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Mechanisms of acupuncture

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ABSTRACT

A lack of scientific studies to prove or disprove the claimed effects of acupuncture has led to its rejection by many of the western scientific community. Now that many effects of acupuncture can be explained in terms of endogenous physiological mechanisms, and that these effects are reported as similar or sometimes superior to established treatments with a very low incidence of side effects, the integration of acupuncture with conventional medicine may be possible. Some of these aspects will be presented in this condensed overview.

1. Introduction

A lack of scientific studies to prove or disprove the claimed effects of acupuncture has led to its rejection by many of the western scientific community. Now that many effects of acupuncture can be explained in terms of endogenous physiological mechanisms, and that these effects are reported as similar or sometimes superior to established treatments with a very low incidence of side effects, the integration of acupuncture with conventional medicine may be possible.

The effects of acupuncture are likely to derive from physiological and/or psychological mechanisms, and the needle stimulation could represent the artificial activation of systems that evolved as natural biological effects in functional situations [1,6].

Acupuncture and some other forms of sensory stimulation elicit similar effects in man and other mammals, suggesting that they bring about fundamental physiological changes. Acupuncture stimulation, eliciting *deqi*, excites receptors and or nerve fibers in the stimulated tissue, which are similarly physiologically activated by strong muscle contractions [1,6]. The effects on certain organ functions are also similar to those obtained by prolonged exercise. On the other hand, light superficial needling excites cutaneous touch receptors that are activated physiologically by stroking that in turn results in a limbic modulation with a suggested role in wellbeing and social bonding [6,4].

The effects of acupuncture in pain cannot be explained by a single mechanism, and pain itself is not entirely a straightforward physiological entity, but a phenomenon that arises from a multitude of varying neuroplastic changes as part of adaptive or sometimes maladaptive reactions [7].

The effects of acupuncture may be attributed to

1. Peripheral effects (release of adenosine and nitric oxide, NO, by axonal and dorsal root reflexes).
2. Spinal effects (modulation of sympathetic tone and motor reflexes)
3. Modulation of endogenous descending pain inhibitory and facilitatory systems
4. Change in the functional connectivity of the brain. Activation or deactivation of:
   a. limbic structures involved in stress/illness responses
   b. the hypothalamus-pituitary-adrenal, HPA, axis
   c. the prefrontal and frontal cortices.
5. Restoration of the default mode state.
6. Modulation of parasympathetic activity.
7. Activation of the reward and mirror systems
8. Modulation of activation of the immune system
9. Expectation, attention, conditioning and extinction of conditioned responses

Clinical trials suggest that variability in treatment outcome following acupuncture may also to a significant degree be attributed to the therapist and the patientís interaction with the therapist. The importance of therapeutic alliance in predicting treatment success is well established. Acupuncture is part of a healing ritual allowing for a therapeutic alliance between the acupuncturist and the patient. Possibly this may be attributed to the ability to mediate empathy and/or consolation.

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2. Background

The human biological system has evolved over a very long period of time, but is still adapted to a hunter-gatherer lifestyle where persistence in physical activity was of fundamental importance for survival. In modern society, psychosocial stress is high and motor activity frequently minimal, and the resulting emotional tension cannot be transformed into physical exercise in accordance with inherited biological needs. Instead, the stress-induced changes remain and can cause long-lasting disturbances in muscle tone and autonomous activity, resulting in various types of pain and functional diseases. A contributing factor to health disturbances is probably limited physical exercise with insufficient afferent input for an optimal performance. Changes in function of biological systems occur as a result of somatic afferent stimulation whether from normal physical exercise, electrical stimulation of afferent nerve fibers or stimulation via acupuncture needles. The direction of change seems to be towards an optimal physiological performance of different functions. The details of the underlying mechanisms are largely unknown, but most likely homeostatic and allostatic mechanisms are involved.

2.1. Pain

The definition of pain has provided a powerful conceptual anchor for scientific and health care professional advances in understanding the nature and treatment of acute and chronic pain. Recently, a review of the definition of pain was proposed:

Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components [2]. By taking this definition into account assessments of a treatment becomes more complex and requires a deep understanding of its use in a clinical context.

