Medical Hypotheses 122 (2019) 68–72

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Activation of the intracellular temperature and ROS sensor membrane protein STIM1 as a mechanism underpinning biological effects of low-level low frequency magnetic fields

Myrtill Simkó*, Mats-Olof Mattsson

SciProof International AB, Östersund, Sweden

ARTICLE INFO

Keywords:
Magnetic field
Biological effects
Mechanism
Ca^{2+} homeostasis
Redox homeostasis

ABSTRACT

The biological effects of low frequency magnetic fields (LF MF) at high flux densities are well known and the underlying mechanism is established. In contrast, health associated effects at lower flux densities, which can be found in the human environment, are controversial, and no accepted interaction mechanism has been presented.

Here we present a hypothesis regarding the biological aspect of interaction between LF MF and cells. We suggest that the endoplasmic reticulum (ER) membrane protein STIM1, which functions as a sensor for several cellular conditions (low Ca^{2+} levels, temperature increase, increased levels of oxygen radicals, hypoxia), is a candidate LF MF sensor. Such a sensor function can be either direct (via local temperature increase caused by intracellularly induced electric fields), or indirect due to responses to increased reactive oxygen species (ROS) levels. Activated STIM1 leads to downstream effects by activation of signal transduction processes and changes in gene expression leading to secondary events. The nature of these changes would be dependent on both cell type and the particular physiological state the cell displays at the time of STIM1 activation.

Results from testing of this hypothesis, as suggested in this paper, would greatly assist in understanding of the possible health-related effects of low-level LF MF. This would benefit both safety assessments regarding MF exposure as well as possible use of MF in medicine.

A better understanding of the biological mechanisms underpinning MF exposure effects of living matter allows the targeted use of the fields in medical applications. There are several examples already in use based on empiric and not on mechanistic knowledge. Knowledge generated from our hypothesis testing makes it possible for MF based medical applications to be optimized.

Introduction

The biological effects of low frequency magnetic fields (LF MF) at high flux densities are well known and the underlying mechanism is established. In contrast, effects at lower flux densities are controversial, although health concerns linger since the International Agency for Research on Cancer [1] (belonging to WHO) evaluated LF MF recently and classified this agent as category 2B, which corresponds to “possibly carcinogenic to humans”. Significantly, no accepted interaction mechanism has been presented that can explain LF MF effects at low flux density levels that are present in the environment.

Low frequency MFs encompass frequencies from 1 to 100 kHz and cause biological effects by the same mechanism irrespective of frequency (see e.g. [2]). These time-varying magnetic fields can induce electric currents in a body which when strong enough can depolarize the membrane of excitable cells and cause excitation of nerve and muscle tissues and the induction of retinal phosphenes. Such effects are transient, limited to the duration of the exposure, and cause various biological responses ranging from perception to annoyance depending on the strength of the induced electric fields. At very high levels, more dramatic and even life-threatening conditions can occur due to interference with cardiac function. The sometimes controversial discussion does not deal with the accepted conditions, but rather with that biological and health related effects may occur at flux density levels that are under established exposure guidelines. The direct cellular targets in producing these effects are not known, and there is no generally accepted biophysical interaction mechanism that can explain such “low level” effects (see, e.g., the last Opinion from the Scientific Committee on Emerging and Newly Identified Health Risks for a recent review of health-related effects of EMF exposure and a discussion about

* Corresponding author at: SciProof International AB, Vaktpoststigen 4, 83132 Östersund, Sweden.
E-mail address: myrtill.simko@sciproof-international.se (M. Simkó).

https://doi.org/10.1016/j.mehy.2018.10.013
Received 21 September 2018; Accepted 20 October 2018

mechanisms [3]). All further discussions about effects of LF MF in this paper concern possible effects below the flux density levels that cause induced currents of such strength that excitation of tissues occur.

Many studies have investigated if there are responses to different kinds of MF exposure regimes in different cell types *in vitro*, showing both presence and absence of effects. The reasons for the diverse outcomes can be based on various factors such as; that there are no effects to detect at all, the effects are too subtle and difficult to detect in comparison to effects caused by other stressors (chemicals, UV or ionizing radiation), or there are too many experimental variables that are not well controlled.

