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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 inappropriate response of the hippocampus/limbic system to EMF, involving glucocorticoids on the hypothalamic-pituitary-adrenal axis.

Keywords: cellular stress response; free radicals; hypothalamic-pituitary-adrenal axis; macromolecule damage and repair; non-ionizing electromagnetic fields (EMF)

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.

Protein damage repair

Induction of heat shock proteins is the major process in repair of damaged proteins, particularly HSP-60 and HSP-70 which refold proteins that were damaged by environmental stressors (Supplementary 3). However, other different forms of HSP are also involved. There are also several papers reporting EMF-induced ubiquitin-related proteosome activity that breaks down damaged proteins for removal [12].

DNA damage repair

Changes in DNA repair after exposure to EMF have been reported in RFR ranges (e.g. [13]), as well as static/ELF EMF (e.g. [14]). Since stress response processes are under feedback control, it should not be surprising that oscillation of the response system occurs, i.e., a response shows a time-dependent increase and decrease in magnitude. Interactions with other chemicals are also possible.

There are reports of changes (increase and decrease) in p53, NFκB, and MAPK after EMF exposure (Supplementary 4). These proteins are related to DNA repair and chromatin stability [15]. Particularly, p53 has major roles also in cell cycle arrest, apoptosis, and tumor suppression [16]. Another cellular response is the mitogen-activated protein kinase (MAPK). It is involved in cellular responses to various stimuli such as mitogens, osmotic stress, heat shock, and oxidative stress and regulates cell functions such as proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis. NFκB production is stimulated by stressors and free radicals. It is involved in the immune responses to infection and affects synapses in the nervous system and memory. Disturbance in NKκB could lead to cancer and auto-immune diseases. These factors are components of the 'cellular stress response'.

The upregulation of DNA repair mechanisms also explains the observations that while most studies reported an increase in DNA damage [17], there are also studies that indicate a decrease after exposure to RFR and ELF-EMF (RFR [18]; ELF-EMF [19]).

Lipid damage repair

The predominant lipid damage after EMF exposure is lipid peroxidation in cellular membranes that could adversely change membrane selective permeability and functions. Lipid peroxidation products can produce DNA adducts that can cause mutation and gene expression changes. Repair can be carried out by certain forms of phospholipase and glutathione peroxidase (phospholipid hydroperoxide glutathione peroxidase). Up-regulation of cellular glutathione peroxidase by EMF has been widely reported (e.g., see supplementary material in [20]). However, the processes of EMF-induced lipid damage repair are not well investigated.

Apoptosis

Apoptosis is the last resort when molecular damage becomes too extensive and is beyond repair. There are many reports on apoptosis induced by exposure to EMF (e.g. [21]). Apoptosis can be induced by activation of caspase. Effects of EMF-exposure on caspase induction are summarized in Supplementary 5.

ELF and RF-EMF can initiate and influence these processes at every step of the way, both detrimentally and beneficially for the entire system.

Some manifestations of 'cellular stress response'

Below are some disease categories that could result from various aspects of 'cellular stress response' – both adverse and beneficial.

EMF and cancer risk

With the repairing processes involved in 'cellular stress response', it is reasonable to posit that EMF exposure should primarily decrease cancer risk. But the reports are quite mixed on end-progressions regarding neoplasia. There are reports of decreased incidence (e.g. [22]); no significant effects (e.g. [23]); and increased incidence (e.g. [24, 25]) in cancer risk in animals chronically exposed to EMF. This also appears to happen with glioma occurrence in humans using cellular and cordless phones [26].

In the case of increased risk, it is also reasonable to think that the cellular stress-induced repair processes may be incomplete, e.g., DNA mis-repair occurs, leading to cancer development from proliferation of damaged cells. Such incomplete repair would decrease the chance of apoptosis and favor cancer development. On the other hand, through other molecular/cellular processes, free radicals can also cause cell transformation (from normal to malignant without triggering the apoptotic process); enhance tumor survival; increase cancer cell proliferation and invasion, angiogenesis, and metastasis (e.g. [27]). Furthermore, anti-apoptotic effects via calcium-dependent processes have also been reported after EMF exposure [28]. All of the above point to EMF acting as both an 'initiator' and 'promotor' in cancer development as observed in brain cancer risk related to cell phone and wireless phone radiation exposure.

