ACUPUNCTURE AND PAIN RELIEF

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Abstract

Pain is one of the most common ailments in a myriad of diseases. Pain relief therefore is very important in ancient and modern medicine. This review will explore the potential beneficial effects of acupuncture on the relieve of pain and its underlying mechanisms.

Pain is a protective mechanism for our survival. Nociceptive substances, like bradykinin, prostaglandin, ATP, and substance P, play an important role in nociceptive pain, caused by any kind of tissue damage. Damage to nervous tissue causes neuropathic pain. The intrinsic pain relieving analgesic system is characterised by action of descending inhibitory nerve fibres and opioids. It is linked to the mechanism of acupuncture analgesia at the level of the brain, spinal cord, nerves, receptors and their ligands.

Acupuncture is used as a therapy for pain relief and for the equilibration of imbalances in visceral and autonomic functions. It is developed around 2,000 B.C. in China and nowadays practiced globally. It influences many brain areas, e.g. the anterior cingulate cortex, the pain perception area. Opioid receptors μ, δ and κ in the brain and spinal cord are activated by acupuncture released enkephalins, β-endorphin, and dynorhpin. The insertion of small acupuncture needles releases anti-nociceptive mediators like adenosine and activates somatic sensory afferent fibres types Aα, Aβ, Aδ and C (or I, II, III and IV respectively). These somatic afferent fibres can elicit a somato sympathetic reflex increasing blood flow, consequently flushing out nociceptive substances, decreasing pain. Moreover, activating nonnociceptive Aα and Aβ fibers will inhibit the nociceptive Aδ and C fibers, reducing the pain.

This article first explicates the types of pain and their pathways, biological structures, and receptors and ligands involved. Secondly, it will explain the mechanism of the intrinsic pain relieving analgesic system and the correlation with acupuncture. Finally, acupuncture analgesia will be explained by reviewing its possible mechanism at the level of the brain, spinal cord, nerves, and receptors and their ligands.

Keywords: Acupuncture, nociception, pain, analgesia

Contents

1. Introduction

1.1. What is acupuncture?

Acupuncture is used as a therapy and intervention for the relief or prevention of pain and for many other health complaints. A normal acupuncture therapy session takes about 30 min. During this time, small inserted metal needles at specific places, called acupoints, are stimulated intermittently to generate the appropriate response. According to traditional Chinese medicine acupoints lie on so-called meridians, which are certain, not physiologically measurable, energy currents along the body. One or more energy currents are blocked during illness and can be relieved by acupuncture on the right acupoint. When the blockade is relieved, the energy "Qi" flows unhindered and the subject is healthy. Stimulation of the needles can be done manually, by rotating the needles shortly; electrically, applying a small current on the needles; by heating the needles. After the development around 2,000 B.C. in China, acupuncture has become worldwide in its practice [(1)]. To date there is an increasing group of patients using forms of complementary medicine, e.g. acupuncture, to better manage their pain [(2)].

The focus of this paper will be on pain and the reduction of pain by acupuncture. It will begin by explaining the physiology of pain subsequently the normal pain relieving systems in the body. Then, the link between acupuncture and pain relief will be discussed, followed by the possible underlying mechanisms used by acupuncture to alleviate pain

2. What is pain?

Pain is a sensation of discomfort, providing the organism with a protective mechanism to survive. The way we perceive pain is different every time, varying from person to person [(3)]. This is the biggest difficulty when studying pain or pain relief. Scientists have made many standardisations to create methods for experiments giving unambiguous results. Nevertheless, interindividual differences continue to exist and this holds true for many aspects in life including the pain we feel either mental or physical.

Focussing on the biology of physical pain, we can describe two forms of pain. The first and the most common is nociceptive pain, the feeling of a papercut, your hand on a hot engine or when bumping into a brick wall, many variations exist of nociceptive pain. It is the result of damage to almost any kind of tissue, or the risk of damage if staying in the specific situation. Nociception is the neural response to this (potential) damage and acts via the activation of its nociceptors, special sensory receptors. The result of nociception is not always the perception of pain, which is accounted for by the brain [(4)]. The second form is neuropathic pain. Patients describe it as an intense burning or (electrically) aching feeling of the skin. This is the results of damage to nervous tissue specifically.

The protecting mechanism to survive is that the person who feels the pain will, often subconsciously, react to remove the pain stimulus and therefore will disengage the risk of (more) tissue damage. Now the body can repair itself and returns to homeostasis, the maintenance of a stable internal environment.

The next sections will explain the physiology of nociceptive pain, neuropathic pain and the suppression of pain.

2.1. Nociceptive pain

2.1.1. Fast pain and slow pain

Nociceptive pain can be divided in two categories: fast pain and slow pain. After applying a painful stimulus, fast pain is felt within approximately 0.1 second, whereas slow pain is felt only after 1 second and rises slowly in intensity over the next seconds to minutes. Reason for this 'delay' in sensing the slow pain is due to the conduction pathways involved [(5)], explained later in this section.

As mentioned before, many variations exist of nociceptive pain and many names can be given to a same sensation by different individuals. The fast pain can be described as sharp, pricking, acute or electric. On the other hand, slow pain can be associated with terms like aching, slow burning, nauseous, dull and chronic. Slow pain can be felt almost anywhere in the body, contrarily fast pain is felt in the skin and not in most deeper tissue [(5)].

Nociceptors are free nerve endings lying superficially widespread in the skin and in some internal tissues. Deep tissue only has few nerve endings which can provide the sensing of slow pain. Different types of nociceptors exist: thermal, mechanical, polymodal and silent nociceptors. Thermal nociceptors are activated by extreme temperatures (>45^{o}C or <5^{o}C) and the following action potential is conducted by type Aδ nerve fibres [(4)] (see *2.1.3. Type Aδ and type C nerve fibres and their pain pathways*). Thermal nociceptors are activated by excessive pressure on the skin and its action potentials also travel via Aδ fibres [(4)]. Polymodal nociceptors can be activated by intense mechanical, chemical, or thermal stimuli. The

subsequent currents are conducted by type C fibres [4]. Lastly, silent nociceptors, only present in internal organs, are only activated when their activation thresholds are highly diminished upon inflammation or by chemical injuries, hence 'silent' in normal conditions [4].

