulate gyrus of the beak, the periaqueductal gray matter (PAG) of the midbrain, and the medial prefrontal lobe and the posterior medial prefrontal lobe [28].

The nucleus raphe magnus (NRM) is a nucleus in the lower brainstem that is associated with the descending pain inhibitory pathway. After stimulating the nucleus raphe magnus related neurons with acupuncture signals, they will emit downward inhibitory impulses and descend along the dorsal lateral funiculus of the spinal cord to the dorsal horn, thereby inhibiting the transmission of pain signals. Related reports suggest that the axons of PAG neurons project to the NRM, and when PAG is nociceptive, the firing frequency of rat NRM neurons increases after analgesia. Meanwhile, Liu et al. found that electroacupuncture at Zusanli (ST-36) activated NRM neurons and produced analgesic effects, which were attenuated by microinjection of naloxone into rat PAG [29]. The periaqueductal gray (PAG) plays a crucial role in the

descending pain suppression system [30]. Niddam et al. also found that alleviating chronic pain through electroacupuncture stimulation of trigger points is mediated by central pain regulation of PAG in the brainstem [31]. Electroacupuncture at acupoints "Zusanli" (ST-36), "Neiguan" (PC6), and "Neiting" (ST-44) can cause significant behavioral and Fos expression analgesic effects, especially in the ventrolateral PAG [32].

Research has shown that during the process of acupuncture analgesia, some neurotransmitters such as serotonin, endogenous opioid substances, acetylcholine, etc. can enhance their analgesic effects. Among them, serotonin (5-HT) can inhibit pain impulses, increase serotonin levels in the spinal cord, and 5-HT has analgesic effects on 2Hz acupuncture [30]. Acupuncture signals excite the nuclei in the CNS and stimulate the activity of 5-HTergic neurons in the brain. In an inflammatory rat model, 5-HT neurotransmitter mediates EA analgesia, which binds to 5-HT1 and 5-HT3 receptors [33,34]. Chang et al. found in their study of a rat inflammatory pain model that EA's analgesic effects were blocked by 5-HT1a and 5-HT3 antagonists at low and high frequencies; At high frequencies (100 Hz), 5-HT2 antagonists enhance the analgesic effect of EA [35]. For the subjects of osteoarthritis model rats, acupuncture and moxibustion treatment will have an important impact on their classic neurotransmitters. Compared with before treatment, the levels of 5-hydroxytryptamine (5-HT) and its metabolite 5-HIAA in the spinal cord of osteoarthritis rats increased significantly after electroacupuncture at Jiaji, which also indicates that the analgesic mechanism of electroacupuncture at Jiaji may be related to the activation of the 5-HT descending analgesic system of rats [36,37]. The nucleus raphe magnus (NRM) contains abundant 5-HT neurons and is a key area in the descending pain modulation system [30]. Acupuncture and moxibustion has a certain effect on the classic neurotransmitters of osteoarthritis model rats, and electroacupuncture at Jiaji can significantly increase the level of 5-hydroxytryptamine in rats with skeletal joints, indicating that the analgesic mechanism of electroacupuncture at Jiaji is related to activating the 5-HT energy descending analgesic system of rats. EA reduces osteoarthritis pain through 5-HT 1 and 5-HT 3 receptors [38-40]. In summary, acupuncture has a significant effectiveness in relieving chronic pain in OA and has a good analgesic effect.

#### 4. Summary

In summary, OA pain has complex pathophysiological mechanisms and is not fixed and unchanging. Both peripheral and central mechanisms are potential mechanisms of OA pain. In order to effectively alleviate the pain of patients, it is necessary to enhance understanding of the pain mechanisms of osteoarthritis and explore the fundamental reasons for poor therapeutic effects. Acupuncture and moxibustion is the treatment choice to prevent cartilage degeneration and relieve pain. Therefore, in the process of treatment, we should accurately master the important mechanism of acupuncture and moxibustion analgesia, use the best acupuncture techniques, acupoint selection, needle retention time, etc., to improve the treatment effect, improve the quality of life of patients, and further focus on the clinical application value of acupuncture and moxibustion analgesia.

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