I. INTRODUCTION

Extremely low frequency (ELF) magnetic field (MF) is a non-ionizing radiation having frequencies up to 300 Hz, which has photon energy too weak to break the atomic bonds. Sources of 60 Hz electromagnetic fields (EMF) were generated from man-made domestic electric devices, electric transport system, etc. [1]. A great increase of the low-frequency EMF occurred from the production, distribution and usage of electricity. Despite the omnipresence of ELF MFs and radio frequency (RF) EMF, there is poor understanding and increasing concerns over their reciprocal actions with biological systems.
tissues and their effects on living organisms. The effects of continued exposure to 60 Hz MF on human beings remain an unresolved issue in biological systems. Without a fundamental understanding of these mechanistic interactions between ELF-MF and organisms, assessment of the potential hazards and benefits on electromagnetic energy will remain challenging. The extrapolation of current results to emerging technologies and different frequency ranges will be nearly impossible. Recently, the safety guidelines of the International Commission on Non-Ionizing Radiation Protection (ICNIRP) indicate that the permissible maximum magnetic flux density for general public exposure is 200 μT [2].

There is increasing evidence about the effect of ELF-EMF on human health and fertility [3]. Exposure to ELF-EMF does not significantly affect implantation and development of a fetus in animal studies. However, it may cause fetus death, congenital anomaly, minor skeletal anomalies and a decrease in the number of female rats impregnated by exposed males [4-8].

The effects of exposure to 60 Hz MF in testicular function are still dubious in the research area. A significant decrease of elongated spermatids was found in exposed 50 Hz at 1.7 mT for 4 hours at 28 days after treatment in mice [9]. However, exposure to ELF-EMF did not induce dominant mutation in the germ cells of male mice [10]. Even though many of these studies often show contradictory results, evidences of adverse effects of ELF-EMF on testicular function were continuously increased in animal studies. It is obvious that the combinational exposure to continuous high-dose MF and long-term period might affect testes, especially by inducing apoptosis of testicular spermatogenic germ cells in mice [6, 11, 12]. Apoptosis of testicular germ cells was influenced by the continuous exposure to 60 Hz MF of 100 μT for 8 weeks or of 14 μT for 16 weeks [11, 12]. Furthermore, the exposure to 60 Hz MF of 14 μT for 16 weeks increased the prevalence of testicular germ cell apoptosis and produced a higher apoptotic rate in mice [12]. Another study showed a consistent decrease in testicular weight, sperm count, sperm motility and morphology exposed to 50 Hz sinusoidal electromagnetic fields of 0.2, 3.2 or 6.4 mT for 2 and 4 weeks in male mice [13].

On the other hand, Ozguner et al. [14] reported that the exposure to 50 Hz EMF at 8.64 mT in Leydig cell can induce cell proliferation and increase testosterone levels and testis weights, while decreasing germ cell populations for 2 hours daily over 10 days in rats. Similar studies revealed that the reduced weight of seminal vesicle and preputial glands, along with decrement of testicular sperm count and testosterone levels scrutinized in adult male rats exposed to 50 Hz of 25 μT MF for 18 consecutive weeks [15]. Hong et al. [16] also observed that DNA strand breakage was induced in testicular cells and abnormal condensation of sperm chromatin structure was increased in mice exposed to 50 Hz of 0.2 mT or 6.4 mT EMF for 4 weeks. However, exposure to a 60 Hz sinusoidal MF of 2 mT for 72 hours or 8 hours of daily exposure for 10 consecutive days did not inflict on any statistically significant differences in meiotic chromosome aberrations in spermatoocytes and any change of sperm morphology in animals [17]. In a pregnant Sprague-Dawley rat study, the continuous exposure to a 60 Hz EMF of 5, 83.3 or 500 μT from day 6 through day 21 of gestation did not affect the spermatogenesis and fertility in the first generation of offspring (F1) [18]. Further, 50 Hz ELF-MF exposure has a significant effect on female sex hormones in rats [19]. Also, mice exposure to 50 Hz MF of 20 mT for 30 minutes per day, three times per week for 2 weeks caused significant decreases in sperm count, motility and daily sperm production and changes in testicular components [20]. It has been reported that Wistar rats exposed to 60 Hz MF of 1 mT three times per day for 30 minutes, between the 13th and 20th day of gestation, showed a decrease volume of testicular components and an increase in connective tissue cells and blood vessels volume [21]. The testicular degeneration was observed in rats exposed to a 60 Hz MF of 1 mT from day 13 of gestation to postnatal day 21 or 90 in three daily applications of 30 minutes [22].

