Ultrastructural Studies On The Effect Of Electromagnetic Field On The Liver Of Albino Rats (*Rattus Norvegicus*)

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Abstract: The aim of the present study was to study the effect of long-term exposure of rats (1 hour per day, 3 days weekly for 4 weeks) to either static or time varying magnetic fields of induced flux densities 2 mT (millitesla) =20G (Gauss) , on the ultrastructure of liver tissue. One hundred and ten male rats were divided into three main groups. Animals of the first group (10 rats) were not exposed to the magnetic field and represented the control group. The second group (50 rats) was exposed to static magnetic field (direct current) at strength of 2 mT. The third group (50 rats) was exposed to alternating magnetic field (alternating current) at strength 2 mT. The results revealed structural irregularity in hepatocyte nuclei as the most prominent ultrastructural change in the liver of treated groups. This was manifested as irregularity of nuclear membranes, widening of the nuclear pores and heterogeneous distribution of the chromatin material. Furthermore, swelling and clumping and deformation of mitochondria were observed in the groups exposed to the magnetic field. In addition, the rough endoplasmic reticulum appeared with marked dilation and the lysosomes appeared distorted.
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1. Introduction

In recent years, there has been a great deal of publicity concerning the possible health effects of magnetic fields; however, there is still very little understanding of the interaction mechanisms between magnetic fields and living matter. Nowadays, a new discipline, which can be called **"magneto biology"** is taking shape (**Genva & WHO, 1987; 1989a; 1989b**).

The concern about the possible harmful effects of electro-magnetic fields (EMFs) on human health has led to a growing interest in the influence of EMFs on life processes and their interaction with cells, organs **,** and embryonic development (**Brent, 1999**).

The most common frequencies in the environment are 50 and 60 Hz, since these frequencies are used in the transmission of electricity (**Coleman *et al*., 1988; Bernhardt, 1991**). Therefore the question arises as to whether fields of similar intensity environmental radiation, e.g. by high power electric lines may influence animals and humans.

It was reported that 60 Hz affect normal development of chicken, hormone levels and circadian rhythmicity in rats, reproduction and development of rats and mice nervous system and decreased resistance of mice against cancer cells (**Marino, 1990**). Exposure to 60HZ magnetic fields was also found to affect cellular processes related to proliferation and tumor promotion (**Frazier *et al.*, 1990; Hori *et al*, 2005**). The reported effect of EMF on cellular activity was reported as due to structural and functional activities of cell membranes leading to intracellular mobilization of intracellular calcium ions (**Tonini *et al.* 2001**).

Changes in cell structure and function was also suggested as due to liberation of free radicals in cells and tissues exposed to EMF (**Zsont *et al*., 2004**). Liberation of free radicals was reported to cause changes in cell surfaces micromorphology in a variety of cells following radiation. These include changes number and size of microvilli, development of surface blebs, membrane ruffling and retraction of pseudopods (**Somosy 2000)**. Free radicals also increased the number and fraction volume of lysosomes in the cells and elevated lysosomal enzyme activity (**Hamberg, 1983; Piao *et al.*, 1983**).

Free radicals and reactive oxygen species result in alterations in the structure and function of mitochondria (**Kergonou *et al.*, 1981; Erickson & Koppenol, 1987**). Elongation and branching of the mitochondria, and a marked increase of their size and the development of giant forms were the most frequently reported changes (**Maeda, 1982; Betzold *et al.*, 1992**). Vacuolization of mitochondria and disruption of their outer and inner membranes were also frequently observed (**Rene´ & Evans, 1970; Yago *et al*., 1972; Shen *et al*., 1989; Kim and Shin, 1994**).

Excessive liberation of free radicals caused dilatation, vesicularization, and fragmentation of the endoplasmic reticulum cisternae and degranulation of RER membranes in a wide varity of cells (**Skog *et al*.,**

1983; Rosen *et al.*, 1989; Mukerjee & Goldfeder, 1974; Skog *et al.*, 1983).

Liver is a very important organ for the healthy and lasting life of mammals. EMF induced liberation of free radicals and reactive oxygen species can induce liver disease (**Muriel, 2009**).

The aim of the present study, the effect of two electromagnetic fields on the rat liver mainly at the ultrastructural level.

2. Material and Methods

One hundred and ten male albino rats (*Rattus norvegicus*) were used in the present study. These animals aged approximately 2½ - 3 months with an average weight 140 -180 gm . The rats were kept in well ventilated cages at room temperature; and fed on a balanced diet, while water was allowed *adlibitum.*

The animals were divided into three main groups according to the type of the magnetic field induced:

Group I: Control group (10 rats)

Animals of this group were not exposed to magnetic fields.

Group II: Direct current magnetic field-treated group (50 rats)

The animals were exposed to static magnetic field (direct current DC) , at strength 2 mT (milli tesla) = 20G (Gauss), 50 Hz (Frequency) at 2V (Volt), and 0.6A (Ampere); for one month (Exposure period) , three days a week ,day after day for one hour in each exposure. The animals of this group were subdivided into 5 subgroups each included 10 animals:

Subgroup One (GR1/DC): Animals of this group were sacrificed after 1 day following the end of exposure period.

