

Electromagnetic fields may act via calcineurin inhibition to suppress immunity, thereby increasing risk for opportunistic infection: Conceivable mechanisms of action



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ARTICLE INFO

Article history:

Received 15 February 2017

Accepted 30 June 2017

Keywords:

Electromagnetic fields (EMF)
Reactive oxygen species (ROS)
Calcineurin
Calcineurin inhibitors
Immunosuppression
Opportunistic infections

ABSTRACT

While a good number of studies have demonstrated that modern, man-made ambient electromagnetic fields can have both stimulatory and inhibitory effect on immune system function, the precise mechanisms have yet to be completely elucidated. It is hypothesized here that, depending on the parameters, one of the means by which long-term electromagnetic field exposure has the potential to eventually lead to immunosuppression is via downstream inhibition of the enzyme calcineurin – a protein phosphatase, which activates the T-cells of the immune system and can be blocked by pharmaceutical agents.

Calcineurin is the target of a class of pharmaceuticals called calcineurin inhibitors (e.g., cyclosporine, pimecrolimus and tacrolimus). When organ transplant recipients take such pharmaceuticals to prevent or suppress organ transplant rejection, one of the major side effects is immunosuppression leading to increased risk of opportunistic infection: e.g., fungal, viral (Epstein-Barr virus, cytomegalovirus), atypical bacterial (*Nocardia*, *Listeria*, mycobacterial, mycoplasma), and parasitic (e.g., toxoplasmosis) infections.

Frequent anecdotal reports, as well as a number of scientific studies, have shown that electromagnetic field exposures may indeed produce the same effect: a weakened immune system leading to an increase in the same or similar opportunistic infections: i.e., fungal, viral, atypical bacterial, and parasitic infections.

Furthermore, numerous research studies have shown that man-made electromagnetic fields have the potential to open voltage-gated calcium channels, which can in turn produce a pathological increase of intracellular calcium, leading downstream to the pathological production of a series of reactive oxygen species. Finally, there are a number of research studies demonstrating the inhibition of calcineurin by a pathological production of reactive oxygen species.

Hence, it is hypothesized here that exposures to electromagnetic fields have the potential to inhibit immune system response by means of an eventual pathological increase in the influx of calcium into the cytoplasm of the cell, which induces a pathological production of reactive oxygen species, which in turn can have an inhibitory effect on calcineurin. Calcineurin inhibition leads to immunosuppression, which in turn leads to a weakened immune system and an increase in opportunistic infection.

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Introduction

In the last thirty years we have seen a substantial increase in a number of disease states and functional impairments, many new or previously rare (e.g., autism spectrum disorder [ASD], chronic fatigue syndrome [CFS], attention deficit hyperactivity disorder [ADHD], etc.) [1–4]. Many of these tend not only to be coupled with

a weakened immune system, but also to involve immune system disorders (e.g., allergies, food and chemical sensitivities, autoimmune disorders, etc.) (e.g. [5,6]). These disease states have paralleled major increases in ambient levels of man-made electromagnetic fields (EMFs) in our immediate environments. Furthermore, a number of experimental and epidemiological studies are continuing to link electromagnetic radiation (EMR) exposure with many of these disease states (e.g., [7–10]), their immune system dysfunctions, and their symptomologies.

Since calcium (Ca²⁺) is necessary for numerous enzymatic functions, a number of researchers have postulated that an EMF effect

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may transpire via Ca^{2+} signaling transcription due to the influence of EMFs on Ca^{2+} cellular flux. While one such study by Manikonda et al. [11], for example, found that a 90-day extremely-low-frequency (ELF) 50 Hz magnetic field exposure (at 50 mT and 100 mT) induced an increase in calcineurin activity concomitant with an increase in intracellular Ca^{2+} ($[\text{Ca}^{2+}]_i$) levels in the hippocampal brain regions, Erkut et al. [12] found that with increasing radiofrequency (RF) EMF (1800 MHz) exposure duration (6, 12, and 24 h, respectively) of pregnant rats exposed for 20 days, “there was... [an increased] reduction in calcineurin activities” in both bone and muscle tissues of newborn rats. Hence, it is assumed here that, depending on the changing complexity of parameters (e.g., cell type; quality, duration, and intensity of exposure, etc.), EMFs can have a stimulatory, inhibitory, or no effect on intracellular calcineurin activity. It is further postulated here that while the influx of Ca^{2+} into the cell can initially have a stimulatory effect on the enzyme calcineurin, a pathological increase in Ca^{2+} can also stimulate the enzyme nitric oxide synthase to produce more nitric oxide (NO), leading to the production of peroxynitrite and other reactive oxygen species (ROS), which may have the downstream potential to inhibit the enzyme calcineurin.

An abundant number of studies have shown a substantial increase in ROS with EMF exposure. And while ROS, depending on concentration, can have both beneficial and deleterious effects, a recent review by Pall [13] has drawn attention to a process by which EMFs can induce the opening of voltage-gated calcium channels (VGCCs) in the plasma membrane via a change in its electric potential, triggering a pathological increase in $[\text{Ca}^{2+}]_i$ via Ca^{2+} influx into cells (Fig. 1a). This in turn can trigger an increase in a number of ROS by means of a chain reaction initiated by the production of nitric oxide (NO) via Ca^{2+} stimulation of enzyme nitric oxide synthase (Figs. 1c–1f). Under normal circumstances, in a

physiological context, one of the feedback-control mechanisms mediating Ca^{2+} entry into the cell through VGCCs is via Ca^{2+} binding proteins (one of which is the protein phosphatase enzyme, calcineurin), which help to control homeostasis of Ca^{2+} within the cell [14] (Fig. 1b). Nitric oxide is involved in a reverse feedback loop by which the enzyme guanylate cyclase is activated, inducing an increase in intracellular cyclic guanosine monophosphate (cGMP), which, in turn, again under normal circumstances, causes an inhibition of Ca^{2+} entry into the cell, thus decreasing intracellular concentrations [15]. However, with the advent of VGCC-opening EMFs into the equation, there is the real possibility that this feedback mechanism becomes impeded or stops working altogether, allowing the uncontrolled flow of Ca^{2+} into the cell.

Calcineurin, a serine-threonine phosphatase, found extensively in a variety of tissues with vital functions in neural, cardiac, skeletal, muscle, and immune cells, has not only been shown to play a central role in immunity, but it is also involved in a wide array of signaling pathways related to both cellular development and cell cycle progression.

Certain pharmaceutical agents known as calcineurin inhibitors, used mainly to prevent organ rejection of transplant recipients, also have an immunosuppressive side effect, known to lead to an increase in the following opportunistic infections: fungal/yeast (e.g., *Cryptococcus neoformans*); viral (esp. herpes-family viruses such as Epstein-Barr virus [EBV], cytomegalovirus [CMV]); atypical bacterial (e.g., *Mycoplasma*, *Nocardia*, *Listeria*, *Mycobacteria*); and parasitic (e.g., toxoplasmosis) infections [16–21].

