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Effects of ELF and static magnetic fields on calcium oscillations in islets of Langerhans

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Abstract

Several experimental studies have produced contradictory results on the effects of extremely low frequency (ELF) magnetic fields on cellular processes involving calcium ions. Furthermore, the few positive results have not been independently replicated. In most of these studies, isolated cells were used. Our study used mouse islets of Langerhans, in which very regular oscillations of calcium concentration can be observed at length. These oscillations are sustained by processes that imply energetic and inter-intracellular communication. Various magnetic fields were applied, either sinusoidal at different frequencies (50 Hz or multiples of the natural oscillation frequency) at 0.1 or 1 mT or static at 1 mT. Islets were also exposed to ''cyclotron resonance'' conditions. There was neither alteration of the fundamental oscillation frequency nor the degree of organisation under all exposure conditions. Using this sensitive model, we could not show new evidence of alterations of calcium processes under exposure to various magnetic fields.
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Keywords: Extremely low frequency; Static magnetic fields; Islets of Langerhans

1. Introduction

Experimental research in bioelectromagnetics has progressed slowly in the last decades due to a lack of suitable biological models and exposure systems. Published results have been negative or contradictory [1], with few successful replications of positive results by independent laboratories. The amplitude of the positive effects was usually small. Because calcium ions play a major role in biology [2], and based on our previous experience of investigations on the effects of magnetic fields on this ion [3], we searched for a robust and sensitive model permitting long exposures. Islets of Langerhans are good candidates: when glucose concentration is increased, insulin is secreted by beta cells and this secretion is sustained by calcium oscillations [4] that occur synchronously in all of the islet's beta cells [5]. Islets maintain these oscillations for a long time with a large amplitude and a very regular frequency. This model can be modified by changing the glucose concentration or by using biochemical agents. These oscillations belong to a family of self-sustained oscillations that should be very sensitive to external perturbations [6]. The biochemistry of this model is well understood since one type of diabetes is due to lack or unregulated production of insulin by beta cells, which is directly linked to the disappearance of calcium oscillations.

We applied different magnetic fields to the islets: a 100-μT magnetic field, at 50 Hz or at a frequency equal to h times the natural frequency (f_n) of the islets (with $h = 0.5$, 1, and 2), static fields at 1 mT, and magnetic fields under resonant conditions for the calcium ion.

2. Materials and methods

2.1. Animals

Female OF1 mice (IFFA CREDO, France) from 5 to 10 weeks old were used. All recommendations of the CNRS regarding animal care and handling were followed.

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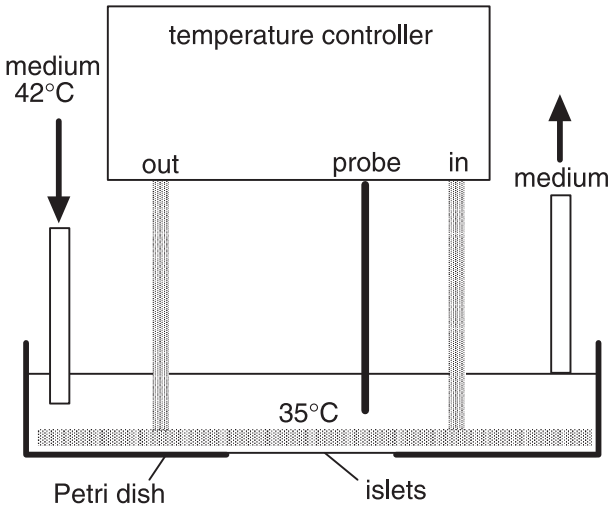

Fig. 1. Setup for controlling the temperature of the medium.

