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Roberto CASALE, Per HANSSON

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A NARRATIVE REVIEW ON THE ANALGESIC EFFECT OF LOCALISED VIBRATION - PART 1: THE NEUROPHYSIOLOGICAL BASIS

Roberto Casale * [1], Per Hansson [2, 3]

[1] Opusmedica PC&R, NPO, Piacenza, Italy; [2] Dept. of Pain Management and Research & Norwegian National Advisory Unit on Neuropathic Pain, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway; [3] Dept. of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

***Corresponding author:**

Roberto Casale

Opusmedica PC&R, NPO, Piacenza, Italy

E-mail: robertocasale@opusmedica.org

Abstract

Background: The analgesic action of localised vibration (LV), which is used in rehabilitation medicine to treat various clinical conditions, is usually attributed to spinal gate control, but is actually more complex.

Objective: The aim of this review is a) to provide neurophysiological insights into the mechanisms underlying the ways in which afferent activity set up by LV induces analgesia through interactions with the nociceptive system throughout the nervous system; b) to give a broader vision of the different effects induced by LV, some of them still related to basic science speculation.

Methods: The Medline, EMBASE, AMED, Cochrane Library, CINAHL, Web of Science and ROAD databases were searched for animal and human neurophysiological and neurohormonal studies related to the direct effects of LV on nociceptive transmission and pain perception and were supplemented by published books and theses.

Results:

The spinal gate control mechanism trough Aß-fibers activation seems to be the most effective antinociceptive system activated by LV at frequencies between 100 and 250 Hz (High frequency HF-LV) when applied in the same segment as the pain. A gating effect can be obtained also when it is applied contralaterally to the painful site or to adjacent dermatomes. Kinaesthetic illusions of movement induced by HF-LV may induce a stronger analgesic effect. Activation of C-mechanoreceptors induced by a massage-like LV of low frequency and low intensity may interfere with pain through the activation of the limbic system. This action doesn't involve any gating mechanism. Frequency is more important than intensity as different frequencies induce activity in different cortical and cerebellar areas; these activations may be related to plastic cortical changes tentatively reversing pain-related maladaptive disorganization. Distraction/shift of attention or cortisol-mediated stress-induced analgesia are not involved in LV analgesic action in humans for both LF and HF. The release of opioidergic neuropeptides (analgesia not reversed by naloxone) as well as a reduction in Substance P in the CSF doesn't seem to play a major role in the HF-LV action. Decrease in Calcitonin and TRPV1 expression in the trigeminal ganglia in animals has been induced by HF-LV but the role of LF-LV is not completely deciphered. Both high and low LV induce the release of oxytocin, which may induce antinociceptive responses in animals and contribute to controlling pain in humans.

Conclusions: Although many aspects of LV-induced pain alleviation deserve more in-depth basic and translational studies, there are sound neurophysiological reasons for using LV in the

therapeutic armamentarium of pain control. Laboratory animal and human data indicate that LV relieves pain not only by acting on the spinal gate, but also at higher levels of the nervous system.

INTRODUCTION

Leaving aside the diagnostic use of a tuning fork, localised vibration (LV) plays a multi-faceted role in medicine. Mechanical vibration can induce work-related diseases, whereas locally applied vibratory stimulation of the skin overlaying muscles and tendons has long been used to study spinal cord reflex activity in clinical neurophysiology. It has also been used to induce therapeutic neuromuscular changes in healthy subjects and in different rehabilitation settings.

In the last decades its use in rehabilitation has been broadened by the introduction of new, easier-to-use devices that produce mechano-acoustic vibrations that can be used to relieve pain. The mechanism underlying this analgesic property is usually attributed to spinal gate control but is likely more complex as LV also has separate effects on perception, as well as on sensory-motor control. The receptors excited during vibratory stimulation of the skin and deep tissues transform the mechanical stimulus into a barrage of impulses to the spinal cord and onto different supra-spinal areas. These areas are related to perception, discrimination, and sensory and motor responses. Limbic structures that distinguish the pleasantness of a mechanical sensory stimulus through the whole span of tactile sensations are also involved. Indeed, the peripheral impulses travel mainly but not exclusively along sensory Aβ afferent neurons, but also C-tactile afferents are involved in the perceptual pleasantness of touch.