2.2. Pain and acupuncture

In recent years, many studies have explored the effects of acupuncture in pain. Some patients may experience amelioration of their suffering which is paralleled by changes in biological functions whereas others "only" report a subjective relief i.e. the changes seen during and after a treatment are highly dependent on the individual and the pathophysiological mechanisms involved. This could account for some of the reasons why variable results of pain alleviation in response to acupuncture have been reported. Also, age and gender related variations in perceived pain have been discussed. Furthermore, factors such as operationalisation of the outcome variable and the statistical method used for evaluation could also be sources of variability. When pain is regarded as subjective, the produced data should be treated as ordinal. A rank-based method, taking the non-metric qualities of the ordinal data into account as well as the variability at the group and the individual level, may therefore be recommended. When using such an approach evaluating changes in electrical sensory thresholds and electrical pain thresholds after low frequency electro-acupuncture separately in healthy women and men, it was found that results were divergent between women and men, i.e. unchanged sensory threshold after acupuncture at the group level in women while changed in men. The assessed pain threshold after acupuncture on the other hand was changed towards higher levels in women and unchanged in men suggesting that evaluation of sensory and pain threshold responses to acupuncture should be analysed separately in women and men [5].

2.3. Pain, acupuncture and traditional Chinese medicine

The paradigm of Traditional Chinses Medicine, TCM, with its balancing of energy may, in its way, explain the origins of diseases and disturbed organ functions, but is seen from a western perspective a philosophical rather than biological approach. In many of the original studies regarding acupuncture and pain the underlying mechanisms, e.g. of pain relief, were often discussed relative to traditional TCM or to the location of the pain (for example low back pain, headache and knee pain) but surprisingly few penetrating discussions have dealt with the pathophysiological background of the actual pain condition.

2.4. Pain classification

In contrast to symptomatic and/or diagnosis-based pain treatments, mechanism-based treatments are more likely to succeed. Pain can be an adaptive sensation, an early warning to protect the body from tissue injury (Nociceptive pain). By the introduction of hypersensitivity to normally innocuous stimuli, pain may also aid in repair after tissue damage (Inflammatory pain). Pain can also be maladaptive, reflecting pathological function of the nervous system (Neuropathic pain or Dysfunctional/Long lasting pain) [10].

Multiple molecular and cellular mechanisms operate alone and in combination within the peripheral and central nervous systems to produce the different forms of pain. Elucidation of these mechanisms (including for example; peripheral and central sensitization, neuroplasticity following nerve injury, contribution of activity in the sympathetic nervous system and dysfunction of the pain modulatory systems (disinhibition and central facilitation) as well as cognitive and affective factors) is key to the development of acupuncture techniques that specifically target or modulate underlying causes rather than just symptoms.

It has been suggested that "an evidence-based approach to pain management is not always possible or beneficial to the individual patient. In the face of inconclusive evidence, a theory-based approach may help determine if the therapeutic effect of a given sensory stimulation has the possibility of being a useful clinical tool in the context of modifying a particular patient's mechanism of pain generation." Further studies on mechanism-based classification and such classification-based treatments are essential [8].

2.5. Physiological mechanisms of acupuncture

2.5.1. Overview

Effects of acupuncture therapy occur at multiple levels in the nervous system, both in the peripheral tissue, at segmental (spinal) and central levels [6].

2.5.2. Peripheral mechanisms

Insertion and manual or electrical stimulation of needles in skin and muscle activates A-alpha, −beta, −delta and C-fibers. In particular, activation of A-delta and C-fibers may be essential for modulating pain and autonomic nervous system activity. Manual and electrical stimulation (electroacupuncture, EA) causes release of neuropeptides including calcitonin gene-related, peptide (CGRP) and vasoactive intestinal polypeptide (VIP) from peripheral nerve terminals and other vasodilatory mediators from the tissue around the needle (including adenosine and nitrous oxide) into the area, increasing blood flow. Low-frequency (2 Hz pulse trains) EA also increases skeletal muscle glucose uptake. In insulin-resistant rats peripheral insulin sensitivity is improved by low-frequency EA for 4–5 weeks with three treatments per week and normalized by five treatments per week.

