From: Pall, Martin L
To: DOH EPH RP Info
Subject: Comments on WiFi Draft Report
Date: Wednesday, February 19, 2014 5:20:30 PM
Attachments: EMF-jcmm12088.pdf
MicrowaveEMF-safety-2.pdf

Dear All:

Let me first introduce myself. I am Professor Emeritus of Biochemistry and Basic Medical Sciences at Washington State University. I have received seven international honors for my research on environmental medicine over the past decade, with five of those after I "retired" from the University. I just received an 8th this morning for a paper I published on how electromagnetic fields impact the cells of our bodies, published in the prestigious medical journal, Journal of Cellular and Molecular Medicine (JCMM), see attached. The 8th such honor is that this JCMM EMF paper was chosen to be placed on the Global Medical Discovery web site as one of the top medical papers of 2013. I have also recently submitted a paper also on the effects of microwave frequency EMFs in producing a whole series of important changes in the body, changes that have been reported in many different studies and now have known mechanisms that explain how they come about. This second paper also discusses the issue of current health standards that are, as you know, based on the assumption that all we have to worry about is heating, however those standards are contradicted by over 20,000 papers in the scientific literature.

I have already given 4 professional talks on biological effects of EMFs and will be giving five more in Europe in a few weeks.

What has been shown in both of these papers, which are based in turn on many hundreds of other studies, is that EMFs act by activating what are known as voltage-gated calcium channels (VGCCs), opening up those channels and allowing calcium to flow into the cells, such that most of the consequences of such opening involve the effects of excessive intracellular calcium including downstream effects. The evidence for a VGCC role is that in two dozen studies, one could block all measured effects of EMFs by using calcium channel blockers, drugs that block these voltage-gated calcium channels. The downstream effects of excessive intracellular calcium include elevated nitric oxide (NO), NO signaling, peroxynitrite derived from NO and consequent oxidative stress. Heating which as you know is the basis of both the U.S. and International safety standards, has nothing to do with the biological effects, and therefore the safety standards are based on a false assumption.

What I considered in addition, in these two papers, with most of the consideration being in the second one, is whether and how the various biological effects that have been widely reported and documented, may be produced as a consequence of VGCC activation. There were 10 biological responses EACH OF WHICH HAVE BEEN WIDELY REPORTED and each of which can be understood as being generated by downstream consequences of VGCC activation and elevated intracellular calcium. Those 10 are: Oxidative stress, therapeutic effects, single strand breaks in cellular DNA (as detected by alkaline comet assays), double strand breaks in cellular DNA (as detected by formation of micronuclei), cancer (which can be generated by the same well-documented mechanism that produces inflammatory carcinogenesis), male and female infertility (in which DNA double strand

breaks have roles and possibly also calcium-triggered apoptosis), breakdown of the blood-brain barrier (produced by oxidative activation of matrix metalloproteinases and consequent degradation of tight junctions), and loss of melatonin leading to consequent sleep dysfunction. Each these has been widely reported, each of them is serious and each of them can be understood as being generated by the VGCC mechanism.

Contrast this with the advocates of heating as the sole or at least the main EMF effect and who cannot understand how any of these are generated. They use circular logic, this cannot be generated by heating therefore these hundreds of reports cannot be true, therefore this strengthens the case for heating.

Let me comment on the issue of inconsistency of the data. I examined the data on the studies of single stranded breaks in cellular DNA in the first paper. And yes, although the majority of studies showed substantial elevation of such breaks, there was a minority that did not. These different studies used different types of cells grown under different conditions or used different cells in the body and they often used different EMF fields. Two studies looked a several types of cells and showed that some cell types produced such single stranded breaks in the DNA and others did not. One study compared different EMF fields and showed that they differed from one another. THAT IS EXACTLY WHAT YOU WOULD EXPECT! Some cells have no VGCCs and will not respond, and some with only low levels may not respond either. The claim that these are inconsistent is simply based on a false expectation. I have not examined the other claims of inconsistency but am skeptical about them, as you should be. Even if there is genuine inconsistency, this does not allow one to throw out many thousands of studies showing real biological effects at EMF field levels that are well within "safety standards" and should not, therefore, occur at all.

Let me say just a few words about Wi-Fi. Barrie Trower whom I met about 3 months ago when he and I gave a talk in Portland, says that from his extensive experience as a military intelligence expert in the UK, that the wavelength used for Wi-Fi is particularly active biologically and is therefore especially problematic. The data showing this has been classified in the UK, the U.S. and other countries so we have no way of ascertaining how convincing it may be. He has been given permission to talk about this, but only at a superficial level. His number one concern is female fertility, because females develop all the eggs they will ever have before puberty, while they are in school. I have discussed the issue of Wi-Fi safety in schools in my second attached paper and ask you to give it careful thought - the health and safety of many thousands of students and teachers is in your hands. Sloppy reasoning is unacceptable.

Martin L. Pall
Professor Emeritus of Biochemistry and Basic Medical Sciences
Washington State University
Personal Information -...

J. Cell. Mol. Med. Vol 17, No 8, 2013 pp. 958-965

Electromagnetic fields act *via* activation of voltage-gated calcium channels to produce beneficial or adverse effects

Martin L. Pall *

Professor Emeritus of Biochemistry and Basic Medical Sciences, Washington State University, Portland, OR, USA

Received: January 8, 2013; Accepted: May 20, 2013

- **Introduction**
- **Possible modes of action following voltage-gated calcium channel stimulation**
- **Therapeutic bone-growth stimulation *via* Ca^{2+}/nitric oxide/cGMP/protein kinase G**
- **Ca^{2+}/nitric oxide/peroxynitrite and pathophysiological responses to EMF exposures: the example of single-strand DNA breaks**
- **Discussion and conclusions**

Abstract

The direct targets of extremely low and microwave frequency range electromagnetic fields (EMFs) in producing non-thermal effects have not been clearly established. However, studies in the literature, reviewed here, provide substantial support for such direct targets. Twenty-three studies have shown that voltage-gated calcium channels (VGCCs) produce these and other EMF effects, such that the L-type or other VGCC blockers block or greatly lower diverse EMF effects. Furthermore, the voltage-gated properties of these channels may provide biophysically plausible mechanisms for EMF biological effects. Downstream responses of such EMF exposures may be mediated through Ca^{2+}/calmodulin stimulation of nitric oxide synthesis. Potentially, physiological/therapeutic responses may be largely as a result of nitric oxide-cGMP-protein kinase G pathway stimulation. A well-studied example of such an apparent therapeutic response, EMF stimulation of bone growth, appears to work along this pathway. However, pathophysiological responses to EMFs may be as a result of nitric oxide-peroxynitrite-oxidative stress pathway of action. A single such well-documented example, EMF induction of DNA single-strand breaks in cells, as measured by alkaline comet assays, is reviewed here. Such single-strand breaks are known to be produced through the action of this pathway. Data on the mechanism of EMF induction of such breaks are limited; what data are available support this proposed mechanism. Other Ca^{2+}-mediated regulatory changes, independent of nitric oxide, may also have roles. This article reviews, then, a substantially supported set of targets, VGCCs, whose stimulation produces non-thermal EMF responses by humans/higher animals with downstream effects involving Ca^{2+}/calmodulin-dependent nitric oxide increases, which may explain therapeutic and pathophysiological effects.

Keywords: intracellular Ca^{2+} • voltage-gated calcium channels • low frequency electromagnetic field exposure • nitric oxide • oxidative stress • calcium channel blockers

Introduction

An understanding of the complex biology of the effects of electromagnetic fields (EMFs) on human/higher animal biology inevitably must be derived from an understanding of the target or targets of such fields in the impacted cells and tissues. Despite this, no understanding has been forthcoming on what those targets are and how they may lead to the complex biological responses to EMFs composed of low-energy photons. The great puzzle, here, is that these EMFs are comprised of low-energy photons, those with insufficient energy to individually influence the chemistry of the cell, raising the question of how non-thermal effects of such EMFs can possibly occur. The author

*Correspondence to: Martin L. PALL, Ph.D.,
Professor Emeritus of Biochemistry and Basic Medical Sciences, Washington State University, 638 NE 41st Ave., Portland, OR 97232 USA
Tel: +01-503-232-3883
E-mail: martin_pall@wsu.edu

doi: 10.1111/jcmm.12088

© 2013 The Author.
Journal of Cellular and Molecular Medicine Published by Foundation for Cellular and Molecular Medicine/Blackwell Publishing Ltd
This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

has found that there is a substantial literature possibly pointing to the direct targets of such EMFs and it is the goal of this study to review that evidence as well as review how those targets may lead to the complex biology of EMF exposure.

The role of increased intracellular Ca^{2+} following EMF exposure was already well documented more than 20 years ago, when Walleczek [1] reviewed the role of changes in calcium signalling that were produced in response EMF exposures. Other, more recent studies have confirmed the role of increased intracellular Ca^{2+} following EMF exposure, a few of which are discussed below. His review [1] included two studies [2, 3] that showed that the L-type voltage-gated channel blocker, verapamil could lower or block changes in response to EMFs. The properties of voltage-gated calcium channels (VGCCs) have been reviewed elsewhere [4]. Subsequently, extensive evidence has been published clearly showing that the EMF exposure can act to produce excessive activity of the VGCCs in many cell types [5–26] suggesting that these may be direct targets of EMF exposure. Many of these studies implicate specifically the L-type VGCCs such that various L-type calcium channel blockers can block responses to EMF exposure (Table 1). However, other studies have shown lowered responses produced by other types of calcium channel blockers including N-type, P/Q-type, and T-type blockers (Table 1), showing that other VGCCs may have important roles. Diverse responses to EMFs are reported to be blocked by such calcium channel blockers (Table 1), suggesting that most if not all EMF-mediated responses may be produced through VGCC stimulation. Voltage-gated calcium channels are essential to the responses produced by extremely low frequency (including 50/60 Hz) EMFs and also to microwave frequency range EMFs, nanosecond EMF pulses, and static electrical and magnetic fields (Table 1).

In a recent study, Pilla [27] showed that an increase in intracellular Ca^{2+} must have occurred almost immediately after EMF exposure, producing a Ca^{2+}/calmodulin-dependent increase in nitric oxide occurring in less than 5 sec. Although Pilla [27] did not test whether VGCC stimulation was involved in his study, there are few alternatives that can produce such a rapid Ca^{2+} response, none of which has been implicated in EMF responses. Other studies, each involving VGCCs, summarized in Table 1, also showed rapid Ca^{2+} increases following EMF exposure [8, 16, 17, 19, 21]. The rapidity of these responses rule out many types of regulatory interactions as being involved in producing the increased VGCC activity following EMF exposure and suggests, therefore, that VGCC stimulation in the plasma membrane is directly produced by EMF exposure.

