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Effects of mobile phone exposure on metabolomics in the male and female reproductive systems

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ABSTRACT

With current advances in technology, a number of epidemiological and experimental studies have reported a broad range of adverse effects of electromagnetic fields (EMF) on human health. Multiple cellular mechanisms have been proposed as direct causes or contributors to these biological effects. EMF-induced alterations in cellular levels can activate voltage-gated calcium channels and lead to the formation of free radicals, protein misfolding and DNA damage. Because rapidly dividing germ cells go through meiosis and mitosis, they are more sensitive to EMF in contrast to other slower-growing cell types. In this review, possible mechanistic pathways of the effects of EMF exposure on fertilization, oogenesis and spermatogenesis are discussed. In addition, the present review also evaluates metabolomic effects of GSM-modulated EMFs on the male and female reproductive systems in recent human and animal studies. In this context, experimental and epidemiological studies which examine the impact of mobile phone radiation on the processes of oogenesis and spermatogenesis are examined in line with current approaches.

1. Introduction to metabolomics: effects of EMF on male and female reproduction

Humans are often exposed to a broad array of electromagnetic fields (EMF) as technology advances. The purpose of this review is to discuss the effects of EMF-induced metabolomics on the male and female reproductive systems caused by mobile phones EMF exposure in the light of current research. Human and animal studies have identified a number of adverse health effects that can be caused by this exposure that require additional evaluations (Sepehrimanesh and Davis, 2017). Many factors, such as body weight, dielectric constant, electrolyte balance and other properties are important in the context of these effects since they change conductivity and reactivity to EMF (Tabrah et al., 1998; Vesselinova, 2015). *In vivo* and *in vitro* studies indicate that EMF exposure can alter cellular homeostasis, activate voltage-gated calcium channels and affect endocrine function, reproduction functions and fetal growth in animals. Moreover, the absorption rate of EMF in human cells is affected by polarization, amplitude, frequency, and power density. Absorption rates of different tissues affect cellular absorption of radiofrequency energy. The effects of EMF may be classified as thermal or non-thermal. In general, the thermal mechanism is understood to increase local temperature with an oscillatory current at the radio frequency of the electrical field (Belyaev, 2005; Gye and Park, 2012). In contrast, non-thermal effects of EMF on human cells can include the generation of large and damaging reactive oxygen species (ROS). ROS generation causes oxidative damage in the target cells. In research on pregnant rats and their offspring exposed to 900 MHz, 1800 MHz and 2450 MHz EMF, Yuksel et al. (2016) reported a higher body temperature and uterus lipid peroxidation levels in newborn rats compared to a control group. This indicates that health risks caused by EMF can arise from either non-thermal or thermal effects of EMF in the female reproductive system (Yuksel et al., 2016) and that both may be involved. EMF has a high penetrating power and can accelerate the movement of charged particles of macromolecules and polymers, such as electrons and ions (Asghari et al., 2016).

EMF-induced changes observed at the cellular level may cause free radicals and Ca^{+2} mediated cell growth inhibition, protein misfolding and DNA damage. EMF has biochemical interactions arising from activation of second chemical messengers in biological materials (Belyaev, 2005; Gye and Park, 2012). Moreover, the effect of EMF exposure on reproductive functions depends on frequency and wave, polarity and information content, as well as energy, power density and total time of exposure. (Gye and Park, 2012). The main side-effects of EMF are seen through protein synthesis, which seriously affects cell

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structure and functions (Mancinelli et al., 2004). In that context, Desai et al. suggested that the EMF might enhance ROS generation by increasing nicotinamide adenine dinucleotide (NADH) oxidase activity in plasma membrane. One possible interaction mechanism between electromagnetic radiation and biological systems is a process involving free radicals (Desai et al., 2009b). Highly reactive free radical formation increases oxidative stress, a physiological or cellular condition, and molecular damage subsequently occurs, together with pronounced effects on macromolecules such as. ROS consist of highly reactive molecules formed by unconjugated electrons in free orbits. While a small concentration of ROS is essential for the maintenance of healthy cells, excessive concentrations can cause tissue damage and impair the ability of cells to undergo repair or apoptosis (Bandyopadhyay et al., 1999; Kesari et al., 2013). In the case of exposure to mobile phone radiation, an EMF-induced iron-mediated process (Fenton reaction) occurs. This reaction leads to an increase in hydroxyl free radical generation in the cells that can cause serious damage. Hydroxyl radicals are generated from hydrogen peroxide through the Fenton reaction in the presence of iron, and also EMF (D'Autreaux and Toledano, 2007; Desai et al., 2009a; Kesari et al., 2013). Kesari et al. (2013) suggested that the Fenton reaction induced by EMF accounts directly for cell death by increasing the production of free radicals that play an important role in the enzymatic and genetic action of EMF (Fig. 1) (Kesari et al., 2013).

