Review Article

Advanced research validates classical principles—the neurobiological mechanisms involved in acupuncture for pain management

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Abstract: Classical acupuncture principle states that acupuncture produces a combination of local effect, distal effect and whole-body effect. How does modern science validate this combination-of-effect principle? This paper presents evidence that the effectiveness of acupuncture results from its local effect, segmental effect and general effect from a neurobiological perspective, which validates the classical principle.

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The biological mechanisms which mediate the effectiveness of acupuncture for pain management have been debated by neuroscientists and acupuncture researchers for decades. There are already so many publications (1-17) in this area that I hesitate to add another to the total, but pain is such a basic and universal fact of human existence that new findings and updated research in this field are always worth discussing. Classical acupuncture principle states that acupuncture produces a combination of local effect, distal effect and whole-body effect. Can modern science validate this combination-of-effect principle? This brief article includes a summary of established understandings of acupuncture management for pain, as well as an outline of newly-discovered knowledge in acupuncture analgesia.

Science has provided us with solid groundwork and breakthrough concepts regarding the neurological structures and mechanisms by which we feel and process the pain response. We now have a detailed understanding of nociceptive pain response, particularly for acute pain. Unfortunately, the mechanisms involved in chronic pain present a more complex scientific challenge, and are still not well-understood. Since clinic practitioners are much more likely to confront chronic pain, rather than acute pain, in the majority of their patients, the sooner we can understand chronic pain mechanisms the better.

Following are three sections which discuss updated material on local, segmental, and general mechanisms of pain relief; and a fourth section which presents a new functional magnetic resonance imaging (fMRI)-based research on the neurobiological localizing of pain.

From a neurobiological perspective, the effectiveness of acupuncture results from its local effect, segmental effect and general effect. These evidence-based conclusions coincide with the classical traditional Chinese medicine (TCM) principle of local effect, distal effect and whole-body effect of acupuncture.

Local mechanisms of pain relief

Many local mechanisms have been proposed as the effectors of pain relief, such as an increase in blood circulation and tension relief of trigger points. At this point, release

of the nucleic acid compound adenosine is the most convincing mechanism. Adenosine receptors comprise a neuromodulator with anti-nociceptive properties. They are a class of purinergic G protein-coupled receptors with adenosine as an endogenous ligand. Four types of adenosine receptors are known in humans: A_1, A_{2A}, A_{2B} and A_3; each is encoded by a different gene. The adenosine A_1 receptor is the one involved in acupuncture analgesia.

It has been established that acupuncture's anti-nociceptive effect is based in the activation of ascending sensory tracks in the spine, which releases opioid peptides in the central nervous system (CNS). But if the CNS is the primary locus of anti-nociceptive effect, several questions remain unanswered: Why is acupuncture effective when it is applied close to or directly on the specific pain site? Why are the analgesic effects of acupuncture concentrated on one side of the body, rather than being bilateral? There is currently no satisfactory explanation for these questions.

In 2010, Goldman *et al.* (18) found that adenosine was released in mice during acupuncture, and that its anti-nociceptive actions required adenosine A_1 receptor expression. Mice which lacked adenosine A_1 receptors did not experience an analgesic effect from acupuncture. When an adenosine A_1 receptor was directly injected with an agonist, it elicited an analgesic effect that was the same as acupuncture. When enzymes which act to degrade adenosine were inhibited, the amounts of adenosine released by acupuncture stimulation were increased, and the anti-nociceptive effect was also potentiated. Pharmacological inhibition of deaminase activity had a similar effect on acupuncture stimulation, increasing adenosine release and prolonging analgesic effects. These observations by Goldman demonstrate that acupuncture stimulation is mediated by the action of adenosine, and that disrupting adenosine metabolism can prolong the effects of acupuncture therapy.

It was well-established that peripheral, spinal, and supraspinal adenosine A_1 receptors produced an anti-nociceptive effect. Goldman *et al.* (18) quantified the extracellular purines in microdialysis samples collected in the vicinity of stimulated acupuncture points, including the transmitter adenosine, and established that insertion and stimulation of acupuncture needles promoted extracellular concentrations of adenosine. The Goldman group then investigated the proposition that injecting an adenosine A_1 receptor agonist would suppress hyperalgesia, and found that the agonist 2-Chloro-N6-cyclopentyladenosine (CCPA) did indeed markedly reduce inflammatory and neurogenic pain.

