Growth stage dependent effects of electromagnetic fields on DNA synthesis of Jurkat cells

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Abstract A 1.8 mT, bone healing, electromagnetic field (EMF) and power frequency EMFs of 0.1 and 0.4 mT significantly inhibit DNA synthesis in otherwise unstimulated Jurkat (E 6.1) cells. Inhibition is generally most prominent in cells from mid log phase growth. In complete medium the bone healing EMF inhibits [^{3}H] thymidine uptake of the latter cells by almost 50% vs. 20–25% inhibition by 60 Hz fields. Cells in conditioned medium are even more sensitive to EMFs with inhibition up to ca. 60%. The effects of the 0.1 and 0.4 mT power frequency EMFs were very similar suggesting saturation at 0.1 mT or lower.

Key words: Electromagnetic field; DNA synthesis; Growth; T-lymphocyte; Jurkat T-cell line

1. Introduction

With increasing generation and use of electricity, interest in how electromagnetic fields (EMFs) affect human health has become an important societal issue. Epidemiological studies indicate a positive association between 50/60 Hz power transmission fields and cancer, especially leukemia and lymphomas [1–3], but in clinical applications certain EMFs induce healing in otherwise non-healing fractures and wounds [4]. These results have combined to stimulate interest in uncovering the mechanism of action of EMFs with the aim of optimizing their role in human health. Although controversial, results from well controlled laboratory studies now strongly support the existence of a significant relationship between EMFs and a wide variety of biological processes at the cellular level. However, it remains unclear how EMF signals are transduced into biological signals, how they are linked to biological responses, and how these events might be related to human health.

In this study we investigated how two distinctly different EMFs affect Jurkat cell proliferation; power frequency (60 Hz) EMFs which are epidemiologically related to negative effects on human health, and a bone healing field (Electro Biology Inc.). Power frequency EMFs were studied at 0.1 and 0.4 mT, while the bone healing field was studied at 1.8 mT, the intensity employed in therapeutic settings.

In the Jurkat lymphoblastoma cell line Lindstroem and coworkers showed that power frequency EMFs modulate signal transduction coupled to the T-cell receptor. Low intensity 50 Hz EMFs increased cellular Ca^{2+} oscillations [5], and inositol triphosphate (IP_3) levels [6] and Ca^{2+} chelators did not block the EMF effect on IP_3. Moreover, in another CD45 deficient Jurkat cell line, EMFs did not induce Ca^{2+} oscillations [7]. Since CD45 regulates tyrosine kinase coupled to the T-cell receptor, these findings suggest that the targets of magnetic fields are very early in the signal transduction pathway. Liburdy and Eckert corroborated this idea by finding that 0.1 mT, 60 Hz EMFs increase high affinity anti-CD3 binding to the T-cell receptor [8], a result reproduced in our laboratory [9].

It is well known that antigens can control lymphocyte signal transduction and upregulate proliferation, while in other situations modification of the signal transduction pathway can lead to apoptosis, removing potentially harmful T-lymphocytes from the cell population. Thus, EMFs acting early in signal transduction might result in either cell proliferation or apoptosis depending upon how they influence downstream events. The research we report here was designed to determine if EMF effects at the level of the Jurkat T-cell receptor can be propagated through the entire signal transduction pathway leading to downstream effects on cell proliferation and/or apoptosis.

Our results indicate that Jurkat cells react to EMF stimulation of the T-cell receptor with cell cycle arrest and thus behave like normal T-lymphocytes stimulated by antigens at the T-cell receptor (e.g. anti-CD3). Specifically, our results show that 60 Hz fields decrease DNA synthesis of Jurkat cells as would be expected if EMFs interact with the T-cell receptor in the absence of a costimulatory signal. Remarkably, the bone healing field which has a 15 cps duty cycle with 4.5 ms bursts of 4444 cps saw tooth pulses during each cycle also inhibited DNA synthesis, but to an even greater extent. We also demonstrated that cell sensitivity to EMFs is highly related to the growth state of cells and that cells in early and late log phase growth are relatively insensitive to EMFs while cells in mid log phase are most susceptible to EMF exposure.