Although that it is not clear how the first interaction takes place, there are some hypotheses available (see e.g. [4]). However, none of these has been confirmed. Since it is known that MF has too low energy to break molecules, the interaction can possibly be via heat development in the form of intracellular "hot spots" caused by Faraday induction of electric fields and associated currents [5]; by induced electric fields that changes the conformations of molecules such as receptors and ion channels, which is used in transcranial magnetic stimulation [6]; by radical pair mechanisms [7]; or by a combination of these or other mechanisms, which can start a reaction. It should be stressed that none of these suggested mechanisms has been generally accepted as explanation for biological and/or health related effects of weak magnetic fields.

Complicating the problem is also that any specific cellular/subcellular target for the biophysical interaction has not been identified. Assuming that the studies suggesting biological effects at low MF levels are correct, the *in vitro* studies have shown that basically all major cellular activities can be affected (see e.g. [8] for recent and critical overviews of relevant studies). Thus, immediate membrane-related events (such as changes in intracellular levels of Ca^{2+} ions), signs of oxidative stress, activation of signal transduction pathways, changes in gene expression, effects on DNA integrity, recruitment of heat shock responses, and effects on cell proliferation and cell survival have all been detected. It is reasonable to assume that most of such observations do not reflect primary MF-influence, but rather that the events are examples of down-stream consequences of an initial interaction between applied MF and biomolecules that will have various effects due to actual status or "preparedness" of the cell.

Here we present a hypothesis for the mode of action of MF on cells that also can account for the diversity of reported effects. We assume that low frequency MF can activate the endoplasmic reticulum (ER)-membrane localized stromal interaction molecules protein STIM1, which has been shown to function as a sensor for several cellular conditions such as intra endoplasmatic reticulum (ER) low Ca^{2+} levels, temperature increase, increased levels of oxygen radicals, and hypoxia.

The relevance of the STIM1 protein

Intracellular Ca^{2+} is essential for diverse cellular functions (see inter alia [9]) and its involvement in MF effects has been investigated repeatedly (see e.g. [10]) for a comprehensive review), but still without any explanation for a mode of action of MF effects. However, the mechanism of Ca^{2+} entry into many cell types including immune cells is triggered by depleting ER Ca^{2+}, a process termed store-operated Ca^{2+} entry (SOCE). Stromal interaction molecules (STIM1 and STIM2) are located mainly in the ER membrane with a single transmembrane domain and are ubiquitous ER **Ca^{2+} sensors** that rapidly translocate to couple with 'store-operated' ORAI Ca^{2+} channels, which are integrated into the plasma membrane when luminal Ca^{2+} levels are low. STIM1 also **senses heat changes**, which trigger a similar translocation and prime STIM1 to activate ORAI, suggesting that STIM1 functions as a sensor of multiple stress signals [11,12].

Local changes in intracellular temperature occur constantly due to normal physiological processes [13,14]. For example, it has been shown in a temperature mapping study that the nucleus and the centrosome of COS7 cells show significantly higher temperature (0.96 °C) than the surrounding cytoplasm, in a cell cycle dependent manner [13]. Tanimoto and colleagues showed heat production in chemically treated (Carbonyl cyanide 3-chlorophenylhydrazone, a protonophore and an uncoupler of oxidative phosphorylation) mitochondria of SH-SY5Y cells [14]. Thus, the function of STIM1 as a ubiquitous sensor and transducer of temperature-linked events is based on normal physiological processes. These processes are fully understood today and are seen as a central tenet of SOCE, a mechanism by which receptor-mediated depletion of ER Ca^{2+} stores leads to the entry of Ca^{2+} across the plasma membrane. However, as discussed by Hooper et al. [11], the role of STIM proteins extends further, with an ever expanding number of physiological roles ascribed to the protein and proven interactions with a range of partners beyond ORAI.

STIM1 can also be activated by **oxidative stress** that promotes the oligomerization of STIM1 and thus the activation of SOCE [15,16]. As reviewed by Bhardwaj et al. [17] several studies showed that the induction of hypoxia or oxidative stress promotes the accumulation of endogenous or overexpressed STIM1 at ER-plasma membrane (PM) junctions in various cell lines. There is now clear evidence for ROS-dependent and store-independent STIM activation, highlighting new mechanisms behind ROS-dependent modulation of Ca^{2+} signals in physiological settings [11]. As reviewed by Hooper et al. mitochondrial ROS production can be stimulated by intracellular Ca^{2+} elevation, while Ca^{2+} elevation is also stimulated by ROS [11]. Thus, moderate amounts of ROS, induced under mild hypoxic conditions, mediate the activation of STIM1 leading to Ca^{2+} elevation in osteosarcoma cells [18]. On the other hand, excessive ROS elevation induces apoptosis via mitochondrial Ca^{2+} overload as cytosolic Ca^{2+} levels rise (see e.g. [19]), a STIM independent process.

