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Effects triggered in the periphery by acupuncture

I. Lund [a,*], T. Lundeberg [b]

[a] Department of Physiology and Pharmacology, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[b] Rehabilitation medicine University Clinic Stockholm, Danderyds Hospital AB, 182 88, Sweden

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ABSTRACT

The clinical effects following acupuncture stimulation can be attributed to peripheral and central effects. Histological studies have revealed that many acupuncture points have dense innervation, and are often located in direct relation to skeletal muscles, connective tissue, as well as to cells with neuro-immune-modulatory role [66], suggesting that these tissue may contribute both to the peripheral and central effects.

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1. Nervous system

1.1. Sensory receptors

Acupuncture stimulation is associated with the activation of different sensory receptors, i.e., the terminal of the spinal dorsal root ganglion neuron or trigeminal sensory neuron, in the skin and deeper tissues. Their properties and the corresponding sensation they give rise to, that may be activated during acupuncture and moxibustion, include five major modalities [51,85,86,105,106].

1.2. Mechanoreceptors; cutaneous and subcutaneous

Five major types of mechanoreceptors have been identified in skin. Two of these are of the encapsulated type and are located in the superficial layers of the skin: Meissnerís corpuscle and the Merkel disk receptor. The other two receptors, the Pacinian corpuscle and the Ruffini ending, also encapsulated, are found in the subcutaneous and deeper tissue layers (including between layers of muscle and on interosseous membranes). The fifth major type of mechanoreceptor is the bare nerve ending responding to stroking of the hairy skin.

1.3. Mechanoreceptors; tendon, joints and skeletal muscle

Four different types of mechanoreceptor are found in skeletal muscles, tendons and joint structures. Their main task is to give rise to the sense of movement and position of oneís own limbs and body (proprioception), and sense of speed and direction of limb movement, and also to enable maintainance of an upright position (postural information) and manipulation of objects. One of these receptors is the ergo-receptor. Ergo-receptors are activated by hard pressure during muscle contraction [56] and also probably by acupuncture, when the sensation of *de qi* is evoked. It has therefore been suggested that the physiological counterpart to acupuncture is exercise [5]. However, the ergo-receptors can also respond to metabolic stimuli of released H^+, lactate, or K^+ ions, i.e., acting as 'metabolic chemoreceptor' and by a release of neurotransmitters [49,108].

1.4. Nociceptors

Nociceptors are the receptors that selectively respond to nociceptive stimulation of peripheral tissue, as mentioned earlier, leading to perceived pain under certain circumstances. Pain is sometimes perceived in the absence of this activity but could then be due to sensitization processes in higher brain structures.

The polymodal nociceptors are the most common class of nociceptor. During intense acupuncture stimulation, acupressure (painful) or strong massage, mechanical nociceptors may be activated resulting in slight increase of pain sensations but also in an increased activity in endogenous pain inhibiting systems.

* Corresponding author.
E-mail address: irene.lund@quicknet.se (I. Lund).

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During acupuncture stimulation a sensation of itch may be perceived. It has been suggested that pruritus/itch receptors [105,69] are part of a larger set of nociceptors where activation of the whole group elicits pain while activation of the itch-selective subset elicits exclusively itch. However, itch or pruritus is not just triggered in the peripheral tissue but also more centrally suggesting that there exist multiple neural pathways for itch induction [77].

1.5. Acupuncture and mechanoreceptors

Acupuncture may activate all types of mechanoreceptor in superficial cutaneous and in deep muscular tissue. It has been reported that most acupuncture points contain abundant free nerve endings, encapsulated cutaneous receptors (Merkel, Meissner, Ruffini, and Pacinian corpuscles), sarcous sensory receptors (muscle spindles and tendon organs) as well as ergo-receptors, and their afferent fibres. Acupuncture sites can be classified into three types: muscle-spindle-rich acupuncture sites, cutaneous-receptor-rich acupuncture sites, and tendon-organ-rich acupuncture sites. In acupuncture practice, manipulation is often performed on the inserted needles to enhance needling sensation and therapeutic responses. Different modes of stimulation technique used (for example superficial versus deep needling depth, light or no stimulation versus rotation and thrusting) will also probably determine which type of receptor is activated. Gentle and repetitive manipulation of the inserted needle would be expected to produce mechanical pressure and tissue distortion that activate mechanoreceptors. Also, manual stimulation may result in distant effects which has been attributed to shear force- and stress-induced tissue displacements. All types of manual technique tested have yielded greater distant effects on sarcous stretch receptors than cutaneous mechanoreceptors; twist/rotation has the greatest distant effects on the cutaneous superficial and deep receptors as well as sarcous stretch receptors compared to other techniques. In addition, the sensitivity status of the peripheral terminals, i.e. intact or sensitized as in a pain condition, will be influenced by the receptor's peripheral milieu such as the presence of lactate, K^+, nitric oxide (NO) ions, chemokines, cytokines, myokines, and a number of other factors. Therefore, the same stimulation technique may produce very different sensations ranging from being barely detectable to being painful.

1.6. Afferent nerve fibres

All somatosensory information from the limbs and trunk is transmitted through individual peripheral afferent nerve fibres of spinal dorsal root ganglion neurons, each of which responds to the modality-specific type of stimulation associated with the morphological and molecular specialization of its peripheral receptors [51]. Somatosensory information from cranial structures is transmitted by the trigeminal sensory neurons in the brain stem, which are functionally and morphologically homologous to spinal dorsal root ganglion neurons, and transmitted further to higher levels in the brain via second order neurons. The principal functions of dorsal ganglion neurons and the trigeminal nerve are transduction of the stimulus and transmission of encoded stimulus information to the higher levels of the CNS. Recent studies also indicate that somatosensory stimulation may be transmitted to the nucleus tractus solitarius without bypassing the dorsal root ganglion.

Mechanoreceptors and proprioceptors are commonly innervated by large-diameter myelinated afferents axons, whereas thermal receptors and nociceptors have small myelinated or unmyelinated axons.. Gentle, dynamic touch is encoded by a distinct tactile type receptor and transmitted in un-myelinated afferent nerves found exclusively in hairy skin, C tactile (CT) afferents. CT afferents increase firing when the skin is stroked at a speed of approximately 30 mm/s with gentle contact at a typical skin temperature [85,71,78,2].

