Activation of cellular stress response by RF-EMF and its possible impact on cell physiology

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ABSTRACT

The question whether microwave radiation, that is emitted by mobile phones (radio-frequency modulated electromagnetic fields: RF-EMF), might exert any detrimental health effects remains unanswered. There is still insufficient number of studies showing that microwave radiation causes not only biochemical but also physiological responses in living cells without heating them (non-thermal effects). One way to demonstrate whether cells respond to the low-level microwave radiation is to determine whether exposure causes activation of the cellular stress response.

Several recent studies have indicated that RF-EMF increases expression or phosphorylation of certain stress response proteins (Daniells et al. Mutation Research 399, 1998, 55-64; de Pomerai et al. Nature 405, 2000, 417-418; Leszczynski et al. Differentiation 70, 2002, 120-129; Leszczynski et al. Proteomics 4, 2004, 426-431; Nylund & Leszczynski, Proteomics 4, 2004, 1359-1365; Czyz et al. Bioelectromagnetics 25, 2004, 296-307). However, there have been also presented, at various scientific meetings, studies that have failed to replicate these published data. These reports, though, are yet unpublished and, therefore, they are still not possible to thoroughly review.

What is often missing in the studies of the effects of RF-EMF, is the evidence that the changes in gene or protein expression or activity are of sufficient magnitude to alter cell physiology. The very limited, to date available, evidence concerning effects of RF-EMF-induced stress response on the down-stream physiological events will be also reviewed.

BRIEF OVERVIEW

Induction of biological effects by the mobile phone radiation (radio-frequency modulated electromagnetic radiation; RF-EMF) remains a controversial issue. However, there exists a significant body of experimental evidence showing that RF-EMF induces biological responses in a variety of cell systems [1, 2, 3, 4]. Therefore, the induction of health effects of RF-EMF exposure remain a possibility that can not be excluded based on the available science.

One of the reasons for this uncertainty is this that the possible biophysical mechanisms for RF-EMF interaction with living cells remain unknown. Energy deposited in tissue by 900MHz GSM mobile phone (4×10^{-6}eV) or by 1800MHz GSM mobile phone (7×10^{-6}eV) is far lower than the energy needed to break a chemical bond (1eV) [3]. For this reason, some consider it still questionable, whether this low energy would be able to induce biological effects at all. Therefore, even when the in vitro or in vivo biological effects are reported, many tend to dismiss the effects as artifacts because the biophysical mechanism is unknown.

The early signs of cell response to a stress factor (e.g. chemical, radiation, heat etc.) are:

- immediately detectable (already within seconds of exposure) changes in phosphorylation level of various proteins, and
- activation of cellular stress response that is designed to prevent and to repair damage done to cell by the exposure to stress factor.

Therefore, by examining changes in protein phosphorylation and in cellular stress response it is possible to determine whether cells can respond to very low energy that is emitted by mobile phones. Such studies, however, are not designed to and do not provide directly any evidence about the potential health effects of RF-EMF exposure.

So far, in spite of tens of years of research there is only one published study that deals with the phosphorylation changes after the RF-EMF exposure [5] and just a few studies dealing with the activation of cellular of stress response proteins and kinases (Table 1; modified after [6).

Table 1. To date published studies of the RF-EMF radiation effects on cellular stress proteins.

Studied Hsp	Biological model	Exposure conditions	Effect	Reference
Hsp70	L5178Y & CHO cells	2.45 GHz (CW); 51-103 W/Kg	no	[7]
Hsp70	HeLa & CHO cells	2.45 GHz (CW) ; 100 W/kg	no	[8]
Hsp70, Hsp27	Human amnion cells	960 MHz ; 2.1 mW/kg	yes	[9]
Hsp27	EA.hy926 cells	900 MHZ (GSM) ; 2-2.4 W/kg	yes	[5]
Hsp70	Human glioma cells	2.45 GHz (CW) ; 20 W/kg	yes	[10]
Hsp70, Hsp27	L-132 cells	3-300 MHz (CW)	no	[119
Hsp16	C. elegans	750 MHz; 1 mW/kg	yes	[12, 13]
Hsp70	Rat brain	900 MHz; 0.3-7.5 W/kg	yes/no	[14]
Hsp70	Rat brain	2.06 GHz; 2.2 W/cm^2	yes	[15]
Hsp70	Chick embryo	915 MHz; 1.57 - 2.5 W/kg	yes	[16, 17]
Hsp70, Hsp27	Human glioma cells	1950 MHz; 1-10 W/kg	yes	[18]

Interestingly, among the studies listed in review by Cotgreave [6] is the work by Cleary et al. [8]. This particular study is continuously, over the years, prominently cited in review reports as work that shows no effect of EMF exposure on stress response. However, this study uses only molecular weight as a "marker" that distinguishes other proteins from the heat-shock proteins. Use of molecular mass alone is absolutely insufficient to say that given protein is a heat shock protein. Thus, it is absolutely unknown what proteins were in the fraction of proteins containing e.g. molecules with weight of 70kDa. Therefore, this study can not and should not be listed as examining any effects related to stress response. Such claims by the authors are not supported by their methods and data. Only use of specific antibodies against stress proteins could be used to prove that stress proteins are or are not affected.