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2.5.3. Segmental mechanisms

Needle stimulation of muscles (which activates descending pain inhibitory systems terminating in the dorsal horn of the spinal cord) with somatic innervations corresponding to the sympathetic innervations of the ovaries, so-called segmental acupuncture points, may alter organ function by modulating sympathetic efferent activity. This is of particular interest since many stress related organ diseases have been shown to have a high concentrations of nerve growth factor (NGF), a marker of sympathetic activity. Segmental low-frequency EA modulates the activity of organ related sympathetic nerves. In the ovaries for example this was reflected by increased ovarian blood flow. The response was demonstrated to be mediated by ovarian sympathetic nerves as a reflex response and was controlled by central pathways. Further evidence that low-frequency EA modulates ovarian sympathetic nerve activity comes from studies in experimentally-induced ovarian dysfunction [9]. Gene and protein expression of markers of sympathetic activity were normalized after 4 weeks of low-frequency EA. For example, in rats with experimentally-induced ovarian dysfunction, ovarian morphology was improved by thrice weekly treatment for 4–5 weeks, as reflected by a higher proportion of healthy antral follicles and a thinner theca interna cell layer than in untreated rats. When treatment was increased to five times per week, low-frequency EA normalized estrus cyclicity, indicating a clear dose-response relationship. It is not known whether manual stimulation of acupuncture needles induces similar effects.

2.5.4. Central mechanisms

When needles are inserted, the peripheral nervous system transfers signals to the brain, which contributes to the effect of acupuncture. Since the central nervous system, CNS, regulates pituitary hormone release, acupuncture may also modulate endocrine and metabolic function. Many brain areas, especially the hypothalamic nucleus, are involved in the effect of acupuncture. Acupuncture-induced release of CNS neuropeptides seems to be essential for inducing functional changes in organ systems. The central hypothalamic beta-endorphin system is a key mediator of changes in autonomic functions, such as effects on the vasomotor centre, which decreases sympathetic tone and is manifested as improved blood pressure regulation and decreased muscle sympathetic nerve activity. Both exercise and low-frequency EA increase hypothalamic beta-endorphin secretion and decrease blood pressure and sympathetic nerve activity; these effects are reversed by mu-opioid receptor antagonists. Interestingly, repeated low-frequency EA plus physical exercise significantly decrease high sympathetic nerve activity.

2.6. Possible mechanisms involved in the alleviation of pain following acupuncture

2.6.1. Overview

Medical acupuncture is based on the activation of mechanoreceptors in the skin, muscle and connective tissue in tendons and muscles. Depending on how the acupuncture treatment is performed, different types of mechanoreceptors are activated.

If acupuncture is carried out using a mild and gentle technique (superficial acupuncture) tactile C-fibers (CT-fibers/cutaneous touch fibers, non-nociceptive) are activated. When the needle penetrates the skin, other touch- and pressure- receptors are activated and also nociceptors.

A majority of the recognised acupuncture points are found in muscle tissue. When an acupuncture needle is inserted into a muscle and rotated, muscle spindles are activated. The information from the spindle is conveyed into the spinal cord through Ia afferent nerves resulting in a reflex whereby the muscle fibers around the acupuncture needle are contracted. Further manipulation of the needle results in the activation of ergoreceptors in the muscle, pressure receptors that are commonly activated by strong muscle contraction. The activation of the ergoreceptors is perceived by the patient (*deqi* or needle sensation) and reported as a dull, aching, burning or stinging sensation. The afferent activity from the ergoreceptors is transmitted to the spinal cord in thin myelinated Aδ-fibers and from there in the spinothalamic tract to the thalamus and further on into the CNS. On their way to the CNS, ascending nerve fibers also project to areas in the mesencephalon (PAG, periaqueductal gray), and neurons in medulla oblongata (RVM, rostroventral medulla). From RVM descending nerve pathways project to the spinal cord modulating nociceptive transmission and sympathetic tone via the release of endogenous opioids (β-endorphins and enkephalins), monoamines (serotonin and norepinephrine), GABA (γ-amino-butyric acid) and glycine. Also, other "pain" inhibitory systems, originating at the brain stem level exist. One of these is the mechanism diffuse noxious inhibitory control, DNIC, system, which is considered to be activated following intense and painful needle stimulation. Experimental studies suggest that this system has minor relevance in clinical practice of acupuncture treatment.

