The mechanism of acupuncture analgesia: a review

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SUMMARY. In order to better understand the therapeutic effectiveness of acupuncture, questions about the means by which it operates need to be addressed. This article provides an overview of the neural, humoral and biomagnetic mechanisms that may contribute to the production of acupuncture analgesia. The concordance of some acupuncture points and trigger points is noted. Possible modulatory areas within the central nervous system are considered and parallels between the influence of acupuncture and the theory of diffuse noxious inhibitory control are explored. The concurrence of peripheral and central nervous activity with acupuncture stimulation suggests a functional if not an anatomical relationship between acupuncture points, meridians, and the nervous system. In addition, many studies demonstrate that acupuncture activates endogenous substances which inhibit nociceptive transmission. Two alternative theories are examined: that acupuncture analgesia occurs as part of a generalized stress response or as a result of an individual's suggestibility. At a practical level, the choice of stimulation modality may influence clinical outcome, as different forms of stimulation, e.g. electroacupuncture and transcutaneous electrical nerve stimulation, can invoke subtly different pathways to produce analgesia. Future studies of the clinical effectiveness of acupuncture could be enhanced by using physiological measurement to assess both process and outcomes. This may also help in providing effective, individualized treatment.

INTRODUCTION

As Lewith & Vincent have recently stated, it is important that questions about whether acupuncture is therapeutically effective are raised alongside those about the means by which it may operate. Several review articles are available which consider the clinical efficacy of acupuncture analgesia (AA). The clinical evidence remains somewhat equivocal. However, this is in part due to the weakness of research methodology in the area, a matter that is being addressed by current researchers. This paper will discuss the various mechanisms that are currently implicated in the production of the analgesic effect.

Acupuncture analgesia in Western medicine

The most well known use of acupuncture in the West is for analgesic purposes. Meta-analyses of controlled trials of acupuncture usage in chronic pain have been published. Acupuncture has many other recorded uses, which have been discussed elsewhere. Reviews emphasize the need for a greater understanding of possible underlying mechanisms.

Mechanisms underlying acupuncture analgesia

Before reviewing the information available on the anatomical and physiological pathways which may mediate an analgesic effect following acupuncture stimulation, a brief mention of the traditional Chinese medicine (TCM) viewpoint on the causes of pain will highlight the difference in underlying philosophies between TCM and Western orthodox medicine.

Within the philosophy of TCM, pain may result from excesses (Shi) or deficiencies (Xu) in the circulation of blood and/or Chi (energy source). Shi is associated with stagnation of Chi, blood or stagnation due to cold. Insufficient nourishment of Chi, blood, or the organs and tissues in general, can create Xu pain. For example, Bensoussan cites the accumulation of cold or heat and the retention of phlegm as associated common causes of pain.

In orthodox terms, the mechanisms whereby acupuncture operates can be categorized into three main areas: neural; humoral; and electromagnetic, although some overlap exists. Furthermore, these categories are not exhaustive: other mechanisms remain to be investigated and explained.
NEURAL MECHANISMS

Denervation experiments have served to support the neural model, i.e. that acupuncture effects operate via the nervous system. An early review of the neurophysiology of AA proposed the involvement of sensory-neural integration. The Figure highlights the pathways involved. An intact nervous system is required for effective AA. Local anaesthetic to a nerve blocks the effects of acupuncture in the area served by the nerve, suggesting neural involvement.

Blocking deep tissue receptors can abolish the characteristic needling sensation associated with acupuncture and the analgesic effect. However, whether the selective blocking required to test this mechanism can be achieved remains questionable.

Sensory (afferent) pathways

From a TCM perspective, for acupuncture to be effective, the needling sensation, or de Qi, must be elicited. From a physiological viewpoint, a high-threshold...
Correspondence of trigger points, motor points and acupuncture points

Liu and colleagues proposed that needling stimulates somatic muscle afferents, e.g. A-δ (group III) and even the smaller C (group IV) nerve fibres, activating central opioid production. Han has implicated both A-δ and the larger A-β fibres in transmission. Experimentation with rabbits suggested that stimulating the smallerafferent fibres produced the greatest analgesic effect.

