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

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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.

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 Ca2+ signaling transcription due to the influence of EMFs on Ca2+ 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 Ca2+ ([Ca2+]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 Ca2+ into the cell can initially have a stimulatory effect on the enzyme calcineurin, a pathological increase in Ca2+ 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 [Ca2+]i via Ca2+ 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 Ca2+ stimulation of enzyme nitric oxide synthase (Figs. 1c–1f). Under normal circumstances, in a physiological context, one of the feedback-control mechanisms mediating Ca2+ entry into the cell through VGCCs is via Ca2+ binding proteins (one of which is the protein phosphatase enzyme, calcineurin), which help to control homeostasis of Ca2+ 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 Ca2+ 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 Ca2+ 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 [O2−], nitric oxide [NO], hydrogen peroxide [H2O2], 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 Ca2+

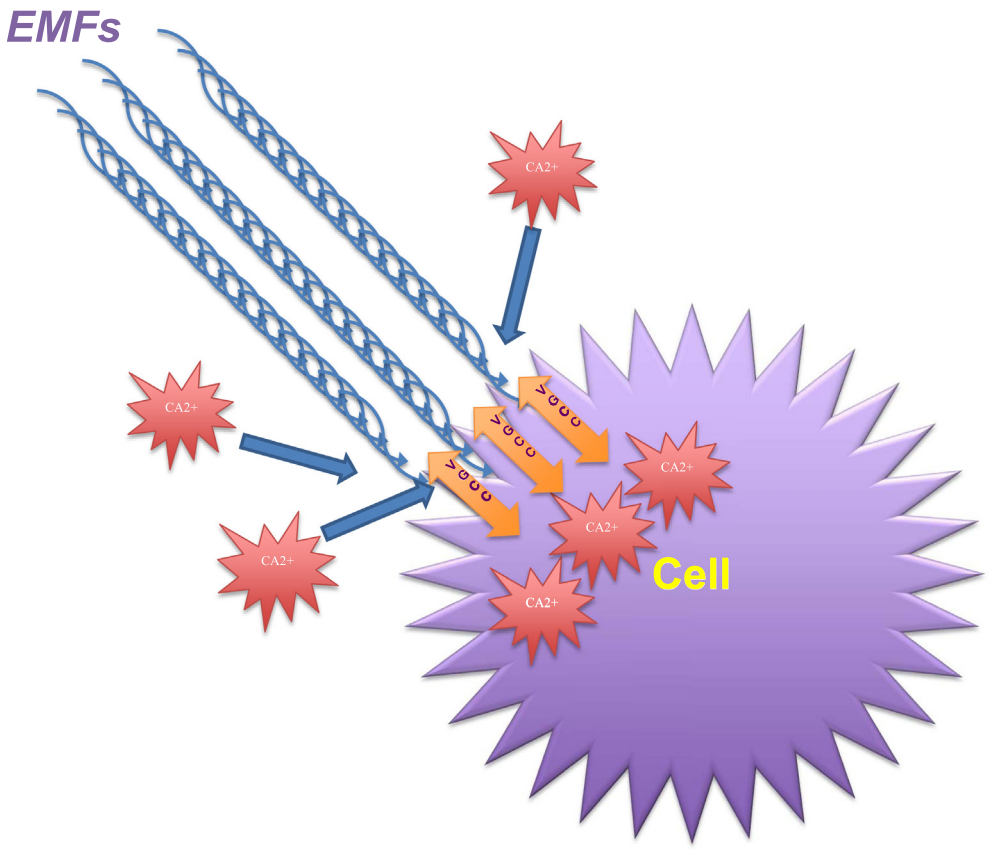

Fig. 1a. Electromagnetic fields (EMFs) open voltage-gated calcium channels (VGCCs) allowing an influx of extracellular calcium ions (Ca2+) into the cell.