Remedee Labs

FROM MILLIMETER WAVES TO PAIN RELIEF

White Paper | *Part 1*

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Preambule

Chronic pain is a global problem with prevalence in Europe estimated at 19% (Breivik et al., 2006) and up to 30,7% in the USA (Johannes et al., 2010). These numbers, which keep growing as the population ages, have a significant economic impact due firstly to a decreased productivity for people of working age, and secondly to the cost of medical care. Chronic pain also has a profound impact on people's lifestyle and quality of life, half of chronic pain sufferers being constantly in pain and a third considering their pain to be severe. A study conducted in the US (Breivik et al., 2006) reports 61% patients being less able or unable to work outside the home, 19% having lost their job due to their condition, 3% having changed jobs because of their pain and 21% having been diagnosed with depression because of their pain.

For a long time, pain had only two identified causes: nociceptive pain, the activation of nociceptors arising from damage to non-neural tissues, or neuropathic pain, lesion or disease of the somatosensory nervous system. As such, opioids came very useful for patients enduring severe acute pain. However, it was without considering other causes and mechanisms for pain and the subsequent inefficacity of opioids that would lead to misusage of those drugs.

It was only in 2016 that the terminology "nociplastic pain", referring to altered nociception, was introduced by the International Association for the Study of Pain. Clinical observations of "unexplained painful conditions" have been connected to recent neuroscientific evidence showing disturbances of the pain system, namely central sensitization. Subsequently, "primary pain", has been included in the new version of the International Statistical Classification of Diseases and Related Health Problems (ICD-11, 2019) and relevant therapies could therefore be recommended.

Acknowledged as arising from biopsychosocial factors, chronic nociplastic pain calls for multifactorial therapies: drug therapies, psychotherapies, physical therapies, etc. Drug therapies involve opioids, but also antidepressant and anticonvulsant for their neuromodulating effects. Therapies that rely on the body's own opioid system have been emphasized: because the release of endogenous opioids is triggered by the stimulation of the peripheral nervous system, treatments such as massages, thermal cures, acupuncture, and cryotherapy are often proposed to patients. These solutions, though effective, require significant expenditure of time, money and effort. The first non-drug treatment recommended to patients with chronic pain is "physical exercise", but it is extremely difficult for sufferers to take physical exercise when even simple everyday movements are painful.

It is in this context that Remedee Labs is developing a safe, convenient, self-managed solution that has the potential to relieve people not only from the burden of chronic pain, but also from conditions involving sleeplessness, stress, mood and reward regulation. The solution uses the emission of millimeter waves (MMW) that stimulate the peripheral nervous system and has neuromodulating effects, through the intracerebral release of various neurotransmitters, (mainly endorphins, but also serotonin and dopamine) together with parasympathetic effects.

In this 1st Volume of our White Paper, we present a summary of endorphins and millimeter wave therapy justifying Remedee Labs' approach and the scope of the projects in development. In Volume II, we demonstrate the potential of our device as a stepping stone to facilitate the holistic change required to overcome nociplastic pain, and show how the Remedee Solution, combining device and a digital, interdisciplinary program, can significantly improve patients' quality of life.

1. Endorphins

1.1. Background

Endorphins are neuropeptides secreted by the body and acting as opioids. Their name come from the contraction between "endogenous", meaning "proceeding from inside" and "morphine", from "Morpheus", the Greek god of sleep and dreams. The analgesic and sedative properties of opioids have been known since Antiquity: opium was extracted from the poppy flower in Mesopotamia and used both for its medicinal and relaxing properties. They are currently considered as "natural pain-killers", "well-being hormones" or "feel-good chemicals".

The existence of the opioid system in the central nervous system was first evidenced by the identification of opioid receptors in the brain (Pert & Snyder, 1975; Simon et al., 1973) and later of their endogenous ligands called Met- and Leu-enkephalin (Kosterlitz & Hughes, 1977; Smith et al., 1976). Since then, many other endogenous opioids have been identified, namely: enkephalin, dynorphin, and β-endorphins.

Endorphins are one kind of opioids derived from the precursor protein pro-opiomelanocortin (Mains et al., 1977) (POMC). They are produced continuously in various parts of the body, but especially in the nervous system and the pituitary gland and interact mainly with cell receptors of the nervous system responsible for blocking pain and its emotional processing. Their production varies dramatically both inter and intra individually, depending on factors such as people's age, activities, mood, or even the time of day.

After binding to specific receptors, endorphins are degraded by enzymes called enkephalinases after about an hour (Chen et al., 2001; Hersh, 1985). Despite this rapid degradation, biological effects of endorphins remain for a longer duration due to the triggering of a chain of second messengers leading to a global activation of the parasympathetic system. neuralgia, (Schlereth et al., 2015).

1.2. Regulation: the involvement of peripheral stimulation

Increases in endorphin levels associated with strain or stress in bodily tissues, especially painful stimulation, physical exercise or childbirth, led to the hypothesis that **intracerebral endorphin levels depend on peripheral nerve stimulations**. Corroborating this idea, several triggers have been identified. **Activation of nociceptors** leads to an increase of β-endorphin levels in blood plasma (Aloisi et al., 1995; Facchinetti et al., 1984), that is negatively correlated with patient's pain score (Szyfelbein et al., 1985). Moreover, intracerebral injection of exogenous β-endorphins leads to an analgesic effect about 30 times stronger than that of morphine (Loh et al., 1976). Activation of t**emperature-specific receptors** leads to an endorphin release and support the wellbeing effects of certain technics, namely e.g. sauna (Vescovi & Coiro, 1993), hot-spring baths (Kubota et al., 1992), cryotherapy (Algafly & George, 2007), as well as the use of capsaicin (Lee et al., 2012), the 'spicy' chemical present in chili peppers, in patches used for neuropathic pain management. The **activation of mechanical receptors and/or ergoreceptors** in connective tissue massage (Kaada & Torsteinbø, 1989), in physical exercise (Harber & Sutton, 1984; Goldfarb & Jamurtas, 1997, for a review, see Harber, 1997) and pregnancy (Berkley et al., 1993; ·Cogan & Spinnato, 1986; Smith et al., 1990; Steinman et al., 1992; Whipple et al., 1990)·have been shown to lead to endorphin release. Lastly, exposure to light leads to an increased production of endorphins mediated by **epidermal keratinocytes** (Fell et al., 2014; Jussila et al., 2016). In an experiment on mice, signs of withdrawal were observed after long term exposure to UV rays was stopped, confirming the hedonic role of β-endorphins that contribute to seasonal affective disorders during seasons with less light (i.e. autumn and winter)(Fell et al., 2014).

1.3. Physiological processes

1.3.1. At the cellular level: neurotransmission and hormonal function

Endorphins secreted in the central and peripheral nervous systems behave as neuromodulators. In the peripheral nervous system, endorphins bind to both pre- and post-synaptic membrane receptors and reduce interneural signal transmission (Goldstein, 1976; Sprouse-Blum et al., 2010), especially that of substance P, a nociceptive neurotransmitter. In the central nervous system, endorphins are involved in the descending regulation of pain, by inhibiting the release of GABA, resulting in abundant release of dopamine (Devine et al., 1993).

Endorphins are also synthesized by the pituitary gland (which sits outside the blood-brain barrier), and are released into the circulatory system in the same way as hormones (Li et al., 1976). Endorphins released in this way circulate through the whole body and their action is similar to that of exogenous opioids (e.g. morphine) in nociception/analgesia (Dickenson & Suzuki, 2005; Zöllner & Stein, 2007).

1.3.2. At the systemic level: changes in the sympathetic/parasympathetic balance

Homeostasis is a dynamic equilibrium which keeps the body maximally functional in various situations. The autonomic nervous system is divided into two sub-systems with opposite effects on homeostasis. On one hand, the sympathetic nervous system regulates the adaptive response to stress - the so-called "fight-or-flight response"(Jansen et al., 1995), preparing the body to react to threatening situations. On the other hand, the parasympathetic nervous system promotes "rest-and-digest" activities (McCorry, 2007). The functional interaction between the sympathetic and the parasympathetic nervous systems works to return the body to the required state of homeostasis.

