EDITORIAL

Low intensity radiofrequency radiation: a new oxidant for living cells

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Received March 12, 2014
Accepted March 24, 2014

Published Online March 29, 2014

DOI 10.5455/oams.240314.ed.002

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Key Words
Cancer;
Electrohypersensitivity;
Oxidative stress;
Radiofrequency radiation

Radiofrequency radiation (RFR), *e.g.* electromagnetic waves emitted by our cell phones and Wi-Fi, are referred to as non-ionizing. This means that in contrast to the ionizing radiation, which does induce ionization of water and biologically important macromolecules, RFR does not have a capacity for such effects. Unlike, for example X-rays, the energy of RFR is not enough to break electrons off the molecules. However, is RFR completely safe for public health? Traditionally, the industry and the public bodies said yes. Nevertheless, new research data change this perception.

Oxidative stress is an induced imbalance between pro-oxidant and antioxidant systems resulting in oxidative damage to proteins, lipids and DNA; and is closely connected to overproduction of reactive oxygen species (ROS) in living cells [1]. The notion that the low intensity RFR can bring about significant oxidative stress in living cells has been doubted for years. The logic is simple: as low intensity radiofrequency electromagnetic waves are not able to ionize molecules, they can do nothing wrong for the living tissues. However, during the last decades a worldwide increase in penetration of wireless communication systems, including cellular telephony and Wi-Fi, attracted massive attention to possible biological effects of low intensity RFR. Consequently, the recent epidemiological studies unexpectedly indicated a significant increase in the occurrence of various tumors among long-term and "heavy" users of cellular phones. These include brain tumors [2, 3], acoustic neuromas [4, 5], tumors of parotid glands [6], seminomas [7], melanomas [8] and lymphomas [9]. Similarly, an increase in tumor incidence among people living nearby cellular base transmitting stations was also reported [10, 11]. As a result, in 2011 the World Health Organization/ International Agency for Research on Cancer classified radiofrequency radiation as a possible carcinogen to humans [12].

To that, a new medical condition, so-called electro-hypersensitivity, in which subjects suffer due to RFR exposure has been described. Typically these people suffer from skin and mucosa related symptoms (itching, smarting, pain, heat sensation), or heart and nervous system disorders after exposure to computer monitors, cell phones and other electromagnetic devices [13]. This malady is growing continuously: starting from 0.06% of the total population in 1985 this category now includes as much as 9-11% of the European population [14].

A number of experimental studies demonstrate metabolic effects induced by low intensity RFR [15-17]. Notwithstanding the non-ionizing nature of RFR, profound mutagenic effects and features of significant oxidative stress in living cells under low intensity RFR exposure were detected using various biological models [18, 19]. Some of the papers however still show an absence of biological effects [20]. To clarify the picture, we analyzed peer-reviewed publications on oxidative effects of RFR and found altogether 80 currently available papers, of which a remarkable part, 76 papers (92.5%), reported the detection of significant oxidative stress. These effects most often included overproduction of ROS, lipid peroxidation/increased concentrations of malondialdehyde, protein peroxidation, increased concentrations of nitric oxide (NO) and changes in the activity of

antioxidant enzymes [21-26]. Some papers point to the role of particular ROS and the ROS related pathways. For example, the mitochondrial pathways of superoxide/ROS generation have been shown to be activated in living cells during exposure to low intensity RFR [17, 27]. Importantly, a non-phagocyte NADH oxidase, a known enzymatic source of ROS, was shown to be significantly activated just after a few minutes of exposure to low intensity RFR [16]. More to that, a possibility of mechanochemical disruption of water molecule clusters with dissociation of water molecules due to low intensity microwave exposure was demonstrated already many years ago [28].

Unexpectedly, a strong non-thermal character of biological effects of RFR has been documented. As low as 0.1 $\mu W/cm^2$ intensity of RFR and absorbed energy (specific absorption rate, SAR) of 0.3 $\mu W/kg$ were demonstrated to be effective in inducing significant oxidative stress in living cells [27, 29]. This observation is particularly important as the modern international safety limits on RFR exposure are based solely on the thermal effects of the radiation and only restrict RFR intensity to 450-1000 $\mu W/cm^2$ and SAR to 2 W/kg [30]. Moreover, studies where thermal intensities of RFR have been used could not reveal oxidative effects [31-33], which might point to the variety of molecular mechanisms of action of radiation induced by different radiation intensities.

It is indicative that many studies demonstrated the effectiveness of different antioxidants to reverse the oxidative stress caused by RFR exposure. Such effects have been reported for melatonin [34-37], vitamins E and C [24, 38], caffeic acid phenethyl ester [36], selenium and L-carnitine [39], and garlic extract [40].

It is still a question how low intensity RFR could activate superoxide-generating enzyme NADH oxidase or significantly increase the level of NO in a cell (*e.g.*, possibly due to activation of NO synthase). But what is understood at the moment is that significantly increased levels of ROS in living cells caused by low intensity RFR exposure could lead to mutagenic effects through expressive oxidative damage of DNA [17, 27, 41]. It is also well documented nowadays that in biological systems, oxidants are not necessarily always the triggers for oxidative damage, and that oxidants such as H_2O_2 could actually serve as signaling messengers and drive several aspects of cellular signaling [42]. This leads to a hypothesis that overproduction of ROS/free radical species in living cells under low intensity RFR exposure can lead to disturbances in cell signaling cascades, which in turn may result in various pathologic consequences.