Possible modes of action following VGCC stimulation

The increased intracellular Ca^{2+} produced by such VGCC activation may lead to multiple regulatory responses, including the increased nitric oxide levels produced through the action of the two Ca^{2+}/calmodulin-dependent nitric oxide synthases, nNOS and eNOS. Increased nitric oxide levels typically act in a physiological context through increased synthesis of cGMP and subsequent activation of protein kinase G [28, 29]. In contrast, in most pathophysiological contexts, nitric oxide reacts with superoxide to form peroxynitrite, a potent non-radical oxidant [30, 31], which can produce radical products, including hydroxyl radical and NO_2 radical [32].

Therapeutic bone-growth stimulation *via* Ca^{2+}/nitric oxide/cGMP/protein kinase G

An example of a therapeutic effect for bone repair of EMF exposure in various medical situations includes increasing osteoblast differentiation and maturation and has been reviewed repeatedly [33–44]. The effects of EMF exposure on bone cannot be challenged, although there is still considerable question about the best ways to apply this clinically [33–44]. Our focus, here, is to consider possible mechanisms of action. Multiple studies have implicated increased Ca^{2+} and nitric oxide in the EMF stimulation of bone growth [44–49]; three have also implicated increased cGMP and protein kinase G activity [46, 48, 49]. In addition, studies on other regulatory stimuli leading to increased bone growth have also implicated increased cGMP levels and protein kinase G in this response [50–56]. In summary, then, it can be seen from the above that there is a very well-documented action of EMFs in stimulating osteoblasts and bone growth. The available data, although limited, support the action of the main pathway involved in physiological responses to Ca^{2+} and nitric oxide, namely Ca^{2+}/nitric oxide/cGMP/protein kinase G in producing such stimulation.

Ca^{2+}/nitric oxide/peroxynitrite and pathophysiological responses to EMF exposures: the example of single-strand DNA breaks

As was noted above, most of the pathophysiological effects of nitric oxide are mediated through peroxynitrite elevation and consequent oxidative stress. There are many reviews and other studies, implicating oxidative stress in generating pathophysiological effects of EMF exposure [see for example 57–64]. In some of these studies, the rise in oxidative stress markers parallels the rise in nitric oxide, suggesting a peroxynitrite-mediated mechanism [64–67].

Peroxynitrite elevation is usually measured through a marker of peroxynitrite-mediated protein nitration, 3-nitrotyrosine (3-NT). There are four studies where 3-NT levels were measured before and after EMF exposure [66, 68–70]. Each of these studies provides some evidence supporting the view that EMF exposure increases levels of peroxynitrite and therefore 3-NT levels [66, 68–70]. Although these cannot be taken as definitive, when considered along with the evidence on oxidative stress and elevated nitric oxide production in response to EMF exposure, they strongly suggest a peroxynitrite-mediated mechanism of oxidative stress in response to EMFs.

© 2013 The Author.

Journal of Cellular and Molecular Medicine Published by Foundation for Cellular and Molecular Medicine/Blackwell Publishing Ltd

Table 1 EMF responses blocked or lowered by calcium channel blockers

Ref. no.	EMF type	Calcium channel	Cell type or organism	Response measured
2	Pulsed magnetic fields	L-type	Human lymphocytes	Cell proliferation; cytokine production
3	Static magnetic field (0.1 T)	L-type	Human polymorphonuclear leucocytes	Cell migration; degranulation
5	ELF	L-type	Rat chromaffin cells	Differentiation; catecholamine release
6	Electric field	L-type	Rat and mouse bone cells	Increased Ca^{2+}, phospholipase A2, PGE2
7	50 Hz	L-type	Mytilus (mussel) immunocytes	Reduced shape change, cytotoxicity
8	50 Hz	L-type	AtT20 D16V, mouse pituitary corticotrope-derived	Ca^{2+} increase; cell morphology, premature differentiation
9	50 Hz	L-type	Neural stem/progenitor cells	*In vitro* differentiation, neurogenesis
10	Static magnetic field	L-type	Rat	Reduction in oedema formation
11	NMR	L-type	Tumour cells	Synergistic effect of EMF on anti-tumour drug toxicity
12	Static magnetic field	L-type	Myelomonocytic U937 cells	Ca^{2+} influx into cells and anti-apoptotic effects
13	60 Hz	L-type	Mouse	Hyperalgesic response to exposure
14	Single nanosecond electric pulse	L-type	Bovine chromaffin cells	Very rapid increase in intracellular Ca^{2+}
15	Biphasic electric current	L-type	Human mesenchymal stromal cells	Osteoblast differentiation and cytokine production
16	DC & AC magnetic fields	L-type	β-cells of pancreas, patch clamped	Ca^{2+} flux into cells
17	50 Hz	L-type	Rat pituitary cells	Ca^{2+} flux into cells
18	50 Hz	L-type, N-type	Human neuroblastoma IMR32 and rat pituitary GH3 cells	Anti-apoptotic activity
19	Nanosecond pulse	L-type, N-type, P/Q-type	Bovine chromaffin cells	Ca^{2+} dynamics of cells
20	50 Hz	Not determined	Rat dorsal root ganglion cells	Firing frequency of cells
21	700–1100 MHz	N-type	Stem cell–derived neuronal cells	Ca^{2+} dynamics of cells
22	Very weak electrical fields	T-type	Sharks	Detection of very weak magnetic fields in the ocean
23	Short electric pulses	L-type	Human eye	Effect on electro-oculogram
24	Weak static magnetic field	L-type	Rabbit	Baroreflex sensitivity
25	Weak electric fields	T-type	Neutrophils	Electrical and ion dynamics
26	Static electric fields, 'capacitive'	L-type	Bovine articular chondrocytes	Agrican & type II collagen expression; calcineurin and other Ca^{2+}/calmodulin responses

EMF: electromagnetic field; ELF: extremely low frequency.

© 2013 The Author.
Journal of Cellular and Molecular Medicine Published by Foundation for Cellular and Molecular Medicine/Blackwell Publishing Ltd

Such a peroxynitrite-mediated mechanism may explain the many studies showing the single-stranded breaks in DNA, as shown by alkaline comet assays or the similar microgel electrophoresis assay, following EMF exposures in most such studies [71–89], but not in all [90–97]. Some of the factors that are reported to influence whether such DNA single-strand breaks are detected after EMF exposure include the type of cell studied [79, 86], dosage of EMF exposure [78] and the type of EMF exposure studied [73, 77]. Oxidative stress and free radicals have roles, both because there is a concomitant increase in oxidative stress and because antioxidants have been shown to greatly lower the generation of DNA single-strand breaks following EMF exposure [72, 75, 81, 82] as has also been shown for peroxynitrite-mediated DNA breaks produced under other conditions. It has also been shown that one can block the generation of DNA single-strand breaks with a nitric oxide synthase inhibitors [82].

Peroxynitrite has been shown to produce single-strand DNA breaks [98–100], a process that is inhibited by many but not all antioxidants [99, 100]. It can be seen from this that the data on generation of single-strand DNA breaks, although quite limited, support a mechanism involving nitric oxide/peroxynitrite/free radical (oxidative stress). Although the data on the possible role of peroxynitrite in EMF-induced DNA single-strand breaks are limited, what data are available supports such a peroxynitrite role.

Discussion and conclusions

How do EMFs composed of low-energy photons produce non-thermal biological changes, both pathophysiological and, in some cases, potentially therapeutic, in humans and higher animals? It may be surprising that the answer to this question has been hiding in plain sight in the scientific literature. However, in this era of highly focused and highly specialized science, few of us have the time to read the relevant literature, let alone organize the information found within it in useful and critical ways.

This study shows that:

1 Twenty-three different studies have found that such EMF exposures act *via* activation of VGCCs, such that VGCC channel blockers can prevent responses to such exposures (Table 1). Most of the studies implicate L-type VGCCs in these responses, but there are also other studies implicating three other classes of VGCCs.

2 Both extremely low frequency fields, including 50/60 cycle exposures, and microwave EMF range exposures act *via* activation of VGCCs. So do static electric fields, static magnetic fields and nanosecond pulses.

3 Voltage-gated calcium channel stimulation leads to increased intracellular Ca^{2+}, which can act in turn to stimulate the two calcium/calmodulin-dependent nitric oxide synthases and increase nitric oxide. It is suggested here that nitric oxide may act in therapeutic/potentially therapeutic EMF responses *via* its main physiological pathway, stimulating cGMP and protein kinase G. It is also suggested that nitric oxide may act in pathophysiological responses to EMF exposure, by acting as a precursor of peroxynitrite, producing both oxidative stress and free radical breakdown products.

4 The interpretation in three above is supported by two specific well-documented examples of EMF effects. Electromagnetic fields stimulation of bone growth, modulated through EMF stimulation of osteoblasts, appears to involve an elevation/nitric oxide/protein kinase G pathway. In contrast to that, it seems likely that the EMF induction of single-stranded DNA breaks involves a Ca^{2+}/elevation/nitric oxide/peroxynitrite/free radical (oxidative stress) pathway.

It may be asked why we have evidence for involvement of VGCCs in response to EMF exposure, but no similar evidence for involvement of voltage-gated sodium channels? Perhaps, the reason is that there are many important biological effects produced in increased intracellular Ca^{2+}, including but not limited to nitric oxide elevation, but much fewer are produced by elevated Na^{+}.

The possible role of peroxynitrite as opposed to protein kinase G in producing pathophysiological responses to EMF exposure raises the question of whether there are practical approaches to avoiding such responses? Typically peroxynitrite levels can be highly elevated when both of its precursors, nitric oxide and superoxide, are high. Consequently, agents that lower nitric oxide synthase activity and agents that raise superoxide dismutases (SODs, the enzymes that degrade superoxide) such as phenolics and other Nrf2 activators that induce SOD activity [101], as well as calcium channel blockers may be useful. Having said that, this is a complex area, where other approaches should be considered, as well.

Although the various EMF exposures as well as static electrical field exposures can act to change the electrical voltage-gradient across the plasma membrane and may, therefore, be expected to stimulate VGCCs through their voltage-gated properties, it may be surprising that static magnetic fields also act to activate VGCCs because static magnetic fields do not induce electrical changes on static objects. However, cells are far from static. Such phenomena as cell ruffling [102,103] may be relevant, where thin cytoplasmic sheets bounded on both sides by plasma membrane move rapidly. Such rapid movement of the electrically conducting cytoplasm, may be expected to influence the electrical charge across the plasma membrane, thus potentially stimulating the VGCCs.

Earlier modelling of electrical effects across plasma membranes of EMF exposures suggested that such electrical effects were likely to be too small to explain EMF effects at levels reported to produce biological changes (see, for example [22]). However, more recent and presumably more biologically plausible modelling have suggested that such electrical effects may be much more substantial [104–109] and may, therefore, act to directly stimulate VGCCs.