Since ROS (e.g., superoxide $[\text{O}_2^-]$, nitric oxide [NO], hydrogen peroxide $[\text{H}_2\text{O}_2]$, and ROS-like singlet oxygen) have also been shown to inhibit calcineurin activity [22–28], it is hypothesized here that one possible mechanism by which EMFs inhibit immune system function is via a downstream pathological increase in Ca^{2+}

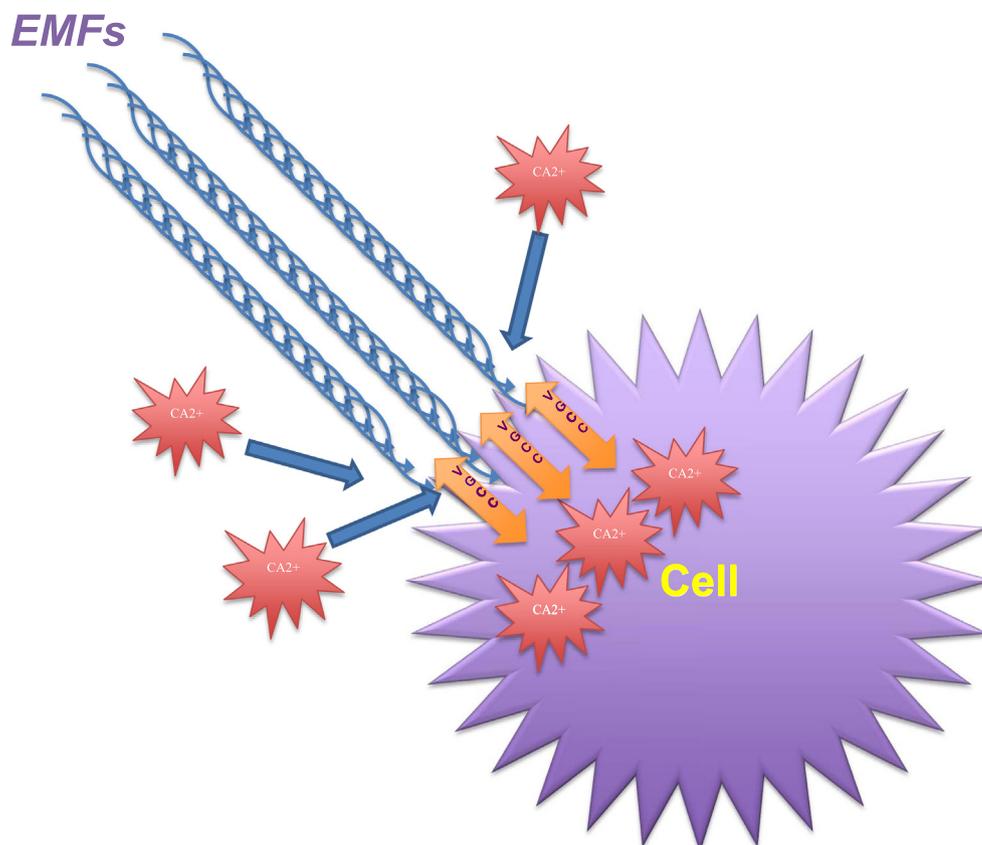


Fig. 1a. Electromagnetic fields (EMFs) open voltage-gated calcium channels (VGCCs) allowing an influx of extracellular calcium ions (Ca^{2+}) into the cell.

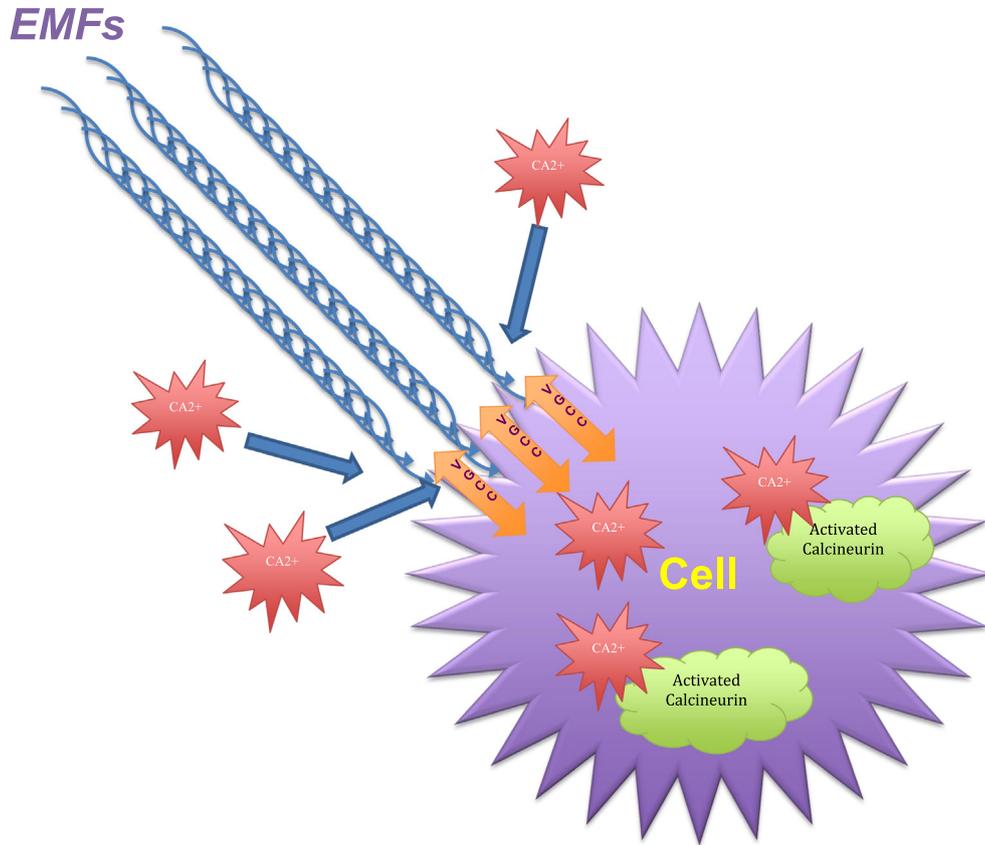


Fig. 1b. Increased levels of intracellular calcium ions (Ca²⁺) activate calcineurin (CN).

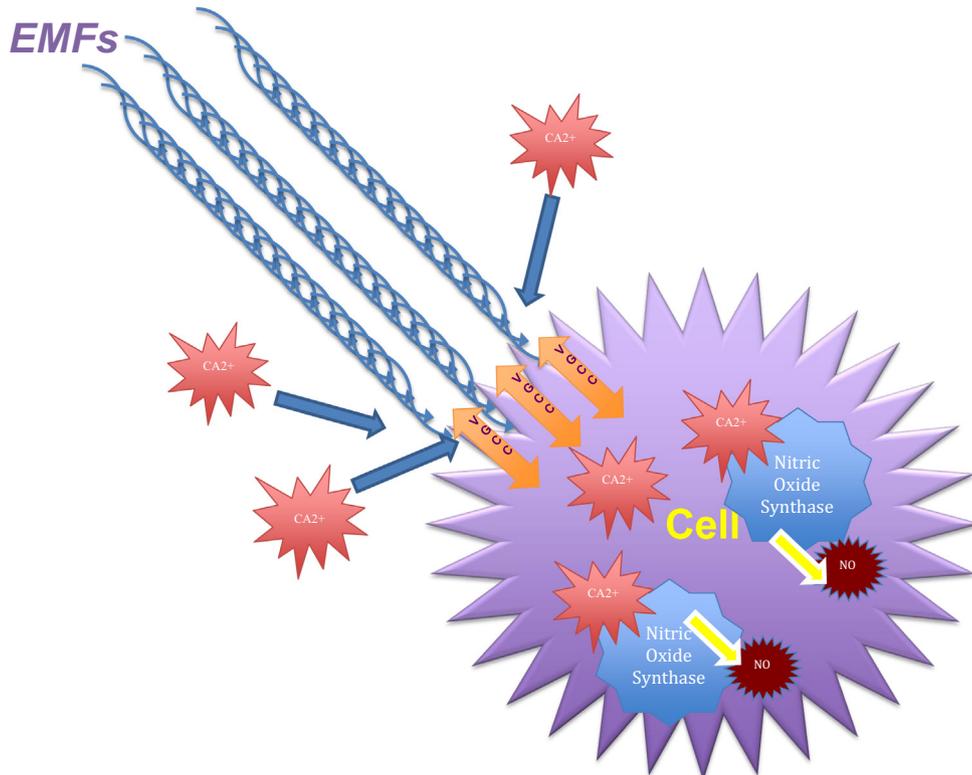


Fig. 1c. Increased levels of intracellular calcium ions (Ca²⁺) stimulate nitric oxide synthase to produce nitric oxide (NO).

