REVIEW REPORT

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CENTRAL MECHANISMS OF ACUPUNCTURE ANALGESIA

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ABSTRACT

Background: Acupuncture is an component of traditional Chinese medicine (TCM) that has been used for three thousand years to treat diseases and relieve pain. Pain is found to be the most common reason for people to use acupuncture. Due to recent scientific findings, acupuncture treatment has been accepted worldwide. Numerous trials have been conducted especially in analgesia. The mechanisms of acupuncture analgesia has been widely investigated, however, the underlying mechanism still not clear. This article summarizes the central mechanisms of acupuncture analgesia and reviews recent studies on the topic.

Method: We have focused on examining the recent literature on acupuncture analgesia. The central mechanisms of acupuncture analgesia and reviews recent studies on the topic. We focused on the studies related to central mechanisms of acupuncture analgesia from these aspects: (neurophysiology, neurochemistry and neuroanatomy).

Result: The result revealed that acupuncture act on various parts of the central nervous system, including the spinal cord, brain stem, cerebral ganglia and cerebral cortex to alleviate pain. The central mechanisms underlying the effects of acupuncture include neurohumors and neurotransmitters, which are involved in analgesia. At spinal level, Spinal opioids, glutamate, norepinephrine and serotonin are the key elements acupuncture-induced analgesia. At brain level, Endogenous opioid peptides, limbic system play essential roles in mediating the analgesia.

Conclusion: Acupuncture is an effective approach to pain management. There is good evidence in both experimental and clinical research that supports acupuncture efficacy in management of chronic pain through central nervous system. Acupuncture should be strongly used as a part of pain management plans. This work helps in improving our understanding of the scientific basis underlying acupuncture analgesia.

Keywords: Acupuncture; Traditional Chinese Medicine; Analgesia; Chronic pain; Central nervous system; Spinal cord.

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INTRODUCTION

Acupuncture is an ancient healing procedure dating back to more than 3000 years in Chinese history.[1] Pain in traditional Chinese medicine (TCM) is due to insufficiency or blockage of Qi along the meridian, which leads to stagnation of Qi. It is difficult to translate the mechanism of acupuncture analgesia in Western terms, because the philosophy of TCM is entirely different. TCM believes in the theory of holistic balance between the Yin and Yang and problems arise when there is an imbalance. Acupuncture is used to balance the Yin and Yang, which are manifested to regulate the Qi (energy) and blood. Qi travels through channels called meridians in the body. There are 20 channels with points, called acupuncture points, aligned along the meridians, which can be manipulated through various techniques to achieve balance of the Qi. The De Qi is a sense of tightness around the needle as it enters deep tissues. The sensation experienced by the patient is often soreness, numbness, heaviness, or even an electrical sensation. Acupuncture relieves pain and illness by unblocking stagnant Qi in the meridians, thereby restoring the balance between Yin and Yang.

The underlying scientific mechanisms and its place in modern medicine had progressed tremendously. Acupuncture has gradually won acceptance in Western countries as an alternative or complementary treatment for analgesia. Acupuncture is widely accepted to treat chronic pain, but the precise mechanism underlying the analgesic effect of acupuncture has not been fully demonstrated. Our understanding of how the brain processes acupuncture analgesia has developed extremely during last decades. Accumulated evidence supports the clinical effectiveness of acupuncture to treat chronic pain. Usually acupuncture points are always located on regions that are abundant in nerves and blood and lymph vessels; this is where nerve endings, nerve receptors, blood vessels, mucopolysaccharides, and mast cells are densely distributed.[2]

Electroacupuncture (EA) enhances the outcome and prolongs the benefit of the treatment. An electrical current is applied to several acupuncture points to gain more vigorous and prolonged stimulation to the needles. Electrical current can be applied to acupuncture needles at either a high or low frequency, each having a different effect on systemic neuromodulation.

Various studies on acupuncture have demonstrated that acupuncture analgesia is initiated by the stimulation of small afferent sensory nerve fibers that innervate the muscles. These then send impulses to the spinal cord and ultimately affect the supraspinal centers. Modulation of the activity of various neurohumoral pathways that are involved in pain perception as these centers are activated there is release of Neurotransmitters that block the pain.[3]

Spinal mechanisms

Spinal cord consists of white matter, gray matter, and a tiny central canal filled with CSF. The gray matter contains the cell bodies of neurons and glia and is divided into four main columns: dorsal horn, intermediate column, lateral horn and ventral horn column. The spinal cord is the first station of nociceptive information processing, interpretation and a pain reflex center. Acupuncture diminishes the transmission of noxious inputs at the spinal level by suppressing dorsal horn neuron activities through descending inhibitory systems. Spinal opioids, glutamate, norepinephrine and serotonin are the main players of acupuncture-induced analgesia at spinal level. Inserting the needles into acupuncture points trigger fast myelinated Aδ fibers that synapse directly in the dorsal horn where as the sensory inputs from C fibers synapse through substantia gelatinosa (SG) cells. The Aδ fibers make collateral connections to intermediate cells, which inhibit the activity of the SG cells. These intermediate cells inhibit the nociceptive pathway in the SG cells that suppresses activity of the spinal nociceptive neurons.[4]