The scope of this review is to provide some neurophysiological insights into the mechanisms underlying the ways in which activity in the nervous system set up by a mechanical stimulus can alleviate pain and at which level of the nervous system (from receptors to the cortex) they manifest themselves. Such insights might enable identification of key concepts that may help to improve decision making in physical therapy practice. Whenever possible, in the presence of basic science data, hypotheses on analgesic mechanisms still to be completely deciphered will also be identified. The review will only consider the direct effects on nociceptive transmission, pain perception, and control of what has been described in the literature as local, selective or segmental vibration, but will here be referred to as LV [1].

METHODS

Following the approach of the PRISMA Extension for Scoping Reviews (PRISMAScR), the Medline, EMBASE, AMED, Cochrane Library, CINAHL, Web of Science, TRIP database, Clinical Evidence and ROAD databases were searched for relevant articles, which were supplemented by published

books and theses. Inclusion/exclusion criteria using Boolean operators for search strategy were: “vibration” “neurophysiological mechanisms”, direct effects of vibration on “nociceptors”, “transmission”, “pain” “pain perception” and “pain control”. Search was limited to “local", “localised” “selective" or "segmental vibration" [1]. Exclusions were made for “Whole body vibration”. In the text data from animals and human research are specified. Results from clinical studies, if not related to LV mechanism of action, were not included in this part as they are discussed in Part 2 of this work.

For the aim of clarity, when possible, the neurophysiological effects of LV so far collected were organised in an anatomy-functional way, reported in sections from receptor transduction and afferent sensory pathway to the spinal cord, and further to sub-cortical and cortical structures. It is worth of mention that some items of particular interest like the role of C-tactile mechanoreceptors, the changes in neurotransmitters and neuromodulators, LV stimulation below perception threshold, the interaction between kinesiologic illusion and pain control have been included with an intent to open new perspectives and to stimulate discussion.

RESULTS

1- The receptive unit - receptors and fibres

1.a Aß-mechanoreceptor units

Human skin types (hairy or glabrous) show not only differences in structure, but also concerning density and types of mechanoreceptor units across different anatomical locations [2] [3]. In addition, some receptors are more deeply localised in the skin, hence cutaneous anaesthesia does not alter vibration threshold in such areas. The four main mechanoreceptors in the skin have a combination of physical properties related to their fast or slow adaptation to mechanical stimuli and low or high stimulation intensity threshold and respond to LV at various frequencies (Table 1). In addition to the cutaneous mechanoreceptors, muscle spindles and Golgi tendon organs also respond to a mechanical vibratory stimulus [4]. In humans, Pacinian corpuscles respond to different vibration frequencies with a bell-shaped stimulus-response curve while primary endings of the muscle spindle discharge with a frequency phase-locked to the vibration. Hagbarth refers to 100-200 Hz at 1-2 mm vibration amplitude as an “appropriate stimulus” to evoke neurophysiological changes in the spinal cord motor neuron excitability in humans [5]. All these cutaneous receptors as well as muscle spindles and Golgi organs are connected to fast conducting

Aß-highly myelinated fibres (correlation between Erlanger & Gasser and Lloyd classification is reported in Table 2). A recent study on the effect of amplitude and frequency of a vibratory stimulus indicates that both parameters may influence experimentally induced pain, but that frequency is more important than the amplitude (intensity): a mild pricking sensation generated by a 10-millisecond burst of radiant heat from a CO_2 laser gradually declined as vibration amplitude increased from 10 to 45 dB (both above sensory threshold) and all frequencies ranging from 20 to 230 Hz may interfere with nociception. These results also point out that signals carried by multiple vibrotactile channels can modulate nociception [6]. However, although no specific mechanoreceptive channel appears to have a privileged role [6], different frequencies have been shown to activate different cortical areas in healthy volunteers [7;8].