Direct stimulation of VGCCs by partial depolarization across the plasma membrane is suggested by the following observations discussed in this review:

1 The very rapid, almost instantaneous increase in intracellular Ca^{2+} found in some studies following EMF exposure [8, 16, 17, 19, 21, 27]. The rapidity here means that most, if not all indirect, regulatory effects can be ruled out.

2 The fact that not just L-type, but three additional classes of VGCCs are implicated in generating biological responses to EMF

© 2013 The Author.

Journal of Cellular and Molecular Medicine Published by Foundation for Cellular and Molecular Medicine/Blackwell Publishing Ltd

exposure (Table 1), suggesting that their voltage-gated properties may be a key feature in their ability to respond to EMFs.

3 Most, if not all, EMF effects are blocked by VGCC channel blockers (Table 1).

4 Modelling of EMF effects on living cells suggests that plasma membrane voltage changes may have key roles in such effects [104–109]. Saunders and Jefferys stated [110] that 'It is well established that electric fields … or exposure to low frequency magnetic fields, will, if of sufficient magnitude, excite nerve tissue through their interactions with … voltage gated ion channels'. They further state [110] that this is achieved by direct effects on the electric dipole voltage sensor within the ion channel.

One question that is not answered by any of the available data is whether what is known as 'dirty electricity' [111–113], generated by rapid, in many cases, square wave transients in EMF exposure, also acts by stimulating VGCCs. Such dirty electricity is inherent in any digital technology because digital technology is based on the use of such square wave transients and it may, therefore, be of special concern in this digital era, but there have been no tests of such dirty electricity that determine whether VGCCs have roles in response to such fields, to my knowledge. The nanosecond pulses, which are essentially very brief, but high-intensity dirty electricity do act, at least in part, *via* VGCC stimulation (Table 1), suggesting that dirty electricity may do likewise. Clearly, we need direct study of this question.

The only detailed alternative to the mechanism of non-thermal EMF effects discussed here, to my knowledge, is the hypothesis of Friedman *et al.* [114] and supported by Desai *et al.* [115] where the apparent initial response to EMF exposure was proposed to be NADH oxidase activation, leading to oxidative stress and downstream regulatory effects. Although they provide some correlative evidence for a possible role of NADH oxidase [114], the only causal evidence is based on a presumed specific inhibitor of NADH oxidase, diphenyleneiodonium (DPI). However, DPI has been shown to be a non-specific cation channel blocker [116], clearly showing a lack of such specificity and suggesting that it may act, in part, as a VGCC blocker. Consequently, a causal role for NADH oxidase in responses to EMF exposure must be considered to be undocumented.

In summary, the non-thermal actions of EMFs composed of low-energy photons have been a great puzzle, because such photons are insufficiently energetic to directly influence the chemistry of cells. The current review provides support for a pathway of the biological action of ultralow frequency and microwave EMFs, nanosecond pulses and static electrical or magnetic fields: EMF activation of VGCCs leads to rapid elevation of intracellular Ca^{2+}, nitric oxide and in some cases at least, peroxynitrite. Potentially therapeutic effects may be mediated through the Ca^{2+}/nitric oxide/cGMP/protein kinase G pathway. Pathophysiological effects may be mediated through the Ca^{2+}/nitric oxide/peroxynitrite pathway. Other Ca^{2+}-mediated effects may have roles as well, as suggested by Xu *et al.* [26].

Conflicts of interest

The author confirms that there are no conflicts of interest.

References

1. **Walleczek J.** Electromagnetic field effects on cells of the immune system: the role of calcium signaling. *FASEB J.* 1992; 6: 3177–85.
2. **Cadossi R, Emilia G, Ceccherelli G, *et al.*** 1988 Lymphocytes and pulsing magnetic fields. In: Marino EE, editor. *Modern bioelectricity*. New York: Dekker; 1998. pp. 451–96.
3. **Papatheofanis FJ.** Use of calcium channel antagonists as magnetoprotective agents. *Radiat Res.* 1990; 122: 24–8.
4. **Catterall WA.** Structure and regulation of voltage-gated Ca^{2+} channels. *Annu Rev Cell Dev Biol.* 2000; 16: 521–55.
5. **Morgado-Valle C, Verdugo-Díaz L, García DE, *et al.*** The role of voltage-gated Ca^{2+} channels in neurite growth of cultured chromaffin cells induced by extremely low frequency (ELF) magnetic field stimulation. *Cell Tissue Res.* 1998; 291: 217–30.
6. **Lorich DG, Brighton CT, Gupta R, *et al.*** Biochemical pathway mediating the response of bone cells to capacitive coupling. *Clin Orthop Relat Res.* 1998; 246–56.
7. **Gobba F, Malagoli D, Ottaviani E.** Effects of 50 Hz magnetic fields on fMLP-induced shape changes in invertebrate immunocytes: the role of calcium ion channels. *Bioelectromagnetics.* 2003; 24: 277–82.
8. **Lisi A, Ledda M, Rosola E, *et al.*** Extremely low frequency electromagnetic field exposure promotes differentiation of pituitary corticotrope-derived AtT20 D16V cells. *Bioelectromagnetics.* 2006; 27: 641–51.
9. **Piacentini R, Ripoli C, Mezzogori D, *et al.*** Extremely low-frequency electromagnetic fields promote *in vitro* neurogenesis *via* upregulation of Ca(v)1-channel activity. *J Cell Physiol.* 2008; 215: 129–39.
10. **Morris CE, Skalak TC.** Acute exposure to a moderate strength static magnetic field reduces edema formation in rats. *Am J Physiol Heart Circ Physiol.* 2008; 294: H50–7.
11. **Ghibelli L, Cerella C, Cordisco S, *et al.*** NMR exposure sensitizes tumor cells to apoptosis. *Apoptosis.* 2006; 11: 359–65.
12. **Fanelli C, Coppola S, Barone R, *et al.*** Magnetic fields increase cell survival by inhibiting apoptosis *via* modulation of Ca^{2+} influx. *FASEB J.* 1999; 13: 95–102.
13. **Jeong JH, Kum C, Choi HJ, *et al.*** Extremely low frequency magnetic field induces hyperalgesia in mice modulated by nitric oxide synthesis. *Life Sci.* 2006; 78: 1407–12.
14. **Vernier PT, Sun Y, Chen MT, *et al.*** Nanosecond electric pulse-induced calcium entry into chromaffin cells. *Bioelectrochemistry.* 2008; 73: 1–4.
15. **Kim IS, Song JK, Song YM, *et al.*** Novel effect of biphasic electric current on *in vitro* osteogenesis and cytokine production in human mesenchymal stromal cells. *Tissue Eng Part A.* 2009; 15: 2411–22.
16. **Höjevik P, Sandblom J, Galt S, *et al.*** Ca^{2+} ion transport through patch-clamped cells exposed to magnetic fields. *Bioelectromagnetics.* 1995; 16: 33–40.
17. **Barbier E, Vetret B, Dufy B.** Stimulation of Ca^{2+} influx in rat pituitary cells under exposure to a 50 Hz magnetic field. *Bioelectromagnetics.* 1996; 17: 303–11.
18. **Grassi C, D'Ascenzo M, Torsello A, *et al.*** Effects of 50 Hz electromagnetic fields on

© 2013 The Author.

voltage-gated Ca^{2+} channels and their role in modulation of neuroendocrine cell proliferation and death. *Cell Calcium*. 2004; 35: 307–15.

