fizjoterapia polska
nr 1/2014 (14)

Wpływ pola magnetycznego na przewodnictwo sygnałów

The effect of magnetic field on the signal transduction

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Streszczenie

Terapia z wykorzystaniem pola magnetycznego znana jest już od wieków. Obecnie jest to technika szeroko wykorzystywana w praktyce z powodu niskiej szkodliwości, szerokich możliwości zastosowania oraz dobrych efektów klinicznych, przy stosunkowo niskich nakładach ekonomicznych. Działanie biologiczne pola magnetycznego związane jest między innymi z efektem przeciwbólowym i przeciwzapalnym. Działanie analgetyczne opiera się przede wszystkim na endogennym układzie opioidowym. Pole magnetyczne reguluje działanie przeciwbólowe opioidów poprzez wpływ na kanały wapniowe i stężenie jonów Ca^{2+}. Co więcej, pole magnetyczne wzmacnia układ immunologiczny wpływając na reakcje zapalne. Jednym z mechanizmów przeciwzapalnej aktywności magnetoterapii może być również działanie antyoksydacyjne. Potwierdzeniem przeciwbólowego i przeciwzapalnego efektu pola magnetycznego są badania kliniczne prowadzone w różnych ośrodkach na świecie. Udokumentowane są między innymi badania, w których zastosowano terapię z wykorzystaniem pola magnetycznego w leczeniu zespołu cieśni nadgarstka, neuropatii cukrzycowej i fibromialgii. Celem niniejszej pracy jest przedstawienie aktualnego stanu wiedzy na temat mechanizmów działania przeciwbólowego i przeciwzapalnego pola magnetycznego.

Słowa kluczowe:

pole magnetyczne, analgezja, zapalenie

Abstract

The therapy using the magnetic field has been known for centuries. Today it is a technique widely used in practice due to low harmfulness, wide applicability and good clinical outcomes with relatively low outlay. The biological effect of the magnetic field is related, inter alia, with analgesic and anti-inflammatory effect. The analgesic activity is primarily based on the endogenous opioid system. The magnetic field regulates opioid analgesic by affecting the calcium channels, and Ca^{2+} concentration. Furthermore, the magnetic field enhances the immune system affecting the inflammatory reactions. One of the mechanisms of anti-inflammatory effect of magnetotherapy may also be an antioxidant activity. The confirmation of the analgesic and anti-inflammatory effect of the magnetic field are clinical trials conducted in various institutions in the world. Have been documented, among others, studies which used magnetic therapy in the treatment of carpal tunnel syndrome, diabetic neuropathy and fibromyalgia. The aim of this study is to present the current state of knowledge on the mechanisms of action of analgesic and anti-inflammatory magnetic field.

Key words:

magnetic fields, analgesia, inflammation

nr grantu statutowego: 506/1136

Introduction

Beneficial effect of magnetic field was already known in antiquity. In ancient Egypt variety of diseases, including internal pain, skin injuries or even fractures was treated using magnetite. Nowadays, the therapeutic treatment using extremely low frequency magnetic field called the magnetotherapy, uses apparatus generating magnetic fields with different values of the physical parameters and the shape of the pulse [1, 2].

Alternating magnetic field applied in rehabilitation is characterized by a low value of the magnetic induction and affects the body on: molecular, subcellular and cellular level. It is manifested by a change in ion balance. Modification of ion flux through the membrane channels is related to the interaction between the transported ions across the cell membrane and membrane channel structural proteins. It affects the content of individual ions in cellular structures and may alter the activity of the metabolic processes, dependent on distribution of ions. The biological effects of magnetic field on living organisms are based on the following physical effects:

- magnetomechanical action of magnetic field on the particles of uncompensated magnetic spins (paramagnetic elements and free radicals and diamagnetic molecules) may result in an increase in the magnetic moment of these elements, as in the case of occurrence in the composition of coenzymes or prosthetic group of enzymes and can lead to activation of the enzymatical reaction,
- effects on the liquid crystal structure created by cholesterol and its derivatives as a component of cell membranes and organelles,
- changes in physical and chemical properties of water that, constitutes the biological environment of most cellular reactions and is the main tissue filler,
- depolarization of membrane cells that possess the ability to receive and conduct of stimuli as a result of spontaneous depolarization, mainly through effects on ion channels,
- effect on the tissue structure having piezoelectric properties and magnetostrictive [3].