The continuous exposure to a 60 Hz MF for 8 weeks [11] or 16 weeks [12] induced testicular germ cell apoptosis in mice. Also, the apoptotic cells among testicular germ cells were increased duration-dependently at an exposure of 100 μT for 6 and 8 weeks, and dose-dependently at exposures of 20 μT and 200 μT for 8 weeks [23].

Apoptosis or cell death maintains tissue homeostasis. Cell death can occur via extrinsic factors such as infection and toxins and intrinsic factors such as DNA damage and absence of survival factors [24]. The testis showed a high incidence of apoptosis, which is 75% of male germ cells produced are removed through the process of apoptosis. Many factors and molecules are involved in testicular germ cell apoptosis [25]. Several genes, such as Bax, p53, Apaf1 and Fas, are reported to be involved in testicular germ cell apoptosis in mice. Primordial germ cells come from the embryo epiblast and eventually move to the developing gonad. During this event, there are apoptotic cells that show abnormal migration. Surplus cells generated during this period die through apoptosis that is largely reliant on Bcl-Xl and Bax [26]. In Bax knock-out or Bcl-2 or Bclx transgenic mice [27], the early changes of apoptosis are eliminated resulting in the accumulation of spermatogonia and spermatocytes as a result of which the animals are infertile [28]. p53 knock-out mouse testes showed about 50% higher numbers of A1 spermatogonia, which means the enhancement of a differentiating type of spermatogonia pro-
mediated by 60 Hz ELF-MF exposure. Other apoptotic genes. This paper suggests that EndoG was significantly increased by the exposure compared decreased by the exposure. We found that message level of apoptosis was significantly increased and sperm counts were decreased by the exposure. We found that message level of EndoG was significantly increased by the exposure compared with other apoptotic genes. This paper suggests that EndoG may play important roles in testicular germ cell apoptosis mediated by 60 Hz ELF-MF exposure.

II. MATERIAL AND METHODS

1. Animals
Six-week-old Sprague-Dawley (SD) male rats weighing 180–200 g were purchased from Samtako Bio Korea (Osan, Korea). The rats were housed two per cage in a specific pathogen-free (SPF) room maintained at 22°C ± 1°C and 50% ± 5% humidity with an alternating 12-hour light-dark cycle. Although the temperatures of cages with rats were 1.1°C ± 0.4°C higher than that of the room inside the animal facility, the amount of MF did not affect the temperature of the cages at all. Food was available ad libitum. After a week of acclimation and quarantine, the rats were randomly divided into the sham and exposure groups. This study was conducted under guidelines for the usage and care of laboratory animals and approved by the Institutional Animal Care and Use Committee of the Experimental Animal Center of Hallym University, Chuncheon, Korea.

2. ELF-MF Exposure System

2.1 Numerical analysis
For the application of ELF-MF exposure systems, we implemented numerical calculation using Biot-Savart Law and designed the device of two orthogonal directional ELF-MF exposure systems with two parallel planes for exposure to animals. In this experiment, we used only horizontal coils for exposure to rats to get transverse MF direction anatomically to simulate human transverse MF exposure under power lines. The dimensions of the horizontal coils, generation of 200 µT ELF magnetic flux density and bucking mode for sham were described previously [23].

2.2 Implementation and measurement
To generate 200 µT MF densities, the MF exposure systems were assembled following the parameters above on the planes in the systems. Rats were housed in uniquely designed non-metallic polycarbonate cages and covers equipped with water bottles and glass nozzles (JD-C-01; Jeung Do Bio & Plant, Seoul, Korea). MF intensity on the planes was numerically determined. The cages should be within 800 mm × 800 mm on the plane for ±10% exposure tolerance. The deviation of measured values of each point at 9 points on the upper and lower planes was less than 5% at 200 µT. Slidac (Daekwang Electronic, Seoul, Korea) and automatic voltage regulators (AVR-HSA100A; Hysung Electric ENG., Seoul, Korea) were used for generating a 60 Hz ELF MF. The magnetic flux densities were measured with HI-3604 system (Holaday Industries, Cedar Park, TX, USA). The Earth MF at the laboratory was 50.1 µT at latitude 37°85′24″N and longitude 127°74′43″E, Hallym University in Chuncheon, Korea which was gauged with GSM-19 Overhauser magnetometer (GEM Systems, Toronto, Canada).