This may be the basis for the different conscious perceptions to different vibration frequencies in humans: a light touch, a rough deep touch and the sensation of flutter and vibration [9] as well as the degree of pleasantness of the stimulation [10]

1.b C-tactile receptor units

Nociceptive Aδ and C-fibres and their central connections are considered to be involved in pain relief when using the so-called counter irritation techniques where the stimulus is recognised as unpleasant if not painful [11]. However, there is a subclass of unmyelinated low threshold slowly conducting (0.5-1 m/sec) mechanosensitive C-fibres innervating human hairy skin, not involved neither in nociception nor in counterirritation techniques but instead subserving the affective and rewarding properties of the sensation of touch [12]. Very low frequencies and intensities of vibration like a gentle repetitive stroking/caressing have been shown to activate this special group of C-fibres. These C-tactile afferents respond with a bell-shaped stimulus-response curve to different stroking velocities with a maximum of response at a stroking velocity of 3cm/s. This peak activation correlates with perceived touch pleasantness in humans [10]. This possible further antinociceptive action has been related to the so called interoception, a concept of importance in rehabilitation. Interoception is defined as the “sense of the physiological condition of the body which includes accuracy, sensibility and awareness for a given stimulus “[for more details on interoception and pain see a review by Di Lernia et al 2017] [13]. The role of low-threshold C fibres in pain modulation was demonstrated in healthy volunteers using two types of conditioning stimuli: stroking stimulus using velvet or sandpaper at speeds of 0.1, 1.0 and 10 cm/s and a LV at low (20 Hz) or high (200 Hz) frequency and amplitude of 200 um for 30 sec. These stimuli were

applied in the normal condition (i.e., no experimental pain) and following the induction of muscle pain by infusing hypertonic saline (5%) into the tibialis anterior muscle. These observations were repeated following the conduction block of myelinated fibres by compression of the sciatic nerve. All participants reliably linked velvet-stroking to pleasantness and sandpaper-stroking to unpleasantness (no pain). Likewise, 20 Hz vibration was linked to pleasantness. During muscle pain, the application of previously pleasant stimuli, including 20 Hz LV resulted in overall pain relief [14].

2 - Segmental level

That afferent activity set up by vibratory stimuli may interact at the spinal level with nociceptive afferents, was initially postulated by Wall & Cronly-Dillon in 1960 [15] and few years later fully developed into the gate control theory [16]. Briefly, the theory states that impulses set up by innocuous stimuli interact at the spinal level with noxious stimuli modulating their progression within the CNS. The“gate” is also subject to descending inhibitory and facilitatory activity from the brain and other cord segments, thus contributing to the control of net ascending activity. Although this relatively simple model has been shown to be “not correct in detail, the general ideas put forward by the concept of a spinal gate and the experiments it prompted in both animals and patients have transformed our understanding of pain mechanisms” [17]. Indeed, after the publication of the gate theory [16], it became the most important concept on which physical therapies, using non-painful mechanical stimulations, based their pain relief action. Experimental evidence on both animals and humans also supports the possibility that spinal gating may take place not only when LV is applied in the same dermatome as the origin of the nociceptive activity but also when applied contralaterally to such inputs [18] or to adjacent dermatomes [19], thus suggesting more pluri-segmental gating. At the spinal cord level, it has also been suggested that LV may induce neuroplastic changes. LV induces a long-term depression-like plasticity in specific spinal cord circuits [20] and inhibits monosynaptic (T and H -reflexes) as well as polysynaptic reflexes, like the flexion withdrawal- and the blink reflex. The flexion reflex can be evoked in both upper and lower limb [21], the blink reflex plays a similar protective role for the eye to that of the withdrawal reflex of limbs in humans [22]. The raise in their excitability threshold is interpreted as an increase in pain threshold in healthy subjects and equivalent to an antinociceptive effect in the presence of pain [21,22]. The gate concept [16] can also be extended to other systems, in particular to an “opioid-dependant gate” in the dorsal horn [17]. The most relevant being the

modulatory action of descending pathways from the rostroventromedial (RVM) medulla, an important neurobiological substrate for the emotional and cognitive modulation of pain. In RVM two populations of neurons (ON and OFF) are present and projecting to the superficial dorsal horn of the spinal cord. The so called OFF cells are turned off by nociceptive inputs and are excited by opiates while ON cells are turned on by nociceptive inputs and are inhibited by opiates. Thus, ON cells enhance nociceptive transmission while OFF cells depress it. (See ref 17). As the RVM is involved in the emotional and cognitive modulation of pain it is possible that an exteroceptive stimulus such as LV could activate these mechanisms contributing to reinforcement of the nociceptive gating at the spinal level, however currently there are no data to support such activation and it remains a matter of speculation.