The biological effect of the magnetic field is widely reported in the the literature, however, the number of observed effects is still unexplained [1, 4]. Review of effects and mechanisms of magnetic field action is shown in Fig. 1.

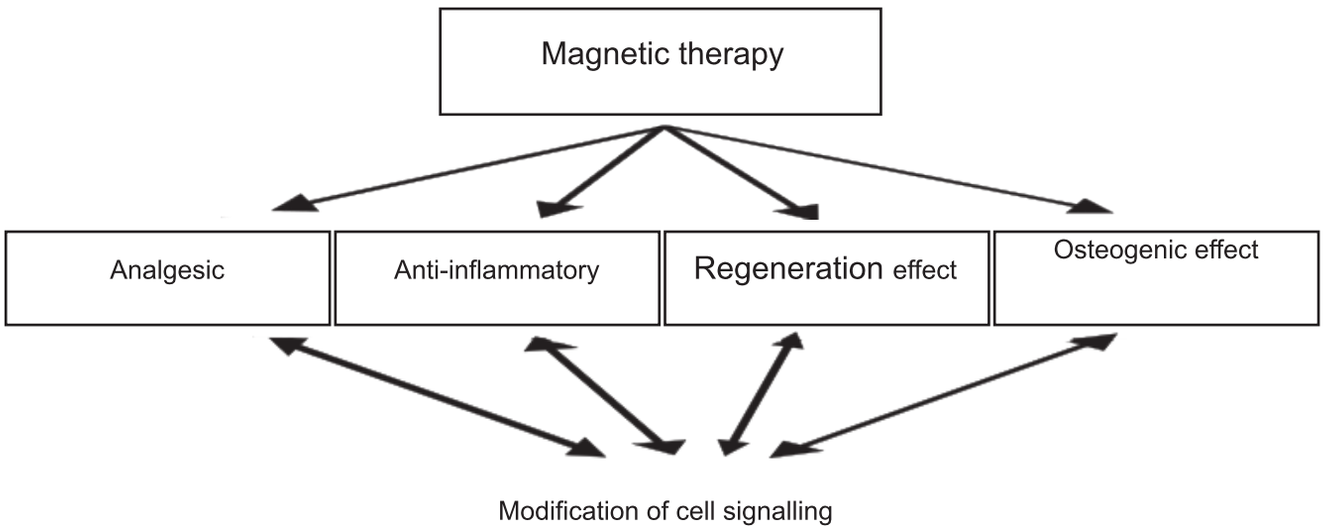
The aim of this paper is to present the current state of knowledge about the mechanisms of analgesic and anti-inflammatory effects of magnetic field.

The analgesic effect

One of the early warning signals of most somatic diseases is a pain. Although it is associated with mental and physical discomfort, undoubtedly has a positive meaning, because is one of the major symptoms providing the ongoing disease process in the body. Pain is also a natural reaction of the body to external damaging factors. According to the International Association for the Study of Pain (IASP) pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [5]. Pain is classified according to the duration and / or the mechanism of formation (Tab. 1) [6].