Subgroup Two (GR2/DC): Animals of this group were sacrificed after one week following the end of exposure period.

Subgroup Three (GR3/DC): Animals of this group were sacrificed after two weeks following the end of exposure period.

Subgroup Four (GR4/DC): Animals of this group were sacrificed after one month following the end of exposure period.

Subgroup Five (GR5/DC): Animals of this group were sacrificed after two months following the end of exposure period.

meter. voltage and current were monitored with a voltmeter.

Group III: Alternating current magnetic field-treated group (50rats)

Rats were exposed to alternating magnetic field (alternating current AC) , at strength 2 mT (millitesla) = 20G (Gauss), 50Hz (Frequency) at 43V (Volt), and 1.28A (Ampere) for one month (Exposure period), three days a week, day after day, one hour for each exposure. Animals of this group were also subdivided into 5 subgroups each includes 10 animals:

Subgroup One (GR1/AC): Animals of this group were sacrificed after 1 day following the end of exposure period.

Subgroup Two (GR2/AC): Animals of this group were sacrificed after one week following the end of exposure period.

Subgroup Three (GR3/AC): Animals of this group were sacrificed after two weeks following the end of exposure period.

Subgroup Four (GR4/AC): Animals of this group were sacrificed after one month following the end of exposure period.

Subgroup Five (GR5/AC): Animals of this group were sacrificed after two months following the end of exposure period.

Effects and exposure technique to different magnetic fields

Static Magnetic Field

An artificial electromagnet apparatus that generates electromagnetic field (EMF) constructed in the Department of Physics, Faculty of Science, Benha University, was applied. The animals were kept in a perforated glass box (5 rats per time), placed in between two poles , each pole was attached to coil which had 1000 turns of the apparatus, connected with DC unit (stabilizer). A horizontal magnetic induction was applied to the whole body of the animal.

Alternating Magnetic Field

The Electromagnetic field (EMF) applied in this study was generated by an artificial Hilm-Holtiz Coil constructed in the Department of Zoology, Faculty of Science, Benha University. The animals were kept in a perforated glass box, (5 rat per time), placed in between two coils, each coil contained 348 turns of the apparatus and connected with AC unit (varic). Then, a horizontal magnetic induction was applied to the whole body of the animal. The field strength in both cases was monitored with a gauss

Electron microscopy

For electron microscopy examination, small pieces of the liver (1mm) were cut and immediately fixed in 2-4 % cold phosphate buffered

glutaraldehyde (**Dawson *et al.*, 1969**) or in cacodylate buffered 2.5% glutaraldehyde solution at pH 7.4 for 2-4 hours (**Sobatini *et al.*, 1963**). Following fixation, the specimens were washed thoroughly at 4°C in three changes of 0.1 N of the buffer solution and then post-fixed in 1% osmium tetra oxide in phosphate buffer for 2 hours (**Millonig, 1961**), dehydrated and embedded in epoxy resin (Epikote 812). Ultra-thin sections were stained with alcoholic uranyl acetate followed by lead citrate and then examined using a transmission electron microscope (JOEL).

3. Results

Control group

Figure (1) represents an electron micrograph of a section in liver of control group. Some hepatocytes are binucleated. The nucleus contains one or two nucleoli. The cytoplasm is completely filled with cell organoids. The mitochondria are numerous and distributed all over the cytoplasm. Rough endoplasmic reticulum, Golgi bodies and some lysosomes are evident. Blood sinusoids including red blood cells and surrounded by endothelial cells, Kupffer cells and fat storing hepatic stellate cells can also be observed.

