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PHYSIOLOGICAL AND PSYCHOLOGICAL EXPLANATIONS FOR THE MECHANISM OF ACUPUNTURE AS A TREATMENT FOR CHRONIC PAIN

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Abstract—Many suggestions have been made about the possible mechanism of acupuncture as an analgesic therapy. This review provides a comprehensive account of the neurological, neurohumoral and psychologically-based hypotheses put forward. Although the exact mechanism of this treatment remains unclear, it is apparent that reproduceable neurological and chemical changes occur in response to acupuncture, and that these changes almost certainly modify the response to, and perception, of pain. The mechanism of chronic pain is completely understood, but within this framework we understand acupuncture as completely as most other types of analgesic treatment.

INTRODUCTION

The objective of this review is not to provide an exhaustive discussion of the physiology and psychology of pain, but to establish a basis upon which the analgesic effects of acupuncture can be better understood. The theories used to explain the pain relief that results from acupuncture fall into three broad categories: neurological, neurohumoral and psychological. It is apparent that although we understand a great deal about pain, no unified theory of pain exists. There are still many painful diseases whose pathology is poorly understood and many clinically effective therapies whose physiology and pharmacology remain elusive.

NEUROLOGICAL MECHANISMS

Chiang has suggested that acupuncture is primarily mediated through the nervous system [1]. He experimented with 21 adult volunteers and noted the local analgesic effect obtained by needling a point in the hand (large intestine 4); the extent of analgesia was measured by the patient's response to a painful electrical stimulus in the hand. Vascular occlusion of the upper arm did not alter the analgesia obtained. Endorphins and enkephalins had not yet been discovered at this time, but as these peptides are neurotransmitters their discovery does not contradict the view proposed by Chiang and supported by much of the research that will be discussed in this review i.e. it is probably correct to think of the physiological changes initiated by acupuncture as being mediated through the peripheral nervous system in the first instance. The first physiological theory used to explain acupuncture was the gate control theory developed by Melzack and Wall [2].

The gate control theory of pain

Until the publication of the gate control theory it was assumed that impulses carrying cutaneous information arrived at the spinal cord and would be transmitted along ascending relay pathways to the cerebral cortex [3]. Work done by Matthews in 1934 had been largely ignored. He showed that sensory input travelling along large diameter afferent fibres depolarised the central terminals of other dorsal root fibres and called this phenomenon 'primary afferent depolarisation' or the 'dorsal reflex'. These ideas were re-examined in considerable detail by Melzack and Wall in the late 1950s and their importance was finally recognised as the basis for a theory of the neural mechanisms underlying pain. They relied on evidence available from earlier workers such as that of Zotterman [4] who had demonstrated that dull, slow, diffuse burning pain is carried from the periphery by small unmyelinated (C) fibres, while the sensation of light touch is carried by large myelinated (A) fibres. Such early observations have been supported by more recent work such as that of Burke [5] who isolated Aβ fibres as transmitting the sensation of light touch.

The gate control theory stated that the transmission of sensation is controlled by the balance of activity in these two types of fibres. According to this theory, low level activity in the small fibres is normally blocked at the first synapse by activity in the large diameter fibres. The 'gate' at the first synapse is opened by intense activity of the C fibres, while a predominance in Aβ fibre activity closes the gate. The gate through which pain signals are transmitted to the transmitter (T) cells is variable. The sensation of pain is dependent on the activity of the A fibres and will result from C fibre dominance over A fibres.

It follows from this that by forcing A fibres to carry sensations of light touch by stimulating the area, pain signals from C fibres can be blocked. The gate is said to be an intermediate structure between so-called T cells in lamina V, which must be stimulated in order that pain interpretation and response can take place, and the sensory fibres which enter lamina I via the dorsal root (see Figs 1 and 2).

Wall and Sweet applied the gate control theory of pain clinically using implanted stimulating devices with low voltage percutaneous electrical stimulation [6]. This led Sweet to develop further the stimulation of both peripheral nerves and the posterior part of the spinal cord in order to promote analgesia [7, 8].

Melzack found it difficult to explain how high intensity electrical stimulation can selectively activate

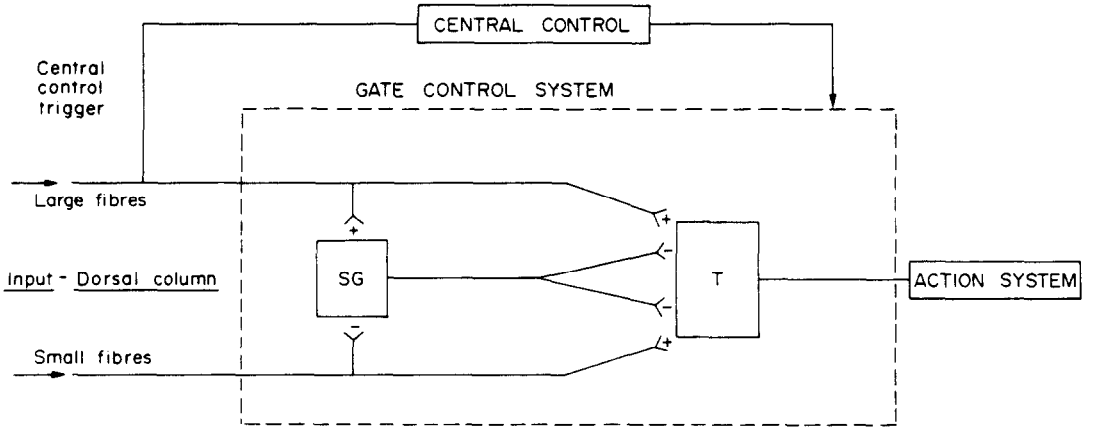

Fig. 1. Schematic representation of gate control theory of pain mechanisms [21]. SG substantia gelatinosa; T transmitter cells; + facilitatory synapse; — inhibitory synapse.