From the tables in the Supplements one can see that many experiments were carried out on cancer cell lines. This is because EMF has also been widely considered as a potential therapeutic tool and/or treatment-adjuvant for cancer. This is supported by the data that most cancer cells were found to become apoptotic after EMF exposure (see Supplementary 5). Static and ELF EMF would be the preferred fields for cancer treatment, since they are easy to generate, and penetrate uniformly into the body for treatments of both solid tumors and

circulating/metastatic malignancies.

Under EMF exposure, some cancer cells within a tumor probably go into apoptosis. Thus, there can be an initial decreased risk of cancer incidence. With continued exposure, however, surviving cancer cells can transform into a more resistant and aggressive state, likely leading to increased cancer risk. The actual response would depend on factors such as cell type, duration of exposure, and the characteristics of the EMF. The exact contributions of these factors are basically unknown. But to reveal whether EMF exposure affects cancer risk, it is imperative that the duration of exposure be included as an independent variable in data analysis [1].

The therapeutic use of EMF for cancer treatment has advantages that include: (1) It is economical and easily applied; (2) Effective; (3) Can be designed to be highly selective in killing cancer cells while sparing normal cells with few side effects; and (4) EMF – particularly static/ELF EMF – can be generated easily at low cost. The efficacy of EMF appears to be high. EMF-induced cell death also appears to be more selectively effective on cancerous than normal cells (e.g. [29]). However, the mechanism of this selectivity is unknown.

Cancer cells may have different cell cycle- and- molecular repair characteristics with alternative gene functions that favor the transition into apoptosis after EMF exposure. A possible reason for why cancer cells are more vulnerable to EMF than normal cells has been discussed elsewhere [30], a mechanism via the Fenton reaction.

Neurodegenerative diseases

Over the years, there has been a significant increase in studies linking EMF to neurodegenerative diseases. These include increased risks of:

- Amyotropic lateral sclerosis: (e.g. [31]).
- Alzheimer's disease: (e.g. [32]).
- Parkinson's disease has been reported mostly in occupational exposure to ELF EMF (e.g. [33]).

Conversely, studies have also reported that EMF exposure improved cognitive disorder and positive chemical changes in various animal models and human patients with:

- Alzheimer's disease: [34].
- Parkinson's disease: [35].
- Huntington's disease: [36].

Cellular stress, and particularly oxidative stress, can lead to protein misfolding [37]. Aggregation of protease-resistant misfolded proteins can cause cell death and development of neurodegenerative diseases [38]. Apparently, long-term high-intensity EMF exposure is

needed to lead to these detrimental effects. On the other hand, as described below, EMF can initiate cellular processes to repair or eliminate misfolded proteins and possibly retard the progress of some of these diseases. It should be mentioned that mitochondria play an important role in some of these processes and that calcium and ion-channels are obligatorily involved. Effects of EMF on mitochondrial functions and intracellular calcium are well known [39]. Even though most studies are on high-level exposures (i.e., higher than environmental levels), effects have been observed at low levels of EMF too [1].

Interaction with other stressors

Another support for EMF-induced elicitation of 'cellular stress response' is EMF interacts with other stressors. Concomitant exposure of EMF with various stressors can have synergistic and/or adaptive effects in which pre-exposure to one stressor lessens the response to a subsequent stressor. These have been shown with ionizing radiation [40], and heat [41]. An interesting finding is that EMF can also interact with psychological stressors used in animal experiments, such as 'immobilization' [42] and 'exposure in open field' [43] experiment designs.

Additional considerations related to 'cellular stress response'

1. Cell proliferation: Another observed stress response is that EMF can trigger apoptosis-induced cell proliferation in other cells, i.e., a process by which apoptosis stimulates neighboring cell division. This can lead to tissue regeneration on the beneficial side but also uncontrolled growth – such as cancer – on the downside. This may partially explain the effectiveness of EMF exposure on bone healing [44], wound repair [45], and in facilitating recovery of spinal cord injury [46], as well as induced sciatic nerve injury [47], ischemia stroke [48], and traumatic brain injury [49].