The presence of somatic afferent and efferent fibres innervating skin, connective tissues, and skeletal muscles has been reported at acupuncture points. Many of the acupuncture sites investigated had relatively dense neural components, particularly nerves fibres, with a ratio of nearly 1.4:1 compared to non-acupuncture points. Also, the ratio of myelinated to un-myelinated fibres was found to be nearly 4-fold higher in the acupuncture point Zu-San-Li (ST36) than surrounding areas. Sarcous sensory receptors (muscle spindles and tendon organs) and their afferent fibres have been reported to be concentrated at acupuncture points located on thick muscles such as the tibials anterior and rectus femoris muscles [66].

Another important neural component of most acupuncture sites, and indeed many somatic areas, is the dense and fine autonomic nerve fibres, found in close proximity to the sensory receptors and afferents. Most autonomic nerves are norepinephrine (NE) containing sympathetic fibres but also cholinergic (ACh) parasympathetic efferent nerves may be found. Interaction between somatic and autonomic neural components may serve to modulate local and afferent signals in points where acupuncture stimulation is applied.

Interaction between activity in the sensory afferents and autonomic efferent nerve fibres may also take place in the dorsal root ganglions and at segmental level in the spinal cord as well as in more central parts of the CNS.

1.7. Electrical stimulation of afferent nerves

As stated above, the difference in the conduction velocities of different nerves may be attributed to internal resistance to current flow along the axon. This is also the reason why electrical nerve stimulation using either surface electrodes as in transcutaneous electrical nerve stimulation (TENS), or with thin needles connected to an electrical stimulator as in electro-acupuncture (EA), with low intensity, activates afferent nerves with large diameter more easily than the thinner ones [8]. When using higher stimulation intensities, thinner sensory afferents are activated by the stimulus.

Due to the fact that EA results in the electrical activation of many different afferent nerves it is therefore not to be regarded as equivalent to manual acupuncture [80]. It is generally accepted that manual acupuncture sets up activity in superficial and deep Aβ and Aδ fibres but that most of the clinical effects including pain alleviation and autonomic modulation may be attributed to the activation of deep Aβ, Aδ and C fibres [5].

1.8. The de qi sensation

A large body of empirical and experimental evidence suggest that during acupuncture stimulation the so called needling sensation, *de qi*, should be strived for.

Although the perception of needling sensation may vary between individuals and with manual techniques, this distinct sensation is generally characterized by soreness, numbness, heaviness, distension, and aching in the deep tissues surrounding the inserted needle [47]. The *de qi* sensation is also often accompanied by an increased blood flow and a feeling of warmth at the acupuncture point. Simultaneously with the patients' sensation of *de qi*, the acupuncturist often perceives an increased resistance to further movement/manipulation of the inserted needle. Thus, the needling sensation is not a single, but a compound sensation that is generated from the activation of various sensory receptors and their afferent fibres in acupuncture sites. It has been demonstrated that numbness, heaviness, and distension during needling are closely associated with the activation of myelinated Aβ and Aδ afferents in deep tissues of acupuncture points, whereas aching and sore-

ness are associated with stimulation of small myelinated Aδ and unmyelinated C fibres.

1.9. Local hyper or hypoesthesia following acupuncture

The insertion of acupuncture needles into various tissues has been reported to result in the release of mediators that can be classified as inhibitory or stimulatory. The stimulatory mediators include various cytokines, prostaglandins, bradykinin, and other pro-inflammatory factors that enhance afferent fibre excitability at the acupuncture site. The inhibitory mediators include ACh, NE, gamma amino butyric acid (GABA), β-endorphin, SP, somatostatin, NO, ATP, cyclic guanosine monophosphate (cGMP), and adenosine, which suppress receptor and/or afferent fibre excitability at the acupuncture site. The predominant effect of acupuncture is to enhance the release of inhibitory mediators. Serotonin (5-HT) and histamine are also released but the effect is more complex as they can exert either inhibitory or stimulatory effects, depending upon which receptors they act on. The increase of mediators in local, peripheral tissues is partly originating from non-neuronal cells. Local mechanisms at acupuncture sites may play an important role in acupuncture induced analgesia, in which afferent noxious signals from sites distal to needling points are blocked mostly by enhancing the activity of inhibitory mediators and activating negative feedback in acupuncture sites based on autoreceptors to SP and CGRP [132].

1.10. Cross talk at spinal cord levels

The spinal cord's dorsal horn in the CNS is a key region in which sensory information is received, integrated, and relayed to higher brain structures. The patterns of termination of primary afferents within the spinal cord are related to axonal diameter, receptive field, and sensory modality. Nociceptive primary afferents terminate primarily in the superficial part of the dorsal horn, specifically in laminae I and II, whereas inputs from myelinated Aβ fibres of mechanoreceptors terminate in deeper layers, i.e., laminae III/IV. Thus, touch sensitive fibres terminate deeper and nociceptive sensitive fibres terminate more superficially within the dorsal horn. Excitatory and inhibitory interneurons are found throughout laminae I, II, and III/IV. Neurons in lamina V receive convergent excitatory input from both non-nociceptive Aβ fibres and nociceptive Aδ and C fibres, conveying the "strongest" stimulation to the higher centres of the CNS. Furthermore, the large diameter Aβ fibres inhibit the firing frequency of neurons in lamina V by activating inhibitory interneurons in laminae I/III. On the other hand the Aδ and C fibres excite lamina V neurons but also inhibit the firing of the inhibitory interneurons in lamina II, which are activated by the Aβ fibres.

In a study using intersectional genetic manipulations to identify some critical components of mechanical pain transduction, it was reported that peripheral mechanical nociceptors and Aβ mechanoreceptors, together with spinal somatisation excitatory and dynorphin inhibitory neurons, form a microcircuit that transmits and gates mechanical pain [26].