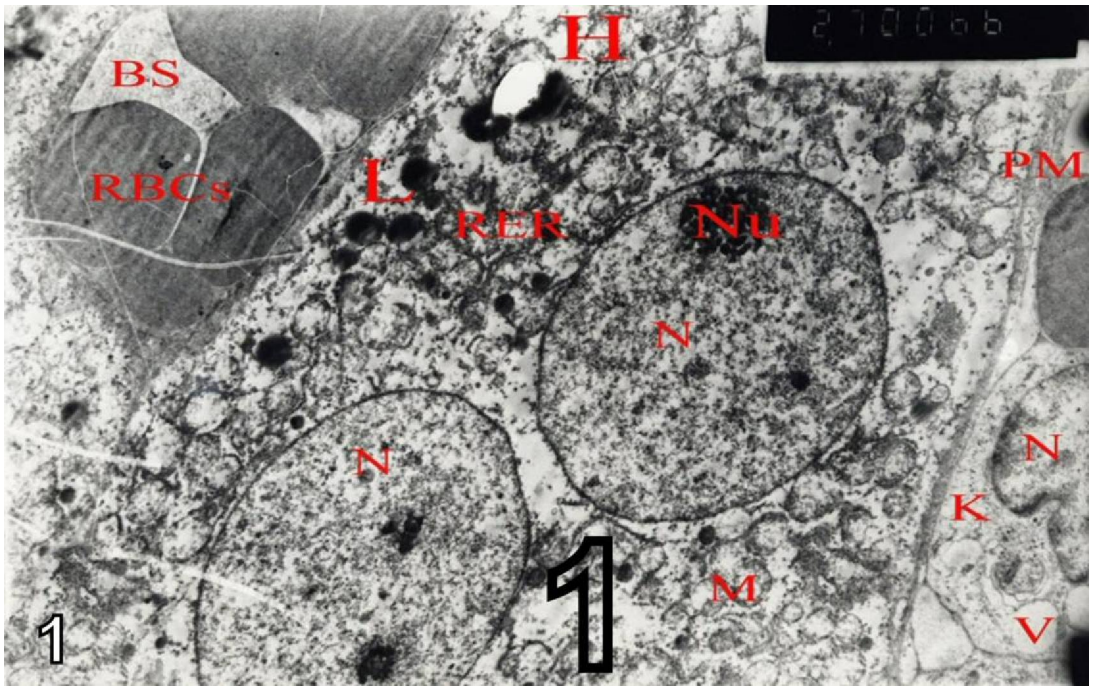


Figure 1. Electron micrograph of a control rat liver showing hepatocytes (H), plasma membrane (PM), double intact nuclei (N), the nucleoli (Nu), scattered mitochondria (M), rough endoplasmic reticulum (RER), numerous lysosomes (L). A blood sinusoid(BS), red blood cells (RBC). (X2700).

One day post-exposure group

Cell injury prevails with different degrees in this group (Figure 2). While cellular changes in the direct current group were in the form of dilatation in RER cisternae (Figure 2A), injury was more rigorous in alternating current group (Figur 2B). In the latter group, the nucleus was indented. Several vacuoles appeared in a swelled cytoplasm. Cell organoids formed cytoplasmic aggregations.

One week post exposure groups

After one week of direct current exposure, some cells appear undergoing apoptosis. Other cells, however appear normal (Figure 3A). The apoptotic cells have foamy cytoplasm and separate apoptotic bodies. Lysosomes appear in both apoptotic cells and apoptotic bodies. In alternating current group (Figure 3B), some nuclei appear enlarged with pale chromatin, showing karyolysis as a sign of necrosis. More signs of cell injury such as fragmentation of rough endoplasmic reticulum are also evident.