2. Unfolded/misfolded protein response: An important cellular mechanism with potential adverse consequences throughout the body is the 'unfolded protein response' in the endoplasmic reticulum and mitochondria, which can be part of the 'cellular stress response' [50]. These are cellular processes to normalize stress-induced protein damage. One feature is that they can cause biphasic consequences, i.e., protecting the cells or cell death, depending on the duration and intensity of stress exposure. Misfolded proteins play important roles in neurodegenerative diseases, cancer development, inflammation, and aging. These processes can be triggered by changes in the redox state in the cell, such as by exposure to EMF. The question is how to tip the balance of the processes to favor one outcome over the other.

3. Gene expression: Data show that changes in gene expression and function are common after EMF exposure [17]. Changes in gene expression certainly would have more significant cellular effects (with possible health impacts) than genotoxicity alone (e.g., DNA strand breaks). Further investigation of genetic processes will provide better insight

into the mechanisms of biological effects of EMF exposure. For example, there are several studies on EMF and microRNA (e.g. [51]) with implications for cellular processes such as lipid metabolism, malignant transformation, and neuronal autophagy. MicroRNAs play important roles in RNA silencing and post-transcriptional regulation of gene expression and reprogramming gene expression patterns in cells under stress. The consequences of these changes on health are unknown.

4. Cellular calcium and ion channels: Cellular calcium is the fundamental "currency" of all biological processes. It surely plays an important role in the effects of EMF since it is known to be involved in most of the cellular processes mentioned throughout this paper, particularly regarding cell differentiation, repair, apoptosis, free radical processes, and cancer development. However, it is not known whether changes in cellular calcium are the direct effects of, or secondary responses to, cellular mechanisms triggered by EMF. Activation of voltage-gated calcium channels by EMF is a concept more recently championed by Martin Pall [39] and should not be overlooked. Most studies on EMF exposure are on the L-type calcium channels (long-lasting), whereas other types of calcium channels are sparsely studied. Particularly, the T-type calcium channels (transient) may deserve some attention, since they are sensitive to small changes in membrane potential [52] and could be more responsive to low-level EMF exposure [53].

EMF and the hypothalamic-pituitary-adrenal axis

From the above presented information, it is clear that a far more nuanced understanding of exposure levels at which effects occur is imperative in the setting of EMF exposure guidelines. The above descriptions are on data regarding the consequences of cellular/biochemical changes caused by EMF-induced 'cellular stress response'. This is probably a component of the traditional effects of EMF as a stressor via the hypothalamic-pituitary-adrenal axis. The concept that EMF is a 'stressor' was proposed many years ago [54] and has been revisited recently [55]. EMF affects the hormones and chemicals involved in the axis. i.e., corticotropin, adrenocorticotropic hormone, and glucocorticoids (e.g. [56, 57]). However, it is not known exactly how EMF affects the hypothalamic-pituitary-adrenal axis. Free radicals may play a role. This also suggests that direct exposure of a tissue is not a necessary prerequisite condition for effects to occur in that organ after EMF exposure. The following sections look at two effects – behavior and electromagnetic hypersensitivity – of EMF as a generalized stressor:

Behavioral effects

EMF as a stressor can lead to changes in arousal and anxiety behaviors (see Tables in [58, 59]). The relationship of behavioral performance (e.g., learning and memory) and arousal can be described by the Yerkes-Dodson Function, an old psychological concept [60]. It is basically an inverted-U function with enhanced performance as arousal increases, after which a peak would be reached, followed by a decline if further increases in arousal occur. This can explain

why both enhancement and retardation in behavioral performance have been reported after EMF exposure [58, 59].

It must be noted that the Yerkes-Dodson Function applies mainly to complex behavioral performance. A linear trend is generally observed with simple tasks. The Yerkes-Dodson Function could be related to circulating levels of glucocorticoids in the body. Cortisol also shows enhancement and retardation effects on memory functions in humans [61]. Many years ago, one of us published a paper [57] reporting that RFR exposure activated the hypothalamic hormone corticotropin-releasing factor that controls secretion of glucocorticoids from the adrenal cortex. More recent research data (see Table in [62]) also shows that RFR affects corticosterone and cortisol in rodents and humans, respectively. Increased glucocorticoid levels in the body have also been reported after static/ELF EMF exposure (e.g. [63]). However, the effects are more complicated.

