

POSSIBLE EFFECTS OF ELECTROMAGNETIC FIELDS ON THE NERVOUS - ENDOCRINE - IMMUNE INTERACTIONS

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1. Introduction

In recent years, complex interactions between the nervous, the endocrine and the immune system have been thoroughly investigated resulting in a large database of knowledge. On the other hand, the effectiveness of electromagnetic stimulation of the neurons has also been widely demonstrated, and the techniques of such stimulation are well established. A combination of the two knowledges offers a possibility to artificially influence the nervous - endocrine - immune (NEI) interactions, in cases when the immunity of a person is impaired, or its glandular functions are disordered. There is a wealth of reports on the use of electromagnetic fields to treat various pathological conditions. The number of diagnostic procedures that rely on the use of electromagnetic fields is also increasing. Therapeutic and diagnostic approaches include: surgical knife, cancer treatment (both hyperthermia and sub-hyperthermal EMF treatment, alone or in combination with other antitumor treatments), chronic and acute wound healing, bone healing, magnetic resonance imaging and spectroscopy, catheter ablation for cardiac arrhythmia, pain treatment, thermotherapy of musculo-skeletal tissue in physical medicine and rehabilitation, edema treatment, etc [1-5]. A number of these therapeutic procedures rely on excessive local heating of the tissue by means of radio frequency electromagnetic field. Other therapeutic procedures however do not have fully established mechanisms of EMFs. It is also very interesting that various signals in terms of amplitudes, pulse shape and frequencies are successfully used. At the moment a large database of EMF interactions with biological systems on various levels are available. Yet, due to very complex interactions between different levels, it is difficult if not impossible to explain reported therapeutic effects. Additional problem is that dosimetric determinations are only available in electrosurgery, catheter ablation, cancer hyperthermia and MR imaging and spectroscopy.

This paper suggests a different approach in explanation of such therapies and offers at the same time the possibility of finding new effective therapies. After a general review of the known NEI interactions, we synthesize the presented knowledge into a model. Based

on this model, we then present a concept of modification of nervous - endocrine - immune interactions by means of electromagnetic stimulation of the autonomic nervous system. Finally, using this model, we attempt to explain the global effect of electromagnetic stimulation on wound healing, which has been observed on several occasions, and possible use of electrical stimulation for cancer treatment.

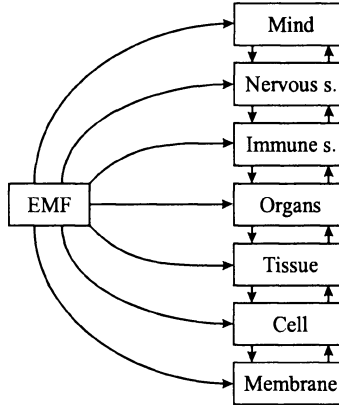


Figure 1. Levels of electromagnetic fields interaction with human body.

2. Nervous-Endocrine-Immune Interactions

Neuroendocrinology (NEI) is a fast-growing field of research that is gaining the interest of many scientists in the fields of biochemistry, physiology, pharmaceuticals, and medicine. It deals with the complex interactions between the nervous, immune and endocrine systems. During the last decade, significant progress has been achieved in this field. Some of the advances have consolidated the established concepts in NEI, and some have added new ones.

The established concepts, often also referred to as "classical", are based on the following series of interactions:

1. the nervous system stimulates or suppresses glandular activity by means of neural signaling, which acts through the innervation of the glands;
2. the glands of the endocrine system respond with increased or decreased production of the hormones;
3. modified hormone production then affects the activity of other glands, or the immune system, which responds by modifying the production of its own regulatory molecules - the cytokines;
4. modified cytokine production affects the activity of the immune system by regulating proliferation and activation of lymphocytes, inflammatory response, phagocytosis, as well as production of erythrocytes.

The described concept is depicted in Figure 2.

