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Minireview

Biological stress responses to radio frequency electromagnetic radiation: are mobile phones really so (heat) shocking?

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Abstract

Cells phenotypically adapt to alterations in their intra- and extracellular environment via organised alterations to gene and protein expression. Many chemical and physical stimuli are known to drive such responses, including the induction of oxidative stress and heat shock. Increasing use of mobile telephony in our society, has brought focus on the potential for radio frequency (microwave) electromagnetic radiation to elicit biological stress responses, in association with potentially detrimental effects of this to human health. Here we review evidence suggesting altered gene and protein expression in response to such emissions, with particular focus on heat shock proteins. Non-thermal induction of heat shock proteins has been claimed by a number of investigations in in vitro cellular systems, and appears pleiotrophic for many other regulatory events. However, many of these studies are flawed by inconsistencies in exposure models, cell types used and the independent reproducibility of the findings. Further, the paucity of evidence from in vivo experimentation is largely contradictory. Therefore, the validity of these effects in human health risk assessment remain unsubstantiated. Where possible, suggestions for further experimental clarification have been provided.

Keywords: Radio frequency electromagnetic radiation; Heat shock proteins; Altered gene and protein expression; Biological stress response

The integrity and functionality of all biological material is meticulously maintained by a complex network of biological "sensing" and "correcting" devices, which respond to changes in chemical and physical parameters in the local environment. The basis of most functional adaptation to cellular processes lies either at (a) altered gene and protein expression, or (b) altered protein activity, resulting from appropriate modulation by signal transduction mechanisms. The overall ability of cells to react in this manner is often collectively termed "stress response."

The true flexibility of the stress response is well illustrated by the wide variety of chemical and physical stimuli, which have been shown to elicit complex and functionally co-ordinated alterations to gene and/or protein expression/function in cells. These stimuli classically include exposure to strong oxidants or reductants, resulting in altered intracellular redox states and the induction of oxidative or reductive stress, respectively [1]. Chemical insult from reactive electrophiles, such as those routinely generated by the metabolism of xenobiotic agents, may also result in dramatic alterations to cell phenotype [1]. In addition to chemical agents, a variety of physical stimuli have been shown to greatly alter cellular phenotype. Perhaps the archetypal example of this is that of altered temperature, resulting in either heat-or cold-shock [2]. Mechanical forces have also been shown to alter cellular phenotype, such as that experienced in vascular material under shear stress [3].

The biological logic embodied in the stress response lies in equipping the cell with a more robust phenotype, by securing or enhancing major cellular house keeping

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functions such as macromolecule (DNA, RNA, and protein) synthesis and repair, and chemical energy supply. This adaptive "battle" against loss of function and initiation of cell death has several features that are noteworthy. First, it is a characteristic of all biological systems, and is avidly preserved throughout evolution, from the simplest prokaryotes, throughout the eukaryotic kingdom. Second, although the stress stimulus may vary considerably, the molecular components of the stress response often contain commonalties [1]. One example effectively illustrating these points is the case of the heat shock proteins (HSPs),[1] which were initially identified in yeast in response to elevated temperature, but are ubiquitously expressed in eukaryotic cells in response to heat, as well as a variety of other chemical and physical stimuli [2]. Here it is also interesting to note that, as well as being involved in the chaperoning of partially folded and denatured proteins [4], HSPs are also intricately involved in regulating important protein–protein interactions [5,6], as well as possessing inhibitory effects on the functionality of proteins directly involved in the execution of apoptotic cell demise [7–9].

One source of a stress stimulus which has received less attention, but which is rapidly coming into focus from a biological and human health perspective, is that of non ionising electromagnetic radiation. Apart from more traditionally investigated aspects of this field involving exposures to ionising radiation [10] and UV radiation [11], exposure of biological material to radio frequency (RF) emissions is presently attracting attention, especially due to the use of microwaves in mobile telecommunications systems. Indeed, the scientific community is presently assessing if exposure of the human population to RF emissions and their incumbent electrical and magnetic fields is detrimental to health or not. Thus, there is a rapidly accumulating literature describing the potential stress response(s) of biological material to RF energy. This is primarily reflected in studies of altered gene expression and protein synthesis, and of HSPs in particular. However, there are both conflicting aspects within the data and a relative lack of mechanistic explanation for the molecular events observed, particularly in the absence of gross cell/tissue heating effects. Therefore, it is the purpose of this treatise to give an overview of presently available data on RF exposure and the induction of expression of HSPs, both in vitro and in vivo. The review will largely focus on radio emissions in the frequency range relevant to telecommunication (ca. 800–900 MHz (GSM) and ca. 1.6 GHz (IRIDIUM), with wavelengths of 33–37 and 19 cm, respectively). However, this does not negate the fact that there are a number of studies at extremely low frequencies (ELF) (50–60 Hz), which suggest concerns for human health, as these ranges are employed in electricity transmission lines. This issue has been debated extensively elsewhere, and it should be only mentioned here that many effects indicating stress responses in biological systems have also been noted with ELF exposure, including effects on HSP expressions [12,13]. At all times efforts will be made to compare and contrast the experiments in terms of (a) the exposure, its physical characteristics, etc., (b) the dose–response characteristics (thresholds, etc.), (c) biological aspects of the response, and (d) methodological aspects of the detection of the molecular stress response. The review will also attempt to describe current thoughts on the mechanism(s) underlying the HSP response, as well as speculate how this might or might not be relevant to other gene/protein expression alterations documented in the literature. Although not a central issue for this, essentially biochemical and biological review, a final summation will attempt to provide some suggestions to improve our knowledge in this area, as well as speculating on the potential impact of stress response data on the overall assessment of risks to the human population from exposure to RF emissions from mobile telephony.

Molecular end-points of RF-induced induced-stress

Heat shock proteins

The HSPs are an important group of cell stress response proteins, originally discovered in yeast exposed to elevated temperature [14]. The generality of induction of these proteins to other stimuli clearly indicate their collective name to be rather misleading. The HSPs were originally thought to act primarily as molecular chaperones for actively unfolding or partially folded proteins. Indeed, the mechanism of action of HSP 70, one of the most ubiquitous HSPs, has been closely studied and shown to involve both target protein recognition, binding, and catalytic refolding [2]. Similarly, the regulation of expression of HSP genes has been closely studied, with the essential characteristics of the activity and response of heat shock factor-1 (HSF-1) well illuminated [15]. The activation of transcription results from a disturbance in the balance between HSF-1 and HSP levels, resulting in release of HSF-1 and its trimerisation and transport into the nucleus, where it binds to multiple heat shock elements (consensus NGAAN) in target genes [15]. The disruption of the inactive complex seems to have a common stimulus involving damage to cellular proteins and their sequestration by free HSP molecules. The damage may result from both physical (heat) or chemical (oxidation, alkylation, etc) stimuli

[1] *Abbreviations used:* HSP, heat shock protein; RF, radio frequency; EMF, electromagnetic field; EMR, electromagnetic radiation; ELF, extremely low frequency; GSM, groupe speciale mobile; CW, continuous wave; FDMA, frequency division multiple access; CDMA, code division multiple access; TDMA, time division multiple access; FM, frequency modulation; TEM, transverse electromagnetic; GFP, green fluorescent protein; NOEL, no observable effect level; ICNIRP, international commission on non-ionising radiation protection; ODC, ornithine decarboxylase; MAPK, mitogen activated protein kinase.