The limbic system – the primordial brain in animal species evolution – contains the highest concentration of glucocorticoid receptors in the brain, particularly in the hippocampus [64]. This explains why there has been a large amount of data showing effects of EMF on the hippocampus [58, 59].

Electromagnetic hypersensitivity

Electromagnetic hypersensitivity syndrome (EHS) may be related to EMF-induced stress, i.e., with the response sequence consisting of effect, compensation/repair, and breakdown [65]. Since EHS can – though not always – involve a fast response to EMF, (i.e., within minutes of exposure), it is likely that it is related to the effect of EMF on radical pair mechanisms.

One can speculate that EHS in humans comes from a primordial characteristic of evolution, that is the ability to sense intensity, orientation, and direction of geomagnetic fields in the environment, which play important roles in the survival of all species [66]. Different neural mechanisms probably play analogous roles in different species. In vertebrates (especially mammals), the limbic system (particularly the hippocampus), is likely the main neural structure in the formation of spatial learning and memory. It is involved in magnetoreception [67] and is capable of responding to static magnetic fields at low intensities (~30 nT in mice) [68]. The limbic system also co-incidentally happens to be the same neural structure involved in anxiety and fear, notably in stress situations [69].

Another possible cause of EHS is an enhancement of nitric oxide (NO) activity, e.g., an increase in the level and/or a prolongation of the free radical half-life. An enhancement of NO activity in the brain, particularly in the limbic system, is known to cause fear/depression/anxiety-like behavior [70]. EMF can also cause fear/depression/anxiety-like responses [57]. Effects of EMF exposure on NO in the brain have been reported (see the ‘research summary’ section of the 2022 update of the BioInitiative Report [5]). The limbic system – and particularly the hippocampus – is probably involved in these behavioral effects.

Thus, it is possible that EHS occurs in people who – by perhaps being genetically pre-ordained – have a limbic system that is hypersensitive to NO and glucocorticoids (via activation of the hypothalamic-pituitary-adrenal axis as described above) and cannot readily adapt and/or compensate for the neurochemical changes. The first response is a fast elicitation of anxiety/fear emotions, with accompanying memory/learning deficits, leading to the possible development of detrimental health problems after continuous repeated exposure. Often this fast response is dismissed as the psychosomatic nocebo effect, but it may be rooted in a more physiological cellular biochemical response. Interestingly – and related to this – is the fact that differential sensitivities of the hypothalamic-pituitary-adrenal axis to stressors in different strains of rat have been reported [71, 72].

While electro- and magneto-reception may have little functional significance today in humans compared with many other species, (e.g., marine wildlife and migratory animals that depend on such perceptual abilities for significant life activities and survival), an overactive human limbic system can misinterpret external electromagnetic fields as stressors, manifesting in anxiety/fear in the EHS response. The responsiveness of the limbic system, particularly the hippocampus, to static magnetic fields can likely generalize to other forms of electromagnetic fields – particularly artificial fields – due to common molecular mechanisms such as cellular oxidative processes. Due to its wide connections to other brain structures, the hippocampus is probably not the sole brain structure affected by EMF. Many brain structures – from the brain stem to the cortex – have neuronal connections with the hippocampus that could also be involved. However, effects of EMF on these brain structures have not been well investigated.

Concluding remarks

The capability and necessity to detect geomagnetic and electric fields started with evolution in living organisms for survival purposes [66]. As complex life forms evolved with the Earth's natural geomagnetic fields, they also developed unique mechanisms at the cellular level necessary to sustain life. The focus of this paper is on integrating much of the knowledge gained over the last several decades in bioelectromagnetics research that points to a likely unifying mechanism to explain both the many adverse and beneficial effects seen with exposure to man-made EMFs. The proliferation of anthropogenic EMF in the past many decades has introduced novel exposures that did not exist until recently in evolutionary terms and which are substantively different from natural fields. Such exposures today interfere with basic biological mechanisms leading to untoward effects. Free radicals (reactive oxidative and nitrogen species) play important roles in cell functions. Human-made EMF can disturb the homeostasis of free radicals leading to dysfunctions such as the 'cellular stress response'.

