EDITORIAL

Low intensity radiofrequency radiation: a new oxidant for living cells

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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 malondialde-hyde, 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.

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