Regularly, fast pain is evoked by mechanical and thermal stimuli, whereas slow pain can be evoked by chemical stimuli as well (Figure

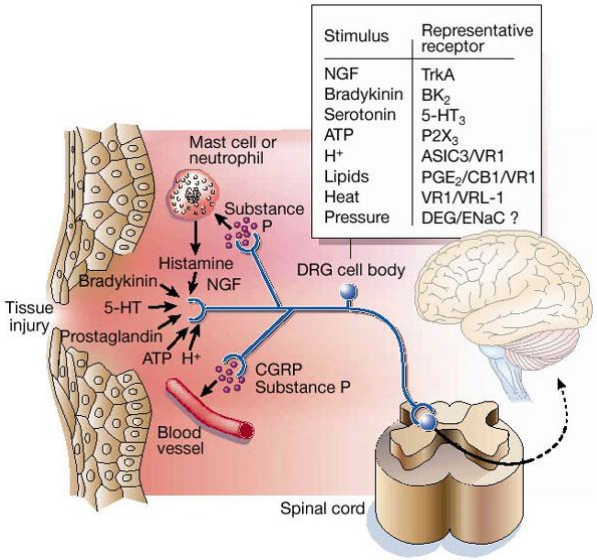

Figure 1. *Inflammatory mediators activate or sensitise the primary afferent nociceptor.*
The process of neurogenic inflammation is also depicted at the terminals. Activated nociceptors can release peptides and neurotransmitters (substance P, ATP and calcitonin-gene-related peptide (CGRP)) to augment the poduction of nociceptive substances in the surrounding tissue and causing vasodilation and plasma extravasation. (Julius and Basbaum, 2001)

1). When your tissue gets damaged or is in an inflammatory state it synthesises and releases nociceptive substances setting off a series of reactions including humoral and neural reactions, considered as tissue-repairing processes and signals of danger [6]. Some of these chemicals or nociceptive substances are bradykinin, serotonin, histamine, prostaglandins, potassium ions, acids, acetylcholine, and proteolytic enzymes. Of these chemicals, bradykinin seems to be the most painful one, because it directly activates type Aδ and type C nociceptors and promotes the synthesis and release of prostaglandins in the local tissue [4]. The local concentration of potassium ions or proteolytic enzymes correlates with the intensity of pain; they increase the permeability of the nerve membrane, exciting pain [5]. Other substances, like prostaglandins, acetylcholine and substance P, can sensitise the nerve endings, but do not activate them. They will decrease the activation threshold of the nociceptors [4]. Higher pain sensitivity will help in healing the damaged tissue faster, because contact with the damaged painful tissue will be avoided until it is healed.

2.1.2. Sensitisation and adaptation

Sensitisation can cause progressively greater excitation of the pain fibres with a continuing stimulus. This increase in sensitivity of pain receptors, the nociceptors, is called primary hyperalgesia. Primary hyperalgesia is caused by a chemically induced reduction of the activation threshold of the nociceptors, a process called peripheral sensitisation [4]. The chemicals involved are bradykinin, histamine, prostaglandins, leukotrienes, acetylcholine, ATP, serotonin, and substance P, which all arise from different cells [4]. Some of these chemicals, e.g. bradykinin, are able to activate the nociceptor as well. Histamine specifically activates the polymodal nociceptor [4]. Prostaglandins are generated by the enzyme cyclooxygenase, which can be blocked therapeutically, therefore having beneficial effects for patients with primary hyperalgesia. Secondary hyperalgesia is caused by continuous stimulation of type C fibres, which increasingly activates the dorsal horn neurons centrally, a process called "wind-up" or central sensitisation [7]. Primary and secondary hyperalgesia are exactly opposite to most sensory receptors in the body which desensitize when a stimulus continues, a process called adaptation. If peripheral or central sensitisation causes normally innocuous stimuli to be painful, this is called allodynia, a form of neuropathic pain.

2.1.3. Nociceptor receptors and their ligands

The pain mediators described earlier and depicted in Figure 1 presumably all act on specific receptors or on receptors with a broad specificity for many of the nociceptive chemicals.. All mediators are able to depolarise the terminal membrane of the nociceptor. This depolarisation will lead to action potentials and the conduction of the pain signal to

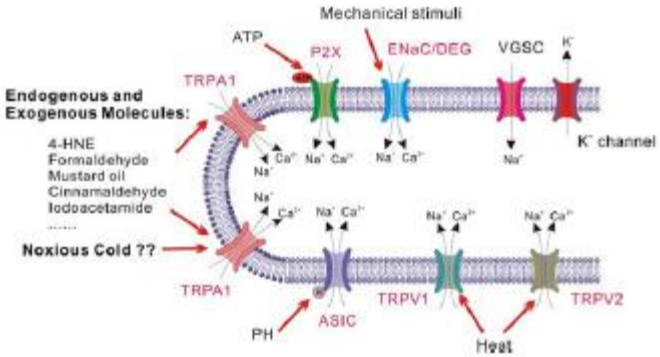

Figure 2. *Multitude of ion channel receptors on the nociceptor. Mechanical, thermal, and chemical stimuli act on different receptors. The TRPA1 receptor has a broad specificity for many stimuli. (Tai et al., 2008)*

the brain. This section will give an oversight of the mediators and their receptors. The figure accompanying this section from a previous study by Tai et al. depicts this very distinctly (Figure 2).

Firstly, mechanical stimuli act on ENaC/DEG receptors [6], and might cause ATP release, which can be detected by P2Y or P2X receptors [6, 8]. Secondly, nocuous heat acts on TRPV1 and TRPV2 receptors, members of the vanilloid transient receptor potential channels [6]. The vanilloid receptor of this family, also called capsaicin receptor, acts on both thermal and chemical stimuli. Heat stimulus and capsaicin, the substance in hot peppers providing its literally hot spice, both act on this vanilloid receptor [4]. Thirdly, for the chemical substances many different receptors exist. Acids act on ASICs, while ATP is detected by P2X receptors [6]. Interestingly, many other endogenous and exogenous molecules might all act on the TRPA1 receptor [9, 10, 11]. It is suggested that perhaps even nocuous cold acts on this receptor [12] as well as cannabinoids, mustard oil and ingredients in wasabi and garlic [13, 14].