2.2. Isolation and culture of the islets

Islets were isolated from the pancreas of mice using a collagenase method [7]. Briefly, the pancreas was removed, cut into small pieces in Hank's Balanced Salt Solution (HBSS) medium (NaCl 138 mM, KCl 5.4 mM, $MgSO_4$ 0.81 mM, $NaHPO_4$ 0.34 mM, KH_2PO_4 0.4 mM, $CaCl_2$ 0.4 mM, $NaHCO_3$ 4.17 mM), digested for 6 min at 37 °C using collagenase (Roche Diagnostics, France), and then gently shaken for 2 min at 37 °C and 1 min at room temperature. Digestion was stopped by adding cold HBSS medium. Isolated islets were handpicked under a stereo microscope. Islets were cultured at 37 °C inside an incubator (95% O_2, 5% CO_2) for 48 h in RPMI-1640 medium from Life Technologies, France, supplemented with 11 mM of glucose, 10% fetal calf serum (Life Technologies), 100 IU/ml penicillin, and 100 μg/ml streptomycin (Merck Eurolab, France).

The effects of the duration and culture conditions on the pattern of calcium oscillations induced by glucose have been investigated [8]. Our study also determined the optimal culture conditions to obtain stable oscillations: islets were cultured for 24, 48, 72, and 96 h in the presence of 5.5 or 11 mM glucose. Optimal culture conditions in terms of amplitude and regularity of oscillations were 48 h with 11 mM glucose. They were used in this study.

2.3. Experimental setup

Islets were loaded in 250 μl HBSS medium (5 mM glucose) with the fluorescent dye Indo-1 in its form AM (10 μM, Elvetec, France) and pluronic acid (0.03%, Sigma, France) for 1 h at 37 °C and washed with dye-free medium. Islets were then activated for 30 min (unless otherwise stated) with 11 mM glucose in HBSS medium.

After activation, islets were allowed to attach onto circular 30-mm cover slips, coated with polyornithine (Sigma) and inserted at the bottom of a perforated Petri dish. The thermostated Petri dish was placed on the stage of an inverted microscope (phase contrast microscope, NIKON, France) and islets were superfused with 11 mM glucose in HBSS medium. Temperature control was achieved by circulating warm water through a glass loop placed on the dish's inner periphery (Fig. 1). The perfusion medium was preheated to 42 °C prior to entering the dish. A temperature probe was placed in the medium, acting on the Ministat (Huber, Germany) to keep the temperature at a constant 35 °C, with a tolerance of 0.1 °C. This temperature was selected according to our preliminary observations that the frequency of the oscillations increased over time when the medium's temperature was kept at 35 °C, in accordance with previous results [8].

The dye was excited at 355 nm and the ratio of fluorescence signals emitted at two wavelengths (480 and 405 nm) was recorded using Axotape software (Axon Instruments, Union City, CA, USA). The ratio was monitored on an oscilloscope to determine the frequency of calcium oscillations in real time. In this study, medium-size islets (around 100-μm diameter) were used since larger islets did not let the dye diffuse to their centres [8], while smaller ones were too prone to UV bleaching.

A magnetic field was applied using two Helmholtz coils positioned to obtain a uniform field at the centre of the Petri dish (Fig. 2). This system was connected to a signal generator with controlled frequency, intensity, shape, and exposure duration. The strength of the magnetic field was measured using a Bartington probe (Bartington Instruments, Oxford, England).

In order to keep a fixed phase between the calcium oscillations and the applied sinusoidal signal, the magnetic field was always turned on at the crest of the calcium oscillation.

2.4. Data analysis

Fig. 3 represents the analysis of a typical control period: frequency spectra were obtained using the Fourier transform. In this example, the fundamental frequency f_f of 35.8 mHz is the basal value. The fundamental frequency of the first control period was normalised to 100 and compared to that of the second period (exposed or sham) and of the third period (control). The instantaneous frequency f_i (one over the time interval between two oscillations crests) was calculated to

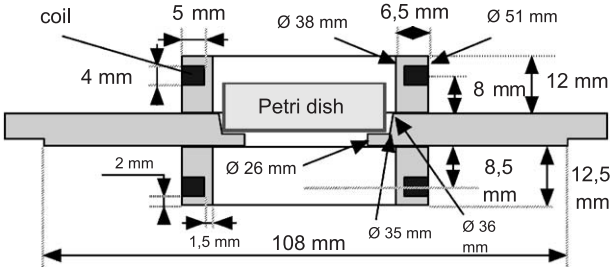

Fig. 2. Schematic of the Helmholtz exposure system.