So far described the spinal gating of nociceptive activity is partially based on the interaction between fast conducing Aß-fibres and lower conduction velocity fibres carrying nociceptive information (A-delta and C- fibres). However as previously mentioned (See chapter 1.b) there is a subclass of unmyelinated low threshold slow conduction velocity (0.5-1 m/sec) mechanosensitive C-fibres innervating human hairy skin, not directly involved in nociception but instead subserving touch in its affective and rewarding properties [12]. This affective mechanism related to mechanosensitivity is completely independent on the gate control. The possibility to use LV to activate these afferents - preferentially responding to tactile forces typical of a gentle caress (low frequency and low intensity stimulation)- alone or in combination with the classical high frequency low intensity gate-based pain control, has not yet been explored. However, it has been reported that activating this type of C-tactile afferents, namely a massage-like mechanical stimulation of low intensity and low frequency an increase in oxytocin-like immunoreactivity levels in plasma and periaqueductal grey matter (PAG) has been demonstrated in animals [see chapter 5 on neurohormones]. This type of stimulation is obtained by a massage technique called effleurage. Effleurage has been successfully used to relieve the affective component of clinical pain as shown in different settings, e.g., in patients undergoing chemotherapy or waiting for ambulatory surgery where both manual and machine-made vibration were able to reduce anxiety and pain [23; 24].

3 - Suprasegmental *and cortical level*

The gain of sensitivity of the nociceptive system can be modulated not only at the spinal level but also at supraspinal levels. Subcortical regions such as the thalamus and the somatosensory

thalamocortical network may be actively involved in such processes [25]. Magnetic functional imaging studies are one of the most sophisticated ways to study the possible central effect of LV. It has been shown that different vibration frequencies differently activate selective afferent pathways, sensory cortical and ipsilateral cerebellar areas [7;8;26;27]. Imaging studies of both animals and humans have demonstrated specific spatial patterns in the activity of the primary somatosensory cortical area (S1) in response to different stimulation frequencies: from a very low frequency (<1 Hz) to flutter (30/50 Hz), and vibration (200 Hz). In healthy volunteers' different frequencies differently activate sub-areas in primary (S1) and secondary (S2) somatosensory areas. While S1 activity seems to decrease with the increase in frequency, S2 doesn't show any clear changes (decrease) as the vibration frequency increases. Particularly S1 shows responses to flutter (30/50 Hz) but little to vibration (>100 Hz) while S2 responds to both frequencies. It is worth of note that the most discriminative cortical pattern has been observed with frequency around 50Hz (cut off frequency between a sensation of flutter or vibration) [7;8]. Infra- as well as supra-tentorial areas are activated by LV. Also, cerebellar areas may be activated by LV. Using functional magnetic resonance imaging (fMRI) in a small group of healthy volunteers, 100Hz LV applied on the dominant forearm has been shown to increase ipsilateral cerebellar activity [27]. Other neuroimaging and neuropsychological studies in humans demonstrate that the range of tasks associated with cerebellar activation includes also non-motor activity such as attention, emotion, and pain. Thus, the increased cerebellar activity induced by LV may account for an active participation of the cerebellar areas in pain modulation induced by LV. Cortical areas other than S1 and S2 somatosensory areas may be activated with different frequency and intensity of the stimulus. Indeed, light skin stroking able to activate C-tactile units may activate posterior insula cortex, pinpointing a different and distinct coding channel of C-tactile afferents projecting primarily to emotional rather than classical somatosensory cortical regions [12]. Thus, pleasantness induced by low frequency low intensity mechanical stimulation, carrying pleasant information through C-tactile afferents, may contribute to reduce the affective part of pain perception. Moreover, it has been shown that, if these specific low-velocity, low-force parameters are met (e.g., a gentle repetitive stroking), the stimulation is primarily processed by the insula rather than by the somatosensory cortex [13]. As an indirect confirmation of the involvement of the limbic system and the possible usefulness of specific low-velocity, low-force LV, changes in the reward circuitry have been shown in migraine as well as in trigeminal neuropathic

pain [28]. These differences in activated areas may give further clues as to the different clinical effects of the various vibration parameters.