small diameter nerve fibres, and suggests that stimulation would cause both A and C fibre activity [9]. Nathan and Rudge tested the gate control theory by artificially inducing C fibre activity and then attempting to abolish it by electrical stimulation of A fibres [10]. They could not abolish the pain produced by C fibre stimulation (in humans) and concluded that their experimental results were inconsistent with the gate control theory. Similar observations were made by Nathan again in 1976 and by Strassbourg *et al.* in 1977 [11, 12].

Brief, intense stimulation with either acupuncture or transcutaneous nerve stimulation (TENS) may cause prolonged pain relief [9], but this reproduceable clinical phenomenon cannot be explained by the gate control theory. Melzack suggests that brief, intense stimulation may cause prolonged pain relief either by activating 'a central biasing mechanism' or by break-

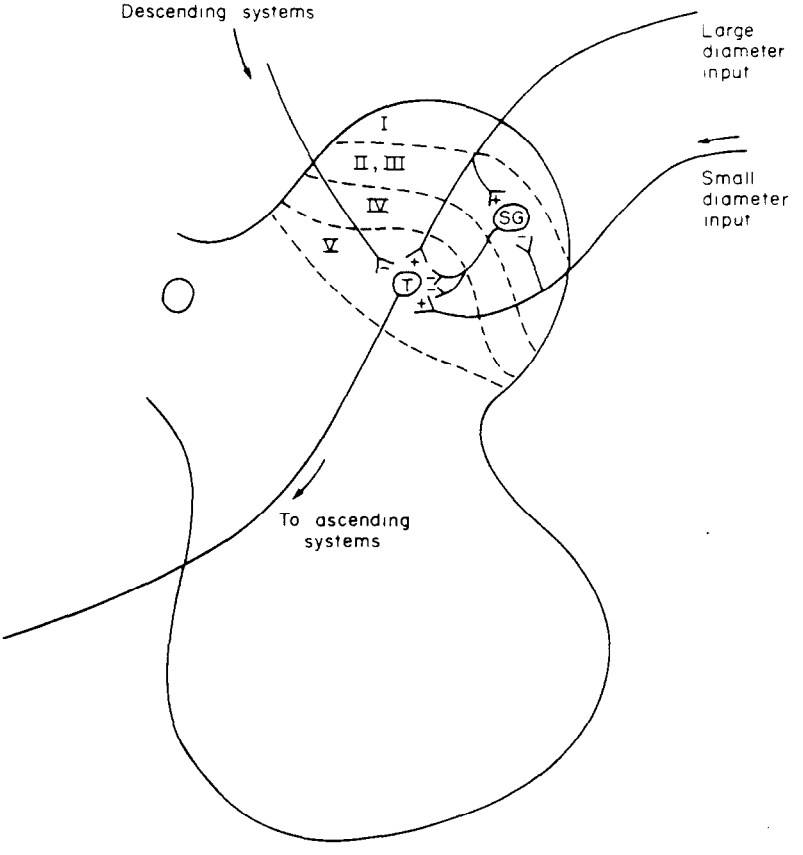

Fig. 2. Schematic representation of location of 'gate' mechanism in the posterior horn of the spinal cord. SG substantia gelatinosa; T transmitter cells; + facilitatory synapse; — inhibitory synapse. Roman numerals refer to laminae within the dorsal spinal grey matter.

ing up a proposed 'memory-like process' through which pain may be mediated. He suggests that pain may be due to prolonged activity within self-exciting neurone chains and that brief, intense input could break up or disrupt this activity and thereby abolish pain perception for prolonged periods [9].

Chien-Ping used electro-acupuncture on decerebrate cats [13]. He was able to demonstrate a clear inhibitory effect in the discharges recorded in the dorsolateral fasciculus when stimulating A fibres in the peripheral nerve; the inhibitory effect was greatest if the whole spectrum of A fibres was stimulated rather than selectively stimulating Aβ fibres. Andersson and Holmgren were unable, selectively, to stimulate Aβ fibres with electro-acupuncture, but do provide some circumstantial evidence for the specific stimulation of these fibres as having a pain inhibitory effect [14]. Janko has shown that TENS does stimulate both Aβ and Aδ fibres and suggests that this may be the mechanism through which TENS causes analgesia [15]. An essentially similar blockade of the sensation of pain can be obtained by various types of stimulation, some of which are thought to be similar to acupuncture; these include vibration and electrical high frequency peripheral or dorsal column stimulation [16, 17].