Whatever the particular first-step molecular mechanisms, it is clear that the substantial overproduction of ROS in living cells under low intensity RFR exposure could cause a broad spectrum of health disorders and diseases, including cancer in humans. Undoubtedly, this calls for the further intensive research in the area, as well as to a precautionary approach in routine usage of wireless devices.

COMPETING INTERESTS

The authors report no conflicts of interest.

REFERENCES

1. Halliwell B. Biochemistry of oxidative stress. Biochem Soc Trans 2007; 35:1147-50.
2. Hardell L, Carlberg M, Soderqvist F, Mild KH, Morgan LL. Long-term use of cellular phones and brain tumours: increased risk associated with use for > or =10 years. Occup Environ Med 2007; 64:626-32.
3. Hardell L, Carlberg M. Mobile phones, cordless phones and the risk for brain tumours. Int J Oncol 2009; 35:5-17.
4. Hardell L, Carlberg M, Hansson Mild K. Case-control study on cellular and cordless telephones and the risk for acoustic neuroma or meningioma in patients diagnosed 2000-2003. Neuroepidemiology 2005; 25:120-8.
5. Sato Y, Akiba S, Kubo O, Yamaguchi N. A case-case study of mobile phone use and acoustic neuroma risk in Japan. Bioelectromagnetics 2011; 32:85-93.
6. Sadetzki S, Chetrit A, Jarus-Hakak A, Cardis E, Deutch Y, Duvdevani S, Zultan A, Novikov I, Freedman L, Wolf M. Cellular phone use and risk of benign and malignant parotid gland tumors--a nationwide case-control study. Am J Epidemiol 2008; 167:457-67.
7. Hardell L, Carlberg M, Ohlson CG, Westberg H, Eriksson M, Hansson Mild K. Use of cellular and cordless telephones and risk of testicular cancer. Int J Androl 2007; 30:115-22.
8. Hardell L, Carlberg M, Hansson Mild K, Eriksson M. Case-control study on the use of mobile and cordless phones and the risk for malignant melanoma in the head and neck region. Pathophysiology 2011; 18:325-33.
9. Hardell L, Eriksson M, Carlberg M, Sundstrom C, Mild KH. Use of cellular or cordless telephones and the risk for non-Hodgkin's lymphoma. Int Arch Occup Environ Health 2005; 78:625-32.
10. Eger H, Hagen K, Lucas B, Vogel P, Voit H. The influence of being physically near to a cell phone transmission mast on the incidence of cancer. Umwelt Medizin Gesellschaft 2004; 4:1-7.

 DOI 10.5455/oams.240314.ed.002

11. Wolf R, Wolf D. Increased incidence of cancer near a cell-phone transmitted station. In: Columbus F (ed) Trends in Cancer Prevention, Nova Science Publishers, New York, NY, pp 1-8, 2007.

12. Baan R, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Islami F, Galichet L, Straif K; WHO International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncol 2011; 12:624-6.

13. Johansson O. Electrohypersensitivity: state-of-the-art of a functional impairment. Electromagn Biol Med 2006; 25:245-58.

14. Hallberg O, Oberfeld G. Letter to the editor: will we all become electrosensitive? Electromagn Biol Med 2006; 25:189-91.

15. Volkow ND, Tomasi D, Wang GJ, Vaska P, Fowler JS, Telang F, Alexoff D, Logan J, Wong C. Effects of cell phone radiofrequency signal exposure on brain glucose metabolism. JAMA 2011; 305:808-13.

16. Friedman J, Kraus S, Hauptman Y, Schiff Y, Seger R. Mechanism of short-term ERK activation by electromagnetic fields at mobile phone frequencies. Biochem J 2007; 405:559-68.

17. De Iuliis GN, Newey RJ, King BV, Aitken RJ. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa *in vitro*. PLoS One 2009; 4:e6446.

18. Ruediger HW. Genotoxic effects of radiofrequency electromagnetic fields. Pathophysiology 2009; 16:89-102.

19. Yakymenko I, Sidorik E, Kyrylenko S, Chekhun V. Long-term exposure to microwave radiation provokes cancer growth: evidences from radars and mobile communication systems. Exp Oncol 2011; 33:62-70.

20. Demirel S, Doganay S, Turkoz Y, Dogan Z, Turan B, Firat PG. Effects of third generation mobile phone-emitted electromagnetic radiation on oxidative stress parameters in eye tissue and blood of rats. Cutan Ocul Toxicol 2012; 31:89-94.

21. Ozgur E, Guler G, Seyhan N. Mobile phone radiation-induced free radical damage in the liver is inhibited by the antioxidants N-acetyl cysteine and epigallocatechin-gallate. Int J Radiat Biol 2010; 86:935-45.