EMF-induced free radicals can create both structural deformities and functional defects in sperm (Gye and Park, 2012). Processes relevant to this damage can involve the stimulation of protein kinases, and an increase in cyclic adenosine mono phosphate (cAMP), phosphorylation, and calcium efflux. The first target of ROS is the sperm membrane. Lipid peroxidation has been shown to be induced when O_2 is not soluble in the hydrophobic membrane or when it is in the protonated form (Evans and Halliwell, 1999; Phillips et al., 2009). Moreover, Kumar et al. (2011) reported that exposure to 2.45-GHz EMF caused apoptosis during spermiogenesis, and that caspase-3 activity affects reproductive physiology. The effect of oxidative stress on health and of microwave EMFs on chronic stress through over-production of ROS have now been revealed (Kumar et al., 2011). Excessive generation of ROS and oxidative stress may contribute to aging and various health conditions affecting female reproduction. Endothelial dysfunction caused by oxidative stress contributes to obstetric complications, such as early and repeated pregnancy loss, pre-eclampsia, intrauterine growth restriction and preterm delivery (Webster et al., 2008). Reactive oxygen and nitrogen species may have adverse effects on embryo implantation and may affect the development of reproductive disorders, such as endometriosis and pre-eclampsia (Webster et al., 2008). Despite the fact that the exact pathogenesis of pre-eclampsia is still unknown, placental ischemia/hypoxia is regarded as a significant factor through

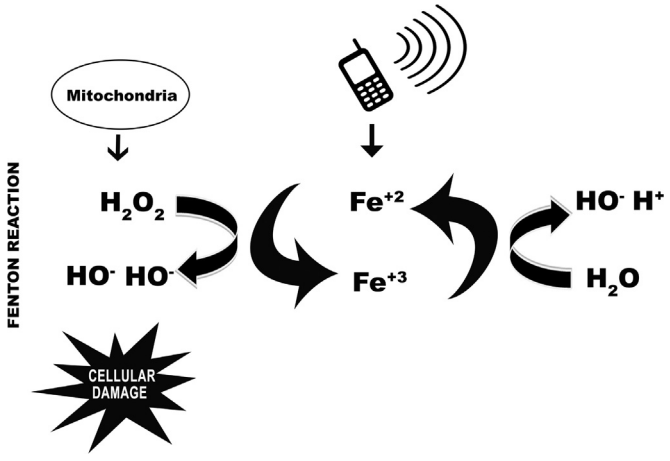

Fig. 1. Diagram showing the role of Fenton reaction EMF-induced cellular damage (modified from Phillips et al., 2009).

the induction of oxidative stress, that may trigger endothelial cell dysfunction in the disease (Webster et al., 2008; Possomato-Vieiraand Khali, 2016). Modified vasomotor functions are demonstrated with unsuccessful embryo implantation in preeclampsia and endometriosis, and low placental perfusion (Massé et al., 2002). Antioxidants are reported to cure such effects and can thus mitigate infertility risks (Agarwal et al., 2008b; Webster et al., 2008). Previous studies have examined the deleterious effects of EMF on reproduction in both genders in different exposure doses, and research has shown that EMF has harmful effects on sex hormones, gonadal function, fetal growth and pregnancy (Rodriguez et al., 2003; Rodriguez et al., 2004; Gye and Park, 2012). In addition, natural antioxidants can be used to reduce the side-effects of EMF exposure (Gye and Park, 2012; Nelson et al., 1995; Pourlis, 2009). In this regard, ROS over-generation can lead to disruption of normal female physiological reactions by penetrating the body's natural antioxidant defense system (Agarwal et al., 2012; Al-Gubory et al., 2010). Oxidative stress has been shown to be a significant cause of infertility in men. Sperm numbers and motility are important determinants of fertilization capacity, and oxidative stress may cause infertility in men by affecting these parameters (Makker et al., 2009; Saalu, 2010).

A significant increase has been observed in mitochondrial and cytosolic superoxide generation in human spermatozoa exposed to EMF (Agarwal et al., 2009; De Iuliis et al., 2009). The relation between loss of sperm motility and ROS over-generation is well-known in sperm biology (Darr et al., 2016). Increases in lipid peroxidation and the sequent malondialdehyde depend on acrolein generation that can covalently bind with electrophilic aldehyde and proteins such as 4-hyrdoxinonena (4-HNE) (Aitken et al., 2012). These components alkalize the sperm axonemal proteins that regulate sperm motility, and especially the heavy chain dynein. In addition, electrophiles such as 4-HNE increase oxidative stress by stimulating ROS generation through sperm mitochondria (Aitken et al., 2012). This occurs since the mitochondrial electron transport chain, another protein group alkalized by 4-HNE, generates succinic acid dehydrogenase components (Aitken et al., 2012). Even a minimal increase in ROS induced with EMF can have a profound effect on reproduction by damaging mitochondria (Aitken et al., 2012). ROS generation originating from EMF is reported to increase lipid peroxidation in spermatozoa and damage mitochondrial DNA (Aitken et al., 2012; Al-Damegh, 2012; Kesari et al., 2011; Moazamian et al., 2015).

2. The effects of EMF-induced oxidative stress mechanisms on the male genital system

The effects of EMF emitted from the mobile phone on the reproductive organs and fetal development have been extensively investigated by our laboratories (Sepehrimanesh et al., 2014) and others, and the number of studies on the impact of EMF exposure on human reproduction has increased considerably. While some studies suggest that EMF has an adverse effect on male reproductive systems, others have reported that EMF has no, or only partial, effects on testicular tissue and functions. As with other endpoints, these inconsistent results may be due to the fact that different researchers have used different frequencies, amplitudes, power densities, and that the density and exposure times of the induced magnetic fields have also not been standardized (Belyaev, 2005; Dasdag et al., 2003; Desai et al., 2009b; Yan et al., 2007). Radiation emitted by mobile phones may cause structural and functional injury in the testes, changes in semen parameters, and decreased epididymal sperm concentrations and male fertility (Kang et al., 2010). These changes depend on the length of exposure, the specific absorption rate (SAR) and the energy level of EMF. In this context, a decrease in testicular size has been reported as one effect, and studies have also reported decreases in the diameter and epithelial thickness of the seminiferous tubules (Dasdag et al., 1999; Ozguner et al., 2005; Salama et al., 2010). According to De Iuliis et al. (2009),