Spinal level

Primary afferent A-β fibres end in the dorsal column nuclei in the spinal cord. High-frequency stimulation, as evoked by transcutaneous electrical nerve stimulation (TENS), operates by this route. Such fibres produce collaterals (branches) which stimulate inhibitory interneurones. One result is inhibition of the nociceptive input of C-fibres operating at a segmental level, i.e. within the same spinal cord segment.

A-δ afferent nerves also make connections at dorsal horn level, where they elicit the release of enkephalins (analgesic substances: see Humoral mechanisms below) from interneurones. Enkephalins act segmentally within the substantia gelatinosa of the spinal cord to inhibit the effects of nociceptive input. A-δ fibres also synapse with nerve cells that convey information via the spinothalamic tract to the periaqueductal grey matter (PAGM) of the midbrain. From there, descending inhibitory control upon the enkephalergic interneurones occurs.

In a cat model, Wu et al observed the discharge of spinal cord dorsal horn neurons to heat stimulus to be temporarily attenuated by electroacupuncture (EA). This suggests modulation of the afferent transmission of pain stimuli. Experiments where the spinal cord was differentially lesioned suggest that the anterolateral as well as the dorsal column may mediate AA.

Brainstem level: midbrain and medulla

The brainstem also mediates AA. TENS-conveying nerves (A-β afferents) end chiefly in the thalamus, but collaterals to the midbrain exist. From the midbrain pretectal region there are connections with the PAGM. Much of A-δ afferent input is conveyed to the reticular formation, where modulation occurs. Chang reported changes in the electrical discharge of reticular neurons during manual needling of the Tsusanli acupuncture point. The pattern was not characteristic of 'pain'; rather, the reticular formation acts more as a relay station. Descending inhibition may also originate from this region. Animal studies provide increasing evidence of a spino-reticulo-spinal feedback loop for the detection and modulation of pain. Bing et al compared the responses of subnucleus reticularis dorsalis (SRD) neurons in the rat medulla to various noxious stimuli and to acupuncture stimulation. Neurons responded to stimulation at different acupuncture points, particularly those contralateral to them; acupuncture stimuli use a similar afferent route. Similar responses were elicited by acupuncture at non-acupuncture points, which accords with a lack of topographical specificity for the analgesic effects of acupuncture.

Diencephalon level

The thalamus contains nociceptors as part of its neuronal relay system. Thalamic nociceptive outflow has been inhibited during acupuncture in animals. Changes in electrical discharge from certain thalamic nuclei have been seen following EA. A weakened aversive behavioural response, i.e. withdrawal from a noxious stimulus, was also observed. Similar effects were reported using CNS stimulation in particular areas and following the administration of the analgesic, fentanyl. In another series of experiments, thalamic nociceptive discharge was inhibited both by stimulating the midbrain raphe nucleus and by the
application of EA.\textsuperscript{30} EA thus appears to influence thalamic transmission of noxious information.

An intact pituitary gland is required for an analgesic effect to occur.\textsuperscript{28} The hypothalamus also seems to modulate AA. The arcuate nucleus receives stimulation from the prefrontal cortex; this may be a channel for the modulation of pain by emotional and cognitive interpretation. Lesions to the arcuate nucleus can reduce AA.\textsuperscript{31,32}