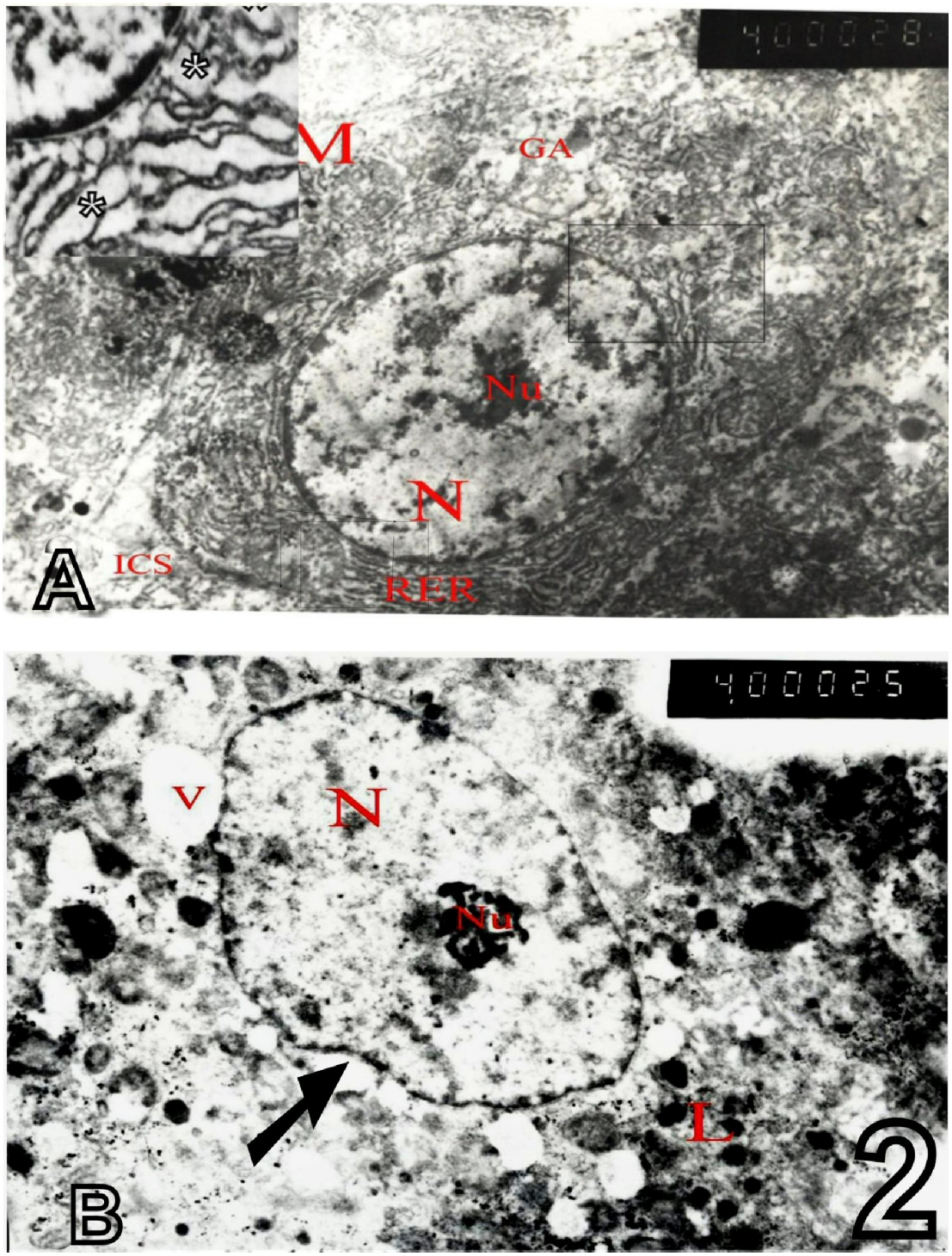
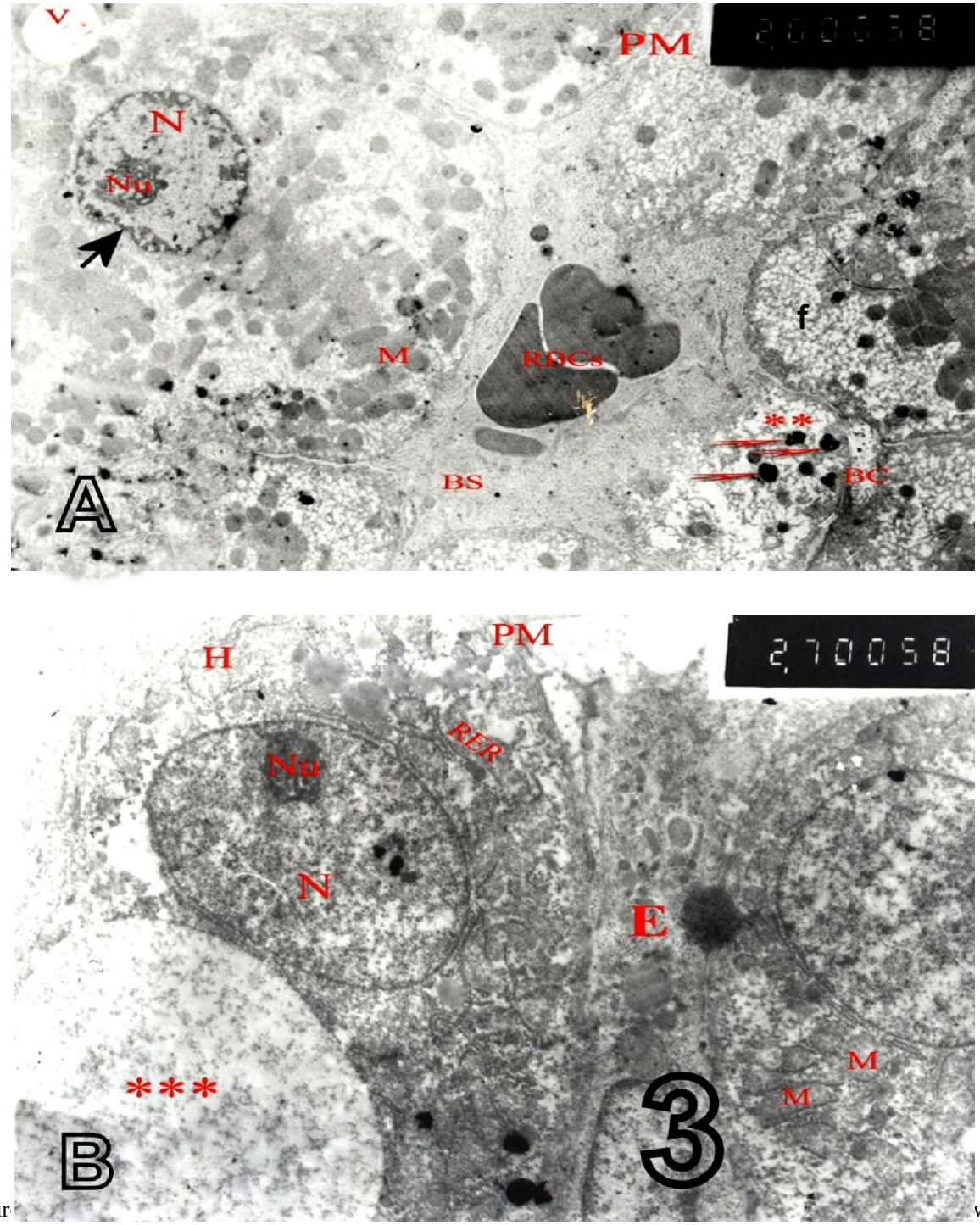


Figure 2. EM of liver after one day following the end of (A) direct current magnetic field exposure, and (B) alternating current magnetic field exposure. (A)showing hepatocyte with smooth contoured nucleus (N) with some clumped heterochromatin, one nucleolus (Nu), vacuoles (V) and many lysosomes (L). (X 4000) The insert at the upper left corner demonstrates a higher magnification (X800) of the RER. Notice the dilated cisternae (*). (B) showing a hepatocyte with indented (arrow) nucleus (N) with one nucleolus (Nu), vacuoles (V) and many lysosomes (L) in an area of aggregated organelles. (X 4000).