2. Material and methods

2.1. Cells

American Type Culture Collection Jurkat cells (E6.1) were grown in complete medium consisting of RPMI 1640 supplemented with 10% heat inactivated FBS, penicillin (50 U/ml), streptomycin (50 μg/ml), fungizone (2.5 μg/ml) and L-glutamine (0.29 mg/ml). Conditioned medium was prepared by growing cells to a defined stage of log phase growth in complete medium, harvesting the medium and storing it for 1 week at −30°C. Cells were grown in a Forma tissue culture incubator at 37°C in a humidified 5% CO_2 atmosphere. In our early experiments, cells were maintained in continuous log phase culture (2×10^5–1×10^6 cells/ml) by passing cells three times each week. However, for most of the experiments presented here we regulated the stage of cell growth more rigorously. Jurkat cells from a −70°C cell

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Abbreviations: Ca^{2+}, calcium; EMF, electromagnetic field; PBL, peripheral blood lymphocyte; T, Tesla

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bank were thawed, seeded at 1×10^5 cells/ml in T 25 tissue flasks, and grown for 24 h, 72 h and 120 h; early, middle and late log phase respectively. In the following, cells harvested at these points of the growth curve are referred to as stages 1, 2 or 3 cells (cf. inset to Figs. 2 and 3). Cells were counted using a hemocytometer or Model Z Coulter Counter. Cell viability was assessed by trypan blue dye exclusion.

2.2. Exposure to EMFs

The clinical bone healing apparatus was provided by Electro Biology Inc., Parsippany, NJ. It consists of a 22 cm (diameter) Helmholtz coil-pair driven by a 15 cps duty cycle. Each duty cycle of the signal consists of 20, 1.8 mT saw tooth pulses delivered for 4.5 ms, followed by a refractory period of about 62 ms [10].

In some experiments (Fig. 1) 0.1 mT and 0.4 mT, 60 Hz sinusoidal EMFs were generated by an AC signal generator (Jackson Electrical Instrument Co.) amplified by a 50 Watt/channel MacIntosh audio amplifier (model MC 250). This signal was delivered to a 29 cm diameter Helmholtz coil-pair. The voltage, current and waveform of the amplifier output were continuously monitored during experiments. Fast Fourier transform analysis of the signal using an Ono Sokki model CF-350 analyzer showed that it contained first, second and third harmonics with intensities of −35 db, −63 db and −67 db respectively. In the same analysis the 60 Hz signal had an intensity of 10.5 db. For all other experiments (Figs. 2 and 3) the same signal generator and monitors were used to drive a double wound 38 cm/side, 3 square coil Merritt system [11] with a uniform magnetic field of ±3.5% over an area of about 100 cm^2 at the exposure site in the center of the field. All magnetic fields were mapped and monitored using a DC and a 60 Hz magnetometer (Integrity Design and Research Corp.).

For EMF exposures cells were at a density of 1×10^6 cells/ml and the experimental EMF was horizontal and oriented in a North to South direction. Exposure to EMFs for 20 min with the Helmholtz or Merritt coil was inside a dedicated tissue culture incubator (37°C, humidified 5% CO_2). Controls were maintained in an identical incubator located next to the incubator with the coils. During experiments the temperature within the coil systems was monitored with a remote sensing, electronic thermometer (Yellow Springs Instrument Co.) and remained constant (±0.5°C) during the 20 min exposure time.

2.3. DNA synthesis assay

Fifty microliters of Jurkat cells at 1×10^6 cells/ml, in complete or conditioned medium were plated in the center wells of 96 well plates. Experimental and control plates were treated as described above. Immediately thereafter 180 μl complete or conditioned growth medium was added to each well. On each of the following 4 days, 20 μl [^{3}H] thymidine (0.1 μCi/ml) was added to wells in an experimental and control plate. After a 3 h incubation period, (37°C, humidified 5% CO_2), cells were harvested on glass filters using a PHD cell harvester (Cambridge Technology Inc., MA). Radioactivity on the filters was measured by liquid scintillation counting.