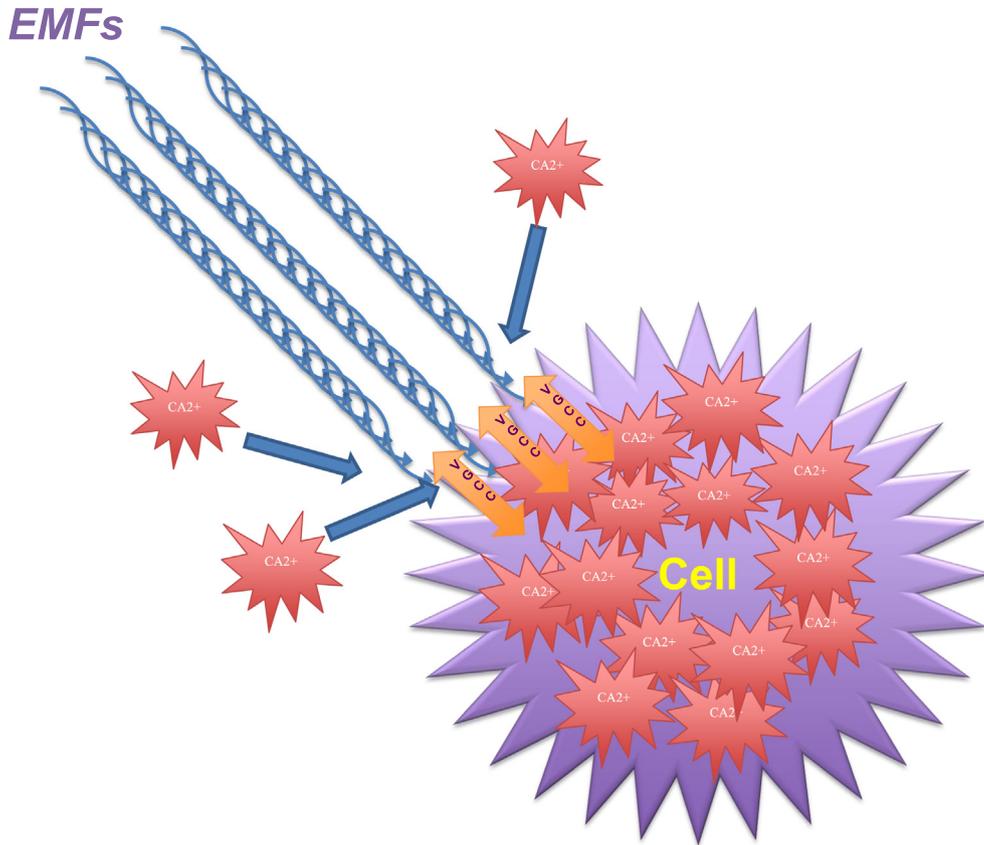


Fig. 1d. Electromagnetic fields (EMFs) can stimulate a pathological increase of calcium ions (Ca²⁺) within the cell.

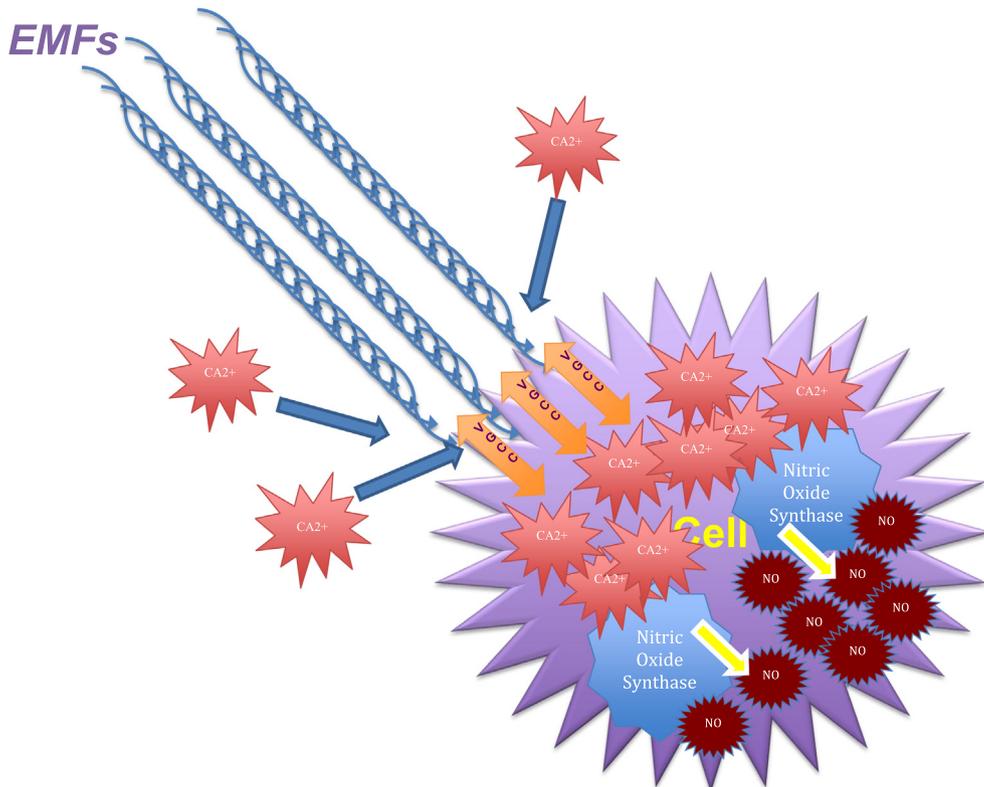


Fig. 1e. A pathological increase in calcium ions (Ca²⁺) can lead to a pathological increase in nitric oxide (NO).

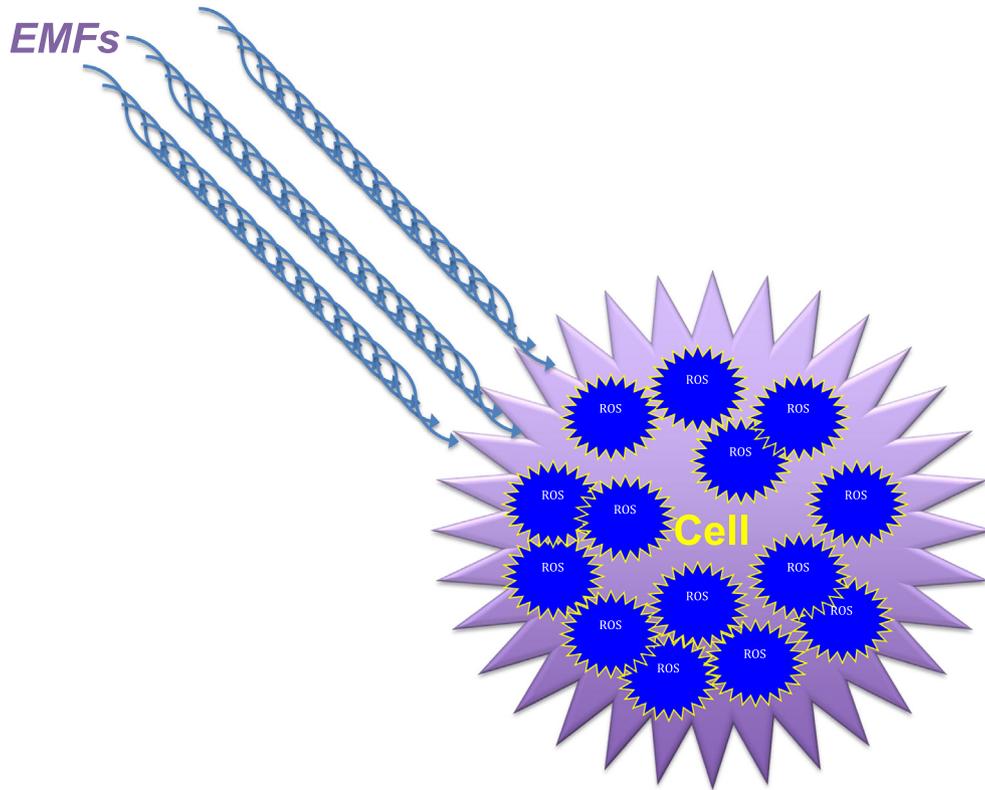


Fig. 1f. A pathological increase in nitric oxide (NO) can lead downstream to the formation of other reactive oxygen species (ROS), such as peroxynitrite.

