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Enhancement of the Hydrolysis Activity of F_0F_1-ATPases Using 60 Hz Magnetic Fields

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The effects of extremely low frequency (ELF) magnetic fields on membrane F_0F_1-ATPase activity have been studied. When the F_0F_1-ATPase was exposed to 60 Hz magnetic fields of different magnetic intensities, 0.3 and 0.5 mT magnetic fields enhanced the hydrolysis activity, whereas 0.1 mT exposure caused no significant changes. Even if the F_0F_1-ATPase was inhibited by *N*,*N*-dicyclohexylcarbodiimide, its hydrolysis activity was enhanced by a 0.5 mT 60 Hz magnetic field. Moreover, when the chromatophores which were labeled with F-DHPE were exposed to a 0.5 mT, 60 Hz magnetic field, it was found that the pH of the outer membrane of the chromatophore was unchanged, which suggested that the magnetic fields used in this work did not affect the activity of F0. Taken together, our results show that the effects of magnetic fields on the hydrolysis activity of the membrane F_0F_1-ATPases were dependent on magnetic intensity and the threshold intensity is between 0.1 and 0.3 mT, and suggested that the F1 part of F_0F_1-ATPase may be an end-point affected by magnetic fields. Bioelectromagnetics 30:663–668, 2009.

Key words: F_0F_1-ATPases; chromatophores; magnetic field; hydrolysis activity

INTRODUCTION

At present, the effects of extremely low frequency electromagnetic fields (ELF-EMFs) on human health have prompted considerable public concern since ELF-EMFs are ubiquitous in modern society [Repacholi and Greenebaum, 1999; Kheifets and Shimkhada, 2005; Saunders and McCaig, 2005; Paniagua et al., 2007]. The effects can be mostly attributed to the dynamics at the nucleic acid and protein levels, with possible influences on DNA, RNA, and protein synthesis [Cridland et al., 1999; Ciombor et al., 2002; Del Re et al., 2003, 2004; Schmitz et al., 2004], the membrane protein structure of living HeLa cells [Ikehara et al., 2003], ornithine decarboxylase enzyme activity [Byus, 1995; Valtersson et al., 1997; Ichinose et al., 2004; Naarala et al., 2004], Na,K-ATPase activity [Blank and Soo, 1993, 1996; Martirosov and Blank, 1995] and biological membranes [Miller, 1991; Paradisi et al., 1993; Astumian et al., 1995; Bersani et al., 1997; Volpe et al., 1998; Baureus-Koch et al., 2003]. However, there are still some disputes concerning the physical mechanism of the effects of electromagnetic fields on organisms [Adair, 1991; Valberg et al., 1997].

In a living cell the F_0F_1-ATPases interconverts two major ''energy currencies'', namely, the transmembrane electrochemical potential difference of protons (or Na^+ in some organisms) and ATP. It is composed of two parts, membrane-embedded F0 and hydrophilic catalytic F1 [Kagawa et al., 1979] (Fig. 1). To further understand the effects of ELF-EMFs on human health, it is important to explore the effects of ELF-EMFs on F_0F_1-ATPases as a possible initial step in a cascade of events that could affect health. Many reports have described the effects of electric fields on ATPase [Witt et al., 1976; Witt, 1979; Vinkler and Korenstein, 1982; Tsong, 1990; Zrimec et al., 2002], but few reports so far have focused on the effects of magnetic fields on ATPase. In fact, research into the bioeffects of ELF magnetic fields is more important than that of electric fields for evaluating health hazards

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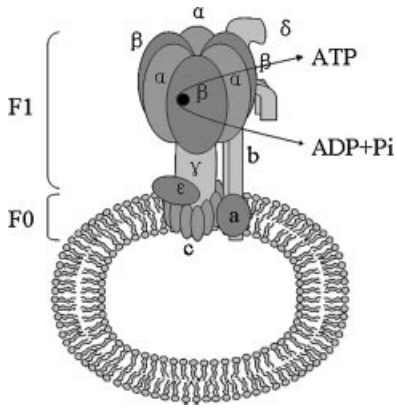

Fig. 1. The schematic subunit organization of F_0F_1-ATPases. F_0F_1-ATPases is composed of eight different subunits, five of which belong to F1, subunits alpha, beta, gamma, delta, and epsilon (3:3:1:1:1), and three to F0, subunits a, b, and c (1:2:10–12).

of ELF-EMFs because there are more disputes on the bioeffects of ELF magnetic fields [Repacholi and Greenebaum, 1999]. The effects of ELF magnetic fields on membrane F_0F_1-ATPase activity are reported in this article.

