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Review

Adaptive response in mammalian cells exposed to non-ionizing radiofrequency fields: A review and gaps in knowledge

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ABSTRACT

Adaptive response is a phenomenon in which cells which were pre-exposed to extremely low and non-toxic doses of a genotoxic agent became resistant to the damage induced by subsequent exposure to a higher and toxic dose of the same, similar (in action) or another genotoxic agent. Such response has been well documented in scientific literature in cells exposed *in vitro* and *in vivo* to low doses of physical (especially, ionizing radiation) and chemical mutagens. The existence of similar phenomenon in mammalian cells exposed *in vitro* and *in vivo* to non-ionizing radiofrequency fields has been reported in several research publications. In *in vitro* studies, human blood lymphocytes exposed to radiofrequency fields and then treated with a genotoxic mutagen or subjected to ionizing radiation showed significantly decreased genetic damage. Similar studies in tumor cells showed significantly increased viability, decreased apoptosis, increased mitochondrial membrane potential, decreased intracellular free Ca^{2+} and, increased Ca^{2+}-Mg^{2+}-ATPase activity. In *in vivo* studies, exposure of rodents to radiofrequency fields and then to lethal/sub-lethal doses of γ-radiation showed survival advantage, significantly decreased damage in hematopoietic tissues, decreased genetic damage in blood leukocytes and bone marrow cells, increased numbers of colony forming units in bone marrow, increased levels of colony stimulating factor and interleukin-3 in the serum and increased expression of genes related to cell cycle. These observations suggested the ability of radiofrequency fields to induce adaptive response and also indicated some potential mechanisms for the induction of such response. Several gaps in knowledge that need to be investigated were discussed.

Contents

Abbreviations: AD, adaptation dose; AR, adaptive response; CA, chromosomal aberrations; CD, challenge dose; CFU-BM, colony forming units in bone marrow; DOX, doxorubicin; FDTD, finite-difference-time-domain; FIT, finite integration technique; GSM, Global System for Mobile Communications; GTEM, Gigahertz Transverse Electromagnetic; MMP, mitochondrial membrane potential; IL, interleukin; MMC, mitomycin C; MN, micronuclei; MNNG, N-methyl-N-nitro-nitrosoguanidine; MUT, mutations; RF, radiofrequency fields; SAR, specific absorption rates; SB, single and double strand breaks; SCE, sister chromatid exchanges; UMTS, universal mobile telecommunication system; WPC, wire patch cell.

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1. Introduction

Exposure to nonionizing electromagnetic radiofrequency fields (RF) in the frequency range 300 MHz–300 GHz has become unavoidable in modern society because of their multitude of uses in defense, industry, medicine and general consumer products such as microwave ovens and wireless communications devices which deliver voice, data and images. There is ongoing concern in the public regarding the potential for adverse human health effects from such exposure. During the last several decades, researchers have been evaluating the extent of genetic damage in human and animal cells exposed *in vivo* and *in vitro* to RF since the damage to the DNA in somatic cells can lead to the development of cancer or cell death while changes in the DNA of germ cells can lead to mutations which can be transmitted to subsequent generations. Investigations were also conducted to examine the impact of RF exposure before, during or after treatment with known genotoxic agent(s), as occur in real life situations. Different genotoxicity end-points including single and double strand breaks (SB), chromosomal aberration (CA), micronuclei (MN), sister chromatid exchanges (SCE) and mutations (MUT) were used to investigate the impact of a range of RF frequencies, modulations, specific absorption rates (SAR), cell types, exposure durations, etc. The conclusions from several peer-reviewed scientific reviews were: (i) the currently available data is not sufficient to provide the evidence that RF exposure *per se* is genotoxic, (ii) RF exposure may not modify (enhance or reduce) the damage induced by known genotoxic agents and, (iii) some of the reported 'adverse' effects may be attributed to RF-induced hyperthermia [1–10]. The conclusions from expert scientific advisory committees in several countries as well as from international organizations were similar to those of the above (reviewed in [11]).

Adaptive response (AR) is a phenomenon in which cells which were pre-exposed to extremely low and non-toxic doses of a genotoxic agent became resistant to the damage induced by subsequent exposure to a higher and toxic dose of the same, similar (in action) or another genotoxic agent. Samson and Crains [12] were the first to demonstrate AR in *Escherichia coli*: the bacteria which were grown in low and non-toxic dose of N-methyl-N-nitro-nitrosoguanidine (MNNG, 1 μg/ml, an alkylating mutagen) became increasingly resistant both to cell killing and mutation by the subsequent exposure to high dose MNNG (100 μg/ml). The low dose is usually referred as adaptation dose (AD) and the high dose as challenge dose (CD). Subsequent researchers demonstrated the induction of AR in many different organisms including mammalian cells exposed *in vitro* and *in vivo* to physical (especially, ionizing radiation) and chemical mutagens using several different end-points such as SB, CA, MN, SCE, MUT, neoplastic transformation, apoptosis, oxidative stress and survival. Further studies also indicated that AR was not elicited instantaneously but require certain time interval between AD and CD to become fully active. Potential action mechanisms have been proposed to elucidate the induction of AR (reviewed in [13]).

In RF investigations, there were some studies in which the cells were first exposed to RF and then treated with a genotoxic agent and, there was no time interval between the two treatments [14–16]. The data from a majority of such studies showed neither enhancement nor reduction of the damage induced by the genotoxic agent. In recent investigations, researchers have given the cells certain time interval between the two exposures in order to examine whether non-genotoxic RF pre-exposure given as AD can elicit AR and induce resistance to the damage induced by a subsequent high challenge dose (CD) of a mutagen. The very first such report was published in 2009 [17]. Since then, there were several other publications in peer-reviewed scientific literature. This paper reviews the RF-induced AR investigations with an outlook on several ionizing radiation- and chemical mutagen-induced AR publications. Gaps in knowledge and future research opportunities are discussed.

2. Studies in human cells

2.1. Peripheral blood lymphocytes

The experimental protocol used was essentially similar in all of the following studies. Peripheral blood was collected from healthy donors. Lymphocyte cultures (before and/or after stimulation with phytohemagglutinin, PHA) were first exposed for 20 h to RF (AD). At 48 h, the cells were treated with a genotoxic dose of mitomycin-C (MMC) or X-rays (CD).

The incidence of MN was determined at the end of 72 h culture period. The results obtained in cells exposed to AD + CD were compared with those treated with CD alone. Overall, RF exposure *per se* did not significantly increase the incidence of MN compared with those in sham-exposed cells and, sham exposure did not decrease mutagen-induced MN and thus was not able to elicit AR.

Sannino et al. [17] were the first to report RF-induced AR in freshly collected human peripheral blood lymphocytes. Lymphocytes from 5 different donors were stimulated with PHA for 24 h and then exposed for 20 h to 900 MHz RF (GSM, Global System for Mobile Communications signal) in a wire patch cell (WPC). The SAR was an average of 1.25 W/kg with peak value of 10 W/kg. At 48 h, all cells were treated with 100 ng/ml MMC. The results were that the cells from 4 donors which were exposed to RF + MMC showed significantly decreased incidence of MN (ranged from 35% to 56%, $p < 0.05$) while those from one donor did show a decrease (25%) but was not significant ($p > 0.05$) (Fig. 1). These observations suggested that RF-exposed cells were able to resist the damage induced by subsequent exposure to MMC and thus exhibited AR. The variability/heterogeneity in the response among the donors was similar to that reported in low dose ionizing radiation- and chemical mutagen-induced AR [18–20].

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