Bundesamt
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Spotlight on EMF Research

Spotlight on “Alternating magnetic fields drive stimulation of gene expression via generation of reactive oxygen species” by Mundell et al. in iScience (2024)

Category [radiofrequency, theory/molecular mechanism]

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Competence Centre Electromagnetic Fields (KEMF)

1 Putting the paper into context by the BfS

Magnetogenetics is a new field of research exploring whether and how biological functions could be controlled in a targeted and non-invasive way by magnetic fields in the future. This is of interest, for example, for medical applications. The present experimental study investigates the effect of magnetic fields on the iron storage protein ferritin. In genetically modified cells, ferritin, due to its iron content, is expected to act as a magnetic field sensor and relay the magnetic field signal to another protein, such as an ion channel, which in turn regulates a desired biological function. The mechanism by which magnetic fields can interact with ferritin to influence biological processes is incompletely understood [2]. Since ferritin stores about 20% of the iron in the human body, insights gained from the field of magnetogenetics can potentially also be relevant for radiation protection.

2 Results and conclusions from the authors‘ perspective

The aim of the present study by Mundell et al. [1] is to understand the molecular mechanism by which the protein ferritin can transmit signals from magnetic fields to other proteins. Building on their previous study [3], Mundell et al. used the cell membrane ion channel "Transient Receptor Potential Vanilloid 1" (TRPV1), to act as a signal receiver for the potentially magnetic field-sensitive ferritin. They coupled the two proteins, TRPV1 and ferritin, to localise ferritin inside the cell in close proximity to TRPV1 ion channels and the cell membrane. Under physiological conditions, TRPV1 can be activated by heat, mechanical stimuli, noxious agents such as reactive oxygen species (ROS) and molecules such as capsaicin (the spicy component of chilli peppers). When activated, TRPV1 allows calcium ions to enter the cell. The linked proteins ferritin and TRPV1 were introduced into the human embryonic kidney 293T (HEK293T) cell line using genetic engineering techniques. Modified HEK293T cells were used, in which the influx of calcium ions activates a calcium-sensitive gene in the cell nucleus. This gene can be specifically measured. In HEK293T cells, which have been turned into a magnetic field sensor, the gene’s activity can be determined in response to an external magnetic field.

In their previous study, such HEK293T cells were exposed to an alternating magnetic field (AMF) for two hours. The AMF was generated by a two-turn coil at 501 kHz and had a magnetic flux density of about 27 mT. A twofold increase in gene activity above the background signal was measured after exposure. In addition, when exposed to AMF at a temperature of 32 °C, it was observed that the substance capsaicin, which is otherwise ineffective at this temperature, was able to stimulate the activity of the TRPV1 ion channel. This resulted in a significant potentiation of the AMF effect by capsaicin with up to a tenfold increase in gene activity. This potentiation could be blocked by experimentally reducing the amount of ROS [3]. The research team concluded that ROS are necessary for magnetic field sensitivity.

To better understand the role of ROS, and since it has been reported that TRPV1 channels can be opened by ROS, in the current study Mundell et al. introduced a mutation of two oxidation- or ROS-sensitive amino acid residues of TRPV1 (cysteines at positions 257 and 741). Using this mutant, both AMF-induced activity and capsaicin potency were largely eliminated. This suggests that ROS are essential for the transfer of the magnetic field signal from ferritin to TRPV1. Spatial coupling of ferritin to the TRPV1 ion channel was also necessary for an effect to occur. This suggests that AMF-stimulated ferritin must generate the ROS in close proximity to the TRPV1 ion channel for the ROS concentration to be high enough to activate TRPV1.

From the data collected, the study derives the concept that alternating magnetic fields with a sufficiently high flux density can stimulate ferritin to generate ROS. In the context of magnetogenetics, the accumulation of ROS around the TRPV1 ion channel leads to the oxidation of its cysteine residues. This increases the conductivity of the TRPV1 ion channel for calcium ions and reduces the temperature required for capsaicin to be effective from 37 °C to 32 °C. Overall, starting with ferritin, this leads to activation and increased overall magnetogenetic activity in response to an AMF.

3 Comments by the BfS

The present study provides new insights and further clues into the possible effects of magnetic fields on biological molecules. In particular, Mundell et al. convincingly show that calcium flux through the TRPV1 ion channel can only be induced by a high frequency alternating magnetic field (AMF) when ferritin is positioned close to TRPV1 ion channels and TRPV1 is sensitive to reactive oxygen species (ROS). This is supported by the lack of effect when certain cysteine amino acids on the TRPV1 channel lose their oxidation sensitivity due to a mutation. Mundell et al. thus identify a possible causal chain that may be relevant for radiation protection. According to this concept, AMF acts on the iron storage protein ferritin in such a way that it leads to the formation of ROS, which react with TRPV1 and can activate it. However, the proximity between the two proteins is artificial and does not occur in nature.

The magnetogenetic effect of ferritin was previously interpreted based on thermal or mechanical processes. These explanations were later challenged by theoretical calculations and experimental results, and a biochemical explanation was proposed [4-6]. According to two other independent research groups, the magnetogenetics of ferritin is based on the iron-dependent generation of ROS [6-7]. Molecular changes in or on ferritin [8] caused by AMF are thought to lead to the release of iron ions and an increase in the concentration of labile (reactive) iron in the cell. This would favour the formation of ROS. A response to the magnetic field has been observed above a certain threshold for the product of frequency and magnetic flux density [2, 3]. However, the exact biophysical and biochemical mechanism of how magnetic fields could cause increased iron release from ferritin remains to be determined.

AMF at the frequencies and magnetic flux densities used in the studies [1-3, 6] may occur mainly in specialised and controlled environments with medical, industrial or scientific applications. The magnetic flux densities that occur during exposure of the general population are usually well below the levels studied here.

From a radiation protection point of view, the results do not allow any conclusions to be drawn about possible health effects of magnetic fields on humans. However, despite the very high magnetic flux

densities used here, the potential sensitivity of ferritin to alternating (magnetic) fields, and a possible resulting generation of ROS, deserves further attention in order to improve the understanding of possible effects of magnetic fields on biological systems. This is relevant, for example, in the context of oxidative stress [9]. We emphasise that the specific exposure conditions discussed here and the highly artificial experimental system do not allow the present work to be used as evidence for ROS generation induced by electromagnetic fields below the limits, as postulated in many studies. Furthermore, the frequency range used in this work is not relevant for mobile communication or power grids.

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