Acupuncture mechanisms for clinically relevant long-term effects – reconsideration and a hypothesis

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Abstract

From the author's direct involvement in clinical research, the conclusion has been drawn that clinically relevant long-term pain relieving effects of acupuncture (>6 months) can be seen in a proportion of patients with nociceptive pain. The mechanisms behind such effects are considered in this paper.

From the existing experimental data some important conclusions can be drawn:

1. Much of the animal research only represents short-term hypoalgesia probably induced by the mechanisms behind stress-induced analgesia (SIA) and the activation of diffuse noxious inhibitory control (DNIC).
2. Almost all experimental acupuncture research has been performed with electro-acupuncture (EA) even though therapeutic acupuncture is mostly gentle manual acupuncture (MA).
3. Most of the experimental human acupuncture pain threshold (PT) research shows only fast and very short-term hypoalgesia, and, importantly, PT elevation in humans does not predict the clinical outcome.
4. The effects of acupuncture may be divided into two main components – acupuncture analgesia and therapeutic acupuncture.

A hypothesis on the mechanisms of therapeutic acupuncture will include:

1. Peripheral events that might improve tissue healing and give rise to local pain relief through axon reflexes, the release of neuropeptides with trophic effects, dichotomising nerve fibres and local endorphins.
2. Spinal mechanisms, for example, gate-control, long-term depression, propriospinal inhibition and the balance between long-term depression and long-term potentiation.
3. Supraspinal mechanisms through the descending pain inhibitory system, DNIC, the sympathetic nervous system and the HPA-axis. Is oxytocin also involved in the long-term effects?
4. Cortical, psychological, "placebo" mechanisms from counselling, reassurance and anxiety reduction.

Keywords

Acupuncture, mechanisms, therapeutic acupuncture, acupuncture analgesia, axon reflexes, long term depression, oxytocin, local endorphins.

Introduction

In the author's thesis[1] the main question was whether acupuncture seemed to have any clinically relevant long-term effects at all. In some of the original works[2;3] it appeared probable that acupuncture could have a long-term pain-relieving effect in some chronic pain patients, mostly those with nociceptive pain. It also became probable that acupuncture could have some influences on the autonomous nervous system for a longer period than just after stimulation.[4;5] To get an explanation for these effects the author analysed the experimental work performed to explain acupuncture analgesia. It soon became very obvious that the animal research (and experimental human research) was not particularly relevant to what we observed (and try to perform) in the clinical setting. Thus, it became necessary to look at other mechanisms than those involved in the standard neurophysiological model. Therefore,

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a new hypothesis of mechanisms behind therapeutic acupuncture was put forward in the thesis. This article is based upon the hypothesis in the thesis where more discussion and more references can be found regarding the subject. This article is also a critical review of important experimental work published from different research groups during the last three decades. A shorter form of this article has recently been published.[6] The article does not attempt to include inactivation of trigger points by direct needling of the tender points.

Acupuncture Analgesia and Therapeutic Acupuncture

The term 'acupuncture analgesia' (AA) was used for electroacupuncture (EA) used to give powerful and immediate pain relief during surgery, first used in China in 1958 but not described until 1973.[7] This form of acupuncture was extensively described in the western media.[8] A success rate of 90% was claimed among those selected for the method in China. However, it soon became clear that only a minority of patients could develop sufficient analgesia to tolerate surgery. Less than 10% of the patients showed a satisfactory response in acupuncture trials.[8;9] For this 10%, only one third had analgesia acceptable according to western standards. Even so, patient selection and psychological preparation was crucial, and often combined with local anaesthetics or other analgesics.[10]

In 1974 Felix Mann reported 100 observations on patients receiving AA.[11] In only 10% of the experiments, the resulting analgesia was considered adequate for surgery. He emphasised, that in therapeutic acupuncture to treat different symptoms, a mild stimulus was all that was usually required. This in contrast to that needed to obtain AA where the stimulation had to be continued for at least 20 min and had to be painful to the maximum level the patient could tolerate. He concluded that, usually, the stimulus required to achieve AA was so intense that the resulting pain would be unacceptable to most western patients. Other studies have come to similar conclusions – acupuncture for surgical analgesia has too many disadvantages and works in too few patients to be of practical value.[12]

In the following text the term therapeutic acupuncture (TA) will be used for the clinical use of acupuncture for other conditions than when immediate analgesia is the goal. It has to be realised that there is a major difference between AA for surgery and the clinical effects sought when practising TA. When performing therapeutic acupuncture for symptom relief, mostly manual acupuncture (MA) is used and the effects are induced slowly and recognised after a course of perhaps 4-8 treatments.[8;9]

The proposed AA effect on surgical pain stimulated physiological research where the goal was to find an explanation for immediate and very strong analgesia. Consequently, much physiological research during the last 25-35 years has concentrated on explaining a phenomenon that may only exist in about 3-10% of the population and that possibly has very little in common with TA. For the main differences between AA and TA, see table 1.

Table 1 **Differences between acupuncture analgesia and therapeutic acupuncture.**

Acupuncture Analgesia	Therapeutic Acupuncture
Immediate and very strong hypoalgesia is the goal.	Immediate hypoalgesia is not the goal.
Starts very fast (minutes).	Symptom relief, often slowly induced after a number of treatments. The effects gradually increase after more treatments.
Short-term=minutes.	Long-term=days-weeks-months.
The stimulation is felt very strongly; it is often painful and uncomfortable.	The stimulation is felt rather weakly; it is rarely painful and often relaxing.
Used most often in different physiological experiments – often electroacupuncture in pain threshold experiments on humans or animals. Used for surgical hypoalgesia.	Used for clinical pain relief and other symptom relief. Most often manual acupuncture but can also be electroacupuncture.