From the thalamus, activity set up by the acupuncture needle is projected to limbic structures, somato-sensory cortex and frontal cortex. In the limbic structures (which have a pivotal role in affective responses) needle stimulation results in a reduced activity (deactivation) [4], which may result in a reduction of the affective component of a symptom. Also, the brain's function called default mode is re-constituted in response to the treatment. Deactivation of the limbic structures as well as a direct inflow from thalamus to hypothalamus will influence homeostasis and thereby influence for example hormonal release and autonomic regulation via the vasomotor centrum in the brain stem. Acupuncture also leads to deactivation of neuronal networks in the brain involved in avoidance behaviour and anxiety. On the other hand functional networks playing a role in reward and consolation are activated.

2.7. A deeper look into some of the possible analgesic effects of acupuncture

2.7.1. Peripheral effects – role of adenosine

Acupuncture is commonly used to treat musculoskeletal pain and acupuncture points are often located in muscle tissue in close proximity to peripheral nerves thereby possibly intercepting pain signals before they reach the spinal cord. Indeed it has been reported that adenosine, a neuromodulator with anti-nociceptive properties, is released locally during acupuncture in mice and that its anti-nociceptive actions required adenosine A1 receptor expression (A_1R-dependent anti-nociception) [3]. Direct injection of an adenosine A1 receptor agonist replicated the analgesic effect of acupuncture. Inhibition of enzymes involved in adenosine degradation potentiated the acupuncture-elicited increase in adenosine, as well as its anti-nociceptive effect. The localized actions of acupuncture are, in principle, ideal for treating pain in specific regions of the body where the pain is triggered from the periphery (nociceptive, inflammatory, ischemic or degenerative).

2.7.2. Spinal and supraspinal effects – frequency dependent mechanisms

Just the fact that different modalities of acupuncture may have different effects suggest that the effects of acupuncture are related to the activation of various endogenous mechanisms. This suggestion is supported by studies showing that the therapeutic effect induced by 2 and 100 Hz electroacupuncture (EA) stimulation may work through different mechanisms. For example, in rats with joint inflammation, there was an increased release of serotonin in the spinal cord occurred during low, but not high frequency stimulation. Also, high-frequency, but not low-frequency stimulation reduces aspartate and glutamate release in the spinal cord. In rats made tolerant to morphine, 2 Hz EA no longer had an anti-nociceptive effect. Furthermore, the two modes of stimulation seem to work through different mechanisms and do not produce cross tolerance with each other, a hypothesis that was experimentally tested. Results showed that prolonged stimulation with 2 Hz EA resulted in a gradual diminution of the analgesic effect, labelled as tolerance. Rats made tolerant to 2 Hz EA were fully responsive to 100 Hz, and vice versa, suggesting that they may be mediated by different receptors. Of added interest is that the efficacy of 2- versus 100-Hz EA seems to be aetiology-dependent. It has been reported that in a rat inflammatory model, 10 Hz EA, but not 100 Hz EA suppressed inflammation by activating the hypothalamus–pituitary–adrenal axis (HPA). Also, in a rat spinal nerve constriction neuropathic pain model, 2 Hz EA stimulation for 30 min suppressed cold hypersensitivity for more than 24 h, whereas 100 Hz was without effect. This was accounted for by the long-term depression in the spinal dorsal horn induced by the 2 Hz EA.

Experimental studies in rats have explored the central pathways mediating low and high frequency EA analgesia: 2 Hz EA seem to sequentially activate the arcuate nucleus of the hypothalamus (beta-endorphinergic neurons), PAG, medulla (enkephalinergic neurons), and the dorsal horn to suppress nociceptive transmission; 100 Hz EA activated a short parabrachial nucleus-PAG-medulla-spinal dorsal horn pathway involving dynorphin. Thus, the accumulating evidence suggests that 2 and 100 Hz EA can be regarded as two distinct therapeutic entities. This conclusion is also supported by a study in patients with dysmenorrhea who reported that both high and low frequency TENS resulted in pain alleviation but only 2 Hz was reversed by the opioid antagonist naloxone. In a clinical context though the individual variability is striking, as has been reported in patients with spinal cord injury subjected to different types of acupuncture – suggesting that the patients should be allowed to try different sensory stimulation techniques before selecting their mode of treatment. This would suggest that acupuncture is effective against some forms of pain in some individuals, where it can offer significant long-term benefit, but it is not a blunderbuss for treating all pain.