The role of endogenous opiates in interaction with the autonomous system has been exhaustively described in a

review by Holaday (1983). This review shows a dense population of opioid receptors in the hypothalamus, hypophysis, brainstem, and in proximity to cardiovascular centers, which is a strong indicator of the role of endogenous opioids in the balance between sympathetic and parasympathetic systems. Endorphins suppress sympathetic nerve activity in a dose-dependent way (Egawa et al., 1993; Wong & Shan, 2001), as well as it stimulate parasympathetic activity (Haddad et al., 1986).

1.4. Functional outcomes

1.4.1. Pain management

Pain is defined by the International Association for the Study of Pain as an "unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage". It is a vital function of the nervous system to provide a warning signal and trigger a response from the individual experiencing the pain. This signal is carried by nerve fibers from the location of the injury, through the spinal cord and to the brain where it is processed and interpreted. The perception of pain depends on many factors including one's individual pain matrix and as a result, is always a subjective experience.

The human body has a system to decrease the pain sensation after the warning information has been processed (Millan, 2002; Ossipov, 2012; Ossipov et al., 2010, 2014). In this system, endogenous opioids play a preponderant role both by reducing ascending transmission of the nociceptive message and by descending inhibition from the brain to the spinal cord (Figure 1). At the peripheral level, endogenous opioids reduce the transmission of nociceptive impulses (Nagi et al., 2015). Descending modulations of pain arise from multiple areas including the somatosensory cortex, the amygdala, and the hypothalamus, and are projected into the periaqueductal grey (PAG). The PAG then projects onto the parabrachial nucleus, locus coeruleus and medulla, and then onto the spinal or medullary dorsal horns. When involved in this descending modulation, endogenous opioids act by reducing interneural signal transmission of the nociceptive message (Sprouse-Blum et al., 2010) and by inhibiting the release of GABA, thus resulting in abundant release of dopamine. Dopamine is a main actor in the feelings of pleasure, reward and euphoria and as such modulates the perception of pain, especially its affective and motivational aspects.

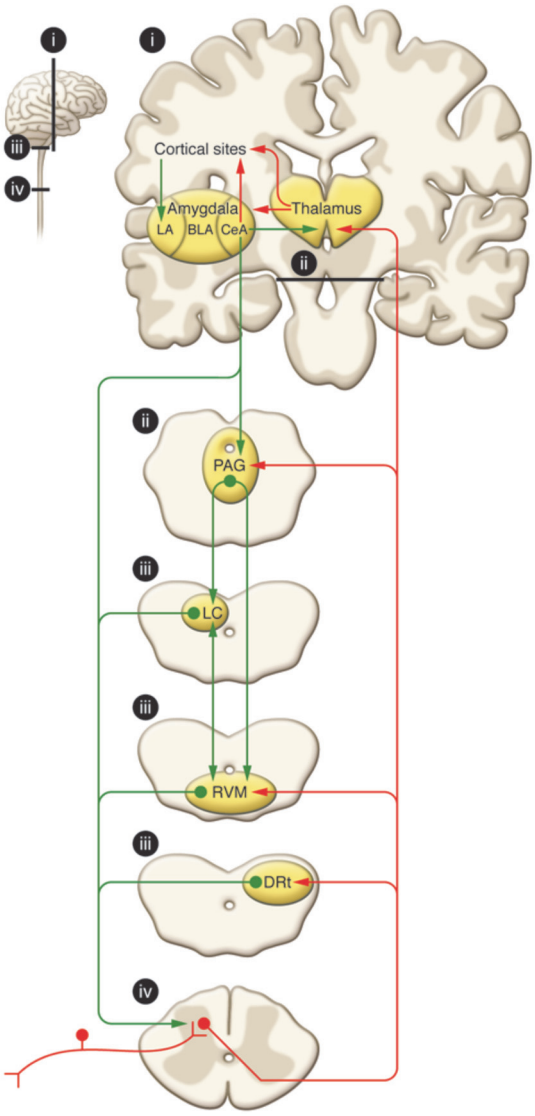

Figure 1. Schematic representation of pain modularity circuitry from Ossipov et al. (2010).
Ascending (red) and descending (green) tracts are shown schematically. Areas labeled "i–iv" in the small diagram correspond with labeled details of the larger diagram. BLA = basolateral amygdala; CeA = central nucleus of the amygdala; DRt = dorsal reticular nucleus; LA = lateral amygdala; LC = locus coeruleus; RVM: rostral ventromedial medulla; PAG = periaqueductal gray region.

1.4.2. Stress and mood regulation

During the normal reaction to stress, the secretion of corticotropin-releasing hormone (CRH) stimulates POMC to release β-endorphin, which helps coping with pain and its emotional response (Hsu et al., 2013). However, prolonged stress leads to a gradual decrease of the peptide and β-endorphin levels over time.

Relationship between endorphin levels and several mood-related conditions have been found. For example, decreased levels of endorphins are found in populations suffering from anxiety and Post-traumatic-stress disorder (PTSD), especially combat-related PTSD in soldiers (Hoffman et al., 1989). Studies conducted in human and animals suggest a link between pathophysiology of major depressive disorder (MDD) and β-endorphin, with individuals suffering from MDD

having lower levels of β-endorphins compared to healthy people (Hegadoren et al., 2009). Administration of opioid agonists is successfully used for therapeutic benefits to relieve anxiety and depression (for a review, see Tenore, 2008).

Several mechanisms by which endorphins are involved in mood regulation have been identified. Endorphins regulate stress-coping strategies by interaction with the hypothalamic-pituary-adrenal (HPA) axis. They modulate hedonia and feelings of reward and satisfaction by interacting with the serotoninergic (Merenlender-Wagner et al., 2009; Zangen et al., 1999) and dopaminergic systems (Roth-Deri et al., 2008). These aspects are found to be strongly affected in MDD patients. The interaction between β-endorphin and dopamine would be bi-directional, with neuronal effects of β-endorphin occurring both downstream and upstream to the dopaminergic synapse in the NAcc (Steinman et al., 2009; Berkley et al., 1993).

1.4.3. Sleep induction

Although "Morphine", the most famous opioid was named after the sleep god Morpheus, the mechanisms by which opioids induce sleep are sparsely investigated and described in the literature.

Endorphins have anticholinergic properties. Indeed, the rate of liberation of acetylcholine is significantly higher during wakefulness and Rapid Eye Movement sleep as compared to deep sleep (Gadea-Ciria et al., 1973; Jasper & Tessier, 1971), and this liberation is regulated by the endogenous opioid system (Lapchak et al., 1989). This mechanism is part of the more global modulatory action of endorphins in the balance between sympathetic/parasympathetic activations. This whole modulating action (described in section 1.3.2.) *per se* promotes sleep induction.

The sleep-inducing effect of endorphins may also be due to their action on the ventrolateral preoptic nucleus (VLPO), a part of the brain that plays an important role in sleep and wakefulness (Sherin et al., 1996). In animals, high doses of morphine seem to induce sleep through the opioidergic projection to the VLPO (Greco et al., 2008; Tissot, 1980).

Pain, stress and (lack of) sleep are closely linked with interactions in all directions (Abell et al., 2016; Gatchel et al., 2007; Harvey, 2002; Leproult et al., 1997; Moldofsky, 2001). Dysfunction in one area negatively impacts the other two, just as improvement in any one has a beneficial effect on the function of the others.

1.4.4. Neuroplasticity

People that suffer from chronic stress (Conrad, 2008; Mizoguchi et al., 2001), sleep deprivation (Leproult et al., 1997)/chronic insomnia (Abell et al., 2016), and chronic pain (for example: chronic migraine(Peres, 2001); chronic back pain (Vachon-Presseau et al., 2013), temporomandibular disorders (Korszun et al., 2002)) have higher basal levels of glucocorticoids than non-sufferers.

