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Cellular and molecular effects of non-ionizing electromagnetic fields

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Abstract

The way that living cells respond to non-ionizing electromagnetic fields (EMF), including static/extremely-low frequency and radiofrequency electromagnetic fields, fits the pattern of 'cellular stress response' – a mechanism manifest at the cellular level intended to preserve the entire organism. It is a set pattern of cellular and molecular responses to environmental stressors, such as heat, ionizing radiation, oxidation, etc. It is triggered by cellular macromolecular damage (in proteins, lipids, and DNA) with the goal of repairing and returning cell functions to homeostasis. The pattern is independent of the type of stressor encountered. It involves cell cycle arrest, induction of specific molecular mechanisms for repair, damage removal, cell proliferation, and cell death if damage is too great. This response could be triggered by EMF-induced alternation in oxidative processes in cells. The concept that biological response to EMF is a 'cellular stress response' explains many observed effects of EMF, such as nonlinear dose- and time-dependency, increased and decreased risks of cancer and neurodegenerative diseases, enhanced nerve regeneration, and bone healing. These responses could be either detrimental or beneficial to health, depending on the duration and intensity of the exposure, as well as specific aspects of the living organism being exposed. A corollary to electromagnetic hypersensitivity syndrome (EHS) could be an

Introduction

There has been a steady increase in intensity of non-ionizing electromagnetic fields (EMF) in the ambient environment due to use of wireless communication devices and electric power. The two main frequency ranges of concern in this paper are the static/extremely low frequency electromagnetic fields (ELF-EMF) (0–300 Hz) and radiofrequency radiation (RFR) (3 kHz–300 GHz) as they are the main frequency ranges of the electromagnetic spectrum in the human environment today.

The question of whether EMF can cause biological effects has been debated for at least six decades. The often-promulgated argument that there are "no known underlying mechanisms" has historically been used to deny the existence of any biological effects (other than electric shock in the ELF range and tissue heating by RFR) and thus hinder change to the status quo regarding allowable exposures.

But hundreds of studies now refute that premise and increasing evidence – especially regarding the more particularized knowledge of the electromagnetic physics nature between inter- and intracellular realms – demonstrates the effects of electromagnetic fields in almost all biological processes [1], such as novel anthropogenic exposure abilities to upset natural genomic functions.

In this paper, research data are summarized to indicate that biological effects of EMF are simply 'cellular stress responses' – a well-investigated cellular/molecular concept [2]. Particularly, EMF-induced 'cellular stress responses' are proposed to be induced by changes in cellular oxidative processes. 'Cellular stress response' induced by oxidative stress is also well established [3].

The amazing electrochemistry of living cells

As the primary building blocks of life, living cells are a true wonder of chemical and electrical activities that in many ways still defy our understanding. All living beings are a complex cacophony of chemical and electrical activities with individual cells acting in stable interdependent homeostasis at the genesis, continuation, and end of life. The higher up the evolutionary ladder, the more developed is the nervous system and the more complex are interactions at the cellular, genomic, and biomic levels. Detailed cell phenotyping and physiology, however, are blindingly complex and therefore beyond the scope of this paper but the brief discussion below is pertinent to this paper's micro-to-macro mechanistic focus.

Depending on function, cells come in different structures, shapes, and sizes, e.g., neurons can be long to facilitate more efficient signal transmission throughout the body while heart cells have more mitochondria due to increased energy needs in blood pumping. Most of this is orchestrated by membrane microcurrent that is inherent to life and which can be affected in various ways by anthropogenic EMFs – speaking the same fundamental electromagnetic "language" in distorted fashion – beginning at the cellular level and affecting the entire

organism [4].

While most exogenous ELF EMF and RFR exposures are below the levels of electrical shock and tissue heating, that does not mean they are without biological/clinical implications, even at low intensities and especially over extended time periods as is common with today's ubiquitous chronic exposures. In fact, much of the potential damage from EMF exposure is hidden in imperceptible sub-clinical activities that may later manifest in chronic clinical disorders. The primary mechanism for such universal response throughout the body and different cell types is likely via cellular oxidative processes and an innate cellular stress response that attempts to offset damage and return the body to stability and equilibrium. As such, the 'cellular stress response' is widely understood as a necessary and beneficial reaction to any number of factors capable of threatening the overall health of living systems. It is also a bellwether marker for the fact that cells are under stress to begin with.