Ryc. 1. Działanie biologiczne pola magnetycznego [4]

Fig. 1. The biological effect of magnetic field [4]



As a result of irritation of the tissue by thermal, chemical, or mechanical stimuli and as a result of inflammation or tumour, the secretion of specific substances (neurokinin, prostaglandins, histamine and serotonin), and stimulation of pain receptors (nociceptors) located at the ends of the peripheral nerve take place. From nociceptors pain signal by sensory neurons is transmitted to the presynaptic receptors in the spinal cord dorsal horns (GABA, serotonin, and α2-adrenoceptors). It causes the release of neurotransmitters in the synaptic space (mainly substance P and glutamine), and the stimulation of postsynaptic receptors: NK-1 (neurokinin-1 receptor), AMPA (A-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) and NMDA (N-methyl-D-aspartate receptor). Both, pre- and prosynaptic receptors are a destinations of painkillers. From spinal cord dorsal horns pain stimulus is transmitted through the medulla to the midbrain, where begins descending way. At this stage, a prolongation or inhibition of pain occurs. If symptoms persist, the pain signal is transmitted to the cerebral cortex, to take perception and emotional reactions (fear, aggression, depression, etc.) (Fig. 2) [7, 8].

So far, there are two mechanisms for modulating of the endogenous pain systems: the descending pain inhibitory system associated with secretion in the medulla and midbrain large amounts of neurotransmitters analgesics, including serotonin and noradrenaline [7] and the second system to silence the pain with the involvement of opioid receptors [8]. Endogenous ligands for opioid receptors are opioid peptides such as endorphins, enkephalins and dynorphins, which are precursors of proopiomelanocortin (POMC), proenkephalin (PENK) and

Tab. 1. Pain classification [6]

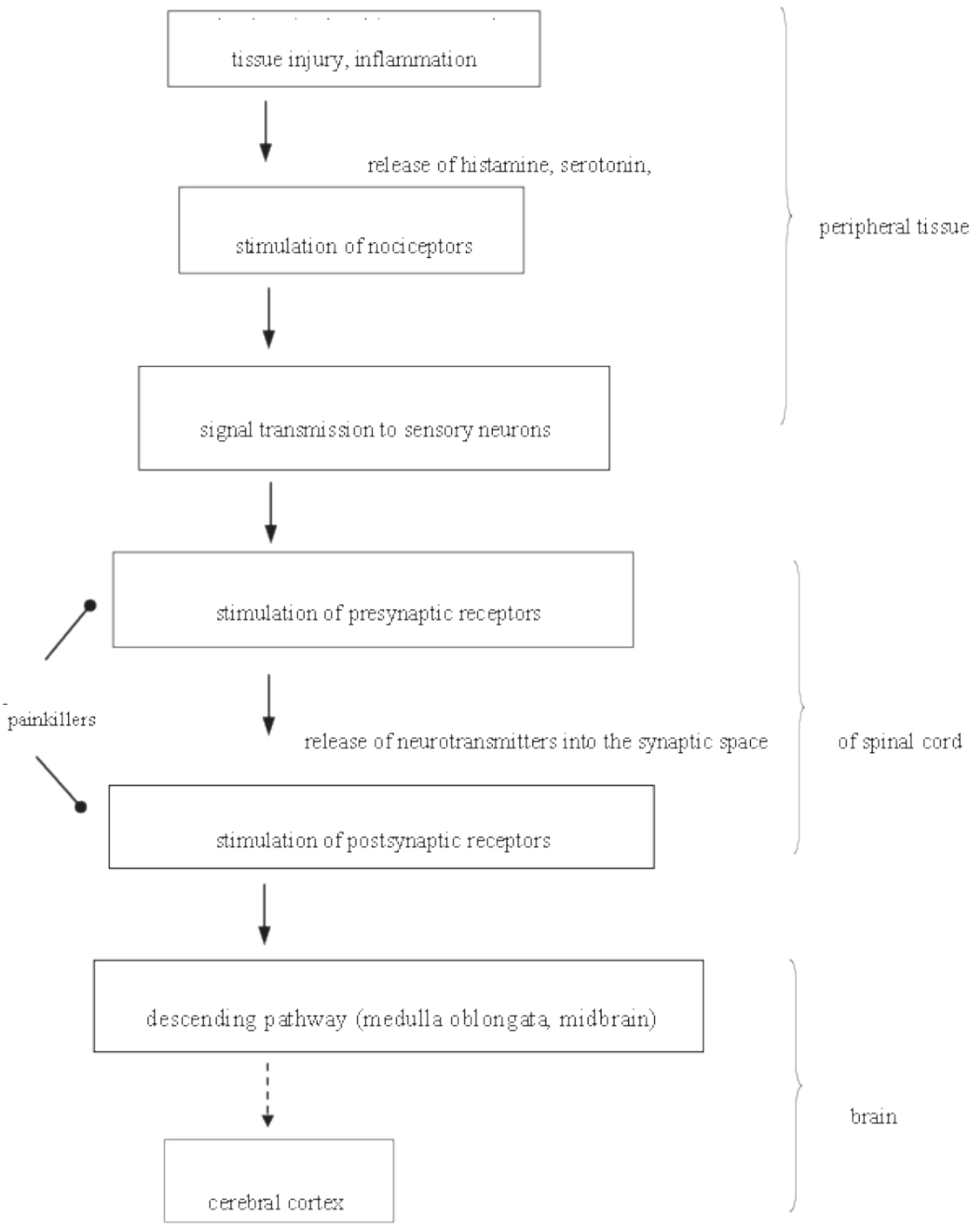
Duration of pain	
Acute pain	Less than 4 weeks
Subacute pain	4-12 weeks
Chronic pain	Over 4 weeks
Mechanism of pain	
Nociceptive pain	Irritation of nociceptors
	The reduction of nociceptor excitability
Neuropathic pain (non-reciceptive)	Damage to the peripheral nerves, nerve roots, and other structures of the nervous system
Psychogenic pain	Somatic sensations without a confirmed pathological state