The nociceptive afferent sensory neurons terminate on dorsal horn neurons and releases the excitatory neurotransmitter glutamate. Glutamate binds to the excitatory ionotropic AMPA type receptor (alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid), which directly opens a Na^+/K^+ channel giving rise to fast synaptic action potentials that propagate the pain signal to the brain [4] (a more detailed route will be explained in the next section). On a more persistent basis, repetitive action of C fibers leads to “wind-up” of the dorsal horn neurons. This phenomenon is mediated by glutamate action on N-methyl-D-aspartate (NMDA) type receptors gating postsynaptic ion channels [4]. At the terminals of the afferent nociceptive fibres not only glutamate is released. C fibres release substance P at the terminals, which augments the actions of glutamate [4]. Substance P and calcitonin-gene related peptide (CGRP) are also released at the peripheral terminals eliciting neurogenic inflammation, described in Figure 1. The neurogenic inflammation causes vasodilation and plasma extravasation leading to edema which increases bradykinin release [4].

2.1.4. Type Aδ and type C nerve fibres and their pain pathways

Fast sharp pain is conducted via small myelinated type Aδ nerve fibres to the spinal cord with a rapidity of approximately 6 to 30 m/sec [5]. Slow chronic pain is transmitted by unmyelinated type C fibres to the spinal cord at velocities between 0.5 and 2 m/sec [5]. This dissimilarity in conducting speed to the brain accounts for the delay in sensing the two different pains. There is a third type of sensory afferent nerve fibres, type Aβ, which predominantly detects innocuous stimuli, hence not that important in the pathways of pain [6]. However, these Aβ fibres may play a role in lateral inhibition of pain, discussed later in *2.3. Suppressing pain, the analgesic system*.

When entering the spinal cord through the dorsal spinal roots, the Aδ and C fibres terminate on relay neurons in the dorsal horns (Figure 3). The fast pain ascends via the neospinothalamic tract and the slow chronic pain via the paleospinothalamic tract.

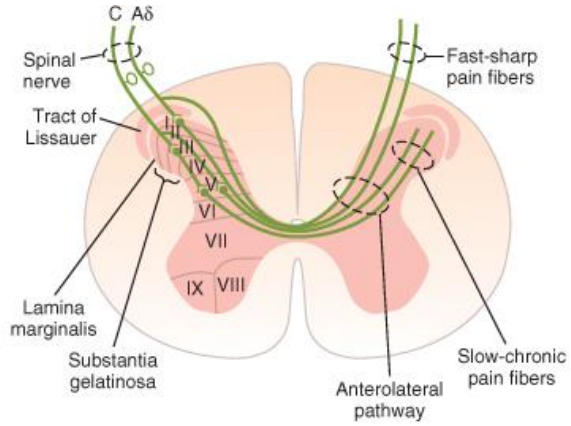

Figure 3. *Crossection of spinal cord. Entering type Aδ and C nerve fibres terminate on relay neurons in lamina I-III, which propagate the signal contralaterally to the brain. (Guyton and Hall, 2005)*

The Aδ fibres terminate in the lamina marginalis (lamina I) of the dorsal horns where they excite, by action of the excitatory neurotransmitter glutamate on AMPA-type glutamate receptors, very long second-order neurons of the neospinothalamic tract [4]. These fibres cross to the contralateral side of the cord through the anterior commissure. From here they propagate the signal upwards via the anterolateral columns through the reticular formation at brainstem level, where some fibres terminate, to the thalamus, terminating in the ventrobasal complex where tactile sensations terminate too [5]. Another terminating point is the posterior nuclear group of the thalamus. From here the signals are conducted to other basal areas of the brain as well as to the somatosensory cortex [5].The C fibres terminate in the spinal cord in the substantia gelatinosa (laminae II and III) of the dorsal horns, here they secrete presumably both glutamate and substance P. Glutamate acts rapidly and lasts for only a few milliseconds, this is because of a very efficient reuptake of amino acids, like glutamate, into nerve terminals or surrounding glial cells [4]. Contrarily, substance P, a neuropeptide, is

released more slowly, building up in concentration over a period of seconds or even minutes. Since there is no specific reuptake mechanism for neuropeptides, substance P can diffuse long distances and can increase in concentration modulating excitability of the neurons [4]. These dissimilarities between the two transmitters can be another explanation for the fast and slow pains. Subsequently, within the dorsal horn, most signals are transduced via one or more short fibre neurons to lamina V. The excited neurons here transmit the signal along their long axons via the anterior commisure to the contralateral side, joining the fast pain fibres, then upward to the brain in the anterolateral pathway [5]. This paleospinothalamic pathway is evolutionary much older than the neospinothalamic pathway and transmits pain mainly from the type C fibres, but some signals from type Aδ as well [5]. Only one tenth to one fourth of these fibres reaches the thalamus via the paleospinothalamic pathway [5]. Most terminate along the way in the (i) reticular nuclei of the medulla, pons and mesencephalon; (ii) tectal area of mesencephalon deep to the superior and inferior colliculi; (iii) periaqueductal gray region surrounding the aqueduct of Sylvius [5]. The latter region is involved in suppression of pain, causing analgesic effects.

2.1.5. Localisation of pain

When it comes to localising the pain, discrepancies arise between fast and slow pain. Fast pain can be localised highly specific, especially when tactile receptors exciting the dorsal column-medial lemniscal system are simultaneously stimulated [5]. Without this simultaneous stimulation of tactile receptors, localisation of the pain is within approximately 10 centimetres of the stimulated area [5]. Pain transmitted by the paleospinothalamic pathway is hard to localise, often only at the specificity of which limb. The reason for this is the multisynaptic nature of the pathway. Paleospinothalamic fibres terminate at a multitude of locations. From the pain areas of the brain stem short fibre neurons can relay the pain signals upward again into the intralaminar and ventrolateral nuclei of the thalamus and into specific parts of the hypothalamus and other basal regions of the brain [5]. Moreover, neuropeptides released at the spinal level have no specific reuptake mechanism, making it easy to diffuse to and act on many different postsynaptic dorsal horn neurons, making it harder to localise this pain [4].