in the cytoplasm of the cell (Fig. 1d), inducing a pathological production of ROS [13] and also possibly singlet oxygen [29] (Fig. 1f), which in turn has an inhibitory effect on calcineurin

[22–28] (Fig. 1g). One other possible mechanism could be an EMF-induced blockage of Ca²⁺ uptake by T-lymphocytes, which might also prevent the activation of calcineurin [30,31]. Either

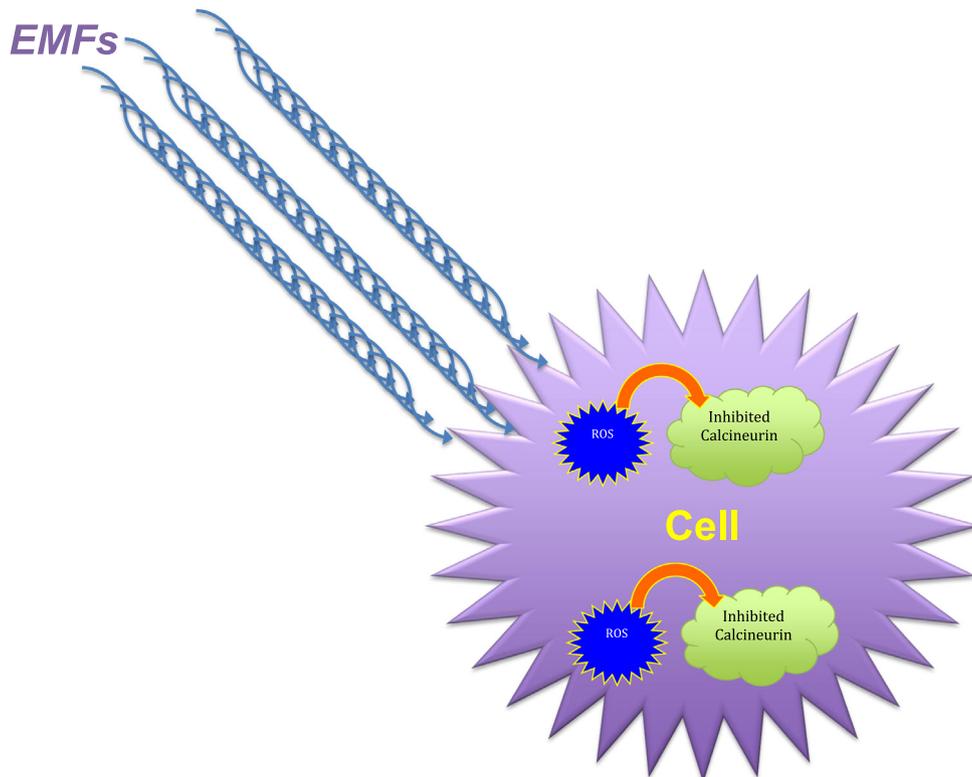


Fig. 1g. Reactive oxygen species (ROS) inhibit calcineurin.

way, calcineurin inhibition leads to immunosuppression, which in turn leads to a weakened immune system and an increase in opportunistic infections.

Calcineurin and T-lymphocytes

Calcineurin is a protein phosphatase enzyme, (named for its attraction to Ca²⁺ and affinity for neurons), which activates the T-lymphocytes involved in cell-mediated immunity (as opposed to humeral immunity). Calcineurin activated by Ca²⁺ thus generates nuclear factor of activated T-cells (NFAT), a transcription factor, via the process of dephosphorylation. The activated NFAT then moves into the nucleus binding to T-cell DNA stimulating production of interleukin 2 (IL-2), an important immune system cytokine. IL-2, in turn, enables the activation, proliferation, and differentiation of inactive or naive T-lymphocytes. (T-lymphocytes are one type of differentiated lymphocyte: the others being natural killer (NK) and B-cells. And it is important to note here that NK cells are also activated by IL-2 and thus would also be indirectly affected by calcineurin inhibition.) T-lymphocytes or T-cells are further differentiated into helper T-cell and cytotoxic T-cell subsets.

Calcineurin inhibitors

Calcineurin inhibitors are pharmaceutical agents (e.g., cyclosporine, tacrolimus, pimecrolimus) that act by inhibiting the func-

tion of calcineurin to produce NFAT, which in turn suppresses the ability of IL-2 to activate, differentiate, and proliferate T cells. They act pharmaceutically as immunosuppressants in order to prevent or suppress organ rejection in transplant patients – and also to suppress inflammation in psoriasis and rheumatoid arthritis. Consequential side-effects of taking calcineurin inhibitors are (1) an increased risk of infection, especially opportunistic infections such as fungal, yeast, viral (Epstein-Barr virus [EBV], cytomegalovirus [CMV]), and atypical bacterial infection (Nocardia, Listeria, mycobacterial, mycoplasma), and (2) an increased risk of neoplasms.

There is evidence which also suggests that calcineurin inhibitors act via increases in oxidative stress. Research by Hong et al. [22] has shown that at least one calcineurin inhibitor, cyclosporine (CsA), acts via the generation of high levels of ROS. Further research by Moreno et al. [23] showing increased oxidative stress markers in transplant recipients taking calcineurin inhibitors (cyclosporine and tacrolimus) vs. healthy subjects lends further evidence to this hypothesis.

EMF-induced calcium flux/uptake blockage

Specific frequency windows, power densities, modulations, and cellular states

Numerous studies [32–57] demonstrate EMF-induced Ca²⁺ flux and/or its possible related effects (Table 1), with the more recent of

Table 1
EMF Effect on Calcium Flux.

Selected research studies	EMF type	Frequency	Power density, Field strength, or SAR	Biological effect/Conclusion
Kaczmarek LK, Adey WR. Weak electric gradients change ionic and transmitter fluxes in cortex. (1974) [32]	Electric field		20–60 mV/cm	Ca ²⁺ and gamma aminobutyric acid (GABA) efflux in cat cerebral cortex.
Bawin SM, Adey WR. Sensitivity of calcium binding in cerebral tissue to weak environmental electric fields oscillating at low frequency. (1976) [33]	Weak sinusoidal electric fields	6 and 16 Hz	10 and 56 V/m	Inhibition of Ca ²⁺ efflux in chick and cat cerebral tissue.
Blackman CF, et al. Induction of calcium-ion efflux from brain tissue by radio-frequency radiation: Effects of modulation frequency and field strength. (1979) [34]	Modulated RF field	147 MHz amplitude modulated by 16 Hz sine waves	0.75 mW/cm ⁻²	Ca ²⁺ efflux from brain tissue, confirming the presence of the frequency “window” (previously described by Bawin et al.), and also a narrow power-density “window.”
Joines WT, Blackman CF. Power density, field intensity, and carrier frequency determinants of RF-energy-induced calcium-ion efflux from brain tissue. (1980) [35]	Modulated RF field	50, 147, and 450 MHz carrier frequencies		The Ca ²⁺ efflux from brain tissue obtained at three frequencies, when adjusted with incident power density (Pi) occur at the same average electric-field intensity within the sample.
Blackman CF, et al. Calcium-ion efflux from brain tissue: power-density versus internal field-intensity dependencies at 50-MHz RF radiation. (1980) [36]	Modulated RF field	50 MHz and 147 MHz	1.44–1.67 mW/cm ² , 3.64 mW/cm ² 1.3 μW/g at 50 MHz, and 1.4 μW/g at 147 MHz	The enhancement of Ca ²⁺ efflux from brain tissue is more dependent on the field intensity in the brain than on the power density of incident radiation.
Joines WT, Blackman CF. Equalizing the electric field intensity within chick brain immersed in buffer solution at different carrier frequencies. (1981) [37]	Modulated RF field	50, 147, and 450 MHz		Supports earlier conclusion that Ca ²⁺ efflux results obtained at different carrier frequencies are in agreement when related by the electric field within the brain.
Joines WT, Blackman CF, Hollis MA. Broadening of the RF power-density window for calcium-ion efflux from brain tissue. (1981) [38]	Modulated RF field	50–147 MHz modulated sinusoidally at 16 Hz	0.83 mW/cm ² 0.55, 0.83, 1.11, and 1.38 mW/cm ²	Enhancement of Ca ²⁺ efflux from brain tissue was induced by changing the spacing between sample tubes.
Blackman et al. Effects of ELF fields on calcium-ion efflux from brain tissue in vitro. (1982) [39]	ELF field	16 Hz sinusoidal	5–7.5 V/m and 35–50 V/m	A 16-Hz sinusoidal field without its carrier wave was found to induce Ca ²⁺ efflux from brain tissue.
Blackman et al. Effects of ELF (1–120 Hz) and modulated (50 Hz) RF fields on the efflux of calcium ions from brain tissue in vitro. (1985) [40]	ELF (1–120 Hz) field Modulated RF (50 Hz) field	45, 50, and 60 Hz	40 Vp-p/m, 45–50 Vp-p/m, and 35–40 Vp-p/m	Demonstrated Ca ²⁺ efflux from brain tissue at certain frequencies and power densities and not at others.
Blackman et al. A role for the magnetic field in the radiation-induced efflux of calcium ions from brain tissue in vitro. (1985) [41]	Local Geomagnetic Field [LGF]	15 and 45 Hz and 1 and 30 Hz	38 μT, 19 μT, 25.3 μT, and 76 μT	Specific frequencies at specific field strengths induced change in calcium ion efflux from brain tissue in vitro, whereas others did not. These