MATERIALS AND METHODS

Preparation of Chromatophores

The chromatophores were prepared from the cells of *Rhodospirillum rubrum* as previously reported [Suzuki et al., 2003; Cui et al., 2005]. In brief, *R. rubrum* was cultured anaerobically in closed vessels at 30 °C under continuous illumination according to the method described elsewhere [Zürrer and Bachofen, 1979]. The harvested cells of *R. rubrum* were suspended in a buffer solution A (0.1 mM Tricine–NaOH, 0.25 M sucrose, 5 mM $MgCl_2$, pH 8.0). The suspension was incubated on ice for 30 min after addition of 1 mg/ml lysozyme. The suspension was sonicated for 10 min (5 s on, 5 s off), causing the plasma membrane to break up and invert to form vesicles with the F_0F_1-ATPases inside out (Fig. 1). The suspension was centrifuged (25,000*g*, 30 min, 4 °C) and the supernatant fluid was transferred to a new tube and centrifuged again (180,000*g*, 90 min, 4 °C). The pellets, which are called chromatophores, were re-suspended in buffer A with 50% glycerol, frozen immediately in liquid nitrogen then stored at −80 °C.

The bacteriochlorophyll (BChl) concentration in the chromatophores was determined by the in vitro extinction coefficient as reported by Clayton [1963]. Measurements in our laboratory showed that there were 2.34×10^{-12} mol of F_0F_1-ATPases in 1 μg Bchl of chromatophores.

Treatment of F_0F_1-ATPases With DCCD and LiCl

Two procedures were used to inhibit the hydrolysis activity of F_0F_1-ATPases. In one procedure, the F_0F_1-ATPases were treated with *N*,*N*-dicyclohexylcarbodiimide (DCCD) as follows. BChl (1.2 μg) of chromatophores was mixed with an equal volume of 100 mM Tris–HCl (pH 8.8) buffer (composed of 100 μM DCCD) and placed on ice for 1 h. In the other procedure, the F_0F_1-ATPases were treated with 2 M LiCl as follows. The 1.2 μg BChl of chromatophores was centrifuged at 18,000*g* for 30 min and the pellet was re-suspended in buffer (250 mM sucrose, 50 mM Tricine, 4 mM $MgCl_2$, 4 mM ATP, 1 mM dithiothreitol, 1 mM phenylmethylsulfonyl fluoride, 2 M LiCl, pH 8.0) then incubated at 25 °C for 30 min to remove the beta subunits of F_0F_1-ATPase from the chromatophores.

Hydrolysis Activity of the F_0F_1-ATPases in Chromatophores

Liu et al. [2004] reported that when the concentration of the ATP is pre-saturated ([ATP] = 10–100 μM) and saturated ([ATP] > 100 μM), the hydrolysis mechanism of the F_0F_1-ATPases behaved in an ATP-dependent manner instead of the widely believed Michaelis–Menten mechanism. In this article, the concentration of the ATP will be raised to saturation level to get good results. Accordingly, the hydrolysis activity of F_0F_1-ATPases is the maximum rate of ATP hydrolyzed per unit of enzyme per unit time and is expressed in moles of ATP hydrolyzed per mole of F_0F_1-ATPases per second (mol ATP/mol F_0F_1-ATPases/s or simply 1/s).

BChl (18 μg) of chromatophores was re-suspended in 35 μl of ATP hydrolysis buffer (50 mM Tricine–NaOH (pH 8.0), 5 mM $MgCl_2$, 4 mM NaH_2PO_4, 15 mM glucose, 5 mM dithiothreitol) at 25 °C. After adding 1 μl of 10 mM ATP and mixing immediately, the F_0F_1-ATPase hydrolysis reaction of ATP began and continued for 30 min at 25 °C. During the reaction, 2 μl of reaction mixture was removed every 3 min and the reaction stopped using 0.2 μl of 4% trichloroacetic acid (TCA). The ATP concentration was measured by the luciferin/luciferase system. Typically, 2.2 μl of mixture was diluted with 100 μl of buffer (100 mM Tricine–acetate, 2 mM EDTA, pH 7.75) and 50 μl of luciferin/luciferase was added. The mixture was mixed quickly and placed in an ultra weak fluorescence analyzer immediately and the photons produced in 10 s at 25 °C

were recorded by computer. In this system, 1 mol ATP will produce 6.77×10^{14} photons.