19. **Craviso GL, Choe S, Chatterjee P, *et al.*** Nanosecond electric pulses: a novel stimulus for triggering Ca^{2+} influx into chromaffin cells *via* voltage-gated Ca^{2+} channels. *Cell Mol Neurobiol*. 2010; 30: 1259–65.
20. **Marchionni I, Paffi A, Pellegrino M, *et al.*** Comparison between low-level 50 Hz and 900 MHz electromagnetic stimulation on single channel ionic currents and on firing frequency in dorsal root ganglion isolated neurons. *Biochim Biophys Acta*. 2006; 1758: 597–605.
21. **Rao VS, Titushkin IA, Moros EG, *et al.*** Nonthermal effects of radiofrequency-field exposure on calcium dynamics in stem cell-derived neuronal cells: elucidation of calcium pathways. *Radiat Res*. 2008; 169: 319–29.
22. **Adair RK, Astumian RD, Weaver JC.** Detection of weak electric fields by sharks, rays and skates. *Chaos*. 1998; 8: 576–87.
23. **Constable PA.** Nifedipine alters the light-rise of the electro-oculogram in man. *Fraefes Arch Clin Exp Ophthalmol*. 2011; 249: 677–84.
24. **Gmitrov J, Ohkuba C.** Verapamil protective effect on natural and artificial magnetic field cardiovascular impact. *Bioelectromagnetics*. 2002; 23: 531–41.
25. **Kindzelskii AL, Petty HR.** Ion channel clustering enhances weak electric field detection by neutrophils: apparent role of SKF96365-sensitive cation channels and myeloperoxidase trafficking cellular responses. *Eur Biophys J*. 2005; 35: 1–26.
26. **Xu J, Wang W, Clark CC, *et al.*** Signal transduction in electrically stimulated articular chondrocytes involves translocation of extracellular calcium through voltage-gated channels. *Osteoarthritis Cartilage*. 2009; 17: 397–405.
27. **Pilla AA.** Electromagnetic fields instantaneously modulate nitric oxide signaling in challenged biological systems. *Biochem Biophys Res Commun*. 2012; 426: 330–3.
28. **McDonald LJ, Murad F.** Nitric oxide and cyclic GMP signaling. *Proc Soc Exp Biol Med*. 1996; 211: 1–6.
29. **Francis SH, Busch JL, Corbin JD, *et al.*** cGMP-dependent protein kinases and cGMP phosphodiesterases in nitric oxide and cGMP action. *Pharmacol Rev*. 2010; 62: 525–63.
30. **Pacher P, Beckman JS, Liaudet L.** Nitric oxide and peroxynitrite in health and disease. *Physiol Rev*. 2007; 87: 315–424.
31. **Pryor WA, Squadrito GL.** The chemistry of peroxynitrite: a product from the reaction of nitric oxide with superoxide. *Am J Physiol*. 1995; 268: L699–722.
32. **Lymar SV, Khairutdinov RF, Hurst JK.** Hydroxyl radical formation by O-O bond homolysis in peroxynitrous acid. *Inorg Chem*. 2003; 42: 5259–66.
33. **Ryabi JT.** Clinical effects of electromagnetic fields on fracture healing. *Clin Orthop Relat Res*. 1998; 355(Suppl. I): S205–15.
34. **Oishi M, Onesti ST.** Electrical bone graft stimulation for spinal fusion: a review. *Neurosurgery*. 2000; 47: 1041–55.
35. **Aaron RK, Ciombor DM, Simon BJ.** Treatment of nonunions with electric and electromagnetic fields. *Clin Orthop Relat Res*. 2004; 10: 579–93.
36. **Goldstein C, Sprague S, Petrisor BA.** Electrical stimulation for fracture healing: current evidence. *J Orthop Trauma*. 2010; 24 (Suppl. 1): S62–5.
37. **Demitriou R, Babis GC.** Biomaterial osseointegration enhancement with biophysical stimulation. *J Musculoskelet Neuronal Interact*. 2007; 7: 253–65.
38. **Griffin XL, Warner F, Costa M.** The role of electromagnetic stimulation in the management of established non-union lf long bone fractures: what is the evidence? *Injury*. 2008; 39: 419–29.
39. **Huang LQ, He HC, He CQ, *et al.*** Clinical update of pulsed electromagnetic fields on osteoporosis. *Chin Med J*. 2008; 121: 2095–9.
40. **Groah SL, Lichy AM, Libin AV, *et al.*** Intensive electrical stimulation attenuates femoral bone loss in acute spinal cord injury. *PM R*. 2010; 2: 1080–7.
41. **Schidt-Rohlfing B, Silny J, Gavenis K, *et al.*** Electromagnetic fields, electric current and bone healing – what is the evidence? *Z Orthop Unfall*. 2011; 149: 265–70.
42. **Griffin XL, Costa ML, Parsons N, *et al.*** Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults. *Cochrane Database Syst Rev*. 2011; CDO08471. doi: 10.1002/14651858.CD008471.pub2.
43. **Chalidis B, Sachinis N, Assiotis A, *et al.*** Stimulation of bone formation and fracture healing with pulsed electromagnetic fields: biologic responses and clinical implications. *Int J Immunopathol Pharmacol*. 2011; 24(1 Suppl. 2): 17020.
44. **Zhong C, Zhao TF, Xu ZJ, *et al.*** Effects of electromagnetic fields on bone regeneration in experimental and clinical studies: a review of the literature. *Chin Med J*. 2012; 125: 367–72.
45. **Diniz P, Soejima K, Ito G.** Nitric oxide mediates the effects of pulsed electromagnetic field stimulation on the osteoblast proliferation and differentiation. *Nitric Oxide*. 2002; 7: 18–23.
46. **Fitzsimmons RJ, Gordon SL, Ganey T, *et al.*** A pulsing electric field (PEF) increases human chondrocyte proliferation through a transduction pathway involving nitric oxide signaling. *J Orthopaedic Res*. 2008; 26: 854–9.
47. **Lin H-Y, Lin Y-J.** *In vitro* effects of low frequency electromagnetic fields on osteoblast proliferation and maturation in an inflammatory environment. *Bioelectromagnetics*. 2011; 32: 552–60.
48. **Cheng G, Zhai Y, Chen K, *et al.*** Sinusoidal electromagnetic field stimulates rat osteoblast differentiation and maturation *via* activation of NO-cGMP-PKG pathway. *Nitric Oxide*. 2011; 25: 316–25.
49. **Pilla A, Fitzsimmons R, Muehsam D, *et al.*** Electromagnetic fields as first messenger in biological signaling: application to calmodulin-dependent signaling in tissue repair. *Biochim Biophys Acta*. 2011; 1810: 1236–45.
50. **Rangaswami H, Schwappacher R, Tran T, *et al.*** Protein kinase G and focal adhesion kinase converge on Src/Akt/β-catenin signaling module in osteoblast mechanotransduction. *J Biol Chem*. 2012; 287: 21509–19.
51. **Marathe N, Rangaswami H, Zhuang S, *et al.*** Pro-survival effects of 17β-estradiol on osteocytes are mediated by nitric oxide/cGMP *via* differential actions of cGMP-dependent protein kinases I and II. *J Biol Chem*. 2012; 287: 978–88.
52. **Rangaswami H, Schwappacher R, Marathe N, *et al.*** Cyclic GMP and protein kinase G control a Src-containing mechanosome in osteoblasts. *Sci Signal*. 2010; 3: ra91.
53. **Rangaswami H, Marathe N, Zhuang S, *et al.*** Type II cGMP-dependent protein kinase mediates osteoblast mechanotransduction. *J Biol Chem*. 2009; 284: 14796–808.
54. **Saura M, Tarin C, Zaragoza C.** Recent insights into the implication of nitric oxide in osteoblast differentiation and proliferation during bone development. *ScientificWorldJournal*. 2010; 10: 624–32.
55. **Zaragoza C, López-Rivera E, García-Rama C, *et al.*** Cbfa-1 mediates nitric oxide regulation of MMP-13 in osteoblasts. *J Cell Sci*. 2006; 119: 1896–902.
56. **Wang DH, Hu YS, Du JJ, *et al.*** Ghrelin stimulates proliferation of human osteo-

© 2013 The Author.

Journal of Cellular and Molecular Medicine Published by Foundation for Cellular and Molecular Medicine/Blackwell Publishing Ltd

blastic TE85 cells *via* NO/cGMP signaling pathway. *Endocrine*. 2009; 35: 112–7.
57. **Simkó M.** Cell type specific redox status is responsible for diverse electromagnetic field effects. *Curr Med Chem*. 2007; 14: 1141–52.
58. **Consales C, Merla C, Marino C, *et al.*** Electromagnetic fields, oxidative stress, and neurodegeneration. *Int J Cell Biol*. 2012; 2012: 683897.
59. **Johansson O.** Disturbance of the immune system by electromagnetic fields-A potentially underlying cause for cellular damage and tissue repair reduction which could lead to disease and impairment. *Pathophysiology*. 2009; 16: 157–77.
60. **Kovacic P, Somanathan R.** Electromagnetic fields: mechanism, cell signaling, other bioprocesses, toxicity, radicals, antioxidants and beneficial effects. *J Recept Signal Transduct Res*. 2010; 30: 214–26.
61. **Wolf FI, Torsello A, Tedesco B, *et al.*** 50-Hz extremely low frequency electromagnetic fields enhance cell proliferation and DNA damage: possible involvement of a redox mechanism. *Biochim Biophys Acta*. 2005; 1743: 120–9.
62. **Iakimenko IL, Sidorik EP, Tsybulin AS.** Metabolic changes in cells under electromagnetic radiation of mobile communication systems. *Ukr Biokhim Zh*. 2011; 83: 20–8.
63. **Jing J, Yuhua Z, Xiao-qian Y, *et al.*** The influence of microwave radiation from cellular phone on fetal rat brain. *Electromagn Biol Med*. 2012; 31: 57–66.
64. **Esmekaya MA, Ozer C, Seyhan N.** 900 MHz pulse-modulated radiofrequency radiation induces oxidative stress on heart, lung, testis and liver tissues. *Gen Physiol Biophys*. 2011; 30: 84–9.
65. **Aydin B, Akar A.** Effects of a 900-MHz electromagnetic field on oxidative stress parameters in rat lymphoid organs, polymorphonuclear leukocytes and plasma. *Arch Med Res*. 2011; 42: 261–7.
66. **Guler G, Turkozer Z, Tomruk A, *et al.*** The protective effects of N-acetyl-L-cysteine and epigallocatechin-3-gallate on electric field-induced hepatic oxidative stress. *Int J Radiat Biol*. 2008; 84: 669–80.
67. **Guney M, Ozguner F, Oral B, *et al.*** 900 MHz radiofrequency-induced histopathologic changes and oxidative stress in rat endometrium: protection by vitamins E and C. *Toxicol Ind Health*. 2007; 23: 411–20.
68. **Sypniewska RK, Millenbaugh NJ, Kiel JL, *et al.*** Protein changes in macrophages induced by plasma from rats exposed to 35 GHz millimeter waves. *Bioelectromagnetics*. 2010; 31: 656–63.
69. **Grigoriev YG, Mikhailov VF, Ivanov AA, *et al.*** Autoimmune processes after long-term low-level exposure to electromagnetic fields part 4. Oxidative intracellular stress response to the long-term rat exposure to nonthermal RF EMF. *Biophysics*. 2010; 55: 1054–8.
70. **Erdal N, Gürgül S, Tamer L, *et al.*** Effects of long-term exposure of extremely low frequency magnetic field on oxidative/nitrosative stress in rat liver. *J Radiat Res*. 2008; 49: 181–7.
71. **Ahuja YR, Vijayashree B, Saran R, *et al.*** *In vitro* effects of low-level, low-frequency electromagnetic fields on DNA damage in human leucocytes by comet assay. *Indian J Biochem Biophys*. 1999; 36: 318–22.
72. **Amara S, Douki T, Ravanat JL, *et al.*** Influence of a static magnetic field (250 mT) on the antioxidant response and DNA integrity in THP1 cells. *Phys Med Biol*. 2007; 52: 889–98.
73. **Focke F, Schuermann D, Kuster N, *et al.*** DNA fragmentation in human fibroblasts under extremely low frequency electromagnetic field exposure. *Mutat Res*. 2010; 683: 74–83.
74. **Franzellitti S, Valbonesi P, Ciancaglini N, *et al.*** Transient DNA damage induced by high-frequency electromagnetic fields (GSM 1.8 GHz) in the human trophoblast HTR-8/SVneo cell line evaluated with the alkaline comet assay. *Mutat Res*. 2010; 683: 35–42.
75. **Garaj-Vrhovac V, Gajski G, Pažanin S, *et al.*** Assessment of cytogenetic damage and oxidative stress in personnel occupationally exposed to the pulsed microwave radiation of marine radar equipment. *Int J Hyg Environ Health*. 2011; 214: 59–65.
76. **Hong R, Zhang Y, Liu Y, *et al.*** Effects of extremely low frequency electromagnetic fields on DNA of testicular cells and sperm chromatin structure in mice. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. 2005; 23: 414–7. [Article in Chinese].
77. **Ivancsits S, Diem E, Pilger A, *et al.*** Induction of DNA strand breaks by intermittent exposure to extremely-low-frequency electromagnetic fields in human diploid fibroblasts. *Mutat Res*. 2002; 519: 1–13.
78. **Ivancsits S, Diem E, Jahn O, *et al.*** Intermittent extremely low frequency electromagnetic fields cause DNA damage in a dose-dependent way. *Int Arch Occup Environ Health*. 2003; 76: 431–6.
79. **Ivancsits S, Pilger A, Diem E, *et al.*** Cell type-specific genotoxic effects of intermittent extremely low-frequency electromagnetic fields. *Mutat Res*. 2005; 583: 184–8.
80. **Kesari KK, Behari J, Kumar S.** Mutagenic response of 2.45 GHz radiation exposure on rat brain. *Int J Radiat Biol*. 2010; 86: 334–43.
81. **Lai H, Singh NP.** Melatonin and a spin-trap compound block radiofrequency electromagnetic radiation-induced DNA strand breaks in rat brain cells. *Bioelectromagnetics*. 1997; 18: 446–54.
82. **Lai H, Singh NP.** Magnetic-field-induced DNA strand breaks in brain cells of the rat. *Environ Health Perspect*. 2004; 112: 687–94.
83. **Lee JW, Kim MS, Kim YJ, *et al.*** Genotoxic effects of 3 T magnetic resonance imaging in cultured human lymphocytes. *Bioelectromagnetics*. 2011; 32: 535–42.
84. **Paulraj R, Behari J.** Single strand DNA breaks in rat brain cells exposed to microwave radiation. *Mutat Res*. 2006; 596: 76–80.
85. **Romeo S, Zeni L, Sarti M, *et al.*** DNA electrophoretic migration patterns change after exposure of Jurkat cells to a single intense nanosecond electric pulse. *PLoS ONE*. 2011; 6: e28419.
86. **Schwarz C, Kratochvil E, Pilger A, *et al.*** Radiofrequency electromagnetic fields (UMTS, 1,950 MHz) induce genotoxic effects *in vitro* in human fibroblasts but not in lymphocytes. *Int Arch Occup Environ Health*. 2008; 81: 755–67.
87. **Svedenstål BM, Johanson KJ, Mattsson MO, *et al.*** DNA damage, cell kinetics and ODC activities studied in CBA mice exposed to electromagnetic fields generated by transmission lines. *In Vivo*. 1999; 13: 507–13.
88. **Svedenstål BM, Johanson KJ, Mild KH.** DNA damage induced in brain cells of CBA mice exposed to magnetic fields. *In Vivo*. 1999; 13: 551–2.
89. **Trosić I, Pavicić I, Milković-Kraus S, *et al.*** Effect of electromagnetic radiofrequency radiation on the rats' brain, liver and kidney cells measured by comet assay. *Coll Antropol*. 2011; 35: 1259–64.
90. **Burdak-Rothkamm S, Rothkamm K, Folkard M, *et al.*** DNA and chromosomal damage in response to intermittent extremely low-frequency magnetic fields. *Mutat Res*. 2009; 672: 82–9.
91. **Fairbairn DW, O'Neill KL.** The effect of electromagnetic field exposure on the formation of DNA single strand breaks in human cells. *Cell Mol Biol (Noisy-le-grand)*. 1994; 40: 561–7.