Figur wing hepatocytes (H) , plasma membranes (PM), indented (arrow) nucleus (N) with clumped large nucleolus (Nu), mitochondria (M), vacuole (V)& numerous lysosomes (arrows) in apoptotic bodies (**), hepatocytes with foamy cytoplasm (f) blood sinusoid (BS) with red blood cells (RBCs) (X 2000). (B) alternating current magnetic field exposure showing hepatocytes (H) with plasma membranes (PM), a nucleus (N) with an eccentric large nucleolus (Nu), ballooned pale nucleus (***), mitochondria (M) & fragmented rough endoplasmic reticulum (RER) and endothelial cell (E). (X 2700).

Two weeks post exposure groups

After two weeks of exposure to direct current magnetic field, some cells show signs of swelling of the cytosol and clumping of the organelles (Figure 4A). On the other hand, signs of hydropic degeneration appear in hepatocytes of the alternating current magnetic fields exposed group (Figure 4B). Signs of chromatin fragmentation and nucleolar margination suggest the onset of necrosis. The cytoplasmic organelles are relatively few with signs of cytoplasmic swelling.

One month post exposure groups

After one month, signs of hepatocyte recovery appear in the direct current exposed group (Figure 5A). Mitochondria are numerous and evenly distributed in the cytoplasm. The rough endoplasmic reticulum is well developed and sequesters mitochondria. On the other hand, hepatocytes from alternating current exposed rat liver, showed several signs of cell injury (Figure 5B). Swelling of the cytoplasm, loss of cell organoids and karyolysis are demonstrated in cell of this group. There is increase appearance of fat storing (hepatic stellate) cells.

Two months post exposure groups

After two months of exposure, the direct current group showed normal hepatocyte structure (Figure 6A). Signs of recovery appear in the hepatocytes of alternating current exposed rat hepatocytes (Figure 6B). The distribution and number of mitochondria is similar to control.The nuclear chromatin and nucleoli suggest biologically active state. There are hepatic stellate cells. However, fibrosis was evident as collagen fibers were detected in sections (see insert of figure 6B).

4. Discussion

The increasing use of electric power for domestic and industrial appliances has resulted in the exposure of many millions of daily users, in homes and work places, to a complex mix of artificially elevated electromagnetic fields (EMF) that span a wide frequency range. The recent concern about the possible harmful effects of magnetic fields (MFs) on human health calls for continuous research on the influence of MFs on life processes and their interaction with organ tissues and cells.

Liver was used in this study because it is an organ with high iron content (**Ngelucci, 2010**). This makes the liver more susceptible to the effects of magnetic fields (**Yoshikawa, 2000**). Its susceptibility is due to increased liberation of free radicals by electromagnetic fields (EMF); because iron is closely involved in free radical formation from hydrogen peroxide, when exposed to EMF, via the Fenton reaction, in cells (**Meneghini, 1997**).

Hepatocytes from the liver of animals exposed to direct or alternating current magnetic fields for one hour every day, 3 days a week for 1 month were examined by electron microscopy after 1day, 1 week, 2 weeks, 1 month and 2 months.

After one day of last exposure, the signs of cell injury were milder in direct current exposed animal hepatocytes than those exposed to alternating current. Such a difference has been previously suggested in several reports (**Tabrah, 1978; Adey, 1979**).

In the direct current group, the injury of the cells was manifested as dilatation of the cisternae of rough endoplasmic reticulum. Although such a change was reported as an early sign of cell death (**Kazunobu, 2004**), it could result from the effect of abnormal osmotic force (McGee 1992). Such osmotic changes may be due to the effect of EMF on membrane permeability (**Ghadially, 1982**).

In hepatocytes from animals exposed to alternating current EMF, the nucleus was indented. Several vacuoles appeared in a swelled cytoplasm. Cell organoids formed cytoplasmic aggregations. Such features were reported in necrotic hepatocytes (**Reynolds & Moslen, 1984**).

After one week of exposure to direct current EMF, apoptotic cells with foamy cytoplasm and separate apoptotic bodies were observed in the electron micrographs. Lysosomes appeared in both apoptotic cells and apoptotic bodies. The ballooning of hepatocytes is one of the earliest, most frequent, and most conspicuous changes seen in liver injured by CCl4 administration. It is also observed in such conditions as viral infection, alcoholic hepatitis, biliary obstruction, starvation, choline deficiency, hypoxia, scurvy, yellow fever, and radiation injury (**Phillips, 1987**). Although the relationship between the ballooning changes and necrosis and the fate of the ballooned hepatocytes have long been debated, the conventional explanation of cell ballooning is that it is a forerunner of necrosis (**Alison, 1994; Shi, 1998**). However, evidence was reported based on electron microscopy and immune-histochemistry that ballooning and foamy cytoplasm is a feature of hepatocyte apoptosis (**Shi, 1998**). The presence of apoptotic bodies in the electron micrographs of the present study demonstrates the apoptotic cell death in direct current exposed animal hepatocytes.

In hepatocytes from animals after one week of exposure to alternating current, some nuclei appeared enlarged with pale chromatin, showing karyolysis. More signs of cell injury such as fragmentation of rough endoplasmic reticulum are also evident.