Amongst the damage that continued activation of HPA axis on the body can inflict, prolonged exposure to glucocorticoids harms the brain. The impairing effect of glucocorticoids on neuroplasticity has been shown at the molecular (Foy et al., 1987; Kim & Yoon, 1998), cellular (Magarinos et al., 1997; Schoenfeld & Gould, 2012) and structural levels (Bremner, 1999; Maleki et al., 2012).

As described above, endorphins have analgesic effects (1.4.1.), modify the sympathetic/parasympathetic balance in favor of a restful state (1.3.2), mediate the stress response (1.4.2) and promote sleep (1.4). As such, endorphins contribute to restore the natural conditions improving neuroplasticity. In addition, interactions between the serotonergic and endorphinic systems are well established (Zangen et al., 1999), and serotonin leads to an increase in neuroplasticity (Ming & Song, 2005; Santarelli, 2004). Finally, endorphins have been the focus of research on neurogenesis in recent studies. *In vitro* studies have shown that endorphins and the activation of endorphins' target receptors increase proliferation of hippocampal progenitors (Persson, Thorlin, Bull, & Eriksson, 2003), while blocking target receptors decreases proliferation (Persson, Thorlin, Bull, Zarnegar, et al., 2003). Koehl et al. (2008) tested the effect of exercise on wild-type and β-endorphin-deficient mice. Their results showed that a lack of β-endorphin in deficient mice completely blocked the running-induced increase in cell proliferation in β-endorphin-deficient runner mice compared to wild-type mice, which shows that β-endorphin released by exercise in wild-type mice is involved in their increased cell proliferation.

2. Millimeter wave therapies

2.1. Historical background

Millimeter Wave (MMW) therapy was developed in the 1970s, in the former Eastern-Bloc countries, at the intersection of biophysics, radio electronics and medicine. Teams of researchers conducted various experiments on the biological effects of MMW exposure and found painkilling results (Betskii & Lebedeva, 2004). At the time, this necessitated the use of huge machines in dedicated rooms at a center people were obliged to visit to receive their treatment. In Eastern Europe, more than 3 million patients received MMW therapy for various conditions, in about 1000 centers (Pakhomov & Murthy, 2000).

However, the cost and bulk of such devices made them inconvenient for therapeutic use and precluded any ambulatory use. Their use was mostly empirical and no clear scientific explanation of the mechanism of action was identified. For these reasons, as well as the development of improved pharmaceutical solutions, MMW therapy stopped being used as a treatment of first intent, or even as an alternative to chemical medication.

After the collapse of the Eastern Bloc, several research teams kept studying MMW therapy for different applications, such as wound healing (Korpan & Saradeth,

1995), diabetes (Moazezi et al., 2008b), cancer (Pakomov et al., 1998) and the treatment of chronic pains (Usichenko et al., 2006). Since then, the action of MMW on organic tissues as well as the physiological mechanisms by which they provoke analgesic effects have been better understood.

2.2. Functional principle

There are various sensory receptors situated in the superficial layers of the skin, the face, and the palms of the hands and feet being more densely innervated than others. Activation of these receptors sends signals from peripheral nerves via the spinal cord to the brain which processes the information. Endorphins are released centrally in response to sensitive peripheral stimulations, generally as a pain coping mechanism, even though pain is not essential to trigger this response, as described in section 1.3.

Penetration depth of electromagnetic waves depends on their frequency such that their penetration depth decreases as their frequency increases (**Figure 2**). Millimeter waves lie within the frequency range of 30–300 GHz and do not penetrate skin beyond a fraction of a millimeter (0.3 – 0.5mm), i.e. the depth of cutaneous sensory receptors. During MMW therapy, skin is exposed to waves that carry enough energy to activate sensory receptors, i.e. thermal endings, but not enough to cause any injury. Normally, "thermal background noise" generates ion fluxes and local currents capable of stimulating voltage-sensitive receptors, and especially voltage-gated calcium channels (VGcc). The twist of the 4 intramembrane chains of VGcc opens the channel like an optical diaphragm. The result is a net influx of calcium, leading by itself to trigger physiological activities in a non-thermal way, e.g. release of neurotransmitters. This painless nerve stimulation leads to an increase in the secretion of intracerebral endorphins, which have hypoalgesic effects.

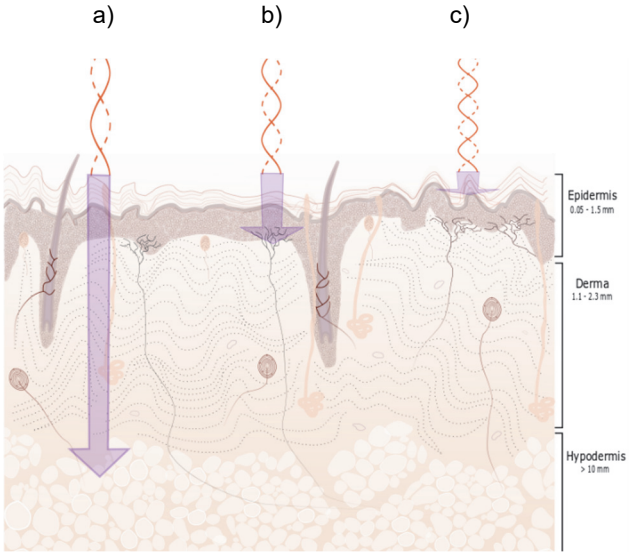

Figure 2. Skin exposed to waves frequency (a) lower than 30GHz, (b) 61GHz, (c) higher than 300GHz. Purple arrows represent energy absorption by the skin.

Hence, a series of of experiments conducted by Radzievsky and colleagues from Temple University (Pennsylvania, USA), contributed to better understand the mechanism of MMW therapy. After demonstrating the suppression of pain sensation in humans exposed to MMWs (Radzievsky et al., 1999) in a double-blind cross-over study, they showed that MMW-induced hypoalgesia is produced by the release of the endogenous opioids, by blocking this effect with naloxone, an opioid receptor antagonist (Rojavin, 2000). They also demonstrated that the effect depends on the innervation density of the area exposed, the most innervated areas leading to the best results (Radzievsky et al., 2000). Further investigations confirmed the role of the peripheral nervous system when deafferentation of the area exposed to MMW totally abolished systemic hypoalgesia (Radzievsky et al., 2001). Lastly, they showed that hypoalgesic effects can't be replicated with laser-increased temperature alone (Radzievsky et al., 2004), are power- and frequency-dependant, and that different types of pain do not respond in the same way to MMW therapy: a single exposure to MMW (15 min, frequency of 61.22 GHz and average incident power of 13.3 mW/cm^2) significantly reduced pain sensitivity in the models of acute and chronic non-neuropathic pain, but 10 exposures were necessary in a model of neuropathic pain in their study (Radzievsky et al., 2008).

2.3. Scientific and clinical data

After the collapse of the Eastern Bloc, worldwide research teams continued to investigate MMW therapies in order to provide an understanding of the mechanisms involved in MMW-induced hypoalgesia in controlled experiments. Several articles have been published reviewing the "medical applications of MMWs"(Rojavin et al., 1998), their effects in "biology and medicine"(Betskii & Lebedeva, 2004), "in interaction with the human body"(Zhadobov et al., 2011), "for pain therapy"(Usichenko et al., 2006). These reviews, as well as other or later published articles, support the effectiveness of MMW therapies, in the absence of associated side effects, used either at *loco dolenti* or by dermal exposure remote from the pain's point of origin.

In **acute pain**, Radzievsky et al.(1999) and Partyla et al. (2017) both ran randomized, placebo-controled trials with healthy participants using the cold pressure test, and showed hypoalgesia effects following exposure to MMW tested compared to sham exposure.