A minimum of 4 replicate cultures were tested at each data point. Data are presented as the mean of replicates. Non-linear regression and ANOVA analysis were performed using Graphpad's Prism, ver. 2.0.

3. Results

3.1. EMF effects in randomly harvested log phase cells

Jurkat cells were randomly harvested at various stages of log phase growth. The growth characteristics of EMF treated and control cells were compared over the next 4 days by assaying [^{3}H] thymidine incorporation into DNA. Often, there was very little difference between experimental and control cultures but sometimes thymidine uptake was significantly decreased in EMF treated cells. In cases where field effects were significant they did not become apparent until more than 24 h after EMF exposure. The difference between experimental and control cultures in these experiments generally increased over the next two days. Fig. 1 shows results of 5 identical, paired, early experiments, in which [^{3}H] thymidine incorporation was measured 72 h after exposure to the 1.8 mT pulsed bone

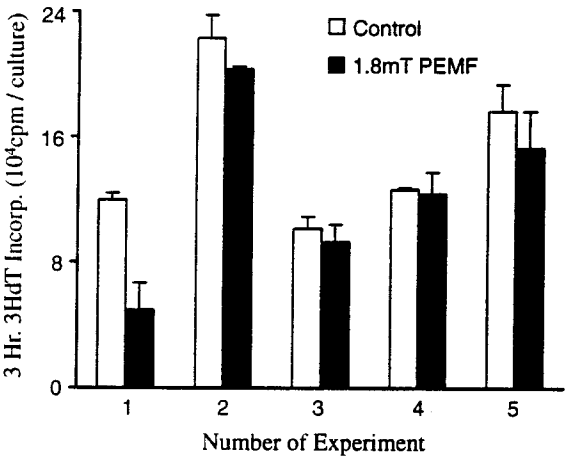

Fig. 1. Effect of the 1.8 mT bone healing field on [^{3}H] thymidine incorporation of Jurkat cells. Cells were randomly harvested in log growth, stimulated for 20 min with the bone healing field and after 72 h [^{3}H] thymidine uptake was measured. In those experiments we obtained variable results from no effect until almost 60% inhibition of DNA synthesis. The bars indicate one standard deviation of 8 replicate cultures.

healing field. Although all of the experiments showed the same trend (i.e. decreased [^{3}H] thymidine uptake in EMF stimulated cultures) the effect was significant only in Experiments 1 and 2 (Fig. 1) and in these cases the extent of the field effect was quite different (58% in Experiment 1 and 9% in Experiment 2). Since all of the experiments were initiated with the same number of viable cells these results suggested that sometimes EMFs either altered the doubling time of the cultures or removed a population of cells from the cell cycle. Statistical analysis on the complete growth curves led to the conclusion that there was no significant difference between the doubling time of EMF treated and control cells, indicating that EMF treatment removed some cells from the dividing population. Parallel experiments in which cultures were exposed to 0.1 mT or 0.4 mT, 60 Hz EMFs exhibited the same trends. EMF treatment usually diminished [^{3}H] thymidine incorporation into DNA, but significant effects were only observed in a small number of cases (data not shown).

3.2. Growth properties of defined log phase cells

Based on the latter results we hypothesized that either the experiments in which we observed an EMF effect were due to chance, or the metabolic state of cells varied significantly from experiment to experiment and that cells in certain metabolic states were more sensitive to EMFs than in others. One way that such a differential cell sensitivity might be explained is if EMFs interact specifically with cells at a relatively narrow well defined point of the cell growth curve (e.g. early, middle or late log phase). To investigate this, we performed a series of identical experiments on cells from defined points of the growth curve. Early, middle or late log phase cells (see Section 2) were isolated, replated at 10^6 cells per culture, exposed to EMFs, and their ability to synthesize DNA (compared to controls) was tested over the next several days. Furthermore, to test if growth factor depletion, or accumulation of metabolites in the medium might also be involved in causing our variable EMF effects, we performed experiments on cells resuspended in complete and conditioned medium.

