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## **Introduction**

The research activities on the biological effects of electromagnetic fields in Japan from 2005 to 2007 are reviewed. *In vivo*, *in vitro*, dosimetrical studies on DC electric and magnetic fields, extremely low frequency (ELF) electric and magnetic fields, intermediate frequency (IF) magnetic fields, radio frequency (RF) and microwaves are discussed. Biomedical applications including magnetic stimulation, hyperthermia, thermal ablation, MEG, MCG, current

distribution MRI, fMRI and radiometry, contactless power transmission, and electromagnetic interference (EMI) are also introduced.

This report does not describe every paper of the member of Japanese Commission K that has been carried out during 2005-2007. It begins with a chapter describing the recent published papers of the biological effects of electromagnetic fields. Next chapter reviews the results of electromagnetic field measurement, dosimetry and exposure assessment. Third and fourth chapters provide a state-of-the-art review of biomedical applications using thermal therapy, hyperthermia with soft-and inductive-heating, MRI, and current distribution MRI, and further discuss some of the EMI issue on implantable medical devices.

## **K1 Biological Effects of Electromagnetic Fields**

### **K1.1 DC and ELF Electric Fields**

To elucidate the mechanism of field perception, Shimizu *et al.* conducted a fundamental study on the movement of body hair in field exposure [Shimizu, 2005]. The electric force exerted on a hair was given from the force component at dielectric discontinuity. With this force, the equation of hair displacement in field exposure was derived. The displacement evaluated by the equation agreed well with experimental results. Finally, the hair movement in field exposure was formulated theoretically. The derived equation describes the real movement of body hair in field exposure. With the equation, the mechanism of the threshold variation in the field perception was made clear.

Kagawa *et al.* have pursued the possibility to control immune functions by ELF electro-stimulation [Kagawa, 2006]. The effect of ELF electro-stimulation on the nitric oxide (NO) producing ability of macrophages was examined. The decrease of NO production due to the electro-stimulation was observed with statistical significance. The measurement showed the decrease of the NO synthesizing enzyme with statistical significance, as well. These facts suggested that the ELF electro-stimulation suppressed the emergence of the NO synthesizing enzyme and that the amount of NO production was consequently decreased by the electro-stimulation. This suggested the feasibility to control the immune function by applying ELF electro-stimulation from outside the body.

Hirata *et al.* investigated the effect of low-frequency (ELF) electric stimulation to muscle oxygenation level by NIRS (near infrared spectroscopy) from comparing with V-Ex (voluntary exercise) [Hirata, 2006]. ELF electric stimulation voltage was started at 20 V (20 Hz, pulse duration: 200  $\mu$ s, duty-cycle: 1s-1s), and then was increased at a rate of 3 V/30 s until maximal tolerance level. In ELF electric stimulation and V-Ex, tissue oxygenation index was decreased with decrease in O<sub>2</sub>Hb (oxy-hemoglobin) and increase in HHb (deoxyhemoglobin), and muscle oxygenation levels at the end of test were very alike. Oxygen consumption, heart rate, systolic and diastolic blood pressure in ELF electric stimulation and V-Ex increased significantly, however, the degree of change in ELF electric stimulation was significantly lower than V-Ex. Blood lactate was significantly increased in both tests. Adrenaline and noradrenaline were significantly increased in V-Ex, even though they showed no change in ELF electric stimulation. These results suggest that ELF electric stimulation is an effective technique activated muscle hypoxia and glycolytic pathway metabolism with low stress on respiratory, circulatory and sympathetic nervous systems.

Muraki *et al.* investigated cardiorespiratory responses and muscle oxygenation during prolonged electrical stimulation (ES)-evoked leg cycling in individuals with paraplegia (PARA) [Muraki, 2007]. PARA individuals demonstrated markedly lower gross mechanical efficiency (approximately 1.3 %) during ES cycling compared with able-bodied (AB) individuals performing voluntary exercise. During ES cycling, muscle oxygen saturation (SO<sub>2</sub>) decreased, whereas SO<sub>2</sub> during volitional cycling was unaltered from resting levels. Muscle oxygenated haemoglobin initially decreased during ES cycling, but returned to resting levels after 10 min.

Deoxygenated haemoglobin initially rose during the first 5 min of ES cycling, and remained elevated thereafter. Upon cessation of ES cycling, lower-limb muscle oxygenation increased, suggesting reactive hyperthermia in PARA individuals after such exercise. During ES cycling, muscle oxygenation followed a different pattern to that observed in AB individuals performing voluntary cycling at an equivalent  $\text{VO}_2$ . Equilibrium between oxygen demand and oxygen delivery was reached during prolonged ES cycling, despite the lack of neural adjustments of leg vasculature in the paralyzed lower limbs.

Miyazaki *et al.* measured somatosensory evoked fields (SEFs) by electric stimulus to the right finger using a 39-channel SQUID system [Miyazaki, 2007]. In order to investigate relationship between phased lag and stimulus repetition frequency (SRF), delay time of a component synchronous the SRFs (2.0 to 30.3 Hz) was calculated by the convolution of the reference signal and the measured SEF waveform.

Oinuma *et al.* studied the influence of high-frequency monopolar stimulation (HFMS) on the rat cerebral cortex [Oinuma, 2007]. Direct stimulation of the brain with 500 Hz HFMS is one of the most common methods to produce motor evoked potentials (MEP). HFMS of 1.5-50 mA were applied to the rat sensorimotor cortex. There was no change in the parameters of MEP in any of the rats exposed to HFMS. Histologically, there was significant swelling of the dendrites in rats immediately after exposure to 40 and 50 mA. The 50 mA stimulation group also exhibited slight swelling of the mitochondria. These findings were not obtained in any of the rats 30 days after stimulation. In rats exposed to 30 mA or less, no morphological or electrophysiological changes were observed.

Nishiyama *et al.* investigated the effects of electrostatic fields on the storage of red blood cell concentrates [Nishiyama, 2007]. The  $\text{Na}^+$  concentration decreased with time but was significantly lower in the 0 V than in the 500, 1500, and 3000 V groups.  $\text{K}^+$  and free hemoglobin concentrations increased with time, with significantly higher values in the 0 V than in the 500, 1500, and 3000 V groups. The pH decreased in the 500, 1500, and 3000 V groups, while it did not change in the 0 V group. The pH decrease was smaller in the 500 V than in the 1500 and 3000 V groups. Electrostatic fields of 500-3000 V could decrease hemolysis in the preparation. Considering the lower pH decrease, it is suggested that 500 V might be the field of choice.

Harakawa *et al.* examined the effects of exposure to extremely low frequency (ELF) electric fields on plasma lipid peroxide levels and antioxidant activity (AOA) in Sprague-Dawley rats [Harakawa, 2005]. The test was based on comparisons among rats treated with a combination of the oxidizing agent, 2,2-azobis(2-aminopropane) dihydrochloride (AAPH) and 50 Hz electric field of 17.5 kV/m for 15 min per day for 7 days, AAPH alone, ELF electric field alone or no treatment. The ELF electric field significantly decreased the plasma peroxide level in rats treated with AAPH, similar to treatment by ascorbic acid or the superoxide dismutase. Ascorbic acid increased AOA; however, ELF electric field and superoxide dismutase did not change AOA compared with sham exposure in stressed rats. No influence on the lipid peroxide level and AOA in unstressed rats was observed with ELF electric field exposure alone. Although the administration of AAPH decreased AOA, this decrease did not change when electric field was added. These data indicate that the ELF electric field influenced the lipid peroxide level in an oxidatively stressed rat.

### **K1.2 Magnetic Orientation-microorganisms and Agarose**

The past studies showed that the collagen fibers and adherent cells can be effectively oriented under the exposure to strong magnetic field. These challenges can lead to the development of bone tissue engineering. In order to achieve more clearly this phenomena, Saito *et al.* investigated the relationship between collagen orientation and magnetic field intensity [Saito, 2006]. The osteoblast cells were prepared and mixed with collagen solution. These mixed solutions were exposed to magnetic field with 2.5, 3 and 8 T. Five days later, the configuration of the osteoblasts was observed under microscope. These results showed the magnetic field intensity over 3 T is necessary to effectively control collagen orientation.

Several studies were carried out on the control of cellular orientation and morphology by applying strong static magnetic fields. Iwasaka *et al.* found that the motion of adherent cells (MC3T3-E1) was influenced by a static magnetic field of 8 T and was parallel to the static magnetic field [Iwasaka, 2005]. During the exposure, most cells showed a back-and-forth motion along the direction of the static magnetic field. Specifically, the direction of cell extension immediately after cell division was parallel to the static magnetic field. Cytoskeletons inside the cells were oriented in parallel with the static magnetic field, and introduced a cell motion parallel with the static magnetic field. The experiments showed that living cells consisting of diamagnetic materials had their motion restricted by the direction of the applied static magnetic field.

Diamagnetic anisotropy in cellular components provided a change in the fluidity of membrane assembly which was detected by fluorescent measurements *in-situ* under magnetic field exposures [Iwasaka, 2006c]. A novel phenomenon was discovered on the structures of giant vesicles which were formed under 8 T magnetic fields, and the contributions of both diamagnetic anisotropies of collagen molecules and lipid molecules were explained on a mathematical model [Suzuki, 2007a].

Effects of static magnetic fields on the optical property of cytochrome oxidase, which is involved in an enzymatic system of mitochondria, were investigated by utilizing purified enzymes and rabbit with a non-invasive oxygen monitor, and the results indicated a slight increment in oxidation of cytochrome oxidase by 14 T magnetic fields [Iwasaka, 2006a]. Iwasaka *et al.* reported the effects of intense static magnetic field (up to 14 T) on the near-infrared (NIR) optical properties of cytochrome oxidase in rabbits. The static magnetic field changed the oxidation of cytochrome oxidase (aa3) periodically depending on the magnetic flux density. Measurements with a cooled CCD system revealed that the absorbance at 830 nm was slightly increased by a static magnetic field of 8 T. A static magnetic field of 14 T was applied to the head of the rabbit, and the results showed the enhanced oxidation of cytochrome oxidase in the mitochondria of cells under the static magnetic field. The effects of the static magnetic field on the paramagnetic behavior of oxygen, electron transfer in cytochromes, and cell membrane conformation in mitochondria may play a role in increasing the sensitivity to NIR light for detecting cytochrome oxidase oxidation, which is one of the primary indicators of cellular activity.

Iwasaka *et al.* further reported a method of controlling the magnetic orientation of osteoblasts by utilizing a ferromagnetic particle chain and a diamagnetic collagen [Iwasaka, 2006b]. A cell culture medium with cells and magnetic particles (MP) was mixed with a collagen solution and incubated for 24 h. During the first 3 h of incubation, the medium in the cell culture dish was exposed to static magnetic field of up to 8 T. The exposure caused the aggregation of MP, which formed chains in parallel with the static magnetic field and at the same time oriented the polymerized collagen fibers perpendicular to the static magnetic fields. A lattice pattern of MP chains and collagen fibers was observed on the bottom of the culture flask. After 24 h of incubation, the spindle like cells had become oriented in parallel with the MP chains or the collagen fibers. The results indicate the possibility of a technique of cellular manipulation with MP-collagen hybrid that could be used to control cellular orientation.

An experiment to clarify the effects of the static magnetic field of up to 8 T on cell membrane fluidity by using red blood cell ghosts and a fluorescence dye, 1-aminonaphthalene-8-sulfonic acid (ANS) was performed [Iwasaka, 2006c]. The emission intensity at 480 nm increased when the temperature of the cell holder was increased from 20 to 38-46°C for 15 min. A change in temperature exhibited an increase in the fluidity of the lipid molecules in the hydrophobic cell membrane and increased the population of ANS molecules emitting light at 480 nm in the cell membrane. A discontinuous change in fluorescence at 38-40°C was exhibited under exposure to a 5 T static magnetic field, while the temperature dependency was continuous without exposure. In addition, under exposure to the static magnetic field, the fluorescence during a decrease in temperature from 38 to 20°C remained at a level close to the fluorescence during an increase in

temperature. The results indicated that the fluidity of the molecules in the cell membrane was decelerated by 5 T static magnetic field. They speculated that the magnetic orientation in a part of the lipid membrane disturbed the release of ANS molecules from a hydrophobic region of the membrane.

According to applications of magnetic forces, which are of a spatial gradient of magnetic flux density, for a biological process, Moses' effect was applied to the patterning of adhered cells by using a field modulator under 1 T [Kimura, 2005]. Also, two kinds of new approaches in magnetic separation techniques for biological materials were reported, one of which was called "magnetic liquid chromatography" [Iwasaka, 2007], and the other was an application of the Magneto-Archimedes separation [Yokoyama, 2007].

Kimura *et al.* presented a new technique of cell micropatterning using a magnetic field [Kimura, 2005]. Mouse osteoblast cells (MC3T3-E1) were seeded on a substrate whose surface was exposed to a periodically modulated magnetic field (a line pattern with a 200- or 600- $\mu\text{m}$  pitch) produced by a field modulator inserted into a homogeneous static magnetic field of 1 T. The cells were trapped consistent with the line profile of the modulated magnetic field. The trapping efficiency was enhanced by adding Mn (II) EDTA (paramagnetic) to the cultivation medium. The cells were subsequently incubated in the magnetic field. The same technique was applied to whole blood to pattern red blood cells.

Eguchi *et al.* examined the role of cytoskeletons, such as stress fibers, on magnetic orientation of Schwann cells after the static magnetic field exposure (8 T in maximum) [Eguchi, 2005]. Schwann cells were cultured from dissected sciatic nerves of neonatal rats. Schwann cells oriented parallel to the static magnetic field after 60 h of more than 4 T. Actin fibers oriented in the direction of the static magnetic field after 60 h of 8 T static magnetic field exposure but randomly oriented without static magnetic field. Orientation of Schwann cells was not observed by inhibiting stress fiber formation using Y-27632, an inhibitor of small guanosine triphosphatases (GTPase) Rho-associated kinase. These results indicate that the static magnetic field elicits reorientation of actin fibers through Rho kinase to allow a response to magnetic orientation of Schwann cells.