The effects of MMW have been shown in **post-operative pain**. Patients with **postoperative septic wounds** exposed to 30-minutes sessions of MMW showed 1.8 times more rapid wound clearance, 1.7 times earlier onset of wound granulation and 1.8 times faster onset of epithelization, and the average daily decrease of wound surface area in the treated patients was twice that of subjects exposed to a sham device (Korpan & Saradeth, 1995). Pradahn, et al. (2014) carried out a study with 120 patients who had to undergo a **cesarean section**. They showed that for 30 patients exposed to MMW for 3 consecutive treatment sessions of

30 minutes, over 3 days, the score of intensity of postoperative pain and the postoperative morbidity were significantly reduced, while postoperative mobility was increased, compared to the 90 patients of a control group.

Regarding neuropathic pain, Moazezi et al. (2008) tested patients with Diabetic Sensorimotor Polyneuropathy and observed a significantly stronger decrease in the Toronto Clinical Neuropathy Score (TCNS) for MMW-exposed patients compared to sham-exposed patients. Megdiatov et al. (1995) investigated **trigeminal nerve neuralgia.** Patients were exposed to either MMW (27 patients) at a frequency of 42.2 GHz, at a power of 10mW/cm^2 for 15 minutes, applied to areas where branches of the affected trigeminal nerve approach skin, or to a sham device (25 patients), for 10 sessions in each condition. Nineteen of the 27 patients treated with MMW reported a decrease of the incidence and severity of pain attacks as opposed to 4/25 in the sham group.

Benefits of MMW exposure have been shown in **joint pain.** Bakaliuk, et al. (1998) showed that repeated sessions of 30 minutes on patients with **osteoarthrosis** led to reduced pain intensity, expressed as a joint pain index, diminished joint stiffness and lower level of C-reactive protein compared to patients with treatment as usual. Similar effects were shown in patients with **rheumatoid arthritis** (Usichenko et al., 2003) and patients with **diffuse connective tissue diseases** (Usichenko & Herget, 2003).

Debouzy et al. (2021; 2022) published case reports relating to the beneficial effects of exposure to MMW, namely hypoalgesia and functional recovery after surgical or sports trauma, pain and physical rehabilitation on chronic pancreatitis, pain and rehabilitation in fibromyalgia.

The medical literature is rich in studies showing the hypoalgesic effects of millimetre waves used under the same conditions as the Remedee band. These results, published as provocation studies, clinical trials or case reports, show good efficacy on several types of pain.

2.4. Remedee One: a technological breakthrough

Remedee Labs is developing technology resulting from two lines of progress: the identification of a biological mechanism of MMW action supported by scientific and clinical research, and a major step forward in the technology necessary to manufacture integrated hyper-frequency components.

Until the beginning of the 21st century, the size of emitters and power supplies precluded any extensive clinical development, especially if ambulatory use was desired. Recently, several applications using frequencies in the tens of GHz range have been developed and widely integrated in products and services. Communication technology has taken advantage of these increases in frequency, as higher bandwidth corresponds to higher data transfer rates. WiFi for instance, which has long been used at 2.4GHz and 5GHz, has recently adopted the 802.11ad standard using frequencies from 57GHz to 70GHz. Wireless backhaul and point-to-point communication systems have also made more and more use of the 60GHz band and benefit from the very high data rates it provides.

Radar has also benefitted from the increase in frequency, as shorter wavelengths allow for the detection of smaller objects and require smaller antennas. Long-range automotive radars now run at 77GHz and are used for cruise-control applications. New applications using miniaturized, personal radars, have been recently developed and integrated in consumer products, such as the Pixel 4 smartphone that uses the Google Soli radar technology as user gesture detection. Other personal radars use the high resolution offered by the small wavelengths to offer new functions such as contactless respiration rate monitoring or even contactless heartrate measurement for newborns.

These new applications come with the benefit of higher system integration and reduced device size, offered by the low power consumption of miniaturized integrated circuits. Microelectronics manufacturing technologies also drive down the costs of the components by several orders of magnitudes. Basic components such as amplifiers or oscillators in the tens of GHz range, that used to cost thousands of dollars are now available for just a few dollars, and are easier and cheaper to build into systems.

Such progress in technologies supporting frequencies and powers necessary for therapeutic use have enabled Remedee Labs to develop its patented Microelectronic Endorphin Trigger (MEET) module. This miniaturized module has been integrated into a wearable device – a wristband called "Remedee One" - making endorphin-stimulation therapy accessible for safe and efficient personal healthcare use.

3. Demonstration of safety, hypoalgesic and parasympathetic effects

3.1. Safety: Analysis of the literature

The safety of exposure to MMWs is well established and has been documented in many preclinical animal studies and clinical studies in human. For the electromagnetic spectrum ranging from 0 to 300 GHz, no study showed any cumulative or long-term effect (Cardis et al., 2013).

Due to the superficial penetration of electromagnetic fields in the millimetric band, specific attention was paid to possible cutaneous and ophthalmological effects. It was of primary importance to determine what power density was perceptible, and that which would cause lesions. It was found in monkeys that energy levels as high as 5J/cm^2 were necessary to induce ocular lesions, while perception occurred for a few mJ/cm^2 (Chalfin et al., 2002; Gandhi & Riazi, 1986; Kues et al., 1999). Similarly, a factor of a 100 was

identified between cutaneous perception/pain and tissular lesions (Debouzy et al., 2007). *In vitro*, very high exposure levels (770 W/kg) are required to induce an inflammatory response (release of interleukin IL1β), which exceeds by several orders of magnitude those allowing perception *in vivo* (Novoselova & Fesenko, 2002). Definitive evidence was drawn from human experiments testing the innocuity of the Active Denial System (ADS), a non-lethal weapon used for crowd dispersion in the USA. The specificity of ADS, which used MMW at significantly higher power levels than those used in the Remedee band, is to provoke pain sensations in order to make people flee, without any tissue damage (Konno et al., s. d.).

3.2. Hypoalgesia and parasympathetic effects: clinical trial

Remedee Labs' first clinical study "Remedee 0" was a randomized, placebo controlled, cross-over study. The aim was to assess the existence of hypoalgesic and parasympathetic effects of Remedee's millimeter waves emitting device when applied to the wrist - a densely innervated area of the body - of healthy volunteers.

Ten healthy participants had the palmar side of their wrist exposed to MMW (61.25 GHz, 17mW/cm^2) for 30 minutes, 1h, & 1h30, and 30 minutes of sham exposure. Experimental pain was induced after the exposure sessions with the Cold Pressor Test, and pain threshold and pain tolerance values were compared to that of the sham condition. Participants' heart rate and blood pressure were measured before and after exposures. Finally, innocuity of the exposure system was controlled with a pre-post exposure visual examination scale and skin temperature measured by a thermal camera. Exposure to 30 minutes, but not 1h or 1h30, of MMW led to significant increases in pain thresholds compared to the sham condition, but no increase of pain tolerance. All conditions led to decreased heart rate, while no change in blood pressure was observed. No change in skin state or temperature was observed for any of the conditions. MMW applied on the inner part of the wrist diminish pain sensations more effectively than placebo, and seem to increase parasympathetic activities, while remaining innocuous. These results justify building a miniaturized MMW emission system to be worn on the wrist that would provide access to ambulatory MMW therapy for pain management. The study is published in the journal Electromagnetic Biology and Medecine (Minier et al., in press).

Conclusion

Remedee Labs is developing a technology allowing neuromodulation via millimeter wave stimulation of the peripheral nervous system. The central secretion of various neurotransmitters elicits hypoalgesic effects regardless of the anatomical origin of the pain.

Over the past three years, our multidisciplinary team, comprised of experts in electronic engineering, software development, machine learning, design, neurophysiology and medicine have developed an easy-to-wear, watch-like device that stimulates one of the most innervated location of the body to maximize endorphin stimulation.