ER and other intracellular membranes/organelles have important functions in cell physiology including lipid homeostasis, regulation of Ca^{2+} dynamics, and control of organelle biogenesis and dynamics. The SOCE cell signalling is essential for e.g. immune and muscle function controlled by the interactions between STIM proteins on the ER and Ca^{2+}-permeable ORAI channels on the PM. These STIM/ORAI interactions are very dynamic processes occurring at **membrane contact sites (MCS).** There is evidence that STIM/ORAI interactions, as they are considered to be restricted to ER-PM MCS, interact also with different intracellular organelles such as mitochondria, phagosomes, endosomes, lysosomes and Golgi apparatus (see recent reviews by [20,21]). Thus, the huge ER-net communicates with intracellular organelles not only by vesicular transport, but also by MCS allowing cross-talk between neighbouring membranes [20]. The most prominent contact sites with the ER are involved in the exchange of membrane lipids and ions. The mitochondria associated membranes (**MAM**) and the ER contact sites are separated by 10–30 nm, which is an optimal distance for efficient transport for lipids and ions by means of diffusion [22]. Both mitochondria and ER are intracellular sites of ROS production, where MAM is the place, where ROS exchange and Ca^{2+} crosstalk between the ER and mitochondria occurs.

The relevance of STIM and ORAI function in **immunity** is emphasized by the fact that the loss of function of either protein in humans (by mutations) leads to severe immunodeficiency [23]. ROS (as an immune modulating signal molecule) modulate SOCE activity in immune cells and in STIM1/ORAI expression systems. The SOCE pathway is exposed to local redox changes appearing within the ER lumen and at the (mitochondria)-plasma membrane where the STIM proteins sense a drop in the luminal ER Ca^{2+} concentration. STIM1 is the only currently known intracellular calcium sensor that functions as a calcium influx regulator which controls immune cell activation [24]. In STIM1$^{-/-}$ microglia, reduced cytokine secretion, chemically or opsonin-dependent phagocytosis, as well as ATP-stimulated chemotactic migration was recently shown [24]. These observations strengthen that STIM1 plays an important role in immune system function.

Since many of the above mentioned downstream events (effects) of

STIM1 has also been observed after MF exposure *in vitro* and *in vivo*, we think that the STIM1 protein is a good candidate for the interaction site of MF induced effect(s), which can possibly be accomplished by activation of the protein via heat development and/or free radical release.

The hypothesis

It has been shown that the ER membrane protein STIM1 functions as a sensor for several cellular conditions (low Ca^{2+} levels, temperature increase, increased levels of oxygen radicals, hypoxia). The available literature shows that cells respond to MF exposure with changes in intracellular Ca^{2+} concentration and free radical production. Different secondary effects have also been described after MF exposure *in vitro* and *in vivo* (e.g. changes in cell proliferation, differentiation etc.). Thus, our hypothesis states that LF MF exposure causes the cell-specific activation of STIM1, either via oxidative stress or via intracellular local temperature increases. The activation can either be an effect of that the MF cause localized intracellular heating ("hot spots", caused by induced electric fields), or that the MF cause increased oxygen radical levels which then trigger the activity of STIM1. Since ROS release itself causes mitochondrial temperature increase, STIM1 can also be activated by that physiological temperature change. Activated STIM1 leads to downstream effects by activation of signal transduction processes and changes in gene expression leading to secondary events (Fig. 1). The nature of these changes would be dependent on both cell type and the particular physiological state the cell displays at the time of STIM1 activation.

Evaluation of the hypothesis

ROS production as the most common MF response

Reactive oxygen species (ROS) are molecules containing oxygen that are highly chemically reactive because they contain free radicals. High levels of ROS can lead to a number of damaging pathological consequences in cells and the organism, including lipid peroxidation, protein damage, deactivation of enzymatic activities, and DNA modification and pro-inflammatory processes as well as the induction of apoptosis. Low levels of ROS function as a second messenger to induce secondary events. STIM1 activation can be a consequence of both these conditions.