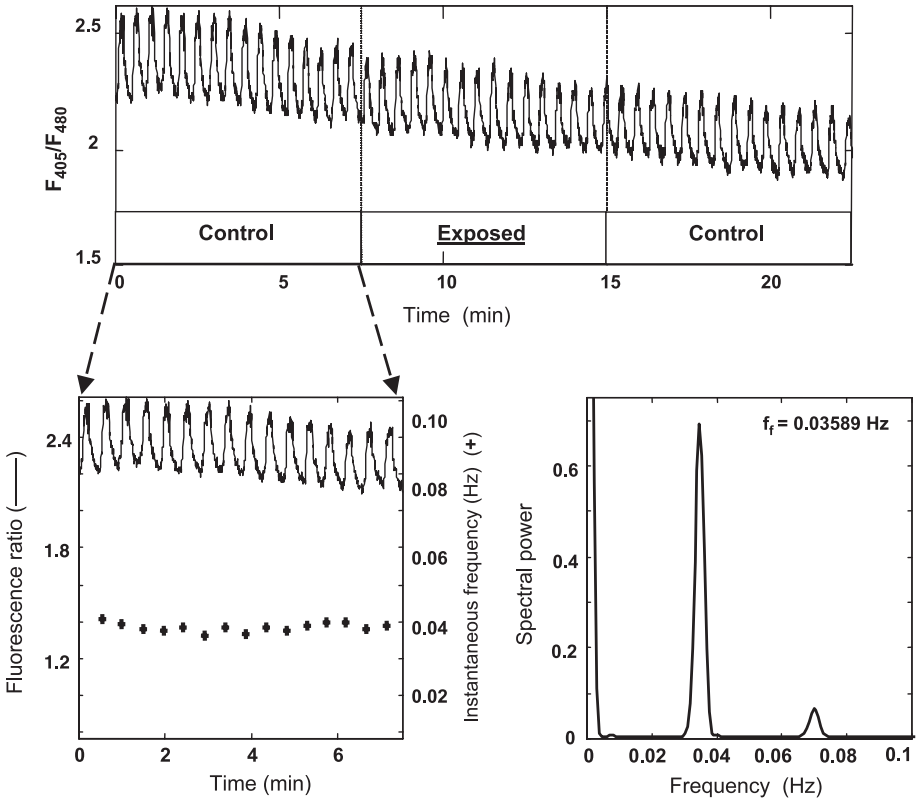

Fig. 3. Analysis of a 7.5-min recording. We plot the instantaneous frequency derived from the derivative of the signal and using Fourier transform of the fundamental frequency (here ca. 36 mHz).

evaluate the "organisational" pattern of the oscillations. "Organisation" is defined as the occurrence of the fundamental frequency among all instantaneous frequencies measured during the reference period.

All analyses were made using the Matlab software (Mathworks, France). Statistical analysis was made with the Student's *t*-test.

3. Results

3.1. Control experiments

Three types of oscillations were recorded. These differed in frequency and shape (Fig. 4). The first type involved slow oscillations ($f_f < 20$ mHz) with a fast rise followed by a slow rise and slow decay (Fig. 4a). These large-amplitude oscillations were not very regular, and a trend toward acceleration of the oscillations and a final plateau was often observed. The second type of oscillations was of the burst type ($20 < f_f < 100$ mHz; Fig. 4b). Their shape, comparable to that of slow oscillations, is composed of a fast rise, followed by a slow decay. Fast oscillations ($100 < f_f < 500$ mHz) were observed in some experiments. This low-amplitude oscillations were irregular (Fig. 4c). Their shape was very specific, with a fast rise followed by a fast decay.