To ensure the proper and effective use of our device, the first step was to ensure its safety. A rigorous analysis of the literature, including fundamental studies conducted on animals and the assessment of the American Active Denial System on human volunteers, showed the absence of noxious effects of the exposure to MMWs. In addition, no scientific study or international norm (IEEE, ICNIRP) reports any long-term effect from electromagnetic millimeter wave exposures. Finally, the harmlessness of our device was confirmed in a clinical trial.

Endorphin stimulation can have several other significant applications beyond pain management, including promoting well-being, alleviating sleeplessness, and managing chronic stress. Moreover, we believe that the Remedee band can have a skateboarding effect, alleviating patients' pain in their daily life, while they prepare to the multidisciplinary change required for their condition (see Remedee Labs White Paper – Volume II).

References

Abell, J. G., Shipley, M. J., Ferrie, J. E., Kivimäki, M., & Kumari, M. (2016). Recurrent short sleep, chronic insomnia symptoms and salivary cortisol : A 10-year follow-up in the Whitehall II study. *Psychoneuroendocrinology*, *68*, 91-99. https://doi.org/10.1016/j.psyneuen.2016.02.021

Algafly, A. A., & George, K. P. (2007). The effect of cryotherapy on nerve conduction velocity, pain threshold and pain tolerance. *British Journal of Sports Medicine*, *41*(6), 365-369. https://doi.org/10.1136/bjsm.2006.031237

Bakaliuk, T. G., Zoria, L. V., & Pogorila, M. A. (1998). Microwave resonance therapy in primary osteoarthrosis : The pathogenetic validation of its clinical use. *Patologicheskaia fiziologiia i eksperimental'naia terapiia*, *4*, 22-25.

Berkley, K. J., Hubscher, C. H., & Wall, P. D. (1993). Neuronal responses to stimulation of the cervix, uterus, colon, and skin in the rat spinal cord. *Journal of Neurophysiology*, *69*(2), 545-556. https://doi.org/10.1152/jn.1993.69.2.545

Betskii, O., & Lebedeva, N. (2004). Low-intensity millimeter waves in Biology and Medicine. *Clinical application of Bioelectromagnetic Medicine", New-York, USA; Macel De-k Ker. Inc*.

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006a). Survey of chronic pain in Europe : Prevalence, impact on daily life, and treatment. *European Journal of Pain*, *10*(4), 287-287. https://doi.org/10.1016/j.ejpain.2005.06.009

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006b). Survey of chronic pain in Europe : Prevalence, impact on daily life, and treatment. *European Journal of Pain*, *10*(4), 287-287. https://doi.org/10.1016/j.ejpain.2005.06.009

Bremner, J. D. (1999). Alterations in brain structure and function associated with post-traumatic stress disorder. *Seminars in Clinical Neuropsychiatry*, *4*(4), 249-255. https://doi.org/10.153/SCNP00400249

Cardis, E., Dore, J.-F., Marc-Vergnes, J.-P., Agnani, J.-B., Bruguiere, P., Crouzier, D., Debaz, J., Debuire, B., Deltour, I., LE Drean, Y., Ledoigt, G., Letertre, T., Marchand, D., Massardier-Pilonchery, A., Nadi, M., Pereira De Vasconcelos, A., Hours, M., Fite, J., Merckel, O., … Saddoki, S. (2013). *Radiofrequency and health. Expertise update. Opinion of the ANSES. Collective expertise report* (INIS-FR--14-0365; Numéro INIS-FR--14-0365). Agence nationale de securite sanitaire de l'alimentation. http://inis.iaea.org/Search/search.aspx?orig_q=RN:45071163

Chalfin, S., D'Andrea, J. A., Comeau, P. D., Belt, M. E., & Hatcher, D. J. (2002). Millimeter wave absorption in the nonhuman primate eye at 35 GHz and 94 GHz. *Health Physics*, *83*(1), Art. 1.

Chen, H., Noble, F., Roques, B. P., & Fournié-Zaluski, M.-C. (2001). Long Lasting Antinociceptive Properties of Enkephalin Degrading Enzyme (NEP and APN) Inhibitor Prodrugs. *Journal of Medicinal Chemistry*, *44*(21), 3523-3530. https://doi.org/10.1021/jm0102248

Cogan, R., & Spinnato, J. A. (1986). Pain and discomfort thresholds in late pregnancy. *Pain*, *27*(1), 63-68. https://doi.org/10.1016/0304-3959(86)90223-X

Conrad, C. D. (2008). Chronic Stress-Induced Hippocampal Vulnerability : The Glucocorticoid Vulnerability Hypothesis. *Reviews in the neurosciences*, *19*(6), 395-411.

Debouzy, J.-C., Crouzier, D., Dabouis, V., Malabiau, R., Bachelet, C., & Perrin, A. (2007a). Effets biologiques des rayonnements millimétriques (94 GHz). Quelles conséquences à long terme ? *Pathologie Biologie*, *55*(5), 246-255. https://doi.org/10.1016/j.patbio.2006.02.006

Debouzy, J.-C., Crouzier, D., Rech, S., & Bachelet Campagne, C. (2021). Low Level Millimetric Waves Exposure in Post Traumatic Surgery Pain Relief : A 2 Cases Report. *Biomedical Journal of Scientific & Technical Research*. 34(1), 2 6362-26365

Debouzy, J-C., Minier, L., Pierre, V., Del Vechhio, F., Nouvellon, R., & Crouzier, D. (2022). Can local millimetric waves exposure be helpful for inflammatory rheumatism care? A 4 case report on rheumatoid arthritis, and ankylosing spondylitis. *Global Journal of Research Analysis*. 11(7), 1-4

Devine, D., P., Leone, P., Pocok, D., Wise, R., A., & Leone, P. (1993). Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release : In vivo microdialysis studies. *Journal of Pharmacology and Experimental Therapeutics*, *266*(3), 1236-1246.

Dickenson, A. H., & Suzuki, R. (2005). Opioids in neuropathic pain : Clues from animal studies. *European Journal of Pain*, *9*(2), 113-116. https://doi.org/10.1016/j.ejpain.2004.05.004

Egawa, M., Yoshimatsu, H., & Bray, G. A. (1993). Effect of beta-endorphin on sympathetic nerve activity to interscapular brown adipose tissue. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *264*(1), Art. 1. https://doi.org/10.1152/ajpregu.1993.264.1.R109

Facchinetti, F., Sandrini, G., Petraglia, F., Alfonsi, E., Nappi, G., & Genazzani, A. R. (1984). Concomitant increase in nociceptive flexion reflex threshold and plasma opioids following transcutaneous nerve stimulation. *Pain*, *19*(3), 295-303. https://doi.org/10.1016/0304-3959(84)90006-X

Fell, G. L., Robinson, K. C., Mao, J., Woolf, C. J., & Fisher, D. E. (2014). Skin β-endorphin mediates addiction to ultraviolet light. *Cell*, *157*(7), Art. 7. https://doi.org/10.1016/j.cell.2014.04.032

Foy, M. R., Stanton, M. E., Levine, S., & Thompson, R. F. (1987). Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behavioral and Neural Biology*, *48*(1), 138-149. https://doi.org/10.1016/S0163-1047(87)90664-9

Gadea-Ciria, M., Stabler, H., Lloyd, K. G., & Bartholini, G. (1973). Acetylcholine Release within the Cat Striatum during the Sleep–Wakefulness Cycle. *Nature*, *243*(5409), Art. 5409. https://doi.org/10.1038/243518a0

Gandhi, O. P., & Riazi, A. (1986). Absorption of Millimeter Waves by Human Beings and its Biological Implications. *IEEE Transactions on Microwave Theory and Techniques*, *34*(2), 228-235. https://doi.org/10.1109/TMTT.1986.1133316

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain : Scientific advances and future directions. *Psychological Bulletin*, *133*(4), 581-624. https://doi.org/10.1037/0033-2909.133.4.581

Goldfarb, A. H., & Jamurtas, A. Z. (1997). β-Endorphin response to exercise. *Sports Medicine*, *24*((1)), 13-18.