Eguchi *et al.* further examined cleavage and survival of fertilized *Xenopus* embryos exposed to 8 T static magnetic field [Eguchi, 2006]. Fertilized *Xenopus* embryos exposed to static magnetic field either in a static chamber or in a rotating culture system. The results showed that the static magnetic field exposure changed the third cleavage furrow from the usual horizontal one to a perpendicular one; however, when the direction of gravity was randomized by exposing embryos to the static magnetic field in a rotating culture system, the third cleavage furrow were formed horizontally. These findings suggest that the observed distortion of the third cleavage furrow in static magnetic field exposed embryos was accomplished by altering gravity effects which were elicited by diamagnetic force due to high gradient magnetic field. These results also showed that the exposure to the static magnetic field did not damage survival. These results demonstrate that static magnetic field and altering gravity cause distortion of the third cleavage furrow and show that effects of exposing cleavage embryos to static magnetic field were transient and did not affect the post-cleavage development. They also showed that static magnetic field is not hazardous to the cleavage and blastula-gastrula transition of developing embryonic cells.

Shinohara *et al.* reported highly oriented collagen structures were successfully synthesized using a conventional superconducting magnet with static magnetic field of 2.5 to 8 T [Shinohara, 2006]. The relationship between the orientation order parameters  $f_{2D}$  of osteoblastic cells (the orientation of collagens) and the magnetic field intensity was mainly investigated. As a result, it was clarified that collagens highly oriented perpendicular to the c direction were obtained by exposure to a static magnetic field of 3 T.

After the short-time exposure of pregnant mice (60 min on 1 day from 7.5 to 14.5 days of pregnancy) to a strong magnetic field of 400 mT (exposure direction was in a dorso-ventral direction), Saito *et al.* evaluated the teratologic effects of developing fetuses [Saito, 2006]. 160

animals were used in the exposure experiment; exposed and control groups consisted of 10 pregnant mice each. Teratological evaluation was performed on day 18.5. The number of live and dead fetuses and fetal resorption sites were counted. All fetuses were examined from gross malformation and gender. They observed various malformations and the type of malformations were polydactylism, abdominal fissure, fused rib, vestigial 13<sup>th</sup> rib, lumber rib, brain hernia and curled tail. In control groups only a low incidence (up to 2.8 %) of curled tail was observed. The mentioned these deformations apparently caused by static magnetic field.

A National Project Group for research on strong static magnetic field effects on physico-chemical processes partially including biological matters collected results of recent topics [Yamaguchi and Tanimoto, 2006].

### **K1.3 DC and ELF Magnetic Fields**

During past three years, three comprehensive review papers have been appeared [Kato, 2006; Miyakoshi, 2005a; Ueno, 2007b]. Kato edited the book entitled “Electromagnetics in Biology”. This comprehensive book covered the fundamental concept of biological issue in electromagnetics and the topical reviews of the published literature. Miyakoshi reviewed the effects of static magnetic field at cellular level. As a result through reviewing many past published studies, he mentioned that static magnetic field alone does not have a lethal effect on basic properties of cell growth and survival under normal culture condition regardless of the magnetic density. Most studies have also suggested that a static magnetic field has no effect on changes in cell growth rate. Most interest area is whether static magnetic fields cause DNA damage. Ueno and Shigemitsu reviewed some of the more recent information on biological effects and medical applications of static magnetic fields. In their review, with exposure to about 1 T and above, there are no adverse effects on reproduction and development, genotoxicity, and molecular and cellular systems, and no consistent evidence on behavioral effects. Most important point they mentioned was that the International Agency for Research on cancer (IARC) has stated the static magnetic field are *not classifiable as to their carcinogenicity to humans* by inconclusive carcinogenic evidence.

#### **K1.3.1 In Vivo Studies**

Okano *et al.* reported that the homeostatic effect of the static magnetic field might influence nitric oxide (NO) pathways [Okano, 2005a]. When the genetically hypertensive rats were exposed to a gradient static magnetic field of 5 mT for up to 12 weeks, blood pressure (BP) and/or plasma concentration of NO metabolites (NO<sub>x</sub>), angiotensin II and/or aldosterone were reduced. Specifically, 5 mT exposures reduced mean BP during 3-6 weeks. Young spontaneously hypertensive rats (SHR) are known to have increased levels of NO<sub>x</sub>, likely due to the upregulation of nitric oxide synthase (NOS). Exposure to a 5 mT static magnetic field for 6 weeks significantly reduced the concentration of NO<sub>x</sub>. A 1 mT static magnetic field did not have an effect on the NO<sub>x</sub>. A 5 mT static magnetic field reduced angiotensin II and aldosterone during 3-6 weeks. Similar significant reductions in angiotensin II and aldosterone were seen with the 1 mT static magnetic field. However, until the 9th week of exposure, irrespective of the longer duration of exposure, all significant antihypertensive effects of static magnetic field disappeared, due to the development of hypertension in young SHR.

The above findings were partially elucidated when SHR were exposed to a 180 mT static magnetic field (a magnet was implanted in the neck) for up to 14 weeks [Okano, 2005d, 2006a]. The static magnetic field enhanced the hypotensive effect of nicardipine and caused a further increase in NO<sub>x</sub> during the 6th week of exposure compared with rats that also received nicardipine but were exposed to a sham field (control). Thus, the synergistic effect of the static magnetic field appeared to be related to NO. The static magnetic field alone (without nicardipine), however, did not induce any change in NO<sub>x</sub> concentration. It is speculated that NO increase by static magnetic field, in part, might be due to the upregulation of inducible NOS rather than neuronal NOS or endothelial NOS [Okano, 2006a].

The homeostatic effects of a static magnetic field were again reinforced when reserpine, an indole alkaloid, was used to induce hypotension and deplete catecholamine reserves in conscious rats [Okano, 2005b]. The static magnetic field exposure (25 mT for 12 weeks) significantly reduced the effect of the reserpine, reducing the hypotension caused by the drug. A 10mT static magnetic field did not have any effect. It is concluded that a 25 mT static magnetic field could potentially reduce hypotension *in vivo*.

The combined effects of a static magnetic field (12 mT for 10 weeks) and two different sympathetic agonists were investigated in conscious rats [Okano, 2007a]. The two different sympathetic agonists, a  $\alpha$ 1-adrenoceptor agonist, phenylephrine and a  $\beta$ 1-adrenoceptor agonist, dobutamine, induced hypertension and different hemodynamics: phenylephrine increased BP and decreased heart rate, skin blood flow, skin blood velocity, and the number of rearing responses; dobutamine increased BP and heart rate, increased skin blood flow and velocity, and the number of rearing responses. Continuous neck exposure to the static magnetic field alone for up to 10 weeks induced no significant changes in any of the measured cardiovascular and behavioral parameters. The static magnetic field exposure for at least 2 weeks (1) significantly depressed phenylephrine effects on BP, skin blood flow and velocity, and rearing activity, and (2) significantly depressed dobutamine effects on BP, skin blood flow and velocity, and suppressed dobutamine-induced increase in the rearing activity. These results suggest that continuous neck exposure to a 12 mT static magnetic field for at least 2 weeks may depress or suppress sympathetic agonists-induced hypertension, hemodynamics, and behavioral changes by modulating sympathetic nerve activity.

In the case of neck application of the static magnetic field, Okano *et al.* found that the exposure to 5.5 mT for 30 min induced significant increases in baroreflex sensitivity (BRS) values during the post-exposure period of 40-60 min in norepinephrine-elevated BP compared with sham exposure in conscious rabbits [Okano, 2005c]. Moreover, the exposure to the static magnetic field for 5-8 weeks significantly suppressed or delayed the development of hypertension together with increased BRS in SHR [Okano, 2005d]. Furthermore, it is postulated through theoretical calculations that the applied static magnetic field can be converted into a changing magnetic field in the baroreceptor region by means of the carotid artery pulsation [Okano, 2005d]. Therefore, it is speculated that the changing magnetic field and the magnetic field modulated by the pulse rate, may influence the activity of baroreceptor and baroreflex function.

Xu *et al.* investigated the effects of the static magnetic field (180 mT for 3 weeks) on the vascularization in bone using an ischemic bone model, where rat femoral artery was ligated [Xu, 2007]. Magnetized and unmagnetized samarium-cobalt rods were implanted transcortically into the middle diaphysis of the ischemic femurs. Collateral circulation was evaluated by injection of microspheres into the abdominal aorta at the third week after ligation. It was found that the bone implanted with a magnetized rod showed a larger amount of trapped microspheres than that with an unmagnetized rod at the proximal and the distal region. There were no significant differences at the middle and the distal region. This tendency was similar to that of the bone mineral density (BMD) in the static magnetic field exposed ischemic bone.

Taniguchi *et al.* examined the effects of the static magnetic field (30 mT for 12 weeks) on osteopenia in an ovariectomized (OVX) rat model [Taniguchi, 2007]. The bone mineral density (BMD) was assessed mainly using dual-energy X-ray absorptiometry (DEXA). Thirty-six female Wistar rats were divided into three groups. The rats in the OVX-M group were exposed to the static magnetic field for 12 weeks after ovariectomy. The ovariectomized rats in the OVX-D group were not exposed to the static magnetic field as a control. The rats in the normal group received neither ovariectomy nor exposure to the static magnetic field. Twelve-week exposure to the static magnetic field in the OVX-M group inhibited the reduction in BMD that was observed in the OVX-D group. Moreover, in the OVX rats, before exposure to the static magnetic field, there was no clear difference in the level of locomotor activity between the active and resting phases, and the pattern of locomotor activity was irregular. After exposure of OVX rats to the

static magnetic field, the pattern of locomotor activity became diphasic with clear active and resting phases, as observed in the normal group. In the OVX-M group, the continuity of the trabecular bone was maintained more favorably and bone mass was higher than the respective parameters in the OVX-D group. These results demonstrate that exposure to the static magnetic field increased the level of locomotor activity in OVX rats, thereby increasing BMD.

Goto *et al.* examined the effects of the static magnetic field (100 mT for 2 h, four times per day for 7 days) affects higher order neural functions in vivo [Goto, 2006]. When embryonic 12-day-old or newborn mice were successively exposed to the static magnetic field at 100 mT for 2 h, four times per day until the postnatal seventh day, Ntan1 mRNA was significantly increased about 1.5-2-fold in the hippocampus in vivo. The mice exposed to the static magnetic field under the same condition showed significantly decreased locomotor activity. These results suggest that the static magnetic field affects higher order neural functions through modulation of genes expression.

Toyomaki *et al.* investigated the static magnetic field (1.5 T) affects brain activity such as arousal level [Toyomaki, 2007]. They compared the electroencephalography (EEG) inside an MRI scanner in the presence/absence of the static magnetic field in two different arousal levels of task and rest conditions in humans. Cardiac-related pulsations of head and blood flow induce an electric voltage at each EEG electrode in a static magnetic field. This induced voltage overlaps with the intrinsic EEG signal and becomes a large confounding factor. No significant difference was observed in the intrinsic EEG in the absence of a magnetic field, whereas in the presence of the static magnetic field, the theta frequency band of the intrinsic EEG increased, especially during the task condition, but other frequency bands did not change. These results demonstrate that a static magnetic field affects brain activity.

Sekino *et al.* investigate the effects of strong static magnetic field (up to 8 T) on the action potentials of the rat sciatic nerve [Sekino, 2006c]. A pair of needle electrodes was inserted beneath the skin of the heel for applying electrical stimulations. Compound action potentials of the left sciatic nerve were measured from a pair of electrodes attached to the nerve bundle under the static magnetic field. We identified the action potentials originating from the A and C fibers. The exposure to static magnetic field did not affect the amplitude of the A fiber's action potentials. An increase in the static magnetic field increases the amplitudes of the peaks of the C fiber. These results indicated that exposure to strong static magnetic field enhances the excitation of nerve fibers, and this effect depends on the type of fibers involved. These result implies that exposure to a strong static magnetic field enhances pain perception because the C fiber is responsible for pain transmission.

Komazaki *et al.* examined the influence of an extremely low frequency (ELF) magnetic field (50 Hz, 5-30 mT) on early development of amphibian embryos [Komazaki, 2007]. When the embryos developed under the influence of an ELF magnetic field, the rate of early development was accelerated. The effect of ELF magnetic field was exerted preferentially at the gastrula stage, and the period of gastrulation was shortened. Histological observations showed that ELF magnetic field promoted morphogenetic cell movements during the gastrulation. ELF magnetic field increased intracellular  $\text{Ca}^{2+}$  ( $[\text{Ca}^{2+}]_i$ ) particularly in the cells isolated from gastrula. These results suggest that ELF magnetic field specifically increased the  $[\text{Ca}^{2+}]_i$  of gastrula cells, thereby accelerating the rate of morphogenetic cell movements during gastrulation.

In order to study the influence of magnetic field (60 Hz, 0.5 T, one hour exposure) on the nervous system of nematode *C.elegans*, Maeda *et al.* observed the behavior of the worm in response to certain chemicals (DA and  $\text{CuSO}_4$ ) both during the exposure and after exposure to magnetic field [Maeda, 2006]. They suggested that the parts of the worm's nervous system are influenced by magnetic fields and there are more effects on the nervous system during than after exposure to magnetic fields.

Suzuki *et al.* investigated the effect of static magnetic field of 4.7 T on the induction of micronuclei induced by some mutagens in order to confirm the co-mutagenic effect [Suzuki, 2006]. Seven-week-old BALB/c male mice with body weights between 22-27 g were exposed



to 4.7 T magnetic fields just after the injection of carboquone (0.5, 1.0 and 2.0 mg/kg), colimid (1.25, 2.5, 5.0 and 7.5 mg/kg), mitomycin C (0.3, 0.5 and 0.7 mg/kg), vincristine (0.02, 0.03 and 0.04 mg/kg), sodium fluoride (10, 20 and 30 mg/kg) or ENU (9, 18 and 36 mg/kg). After exposure to magnetic field, the mice were sacrificed by cervical dislocation. Bone marrow smears were prepared. The number of micronucleated polychromatic erythrocytes in 1000 polychromatic erythrocytes per animal was counted under a light microscope. The frequency of micronuclei induced by above six mutagens increased after co-exposure to magnetic field. The authors concluded that an additive/synergistic effect of magnetic field was observed from the results of increased frequency of micronuclei by mutagens in mouse bone marrow erythrocytes.

