CHAPTER 1

MECHANISMS OF ACUPUNCTURE IN PAIN: A PHYSIOLOGICAL PERSPECTIVE IN A CLINICAL CONTEXT

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Abstract

Acupuncture is part of Traditional Chinese Medicine, a medical system with an empirical basis. A lack of scientific studies to prove the claimed effects of acupuncture has led to its rejection by many of the Western scientific community. Now that the mechanisms can be partly explained in terms of endogenous mechanisms, and the reported effects are similar or sometimes even superior to established treatments, the integration of acupuncture with conventional medicine may be possible. The effects of acupuncture are likely to devolve from physiological and/or psychological mechanisms with biological foundations, and the needle stimulation could represent the artificial activation of systems obtained by natural biological effects in functional situations. Acupuncture and some other forms of sensory stimulation trigger similar effects in man and other mammals, suggesting that they bring about fundamental physiological changes. Acupuncture stimulation, eliciting ‘de qi’, excites receptors and or nerve fibers in the stimulated tissue, which are also similarly physiologically activated by strong muscle contractions. The effects on certain organ functions are also similar to those obtained by protracted exercise. On the other hand light superficial needling, as often used during ‘sham’ acupuncture, excites cutaneous touch receptors resulting in a limbic ‘touch response’ with a suggested role in wellbeing and social bonding. The effects of acupuncture in pain...
cannot be explained by one mechanism, as pain itself is not a physiological entity, but a multitude of varying neuroplastic changes being part of adaptive or maladaptive reactions.

**THE EFFECTS OF ACUPUNCTURE ON PAIN**

The effects of acupuncture on pain may be attributed to:

1. peripheral effects (release of adenosine, NO, axonal and dorsal rot reflexes);
2. spinal effects (modulation of sympathetic tone and motor reflexes);
3. modulation of descending pain inhibitory and facilitatory systems;
4. change in the functional connectivity of the brain, with activation or deactivation of:
   a. limbic structures involved in stress/illness responses,
   b. the HPA-axis, or
   c. the prefrontal and frontal cortices;
5. restoration of the default mode state;
6. increase in parasympathetic activity;
7. activation of the reward and mirror systems;
8. modulation of the immune system;
9. extinction of fear and anxiety induced behaviour; or
10. expectation and attention.

Clinical trials suggest that variability in treatment outcome following acupuncture may also to a significant degree be attributed to the therapist. The importance of therapeutic alliance in predicting treatment success is well established. Also, 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.

**BACKGROUND**

The human biological system has evolved over a very long period of time, yet remains adapted to a hunter-gatherer lifestyle where persistence in physical activity was of fundamental importance for survival. In modern
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In recent years, many publications have explored the effects of acupuncture in pain. ‘Acupuncture’ as a treatment encompasses much more than simply needling: it involves a complex interaction and context that may include empathy, touch, intention, expectation and conditioning. This is almost certainly why clinical research consistently demonstrates large effects from ‘acupuncture’ as a package of care, and small but statistically significant effects (Vickers et al., 2012) of needling over “sham” techniques — that often involve needling as well — and as such may be considered a modality of sensory stimulation.¹

Some patients may experience a reduction of their suffering which is paralleled by changes in biological parameters whereas others ‘only’ report a subjective relief i.e. the changes seen during and after a treatment are highly dependent on the subjective report of the patient and the pathophysiological pain 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. Variability in outcome may also be attributed to

¹Lewith and Cummings. Personal communication, 2012.
factors such as operationalisation of the outcome variable and the statistical method for evaluation. 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 then be used. When using such an approach evaluating changes in electrical sensory thresholds and electrical pain thresholds after low-frequency electro-acupuncture separately (in men and women) it was found that outcomes were divergent between women and men, i.e. unchanged sensory threshold after acupuncture at the group level in women while changed in men. On the other hand the assessed pain threshold after acupuncture was changed towards higher levels in women and unchanged in men suggesting that there might be gender specific effects (Lund and Lundeberg, 2010). Likely there are many other causes of variability (including different aetiological factors) that have not yet been investigated and that are hidden within many of the statistical approaches.