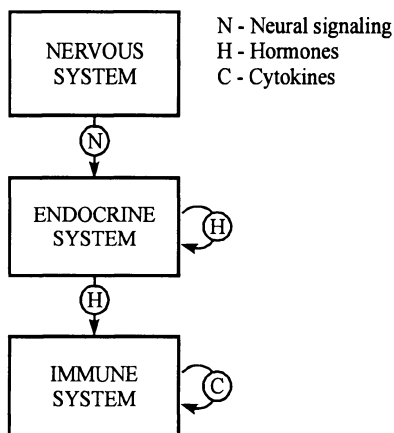


Figure 2. The "classical" pathways of nervous-endocrine-immune interactions.

A substantial evidence exists, however, that some of the roles presumed in the "classical" concept can also be reversed, making the scheme more complex. Namely, it has been known for a long time that some of the neurons of the hypothalamus function as endocrine glands, secreting hormones into the blood [6]. In addition, a series of recent studies suggests that the immune system is also able under some circumstances to produce hormones [7], and endocrine system to produce cytokines [8]. Also, it has been demonstrated that some cytokines can inhibit the activity of the hypothalamus [9]. These pathways are named "alternative" or "auxiliary".

Addition of these pathways yields a modified model, shown in Figure 3. The solid arrow-lines represent the "classical" pathways of the interactions, while the dashed arrow-lines designate the "alternative" pathways.

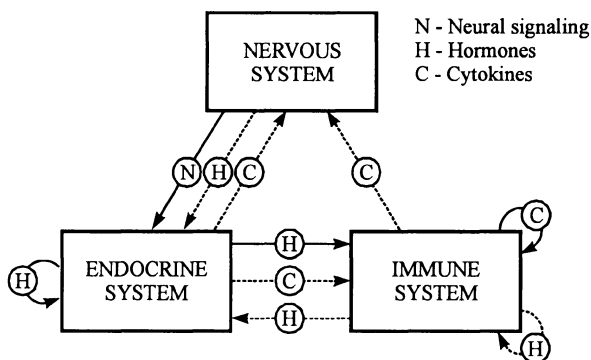


Figure 3. "Classical" (solid) and "alternative" (dashed) pathways of nervous-endocrine-immune interactions.

3. Modulation of the NEI Interactions by EMF

It is by now well established that various types of electric currents using different techniques of application improve healing of chronic wounds and reduce or even eradicate tumors [1,10,11].

However, there is no single mechanism which could explain and justify the large assortment of electrotherapeutic regimes. Some of the hypotheses that have been advanced and have some experimental support include:

- Transmembrane voltage in a cell exposed to external electric fields is modified [12-14].
- Host immune response in wound and bone healing and tumor treatment is stimulated [1,11,15].
- Electric currents might induce an increased production of peptide signaling molecules - growth factors [16].
- Electric currents might also enhance the processes of activation of immune cells [17].

All these phenomena are based on local application of electromagnetic fields. However, there are documented reports that wound healing occurs even when electrical stimuli are applied quite distantly from the wound site. Illis and co-workers observed that after spinal cord stimulation that was originally intended for pain suppression and improvement of locomotion, indolent ischaemic wounds on the leg began to heal [18]. Kaada applied electroacupuncture to a point on the hand and observed wound healing on the legs [19]. Regarding cancer, a large body of evidence is connecting the disease to neural and psychological factors [20]. These observations suggest an involvement of a global mechanism. In the cases of electroacupuncture and spinal cord stimulation, neural pathways have to be involved in healing of distant wounds. As these pathways alone do not suffice to produce such an effect, it is probably the whole NEI system that achieves the healing.

Figure 4 shows in detail some of the "classical" NEI pathways that could lead to systemic effects of neurostimulation. The model takes into account the previously published schemes by Husband [21], Old [22], and Chambers with co-workers [23].