The gate control theory implies that acupuncture and TENS should have their greatest effect if painful (C fibre) and pain inhibitory (A fibre) stimulation occurs in the same segment. Chien-Ping noted that the apparent analgesic effects of electro-acupuncture close to the site of pain (in decereberate cats) was more marked when the site of acupuncture and the site of pain were innervated by the same or adjacent segments [13]. Chan and Fung report a similar phenomena, again using decerebrate cats as the experimental model [18]. They measured dorsal root potentials in response to peripheral electro-acupuncture. However it is apparent that in some cases pain can be successfully relieved by acupuncture on a bizarre heterosegmental basis [19]. Therefore the mechanism cannot be the same as that proposed in the gate control theory. In such instances Bowsher suggests that acupuncture may be causing analgesia via a number of intersegmental feed-back loops within the cord, in which input into the excitatory reticular neurones will inhibit C fibre transmission [20].

The observations made by Melzack and Wall when developing their gate control theory goes some way to explaining how acupuncture may produce its analgesic effects. However it is apparent that the specific cordal mechanisms modulating pain are incompletely understood and almost certainly very complex. It would seem that they involve a balance of excitatory and inhibitory influences that are modulated through a number of different neurological circuits on entry into the cord. However the evidence available does suggest that both electro-acupuncture and TENS seem to have an influence on these neurological mechanisms.

Descending inhibitory influences and the thalamus

Further work by Melzack into relief of chronic pain by repeated electrical stimulation has brought forward speculation that a central biasing mechanism exists within the brain stem [9]. He believes that chronic pain may be partially due to 'a neural reverberating circuit', involving the periaqueductal grey areas and suggests that both TENS and acupuncture could activate a central biasing mechanism thereby inhibiting the transmission of painful stimuli through the neuraxis. The second possible explanation is that prolonged pathological pain may result in permanent or semi-permanent changes in central neural activity [21]. Fox and Melzack suggest that these changes may take the form of self-exciting circuits that result in memory-like processes which could be disrupted by brief intense input from either acupuncture or TENS; such disruption could long outlast the duration of stimulation [22]. If central activities were to restart they might involve fewer neurones and invoke less pain, therefore gradually diminishing the perception of pain. These concepts have yet to be verified.

Man and Chen postulated a second gate within the reticular activating system, with a main gate at the thalamus [23]. The main evidence cited for the thalamic gate is that stimulation of areas supplied only by the cranial nerves would cause impulses to go directly to the main gate, the thalamus. They also rely on studies from the Shanghai College of Acupuncture Group [24] which demonstrate that the response of mid-brain reticular formation to painful stimuli is largely abolished by electro-acupuncture, but on closer analysis the evidence quoted does not really support Man and Chen's hypothesis of the second (thalamic) gate. Nevertheless the reticular activating system may well be important in mediating analgesic effects of acupuncture. Chen-Yu *et al.* [25] and Ke-Fei *et al.* [26], in the Shanghai Institute of Physiology, studied the effects of noxious stimulation modulated by electro-acupuncture on rabbits and have shown that stimulating the reticular formation has a marked inhibitory effect on pain. Chen-Yu observed that section of the dorsal column alone did not produce any detectable change in either the pain threshold or the effect of electro-acupuncture on pain threshold, neither did superficial cordotomy significantly modify the analgesic effect of acupuncture [25]. Ke-Fei *et al.* noted that electro-stimulation of the medial medullary reticular formation had a marked inhibitory effect on pain perception and neuronal discharges in the region of the thalamus [26].

Reynolds demonstrated that electro-stimulation of the periaqueductal grey (PAG) and a region close by, the nucleus raphe mangus (NRM) resulted in analgesia in rats [27]. This observation has been subsequently verified by a number of studies in both humans as well as animals [28–30]. More recent studies by Akil *et al.* [31, 32] demonstrate that such focal brain stimulation releases endorphins. These studies imply a 'descending inhibitory control system' for pain may exist. Such a system is also probably endorphin mediated; micro injection of opiates into the PAG elicits analgesia [33] and opiate antagonists can abolish the analgesia elicited by brain stimulation [31]. Neurones from the PAG and NRM are closely linked [34] and excitation of the PAG enhances the activity of NRM neurones [35]. Furthermore, neurones originating in the NRM are found in laminae I, II and V of the dorsal horn and direct stimulation of the dorsal horn elicits inhibition of nociceptive

neurones in the dorsal horn; the neurones originating in the NRM pass into the dorsal horn via the dorsolateral funiculus [36]. It is therefore likely that a descending inhibitory control system exists and that this can be activated either centrally by direct stimulation of the periaqueductal grey or peripherally by acupuncture. Furthermore it is probable that endorphins may be involved as neurotransmitters within this system.

Chang suggests that the thalamus performs an important integrative function in the process of acupuncture analgesia [37]. He implicates the nucleus parafascicularis and the nucleus centralis lateralis, and has demonstrated that discharges mediating painful stimuli, from both these thalamic nuclei, can be inhibited by electro-acupuncture. The nucleus parafascicularis and the nucleus centralis lateralis gave rise to characteristic unit discharges in response to painful stimuli. These discharges were abolished by electro-acupuncture, but if the stimulus applied was too powerful then the response to pain seemed to be exaggerated. Pain discharges from the thalamic neurones persisted after section of the dorsal column and could not be produced by electrical stimulation of the severed dorsal column above the lesion; this implies that the main pathway of pain as mediated through the thalamus is not within the dorsal column. Chang goes on to suggest that the thalamus probably has an integrative function in pain perception and it is these functions that can be modified by acupuncture to produce an analgesic effect [37]. Most of the cortically projecting thalamic nuclei also receive afferents from the ascending reticular neurones [20]. Bowsher suggests that, "If as seems likely, most reticulo-thalamic axons collateralise widely, then it is probable the endings in the cortically projecting nuclei may be collateral to those which terminate in the intralaminar nuclei". It is therefore possible that a series of excitatory and inhibitory feedback loops are present, starting in the cord and subsequently travelling up the nervous system via the thalamus to where pain is finally perceived within the cortex. Acupuncture can modulate the transmission of noxious stimuli at many levels in the central nervous system, and it would be wrong to think of any one theory acting as the complete or unified explanation for this complex series of interactions.

