PHYSIOLOGICAL MECHANISMS UNDERLYING MILLIMETER WAVE THERAPY

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Abstract. Millimeter Wave (MW) Therapy is the application of low-intensity millimeter-wavelength electromagnetic waves in the treatment of a large variety of diseases including cardiovascular disorders, diabetes, dermatitis, gastrointestinal disorders, wound healing, pain relief, and the reduction of toxic side effects of chemotherapy in cancer patients. MWs, a form of microwaves, are non-ionizing and are administered onto a localized area of the skin at a sufficiently low intensity that there is no perceptible heating. The three most common frequencies used are 42.2, 53.6, and 61.2 GHz. In addition to its demonstrated effectiveness, it is a non-invasive, painless, relatively inexpensive modality with exceedingly rare and minor side effects. Although MW therapy has been and continues to be used extensively throughout the former Soviet Union with very impressive successes, it is virtually unknown to Western physicians. Reasons for the lack of acceptance in Western Countries include: (1) the lack of well described reports in peer-reviewed scientific journals, (2) the lack of well controlled, double-blind clinical trials, and (3) the lack of any known and accepted mechanism explaining how a localized MW exposure on the skin can be therapeutic in a large number of remote or generalized pathologies. Consequently, the Center for Biomedical Physics at Temple University Medical School was established in 1992 to study all aspects of MW therapy: its validity, its effectiveness, and most of all the mechanisms underlying its effectiveness. The chain of events initiated by MW exposure of the skin is still not fully understood. However, there is sufficient evidence to suggest a cascade of physiological reactions that are capable of resulting in a

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therapeutic response. The penetration of MWs into the skin is less than one millimeter, and therefore the initial interaction must occur within the skin. Free nerve endings, which penetrate into the epidermis, are stimulated directly or indirectly by the MWs. Denervation of the exposed area of the skin completely blocks the effect. The indirect stimulation may result from excitation of immunocompetent dermal cells, such as langerhans cells and keratinocytes, which can be induced to release various cytokines capable of modifying neural membranes. The MW signal is transmitted to the spinal cord and subsequently to various regions of the brain where neurosecretions are released, the most important of which are the endogenous opioids. Naloxone, an opioid inhibitor, greatly diminishes the effect. Opioids are well known chemical mediators that can reduce pain and modify the immune system, and are most likely responsible for most of the therapeutic benefits of MW therapy.

Keywords: Millimeter waves, Therapy, Skin heating, Nerve stimulation, Keratinocytes, Delayed Type Hypersensitivity, Melanoma, Pain relief

1. Introduction

Millimeter wave (MW) therapy is the application of low-intensity millimeter wavelength electromagnetic waves in the alternative treatment of a variety of diseases. MW, a form of microwaves, are non-ionizing and administered onto a localized area of the skin at a sufficiently low intensity that there is no perceptible heating. The three most common frequencies used are 42.2, 53.6, and 61.2 GHz. Strikingly high success rates have been reported in the treatment of cardiovascular diseases, diabetes, dermatitis, gastrointestinal disorders, wound healing, pain relief, and the reduction of toxic side effects of chemotherapy and radiotherapy in cancer patients. Although MW therapy has been and continues to be used extensively throughout the former Soviet Union, it is virtually unknown to Western physicians. In addition to its demonstrated effectiveness, it is a non-invasive, painless, relatively inexpensive modality with exceedingly rare and minor side effects.

The usual MW treatment regimen consists of daily applications of 15 to 30 minutes for 5 to 15 days. The MW device is typically a “book-sized” instrument which is brought in close contact with the skin surface. The site of application varies with the disease being treated. Surface wounds and skin diseases are usually treated at the site of the lesion. In treating arthritis the site of application is at the affected joint. In treating internal diseases, the recommended site of application may be at any one of a number of anatomic or acupuncture points. A common site of application is the lower end of the sternum, as is pictured in figure 1.

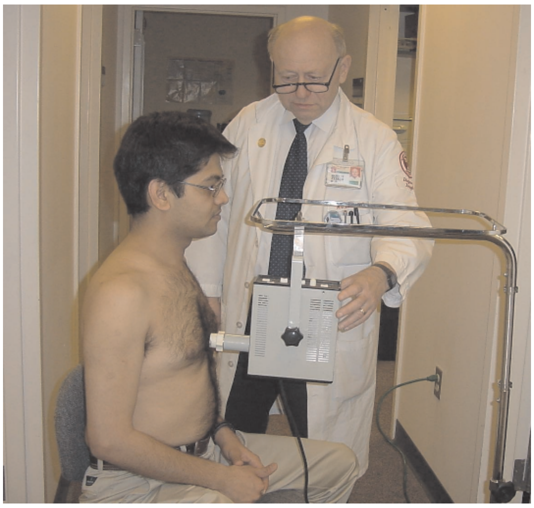

Figure 1. Typical Application of Millimeter Wave Treatment. The MW device is brought in contact with the lower end of the sternum, and the millimeter waves are applied for 20 minutes. The patient perceives no pain or temperature elevation.