One important question of interest was whether cells in

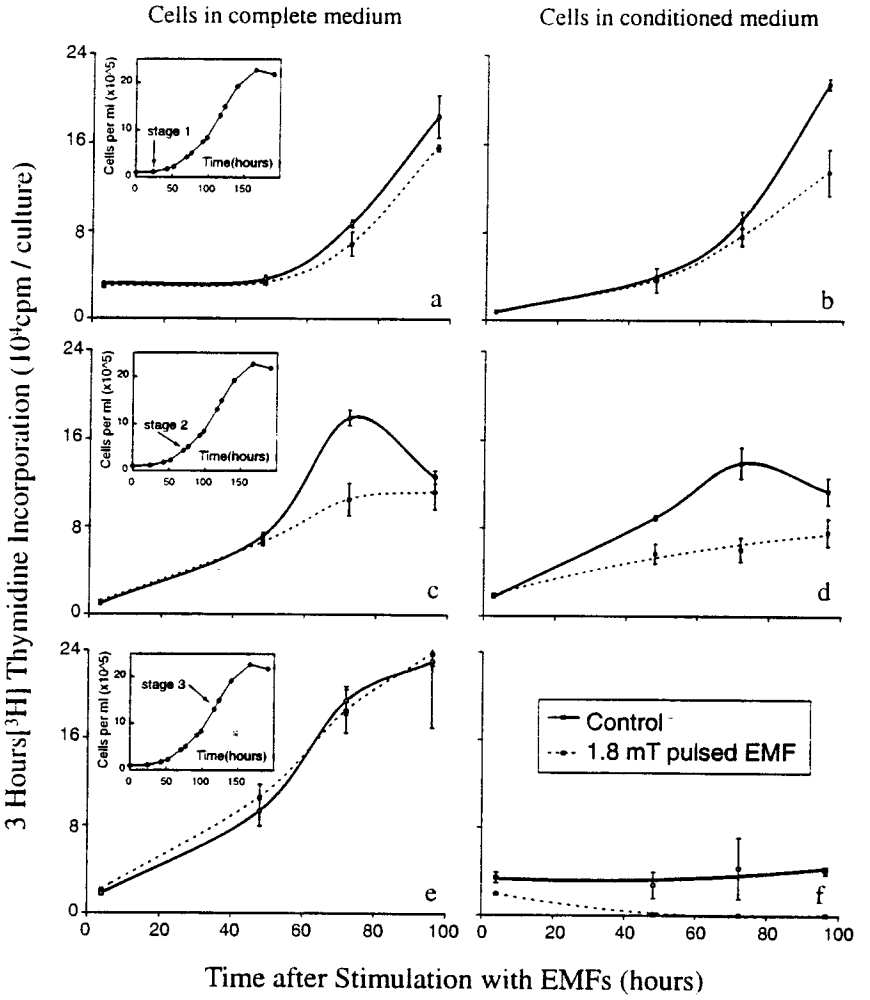

Fig. 2. Effect of the 1.8 mT bone healing field on [^{3}H] thymidine incorporation of Jurkat cells. Cells were isolated at stage 1, 2 or 3 of the growth curve (see insets), resuspended in complete medium (left panels) or conditioned medium (right panels), stimulated for 20 min with the bone healing field and [^{3}H] thymidine uptake (3 h pulses) assayed over the next four days. The bars indicate the standard deviations of four replicate cultures, eight in case of controls.

different stages of log phase cell growth were metabolically different, and if this might account for our variable results shown above. To study this, cells harvested from one culture at stage 1, 2 or 3 of log phase growth were transferred to new medium (either complete or conditioned) and tested for their subsequent [^{3}H] thymidine uptake and sensitivity to EMFs. Fig. 2, panels a–d, demonstrate that the daily, pulsed, [^{3}H] thymidine uptake of control cells generally increased exponentially, reflecting continued exponential growth of these cultures. However, the length of the period of log phase growth varied depending on the growth stage from which the cells were harvested and on the medium in which the cells were resuspended prior to EMF treatment.