Ogiue-Ikeda *et al.* investigated the acquisition of ischemic tolerance in the rat hippocampus using repetitive transcranial magnetic stimulation (rTMS) which is a type of ELF-pulsed magnetic fields (ELF-PEMF) [Ogiue-Ikeda, 2005]. Rats received ELF-PEMF (0.75 T, 1000 pulses/day) for 7 days, and the field excitatory postsynaptic potentials were measured in the hippocampal CA1. After slices were exposed to ischemic conditions, long-term potentiation (LTP) was induced. The LTP of the stimulated group was enhanced compared with the LTP of the sham control group in each ischemic condition, suggesting that ELF-PEMF has the potential to protect hippocampal function from ischemia.

Funamizu *et al.* examined the effects of an ELF-PEMF on neurological and psychiatric disorders [Funamizu, 2005]. As an animal model, the lesioned rats were made by administering the neurotoxin MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine). Forty-eight hours after MPTP injection, the rats received ELF-PEMF (1.25 T, 2000 pulses/day) for 1 day, and tyrosine hydroxylase (TH) and NeuN expressions were investigated in the substantia nigra. The functional observational battery-hunched posture score for the MPTP-ELF-PEMF group was significantly lower and the number of rearing events was higher compared with the MPTP-sham group, these behavioral parameters reverted to control levels. These results suggest that ELF-PEMF treatment could reactivate the dopaminergic system in lesion rats.

Yamaguchi *et al.* investigated the effects of an ELF-PEMF on tumor development processes and immune functions *in vivo* [Yamaguchi, 2005ab, 2006a]. ELF-PEMF were applied at pulse width = 238  $\mu$ s, peak magnetic field = 0.25 T, frequency = 25 pulses/s, 1,000 pulses/sample/day and magnetically induced eddy currents = 0.79-1.54 A/m<sup>2</sup>. B16-BL6 melanoma model mice were exposed to the ELF-PEMF for 16 days from the day of injection of cancer cells. A tumor growth study revealed a significant tumor weight decrease in the ELF-PEMF group. These results showed the anti-tumor effect and immunomodulatory effects of ELF-PEMF.

Yamaguchi *et al.* further examined the combination effect of an ELF-PEMF and an anticancer agent on human chronic myelogenous leukemia-derived cell line TCC-S using molecular target drug (selective tyrosine kinase inhibitor) imatinib mesylate (imatinib) [Yamaguchi, 2006b]. The stimulus conditions were determined as follows: 0.1, 0.25, and 0.5 T, 25 pulses/s, 1000, 3000, and 6000 pulses/day. TCC-S cells were cultured with imatinib (100 nM) and exposed to ELF-PEMF for up to 56 h after drug treatment. The significant combination effects of ELF-PEMF and imatinib occurred by the stimulus intensity and pulse dose depended manner. To clarify the effects of ELF-PEMF on human normal lymphocytes, PBMCs were also exposed to ELF-PEMF with or without imatinib. ELF-PEMF had no effect on the viability of PBMCs. These results indicate that ELF-PEMF possibly improve the effectiveness of anticancer agents.

Mano *et al.* investigated the effect of ELF magnetic field (60 Hz, 5 mT) on the germination of seeds [Mano, 2006]. The germination of seeds of *Arabidopsis thaliana*, *Lactuca sativa* and *Zinnia elegans* were decreased by 8-21 day-incubation in 90 % relative humidity at 37 °C. ELF magnetic field applied to seeds during the incubation suppressed these decreases in the germination. The ELF magnetic field suppressed irreversible deterioration of the seeds, rather than dormancy, probably preventing water absorption. ELF magnetic field can be helpful for the storage of humidity-vulnerable seeds.

### **K1.3.2 In Vitro Studies**

Hirai *et al.* reported repetitive daily exposure to a static magnetic field (100 mT for 15 min per day for 8 days) led to a decrease in the expression of microtubule-associated protein-2 (MAP-2), without significantly affecting cell viability or the expression of neuronal nuclei (NeuN) and growth-associated protein-43 (GAP-43) [Hirai, 2005a]. However, the repetitive static magnetic field exposure prevented decreases in both brain-derived neurotrophic factor (BDNF) mRNA and MAP-2 and additionally increased the expression of NR2A subunit, without altering NR1 expression in neurons cultured in the presence of the antagonist for N-methyl-D-aspartate (NMDA) receptors dizocilpine (MK-801). Repetitive static magnetic field exposure was also effective in preventing the decrease by MK-801 in the ability of NMDA to increase intracellular free  $Ca^{2+}$  ions, without affecting the decrease in the maximal response. These results suggest that repetitive static magnetic field exposure may at least in part counteract the neurotoxicity of MK-801 through modulation of the expression of particular NMDA receptor subunits in cultured rat hippocampal neurons.

Hirai *et al.* examined the effects of a static magnetic field (100 mT for 15 min) on cultured rat hippocampal neurons using polymerase chain reaction [Hirai, 2005b]. The results suggest that the static magnetic field may modulate cellular integrity and functionality through expression of a variety of responsive genes required for gene transcription and translation, proliferation, differentiation, maturation, survival, and so on. in cultured rat hippocampal neurons. Hirai *et al.* screened genes responsive to a brief static magnetic field (100 mT for 15 min) in cultured rat hippocampal neurons using differential display analysis [Hirai, 2006]. These results suggest that a brief static magnetic field leads to the induction of amidohydrolase for N-terminal asparagines (Ntan1) responsible for MAP2 protein degradation through ubiquitin-proteasome pathway in rat hippocampal neurons.

Okano *et al.* reported the effects of the static magnetic field (120 mT for 10 days) on increased endothelial tubular formation mostly in the absolute field gradient range of more than 28 mT/mm (28 T/m) in the target cells [Okano 2006b, 2007b, 2007c]. These studies investigated the spatial magnetic gradient effects of static magnetic field on endothelial tubular formation. The effects of gradient static magnetic field on tubular formation were compared with those of uniform static magnetic field that has no spatial gradients on the entire bottom area of culture wells [Okano 2007c]. Five experimental groups of 25 samples each were examined: (1) sham exposure (control); (2) peak gradient exposure in the peripheral part; (3) peak gradient exposure in the central part; (4) uniform exposure to 20 mT; (5) uniform exposure to 120 mT. The static magnetic field or sham exposure was carried out for 10 days. Photomicrographs of tubular cells, immunostained with an anti-platelet-endothelial cell adhesion molecule-1 (PECAM-1 [CD31]) antibody as a pan-endothelial marker, were analyzed after the 10-day culture. Gradient static magnetic field in the peripheral or central part was found to significantly promote tubular formation in terms of the area density and length of tubules in each peak gradient/force part of the wells, compared with the sham exposure. In contrast, uniform static magnetic field did not induce any significant change in the tubular formation. These findings suggest that tubule formation can be promoted by applying the peak gradient/force to a target site of culture wells.

Haneda *et al.* examined the effects of the static magnetic field (300 mT for several hours) on single suspension-cultured plant cells (*Catharanthus roseus*) [Haneda, 2006]. Exposure of intact cells to the static magnetic field did not result in any changes within experimental error, while exposure of regenerating protoplasts significantly increased the measured forces and stiffened regenerating protoplasts. The diameters of intact cells or regenerating protoplasts were not changed after exposure. Measured forces for regenerating protoplasts with and without exposure increased linearly with incubation time, with these forces being divided into components based on the elasticity of synthesized cell walls and cytoplasm. No changes in cell wall synthesis were noted after exposure. Analysis suggested that the static magnetic field roughly tripled the Young's modulus of the newly synthesized cell wall without any lag.

Sakurai *et al.* reported that exposure to the static magnetic field of up to 10 T promoted

osteoblast differentiation in vitro [Sakurai, 2007a]. Prostaglandins respond early to exogenous mechanical loading, and play an important role in bone formation. The magnetic field gradient was highest (41.7 T/m) at 6 T. Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) secretion was not affected at 10 T compared with sham exposure, but was enhanced at 6 T. Similarly, PGE<sub>2</sub>-synthesizing enzyme, cyclooxygenase 2 (Cox-2) expression and the transcription factor nuclear factor κB (NF-κB) translocation were not enhanced at 10 T, but increased at 6 T. These findings suggested that exposure to a high magnetic field gradient induced secretion of PGE<sub>2</sub> and expression of the Cox-2 protein via increased translocation of NF-κB.

Sakurai *et al.* evaluated the effects of an extremely low frequency (ELF) magnetic field on glucose-stimulated insulin secretion from HIT-T15 cells and investigated the mechanisms of these effects [Sakurai, 2005b]. They demonstrated that ELF magnetic field at 5 mT and 60 Hz decreased glucose-stimulated insulin secretion by preventing the increases in cellular adenosine 5'-triphosphate/adenosine 5'-diphosphate, membrane depolarization, and cytosolic free Ca<sup>2+</sup> concentration. The glucose-induced upregulation of insulin mRNA expression was also attenuated by exposure to ELF magnetic field, although cell viability was not affected. These findings demonstrate the potential of exposure to ELF magnetic field for clinical use as a novel inhibitory method of insulin secretion.

Because there are few studies about the effects of an ELF magnetic field on β-cell survival and function, Sakurai *et al.* investigated the effects of 5 mT of 60 Hz magnetic fields on cell survival and function [Sakurai, 2005a]. The used cultured cell was a hamster-derived insulin-secreting cell line (HIT-T15). They cultured HIT-T15 cells under the exposure to sham and ELF magnetic field conditions. It was found that exposure to ELF magnetic field for 5 days in the absence of glucose increased cell number, exposure for 2 days without glucose and for 5 days with 100 mg/dl glucose increased the insulin secretion, and exposure for 2 and 5 days with 40 and 100 mg/dl glucose increased intracellular insulin concentration in HIT-T15 cells. The increase in cell number under apoptotic culture condition by exposure to ELF magnetic field can lead to new therapeutic applications in the treatment of diabetes.

Koyama *et al.* investigated the effects of an ELF magnetic field (5 mT and 60 Hz) on the number of apurinic/aprimidinic (AP) sites in human glioma A172 cells [Koyama, 2007a]. There was no difference in the number of AP sites between cells exposed to ELF magnetic field and sham controls. With methyl methane sulfonate (MMS) or H<sub>2</sub>O<sub>2</sub> alone, the number of AP sites increased with longer treatment times. ELF magnetic field in combination with the genotoxic agents increased AP-site levels compared with the genotoxic agents alone. The results suggest that the number of AP sites induced by the genotoxic agents is enhanced by ELF magnetic field, presumably thereby lengthening the lifetime of radical pairs.

Fukushima *et al.* examined the effects of an ELF magnetic field applied phosphate buffered saline solution (PBS) or water on ATP activity [Fukushima, 2005]. PBS and highly purified water were exposed to ELF magnetic field at 1 μT and 6 Hz under visible light (ELF magnetic field + light). When ELF magnetic field/light-applied pure water or PBS was added to the medium, CHO cells which respond to exogenous adenosine triphosphate (ATP) resulting in increase of [Ca<sup>2+</sup>]<sub>i</sub>, were found to elevate [Ca<sup>2+</sup>]<sub>i</sub> without exogenous ATP. This activity of ELF magnetic field applied water or PBS was equivalent to 100 nM ATP. Furthermore, when the ELF magnetic field was applied on highly purified water under visible light, for more than 12 h at 40°C, the pure water became to exert luminescence of luciferin in the presence of luciferase. This reaction did not require ATP nor Mg<sup>2+</sup> in the reaction mixture at all. These facts indicate that ELF magnetic field/light-applied PBS or water mimics ATP activity.

Ono *et al.* evaluated the effect of 44 mT static magnetic field on glucose uptake as the energy source of the metabolic change, and on gene expression of glucose transporters (GLUT1 and GLUT3) [Ono, 2006]. The static magnetic field was applied to the cultured cells (30 x 10<sup>4</sup> cells/mL) for 8 or 24 h. The target cell was neuroblastoma NG108-15. Glucose uptake of the cells and mRNA expression was measured by the phenol-sulfuric acid method and RT-PCR technique, respectively. The results showed that the glucose uptake of the cells was enhanced in 8

h exposure, while the GLUT1 and GLUT3 mRNA expression shows no change. In contrast, in 24 h exposure to static magnetic field, the glucose uptake and GLUT1 and GLUT3 mRNA expression were suppressed. The authors suggested that the metabolic activity change observed during the 24 h exposure may attribute to the change in glucose uptake and modification of GLUT1 and GLUT3 gene expression.

### **K1.3.3 Other Studies**

Koyama *et al.* examined the effects of an ELF magnetic field (5 mT and 60 Hz) and/or X-rays on mutations in the supF gene carried by pTN89 plasmids in *Escherichia coli* (*E. coli*) [Koyama, 2005]. The plasmids were subjected to sham exposure or exposed to ELF magnetic field, with or without X-ray irradiation (10 Gy). Increased mutant fraction was not detected following exposure to ELF magnetic field alone, or after sham exposure. The mutant fraction for X-rays followed by an ELF magnetic field was significantly higher than those of other treatments. Sequence analysis of the supF mutant plasmids revealed that base substitutions were dominant on exposure to X-rays alone and X-rays plus an ELF magnetic field. Several types of deletions were detected in only the combined treatments, but not with X-rays alone. There were no mutant colonies in sham irradiated and an ELF magnetic field alone treatment, but exposure to ELF magnetic field immediately before or after X-ray irradiation may enhance the mutations. These results indicate that an ELF magnetic field increases mutation and alters the spectrum of mutations.

Ohkubo *et al.* reviewed the effects of static magnetic field of 0.3-180 mT, ELF magnetic field of 0.1-30 mT and microwave, 1.5 GHz with SAR of 0.08-8 W/kg on microcirculatory system in different tissues in experimental animals of rat, rabbit, house and human [Ohkubo, 2007]. He emphasized that there is an importance of understanding the effects of magnetic fields on microcirculatory system. It may have direct and indirect role in interaction of magnetic fields with different tissues. The results obtained from ELF and RF electromagnetic field failed to show any changes in microcirculatory system except for leukocyte and endothelial cell interaction. The animal study can contribute to evaluate possible health risks of electromagnetic field.

### **K.1.4 IF Magnetic Field**

Chuman *et al.* first, investigated the effect of 20 kHz intermediate frequency (IF) magnetic field on *Xenopus laevis* [Chuman, 2007]. They compared the tail-length of frogs between exposed and control groups after exposure to IF magnetic field. The parameters were the exposure time and strength of magnetic field intensity. They used two exposure equipments, the commercial available induction heater (IH) cooker and Merritt coil type exposure facility. The results showed that the exposure may speed up metamorphosis of frog.