The second type of oscillations was the most frequent and the only one considered in our analysis. Very regular oscillations were obtained for 90 min under constant exposure to UV.

The following exposure protocol was used: (1) 30-min control, (2) 30 min with sham exposure or exposure during the central 10-min period, and (3) 30 min of control without exposure. In each of the three periods, a different part of the islet was illuminated and observed. Fig. 5 shows these three periods for one islet at three different locations within the same islet with 15-min intervals between recordings (in this particular case, 11 mM glucose was added at the beginning of the recording period rather than during the loading period). Following the initial increase in glucose concentration, an increase in calcium concentration took place. Oscillations started thereafter, becoming increasingly regular, as shown by the calculation of instantaneous frequency f_i.

3.2. Cyclotron resonant conditions

Since the early work of Liboff _Ref20477684-[9], it has been hypothesised that the movement of ions through channels or other ionic processes could be affected by exposure to combined parallel static and AC magnetic fields at a specific frequency and amplitude. This ''cyclotron resonance''

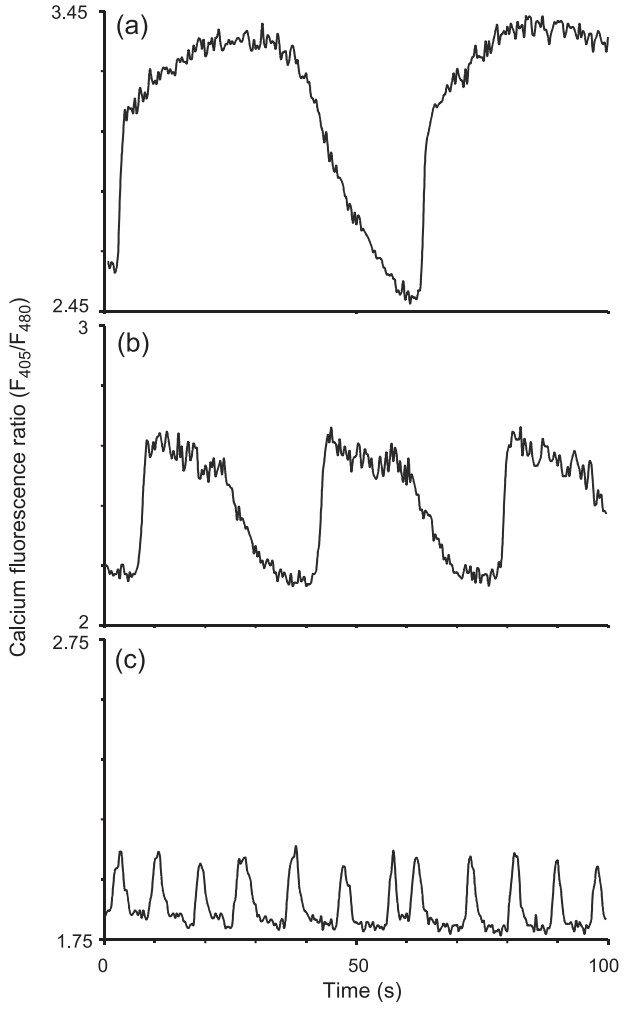

Fig. 4. The three different types of oscillations. (a) Slow oscillations, (b) burst oscillations, (c) very fast oscillations over 100 s.

hypothesis has never been verified independently despite several attempts.

We tested the "resonance conditions" in our experimental model of calcium oscillations. The amplitude of static field B_{DC} was 20.7 μT with a vertical orientation, and that of the AC field B_{AC} was 20.7 μT_{pk-pk} at a sine wave of 16 Hz, also with vertical orientation. Using these exposure conditions, no effects on the organisation and fundamental frequency were observed between field and sham-exposed islets (Table 1). In the analysis of the 21 "exposed" runs, f_f was on average 135 ± 12 (f_f being normalised to 100 in the control period preceding exposure with ± 9% variability), while for the 12 "sham-exposed" runs, f_f was 131 ± 7. The difference between exposed and sham-exposed f_f was not statistically significant.