**Pain Classification**

The paradigm of Traditional Chinese Medicine (TCM) with its balancing of energy may, in its way, explain diseases or disturbances, but it is 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. 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 studies have dealt with the effects of acupuncture in relation to the pathophysiological mechanisms involved.

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).

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 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 modulates 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 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 treating a particular patient’s mechanism of pain generation. Further studies on mechanism-based classification and such classification-based treatments are essential (Thomas and Lundeberg, 1996).

**PHYSIOLOGICAL MECHANISMS OF ACUPUNCTURE**

**Overview**

Effects of acupuncture therapy occur at multiple levels in the nervous system, both in the peripheral tissue, at segmental (spinal) and central levels (Stener-Victorin and Wu, 2010).

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 (electro-acupuncture, 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, NO) into the area increasing blood flow. Interestingly, low-frequency (2 Hz pulse trains) EA also increase 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. Taken together, these finding suggest that local needling may improve nutritive blood flow
and glucose uptake, factors that may be impaired in ischemic and degenerative pain conditions.

Segmental mechanisms: Needle stimulation of muscles results in the activation of descending; nociceptive (‘pain’) and sympathetic inhibitory systems — terminating in the spinal cord — within the same segments. This is how acupuncture, by using so-called segmental acupuncture points, may alter organ function by modulating sympathetic efferent activity. Also, using points segmentally related to a specific organ may modulate parasympathetic activity. As discussed above many organ diseases, results in visceral pain may be attributed to stress and increased sympathetic tone. This is of interest since many stress related organ diseases has been shown to have an increased concentrations of nerve growth factor (NGF), a marker of sympathetic activity, within the organ. In the ovaries for example, segmental low frequency EA for 20 minutes resulted in increased ovarian blood flow and decreased sympathetic activity. Further evidence that low-frequency EA modulates ovarian sympathetic nerve activity comes from studies in experimentally induced ovarian dysfunction. Gene and protein expression of markers of sympathetic were normalized after four weeks of low-frequency EA. Also, in rats with experimentally induced ovarian dysfunction, ovarian morphology was improved by thrice weekly treatment for 4–5 weeks as seen by a higher proportion of healthy ovarian follicles than in untreated rats. When treatment was increased to five times per week, low-frequency EA normalised oestrus cyclicity. This suggests that there exists is clear dose-response relationship.

Central mechanisms: When acupuncture needles are inserted, signals are transferred from the periphery to the central nervous system (CNS). Since CNS regulates homeostasis, pituitary hormone release may be affected. Acupuncture also modulates immune, endocrine and metabolic function via the CNS. Many brain areas, especially the hypothalamus, are involved in the effect of acupuncture. Acupuncture-induced release of CNS neuromodulators (peptides and hormones) seems to be essential for inducing functional changes in organ systems. The central hypothalamic beta-endorphin system is likely a key mediator of changes in autonomic functions, such as effects on the vasomotor centre, which decreases sympathetic tone. The latter and is reflected by 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 following a treat-
ment. Naloxone, a my-opioid receptor antagonist, reverses these effects.
Interestingly, repeated low-frequency EA and/or physical exercise signifi-
cantly decrease high sympathetic nerve activity for a sustained period of
time. This suggest that acupuncture both have short- and long-term effects
and that the long-term effects are not seen until a sufficient number of
treatments have been carried, i.e. assessing the effects of acupuncture after
one or a few treatments is not possible.