2.7.3. Central effects – changes in brain activity following acupuncture

Neuroimaging has been used to both characterize evoked brain response to acupuncture needling, as well as assess longitudinal changes in brain activity in response to acupuncture therapy.

A recent meta-analysis investigating fMRI response to acupuncture needle stimulation found that the brain response to acupuncture needle stimulation was characterized by a common pattern of activation and deactivation with overlapping responses within multiple cortical, subcortical/limbic and brainstem areas [4]. This includes primary and secondary somatosensory cortices (SI, SII) and limbic brain regions (e.g. hypothalamus, amygdala, cingulate, hippocampus). The hippocampus plays an important role in learning and memory while the amygdala plays a role in mood (affective encoding). Limbic structures are directly connected to the brainstem as well as the hypothalamus, which modulates neuroendocrine and homeostatic function. Coordinated interaction between the amygdala/hippocampus and the hypothalamus may affect arousal and motivational state. In general, many components of the limbic system are down-regulated in response to acupuncture, specifically if *deqi* sensation is induced. Furthermore, many acupuncture studies have demonstrated modulation of anterior and posterior insula, and the prefrontal cortex (PFC). The insula has been implicated in the sensory-discriminative dimension of visceral pain. Finally, the prefrontal cortex, which has multiple distributed connections with the limbic system, is likely to play an important role in expectancy-related modulation of pain processing. The insula and cingulate have been shown to support the peripheral autonomic response to acupuncture, while dorsomedial prefrontal areas may specifically support *deqi* sensation. While comparisons to sham acupuncture have been less common, evidence of greater insula and mid-cingulate activation and greater amygdala deactivation in response to real compared to sham acupuncture have been found.

2.8. Possible clinical implications

2.8.1. Site of needle insertion

A combination of needles inserted locally in the area of pain/within segmental receptive fields related to the pain – and needles inserted distally in myotomes or sclerotomes matching the origin of pain or inserted in distal body parts extrasegmental to the pain.

2.8.2. Intensity of stimulation

Pain may decrease with either superficial needle insertion or deep mode acupuncture with *deqi*, but more patients respond to deep needling.

2.8.3. Duration of treatment

Thirty-minute treatment is effective. Longer treatment relieves similar numbers of patients, but greater numbers have increased pain.

2.8.4. Timing of intervention

Pre-emptive acupuncture analgesia may result in increased or decreased postoperative pain and analgesic consumption depending on time of intervention, as has also been reported with opioids. On the other hand, treatment of chronic episodic dysmenorrhea or migraine with acupuncture one week prior to menses/migraine reduced pain and analgesic consumption, or had no effect.

2.8.5. Mode of stimulation

Chronic nociceptive musculoskeletal pain is reduced by low-frequency electrical stimulation but also by manual acupuncture or high frequency electrical stimulation. Periosteal stimulation has the greatest effect upon nociceptive visceral pain of dysmenorrhea, although other modes of acupuncture and low-frequency TENS also reduced pain.

2.8.6. Aetiology of pain

In general patients with nociceptive or inflammatory/ischemic pain have a better effect of acupuncture as compared to patients with maladaptive pain (neuropathic or long term pain). However, in patients with maladaptive pain other treatment options may not be around and even a minor relief may be clinically relevant to the individual patient.

3. Summary

'Acupuncture' as a treatment for pain encompasses much more than simply needling: it involves a complex interaction and context that may include compassion, touch, intention, attention, expectation and conditioning. This is almost certainly why clinical research consistently demonstrates large effects from 'acupuncture' as package of care, and small (but statistically significant) effects of needling over sham techniques (that often involve needling as well). It should be emphasized that acupuncture is a relatively safe treatment with few side effects and not associated with an "environmental load" (drug residues in the nature).Acupuncture has been demonstrated to be cost-effective as a treatment modality in its own right and as a complement to drugs and other interventions.

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