Tachi *et al.* investigated whether 20 kHz magnetic field of 0.5 mT and 1 mT induce DNA damage or physiologically abnormality in bacterial cells containing bacteriophage  $\lambda$  [Tachi, 2005]. Their results showed that after exposure to magnetic field for about 4 and 8 hours, the prophages shifted to lytic growth more often than control group. The results were compared to the result of 60 Hz, 45 mT magnetic field exposure experiments. The comparison gave the both IF and ELF magnetic fields induce physiological damage in bacterial cells.

Morimoto *et al.* examined the effects of an intermediate frequency (IF) electromagnetic field (10 MHz for 24 h) on production of endothelin-1 (ET-1) in cultured endothelial cells [Morimoto, 2005]. IF electromagnetic field reduced ET-1 basal levels in human umbilical vein and microvascular endothelial cells, but failed to reduce ET-1 basal levels in bovine and human aortic endothelial cells. IF electromagnetic field significantly inhibited thrombin-stimulated ET-1 production in all four endothelial cell types in a dose-dependent manner. IF electromagnetic field significantly inhibited thrombin-induced endothelin-1 mRNA expression in all four cell types. The inhibitory effect of IF electromagnetic field on ET-1 production was abolished by the NOS inhibitor, NG-monomethyl-L-arginine ( $10^{-3}$  M). These results

demonstrate that IF electromagnetic field modulates ET-1 production in cultured vascular endothelial cells and the inhibitory effect of IF electromagnetic field is, at least partly, mediated through a NO-related pathway.

Miyakoshi *et al.* examined the cellular genotoxicity of an IF magnetic field (532±20 µT at 23 kHz) in cultured cells [Miyakoshi, 2007]. Exposure to IF magnetic field for 2 h did not affect the growth of Chinese hamster ovary (CHO)-K1 cells and caused no mutagenic effects in bacterial mutation assays. Exposure to the IF magnetic field for 2 h induced neither single nor double DNA strand breaks in comet assays, and caused no significant change in the mutation frequency at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus compared to sham exposure. The results suggest that exposure to an IF magnetic field for 2 h does not cause cellular genotoxicity in bacteria and in CHO cells.

Haga *et al.* investigated the effects of IF magnetic fields with 20 kHz, 600µT on living biological cells using a highly sensitive mutagenesis assay method [Haga, 2005]. A bacterial gene expression system for mutation repair (umu system) was used for the sensitive evaluation of damage in DNA molecules. *Salmonella typhimurium* TA 1535 (pSK 1002) was used in this study. No effect from exposure to 20 kHz, 600 µT magnetic field in terms of damage in DNA molecules were observed.

Shigemitsu *et al.* reviewed the biological effects of IF electromagnetic fields with around 20 kHz from *in vivo* and *in vitro* studies [Shigemitsu, 2007]. After the short review based on published papers, they concluded that the available research data is inadequate for health risk assessment of IF electromagnetic fields. They also recommended that the study and exposure experiment of the biological and health effect of IF electromagnetic fields are very important.

## **K1.5 RF and Microwaves**

### **K1.5.1 *In Vivo* Studies**

Hata *et al.* studied the effects on melatonin synthesis in rats after short term exposure to a 1439 MHz time division multiple access (TDMA) electromagnetic field [Hata, 2005]. The average specific absorption ratio (SAR) of the brain was 7.5 W/kg, and the average SAR of the whole body were 1.9 and 2.0 W/kg for male and female rats, respectively. No significant differences in melatonin and serotonin levels were observed between the exposure, sham, and cage control groups. These results suggest that short term exposure to a 1439 MHz TDMA electromagnetic field (about four times stronger than that emitted by mobile phones) did not alter melatonin and serotonin synthesis in rats.

Kuribayashi *et al.* investigated the effects of 1439 MHz electromagnetic field exposure on the blood-brain barrier (BBB) were using immature (4 weeks old) and young (10 weeks old) rats [Kuribayashi, 2005]. Alteration of BBB related genes, such as those encoding p-glycoprotein, aquaporin-4, and claudin-5, was assessed at the protein and mRNA levels in the brain after local exposure of the head to electromagnetic field at 0, 2, and 6 W/kg SAR for 90 min/day for 1 or 2 weeks. Although expression of the 3 genes was clearly decreased after administration of 1, 3-dinitrobenzene (DNB) as a positive control, when compared with the control values, there were no pathologically relevant differences with the electromagnetic field at any exposure levels at either age. Vascular permeability was not affected by electromagnetic field exposure. Thus, these findings suggest that local exposure of the head to 1439 MHz electromagnetic field exerts no adverse effects on the BBB in immature and young rats.

Yuasa *et al.* investigated whether the radiofrequency electromagnetic fields (RF-EMF) emitted by a mobile phone for 30 min has short-term effects on human somatosensory evoked potentials (SEP) [Yuasa, 2006]. Neither SEP nor their recovery function was affected by exposure to RF electromagnetic field or sham phone use. The results suggest that 30 min mobile phone use has no short-term effects on the human sensory cortex.

Inomata-Terada *et al.* investigated whether RF electromagnetic fields emitted by a mobile phone has short-term effects on the human motor cortex [Inomata-Terada, 2007]. They

measured motor evoked potentials (MEP) elicited by single pulse transcranial magnetic stimulation (TMS), before and after mobile phone exposure (active and sham) in 10 normal volunteers. Three sites were stimulated (motor cortex (CTX), brainstem (BST) and spinal nerve (Sp)). The short interval intracortical inhibition (SICI) of the motor cortex reflecting GABAergic interneuronal function was also studied by paired pulse TMS method. MEP to single pulse TMS was also recorded in two patients with multiple sclerosis (MS) showing temperature dependent neurological symptoms (hot bath effect). Neither MEP to single pulse TMS nor the SICI was affected by 30 min of RF electromagnetic field exposure from mobile phones or sham exposure. In two MS patients, mobile phone exposure had no effect on any parameters of MEP even though conduction block occurred at the corticospinal tracts after taking a bath.

Terao *et al.* investigated whether exposure to pulsed high-frequency electromagnetic field (pulsed EMF) emitted by a mobile phone has short-term, 30 min, effects on saccade performances [Terao, 2007]. Using 10 normal subjects (4 male, 6 female, with  $33.1 \pm 8.6$  years (23-52 years), they studied the performance of visually guided saccade (VGS), gap saccade (GAP), and memory guided saccade (MGS) tasks before and after exposure to 800 MHz EMF with  $0.054 \pm 0.02$  W/kg of 10 g. They also implemented a hand reaction time (RT) task in response to a visual signal. In conclusion, Thirty minutes of mobile phone exposure has no significant short-term effect on the performance of various saccade tasks, which suggests that the cortical processing for saccades and attention is not affected.

Shirai *et al.* evaluated the effects of a 2-year exposure to a RF electromagnetic equivalent to that generated by cellular phones on tumor development in the central nervous system (CNS) of rats [Shirai, 2005, 2007]. Pregnant F344 rats were given a single administration of N-ethylnitrosourea (ENU) on gestational day 18. A 1.439 GHz time division multiple access (TDMA) signal for the Personal Digital Cellular (PDC), Japanese standard cellular system was used for the exposure of the rat head starting from 5 weeks of age, 90 min a day, 5 days a week, for 104 weeks [Shirai, 2005]. A 1.95 GHz wide-band code division multiple access (W-CDMA) signal for the International Mobile Telecommunication 2000 (IMT-2000) cellular system was also employed [Shirai, 2007]. Under the present experimental conditions, exposure of heads of rats to both RF electromagnetic field signals for a 2-year period was not demonstrated to accelerate or otherwise affect ENU-initiated brain tumorigenesis.

Jia *et al.* monitored local temperature changes in rabbit pinnae, which were evoked by RF electromagnetic field for 20 min at local SAR levels of 0 (sham exposure), 2.3, 10.0, and 34.3 W/kg over 1.0 g rabbit ear tissue [Jia, 2007]. The effects of exposure RF electromagnetic field on skin temperature were measured under normal blood flow and without blood flow in the ear. The results showed: (1) blood flow clearly modified the RF electromagnetic field-induced thermal elevation in the pinna as blood flow significantly suppressed temperature increases even at 34.3 W/kg; (2) under normal blood flow conditions, exposures at 2.3 and 10.0 W/kg, approximating existing safety limits for the general public (2 W/kg) and occupational exposure (10 W/kg), did not induce significant temperature rises in the rabbit ear. However, 2.3 W/kg induced local skin temperature elevation under no blood flow conditions. These results demonstrate that the effects of blood flow should be considered when extrapolating modeling data to living animals, and particular caution is needed when interpreting the results of modeling studies that do not include blood flow.

Masuda *et al.* examined the influence of RF electromagnetic field on rat skin using Global System for Mobile Communication (GSM)-900 or -1800 Radio Frequency Radiation (RFR) [Masuda, 2007a]. Hairless female rats were exposed or sham-exposed for 2 h to GSM-900 or -1800 signals, using a loop-antenna located on the right part of the rats' back. The local SAR at skin level was 5 W/kg. A skin biopsy was done at the end of the experiment not only at the location of exposure, but also on the symmetrical part of the back. Analysis of skin sections using hematoxylin eosin saffron (HES) coloration showed no difference in skin thickness or apparent cell toxicity among the animal groups. Histological analysis of the epidermis showed

that the ratio between cells expressing the antigen Ki-67 (cellular proliferation marker) and the total number of cells remained within the range of normal proliferation ratio for the exposed side of the animal. No Ki-67 labelling was observed at the dermis level. Results on filaggrin, collagen and elastin levels also showed an insignificant influence of RFR. These results do not demonstrate any major physical and histological variations at skin level induced by RFR used in mobile telephony.

Masuda *et al.* further investigated the effects of RF electromagnetic field on cerebral microcirculation in rat brain [Masuda, 2007bc]. The head of the rat was exposed for 10 min to 1439 MHz RF electromagnetic field at 0.6, 2.4 and 4.8 W/kg of brain averaged SAR [Masuda, 2007b], and for 4 weeks (60 min/day, 5 days/week) to RF electromagnetic field at 2.4 W/kg of brain averaged SAR [Masuda, 2007c]. Four microcirculatory parameters (BBB permeability, leukocyte behavior, plasma velocity, and vessel diameter) were measured before and after RF electromagnetic field exposure using a closed cranial window method. No extravasation of intravenously injected dyes from pial venules was found at any SAR level. No significant changes in the number of endothelial-adhering leukocytes after exposure were found. The hemodynamics indicated that the plasma velocities and vessel diameters remained constant within the physiological range throughout each exposure. These findings suggest that there were no effects on the cerebral microcirculation under the given RF electromagnetic field exposure conditions.

Ushiyama *et al.* investigated the effect on Blood Cerebrospinal fluid Barrier (BCB) function of rat by RF electromagnetic fields exposure [Ushiyama, 2007]. They set up a real-time measuring system for BCB function using a micro-perfusion method. After the short time exposure (30 min), 1.5 GHz RF electromagnetic field at the brain average SARs of 9.5 W/kg for adult and 10.4 W/kg for juvenile did not affect BCB function in rats.

The uncertainty of a large-scale long-term *in vivo* study on brain tumor has been evaluated by Wang *et al.* and Wake *et al.* [Wang 2006d 2006e; Wake, 2007a]. They found that the uncertainty of brain SAR in the rats in the exposure setup is higher for male rats than for female rats. Wake *et al.* developed an exposure setup for local exposure of a rabbit eye in order to evaluate the threshold of ocular effects such as cataract at 2.45 GHz [Wake, 2007b].

### **K1.5.2 In Vitro Studies**

Wang *et al.* examined the effects of 2450 MHz RF electromagnetic field on malignant changes in mouse C3H10T1/2 cells [Wang, 2005a]. The cells were exposed to the RF electromagnetic field alone in SAR from 5 to 200 W/kg for 2 h and/or were treated with a known initiating chemical, methylcholanthrene (MC) (2.5 µg/ml). No significant differences were observed in the malignant transformation frequency between the controls and RF electromagnetic field with or without 12-O-tetradecanoylphorbol-13-acetate (TPA) (0.5 ng/ml), a tumor promoter that could enhance transformation frequency initiated by MC in multistage carcinogenesis. However, the transformation frequency for RF electromagnetic field in SAR of more than 100 W/kg with MC or MC plus TPA was increased compared with MC alone or MC plus TPA. In contrast, the corresponding heat groups (heat alone, heat + MC, and heat + MC + TPA) did not increase transformation compared with each control level. The results suggest that 2450 MHz RF electromagnetic field could not contribute to the initiation stage of tumor formation, but it may contribute to the promotion stage in very high SAR (>100 W/kg).

Wang *et al.* further investigated the effects of 2450 MHz RF electromagnetic field on a stress response in A172 cells, using heat shock proteins (HSP)70 and HSP27 as stress markers [Wang, 2006b]. The cells were exposed to the RF electromagnetic field with a wide range of SAR (5-200 W/kg) or sham conditions. Since the RF electromagnetic field in 50-200 W/kg SAR causes temperature increases in culture medium, appropriate heat control groups (38-44 °C) were also included. The results showed that the expression of HSP70 increased in a time and dose-dependent manner in >50 W/kg SAR for 1-3 h. A similar effect was also observed in corresponding heat controls. There was no significant change in HSP27 expression caused by

RF electromagnetic field at 5-200 W/kg or by comparable heating for 1-3 h. However, HSP27 phosphorylation increased transiently at 100 and 200 W/kg to a greater extent than at 40-44°C. Phosphorylation of HSP27 reached a maximum after 1 h exposure at 100 W/kg RF electromagnetic field. The results suggest that exposure to a RF electromagnetic field has little or no apparent effect on HSP70 and HSP27 expression, but it may induce a transient increase in HSP27 phosphorylation in A172 cells in very high SAR (>100 W/kg).

Komatsubara *et al.* investigated the effects of RF electromagnetic field on chromosomal aberrations in mouse m5S cells [Komatsubara 2005a]. The RF electromagnetic field exposure was performed at 2.45 GHz for 2 h at average SAR of 5-100 W/kg with continuous wave-form (CW), or at a mean SAR of 100 W/kg (with a maximum of 900 W/kg) with pulse wave-form (PW). The effects of RF electromagnetic field exposure were compared with those in sham-exposed controls and with mitomycin C (MMC) or X-ray treatment as positive controls. No significant differences were observed following exposure to RF electromagnetic field in SAR from 5 to 100 W/kg CW and at a mean SAR of 100 W/kg PW compared with sham-exposed controls, whereas treatments with MMC and X-rays increased the frequency of chromatid-type and chromosome-type aberrations. RF electromagnetic field exposures at 2.45 GHz for 2 h with up to 100 W/kg SAR CW and an average 100 W/kg PW do not induce chromosomal aberrations in m5S cells. Furthermore, there was no difference between exposures to CW and PW RF electromagnetic field.

