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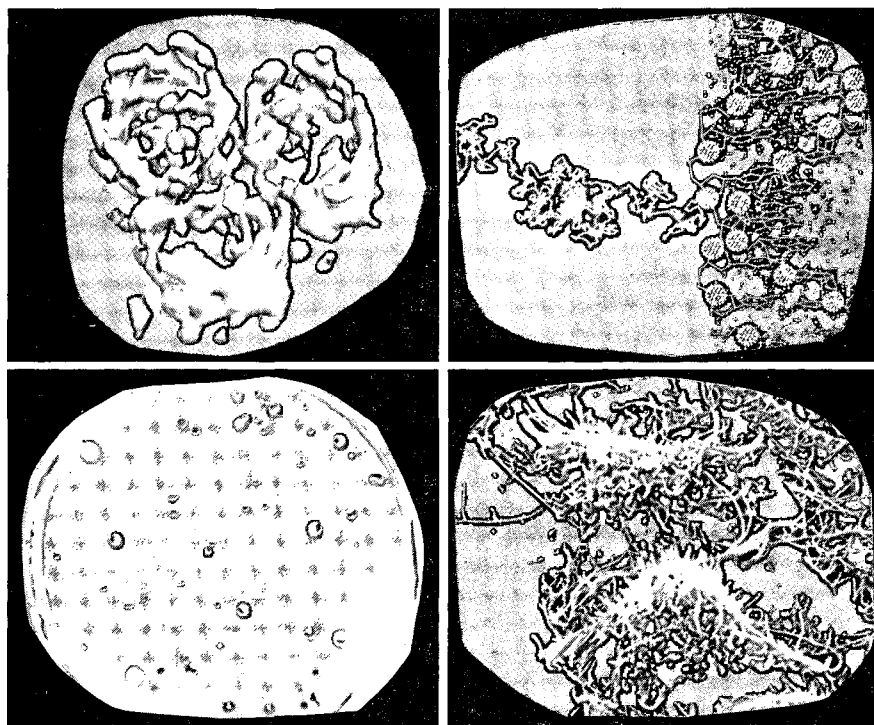
CELL & MOLECULAR BIOLOGY DIVISION

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February 1993



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Time-Varying and Static Magnetic Fields Act in Combination to Alter Calcium Signal Transduction in the Lymphocyte

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ABSTRACT. We tested the hypothesis that ELF time-varying magnetic fields act in combination with static magnetic fields to alter calcium signaling in the lymphocyte. A 60 minute exposure of thymic lymphocytes at $37 \pm 0.05^\circ\text{C}$ to a 16 Hz, 421 mG (42.1 μT) magnetic field simultaneously with a colinear static magnetic field of 234 mG (23.4 μT) [AC/DC field intensity ratio = 1.8] inhibits calcium influx triggered by the mitogen Concanavalin-A [1]. Resting lymphocytes do not respond to the fields indicating that mitogen activation is required. In parallel studies, we show that the nominal rise in $[\text{Ca}^{2+}]_i$ induced by Con-A is inhibited during field exposure. Split field exposures show that the presence of the AC field or the DC field alone does not produce an effect. Exposures at AC/DC ratios of 3.8 (Bessel function first zero) and 5.3 (Bessel function first minimum) yield results "consistent" with a proposed parametric resonance theory of interaction of low intensity magnetic fields with biological systems [2].

INTRODUCTION. A central question to interaction mechanisms of magnetic fields with biological systems is whether a time-varying (AC) magnetic field interacts in a fundamentally different manner at the cellular level when a static (DC) magnetic field is present [1, ref therein] This question is of interest since both ELF magnetic fields and geomagnetic static magnetic fields are present in the environment and workplace, and since it is critical to identify field metrics that have biological relevance.