Viscero-somatic reflexes

Mann has stated that cutaneo-visceral and intersegmental reflexes are particularly important in mediating the effects of acupuncture [38]. The clinical evidence for this hypothesis is that in the insertion of needles into points far distant from the site of pain can frequently result in a swift and dramatic analgesic effect [19]. Studies mentioned previously in this paper imply that acupuncture produces the greatest possible A fibre activity (thereby implying it should have the greatest analgesic effect) when the stimulus is applied to the same dermatome as the pain, however some attempt must be made to explain the bizarre intersegmental effects that are observed in clinical practice.

Sherrington described the scratch reflex in the spinal dog in which stimulation anywhere in a saddle shaped area extending from the pectoral to the pelvic girdle caused rapid scratching movements in the ipselateral hind leg and rigidity in the contra-lateral limb [39]. If the stimulus was moved to the opposite side of the back, the hind legs reversed their roles; ipselateral hemisection of the spinal cord abolished the reflex whereas contralateral hemisection left it unaffected. Dowman studied cats who had had spinal transection at the level of their first thoracic vertebrae. He demonstrated that splanchnic nerve stimulation spread up the cord by two pathways, one a fast extraspinal route in the sympathetic chain on the same side and the other a slower intraspinal route [40].

Miller and Ward stimulated the viscera and obtained muscle contractions in the expected appropriate dermatome [41]. They also found that distension of the stomach by air, traction on the stomach, mustard oil on the gastric mucosa and squeezing the small intestine all elicited the same reflex. Brown-Sequard [42] was probably the first to describe viscero-somatic reflexes; he relates an experiment with a dog which had a tube tied into its ureter. When the internal abdominal wall was pricked within the sensory distribution of the first lumbar nerve, the secretion of urine was considerably diminished. Mann suggests that these bizarre and largely unexplained reflexes may explain how acupuncture at a distant site may alleviate pain [38].

More recently, Travell and Rinzler have observed that trigger areas occur on the front of the chest in true cardiac pain, and furthermore that stimulation of these areas with needles has an analgesic effect [43, 44]. Shen-Eh *et al.* looked at the possibility of relaxing abdominal muscles during abdominal surgery under acupuncture anaesthesia [45]. He studied the cat and demonstrated that acupuncture could cause muscle relaxation but that high spinal cord transection abolished this reflex. Further work by Huan-Ji and Yan-Shang, again studying cats, has shown that such viscero-somatic reflex can be largely abolished by lesioning the medulla (including the nucleus raphe magnus) and completely abolished by transection of both the lower medulla and cervical cord [46]. At present we have an incomplete picture of the relevance of these reflexes and how they can be integrated into a unified system which might be effected by peripheral stimuli such as acupuncture. However we can observe that viscero-somatic reflexes exist and in some instances are effected by acupuncture.

Diffuse noxious inhibitory control (DNIC)

Le Bars *et al.* have suggested that noxious stimuli, when applied to any part of the body, can produce analgesic effects at distant sites [47]. They recorded the input from 68 convergent dorsal horn neurones in anaesthetised rats and noted that both A and C fibre afferents could be activated by both low and high frequency peripheral electro-stimulation. Furthermore the stimulation of these neurones was inhibited by any noxious stimuli applied to the body. They therefore called this response diffuse noxious inhibitory control (DNIC). The most effective areas for eliciting this response were the tail and muzzle of the rat. The stimulation of the tail or muzzle both electrically (TENS) and by noxious radiant heat

significantly modified the C fibre response and long lasting effects could be observed which were directly related to the duration of the conditioning painful stimulus.

Le Bars *et al.* therefore suggest a more non-specific system than, for instance, the gate control theory. DNIC seems to be dependent on supraspinal structures and furthermore the results obtained would imply that it works on an inter-segmental basis. These observations do not contradict many of the other theories put forward to explain how a noxious stimulus can potentially modify pain elsewhere in the body [47].

Other neurological mechanisms suggested as explanations for the effect of acupuncture

Becker *et al.* suggest that acupuncture is mediated through a primitive nervous system [48]. He and his co-workers hypothesise that as in many control systems involving a high energetic process, a control system involving signals of low energy content may be present. He uses as support for this argument various experiments on bone healing, leg regeneration in the salamander and some detailed studies on the electro-physiological correlates of acupuncture points. Whether the proposed transmission and control system for the nervous system is present, or can be modified by acupuncture, remains unproved.

Arguments that acupuncture can modify the activity of the autonomic nervous system can be supported by studies already mentioned on the effect of acupuncture on viscero-somatic reflexes. A number of observations have been made on experimental animal models that lend support to the idea that acupuncture is at least partially mediated through the autonomic nervous system. Acupuncture has been shown to reduce the mortality from shock in experimentally exsanguinated cats and dogs [49, 50]. It can also be shown to have a significant effect on gastro-intestinal function in both man and animals [51]. Specific effects can be shown on gastro-intestinal circulation, gastric motility, gastric secretion and absorption of fluid from the peritoneal cavity in rabbits [52]. Consequently it is probable that acupuncture is having a very widespread effect throughout both the somatic and autonomic nervous system.