22. Bilgici B, Akar A, Avci B, Tuncel OK. Effect of 900 MHz radiofrequency radiation on oxidative stress in rat brain and serum. Electromagn Biol Med 2013; 32:20-9.

23. Deshmukh PS, Banerjee BD, Abegaonkar MP, Megha K, Ahmed RS, Tripathi AK, Mediratta PK. Effect of low level microwave radiation exposure on cognitive function and oxidative stress in rats. Indian J Biochem Biophys 2013; 50:114-9.

24. Jelodar G, Nazifi S, Akbari A. The prophylactic effect of vitamin C on induced oxidative stress in rat testis following exposure to 900 MHz radio frequency wave generated by a BTS antenna model. Electromagn Biol Med 2013; 32:409-16.

25. Megha K, Deshmukh PS, Banerjee BD, Tripathi AK, Abegaonkar MP. Microwave radiation induced oxidative stress, cognitive impairment and inflammation in brain of Fischer rats. Indian J Exp Biol 2012; 50:889-96.

26. Ni S, Yu Y, Zhang Y, Wu W, Lai K, Yao K. Study of oxidative stress in human lens epithelial cells exposed to 1.8 GHz radiofrequency fields. PLoS One 2013; 8:e72370.

27. Burlaka A, Tsybulin O, Sidorik E, Lukin S, Polishuk V, Tsehmistrenko S, Yakymenko I. Overproduction of free radical species in embryonal cells exposed to low intensity radiofrequency radiation. Exp Oncol 2013; 35:219-25.

28. Vaks VL, Domrachev GA, Rodygin YL, Selivanovskii DA, Spivak EI. Dissociation of water by microwave radiation. Radiophys Quantum Electron 1994; 37:85-8

29. Oksay T, Naziroglu M, Dogan S, Guzel A, Gumral N, Kosar PA. Protective effects of melatonin against oxidative injury in rat testis induced by wireless (2.45 GHz) devices. Andrologia 2014; 46:65-72.

30. Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). International Commission on Non-Ionizing Radiation Protection. Health Phys 1998; 74:494-522.

31. Luukkonen J, Hakulinen P, Maki-Paakkanen J, Juutilainen J, Naarala J. Enhancement of chemically induced reactive oxygen species production and DNA damage in human SH-SY5Y neuroblastoma cells by 872 MHz radiofrequency radiation. Mutat Res 2009; 662:54-8.

32. Hong MN, Kim BC, Ko YG, Lee YS, Hong SC, Kim T, Pack JK, Choi HD, Kim N, Lee JS. Effects of 837 and 1950 MHz radiofrequency radiation exposure alone or combined on oxidative stress in MCF10A cells. Bioelectromagnetics 2012; 33:604-11.

33. Kang KA, Lee HC, Lee JJ, Hong MN, Park MJ, Lee YS, Choi HD, Kim N, Ko YG, Lee JS. Effects of combined radiofrequency radiation exposure on levels of reactive oxygen species in neuronal cells. J Radiat Res 2014; 55:265-76.

34. Oktem F, Ozguner F, Mollaoglu H, Koyu A, Uz E. Oxidative damage in the kidney induced by 900-MHz-emitted mobile phone: protection by melatonin. Arch Med Res 2005; 36:350-5.

35. Ayata A, Mollaoglu H, Yilmaz HR, Akturk O, Ozguner F, Altuntas I. Oxidative stress-mediated skin damage in an experimental mobile phone model can be prevented by melatonin. J Dermatol 2004; 31:878-83.

36. Ozguner F, Bardak Y, Comlekci S. Protective effects of melatonin and caffeic acid phenethyl ester against retinal oxidative stress in long-term use of mobile phone: a comparative study. Mol Cell Biochem 2006; 282:83-8.

37. Sokolovic D, Djindjic B, Nikolic J, Bjelakovic G, Pavlovic D, Kocic G, Krstic D, Cvetkovic T, Pavlovic V. Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain. J Radiat Res (Tokyo) 2008; 49:579-86.

38. Oral B, Guney M, Ozguner F, Karahan N, Mungan T, Comlekci S, Cesur G. Endometrial apoptosis induced by a 900-MHz mobile phone: preventive effects of vitamins E and C. Adv Ther 2006; 23:957-73.

39. Turker Y, Naziroglu M, Gumral N, Celik O, Saygin M, Comlekci S, Flores-Arce M. Selenium and L-carnitine reduce oxidative stress in the heart of rat induced by 2.45-GHz radiation from wireless devices. Biol Trace Elem Res 2011; 143:1640-50.

40. Avci B, Akar A, Bilgici B, Tuncel OK. Oxidative stress induced by 1.8 GHz radio frequency electromagnetic radiation and effects of garlic extract in rats. Int J Radiat Biol 2012; 88:799-805.

41. Guler G, Tomruk A, Ozgur E, Sahin D, Sepici A, Altan N, Seyhan N. The effect of radiofrequency radiation on DNA and lipid damage in female and male infant rabbits. Int J Radiat Biol 2012; 88:367-73.

42. Stone JR, Yang S. Hydrogen peroxide: a signaling messenger. Antioxid Redox Signal 2006; 8:243-70.