Taken together, non-nociceptive afferents close and nociceptive afferents open a 'gate' to the central transmission of noxious input. Approximately 30% of the neurons in the superficial dorsal horn are immune-reactive for the inhibitory transmitter GABA, and/or glycine. These inhibitory neurons are driven by the activity in low-threshold primary Aβ afferents. However, it has recently been demonstrated that nearly all of the GABA containing neurons also receive input from high-threshold Aδ and/or C fibres, a combination that is not predicted by the gate control theory of pain. On the other hand, glycine containing inhibitory neurons located near the laminae II/III border may directly inhibit an enzyme that is a member of protein kinase family and involved in diverse cellular signalling pathways, the protein kinase C (PKC) γ^+ neurons, to close the gate. Some lamina II neurons receive tonic descending inhibition from higher brain areas via GABA and glycine containing neurons, suggesting that superficial dorsal horn neurons are inhibited through two different modes, phasic and tonic, that could be activated through peripheral and central mechanisms. Depending on the pain condition treated, possibly the short term effects of acupuncture are mediated through the phasic activity whereas the long term effects are related to modulation of the tonic activity. This gate mechanism described above is the rationale for the use of TENS for the relief of pain [8].

The mechanism of analgesia is topographically specific, meaning that the area of the body in which pain is regulated is linked anatomically to the segments where the nociceptive and non-nociceptive afferents terminate. This would suggest that the sensory stimulation should be applied in the same segments (dermatome, myotome or sclerotome) as the pain. Furthermore, activity in non-nociceptive afferents results in inhibition of sympathetic efferents in lamina VII of the spinal cord whereas nociceptive activity results in an activation (for example during needling). However, long-term needling (20–40 min) may result in the activation of centrally based inhibition of the sympathetic tone. This inhibition is more pronounced after the end of treatment and may last for hours. An even more potent counterbalance to nociception is mediated by stimulation of the periaqueductal grey (PAG), region, the gray matter that surrounds the third ventricle and the central aqueduct. This stimulation-produced analgesia activates descending pain inhibitory systems that inhibit firing of nociceptive neurons in the dorsal horn of the spinal cord. Few neurons in the PAG matter project directly to the dorsal horn of the spinal cord. Instead, they make excitatory connections with neurons, in particular serotonergic neurons, in the nucleus of raphe magnus. From the neurons in nucleus raphe magnus they project to the spinal cord via the dorsal part of the lateral funiculus and make inhibitory connections with neurons in laminae I, II, and V of the dorsal horn. Other descending inhibitory systems that suppress the activity of the nociceptive neurons in the spinal cord originate in the noradrenergic locus coeruleus and block the output of the neurons in laminae I and V by direct and indirect inhibitory actions. They also interact with opioid-containing circuits in the dorsal horn. Opiates and opioid peptides (endorphins, enkephalins and dynorphins) regulate nociceptive transmission via different mechanisms—one of these is postsynaptic inhibition, produced by increasing K^+ conductance in the second order neuron, and one is presynaptic inhibition. The opioid-induced decrease in transmitter release (glutamate and SP) from primary afferents results either indirectly from a decrease in Ca^{2+} entry into the sensory terminals or directly from a decrease in Ca^{2+} conductance.

Both experimental and clinical studies suggest that part of the analgesic effect of acupuncture is mediated through activity in these descending systems that also seem to play a role in the modulation of the autonomic activity. A role for opioids is supported by the fact that morphine produces analgesia by activating descending inhibitory systems.

1.11. Spinal reflexes–dorsal root, motor and autonomic reflexes

It has been demonstrated that descending inhibitory systems modulate dorsal root reflexes (DRR) through presynaptic inhibition and thereby inhibition of the antidromic activity in A and C primary afferent nerve fibres that contributes to the release of SP and CGRP at their peripheral terminals, so called neurogenic inflammation. This descending control of DRR is seen following activation of neurons in PAG and is mediated by GABA and 5-HT. GABA (A) receptors

play a key role in the generation of DRRs, but 5-$HT_{(3)}$ receptors also contribute.

The spinal cord processes somatic and visceral reflexes as well as outputs from the CNS to effector organs involved in visceral functioning including cardiovascular regulation. Since opioid or nociceptin-like immuno-reactivity is present in the spinal sympathetic nuclei (i.e., intermediolateral column, IML) it has been suggested that acupuncture, especially low frequency (2 Hz) EA, also influences the neurotransmission between the brain stem and the IML. Interestingly, both opioids and nociceptin reduce the response to rostral ventrolateral medulla (rVLM)-induced sympathetic excitation, indicating that the two peptides can regulate sympathetic outflow. Furthermore, afferent stimulation can modulate sympathetic activity directly through the inhibition of excitatory interneurons. These interneurons appear to form important links in the spinal cord circuitry involved in autonomic control. Taken together this suggests that acupuncture, via modulation of somato-autonomic reflexes, may modulate for example gut motility and bladder activity, a modulation that is directly related to the physiological/pathophysiological state of the organ/system [22].

During acupuncture stimulation there is an increased sympathetic activity during stimulation (manual or electro). After the end of stimulation the effects are dependent on the basal activity before the start of stimulation. In subjects with an increased activity before the start of stimulation there is a sympathetic inhibition that may last as long as 12 h. In patients with a normal tone there is a minor inhibition which is short-lasting. In subjects with a low activity the activity stays increased after the end of stimulation. The parasympathetic tone is also affected but with a lesser magnitude but possibly with a longer duration (up to 72 h). The total net effect is a response towards the "normal level".

It has also been demonstrated that acupuncture may modulate motor reflexes at the spinal cord level as well as motor behaviour, a modulation dependent on the condition treated. For example, manual acupuncture provides sufficient neuromuscular stimuli to promote immediate changes in motor unit gross recruitment without repercussion in maximal force output in healthy subjects, whereas post-stroke patients did not exhibit significant reduction on the myoelectric activity and maximal force output after manual acupuncture. A common clinical experience is that acupuncture reduces muscle tenderness. This has in part been attributed to the suppression in motor neuronal activities of the skeletal muscles by needle insertion. In a healthy human, application of vibratory stimulation on the volar side of the fingertip induces a flexion reflex. Typically, the finger flexion force occurs with the onset of vibration and increases progressively during vibration. This reflex is assumed to have two reflex arcs, that is, the spinal short loop and supraspinal long loop. Interestingly, the activities in both these loops are suppressed by ipsilateral segmental acupuncture stimulation in the upper extremity, and suppression on the supraspinal long loop is relatively long lasting (a continuous decrease of the vibration-induced finger flexion reflex was observed after removal of a needle) compared with that on the short loop. This motor reflex inhibiting effect has been attributed to the activation of nociceptive A delta or C fibres indicating that there is convergence between nociceptive and non-nociceptive afferents of different origins onto the common interneurons in segmental reflex pathways to α-motor neurons. This would suggest that noxious somatosensory input by using acupuncture could suppress motor neurons that innervate the flexor muscles through common interneurons and that acupuncture treatment could be a useful intervention for reducing muscle spasticity at least in the upper extremity [113]. The effect of acupuncture on motor reflexes and motor control needs further evaluation.