4 Pain control and Kinesiological illusion induced by LV

The relationship between vibration and induced kinesiological illusion has been reported in the early seventies and a relationship between movement and vibration to control pain was suggested early in the nineties. However, only recently activation of motor-related regions with kinesiologic illusions has been assessed to contribute toward pain alleviation in a clinical setting [29].
LV may reduce pain while activating muscle- as well as skin mechanoreceptors separately, and a better pain control may be achieved when both components are activated simultaneously. However, the strongest analgesic effects of LV occur when also illusory joint movements are perceived by the subject [30]. It has been shown that muscle tendon vibration induces proprioceptive messages mediating kinaesthetic illusory movements [29,30] very similar to those activated during actual movements and activating the same cortical areas. Thus, a stronger analgesic effect from a LV may be induced when illusory movements are perceived putting a strong emphasis on sensory-motor integration. Disturbances in position sense and cortical body representation has been reported in several chronic pain states such as CRPS phantom limb pain and fibromyalgia suggesting the presence of maladaptive neuroplastic changes [31] . This has been reported not only as altered body scheme but also as alteration in the interoceptive body representation [13]. Although an ongoing debate [32,33] on to what extent cortical reorganization exist in chronic pain patients and to what extent it is involved in pain generation and maintenance, treatments likely to normalize defective endogenous pain controlling pathways by means of physical modalities are commonly proposed to control pain. In particular LV has been shown to significantly improve range of motion and pain in patients with CRPS-I, as the result of a "re-established consonance between sensory input and motor output at cortical level "[34]
Kinesiological illusion-related pain control can raise the question if LV may influence pain perception by distracting the subject or influencing negative pain-related emotions. While the first hypothesis has been considered inconsistent by recent work using the distractibility subscale of the Cognitive Failures Questionnaire (CFQ-D:) [35], the possibility that LV may influence negative pain-related emotions has been supported by a study on acute pain after surgery for distal fracture of the radius [29].

5 LV at a sub-threshold sensory perception.

Healthy subjects can discriminate different stimulation intensities -a light from a rough deep touch- or to perceive and discriminate different frequencies – a sensation of low frequency repetitive touch from a flutter or a vibration [9]- or even to feel if a LV is more or less pleasant [10]. All the herein reported studies dealt with the neurophysiological modifications induced by LV in humans in the presence of a clearly perceived sensation by the subject, even though of different intensity and frequency. The stimulus-induced perception was therefore a prerequisite for its therapeutic use. However, the lowest intensity of a tactile stimulus that is perceivable to a person has been shown to be higher than the minimum intensity needed to activate sensory neurons (i.e., neuronal threshold) [36]**.** In a recent line of research cortical neurophysiological changes have been studied using a vibration stimulus with a frequency within the Pacinian activation range with an intensity 40% below the sensory threshold, i.e., without a conscious perception of the vibratory stimulus and without any kinesiological illusion of movement. It was demonstrated that a subliminal, consciously unperceived LV, can modify sensory-motor cortical activity thus indicating that LV may have a strong modulatory effect at that level without the need of a stimulus to be perceived or even to have a high intensity [37]. On this particular use of LV for pain control there aren't specific studies, however the result of the so far mentioned research line, although not directly related to pain control, may be relevant for the use of LV to control pain in specific groups of patients (e.g., children or patient with mechanical allodynia) or during rehabilitation aimed at a cortical reorganization as in the case of pain-related motor impairment in osteoarthritis [38]. In this clinical model, pain is associated with connectivity changes in primary sensory areas (S1) as well as in cortical regions related to the limbic system like the para-hippocampal gyrus and the insula [38] reinforcing the suggestion that also subthreshold LV could act outside the gating mechanism.

6 - Neurotransmitters & neurohormones

***6.a Calcitonin* gene related peptide (CGRP) and substance P (SP)**

Neuropeptides play a pivotal role in nociception as well as in antinociception. Calcitonin gene related peptide (CGRP) and substance P (SP) release from nociceptive fibres in the peripheral tissues are at the basis of inflammatory/nociceptive pain [39]. In an early study 7 patients suffering from chronic pain of mixed origin (1 polyarthritis,1 scapular bursitis, 1 spondylarthritis, 1 cervicobrachialgia, and 3 low back pain) the effect of 30 minutes of 100 Hz LV on SP-like

immunoreactivity levels in the CSF was studied. Results indicate that LV was able to reduce pain and SP levels. However, the reduction in SP level was considered by the authors too minute to account for the analgesic effect obtained [40]. Recently an experimental study on animals' behavioural response to mechanically induced orthodontic inflammation, demonstrated that 120 Hz vibratory stimulation significantly decreased the duration of face grooming and reduced expression of TRPV1 (Transient Receptor Potential Vanilloid -1) and CGRP in the rat trigeminal ganglia [41].