**Descending pathways**

Higher centres may exert a descending inhibitory gating effect.\textsuperscript{33} The PAGM is central to pain modulation by both ascending and descending inhibition.\textsuperscript{34} Stimulation of the PAGM enhanced AA in rats.\textsuperscript{35} Recently, the evidence for somatotopic organization within the PAGM has been suggested as a possible explanation of the need for using specific heterosegmental acupuncture points.\textsuperscript{13} The midbrain, in particular the nucleus raphe magnus (NRM), acts as a relay station for descending inhibitory messages.\textsuperscript{36} Liu et al\textsuperscript{37} proposed that EA may activate the NRM, thereby inducing analgesia. Medullary lesion involving the NRM has been shown to reduce EA effects.\textsuperscript{38} EA analgesia in cats was markedly attenuated by the transection of the dorsolateral columns of the spinal cord, an area that contains descending fibres from the NRM.\textsuperscript{39} A somatotopic relationship between areas of the raphe nuclei and the spinal dorsal horns may be somehow connected to the relative specificity of acupuncture points in producing regional analgesia.\textsuperscript{40}

**Diffuse noxious inhibitory control**

Diffuse noxious inhibitory control (DNIC) theory proposes a counter-irritant stimulation which acts to inhibit pain messages. Counter-irritation has been tested in both human and animal studies. Research has highlighted the need for a noxious afferent input stimulus.\textsuperscript{35,41} DNIC may act as a filter, extracting pain signals en route to higher centres.\textsuperscript{42} In addition, the signals could amplify the response to incoming noxious stimuli. Opioid receptors and other neurotransmitters are involved,\textsuperscript{42,43} as will be subsequently discussed. The impact of what may be DNIC due to sham needling, plus the overall placebo effect, may confound investigations of the clinical effectiveness of AA.\textsuperscript{2,5,44}

DNIC-associated activity does not tally directly with the acupuncture response. DNIC effects tend to be transient, whilst the effects of acupuncture can be long-lasting. Secondly, acupuncture does not appear to necessarily involve C-fibre activation. TENS and EA seem to utilize primarily A-\(\alpha\) and -\(\beta\) afferents, with C-fibres only being activated at higher threshold levels.\textsuperscript{12}

**HUMORAL MECHANISMS**

During the 1970s, it became clear that the delayed onset and duration of acupuncture analgesic response necessitated a hypothesis for a humoral influence. There is a need for more investigation in this area, given its complexity. The humoral model addresses the role of neurotransmitters, hormones and other chemical substances that circulate in the blood and cerebrospinal fluid (CSF). Many acupuncture studies have involved chemical blockade or enhancement to assess the impact of various neurotransmitters.

**Opioid activity**

He\textsuperscript{45} reviewed the CNS circuitry through which acupuncture appears to evoke analgesic activity via the release of endogenous opiate peptides. Various CNS sites are rich in opioids and their receptors. These will be briefly reviewed in relation to acupuncture studies. The research can be divided into three main categories:

1. The measurement of opioid levels, e.g. enkephalins, during/following acupuncture
2. The enhancement of opioid levels during/following acupuncture
3. The inhibition of AA using the opiate (morphine) antagonist naloxone.

**Measurement of opioid levels**

Raised CSF endorphin levels following EA have been reported.\textsuperscript{46} All studies demonstrated pain relief. Differential opiate release occurred in a study of low-frequency EA.\textsuperscript{44} CSF \(\beta\)-endorphins were raised; met-enkephalin levels remained unchanged. However, others\textsuperscript{48} reported raised plasma met-enkephalins and stable \(\alpha\)-endorphins in their patients. In an animal experiment, increased CSF leu-enkephalins were observed following EA.\textsuperscript{49}

The PAGM is a focal site for various endogenous opioids and their receptors. Zhang et al\textsuperscript{50} investigated the hypothesis that acupuncture elicits PAGM opioid release. Opioid assays from PAGM perfusate increased during EA, concordant with the degree of analgesic effect produced.