1.12. The dorsal column-medial lemniscal system

The principal central branch of the axon of neurons mediating tactile sensation and proprioception from the limbs and trunk ascends in the spinal cord in the ipsilateral dorsal column to the medulla [51]. At the upper spinal levels the dorsal column is divided into two fascicles (bundles) - the gracile fascicle and the cuneate fascicle. The medially located gracile fascicle contains fibres that ascend from the ipsilateral sacral, lumbar and lower thoracic segments. The cuneate fascicle is located laterally and contains fibres from the upper thoracic and cervical segments. Axons from the two bundles terminate in the lower medulla, in the gracile nucleus and the cuneate nucleus, respectively. The axons from the two nuclei cross to the other side of the brain stem and ascend to the posterior lateral nucleus of the thalamus. Mechanosensory information from the face and scalp is transmitted to the principal trigeminal nucleus which is located in the pons.

The trigeminal lemniscus crosses over and later joins axons from the arm and back of the head in the medial lemniscus. Because of the crossing of fibres in the medulla and pons the right side of the brain receives sensory input from the limbs and trunk of the left side of the body and vice versa. From the thalamus the proprioceptive sensory input projects, directly and indirectly, to the somatosensory cortex, the frontal cortex, the limbic structures and the hypothalamus.

1.13. The anterolateral system

Neurons mediating information of nociception/pain, hard pressure, cutaneous touch and temperature from the limbs and trunk terminate in the ipsilateral dorsal horn of the spinal cord. The fibres are small and branch extensively in the white matter, forming the tract of Lissauer, and terminate in the most superficial layers of the dorsal horn. Thus neurons in the marginal zone (lamina I) and substantia gelatinosa (laminae II and III) respond almost exclusively to painful or thermal stimulus. From the dorsal horn the information ascends to the anterolateral quadrant of the contralateral side of the spinal cord. The anterolateral pathway is thus made up by neurons in the marginal zone, the nucleus proprius (lamina IV), the deep layers of the dorsal horn (laminae V and VI) and the intermediate zone (laminae VII). The anterolateral tract includes three ascending pathways, terminating in the thalamus: the spinothalamic pathway, the spinoreticular pathway and the spinomesencephalic pathway. The spinothalamic pathway mediates information about the nociceptive/painful and thermal stimuli directly to the ventral posterior lateral nucleus of the thalamus. Axons in the spinoreticular tract will synapse with neurons in the reticular formation of the medulla and pons, which then relay information to the intralaminar and posterior nuclei of the thalamus and to other structures in the diencephalons, such as the hypothalamus.

Trigeminal sensory afferents that carry information of nociception/pain and temperature from the head and face form the spinal trigeminal tract terminating in the trigeminal nucleus in the medulla. The spinal trigeminal nucleus contains a marginal zone and a substantia gelatinosa that receive nociceptive information and a magnocellular division that is innervated by mechanoreceptors and corresponds to the nucleus proprius. The axons of trigeminal neurons also decussate in the brain stem and join ascending fibres from the most rostral spinal segments.

Thalamic neurons sensitive to nociceptive/painful or thermal stimuli project to the primary somatic sensory cortex, to the dorsal anterior insular cortex and to the anterior cingulate gyrus. In addition to these regions, activity is conveyed to the frontal cortex, the limbic structures and the hypothalamus.

1.14. Brain

Studies using fMRI for evaluation of treatment effects have demonstrated that acupuncture can induce haemodynamic changes in brain functional networks. Although brain responses vary slightly in response to stimulation of different acupuncture points, similar central effects are generally obtained when acupuncture stimulation is associated with sensations of *de qi*. Under these circumstances acupuncture stimulation evokes deactivation of a limbic-paralimbic-neocortical network, which encompasses the limbic system, as well as activation of somatosensory brain regions. Also, extensive signal attenuations, mainly distributed in the medial temporal lobe, the posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC), and a large section of the parietal cortex has also been reported. These networks closely match the default mode network and the anti-correlated task-positive network [47]. The amygdala and hypothalamus, in particular, show decreased activation during acupuncture stimulation that is not commonly associated with default mode network activity. On the other hand when sharp uncomfortable pain is elicited there is no deactivation and instead activation and arousal may be seen. The default network, the dominant functional network during the resting state, plays an important role in attention, memory, consciousness, and self-referential processes. During illness, pain and stress, the network's activity is disturbed resulting in malfunctioning. When subjected to acupuncture the default mode has been reported reset and patients may report the "return of their mental functioning". Similarly, acupuncture, but not the sham version, can also induce the increased connectivity within both the default mode network (DMN) and the sensorimotor network (SMN). Acupuncture can also cause prominent and long-lasting modulation effects on the intrinsic coherence of the wide interceptive-autonomic areas of the brain and spinal cord. Acupuncture may furthermore inhibit activity in the frontal cortex thereby modulating anxiety responses and fear avoidance reactions. Recently, behavioural and functional brain responses to the insertion of needles into the body have been recorded in two different contexts, treatment and stimulation. Although the applied stimuli were physically identical in both groups, the verbal instructions differed: participants in the stimulation group were primed to consider the acupuncture as a painful stimulus, whereas the participants in the treatment group were told that the acupuncture was part of therapeutic treatment. Acupuncture yielded greater brain activation in reward-related brain areas (ventral striatum) of the brain in the treatment group when compared to the stimulation group. Also, brain activation in response to pain stimuli was significantly attenuated in the bilateral secondary somatosensory cortex and the right dorsolateral prefrontal cortex in the treatment group but not in the stimulation group demonstrating the power of context in acupuncture practice [64].

Taken together, the peripheral effects of acupuncture on the sensory nerves may be attributed to changes in the peripheral milieu of the sensory re ceptors and their afferents, reflex mechanisms at the spinal cord level, activation of descending modulation as well as deactivation of the limbic-paralimbic-neocortical network. Also, acupuncture may result in deactivation of the frontal-prefrontal areas of the brain as well as modulation of hypothalamic homeostatic mediated responses.