Despite the initial observation in humans, and the recent discovery of a downregulation of TRPV1, no other clinical work has been published so far on the subject.

6.b Endogenous opioids

The most thoroughly studied hormones related to pain alleviation by vibration are those that belong to the endogenous opioid system. Although some proof has been published that LV may influence pro-nociceptive neuropeptides [41], conversely, in humans the possible involvement of endogenous opioids in the long-lasting pain relief induced by LV was not confirmed: pain reduction following operative removal of impacted third molar obtained by a 100 Hz LV was not reversed by naloxone, a mostly μ antagonist when used in clinical doses, suggesting that no endogenous u-opioid agonist release was involved [42]. Other studies on chronic musculoskeletal pain in humans have not found any involvement of met-enkephalin or β-endorphin [43].

6.cTestosterone & Cortisol

There are strong evidence of gender differences in the epidemiology, symptomatology, pathophysiology, and treatment outcome in both clinical pain conditions and experimental studies [44]. Testosterone has a protective action toward pain perception. Several studies support a role for testosterone in dampening pain and raising the pain threshold [45]. Its level is higher in men than in women and this may account for differences in responses to vibratory stimulation on sensory detection and pain thresholds between women and men [46]. These differences in response to LV may also account for the lack of any clear-cut evidence of changes in testosterone concentrations when using frequency of stimulation at 20 and 45 Hz LV. Increased basic level of cortisol has been found in many chronic pain conditions such as fibromyalgia [47]. A significant decreased level of cortisol levels has been reported in normal subjects using high vibration frequencies (300 Hz) suggesting a possible role of high frequency LV in a cortisol-mediated antinociceptive effects [48].

6.d Oxytocin

Oxytocin (OXT), a hypothalamic neuropeptide acts in the central and peripheral nervous systems with anti-inflammatory and anti-oxidant properties, regulating immune and anti-inflammatory responses [49]. In experimental conditions in animals a non-noxious 100 Hz LV leads to an increase of oxytocin in plasma and cerebrospinal fluid (CSF). This has been associated with an antinociceptive effect shown by an increased latency to the tail flick test, reversed by an oxytocin antagonist, thus suggesting that oxytocin related mechanisms may be involved in high frequency/low intensity LV-induced pain relief. In humans, plasma oxytocin concentration and associated neural responses have been studied using functional near infrared spectroscopy (fNIRS) during hand- or machine-administered light massage of low frequency. Plasma oxytocin as well as neural responses in posterior superior temporal sulcus and medial/lateral orbitofrontal cortex were increased after both massage by hand and machine. Plasma oxytocin however increased more after massage by hand. [50]. This last action may be related to the activation of C-tactile units and may involve insular/limbic system of rewarding and pleasantness [12, 14].

6.e Adenosine

Adenosine, a purine nucleoside, is responsible for the regulation of multiple physiological and pathological cellular and tissue functions including nociception. Most of the antinociceptive effects of adenosine are dependent upon G protein-coupled receptors A1-AR activation located at peripheral, spinal, and supraspinal sites [51]. In animals at spinal cord level, it has been shown that vibration at frequencies between 80-250 Hz induces a release of an endogenous purine compound -adenosine- with simultaneous inhibition of the on-going activity of nociceptive neurons [52].