It is likely that some off the long-term effects of acupuncture may be
attributed to changes in the expression and synthesis of hypothalamic
beta-endorphin. Interestingly, growing evidence suggests that the opioid
system is deregulated both centrally and peripherally in many stress
related conditions. This suggestion is supported by experimental and
clinical studies of polycystic ovary syndrome (PCOS) where it has been
reported that the opioid system is deregulated both centrally and peripher-
ally. Hypothalamic beta-endorphin interacts with the hypothalamic-
pituitary-ovarian axis by exerting a tonic inhibitory effect on the
gonadotropin-releasing hormone (GnRH) pulse generator. As has been
demonstrated, acupuncture affect the hypothalamic-pituitary-ovarian axis
by modulating central beta-endorphin production and secretion, thereby
influencing the release of hypothalamic GnRH and pituitary secretion of
other hormones including the gonadotropins. Furthermore, in rats with
experimentally induced PCOS, five low-frequency EA treatments per
week for 4–5 weeks restored hypothalamic androgen receptor and GnRH
protein expression. These changes were paralleled by normalised expres-
sion and synthesis of hypothalamic beta-endorphin supporting a pivotal
role of hypothalamus in the long-term effects of acupuncture.

POSSIBLE MECHANISMS IN THE ALLEVIATION
OF PAIN FOLLOWING ACUPUNCTURE

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. A majority of the described 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 ergo-receptors in the muscle, pressure receptors that are commonly activated by strong muscle contraction. The activation of the ergo-receptors is perceived as a strong stimulus by the patient, the so-called needle sensation or *de qi*. *De qi* is often reported as a dull, aching, burning or stinging sensation. Afferent activity from the ergo-receptors is transmitted to the spinal cord in thin myelinated Aδ-fibers. From the dorsal horn of the spinal cord the information is conveyed in the spinothalamic tract to the thalamus and further on into the CNS. On its 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 pursuing a modulating effect on nociceptive transmission.
and sympathetic tone via the release of endogenous opioids (β-endorphins and enkephalins), monoamines (serotonin and nor epinephrine) and GABA (γ-amino-butyric acid) and glycine. Also, other ‘pain’ inhibitory systems, originating at the brain stem level exist. One of these is the DNIC mechanism (diffuse noxious inhibitory control system), which may be activated following intense and painful needle stimulation. Experimental studies suggest that this system has minor relevance in clinical practice.

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 needle stimulation results in a reduced activity (deactivation), which may result in a reduction of the affective component of a symptom. Also, the default mode is re-constituted. Deactivation of the limbic structures as well as a direct inflow from thalamus to hypothalamus will influence homeostasis and thereby influence 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 behaviours and anxiety. Functional networks playing a role in reward and consolation are also activated.

A DEEPER LOOK INTO SOME OF THE POSSIBLE ANALGESIC EFFECTS OF ACUPUNCTURE

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 nociceptive (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 (A1R-dependent anti-nociception). 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 localised actions of acupuncture would hypothetically make acupuncture ideal for treating pain in specific regions of the body.
These findings triggered Hurt and Zylka (2012) to elucidate if the antinociception of adenosine/acupuncture could be transiently boosted with additional substrate (AMP), blocked with an A1 antagonist or an inhibitor of phospholipase C. They reported that injection of prostatic acid phosphatase (PAP), an ectonucleotidase that dephosphorylates extracellular AMP to adenosine, administered into the Weizhong acupuncture point at the popliteal fossa, had dose- and A1R-dependent antinociceptive effects in mice models of acute and chronic ‘pain’. These inhibitory effects lasted up to six days following a single injection, much longer than the hour-long inhibition provided by acupuncture. Likely, PAP inhibits nociception via an A1R- and PLC-dependent mechanism in the periphery highlighting a role for this ectonucleotidase in peripheral pain mechanisms.

These novel findings show how deeper knowledge of acupuncture mechanisms may stimulate development of new treatments.

Given that a selective A1R antagonist blocked the antinociceptive effects of acupuncture and PAP, other compounds that block A1R, such as theophylline and caffeine (a non-selective A1 and A2 antagonist), could reduce the efficacy of acupuncture. Therefore, patients should probably eliminate xanthine-derived alkaloids (like caffeine) intake before treatment to maximise the analgesic effect of acupuncture. This suggestion is supported by a study showing that caffeine (but not placebo) at a dose equivalent to two to three cups of coffee can block the analgesic effects of transcutaneous electrical nerve stimulation (TENS).