2. Neuro-immunological reflexes

2.1. Axon reflex

In addition to orthodromic inputs to the spinal cord and brain from the periphery, action potentials in sensory neurons can also be transmitted antidromically at branch points back down to the periphery, thereby forming the axon reflex. These activities together with sustained local depolarizations lead to a rapid and local release of neural mediators from both peripheral axons and terminals.

2.2. Axon reflex -Aδ/type III fibres

Intense antidromic stimulation of afferent nerves sufficient to excite thin myelinated Aδ/type III fibres will produce an increase in skin and muscle blood flow in the distal territory of the nerve. The magnitude and time course of the vasodilatation depend on the number and frequency of the nerve stimulation. There is no evidence of an accompanying plasma extravasation, suggesting that Aδ/type III afferent nerve fibres are involved in axon reflex/axon [49,108] response reactions without inducing a neurogenic inflammation (includes the activation of C afferent fibres, see below). This could explain part of the positive effects of acupuncture when treating ischemic conditions, i.e., acupuncture stimulates ergoreceptors and so releases CGRP and triggers Aδ/III axon reflexes that in turn results in vasodilation and increased capillary flow mainly within the muscle. Two pathways for the vasodilation of CGRP have been described, either NO-endothelium dependent or not:

1.) CGRP binds to the CGRP1 receptor on vascular smooth muscle cells and induces an increase in intracellular cyclic adenosine 5′ -monophosphate (cAMP) and protein kinase A (PKA). This cascade results in opening of K^+ ion channels and Ca^{2+} ion sequestration followed by relaxation of vascular smooth muscle (vasodilation). This pathway is NO-endothelium-independent.
2.) The binding of CGRP to the CGRP1 receptor on vascular endothelium cells triggers NO production via NO synthase. NO released from vascular endothelium leads to relaxation of vascular smooth muscle. This pathway is NO-endothelium-dependent.

A peripheral role for CGRP in the vasodilatory response following acupuncture is also partly supported by studies showing that CGRP participated in increasing local muscle blood flow following manual acupuncture [108] without changing arterial blood pressure in intact rats. Other mechanisms involved in the vasodilatory response such as release of adenosine phosphate compounds from connective tissue or by an increase in mechanical signalling through the extracellular matrix were also suggested. These compounds may induce its vasodilatory effect by binding to adenosine (A1 receptors) and purine receptors (P2Y receptors). The binding of adenosine phosphate compounds to their receptors on vascular endothelium cells induces in turn release of NO. The release of NO could also be the result of a sequential reaction, beginning with a change in sympathetic activity and leading to NO production. Another explanation could be that NO production may be caused by mechanical stimulation of the vascular endothelium, i.e. shear stress imposed on the vascular wall, during acupuncture [63].

The above results suggest that acupuncture may have an important role in the peripheral tissue milieu by inducing vasodilation. NO is possibly the most important factor in the short term (reversing ischaemia), whereas CGRP may be more important in the longer term as it has trophic effects on the endothelium, thereby promoting angiogenesis. The relevance of this mechanism needs to be elucidated in pathophysiological models and in clinical conditions.

2.3. Axon reflex - C/type IV fibres

Acupuncture may also result in the activation of nociceptors and C-fibres [115]. Action potentials transmitted in nociceptor neurons result in a rapid and local release of neural mediators from both peripheral axons and terminals inducing vasodilation, extravasa-

tion and oedema, i.e., "neurogenic inflammation", an inflammatory response independent of that produced by the immune system. In the acute setting of tissue damage, it has been suggested that neurogenic inflammation is protective, facilitating physiological tissue healing.

Neurogenic inflammation is mediated by the release of CGRP and SP, which act directly on vascular endothelial and smooth muscle cells. CGRP has potent vasodilatory effects as described above whereas SP increases capillary permeability leading to plasma extravasation and oedema. Also mediators such as glutamate, NO and cytokines are released from the peripheral sensory neurons that in turn directly will attract and activate innate (mast cells, dendritic cells) and adaptive immune cells (T lymphocytes).

Cytokines have a key role in communication between immune cells and nociceptor neurons. Upon activation of cytokine receptors, signal transduction pathways are activated in sensory neurons leading to downstream phosphorylation of membrane proteins including Tryptophan (Trp) and voltage-gated channels. The resulting sensitization of nociceptors means that normally innocuous mechanical and heat stimuli can now activate nociceptors. Interleukin (IL) 1 beta and tumour necrosis factor (TNF) -alpha are two important cytokines released by innate immune cells during inflammation that are directly sensed by nociceptors which in turn express the cognate receptors, induce activation of p38 map kinases leading to increased receptor membrane excitability. Nerve growth factor (NGF) and prostaglandin E2 are also major inflammatory mediators released from immune cells that act directly on peripheral sensory neurons to cause sensitization. An important effect of nociceptor sensitization caused by immune factors is an increased release of neuropeptides at peripheral terminals that further activate immune cells, thereby inducing a positive feedback loop that drives and facilitates hypersensitivity.

In the early phases of inflammation, sensory neurons signal to tissue resident mast cells and dendritic cells, which are innate immune cells that are important in initiating the immune response. During the effector phase of inflammation, immune cells need to find their way to the specific site of injury. Many mediators released from sensory neurons, neuropeptides, chemokines, and glutamate, are chemotactic for neutrophils, eosinophils, macrophages, and T-cells, and enhance endothelial adhesion which facilitates immune cell homing. Furthermore, neurons may directly participate in the effector phase of the inflammatory reaction, as neuropeptides themselves may have direct antimicrobial functions. Neuronally derived signalling molecules can also direct the type of inflammation, by contributing to the differentiation or specification of different types of adaptive immune T cells. An antigen is phagocytised and processed by innate immune cells, which then migrate to the nearest lymph node and present the antigenic peptide to naïve T cells. Depending on the type of antigen, co-stimulatory molecules on the innate immune cell, and the combinations of specific cytokines, naïve T cells mature into specific subtypes that best serve the inflammatory effort to clear the pathogenic stimulus. This T cell maturation process is heavily influenced by sensory neuronal mediators.