Labeling the Chromatophores With pH Indicator F-DHPE

Frozen chromatophores (20 µl) was diluted with 980 µl buffer (0.1 mM Tricine–NaOH, 50 mM KCl, 5 mM $MgCl_2$, pH 8.0) and 1 µl saturated *N*-(fluorescein-5-thiocarbamoyl)-1,2-dihexadecanoyl-*sn*-glycero-3-phosphoethanolamine, triethylammonium salt added (F-DHPE) (Molecular Probes, Eugene, OR). This was then incubated on ice for 30 min and centrifuged at 15,000*g* for 15 min. The resulting pellet was re-suspended in buffer solution (0.1 mM Tricine–NaOH, 50 mM KCl, 5 mM $MgCl_2$, pH 8.0). The fluorescence of the pH indicator F-DHPE was detected by a F-4500 FL Spectrophotometer (Hitachi, Tokyo, Japan).

MF Exposure System and Experimental Design

An ELF magnetic exposure system was constructed in our laboratory for the experiments. This system consists of a high-precision AC current source and two rectangular coils, as described by Misakian et al. [1993]. Each rectangular coil was made up of two sub-coils each with 100 turns of copper wire (diameter 1 mm), which could produce equal magnetic field strength. The two rectangular coils consisted of 200 turns of copper wire with dimensions 12 cm × 6 cm separated by a distance of 7 cm. To control the currents in the coil, a bi-directional switch was designed. When the currents in the two sub-coils were in same direction, the coil would generate and expose the sample to a uniform, sinusoidal, vertical AC magnetic field. When the currents of the sub-coils were in opposite directions, the coil would generate magnetic fields with zero strength for a sham exposure experiment. In our experiments, the exposure fields were characterized as 60 Hz, 0.1–0.5 mT, and detected by a Gauss/Tesla meter (F.W. Bell Model 7010, Bell Technologies, Orlando, FL). The non-uniformity of the magnetic fields in the exposed space (50 mm × 10 mm × 5 mm) is less than 2%. The vertical component of the geomagnetic field is 31 µT, the north-south component is 28 µT and the east–west component is 11 µT, values which were measured by a fluxgate magnetometer (National Institute of Metrology, Beijing, P. R. China).

In this article, the exposure experiments were done in a temperature-controlled (25 ± 1 °C) room, and the temperature difference between exposure group and sham group is less than 0.2 °C in the exposed space. During the measurement, the researcher who measured the ATP concentration was not informed of the exposure conditions. Each exposure experiment was repeated at least three times.

Statistical Analysis

All the data were analyzed using the software SPSS 13.0 for Windows (SPSS, Chicago, IL). The statistical significance was determined by a paired-sample *t*-test. Error bars represent standard deviation (SD) of the mean. The significance was set at $^*P < 0.05$, $^{**}P < 0.01$.

RESULTS

Hydrolysis Activity of F_0F_1-ATPases

The hydrolysis activity of the chromatophores at room temperature (25 °C) was calculated to be $14.11 \pm 1.67\ s^{-1}$. When the F_0F_1-ATPases were treated by the inhibitor DCCD and LiCl, the activities fell to only $4.80 \pm 0.68\ s^{-1}$ and $0.86 \pm 0.51\ s^{-1}$, respectively.

Effects of Magnetic Fields on the Hydrolysis Activity of F_0F_1-ATPases

The rate of autohydrolysis of ATP at 25 °C in the buffer system was $1.07 \pm 0.89 \times 10^{-13}$ mol/s. When the ATP buffer was exposed to 0.5 mT 60 Hz magnetic field, the rate was $1.17 \pm 0.95 \times 10^{-13}$ mol/s. There are no significant differences between the rates of the exposed and the sham group ($P > 0.05$, $n = 6$). Therefore, the autohydrolysis of ATP was not affected by the magnetic field.

When the membrane F_0F_1-ATPases were exposed to 60 Hz magnetic fields at different magnetic intensities (0.1, 0.3, and 0.5 mT), the results, presented in Figure 2, showed that both 0.3 and 0.5 mT, 60 Hz