Table 1 (continued)

Selected research studies	EMF type	Frequency	Power density, Field strength, or SAR	Biological effect/Conclusion
Conti P, et al. A role for Ca ²⁺ in the effect of very low frequency electromagnetic field on the blastogenesis of human lymphocytes. (1985) [30]	Pulsed ELF field	3 Hz	6 mT	effective frequencies could be rendered ineffective by altering the field strength whereas other ineffective frequencies could be made effective via the same means.
Conti P, et al. Mitogen dose-dependent effect of weak pulsed electromagnetic field on lymphocyte blastogenesis. (1986) [31]	Pulsed ELF field	3 Hz	50 G	Field exposure caused DNA synthesis and Ca ²⁺ uptake inhibition in mitogen-stimulated thymocytes, the effect being seemingly synergistic with calcium blocker agent, verapamil.
Blackman et al. Influence of electromagnetic fields on the efflux of calcium ions from brain tissue in vitro: a three-model analysis consistent with the frequency response up to 510 Hz. (1988) [42]	ELF Field	15 Hz intervals over range 1–510 Hz	15 Vrms/m, 59 and 69 nTrms	Field exposure induced intense inhibition of DNA synthesis with use of optimal doses of mitogens, while opposite effects were induced with suboptimal concentration of mitogens.
Blackman et al. Effect of ambient levels of power-line-frequency electric fields on a developing vertebrate. (1988) [43]	Sinusoidal electric fields	Either 50 or 60 Hz	Average intensity of 10 Vrms/m	“Hypothetical ordering of the frequency-response profile provides the basis for future experimental designs to test each possible interaction model and for their connection to the calcium-ion efflux endpoint.”
Cadossi R, et al. Lymphocytes and pulsing magnetic fields. (1988) [47]	Pulsed magnetic field	75 Hz	1 mV/m	The brains of chicks born of eggs exposed to either 50 or 60 Hz for a 21-day incubation period had differing Ca ²⁺ efflux reactions, demonstrating that the “exposure of a developing organism to ambient power-line-frequency electric fields at levels typically found inside buildings can alter the response of brain tissue to field-induced calcium-ion efflux.”
Blackman et al. Multiple power-density windows and their possible origin. (1989) [44]	Modulated RF field	50 MHz modulated sinusoidally at 16 Hz	1.75, 3.85, 5.57, 6.82, 7.65, 7.77, and 8.82 mW/cm ²	Exposure increased response of lymphocytes to suboptimal phytohemagglutinin (PHA) levels via the influx of Ca ²⁺ . Calcium blocker verapamil blocked PHA-stimulated Ca ²⁺ influx while PEMF antagonized the verapamil block suggesting that the PEMF effect was on Ca ²⁺ flux across the plasma membrane.
Dutta SK, Ghosh B, Blackman CF. Radiofrequency radiation-induced calcium ion efflux enhancement from human and other neuroblastoma cells in culture. (1989) [45]	Modulated RF field	13–16 Hz and 57.5–60 Hz modulation ranges	SAR of 0.05 and 0.005 W/kg	Ca ²⁺ efflux from brain tissue at a new set of power densities converted to specific absorption rate (SAR) by 0.36 mW/kg per mW/cm ² .
Dutta SK, et al. Dose dependence of acetylcholinesterase activity in neuroblastoma cells exposed to modulated radio-frequency electromagnetic radiation. (1992) [46]	Modulated RF field	147 MHz sinusoidally modulated at 16 Hz		Amplitude-modulated radiofrequency radiation can induce responses in cells of nervous tissue origin from widely different animal species, including humans.
Walleczek J, Liburdy RP. Nonthermal 60 Hz sinusoidal magnetic-field exposure enhances 45Ca ²⁺ uptake in rat thymocytes: dependence on mitogen activation. (1990) [63]	Sinusoidal magnetic field	60 Hz	1.0 mV/cm	Exposed neuroblastoma cells (NG108) (30 min) showed increased AChE activity.
Papatheofanis FJ. Use of calcium channel antagonists as magnetoprotective agents. (1990) [48]	Static magnetic field		0.1 T	A 60 min exposure enhanced 45Ca ²⁺ uptake in lymphocytes activated with the mitogen Concanavalin A (Con A) while having no effect on 45Ca ²⁺ uptake in resting lymphocytes.
Liburdy RP. Calcium signaling in lymphocytes and ELF fields. Evidence for an electric field metric and a site of interaction involving the calcium ion channel. (1992) [49]	ELF field	60 Hz magnetic	22 mT 1.7 mV/cm	Furthermore, thymocytes with a reduced capacity to mobilize Ca ²⁺ in response to Con A were most affected by the magnetic field.
Walleczek J, Budinger TF. Pulsed magnetic field effects on calcium signaling in lymphocytes: dependence on cell status and field intensity. (1992) [62]	Pulsed Magnetic ELF field	3 Hz	Bpeak = 6.5 mT, Emax = 0.69 mV/cm, Jmax = 2.6 microA/cm ²	Human polymorphonuclear leukocytes (PMNs) treated with the calcium channel antagonists diltiazem, nifedipine, and verapamil prior to being exposed to a magnetic field had no significant change in degranulation when compared to control and sham-exposed PMNs similarly treated.
Fitzsimmons RJ, et al. Combined magnetic fields increased net calcium flux in bone cells. (1994) [56]	Combined magnetic field (CMF)	Between 15.3 and 16.3 Hz	10(-5) V/m	Calcium influx increased during mitogen-activated signal transduction in thymic lymphocytes exposed for 60 min.

