International Journal of Biological, Life and Agricultural Sciences
ISSN: 2415-6612
Vol:4, No:8, 2010

# Effects of Intrauterine and Extrauterine Exposure to 1800 MHz GSM-Like Radiofrequency Radiation on Liver Regulatory Enzymes Activities in Infant Female Rabbits

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***Abstract*—**In the present study, we aimed to design the intrauterine and extrauterine exposure to 1800 MHz GSM-like RF radiation and investigate its possible bio-effects on infant female rabbits. Totally thirty-six New Zealand White female rabbits, one-month old, were randomly divided into four groups which are composed of 9 rabbits; i. Group I [Intrauterine (IU) exposure(-); Extrauterine (EU) exposure (-)], Group II [IU exposure (-); EU exposure (+)], Group III [IU exposure(+);EU exposure(-)], Group IV [IU exposure (+);EU exposure(+)]. The master regulatory enzymes activities of pentose phosphate pathway (glucose-6-phosphate dehydrogenase, G-6PD; 6-phosphogluconate dehydrogenase, 6-PGDH) and glutathione-dependent metabolism (glutathione peroxidase, GSH-Px; glutathione reductase, GR; glutathione S-transferase, GST, thioredoxin reductase, TRx) were analyzed in liver tissues of young female rabbits. Decreased G-6PD, 6-PGD, GSH-Px, GR activities were found in Group III compared to Group I ($p<0.05$, Mann Whitney). Increased GSH-px and TRx activities were found in Group IV compared to Group I ($p<0.05$, Mann Whitney). It can be concluded that the intrauterine and extrauterine exposure to GSM-like RF radiation may influence the liver regulatory enzymes activities.

***Keywords*—**Radiofrequency (RF), intrauterine (IU) and extrauterine (EU) exposure, infant female rabbits.

## I. Introduction

HEALTH risk assessment of Radiofrequency (RF) exposure from childhood to adulthood is one of the most important issues both for scientists and the general public. It is because of the majority of toddlers, preschool-age children (2-5 years) being diagnosed with leukemia in the 20th century [1] Epidemiologic evidences indicate that childhood leukemia may be associated with an increased intensity of exposure to environmental electromagnetic (EM) fields. EM fields that people expose in their daily lives can be classified in two categories as: a) Extremely low frequency (ELF) fields from electrical and electronic appliances and power lines and b) RF fields from mobile phones, base stations and broadcast transmission towers [2] The International Agency for Research on Cancer (IARC) has declared ELF magnetic (B) fields as the possible carcinogenic agent to humans mainly based on epidemiological studies on childhood leukemia [3] However, there is no classification for RF field exposures. Recent epidemiological studies of residential exposure to RF radiation from broadcast transmitters have provided limited information, only for the leukemia incidence rates [4-6], but more information is required about the individual' s exposure [7].

In evaluating the potential health risks of general public exposed to RF radiation, children may be considered as more sensitive group because of their ongoing development process. In the development stages (from conception to adulthood), their brain tissues with high content of water and ions absorb more RF radiation at mobile phone frequencies [8]. Increased intensity and extended duration of exposure to RF radiation during these stages may lead to inherited disorders by altering the conformation of structural molecules. The direct causal relations between RF fields and genetic disorders are still inconsistent because of their insufficient energy level to affect the macromolecular bonds [9-11].

The pentose phosphate pathway (PPP) is an important metabolic pathway in cellular sugar metabolism. This pathway provides ribose for nucleoside synthesis and NADPH for reductive biosynthetic reactions and maintenance of glutathione at reduced state [12]. Protection against free radicals requires maintenance of endogenous thiol pools, most importantly, reduced glutathione (GSH), by NADPH [13]. NADPH is the main source of reducing power in various processes and has enormous physiological significance, including the biosynthesis of L-ascorbic acid, cholesterol, fatty acids, deoxyribonucleotide biosynthesis, and detoxification of xenobiotics, protection against oxidative stress and synthesis of nitric oxide [14]. The two master regulators involved in oxidative part of PPP are glucose-6-phosphate dehydrogenase (G-6PD) and 6- phospho-gluconate

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dehydrogenase (6PGDH). Alterations in the activities of antioxidant enzymes GR, GPx, GST, G6PD and 6PGD may affect cellular defense system. Free radicals and various electrophiles are involved in the etiology of diseases [15].

In the present study, it was aimed to design the intrauterine and extrauterine exposure to GSM-like RF radiation and investigate its effects on the activities of enzymes that are involved in cellular metabolic pathway.