Currently available MW devices are made in Russia and other countries of the former Soviet Union. The best amongst these is the YAV-1 MW applicator manufactured by ISTOK, a major Russian Military Electronic Research and Development Center.

Figure 2. The YAV-1 MW Device. The instrument panel is shown on the left. Millimeter waves emerge from the rectangular horn seen within the circular white plastic applicator seen in the picture on the right.

In spite of the large numbers of patients treated and the very high success rates attributed to MW therapy by hospitals and clinics in the former Soviet Union, there have been just a handful of publications in peer-reviewed scientific journals with sufficient details to satisfy Western physicians and scientists. Because of this lack of details and quantitation, the interpretation and evaluation of the results are difficult and unreliable. Therefore, it is necessary to independently test the validity of the Soviet claims before MW therapy can become an accepted alternative modality in clinical applications in the United States. The Center for Biomedical Physics at Temple University Medical School in Philadelphia has been established to study the scientific basis of MW therapy, to determine its mechanism(s) of action, and to quantitatively evaluate its effect on certain selected diseases.

Our approach to understanding MW therapy has been broad, including studying the fundamental interactions of MWs with tissue, studying the local and systemic biological effects of MW exposure, and the performance of clinical trials of MW therapy in selected diseases.

An excellent review of the invitations of the research and in the biological effects of millimeter waves was written by Pakhomov and his colleagues (1998). Other reviews and reports have come from our laboratory (Rojavin and Ziskin, 1998). There have been reported three general types of effects resulting from millimeter wave therapy: 1) anti-inflammatory and repair stimulating action, 2) immune system stimulation, and 3) sedative and analgesic effects. The following is a survey of some of the interesting results of our endeavors.

2. Fundamental Physical Interactions of MW with the Skin

Millimeter waves are rapidly absorbed by the skin. Penetration depths are only a few tenths of a millimeter. Consequently, any biological response to MW irradiation must be initiated within the skin. Gaining an understanding of the mechanisms of how MW can have a therapeutic effect starts with learning how it interacts with the skin and its structures.

The high absorption of MW in the skin mostly results from the MW interaction with water (Alekseev and Ziskin, 2001b). Among the tissue and skin components, water has a greatest absorption coefficient and constitutes 70-80% of tissue and skin. The applied MW electromagnetic field induces the rotational movement of water molecules due to partial orientation of their permanent dipoles. The water of hydration associated with proteins and other organic molecules exhibits little absorption in the MW frequency range due to strong restriction of their motion. Thus, the amount of water contributing to MW absorption in tissues equals the total water content minus the fraction of "bound" or motionally restricted water.

Because the structure and the free water content of each skin layer are different, internal reflections between skin layers can change the total reflection from the skin. The MW absorption in some layers may increase due to multiple reflections within these layers (Alekseev and Ziskin, 1999c). In this case, the reflection or absorption may exhibit sharp frequency dependence.

3. Skin structure

The physical properties of skin and its appendages greatly affect the amount and distribution of MW absorbed. The thickness of the human epidermis and dermis varies in the range of 40-150 µm and 1.13-2.8 mm, respectively. The stratum corneum has low water content (15-40%), and the total water concentration in the rest of the epidermis and dermis is 70 – 80%. Thus, MW energy penetrates the stratum corneum fairly easily, but is rapidly absorbed within the deeper epithelium and dermis. The stratum corneum, especially in palmar skin, due to low water content may improve the coupling conditions with the antenna of a clinical MW applicator, thereby increasing the energy deposition in the skin.

4. MW heating of the skin

Millimeter wave irradiation has a certain number of physical features – one is that heating is a major mechanism for bioeffects; also most of the energy is absorbed within a few tenths of the millimeter. Also, wavelengths and tissue are compatible with biological structures. Finally, irradiation is frequently applied in a near field.