In addition, both opioid and cholinergic mechanisms in the caudate nucleus (one of the basal nuclei) have been proposed to operate during AA.\textsuperscript{51,52} Xie et al\textsuperscript{53} reported an association between caudate levels of met-enkephalin and the degree of AA produced in rats. The hypothalamic arcuate nucleus has been shown experimentally to assist in \(\beta\)-endorphin-mediated analgesia.\textsuperscript{46} Other mediation sites include the preoptic area\textsuperscript{55} and parts of the limbic system.\textsuperscript{56}
Enhancement of opioid levels

The administration of bacitracin which inhibits degradation of endogenous opioids enhanced AA in rabbits. Enkephalin levels were enhanced in the intervention group. This finding can be supported by rat experiments. Cyclohexamide, which acts to reduce met-enkephalin production, attenuated both the EA-induced increase in met-enkephalins and the analgesic effect, as measured by a tail-flick test in rats. Zhou et al reported similar findings from radioimmunoassay studies, albeit with very small sample sizes. They hypothesized that acupuncture may raise enkephalin levels by accelerating opioid biosynthesis.

One type of amino acid, the D-amino acids, block the enzymes that would normally degrade endorphins: they can prolong AA. In one experiment, tail-flick response to painful stimuli in rats was inhibited by EA, morphine and PAGM stimulation. Administration of d-phenylalanine enhanced all three analgesics, suggestive of a common underlying mechanism.

Inhibition of AA using naloxone

The drug naloxone competes for opioid receptors, blocking opioid activity. In animal models, opioid involvement was inferred, given the reversal of AA and behavioural responses following naloxone administration. Similar findings have been reported from other animal models, where the behavioural response to nociceptive stimulation was observed. Injection of naloxone into the septal area, the nucleus accumbens and the amygdala partially reversed the effects of both morphine and EA in rabbits. This work supports clinical findings from human tooth pulp stimulation experiments where AA was seen to be naloxone-reversible.

Acupuncture appears to influence the release of endogenous opioids onto receptor sites to elicit analgesia. Specific receptors, namely the μ-1 type, seem responsible for the mediation of analgesic effects. CXBX-strain mice who are deficient in opioid receptors have a poor analgesic response to EA.

Not all the research favours an opioid explanation. Chapman and co-workers failed to reverse AA using naloxone in a tooth pulp stimulation experiment. In a small randomized double-blind trial of patients with chronic pain, no change in the pain relief afforded by manual acupuncture was encountered in those given naloxone. When comparing studies, however, in addition to noting the naloxone dosage used (and possibly the time of administration), the type of stimulation and the points chosen must be considered, since these could also modify outcome. Cheng & Pomerantz reported that whilst analgesic effects could be produced by EA at both high (200 Hz) and low (4 Hz) frequencies, only the analgesia under the latter condition was reversed by naloxone.

Another set of experiments may also clarify reasons for the discrepant findings. Increased levels of both endogenous opioids and serotonin (5-HT) have been associated with acupuncture. A lowering of either one of these substrates resulted in a compensatory increase in the other. A reduced analgesic effect generally occurred with both naloxone and a 5-HT synthesis inhibitor. Pharmacological interference with both substances almost abolished analgesic effects.

Other humoral activity

Over 20 neurotransmitters have been associated with the response to acupuncture. The key players are: serotonin (5-HT); dopamine (DA); noradrenaline (NA); and somatostatin, in particular CNS regions. (It should be recalled, however, that neurotransmitters tend to be found in some quantity in most areas of the brain.) Serotonin is thought to have a largely inhibitory effect. However, in terms of specificity, it should be noted that, clinically speaking, it is the non-specific tricyclics that act as analgesics, rather than, say, SSRIs). Blood serotonin levels change with acupuncture intervention; the increase may be due to the release of a precursor or associated pituitary activity, since serotonin does not cross the blood–brain barrier. Jin et al demonstrated enhanced 5-HIAA (indicative of catecholamine metabolism per se) and tryptophan (indicative of 5-HT activity) levels with EA and suggested that EA enhances 5-HT activity.