Usual clinical observations concerning therapeutic acupuncture for chronic pain

After the first few acupuncture treatments there might be several hours of pain relief or nothing at all may happen. Some patients even get worse and have a temporary aggravation of their symptoms for some days before they start to improve. This aggravation can be seen for 2-3 days or even up to a week. For those responding to acupuncture, usually both the degree and duration of the pain relief increase after each single treatment,[13;14] a clinical observation that has gained some experimental support.[15] In chronic pain patients the improvements are often incomplete with symptom relief for weeks or months. A proportion of patients, 20-30% can be regarded as non-responders to acupuncture regardless of the condition from which they suffer.[14] Some people, often called strong reactors, respond very well to acupuncture if the correct 'dose' of acupuncture is given; this is perhaps the 'art of acupuncture'.[16;17;18]

As acupuncture needles are inserted into the tissue, mostly down to the muscular layer, they excite receptors and nerve fibres. A special method is painful sensory stimulation, which has been used through the centuries, an old idea that a short but very painful stimulus would reduce pain. These methods have been called 'counterirritation' or 'hyperstimulation analgesia', and acupuncture is sometimes regarded as such a method.[19] However, it is important to realise that most patients who are treated with acupuncture describe the procedure as relaxing and pleasant, not painful and stressful. Indeed, most patients feel calm, warm, relaxed, tired and heavy in arms and legs during and after treatments, some even feel euphoric.[17;18]

Acupuncture mechanisms – the standard neurophysiological model

Several physiological mechanisms have been suggested accounting for the pain relieving effect of acupuncture. Spinal and supraspinal endorphin release have been proposed,[20-26] as has the activation of DNIC (Diffuse Noxious Inhibitory Control) through bulbospinal pathways.[27] The involvement of neurochemicals like serotonin, noradrenalin and different endorphins, as well as hormones such as adrenocorticotrophin (ACTH) and cortisone, has been studied in detail and is summarised in the relevant literature.[28-31]

The acupuncture physiology is often summarised in the following manner.[18;29;31-33]

For acupuncture needles inserted within the segment of pain:

- Spinal gate-control mechanism (involving enkephalin and dynorphin)

For extrasegmental acupuncture:

- Activation of midbrain structures, particularly the periaqueductal grey (PAG), and the descending pain relieving system (involving endorphins, serotonin and noradrenaline).
- Diffuse noxious inhibitory control (DNIC) is sometimes claimed to be involved.
- Activation of the HPA-axis (hypothalamic-pituitary-adrenal) with increased levels (in the blood) of β-endorphin and ACTH/cortisone.

Gate-Control

Melzack and Wall introduced the gate control theory in 1965.[34] This theory gave a theoretical framework for explaining the observed pain-relief resulting from stimulation of somatic afferent nerves. The mechanism for this modulation of afferent input was said to be located in the dorsal horn and to involve the Wide Dynamic Range (WDR) neurones. WDR neurones receive input from both nociceptive and non-nociceptive afferents. In short, the theory implies that the WDR neurones are inhibited by interneurones that are excited by non-noxious inputs in the same segment. This mechanism was proposed to be under supraspinal control. The inhibition would work fast and be short-term, with effects occurring mainly during stimulation.

This mechanism only explains pain relief during stimulation and it does not explain why pain inhibition may outlast the duration of stimulation by hours or even days.

Descending pain inhibitory and facilitating systems

The existence of descending pain inhibitory systems from the brainstem was determined by experiments in the late 1960s and beginning of the 1970s. It was found that electric stimulation in an area called the peri-aqueductal grey (PAG) could abolish pain when performing exploratory

laparotomies in unanaesthetized rats. This new form of analgesia was called stimulation-produced analgesia (SPA).[35;36] It was later shown that this pain relief could also be produced in chronic pain patients.[37] The descending pain inhibitory tracts in the spinal cord seemed to originate in neurones in the nucleus raphe magnus (NRM). These neurones project to the dorsal horn and use serotonin as the principal neurotransmitter.[38-40]

The endorphinergic systems with opioid receptors and endogenous opioid peptides were discovered somewhat later than SPA.[41-43] It was soon discovered that the areas with a rich amount of endorphin receptors overlapped those from which SPA could be elicited.[44] It was also shown that naloxone (a μ-receptor blocking agent) could partially block the action of opioid injections into the PAG, also indicating the role of endorphins in this form of analgesia.[45] The most common endorphins (in the pain control system) are β-endorphin, enkephalins and dynorphins. The most important endorphin receptors are called μ, δ and κ.

Much interest has focused on β-endorphin, which binds mostly to the μ-receptor. It is released through two different systems. One is from the arcuate nucleus of the hypothalamus to the midbrain and brainstem nuclei (i.e. the PAG). It is also released into the blood via the pituitary. Pro-opiomelanocortin (POMC) is a peptide precursor molecule in the pituitary that is broken down to produce equimolar quantities of β-endorphin, ACTH and melanocyte stimulating hormone (MSH). These substances are thus released into the bloodstream. Beta-endorphin cannot pass the blood brain barrier, and thus the two compartments of β-endorphins do not influence each other.

There is now considerable evidence for the existence of multiple descending pain inhibitory systems, of both opioid and non-opioid nature.[46] The different pain inhibitory systems can be activated clinically through dorsal column stimulation (DCS) where the mechanism is thought to be both segmental[47] and of supraspinal origin.[48]

Besides these inhibitory systems, the existence of descending excitatory systems has also been shown.[49] These systems are involved in the induction of hyperalgesia. Thus, in the dorsal horn there is a balance between the inhibitory and excitatory systems.