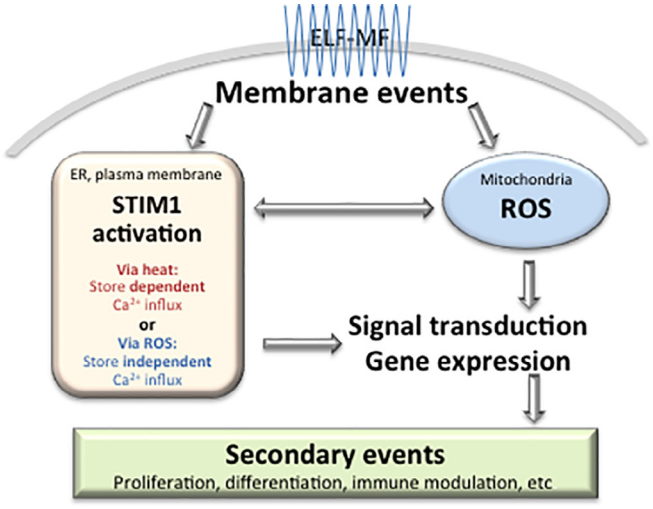

Fig. 1. STIM1 activation as suggested is the key initial event for cellular effects of exposure to low frequency (LF) magnetic fields (MF). The model suggests that exposure to LF MF either causes direct activation of STIM1 by heat development (via induced electric fields), or by ROS release. STIM1 can also be activated via changes in the redox status of the cell (ROS production) in an indirect manner. Dependent on cell status, a number of different signal transduction pathways and secondary events can be influenced.

Numerous investigations have shown the release of ROS, or other oxidative processes, after MF exposure and were often connected to other investigated effects. ROS production has been investigated directly and also indirectly by e.g. detecting DNA damage in different cell types during various exposure conditions. Therefore, we assume that oxidative processes triggered by MF play a key role for the effectiveness of MF [25,26]. As shown earlier, short-time exposure (45 min) to MF (1 mT) resulted in significantly increased phagocytic activity accompanied by a significantly increased ROS release [27]. Many studies confirmed this finding, as recently reviewed and analysed in a total of 41 scientific original publications [28]. The review tested the hypothesis that LF MF exposure *in vitro* causes changes in oxidative status as an early response, and the strongest association between MF exposure and effects occurred at 0.1 or 1 mT. Furthermore the effects were not cell type or exposure duration dependent, and they are modest in comparison with the corresponding positive controls. Also other more recent studies have investigated the induction of ROS after MF exposure. Zeng et al. [29] applied repeated MF exposure (50 Hz, 2 mT ELF MF for 8 h per day) to primary cultured hippocampal neurons and investigated oxidative stress, among other endpoints, and detected increased ROS levels. Mannerling et al. [30] reported that 0.025–0.10 mT MF (50 Hz, 1 h exposure) increased (30–40%) the levels of the superoxide radical anion, comparable to the positive control PMA in the human leukaemia cell line K562 and increased two-fold the level of the heat stress protein HSP70. MF exposure together with free radical scavengers (melatonin or 1,10-phenantroline) inhibited the MF-induced increase in HSP70 and superoxide radical anion release. These findings were recently confirmed by Pooam et al. [31] using RAW264 macrophages. The authors showed similar effects, namely that 50 Hz MF diminished the mitochondrial membrane potential leading to the increase in the production of O^{2-} and the expression of HSP70 protein. Calcabrini et al. [32] investigated ROS levels in human keratinocytes exposed for 1 h to 50 Hz ELF-MF (from 0.025 to 0.2 mT) and detected significant ROS increases at 0.05 and 0.1 mT. Moreover, glutathione content, antioxidant defense activity, and lipid peroxidation markers were assessed for different exposure lengths. The authors detected that there was a greater sensitivity of the cells exposed to 0.05 mT than to other flux densities. Reale et al. [33] evaluated the effects of MF (50 Hz, 1 mT) on human SH-SY5Y cells, and found increased NOS and oxygen radicals release accompanied by changes in antioxidant catalase (CAT) activity and enzymatic kinetic parameters related to CYP-450 and CAT activity.

Also static magnetic fields (SMF) have been shown to influence a number of cellular activities, including formation of ROS and transmembrane Ca^{2+}-transport (inter alia [34]). Such interactions are suggested to be dependent on that biomolecules contain magnetic dipole moments (see e.g. [35]). Whether or not this is a prerequisite also for LF MF interactions with cells in the context we are discussing here is unknown. Furthermore at present it is not known if, STIM1 does contain epitopes that suggest the presence of magnetic dipole moments. However, effects originating with local temperature increases would be more likely occurring independent of the presence of any dipole characteristics of the protein.