© 2013 The Author.
Journal of Cellular and Molecular Medicine Published by Foundation for Cellular and Molecular Medicine/Blackwell Publishing Ltd

92. **Fiorani M, Cantoni O, Sestili P, *et al.*** Electric and/or magnetic field effects on DNA structure and function in cultured human cells. *Mutat Res*. 1992; 282: 25–9.
93. **Malyapa RS, Ahern EW, Straube WL, *et al.*** Measurement of DNA damage after exposure to 2450 MHz electromagnetic radiation. *Radiat Res*. 1997; 148: 608–17.
94. **McNamee JP, Bellier PV, Chauhan V, *et al.*** Evaluating DNA damage in rodent brain after acute 60 Hz magnetic-field exposure. *Radiat Res*. 2005; 164: 791–7.
95. **Scarfí MR, Sannino A, Perrotta A, *et al.*** Evaluation of genotoxic effects in human fibroblasts after intermittent exposure to 50 Hz electromagnetic fields: a confirmatory study. *Radiat Res*. 2005; 164: 270–6.
96. **Stronati L, Testa A, Villani P, *et al.*** Absence of genotoxicity in human blood cells exposed to 50 Hz magnetic fields as assessed by comet assay, chromosome aberration, micronucleus, and sister chromatid exchange analyses. *Bioelectromagnetics*. 2004; 25: 41–8.
97. **Testa A, Cordelli E, Stronati L, *et al.*** Evaluation of genotoxic effect of low level 50 Hz magnetic fields on human blood cells using different cytogenetic assays. *Bioelectromagnetics*. 2004; 25: 613–9.
98. **Szabó G, Bährle S.** Role of nitrosative stress and poly(ADP-ribose) polymerase activation in myocardial reperfusion injury. *Curr Vasc Pharmacol*. 2005; 3: 215–20.
99. **Moon HK, Yang ES, Park JW.** Protection of peroxynitrite-induced DNA damage by dietary antioxidants. *Arch Pharm Res*. 2006; 29: 213–7.
100. **Sakihama Y, Maeda M, Hashimoto M, *et al.*** Beetroot betalain inhibits peroxynitrite-mediated tyrosine nitration and DNA strand damage. *Free Radic Res*. 2012; 46: 93–9.
101. **Hybertson BM, Gao B, Bose SK, *et al.*** Oxidative stress in health and disease: the therapeutic potential of Nrf2 activation. *Mol Aspects Med*. 2011; 32: 234–46.
102. **Ridley AJ, Paterson HF, Johnston CL, *et al.*** The small GTP-binding protein rac regulates growth factor-induced membrane ruffling. *Cell*. 1992; 70: 401–10.
103. **Wennström S, Hawkins P, Cooke F, *et al.*** Activation of phosphoinositide 3-kinase is required for PDGF-stimulated membrane ruffling. *Curr Biol*. 1994; 4: 385–93.
104. **Joucla S, Yvert B.** Modeling of extracellular neural stimulation: from basic understanding to MEA-based applications. *J Physiol Paris*. 2012; 106: 146–58.
105. **Pashut T, Wolfus S, Friedman A, *et al.*** Mechanisms of magnetic stimulation of central nervous system neurons. *PLoS Comput Biol*. 2011; 7: e1002022.
106. **Fatemi-Ardekani A.** Transcranial magnetic stimulation: physics, electrophysiology, and applications. *Crit Rev Biomed Eng*. 2008; 36: 375–412.
107. **Silva S, Basser PJ, Miranda PC.** Elucidating the mechanisms and loci of neuronal excitation by transcranial magnetic stimulation using a finite element model of a cortical sulcus. *Clin Neurophysiol*. 2008; 119: 2405–13.
108. **Radman T, Ramos RL, Brumberg JC, *et al.*** Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation *in vitro*. *Brain Stimul*. 2009; 2: 215–28.
109. **Minelli TA, Balduzzo M, Milone FF, *et al.*** Modeling cell dynamics under mobile phone radiation. Nonlinear cell dynamics under mobile phone radiation. *Nonlinear Dynamics Psychol Life Sci*. 2007; 11: 197–218.
110. **Saunders RD, Jefferys JGR.** A neurobiological basis for ELF guidelines. *Health Phys*. 2007; 92: 596–603.
111. **Havas M.** Dirty electricity elevates blood sugar among electrically sensitive diabetics and may explain brittle diabetes. *Electromagn Biol Med*. 2008; 27: 135–46.
112. **Havas M.** Electromagnetic hypersensitivity: biological effects of dirty electricity with emphasis on diabetes and multiple sclerosis. *Electromagn Biol Med*. 2006; 25: 259–68.
113. **de Vochta F.** "Dirty electricity": what, where, and should we care? *J Expo Sci Environ Epidemiol*. 2010; 20: 399–405.
114. **Friedman J, Kraus S, Hauptman Y, *et al.*** Mechanism of short-term ERK activation by electromagnetic fields at mobile phone frequencies. *Biochem J*. 2007; 405: 559–68.
115. **Desai NR, Kesari KK, Agarwal A.** Pathophysiology of cell phone radiation: oxidative stress and carcinogenesis with focus on the male reproductive system. *Reproduct Biol Endocrinol*. 2009; 7: 114. doi:10.1186/1477-7827-7-114.
116. **Wyatt CN, Weir EK, Peers C.** Diphenylamine iodonium blocks K^+ and Ca^{2+} currents in type I cells isolated from the rat carotid body. *Neurosci Lett*. 1994; 172: 63–6.

© 2013 The Author.

Journal of Cellular and Molecular Medicine Published by Foundation for Cellular and Molecular Medicine/Blackwell Publishing Ltd

Microwave Electromagnetic Fields Act by Activating Voltage-Gated Calcium Channels: Why the Current International Safety Standards Do Not Predict Biological Hazard

Martin L. Pall
Professor Emeritus of Biochemistry and Basic Medical Sciences
Washington State University
Personal Informatio... Portland, OR 97232 USA
Personal Information - Privacy - RCW 42.56....

Abstract:

Microwave and other low frequency electromagnetic fields (EMFs) have been shown to act by activating voltage-gated calcium channels (VGCCs) with most biological effects being due to elevated intracellular calcium, consequent nitric oxide (NO) elevation and either peroxynitrite or NO signaling. This, the role of excessive intracellular calcium in microwave effects and some 20,000 papers on microwave biological effects show that the current international safety standards do not predict biological hazard. Such standards are based on the false assumption that the predominant effects of microwave and other low frequency EMF exposures are due to heating. A whole series of biological changes reportedly produced by microwave exposures can now be explained in terms of this new paradigm of EMF action via VGCC activation, including: oxidative stress; single and double stranded breaks in cellular DNA; therapeutic effects; blood-brain barrier breakdown; greatly depressed melatonin levels and sleep disruption; cancer; male and female infertility; immune dysfunction; neurological dysfunction; cardiac dysfunction including tachycardia, arrhythmia and sudden cardiac death. A two-phase program for greatly improving EMF safety standards is proposed.

Key Words: Low frequency electromagnetic fields; pulsed field effects; calcium signaling; nitric oxide signaling

There have been demonstrations by "activists" in many parts of the world against what they consider to be unsafe exposures to microwave frequency electromagnetic fields (EMFs). Such exposures have increased by large amounts in recent years. Such demonstrations have been met with assertions by government organizations and by industry that these exposures are well within international and national safety standards and

therefore can be assumed to be safe. They are correct that these are well within safety standards. A central question being examined here is whether these standards are based on well documented science such that if they are, we should be assured of safety.

Current U.S. and International safety standards are based on the assumption that the only important thing that microwave and other low frequency EMFs can do biologically is to heat things (1-5), like heating things in a microwave oven. Based on that assumption, safety standards are based on heating (1-5) and the reasonable inference, *if that assumption is correct*, is that levels of exposures which only produce insignificant heating have no biological impact and therefore are "safe." In fact advocates for current standards argue that current safety standards are about 100 times more stringent than is needed (1), because even exposure levels 100 times higher than allowed by current safety standards produce only slight heating.

However, over 20,000 publications in the scientific literature have reported substantial biological effects of at exposures well within safety standards, such that none of these should be possible if current safety standards are scientifically based. These include some 4000 studies on therapeutic effects of microwave EMFs, effects that are well known to be non-thermal (6).