prodynorphin (PDYN). It was previously thought that opioid receptors are present only in the brain but the present knowledge enable to conclude that these receptors in the spinal cord and peripheral tissues also occur. There are three types of receptors: μ (occurring in the brain, with the main ligand β-endorphin), δ (present in the spinal cord) and κ (located on the periphery). Depending on the type of receptor and thus the place of its occurrence, supraspinal cord, spinal cord and peripheral, regulation receptors are distinguished [8-10].

In the brain β-endorphins are produced in anterior pituitary and are characterized by a stronger analgesic effect of morphine. They are released under the action of stress, pain, and exercise. The analgesic activity is associated with hyperpolarisation of peripheral somatosensory fibers and caused by the binding of β-endorphin to opioid receptors. Opioid peptides induce the changes of membrane permeability by interacting with the G protein. It results in the inhibition of blocking calcium L gated channels, induce conformational changes in the receptor and modification of binding energy [11, 12].

Hargeaves *et al.*, demonstrated the participation of endogenous opioids in the analgesic reactions. They observed an increase in the concentration of β-endorphin in the plasma of patients undergoing surgery in the oral cavity under local anesthesia (2% lidocaine) with simultaneous increase in the pain threshold. Further studies of these authors showed that the administration of fentanyl (an opioid agonist), contrary to the administration of lidocaine causes the reduction in levels of

Fig. 2. The pain signal transduction [7, 8]



these peptides in the plasma [13, 14]. Moreover, these peptides affect the transmission sensations of visual, auditory and olfactory sensations [11].

Biological effects of magnetic field used in physical therapy are related mainly to the, analgesic effect. The analgesic activity of magnetotherapy has been confirmed by fundamental and clinical research conducted in various centre in the world [15-19].