Endogenous opiate peptides

Endogenous opiate peptides (EOP) include β-endorphins, enkephalins, and dynorphins that bind to μ-, δ-, and κ-receptors to create analgesia. Neural imaging studies have confirmed the importance of the endogenous opioid system and the central nervous system in acupuncture analgesia.[5] Many studies found high concentrations of EOP after an acupuncture treatment in both the CSF and plasma. EA induces endogenous opioids; Low frequency (2–15 Hz) may release enkephalin, β-endorphin and endomorphins working on μ- and δ-opioid receptors. High frequency (100 Hz) caused release of dynorphin to κ-opioid receptors on the spinal cord. Nociceptin/orphanin FQ (N/OFQ) and opioid-like receptors play important roles in pain modulation. N/OFQ has been observed in fibers and neurons in superficial laminae of the dorsal horn, which inhibit C fibers thus induce analgesia. Acupuncture reduces pain by inducing release of spinal N/OFQ through both pre- and post-synaptic mechanisms.[6,7] The needs of opioid–like medications in patients with chronic pain will be decreased after acupuncture course.[8]

Amino acids

Amino acids are divided into excitatory amino acids (such as glutamate) and inhibitory amino acids (such as GABA). Many studies suggest that acupuncture may decrease the activity of excitatory amino acids and increase that of the inhibitory amino acids in the central nervous system. Glutamate and its receptors are in the spinal dorsal horn and play important roles in transmission of noxious stimuli. EA could produce a significant analgesic effect in neuropathic pain, which reduce the release of glutamate from the dorsal horns of the spinal cord and the decreased content of the excitatory amino acids.[9] EA inhibits transmission of noxious Stimuli at the spinal level by decreasing glutamate receptor activities.[10,11]

The gamma aminobutylic acid (GABA) receptors are involved in acupuncture analgesia, current studies show that EA analgesia induces an increase of $GABA_A$ and $GABA_B$ receptors in the spinal cord are associated with acupuncture analgesia[12]

Noradrenalin and Serotonin

Noradrenalin (norepinephrine) is a neurotransmitter of the post-ganglion sympathetic nerves and many central neurons, Noradrenaline containing neurons originate from various brain areas which descend along the dorsolateral tracts of the spinal cord, playing a role in pain modulation.[13] Electrophysiological studies show that norepinephrine significantly reduces spinal dorsal horn neuron excitability in a neuropathic pain.[14] Studies also suggest that EA may reduce the activity of noradrenalin system in the brain via the activity of endogenous opioid peptide.

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter synthesized in the serotonergic neurons that are mainly located in the median regions of the brain. Serotonin and its receptors play an important role in acupuncture analgesia. Acupuncture and EA increase the spinal concentrations of serotonin and serotonin receptor activation indicating central descending pathway activation. When serotonin receptors were blocked, acupuncture-induced analgesia was dramatically reduced.[15] Numerous studies show serotonin and norepinephrine involvement in electroacupuncture analgesia [16,17]

Supraspinal mechanisms

The regions of the brain modulated by painful sensation, taken together, are composing primary/secondary somatosensory area, thalamus, insula, prefrontal cortex, anterior cingulate cortex, basal ganglia, limbic system, brainstem, and cerebellum.[18] The descending inhibition of analgesia from the CNS focused on transmitters, modulators, and receptors; central effects reinforce segmental and local analgesia.

Central pain processing occurs in the brain via the complex interaction between the cortex and subcortical nuclei. Most fMRI of acupuncture may recruit distributed cortical and subcortical brain networks that are also implicated in both inhibitory and facilitating effects in the pain-modulation system for both sensation and affective pain perception.[19]

Brain stem

The brain stem consists of medulla oblongata, mid brain and pons. It is a relay station for sorting, synthesizing and discriminating information associated with pain. The nucleus raphe magnus (NRM) in the midbrain is a significant neural site for descending analgesia via expression of serotonin. The dorsolateral pontine tegmentum is another site mediating pain by providing noradrenergic innervations of the spinal cord. EA could regulate neurons in the nucleus tractus solitarius in medulla oblongata through polysynaptic cross-talk mechanism, which mediates EA analgesia on visceral pain in anesthetized rats.[20] A study conducted on rat and found that EA 10 Hz at ST36 significantly suppressed visceral hyperalgesia and inhibited Fos expression in dorsal raphe nuclei of the brainstem and other centers on the brain.[21]

The periaqueductal gray (PAG) is the primary control center for descending pain modulation. It has enkephalin-producing cells that suppress pain. Imaging studies have documented concurrent analgesia with increased activity in the PAG with EA.[22] Behavioral studies in animal models showed that the PAG – rostral ventromedial medulla (RVM) system plays a key role in acupuncture or EA analgesia.[23] EA resulted in strong expression of c-Fos immunoreactivity in the ventrolateral to lateral subdivision throughout the PAG. It was of particular interest in the experiment of the acupoint that strong expression of gamma aminobutylic acid (GABA) frequently showed similar pattern of distribution to that of c-Fos in the PAG. This, suggesting that the PAG neurons activated by EA might play an important role in the descending pain control system involving the GABA since the PAG has special reference to the dorsal horn of the spinal cord and function of pain control.[24] Current research documents that PAG, acting in concert with other midbrain sections, to be the primary CNS structure responsible for descending pain in the reduction of catecholamine content in the preoptic area may enhance acupuncture analgesia.