Exposure of human skin with MW at incident power densities (IPD) ≥ 10 mW/cm^2, as frequently used in MW therapy and laboratory experiments, can lead to localized heating of the skin. Rapid temperature increase during irradiation, even if only a small total increment, can cause certain biological effects [Alekseev et al., 1997]. Therefore, determination of the heating rates and temperature rise distributions within the skin during exposure with various radiators plays an important role in evaluating thermal mechanisms of mm-wave action, and in assessing dosimetry of the skin (Alekseev and Ziskin, 2003).

5. Dosimetry

The absorption of microwave EMF in biological tissue is characterized by the specific absorption rate (SAR) (Durney *et al*., 1986):

$$SAR = \frac{\sigma |E|^2}{\rho} \qquad (1.4)$$

where σ is the conductivity of tissue, E is the internal electric field, and ρ is the mass density. In the cases, when the experimental determination of E is complicated, the SAR can be obtained from measuring the initial temperature rise rate $dT/dt|_{t=0}$ as follows (IEEE, 1992):

$$SAR = C \cdot \frac{dT}{dt}\Big|_{t=0} \qquad (1.5)$$

where C is the specific heat of tissue. SAR within tissue can be also determined from the incident power density (IPD) measurements as follows (Gandhi and Riazi, 1986).

The use of an infra red camera provides an excellent way of determining the dosage of millimeter waves. Because the radiation is within the near field, the resulting heating pattern is very non-uniform. SAR values in hot spot areas can exceed a thousand watts per kilogram with an incident power density of 10 mW/cm^2 (Alekseev and Ziskin, 1999a).

The mechanism by which millimeter waves are able to produce systemic whole body effects from local exposures where the penetration is very shallow is not well understood. However, two major mechanisms seem to be involved: 1) stimulation of the nervous system and 2) stimulation of the immune system. In either case, the initial interaction with the millimeter waves occurs within the skin. Free nerve endings extending into epidermis can be stimulated directly. Also, immunocompetent cells such as langerhans cells and keratinocytes within the skin epidermis can also be stimulated directly. The neurons in the skin are thus either stimulated directly or indirectly by the release of cytokines from stimulated dermal cells. The resulting "millimeter wave signal" is transmitted through the cutaneous nerve through the dorsal root ganglion into the spinal cord. At the first synapse in the spinal cord, there is a release of endogenous opioids. The release of endogenous opioids occurs at least two other spots in the brain. The release of endogenous opioids into the blood stream spreads these chemicals throughout the body, and certainly is adequate for explaining why pain relief can result from millimeter wave exposures. The involvement of endogenous opioids in MWT is verified by the fact that the beneficial effect of MWT is completely abolished upon the administration of Naloxone, a general opioid inhibitor. Opioids are also known to have wide ranging effects on various systems in the body including the immune system.

6. Direct Stimulation of Neurons by MW

Laboratory demonstration of millimeter wave stimulation of neurons can be seen in experiments using pond snails (Alekseev, *et al*, 2000). Special neural ganglia in the neck region of these mollusks are well known biologically. They act as pacemaker neurons for the entire organism. The neurons firings can be detected by microelectrodes and recorded (Alekseev and Ziskin, 1999b). The displayed traces show a pattern of regular spike firing. However, with increasing intensities of MW, the frequency of the firing rate slows. The slowing is dose dependent to the SAR level. At sufficiently high SAR levels there is a complete cessation of firing until the MW exposure is stopped. At moderate SAR levels there is an initial slowing of the firing rate followed by a later compensatory increase in firing rate. This can be explained on a thermal basis in that there are two opposing thermally sensitive mechanisms involved. The most rapid mechanism is the thermal stimulation of the sodium a pump which increases the membrane potential and causes the slowing of the neuron firing. The slower mechanism is the thermally increased permeability of the neuron membrane which allows ion transfer which will decrease the membrane potential and ultimately cause an increase in the firing range. It was found that the rate of rise of temperature, even though the absolute temperature rise is not high, is the significant factor. And the threshold of the firing of these neurons is 0.0025 ^{0}C per second. This is very similar to what is found in the literature for human warmth receptors and human cold receptors. In summary, millimeter wave irradiation causes a biphasic change in the firing range of neurons. The temperature rise rate plays an important role in development of the neural response. Therefore, millimeter wave irradiation as used in therapy is capable of activating thermoreceptors and other thermosensitive nerve endings in the upper layers of the skin.