Goldstein, A. (1976). Opioid Peptides (Endorphins) in Pituitary and Brain. *Science*, *193*(4258), 1081-1086. JSTOR.

Greco, M.-A., Fuller, P., Jhou, T. C., Martin-Schild, S., Zadina, J. E., Hu, Z., Shiromani, P., & Lu, J. (2008). Opioidergic projections to sleep-active neurons in the ventrolateral preoptic nucleus. *Brain research*, *1245*, 96-107. https://doi.org/10.1016/j.brainres.2008.09.043

Haddad, G. G., Jeng, H. J., & Lai, T. L. (1986). Effect of endorphins on heart rate and blood pressure in adult dogs. *American Journal of Physiology-Heart and Circulatory Physiology*, *250*(5), H796-H805. https://doi.org/10.1152/ajpheart.1986.250.5.H796

Harber, V. J., & Sutton, J. R. (1984). Endorphins and Exercise. *Sports Medicine*, *1*(2), 154-171. https://doi.org/10.2165/00007256-198401020-00004

Harvey, A. G. (2002). A cognitive model of insomnia. *Behaviour Research and Therapy*, *40*(8), 869-893. https://doi.org/10.1016/S0005-7967(01)00061-4

Hegadoren, K. M., O'Donnell, T., Lanius, R., Coupland, N. J., & Lacaze-Masmonteil, N. (2009). The role of β-endorphin in the pathophysiology of major depression. *Neuropeptides*, *43*(5), 341-353. https://doi.org/10.1016/j.npep.2009.06.004

Hersh, L. B. (1985). Characterization of Membrane-Bound Aminopeptidases from Rat Brain : Identification of the Enkephalin-Degrading Aminopeptidase. *Journal of Neurochemistry*, *44*(5), 1427-1435. https://doi.org/10.1111/j.1471-4159.1985.tb08779.x

Hoffman, L., Watson, P. B., Wilson, G., & Montgomery, J. (1989). Low plasma β-endorphin in post-traumatic stress disorder. *Australian & New Zealand Journal of Psychiatry*, *23*(2), Art. 2.

Holaday, J. W. (1983). Cardiovascular Effects of Endogenous Opiate Systems. *Annual Review of Pharmacology and Toxicology*, *23*(1), 541-541. https://doi.org/10.1146/annurev.pa.23.040183.002545

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Wang, H., Ni, L., Walker, S. J., Mickey, B. J., Korycinski, S. T., Koeppe, R. A., Crocker, J. K., Langenecker, S. A., & Zubieta, J.-K. (2013). Response of the μ-opioid system to social rejection and acceptance. *Molecular Psychiatry*, *18*(11), 1211-1217. https://doi.org/10.1038/mp.2013.96

Jansen, A. S. P., Nguyen, X. V., Karpitskiy, V., Mettenleiter, T. C., & Loewy, A. D. (1995). Central Command Neurons of the Sympathetic Nervous System : Basis of the Fight-or-Flight Response. *Science*, *270*(5236), 644-646. https://doi.org/10.1126/science.270.5236.644

Jasper, H. H., & Tessier, J. (1971). Acetylcholine Liberation from Cerebral Cortex during Paradoxical (REM) Sleep. *Science*, *172*(3983), 601-602. https://doi.org/10.1126/science.172.3983.601

Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., & Dworkin, R. H. (2010). The Prevalence of Chronic Pain in United States Adults : Results of an Internet-Based Survey. *The Journal of Pain*, *11*(11), 1230-1239. https://doi.org/10.1016/j.jpain.2010.07.002

Jussila, A., Huotari-Orava, R., Ylianttila, L., Partonen, T., & Snellman, E. (2016). Narrow-band ultraviolet B radiation induces the expression of β-endorphin in human skin in vivo. *Journal of Photochemistry and Photobiology B: Biology*, *155*, 104-108. https://doi.org/10.1016/j.jphotobiol.2016.01.007

Kaada, B., & Torsteinbø, O. (1989). Increase of plasma beta-endorphins in connective tissue massage. *General Pharmacology*, *20*(4), 487-489. https://doi.org/10.1016/0306-3623(89)90200-0

Kim, J., & Yoon, K. (1998). Stress : Metaplastic effects in the hippocampus—ScienceDirect. *Trends in Neurosciences*, *21*(12), 505-509. https://doi.org/10.1016/S0166-2236(98)01322-8

Koehl, M., Meerlo, P., Gonzales, D., Rontal, A., Turek, F. W., & Abrous, D. N. (2008). Exercise-induced promotion of hippocampal cell proliferation requires β-endorphin. *The FASEB Journal*, *22*(7), 2253-2262. https://doi.org/10.1096/fj.07-099101

Konno, T., Hanazawa, M., Watanabe, S., Taki, M., & Shirai, H. (s. d.). *A study of warmth sensation produced by millimeter wave exposure*. 4.

Korpan, N. N., & Saradeth, T. (1995). Clinical effects of continuous microwave for postoperative septic wound treatment : A double-blind controlled trial. *The American journal of surgery*, *170*(3), Art. 3.

Korszun, A., Young, E. A., Singer, K., Carlson, N. E., Brown, M. B., & Crofford, L. (2002). Basal circadian cortisol secretion in women with temporomandibular disorders. *Journal of Dental Research*, 279-283.

Kosterlitz, H. W., & Hughes, J. (1977). Opiate Receptors and Endogenous Opioid Peptides in Tolerance and Dependence. In M. M. Gross (Éd.), *Alcohol Intoxication and Withdrawal—IIIb : Studies in Alcohol Dependence* (p. 141-154). Springer US. https://doi.org/10.1007/978-1-4615-9038-5_10

Kubota, K., Kurabayashi, H., Tamura, K., Kawada, E., Tamura, J., & Shirakura, T. (1992). A transient rise in plasma β-endorphin after a traditional 47°C hot-spring bath in Kusatsu-spa, Japan. *Life Sciences*, *51*(24), 1877-1880. https://doi.org/10.1016/0024-3205(92)90039-R

Kues, H. A., D'Anna, S. A., Osiander, R., Green, W. R., & Monahan, J. C. (1999). Absence of ocular effects after either single or repeated exposure to 10 mW/cm2 from a 60 GHz CW source. *Bioelectromagnetics*, *20*(8), 463-473. https://doi.org/10.1002/(SICI)1521-186X(199912)20:8<463::AID-BEM1>3.0.CO;2-T

Lapchak, P. A., Araujo, D. M., & Collier, B. (1989). Regulation of endogenous acetylcholine release from mammalian brain slices by opiate receptors : Hippocampus, striatum and cerebral cortex of guinea-pig and rat. *Neuroscience*, *31*(2), 313-325. https://doi.org/10.1016/0306-4522(89)90376-X

Lee, J.-S., Kim, S.-G., Kim, H.-K., Baek, S.-Y., & Kim, C.-M. (2012). Acute Effects of Capsaicin on Proopioimelanocortin mRNA Levels in the Arcuate Nucleus of Sprague-Dawley Rats. *Psychiatry Investigation*, *9*(2), 187-190. https://doi.org/10.4306/pi.2012.9.2.187

Leproult, R., Copinschi, G., Buxton, O., & Van Cauter, E. (1997). Sleep Loss Results in an Elevation of Cortisol Levels the Next Evening. *Sleep*, *20*(10), 865-870. https://doi.org/10.1093/sleep/20.10.865

Li, C. H., Chung, D., & Doneen, B. A. (1976). Isolation, characterization and opiate activity of β-endorphin from human pituitary glands. *Biochemical and Biophysical Research Communications*, *72*(4), 1542-1547. https://doi.org/10.1016/S0006-291X(76)80189-1

Loh, H. H., Tseng, L. F., Wei, E., & Li, C. H. (1976). Beta-endorphin is a potent analgesic agent. *Proceedings of the National Academy of Sciences*, *73*(8), Art. 8.