DNIC

A special form of descending pain inhibition seems to work according to the principle 'pain inhibits pain'. This physiological system has been called diffuse noxious inhibitory control (DNIC).[50;51] DNIC does not appear to be somatotopically organised since it can be triggered by many types of noxious stimulus from any part of the body outside the area of pain. The phenomenon has been studied in animals as well as in humans.[25;52] The strength of the inhibition is directly related to the intensity of the pain provoking stimuli but the inhibition persists for only some minutes, after the stimulation ceases. The mechanism involves a supraspinal loop, which involves endorphinergic as well as serotoninergic neurones. The relation between DNIC and stress induced analgesia is not clear, but in stress-induced analgesia there are often pulse and blood pressure increases, changes that are not necessary for DNIC activation. The mechanism of this system has been suggested to be a kind of lateral inhibition in the nociceptive system, detecting the most intense pain producing area by blocking all other pain input. In clinical practice sometimes a technique is used where a painful stimulus is indeed applied within the painful area, i.e. the injection of sterile water intracutaneously in the skin of the neck to treat neck pain.[53] This clinical method has probably very little in common with DNIC since DNIC is very short acting, and according to it´s physiological basis, it should be performed outside the area of pain.

Problems with the standard neurophysiological model to explain clinical experience

When we try to understand therapeutic acupuncture there are some severe shortcomings of the model mentioned above:

- The model can only explain very short-term pain relief after each stimulation period. The gate-control mechanism is only active during stimulation and the descending inhibitory system for up to about eight hours.
- The model cannot explain why, in some patients, pain relief starts some days after the treatment whether the patient is first worse or not. The gate-control does not start some days after the stimulation, and that is not the case for the descending pain inhibitory systems either.

- The model cannot explain why there seems to be more prolonged pain relief after more treatments and why there seems to be long-term pain relief after a course of 8-12 treatments. If the model had been correct for therapeutic acupuncture then other forms of stimulation induced analgesia, for example TENS, peripheral nerve stimulation, dorsal column stimulation, deep brain stimulation, stress-induced analgesia or painful stimulation, claimed to work through the same physiological systems, ought to be acupuncture-like in effects. All these forms of stimulation can cause immediate and short-lasting pain relief directly after stimulation.[54-60] But, they are not all reported to cause long-term pain relief or to create pain relief some days after a stimulation period. Thus, there are important differences, see table 2.

The standard neurophysiological model can probably be used to explain AA (surgical analgesia or pain relief during delivery), but it should be realised that AA is mostly painful stimulation, and if the gate-control mechanisms are implicated, then the stimulation should be non-painful.

Experimental animal acupuncture pain research: Stress-induced analgesia or specific acupuncture induced analgesia?

Many research groups have tried to monitor central neurochemical changes particularly after EA to understand mechanisms of pain relief after acupuncture. However, most groups have used conscious animals where no special attention has been taken to rule out stress-induced analgesia.

Different kinds of 'stress' (nociceptive as well as non-nociceptive) have been shown to induce analgesia – referred to as stress-induced analgesia (SIA).[59] Experimentally it was shown (in rats) that electric shocks to the feet over a period of 15 minutes induced analgesia that was comparable in potency to large doses of morphine and that was partially reversible with naloxone. Stress was also shown to induce increases in brain endorphins. Repeated daily applications of shocks to the feet gradually led to adaptation. Thus, SIA develops tolerance and not an increased effect after repeated applications to rats. Later it was shown that short periods of shocks to the feet resulted in non-opioid analgesia whereas longer periods of shocks to the feet activated the opioid analgesia system. It was even shown that the same stressor

Table 2 **Some examples of stimulation based pain-relieving methods.**

Method or system activated for pain relief	Usual stimulation characteristics What is stimulated, how and where?	Reported start of pain relief after some days?	Reported post-treatment pain relief	Reported long-term pain relief after 8-12 treatments?	References
TENS Hi	Skin afferents, mostly non-noxious, within the segment of pain	No	Immediate + hours	No	54
TENS Lo	Muscle afferents, mostly non-noxious, within the segment of pain	No	Immediate + hours	No	54
Peripheral nerve stimulation	Whole affected nerve, non-noxious	No	Immediate + hours	No	55
DCS	Dorsal columns, non-noxious, paresthesia to the painful area	No	Immediate + hours	No	56;57
DBS (Thalamus)	Thalamus	No	Hours – 3 days	No	58
DBS (PAG)	PAG	No	Hours – 1 day	No	58
SIA	Stress and noxious stimulation, whole body	No	Immediate + hours	No	59
DNIC	Skin/muscle afferents, noxious, outside pain area.	No	Very short (minutes)	No	60
Therapeutic acupuncture	Skin/muscle afferents, mostly non-noxious, local around pain area and distant places.	Yes	Longer with more treatments	Yes	1;14

TENS=Transcutaneous electrical nerve stimulation; Hi=High frequency; Lo=Low frequency; DCS=Dorsal column stimulation; DBS=Deep brain stimulation; PAG=Periaqueductal grey; SIA=Stress induced analgesia; DNIC=Diffuse noxious inhibitory control.

could cause different forms of analgesia depending on the area of the body to which it was applied.[59] It was later shown that SIA also exists in man.[60]

Interestingly, it has now been shown that the different endorphin receptors (μ, δ, κ) can be involved in different kinds of SIA. Thus, the non-opioid form of SIA previously referred to may simply represent activation of naloxone resistant opioid receptors.[29] For example, κ-receptors mediate stress induced antinociception at spinal levels, whereas δ-receptors mediate the same phenomenon at a supraspinal level.[61-63] Compare this with the arguments for the activation of specified opioid receptors at different CNS locations after EA with different frequencies.[29;30]