Conclusion

Many of these neurological explanations may at first seem confusing. In some instances the same set of observations seem to be used to support rather different hypotheses. Furthermore in most of the studies, animal models have been used and it may be wrong to assume that information obtained from the study of noxious stimuli in animals (often decerebrate animals) can be used to explain the neurological implications of inserting an acupuncture needle into man for the treatment of chronic pain. Andersson and Holmgren [14] make it quite clear that they do not consider acute experimental pain, even in human volunteers, to be necessarily working through the same mechanism as chronic pain.

In spite of these criticisms, it is apparent that acupuncture and TENS seem to be having an effect at many sites in the central nervous system, and as we have suggested earlier, it is probable that a complex series of feedback loops operate at segmental, inter-segmental, medullary, mid-brain and thalamic levels. It is likely that each of the theories discussed represents part of the truth, rather than the complete explanation of all the observed phenomena.

NEUROHUMORAL MECHANISMS

Endorphins

It has been recognised for many years that morphine and other opiates are excellent analgesics, but the mechanism through which they produce analgesia has only recently been elucidated [3]. In 1975 Hughes *et al.* discovered two pentapeptides in porcine brain, leu- and met-enkephalin [53]. Met-enkephalin is also found in human brain, in extracts of the pituitary and other neural tissues, and is part of a larger molecule (30 amino acids) β endorphin [54]. Both β endorphin and dynorphin (the extended form of leu-enkephalin) seem to have greater analgesic potency than their pentapeptides. In addition there are a number of related opiate peptides (α and γ endorpin and α and β neo-endorphin). Endorphin seems to be mainly found in the basal hypothalamic nuclei and in ascending collaterals to many nuclei throughout the brain [55]. The enkephalins are mainly found in the short interneurones within the limbic system, hypothalamus, basal ganglia, periaqueductal grey area, medulla oblongata and spinal cord [56].

Martin originally proposed that opiate receptors were heterogeneous [57]. More recent work has suggested that opiate activity on guinea pig ileum can be reversed by naloxone, but opiate activity on mouse vas deferens cannot. The receptors in guinea pig ileum had been termed μ receptors and those in vas deferens δ receptors. Pert and Taylor have classified opiate receptors as type 1 or type 2, according to their GTP sensitivity [58]. Type 1 receptors, that is receptors in which the enzyme GTP will reduce opiate agonist binding, are predominantly found in ileum and are said to be more or less equivalent to μ receptors. Type 2 receptors are unaffected by the action of GTP and are found primarily in vas deferens, and may therefore be equivalent to δ receptors. One of the main difficulties in defining further more detailed or more exact sub-groupings of opiate receptors has been that one of the major methods currently available for isolating their activity is their differential sensitivity to the receptor blocking drug naloxone [59].

It has been shown by a number of studies that both manual and electro-acupuncture as well as other stimulation techniques such as TENS are probably at least partially mediated through the release of endorphins. Pomeranz and Chiu [60] have demonstrated in a meticulous manner that electro-acupuncture (using the mouse squeak model) was completely blocked by naloxone and that sham electro-acupuncture was unaffected by this drug. Furthermore naloxone alone (a partial opiate agonist) could not produce the same effects as electro-acupuncture. Studies by Akil *et al.* [32], Sjolund *et al.* [61] and Nappi *et al.* [62] all on humans, provide strong evidence demonstrating that electrical stimulation both peripherally and centrally as well as manual needling, cause a rise in cerebrospinal fluid (CSF) endorphins.

Cheng and Pomeranz [63] again using the mouse squeak model, observed that small doses of cyclazocine, diprenorphine or naltrexone all blocked acupuncture analgesia in the same manner as naloxone. Type 1 opiate receptors are naloxone reversible (*vide supra*) and therefore it seems likely that type 1 opiate receptors are involved in the acupuncture analgesia studied in these experiments. Furthermore injection of dextro-naloxone (an inactive stereoisomer) had no effect on reversing acupuncture analgesia [64]. These observations add further support to the argument that stereospecific opiate receptors mediate acupuncture analgesia, as well as providing support for the involvement of endorphins. Using a strain of mice (CX BK) who have congenital deficiency of opiate receptors, Peets and Pomeranz [65] showed that these mice demonstrated a singificantly lower response to acupuncture analgesia, thereby implying that endorphin receptors are necessary if acupuncture is to have an analgesic effect. They speculated that some people may have a deficiency within their endorphin system similar to that observed in the CX BK mice strain; this might explain why 30% of humans do not experience either morphine or acupuncture analgesia. Takeshige *et al.* [66] studied acupuncture analgesia in rats. 40% of the rats failed to demonstrate acupuncture analgesia and when these animals were sacrificed they were found to be deficient in opiate receptors, again suggesting that both endorphins and opiate receptors are essential for effective acupuncture analgesia. Sjolund *et al.* [61] have provided some evidence for the segmental release of endorphins. They treated backache by inserting acupuncture needles into the lumbar region and observed the doubling of endorphin levels in the lumbar CSF. However when they treated facial pain by using acupuncture points in the hand, no increased endorphin levels in the CSF of the lumbar region was noted. In both instances, the acupuncture seems to be equally clinically effective, thereby implying endorphins may be released in a regional manner in response to acupuncture.