Control cells harvested at stage 1 continued exponential growth with a doubling time of 21 h (R^2, 0.99) over the 96 h experimental period regardless of the medium used to resuspend them (Fig. 2, panels a and b). However, stage 2 cells exhibited markedly different results than might have been expected from experiments with stage 1 cells. For example we expected control cells harvested in mid log phase and resuspended in fresh complete medium (Fig. 2, panel c) to continue growth like the control cells shown in Fig. 2, panel a. However, stage 2 cells had a much shorter doubling time (16.9 h, R^2, 0.99) and log phase growth ended around 72 h. Stage 3 cells (Fig. 2, panel e) exhibited a doubling time similar to that of stage 1 cells (21.8 h, R^2, 0.98) but after 72 h these cells also exhibited growth arrest. These results indicate that cells at different stages of log phase growth have significantly different metabolic states.

3.3. *Effects of the 1.8 mT bone healing field on defined log phase cells*

The duty cycle, waveform and frequency of the 1.8 mT bone healing field are markedly different from those of the 0.1 and 0.4 mT, 60 Hz, power frequency fields that we used. Moreover, the mechanism by which EMFs induce their biological activity is unknown and thus the biologically important property(s) of the EMFs are also unknown. Because of these considerations we present the results of the bone healing field and power frequency fields in two separate sections.

The effects of bone healing EMFs on [^{3}H] thymidine incorporation depended on the metabolic state of the cells studied (i.e. phase 1, 2, or 3 cells). In the 1st and 2nd generation after replating in complete medium no obvious difference was seen