Many of the experimental results in acupuncture research could be interpreted as stress-induced analgesia. For example, in the initial experiments where humoral factors were indicated Cerebrospinal Fluid CSF, was taken from rabbits that had received acupuncture and was injected into recipient rabbits.[64] The rabbits were restrained and fingers pressed, twice a second, against the area of the Achilles tendon insertion on the lower leg ("finger acupuncture"). This was because when acupuncture had been performed in initial trials there was too much bleeding afterwards from points in the lower leg (indicating severe struggling of the animal). Thus, the experiments did not in reality even include real acupuncture. The word acupuncture comes from acus (=sharp) and pungere (=puncture). Therefore, the use of the word acupuncture should imply that needles are involved in the process.

On the other hand, Galeano et al showed that in quiet, non-struggling rabbits, EA did not produce any analgesia.[65] However, if they were agitated during stimulation they became hypoalgetic. In opposition to this, Han et al claimed that a naloxone reversible hypoalgesia occurred in rabbits after EA.[66] Even if the authors state that their experiment was not associated with a stress reaction, they admit that, initially, just after needle insertions, a stress reaction with increased pain thresholds occurred. When this stress reaction had subsided, one group of animals continued with only needles inserted while the EA group was subjected to muscle contractions from the stimulation. In another study it was shown that EA with a strength of at least 10 times the threshold to evoke visible muscle contraction was needed to produce antinociception.[67]

Mostly, EA with intensity gradually increased from 1-2-3 mA, has been performed on conscious rats with acupuncture needles inserted in locations on the lower legs corresponding to the acupuncture points SP6 and ST36 in humans. In several reports,[68;69] it was explicitly written that: "Squeaks occurred at the beginning of a new stimulation intensity and subsided in 2-3 minutes." In 1991, Bossut and Mayer noted that during EA stimulation rats showed obvious signs of discomfort (with intensity of only about 1 mA).[70] They concluded that intensities that did not induce stress reactions in the rats did not produce any analgesia. Their conclusion was that the intensities used to increase pain thresholds in rats were too strong to be clinically applied in humans.

Needle thickness

To perform acupuncture in animals, needles of the same thickness as those used in humans have been used most commonly (often 0.3mm=30G), in spite of the fact that the animal weighs about 200-300g (typical laboratory rat).[32] It can therefore be suspected that much more tissue damage, nociception and stress are generated in the rat than in the human being with the same needle thickness. Consider that the rat paw is about 20 times smaller than a human hand and hence the corresponding needle thickness for a human hand would be about 6mm in diameter to produce the corresponding amount of tissue damage and nociception as in most animal 'acupuncture' experiments. These needles are most often applied to places where human acupuncture points like LI4, SP6, and ST36 are situated.

Manual acupuncture or electroacupuncture (EA)?

Almost all research has been performed with EA – although therapeutic acupuncture is mostly manual acupuncture. However, many of these EA-studies have included a control group with only needles inserted without electric stimulation. In none of these has it been found that increase of pain thresholds has occurred.[69;71-74]

Acupuncture and physical training – the same physiology?

It has been argued that the mechanisms behind acupuncture are the same as those in muscle training.[33] This idea has been proposed since EA excites receptors or nerve fibres in the tissues, which are stimulated under physiological conditions by strong muscle contraction. The hypothesis was based on experiments with sciatic nerve stimulation (proposed to mimic acupuncture), running in wheels and electric muscle stimulation (also proposed to mimic acupuncture).

For example, strong, 6-16 times muscle contraction threshold, low-frequency electric stimulation to the sciatic nerve in conscious spontaneously hypertensive rats induced a pain threshold elevation and a post stimulatory reduction of blood pressure, after an initial period with sympathetic activation during the stimulation.[75] However, if diazepam had been given to the rats before and during the experiments,[76] or the animals were anaesthetised,[77] no such blood pressure reduction was seen. This strongly suggests that the effects were stress-induced. The hypothesis also claims that acupuncture releases β-endorphin and ACTH into the peripheral circulation, but this is also a sign of stress or pain. The stimulation intensity described – 6-16 times muscle contraction threshold, is considerably higher than that used clinically in humans. Patients receiving therapeutic acupuncture often feel calm, warm, relaxed, tired and heavy in arms and legs. They do not appear to be 'stimulated' in the same way as during or after a period of running. Thus, the proposed hypothesis does not seem to explain the features relevant to therapeutic acupuncture.