M. A. Rojavin, M. C. Z., A. A. Radzievsky, A. Cowan. (2000). Pain relief caused by millimeter waves in mice : Results of cold water tail flick tests. *International Journal of Radiation Biology*, *76*(4), 575-579. https://doi.org/10.1080/095530000138592

Magarinos, A. M., Verdugo, J. M. G., & McEwen, B. S. (1997). Chronic stress alters synaptic terminal structure in hippocampus. *Proceedings of the National Academy of Sciences*, *94*(25), 14002-14008. https://doi.org/10.1073/pnas.94.25.14002

Mains, R. E., Eipper, B. A., & Ling, N. (1977). Common precursor to corticotropins and endorphins. *Proceedings of the National Academy of Sciences*, *74*(7), 3014-3018. https://doi.org/10.1073/pnas.74.7.3014

Maleki, N., Becerra, L., Brawn, J., Bigal, M., Burstein, R., & Borsook, D. (2012). Concurrent functional and structural cortical alterations in migraine. *Cephalalgia: An International Journal of Headache*, *32*(8), 607-620. https://doi.org/10.1177/0333102412445622

McCorry, L. K. (2007). Physiology of the Autonomic Nervous System. *American Journal of Pharmaceutical Education*, *71*(4). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1959222/

Megdiatov, R. S., Vasilenko, A. M., Arkhipov, V. V., Kislov, Vy., & Smirnov, V. F. (1995). *Use of a 'Sharm' therapeutic-diagnostic system in complex therapy of trigeminal nerve neuralgia*. 83-87.

Merenlender-Wagner, A., Dikshtein, Y., & Yadid, G. (s. d.). *The beta-Endorphin Role in Stress-Related Psychiatric Disorders*. 14.

Millan, M. J. (2002). Descending control of pain. *Progress in Neurobiology*, 120.

Ming, G., & Song, H. (2005). ADULT NEUROGENESIS IN THE MAMMALIAN CENTRAL NERVOUS SYSTEM. *Annual Review of Neuroscience*, *28*(1), 223-250. https://doi.org/10.1146/annurev.neuro.28.051804.101459

Mizoguchi, K., Yuzurihara, M., Ishige, A., Sasaki, H., Chui, D.-H., & Tabira, T. (2001). Chronic stress differentially regulates glucocorticoid negative feedback response in rats. *Psychoneuroendocrinology*, *26*(5), 443-459. https://doi.org/10.1016/S0306-4530(01)00004-X

Moazezi, Z., Hojjati, S. M. M., & Ayrapetyan, S. (2008a). *Low Intensity Millimeter Wave as a Potential Tool in Treatment of Diabetic Sensorymotor Polyneuropathy. 1*, 6.

Moazezi, Z., Hojjati, S. M. M., & Ayrapetyan, S. (2008b). Low-intensity millimeter wave as a potential tool in treatment of diabetic sensorymotor polyneuropathy. *Int. Dent. Med. Disord*, *1*, 50-55.

Moldofsky, H. (2001). Sleep and pain. *Sleep Medicine Reviews*, *5*(5), 385-396. https://doi.org/10.1053/smrv.2001.0179

Nagi, K., Charfi, I., & Pineyro, G. (2015). Kir3 channels undergo arrestin-dependant internalization following delta opioid receptor activation. *Cellular and Molecular Life Sciences*, *72*(18), 3543-3557. https://doi.org/10.1007/s00018-015-1899-x

Novoselova, E., & Fesenko, E. E. (2002). Immunomodulating effetcs of EM Waves in EMF and human health. *Fundamental and Applied Research*.

Ossipov, M. H. (2012). The Perception and Endogenous Modulation of Pain. *Scientifica*, *2012*, 1-25. https://doi.org/10.6064/2012/561761

Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *The Journal of Clinical Investigation*, *120*(11), 3779-3787. https://doi.org/10.1172/JCI43766

Ossipov, M. H., Morimura, K., & Porreca, F. (2014). Descending pain modulation and chronification of pain. *Current opinion in supportive and palliative care*, *8*(2), 143-151. https://doi.org/10.1097/SPC.0000000000000055

Pakhomov, A. G., & Murthy, P. R. (2000). Low-intensity millimeter waves as a novel therapeutic modality. *IEEE transactions on plasma science*, *28*(1), Art. 1.

Pakomov, A. G., Akyel, Y., Pakhomova, O. N., Stuck, B. E., & Murphy, M. R. (1998). Current state and implications of research on biological effects of millimeter waves : A review of the literature. *Bioelectromagnetics*, *19*(7), 393-413.

Partyla, T., Hacker, H., Edinger, H., Leutzow, B., Lange, J., & Usichenko, T. (2017). Remote Effects of Electromagnetic Millimeter Waves on Experimentally Induced Cold Pain : A Double-Blinded Crossover Investigation in Healthy Volunteers. *Anesthesia & Analgesia*, *124*(3), Art. 3. https://doi.org/10.1213/ANE.0000000000001657

Peres, M. F. P. (2001). Hypothalamic involvement in chronic migraine. *Journal of Neurology, Neurosurgery & Psychiatry*, *71*(6), 747-751. https://doi.org/10.1136/jnnp.71.6.747

Persson, A. I., Thorlin, T., Bull, C., & Eriksson, P. S. (2003). Opioid-induced proliferation through the MAPK pathway in cultures of adult hippocampal progenitors. *Molecular and Cellular Neuroscience*, *23*(3), 360-372. https://doi.org/10.1016/S1044-7431(03)00061-7

Persson, A. I., Thorlin, T., Bull, C., Zarnegar, P., Ekman, R., Terenius, L., & Eriksson, P. S. (2003). Mu- and delta-opioid receptor antagonists decrease proliferation and increase neurogenesis in cultures of rat adult hippocampal progenitors. *European Journal of Neuroscience*, *17*(6), 1159-1172. https://doi.org/10.1046/j.1460-9568.2003.02538.x

Pert, C. B., & Snyder, S. H. (1975). Identification of opiate receptor binding in intact animals. *Life Sciences*, *16*(10), 1623-1634. https://doi.org/10.1016/0024-3205(75)90080-6

Pradhan, M., Shao, Y., & Luo, Y. P. (2014). Millimeter wave therapy for abdominal incision wound : A clinical study. *Asian Journal of Medical Sciences*, *6*(1), 43-48. https://doi.org/10.3126/ajms.v6i1.10311

Radzievsky, A. A., Gordiienko, O. V., Alekseev, S., Szabo, I., Cowan, A., & Ziskin, M. C. (2008). Electromagnetic millimeter wave induced hypoalgesia : Frequency dependence and involvement of endogenous opioids. *Bioelectromagnetics*, *29*(4), 284-295. https://doi.org/10.1002/bem.20389

Radzievsky, A. A., Rojavin, M. A., Cowan, A., Alekseev, S. I., Radzievsky, A. A., & Ziskin, M. C. (2001). Peripheral neural system involvement in hypoalgesic effect of electromagnetic millimeter waves. *Life Sciences*, *68*(10), 1143-1151. https://doi.org/10.1016/S0024-3205(00)01016-X

Radzievsky, A. A., Rojavin, M. A., Cowan, A., Alekseev, S. I., & Ziskin, M. C. (2000). Hypoalgesic effect of millimeter waves in mice : Dependence on the site of exposure. *Life Sciences*, *66*(21), Art. 21. https://doi.org/10.1016/S0024-3205(00)00536-1

Radzievsky, A. A., Rojavin, M. A., Cowan, A., & Ziskin, M. C. (1999). Suppression of pain sensation caused by millimeter waves : A double-blinded, cross-over, prospective human volunteer study. *Anesthesia & Analgesia*, *88*(4), Art. 4.