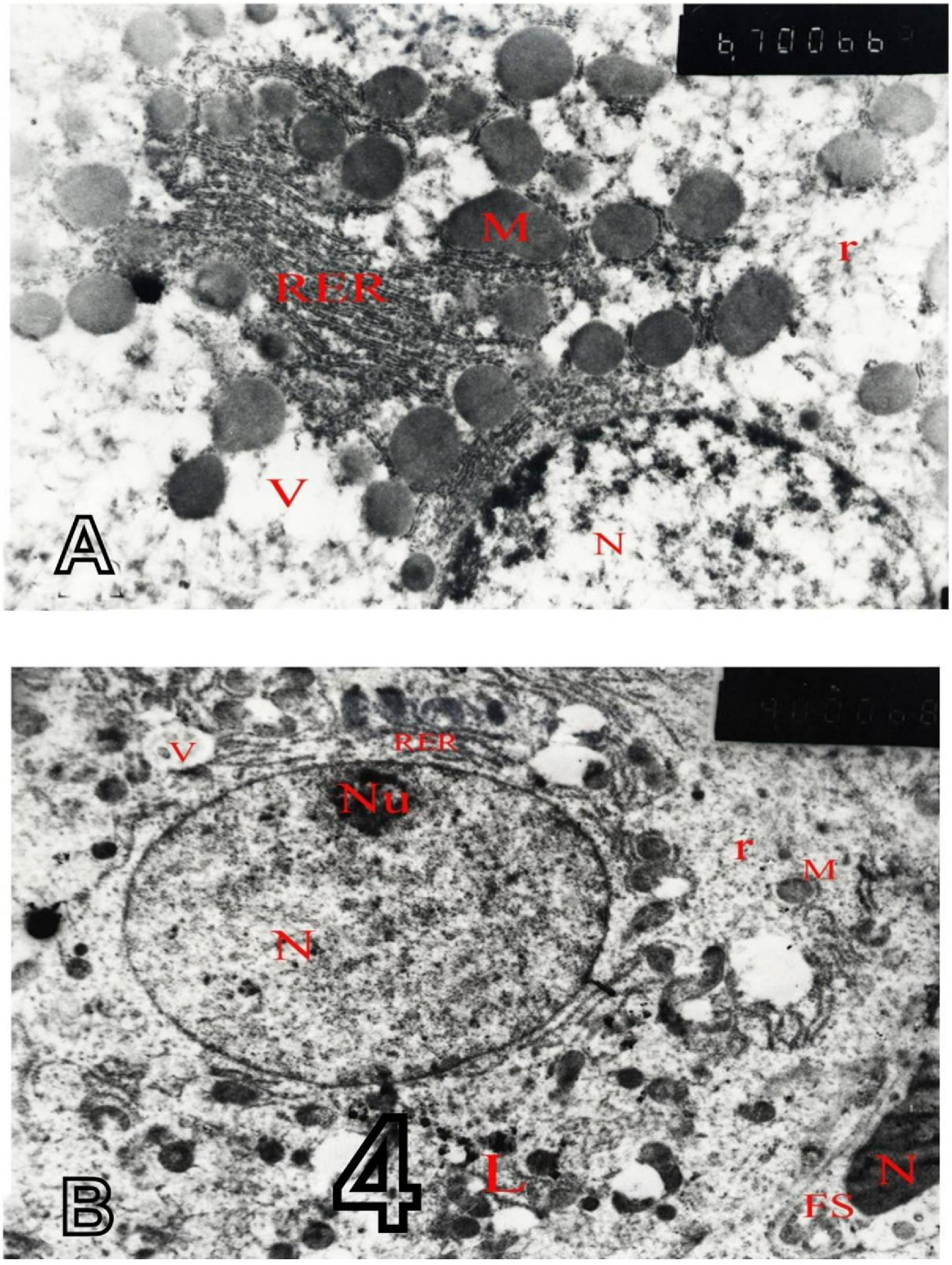


Figure 4. EM of rat liver dissected after two week following the end of (A) direct current magnetic field exposure showing hepatocyte with sighns of swelling, has a nucleus (N) with somewhat clumped heterochromatin, mitochondria (M), packed rough endoplasmic reticulum (RER) & vacuole (V) clumped at one pole of the nucleus. (X 6700). (B) alternating current magnetic field exposure showing a hepatocyte with an eccentric large nucleolus (Nu) in the nucleus (N), few scattered mitochondria (M), rough endoplasmic reticulum (RER), vacuoles (V), and numerous lysosomes(L).Signs of hydropic degeneration are also observed. (X 4000).