Cerebral ganglia

The cerebral ganglia modulated by a number of neurohumoral substances. The arcuate nucleus, paraventricular nucleus and preoptic area are located within the hypothalamus, and are associated with the modulation of pain. Functional magnetic resonance imaging studies have demonstrated that acupuncture produces deactivation of limbic structures (including the amygdala, the hippocampus, and cingulate) to a painful stimulus via a mechanism that is distinct from pain and sham stimulation.[25] The preoptic area contains numerous neurotransmitters that have roles for analgesia.

Vasopressin (VP) is a nonapeptide posterior pituitary hormone which enhance acupuncture analgesia in the central nervous system through this mechanism[26], Acupuncture causes PVN secreting VP by norepinephine action. VP is transported to the other brain regions to regulate the local antinociceptive system. VP enhances the enkephlin and endorphin synthesis and secretion in PAG to participate in acupuncture analgesia. VP influences the release of serotonin and acetylcholine (Ach). Serotonin and Ach can be transferred to the spinal cord to influence endogenous opiate peptides release to regulate acupuncture analgesia. The hypothalamus releases beta-endorphins, which directly activates the periaqueductal gray (PAG) in the midbrain; the PAG is also activated via input from the limbic system, which encompasses the emotional aspect of pain and the reason pain is often an unpleasant experience rather than a simple sensation.[27]

Another study reported that acupuncture have an effect of pain modulation in irritable bowel syndrome by regulating the serotonin pathway at insula and the mood in higher cortical center via ascending pathway at the pulvinar and medial nucleus of the thalamus.[28] Imaging studies provides a good evidence for acupuncture analgesic effect via the limbic system with different brain areas activation.[29] Many studies documented greater central brain signal increases with EA than manual acupuncture.[30]

Cerebral cortex

The cerebral cortex is the center of higher nervous activity, including consciousness, intelligence, reasoning, judgment, planning, movement, emotions, and problem solving.

A study postulated that acupuncture might have the potential effect of pain modulation in irritable bowel syndrome by modulating the serotonin pathway at insula and the mood and affection in higher cortical center via ascending pathway at the pulvinar and medial nucleus of the thalamus.[31]

Central mechanisms include initiating descending pain control through the insular and frontal cortex activation of the periaqueductal gray, the strongest center to suppress pain, via the spinoreticulothalamic tract. The cumulative effect of repeated acupuncture stimulation was consistent with the characteristic habituation effects associated with functional magnetic resonance imaging examination.[32] Acupuncture might have the potential effect of pain modulation by (1) modulation of serotonin pathway at insula and (2) modulation of mood and affection in higher cortical center via ascending pathway at the pulvinar and medial nucleus of the thalamus.[31,33]

A functional magnetic resonance Imaging Study had confirmed that the rostral anterior cingulated cortex was engaged in acupuncture analgesia.[34]

DISCUSSION

Acupuncture has a powerful role to play in practice, and it is well-accepted approach to mange chronic pain patients. More evidence arises eventually for acupuncture analgesia. The acupuncture basis of analgesia grows with our better understanding of pain mechanisms and the effect of chronic pain on the central nervous system. Evidence has indicated that the main feature of acupuncture analgesia is its longevity, gradual peaking and gradual returning. Acupuncture works through a variety of mechanisms to relieve chronic pain.

Acupuncture has an analgesic effect via endogenous descending pain control pathways that modulate nociceptive signals at the level of the brain and spinal cord. Endogenous opioid peptides in the central nervous system play an essential role in mediating the analgesia. Manual acupuncture and EA can regulate the opioid system in the central nervous system. Different kinds of neuropeptides are released by EA with different frequencies. Analgesic effect after using lower frequencies was longer lasting and more cumulative in analgesia provided. Data suggest that acupuncture can activate or strengthen the activity of the EOP system in the central nervous system by increasing the release and production of EOP, and by up regulating the opioid receptor expression.

The serotoninergic descending inhibitory pathway is also suggested to be an important mechanism of acupuncture analgesia.

Central analgesia reinforces segmental and local analgesia. Although there is a good evidence for

central analgesia of acupuncture, it is limited by our understanding of central regulatory events of analgesia.

Recommendations

1. To help patients to benefit from acupuncture analgesia the experimental research need to be translated to clinical trials.
2. A combination of the high and low frequencies of EA produces a simultaneous release of all four opioid peptides, resulting in a maximal therapeutic effect.
3. Brain mechanisms of acupuncture analgesia need more investigation.

CONCLUSION

Acupuncture analgesia is an effective approach to pain management. There is good evidence in both experimental and clinical research that supports acupuncture efficacy. Therefore, acupuncture should be accepted and used as part of treatment of a wide variety of painful conditions.

Disclosure statement

The authors affirm there are no conflicts of interest and the authors has no financial interest related to the material of this manuscript.

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