2.1.6. Pain perception

As mentioned in the introduction, pain perception is different for every person. One explanation is the intrinsically pain suppressing, analgesia, systems in the body, which we will discuss later. Another possibility is that in the brain the ability to perceive pain is encompassed by many divergent pathways able to have different interactions. The somatic sensory areas of the cerebral cortex are not primarily responsible for the perception of pain. Without this part of the cerebral cortex, pain is still perceived [5]. Most probably, the reticular formation, thalamus and other lower brain areas where pain impulses enter give rise to the conscious perception of pain [5]. However, stimulation of the somatosensory cortex does bring about a mild perception of pain in itself [5]. Additionally, the cortex presumably plays a major role in the interpretation of pain quality, whereas perception per se might primarily be the function of lower centres [5].

2.1.7. Fight or flight

Besides the fact that you know something is not right when perceiving pain, another interesting finding is observed. When electrically stimulating the reticular areas of the brain stem and the intralaminar nuclei of the thalamus, areas where slow pain pathways terminate, strong arousal effects occur throughout the entire brain on nervous activity [5]. These areas are also known to be part of the arousal system. When this system is activated, the person feels more awake, better concentrated and gets into a state of fight or flight. Again a mechanism focused on the survival of the organism. Unfortunately, when having chronic or severe pain, this same system will keep you from falling asleep, on the long run having a detrimental effect on your physical and mental health state.

2.2. Neuropathic pain

Neuropathic pain is the result of damage to nervous tissue from the peripheral or the central nervous system, giving rise to the names peripheral neuropathic and central neuropathic pain respectively. The causes can vary from infections and metabolic diseases to multiple sclerosis and chemotherapy [15]. The pain felt is described as a burning or (electrically) aching feeling, which can be felt continuously or provoked by an innocuous, not painful, stimulus [16]. The intensity of the pain can rise even with the slightest touch, either by primary or secondary hyperalgesia, this phenomenon is similar to the sensitisation process during nociceptive pain. Even the touch of clothes on the

skin can be too much to bear [author's observation]. During neuropathic pain alterations in the neurons occur in the expression of ion channels, neurotransmitters, peptides and their receptors [7]. The proposed reason for this is neuronal plasticity, that the function and molecular composition of a neuron can subsequently change when its environment changes. When the cause of the neuropathic pain is a normally innocuous stimulus, this type of pain is called allodynia. Central sensitisation in spinal cord after limb amputation results in the so-called phantom limb pain [4]. Phantom limb pain can nowadays be prevented by accompanying general anaesthesia with local spinal analgetics or anaesthetics [4].

The exact mechanism underlying peripheral and central neuropathic pain is still to be revealed. Probable causes are on one hand heightened peripheral sensory input leading to more pain impulses. On the other hand, diminished peripheral sensory input causes neurons of the central nervous system, like the hypothalamus and dorsal horn neurons, to spontaneously excite and induce pain, called deafferentiation pain [16]. Any injury blocking or reducing the conductance of the spinothalamic pathway can cause this deafferentiation pain [17]. Even though some patients with central neuropathic pain have spontaneous remission after some time, most others endure the pain for the rest of their lives [17]. Besides the neuropathic pain itself, the consequences are vast, leading to a reduction in personal health and quality of life. The need for adequate therapies is self-evident, but the currently available therapies are confined by their side effects preventing long term use and satisfactory dosing. Available therapies are mostly antidepressants, anticonvulsants and opioids [18, 19, 20, 21].

2.3. Suppressing pain, the analgesic system

An analgesic system can suppress upon activation the input of pain signals to the nervous system. There are three important components of this system. First of all, areas of the mesencephalon (midbrain) and upper pons, namely the periaqueductal gray, surrounding the aqueduct of Sylvius, and the periventricular areas, surrounding parts of the third and fourth ventricles [5]. From here neurons descend to the second important structures, the raphe magnus nucleus in the lower pons and upper medulla, along with the nucleus reticularis paragigantocellularis in the medulla [4, 5]. These nuclei propagate second-order signals downward via dorsolateral columns in the spinal cord to the third part, a pain inhibitory complex in the dorsal horns of the spinal cord [5]. Here the pain signals can be blocked before they pass to the brain to be perceived.

Pain signals entering the spinal cord via the dorsal roots can specifically be blocked by electrically stimulating the periaqueductal gray area or the raphe magnus nucleus [5, 4]. Areas exciting the periaqueductal gray, such as the periventricular nuclei and the medial forebrain bundle in the hypothalamus, can suppress the pain as well when stimulated [5]. The nerve fibres descending from the periventricular nuclei and periaqueductal gray area secrete the transmitter enkephalin when terminating on neurons of the raphe magnus nucleus [5] (Figure 4).

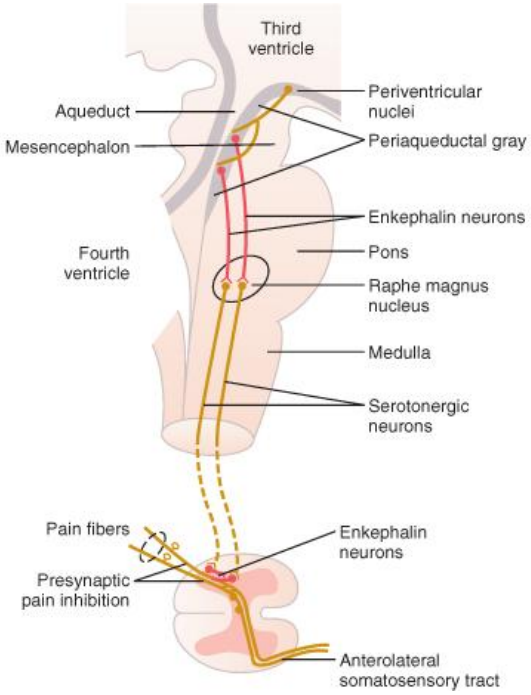

Figure 4. *Descending analgesic pathway from mesencephalon through brainstem to spinal cord. Enkephalin secreting neurons inhibit transmission of incoming pain fibres in the spinal cord. (Guyton and Hall, 2005)*