Experimental human acupuncture pain research

In 1965, the first human experiments were performed which showed that MA (to LI4) produced a generalised pain threshold (PT) increase in about two-thirds of the volunteers. The PT increased gradually over 15-30 minutes of stimulation and gradually decreased after removal of the needles, halving in value over 15-17 minutes. These findings were not published until 1973.[78] Andersson et al found that the dental PT of volunteers gradually increased when performing low frequency (1-5Hz) electrical stimulation intrasegmentally to the area of experimental pain.[79;80] The PT increased after a latency of about 15-30 minutes and remained elevated until 30 minutes after stimulation had finished. Only if the stimulation intensity had been strong, just tolerable and had produced uncomfortable muscle contractions, was PT elevation seen. Chiang showed that AA was dependent on muscle afferents but not skin afferents in the stimulated area by using local anaesthetics to block the afferents from the first dorsal interosseous (LI4) area of the hand.[81] Pomeranz and Paley confirmed this finding.[71] The efficacy of needling was also shown to be very much dependent upon the intensity of the needling sensation produced locally. Further, it was found that the AA was stronger if two points were needled instead of only one.[81] However, the PT elevations seemed to be rather small and variable, and were only found in a proportion of subjects. For example, Chapman et al [82] showed the pain relief of acupuncture to be about the same as when inhaling 33% nitrous oxide,[82] and Mayer et al found dental PT elevation above 20% after MA in 20 out of 35 volunteers (57%).[21] When EA stimulation was performed with intensity just below painful muscle contractions, only 42% of the volunteers increased their PT above 20%.[83] Lundeberg et al used MA and EA at 2Hz or 100Hz with an intensity twice sensory threshold.[84] They found that extrasegmental stimulation did not increase PT at all. Segmental stimulation did induce PT elevation, but there was no effect beyond the end of the stimulation period. After clinical application of EA, creating strong muscle contractions, Widerström et al found very small PT increases (mean 10%).[85] Even in acupuncture responders, only small PT elevations were found (mean 20%).[86]

Two systematic reviews have been published in a recent text.[32] They concern experimental pain and MA (twelve studies) or EA (also twelve studies). It was concluded that MA had no effect on experimental pain thresholds compared to sham stimulation, whether stimulation was extrasegmental or intrasegmental. The conclusion regarding EA was that it could create minor (20-30%) elevation of PT. It was argued that these

small effects probably have no clinical relevance. These small changes are even smaller than those seen after hypnosis.

Are endorphins involved or not?

Human studies have been performed to evaluate whether endorphins are involved in the mechanisms of acupuncture induced pain relief. The results are conflicting. Mayer et al reported antagonism of PT elevations resulting from painful MA when naloxone was administered.[21] Chapman et al could not confirm this result.[83;87] Clement-Jones et al demonstrated increased β-endorphin in CSF after acupuncture for chronic pain.[24] Kiser et al showed that the degree of pain relief after EA in 14 of 20 chronic pain patients was correlated to the increase in plasma met-enkephalin.[88] In a review of the subject,[26] Price and Mayer concluded that endorphins are partially involved in acupuncture analgesia in humans, even if we don't know where. Thus, AA in humans is believed to rely both on opioid and non-opioid mechanisms. However, it is not known whether endorphins are involved locally (in the tissues), within the central nervous system, or both.

Does pain threshold elevation predict clinical pain relief?

An important study on the issue of pain thresholds and pain relief in chronic low back pain patients showed that, after acupuncture, 60% of the patients had a raised tolerance to experimentally induced pain both on the back and forearms.[15] These changes persisted for only 90 minutes. Eleven out of 12 patients got relief of their clinical low back pain condition. This therapeutic relief followed a different time course; it reached a maximum 2 to 24 hours after acupuncture and persisted for several days (up to 10-14 days). Over the two-month period when acupuncture was performed, there was an increase in pain relief (measured with VAS) with the treatments. Some patients developed both types of analgesia while others experienced only one type. The authors concluded that acupuncture produced two distinctive patterns of analgesia in man. One was a 'central – inhibitory pattern' of analgesia, which was a short-lasting (90 minute) increase in pain tolerance to experimentally induced pain. This was probably a central effect as it occurred both locally and in remote regions. The other was an 'origin-specific pattern', and was regarded as a local therapeutic effect around the painful region. The authors thought this effect was mediated by peripheral changes, caused directly or indirectly by the acupuncture stimulus.

Interestingly, Dyrehag et al attempted to see whether it was possible to predict which patients with chronic neck and shoulder pain would respond to EA.[89] They performed an initial test session where dental PT was measured before and after EA. No correspondence at all was found between initial PT changes and clinical outcome. Thus, PT elevation does not seem to have any clinical relevance at all in terms of long-term outcome as it cannot predict which patients will benefit from acupuncture treatment.

Acupuncture and the sympathetic nervous system

Acupuncture often induces local vasodilatation around the needles, and a feeling of warmth all over the body. Thus, it seems as if acupuncture involves both local (through axon reflexes) and general vasodilatation.[90] After studying skin temperature changes, Ernst and Lee proposed that acupuncture has a central sympathetic inhibitory effect.[91,92] However, in some instances EA first caused a cooling effect during stimulation.[92] Dyrehag et al noticed a decrease in the skin temperature during a test EA session before a treatment series.[93] However, after eight EA treatment sessions, an increase in skin temperature was demonstrated in a new EA test stimulation. Direct measurements of sympathetic nerve activity, recorded with a microelectrode inserted in a muscle fascicle of the peroneal nerve, in human volunteers, were reported in a placebo-controlled study.[94] It was shown that after 2Hz EA, at maximal intensity without discomfort, to points in the upper extremity (LI4 and LI11), dental PT was elevated and a transitory increase of muscle sympathetic nerve activity occurred.

It seems probable that the results from Sato et al are valid here – low intensity stimulation leads to a reduced sympathetic outflow while strong (noxious) stimulation leads to increased activity.[95]

Acupuncture and modulation of the stress-system (HPA-axis)

It is often proposed that β-endorphin and ACTH (and thus cortisone) are released into the blood after acupuncture. This would strongly imply that acupuncture is a stressful event.[97;98] This can be exemplified by the frequently cited animal study of Cheng et al,[96] in which the conclusion was that the blood level of cortisone was increased (40%) after EA. However, the trials were performed on conscious horses where four or five very thick needles, 14G (about 2.10mm diameter), were inserted 3 to 5cm into the lower limb, including sites under the foot. Electric stimulation was adjusted to above the threshold for muscle contractions. In contrast, using non-noxious MA and EA in humans, Lundeberg et al did not find any changes in plasma β-endorphins or ACTH after stimulation.[84]

It is now realised that the effect on plasma ACTH (and cortisone) of sensory stimulation is dependent on the strength of stimulation.[95] Thus, even in anaesthetised rats and humans, an increase of plasma ACTH and cortisone can be observed when noxious stimulation is performed, however, innocuous mechanical stimulation produced no significant change in plasma cortisone. The same seems to be true for release of adrenaline and noradrenaline from the adrenal glands – low intensity repetitive electrical stimulation or brushing of the skin gives rise to a decreased release of adrenaline and noradrenaline, while high intensity repetitive electrical stimulation, or noxious stimulation, produces increased levels of these stress hormones.