Considering that signalling molecules released from peripheral sensory nerve fibres regulate not only small blood vessels, but also the chemotaxis, homing, maturation, and activation of immune cells, it is becoming clear that neuro-immune interactions are very intricate. Furthermore, it is specific combinations of signalling molecules released from nociceptors that influence different stages and types of immune responses rather than individual neural mediators. This would suggest that the effects of acupuncture are different depending on when, where and how it is applied. Clinical observations have demonstrated that the acupuncture-induced axon reflex is strongly apparent in the areas of acupuncture points, particularly in the back and abdominal acupuncture points. It is characterized by a hyperaemia (flare) that rapidly (generally within 2–5 min) spreads beyond needling points of the skin with a diameter of 1–3 cm. The axon-dorsal root reflex at acupuncture sites may also be closely related to dense sympathetic nerve-rich arterioles.

Hypothetically the local neurogenic inflammation induced by acupuncture may play an important role in tissue healing, such as in tendinopathies. This would further suggest that needling in the proper site (injured site) is critical for these specific effects.

2.4. Autonomic reflexes

Acupuncture and electro-acupuncture may result in the activation of interneurons in the brainstem including the nucleus tractus solitarius that results in outgoing neural signals from the dorsolateral motor nucleus. The outgoing signals generated in the brainstem suppress innate immune responses and inflammation, either: via the vagus nerve to the adrenal medulla (vagal-adrenal medulla reflex), resulting in the release of dopamine; or via the adrenergic nerve to the blood vessel near the fifth lumbar segment (exercise gateway reflex); or via the vagus nerve to the coeliac ganglion to the spleen to acetylcholine-producing (AChT+) T cells (inflammatory reflex); or they induce a local axon reflex (see above). Also, there is neural influence on B cell trafficking and antibody secretion affecting the immune response. Furthermore, outgoing signals are also relayed to the nuclei in the hypothalamus that control the function of the HPA axis, resulting in increased glucocorticoid hormone release by the adrenal gland, which suppresses innate immune responses.

2.5. Vagal-adrenal medulla reflex

The efferent vagus nerve signals induce the release of dopamine in the adrenal medulla resulting in the activation of dopaminergic type 1 (D1) receptors and suppressed systemic inflammation. The route by which sensory signals elicited from electro-acupuncture transits to the brainstem to activate outgoing vagus signals remains unknown. Interestingly, there is a significant correlation between depressed vagus nerve activity and increased morbidity and mortality in non-resolving inflammatory diseases. An intriguing possibility is that vagus nerve deficiencies might be reversed by vagus nerve stimulation using for example EA, aerobic exercise, meditation, music therapy, and biofeedback training.

3. Inflammatory reflex

In the inflammatory reflex, products of inflammation activate afferent action potentials travelling in the vagus nerve to the nucleus tractus solitarius, which relays the neuronal signals to other brain nuclei located in the hypothalamus and brainstem [125,126,34]. Efferent signals travel from the nucleus ambiguus and dorsal motor nucleus back down the vagus nerve, which terminates in the coeliac ganglia [13,15]. Stimulation of the vagus nerve activates adrenergic splenic neurons residing in the coeliac ganglion, which travel into the spleen and terminate in synapse-like structures adjacent to T cells in the white pulp [98]. Norepinephrine released from splenic neurons binds to α_2 adrenergic receptor expressed on a subset of T cells that expresses choline acetyltransferase, the rate-limiting enzyme in acetylcholine biosynthesis.

Activation of the sympathetic outflow by flight-or-fight responses or pain, or through direct signalling, can increase local concentrations of adrenaline and noradrenaline, which can suppress inflammation further. Anatomical, functional, and molecular lesions in the vagus nerve enhance cytokine production associated with non-resolving inflammation [120]. Under basal conditions,

the vagus nerve transmits tonic inhibitory activity that dampens the activity of the innate immune response to pathogen associated molecular products [98]. The inhibitory activity of the inflammatory reflex can be enhanced by manual acupuncture or EA that increase the generation of adrenergic signals in the splenic nerve [14,15,12,75,123]. The activity of the splenic adrenergic neurons can be functionally modified by either preganglionic neurons arising on the sympathetic chain, or by signals arriving there from the vagus nerve that terminate on interneurons residing in the coeliac ganglion that can modulate the signals arising from the sympathetic chain. Activation of the sensory sciatic nerve by EA in the leg inhibits cytokine release and improves survival in an experimental model of sepsis through a sciatic-to-vagus nerve circuit that regulates the innate immune response [117]. Signals in the sciatic nerve results in efferent vagal nerve activity and dopamine release in the adrenal medulla (see above).

3.1. Exercise gateway reflex

The muscle contraction dependent reflex or the "Exercise gateway reflex" circuit that regulates T-cell recruitment into the CNS [7] has several components. In this reflex circuit, sensory signals arise in the hind limb, are transmitted to the spinal cord and brain stem and then descend in the sympathetic chain to be relayed via adrenergic neurons that terminate on endothelial cells to regulate expression of chemokine receptors [122]. A similar circuit, termed the "Exercise pressor reflex" is activated during exercise by stimulation of mechanoreceptors and metabolically sensitive ergoreceptors in skeletal muscle [53]. Arrival at the brain stem level of sensory input from muscles increases the activity of cholinergic neurons descending in the sympathetic chain at the same segmental level, i.e., it has a somatotopic organization. This suggest that EA via sensory sciatic nerve stimulation may initiate anti-inflammatory efferent vagus nerve signals [21].

3.2. Neural influence on B cell trafficking and antibody secretion.

Electrical stimulation of the vagus nerve may influence B cell trafficking and antibody secretion. Stimulation of the vagus nerve results in the activation of the adrenergic splenic nerve. This leads to accumulation of CD11+ B cells in the marginal zone of the spleen and decreased antibody production. On the other hand, in the setting of diminished signalling from the vagus nerve to splenic nerve, antibody-secreting CD11+ B cells traverse the marginal zone and enter the red pulp of the spleen, where they release antibodies into the circulation [76]. The net effect of this neural regulation is that the antibody levels to specific antigenic challenge is significantly reduced thereby influencing the adaptive immune response.

3.3. Connective tissue

Acupuncture stimulation has been reported to induce mechanical deformation in connective tissue resulting in mechanical stimulation of fibroblasts resulting in autocrine purinergic signalling, active changes in fibroblast cell shape, anisotropic tissue motion, and a small tissue lesion.

3.4. Autocrine purinergic signalling

Acupuncture, as well as other modes of mechanical stimulation of fibroblast and other cell types, is associated with the release of purines like ATP [18] that is present within the cytosol of all cell types [103] The mechanical stimulation may result in opening of mechanosensitive channels of the plasma membrane and thus in release of cytosolic ATP [35,114].