It should be noted that there is a reasonable basis for the heating assumption underlying current safety standards. The photons that make up microwave frequency and other low frequency fields are very low energy photons, without insufficient energy to individually change the chemistry of our bodies. That is they are different from ionizing radiation or even ultraviolet or visible radiation, where individual photons have sufficient energy to produce chemical changes. How, then can we understand the thousands of studies showing well-documented non-thermal biological effects of microwave frequency and other low frequency EMFs?

<u>EMFs Act via Stimulation of Voltage-Gated Calcium Channels (VGCCs)</u>

The author showed in a recent review (7), that in 2 dozen studies, EMF effects on cells and organisms could be blocked by calcium channel blockers, agents that block voltage-gated calcium channels (VGCCs; also known as voltage-operated, voltage-dependent or voltage-regulated

calcium channels). In each of these two dozen studies, all of the measured effects were greatly lowered by the calcium channel blockers, suggesting that activation of these channels is responsible for most if not all of the EMF effects (7). In most but not all cases, it was L-type VGCCs that were primarily involved.

Activation of these channels is thought to produce most biological effects through increases in intracellular calcium levels.

In these studies, the EMFs studied were of various types, including extremely low frequency fields such as coming from the 50 or 60 cycle electrical wiring, microwave frequency EMFs, very short nanosecond pulses, and even static electric or magnetic fields. The findings for microwave EMFs create the most concerns, however, because our exposures have increased so quickly in recent years, and new technologies involving new exposures are becoming available at an ever increasing rate. The action of such microwave exposures via VGCC activation is also supported by a large number of studies, reviewed earlier (8,9), showing that elevated intracellular calcium levels were found following low level microwave EMF exposures, leading to changes in calcium signaling. This mode of action is also supported by two studies by Panagopoulos et al (10,11) who predicted that EMFs, including microwave EMFs can act by influencing the charged amino acid residues that control voltage-gated ion channels, to activate some of those channels. These were biophysical modeling studies and they not only support these VGCC findings, they also argue that the activation of these channels by microwave and other low frequency EMFs is biophysically plausible.

We are, therefore, in a situation where the old paradigm of such EMF action, where only heating effects were considered plausible and real (1-5), is replaced by a a new paradigm where VGCC activation by microwave and other EMFs is both plausible and real <u>and</u> provides an explanation for over 20,000 papers in the scientific literature that are inexplicable by the old paradigm.

That does not mean that there may not be other biological actions of EMFs, not involving VGCCs, through their actions on various charged chemical groups including amino acid residues in proteins. Pilla reviewed two studies in which microwave EMFs increased calmodulin activation (6). Calmodulin is regulated by intracellular calcium such that its activation may

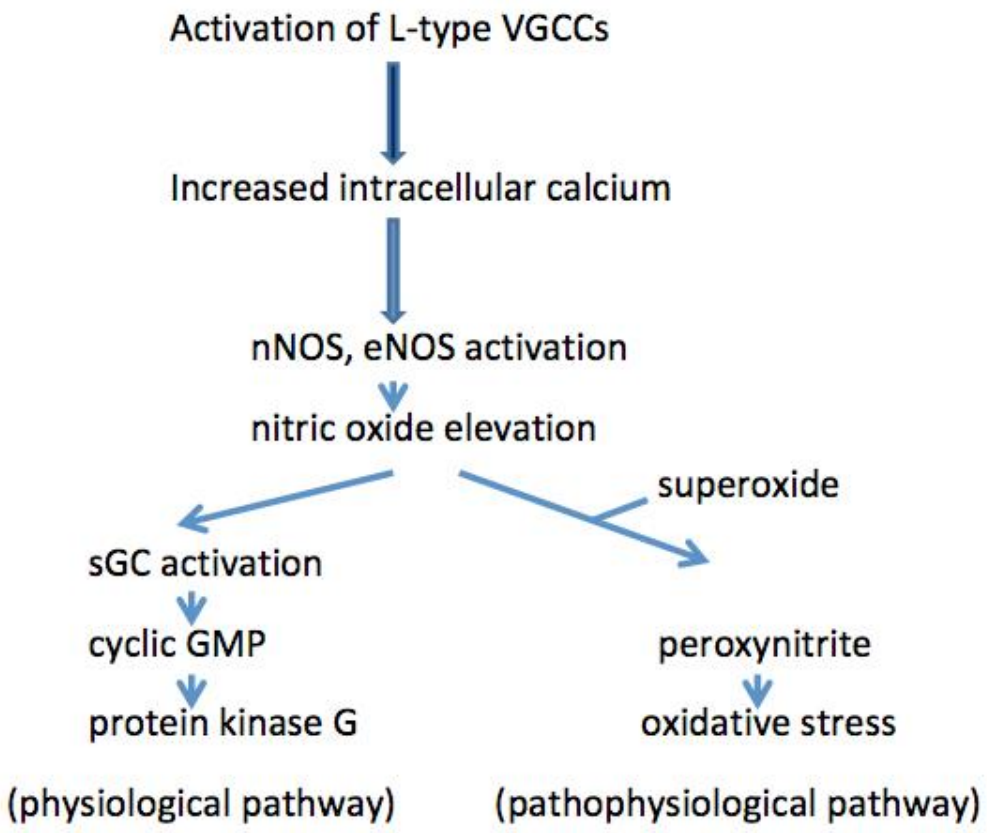
act along with VGCC activation in two related pathways of action discussed below.

Two Related Pathways of Action that Can Be Activated by VGCC Activation

VGCC activation is thought to act, to a great extent by increasing intracellular calcium levels. This is especially true for activation of the L-type VGCCs where the channels stay open relatively long periods of time. Whereas most other ion channels tend to stay open for only perhaps 1 or a few milliseconds, L-type VGCCs tend to stay open typically for a hundred milliseconds or more. Consequently their activation can easily produce a substantial impact on the levels of intracellular calcium.

While other effects of intracellular calcium are also likely to occur following VGCC activation, much of the effect of elevated intracellular calcium has been shown to be produced by calcium/calmodulin stimulation of the two calcium/calmodulin-dependent nitric oxide synthases, nNOS and eNOS (see Fig. 1, below), leading to large increases in nitric oxide (NO). NO can act along two pathways, as indicated in Fig. 1 below, to either stimulate NO signaling along the NO/cGMP, G kinase pathway which is thought to be the main pathway of action of NO in producing normal physiological responses. This is thought to be the pathway involved in producing therapeutic effects of EMFs (6,7). In contrast, the pathway leading from NO to peroxynitrite and oxidative stress is thought to be the main pathway of action in pathophysiological responses to EMFs (7); it is the likely pathway of action of EMFs in producing single strand breaks in cellular DNA (7,15). So immediately we can see plausible mechanisms of action for some EMF effects, effects that were inexplicable by the old heating paradigm.

Figure 1. Possible pattern of action of VGCCs via nitric oxide (NO)



Other Well-Documented Responses to Microwave EMFs Can Also Be Produced via Plausible Mechanisms via VGCC Activation

It can be seen from the previous section that three well-documented responses to microwave EMFs, namely therapeutic effects, single stranded breaks in cellular DNA and oxidative stress, can each be explained as being plausible consequences of VGCC activation by such EMFs. What about other such well-documented effects?

Double strand breaks in DNA, which are detected through the accumulation of micronuclei in cells after microwave and other EMF exposures, can be generated through the same mechanism as single stranded breaks.

Cancer is now well-established to be caused by weak microwave radiation exposures (reviewed in: 12-14). Adey many years ago showed that calcium effects were involved in cancer causation by such weak EMFs (9). It is known that cancer can be produced by a combination of single and double stranded breaks and other changes in DNA produced by peroxynitrite and its radical breakdown products. This NO/peroxynitrite pathway of action has been implicated in what is called inflammatory carcinogenesis (15-17) and provides, therefore a plausible mechanism of action for EMF/VGCC carcinogenesis.

Breakdown of the blood-brain barrier is another commonly reported response to microwave EMF exposure. Such breakdown occurs through peroxynitrite/oxidant product stimulation of the activation of matrix metalloproteinases (MMPs) (18-20), with the MMPs degrading the tight junctions between cells that are essential to maintain the blood-brain barrier (20,21). So again, we have a plausible mechanism leading from microwave EMF exposure to breakdown of the blood-brain barrier.

There are many studies showing that melatonin levels at night are greatly depressed in people exposed to microwave EMFs, with substantial sleep disruption as an apparent consequence. It has been shown that VGCCs and consequent intracellular calcium have effects on both the entrainment of the circadian rhythm which controls melatonin production as well as a more directly on melatonin production (22,23), providing simple explanations for this effect.

There has been much concern over the both male and female infertility in response to microwave EMF exposure. Such infertility may be caused by multiple effects of VGCC activation, including those produced through the peroxynitrite/oxidative stress pathway. Kesari et al (24) showed important roles of oxidative stress in cell-phone exposure caused male infertility. Double stranded breaks in the DNA of the gamete precursor cells, have been shown to have infertility roles (25). Such double stranded breaks in DNA produce a breakdown of the integrity of the genome and produces, therefore spontaneous early abortion and consequent infertility. However high levels of intracellular calcium can also induce apoptotic cell death through effects of elevated calcium in the mitochondria of those cells (26,27). In males, there may also be a breakdown of the blood-testis barrier via a mechanism identical to the breakdown of the blood-brain barrier, discussed above.

It can be seen from the above that 10 different well-documented microwave EMF effects can be easily explained as being a consequence of EMF VGCC activation: oxidative stress, elevated single and double strand breaks in DNA, therapeutic responses to such EMFs, breakdown of the blood-brain barrier, cancer, melatonin loss, sleep dysfunction, male infertility and female infertility.

This May Be Just the Beginning

When one looks at what cell types carry functional VGCCs, there are many. Let's discuss a few of these where there has been substantial study. Most of the cells of the immune system carry VGCCs. O. Johansson (28) reviewed effects of microwave EMFs on the immune system and suggests that increases in allergies and inflammation may be produced by such EMFs.

VGCCs are found widely in the nervous system where almost every neurotransmitter is released in response to VGCC activation (29). There have been studies on the impact of cell phone or cordless phone use on various aspects of brain function but we are still in the very early stages in studying such effects. But given the widespread and important role of VGCCs in the central nervous system, one needs to carefully consider all types of neuropsychiatric and neurodegenerative responses as to whether or not these may possibly be linked to microwave EMF exposure. There have been many studies showing various changes in neurological function

and other brain changes following low level microwave EMF exposures (see for example, refs. 30-48).