Conclusions from the existing acupuncture experimental data:

1. Most of the animal research on acupuncture probably only shows the consequences of nociceptive stimulation and the activation of SIA and DNIC.
2. Stimulation strength is very important as noxious or stressful stimulation induces activation of the stress-system while gentle stimulation seems to reduce it.
3. The majority of acupuncture research on animals has been performed using (strong) EA even though human therapeutic acupuncture is most often performed with gentle manual acupuncture.
4. When manual acupuncture has been used in animal research no pain threshold elevation has been described.
5. Pain threshold elevation in humans only seems to occur if the stimulation is painful.
6. Further, proof only exists for very short-term and very small PT elevations after EA. The PT elevations do not seem to have much clinical relevance.
7. Pain threshold elevations in humans do not correspond at all with clinical outcome after therapeutic acupuncture.
8. Acupuncture analgesia in humans probably has both opioid and non-opioid mechanisms.
9. The experimental research has only investigated mechanisms for acupuncture analgesia, and not for therapeutic acupuncture.

A hypothesis on the mechanisms of acupuncture

A. Acupuncture induces peripheral events that might improve tissue function and induce local pain relief: (local needles)

Axon reflexes, neuropeptides and dichotomising nerve fibres

Just the insertion of a needle in the tissue induces changes close to the needle (in all different tissues penetrated) and through axon reflexes. The flare reaction (reddening, vasodilatation) is often seen locally around the acupuncture needles. This vasodilatation in the skin due to axon reflexes has been recognised for quite some time and the mechanisms have been clarified in detail.[99;100] The stimulation of Aδ or C fibres releases vasoactive and pro-inflammatory neuropeptides such as calcitonin gene-related peptide (CGRP), substance P (SP), neurokinin A (NKA), opioids, galanin, somatostatin and vasoactive intestinal peptide (VIP). The profound and prolonged vasodilatation is probably mediated mostly by CGRP.[101-104] EA (and TENS) produces peripheral vasodilatation, in skin and muscle, both experimentally and clinically, that probably is caused by this neuropeptide release.[105-113]

Remarkably, CGRP is pro-inflammatory,[100] but it has also been shown that CGRP (in low doses) has a potent anti-inflammatory action.[114] Thus, it

seems as though a form of balance exists between anti-inflammatory and pro-inflammatory effects (low dose or high dose of CGRP) in the tissues.

Dichotomising spinal nerves have been identified with branches to two different types of tissues, for example, nerve fibres to both intercostal muscles and internal organs,[115;116] stimulation of the saphenous nerve gives rise to vasodilatation around the sciatic nerve,[117] and nerve fibres supplying the intervertebral disc also supply skin in the groin.[118] Such connections may mean that axon reflexes provoked by acupuncture can have influences on structures deeper and more distant than local areas of skin and muscle.

Neuropeptides and trophic effects

Acupuncture can improve salivary flow, long-term, for patients with xerostomia of different causes.[119;120]

Manual acupuncture was shown to significantly increase the blood flow in the area overlying the parotid glands.[121] Moreover, the salivary concentrations of neuropeptides VIP and CGRP in patients with xerostomia increased after acupuncture.[122-124] It has previously been shown that neuropeptides such as SP, VIP and CGRP have trophic effects on glandular tissues (leading to regeneration).[125-128] A possible explanation for the long-term effects of acupuncture might be that the release of these neuropeptides induces regeneration of traumatizised glandular tissue.

Local endorphins

Local endorphins and their receptors (μ, δ, κ) have been found on nociceptive afferents in inflammatory conditions.[129] The different endorphins are secreted from inflammatory cells in the tissue after an injury. Increased synthesis of the endorphin receptors occurs at the dorsal root ganglion as a response to the nociceptive input to the dorsal horn. The endorphins and their receptors accumulate at the injury site after a few days.[129-131] This accumulation may lead to a peripheral opioid analgesia some days after an injury. The penetration of acupuncture needles induces small tissue injuries, thus there may, in some instances, be an increase in local endorphins after a few days. This could be one explanation for pain relief occurring 2-3 days after a treatment session, and a possible reason why it appears to be so useful to use many local acupuncture points.

B. Spinal mechanisms: (regional, segmental and extrasegmental needles)

Gate-Control

The inhibition produced through this mechanism works rapidly in the short-term, with effects occurring mainly during stimulation. Thus, this mechanism only explains pain relief during the non-painful stimulation period.