In 1975 a Chinese neurosurgeon in Hong Kong, Dr Wen, reported symptoms of heroin withdrawal could be alleviated by electro-acupuncture. This resulted in a collaborative study with Professor Besser's unit at St Bartholomew's Hospital (London) in which it was shown that electro-acupuncture caused a significant rise of met-enkephalin in the CSF of such addicts [67]. Electro-acupuncture in patients with chronic pain showed an increase in CSF β endorphin, but met-enkephalin levels were unchanged in these patients [68]. These results suggest that the mechanism implicated in heroin withdrawal and pain relief may be different.

Having established that endorphin release can be stimulated by acupuncture it is necessary to demonstrate that these physiological changes do correlate with clinical pain relief. Electrical stimulation of the periventricular brain in man causes profound analgesia accompanied by a massive increase in β endorphin levels [32] and intrathecal administration of β endorphin produces a long-lasting analgesic effect in cancer patients [69]. It has also been noted that patients with chronic pain seem to have a low CSF β endorphin level, but that these levels do not seem to correlate with the severity of duration of pain [32]. Such observations in humans are further supported by animal work from Shanghai Academy [70]. A similar case has been made for the mechanism of TENS, in that it has been also shown that this form of stimulation therapy causes a rise in β endorphin levels within the CSF.

It has been suggested that naloxone can reverse the effects of acupuncture induced analgesia; it does reduce or abolish the effects of low frequency (2–6 Hz) electro-acupuncture in various animals which have been subjected to experimental pain [71–73]. However analgesia produced by high frequency electro-acupuncture (above 100 Hz) in mice cannot be reversed by naloxone [63]. In human subjects with chronic or experimental pain the situation is more complex; some studies suggest that acupuncture may be partially reversed by naloxone [74], some studies suggest a complete reversal [75], while other studies suggest that there is no change in the perceived level of chronic pain after the administration of naloxone [76, 77].

These observations could be explained by the differential sensitivity of various opiate receptors to naloxone. It may be that low frequency electro-acupuncture results in endorphin binding to type 1 (μ) opiate receptors. If this were the case then one would expect the effect to be completely reversed by naloxone. In other instances, such as those cited by Kenyon *et al.* (manual acupuncture) and Chapman *et al.* (low frequency electro-acupuncture) the analgesic effects of acupuncture should have been reversed by naloxone, but clearly were not. Indeed Chapman now [78] believes that there is little convincing evidence that endorphins play a significant role in acupuncture analgesia.

In spite of some evidence to the contrary there is enough data available to suggest that acupuncture does indeed release endorphins and that endorphin release has an analgesic effect. However it is apparent that the story is far from complete and there are still a number of rather confused areas that require further research and more detailed explanation.

We have mentioned that there is some circumstantial evidence to suggest that acupuncture modifies the activity of the autonomic system. It is clear that the endogenous opiate system also reacts with the autonomic nervous system; opiate peptides are concentrated in the sympathetic ganglia and adrenal medulla and are co-stored with catecholamines [79]. In some species, other neuropeptides such as somatostatin and neurotensin are also stored and released with catecholamines from the sympathetic system [80].

Substance P, the link

Substance P and somatostatin were discovered by Von Euler and Gaddum in 1931. Substance P has recently been shown to be of importance in pain transmission and may provide a link between the endogenous opiod system and other purely neurological theories such as the gate control theory of Melzack and Wall. Substance P is present in all mammalian species, including man, and is found in the terminals of the sensory neurones located in laminae 1 and 2 of the dorsal horn [81]. It is also

released in response to stimulation of unmyelinated fibres [82]. However the artificial application of substance P produces an excitation of dorsal horn neurones in a gradual and very prolonged manner; this does not mimic the response of the same dorsal horn neurones to activation of the nociceptive sensory fibres [83]. On the basis of this evidence, Jessell suggests that the role of substance P may be to modulate the excitability of dorsal horn neurones, although more evidence is required to resolve this possibility [84].

Many enkephalin containing neurone terminals are also concentrated in lamina 1 and 2 of the dorsal horn [85]. Direct spinal administration of opiates in animals and man has been shown to elicit powerful analgesia [86]. Both the local application of morphines and met-enkephalin reduces the dorsal horn response to noxious stimuli [87], but have no effect on the response to light tactile stimuli. This suggests that the opiates may be acting presynaptically on the terminals of nociceptive afferent fibres to reduce the release of substance P. Capsaicin, which depletes P, causes marked analgesia. It is therefore possible that substance P may be acting as a transmitter of nociceptive afferent input (possibly via the gate control theory) and that this can be modified by the release of enkephalins presynaptically in the dorsal horn.

Within the dorsal horn a large number of nerve terminals originating from the nucleus raphe magnus exist; direct electrical stimulation of the nucleus raphe magnus elicits potent inhibition of nociceptive neurons in the dorsal horn [36]. Many of the neurones in the brain stem that form this inhibitory projection contain 5-HT [5-hydroxy-tryptamine of serotonin) as their primary transmitter, as well as substance P [88]. The functional consequence of the presence of these two transmitters within the same group of neurones is not yet clear, but implies that substance P may be a transmitter substance in the analgesia produced by stimulation of the periaqueductal grey and nucleus raphe magnus.