Takashima *et al.* examined the effects of 2.45 GHz RF electromagnetic field with SAR from 0.05 to 1500 W/kg *in vitro* [Takashima, 2006]. When cells (CHO-K1 and MO54) were exposed to a continuous RF electromagnetic field in SAR from 0.05 to 100 W/kg for 2 h, cellular growth rate, survival, and cell cycle distribution were not affected. At 200 W/kg, the cell growth rate was suppressed and cell survival decreased. When the cells were exposed to an intermittent RF electromagnetic field at 300 W/kg (pk), 900 W/kg (pk) and 1500 W/kg (pk) (100 W/kg [mean]), no significant differences were observed between these conditions and intermittent wave exposure at 100 W/kg. When cells were exposed to a SAR of 50 W/kg for 2 h, the temperature of the medium around cells rose to 39.1°C, 100 W/kg exposure increased the temperature to 41.0°C, and 200 W/kg exposure increased the temperature to 44.1°C. Exposure to RF electromagnetic field results in heating of the medium, and the thermal effect depends on the mean SAR. Hence, these results suggest that the proliferation disorder is caused by the thermal effect.

Koyama *et al.* investigated the effects of 2.45 GHz RF electromagnetic field on bacterial mutations and the HPRT gene mutations [Koyama, 2007b]. Bacteria were exposed to RF electromagnetic field for 30 min in SAR from 5 to 200 W/kg. In all strains, there was no significant difference in the frequency of revertant colonies between sham exposure and RF electromagnetic field-exposed groups. In examination of mutations of the HPRT gene, CHO-K1 cells were exposed to RF electromagnetic field for 2 h in SAR from 5 to 200 W/kg. A combination effect of simultaneous exposure to RF electromagnetic field and bleomycin was detected at the respective SAR. A statistically significant difference was observed between the cells exposed to RF electromagnetic field at the SAR of 200 W/kg. Cells treated with the combination of RF electromagnetic field in SAR from 50 to 200 W/kg and bleomycin exhibited increased HPRT mutations. As the exposure to RF electromagnetic field induced an increase in temperature, these increases of mutation frequency may be a result of activation of bleomycin by a thermal effect.

Sakuma *et al.* conducted a large-scale *in vitro* study focused on the effects of RF electromagnetic field from mobile radio base stations employing the IMT-2000 cellular system [Sakuma, 2006]. First, they evaluated the responses of human cells to microwave exposure at a SAR of 80 mW/kg, which corresponds to the limit of the average whole body SAR for general public exposure defined as a basic restriction in the ICNIRP guidelines. Second, they investigated whether continuous wave (CW) and Wideband Code Division Multiple Access (W-CDMA) modulated signal RF electromagnetic field at 2.1425 GHz induced different levels



of DNA damage. Human glioblastoma A172 cells and normal human IMR-90 fibroblasts were exposed to RF electromagnetic field. A172 cells were exposed to W-CDMA radiation at SARs of 80, 250, and 800 mW/kg and CW radiation at 80 mW/kg for 2 and 24 h, while IMR-90 cells were exposed to both W-CDMA and CW radiations at a SAR of 80 mW/kg for the same time periods. Under the same RF electromagnetic field exposure conditions, no significant differences in the DNA strand breaks were observed between the test groups and the sham-exposed control groups. These results confirm that low level exposures do not act as a genotoxicant up to a SAR of 800 mW/kg.

Hirose *et al.* investigated the effects of RF electromagnetic field on apoptosis or other cellular stress response through p53 activation or the p53-signaling pathway [Hirose, 2006]. Under the RF electromagnetic field conditions described above (IMT-2000), no significant differences in the percentage of apoptotic cells were observed between the test groups and the sham-exposed control groups. No significant differences in expression levels of phosphorylated p53 at serine 15 or total p53 were observed between the test groups and the sham-exposed control groups. Moreover, there were no noticeable differences in gene expression of the subsequent downstream targets of p53 signaling involved in apoptosis between the test groups and the sham-exposed control groups. These results confirm that RF electromagnetic field up to 800 mW/kg does not induce p53-dependent apoptosis, DNA damage, or other stress response in human cells.

Hirose *et al.* further examined the effects of RF electromagnetic field on phosphorylation and overexpression of a heat shock protein HSP27 [Hirose, 2007]. Under the RF field exposure conditions described above (IMT-2000), no significant differences in the expression levels of phosphorylated HSP27 at serine 82 (HSP27 [pS82]) were observed between the test groups and the sham-exposed control groups. Moreover, no noticeable differences in the gene expression of hsp were observed between the test groups and the sham-exposed control groups. These results confirm that RF electromagnetic field up to 800 mW/kg does not induce phosphorylation of HSP27 or expression of hsp gene family.

Using of human glioma MO54 cells, Miyakoshi *et al.* investigated whether radio frequency field exposure (1950 MHz with SAR of 1, 2 and 10 W/kg) could activate stress response genes [Miyakoshi, 2005b]. After the exposure up to 2 h, cell growth and cell number were counted at 0-4 days after exposure. Expression of HSP27, HSP70 and the level of phosphorylated HSP27 (78Ser) protein were determined. The results suggested that although exposure to a 1950 MHz RF electromagnetic field has no effect on cell proliferation and expression of HSP27 and HSP70, it may inhibit the phosphorylation of HSP27 at Serine 78 in MO54 cells.

Hikage *et al.* performed in vitro experiments on free radical production due to 900 MHz and 2.45 GHz mobile radio wave exposure [Hikage, 2006, 2007b]. Using of human white blood cell exposed to 900 MHz RF electromagnetic field, they investigated the estimation of hydroxyl free radical production due to non-thermal effects. Including 900MHz wave, the six different sets of exposure conditions were used: 1) continuous wave, 2) pulse modulation, 3) GSM (Global System for Mobile Communication) basic signal modulation, 4) PDC (Personal Digital Cellular) signal modulation and 5) CDMA (Code Division Multiple Access) 2000 signal modulation. The exposure level can be changed from cellular level to high SAR level (up to 150 W/kg). The cell's temperatures were kept below 39 °C. The experimental data confirms that there is no statistically significant influence of 900 MHz RF electromagnetic field exposure on human white blood cells and that there is a correlation between radical production and cell temperature. In addition, Hikage *et al.* tried to confirm the effects of 900 MHz and 2.45 GHz RF electromagnetic field exposures on the production of free radical in human fibroblasts cells.

### **K1.5.3 Other Studies**

There have been increased in the number of cellular phone users. With increasing there have been many reports of health disorders related to RF electromagnetic fields. Kawasaki *et al.*

considered and confirmed the dependency of students (Thai university and high school) on cellular phones and compared the results with the dependency of Japanese students (University and high school) [Kawasaki, 2006]. A survey form (cellular phone dependence questionnaire; CPDQ) was distributed to 181 female and 177 male Thai university students and to 240 female and 140 male Thai high school students. After factor analysis, the total scores for the Thai university was higher than the scores for the Thai high school students. The total score of the questionnaire was high, indicating a strong tendency toward cellular phone dependence.

Due to the rapid increase of cellular phone use in Japan, the public concerns about the possible health effects. Takebayashi *et al.* initiated a case-control study to examine the relationship between cellular phone use and acoustic neuroma [Takebayashi, 2006]. This study followed the INTERPHONE study with the international collaboration. Fifty one cases and 192 controls were regular cellular phone users on the reference date, one year before the diagnosis. No significant increase of acoustic neuroma was observed. The odds ratio (OR) was 0.73 (95 % CI 0.43 to 1.23). As an exposure index, cumulative lengths of use (<4 years, 4-8 years, >8 years), or cumulative call time (<300 hours, 300-900 hours, >900 hours) were used. This epidemiological study suggests that there is no significant increase in the risk of acoustic neuroma in association with cellular phone use in Japan.

## **K2 Field measurement, Dosimetry and Exposure Assessment**

### **K2.1 DC and ELF Fields**

Moriyama *et al.* assessed ELF magnetic field originating from equipment used for assisted reproduction, umbilical cord-blood and peripheral-blood stem cell transplantation, transfusion, and hemodialysis [Moriyama, 2005a]. The ELF magnetic field values were 0.1-1.2  $\mu\text{T}$  on clean benches, <0.1-8.0  $\mu\text{T}$  on inverted microscopes, <0.1-13.6  $\mu\text{T}$  in  $\text{CO}_2$  incubators, 4.3-11.5  $\mu\text{T}$  in centrifuges, 0.4-18.8  $\mu\text{T}$  in programmed freezers, <0.1-0.3  $\mu\text{T}$  in deep freezers, 0.3-3.1  $\mu\text{T}$  on cell separators, and 0.2-0.9  $\mu\text{T}$  in hemodialysers. Frequencies of ELF magnetic field were nominally 60 Hz, but some devices showed non-sinusoidal 120 Hz. Such ELF magnetic field can be reduced by shielding the sources or altering the protocols employed.

Moriyama *et al.* measured ELF magnetic field at 696 points in a room of a typical Japanese apartment building [Moriyama, 2005b]. ELF magnetic field exceeded 0.4  $\mu\text{T}$  in 24 % of the living space, and the maximum value, 1.8  $\mu\text{T}$ , was detected at floor level. Analysis of the ELF magnetic field distribution revealed that 60 Hz 100 V electrical wiring for room lights within the floor and ceiling had been laid out in large rectangles, equivalent to 1 turn coils. Further plotting of the vertical components every 0.01 m on the floor indicated that the depth of the cable was 0.23 m. Further studies should be conducted in order to confirm that the building investigated in this pilot study is typical of Japanese apartment buildings in terms of ELF magnetic field.

Kabuto *et al.* evaluated the effects of residential power-frequency ELF magnetic field as a possible human carcinogen by the International Agency for Research on Cancer (IARC) [Kabuto, 2006]. In response to great public concern, the World Health Organization (WHO) urged that further epidemiologic studies should be conducted in high-exposure areas such as Japan. They conducted a population-based case-control study analyzing 312 case children (0-15 years old) newly diagnosed with acute lymphoblastic leukemia (ALL) or acute myelocytic leukemia (AML) in 1999-2001 (2.3 years) and 603 controls matched for gender, age and residential area. The odds ratios for children whose bedrooms had ELF magnetic field levels of 0.4  $\mu\text{T}$  or higher compared with the reference category (<0.1  $\mu\text{T}$ ) was 2.6 (95 % CI=0.76-8.6) for AML+ALL and 4.7 (1.15-19.0) for ALL only. Controlling for some possible confounding factors did not alter the results appreciably. Even an analysis in which selection bias was maximized did not fully explain the association. Most of the leukemia cases in the highest exposure category had ELF magnetic field levels far above 0.4  $\mu\text{T}$ . These results provided additional evidence that high ELF magnetic field exposure was associated with a higher risk of

childhood leukemia, particularly of ALL.

Yamazaki *et al.* examined the association between residential proximity to 60 Hz high voltage (22-500 kV) overhead transmission lines (HVOTL) and mental health [Yamazaki, 2006]. The prevalence of poor mental health was 15 %. Among the 223 subjects, 10 lived within 100 m of a HVOTL. The adjusted odds ratios (OR) for poor mental health among those who lived 101-300 m or within 100 m from HVOTL were 1.29 (95 % confidence interval (CI): 0.35-10.13) and 1.87 (95 % CI: 0.35-10.13), respectively, against the reference category (>300 m). Mental health status was not significantly associated with the distance between the subject's residence and the closest HVOTL.

Hamada presented a fast-multiple surface-charge-simulation method for calculating three-dimensional Laplacian fields in voxel models. This method treats a surface of a voxel that has different inside and outside conductivities as a surface element of the indirect boundary element method [Hamada, 2006]. This method was successfully applied to calculate the electric field induced by an applied homogeneous EMF magnetic field in a human head model that has 1 m x 1 m x 1 m voxel size.

In Japan, the radio frequency protection guideline recommends the limits of contact current for contact hazard due to an ungrounded metallic object under an electromagnetic field in the range from 10 kHz to 15 MHz. The contact body impedance for the Japanese in the frequency range from 75 kHz to 15 MHz is obtained to arrange the standard measurement method for contact current [Kamimura, 2005]. The contact body impedance of 27 Japanese subjects (eight adult male, five adult female and fourteen children) was measured. The human body impedance is obtained from numerical simulation using the impedance method and voxel model, and is compared it with measured value.

Kitano *et al.* formulated mathematically the induced electric field in a spherical conductor exposed to orbital EMF dipole magnetic field source [Kitano, 2006]. They confirmed its validity by comparing the analytical solution with numerical solution by the equivalent multiple moment method.

Kobayashi *et al.* carried out the rejection of magnetic noise from the wire in magnetocardiogram (MCG) measurement [Kobayashi, 2005]. MCG were measured from two subjects with and without attachment of the wire. In order to reduce the effects of magnetic noise from the wire, signal processing by independent component analysis, digital-high-pass filter, and singular value decomposition was carried out. Due to the reduction of the magnetic noise from the wire by independent component analysis, independent component analysis is the effective technique.

Miyata *et al.* proposed the free scanning method for the magnetic field distribution measurements by recording the position of the moved sensor automatically [Miyata, 2007]. The magnetic field sensor has two kinds of range of the measurement frequency, low frequency (30 Hz to 1 kHz) and high frequency (1 kHz to 100 kHz). In their study, they tried to measure two dimensional magnetic flux density distributions in the vicinity of the induction heating (IH) cooker.

Oikawa *et al.* measured the environmental magnetic field of 50 Hz and 60 Hz in the room very close to power-receiving and transformer rooms in two buildings [Oikawa, 2006].

In highly non-uniform ELF magnetic field, the compliance test in accordance with guidelines has been a critical issue. When the measured maximum magnetic fields on the surface of the human body exceed the reference level, the basic restriction should be investigated in a different way. Yamazaki *et al.* proposed a new simplified method for the estimation of the maximum induced current from magnetic field measurements in practical complex [Yamazaki, 2005, 2007]. The method is based on the reduction rate of the magnetic field within a spherical model. The relationship between the reduction rate of magnetic field and the rate of maximum induced current to that of uniform field exposure was approximated using a simple regression curve. The results have practical values for assessing compliance with guidelines.