## II. Materials and Methods

### A. Animals

A total 36 New Zealand female white baby rabbits (1-month old) were used in this study. The animals were obtained from the Laboratory Animals Breeding and Experimental Research Center of Gazi University. The experimental protocol was reviewed and approved by the Laboratory Animal Care Committee of Gazi University (G.U.ET-06.027).

Eigtheen of baby rabbits were exposed to 1800 MHz GSM-like RF radiation for 15 min/day during a week in the intrauterine period (between $15^{th}$ and $22^{nd}$ days of the gestational period when the transition from embryogenesis to organogenesis takes place) whereas the others were not exposed. After birth, all of these 36 infant rabbits kept with their mothers until they became 1-month old. They had breastfeeding, and their optimum growth was obtained during this 1-month-period.

Baby rabbits aged 1- month were housed under the same conditions in a temperature and humidity-controlled room (20±1°C, 50 ± 10% relative humidity) and 14-16 h light/dark cycle conditions. The animals were provided with tap water and Standard pelletized food *ad libitum* except during exposure periods.

Only one animal was placed in each cage during each RFR exposure period because placing more than one animal in a cage would create a stress factor.

### B. Exposure Level and Quality Control

GSM like signals in 1800 MHz frequency were formed by using a signal generator (Agilent Technologies 8648C, 9 kHz-3.2 GHz) with the integrated pulse modulation unit and horn antenna (Schwarzbeck, Doppelsteg Breitband Horn antenna BBHA 9120 L3F, 0.5 - 2.8 GHz) in a shielded room. The generated power was controlled by a spectrum analyzer (Agilent Technologies N9320A, 9 kHz-3 GHz) integrated to the signal generator. The signals were amplitude-modulated by rectangular pulses with a repetition frequency of 217 Hz and a duty cycle of 1:8 (pulse width 0.576 ms), corresponding to the dominant modulation component of the GSM.

RFR Generator provided 20 dBm (0.1 W) power during the exposure period. The signal was controlled by means of the spectrum analyzer connected to the signal generator, and NARDA EMR 300 and type 26.1 probe were used for measurement of the output radiation. Measurements were taken during the entire experiment and the data was saved in the computer which was connected to the device via fiber optic cable. The evaluated data was 14 ±0.5 V/m (Figure1).

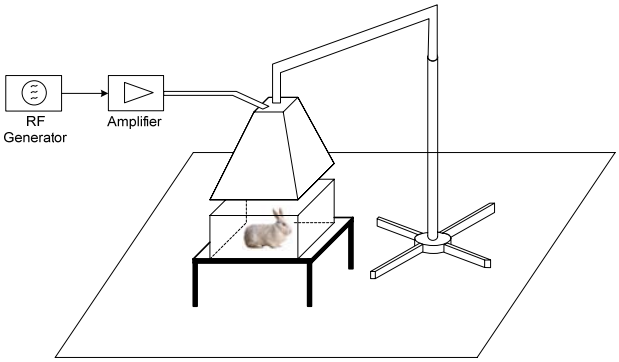


Fig.1 GSM-like RF exposure system

### C. Experimental Design

Thirty-six (1-month old) New Zealand female white baby rabbits were randomly divided into four groups;

Group I [Intrauterine exposure (-); Extrauterine exposure (-)]: Infant rabbits were exposed to 1800 MHz GSM-like RF signals neither in the intrauterine (IU) nor in the extrauterine (EU) periods.

Group II [Intrauterine exposure (-); Extrauterine exposure (+)]: Infant rabbits were exposed to 1800 MHz GSM-like RF signals for 15min/day during a week when they reached 1-month of age.

Group III[Intrauterine exposure(+); Extrauterine exposure (-)]: Infant rabbits were exposed to 1800 MHz GSM-like RF signals for 15min/day during a week in the IU period (between $15^{th}$ and $22^{nd}$ days of the gestational period).

Group IV[Intrauterine exposure(+);Extrauterine exposure (+)]: Infant rabbits were exposed to 1800 MHz GSM-like RF signals for 15min/day during a week both in the IU period (between $15^{th}$ and $22^{nd}$ days of the gestational period) and in the EU period when they reached 1-month of age.

### D. Biochemical Analysis

Liver tissues washed out from contaminating blood with ice-cold sterile physiological saline solution and were placed in liquid nitrogen, where they remained until the procedures for determining enzyme activities. Each sample was then homogenized with an ultra turax homogenizer with S18N-10G probe for approximately 3 min with 3 volumes of 50 mM potassium phosphate buffer, pH 7.4. The homogenate was centrifuged at 105,000 × g for 60 min at 4oC in a Beckman ultracentrifuge (Beckman Coulter, Inc., Fullerton, CA), and supernatants were used for the measurement of enzyme activities.