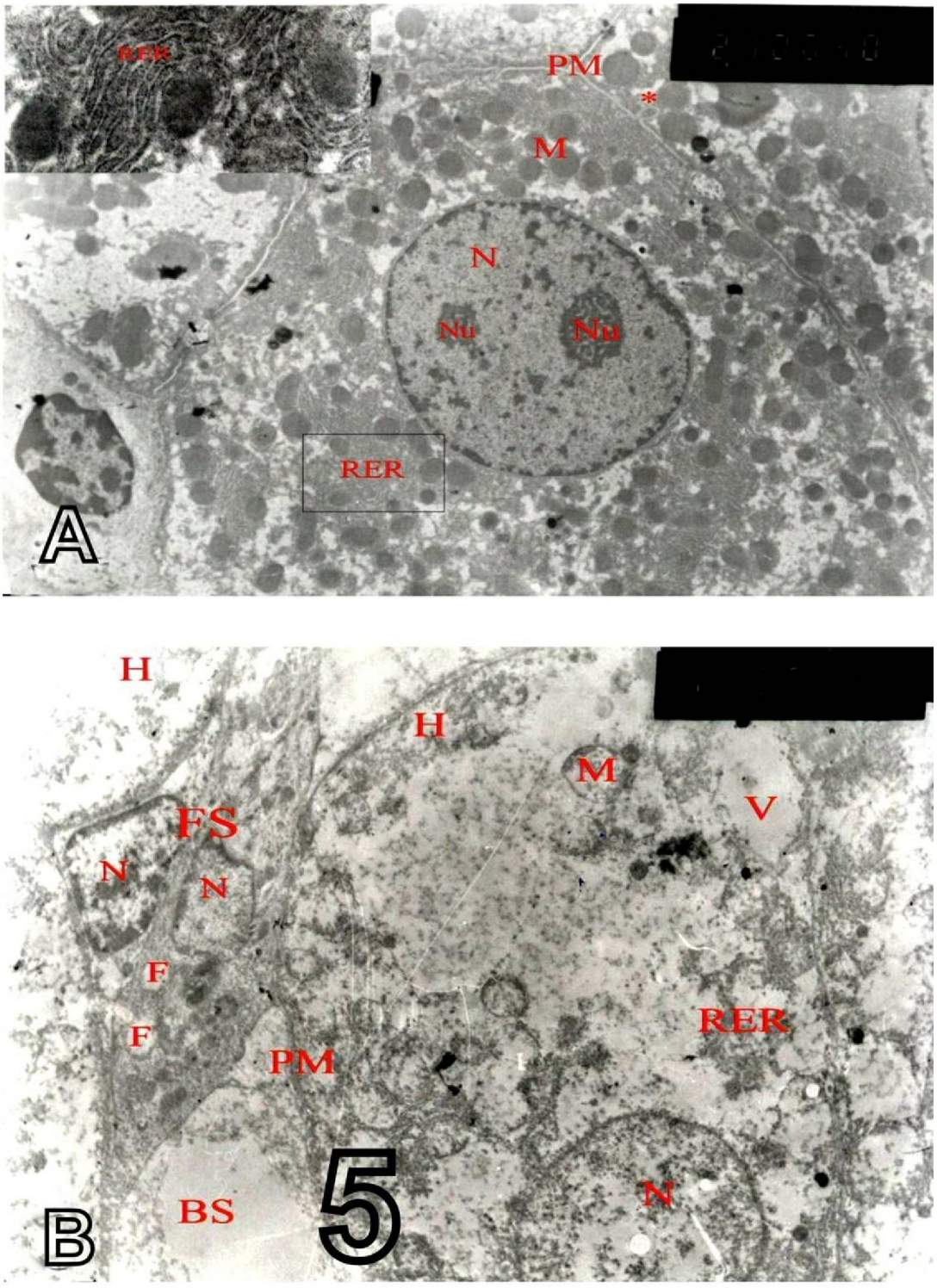


Figure 5. EM of treated rat liver after one month following the end of (A) direct current magnetic field exposure showing hepatocytes (H) with large nucleus (N) containing two nucleoli (Nu), numerous mitochondria (M) and rough endoplasmic reticulum (RER). (X 2700). The insert at the upper right corner is enlarged view of the RER in the rectangle. (X14000). (B) alternating current magnetic field exposure showing a hepatocytes (H) with swelling cytosol, a marginated karylytic nucleus (N), few scattered mitochondria (M), dispersed rough endoplasmic reticulum (RER), vacuoles (V) and a sinusoid Larger view (BS). In addition, a hepatic stellate (fat storing cell FS) enclosed in between hepatocyte, which contains one irregular nucleus (N) and fat droplets (F). (X 2700).