Recently, it was found that acupuncture on mouse ST36 significantly reduced chronic pain in the ipsilateral paw and it increased the extracellular concentrations of ATP and adenosine in acupuncture point tissues. ATP is well established as an intracellular energy source that powers biochemical processes but is also proposed to act as an extracellular signalling molecule between cells. The specific receptors on the cell surfaces that receive messages carried by ATP are termed purinoceptors since ATP belongs to purine group. It is been reported that ATP can be released from different types of cell (e.g., osteoblasts, fibroblasts, endothelial, epithelial, and glial cells) in response to gentle mechanical stimulation without damaging the cells. ATP is also released in response to heat and electrical stimulation techniques in conjunction with acupuncture to enhance its effect. Recent evidence has also confirmed the finding that sensory nerve terminals in the skin are activated by ATP or inhibited by adenosine. Interestingly, the local application of 2-chloro-*N*(6)-cyclopentyladenosine (CCPA), an adenosine A1 receptor agonist, replicated the analgesic effect of acupuncture. The local inhibition of enzymes involved in adenosine degradation also potentiated the acupuncture-elicited increase in adenosine, as well as its anti-nociceptive effect. These data strongly suggest that acupuncture-released ATP and its metabolite adenosine in local acupoint tissues block nociceptive impulses from sites distal to needling point [35,135]. Also, adenosine binds to endothelial cells resulting in the release of NO and thereby a marked vasodilation. ATP is thereby increased in extra-cellular fluid as it leaks out when the plasma membrane is damaged during the mild tissue injury associated with acupuncture. Alternatively, or in addition, ATP can be actively released by local cells [18]. Samples collected near the location of the needle have shown that the concentrations of all purines are increased in tissue close to the stimulated area [114]. Potent enzymes, ectonucleotidases, present in the interstitial space degrade ATP to adenosine 5′ -diphosphate (ADP), adenosine 5′ -monophosphate (AMP), and adenosine, each of which has their own respective sets of receptors [134]. In particular the adenosine A1 receptor has been shown to suppress the conductance of nociceptive input by activating A1 receptors on peripheral pain fibres [72,48,135]. In support of a key role of A1 receptors in the peripheral mechanisms by which acupuncture may reduce pain is the observation that A1 receptor knockout mice do not benefit from acupuncture or from local injection of adenosine A1 receptor agonists [35].

3.5. Changes in fibroblast cell shape

A series of studies have demonstrated that connective tissue is affected by acupuncture. For example it has been shown that rotation of an inserted acupuncture needle stretches nearby connective tissue by pulling collagen fibres from the periphery toward the needle, [57]. Also, acupuncture needle rotation cause fibroblasts to increase their cross-sectional area, as their cell bodies expand and spread out [61,59,58]. Tissue stretching is associated with a transient increase in tissue tension, but the viscoelastic properties of the tissue return to pre-stretching level within minutes, which occurs in parallel with active remodelling of the cytoskeleton of fibroblasts [62]. Tissue tension is likely sensed by fibroblasts by their adhesion to collagen fibres [116]. Interestingly, pre-treatment with rho kinase inhibitors [133] or colchicine (inhibitor of microtubule polymerization) is linked to a 60–80% greater resting tissue tension after tissue stretching and prevents the expansion of fibroblasts [62]. These observations suggest that the remodelling of fibroblasts in response to mechanical stimulation dampens the increase in tissue tension induced by tissue stretch and thereby is important for maintaining stable viscoelastic properties of the tissue [1]. Thus, the cytoskeleton of fibroblasts plays an important role in dynamic tissue remodelling.

Fibroblasts located close to the location of needle stimulation are not only exposed to the changes in tissue tension induced by needle rotations, but also to ATP. Recent findings suggest that activation of purinergic receptors will in turn trigger a transient disassembly of polymerized actin, an effect that may contribute to the rapid cytoskeletal remodelling and cell body expansion induced by tissue stretch. It has therefore been suggested that acupuncture-induced purine signalling [79] triggers fibroblast cytoskeletal remodelling that counteracts fibrosis such as in scar tissue, and that purinergic signalling via increases in cytosolic Ca^{2+} may contribute to such dynamic changes of the actin cytoskeleton [23,36].

3.6. Anisotropic tissue motion

It has previously been shown using ultrasound elastography in humans that acupuncture needle manipulation causes measurable movement of tissue up to several centimetres away from the needle. Rotation of the needle following insertion promotes the mechanical coupling between the needle and connective tissue, and causes winding of tissue surrounding the needle. This mechanical signal (passive deformation) is transmitted to connective tissue cells and is amplified due to increased tissue displacement. The superficial area of tissue deformation may reach 25 mm^2 or more around a single needle and stimulates several muscle and tendon receptors, evidenced by the variety of subjective descriptions (of aching, pressure, heaviness or soreness) of the *de qi* sensation. Also, it has been shown that fibroblasts within whole areolar connective tissue expand and develop larger cross-sectional areas in response to acupuncture [61]. Recently, anisotropic tissue motion was observed during acupuncture, a motion that may influence the spatial distribution of local connective tissue cellular responses following acupuncture needle manipulation [30]. This response suggests that different directions of rotation of an acupuncture needle may have different effects at the same site.

It is well known that manual acupuncture and electro-acupuncture may produce local and distant effects (see below). EA stimulation produces the distant effects in exciting cutaneous mechanoreceptors and sarcous stretch receptors at acupuncture sites, with a range of approximately 25–45 mm from needling point. The EA intensity-dependent distant effect was observed on only the cutaneous superficial receptors, but not the cutaneous deep receptors and sarcous stretch receptors in rabbits [5]. In general, while most nociceptors are innervated by thin myelinated Aδ and C fibres, most somatic mechanoreceptors are innervated by Aβ fibres. Therefore, the activation of mechanoreceptors and their Aβ afferent fibres appears to play a dominant role in the biophysical reactions of acupuncture sites, particularly in muscle-spindle-rich acupuncture sites.