3.3. Fifty-hertz exposure

Fifty-hertz sinusoidal magnetic fields with a strength of 100 μT were applied to the islets (Table 2). Fig. 6 represents an experiment with the three analysis periods. No significant differences were observed between sham-exposed and exposed islets in terms of organisation of the oscillations and alteration of the fundamental frequency (105 ± 5 for 31 "exposed" runs vs. 109 ± 8 for 42 "sham-exposed" runs, n.s.).

3.4. Exposure to near natural frequencies

Free-running calcium oscillations occurred at "natural" frequencies in the range 20–100 mHz. We tested the hypothesis that some entrainment by the magnetic field may be caused by exposure to low-frequency signals at the same frequency or its harmonics and subharmonics ($h = 0.5$, 1, or 2). Therefore, the natural frequency f_n was recorded during the first 5 min on the oscilloscope and the signal was then applied with $h = 0.5$, 1, or 2. No difference was observed on the pattern of calcium oscillations under any of the conditions (Table 2). The values of f_f for the exposed period were 109 ± 8 ($h = 0.5$), 105 ± 12 ($h = 1$), and 97 ± 8 ($h = 2$) vs. a sham-exposed value of 109 ± 8 (n.s.). All these experiments were done at field strengths of 100 μT, but some experiments were also done at $f_f/2$ at 1 mT, without further effects on the oscillations (Table 3). The fundamental frequency of exposed islets was 107 ± 12 vs. 105 ± 10 for the sham-exposed runs (n.s.).

3.5. Exposure to a static magnetic field

Static magnetic fields were applied with an intensity of 1 mT. No effects were seen on the pattern of the calcium oscillations under these exposure conditions (Table 2). The fundamental frequency of exposed islets was 124 ± 15 vs. 109 ± 8 for the sham-exposed runs (n.s.).

4. Discussion

In this work, we studied the effects of several types of magnetic fields on calcium oscillations. We used insulin-secreting cells from the pancreatic islets of Langerhans. This model is known to produce prolonged and regular cytosolic calcium oscillations in all beta cells. We tested the hypothesis that extremely low frequency (ELF) and/or static magnetic fields can alter the frequency and shape of these oscillations. The outcome of our experiments did not demonstrate any significant effect of magnetic fields.

Calcium homeostasis in the presence of magnetic fields has been the subject of several studies in view of the major role of this ion in biology [1]. Calcium ion concentration is highly regulated in all cell types, and this ion acts as a messenger or an effector in many biological processes [2] (e.g., differentiation, proliferation, transcriptional activation, and apoptosis). Calcium ions can interact as second messengers in both excitable and nonexcitable cells. The cytosolic concentration of calcium regulates the activities of various molecules, including kinases, phosphatases, phos-