Recently a report has specified field parameters in sufficient detail for testing the hypothesis that AC/DC field combinations interact with biological systems [2]. The parametric resonance theory states that protein-bound ions can behave as a spatial oscillator with a set of vibrational frequencies that depend on the bond energy, charge q , and mass m of the ligand bound ion. The bound ion continuously oscillates about an energy level as coordination bonds are broken and reformed due to random thermal motion. The presence of a static magnetic field splits the energy level of the bound ion into two sublevels corresponding to electromagnetic frequencies w_1 and w_2 in the infrared band. The difference between these two energy levels equals the cyclotron frequency, $w_c = (w_1 - w_2) = (q/m)Bdc$.

Applying a colinear AC field at the cyclotron frequency modifies the probability, P , of ion transitions between energy states that depends on a Bessel function argument defined by the intensity ratios of the AC and DC fields [2]. The Bessel function curve looks like a damped sinusoidal curve with a first maximum at $BAC/BDC = 1.8$, a first cross-over point or zero at 3.8, and a first minimum at 5.3. We interpret this to mean that at these field intensity ratios a change in biological response (positive or negative) will be observed at the maximum and minimum ratios, with no change observed at the zero ratio.

EXPERIMENTAL PROCEDURES. Preparation of rat thymocytes, description of the $^{45}\text{Ca}^{2+}$ transport assay, and description of the temperature-regulated, μ -metal shielded, Helmholtz multiple-coil exposure system and dosimetry procedures are recently described in [1]. Fura-2 loading and real-time measurement of intracellular calcium during field exposures are recently described in [3]. A special Helmholtz exposure coil was fabricated and positioned around a fluorescence cuvette to permit AC/DC field exposures during on-line fluorescence measurements.

RESULTS AND DISCUSSION. Figures 1-3 present the results of AC/DC field exposures on mitogen activated calcium influx in rat thymocytes (60 minutes, 37C). **Figure 1** shows data for the AC/DC ratio of 1.8 (234 mG DC; 421 mG AC, 16 Hz; resonance for $^{45}\text{Ca}^{2+}$), corresponding the first Bessel function maximum. The two left bar graphs reveal that calcium influx increased for cells treated with Con-A (1-3 $\mu\text{g}/\text{ml}$). The two right bar graphs show the effect AC/DC fields have on calcium influx in resting and activated cells. Only activated cells responded to the fields - AC/DC fields significantly inhibited calcium influx triggered by Con-A. Experiments employing separate AC and DC magnetic fields were not effective [1]. We next performed exposures at AC/DC magnetic field ratios of 5.3 and 3.8, and this data is presented in **Figures 2 - 3**, respectively. At the first Bessel zero-crossing we observed no change in calcium influx (**Figure 3**), while at the first Bessel minimum we observed an enhancement of calcium influx (**Figure 2**).

These preliminary data suggest that AC/DC field combinations have the potential to influence calcium influx in mitogen-activated lymphocytes.

The above findings also raise the important question of whether intracellular calcium is altered. To address this question we monitored FURA-2 fluorescence in thymocytes in real-time during AC/DC field exposures. The significance of this approach is two fold: (a) it permits an instantaneous evaluation of an important signal transduction parameter, $[Ca^{2+}]_i$, during field exposure, and (b) it enables information about field interaction kinetics to be obtained.

Figure 4 shows the time course of $[Ca^{2+}]_i$ following AC/DC field exposure and mitogen activation. Resting thymocytes display a stable level of $[Ca^{2+}]_i$ of approximately 135 nM; this is unaltered by exposure at 180 seconds to AC/DC fields (208 mG DC; 375 mG AC, 16 Hz; AC/DC = 1.8; resonance conditions at 16 Hz for the $^{40}Ca^{2+}$ ion). This result is consistent with the calcium influx findings for resting cells in **Figure 1**. When Con-A is added at approximately 260 seconds unexposed cells show a characteristic rise in $[Ca^{2+}]_i$ to a level of 210 nM at 370 seconds. This nominal rise in $[Ca^{2+}]_i$ is significantly blunted by the AC/DC fields, although the early kinetics appear unaffected through the first 100 seconds. After 100 seconds the two traces diverge as time increases. A reduction in $[Ca^{2+}]_i$ levels during AC/DC field exposure is consistent with reduced calcium influx shown in **Figure 1**.