Within the "classical" pathways, the autonomic nervous system influences the activity of the endocrine glands through direct innervation. Coordination and regulation of the glandular activity is based on the release of hypothalamic, pituitary and peripheral endocrine hormones. Some of the hormones released by thymus, adrenal cortex and adrenal medulla also affect the activity of leukocytes, mainly T and B lymphocytes. This activity is demonstrated by increase or decrease in the production of cytokines, a large family of protein factors involved in numerous aspects of the immune response. Some of the members of cytokine subfamilies, such as interferons (IFN), tumor necrosis factors (TNF) and interleukins (IL), are directly involved in the processes of tumor growth inhibition, including the destruction of tumor cells. Some of the cytokines reputedly also regulate the synthesis of growth factors in different cell types, such as fibroblasts and endothelial cells [22]. Growth factors then accelerate the pace of growth and division of tissue cells, thus promoting the repair of damaged

tissues, including wound healing. It has also been reported that some cytokines, especially interleukin-1 (IL-1), influence the activity of the hypothalamus [4].

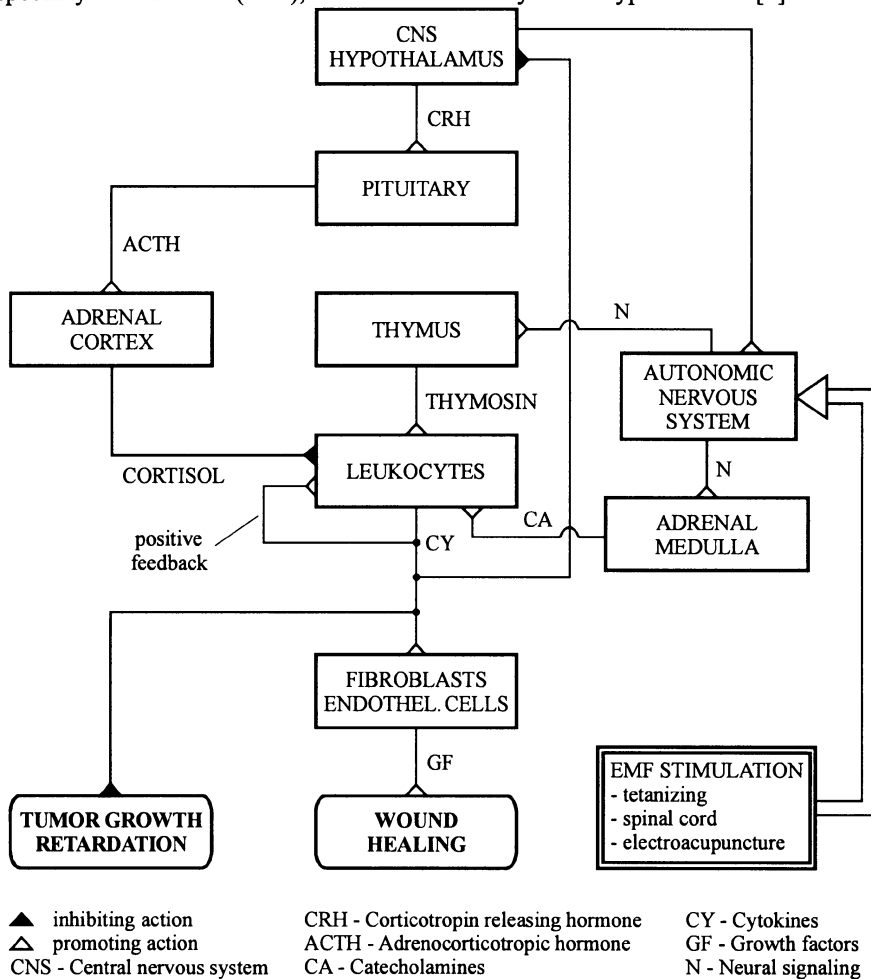


Figure 4. Some of the possible ways to affect wound healing and tumor growth via the immune system.

The model presented in Figure 4 shows possible pathways leading from electromagnetic stimulation to wound healing and tumor reduction. Neural activity, which is influenced by means of electromagnetic stimulation, then affects the immune system, which can finally induce accelerated healing of wounds, as well as decrease of tumor size, or at least the retardation of tumor growth.

Based on this example we can therefore conclude that electromagnetic stimulation of the nervous system could be an additional modality for systemic treatment of various pathologies.

4. Acknowledgement

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5. References

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