Taken together, moderate free radical release induced by LF MF is a key measurable response to exposure. We think that MF either influences the membrane STIM1 protein by intracellular local heat development via induced electric fields, secondarily leading to ROS release, or that MF-caused ROS release activates STIM1. Thus, STIM1 does not react directly to low level LF MF but to temperature change and ROS (as well as calcium concentration change). There are no studies investigating either intracellular induced "hot spots" or induced electric fields caused by MF. Since, as described above, the mitochondria and ER are the major ROS production sites within cells, ROS exchange and also Ca^{2+} crosstalk (as a secondary measurable event) can occur at the sites of MAMs and MCSs, where STIM1 is located. Therefore STIM1

activation by ROS or by heat could play a key role in the mode of action.

Experiments to test the hypothesis

There are several possible approaches to investigate the possible activation of STIM1 during or after exposure to MF *in vitro*. The first requisite is to have a cell line that consistently responds to MF exposure with an effect such as ROS release, which we assume is at least one of the very first biological responses to exposure. It is known that different cell lines react similarly to specific chemicals, however, the responses to MF seem to be different among different cells types. Thus, the cell line in question needs to have the potential to generate ROS upon stimulation, and to respond to MF with increased ROS production.

In the case of a positive response to MF (induced ROS production), the direct activation of the STIM1 protein can be visualized by studying the formation of puncta (based on e.g. imaging techniques using relevant antibodies) containing the complexes formed by STIM1/ORAI at the junction between the plasma membrane and the ER membrane.

However, although such a finding provides support for the STIM1-activating potential of MF, it does not directly address if STIM1-activation is responsible for, or at least involved in, stimulation of ROS production. A way to approach the latter is to inhibit STIM1, either on the gene expression level (e.g. si-RNA, cell lines with STIM1 gene deficiencies such as STIM1$^{-/-}$ knockout cell lines that are commercially available) or on the functional level using specific inhibitors (see e.g. [36]).

The outcomes of such experiments answer the question if MF-induced STIM1 activation is a factor in MF-caused ROS production, but do not address in what way MF can trigger STIM1 activation. Our hypothesis is that MF either causes intracellular heating, or starts a chain of ROS-production events where the first initial step leads to increases in ROS that activate STIM1, which in turn leads to further stimulation of ROS production. Investigations in the presence of scavengers or NAD(P)H inhibitors that suppresses or inhibits the MF induced ROS production but not STIM1 activation via heat, could give hints to the question if ROS or heat is the “inducer” of STIM1 activation.

Intracellular temperature in real time can be investigated by confocal laser microscopy techniques.

These sets of experiments are realistically testing the different aspects of the hypothesis, and will, independent of outcome at each step, provide valuable insight into mechanisms behind possible biological effects of LF MF at lower flux density levels.

Consequences of the hypothesis and discussion

LF MF exposure induces biological effects/reactions, however the mechanistic mode of action is still not clear. Therefore, it is still a discussion about its relation to health related issues: Is it inducing any effects or reactions in living matter? Is it causing detrimental or beneficial effects? Studies have shown bidirectional effects *in vivo* and *in vitro* as well as no effects at all. A further question, which remains is, why cells/tissues/organisms are reacting differently to the same agent?

To answer these questions one has to keep in mind that different cells/tissues/organisms react differently to other physical or chemical agents as well. This is depending on several physiological factors such as the cellular metabolic and redox state, cell cycle stage, genetic and molecular background at the time of exposure etc. A strong effect/reaction to an agent is easier to detect in certain cells/tissues/organisms but not in other ones, whereas a very weak effect can easily be hidden within the background noise and will not be detected as an effect.

The presented hypothesis allows investigating the direct involvement of a specific protein, namely STIM1, since activation of STIM1 leads to puncta-formation, which can be studied by various techniques. Thus, it is not necessary to focus on a measurable downstream effect, to understand an early interaction of MF and cells/tissues/organisms. Correspondingly, it is known that downstream effects can differ from cell type to cell type. It has been shown that the ubiquitous STIM1 promotes the growth of human oral tongue squamous cell carcinoma (OTSCC) cells by regulating apoptosis and the cell cycle [37]. However no involvement of STIM1 was shown on cell proliferation in vascular smooth muscle cells [38], human myoblasts [39], HEK293 cells [40], human umbilical vein endothelial cells (HUVEC) derived cell line EA.hy926 [41], and in normal HUVEC [42].