The examples given above demonstrated how research into acupuncture mechanisms may result in new treatments, like local PAP administration, and how new findings may have direct impact on clinical practice i.e. that the analgesic effect of acupuncture partly may be attributed to a release of adenosine, a release possibly ‘being at risk’ by intake of coffee or soft drinks containing xanthine-derived alkaloids before treatment.

**Spinal and Supraspinal Effects — Frequency Dependent Mechanisms**

Just the fact that different modalities of acupuncture may have different effects suggests that the effects of acupuncture are related to the activation of various endogenous mechanisms (Han, 2011). If so selecting the
appropriated modality is crucial when treating different pain conditions. The suggestion that different modalities of acupuncture activate different antinociceptive mechanisms is supported by studies showing that in rats with joint inflammation, there was an increased release of serotonin in the spinal cord during low (2 Hz), but not high frequency (100 Hz) EA. On the other hand, high-frequency, but not low-frequency EA reduced aspartate and glutamate release in the spinal cord. Also, in rats made tolerant to morphine, 2 Hz EA no longer had an anti-nociceptive effect, suggesting that low-frequency EA stimulates beta-endorphin release. If the two modes of stimulation indeed work through different mechanisms, they should not produce cross-tolerance with each other. This has been tested and the results show 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 was fully responsive to 100 Hz, and vice versa, suggesting that they may be mediated by different receptors. This conclusion is also supported by a study in patients with dysmenorrhoea who reported that both high- and low-frequency TENS resulted in pain alleviation but only 2 Hz was reversed by the opioid antagonist naloxone. A modality specific effect on inflammation has also been reported. In a rat inflammatory model, 10 Hz EA, but not 100 Hz EA suppressed inflammation likely by activating the hypothalamus–pituitary–adrenal axis (HPA). Also, in a rat model of neuropathic ‘pain’ 2 Hz EA stimulation for 30 min suppressed cold hypersensitivity for more than 24 hours, whereas 100 Hz was without effect. Experimental studies in rats have explored the central pathways mediating low- and high-frequency EA analgesia. Two hertz EA sequentially activates the arcuate nucleus of the hypothalamus (beta-endorphinergic neurons), PAG, medulla (enkephalinergic neurons), and the dorsal horn to suppress nociceptive transmission whereas 100 Hz EA activate parabrachial nucleus-PAG-medulla-spinal dorsal horn to suppress nociceptive transmission. The ‘100 Hz pathway’ involve the release of dynorphin.

Thus, the accumulating evidence suggests that 2 Hz and 100 Hz EA can be regarded as two distinct therapeutic entities. However, there is an individual variability in our ability to activated these systems as has been reported in patients with spinal cord injury pain subjected to different types of acupuncture, some preferring low frequency and others high
frequency. This would suggest that the patients should be allowed to try different acupuncture stimulation techniques before selecting their mode of treatment.

**Changes in Brain Activity Following Acupuncture**

Neuroimaging has been used to both characterise evoked brain response to acupuncture needling, as well as assess longitudinal changes in brain activity in response to so-called acupuncture therapy ‘translational’ studies.

A recent meta-analysis (Huang *et al*., 2012) investigating fMRI response to acupuncture needle stimulation found that brain response to acupuncture needle stimulation was characterised by a common pattern of activation and deactivation and different acupuncture points elicits overlapping response within multiple cortical, subcortical/limbic and brainstem areas. This would imply that acupuncture point specificity is not crucial from a brain perspective and that many of the effects of acupuncture in the brain are general. Areas with altered activity during and after activity include 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 play a role in mood (affective processing). The limbic structures are directly connected to the brainstem as well as the hypothalamus. Neural network interaction between the amygdala/hippocampus and the hypothalamus affect arousal and the motivational state.