Nishizawa *et al.* investigated the magnetic field properties and dosimetry at 50 Hz, ELF with

the coil model [Nishizawa, 2007]. This coil model is prescribed as substitute source model for real household appliances in European standard EN50366 (CENELEC). The accuracy of the magnetic field vectors and the values of the induced current density were compared with the results of two test appliances (a drill machine and a hand mixer) obtained from the equivalent source model. The magnetic fields obtained using the coil model and real appliance show an agreement with each other with a maximum difference of 5 dB. The calculated induced current densities in the numerical human body models (homogeneous and anatomical body models) and the real appliances also show a good agreement with each other with a maximum difference by a factor of 1.6. Based on the totally obtained results in this study, the applicability of the coil model prescribed in EN50366 confirms that of the two applied test appliances.

Takuma *et al.* reviewed and summarized the recent developed topics related the basic formulas for field calculation, effects of electromagnetic fields, calculation methods, activity of Investigation Committee in the IEEJ, and future research subjects [Takuma, 2006].

## **K2.2 IF Magnetic Field**

Yamazaki *et al.* developed IF magnetic field exposure facility for *in vivo* exposure experiment with small animal [Yamazaki, 2006a, 2006b]. Before constructing facility, they first, investigated the effect of architectural structure on the uniform magnetic field generated from their proposed coils by the 3D magnetic field analysis. It is shown that the distance between coil and architectural structure in the direction of magnetic field should be determined taking into account the frequency. Also, the architectural structure has shielding effect. IF magnetic field generates the eddy current inside the reinforcing steel bar, so, the magnetic field disturbance is substantially greater in reinforced concrete building. After these preliminary considerations, Shigemitsu *et al.* have developed a 20 kHz (IF) magnetic field exposure system for *in vivo* studies [Shigemitsu, 2007]. The dimensions of the exposure system are 1.6 m x 1.6 m x 1.616 m high located in the specific pathogen free (SPF) exposure room. The system is designed to provide magnetic fields with vertically polarized sinusoidal 20 kHz wave form up to 200  $\mu\text{T}$  with the uniformity within  $\pm 5\%$  over the space occupied by an animals.

Fujita *et al.* have developed an IF magnetic field exposure system *in vitro* [Fujita, 2007]. This system mainly consists of an IF magnetic field generating coil housed inside an incubator, inside which cultured cells can be exposed to IF magnetic field. Two systems were prepared to allow the experiment to be conducted in a double-blind manner. The level of the generated IF magnetic field was set to 532  $\mu\text{T}$  rms in the exposure space, 23 kHz, 80 times the value in the International Commission on Non-ionizing Radiation Protection (ICNIRP) guidelines, with spatial field uniformity better than 3.8%. The waveforms were nearly sinusoidal. The parasitic electric field was 157 V/m rms and the induced electric field was 1.9 V/m rms. The temperature was maintained at  $36.5 \pm 0.5$  °C for 2 h. The leaked magnetic flux density was 0.7 mT rms or lower in the stopped system when the other system was being operated, and the environmental magnetic flux density was 0.1 mT rms or lower. This system could be successfully used to evaluate the biological effects of exposure to IF magnetic field.

Kamimura *et al.* evaluated the magnetic field exposure of human body near an induction heating (IH) cooker with 20 kHz by using of SPFD method [Kamimura, 2006]. They calculated the maximum induced current density among three kinds of human body models (Japanese adult male/female and American adult male) and compared the calculated current density with the guideline of ICNIRP. They showed that the maximum induced current densities are different among three models. They also showed that the induced current exceeding the guideline of ICNIRP may not flow inside human body in the case with a portable type IH cooker and a pan designed for the IH cooker.

Nishizawa *et al.* investigated the magnetic field properties and dosimetry at 21 kHz, intermediate frequency for an induction heater (IH) with the coil model [Nishizawa, 2006]. This coil model is prescribed as substitute source model in European standard EN50366 (CENELEC). The accuracy of the magnetic field vectors and the values of the induced current density were

compared with the results of realistic model for IH obtained from the equivalent source model. The coil model coincided well for the magnitude of the magnetic field strength around the IH. On the other hand, the dominant field vector of the coil model differs significantly from the real IH, which leads to induced current densities in the body model, three times larger. These results showed that the application of the coil model prescribed in the EN50366 is confirmed for the IH.

Suzuki and Taki measured the magnetic field around induction heating hobs operated at 20 kHz and evaluated the compliance with ICNIRP guideline [Suzuki, 2005]. At the very proximity to the device, the distribution of the magnetic flux density was highly inhomogeneous and the maximum flux density can exceed the reference levels of the guideline. Using of anatomical human model, the induced current densities exposed to magnetic field were calculated numerically by impedance method. The induced current densities were sufficiently lower than the basic restriction of INCIRP guideline.

Tarao *et al.* calculated the induced current in an anatomically high-resolution human model exposed to 20.9 kHz operated house-hold (IH) induction cooker [Tarao, 2006ab]. In case of the adult human model exposed to highly inhomogeneous 20.9 kHz magnetic field, they calculated that the induced current ranging from 5 to 19 mA/m<sup>2</sup> is obtained for between the shoulder and lower abdomen. However, for child model, it can be obtained that the currents between 5 and 21 mA/m<sup>2</sup> are induced for between the head and abdomen. They also obtained the result that the induced current in the child model are 2.1 to 6.9 times larger compared of the adult model under the exposure condition. They further studied the induced current in an anatomically human model of 2.5 x 2.5 x 2 mm voxel size exposed to 20.9 kHz magnetic fields generated from IH cooker by impedance method. In calculation, the maximum about 2  $\mu$ T magnetic field near the lower abdomen of the body was assumed. ICNIRP guideline gives that the basic restriction is expressed in term of a current densities averaged over a cross-section of 1 cm<sup>2</sup> perpendicular to the direction of the current. Tarao *et al.* proposed the conversion of computed results to corresponding current densities by averaging the current over the cross section of any 1 cm<sup>2</sup> of the model. The calculation results showed that the maximum averaged current densities, 5.31 mA/m<sup>2</sup> appears at the muscle of the abdomen, close to the magnetic sources. This value is 1/8 of the ICNIRP basic restriction level for the public exposure. In calculation at certain voxel, the averaging is key procedure. For example, the maximum value with the averaging decreased by 60 % from 13.2 mA/m<sup>2</sup> without the averaging to 4.31 mA/m<sup>2</sup>.

Induction heating (IH) cooker is recently very popular in Japan. Along the study of the biological and health effects of IF magnetic field generated from IH, the evaluation of the best heating performance and practical design are also necessary to achieve the higher quality heating. Yonetsu *et al.* proposed the effectiveness and practical design method of higher quality heating for IH cooker [Yonetsu, 2006]. They evaluated the better heating performance by adjusting the arrangement of the heating coil and coil winding. The heat distribution of heating plate and heat transfer were also calculated by the finite element methods. For obtaining the optimum coil arrangement, multi-objective genetic algorithm was employed. By these approaches, they showed that the optimum coil arrangement can be obtained easily.

### **K2.3 Radio frequency electromagnetic fields and Microwaves**

Wang *et al.* reported some detailed dosimetry results for the Salford-used transverse electromagnetic (TEM) cell in rats [Wang, 2006a]. The whole-body average SAR and the brain-average SAR varied up to 1.5 times and 2.7 times, respectively. For an input of 1 W to the TEM cell, the whole-body average SAR was 1.1 W/kg, while the brain-average SAR was 1.0 W/kg. This means that the TEM cell structure obviously produces not a local but a whole body exposure.

Wang *et al.* evaluated RF electromagnetic field in experimental fusion facilities for safety guidelines to ensure workers' safety [Wang, 2005b]. Since the leaked RF electromagnetic field has time-varying characteristics whose amplitudes vary according to a stochastic process, a

measurement of the amplitude probability distribution (APD) was conducted. An approach was then presented to derive from the measured APD and SAR in an exposed human body. The statistically-averaged whole-body-averaged SAR showed that the leaked field intensities were low enough to not cause any thermal hazards for the workers in the specific RF electromagnetic field environment. The statistically averaged SAR also showed fair agreement with the SAR derived from the time average over 6 min as specified in the safety guidelines. This finding suggests the usefulness of the APD measurement in lieu of a field measurement over a 6-min period because the APD can be obtained in a time period much less than 6 min.

Wang *et al.* made a detailed error analysis in the whole-body average SAR calculation for the finite-difference time-domain (FDTD) method in conjunction with the perfectly matched layer (PML) absorbing boundaries [Wang, 2006b]. They derived a basic rule for the PML employment based on a dielectric sphere and the Mie theory solution. They then attempted to clarify to what extent the whole-body average SAR may reach using an anatomically based Japanese adult model and a scaled child model. The results showed that the whole-body average SAR under the ICNIRP reference level exceeds the basic safety limit nearly 30 % for the child model both in the resonance frequency and 2 GHz band [Wang, 2006c].

Hirata investigated the effect of frequency, polarization, and angle of incidence of an ELF electromagnetic field on the SAR and maximum temperature increase in the human eye at 900 MHz, 1.5 GHz, and 1.9 GHz [Hirata, 2005a]. The SAR and temperature increased in the eye, largely dependent on the separation between the eye and a source, and the frequency, polarization, and angle of incidence of the ELF electromagnetic fields wave. The maximum temperature increased (0.303-0.349 °C) in the lens of the adult for the SAR value of 2.0 W/kg for the eye tissue (about 10 g) was marginally affected by the above-mentioned factors. No clear difference of a maximum temperature increase in the lens at the SAR limit was observed between the adult and children models.

Hirata *et al.* investigated statistically the maximum temperature increases in the head and brain for the SAR averaging schemes prescribed in the ICNIRP and IEEE guidelines [Hirata, 2005b]. They paid much attention to the correlation between peak SARs and maximum temperatures. They found that maximum temperature increases in the head are well correlated with peak spatial average SARs calculated with different schemes. Maximum temperature increases in the head for peak SAR values are largely dependent in the averaging scheme.

Hikage *et al.* estimated the electromagnetic field excitation by cellular radios in actual train carriages [Hikage, 2005b]. They mentioned; with regard to the electromagnetic compatibility (EMC) of the portable radio terminals such as cellular phones and data communication transceivers, the important issue is to prevent the occurrence of unwanted effects on the human health due to the RF exposure. As example, they conducted the precise computer numerical stimulating, FDTD method, using 800 MHz and 2 GHz transmitter in an actual train carriage and estimated the electromagnetic field distribution excited inside train carriage. The parallel FDTD computer simulation could be considered to be effective for estimating the complicated electromagnetic field excitation problems precisely.

Hikage *et al.* developed a 900 MHz ridged-waveguide microwave exposure equipment to achieve high power density irradiation for *in vitro* experiments [Hikage, 2007d]. This exposure system consists of a vector signal generator, 100 watts transistor amplifier, stub tuner, the ridged waveguide and terminator.

Ishikawa and Tanimura visualized the magnetic leakage flux from cellular phone [Ishikawa, 2006]. As a result of the visualization, the magnetic leakage flux from some parts of cellular phones can be clearly observed even when the cellular phone is turned off. The magnetic leakage flux can be estimated roughly to be about 0.01 mT. They emphasized this visualizing technique is useful for the research areas of human health, environmental medicine, scientific education and engineering.

Although there are several papers on the evaluation of electromagnetic wave exposure in the fetuses, the abdomen model, of pregnant women, the structure inside the models is not

representative of actual situation due to the organ and tissue complexity of the mother and fetus. So, Kawai *et al.* presented a simple abdomen model of pregnant women and evaluated the SAR inside the proposed model close to normal mode helical antennas (NHAs) [Kawai, 2006]. The SAR was calculated using FDTD method. They confirmed that the 10-g average SAR in the fetus is sufficiently less than 2 W/kg, when the output power of NHAs is 5 W which is the maximum power of portable radio terminals in Japan.

Nagaoka *et al.* developed an anatomically realistic whole-body pregnant-woman model for electromagnetic dosimetry [Nagaoka, 2007]. The numerical dosimetry of pregnant women is an important issue in electromagnetic field safety. They constructed a new fetus model including inherent tissues of pregnant women based on abdominal magnetic resonance imaging data of a 26-week-pregnant woman. The whole-body pregnant woman model was developed by combining the fetus model and a nonpregnant-woman model. The model consists of about 7 million cubical voxels of 2mm size and is segmented into 56 tissues and organs. First, this pregnant-woman model is completely anatomically realistic voxel model that includes a realistic fetus model and enables a numerical simulation of electromagnetic dosimetry up to the gigahertz band. In this paper, the basic specific absorption rate characteristics of the pregnant-woman model exposed to vertically and horizontally polarized electromagnetic waves from 10 MHz to 2 GHz.

With rapid increase in the use of the mobile phones in enclosed environments such as trains and elevators, public concern regarding the possibility of the RF exposure in such areas exceeding the basic restriction of the ICNIRP exposure guideline has been growing. Using of FDTD calculation method, Simba *et al.* carried out to determine whether the exposure in the elevator can exceed the basic restriction, 0.08 W/kg, whole-body average SAR [Simba, 2007a, 2007b]. They performed the FDTD calculation of the 10 g average SAR as a function of the human body position inside an elevator at 900, 1500 and 2000 MHz. The SAR results are below the ICNIRP exposure guideline.

Wang *et al.* have developed a formulation to approximate complex permittivities of biological tissues and organs as function of age [2006e]. The model is based on the dependence on water-content ratio which is dominant to determine the complex permittivity in GHz band.

A novel technique to evaluate SAR experimentally has been developed by Suzuki *et al.* [Suzuki, 2006]. Using liquid crystal sensitive to temperature, they measured temperature elevation due to microwave exposure.

Standardization of procedures for compliance tests of wireless terminals is also one of important topics. Mochizuki *et al.* clarified the effects of the size and shape of head phantoms on SAR distributions during exposure to near-field from a cellular phones [Mochizuki, 2007]. Ishii *et al.* investigated on applicability of a small antenna in phantom liquid for calibration of SAR probes [Ishii, 2007].