3. Animal Exposure to MF - Experimental Design
Six-week-old SD male rats weighing 180–200 g were sequentially divided into two groups by body weight. The 12 rats in each group were housed in six cages with two rats per cage. The experimental group was exposed to 60 Hz MF at 200 µT for 24 hr/day (except for 3 hours per week for management) for 20 weeks, and the sham operated group was exposed to MF energized in a bucking mode as the control. The cages were sequentially relocated every week. The body mass of all animals was examined every week. The rats were sacrificed at the end of exposure. Epididymes and testes of each animal were excised, weighed and immediately fixed with formalin. The fixed organs were embedded with paraffin for further histochemical experiments. The noise from the exposed cage had no effect on the rats during 60 Hz exposure.

4. Detection of Apoptotic Cell Death in Testis by TUNEL Staining
In situ terminal deoxynucleotidyl transferase mediated deoxy-UTP nick end labeling (TUNEL) staining was performed
to assess apoptotic cells in testis using the *in situ* apoptosis detection kit (Takara, Shiga, Japan) as described in a previous study [12]. The paraffin-embedded tissues were used for staining. TUNEL staining was performed according to manufacturer’s protocol. Cells that stained an intensely dark brown color were designated as TUNEL positive. TUNEL-positive cells were counted in 50 seminiferous tubules under a BX51 light microscope (Olympus, Tokyo, Japan). Hematoxylin and eosin (H&E) staining was performed to show general morphology of cell and tissue.

5. Sperm Count
The cauda epididymis of the right testis was eliminated, weighed and homogenized in a 50 mL conical tube containing 10–20 mL of distilled water. The sperm were counted and the total number of sperm per caudal epididymis was counted.

6. Examination of Apoptotic Genes in Testis using RNA Preparation and RT-PCR
After 20 weeks of exposure to 60 Hz at 200 μT, the testis was isolated for extracting total RNA. Using TRIZOL (Invitrogen, Waltham, MA, USA) reagent, the testis was homogenized and isolated following manufacturer’s protocol. Isolated RNA was stored in RNase-free water for further use. Isolated RNA was reverse transcribed to make cDNA for real-time polymerase chain reaction (PCR). Using FastLane Cell cDNA Kit (Qiagen, Hilden, Germany), cDNA was synthesized from 10 μg of total RNA as template, 1 μL of RT primer mix, 4 μL of QuantiScript RT Buffer (5×) and QuantiScript RT Master Mix. Synthesized cDNA was used as template for real-time PCR. For real-time PCR, QuantiTect SYBR Green PCR Kit (Qiagen) was used. Primer was synthesized from Qiagen, Germany, using QuantiTect Primer Assay. Sizes of each of the genes used were as follows: GAPDH (149 bp), p53 (80 bp), Bax (183 bp), Bcl-2 (80 bp), caspase-3 (115 bp), AIF (apoptosis-inducing factor: 75 bp) and EndoG (85 bp). The real-time PCR reaction mixture is 10 μL of QuantiTect SYBR Green PCR Master Mix (2×), 2 μL of primer, 1 μL of cDNA, and 7 μL of RNase-free water. PCR reaction was performed using Rotor-Gene Q (Qiagen) as follows: denaturation (95°C, 15 minutes; 94°C, 15 seconds), annealing (51°C, 30 seconds), and extension (72°C, 30 seconds) for 45 cycles. The result was analyzed with the Rotor-Gene 6 program.

7. Statistical Analysis
Statistical analyses were executed by one-way analysis of variance (ANOVA) with post-Bonferroni multiple comparison tests using GraphPad Prism software version 4.0 for Windows (GraphPad Software, San Diego, CA, USA). Differences were considered as significant if *p*-value <0.05. All values were expressed as the mean ± SE. Chi-square tests were analyzed to evaluate the data.

III. RESULTS

1. Continuous Exposure to 60 Hz at 200 μT Does not Affect Rat’s Body Weight and Testicular Mass
Body mass of animals was recorded every week for 20 weeks (data not shown), and testes were weighed after the end of exposure (Table 1). There were no significant effects on the body weight of the exposed group compared with the sham control group. In addition to body weight, the continuous exposure to 60 Hz MF did not affect the testicular mass compared to the sham control (Table 1). These results indicate that continuous exposure to 60 Hz MF did not affect the body and testicular masses of the rats as in previous reports on mice [11, 12, 23].