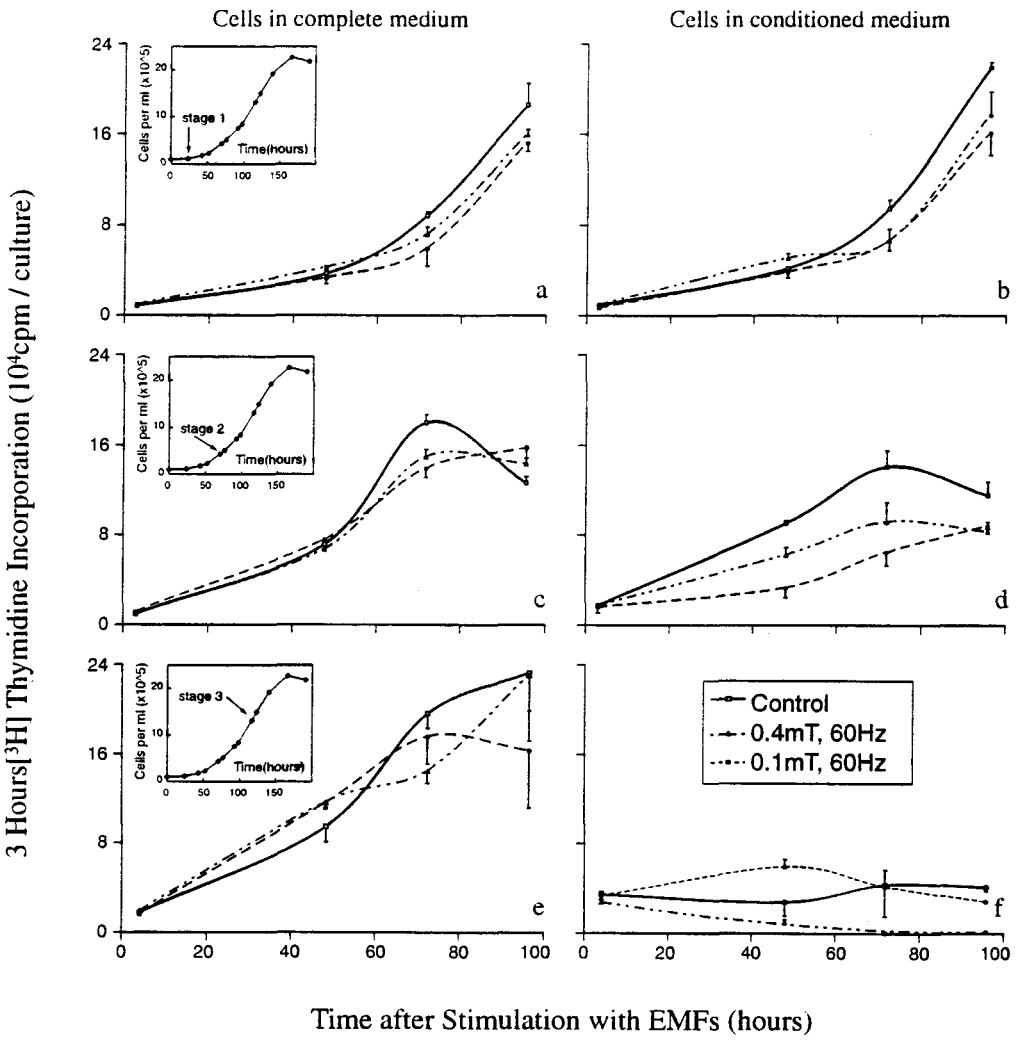

Fig. 3. Effects of the 0.1 mT and 0.4 mT 60 Hz electromagnetic fields on [^{3}H] thymidine incorporation of Jurkat cells. Cells were treated in the same way as described in Fig. 2.

between control and treated cells regardless of their metabolic state (Fig. 2). However, at 48 h and later [^{3}H] thymidine uptake of EMF treated stage 1 and stage 2 cells was clearly decreased compared to paired controls and inhibition was most prominent in stage 2 cells (42% at 72 h in stage 2 cells vs. 22% in stage 1 cells; one-way ANOVA, $P < 0.01$). Furthermore, when the log phase growth period of these cultures was analyzed by two-way ANOVA, [^{3}H] thymidine uptake of EMF treated cells was found to be significantly different from controls ($P < 0.0001$). In contrast, stage 3 cells replated in complete medium were refractory to EMFs (Fig. 2, panel e).

A further question was if EMF effects on Jurkat cells are influenced by factors that accumulate or are depleted from conditioned medium. To study this we tested the effect of EMFs on cells replated in conditioned medium. The EMFs inhibited [^{3}H] thymidine uptake in cells taken from all stages of growth (Fig. 2, panels b, d, f) and the magnitude of inhibition increased with increasing culture age (16, 57 and 99% in stage 1, 2 and 3 cells respectively).

In comparing [^{3}H] thymidine uptake of cells grown in complete vs. conditioned medium it is clear that the medium had a marked effect on thymidine uptake and sensitivity of cells to EMFs. EMFs depressed thymidine uptake of stage 2 cells in complete medium by 42% vs. 57% in conditioned medium. Although EMFs have little or no effect on stage 3 cells in complete medium, in conditioned medium the EMF effect is very striking (99% inhibition).

3.4. *Effects of sinusoidal 60 Hz fields on defined log phase cells*

Like 1.8 mT fields, power frequency EMFs generally inhibited [^{3}H] thymidine uptake by Jurkat cells (Fig. 3). In two-way ANOVA analysis the inhibition of [^{3}H] thymidine uptake of stage 1 and stage 2 cells by 60 Hz fields was always significantly different from controls ($P < 0.0001$). Power frequency

Table 1
Inhibition of DNA synthesis in stage 2 cells in complete medium

	0.1 mT 60 Hz % Inhibition	0.4 mT 60 Hz % Inhibition	1.8 mT Bone healing EMF % Inhibition
Experiment 1	22.7	17	41.4
Experiment 2	21.2	27.5	33.9
Experiment 3	24	14	30

Experiment 1 is the 72 h maximum inhibition time point taken from Figs. 2 and 3, panels c, while Experiments 2 and 3 represent the maximum inhibition time point which occurred at 48 h after field treatment. Other conditions were as described in Section 2.