### **K3 Tissue Properties, Materials, and Phantoms**

#### **K3.1 Design Methods of the Electromagnetic Environment**

Tosaka *et al.* developed a measuring system using a tri-axial search coil in order to measure the magnetic field noise around electric devices [Tosaka, 2005]. They chose the measuring frequency is less than 100 kHz and the sensitivity is of the order of pico Tesla. In conclusion, the crosstalk of the orthogonal search coil is less than -40dB between the tri-axial search coil sensors. The sensitivity of the search coil is 10 pT/ $\sqrt{\text{Hz}}$  at 1 kHz.

#### **K3.2 Phantoms and Tissue Properties-Bioelectromagnetics Parameters**

Hirata *et al.* quantified induced current in anatomically based Japanese male and female models for exposure to low-frequency electric fields [Hirata, 2007b]. A quasi-static FDTD method was applied to analyze this problem. For the computational results, the difference of the induced current density averaged over an area of 1 cm<sup>2</sup> between Japanese male and female

models was less than 30 % for each nerve tissue. The difference of induced current density between the present study and earlier works was less than 50 % for the same conductivities, despite the different morphology. Particularly, maximum current density in central nerve tissues appeared in the retina of Japanese models, the same as in the earlier works.

Hirata *et al.* computationally verified the effect of anesthesia on temperature variations in the rabbit eye due to microwave energy [Hirata, 2006a]. The FDTD method was used for calculating the SAR and temperature variation in rabbits. They used a computational rabbit phantom, which is comprised of 12 tissues (including 6 eye tissues) with a resolution of 1 mm. Thermal constants of the rabbit were derived by comparing measured and calculated temperatures. For intense microwave exposure to the rabbit eye, time courses of calculated and measured temperatures were in good agreement for cases both with and without the administration of anesthesia. The point to be stressed is that under anesthesia the thermoregulatory response was inactivated, and blood flow and basal metabolism was reduced.

The correlation between the peak spatial-average SAR and maximum temperature increase for antennas attached to the human trunk was reported [Hirata, 2006b]. Frequency bands considered are 150, 400, and 900 MHz, which are assigned for occupational communications. The effect of variation of thermal constants on the temperature increase is revealed by using one-dimensional model. Computational results suggests that one of the most dominant factors which affect the correlation between peak SAR and maximum temperature increase is blood flow in tissues.

Hirata proposed an improved heat transfer model of the eye for exposure to RF electromagnetic field. Particular attention was paid to the difference from the simplified heat transfer model commonly used in this field [Hirata, 2007a]. From the computational results, the temperature elevation in the eye calculated with the simplified heat transfer model was largely influenced by the RF electromagnetic field-induced SAR outside the eyeball, but not when using their improved model.

Hirata *et al.* reported that a RF electromagnetic field-induced SAR of the human body for far-field exposure at the International Commission on the ICNIRP reference level has two peaks in the resonance frequency and GHz regions [Hirata, 2007d]. Dominant factors influencing whole-body average SAR in these two frequency regions have not yet been revealed sufficiently. The main purpose of this study is to clarify the dominant factors influencing the SAR in terms of whole-body average SAR in an anatomically based model compared with those in a homogeneous anthropomorphic model and corresponding cuboid models. Computational results show that the SAR peak in the resonance frequency region greatly depends on the electric properties of tissue, while the peak in the GHz region is affected mainly by the surface area of the model.

Hirata *et al.* investigated the effect of blood temperature variation modeling on body-core temperature [Hirata, 2007c]. The computational results show that the modeling of blood temperature variation was the dominant factor influencing the body-core temperature. This is because the temperature in the inner tissues is elevated via the circulation of blood whose temperature was elevated due to the RF electromagnetic field-induced SAR. Even at different frequencies, the body-core temperature elevation at an identical whole-body average SAR was almost the same, suggesting the effectiveness of the whole-body average SAR as a measure in the ICNIRP guidelines. Next, they discussed the effect of sweating on the temperature elevation and thermal time constant of blood. The variability of temperature elevation caused by the sweating rate was found to be 30%. The blood temperature elevation at the basic restriction in the ICNIRP guidelines of 0.4 W/kg is 0.25°C even for a low sweating rate. The thermal time constant of blood temperature elevation was 23 min and 52 min for a man with a lower and a higher sweating rate, respectively, which is longer than the average time of the SAR in the ICNIRP guidelines. Thus, the whole-body average SAR required for blood temperature elevation of 1 °C was 4.5 W/kg in the model of a human with the lower sweating coefficients for 60 min exposure. From a comparison of this value with the basic restriction in the ICNIRP



guidelines of 0.4 W/kg, the safety factor was 11.

Hirata *et al.* investigated the temperature elevation in the eye of anatomically based human head models for plane-wave exposures [Hirata, 2007e]. The finite-difference time-domain method is used for analyzing the RF electromagnetic field-induced SAR and temperature elevation. The eyes in the anatomic models have average dimensions and weight. Computational results show that the ratio of maximum temperature in the lens to the eye-average SAR is almost uniform (0.112-0.147°C W/kg) in the frequency region below 3 GHz. Above 3 GHz, this ratio increases gradually with an increase of frequency, which is attributed to the penetration depth of RF electromagnetic field. Particular attention is paid to the difference in the heating factor for the lens between this study and earlier works. Considering causes clarified in this study, compensated heating factors in all these studies are found to be in good agreement.

Hirata *et al.* investigated the SAR and temperature elevation in an anatomically-based human model for RF electromagnetic field exposure [Hirata, 2007f]. First, they investigated the effect of blood temperature variation and thermoregulation modeling on body-core temperature. The modeling of blood temperature variation was found to be the dominant factor influencing the body core temperature. This is because the temperature in the inner tissues is elevated via the circulation of blood warmed due to the RF electromagnetic field-induced SAR. For the same whole-body average SAR at different frequencies, the body-core temperature elevation was almost same, suggesting the effectiveness of the measure used in the ICNIRP guidelines. Then, they discussed the effect of sweating rate on the temperature elevation and thermal time constant of blood temperature. The uncertainty of temperature elevation due to the sweating rate was 30% or so.

Saito and Ito have been studying various coaxial-slot antennas for microwave hyperthermia. Saito *et al.* presented the effectiveness of the coaxial-slot antenna and the array applicators composed of two or four coaxial-slot antenna through clinical trials [Saito, 2005]. Then, as an example, they have developed a coaxial-slot antennas aiming at intracavitary heating for bile duct carcinoma [Saito, 2006; Hiroe, 2006]. They estimated the heating performance of such antenna for the actual treatments and confirmed the possibility of this treatment by use of the proposed coaxial-slot antenna.

Phantoms are used to evaluate amounts of absorbed electromagnetic energy. Ito and his research groups developed phantoms for use in the frequency range from 3 to 10 GHz. Takimoto *et al.* evaluated the effectiveness of the biological tissue-equivalent solid phantom for Ultra WideBand (UWB) communications [Takimoto, 2006]. Solid phantom can be obtained manufacturally the arbitrary shapes. Such solid phantom have been developed and used for the frequency bands between 3-10 GHz. It was shown that it is possible to investigate antenna characteristics using this developed phantom in wide frequency ranges in mobile terminal. Ito *et al.* reviewed the development of solid biological tissue-equivalent phantoms for UWB communications band and evaluated the interaction between human bodies (called biological tissue-equivalent phantom) and radio terminals [Ito, 2007b].

Hiroe *et al.* developed the phantom for measurement of temperature rises inside biological tissue by electromagnetic wave exposure [Hiroe, 2007]. Iwai *et al.* also developed a realistic human phantom in a PDA (Personal Digital Assistance) position for electromagnetic wave evaluation of handset antennas [Iwai, 2006].

There are few data of electrical properties of biological tissues and organs in millimeter-wave (MMW) while new wireless technology will be operated in the frequency regions. Wakatsuchi *et al.* recently tried to measure complex permittivities of whole-blood sample upto 50 GHz [Wakatsuchi, 2007].

## **K4 Biomedical Applications**

### **K4.1 Magnetic stimulation**

Hirayama *et al.* examined the effects of rTMS on pain in patients with intractable deafferentation pain [Hirayama, 2006]. Twenty patients received ten trains of rTMS (5 Hz for 10 seconds at 50 second interval) of the primary motor cortex (M1), the postcentral gyrus (S1), premotor area (preM), and supplementary motor area (SMA). Results indicated a statistically significant effect lasting for 3 hours after the stimulation of M1. Stimulation of other targets was not effective. The M1 was the sole target for treating intractable pain with rTMS, in spite of the fact that M1, S1, preM, and SMA are located adjacently.

Saitoh *et al.* also investigated the effects of rTMS on pain in patients with intractable deafferentation pain [Saitoh, 2006, 2007a]. Ten trains of rTMS (5Hz for 10 seconds at 50 second interval) were applied to the M1, S1, preM and SMA. Only M1 stimulation was effective for pain reduction (50%). Motor cortex stimulation (MCS) procedures were performed. The success rate of MCS was around 63%, and seemed to be higher in cases of pain with spinal cord and peripheral origins, while it was lower in cases of post-stroke pain.

Saitoh *et al.* further evaluated the effects of rTMS on pain in patients with a cerebral lesion or with a noncerebral lesion [Saitoh, 2007b]. Ten trains of rTMS (5Hz for 10 seconds at 50 second interval) were applied to the M1, S1, pre-. The rTMS was applied to all the patients at frequencies of 1, 5, and 10 Hz and as a sham procedure in random order. High-frequency (5 or 10 Hz) rTMS of the precentral gyrus can reduce intractable deafferentation pain, but low-frequency stimulation (at 1 Hz) cannot. Patients with a noncerebral lesion are more suitable candidates for high-frequency rTMS of the precentral gyrus.

Sakihara *et al.* investigated whether the vestibulospinal tract mediates late electromyographic response with a latency of 100ms evoked bilaterally in soleus muscles following rTMS (1.4 T ELF-PEMF) over the left cerebellum [Sakihara, 2007]. The vestibulospinal tract was activated by optokinetic stimulation. The results show that the latency of the soleus electromyographic response is shortened by optokinetic stimulation, but the latency of the motor response evoked by the corticospinal tract is unchanged. These findings support our hypothesis that vestibulospinal tracts mediate late electromyographic responses, and allow the development of techniques to assess the human vestibulospinal system function.

Ueno and Sekino reviewed medical applications of the recently developed techniques in biomagnetics and bioimaging such as transcranial magnetic stimulation, magnetoencephalography, magnetic resonance imaging, cancer therapy based on magnetic stimulation, and magnetic control of cell orientation and cell growth. They emphasized that these techniques are leading medicine and biology into a new horizon through the novel application of magnetism [Ueno, 2006].

First, Sekino *et al.* calculated eddy current distributions in transcranial magnetic stimulation (TMS) under various conditions and compared their calculated results with the current distribution in electroconvulsive therapy (ECT) in order to find an optimum conditions of TMS as an alternative to ECT [Sekino, 2005d]. Then, they performed numerical simulation of the eddy current induced by transcranial magnetic stimulation (TMS) to the cerebellum [Sekino, 2006a]. Solutions were obtained on a three-dimensional human head model with inhomogeneous conductivity. The maximum current density in the cerebellum was 2.9A/m<sup>2</sup> in a magnetic field intensity of 0.56 T. Distribution of the eddy current in the cerebellum was limited to approximately 1 cm beneath the surface of the cerebellum.

Maeda *et al.* designed and developed the magnetic separator for biomaterials labeled by magnetic beads [Maeda, 2007]. Magnetic separation is an important method for purifying of cells or NDA. Their developed magnetic separator consisted of three rectangular coils, two circular coils, and a separation chamber. A separation rate over 90 % was obtained with this system in a separation test using magnetic beads.

#### **K4.2 Thermal Therapy**

Tanaka *et al.* investigated the therapeutic effects of dendritic cell (DC) therapy combined with magnetite cationic liposomes (MCL)-induced hyperthermia on mouse melanoma [Tanaka,

2005]. In an *in vitro* study, when immature DC was pulsed with mouse B16 melanoma cells heated at 43°C, major histocompatibility complex (MHC) class I/II, costimulatory molecules CD80/CD86 and CCR7 in the DC were upregulated, thus resulting in DC maturation. C57BL/6 mice bearing a melanoma nodule were subjected to combination therapy using hyperthermia and DC immunotherapy *in vivo* by means of tumor-specific hyperthermia using MCL and directly injected immature DC. Mice were divided into 4 groups: group I (control), group II (hyperthermia), group III (DC therapy) and group IV (hyperthermia + DC therapy). Complete regression of tumors was observed in 60% of mice in group IV, while no tumor regression was seen among mice in the other groups. Increased cytotoxic T lymphocyte and natural killer activity was observed on *in vitro* cytotoxicity assay using splenocytes in the cured mice treated with combination therapy, and the cured mice rejected a second challenge of B16 melanoma cells. This study has important implications for the application of MCL-induced hyperthermia plus DC therapy in patients with advanced malignancies as a novel cancer therapy.

Mochiki *et al.* applied a new treatment modality using a combination of gastrectomy with postoperative intraperitoneal hyperthermo-chemotherapy (PIHC) using a heating device Thermotron RF-8 (8 MHz EMF) [Mochiki, 2007]. They evaluated the feasibility of PIHC in advanced gastric carcinoma patients with peritoneal seeding. The PIHC group received a 60-min PIHC with a cisplatin (80 mg/m<sup>2</sup>) two weeks after surgery, and the control group received surgery alone. The PIHC group had a significantly higher survival rate and better prognosis compared with the control group.

Ito and Saito described two types of heating schemes which can be used with microwave energy, and provided brief explanations of the basic engineering involved [Ito, 2007a]. In addition, they pointed out the evaluation method of antenna performance. Ito reviewed the antenna technology to medicine [Ito, 2006]. His review included the diagnosis, hyperthermia, MRI, computed tomography and telemetering system.

#### **K4.3 Thermal Therapy-Soft heating and Inductive Heating**

In hyperthermia, high frequency electromagnetic fields are used to heat the cancer cells. These electromagnetic fields fall into two frequency ranges and produced some side effects such as the heating of healthy cells or the impact on the body of invasive surgery required to exposed deep-lying cells. To reduce these side effects, Matsumoto *et al.* proposed the use of lower microwave frequencies with phase control [Matsumoto, 2007]. They confirmed that the phase control technique for long-wavelength, 430 MHz, microwaves was effective in producing localized heating. In order to use the brain tumor, Kikuchi *et al.* estimated the heating pattern for interstitial microwave hyperthermia by a coaxial-dipole antenna [Kikuchi, 2006]

Saito and Ito described the fundamental characteristics of microwave inside the biological tissue and two types of heating schemes for the hyperthermic treatments [Saito, 2007]. In Addition, they introduced the actual treatment of newly developed microwave antenna. Microwave energy is one of the heating sources used for thermal therapy of cancer.