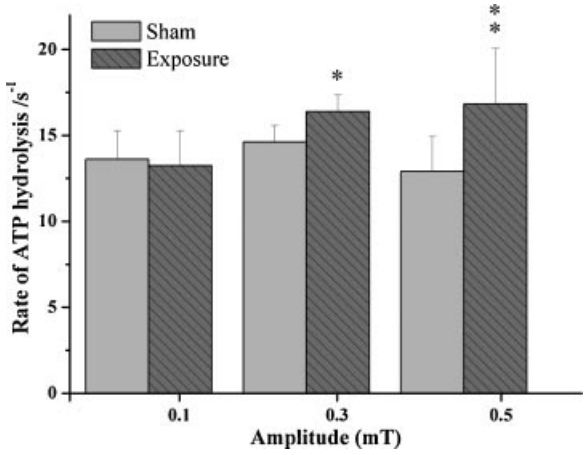

Fig. 2. The effects of 0.1–0.5 mT, 60 Hz magnetic fields on F_0F_1-ATPase. Error bars represent SD of the mean. Significance was set at $^*P < 0.05$, $^{**}P < 0.01$, $n = 6$.

magnetic fields enhanced the hydrolysis activity significantly (both $P < 0.05$, $n = 6$), but the 0.1 mT, 60 Hz magnetic field had no significant effect ($P > 0.05$, $n = 6$).

It is well known that the inhibitor DCCD can reduce both the synthesis and hydrolysis activity of F_0F_1-ATPase by inhibiting the transfer of H^+ across membrane. When the F_0F_1-ATPase had been inhibited by DCCD for 1 h, the hydrolysis activity was $4.80 \pm 0.68\ s^{-1}$, which represented a 68.1% deactivation. When the F_0F_1-ATPase, inhibited by DCCD for 1 h, was exposed to a 0.5 mT 60 Hz magnetic field, the hydrolysis activity increased to $6.97 \pm 1.24\ s^{-1}$ ($P < 0.01$, $n = 6$). Therefore, exposure to a 0.5 mT 60 Hz magnetic field still stimulated the hydrolysis activity of the F_0F_1-ATPase even after the F_0F_1-ATPase had been inhibited by DCCD for 1 h.

When the F_0F_1-ATPases were treated with 2 M LiCl for 24 h, the hydrolysis activity was reduced to $0.86 \pm 0.51\ s^{-1}$ due to the removal of the beta subunits of F_0F_1-ATPase. When these treated F_0F_1-ATPases were exposed to a 0.5 mT 60 Hz magnetic field, the hydrolysis activity of F_0F_1-ATPase was $0.66 \pm 0.34\ s^{-1}$. Thus, there is no significant difference between the exposed group and the sham group ($P > 0.05$, $n = 6$).

Effects of MF on the pH of the Chromatophores

To further investigate how magnetic fields affect membrane F_0F_1-ATPase, a H^+ transfer experiment was performed without the addition of ATP. F-DHPE is a pH indicator and has been used to measure pH changes adjacent to the bilayer surface. In the range of pH 7.0–9.0, F-DHPE is sensitive to pH changes and has a positive correlation with the change of pH [Cui et al., 2005]. When the chromatophores labeled with F-DHPE were exposed to a 0.5 mT, 60 Hz magnetic field, the fluorescence of exposed samples and the sham samples are as shown in Figure 3. Each fluorescence response curve was fitted to a linear function and the slopes calculated. It was found that the fluorescence decreased whether or not the chromatophores were exposed. However, there was no significant difference between the slopes of the fluorescence time dependence of the exposed and sham samples ($P > 0.05$, $n = 10$). This means that the pH of outer membrane of chromatophore was not changed when the chromatophores were exposed to the 0.5 mT, 60 Hz magnetic field.

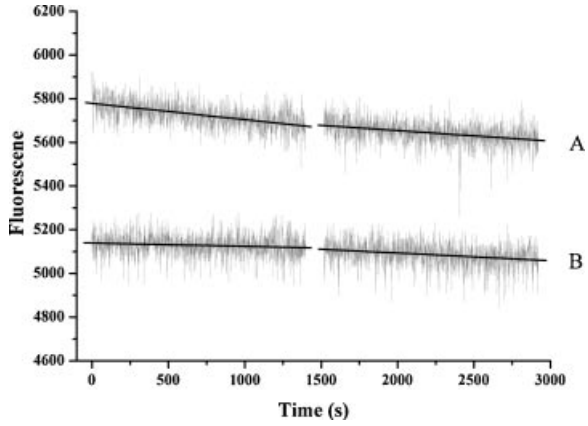

Fig. 3. The effect of 0.5 mT, 60 Hz magnetic fields on the pH of the chromatophores. The gray curve line A is fluorescence of chromatophores exposed by MF for 20 min first and then sham-exposed for the same time after 2 min interval; the dark line is linear fitting to each curve line. Curve line B was the reverse turn.