From here, fibres descend to the dorsal horn of the spinal cord where they terminate and secrete the transmitter serotonin [5]. The serotonin acts on small spinal cord neurons secreting enkephalin [5]. This enkephalin is presumably the causative agent of presynaptic and postsynaptic inhibition of entering type C and type Aδ nerve fibres synapting in the dorsal horns [5]. Not only the pain signal itself is hereby blocked but also the local reflexes, e.g. withdrawal reflexes, of which the pain fibres are its afferents [5, 4]. Not only nerve fibres from the former described pathways terminate in the dorsal horn of the spinal cord to inhibit the activity of

nociceptive neurons. Also neurons from the noradrenergic locus ceruleus directly and indirectly reduce the conductance of neurons in laminae I and V.

If this normal analgesic system would not function, one can readily understand that more pain is perceived. This seems to be the case during neuropahtic pain. A change occurs in the inhibition of the incoming pain fibres or the fibres in which they terminate on. Peripheral pain fibres terminate on lamina I neurons, which are inhibited during normal physiological circumstances by glycine releasing interneurons. However, during a neuropathic pain model, a study by Coull et al., the mediating transmitter glycine is accompanied by γ-aminobutyric acid (GABA), a general inhibitory transmitter [22]. The lamina I neurons inhibited by these substances no longer get inhibited that much and even reach the threshold for action potentials sooner. The inhibition alters and reduces, leading to more pain signals entering the brain, hence perceiving more, longer, and more intense pain [23, 22].

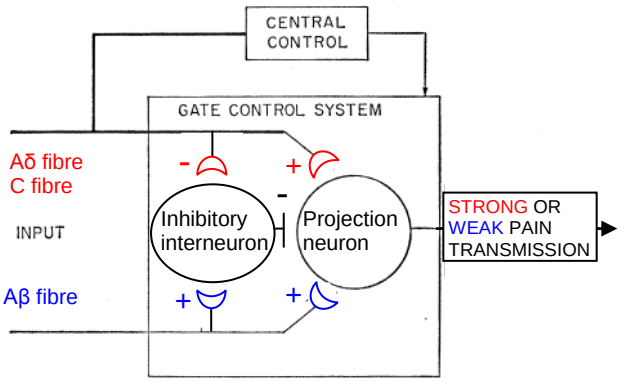

Figure 5. *Gate control theory of modulating pain. Nociceptive Aδ and C type fibers activate directly and indirectly the projection neuron to propagate pain signals. Nonnociceptive Aβ type fibers have bot excitatory and inhibitory effects on the projection neuron. The equilibrium between both nociceptive and nonnociceptive inputs establishes the intensity of pain. (Adapted from Melzack and Wall, 1965)*

Another very different way of inhibiting pain transmission on spinal cord level is presumably by lateral inhibition. This process is the basis of the gate control theory of Melzack and Wall in the 1960s (Figure 5). The theory encompasses different components. Firstly, nociceptive (Aδ and C) and nonnociceptive (Aβ) fibers terminate on neurons of lamina V and presumably lamina I of the spinal cord [24, 22]. Secondly, nonnociceptive Aβ fibers activate inhibitory interneurons in lamina II, which inhibit the neurons of lamina V [24]. Contrarily, nociceptive Aδ and C fibers inhibit these inhibitory interneurons in lamina II, therefore activating neurons in lamina V [24]. All in all, nociceptive input "opens" this gate for the propagation of painful signals, whereas nonnociceptive input "closes" the gate [24].

2.3.1. Pain killers from the brain

The analgesic system of the brain can be activated by electrical stimulation or injecting small amounts of morphine into the periventricular nucleus or the periaqueductal gray area; this leads to impressive pain suppression [5, 4]. This analgesic effect can be blocked by the opioid μ-receptor antagonist naloxone, when injected into the periaqueductal gray or in the raphe magnus nucleus [4]. By transecting descending inhibitory pathways in the bilateral dorsolateral funiculus, the electrically- and morphine-induced analgesia is blocked [4]. At different points in the analgesic system morphine-like substances have effects, particularly the opiates. Looking for the natural derivative of these opiates, studies came across a multitude of opiate-like substances in the nervous system. The important ones are, in the hypothalamus and pituitary gland, β-endorphin, and in the brain stem and spinal cord portions of the analgesic system, methionine-enkephalin, leucine-enkephalin, and dynorphins [5]. All of these substances were broken down from the same three protein molecules: pro-opiomelanocortin, proenkephalin, and prodynorphin [5]. An analgesic effect by these substances can only occur if specific receptors are present in the human body detecting them.

2.3.2. Analgesic receptors and their ligands

The three most important opioid receptors are μ, δ and κ. In mice without the opioid μ-receptor morphine has no analgesic effect [4]. The endogenous opioid peptides mentioned before all act on these receptors. Methionine-enkephalin, leucine-enkephalin, and β-endorphin act on μ- and δ-receptors, whereas dynorphin is merely detected by κ-receptors [25]. Despite divergent locations of the receptors, all are present in nociception associated areas of the nervous system [4]. Opiates and opioid peptides reduce the nociceptive conduction by presynaptic and postsynaptic inhibition on nociceptive afferents and dorsal horn neurons respectively [4].

2.3.3. Treatment of pain

As mentioned before, during tissue damage nociceptive substances are synthesised and released, inducing a nociceptive response. Pharmacological intervention is the major treatment of pain, often reducing the production of nociceptive substances peripherally and/or centrally; or

inhibiting the induced nociceptive transmission through each level of the nervous system [26]. When administering aspirin or some nonsteroidal anti-inflammatory drug, cyclooxygenase is blocked impairing the production of prostaglandins [4]. Due to the lack of prostaglandins nociceptors will not be sensitised, hence pain reduction is established.