Stents are one method of treatment for stenosis of lumens organ from various causes. The cylindrical metallic stents are composed of alloy wire. After stents are implanted, however, the stenosis may recur due to a tumor or abscess again. It is particularly difficult to remove tumors or abscesses of the bile duct by surgical repair, because the duct is in a deep portion of the abdomen. Oya *et al.* proposed a noninvasive remedying method for tumors and abscesses by using thermotherapy with magnetically excited metallic stents [Oya, 2006; 2007]. Currently, clinical stents are not manufactured to allow for heating. We made experimental stents by magnetic shunt steel to heat the stents and control the heat of stents by external magnetic excitation for thermo-therapeutic applications [Hodaka, 2005].

A series of research papers about the soft-heating from Tohoku University were published [Matsuki, 2006; Maruyama, 2006; Sawaya, 2005; Takura, 2007a, 2007b]. Soft-heating method is one kind of heating technique of hyperthermia. The feature of this method is to use thermosensitive magnetic material as the heat element. The heater consists of thermosensitive

ferrite and is implanted into the body. The heating can be obtained by a high-frequency magnetic field. This means the heat element can control the temperature automatically, referring the Curie-point of the thermosensitive ferrite. The heat element consists of a thermosensitive ferrite and metal ring. The purpose of the metal ring wrapped to ferrite is increase heat quantity compared with that of ferrite alone. The effect of the heat element in mouse tumor model (B-16 melanoma) is examined. As a result, the tumors of mice were locally heated to the point at which tumor is necrotized in the condition of 6 mT at 200 kHz. Sawaya *et al.* examined the exciting conditions for the high-temperature magnetic hyperthermia [Sawaya, 2005]. The creation of a complex type of heater consists of thermosensitive ferrite wound on a metallic ring which gives the production of heat due to lossess of hysteresis and inductive currents. They examined the effect of exciting frequency on the heating. The area if 12 x 7 mm is heated over 60° in phantom in the condition of 6 mT at 100 kHz. As example, the tumors of mice were heated due to the point at which the tumor is necrotized.

Takura *et al.* created a complex heater composed of thermosensitive ferrite wound on a metallic ring which produces a greater amount of heat due to losses through hysteresis and inductive current than thermosensitive ferrite alone [Takura, 2007a]. The temperature of the heater was controlled by using the Curie-point. They comment that it is necessary to miniaturize the element and achieve optimal performance if their technique is used. They also developed the miniaturization of micro implantable devices with thermosensitive ferrite for soft-heating hyperthermia [Takura, 2007b].

#### **K4.4 MRI and Current Distribution MRI**

Two strategies-motor and visual- are considered to be used for performing mental rotation. The former involves the function of the motor-related areas of the brain, whereas the latter does not. Subject's experience influence strategy selection during the mental rotation of three-dimensional (3D) shapes. However, it remains questionable as to whether the attributes of 3D objects enhance the motor-related activities. Kawamichi *et al.* compared the brain activities during two types of mental rotations-two-dimensional (2D) and 3D rotation using functional magnetic resonance imaging (fMRI) [Kawamichi, 2007a]. Then, they measured spatio-temporal brain activities during two types (two dimensional (2D) and 3D rotation tasks) of mental rotation of 3D objects using magnetoencephalography (MEG), task difficulty enhanced by rotation dimensionality is a major factor related to the selection of motor strategy [Kawamichi, 2007b].

Sekino *et al.* performed numerical simulations of the eddy current induced by TMS/ELF-PEMF to the cerebellum [Sekino, 2006a]. Solutions were obtained on a three-dimensional human head model with inhomogeneous conductivity. The stimulating coil consisted of a pair of circular coil elements with a diameter of 110 mm. The electric current applied to the coil had an intensity of 44.2 kA Turn, which resulted in a magnetic field intensity of 0.56 T at the center of a coil element. The maximum current density in the cerebellum was 2.9 A/m<sup>2</sup>. Distribution of the eddy current in the cerebellum was limited to approximately 1 cm beneath the surface of the cerebellum. The eddy current had a localized distribution in the cerebellum, while the magnetic field had a broad distribution.

Detection of weak magnetic fields induced by electrical currents using MRI is necessary for mapping neuronal activities in the brain. Such detection is dependent on the signal-to noise ratio and sensitivity of MRI. Hatada *et al.* computed the brain eddy current distributions induced by RF magnetic field from a birdcage coil in MRI by simulations based on the finite element method (FEM) and calculated Johnson noise from the head [Hatada, 2005a, 2005b].

Imae *et al.* obtained the minimization of discrete errors in diffusion simulation of nuclear magnetization [Imae, 2007]. Simulations of finite-difference diffusion are used for solving the diffusion equation of nuclear magnetization in discrete space and time. They evaluated the difference between a discrete solution and an exact solution that had been derived from the

manetization diffusion equation..

Tanaka *et al.* proposed a method of estimating mechanical strain in biological tissue using diffusion MRI [Tanaka, 2007]. Mechanical strain in biological tissues causes a change in the diffusion properties of water molecules. Measurements were carried out on uncompressed and compressed chicken skeletal muscles. A theoretical model of the diffusion of water molecules in muscle fibers was derived based on Tanner's equation. The intracellular diffusion coefficient was changed by mechanical strain.

Kodama and Takeuchi assessed relationships between six texture features and changes in atrophy of the cerebral parenchyma, the hippocampus, and the parahippocampal gyrus in the Alzheimer-type dementia (ATD) brain to determine whether or not the features reflect cerebral atrophy in ATD patients [Kodama, 2005]. The subjects were 10 ATD patients consisted of three men and seven women (the mean age of  $71.4 \pm 6.7$  years) underwent an MRI test of the head annually for at least 3 consecutive years. These results indicate that the six texture features were shown to reflect gray matter atrophy associated with ATD and to change with the progress of the disease. The texture features should be a more effective instrument for identifying the progress of ATD.

Kumagai *et al.* prepared PEG-coated beta-FeOOH nanoparticles through electrostatic complex formation of iron oxide nanoparticles with poly (ethylene glycol)-poly (aspartic acid) block copolymer [PEG-P (Asp)] in distilled water [Kumagai, 2007]. The nanoparticle size was determined to be 70 nm with narrow distribution. The PEG-coated nanoparticles revealed excellent solubility and stability in aqueous solution as well as in physiological solution. The experiments on tumor-bearing mice demonstrated that this nanoparticle achieved an appreciable accumulation into solid tumor.

Using of Wistar rats at nine weeks olds, Saotome *et al.* obtained  $^1\text{H}$  magnetic resonance spectra of skeletal muscles, with and without atrophy and evaluated the content of creatine in the muscles [Saotome, 2005]. Tissues have diffusional anisotropy. Their diffusion properties are denoted by a tensor. Saotome *et al.* evaluated the diffusional anisotropy and microscopic structure in atrophied skeletal muscles using the pulsed-gradient spin-echo (PGSE) nuclear magnetic resonance (NMR) method [Saotome, 2006]. In this study, the left sciatic nerve was severed in twelve 9-week-old rats. The proposed method is effective for evaluating changes in the microscopic structure of skeletal muscles.

Sekino *et al.* obtained the spatial distribution of anisotropic conductivity of the human brain using MRI [Sekino, 2005a]. Estimation of conductivity is based on the proportionality between the conductivity and the diffusion coefficient of water. The gray matter did not have a clear dependence of conductivity on direction. In some region in the white matter, conductivity exhibited high anisotropy. This method has potential applications in current source estimations of EEG and MEG. Then, Sekino *et al.* investigated the effect of strain on diffusion tensor MRIs of muscles using numerical simulations and animal experiments [Sekino, 2005b]. A compression of a tissue caused a decrease in the effective coefficient in the direction of compression and an increase in the fractional anisotropy of diffusion.

Generally, non-invasive imaging techniques is useful for analysis of electromagnetic fields, current distributions in electric stimulation and magnetic stimulation, the calculation of the absorption of electromagnetic waves from mobile phones, current source estimation in EEG and MEG. Sekino and Ueno reviewed the new methods for MRI of electric properties in living bodies [Sekino, 2007]. They recommend that new methods have potential applications in biomedical engineering involving electromagnetic field analysis and new diagnostic imaging techniques.

#### **K4.5 Contactless power transmission system**

Matsuki and Sato explain the fundamental operation of circuit, and outlines trends in circuits for various contactless power supply application including home electrical appliances and electric automobiles [Matsuki, 2007].

Contactless power supply systems transmit electric power by electromagnetic induction with a pair of coils. The efficiency and the output voltage depend on parameters of coils. The suitable parameter values that realize stable high efficiency contactless power supply have been obtained. In the application with low output voltage, the voltage drop of the diodes becomes dominant power loss. A synchronous rectification was proposed as a solution of this problem. The contactless power supply system for an artificial heart operates at 190 kHz. The planar coils with Mn-Zn ferrite core were applied. Highly stable output voltage and 93.4% of maximal efficiency (dc-dc) were realized.

The devices were designed in view of the biomedical compatibility, gradually sloped coils and the flexibility of the primary coil prevent pressure necroses of the skin. The rectifier circuit board was placed in the internal space of the ferrite core to reduce the number of the implanted devices.

Implant medical devices are physically isolated from power sources required to supply driving energy to them. A well-known contactless power transmission technology is the transcutaneous energy transmission system (TETS), which applies electromagnetic induction between two disk-like spiral coils (a primary coil outside the body, and a secondary coil inside the body). Implant devices that require a temperature rise for their actuation must be prevented from overheating, and transcutaneous control and monitoring of the devices' temperature is necessary. A small inductor with a thermosensitive ferrite core was developed as a thermo-sensing device. This inductor controls the temperature automatically inside the body in combination with TETS. A coupling factor change between the two coils of a TETS transformer also affects the stability of power transmission characteristics. A suitable excitation frequency was designed to ensure stable driving. The control system referred to above has been applied in an artificial anal sphincter system that is now being developed, and appropriate driving has been observed [Arai, 2005; Kakubari, 2006a, 2006b; Matsuki, 2007; Miura, 2005a, 2005b, 2006].

#### **K4.6 Electromagnetic interference**

The use of implantable cardiac pacemakers has become more widespread in the world. In Japan, more than 50,000 devices are implanted per year as of 2005. Now, many communication devices including Radio Frequency Identification (RFID), Electronic Article Surveillance (EAS) and contactless IC cards are expected to be more popular. The implantable cardiac pacemaker patients are exposed to the electromagnetic field generated from these communication devices. From the safety issue, it must be clarified that the impact of electromagnetic field from these devices (EMI) on implantable cardiac pacemaker.

Hanada proposed that most problems with the electromagnetic environment of medical institutions have been related to radiated electromagnetic field and have been constructed from reports about electromagnetic interference (EMI) with electronic medical equipment by the radio waves emitted from mobile telephone handsets [Hanada, 2007]. Examples of measurements and measuring methods were shown for radiated electromagnetic field, the static magnetic field, power-source noise, and common components of the medical electromagnetic environment.

Tarusawa *et al.* clarified the impact of electromagnetic interference (EMI) from cellular base station (BS) antennas on implantable cardiac pacemaker [Tarusawa, 2005b]. The estimation of the impact is based on *in vitro* experiments conducted using simulated multicarrier and multicode signals. These signals are transmitted from actual BS antennas and dipole antennas as the radiation source of the BS antenna. The results showed that pacemaker EMI depends on the average power of the transmission signal and does not depend on the peak-to-average power ratios of the transmission signals. No pacemaker EMI is detected in the immediate vicinity under the BS antenna at an input power level for typical operation. It is clear that the pacemaker EMI should not pose a concern in residential environments.

Futatumori *et al.* investigated the EMI effect of RFID reader/writer on pacemakers and ICDs using newly constructed *in vitro* experimental system based on an Irnich's flat torso phantom [Futatumori, 2006abcd]. The *in vitro* EMI test, experiments on 10 types of RFID

reader/writer and 13 types of implantable pacemakers and defibrillators were conducted. The frequency bands were 125 kHz, HF (13.56 MHz), UHF (950 MHz) and 2.45 GHz. Futatsumori *et al.* have been carried out the detailed *in-vitro* experiments to assess the EMI due to RFID reader/writers for implantable medical devices (RFID/IMD-EMI). They proposed a novel RFID/IMD-EMI assessment methodology based on the total magnetic flux integrated across the pacemaker and the lead cross-section [Futatsumori, 2007ab]. Taguchi *et al.* developed three-dimensional automatic measurement system for the assessment methodology of implantable medical devices EMI due to RFID reader/writers [Taguchi, 2007].

Hikage *et al.* estimated the EMI risk to pacemakers by cellular radio transmission considering the effect of electromagnetic field absorption and shielding due to a human's body inside the elevator [Hikage, 2007a]. Large scale FDTD analysis for implantable cardiac pacemakers EMI due to mobile radios in train carriage of complicate situation were carried out by Higaki et al [Hikage, 2007c].

Hirose *et al.* investigated quantitatively the EMI caused by an induction oven in implantable unipolar cardiac pacemakers and measured the distribution profile of the magnetic field strength both with and without a pan on the induction oven [Hirose, 2005]. Then, they performed the inhibition test and asynchronous test using four kinds of pacemakers housed in the standardized Irnich human body model and the maximum distance from the induction oven up to which the EMI occurred. The maximum EMI distance from the oven was 34 cm for one of the pacemakers. The safe distance from an induction oven of a patient with an implanted cardiac pacemaker is considered to be 50 cm or more.

Although the Computed Tomography (CT) is widely used in clinical practice, there has not been a detailed report of its effect on the function of pacemakers. Yamaji *et al.* investigated the effect of CT on a pacemaker in a human body mode with and without shielding by rubber or lead and measured ECGs in 11 patients with pacemakers and electromagnetic field in the CT room during CT scanning [Yamaji, 2006]. Transient malfunctions of pacemakers during CT occurred in 6 of 11 patients. The malfunction was prevented by lead but not by rubber. The alternating electric field was 150 V/m and the alternating magnetic field was 15 $\mu$ T on the CT scanning line. These field strengths were lower than the level of influencing pacemaker functions.

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