As with all the studies in this area, the results are both positive and negative. Therefore, studies of mobile-phone-radiation-induced cellular stress response have been included in the updated research agenda of the WHO EMF Project in 2003.

When studying cellular stress response and before making final conclusions as to the effect of EMF on stress response, it is necessary to keep in mind several issues:

- different types of cells express different pattern of stress proteins and therefore they might respond differently to the same stress factor,
- induction of certain stress protein in one cell type does not mean that the same stress factor will induce the same stress protein in another cell type,
- comparison of the extent of RF-EMF induced stress response (weak stimulus) with the extent of stress response induced by heat (strong stimulus) for the purpose of claims that the RF-EMF -induced stress is negligible is incorrect; it would be like comparing response to "tickling with feeder" with response to "hitting with hammer",
- stress response increases gradually with the increase of imposed stress and it is not the type of reaction that causes "either-everything-or-nothing".

We have previously shown that RF-EMF exposure causes global change in the phospho-proteome (all phosphorylated proteins in the cell) [5] We have also shown that RF-EMF activates p38 MAP kinase/Hsp27 stress signaling pathway and causes changes in the physiology of endothelial cells that are consistent with the possibility of blood-brain barrier leakage [5, 19, 20, 21](Figure 1).

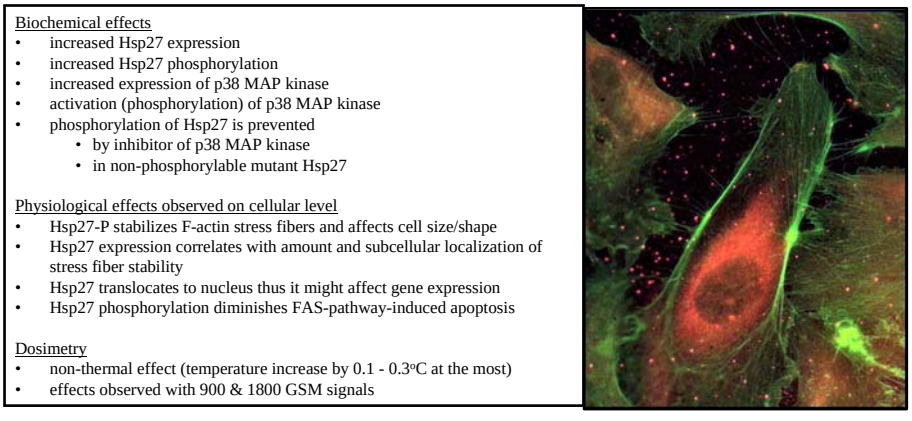

Figure 1. Left panel - list of stress response and stress response-related down-stream effects that were induced by mobile phone radiation in endothelial cell line. Effects are not caused by heating. Right panel - distribution of stress fibers (green fluorescence) and Hsp27 (orange fluorescence) in cell exposed for 1h at 2 SAR.

Based on the known functions of Hsp27 in endothelial cells we have proposed hypothesis suggesting what changes might be induced in endothelial cells in response to RF-EMF exposure (Figure 2). This hypothesis is now being tested.

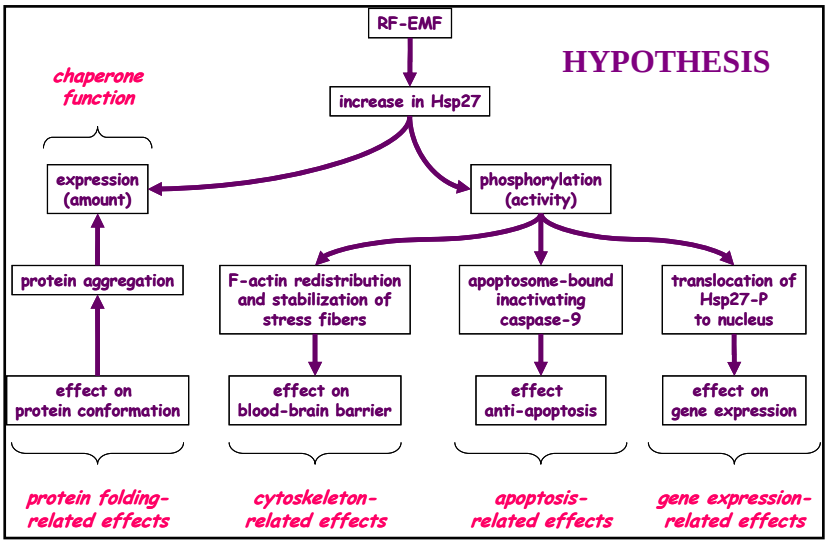

Figure 2. Endothelial cell functions that might be affected by the changes in expression and/or in activity of stress protein Hsp27. This hypothesis is being currently tested.

In conclusion, it appears that cells can recognize mobile phone radiation as an external stress factor and launch protective response in form of activation of stress proteins. Simultaneously occurring broad changes in protein phosphorylation indicate that a large variety of cellular signaling pathways are activated in response to this radiation. Identification of these signaling pathways is possible only by using modern high-throughput screening techniques of transcriptomics and proteomics. This will allow formulating of much better, knowledge-based, hypotheses to determine whether there exists a possibility of induction of health hazard by mobile phone radiation.

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