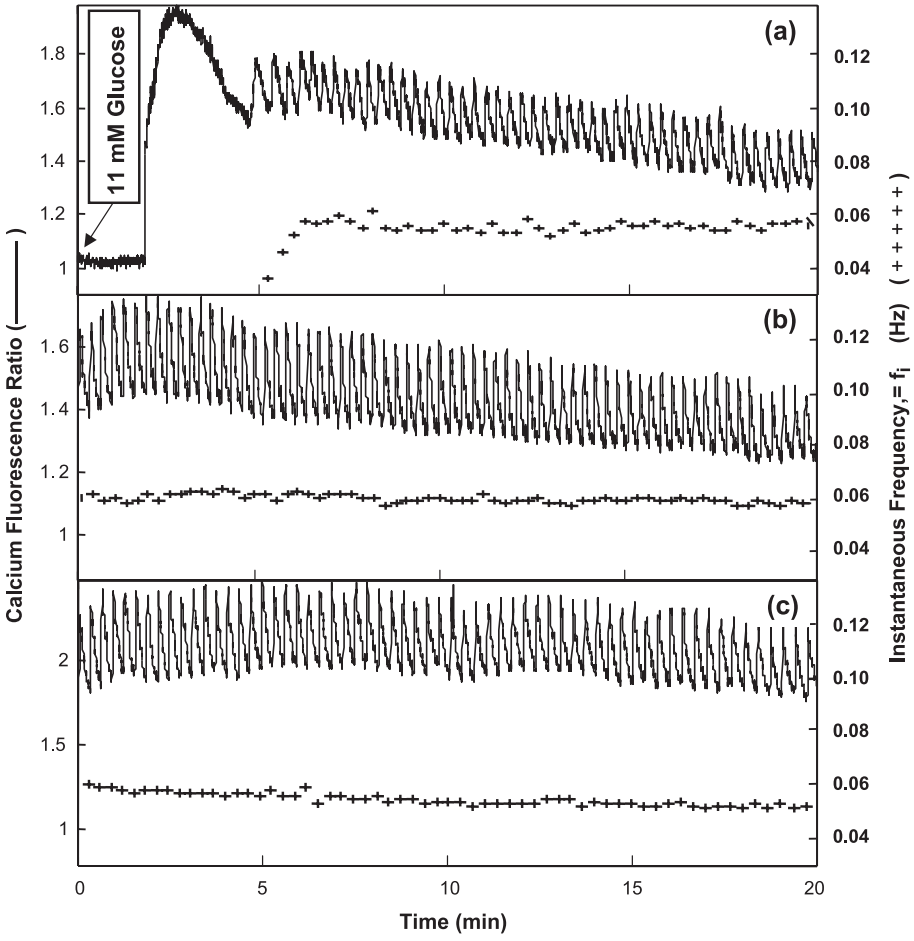

Fig. 5. Regularity of the oscillations. Three successive 20-min periods recorded on the same islet but in three different places.

phodiesterases, cytoskeletal components, and ion channels. The importance of this ion in cell physiology results from the ability that all cells have to modulate Ca^{2+} signals in space, time, and amplitude as well as to modify signals transmitted in this way [2]. Following earlier studies on the effects of strong magnetic fields on calcium ion entry into cells [10], most of subsequent works have concentrated on alterations of this ion's intracellular concentration. Jurkat T lymphocytes were initially a key model for such studies, in particular, those by Lindstrôm et al. [11–15]. These studies showed that oscillations of calcium concentration were facilitated by exposure to ELF magnetic fields at around 50 Hz and 100 μT. They also showed that CD45 phosphatase was necessary and that, overall, an intact signal transduction pathway was needed. This includes molecules involved in early events in the signalling pathway from the T cell antigen receptor. Parallely, recent studies have shown that 50-Hz magnetic fields were unable to regulate PKC- and Ca^{2+}-dependent gene expression in Jurkat cells [15]. However, all attempts to replicate previous positive studies on calcium oscillations in Jurkat cells have failed [16,17], even though Galvanovskis et al. [18,19] observed

Table 1
Exposure under resonance conditions (percentage of changes in various runs)

	Exposed	Sham-exposed
Number of runs	21	12
Organisation	19%	17%
Disorganisation	81%	83%
Acceleration	90%	100%
Slowing down	10%	0%

The amplitude of the static field B_{DC} was 20.7 μT, with a vertical orientation, and that of B_{AC} was 20.7 μT_{pk-pk} at 16 Hz (sine wave and vertical).

Table 2
Effect of exposure as a function of frequency (50 Hz, natural frequency f_n, and DC) and intensity (100 and 1000 μT)

	Control	50 Hz	$2f_n$	f_n	$f_n/2$	Static
Field strength (μT)	0	100	100	100	100	1000
Number of runs	42	31	15	18	18	17
Organisation	52%	29%	47%	50%	50%	47%
Disorganisation	33%	45%	40%	33%	44%	18%
Acceleration	48%	42%	47%	39%	50%	47%
Slowing down	50%	42%	47%	61%	39%	35%

Percentage of changes in various runs.
f_n is the natural frequency measured during 5 min prior to exposure.