fields generally had no significant effect on stage 3 cells, except in conditioned medium where the 0.4 mT field inhibited the 72 h [^{3}H] thymidine uptake by 76%. With the 1.8 mT bone healing field stage 2 cells appeared most sensitive to EMFs and the effect was most prominent at 72 h. Similar trends were observed with cells exposed to the 0.1 and 0.4 mT power frequency fields (Fig. 3, panels c, d). Likewise, with power frequency fields the magnitude of the EMF effect in all stages was greater in conditioned medium compared to cells in complete medium. For example, in stage 2 cells the inhibition induced by 0.1 mT fields in complete medium was 23% compared to 54% in conditioned medium and the 0.4 mT field induced inhibition by 17 and 35% respectively. Unexpectedly, the 0.4 mT and 0.1 mT field effects on [^{3}H] thymidine uptake were not significantly different from each other even though both fields were significantly different from controls. This result suggests that the 60 Hz EMF effect is already saturated at a field strength of 0.1 mT.

In continuing experiments with stage 2 and stage 3 cells in complete medium (Table 1) we again found stage 2 cells to be responsive to all the EMFs tested and stage 3 cells to be refractory to EMF treatment. In all experiments DNA synthesis of stage 2 cells treated either with the 60 Hz or bone healing EMFs was significantly decreased compared to controls. Moreover, although the time varies at which maximum inhibition is observed (72 h in Experiment 1 and 48 h in Experiments 2 and 3) the inhibition of DNA synthesis associated with exposure to EMFs is remarkably constant from experiment to experiment as shown in Table 1.

4. Discussion

We investigated the effect of two different kinds of EMFs on DNA synthesis of Jurkat cells. The bone healing field (described in Section 2) is widely employed therapeutically to treat non-healing bone fractures and weak 60 Hz power frequency fields have been epidemiologically associated with increased risk of cancer. Remarkably, under the conditions of our experiments both kinds of fields had similar effects on Jurkat cell growth, decreasing the extent of [^{3}H] thymidine incorporation into treated cells in 20 of 24 experiments shown in Figs. 2 and 3 and Table 1.

Generally, the physiological effect of exposure to fields was delayed with significant effects on DNA synthesis first becoming apparent 24–48 h after exposure to EMFs and increasing in magnitude over the next 48 h. Thus, the result of EMF exposure during one round of the cell cycle was not apparent as an effect on DNA synthesis until the next and succeeding rounds of the cell cycle. The fact that [^{3}H] thymidine incorporation into DNA continued to be inhibited and that EMF effects became more prominent during the remainder of culture growth strongly indicates that EMFs permanently prevented subpopulations of the cultures from cycling.

Alternative interpretations of our results include the possibility that EMFs only inhibited the [^{3}H] thymidine uptake involved in DNA repair and/or that extracellular [^{3}H] thymidine transport was inhibited [12]. Since the EMF effect was not most prominent immediately after EMF exposure, but occurred several generations later, we conclude that the EMF effect is not due to inhibition of DNA repair or transiently altered [^{3}H] thymidine transport.

In most of our experiments EMFs decreased DNA synthesis and the magnitude of this effect was only weakly dependent on the physical characteristics of the fields. We were surprised at this outcome since many studies indicate that special frequencies, waveforms and intensities (windows) are required to generate a specific biological reaction [13,14]. Although all the fields were qualitatively similar in their effect on DNA synthesis, the 1.8 mT bone healing field generally caused more prominent biological effects than the 60 Hz fields. Since the 0.1 and 0.4 mT, 60 Hz fields did not show a dose response relationship, we conclude that the 60 Hz EMF effect on [^{3}H] thymidine uptake of Jurkat cells, is already saturated at 0.1 mT. Similar results are reported from EMF induced Ca^{2+} oscillations in Jurkat cells [15]. To further support this idea, Liburdy and others have shown, in other cell types, that 60 Hz sinusoidal fields with intensities as low as 1.2 μT have reproducible biological effects [16,17]. Finally, we calculated the electric fields induced in our samples and found that the bone healing field had a 90-fold greater field density than the 0.1 mT 60 Hz field and a corresponding 22.5-fold greater field density than the 0.4 mT 60 Hz field. From this perspective the bone healing field is again clearly more energetic than the 60 Hz fields and again the 60 Hz fields appear to be saturated with the 0.1 mT magnetic field.