A note

It is beyond the scope of this paper to consider the possible clinical effects of LV, as they are considered in the clinical part of this work (Part 2). However, in a neurophysiological context it is worth mentioning that the ability of LV to modulate cortico-spinal mechanisms may be influenced not only by a specific activation of mechanoreceptors units and the frequency used [53] but also on the proximal or distal site of its application. Also, its application on the skin overlying flexor or extensors muscles, may influence its ability to interfere with the cortico-spinal mechanisms as nociceptive flexor responses are enhanced by flexor vibration and depressed by extensor vibration [54]. Hairy or glabrous human skin types are remarkably different in structure and varying in mechanoreceptive unit densities and types across different anatomical locations. This difference in mechanoreceptor innervation density correlates with tactile acuity [2]: mechanoreceptor unit

afferents densely innervate distal limbs, providing high tactile acuity, with hands and feet showing gradients in innervation. Likewise, humans exhibit spatially distinct response properties to nociceptive stimuli, with the spatial acuity for nociceptive inputs higher on fingertips than in neighbouring skin [3]. Thus, also site of application - dermatome/extra-dermatome; distal/proximal; hairy/glabrous; more/less densely innervated part of the body- may influence the magnitude of the afferent volley and therefore the possible neuromodulatory effect of LV.

CONCLUSION

Results of this narrative survey on some neurophysiological/neurochemical mechanisms underlying the use of LV show different interactions by which LV may interfere with nociceptive transmission and pain perception [Box 1].

Some of them are universally recognised, such as the gate mechanism exerted at different levels of the nervous system [25] and based on the interaction between Aß and Ad/C nociceptive fibers. Some others are based on completely different neurophysiological background such as the activation of C-tactile fibers and the use of stimulations at subthreshold sensory or the reinforcement on pain control induced by kinesiological illusion of movement during a high frequency LV. However, these interactions across modalities are not sufficiently explored in preclinical research or in the clinic on a broad number of patients and in selected pain pathologies. Also quite interesting is the release of antinociceptive neurohormones induced by LV even if only a fraction of the neurohormones and transmitters possibly involved in pain modulation has been studied. In this respect it is mandatory to note that the so far reported data – both pros as well as cons- on the release of neuro-hormones and neurotransmitters induced by LV may not be generalized due to the use of different frequencies of stimulation as well as different experimental settings (e.g., gender).

Of great rehabilitation interest is the emerged link between pain control and movement both in term of kinesiological illusion as well as in term of LV associated with motor imageries. This great interest is testified by the recent publication of a methodology, the Standardized Kinesthetic Illusion Procedure (SKIP), to favor the use of LV-induced illusions in clinical rehabilitation settings [55]. Someothers, finally, are extremely interesting in a rehabilitation context but, in some way, are difficult to merge in a homogeneous neurophysiological background, such as the use of sensory sub-threshold vibrations to control pain. This approach actually does not have a direct

application on pain as it may have more links to enhancing motor control and only as a secondary effect may interfere with pain.

In physical therapy, many treatments evolved and were used clinically before we understood how their effects are produced as it happens not only for LV but also for other more frequently used physical modalities [56] such as transcutaneous electric nerve stimulation (TENS) or other therapies based on mechanical stimulation. LV data coming from animal and human studies, provide sound neurophysiological reasons for adding LV to the armamentarium of physical analgesic therapies. Although scientific bases for its more widespread use therefore exist, the possible incomplete knowledge of all the physiological actions here reviewed make this promising physical therapy still little used with the consequent lack of RCT studies on which to formulate shared and applied guidelines. Moreover, also for the most accredited neurophysiological mechanisms there is a substantial lack of appropriate exchange between basic science and translational medicine.

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BOX 1. Herein are summarised the most relevant neurophysiological mechanisms currently reported as the basis of the analgesic actions of LV.