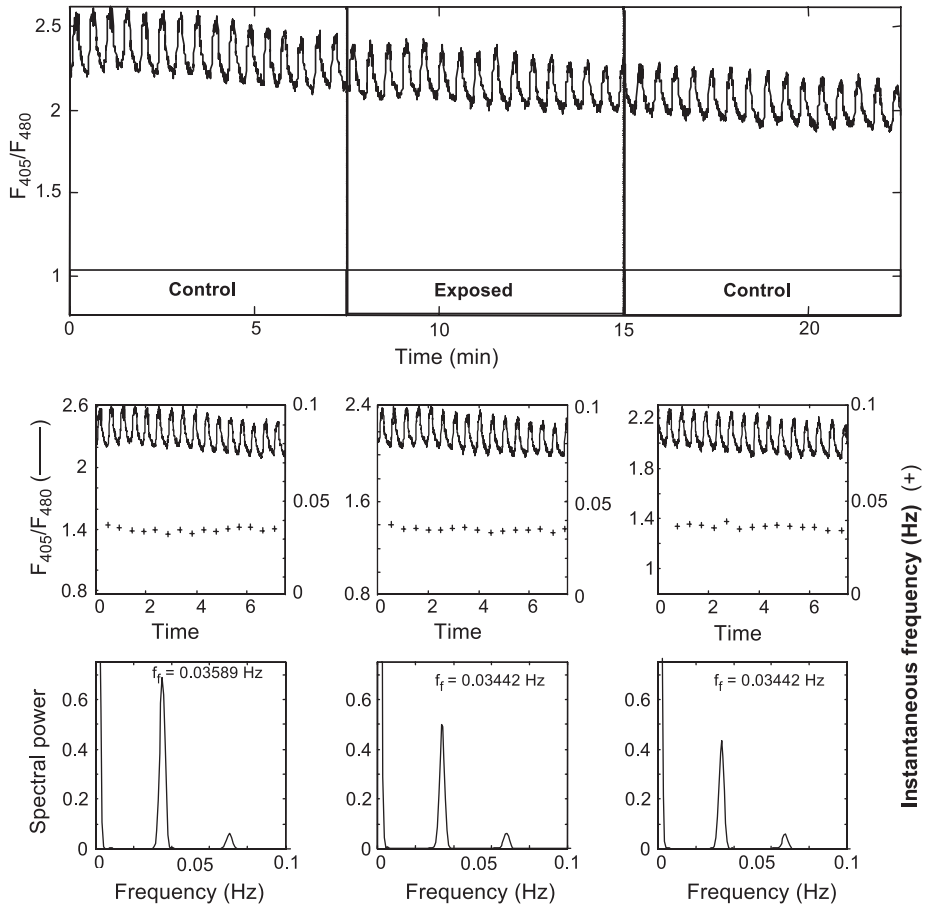

Fig. 6. Full analysis during one experiment of exposition. The first and the third periods were controls with no field. During the second period, we exposed islets to a sinusoidal magnetic field of 100 μT with a frequency of 50 Hz.

minor alterations of oscillation frequency spectra on Jurkat cells. The latter group showed that the method of fixing the cells to the glass substrate was crucial to the effect's elicitation, while the results of Refs. [3] and [20,21] showed that UV light used in the monitoring of calcium by fluorescence was also a potential confounder, in that UV alone might trigger concentration increases.