3.7. Skeletal muscle

Skeletal muscle is the largest organ in the body and primarily associated with locomotion. Also, recent evidence suggest that skeletal muscle act as a secretory organ through the release of "myokines", i.e., cytokines and other peptides that are produced, expressed, and released by skeletal muscle especially during contractions [89]. This provides a basis for how acupuncture, through the activation of skeletal muscle, may communicate with the stimulated muscle and with other organs in the peripheral parts of the body.

During the past decade, skeletal muscle cells have been identified as cells that have the capacity to produce several hundred transmitters, myokines, including: interleukins, growth factors, modulatory factors including hormones. Several of these myokines are released during both manual and electro-acupuncture [70]. Furthermore, the efficacy of acupuncture has been attributed to the elicitation of strong muscle contractions and the effects on organ functions by acupuncture are similar to those obtained by protracted exercise [5]. Preliminary trials suggest that part of the beneficial effects of repeated low frequency EA stimulation of muscle tissue also may be attributed to significant alterations in DNA methylation (in gene bodies and intergenic regions) and gene expression. The direction of the changes of DNA methylation was inversely correlated to expression changes which is concordant with phenotypic adaptations i.e. the muscle adapts to being active. This would suggest that EA, low-frequency TENS or other types of electrical muscle stimulation may be used to reduce the consequences of inactivity as seen following post-surgical immobilization.

3.8. Interleukins

Interleukin-6 (IL-6) is released into the blood stream in response to muscle contractions and possibly low frequency EA [90]. Following exercise, the basal plasma IL-6 concentration may increase up to 100-fold, but smaller increases of approximately 10-fold are seen following EA. The exercise-induced increase of plasma IL-6 occurs in an exponential manner and the peak IL-6 level is reached at the end of the exercise or shortly thereafter [29,87,88,99]. The amount of IL-6 produced is correlated to the amount of muscle mass engaged in the exercise. Interestingly, the concentration of IL-6 within the contracting skeletal muscle is 5- to100-fold higher than the levels found in the circulation [11,42,84]. Also, it has been shown that IL-6 appears to accumulate within the contracting muscle fibres as well as in the interstitium during exercise [50]. Muscle-derived IL-6 appears to function as an exercise sensor [43,93,100]. Thus, enhanced glucose availability and training adaptation attenuate the exercise-sensitive increase in IL-6 plasma concentration [29]. Contraction may lead to IL-6 gene transcription via Ca^{2+} being released from the sarcoplasmic reticulum to activate IL-6 through activation of nuclear factor of activated T cells [45]. A role of IL-6 in the local glucose metabolism is supported by the finding that a trained muscle is more sensitive to IL-6 and that insulin-resistant individuals show IL-6 resistance [104]. This could explain why elevated circulating levels of IL-6 has been reported to accompany obesity and physical inactivity, i.e. serving as a compensatory mechanism. This suggestion is in line with studies showing that IL-6 enhances glucose production and uptake and cytokine signalling through AMP activated protein kinase (AMPK) [93]. It appears that IL-6 activates AMPK in skeletal muscle by increasing the concentration of cAMP, and secondarily, the AMP: ATP ratio [54]. It has also been reported that IL-6 stimulates lipolysis in skeletal muscle [96] and has a role in myogenesis and mediates anti-inflammatory effects [94].

Other interleukins with a possible role in the peripheral acupuncture effects are: Interleukin-7 (IL-7) [40], Interleukin-8 (IL-8) [81–83,112,55,65] and Interleukin-15 (IL-15) [37,6,31,19,17].

3.9. Growth factors

Neurotrophins are a family of structurally related growth factors, including nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF), which exert many of their effects on neurons primarily through Trk receptor tyrosine kinases. BDNF and its receptor TrkB are expressed in the brain as well as in skeletal muscle following EA and exercise [46,91,92,74,102,25,95]. Other growth factors include myostatin, a member of the transforming growth factor beta (TGF-β) superfamily that is produced by skeletal muscle and secreted into the circulation [97,3,27,38,67,4,124,107].

Other compounds released into the circulation following muscle contractions include Irisin [16,129,68,127], Leukaemia

Inhibitory Factor (LIF) [41,52,109,110,24,111] and Erythropoietin (EPO) [44,101].

3.10. Exercise, acupuncture and myokines

Myokines may provide a conceptual basis for understanding how acupuncture may induce local effects within skeletal muscles during and after needling but also how EA especially may induce the release of myokines that communicate with other organs. This would suggest that exercise and EA might be an interesting treatment option, possibly also for prevention, in patients with diseases associated with inactivity like type 2 diabetes, cardiovascular diseases, breast and colon cancer, postmenopausal problems, dementia, and depression [9,32,128,130]. Without doubt there is a major overlap between several diagnoses, which points at the possibility that although these disorders have very different phenotypical presentations, they share some underlying pathogenic mechanisms.

It is well known that both physical inactivity and abdominal adiposity are associated with persistent systemic low-grade inflammation [131,28,39]. Models of lipodystrophy suggest that if the subcutaneous fat becomes inflamed and adipocytes undergo apoptosis/necrosis, the fat storing capacity is impaired and fat will consequently be deposited as ectopic fat [20]. One obvious explanation to the differential outcome of accumulating fat subcutaneously or as ectopic fat could be that when fat is stored in "the wrong places", it will stimulate an inflammatory response [131]. Evidence exists that visceral fat is more inflamed than subcutaneous fat and constitutes an important source of systemic inflammation. In this respect it is interesting to note that acupuncture may have an anti-inflammatory effect and that exercise may be recommended in the protection against diseases associated with chronic inflammation, including rheumatic diseases [33,73,10]. A hypothetical scenario could be that each bout of exercise or EA session induces an anti-inflammatory reaction, as muscle-derived IL-6 inhibits TNF production and stimulates the production of the anti-inflammatory cytokines IL-1beta and IL-10. Exercise and EA probably have pleiotropic positive effects in almost every organ system, potentially having myokine-mediated direct and indirect anti-inflammatory effects in inflammatory diseases. As part of the effects of exercise that are locally mediated, local needling (muscle points around the knee) and EA stimulation, inducing visible contractions, should be advocated when treating low-grade inflammatory conditions like knee osteoarthritis. This would also suggest that distant needling or manual acupuncture is suboptimal and superficial needling even more so.

4. Conclusion

Taken together there are specific peripheral effects of acupuncture (neural, skeletal muscle, connective tissue and/or immunological) that may be therapeutic. To obtain such effects the stimulation technique and site must be adopted to the condition treated.

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