Most of the hormones of the body are released under the control of mechanisms triggered by VGCC activation (29). What effects there may be of such possible linkage between EMFs and hormonal control is difficult to fathom. One hormone release system that has been studied in this context is the release of epinephrine/norepinephrine from the chromaffin cells of the adrenal gland. It has been shown in two studies that EMFs stimulate the release of these two hormones by chromaffin cells by a VGCC-dependent mechanism (7) as well as in many other EMF chromaffin cell studies where a VGCC role was not tested. These two hormones, when elevated produce major stress on the body, including psychological stress.

Another cell type where VGCCs have major roles are the pacemaker cells of the heart, endocrine system and central nervous system (29). These pacemaker cells have very high densities of VGCCs in them and may, therefore, be particularly susceptible to EMF activation. In the heart hyperactivity of the VGCCs produces tachycardia and arrhythmias, leading in some cases to sudden cardiac death (49,50). There are studies, in two cases going back to the 1960s (51,52), showing that isolated animal hearts exposed to microwave EMFs (again, well within current safety standards) developed tachycardia and arrhythmia and Havas has shown that some electromagnetic hypersensitive (EHS) individuals developed instantaneous tachycardia when unknowingly exposed to an activated cordless phone (53,54). We currently have an epidemic of tachycardia, arrhythmia and sudden cardiac death despite the fact that ischemic heart disease is decreasing. Could this be due to microwave EMF exposure? This is a possibility that cannot be ruled out at this point.

We are still in the early stages of studying many of these issues but safety standards should, of course, be genuinely tied to real safety, not simply to incomplete knowledge of extremely important potential and plausible hazards.

Are we going to jettison our false safety standards in favor of some that are at least somewhat biologically relevant?

<u>Pulsed Fields and Different Frequencies and Intensities</u>

It has been known for well over a quarter of a century that pulsed microwave fields are much more biologically active than are non-pulsed fields. This is still another type of observation that is completely inconsistent with heating being the main effect. Pulsed fields are, of course, produced by any type of wireless communication device since it is the pattern of pulsations that conveys the information. However because different devices often use different types of pulsation patterns, we are left with the information that pulsations are important but we don't know how biologically active the different pulsation patterns are. So how can we rationally compare the dangers of one device vs another? The answer is we can't at this time because we don't have the required information.

Furthermore Barrie Trower, a retired military intelligence expert from the U.K. has stated that different wavelengths vary in their biological activities as well, but the specifics are all classified by multiple countries because of "national security." The problem of course is that this does not help the security of our bodies. However, this again says that we cannot compare different wireless communications devices with each other when they work on different wavelengths. Finally, it has been shown that there can be intensity "windows" where biological activity is greater than at intensities both higher <u>and</u> lower than the window intensity (55). This again argues against heating and also makes it impossible to currently predict biological activity without doing actual measurements of biological activity. While in general, lower intensities are safer than higher intensities, this "window" effect shows that there are some biologically important exceptions to this pattern.

<u>Where Do the Threats Come From and What Can We Do About Them?</u>

The threats come mainly but not solely from cordless communications devices, cell phones, cordless phones, cordless phone bases, Wi-Fi fields, Wi-Fi signaling from computers and tablets, cell phone and other microwave towers, radar units, microwave ovens, so called "smart meters" and all types of other cordless communications devices.

There are also concerns about extremely low frequency fields including 50/60 cycle fields coming from our wiring. In addition, essentially all such wiring nowadays, have various amounts of dirty electricity, which comes from high frequency transients in the electric wiring. These high frequency transients come from all types of digital devices. Digital power supplies, compact fluorescents and also digital inverter boxes used to

convert photovoltaic energy from DC to AC and similar devices used in wind generated electricity may be particularly problematic. Dirty electricity can move along the power lines and enter houses and other buildings from outside, so you have to deal with your own generation but also levels generated elsewhere in the vicinity. The biological effects of dirty electricity, as reported by Samuel Milham (56), Magda Havas and others are similar to those from microwave EMFs, so it seems likely that dirty electricity works, at least in part via VGCC activation, as well. I am not going to comment further on the dirty electricity problem here, although it is a substantial one.

The various types of devices listed in the first paragraph of this section, all put out pulsed fields with different patterns of pulsation from one device to another, making it impossible to currently predict biological effects of one device based on effects of another. Similarly since the different types of devices use different frequencies, they may differ from one another in biological impact in ways that cannot currently be predicted, given our current dearth of measurements of such effects by different devices. Accordingly, what is needed is a two-phase solution to this public health crisis:

1. Lowering exposures from current allowed levels, which use heating effects to compare different devices, by factors of 100 to 1000-fold. We know of, course, that this may be inadequate and that there may still be biological effects with many devices. But such lowering will produce a substantial improvement over current safety standards.
2. Use a series of biological response measures to compare biological responses to different devices to allow us to devise more biologically defensible safety standards in the future.

<u>Lowering Exposures by Factors of 100 to 1000-fold</u>

There are quite a number of things that can be easily done to improve the current situation. One can put shielding materials on the bottom of laptop computers and the back of tablets to lower exposures to our bodies. Wi-Fi fields are poorly designed with exposure levels of 1000 to 10,000 times that necessary for function when one is located near the Wi-Fi antenna. They can be redesigned to greatly lower such maximum exposures – the problem is that there has not been any focus on this issue. There are still problems using Wi-Fi in schools even if one does this, because a whole classroom of laptops communicating back to the Wi-Fi antenna still

generates very high fields in a small space. My opinion is that it is better to go back to hard wiring computers in schools to completely avoid such unnecessary exposures.

Cell phones can be used with headsets or on speakerphone, both of which substantially lower exposures. Headsets should be given to anyone purchasing or otherwise receiving a cell phone, to encourage use. Cell phones can be carried in pouches shielded on one side, so by carrying the cell phone near the body with the shielded side towards the body, exposures can be greatly lowered.

Cordless (DECT) phones in the U.S. and many other countries are poorly designed, having bases which broadcast 24 hours per day. There are cordless phones available in Europe where the bases only broadcast when the phone is in use – this type of design should be standardized. Most cordless phones are designed so that they can be used circa 200 ft (60 m) away from the base. Most people do not need such long distance usage. By lowering the signal, cutting the distance to 20 ft (6 m), one can cut exposures from the phone 100-fold; redesigning antennae and other properties in such phones could, no doubt, produce further improvements. Changing the design of the phone antennae in either cordless phones or cell phones could lower exposures to the head when these are used without headsets or on speakerphone.

"Smart meters" should be abolished because they use short high-intensity pulses of microwave radiation. We know from the nanosecond pulse studies can be very damaging and act via VGCC activation, with activation continuing long after the pulse has ceased (7). It has been known for over 30 years that short microwave pulses can cause massive cellular damage (57). Until we have some biological measures of "smart meter" effects, it is foolhardy in my view to continue using them.

Cell phone and other microwave towers can be redesigned to lower maximum exposures near the tower. Austria has done such redesigns, lowering such exposures by 1000-fold and there is no reason that similar redesigns cannot be done elsewhere.

Microwave ovens also put out pulsed fields, pulsing with the alternating current that runs them. Exposures from microwave ovens can easily be lowered 100-fold or more through simple redesigning, including putting finer grounded metal mesh over windows.

We had, in the U.S., a huge shift in automobile safety from the 1950's and 60's to the 1980's when safety became a big marketing issue, so companies were competing based on safety, not just style and performance. We need a similar shift in the electronics industry. It can be done if the public knowledge is such that the public demands it, but probably not otherwise.

Biological Testing

Hardell and Sage (58) argued for biologically based EMF safety standards before the VGCC central mechanism of action was realized. It is possible, of course, that EMF action may occur via other mechanisms, not just VGCC activation, but until such alternatives are identified, they cannot be easily assessed. Because we know that VGCC activation occurs and is very important biologically, this must be the current focus of biological testing. There are 10 types of VGCCs, including four types of L-type channels and also four other types of VGCCs (N-type, P/Q-type, R-type, T-type), with T-types having three forms. These 10 VGCCs differ from one another in their properties and may therefore differ from one another in how easily they become activated by various EMFs. These channels are also subject to multiple forms of biological regulation which may also produce still more heterogeneity in terms of biological responses to EMFs. In general then, cells differ from one another in whether they have VGCCs or not (most but not all do), the types of VGCCs found in specific cell types and the density of the different VGCCs in the plasma membrane and how these VGCCs are regulated in specific cells under specific conditions.

It is highly desirable to test EMF effects using diverse biological responses, to lower the probability of missing important responses to specific types of EMF exposures.

The proposal here is to use three types of biological response tests. Our discussion here is on these three general approaches, but does not provide detailed descriptions of each.

1. Cell culture tests: Should use cells known to be sensitive to EMFs. Probably the simplest way to measure responses is to use a nitric oxide electrode positioned in the gas phase over the cells in culture to measure increases in nitric oxide production, as shown earlier by Pilla (59).

2. Specific biological effects measured in experimental animals: Some effects that should be considered are:

Tachycardia and other changes in heart beat in experimental animals

Increased levels of epinephrine/norepinephrine in the blood

Changes in neurological function, such as those reported during cell phone or cordless phone use

3. Whole animal studies can be done, by measuring whole body nitric oxide production. Nitric oxide is unstable in the body and it is typically measured through nitrate/nitrite in the blood.

We very much need to get started with such studies which are essential in order to approach genuine safety instead of the fictional safety we have now.

Citations:

1. Osepchuk JM, Petersen RC 2003 Historical review of RF exposure standards and the International Committee on Electromagnetic Safety (ICES). Bioelectromagnetics Supplement 6:S7-S16.
2. Osepchuk JM, Petersen RC 2001 Safety standards for exposure to RF electromagnetic fields. Microwave Magazine IEEE 2:57-69.
3. D'Andrea JA, Ziriax JM, Adair ER. 2007 Neurobiology of hyperthermia Prog Brain Res 162:107-135.
4. Tripathy H, Pathak PP 2012 Thermal effect due to induced field of broadcasting radiation. Int J Environ Sci 1:50-55.
5. Lin JC 2006 A new IEEE standard for safety levels with respect to human exposure to radio-frequency radiation. Antennas and Propagation Magazine 48:157-159.
6. Pilla AA 2013 Nonthermal electromagnetic fields: from first messenger to therapeutic applications. Electromagn Biol Med 32:123-136.
7. Pall ML 2013 Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. J Cell Mol Med 17:958-965.
8. Walleczek J. 1992 Electromagnetic field effects on cells of the immune system: the role of calcium signaling. FASEB J 6:3177-3185.
9. Adey WR. 1993 Biological effects of electromagnetic fields. J Cell Biochem 51:410-416.