The tests of our hypothesis will provide a number of knowledge gains, which of course differ dependent on the outcomes of the tests. First of all, we suggest to focus on the possible involvement of a distinct protein species based on what we already know regarding outcomes from *in vitro* and *in vivo* studies that have investigated LF MF effects. In the absence of effects on STIM1 activation, we would nevertheless be able to design further studies related to ROS production that are more directly focused on ROS production per se.

On the other hand, if the data suggest that STIM1 is involved in the MF response, further studies aiming for direct coupling to signal transduction events, with or without Ca^{2+}-involvement, are relevant to perform. Also the up-stream events leading to STIM1 activation will then be possible to address, which would provide meaningful information about where the initial biophysical interaction takes place.

We have not discussed the various aspects of exposure that are important for our question in this hypothesis paper. Our discussion has been focused on LF MF, without specifying either a frequency, the flux density, the wave form or modulation of the field, or the exposure duration. All these factors are relevant and would be amenable for more detailed studies if the results indicate that there are effects of the MF exposure that we can better understand in terms of biological mechanisms compared to before the testing of our hypothesis. Based on a multitude of studies (e.g. summarized in [28]), it is relevant to design exposure conditions that include power frequency MF (50 or 60 Hz), sine wave configuration, a flux density of 1 mT, and exposure durations of up to 1 h. Such a combination of conditions reflects pretty well conditions used in many of the studies that have recorded exposure effects. A much more detailed study into exposure conditions should be part of a continuation after the initial hypothesis testing. The results from such studies serve both to test the credibility of claims of health related effects of environmental exposures, and would also be helpful in designing novel hypotheses regarding primary biophysical interaction mechanisms.

A better understanding of the biological mechanisms underpinning MF exposure effects of living matter allows the targeted use of the fields in medical applications. There are several examples already in use based on empiric and not on mechanistic knowledge. Knowledge generated from our hypothesis testing makes it possible for MF based medical applications to be optimized.

Conflict of interest statement

The authors declare no conflicts of interest.

Funding

This work was not supported by grants.

References

[1] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Non-ionizing radiation, part 1: static and extremely low-frequency (ELF) electric and magnetic fields. IARC Monogr Eval Carcinog Risks Humans 2002;80:1–395. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12071196.

[2] ICNIRP. Guidelines for limiting exposure to time-varying electric and magnetic fields (1 Hz to 100 kHz). Health Phys 2010;99(6):818–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21068601%5Cnhttps://drive.google.com/open?id=0B-_EfabIdYlFTkU4NmlYMVBsVjA&authuser=0%5Cnhttps://drive.google.com/open?id=0B-_EfabIdYlFZDFlamwzZTM5Ym8&authuser=0.

[3] Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).