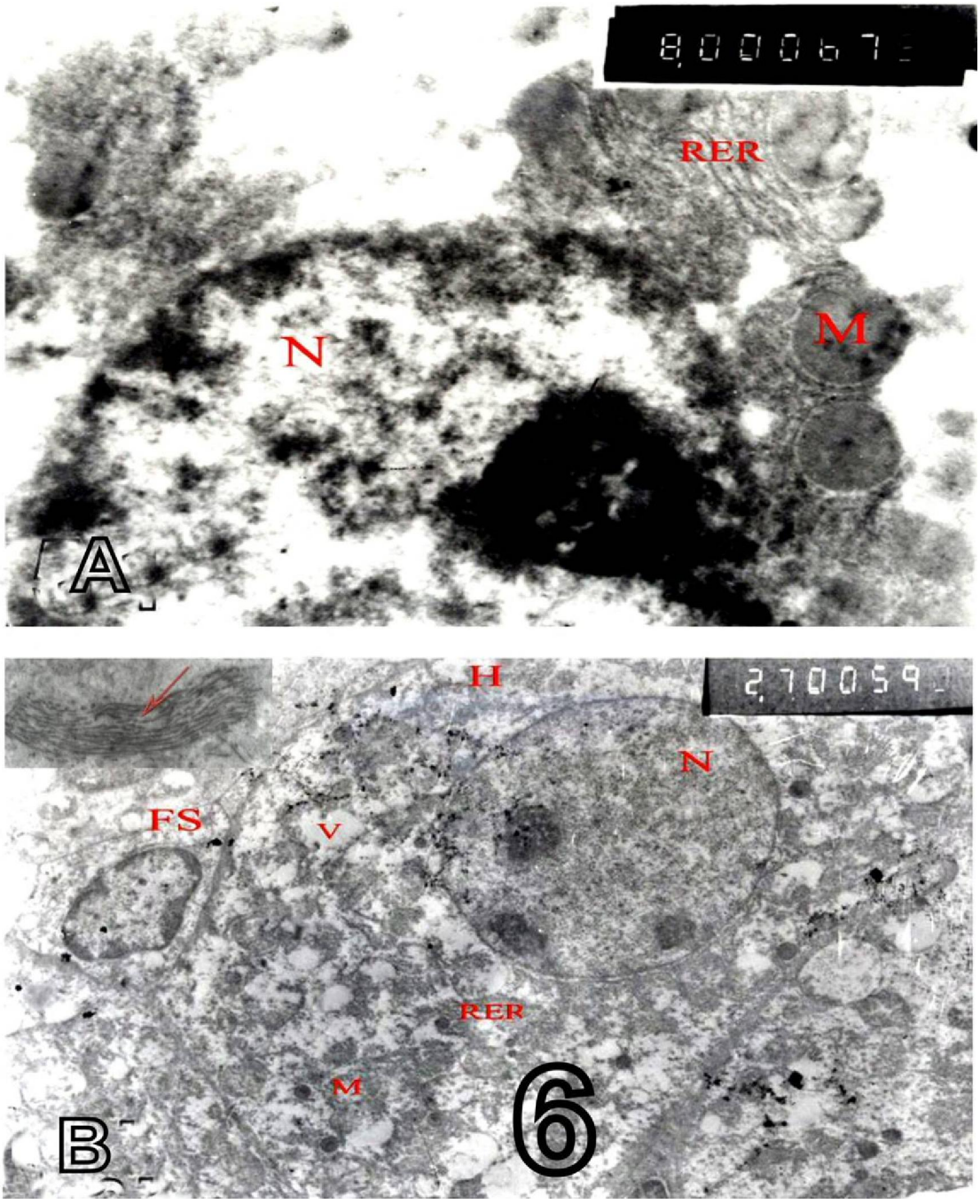


Figure 6: EM of treated rat liver after two month following the end of (A) Direct current magnetic field exposure showing enlarged nucleus (N), mitochondria (M) and rough endoplasmic reticulum (RER). (X 8000). (B) alternating current magnetic field exposure showing hepatocyte (H) a nucleus (N), with three nucleoli, mitochondria (M), rough endoplasmic reticulum (RER) & vacuoles (V). A fat storing cell (hepatic stellate cell) (FS), is adjacent to the hepatocyte (X 2700). The insert at the upper right corner illustrates a magnified view of collagen fibers found in sections of this group. (X8000).

The observed features were described for hepatocytes undergoing necrosis (**Francavilla, 1989**). Induction of hepatocyte necrosis may be through the increased production of tumor necrosis factor alpha induces by alternating current EMF (**Yamaguchi, 2006**) which results in cell necrosis (**Yu, 1996**).

After two weeks of exposure to direct current magnetic field, some cells showed signs of swelling of the cytosol and clumping of the organelles. Such a change could be due to disturbance of the cytoskeleton especially microtubular organization (**Stockem, 1992**). Such disturbance is probably due to mobilization of intracellular calcium by EMF (**Tonini, 2001**) which is essential for microtubular organization (**Masini, 2006**).

signs of hydropic degeneration appear in hepatocytes of the alternating current magnetic fiels exposed group. Signs of chromatin fragmentation and nucleolar margination suggest the onset of necrosis. The cytoplasmic organelles are relatively few with signs of cytoplasmic swelling.

Signs of hydropic degeneration appear in hepatocytes of the alternating current magnetic field exposed group. Signs of chromatin fragmentation and nucleolar margination suggest the onset of necrosis. The cytoplasmic organelles are relatively few with signs of cytoplasmic swelling. All these signs indicate the onset of cell necrosis (**Schaff, 1990**).

After one month, signs of hepatocyte recovery appear in the direct current exposed group. On the other hand, hepatocytes from alternating current exposed rat liver, showed several signs of cell injury. Swelling of the cytoplasm, loss of cell organoids and karyolysis are demonstrated in cell of this group. There is increase appearance of hepatic stellate cells. This indicates that alternating current EMF at 2mT, 50Hz results in a more lasting injury in the liver of treated animals. The appearance of activated hepatic stellate cells indicate the onset of liver fibrosis (**Gressner, 1998**). This is evident in the present study from the appearance of collagen fibers in sections of liver after 2 months of exposure to alternating current EMF.

Finally, the high risk exposed personnel should be regularly examined for liver function tests . Furthermore , for the safe medical use of Magnetic Resonance equipment , monitoring of cardiac and circulatory functions of the patients during examination , should be recommended especially in patients with impairment of excitation stimulation or impairment of conduction of the excitation as they are more susceptible to the imposed cardiovascular stress.

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