The Goldman experiments established that, in mice, acupuncture manipulation stimulates the release of adenosine, that adenosine A_1 receptor expression is required for analgesia, and that therefore it is the activation of adenosine A_1 receptors on ascending nerves which produces the clinical anti-nociceptive benefits of acupuncture. Suppressing adenosine-degrading enzymes with drugs increased the availability of adenosine and improved the effectiveness of acupuncture in mitigating chronic pain.

Once the Goldman study (18) demonstrated in mice that acupuncture stimulates extracellular concentrations of adenosine, activating adenosine A_1 receptor expression and producing an analgesic effect, their next question was whether acupuncture produced the same local extracellular concentrations of adenosine in humans. This question was taken up by Takano *et al.* (19), who conducted an analgesia study with human participants. In this study, acupuncture was applied for 30 minutes to acupuncture point Zusanli (ST36). Microdialysis samples of interstitial fluid were collected before, during, and after the treatments. As in mice, it was noted that adenosine concentration increased during acupuncture. In humans, it was also noted that the adenosine levels remained high for 30 minutes after the acupuncture treatment. If acupuncture was not delivered to Zusanli, or if the needle was inserted in the acupoint but not rotated, there was no noticeable increase of adenosine concentrations. The Takano study on humans strengthened the evidence for acupuncture-mediated analgesia *via* adenosine release.

Segmental mechanisms of pain relief

The main theory relating to the segmental mechanism of pain relief is the gate control theory. The gate control theory, proposed by Melzack and Wall (20) in 1965, is the one of the most widely-accepted theories of pain modulatory mechanisms. The "gate" is located in the dorsal horn of the spinal cord. It is the substantia gelatinosa (SG), a collection of neural cells located in the dorsal horn of the spinal cord, which controls the transmission of neural impulses from the peripheral nervous system to the CNS. Non-noxious input/stimulation closes the SG gates to painful input, which results in preventing the pain sensation from traveling to the CNS (in this study, "non-noxious input" such as touch or needling is contrasted with "noxious input", which is stimulation that injures or threatens to injure the body's tissues). The main structures involved in

the gate control theory are A-beta nerve fibers, C nerve fibers, and the dorsal horn neurons, SG.

Anatomical features of the spinal cord which are involved in the segmental mechanism of pain relief are: ascending pain fibers (primarily the A-delta and C fibers); Rexed laminae; nocineurons (pain receptors); and opiate receptors. Rexed laminae are layers of grey matter in the spinal cord. The pain fibers innervate the nocineurons in Rexed laminae I & II of the dorsal horn of the spinal cord. Cells from lamina II make synaptic connections in laminae IV to VII, and cells in laminae I and VII initiate ascending spinothalamic tracts. Opiate receptors at the presynaptic ends of the nocineurons and at the interneural level layers IV to VII in the dorsal horn are activated at the spinal level. The activation of opiate receptors at the interneuronal level leads to hyperpolarization of the neurons, which result in the inhibition of firing and the release of a neurotransmitter involved in pain transmission, thereby blocking pain transmission.

Gate control theory (21) deals with nerve fibers in the SG of the spinal cord which can both transmit pain and inhibit pain. The main nerve fibers involved are A-beta, A-delta and C nerve fibers. A-beta nerve fibers are large, fast-conducting, and have a low-volt threshold, while the C nerve fibers are small, slow-conducting, and have a high-volt threshold. Gate control theory posits that a high volume of pain impulses from A-beta fibers has the effect of closing the gate of the SG, preventing the pain impulses from the smaller, slower C nerve fibers from getting through to the brain. That is, the SG is "opened" by A-delta and C fibers, and "closed" by A-beta fibers.

There are two "gate" responses noted: Sensory nerve fibers from the skin activate inhibitory interneurons, which inhibit pain-related information carried by the sensory fibers. At the spinal cord level, non-noxious stimulation such as acupuncture needling provides sensory input that "closes the gate" to noxious input and prevents it from reaching the CNS. The mechanical, non-noxious stimulation produces presynaptic inhibition of pain information, blocking the synapse of dorsal root nociceptor fibers with nociceptor spinal neurons.