Long-term potentiation (LTP) and long-term depression (LTD) in the dorsal horn

Long-term potentiation (LTP) is a form of synaptic plasticity where the synaptic strength increases. Long-term depression is the opposite – a synaptic plasticity where the synaptic strength decreases. The LTP phenomenon is probably one background to central sensitisation and memory in the pain transmission system.[132] Central sensitisation can occur within the CNS from the dorsal horn level up to the thalamus and even to the cortex, and is probably involved in some forms of chronic pain. Central sensitisation results in a reduced mechanical threshold, an increased responsiveness to suprathreshold stimuli and an expansion of the receptive fields of WDR neurons.[133] These changes can make non-painful stimuli to be interpreted as pain (allodynia). The NMDA receptor (N-methyl-D-aspartic acid) seems to have a major role in the development of LTP and central sensitisation.[131;134;135]

Recently long-term depression of Aδ-fibre evoked mono- or polysynaptic excitatory postsynaptic potentials in the superficial spinal dorsal horn has been found with low frequency stimulation of afferent Aδ-fibres (mildly painful) in the same segment.[136;137] At least in awake animals this LTD may last for days or weeks,[138;139] and might thus explain pain relief with a longer duration, than the gate control mechanism does. The NMDA receptor is instrumental in the development of the LTD.[137] If, however, the spinal cord was cut, and thus, no descending inhibition occurred the same stimulation led to a LTP instead of a LTD.

The stimulation of Aδ-fibres does not only have the capacity to give rise to LTD but it can

also reverse an ongoing LTP. This means that there may be the potential to reverse central sensitisation and hyperalgesia.[132;139]

It is usual to note that, clinically, there is a great variability within, and between, patients even if the same stimulation parameters are used. This may depend on the balance that seems to exist between LTP and LTD. The result of an Aδ stimulation period appears to be dependent on the initial resting membrane potential of the WDR cells. If the WDR cell was hyperpolarised (e.g. activity in the segmental inhibitory system and/or descending inhibitory systems) the result of the stimulation was a LTD. If instead the cell was a little depolarised (e.g. ongoing pain, descending excitatory influences) then the result was a LTP. Thus, the same stimulation parameter sometimes induces LTP (with more pain) and sometimes LTD (with less pain), dependent on the initial condition of the WDR cells.[132;139]

Propriospinal pain inhibition (extrasegmental needles)

As pointed out by Sandkuhler,[140] numerous propriospinal intersegmental systems have been identified to be involved in pain inhibition. These propriospinal neurones may be activated by afferent stimulation or by supraspinal pathways. With superperfusion techniques, it has been shown that axons from thoracic, cervical or sacral levels can induce a lumbar antinociceptive effect. The efficacy of this propriospinal inhibition was shown to be similar to the inhibition produced by stimulation of the PAG. Thus, the propriospinal antinociceptive neurones may constitute a third component of endogenous antinociception in addition to segmental and supraspinal descending inhibition.

C. Supraspinal mechanisms: (needles distributed all over the body)

The descending pain inhibitory systems

This descending pain inhibitory system may be activated by noxious or stressful events.[59]

As direct electrical stimulation to PAG only gives rise to short-term pain-relief, it does not seem very realistic that acupuncture could give rise to long-term effects through this system. However, this system is probably involved in AA.

The DNIC system

DNIC gives only an extremely short-lasting pain-inhibitory effect. It is activated by noxious stimulation applied outside the segment of pain.[27] This system may also be involved in AA.

The sympathetic nervous system and the HPA-axis

Low intensity stimulation gives rise to reduced sympathetic outflow and reduced secretion of adrenaline and noradrenaline from the adrenal glands. High intensity (noxious) stimulation give rise to the opposite. ACTH and cortisone increases after painful or stressful acupuncture, but not after non-painful or non-stressful stimulation.[95] Thus, the intensity of stimulation seems to be very important in determining which system is activated.

Oxytocin

Recent research has indicated that oxytocin is secreted in response to non-noxious sensory stimulation. Interestingly, this hormone seems to give rise to long-term effects of an 'anti-stress' nature that resemble those after acupuncture.[141;142] It was shown that a five-day treatment period with oxytocin gave rise to a long-term increase in PT in rats up to seven days after the last injection.[143] If an additional injection of oxytocin was given 10 days after the series, the significant difference persisted even after 3 weeks. In humans, intrathecal oxytocin has been shown to induce pain relief in lumbar pain.[144] It has also been shown that different kinds of sensory stimulation (2Hz EA, thermal stimulation, massage or vibration) increase oxytocin in plasma and CSF.[141;145] Further, oxytocin has given rise to anxiolysis and sedation.[146;147] Thus, oxytocin might be a candidate for inducing long-term effects after therapeutic acupuncture.

D. Cortical, psychological and placebo mechanisms (from the treatment sessions)

Acupuncture, like all other treatments, may have a significant placebo effect. However, recently the concept of placebo effects has been criticised.[148] Further, a recent meta-analysis (114 studies reviewed) has analysed whether the administration of placebos has any advantage over no treatment.[149] No effects were seen on objective or

binary outcomes. Small effects were seen in studies with continuous subjective outcomes, and for the treatment of pain (mean reduction of 6.5mm on the VAS). Thus, pure placebo effects seem to be very small, and probably not at all of any clinical relevance in terms of long-term effects.

Nevertheless, therapeutic acupuncture involves regular visits to the therapist for about 6-8 sessions. These sessions do not only consist of needle insertions but also discussions about possible changes, alternative diagnoses and perhaps therapeutic alternatives. If there is a good patient-therapist relationship, these regular visits probably constitute a form of therapeutic counselling, which may reduce anxiety and improve well-being. In support of this it has been shown that, among physical therapies (including placebos), interventions involving more time with the therapist, or more treatments, had a significant advantage in terms of the outcome.[150]
For a summary of the hypothesis, see table 3.