Unfortunately these interventions present themselves with many side effects [27, 28, 29, 30]. Some of these side effects reduce the pharmacokinetic action of the medication by impairing regional blood circulation, hence decreasing the medication effectiveness [31]. Others act on receptors distributed widely and responsible for diverse effects. The search for therapies with higher efficacy and less side effects goes on. Besides new pharmacological drugs this search also encounters alternative and complementary therapies with less adverse effects, like acupuncture.

3. Does acupuncture relieve pain?

Before investigating the mechanism behind a potentially pain relieving acupuncture session, this paragraph will present some recent studies on the allegedly analgesic effects, visceral and autonomic effects and the factors involving these outcomes of acupuncture.

The insertion of acupuncture needles itself is not an adequate way to relieve pain [32]. With intermittent stimulation, either manual, electrical or heated, acupuncture can have analgesic effects, provided that an intrinsic feeling results in the patient [33, 34]. This feeling is described as soreness, numbness, heaviness and distension in the deep tissue underlying the acupoint. After applying acupuncture, the pain threshold is slowly increasing and remains higher, even after application has finished, therefore providing a long lasting analgesic effect [35]. Also in rats suffering from visceral pain electro acupuncture has prophylactic effects, when applied on Jiaji acupoints (along the spine) before researchers induced the visceral pain [36]. In unilateral migraine pain acupuncture seems to have some beneficial effects too [37]. Since the mechanism of these pains is not yet fully understood, the search for good therapies is still going on. One study observed the effect of acupuncture on thalamic pain, which is a neuropathic pain due to damage, e.g. by a haemorrhage or infarction, in the thalamus, a brain structure concerning all sensory information from the body. They compared acupuncture with normal western therapy using Carbamazepine, an anticonvulsant drug also used against neuropathic pains such as thalamic pain. No significant difference was found between both therapies, but acupuncture reached the same analgesic effects as Carbamazepine usage [38]. In another model for neuropathic pain, low-frequency electrical acupuncture leads to a reduction of thermal hyperalgesia in rats [39]. In a large german study, the Acupuncture Research Trials, acupuncture showed significantly and clinically relevant beneficial effects on different ailments [40]. The study included effects on low-back pain, osteoarthritis of the knee, migraine, and tension-type headache [40]. The big study German Acupuncture Randomised Trials shows beneficial effects of acupuncture too. True (according to Traditional Chinese Medicine (TCM)) acupuncture and sham (superficially in non-TCM acupoints) acupuncture therapy both were significantly more effective than standard therapy in low-back pain and gonarthrosis and in all trials the patients took less medication for their illness [40]

Even though this all seems hopeful in respect to future therapies, not all studies find these beneficial effects. A recent study by Cho et al. 2010 [41] critically evaluated the evidence for or against acupuncture for labour pain management. They concluded that the results from randomised controlled trials, besides being diverse and often flawed, do not support the use of acupuncture for controlling labour pain. Furthermore, acupuncture can even diminish the effect of pain relief when administration is not performed properly [33].

3.1. A multitude of effects

Besides relieving pain, acupuncture is also used to improve imbalances in visceral and autonomic functions [42, 43]. According to a recent study, acupuncture can have an assisting role when using general anaesthesia [44]. For breast carcinoma operations it can help to steady the blood pressure, to reduce the analgesics dosage, and to ameliorate the pain relief [44]. Indeed, when applying traditional acupuncture before the induction of anaesthesia, the requirements for general anaesthesia and postoperative analgesia reduce [45, 46], even postoperative nausea and vomiting are reduced [46]. When using electro acupuncture on anesthetized patients before going to surgery, plasma adrenaline levels increase [47]. Adrenaline has positive inotropic and chronotropic properties on the heart, increasing the contractility and frequency respectively. This might help steady the blood pressure during surgery. On the other hand, there is clinical evidence that in some types of hypertension the blood pressure can be ameliorated by application of acupuncture [48], although more recent data suggest only amelioration of systolic blood pressure [49].

Acupuncture can also be used to change the blood flow in specific organs [50]. A recent study by Kagitani et al. 2010 reviews different effects of acupuncture mediated by activation of afferent nerve fibres innervating the skin and muscles by manual or electro-acupuncture [42]. Some of the effects listed are a decrease of micturition contraction [51], change of gastric motility [52], decreasing mean arterial pressure [53], different effects on the secretion of adrenal medullary catecholamine hormones (adrenaline and noradrenaline) [54, 55], decreasing heart rate [56], increasing cortical cerebral blood flow [57], a decrease in renal blood flow and increases in blood flow in specific muscles [58]. In most of these studies manual or electro-acupuncture was applied to one hindlimb or hindpaw, indicating that not all effects are locally. When severing the afferent nerve fibres innervating the skin or muscles where manual or electro acupuncture was applied, no effects could be measured. This last part of the experiments suggests the major involvement of afferent nerve fibres in the effects of acupuncture. (for more information on this part, see paragraph *4.3. Nerves*). These visceral responses have been proven to be reflexes where the afferents, as just mentioned, are cutaneous and muscle somatic afferent nerves and the efferents are autonomic efferent nerves. Also motor functions are affected by acupuncture. Electro-acupuncture stimulation at the Zusanli (hindlimb) or the Hoku (forepaw) point evoked Aβ (type II) afferent nerve impulses, repressing the tail flick reflex, which is a withdrawal response to the application of noxious heat to the tail [49].

Apparent is the multitude of effects elicited by acupuncture application, irrespective of the the type of stimulation. When focussing on the physiology of one of the most important symptoms of a disease, pain, one can readily understand the complexity and difficulty of studying the true mechanism behind acupuncture and pain relief. The next section will describe the physiology of pain and pain relief and present recent studies demystifying the potential mechanisms behind acupuncture and pain relief.

3.2. Factors involved in the effects of acupuncture

A recent study by Witt et al. 2010 investigating physician characteristics such as duration of training and experience found that these factors did not influence patients' outcome after acupuncture, suggesting that formal training parameters have only a limited influence on treatment effect [59]. Other skills such as the therapeutic relationship, which are difficult to measure, may probably play a more important role and should be taken into consideration.