The mechanism of the analgesic effect of magnetic field is not fully understood. At present many studies have focused on the analgesic action of magnetotherapy through the endogenous opioid system. The magnetic field may regulate opioid anal-

gesic effect by its influence on calcium channels and the concentration of Ca^{2+} [12, 20-22]. However, Thomas et al. found that in land snail (*Capaea nemoralis*) magnetic field may enhance opioid analgesic response by δ receptors, or even initiate an analgesic effect. Moreover, using a magnetic field after administration of naloxone – (strong opioid agonist which does not have the analgesic effect and removes central and peripheral effects of opioids), an analgesic effect of field was reduced, but not eliminated. Thus, the results of the studies have shown that the analgesic effect of magnetic field is not only linked with the opioid system [21]. According to Prato *et al.* studies the effect of magnetic field on the level of the opioids depends on the parameters of the applied magnetic field and analgesic effect is associated with the flow of potassium and calcium ion. Reducing the flow of Ca^{2+} causes an increase in the level of analgesia, while the increase or administration of calcium channel agonist causes the removal of the analgesic effect. Contrary, an increase in the flow of K^{+} ions potentiates the analgesic effect of the opioids, the administration of potassium channel antagonists - glibenclamide - removes this activity [22, 23].

Treatment of rats with extremely low frequency magnetic field has been demonstrated that analgesic effect of magnetotherapy depends on both, the opioid and non-opioid systems. Non-opioid analgesic effect of magnetic field is related to the increase of secretion of substance P and serotonin (5-HT), that play an important role in the regulation of nociception processes. Bao *et al.* demonstrated that the β-endorphin neurons located in the arcuate nucleus, and their completion occur in the brainstem, in the raphe nucleus, where a large numbers of serotonin receptors exists. Thus, the increase in opioid peptide secretion is associated with an increase in serotonin binding, and supraspinal cord analgesic effect of magnetic field correlates with the level of serotonin in the brain [24]. The level of substance P, involved in the central regulation of pain, is also increased after magnetotherapy. Substance P regulates central neurotransmission of serotonin and β-endorphin [10]. Thus, the levels of three neurotransmitters: β-endorphin, serotonin and substance P in blood are increased, but until now there are insufficient data to maintain whether these changes occur simultaneously, or individual substances mutually regulate the process of formation [24].

Inflammation

Immune system is activated in response to harmful exogenous or endogenous agents. During an inflammatory response activated cells are capable to phagocytosis - macrophages and mast cells. These cells release inflammatory mediators - cytokines and chemokines, generate reactive oxygen species and activate leukocytes that migrate to the site of inflammation.

Magnetic fields are often used for the rehabilitation and inflammatory treatment. One of the probable mechanism for the efficient action of the magnetic fields in the rehabilitation and antiinflammatory therapies is its supporting the activation of the immune system. Murabayashi *et al.* investigated the effect of magnetic field on the activity of monocytes / macrophages

and lymphocytes *in vitro*. They found that the use of magnetotherapy increases monocyte activation by enhancing influx of calcium ion into the cell. The influx of Ca^{2+} enhances the secretion of neurotransmitters, such as substance P, which stimulates the immune cells to the production of proinflammatory cytokines, including interleukin-1 universal factor stimulating the inflammatory response. Thus, the anti-inflammatory response of organism is increased. In addition, the authors observed that there is a correlation between exposure time and increase of the proliferation and activity of lymphocytes whose deficiency is responsible for the reduced immunity. The best results were obtained at 20-minute exposure to a magnetic field. The effect of 60-minute exposure was completely abolished. The effect of magnetic field on lymphocytes is associated with increased concentrations of interleukins: Il-1β and IL-2 [25]. Interleukin-1β is produced by monocytes in response to inflammatory signals, affects lymphocyte differentiation and increases expression of interleukin-2, which in turn, is the most important growth factor for lymphocytes [26, 27].

Extremely low frequency of magnetic field affects the immune system by increasing the density of adenosine receptors, in particular A_{2A} and A_3, leading to increased levels of cAMP. Adenosine receptors are involved in the immune response by inhibitory effects on the secretion of mediators of the immune response. Adenosine affects the production of cytokines, reactive oxygen species and metabolites of arachidonic acid. The magnetic field inhibits the secretion of pro-inflammatory cytokines, in particular, IL-6, IL-8 and prostaglandin E2, and activates the secretion of interleukin IL-10 with anti-inflammatory properties [28, 29].