2. Continuous Exposure to 60 Hz MF Effects Testicular Germ Cell Apoptosis and Sperm Behaviors
To investigate the effect of the MF on the male reproductive system, rats were exposed to 60 Hz at 200 μT for 20 weeks and apoptotic cells were examined with a TUNEL assay. A significant increase in the number of TUNEL-positive cells existed in seminiferous tubules in rats exposed to 200 μT (Table 2). The apoptotic cells were mostly detected in spermatogonia, which are testicular germ cells placed on basement membrane. Apoptotic cells are characterized as condensed chromatin, shrinkage of cytoplasm and presence of apoptotic bodies. TUNEL-positive cells per seminiferous tubule significantly increased in exposed rats (*p*<0.001). The total number of sperm in a cauda epididymis was counted after 20 weeks of exposure (Table 3). The total number of sperm in the epididymis of rats was significantly decreased in the exposed group compared with the sham control group. However, continuous exposure to MF did not affect sperm movement or ratio of abnormal sperm (Table 3). Taken together, these results indicate that an increased number of apoptotic testicular

Table 1. Testicular weight after continuous exposure to 60 Hz magnetic field

| | Sham | 200 μT |
|---|---|---|
| Average (g) | 1.905 | 1.941 |
| Standard deviation | 0.112 | 0.153 |
| Standard error | 0.038 | 0.048 |
| *p*-value | - | 0.562 |

No significant differences were found between sham control and exposed group (*p*<0.05). Standard error for comparing sham and exposure control (n = 12).
Table 2. Number of apoptotic cell in testicular germ cell after continuous exposure to 60 Hz magnetic field

|                  | Sham  | 200 μT |
|------------------|-------|--------|
| Apoptosis (cell number) | 0.20  | 0.73   |
| Standard deviation   | 0.088 | 0.301  |
| Standard error       | 0.250 | 0.100  |
| p-value             | -     | 0.001  |

The significant difference was the increase in the numbers of apoptotic cells in the exposed group (p<0.001 vs. sham). Standard error for comparing sham and exposure control (n=12).

Table 3. Statistical analysis of sperm after continuous exposure to 60 Hz magnetic field

|                  | Sham   | 200 μT |
|------------------|--------|--------|
| Sperm count (10^7) | 12.15 ± 3.31 | 8.03 ± 1.67* |
| Sperm movement (%) | 99.2 ± 4.2  | 92.3 ± 3.0      |
| Abnormal sperm (%) | 3.9 ± 3.6   | 7.4 ± 7.8       |

Data are presented as mean ± standard error.

There were no significant effects on the mobility and the morphological abnormality of sperm. The significant difference was the decrease in the numbers of sperm in the exposed group. Standard error for comparing sham and exposure control (n=12).

* p<0.01.

3. EndoG Is Induced by MF Exposure

To further investigate the apoptotic gene expression in continuous exposure to MF in rat, testes were isolated and RNA was extracted from the tissue.

Integrity of total RNA was examined in agarose gel (Fig. 1(a)). Total RNA was extracted and the amount of RNA was similar in the exposed group and the sham control group. The expression level of each message was examined with RT-PCR. cDNA from mRNA was amplified with PCR and quantified the relative level of mRNA. As shown in Fig. 1(b), EndoG mRNA was significantly induced by the continuous exposure to MF. However, anti-apoptotic gene Bcl-2 and pro-apoptotic genes including p53, Bax, capase-3, and AIF are not affected by continuous exposure to 60 Hz MF. These results suggest that testicular germ cell apoptosis might be a caspase-independent and EndoG-dependent process.

IV. DISCUSSION

We previously reported that continuous exposure to 60 Hz of 0.1 or 0.5 mT for 8 weeks, 14 μT for 16 weeks and dose- and duration-dependent treatment in mice significantly activates apoptotic cell death of testicular germ cells, which was detected by TUNEL staining [11, 12, 24]. The ICNIRP safety guideline indicates that the permissible maximum magnetic flux density for general exposure is 200 μT [2]. In the present study, we further examined the expression of apoptosis-related genes after continuous exposure to MF at 200 μT for 20 weeks in rats. The continuous exposure to 60 Hz at 200 μT does not affect body weight and testicular mass. However, similar to previous studies in mice, the testicular germ cell apoptosis and sperm count were significantly changed in the exposed group. This process may also be related to EndoG expression.