All cells, though independent, act with interdependent functions in relation to the whole functioning organism. Although cellular stress responses are a brilliant evolutionary process through which living systems repair damage for the corrective benefit of an organism, there is a cumulative point where damage is too great and cellular repair impossible, thereby leading to cell death (e.g., apoptosis). However, EMF exposures may be more detrimental when they do not fully initiate cellular damage repair and/or trigger apoptosis, thereby allowing cells to replicate in a damaged/mutated state as seen in cancers. This paper is a roadmap for what happens at the cellular level.

EMF cellular/molecular effects

The concept of EMF and 'cellular stress response' was first mentioned by Martin Blank over a decade ago [5] on the effects of EMF on cell functions. Many papers have been written since on this subject. Including the recent paper by Barati et al. [6] to explain the effects of EMF on apoptosis. 'Cellular stress response' follows a pattern of cellular biochemical changes. It could be the cellular component of the generalized response of all organisms to stressors.

The stress effect from EMF is most likely initiated by changes in oxidative status in cells after exposure. Oxidative changes are the most well-established effect of EMF (see the 'research summary' section of the 2022 update of the BioInitiative Report [5]). There are various speculations on how EMF affects cellular oxidative processes. Electromagnetic field-induced formation of radical pairs in susceptible cellular molecules, e.g., cryptochromes, is a likely mechanism. The processes are important in the survival of many species as well and highly conserved, but discussion of them is beyond the scope of this paper. Readers can easily find publications on the processes (e.g. [7]).

How 'cellular stress response' unfolds

'Cellular stress response' involves: (1) Cell cycle arrest – usually at the G1/S and G2/M check

points – allows time for cells to conserve energy for repair to occur. (2) Initiation of repair processes: induction of molecular chaperones such as heat shock proteins (HSP) for protein damage repair; repair of nucleic acid and chromatin involving the p53 and NF-kappaβ pathways, among others. (3) Removal of damaged molecular debris using mechanisms such as the ubiquitin/proteasome pathway. (4) In case of severe stress when damage is beyond repair, apoptosis occurs.

These processes can decrease genetic instability and possibly reduce risks of mutation and tumor formation. But artificially caused premature cell death can also lead to degenerative diseases. Thus, avoiding environmental stressors is more beneficial than relying on repair mechanisms after the fact. Exposure to multiple stressors can – and do – act synergistically and pre-exposure to one stressor can lead to cross tolerance to another stressor (see "Interaction with other stressors" below). The following sections describe the different stages of 'cellular stress response' relating to EMF exposure.

Oxidative molecular damage

Changes in oxidative processes can cause molecular damage, which is the initial step of the 'cellular stress response'. Such damage after EMF exposure has been extensively reported. Supplementary 1 contains some examples.

Cell cycle arrest

Cell cycle arrest is an immediate response to cellular molecular damage. Some studies on EMF-induced cell cycle arrest are listed in Supplementary 2. In addition, any alterations in cell cycles are supported by expression of gene/factors involved in cell cycle regulation that include cyclin, p53, p21, GADD45 (e.g. [8], [9]).

Supporting evidence that effects are initiated by oxidative stress is that the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) has been shown to be activated by EMF exposure [10]. NRF2 regulates cellular defense against cellular oxidative damage by bonding to nucleus DNA at the location of the Antioxidant Response Element (ARE) leading to expression of genes involved in oxidative stress response [11].

Molecular damage repair

The next step in the 'cellular stress response' is initiation of molecular repair mechanisms, the triggering of which have been reported after EMF exposure. These are highly complicated processes and involve many different molecular pathways and factors. There are three main types of molecular damage repair for protein, DNA, and lipid.