(continued on next page)

Table 1 (continued)

Selected research studies	EMF type	Frequency	Power density, Field strength, or SAR	Biological effect/Conclusion
Kenny JS, et al. Quantitative study of calcium uptake by tumorigenic bone (TE-85) and neuroblastoma x glioma (NG108-15) cells exposed to extremely-low-frequency (ELF) electric fields. (1997) [57]	Capacitively coupled electric fields (CCEF)	16 Hz	18.3 mV/cm	45Ca ²⁺ uptake enhanced in tumorigenic bone [TE-85] and neuroblastoma x glioma [NG108-15]) cells at frequency-specific 16 Hz also increasing TE-85 [Ca ²⁺] _i from 140 to 189–210 nM and NG108-15 [Ca ²⁺] _i from 67 to 189–210 nM.
Fanelli C, et al. Magnetic fields increase cell survival by inhibiting apoptosis via modulation of Ca ²⁺ + influx. (1999) [50]	Magnetic field		6 G	Magnetic fields were show to increase cell survival via the inhibition of apoptosis via their modulation of Ca ²⁺ influx.
Cho MR, et al. Transmembrane calcium influx induced by ac electric fields. (1999) [51]	Electric field	1 or 10 Hz	10 V/cm	A continuous 30 min. electric field applied to human hepatoma (Hep3B) cells prompted a fourfold increase in [Ca ²⁺] _i . This [Ca ²⁺] _i increase was inhibited by a depletion in extracellular Ca ²⁺ , and also partially by cation channel inhibitor GdCl ₃ or the nonspecific calcium channel blocker CoCl ₂ , with simultaneous treatment of both GdCl ₃ and CoCl ₂ completely inhibiting the increase in [Ca ²⁺] _i .
Grassi C, et al. Effects of 50 Hz electromagnetic fields on voltage-gated Ca ²⁺ channels and their role in modulation of neuroendocrine cell proliferation and death. (2004) [52]	ELF	50 Hz		Proliferation of human neuroblastoma IMR32 (+40%) and rat pituitary GH3 cells (+38%) was significantly enhanced by exposure to ELF EMFs. Furthermore, puromycin- and H(2)O(2)-induced apoptosis in IMR32 cells was also inhibited by field exposure. Ca(2+) channel blockade counteracted the field exposure effects on both proliferation and apoptosis.
Craviso GL, et al. Nanosecond electric pulses: a novel stimulus for triggering Ca ²⁺ influx into chromaffin cells via voltage-gated Ca ²⁺ channels [53]	Pulsed electric field		5 MV/m	A single 5 ns, high-voltage electric pulse exposure stimulated Ca(2+) entry into bovine chromaffin cells via the opening of L-type voltage-gated Ca(2+) channels (VGCC) while VGCC blockers inhibited this response.
Craviso GL, et al. Modulation of intracellular Ca ²⁺ levels in chromaffin cells by nanoelectropulses. (2011) [54]	Pulsed electric field	1 Hz, 10 Hz, and 1 kHz.	5 MV/m	A single 5 ns pulse exposure induced Ca(2+) influx and a rapid, transient increase in intracellular calcium concentration ([Ca(2+)] _i) in chromaffin cells. A temperature sensitivity was also noted with a number of cellular responses.
Morotomi-Yano K, Akiyama H, Yano K. Different involvement of extracellular calcium in two modes of cell death induced by nanosecond pulsed electric fields. (2014) [55]	Pulsed electric field			Various cellular responses (e.g., Ca ²⁺ influx and cell death) were induced by nanosecond pulsed electric fields (nsPEFs). Necrosis was enhanced with the presence of extracellular Ca ²⁺ in HeLa S3 cells. The presence of a Ca ²⁺ ionophore boosted necrosis while the absence of extracellular Ca ²⁺ made HeLa S3 cells less susceptible to nsPEFs. It was concluded that cell death induced by nsPEFs is cell-type dependent and that extracellular Ca ²⁺ is essential for nsPEF-induced necrosis.

these studies [47–57] implicating the EMF effect of opening of VGCCs as being responsible for this flux. These have predominantly shown not only an influx of Ca²⁺ with EMF exposures, but also that both calcium channel blockers and a reduction in extracellular Ca²⁺ can impede this effect. Furthermore, EMF stimulation of Ca²⁺ flux occurs dependent on specific frequency windows, specific power densities, specific modulations, (but not in others lying between them), and the specific biological parameters of the cell. A limited number of studies [30,31] have also shown blockage of Ca²⁺ uptake by cells – similar to the effect of the voltage-gated calcium channel (VGCC) blocker verapamil – along with inhibition of lymphocyte blastogenesis when a 3-Hz (6 mT) EMF was used.

(It should be noted that with Ca²⁺ influx and efflux, both processes are induced via VGCC activation. Ca²⁺ efflux has been studied via the loading of cells with radioactively labeled 45Ca²⁺. When VGCCs are activated raising intracellular Ca²⁺ levels via non-radioactive Ca²⁺ influx, 45Ca²⁺ efflux ensues.)

In summary, ELF EMFs can induce calcium influx via the opening of VGCCs at specific frequencies coupled with specific field strengths and not at others. A change in frequency can stimulate VGCC openings at different field strengths and vice versa: i.e.,

specific frequencies can be made ineffective with a change in field strength, while, conversely, also rendering previously ineffective signals effective with, for example, the same change in the field strength. Radiofrequency (RF) EMFs at specific frequencies can also cause Ca²⁺ influx via the opening of VGCCs, but at only a specific range of intensities and only when they are amplitude-modulated with low frequencies. While continuous wave ELFs have been shown to induce Ca²⁺ influx, unmodulated RF EMFs have so far shown no effect on Ca²⁺ influx. Furthermore, biological effects induced by Ca²⁺ influx are also dependent on the qualitative state of the cell (e.g., whether or not blastogenesis is taking place).

EMF effect on immune system cells

T-lymphocytes and VGCCs

While by 1985, calcium channels had yet to be uncovered in T-lymphocytes [58], it is now well established that T-lymphocyte activation is associated with both antigen receptor – or mitogen – stimulation and a continuous increase in free [Ca²⁺]_i levels via heightened transmembrane Ca²⁺ influx via both VGCCs [59] and

also a non-voltage-gated calcium channel (nVGCC) influx [60,61], the latter of which is most likely opening in response to T-cell activating mitogens, and facilitated by inositol trisphosphate (InsP3) – a secondary messenger molecule used in signal transduction and lipid signaling.

Qualitatively different field responses: inhibition, stimulation or no field effect

Walleczek and Budinger [62], in investigating the effects of pulsed magnetic fields on Ca²⁺ signaling in T-lymphocytes, found that magnetic fields at 3 Hz inhibited Ca²⁺ uptake (i.e., influx) in mitogen-stimulated thymocytes (immature T-lymphocytes) and that this inhibition increased with increasing magnetic flux densities, noting that variations in both physical field exposure characteristics as well as biological parameters (e.g., the state of the cell) can determine the outcome of cellular EMF exposure experiments. Inhibition, stimulation, or no field effect can be observed in direct dependence on physical and biological boundary conditions [62].

This is in line with the Conti et al. [28] experiment also applying a 3-Hz (6-mT) pulsed magnetic field on mitogen-dependent human lymphocytes and finding a reduction in uptake of Ca²⁺.

In an earlier study, however, Walleczek and Liburdy [63], this time looking at 60-Hz sinusoidal magnetic field (22-mT) effect on thymocytes, found that Ca²⁺ uptake (i.e., influx) under the same experimental conditions was enhanced, and not reduced as with the case of the 3-Hz model, further highlighting the fact that varying EMF frequency differentials can induce field responses that are qualitatively different. This is in line with the conclusion of Blackman et al. [41] that there are specific frequency windows that can change in accordance with changes in power density.

Over the past 35 years, a large number of papers [64–108] have addressed effects – often contradictory – on immune system function with exposures to EMF of both extremely low frequency (ELF) and modulated radiofrequency (RF). Outcomes have been both stimulatory and inhibitory, with both pathological and – some – potentially therapeutic effects. Contradictory EMF effect can be attributed to the fact that the immune system will show varied responses based on the interactions of a number of parameters: (1) EMF exposure quality, (2) EMF exposure duration, (3) EMF exposure frequency, (4) EMF exposure power density, and (5) the specific state of the cell. And this is seemingly closely related to changes in Ca²⁺ ion flux.

Based on accumulated evidence showing that nonthermal exposure of ELF-EMF can elicit changes in immune cells, in 1992, Walleczek [64] had hypothesized that EMFs indirectly affect the immune system via cell membrane-mediated Ca²⁺ signaling processes. Eichwald and Walleczek [65], in 1996, further noting that in studies of immune system cellular Ca²⁺ uptake regulation, depending on the degree of cellular activation, various field effects – stimulatory, inhibitory, or no field effect – have been observed under identical field parameters. They hypothesized that cellular biochemical stimulation results in specific signaling pathway activation, which regulates cellular Ca²⁺ dynamics (the release of Ca²⁺ from [Ca²⁺]_i stores and capacitative Ca²⁺ entry), hypothesizing that a specific EMF-sensitive enzyme may be activating a feedback control loop on signaling processes, which in turn would modulate entry of Ca²⁺ into the cell, and affect other Ca²⁺-dependent cellular processes (e.g., DNA synthesis). More recent studies, detailed in a review by Nejabakhsh and Feng [14], have established that this is indeed the case. Nejabakhsh and Feng state that calcium ion entry through voltage-gated calcium channels is essential for cellular signaling in a wide variety of cells and multiple physiological processes. Perturbations of voltage-gated calcium channel function can lead to pathophysiological consequences. Calcium binding pro-

teins serve as calcium sensors and regulate the calcium channel properties via feedback mechanisms [14].