According to Traditional Chinese Medicine the acupoints lie on meridians, and if these specific locations are stimulated by a needle, energy blockages will be relieved, the energy “Qi” will flow and the person is healthy. When comparing acupuncture versus sham-acupuncture (not in a meridian), a randomised controlled trial shows no difference in effect [60]. However, both therapies show a decrease in pain-sensing using different pain-measuring methods. The best decrease in pain and highest patient satisfaction is observed when acupuncturists’ communication style is with high expectations, compared to a neutral expectations communication-style. This study suggests that the benefits of pain relief by acupuncture can be influenced through placebo effects due to the behaviour of the acupuncturist [60]. Moreover, individual sensitivity to acupuncture, the type of needle stimulation and even genetic factors can influence the outcome of acupuncture analgesia [32].

4. How does acupuncture relieve pain?

4.1. Brain

Acupuncture inducing deqi, a proper sensation in the fingers of the acupuncturist during manual acupuncture [32], gives rise to deactivation of the limbic system (particularly hypothalamus and amygdala), which is involved in emotions. Contrarily, when inducing sharp pain it can activate the limbic system [33, 61]. Many brain regions are involved in the modulation of acupuncture analgesia [32].

Chemical mediated electro acupuncture analgesia was confirmed by a study in 1974. In this study cebrebrospinal fluid was obtained from rabbits subjected to acupuncture stimulation and was infused to a naïve recipient rabbit in its third brain ventricle. The analgesic effect from the donor rabbit was transferred to the recipient rabbit, confirming the chemical mediated electro acupuncture analgesia [25, 62]. Indeed, electro-acupuncture leads to increased serotonergic activity of median raphe nuclear groups. This area of the brainstem is involved in the analgesic system (Figure 4). Contrarily, deactivation by acupuncture is shown in the subgenual cingulate and the reticular formation, leading to sympathetic tone down-regulation [61]. This reduced sympathetic activity can stimulate the analgesia effect, see paragraph *4.5. Somato sympathetic reflex.*

When applying painful stimulation to the right foot of a mouse, scientists recorded the

response in vivo of the contralateral (left) anterior cingulate cortex (ACC) [63]. The ACC is important for the perception of pain [64] and in humans painful electrical stimulation is related to its activation [65]. High-intensity stimulations excited the ACC in mice [63], verifying the idea that ACC neurons respond chiefly to painful stimuli [65]. Manual acupuncture, by rotating a needle once every 5 min for 30 min, reduced the ACC activity even after the acupuncture session. Combining these results with other experiments, the decreasing activation of the ACC is likely to be caused peripherally by acupuncture. Manual acupuncture releases anti-nociceptive mediators in the tissue of needle insertion, locally inhibiting pain signal transmission [63] (see paragraph *4.4. Receptors and their ligands*).

4.2. Spinal cord

The effects of manual acupuncture at the Zusanli (hindlimb) acupoint or at a non-acupoint on the activity of enkephalinergic neurons in the spinal cord of rats were investigated. Manual acupuncture activated heterosegmentally enkephalinergic neurons in the spinal cord, irrespective of stimulated location, whether acupoint or not [66]. Along with the results of other studies this finding suggests there are no true acupoints or meridians as described by ancient Traditional Chinese Medicine, a statement proposed earlier by Felix Mann [67], founder of the Medical Acupuncture Society.

An opioid μ-receptor antagonist, naloxone, blocks the acupuncture induced analgesia [68, 69]. Naloxone has this same anti analgesic effect on morhpine, described in *2.3.1. Pain killers from the brain.* Moreover, electro acupuncture triggers the release of different opioid peptides when different frequencies are used [62]. A frequency of 2 Hz increases met-enkephalin, β-endorphin and endomorphin concentrations in the subarachnoid space of the spinal cord [62]. Additionally, 100 Hz electro acupuncture increases the release of dynorphin A, whereas 15 Hz stimulation heightens both enkephalins and dynorphins [62]. Another study confirms the role of μ- and δ-opioid receptors, but not the κ-opioid receptor, in electro acupuncture induced anti-hyperalgesia [70]. Indeed, when neurons containing μ-opioid receptors die by treatment with a toxin, the anti-hyperalgesic effect of electroacupuncture is not observed [71].

4.3. Nerves

When trying to elucidate the mechanism behind acupuncture analgesia, most studies focussed on sensory stimulation as a primary mechanism [72, 32]. Indeed, activating afferent nerve fibres innervating skin and muscles seems to be the primary mechanism through which acupuncture elicits its analgesic and visceral effects [73, 74]. A needle inserted into the skin causes afferent activity of peripheral nerve fibres type A and C [32]. Activation of these somatic afferent nerves by acupuncture stimulation results in closing the “gate” (Figure 5) of nociceptive transduction. This inhibitory effect causes suppression of pain, production of various reflex responses including somatic, autonomic and hormonal responses.

When looking at the different types of afferent somatic nerve fibres, (types Aα, Aβ, Aδ and C or I, II, III and IV respectively), Kagitani and colleagues summarise the different visceral and motor responses elicited after activation of these nerve fibres [42]. They recorded from the dorsal spinal root where no antidromically activated efferent nerves are present, these can be present peripherally and cause false activity detection. Conclusion of this study was that manual acupuncture needle stimulation to the hindlimbs activated afferent nerve fibres of all four groups of afferents in rats [42]. This supports the idea that acupuncture closes the nociceptive control gate.

4.4. Receptors and their ligands

A group of skeletal muscle receptors have both low and high thresholds for mechanical stimulation. They are innervated by type Aδ and possible type C nerve fibres. Activation of these receptors happens in physiological settings during strong muscle contraction. The results of their stimulation by acupuncture are physiological responses similar to those resulting from physical exercise [72, 75, 76]. Another type of receptor, the polymodal receptor, is proposed as a possible mediator of acupuncture effects with moxibustion (heating) [77, 78]. Polymodal receptors are activated by mechanical or thermal stimuli [77, 78], which could explain an overlap in effects of manual acupuncture and moxibustion [79].