Apoptosis is an essential process for regulating both the size and the quality of germ lines. However, the mechanistic process of germ cell apoptosis is not well understood. One of reasons for germ cell death is a shortage of gonadotropin or testosterone [33]. Previous study demonstrated that exposure to 60 Hz ELF MF for 16 weeks did not significantly affect testosterone levels. Interestingly, testicular germ cell apoptosis appeared mainly in spermatogonia [11]. These findings suggest that the apoptotic pathway is strictly regulated and there is a possibility that a certain spermatogenic stage or germ cell type might be more vulnerable to ELF MF. Spontaneous apoptosis is most commonly observed in spermatocytes, less
frequently in spermatogonia, and seldom in spermatid in mice [34, 35]. Those results suggested that germ cell apoptosis induced by ELF MF may not be hormonally mediated. Kato et al. [36] reported that continuous exposure to circularly polarized 50 Hz magnetic fields of 50 μT for 6 weeks did not affect the plasma testosterone level in rats. In other report, exposure to a 50 Hz magnetic field of 5 mT had no effect on the testosterone level of rats for periods of 1, 2, and 4 weeks [37]. However, the effects of ELF MF on the serum testosterone level are contradictory among various studies. The disagreement in results might be due to the variation in exposure conditions, the time and intensity of exposure and the animals tested.

The process of apoptosis involves reduction of cell volume, chromatin condensation and margination and formation of apoptotic body [38]. In a previous study [12], the degeneration of spermatogonia showing condensation of nuclear chromatin was found at apoptosis induced by 60 Hz MF. Also, we observed that apoptosis of phagocytic Sertoli cells appeared in exposure groups. It can be suggested that exposure to MF may be related to the activation of apoptosis without decreasing testis mass, and then the disruption of seminiferous tubule organization. The apoptotic pathway induced by ELF-MF is tightly regulated at a certain spermatogenic stage, and therefore, a germ cell type might be more vulnerable to MF.

In our result, testicular weight is not affected by MF exposure. However, testicular germ cell apoptosis and sperm counts were affected by continuous exposure to MF. p53 was related to radiation-induced cell death in the mouse testis [39, 40]. These results suggest that spermatogonia are sensitive to irradiation in mice. p53 protein was not detected in testicular germ cells (spermatogonia). However, p53 protein was induced in γ-irradiated testicular germ cells (spermatogonia) and decided the cell fate as check-point protein [41]. The increased cell death was shown in p53-dependent and caspase 3-dependent manners [42]. EndoG is a nuclear-encoded mitochondrial nuclease reported to be important for both nuclear DNA fragmentations during apoptosis and mitochondrial DNA replication [30, 31]. One report suggested that spermatocytes, round spermatids and bone-marrow cells had normal, fast repair of single-strand breaks (SSBs) when compared with the repair reported for cultured rodent cells and human lymphocytes. In contrast, the elongated spermatids showed hardly any SSB repair. The round spermatids hardly repair the base damage (BD) within the first hour after irradiation, but at 7 hours only a small amount of BD could be detected. In elongated spermatids repair of BD could not be measured due to a high background level of this type of damage. The substantial loss of repair capacity showed during passage through the different stages of spermatogenesis. This loss manifests at an earlier stage for the more complicated repair of BD than for the repair of SSB [43]. A recent report indicates that EndoG requires disappearance of the male mitochondria during the spermatids’ development in Drosophila [44]. Another report showed that EndoG homozgyous mutant embryos die between embryonic day 2.5 and 3.5. Mitochondrial DNA copy numbers in ovulated oocytes from EndoG heterozygous mutant and wild-type mice are similar, suggesting that EndoG is involved in a cellular function unrelated to mitochondrial DNA replication. Furthermore, spontaneous cell death of spermatogonia in EndoG heterozygous mutant mice is significantly reduced compared with wild-type mice. These results indicate that EndoG is essential during early embryogenesis and plays a critical role in normal apoptosis and nuclear DNA fragmentation [32].

In this study, we elucidate the testicular germ cell apoptosis by 60 Hz EMF-MF exposure in rats. Furthermore, we suggest that this apoptosis is regulated by EndoG. We need to further scrutinize the mechanism of EndoG function in EMF-MF-induced testicular germ cell apoptosis (Fig. 2).

![Fig. 2. Proposed model of 60 Hz induced testicular germ cell apoptosis. 60 Hz induced testicular germ cell apoptosis might be mediated by a caspase-independent pathway through mitochondrial protein, endonuclease G (EndoG).](image)

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