The above findings taken together indicate that AC and DC magnetic field combinations can act to influence calcium signaling in mitogen-activated lymphocytes. Two key factors in these studies are the concepts of signal transduction and cellular activation. Several groups have reported studies using AC/DC fields but have not employed a model system with these key factors [1, refs therein]. The results presented here are "consistent" with the parametric ion theory, however, further research is need to adequately test predictions and this will involve varying the AC frequency to "detune" the interaction, and systematically varying the AC/DC field ratios to cover the Bessel function curve.

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FIGURE LEGENDS.

Figure 1: Effect of Magnetic Field Combination AC/DC = 1.8: the First Bessel Function Maximum. Resonance for the $^{45}\text{Ca}^{+2}$ ion: Frequency = 16 Hz, AC = 421 mGauss, DC = 234 mGauss. Temperature = $37 \pm 0.05^\circ\text{C}$, 60 minutes.

Figure 2. Effect of AC/DC = 5.3: the First Bessel Function Minimum. Conditions as in Figure 1 except AC = 1240 mGauss.

Figure 3. Effect of AC/DC = 3.8: the First Bessel Function Zero. Conditions as in Figure 1 except AC = 901 mGauss.

Figure 4. Real-time Measurement of Intracellular Calcium During Exposure to AC/DC = 1.8 (First Bessel Maximum). Resonance for the $^{40}\text{Ca}^{2+}$ ion: Frequency = 16 Hz, AC = 375 mGauss, DC = 208 mGauss.