Pall [13], in a review of the literature, has described how EMFs may produce – what is usually – a pathological increase in [Ca²⁺]_i via the opening of VGCCs that trigger an influx of Ca²⁺ from extracellular medium, leading downstream to the production of nitric oxide and peroxynitrite and consequent oxidative stress, and further that a wide range of these EMF effects have been shown to be blocked by calcium channel blockers, concluding that “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 [13].”

EMFs and ROS

Over the past 10 years there has been an exponential increase in studies [109–211] showing increased ROS activity with EMF exposure at power density levels more in line with what people are now receiving in their daily lives. Increased intracellular ROS activity has been found to increase lipid peroxidation and protein oxidation, impair antioxidant enzyme function, and is correlated with DNA damage, reduced cell membrane integrity, and reduced mitochondrial function. The majority of these studies show increased levels in markers for oxidative stress, e.g., malondialdehyde (MDA) and nitric oxide (NO), and decreases in levels of the antioxidant enzymes, e.g., superoxide dismutase (SOD), glutathione peroxidase (GSH-px), and catalase (CAT) – with a number of studies showing a protective and ameliorative effect of these induced by certain antioxidant nutritional substances like *Ginkgo biloba*, caffeic acid phenethyl ester (CAPE), garlic, ginseng, lotus seedpod procyanidins (LSPCs), β-glucan, L-carnitine, melatonin, vitamin E, C, zinc, and selenium. In a recent review by Yakymenko et al. [211] (and the only one of its kind at present), 100 peer-reviewed studies were surveyed examining the oxidative effects of low-intensity RF EMF with 93 confirming RF EMF-induced oxidative stress in biological systems.

ROS and calcineurin inhibition

Sommer et al. [24] found that the ROS – superoxide (O₂⁻), nitric oxide (NO), and hydrogen peroxide (H₂O₂) – all had a potent inhibitory effect on calcineurin, concluding that ROS and reactive nitrogen species (RNS) have an inhibitory effect on calcineurin via the oxidation of both catalytic metals and critical thiols.

Lee et al. [25], in noting a correlation in increased ROS with calcineurin inactivity, describe the inactivation of calcineurin by hydrogen peroxide triggering the proteolytic cleavage and decreased enzymatic activity of calcineurin, with the cleaved form of calcineurin having no enzymatic ability to dephosphorylate NFATc.

Smit et al. [212] found – in noting similarities in the immunosuppressive effect of UV radiation with calcineurin inhibitors, when they investigated the UV effect on calcineurin in skin – a significant reduction in calcineurin activity in skin with exposure to UV radiation, along with a reduction in production of cytokines IL-2, gamma-interferon, IL-4, and IL-10, all controlled by the Ca²⁺-calcineurin pathway – indicating that UV radiation can result in calcineurin inactivation in skin, suppressing skin immunity in a manner similar to calcineurin inhibitors. Musson et al. [26], in noting that calcineurin is a target of modulation by ROS, were able to show, both in vivo and in vitro, that UVA1 radiation suppresses calcineurin activity via the production of singlet oxygen and superoxide. Musson et al. [27], also further emphasizing calcineurin's documented sensitivity to oxidative stress, assessed and contrasted the influences of UVA1 and arsenite on calcineurin, showing that these two agents had a strong inhibitory effect on calcineurin activity in Jurkat and skin cells with a reduction in

NFAT nuclear translocation in Jurkat cells, and that these effects could be partially ameliorated with an increase in the dismutation of superoxide in Jurkat and skin cells.

EMFs and immune system dysfunction/suppression

While a diverse number of studies [66–108] show nonthermal EMF effect on the immune system function, many of these studies find effect with short-term exposure to EMFs at power densities many times more powerful than we would at present expect to encounter in our everyday lives. Notwithstanding, it has been proposed that long-term low-level non-ionizing radiation exposures may be equivalent to short-term high-intensity ionizing radiation exposures [101], and similarly that long-term low-level non-ionizing radiation effects to what are considered “low” power densities can also be equivalent to effects produced by short-term high-intensity non-ionizing radiation exposures at what are considered “high” power densities [102]. In other words, many of the biological effects produced in many of these short-term exposure conditions using power densities at levels higher than we would normally experience in everyday life may very well be mimicked by present-day long-term exposures to lower power densities many of us are currently encountering.

Experimental immunological research studies have demonstrated that nonthermal EMF exposures can affect immune-specific organs [66–70], innate and adaptive immune cell activity [30,31,68,69,71–73,77–79], antibodies [69,82,83], cytokines [87–89,95], and enzymes [65,131], with other research studies showing effects on the autoimmune system [86,91], cellular Ca²⁺ uptake [30,31], augmentation of chemical toxicity [84], food sensitivities [92], and increased free-radical production [109–211].

The same opportunistic infections induced as side effects in transplant recipients taking immunosuppressant calcineurin inhibitors to prevent organ rejection – reactivated viral (EBV, CMV, Coxsackie, etc.), candida, mold, bacterial (mycoplasma), and parasitic (toxoplasmosis) infections – have also been uncovered in a number of what have been described as neuro-immune dysfunction syndromes (NIDS)[213]: e.g., CFS, ASD, ADHD, and Alzheimer’s disease [AD], [214–264] etc.

For example, Nicholson and Haier [214,215] have uncovered various systemic and central nervous system bacterial and viral infections (e.g., Mycoplasma species, Chlamydia pneumonia, Borrelia burgdorferi, human herpes virus-1, -6, and -7, and other bacterial and viral infections) in patients with amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Alzheimer’s disease (AD), Parkinson’s disease (PD), autism spectrum disorders (ASD), a number of psychiatric disorders (paranoia, dementia, schizophrenia, bipolar disorder, panic attacks, major depression, anorexia nervosa, and obsessive-compulsive disorder), neuropsychiatric movement disorders (e.g., Gilles de la Tourette’s syndrome), autoimmune diseases (Guillain-Barré syndrome, paediatric autoimmune neuropsychiatric disorders associated with Streptococci [“PANDAS”]), fatiguing illnesses (CFS/myalgic encephalomyelitis [ME]), Gulf War Syndrome, and Lyme disease – with many of these showing cytokine changes, increases in ROS with its resulting oxidative stress, changes in neurotransmitter levels, and decreased NK cell activity.

Many of these mysterious disease states of unknown etiology have increased exponentially in the last thirty years in proportion with increases in ambient man-made electromagnetic fields. And with this correlation, the question “Is there causation?” begs to be asked. There is more research that suggests there is. For example, Grimaldi et al. [104] found that a 50-Hz EMF exposure could activate the Epstein-Barr virus genome in latently infected human lymphoid cells, and Canseven et al. [105] further found that a 50-Hz magnetic field could suppress NK cell activity on candida stel-

latoidea – and as noted earlier, NK activation is dependent on IL-2 production by T-cells.

Nageswari [106–108], for example, in several experiments, found that chronic low-power microwave radiation exposure (2.1 GHz @ 5 mW/cm² 3 h daily, 6 days a week for 3 months) on the immunological systems of rabbits produced significant suppression of T-lymphocyte numbers; lymphoid cell depletion in lymph node, spleen, and appendix; recurrent infections; an increased susceptibility to bacterial infection; an increase in the number of large leukocytes; a decrease in the number of small leukocytes, neutrophils, and erythrocytes; leukocytosis; cataracts; and weight loss, etc.