*E. Chemicals*

Glucose-6-phosphate (G-6-P), nicotinamide adenine dinucleotide phosphate ($NADP^+$), reduced nicotinamide adenine dinucleotide phosphate (NADPH), magnesium chloride ($MgCl_2$), oxidized glutathione (GSSG), sodium phosphate monobasic and dibasic, and Tris [Tris (hydroxymethyl) aminomethane] were obtained from Sigma Chemical (St. Louis, MO, USA) All other chemicals were of analytical grade and obtained from Sigma, USA.

Glutahione-S-transferase assay: Enzyme activity was assayed by measuring the conjugation of reduced glutathione with 1-chloro-2,4-dinitrobenzene, as described by Habig et al. [16]. The 0.5 ml incubation mixture contained 0. 25 ml of 0.2 M sodium phosphate buffer (pH 6.5), 25 µl of 20 mM GSH, 25 µl of 20 mM CDNB, 5 µl supernatant and 195 µl distilled water. Assays were carried out in duplicate and the activities were followed for 30 s. The reaction was linear entire the experimental period.

Thioredoxin reductase assay: Enzyme activity was determined spectrophotometrically by monitoring the NADPH-dependent production of 2-nitro-5- thiobenzoate (extinction coefficient of 13.600 M–1 cm–1) at 412 nm and at 37ºC. The enzyme added to an assay mixture of 100 mM sodium phosphate pH 7.4, 2 mM EDTA, 3 mM DTNB. The reaction is initiated by addition of 0.2 mM NADPH [17]. Assays were carried out in duplicate and the activities were followed for 60 s. The reaction was linear entire the experimental period.

Glutathione peroxidase assay: Each 0.05 ml sample was incubated for 10 min at 37 C in a 0.495 ml incubation mixture containing 0.05 ml of 100 mM potassium phosphate buffer (pH 7.0), 5 µL of 100 mM GSH, 10 µL of 200 mM EDTA, 5 µL of 400 mM sodium azide, 50 µL of 2 mM NADPH, 320 µL distilled water and 50 µL GR (10 U/mL) [18] After the 10 min incubation period, the reaction was initiated by the addition of 5 µL of 10 mM $H_2O_2$. The decrease in the optical density (OD) of the system was measured for 30 s at 340 nm. A similar mixture excluding GSH was used as a blank. One unit of activity (U) was defined the same as for GR.

Glucose-6-phosphate dehydrogenase assay: Enzyme activities were determined spectrophotometrically using an LKB Ultraspec Plus (4054 UV/visible; Cambridge, UK) spectrophotometer, monitoring NADPH production at 340 nm and 37 ºC [19]. The assay mixture contained 10 mM $MgCl_2$, 0.2 mM $NADP^+$ and 0.6 mM G-6-P in 100 mM Tris/HCl buffer, pH 8.0. Assays were performed in duplicate and activities were followed for 60 s. The reaction was linear during this time. One unit (U) of activity was defined as the amount of enzyme required to reduce one mmol NADP+/min under the assay conditions. Specific activity was defined as the number of units/mg protein.

6-Phosphogluconate dehydrogenase assay: 6-Phosphogluconate dehydrogenase activity was measured by substituting 0.6 mM 6-PGA as substrate in the assay mixture given above for G6PD measurement [20].

Glutathione reductase assay: Glutathione reductase activity is determined according to modified Stall method [21]. The incubation mixture contained 100mM sodium phosphate buffer, pH 7.4; 1 mM GSSG; 0.2 mM NADPH; bovine liver GR. Decrease in the absorbance of NADPH at 340 nm is monitored spectrophotometrically, at 37ºC. Assays were performed in duplicate and activities were followed for 60 s. The reaction was linear during this time. A unit of activity (U) is defined as the amount of enzyme that catalyses the oxidation of 1 µmole of NADPH in 1 min under these conditions.

*F. Statistical Analysis*

Data analysis was carried out using the SPSS 11.5 statistical package (SPSS, Chicago, IL, USA). The Kruskal-Wallis (non-parametric) test was applied to evaluate differences among all groups while differences between pairs of groups were evaluated by means of the Mann-Whitney test. The results were expressed as Mean ± Standard Deviation (SD) values.

## III. RESULTS

Glutathione-related enzymes analyzed in this present study, except for GST and TRx activities, were found significantly decreased in Groups III and IV with respect to (w.r.t) Group I ($p<0.05$, Mann- Whitney). There was no difference in GST activity while liver TRx activity increased significantly in Groups III and IV w.r.t Group I ($p<0.05$, Mann- Whitney). Although TRx and GPx activities increased significantly, it was found to decrease in the activities of both G6PD and GR in Group IV w.r.t Group II and Group III ($p<0.05$, Mann-Whitney). The results are tabulated in Table1.