DISCUSSION

The effects of ELF electromagnetic fields on membrane Na,K-ATPase have been well documented. These reports have demonstrated that the activity of Na,K-ATPase is stimulated by magnetic fields whether the activity is high or low, and the stimulating effects decrease with increasing Na,K-ATPase activity [Blank and Soo, 1993, 1996; Martirosov and Blank, 1995]. In this article, the effects of ELF magnetic fields on membrane F_0F_1-ATPase were stimulated by 60 Hz magnetic fields, an effect similar to the stimulating effects of magnetic fields on the activity of Na,K-ATPases. When the F_0F_1-ATPases were exposed to 60 Hz magnetic fields of different intensities, the hydrolysis activity was enhanced by 0.3 and 0.5 mT magnetic fields but when the magnetic intensity was as low as 0.1 mT it did not show any effect. Accordingly, the effect of magnetic fields seems to depend on the magnetic intensity with the threshold lying between 0.1 and 0.3 mT.

It is well known that the DCCD is a potent inhibitor of F_0F_1-ATPase and acts on the membrane sector, F0 [Matsuno-Yagi and Hatefi, 1993]. When the hydrolysis activity of F_0F_1-ATPase was inactivated by 68.1% using DCCD, the 0.5 mT 60 Hz magnetic field still stimulated the hydrolysis activity of F_0F_1-ATPase. The increase was unchanged regardless of whether the F_0F_1-ATPase was inhibited by DCCD or not. These results suggest that the magnetic fields mainly affect F1 because DCCD acts only on F0 [Matsuno-Yagi and Hatefi, 1993].

When the chromatophores were exposed to a 0.5 mT, 60 Hz magnetic field, the pH of the outer membrane of the chromatophore was not changed. It is suggested that the magnetic fields used in this article did not affect the activity of F0 because the main function of the F0 is to transfer H^+. Since the magnetic fields did enhance the hydrolysis activity of F_0F_1-ATPase, it is

concluded that the effects of magnetic fields on F_0F_1-ATPase mainly result from the effect on F1.

Many reports have described experiments showing that an external electric field can stimulate the synthesis of ATP by F_0F_1-ATPase [Witt et al., 1976; Witt, 1979; Vinkler and Korenstein, 1982; Tsong, 1990; Zrimec et al., 2002]. Vinkler and Korenstein also reported that the inhibitors Dio-9 and DCCD did not have an inhibitory effect on the ATP synthesis stimulated by external fields. They suggested that the binding site of these two inhibitors does not seem to participate in the reaction. Our results seem to be in agreement with these previous results. However, the inductive electric field in our experiment, which was computed to be at the level of $\sim 10^{-4}$ V/m, was much smaller than the external electric fields used in those articles (always greater than 100 V/m). Some reports suggested that there may be other mechanisms that respond directly to the effects of magnetic fields on F0F1-ATPase. Blank and Goodman [2004] suggested, from the effects of magnetic fields on Na,K-ATPase, cytochrome oxidase and the Belousov–Zhabotinski (BZ) reaction, that the responses of these simpler biological systems to magnetic fields also support a mechanism initiated by interaction with electrons. Accordingly, the description of a mechanism for the effects of magnetic fields on F_0F_1-ATPase needs further research.

It is known that there have been considerable concerns and controversies recently about the effects on human health from increasing exposure to ELF-EMFs [Merchant et al., 1994; Lacy-Hulbert et al., 1998; Saunders and McCaig, 2005; Paniagua et al., 2007]. These effects may be related to the change of activity of F_0F_1-ATPase induced by the magnetic fields, since F_0F_1-ATPase is an important protein for energy transport across membrane. For example, Sobel et al. [1996] and Qiu et al. [2004] reported that EMFs could increase the risk of Alzheimer's disease (AD) among workers. Martinez-Cano et al. [2005] reported that the hydrolytic activity of F_0F_1-ATPase increases significantly in patients with probable AD, and increased as cerebral deterioration progressed in the male population with probable AD. Since the results in this study indicate that magnetic fields affect the hydrolysis activity of F_0F_1-ATPase, it is possible to speculate that the association between magnetic fields and AD might be related to a change of the hydrolysis activity of F_0F_1-ATPase. Regardless of this speculation, the normal status of the living cell may be negatively impacted when the activity of F_0F_1-ATPase is changed by magnetic fields.

In conclusion, 60 Hz magnetic fields were found to enhance the activity of F_0F_1-ATPase. The effects depended on magnetic intensity and the magnetic fields mainly affected the F1. Our results may provide a new way to explore a relationship between the effects of magnetic fields on human health and the effects of magnetic fields on membrane F_0F_1-ATPase.

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