FIRST BESSEL MAXIMUM (AC/DC=1.8):
INHIBITION OF MITOGEN-ACTIVATED CALCIUM INFLUX

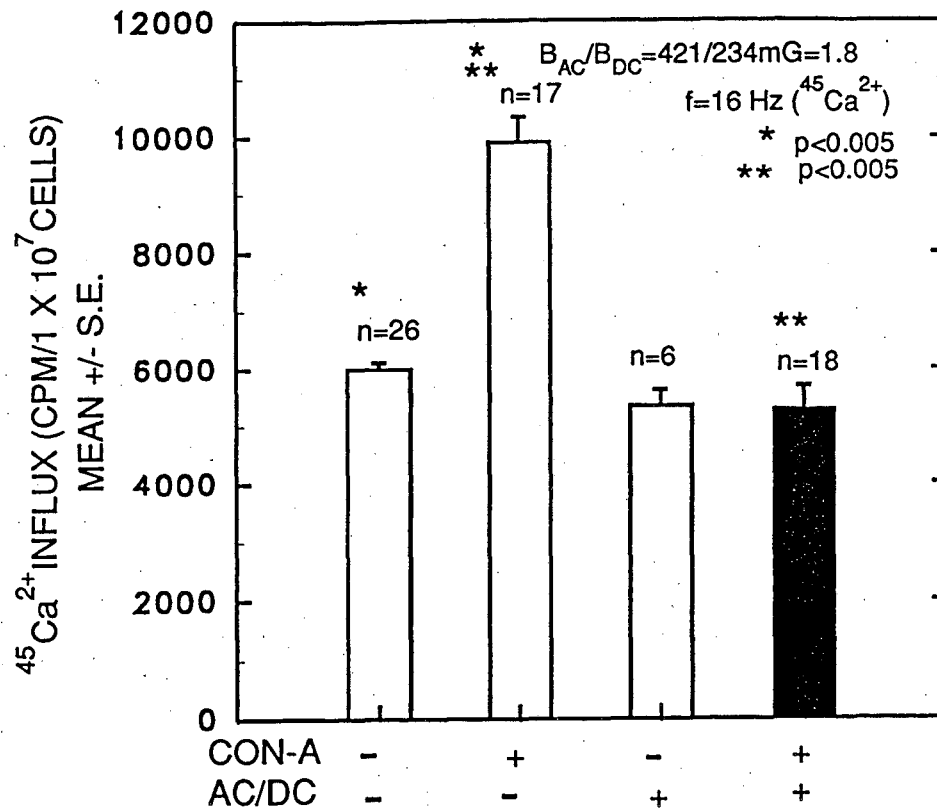


FIGURE 1

FIRST BESSEL MINIMUM (AC/DC=5.3):
ENHANCEMENT OF CALCIUM INFLUX

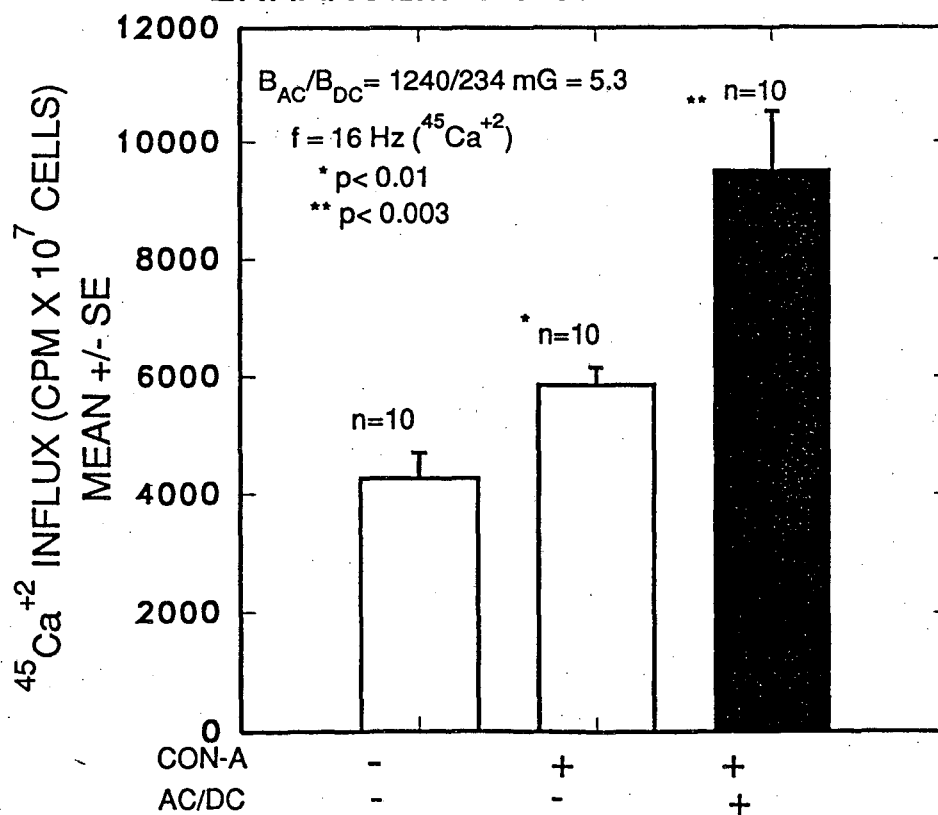


FIGURE 2