Gate control theory is a plausible explanation of how acupuncture works through the nervous system to alleviate pain. In this scenario, acupuncture stimulates the acupuncture points, creating a steady stream of non-noxious pain impulses. A-beta nerve fibers transmit the non-noxious pain impulses to the SG, over-riding or short-circuiting any pain impulses from A-delta and C fibers, and causing the gate to close. This can explain the effectiveness of acupuncture in immediate pain relief.

General, or whole-body mechanisms of pain relief

The main mechanism in this category is the descending inhibition, which refers to the ability of activation in various brain areas to attenuate spinal dorsal horn neuronal responses to peripheral noxious stimuli. The main structures involved in descending inhibition are: periaqueductal gray (PAG) matter in the upper brain stem; the rostroventromedial medulla (RVM); the locus coeruleus (LC); the nucleus raphe magnus (NRM); and the nucleus reticularis gigantocellularis (Rgc). As a group, these structures contribute to the descending pain suppression pathway, which inhibits incoming pain information at the spinal cord level. Neurotransmitters, neuropeptides, and monoamines are involved in this process. The neurotransmitters involved include acetylcholine (ACh), gamma-aminobutyric acid (GABA), and serotonin. Neuropeptides include beta-endorphins, enkephalins and dynorphins. Monoamines include serotonins, dopamine, and norepinephrine.

Pain perception is based in activation of the midbrain and medullary areas. These areas can control both the perception and the reaction to pain as they communicate through the brainstem. The PAG brain area receives input from the higher brain centers and can activate a strong analgesic effect. The RVM is a gatekeeper that can facilitate or inhibit pain perception, and exerts final control of descending pain facilitation.

Studies (22) have documented the structure and function of the PAG and RVM areas of the brain/brainstem in regard to nociception. The PAG is a significant control center, with connections to the cerebral cortex, the amygdale, the RVM, and the spinal dorsal horns. It receives ascending nociceptive inputs from the spinal dorsal horns, and mediates descending pain modulation mainly through the RVM. A primary function of the PAG is to modulate or inhibit nociceptive inputs and pain perception. Opioid receptors in the CNS are key elements in pain inhibition. It has been demonstrated that electrical stimulation to the PAG can trigger its endogenous pain inhibitory system and elicit strong anti-nociceptive effect.

Takeshige *et al.* (23) demonstrated that the descending inhibition associated with acupuncture analgesia starts in the posterior arcuate nucleus and descends to the

hypothalamic ventromedial nucleus (HVM). At that point, it divides into two pathways: the serotonin-mediated path descends through the ventral periaqueductal central gray (V-PAG), and then to the raphe magnus (RM); and the noradrenaline-mediated path descends through the reticuloparagigantocellular nucleus (NRPG) and part of the reticulogigantocellular nucleus (NRGC).

Locating pain remains elusive

Recently, a study (24) was published in the journal *Nature Communications* by scientists at the University of Colorado. They analyzed data from six fMRI studies of 183 participants to determine which specific areas of the brain were responding when a pain stimulus was applied (in this study, the pain stimulus was heat). Mapping global brain activity in this manner disclosed that our brains process different aspects of "pain" in different areas. In addition to experiencing the actual pain stimulus, participants were also given the psychological stimulus of monitoring their expectations of pain and perceived control over pain. Researchers found that some areas of the brain responded specifically to the intensity of the pain stimulus, such as the insula, cingulate cortex, and thalamus. Other brain structures were not sensitive to pain intensity, but were involved in the psychological areas of expectation and control: the dorsomedial prefrontal cortex, the middle temporal gyrus, and the caudate and ventrolateral prefrontal cortex. Another group of brain regions, including the ventromedial prefrontal cortex, the nucleus accumbens, the parahippocampal cortex, and the posterior dorsolateral prefrontal cortex, associated increased brain activity with decreased pain. This study is just another illustration that pain exploration and understanding is still evolving.

Summary

Scientists and medical professionals the world over are contributing valuable research and understanding of the neurobiological mechanisms of pain and pain control. The database of scientific studies in the area of acupuncture for pain management is constantly revisited and expanded, refining our knowledge and revealing the intricate connections of our neuro-anatomy. However, beyond the new terminologies of brain structures and brain chemistry, useful as they are, acupuncturists can still recognize the underlying principles and practices of TCM. Neurobiology and TCM may have completely different vocabularies, but they are equally able to address the enduring problem of treating human pain.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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