From their experiments, Zhu & Shi proposed that acupuncture activates the chain of events from opioid, and to a lesser extent 5-HT and NA release in the PAGM to descending 5-HT influence from the PAGM to the NRM. Han et al demonstrated this experimentally in a double-blind study using clomipramine, a 5-HT reuptake inhibitor. Several authors have used 5, 6-DHT to deplete serotonin and have noted an attenuation of EA effect. Interestingly, the impact of acupuncture can be less in a depressed patient. This may accord with research that suggests that patients suffering from depression have lower serotonin levels.

Painful impulses are also modulated, both positively and negatively, by catecholamines: DA, NA and somatostatin. In experiments, AA was enhanced following the introduction of exogenous cAMP and ATP. These substances may activate intermediary hypothalamic-pituitary protein hormones. In a series of experiments, serotonin and catecholamine levels were measured during acupuncture. EA appeared to activate dopaminergic (DA) neurons. The analgesic effects of EA were enhanced using apomorphine, a DA agonist and reduced by 5,6-DHT; a dopamine receptor (D2) antagonist. Also, AA was accompanied by a reduction in brain NA levels. Unfortunately, interpretation of the findings is limited due to the small sample sizes.
Cholinergic mechanisms may also be involved in AA, the caudate nucleus being a key area. An association between AA and raised levels of acetylcholine (ACh) has been reported. Ge et al conducted histochemical analysis of rat brain after acupuncture. They found raised levels of acetylcholinesterase (AChE, the enzyme which aids ACh degradation) in the locus coeruleus and raphe nucleus, compared to a control group. Atropine (ACh antagonist) decreased the analgesic effect of acupuncture. However, given the widespread activity of ACh within the CNS, it is difficult to assess any specific role it might have.

Analgesic antagonists include substance P, cholecystokinin and cAMP. Yonehara et al suggested that EA inhibits substance P release evoked by tooth pulp stimulation in animals. They discussed the possibility that EA exerts an opioid inhibitory effect on substance P at the level of the trigeminal nucleus (brainstem region) and, via a relay system, may elicit monoamine release, with a consequent inhibitory, descending influence.

Other experiments showed AA to be antagonized by gamma-aminobutyric acid (GABA) release from the diencephalon region. Antagonistic monoamine (DA, NA) involvement, chiefly via the locus coeruleus, may also occur. Dopaminergic influences may antagonize the opioid effect in the caudate nucleus.

Inhibition of adrenergic (sympathetic) activity by acupuncture may account for some of the analgesic pattern. Cao et al reported corroboratory physiological evidence following acupuncture. However, at spinal level, NA may have a facilitatory effect. Catecholamines act differentially; AA was enhanced following direct microinjection of NA into the ventromedial hypothalamus.

Ge et al histochemically compared catecholamine levels in the locus coeruleus and raphe magnus using tissue from acupunctured animals and controls. Catecholamine levels appeared to be lower in the former group, perhaps as a result of increased monoamine oxidase activity (the enzyme which assists catecholamine degradation). The authors cite clinical evidence of a decrease in monoamines during acupuncture anaesthesia and reserpine (a monoamine antagonist) experiments, wherein analgesia has been enhanced. They conclude that the findings have been mixed, probably due to the various functions of the locus coeruleus, but favour a limited role for catecholamines in AA.

Several experimenters have sought to develop an understanding of the opposing roles of monoamines using antagonist drugs, i.e. α- and β-blockers. The evidence suggests that antagonistic (non-analgesic) functions operate via α receptors, whilst analgesic effects operate via β receptors, the overall balance favouring the former activity.

**Donor experiments**

Some interesting experiments have demonstrated the importance of circulating chemicals by giving acupuncture to one animal and then donating the body fluid to a recipient animal, with therapeutic outcome occurring in both. Unfortunately, methodological details appear to have been lost in the translation from Chinese.