Some groups have studied calcium homeostasis under "resonance" conditions involving the combined action of ELF and static magnetic fields. The most widely used model is the "ion cyclotron resonance" (ICR) model proposed by Liboff [9] as a process able to facilitate the movement of ions such as Ca^{2+} through membrane channels. The resonance condition is expressed by the relationship $f_c = qB/2\pi m$, where f_c is the frequency, q is the ion charge, and m is its mass. Although some results of Ca^{2+} uptake by lymphocytes [22] and diatoms [23] seem to support this model, there have also been several negative results (e.g., Refs. [24,25]). Moreover, several fundamental physical arguments have been raised against the ICR model. Two other resonance models have been proposed based on the same relationship between the frequency and the parameters of the fields (within a factor of 2).

All these studies on the effects of low-frequency magnetic fields have shown contradictory results (see the review by Berg [1]). Most of these studies used single cells, which undoubtedly present some advantages (e.g., ease of culture, ease in monitoring biochemical parameters, ease in the quantitative assessment of calcium concentration, and a wide statistical basis). However, isolated cells have several further disadvantages: they are very sensitive to external parameters, experimental setup, culture conditions, and number of passages for cell lines, but isolated cells are not as informative as organs since there is no communication between cells.

Table 3
Exposure at $f_n/2$ with an intensity of 1000 μT compared to controls with no field applied (percentage of changes in various runs)

	$f_n/2$ (1000 μT)	No field
Number of runs	22	19
Organisation	50%	37%
Disorganisation	36%	53%
Acceleration	73%	90%
Slowing down	19%	5%

f_n is the natural frequency measured during 5 min prior to exposure.

We thus chose the islet of Langerhans as a model which has the advantages of both single cells' good side and organs (intercellular communication and multicellular structure). This tissue is very conducive to experimentation since it can be exposed for a relatively long time, even under UV illumination. Beta cells oscillate synchronously in the islet [5], which increases the signal-to-noise ratio because the emitted fluorescence is monitored in several dozen cells. Calcium oscillations in islets of Langerhans involve cellular energetics [26] (total glycolysis are used in this tissue to produce ATP within the Krebs cycle), intracellular communication (calcium ion, G protein, PLC [27], cAMP, charges, etc.), and intercellular communication (gap junctions [28], diffusible components [29], etc.). As specified by Grundler et al. [30], the autonomous limit cycle oscillation necessitates an open system and two further conditions: the existence of feedback loops within the signalling pathway enhancing the incoming signal and the presence of strongly dissipative processes. Under these conditions, nonlinear self-sustained oscillators show extreme sensitivity to coherent perturbations. Our study showed that, in spite of this sensitivity, calcium oscillations remained well organised when subjected to various external coherent signals.

Several theoretical models have been published presenting numerical simulations of islet functioning. We used two of these models (Refs. [31] and [32]) to build our own more comprehensive model in order to test the impact of disturbances induced by magnetic fields on biochemical processes and to determine their effect on oscillation patterns. These simulations (not presented) showed that several elementary reactions were very sensitive, as the modulation of their kinetic parameters by the time-varying magnetic field caused profound alterations in oscillation patterns. However, there was no evidence of such alterations in cell-exposure experiments. We have thus shown that the islets of Langerhans model, which is very sensitive to disturbances (temperature, glucose concentration, culture conditions, etc.), seems to be unaffected by magnetic fields under various exposure conditions. These data provide further evidence that biological systems involving calcium ions are not easily affected by magnetic fields, even at levels far above ambient. This negative testing of the hypothesis could be investigated further over a wider frequency range. However, as this method, measuring the frequency and regularity of the oscillations, is very sensitive, it is unlikely that effects will be found using ELF with regular calcium oscillations.

Since low-frequency magnetic fields are unable to alter well-established calcium oscillations, it would be desirable to perform the same experiment on less-organised oscillations, which might be more sensitive to coherent external disturbances. Such disorganised oscillations can easily be obtained by lowering the concentration of glucose in the medium. In conclusion, using a very sensitive model, we could not produce new evidence of alterations of calcium processes under exposure to various magnetic fields, in contrast with a few positive results previously published on other models.

Acknowledgements

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