Conclusion

Most of the experimental acupuncture research seems only to give us an understanding of what nociceptive and stressful stimulation (with the activation of DNIC and SIA) can give rise to. Thus, the research can probably explain something important about mechanisms behind acupuncture analgesia, but cannot explain clinical observations regarding therapeutic acupuncture. Furthermore, as it has been shown that changes in pain thresholds do not predict clinical pain relief, it does not seem relevant to make any statements about mechanisms for therapeutic acupuncture based on research into alteration of pain thresholds. The differentiation of acupuncture between acupuncture analgesia and therapeutic acupuncture seems clinically relevant as these two main forms have such different effects and (probably) physiological backgrounds. However, it must be pointed out that in reality there is a continuum from low intensity (therapeutic acupuncture) to high intensity (acupuncture analgesia) stimuli.

The proposed hypothesis gives us a much more dynamic understanding of clinical observations. The hypothesis also gives a possible understanding of much more of what we observe in the clinic than the standard neurophysiological hypothesis does. See some examples of this in table 4.

Probably some of the proposed mechanisms are relevant in some conditions, and in some patients, and others are relevant in other conditions and patients. For example, if no tissue injury exists the local mechanisms are unlikely to have a substantial role. In neurogenic pain we can only expect shorter effects as only the spinal, supraspinal and cortical mechanisms are relevant. In a few patients central sensitisation may be changed. For some patients perhaps only the cortical effects (anxiety reduction through counselling) are the ones that give the patient relief.

Table 3 **Summary of hypothesis for mechanisms of therapeutic acupuncture and acupuncture analgesia.**

Acupuncture method	Local events in the tissue (Local needles)	Segmental mechanisms and somato-autonomous reflexes (Regional needles)	Central mechanisms (Distal, regional and some local needles)
Therapeutic acupuncture =gentle manual or electro-acupuncture. **Usual clinical use.**	Axon reflexes in the tissue around needles and deeper through dichotomising fibres giving increased circulation and neuropeptide release. Can act as trophic factors (e.g. regeneration of glands). Anti-inflammatory effects (low dose of CGRP). Release of local endorphins to local receptors.	Gate mechanism and perhaps long term depression (LTD) and propriospinal inhibition. Reverse of LTP to LTD (reduces central sensitisation). Sympathetic inhibition with increased segmental circulation	Sympathetic inhibition. Decreased levels of stress-hormones, adrenaline and cortisone in plasma. Perhaps oxytocin induces long-term pain threshold elevations and anti-stress effects.
Acupuncture Analgesia= high intensity, manual or electro-acupuncture. Most physiological experiments.	Tissue trauma around the needles giving rise to more local pain (CGRP in higher doses has pro-inflammatory actions). Increased local pain for some days.	Gate mechanism and perhaps LTD and propriospinal inhibition. Reverse of LTP to LTD (reduces central sensitisation) or the opposite. Sympathetic stimulation with decreased segmental circulation.	Sympathetic stimulation. Increased levels of the stress-hormones, ACTH, adrenaline and cortisone in plasma. DNIC is activated. Descending pain inhibition from PAG with endorphins, serotonin and noradrenaline.

Table 4 **Examples of what the proposed hypothesis for therapeutic acupuncture might explain that cannot be explained from the standard neurophysiological hypothesis.**

Clinical observations that cannot be explained by standard hypothesis	Possible explanation of the observations with the proposed hypothesis
Pain relief (and other effects) for more than a day or two. More prolonged pain relief after more treatments.	All the local mechanisms=tissue healing effects. Perhaps LTD and shift from LTP to LTD. Perhaps oxytocin with long-term anti-stress effects.
Pain relief starting some days after the treatment.	Local endorphins and all the other local mechanisms.
Effects of local points. Effects of gentle manual acupuncture.	All local mechanisms.
Increased local pain and exacerbation of generalised pain after treatment.	Pro-inflammatory effect of too much CGRP and a shift of the balance between LTP and LTD.
Sometimes sympathetic stimulation, sometimes inhibition.	Perhaps a matter of stimulation strength.
Sometimes relief, sometimes more pain.	The initial resting membrane potential (state of the WDR neurones) determines whether there is LTD (pain relief) or a LTP (more pain).

Interestingly, there seems to be many balances involved in the physiology. For example, a low concentration of CGRP is anti-inflammatory and higher concentrations are pro-inflammatory; the induction of a LTP (with more pain) or a LTD (with less pain) seems to be influenced by stimulation parameters and the initial condition of the relevant WDR cells; whether we get sympathetic stimulation or inhibition is dependent on stimulation strength; whether the overall effects are stressful or anti-stressful also depends on stimulation strength.

The understanding of what small differences in the WDR cells initial condition might lead to is perhaps a way to understand very fast dramatic effects in some of our patients. Thus, the theories about non-linearity and chaos might be applicable in some instances and not only simple dose-response relations.

Future research concerning mechanisms

It would be worthy if future research examined more in detail the different possible mechanisms mentioned in the hypothesis. It would be of great interest to know more about the peripheral mechanisms as well as the central changes of sensitisation (pain memory).

Examples of testable aspects of the hypotheses:

- Do local acting endorphins accumulate (after a time) in the tissue surrounding an acupuncture needle?
- Do the signs of central sensitisation decrease after low frequency electroacupuncture when Aδ fibres are activated?
- Is pain relief after EA prolonged if we first stimulate the Aβ fibres to “close” the gate (for perhaps 15 minutes) and then increase the strength to Aδ stimulation for a 15-minute period? This has been called ‘sequential’ EA (or TENS) by Sandkuhler.[139]

The examination of the different proposals in the hypothesis would be relevant clinically as it could help us to select patients for treatments, and also for us to select which stimulation parameters would seem most suitable for different conditions.

I hope this article will lead to a better understanding of the possible mechanisms of acupuncture.

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