In general, many components of the limbic system are down regulated in response to acupuncture, specifically if the *de qi* sensation is induced. Furthermore, many acupuncture studies have demonstrated that acupuncture modulates the activity of anterior and posterior insula, and the pre-frontal cortex (PFC). The prefrontal cortex, which has multiple connections with the limbic system, plays an important role in pain behaviour (avoidance reactions) as well as in expectancy. To elucidate the role of expectancy in acupuncture, comparisons to sham acupuncture have been made, and in a meta-analysis evidence of insula and cingulate activation and greater amygdala deactivation was found in response to real compared to sham acupuncture.
Other studies have found that resting brain connectivity (defined as ongoing neural and metabolic activity in the resting brain) is also modulated by acupuncture. Studies have reported that real, but not sham acupuncture, increased resting default mode network (DMN) connectivity immediately after needling (Dhond et al., 2008). This result suggests that even after the needling procedure, there are sustained effects on brain activity. This is supported by studies showing decreased resting connectivity between the DMN and insula (areas involved in pain) over time following repeated acupuncture sessions.

To study the neurochemical processes involved in acupuncture PET have been used. Harris and coworkers (2009) investigated the action of acupuncture and sham acupuncture on mu-Opioid receptor (MOR) binding in fibromyalgia patients. They demonstrated that sham acupuncture caused a decrease in MOR binding ability whereas acupuncture increased receptor binding ability, within the same brain regions. In the acupuncture group, those individuals that displayed a greater increase in MOR binding were the also the patients that had improvements in clinical pain. Interestingly, while clinical pain was reduced to a similar extent in the acupuncture and the sham group, the MOR mechanisms were different. In another study Harris and collaborators used 1H-MRS to study glutamate and combined glutamate + glutamine (Glx) levels in patients with fibromyalgia following acupuncture (Harris et al., 2008). They demonstrated that patients with greater reductions in glutamate and Glx displayed greater improvements in pain outcomes.

**POSSIBLE CLINICAL IMPLICATIONS**

Site of needle insertion: A combination of local needles in the area of pain, or within segmental receptive fields and distal (extrasegmental) needles in myotomes or sclerotomes to the origin of pain may be tried.

Intensity of stimulation: Pain decreased with either superficial needle insertion or deep mode acupuncture with *de qi*, but more patients responded to deep needling.

Duration of treatment: Thirty-minute treatment is effective. Longer treatment relieves similar numbers of patients, but greater numbers had increased pain.
Timing of intervention: Pre-emptive acupuncture analgesia may result in increased or decrease 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 dysmenorrhoea or migraine with acupuncture one week prior to menses/migraine reduced pain and analgesic consumption, or had no effect.

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 dysmenorrhoea, although other modes of acupuncture and low-frequency TENS also reduced pain.

Aetiology of pain: In general patients with nociceptive or inflammatory/ischemic pain had a better effect of acupuncture as compared to patients with maladaptive pain (neuropathic or long-term pain).

SUMMARY

The term ‘acupuncture’ covers a diverse academic field that spans from ancient medical history to the most advanced contemporary neurophysiology. Practice ranges from simple techniques that can be taught to patients to more sophisticated invasive techniques that are the basis for much of the field of neuromodulation.

‘Acupuncture’ as a treatment for pain encompasses much more than simply needling: it involves a complex interaction and context that may include empathy, 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). Simple techniques can be taught to most healthcare workers, and this can empower pain services in the remotest regions where more expensive medicines or even the simplest analgesics may not be accessible. By contrast, within the centre of modern healthcare, where there is access to the latest scanning technology, the use of the simple slim filiform needles can greatly enhance the assessment of pain by applying a mechanical stimulus in different tissue layers and recording the patient’s perception and recognition of symptoms (as proposed by the unofficial
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IASP SIG for Pain). Acupuncture has been demonstrated to be cost-effective as a treatment modality in its own right and as a complement to drugs and other physical interventions. It should be emphasised that acupuncture is a relatively safe treatment with few side effects and not associated with an ‘environmental load’ (drug residues in the nature).

REFERENCES