No studies to date have specifically implicated acupuncture as a method by which substance P can be released and thereby effect pain perception. However the circumstantial evidence available implies that acupuncture is likely to affect the release of substance P and consequently affect pain transmission and perception within the central nervous system.

Effects on other neurotransmitters

An excellent review of the role of central neurotransmitters in acupuncture analgesia has been published by Jisheng [73]. He demonstrates that a lowering of central 5-HT (in both humans and animals) increases the effect of acupuncture analgesia. Acupuncture was shown to cause a significant increase in 5-HT concentration in rat brain and other studies revealed that both the synthesis and utilisation of central 5-HT was accelerated during acupuncture. Furthermore in a double-blind study the effect of acupuncture anaesthesia for dental extraction was significantly strengthened by the prior oral administration of clomipramine, which blocks the re-uptake of 5-HT thus raising its functional activity.

Acetylcholine also has an effect on acupuncture analgesia; blockade of acetylcholine synthesis by intravenous injection of hemicholine (in rats) impedes the effect of acupuncture analgesia. The effect of acupuncture analgesia in both rabbits and rats could be partially blocked by atropine and potentiated by eserine.

Dopamine agonists such as apomorphine increased the effect of acupuncture analgesia in rabbits, while administration of droperidol (a dopamine antagonist) decreased its activity. Intravenous injection of the chemical precursors of norepinephrine partially block the effects of acupuncture analgesia and the administration of an agonist (clonidine) for central α receptors also depressed the analgesic effect that could be obtained from acupuncture on rats. Phentolamine (an α receptor antagonist) augmented the effect of acupuncture analgesia. It therefore seems likely that dopamine, through dopamine receptors, and noradrenalin, through α receptors, exert antagonist effects on acupuncture analgesia.

Propanolol caused a decrease in the effect of acupuncture analgesia in rats, which is in line with the clinical findings that propranolol makes acupuncture anaesthesia in man less effective. This suggests a facilitating effect of α receptors occurs during acupuncture analgesia. Acupuncture has also been shown to lower the cerebral noradrenaline content, it would seem as a result of greater utilisation and synthesis of this chemical.

These arguments strongly support the notion that acupuncture has a fundamental effect on many central neurotransmitters, probably as a secondary result of the neural effects of acupuncture discussed earlier in this review.

PSYCHOLOGICAL MECHANISMS

Although the majority of mechanisms suggested for acupuncture have concentrated on physiological theories, some more psychologically orientated explanations are available.

It is important to understand that patients in pain are physiologically disturbed [89], for instance, they are more likely to be depressed [90]. Timmermans and Sternback analysed the personality and pain reaction variables in 119 patients with chronic pain [91]. They demonstrated that these patients were likely to have qualities such as 'inter-personal alienation and manipulativeness'. Whether these attributes are present prior to the complaint of pain, or are produced by the presence of a chronic intractable pain state is unclear. In some instances pain complaint is part of a 'pain game', played by the patient on both the patient's immediate family and the physician [92]. It has been recognised for some years the experience of chronic pain can be alleviated by the use of anti-depressant medication [93]. Perhaps this somatic complaint represents a legitimate avenue through which the depressed patient can seek medical help [94]. Such background information must necessarily preface any purely psychological theory that might be used to explain the mechanism of acupuncture.

Do particular types of patients respond to acupuncture?

Toomey *et al.* analysed the psycho-social factors affecting response to acupuncture [95]. Patients who

responded to acupuncture were found to be less depressed, less passive and have shorter duration of pain than those that failed to respond to this therapy. However there was little difference in the way responders and non-responders described their pain. The 'noxiousness' of the stimulus causing pain also did not correlate with the response to therapy. The non-responders were more prone to stress; for instance the presence of non-pain related co-existent physical illness is more likely to be associated with a failure to respond to acupuncture. Mendelson *et al.* studied 77 patients with low back pain using a double-blind cross over study comparing acupuncture and placebo acupuncture [96]. They measured anxiety, depression and pain duration, and subsequently correlated these measures with response to treatment. None of these psychological varibles predicted which patients would respond to acupuncture and/or placebo. Levine *et al.* [97] suggest that acupuncture works best on depressed, anxious patients while other studies imply the reverse [98]. Our knowledge of pain and depression would suggest that a less depressed patient is more likely to respond to any therapy for chronic pain. However from the limited information available it is not possible to predict whether certain specific patients will respond to acupuncture.

Hypnosis

Hypnotic suggestion has been implicated as one of the possible mechanisms involved in acupuncture. Kroger has suggested that acupuncture analgesia works by 'suggesting in slow motion hypnosis' [99]. Wall has stated that, "acupuncture is an effective use of hypnosis. This in no way diminishes that value of acupuncture, but it does place it in a class of phenomena with which we are familiar" [100]. Kroger, reviewing the common denominators in acupuncture and hypno-anaesthesia, suggest there are many similarities; for instance neither can be used to best effect on tense or apprehensive patients [99]. He implies that the high rate of success of acupuncture analgesia in China stem from the regimented environment of Chinese society, and the consequent limitations on complaint behaviour of Chinese citizens! Therefore acupuncture could be closely related to the operant conditioning techniques for shaping and altering desired behavioural responses. However little hard evidence is provided to support these suppositions.