Radzievsky, A., Gordiienko, O., Cowan, A., Alekseev, S. I., & Ziskin, M. C. (2004). Millimeter-Wave-Induced Hypoalgesia in Mice : Dependence on Type of Experimental Pain. *IEEE Transactions on Plasma Science*, *32*(4), 1634-1643. https://doi.org/10.1109/TPS.2004.830972

Rojavin, M. A., Cowan, A., Radzievsky, A. A., & Ziskin, M. C. (1998). Antipruritic effect of millimeter waves in mice : Evidence for opioid involvement. *Life sciences*, *63*(18), Art. 18.

Roth-Deri, I., Green-Sadan, T., & Yadid, G. (2008). β-Endorphin and drug-induced reward and reinforcement. *Progress in Neurobiology*, *86*(1), 1-21. https://doi.org/10.1016/j.pneurobio.2008.06.003

Santarelli, L. (2004). S8 The Neurobiology of anxiety and depression : Role of serotonin and hippocampal neurogenesis. *Behavioural Pharmacology*, *15*(5), A3.

Schoenfeld, T., & Gould, E. (2012). Stress, Stress Hormones, and Adult Neurogenesis. *Experimental neurology*, *233*(1), 12-21. https://doi.org/10.1016/j.expneurol.2011.01.008

Sherin, J. E., Shiromani, P. J., McCarley, R. W., & Saper, C. B. (1996). Activation of Ventrolateral Preoptic Neurons During Sleep. *Science*, *271*(5246), 216-219. https://doi.org/10.1126/science.271.5246.216

Simon, E. J., Hiller, J. M., & Edelman, I. (1973). Stereospecific Binding of the Potent Narcotic Analgesic [3H]Etorphine to Rat-Brain Homogenate. *Proceedings of the National Academy of Sciences*, *70*(7), 1947-1949. https://doi.org/10.1073/pnas.70.7.1947

Smith, R., Cubis, J., Brinsmead, M., Lewin, T., Singh, B., Owens, P., Chan, E.-C., Hall, C., Adler, R., Lovelock, M., & others. (1990). Mood changes, obstetric experience and alterations in plasma cortisol, beta-endorphin and corticotrophin releasing hormone during pregnancy and the puerperium. *Journal of psychosomatic research*, *34*(1), Art. 1.

Smith, T. H., Hughes, J., Kosterlitz, H. W., & Sosa, R. P. (1976). Enkephalins : Isolation, distribution and function. In *Opiates and Endogenous Opioid Peptides* (Kosterlitz, H. W., p. 57-62). North-Holland Publishing Co.

Sprouse-Blum, A. S., Smith, G., Sugai, D., & Parsa, F. D. (2010). Understanding Endorphins and Their Importance in Pain Management. *Hawaii Medical Journal*, *69*(3), 70-71.

Steinman, J. L., Carlton, S. M., & Willis, W. D. (1992). The segmental distribution of afferent fibers from the vaginal cervix and hypogastric nerve in rats. *Brain Research*, *575*(1), Art. 1. https://doi.org/10.1016/0006-8993(92)90418-9

Szyfelbein, S. K., Osgood, P. F., & Carr, D. B. (1985). The assessment of pain and plasma β-endorphin immunoactivity in burned children. *Pain*, *22*(2), 173-182. https://doi.org/10.1016/0304-3959(85)90177-0

Tenore, P. L. (2008). Psychotherapeutic Benefits of Opioid Agonist Therapy. *Journal of Addictive Diseases*, *27*(3), 49-65. https://doi.org/10.1080/10550880802122646

Tissot, R. (1980). Opiate receptors and sleep. Effects of microinjections of morphine in the median thalamus and the periaqueductal gray matter of the rabbit (author's transl). *Neuropsychobiology*, *6*(3), Art. 3.

Usichenko, T. I., Edinger, H., Gizhko, V. V., Lehmann, C., Wendt, M., & Feyerherd, F. (2006). Low-Intensity Electromagnetic Millimeter Waves for Pain Therapy. *Evidence-Based Complementary and Alternative Medicine*, *3*(2), 201-207. https://doi.org/10.1093/ecam/nel012

Usichenko, T. I., & Herget, H. F. (2003). Treatment of chronic pain with millimetre wave therapy (MWT) in patients with diffuse connective tissue diseases : A pilot case series study. *European Journal of Pain*, *7*(3), 289-294. https://doi.org/10.1016/S1090-3801(02)00125-8

Usichenko, T. I., Ivashkivsky, O. I., & Gizhko, V. V. (2003). Treatment of rheumatoid arthritis with electromagnetic millimeter waves applied to acupuncture points-a randomized double blind clinical study. *Acupuncture & electro-therapeutics research*, *28*(1), 11-18.

Vachon-Presseau, E., Roy, M., Martel, M.-O., Caron, E., Marin, M.-F., Chen, J., Albouy, G., Plante, I., Sullivan, M. J., Lupien, S. J., & Rainville, P. (2013). The stress model of chronic pain : Evidence from basal cortisol and hippocampal structure and function in humans. *Brain*, *136*(3), 815-827. https://doi.org/10.1093/brain/aws371

Vescovi, P. P., & Coiro, V. (1993). Hyperthermia and endorphins. *Biomedicine & Pharmacotherapy*, *47*(8), Art. 8. https://doi.org/10.1016/0753-3322(93)90078-Y

Whipple, B., Josimovich, J. B., & Komisaruk, B. R. (1990). Sensory thresholds during the antepartum, intrapartum and postpartum periods. *International Journal of Nursing Studies*, *27*(3), 213-221. https://doi.org/10.1016/0020-7489(90)90036-I

Wong, T. M., & Shan, J. (2001). Modulation of sympathetic actions on the heart by opioid receptor stimulation. *Journal of Biomedical Science*, *8*(4), Art. 4. https://doi.org/10.1159/000054047

Zangen, A., Nakash, R., & Yadid, G. (1999). Serotonin-Mediated Increases in the Extracellular Levels of β-Endorphin in the Arcuate Nucleus and Nucleus Accumbens : A Microdialysis Study. *Journal of Neurochemistry*, *73*(6), 2569-2574. https://doi.org/10.1046/j.1471-4159.1999.0732569.x

Zhadobov, M., Chahat, N., Sauleau, R., Le Quement, C., & Le Drean, Y. (2011). Millimeter-wave interactions with the human body: State of knowledge and recent advances. *International Journal of Microwave and Wireless Technologies*, *3*(02), Art. 02. https://doi.org/10.1017/S1759078711000122

Zöllner, C., & Stein, C. (2007). Opioids. *Handbook of Experimental Pharmacology*, *177*, 31-63. https://doi.org/10.1007/978-3-540-33823-9_2

About Remedee Labs

Based on 10 years of pre-clinical and clinical research, Remedee Labs has designed and developed the first endorphin stimulator for personal use. Building on the experience of its clinical partners, the company now uses its unique technology to offer the first patient-centered digital service platform for chronic pain management, working alongside medical practitioners.

Remedee Labs technology, embedded in the first endorphin stimulator wristband, stimulates the nerve endings of the wrist during 30 minutes session. In response to this painless nerve stimulation, the brain releases intracerebral endorphins recognized as the body's highly effective natural pain killer – in a safe, fast and simple way.

But chronic pain requires comprehensive treatment that is tailored to individual needs and provided by a specialized team. Remedee Labs' solution is the only holistic approach that combines innovative technology, digital solution, human support and therapeutic education placing the patient at the center of the treatment for a sustainable improvement of his quality of life.

Remedee Labs initial focus is Fibromyalgia a debilitating chronic condition that affects many aspects of healthy living and quality of life. In may 2022 FDA has granted Breakthrough Device Designation for fibromyalgia patients based on initial real-world evidence results. The initial results showed a clinically significant improvement in their quality of life (FIQ) and an improvement in their sleep quality (PSQI).

Additionally, Remedee Labs is expanding its range of services to address other chronic pain conditions. Early data suggests strong efficacy in reducing pain across a variety of pathologies through digitally stimulated endorphin pathways.