Our data indicate that the metabolic state and/or culture conditions of cells is an important variable in determining the outcome of exposure to EMFs. We found that cells taken from various stages in the growth curve, reintroduced into new culture medium (complete or conditioned), and then exposed to magnetic fields exhibited growth stage dependent EMF effects. Early log phase cells (stage 1) displayed only small EMF effects, middle log phase cells exhibited larger EMF effects, and late log phase cells were relatively insensitive to EMFs. Additionally, cells replated in conditioned medium generally exhibited reduced growth compared to cells in complete medium and the EMF effect was more prominent under these conditions. These results might explain the experimental variability of the EMF effects that we observed in our early experiments (Fig. 1) and the apparent irreproducibility of many EMF studies found in the literature. While rigorous control of cell growth greatly improves the reproducibility of the EMF effects (see Table 1) there are still some uncontrolled conditions left in our experiments as can be seen by the variability in the time when the most prominent EMF effects are seen. In future experiments we plan to control the cell cycle and growth stage to determine if EMF sensitivity is also cell cycle dependent and if further gains can be made in the robustness of the model.

While this is the first report of EMF effects on proliferation of Jurkat cells, there are comparable studies showing EMF dependent changes in cell proliferation of mitogen stimulated human peripheral blood lymphocytes (PBLs), although there is great variability in the reported effects [18]. For example, in these studies EMFs have been shown to increase or inhibit [^{3}H] thymidine uptake of PBLs. While these differences are generally attributed to the physical properties of the fields used in the studies, our results suggest that the metabolic state of the cells is at least as important as the characteristics of the EMFs used in electromagnetic experiments.

Consistent with our results Pasquinelli et al., 1993 [19] found in two leukemic cell lines that exposure to 2 mT, 75 Hz lowered the DNA synthesis of cells stimulated with doxorubicin, an apoptosis inducing drug. Our results are also in

agreement with earlier observations on mitogen activated PBLs taken from stressed humans or rats. Fields of 22 mT (60 Hz) were shown to increase Ca^{2+} flux in rats and this effect was greater in aged animals [20]. Likewise, age related EMF effects were shown on cell proliferation in lymphocytes from young and aged humans exposed to 2.5 mT, 50 Hz, pulsed EMFs [21]. Moreover, Cadossi et al. showed that [^{3}H] thymidine uptake of slowly cycling PBLs obtained from diseased donors was more sensitive to power frequency EMFs than the rapidly cycling PBLs obtained from healthy donors [22].

The main objective of this study was to determine if Jurkat cells respond to EMFs with biologically significant, long lasting, effects. It is known that EMFs induce the appearance of CD3 epitopes on Jurkat cells [8,9]. Additionally, activation of Jurkat cells with anti-CD3 is known to induce cell cycle arrest with inhibition of DNA synthesis [23]. However, it has not been reported that EMFs capable of inducing anti-CD3 epitopes could also bring about downstream effects on DNA synthesis. This study bridges that gap by demonstrating that power frequency EMFs, capable of inducing CD3 epitopes on Jurkat cells are also capable of inducing cell cycle arrest with attendant inhibition of DNA synthesis. A secondary objective was to determine if EMFs with widely differing physical characteristics can have similar biological end points. The bone healing field and the power frequency field are markedly different but, surprisingly, have qualitatively similar, inhibitory effects on DNA synthesis in Jurkat cells. All the effects we observe can be explained by EMF activation of the T-cell receptor or by direct interaction with downstream components of signal transduction pathways [5–7]. Since many disease states involve inappropriate regulation of cell growth and differentiation it is likely that continuing study of the role of EMFs in activation and proliferation of T-lymphocytes will account for many of the health related effects of exposure to EMFs [1–4].

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