Opinion on: potential health effects of exposure to electromagnetic fields (EMF). [Internet]. 2015 [cited 2017 Aug 10]. p. 288. Available from: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_041.pdf.
[4] Valberg P, Kavet R, Rafferty CN. Can low-level 50/60 Hz electric and magnetic fields cause biological effects? Radiat Res 1997;148(1):2. Available from: http://www.jstor.org/stable/3579533?origin=crossref.
[5] Racuciu M, Miclaus S, Creanga D. On the thermal effect induced in tissue samples exposed to extremely low-frequency electromagnetic field. J Environ Health Sci Eng 2015;13(1):85. https://doi.org/10.1186/s40201-015-0241-8.
[6] O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev 2018;4(4) CD008208. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29652088.
[7] Barnes FS, Greenebaum B. The effects of weak magnetic fields on radical pairs. Bioelectromagnetics 2015;36(1):45–54. https://doi.org/10.1002/bem.21883.
[8] Ahlbom A, Bridges J, de Seze R, Hillert L, Juutilainen J, Mattsson MO, et al. Possible effects of electromagnetic fields (EMF) on human health–opinion of the scientific committee on emerging and newly identified health risks (SCENIHR). Toxicology 2008;246(2–3):248–50.
[9] Berridge MJ, Bootman MD, Lipp P. Calcium–a life and death signal. Nature 1998;395(6703):645–8. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9790183.
[10] Golbach LA, Portelli LA, Savelkoul HFJ, Terwel SR, Kuster N, de Vries RBM, et al. Calcium homeostasis and low-frequency magnetic and electric field exposure: a systematic review and meta-analysis of in vitro studies. Environ Int 2016;92–93:695–706.
[11] Hooper R, Samakai E, Kedra J, Soboloff J. Multifaceted roles of STIM proteins. Pflügers Arch Eur J Physiol 2013;465(10):1383–96.
[12] Xiao B, Coste B, Mathur J, Patapoutian A. Temperature-dependent STIM1 activation induces Ca2+ influx and modulates gene expression. Nat Chem Biol 2011;7(6):351–8. https://doi.org/10.1038/nchembio.558. Nature Publishing Group.
[13] Okabe K, Inada N, Gota C, Harada Y, Funatsu T, Uchiyama S. Intracellular temperature mapping with a fluorescent polymeric thermometer and fluorescence lifetime imaging microscopy. Nat Commun 2012;3:705. https://doi.org/10.1038/ncomms1714. Nature Publishing Group.
[14] Tanimoto R, Hiraiwa T, Nakai Y, Shindo Y, Oka K, Hiroi N, et al. Detection of temperature difference in neuronal cells. Sci Rep 2016;6:22071. Nature Publishing Group, Available from: http://dx.doi.org/10.1038/srep22071%5Cnhttp://www.nature.com/articles/srep22071%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/26925874%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4772094.
[15] Hawkins BJ, Irrinki KM, Mallilankaraman K, Lien YC, Wang Y, Bhanumathy CD, et al. S-glutathionylation activates STIM1 and alters mitochondrial homeostasis. J Cell Biol 2010;190(3):391–405.
[16] Prins D, Groenendyk J, Touret N, Michalak M. Modulation of STIM1 and capacitative Ca2+ entry by the endoplasmic reticulum luminal oxidoreductase ERp57. EMBO Rep 2011;12(11):1182–8.
[17] Bhardwaj R, Hediger MA, Demaurex N. Redox modulation of STIM-ORAI signaling. Cell Calcium 2016;60:142–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27041216.
[18] Mungai PT, Waypa GB, Jairaman A, Prakriya M, Dokic D, Ball MK, et al. Hypoxia triggers AMPK activation through reactive oxygen species-mediated activation of calcium release-activated calcium channels. Mol Cell Biol 2011;31(17):3531–45. https://doi.org/10.1128/MCB.05124-11.
[19] Grimm S. The ER-mitochondria interface: the social network of cell death. Biochim Biophys Acta Mol Cell Res 2012;1823(2):327–34.
[20] Wu Y, Whiteus C, Xu CS, Hayworth KJ, Weinberg RJ, Hess HF, et al. Contacts between the endoplasmic reticulum and other membranes in neurons. Proc Natl Acad Sci 2017;114(24):E4859–67. https://doi.org/10.1073/pnas.1701078114.
[21] Demaurex N, Guido D. Store-operated Ca^{2+} entry (SOCE) pathways. Groschner K, Graier WF, Romanin C, editors. Advances in Experimental Medicine and Biology, vol. 993. Cham: Springer International Publishing; 2017. p. 277–96. Available from: http://link.springer.com/10.1007/978-3-319-57732-6.
[22] Gatta AT, Levine TP. Piecing together the patchwork of contact sites. Trends Cell Biol England 2017;27(3):214–29.
[23] Demaurex N, Nunes P. The role of STIM and ORAI proteins in phagocytic immune cells. Am J Physiol Cell Physiol 2016;310(7):C496–508. https://doi.org/10.1152/ajpcell.00360.2015.