Finer has suggested that hypnotic analgesia may be acting via Melzack and Wall's gate control theory [101]. Hagbarth has shown that dorsal column activity in the cat can be inhibited by stimulation of the reticular formation, an area of the nervous system that is affected by hypnotherapy. Furthermore in man the abdominal spinal reflex can be affected by suggestion thus implying that hypnosis may affect viscero-somatic reflexes [102]. The evidence available to support these mechanisms for hypnotic analgesia is limited, but nevertheless the suggested mechanisms are similar to some of the physiological mechanisms proposed for acupuncture.

Studies by Pomeranz and Chiu [60] show that naloxone reversed acupuncture analgesia but had no effect on hypnotic analgesia. This has subsequently confirmed by Sjolund and Eriksson [103] and Goldstein and Hilgard [104]. Therefore it would seem that hypnosis is not mediated through the same kind of endorphin mechanisms that have been proposed for acupuncture.

A number of clinical studies have attempted to correlate hypnotic suggestibility with response to acupuncture. Goldberger and Turskey [105] investigated the relationship between these two phenomena in a group of healthy volunteers. They created analgesia in the forearm by using surface electrodes located over acupuncture points, stimulated electrically. One group of patients were given the explicit suggestion that acupuncture would fail to produce analgesia, but subsequent noxious stimulus demonstrated that analgesia was present and that the hypnotic suggestion that the arm was particularly sensitive could not overcome the analgesic effects of acupuncture. A control group was included who received stimulation over random loci and were also given explicit suggestions that analgesia would be present in the arm. No alteration in the perception of pain intensity was demonstrable in the control group at any time during the experiment. However subsequent stimulation of the correct acupuncture points in the control group again produced significant analgesia and also overcame the counter suggestion of sensitisation. Moore and Burke [106] studied the effects of acupuncture and suggestibility on chronic shoulder pain. Patients were placed in one of two environments; one was positive and supportive, suggesting the therapy would work and the other was negative, suggesting the therapy would be ineffective. Neither of these settings affected treatment outcome. Those patients rated as highly susceptible to hypnosis tended to fail to achieve the highest levels of pain relief, but hypnotic suggestibility could not be significantly correlated with treatment outcome in the context of this study. Liao and Wan also reached a similar conclusion; that is, that highly suggestible patients did not necessarily do well with acupuncture [107].

Only one study to date has noted a correlation between suggestibility and response to acupuncture, that of Katz *et al.* [108]. They noted a close correlation between hypnotizability and pain relief, and suggested that acupuncture and hypnosis may be working through parallel mechanisms.

The exact mechanism of hypnosis remains unclear, but there is some evidence to suggest that acupuncture and hypnosis may be affecting the same neurological pathways. However, hypnosis does not seem to be endorphin mediated (naloxone reversible) whereas acupuncture almost certainly is. The evidence available suggests that acupuncture and hypnosis are probably unrelated in that suggestibility is not an essential factor in the success or failure of acupuncture therapy for pain.

The placebo effect

Beecher was one of the first modern physicians to recognize the power and importance of the placebo and to attempt to quantify its effect [109]. It is quite possible that because acupuncture is such a dramatic (and in lay terms) mystical therapy, it may have some element of suggestion within it. If this were the case

then physical placebos, similar to acupuncture, should result in a higher placebo effect than that noted from placebo medication, in properly controlled, double-blind studies, on pharmacological preparations. Mock TENS, a procedure very similar to that of electro-acupuncture, produces a placebo response of the order of 30%, [110–112]. Therefore, within the context of these controlled studies, the placebo effect of a technique very similar to that of acupuncture is almost exactly equivalent to that expected from placebo medication. It has been suggested that placebo analgesia is endorphin mediated as it is naloxone reversible [113]. Perhaps placebos and acupuncture are mediated through the same biochemical systems. It is possible that acupuncture is a particularly powerful form of placebo therapy.

Any therapy, particularly for pain, is more likely to be effective if the relationship between the doctor and the patient is effective in reducing anxiety [93]. Acupuncture is frequently practised (in the United Kingdom) in the setting of a private clinic where the patient receives both time and sympathy from the doctor. Consequently, some of the successes claimed by acupuncture could be attributed to the relationship between the therapist and the patient rather than the therapy itself. However the extent of this factor remains undefined and represents a phenomenon that is difficult to investigate objectively.

Race

Early reports of acupuncture in China have implied that acupuncture was a useful therapy for the Chinese but would never work in the West. Perhaps because of the inscrutable face of the Orient the Chinese were thought to be almost resistant to pain. Studies by Chapman *et al.* [114] and Knox *et al.* [115] show that Orientals are at least as susceptible to experimental pain as Occidental races; in fact Knox's work shows that Orientals have a significantly lower pain tolerance than Caucasians. It therefore seems unlikely that race has any significant effect on the outcome from this form of therapy.

Conclusion

In the United Kindgom acupuncture is mainly used as a therapy for the treatment of chronic pain. Patients in chronic pain are likely to be depressed, but it is unclear as to whether any specific psychological variables affect the outcome of acupuncture therapy. Acupuncture and hypnosis are almost certainly different phenomenon and acupuncture cannot be thought of as a complex form of hypnotic suggestibility. All therapies have a placebo effect, and acupuncture is no exception to this general rule. Alternative medicines are becoming more popular throughout Europe, and it may be that patients who seek such therapy are more likely to respond to it, particularly within the context of private practice where the patient will be given the facility for a more relaxed consultation.

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