In addition to the number of experimental studies showing immunological effects, long-term epidemiological – especially residential and occupational – studies have indicated a host of symptoms and biological markers associated with long-term EMF exposures. For example, residential studies on people living in the vicinity of cellular base stations report the following symptoms: fatigue; headache; sleep disturbances; discomfort; irritability; anxiety; depression; memory loss; concentration difficulties, dizziness; vertigo; nausea; loss of appetite; decreased libido; visual perturbations; blurred vision; tremors; skin rashes; elevated blood pressure; motor, memory, and learning impairment in children; cold hands and feet; and cardiovascular symptoms [102,265–275].

Interesting to note here is that many of these symptoms are also found in the above-mentioned neuro-immune dysfunction syndromes, especially CFS. For example, even the CDC lists on its CFS website the following (strikingly similar to the above) symptoms: increased malaise, headache, problems with sleep, depression or mood problems (irritability, mood swings, anxiety, panic attacks), difficulties with memory and concentration, brain fog, dizziness, and visual disturbances (sensitivity to light, blurring, eye pain) [276].

Also found in the vicinity of base stations were increased rates of suicide, increased risk of cancer, elevated brain tumor incidence, and decreased lung function in children [102]. With regard to biological markers associated with occupational exposures, there have been reductions in total lymphocytes [277,279]; in T-lymphocyte subsets, T8 [79], CD4 and CD3 [277,279] counts; NK cell [277,278,280,281] counts; interferon gamma (IFN γ) [277]; ornithine decarboxylase (ODC) activity [278]; PHA-stimulated IFN γ release from PBMC [280]; and blood cytotoxic activity of NK lymphocytes [280] found in workers occupationally exposed to a variety of EMFs.

Summary and discussion

Planetary life is incessantly exposed on a daily basis to an increasingly thickening soup of invisible EMF frequencies at a variety of power densities, pulse modulations, and durations. It has been estimated that we are now being exposed to between one quadrillion (10¹⁵) to one quintillion (10¹⁸) times the amount of EMR we would normally receive from natural background sources. Health effects reported in the literature include opening of the blood-brain barrier, genotoxicity, cancer, and infertility, and involve neurological, neurodegenerative, immune system, allergic, inflammatory, and cardiovascular effects [152].

Calcineurin inhibitors act by preventing calcineurin from activating the transcription factor NFAT to move into the T-cell nuclear DNA and to stimulate production of IL-2, in order to enable the activation, proliferation, and differentiation of inactive T lymphocytes. There is evidence to suggest that some calcineurin inhibitors themselves produce this inhibition via the actuation of ROS – as do EMFs via Ca²⁺ influx, leading to pathological levels of [Ca²⁺]_i. A number of studies [141,173,174] further indicate that Ca²⁺ influx

can occur with everyday wireless (e.g., cell phone and WiFi) radiation exposures.

The ROS nitric oxide, superoxide, hydrogen peroxide, and singlet oxygen have been shown in a number of studies to inhibit calcineurin. EMFs have been shown to induce an intracellular increase in nitric oxide [112,118,121,132,144,181] and changes in superoxide dismutase [109,121,126,132,133,144,158,163,194,198,208], the latter strongly suggesting an increase in superoxide. Both nitric oxide and superoxide are known calcineurin inhibitors. Furthermore, superoxide can dismutate into hydrogen peroxide, another known calcineurin inhibitor. Finally, there is evidence to suggest that nitric oxide and hydrogen peroxide react to produce singlet oxygen [29]. Hence, it is hypothesized that EMFs have the potential to indirectly inhibit calcineurin via the downstream production of any one or more of the following ROS or ROS-like molecules – nitric oxide, superoxide, hydrogen peroxide, and singlet oxygen – as a result of a pathological influx of Ca²⁺ into the cell.

Electromagnetic fields have been shown to induce either stimulatory, inhibitory, or no effect on the immune system in relationship to how specific EMF frequencies, specific EMF power densities, and specific EMF durations interact with specific field parameters of the cell – especially with regard to either Ca²⁺ flux into or blockage of Ca²⁺ uptake by the cell. While the research seems to suggest that at specific frequencies and certain power densities, nonthermal EMF exposures can have an initially stimulating effect on the immune system, at higher power densities and/or with longer durations, this effect can be or become inhibitory – most likely due to increases in intracellular ROS and singlet oxygen, with the research also suggesting certain antioxidant substances ameliorating these effects.

Johansson [282], in a recent review of the literature, concluded that EMFs disturb immune function through stimulation of various allergic and inflammatory responses, as well as having effects on tissue repair processes, which may potentially lead to an underlying cause for cellular damage and tissue repair reduction. Such disturbances increase the risks for various diseases and functional impairments, including cancer and electrohypersensitivity (EHS).

Besides leaving the organism open to opportunistic infection, calcineurin inhibition has been correlated with an increase in neoplasms and skin cancer – and it has also been shown that UV radiation can inhibit calcineurin via the production of singlet oxygen and superoxide [26]. The fact that a number of ROS and singlet oxygen can be produced via means other than UV radiation – i.e., downstream effects of pathological increases in intracellular Ca²⁺ levels [e.g. 29] – supports the hypothesis that these can also inhibit calcineurin. The hypothesis that EMFs also inhibit calcineurin via the production of ROS furthermore adds support to research by Hallberg and Johansson [283–286], finding increases in skin cancers in correlation with increasing exposures to ambient man-made EMFs.

In summary, there has been a significant rise in a number of disease states (autism spectrum disorder, chronic fatigue syndrome, etc.) over the last thirty years, and these have coupled increases in levels of artificial electromagnetic pollution. Many of these disease states are paired with a weakened immune system, not to mention immune system disorders. Moreover, an increasing number of experimental and epidemiological studies are connecting many of these disease states, and their symptomologies, with electromagnetic radiation exposures. Calcium (Ca²⁺) is necessary for a number of enzymatic functions, and numerous researchers have proposed an EMF effect due to Ca²⁺ influx and Ca²⁺ signaling transcription. Two studies to date have found an EMF effect on calcineurin: one finding ELF to have a stimulatory effect and the other finding RF to have an inhibitory effect. While this paper proposes that depending on the complexity of parameters, EMF exposures can have stimulatory, inhibitory, or no effect on calcineurin

activity, it also proposes that a pathophysiological increase in intracellular Ca²⁺ levels due to EMF activation of VGCCs can stimulate the production of ROS, which may lead downstream to calcineurin inhibition and a weakened immunity – as ROS have been shown in a number of studies to inhibit calcineurin. The infections induced by patients taking calcineurin inhibitors have interestingly also been found in a number of disease states termed neuro-immune system disorders (NIDS), (e.g., CFS, ASD, ADHD, and AD).

In conclusion, this hypothesis proposes that one means by which man-made electromagnetic fields have the potential to disturb immune system homeostasis is by opening VGCCs (Fig. 1a) and pathologically increasing intracellular Ca²⁺ levels (Fig. 1d), leading to pathological intracellular levels of ROS (Figs. 1e and 1f), which in turn have the potential to inhibit calcineurin (Fig. 1g), leaving the body increasingly susceptible to opportunistic infection. Given this possibility, while it can be said that candida, mold, mycoplasma, EBV, CMV, and other opportunistic pathogens are certainly part of the etiological conundrum of many unexplained disease states, perhaps the root of the problem may have more to do with an overlooked invisible environmental factor potentially weakening immune systems and making many more susceptible to these pathogens. While there is much research showing that EMFs alter immune system function, original experimental research demonstrating whether or not long-term low-level EMF exposure may indeed lead to immunosuppression and increase in opportunistic infection is required. Furthermore, original experimental research needs to be undertaken to determine for certain whether or not long-term exposure to EMFs (especially RF) can effect a decrease in calcineurin levels within immune cells, as was found with calcineurin in muscle and bone cells exposed to RF EMFs. This would determine a clear mechanism by which EMF exposure can in fact lead to immunosuppression.

Conflict of interest statement

The authors confirm that there are no conflicts of interest.

Acknowledgments

The Karolinska Institute, Stockholm, Sweden, supported this study. We would also like to thank Laurie Masters for proofreading the document.

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