7. Effects on Keratinocytes

Extensive histological and histochemical studies of skin reveal that millimeter waves at therapeutic levels cause no damage to the skin [Szabo, et al, 2003]. However, at higher intensities it is possible to see that apoptosis is induced in keratinocytes if the temperature exceeds 43 ^{0}C. Significantly, the apoptosis does not reveal itself until 24 hours following the exposure. Therefore, studies looking for small effects should include studies lasting for 24 hours following the exposure (Szabo, *et al,* 2001). Effects of millimeter waves at therapeutic levels on cell cultures of human keratinocytes are mostly negative. However, we did find in one study an increased release of the cytokine IL-1β.

8. Delayed Type Hypersensitivity

Millimeter waves have been found to produce a number of changes influencing the immune system. A particular interesting one involves the delayed type hypersensitivity (DTH). DTH is a memory dependent immune response. It is T-cell mediated. Common examples are poison ivy and poison oak dermatitis. There is a two stage process involved. The first is sensitization in which a topical application of an allergen induces an immunological memory for the allergen but little to no reaction. The second stage is the challenge stage in which exposure to the same allergen, even in very small doses, at a later time evokes a significant inflammatory skin reaction.

Our study (Logani and Ziskin, 1999) involved sensitization with dinitrochlorobenzene (DNCB) on the right ears of mice at the fifth, sixth and seventh days following exposure to MW for 30 minutes on its back. On day 7, a small amount of DNCB was placed on the Left Ear. This induced a generalized immune response in the mice. Measurement of the effect was accomplished by measuring the thickness of the ear, as the ear provides the convenient spot to measure the overall tissue edema resulting from the immune reaction. In hairless mice which are somewhat compromised in their immune system, we see a significant increase in the ear thickness which appears to be dose-dependent and greater than in sham controls. However, when immunocompetent mice, such as Balb/C were tested, we found no significant response to MW. However, when the BALB/C mouse was pretreated with a chemotherapeutic agent such as cyclophosphamide (CPA), we found that the therapeutic effect of the millimeter waves was observed. This is consistent with reports from Russia that millimeter wave therapy has no effect on normal functioning conditions but it will have a positive effect on altered states of the body. In summary, millimeter waves enhance DTH reaction in the hairless mutant mice. Millimeter wave effects do not effect DTH reaction in BALB/C mice. However, millimeter wave enhance DTH reaction in BALB/C mice pretreated with cyclophosphamide (CPA). These findings support the hypothesis that millimeter waves normalize disturbed immune functions.

9. Effect on Subcutaneous Melanoma

An experimental model that has a proved quite useful in our experience has been the effect of millimeter waves on subcutaneous B16 melanoma growth in mice (Radzievsky, *et al,* 2004). The B16 melanoma is a fast growing tumor in mice that mimics malignant cutaneous melanoma in humans. Because of its black color, melanomas are readily visible in just 24 -48 hours following the subcutaneous injection of the B16 melanoma cells. Thus, tumor growth can be easily monitored. Without millimeter wave treatment, melanomas grow continually in size. However, we were able to show that millimeter wave significantly decreased the rate of growth of these tumors. Furthermore, in tumor challenge studies, we were able to show that something is released from a tumor that has been treated by millimeter waves that causes tumor inoculations in other parts of the body to be significantly suppressed. Further investigation showed that TNF alpha concentrations in the solid tumors in the groups of MW-treated mice were significantly increased over sham-controls. This has potential clinical benefit in the treatment of cutaneous melanomas and in suppressing their metastasis (Szabo, *et al,* 2004).

10. Suppression of Pain

Numerous studies have been performed in our lab demonstrating the ability of millimeter waves to suppress various types of pain, including acute, chronic non-neuropathic, and chronic neuropathic pain (Radzievsky, *et al,* 1999, 2000, and 2001). The best experimental model for acute pain is the Hot water Tail-

Flick Test, the best for chronic non-neuropathic pain is the Cold water Tail-Flick Test, and the best for chronic neuropathic pain the Chronic Constriction Injury of the sciatic nerve. 61.22 GHz MW irradiation at 15 mW/cm^2 has been applied to the nasal region of mice to determine the hypoalgesic effect of millimeter waves. Millimeter waves significantly increased the duration which the mice could withstand the hot water. It was found that naloxone, a general inhibitor of opioids, was effective and completely blocked the effects of millimeter waves on reducing acute pain. This substantiated the concept that the effect of millimeter waves was mediated by endogenous opioids. This is similar in respect to other forms of localized stimulation such as acupuncture. A double blind prospective human volunteer study showed that MW exposure was able to suppress pain sensation when the subjects' hands were placed in ice water (Radzievsky, *et al,* 1999).

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