The fundamental biological dynamic inherent in the 'cellular stress response' is a fine balance between two potentially opposing mechanisms – the repair of cellular damage leading to healthy cell proliferation and survival, or cell death when the former is no longer viable. Cellular response to EMF follows the basic pattern of the 'cellular stress response' consisting of macromolecular damage to proteins, lipids, and DNA; cell cycle arrest; molecular repair; and cell death when damage becomes too extensive to repair. The process is likely initiated by

the oxidative stress induced by EMF. These processes can facilitate an astounding array of effects for benefit and/or harm including: both specific wound- and generalized-healing, as well as decreased cancer risk; vs. uncontrolled cell proliferation leading to abnormal growth and cancer, in addition to apoptosis leading to degenerative diseases. The challenge, of course, is to guide the processes in a positive direction while minimizing destructive potential.

All of the above effects noted throughout this paper indicate that 'cellular stress response' is a universal change process central to how EMF affects living systems. It is essential to better investigate the interactions among the different parameters of EMF exposure, such as frequency, intensity, exposure duration, and modulation, to prevent harmful effects and achieve beneficial effects, e.g., bone and wound repair, cancer treatment, and reversal/retardation of neurodegenerative diseases [1]. It is especially important to recognize more subtle effects at cellular levels in exposure standards setting – something that is not happening today.

For decades, the argument that "there is no known mechanism" has been used to paralyze changes in public health policy by denying any reported biological effects of EMF below certain thresholds. But increasing recognition of EMF as a 'cellular stress response' via oxidative stress serves to de-mystify that argument which has been specious all along. Logically, perfect understanding of mechanisms is not required to accept the reality of observed effects. One cannot deny that apples fall from trees to the ground without Isaac Newton's gravity explanation, nor is the mechanism of Charles Darwin's 'natural selection' necessary for one to understand that living species have formed in many varieties over time.

One pertinent question is: "What intensities of EMF trigger the cellular stress response?" Since cellular oxidative changes are the likely culprit of the effect, the response can occur at relatively low EMF intensities – many now common in the environment today. There are numerous reports showing oxidative changes at RFR specific absorption rates below 0.4 W/kg (some even at low mW/kg levels) see supplementary material 1 in [1]. Oxidative changes with static/ELF EMF at low μT levels have been reported see supplementary materials in [20]. It is reasonable to speculate that effects are 'non-thermal' particularly in cases when freely moving animals are exposed (see also the discussion in [1] that EMF is more potent and that effects are fundamentally different from heating mechanisms in causing biological effects.). Furthermore, since most static/ELF EMF free radical effects studies were carried out at mT levels, it is also reasonable to speculate that mT-fields could be suitable for medical treatments for neurological diseases, and tissue regeneration, among others.

This paper touches on many aspects of the biological effects of EMF. The goal was to synthesize a hypothesis on their mechanisms of action (Figure 1). In doing so, it is always essential to objectively scrutinize whether available data – experimental or theoretical – form a logical coherent picture similar to solving a jigsaw puzzle. We think we have preliminarily achieved this goal with what we described in this paper.