Four main skin mechanoreceptors, Golgi organs and muscle spindle receptors respond to LV. All of them are connected to fast conducting highly myelinated fibres (A ß fibres)
In general, highly myelinated skin mechanoreceptive units don't have a privileged role in the transmission of a vibratory stimulus.
Vibratory frequency is more important than its intensity as different frequencies differently activate cortical areas. This may account for different functional responses and to be possibly related to plastic cortical changes.
In humans the best pain reducing frequencies are between 100 and 250 Hz (high frequency - HF) with a peak response at 100-150 Hz for which the most sensitive being the Pacinian corpuscles and the primary endings of the muscle spindle.
The spinal gate mechanism seems to be the most relevant mechanism of pain control induced by a HF-LV. Pain relief may be obtained also when LV is applied contralaterally to the painful site or to adjacent dermatomes. Other gate-like opioid-dependant mechanisms may contribute to reduce pain at this level.
HF- LV induces proprioceptive messages mediating kinaesthetic illusory movements. HF-LV shows stronger analgesic effects when it induces kinesthetic illusions of movement.
LV of low frequency and low intensity massage-like (LF-LV) may activate C - mechanoreceptors and interfere with pain through activation of the limbic system. This action does not involve any gating mechanism.
The analgesic effects of HF-LV (100 Hz) are not mediated by an opioidergic neuropeptide production as its action is not reversed by naloxone in humans (note: μ-receptors mainly). A reduction in SP has been reported but without clinical relevance.
Calcitonin related peptides (CGRP) and TRPV1 expression are modulated by a HF-LV (120Hz) in a dental pain model in animals. No data in humans.
Both HF-LV (100 Hz) and LF-LV (LV-like massage) induce the release of oxytocin, which may induce antinociceptive responses in animals and contribute to controlling pain in humans.
HF- LV (between 80 and 250 Hz) may induce a release of an endogenous purine compound - adenosine. Higher frequencies (300 Hz) may induce a decrease in plasma cortisol and interfere with pain perception in humans
The analgesic effects of LV in humans are not related to distraction/shift of attention. Gender differences (e.g.in testosterone level) may account for lack of clear-cut clinical results.

Table 1: Skin mechanoreceptors classification according to sensitivity to type of mechanical forces and frequency of stimulation. Each SA, SA2, RA and PC convey specific tactile signals of light touch, flutter and vibration, respectively. The afferents transmit tactile sensory signals to the cortex in a segregated way. These separate afferent pathways cause different cortical somatosensory responses in S1 and in bilateral S2 (6;7).
It is worth of note that a) different frequencies differently activate cortical areas and that these differences are found in sub-areas of S1 and S2; b) while S1activity seems to decrease with the increase in frequencies, S2 activity doesn't show any clear changes (decrease) as the frequency increases; c) S1 shows responses to flutter but little to vibration while S2 responds to both frequencies; d) frequency around 50Hz induces the most discriminative cortical pattern. (Table modified from 27).

Name	Action	Type	Cortical areas
Merkel cell-neurite complexes	Detect a light touch and a sustained indentation	type 1 slowly adapting receptors (SA1)	contralateral S1 and bilateral S2
Ruffini corpuscles	Detect kinaesthetic senses and static forces	type 2 slowly adapting receptors (SA2)	contralateral S1 and bilateral S2
Meissner corpuscles	detect texture and a relatively low frequency stimulation of cutaneous flutter whose frequency range is 5–50 Hz	type 1 rapidly adapting receptors (RA);	S1: Flutter (40 Hz) increased bilaterally the activity in PC but greater contralaterally. S2: bilateral activation of PPC and LS
Pacinian corpuscles	detect high-frequency rapid stimulation of cutaneous vibration whose frequency range is > 80 Hz* *Studies in humans range from 20 to 200 Hz.with a bell-shape response curve	type 2 rapidly adapting receptors (PC)	S1 : Vibration (80 Hz) increased activity in PC but lower that that induced by a 40 HZ. Vibrations >80 Hz. induced little S1 activation. S2: bilateral activation of PPC and LS

Captions:
S1 (primary somatosensory cortex);
S2 (secondary somatosensory cortex);
SA1 (slowly adapting mechanoreceptor 1);
SA2 (slowly adapting mechanoreceptor 2);
RA (type 1 rapidly adapting mechanoreceptor);
PC (type 2 rapidly adapting mechanoreceptor);
PC (post central gyrus);
PPC (posterior parietal cortex)
LS (upper bank of the lateral sulcus)

Table 2 Fibres classification according to general classification of fibres (Erlanger & Gasser, 1941) and the classification of sensory fibres (Lloyd, 1943) [For an historical note see: Manzano, GM, et al

"A brief historical note on the classification of nerve fibres." Arquivos de neuro-psiquiatria (2008): 117-119].

General fibers classification (Erlanger & Gasser)				Sensory fibres classification (Lloyd)
Group	Diameter (µm)	Speed (m/s)	Function	
A				
α	12-20	70-100	Motor; sensory	I
β	5-12	30-70	Sensory	II
γ	3-5	15-30	Motor; sensory	
δ	2-3	5-10	Sensory	III
B	1-2	2-5	Autonomic preganglionic	
C	0,2-1	0,5-2	Sensory; Autonomic postganglionic	IV