[24] Lim HM, Woon H, Han JW, Baba Y, Kurosaki T, Lee MG, et al. UDP-induced phagocytosis and ATP-stimulated chemotactic migration are impaired in STIM1(−/−) microglia in vitro and in vivo. Mediators Inflamm 2017;2017.
[25] Simkó M. Cell type specific redox status is responsible for diverse electromagnetic field effects. Curr Med Chem 2007;14:1141–52. Available from: http://www.ingentaconnect.com/content/ben/cmc/2007/00000014/00000010/art00008.
[26] Simkó M, Mattsson M-O. Extremely low frequency electromagnetic fields as effectors of cellular responses in vitro: possible immune cell activation. J Cell Biochem 2004;93(1):83–92. https://doi.org/10.1002/jcb.20198.
[27] Simkó M, Droste S, Kriehuber R, Weiss DG. Stimulation of phagocytosis and free radical production in murine macrophages by 50 Hz electromagnetic fields. Eur J Cell Biol 2001;80(8):562–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11561907.
[28] Mattsson M-O, Simkó M. Grouping of experimental conditions as an approach to evaluate effects of extremely low-frequency magnetic fields on oxidative response in in vitro studies. Front Public Health 2014;2:132. Available from: http://journal.frontiersin.org/journal/10.3389/fpubh.2014.00132/full%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/25229055%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4151017.
[29] Zeng Y, Shen Y, Hong L, Chen Y, Shi X, Zeng Q, et al. Effects of single and repeated exposure to a 50-Hz 2-mT electromagnetic field on primary cultured hippocampal neurons. Neurosci Bull 2017;33(3):299–306. https://doi.org/10.1007/s12264-017-0113-6.
[30] Mannerling A-C, Simkó M, Mild KH, Mattsson M-O. Effects of 50-Hz magnetic field exposure on superoxide radical anion formation and HSP70 induction in human K562 cells. Radiat Environ Biophys 2010;49(4):731–41. https://doi.org/10.1007/s00411-010-0306-0.
[31] Pooam M, Nakayama M, Nishigaki C, Miyata I, Miyata H, Miyata I. Effect of 50-Hz sinusoidal magnetic field on the production of superoxide anion and the expression of heat-shock protein 70 in RAW264 cells. Int J Chem 2017;9(2):23. Available from: http://www.ccsenet.org/journal/index.php/ijc/article/view/66925.
[32] Calcabrini C, Mancini U, De Bellis R, Diaz AR, Martinelli M, Cucchiarini L, et al. Effect of extremely low-frequency electromagnetic fields on antioxidant activity in the human keratinocyte cell line NCTC 2544. Biotechnol Appl Biochem 2016 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27001710.
[33] Reale M, Kamal MA, Patruno A, Costantini E, D'Angelo C, Pesce M, et al. Neuronal cellular responses to extremely low frequency electromagnetic field exposure: implications regarding oxidative stress and neurodegeneration. PLoS One 2014;9(8).
[34] Bekhite MM, Figulla H-R, Sauer H, Wartenberg M. Static magnetic fields increase cardiomyocyte differentiation of Flk-1+ cells derived from mouse embryonic stem cells via Ca2+ influx and ROS production. Int J Cardiol 2013;167(3):798–808. Available from: http://linkinghub.elsevier.com/retrieve/pii/S016752731200188X.
[35] Zhang L, Wang J, Wang H, Wang W, Li Z, Liu J, et al. Moderate and strong static magnetic fields directly affect EGFR kinase domain orientation to inhibit cancer cell proliferation. Oncotarget 2016;7(27):41527–39. Available from: http://www.oncotarget.com/fulltext/9479.
[36] Varnai P, Hunyady L, Balla T. STIM and Orai: the long-awaited constituents of store-operated calcium entry. Trends Pharmacol Sci 2009.
[37] Cui X, Song L, Bai Y, Wang Y, Wang B, Wang W. Stromal interaction molecule 1 regulates growth, cell cycle, and apoptosis of human tongue squamous carcinoma cells. Biosci Rep 2017;37.
[38] Li J, Sukumar P, Milligan CJ, Kumar B, Ma ZY, Munsch CM, et al. Interactions, functions, and independence of plasma membrane STIM1 and TRPC1 in vascular smooth muscle cells. Circ Res 2008.
[39] Darbellay B, Arnaudeau S, König S, Jousset H, Bader C, Demaurex N, et al. STIM1- and Orai1-dependent store-operated calcium entry regulates human myoblast differentiation. J Biol Chem 2009.
[40] El Boustany C, Katsogiannou M, Delcourt P, Dewailly E, Prevarskaya N, Borowiec AS, et al. Differential roles of STIM1, STIM2 and Orai1 in the control of cell proliferation and SOCE amplitude in HEK293 cells. Cell Calcium 2010.
[41] Antigny F, Girardin N, Frieden M. Transient receptor potential canonical channels are required for in vitro endothelial tube formation. J Biol Chem 2012.
[42] Abdullaev IF, Bisaillon JM, Potier M, Gonzalez JC, Motiani RK, Trebak M. Stim1 and orai1 mediate crac currents and store-operated calcium entry important for endothelial cell proliferation. Circ Res 2008.