FIRST BESSEL ZERO (AC/DC=3.8):
NO CHANGE IN CALCIUM INFLUX

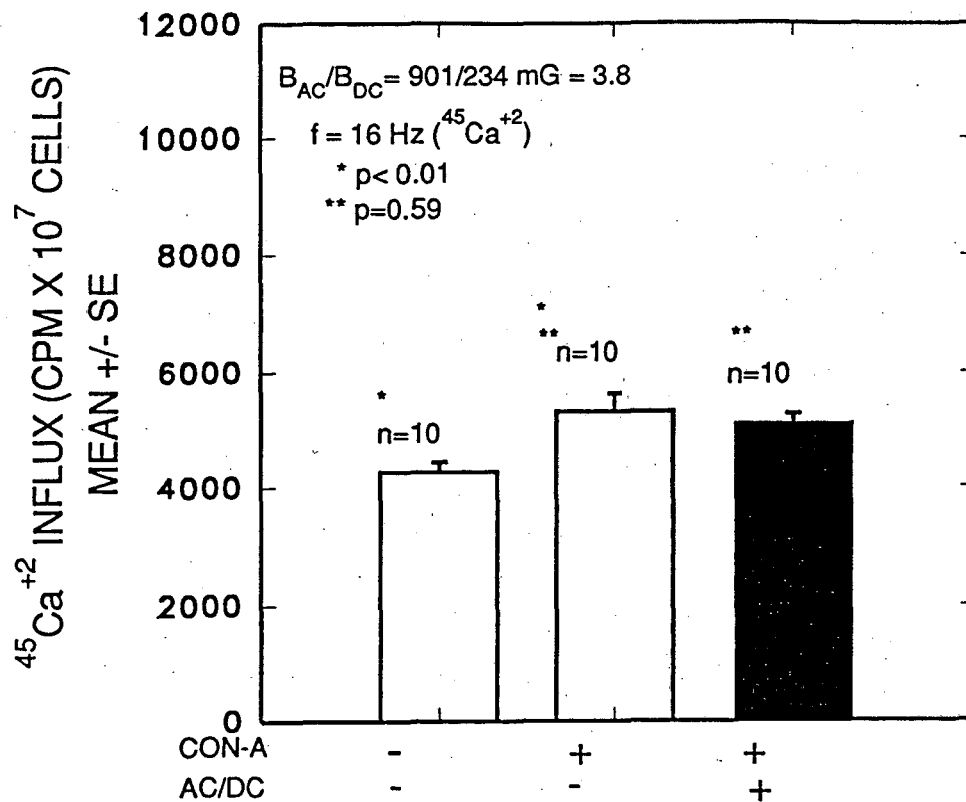


FIGURE 3

INTRACELLULAR CALCIUM IN FURA-2 THYMOCYTES

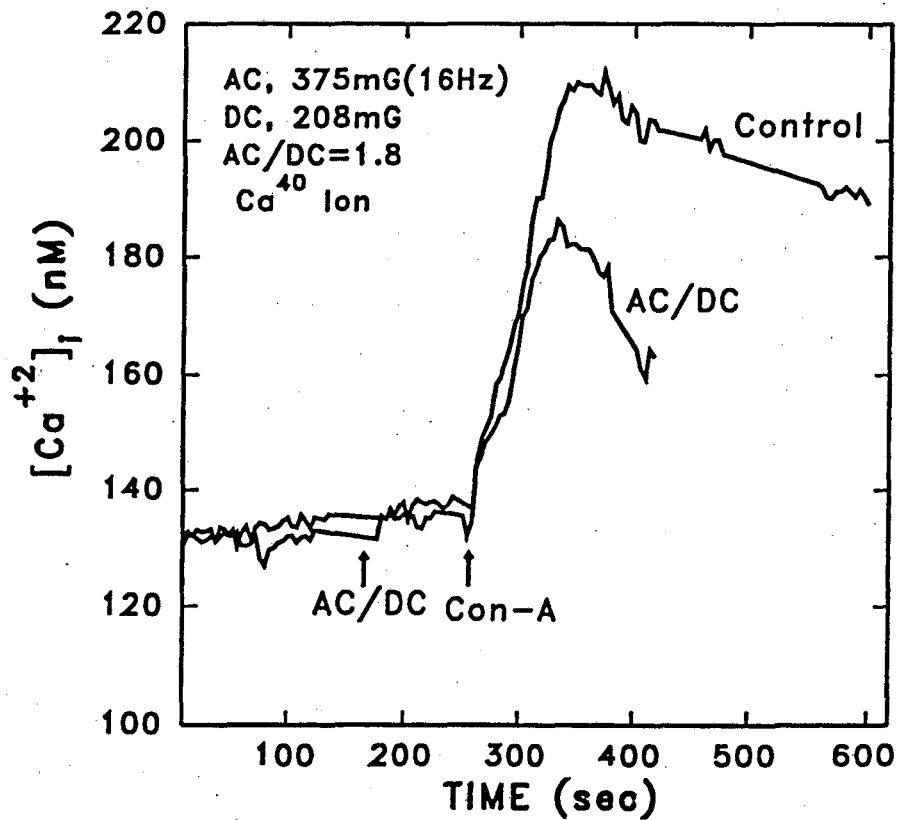


FIGURE 4

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