10. Panagopoulos DJ, Messini N, Karabarbounis A, Philippetis AL, Margaritis LH. 2000 A mechanism for action of oscillating electric fields on cells. Biochem Biophys Res Commun 272:634-640.
11. Panagopoulos DJ, Karabarbounis A, Margaritis LH. 2002 Mechanism for action of electromagnetic fields on cells. Biochem Biophys Res Commun 298:95-102.
12. Kesari KK, Siddiqui MH, Meena R, Verma HN, Kumar S. 2013 Cell phone radiation exposure on brain and associated biological systems. Indian J Exp Biol 51:187-200.
13. Yakymenko I, Sidorik E, Kyrylenko S, Chekhun V. 2011 Long-term exposure to microwave radiation provokes cancer growth: evidences from radars and mobile communication systems. Exp Oncol. 2011 Jun;33(2):62-70.
14. Khurana VG, Teo C, Kundi M, Hardell L, Carlberg M. 2009 Cell phones and brain tumors: a review including the long-term epidemiologic data. Surg Neurol 72:205-214
15. Graham PM, Li JZ, Dou X, Zhu H, Misra HP, Jia Z, Li Y. 2013 Protection against peroxynitrite-induced DNA damage by mesalamine: implications for anti-inflammation and anti-cancer activity. Mol Cell Biochem 378:291-298.
16. Ohshima H, Sawa T, Akaike T. 2006 8-nitroguanine, a product of nitrative DNA damage caused by reactive nitrogen species: formation, occurrence, and implications in inflammation and carcinogenesis. Antioxid Redox Signal 8:1033-1045.
17. Kim HW, Murakami A, Williams MV, Ohigashi H. 2003 Mutagenicity of reactive oxygen and nitrogen species as detected by co-culture of activated inflammatory leukocytes and AS52 cells. Carcinogenesis 24:235-241.
18. Suofu Y, Clark J, Broderick J, Wagner KR, Tomsick T, Sa Y, Lu A. 2010 Peroxynitrite decomposition catalyst prevents matrix metalloproteinase activation and neurovascular injury after prolonged cerebral ischemia in rats. J Neurochem 115:1266-1276.
19. Hossain M, Mazzone P, Tierney W, Cucullo L. 2011 In vitro assessment of tobacco smoke toxicity at the BBB: do antioxidant supplements have a protective role? BMC Neurosci 2011 Sep 24;12:92. doi: 10.1186/1471-2202-12-92.
20. Nag S, Kapadia A, Stewart DJ. 2011 Review: molecular pathogenesis of blood-brain barrier breakdown in acute brain injury. Neuropathol Appl Neurobiol 37:3-23.

21. Polimeni M, Prato M. 2014 Host matrix metalloproteinases in cerebral malaria: new kids on the block against blood-brain barrier integrity? Fluids Barriers CNS. 2014 Jan 27;11(1):1. doi: 10.1186/2045-8118-11-1.
22. Zatz M, Heath JR 3rd. 1995 Calcium and photoentrainment in chick pineal cells revisited: effects of caffeine, thapsigargin, EGTA, and light on the melatonin rhythm. J Neurochem 65:1332-1341.
23. Zatz M, Mullen DA. 1988 Does calcium influx regulate melatonin production through the circadian pacemaker in chick pineal cells? Effects of nitrendipine, Bay K 8644, Co2+, Mn2+, and low external Ca2+. Brain Res 463:305-316.
24. Kesari KK, Kuman S, Behari J. 2011 Effects of radiofrequency electromagnetic wave exposure from cellular phones on reproductive pattern in male Wistar rats. Appl Biochem Biotechnol 164:546-549.
25. Avendaño C, Mata A, Sanchez Sarmiento CA, Doncel GF. 2012 Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertil Steril 97:39-45.
26. Hajnóczky G, Csordás G, Das S, Garcia-Perez C, Saotome M, Sinha Roy S, Yi M. 2006 Mitochondrial calcium signalling and cell death: approaches for assessing the role of mitochondrial Ca2+ uptake in apoptosis. Cell Calcium 40:553-560.
27. Webster KA. 2012 Mitochondrial membrane permeabilization and cell death during myocardial infarction: roles of calcium and reactive oxygen species. Future Cardiol 8:863-884.
28. Johansson O. 2009 Disturbance of the immune system by electromagnetic fields-A potentially underlying cause for cellular damage and tissue repair reduction which could lead to disease and impairment. Pathophysiology 16:157-77.
29. Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J. 2005 International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. Pharmacol Rev 57:411-25.
30. Khurana VG, Hardell L, Everaert J, Bortkiewicz A, Carlberg M, Ahonen M. 2010 Epidemiological evidence for a health risk from mobile phone base stations. Int J Occup Environ Health 16:263-267.
31. Papageorgiou CC, Hountala CD, Maganioti AE, Kyprianou MA, Rabavilas AD, Papadimitriou GN, Capsalis CN. 2011 Effects of Wi-Fi signals on the p300 component of event-related potentials during an auditory hayling task. J Integr Neurosci 10:189-202.

32. Divan HA, Kheifets L, Obel C, Olsen J. 2008 Prenatal and postnatal exposure to cell phone use and behavioral problems in children. Epidemiology 19:523-529.
33. Odaci E, Bas O, Kaplan S. 2008 Effects of prenatal exposure to a 900 MHz electromagnetic field on the dentate gyrus of rats: a stereological and histopathological study. Brain Res 1238:224-229.
34. Bas O, Odaci E, Mollaoglu H, Ucok K, Kaplan S. 2009 Chronic prenatal exposure to the 900 megahertz electromagnetic field induces pyramidal cell loss in the hippocampus of newborn rats. Toxicol Ind Health 25:377-384.
35. Bas O, Odaci E, Kaplan S, Acer N, Ucok K, Colakoglu S. 2009 900 MHz electromagnetic field exposure affects qualitative and quantitative features of hippocampal pyramidal cells in the adult female rat. Brain Res 1265:178-185.
36. Bodera P, Stankiewicz W, Antkowiak B, Paluch M, Kieliszek J, Sobiech J, Zdanowski R, Wojdas A, Siwicki AK, Skopińska-Rózewska E. 2012 Suppressive effect of electromagnetic field on analgesic activity of tramadol in rats. Pol J Vet Sci 15:95-100.
37. Fragopoulou AF, Samara A, Antonelou MH, Xanthopoulou A, Papadopoulou A, Vougas K, Koutsogiannopoulou E, Anastasiadou E, Stravopodis DJ, Tsangaris GT, Margaritis LH. 2012 Brain proteome response following whole body exposure of mice to mobile phone or wireless DECT base radiation. Electromagn Biol Med 31:250-274.
38. Paulraj R, Behari J. 2006 Protein kinase C activity in developing rat brain cells exposed to 2.45 GHz radiation. Electromagn Biol Med 25:61-70.
39. Khurana VG, Hardell L, Everaert J, Bortkiewicz A, Carlberg M, Ahonen M. 2010 Epidemiological evidence for a health risk from mobile phone base stations. Int J Occup Environ Health 16:263-267.
40. Mausset-Bonnefont AL, Hirbec H, Bonnefont X, Privat A, Vignon J, de Sèze R. 2004 Acute exposure to GSM 900-MHz electromagnetic fields induces glial reactivity and biochemical modifications in the rat brain. Neurobiol Dis 17:445-454.
41. Thomas JR, Schrot J, Banvard RA. 1982 Comparative effects of pulsed and continuous-wave 2.8 GHz microwaves on temporally defined behavior. Bioelectromagnetics 3:227-235.
42. Ito H, Bassett CA. 1984 Effect of weak, pulsing electromagnetic fields on neural regeneration in the rat. Lancet 1(8379):695-698.
43. Jiang DP, Li J, Zhang J, Xu SL, Kuang F, Lang HY, Wang YF, An GZ, Li JH, Guo GZ. 2013 Electromagnetic pulse exposure induces overexpression of beta amyloid protein in rats. Arch Med Res 44:178-184.

44. Lai H, Singh NP. 1995 Acute low-intensity microwave exposure increases DNA single-strand breaks in rat brain cells. Bioelectromagnetics 16:207-210.
45. Sokolovic D, Djindjic B, Nikolic J, Bjelakovic G, Pavlovic D, Kocic G, Krstic D, Cvetkovic T, Pavlovic V. 2008 Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain. J Radiat Res 49:579-586.
46. Lai H, Carino MA, Horita A, Guy AW. 1992 Single vs. repeated microwave exposure: effects on benzodiazepine receptors in the brain of the rat. Bioelectromagnetics. 1992;13(1):57-66.
47. Sanders AP, Schaefer DJ, Joines WT. 1980 Microwave effects on energy metabolism of rat brain. Bioelectromagnetics 1:171-181.
48. Salford LG, Brun AE, Eberhardt JL, Malmgren L, Persson BR. 2003 Nerve cell damage in mammalian brain after exposure to microwaves from GSM mobile phones. Environ Health Perspect 111:881-883.
49. Dixon RE, Cheng EP, Mercado JL, Santana LF. 2012 L-type Ca2+ channel function during Timothy syndrome. Trends Cardiovasc Med 22:72-76.
50. Hsiao PY, Tien HC, Lo CP, Juang JM, Wang YH, Sung RJ. 2013 Gene mutations in cardiac arrhythmias: a review of recent evidence in ion channelopathies. Appl Clin Genet 6:1-13.
51. Levitina NA 1966 Investigation of the nonthermal effect of microwaves on the cardiac rhythm of frogs. Byull Eksp Biol Med 62(12):64-66.
52. Frey AH, Seifert E 1968 Pulse modulated UHF energy illumination of the heart associated with change in heart rate. Life Sci 7:505-512.
53. Havas M, Marrongelle J, Pollner B, Kelley E, Rees CRG, Tully, L 2010 Provocation study using heart rate variability shows microwave radiation from 2.4 GHz cordless phone affects autonomic nervous system. Eur J Oncol Lib 5:273-300.
54. Havas M, Marrongelle J 2013 Replication of heart rate variability provocation study with 2.4-GHz cordless phone confirms original findings. Electromagnetic Biol Med 32:253-266.
55. Panagopoulos DJ, Margaritis LH. 2010 The identification of an intensity 'window' on the bioeffects of mobile telephony radiation. Int J Radiat Biol 86:358-366.
56. Milham S. Dirty Electicity: Electrification and the Diseases of Civilization, 2nd Ed., IUniverse, Inc., 2012, Bloomington IN USA.
57. Webber MM, Barnes FS, Seltzer LA, Bouldin TR, Prasad KN. 1980 Short microwave pulses cause ultrastructural membrane damage in neuroblastoma cells. J Ultrastruct Res 71:321-330.

58. Hardell L, Sage C. 2008 Biological effects from electromagnetic field exposure and public exposure standards. Biomed Pharmacother 62:104-109.
59. Pilla AA. 2012 Electromagnetic fields instantaneously modulate nitric oxide signaling in challenged biological systems. Biochem Biophys Res Commun 426: 330-333.