TABLE I EFFECTS OF 1800MHZ GSM-LIKE RF RADIATION ON THE GLUTATHIONE RELATED ENZYME ACTIVITIES

| Groups | GST (U/mg) | TRx (U/mg) | GSH-px (U/mg) | G6PD (U/mg) | 6PGD (U/mg) | GR (U/mg) |
|---|---|---|---|---|---|---|
| I | 23.50 ± 3.14 | 0.069 ± 0.006 | 1.18 ± 0.17 | 0.070 ± 0.004 | 0.076 ± 0.004 | 0.59 ± 0.05 |
| II | 21.62 ± 1.87 | 0.074 ± 0.007 | 1.06 ± 0.12 | 0.075 ± 0.007 | 0.079 ± 0.003 | 0.58 ± 0.04 |
| III | 20.86 ± 2.32 | 0.077 ± 0.006 | 0.98 ± 0.12 | 0.052 ± 0.004 | 0.062 ± 0.003 | 0.46 ± 0.08 |
| IV | 21.28 ± 1.03 | 0.085 ± 0.004 | 1.30 ± 0.15 | 0.063 ± 0.005 | 0.075 ± 0.004 | 0.45 ± 0.02 |

Values of Mean± standard deviation (SD)

I : [Intrauterine exposure (-); Extrauterine exposure (-)]
II: [Intrauterine exposure (-); Extrauterine exposure (+)]
III: [Intrauterine exposure(+);Extrauterine exposure(-)]
IV: [Intrauterine exposure(+);Extrauterine exposure (+)]

## IV. CONCLUSION

The possible bio-effects of short-term exposure to GSM-like signals were examined in both the prenatal and postnatal stages of female rabbits aged 1-month old. The activities of glutathione-related enzymes were analyzed in all experimental

subjects' liver tissues. Our results indicate that RF radiation would be particularly effective in cellular metabolic pathways.

The exponential growth in the use of wireless communication technologies namely, mobile phones and other types of hand-held phones has become one of the most important issues both for scientists and public. Recent studies show that acute or chronic exposure to RF radiation in different frequencies and duration may cause different biological outcomes [22-35]. With respect to the published studies, it is suggested that the effect and the amount of damage caused by radiation are positively correlated with the exposure time [36, 37]. However, the interaction mechanism of RF fields with biological systems is still unclear. Therefore, this unclear issue has still been investigated by scientists with a high performance.

The assessment of RF interaction with the living organism has been characterized by its frequency, polarization, and power density. Besides, interaction mechanisms are mainly based on the absorption of RF energy by biological matter [38]. The energy deposited in tissue by a 900 MHz GSM mobile phone (4 $x10^{-6}$ eV) or by a 1800 MHz GSM mobile phone ($7x10^{-6}$ eV) is far lower than the energy needed to break a chemical bond (1 eV) [39]. In contrary, recent studies showed that some alterations may be observed at the cellular level through the exposure to low frequency RF radiation. These alterations have included the DNA breakages, chromosomal abnormalities, various cell deaths, activation of endogenous chemical products, cellular stresses and the formation of free radicals can be observed [22-35]. The incidences of childhood leukemia, brain tumours, neurological effects, neurodegenerative diseases, immune system deregulation, allergics, inflammatory responses, some behavioural and learning disabilities have also increased due to RF radiation [8].

Whether the exposure to EM fields could affect the development of children has remained unanswered since there are very limited experimental and epidemiological data. However, it is known that children can be considered as the most sensitive group of society and they would be more exposed to environmental toxic agents (drugs, tobacco, radiation, or environmental chemicals) throughout their development stages. Exposure to these environmental toxic agents may lead to the retardations in tissue or organ developments and the other deterministic effects including death, interference with fertility and endocrine function, alterations in sexual maturation, interference with development of the immune system and alterations of neurological development. The evaluation of children's health risks from environmental exposures should be structured, informed, and guided by the best available information on the many factors influencing children's exposures and sensitivities [40].

In the present study, the master regulatory enzymes of Pentose phosphate pathways were analyzed to clarify the biochemical changes associated with RF radiation. An imbalance in the activities of enzymes involved in pentose phosphate pathway, G6PD and 6PGD, alters multiple cell pathways and may contribute to the pathogenesis of many diseases.

## ACKNOWLEDGMENT

The present study was granted from Gazi University Research Foundation, Project No: 01/2005–07.
RF radiation measurements were performed with the devices granted from Gazi University Research Foundation, Project No: 01/2003-62.

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