One of the mechanisms of anti-inflammatory activity of magnetic fields is also an antioxidant effect. There are many reports confirming the antioxidant properties of magnetic fields [30, 31]. In mouse fibroblasts Kurzeja *et al.* showed the normalization of the level of oxidative stress markers together with the elevated activities of antioxidant enzymes: superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) [30]. Similarly, studies by Sosnowski *et al.* confirmed the influence of magnetic fields on the normalization of the activity of antioxidant enzymes in the blood of tested rats and reduction of hydrogen peroxide generation [31]. It should be underlined that not all researchers agree with the antioxidant role of the magnetotherapy. The opposite results were presented by Ciejka *et al.* and Bediz *et al*., who observed an increase of lipid peroxidation under the influence of magnetic fields [32, 33]. The observed differences in the magnetic field action may result from the application of various test model.

Peripheral action

In recent years, the number of reports on the peripheral analgesic activity of endogenous opioids including β-endorphin increases, particularly in response to the presence of painful inflammation. In addition to the central nervous system opioid peptides have been found in the cells of the immune response

[9]. In the initial phase of development of the inflammatory response opioid peptides are synthesized by granulocytes, then in the next stage of inflammation by monocytes and by lymphocytes, which become the main site of production of these peptides during the inflammatory process [9, 34]. Various factors, including cytokines and environmental stress, may lead to the release of the granule contents and local analgesic activity [34]. Despite the lack of reliable evidence it can be postulated that magnetic field is involved in the local analgesic effect through the release of opioid peptides from granules. The mechanism of action could be the similar to systemic analgesic activity.

Clinical trials

The analgesic effect of magnetic field is confirmed in clinical studies. Weintraub and Cole determined the impact of extremely low frequency magnetic field therapy on neurons function and reduction of neuropathic pain in patients with carpal tunnel syndrome (CTS). Randomized double-blind study was performed on 36 patients with symptomatic CTS. There was a statistically significant short- and long-term reduction in pain and improvement of neuronal function under the influence of magnetotherapy [35]. Similar results were obtained by Dakowicz *et al.* , who compared the effects of laser and magnetotherapy on patients with CTS and showed, like previous authors, the reduction in pain in both groups where laser or magnetic field were used. The same effect was seen after the second series of standard therapy lasting for about 6 months [36]. Moreover, Weintraub *et al.* conducted a randomized study on the effects of pulsed magnetic field on the reduction of neuropathic pain, and regeneration of nerve damage caused by diabetic neuropathy. Clinical trials included 225 patients with symptomatic diabetic neuropathy. The experimental results showed that the use of magnetic field therapy reduces pain in patients neuropathy [37]. Similar observations were made by Wrobel *et al.* , who conducted a randomized clinical trial, with 32 patients with diabetic neuropathy. They found that the magnetic field has a positive effect on the inhibition of pain intensity, and thus improve the quality of life and sleep disorder [38].

Sutbeyaz *et al.* assessed the effect of the pulse of magnetic field in patients with fibromyalgia (FM), ie. generalized muscle pain and arthritis. A randomized, double-blind study was performed on 56 women, aged 18-60 years of FM. They claimed that megnetotherapy may reduce pain, fatigue, and improve the general condition of the patients [39].

Summary
This study gives the overview of the literature on analgesic and anti-inflammatory effects of magnetic field. Presented results indicate that the application magnetotherapy as a form of therapy for many diseases associated with painful inflammation may be beneficial alternative to standard forms of treatment, particularly applied in order to reduce pharmacotherapy. Interest in the magnet may be due to low hazard, wide applicability and good clinical outcomes, simultaneously with a low cost.

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