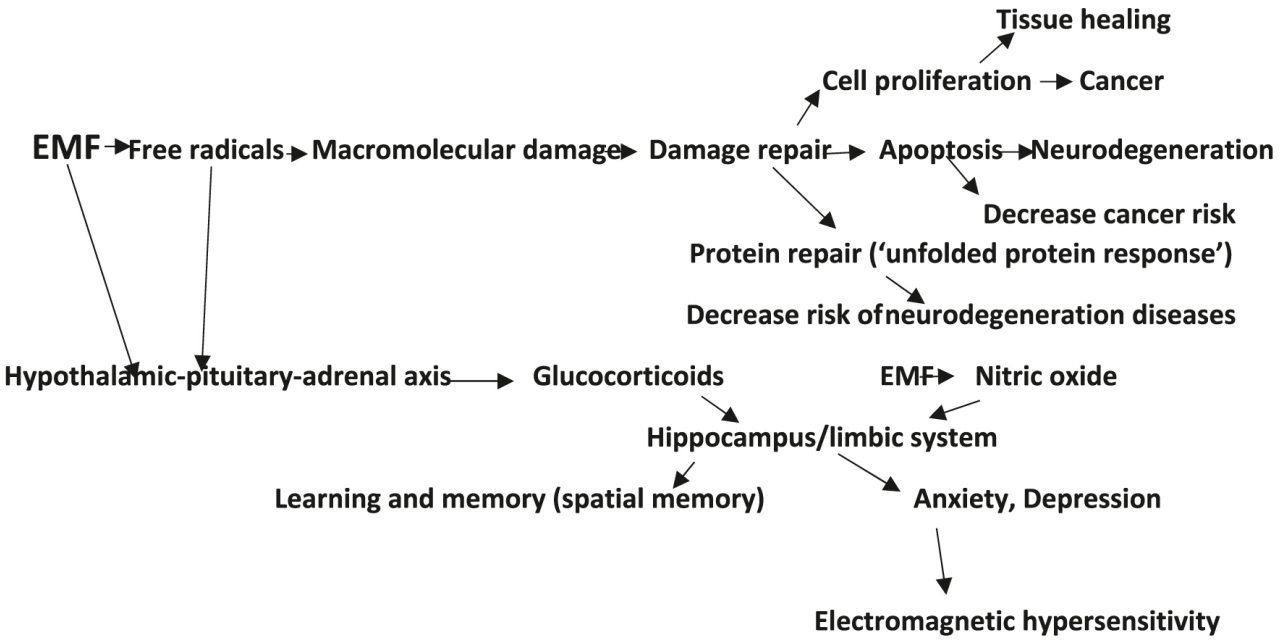

Figure 1:

A schematic representation of the hypothesis of mechanisms and effects of EMF discussed in the paper. The upper pathway presents the possible consequences of EMF-induced 'cellular stress response'. The lower pathway describes the responses of the 'hypothalamic-pituitary-adrenal axis'.

While quality of research can vary with different studies, in general, there are inherent self-correcting dynamics involved with the data of poorly designed and/or executed studies; they tend to eventually be found not to fit into the general picture and consequently are eliminated or ignored. In reviewing studies, there is also a popular fallacy that any replication of experimental results is of the highest importance. But advancement of scientific knowledge traditionally does not depend on replication, which can often be a waste of resources, plus, practically speaking, funding to replicate experiments is generally not available. (Replication experiments, in fact, are rare in scientific research, and in EMF research most replication experiments are industry-funded.) In addition, exact replication of an experiment carried out by a different laboratory is difficult and often introduces additional complexities to the original inquiries which may have already gotten clear and simple results. There are actually very few replications carried out in EMF research. Therefore, it is neither logical nor accurate to justify the often-used arguments that "EMF effects are not reliable because they cannot be replicated" and "data are not believable until they have been replicated".

The most important feature in science is to look for data consistency that simplifies/explains existing data/observations, thereby allowing synthesis of working hypothesis and predictions of future experimental outcomes. Effects should always be robust, i.e., they should occur under different experimental conditions in order for patterns to be understood. This is exactly what the literature of EMF reveals, e.g., similar and collaborating effects have been observed under different conditions (see 'Research Summary' of the 2022 update of the BioInitiative Report [5]). There are, of course, experiments that showed no effects. However, responses in all experimental conditions are not expected, particularly when oscillation of the response

system can occur as discussed above. Depending on exposure conditions and when, after exposure, measurements are carried out, decrease, increase, or no significant effects are results that can all be observed.

Moving toward forming a more comprehensive EMF public health policy, from the discussion above, it is clear that the biological effects of EMF involve an extremely complex matrix of interacting factors across all cell lines/functions. These require careful analysis of comprehensive data, as well as the appropriate level and kind of expertise in standards exposure-setting groups such as ICNIRP and IEEE/FCC in order to interpret such information fully and accurately. When it comes to committee members in positions to make decisions, such membership should always include sufficient knowledge of the physics of EMF and its interactions with whole organic biological systems in order to understand biomic functional processes. It is more critical than ever, given rising EMF levels in all frequency ranges today, that any committee or government entity in a position to influence exposure recommendations be appropriately credentialed in the right disciplines with a proven EMF research track record, and that anyone invited onto such committees understand their own limitations/biases, if any, and refuse to be seated if the subject is outside their purview. There should be a preponderance of committee members with backgrounds in biology, not just physics/engineering as is the case today. There are unfortunate indications that such high standards of appropriate qualification to sit on such committees are not being met today (see [73, 74]), but to do anything less is highly unethical as this subject will continue to be in the hands of people acting outside of their areas of expertise. This issue concerns biological interactions from exogenous EMF exposures at low intensity, not engineering quandaries.

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