In the central and peripheral nervous system the synthesis, release and action of neurotransmitters and neuropeptides can be affected by acupuncture [80, 81, 82, 62, 32, 83]. Moreover, endogenous opioids are released by physical exercise and acupuncture and appear to cause functional changes in different organ systems [72]. An essential finding in the search for causative agents of pain relieve by acupuncture is β-endorphin [82]. The endogenous opioid β-endorphin influences a variety of hypothalamic and autonomic functions and is important in the regulation of pain

perception, stress response, mood and immune functions [84, 85].

A recent study shows that during acupuncture in mice adenosine, a neuromodulator with anti-nociceptive properties, is released [63]. Paradoxically, this anti-nociceptive adenosine is a metabolic product of the nociceptive ATP (Figure 1-2). The anti-nociceptive actions of adenosine are mediated through A1-adenosine receptors, present on the ascending nerves. The mice had inflammatory (nociceptive) pain leading to mechanical and thermal allodynia, both are forms of neuropathic pain. Acupuncture reduced the nociceptive and neuropathic pain by anti-nociceptive action of adenosine released from the local tissue. Besides peripheral effects they investigated effects in the brain as well (see paragraph *4.1. Brain*) [63]. Suppressing the breakdown of adenosine effectively increases the clinical benefits of acupuncture [63], because there will be a higher concentration of adenosine at the local site of stimulation increasing the anti-nociceptive responses. Suppressing deaminase, the enzyme for adenosine breakdown, can be used in a complementary way with acupuncture therapy and is therefore of future interests when looking for new analgesic treatments.

4.5. Somato sympathetic reflex

The control of vessel diameter, vasomotor action, is among others regulated by orthosympathetic activity. Acupuncture activates somatic afferent fibres [86, 42], which evoke in many regions of the body excitatory and inhibitory sympathetic reactions [31] that can be topographically depicted [31]. Acupuncture reducing vasomotor activity, increases the vessel diameter and blood flow to local and remote muscle [31]. Subsequently, nociceptive substances are flushed out of the tissue resulting in pain relief [87].

Acupuncture as a complementary therapy can increase blood flow in certain tissues [57, 50, 88] and can enhance hereby the pharmacokinetic action of medication [31]. An alternative therapy replaces the standard therapy, while a complementary therapy is used in combination with the standard therapy for better results. In both cases acupuncture could be an option.

5. Discussion

Pain is a protective mechanism for our survival. There are many different forms of pain and this review described their most important features and physiological backgrounds. Tissue damage causes fast and slow nociceptive pain by action of nociceptive substances like bradykinin, prostaglandin, ATP, and substance P. Nervous injury leads to neuropathic pain. Fortunately, the body encompasses a natural pain relieving system, the analgesic system characterised by action of descending inhibitory nerve fibres and opioids. This system can be activated artificially, by injection of pharmacological drugs, like morphine, or by electrical stimulation of certain brain areas [5, 4]. Specific receptors and their ligands concerning nociception are discovered in the past centuries, providing more auspicious therapeutic targets. Most analgesic drugs comprise adverse effects hampering the opportunity to administer the high doses needed for most beneficial effects. The quest for new options of pain management encounters alternative and complementary therapies, like acupuncture.

Acupuncture is used as an ancient pain relieving therapy, but is also used to equilibrate imbalances in visceral and autonomic function. With modern techniques acupuncture analgesia is put to the test. Progressively increasing knowledge about the neurobiochemical mechanism of acupuncture analgesia is acquired. It influences many brain areas, e.g. inhibiting the anterior cingulate cortex, the pain perception area. Opioid receptors μ, δ and κ in the brain and spinal cord are activated by acupuncture released enkephalins, β-endorphin, and dynorhpin. The insertion of small acupuncture needles releases anti-nociceptive mediators like adenosine and activates somatic sensory afferent fibres types Aα, Aβ, Aδ and C (or I, II, III and IV respectively). These somatic afferent fibres can elicit a somato sympathetic reflex increasing blood flow, consequently flushing out nociceptive substances, decreasing pain. Moreover, activating nonnociceptive Aα and Aβ fibers will inhibit the nociceptive Aδ and C fibers, known as the gate control theory [24], reducing the pain. Psychologically, placebo effects might modulate the beneficial effects.

Hard evidence based statements are difficult to make about effects and an underlying mechanism of acupuncture analgesia. Due to the multitude of divergent research methods used in studies, interindividual pain perception differences, and patients sensitivity of acupuncture analgesia outcome, acupuncture analgesia remains difficult to investigate.

An acupuncture session, either by manual, electrical or heated stimulation, can bring about many different physiological effects. Different sympathetic responses can occur after somatic

afferent stimulation [31]. Visceral functions can be affected [42, 43]; and blood flow to specific parts of the body can be altered [50, 57, 88]. Excitatory and inhibitory responses at different locations in the body can cause unwanted effects. Before applying acupunctural stimulation to a specific area, one should understand all the possible consequences in the body. Therefore, in the development of acupuncture as an alternative or complementary therapy, more knowledge should be available before practising it as a true therapy for specific health complaints.

Even though a special feeling of numbness and distension of the acupoint should occur before acupuncture analgesia works [33, 34, 89], visceral functions do not seem to be absent without this sensation when patients are under general anaesthetics [44]. Moreover, in anaesthetised animal studies the debated placebo effect cannot be observed, while beneficial effects are apparent [86].

Besides alternative therapies with fewer side effects, including physical therapies [90], complementary therapies like acupuncture can be used as pain management as well. Possibly acupuncture itself can be enhanced. With the use of pharmacological intervention it is possible to block specific receptors or enzymes. When the exact mechanism behind acupunctural analgesia has come to light, perhaps pharmacological interventions can put the finishing touch to acupuncture, instead of the other way around.

Concluding, the studies mentioned in this review suggest that acupuncture can have beneficial effects concerning pain management. However, not all pains can be reduced by acupuncture. Therefore, more knowledge is needed on the mechanism of pain relief by acupuncture to fully understand when and how acupuncture can be used as an alternative or a complementary therapy for the reduction of pain.

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