**BIOELECTRIC AND BIOMAGNETIC MEDIATION**

Bioelectric mediation supposes that the meridians are electrically distinct entities. Bioelectric changes associated with the meridians may precede any neurological or humoral reactivity to acupuncture. Acupuncture points correspond well with areas of low resistance (high permeability) around the body. The resistance at a particular point seems to be lowered further in disease conditions. Many modern acupuncturists make use of this phenomenon in detecting the acupuncture points to use.

Places with the greatest electromagnetic activity/bioluminescence correspond to TCM acupuncture points. Kirlian photography has been used to measure bioluminescence. This is thought to reflect the energy flow along the meridians, although evidence for its utility remains equivocal. Attempts to measure changes in the body’s biomagnetic fields during acupuncture have been limited because the body’s magnetic fields are very weak and are not readily detectable. It remains to be seen whether meridian flow is associated with charge movement during acupuncture.

More recently, it has become possible to detect acupuncture meridians using radioisotopes. Darras et al reported upon the use of technetium-99m to investigate acupuncture pathways. A particular migratory pattern was seen from various acupuncture points, which accorded with the traditional channels. Furthermore, these paths were distinct from the vascular and lymphatic circulation, in terms of rate and direction of flow. Concentrated areas of the tracer related not only to organs known to take up the tracer, but also to acupuncture points along a given meridian. The migratory pattern appeared to be altered in pathological conditions. In addition, changes in the tracer’s migration rate from contralateral points of the body followed unilateral stimulation of an acupuncture point on the same meridian. The authors proposed that acupuncture stimulation evokes an effect via a neurochemical process. The pathways may be related to connective tissue diffusion following the neurovascular bundles along the extremities. This interstitial route needs further investigation.
Differential responses to various modes of acupuncture stimulation

Bioelectrical mediation may partially explain why acupuncture outcome may vary depending upon the type of stimulation employed, e.g. manual or electroacupuncture. Furthermore, research evidence suggests that the intensities and frequencies used in EA may produce subtly different physiological outcomes. In a therapeutic setting, therefore, one technique may be more appropriate than another.

Alternative hypotheses

Acupuncture analgesia as a generalized response to stress

Some critics have suggested that AA may be purely a generalized response to trauma. However, researchers have described the distinctions between acupuncture and stressful stimuli, highlighting different processes and outcomes.

Alternative hypotheses: hypnotic suggestibility

Some researchers contest that acupuncture effect is due to a hypnotic-type suggestibility. Knox & Shum were unable to reverse hypnotic analgesia using naloxone, an indication that at least one different mechanism operates. There was some intra-individual commonality of responsiveness to acupuncture and hypnotism, however. Others have found this to be unrelated to analgesic outcome.

CONCLUSION

Whilst both neural and humoral mechanisms are important, neither can fully explain such a fundamental phenomenon as differential point efficacy in certain painful conditions. There may be no distinct neural or circulatory difference between a real point and a nearby sham point, yet needling outcomes can be different. Needling changes the electrical activity at points and along channels; this may serve to correct a homeostatic imbalance. The clinical effectiveness of acupuncture per se is said to depend upon the specific placement of the needles at designated acupuncture points. For analgesic activity, point specificity appears to be less crucial than for other types of therapeutic intervention, e.g. for vomiting. Hence DNIC may be a valid model for partially explaining AA.

The therapeutic benefits of AA may relate to activity other than neurological blockade, e.g. decreasing gastric acidity or eliciting vasodilation. "Correct acupuncture, properly directed to the management of pain, will also increase oxygenation of cardiac muscle, reduce gastric acidity and control inflammatory responses." Hopefully, future studies of the clinical effectiveness of acupuncture will be enhanced by the measurement of physiological parameters to assess both the process and outcomes. This will aid the comparison of acupuncture and alternative analgesics and may assist in the provision of effective, individualized treatment.

ACKNOWLEDGEMENTS

The author would like to thank J. Tissier, R. Walker and J. Sizer for their valuable comments on this article.

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