STOCHASTIC RESONANCE OF ELF-EMF IN VOLTAGE-GATED CHANNELS: THE CASE OF THE CARDIAC $I_{Ks}$ POTASSIUM CHANNEL

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ABSTRACT

We applied a periodic magnetic field of frequency 16 Hz and amplitude 16 nT to a human $I_{Ks}$ channel, expressed in a *Xenopus* oocyte and varied the membrane depolarization between -100 mV and +100 mV. We observed a maximal increase of about 9% in the potassium current at membrane depolarization between 0 mV and 8 mV (see Figure 3). A similar measurement of the potassium current in the KCNQ1 channel, expressed in an oocyte, gave a maximal increase of 16% at the same applied magnetic field and membrane depolarization between -14 mV and -7 mV (see Figure 4). We attribute this resonant behavior to stochastic resonance between the thermal activations of the configuration of interacting ions in the $I_{Ks}$ channel over a low potential barrier inside the closed state of the channel and the periodic electromotive force induced across the membrane by the periodic magnetic field. The partial synchronization of the random jumps with the periodic force changes the relative times spent on either side of the barrier, thereby changing the open probability of the spontaneously gating open channel. This, in turn, changes the conductance of the channel at the particular

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depolarization level and frequency and is expressed in the Hodgkin-Huxley equations as a bump at the given voltage in the conductance-voltage relation. We integrate the modified Hodgkin-Huxley equations for the $I_{Ks}$ current into the Luo-Rudy model of a Guinea pig ventricular cardiac myocyte and obtain increased conductance during the plateau of the action potential in the cell. This shortens both the action potential and the cytosolic calcium concentration spike durations, lowers its amplitude, increases cytosolic sodium, and lowers cytosolic potassium concentrations. The shortening of the ventricular calcium signal shortens the QT period of the ECG. These theoretical predictions, supported by experimental measurements, show that $I_{Ks}$-current boosting by ELF-EMF may be beneficial for increasing the repolarization reserve and thereby for preventing the prolongation of the action potential and the risk of ventricular arrhythmias.

1 Introduction

The recent spate of communications on ELF-EMF effects on heart [1], [2], [3], [4], on cardiac myocytes in vitro [5], on cardiovascular disease mortality [6], on human blood pressure [7], on increase in vitro and in vivo of angiogenesis [8], on calcium-ion efflux from brain tissue in vitro [9], [10], on human leukemia T-cells [11], on the control of neutrophil metabolism [12], on cell membranes [13], on characteristics of membrane ions [14], on system of ions [15], on ion cyclotron resonance [16], on ion thermal motion in a macromolecule [17], [18], raises the question of pinpointing the source of the interactions at the molecular level.

The immediate suspects of the said interaction are the KCNQ1 channels (Kv7.1) that belong to a subfamily of voltage-gated K$^+$ channels, Kv7, and co-assemble with KCNE1 $\beta$ subunits to generate the $I_{Ks}$ potassium current that is critical for normal repolarization of the cardiac action potential [19], [20], [21], [22], [23]. The reason for suspecting the $I_{Ks}$ channel of complicity in affecting calcium transients in cardiac myocytes and in the general cardiac response to ELF-EMF, such as the shortening of the QT interval (mutations in either KCNQ1 or KCNE1 genes produce the long QT syndrome (LQT) [24]), a human ventricular arrhythmia [22], [23], [25], and similar phenomena communicated in [24], [4], [5], is that they stay open for the duration of the plateau in the action potential of cardiac myocytes. This leaves sufficient time for the $I_{Ks}$ current to interact with the ELF-EMF.

The main result of this paper is to pinpoint the interaction of the ELF-EMF at the suspected KCNQ1 and $I_{Ks}$ channels. To do this, we applied a periodic magnetic field of frequency 16 Hz and amplitude 16 nT to a human $I_{Ks}$ channel, expressed in a Xenopus oocyte and varied the membrane depolarization between -100 mV and +100 mV. We observed a maximal increase of about 9% in the potassium current at membrane depolarization between 0 mV and 8 mV (see Figure 3). A similar measurement of the potassium current in the KCNQ1 channel, expressed in an oocyte, gave a maximal increase of 16% at the same applied magnetic field and membrane depolarization between -14 mV and -7 mV (see Figure 4).

The effect of ELF-EMF on cardiac myocytes at the $I_{Ks}$ was demonstrated in [3]. Specifically, neonatal rat cardiac myocytes in cell culture were exposed to electromagnetic fields at
frequencies 15 Hz, 15.5 Hz, 16 Hz, 16.5 Hz and amplitudes of the magnetic field from below 16 pT and up to 160 nT. In the range 16 pT – 16 nT both stimulated and spontaneous activity of the myocytes changed at frequency 16 Hz: the height and duration of cytosolic calcium transients began decreasing significantly about 2 minutes after the magnetic field was applied and kept decreasing for about 30 minutes until it stabilized at about 30% of its initial value and its width decreased to approximately 50%. About 10 minutes following cessation of the magnetic field the myocyte (spontaneous) activity recovered with increased amplitude, duration, and rate of contraction. Outside this range of frequencies and magnetic fields no change in the transients was observed (see Figure 1). When the stereospecific inhibitor of KCNQ1 and $I_{Ks}$ channels chromanol 293B was applied, the phenomenon disappeared, which indicates that the $I_{Ks}$ and KCNQ1 potassium channels in the cardiac myocyte are the targets of the electromagnetic field, in agreement with the results of the oocyte experiment mentioned above.

The peaking of the effect of the ELF-EMF at definite frequencies ties interaction phenomenon to possible stochastic resonance. Stochastic resonance (SR) constitutes a cooperative phenomenon, whereby the addition of noise to a periodic signal measured by a nonlinear bistable (or multistable) system can, paradoxically, boost the detected signal [26]. A voltage-gated ion channel in a biological membrane can be viewed as a bistable nonlinear system driven by noise (thermal fluctuations), which causes random transitions between the open and closed states at rates that depend on membrane voltage. Thus voltage-gated ionic channels can be naturally expected to exhibit SR.

Voltage-gated channels are known to gate spontaneously, that is, to open and close to

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Figure 1: Cardiac cells, 4 days in culture, were exposed to magnetic fields of magnitude 160 pT and frequency 16 Hz for 30 min. Characteristic traces of spontaneous cytosolic calcium activity (A,B,C,D) and of electrically stimulated (1 Hz) cytosolic calcium activity (E,F,G,H). Times are measure in seconds from the moment of application of the magnetic field.
permeating ions at random times, without the application of any apparent external force \[27\]. There are many theories of spontaneous random gating of protein channels of biological membranes \[28\], \[29\], \[30\], \[31\], \[32\], \[33\]. When an alternating magnetic field is applied transversally to the channel, an alternating electromotive force is created, according to Faraday’s law, which superimposes an alternating electric force on the mobile ions in the channel. The specific response at 16 Hz may indicate some form of resonance or stochastic resonance of a gating mechanism of open voltage-gated potassium channels (e.g., a secondary structure or mechanism) with time-periodic induced electric field. A summary of the SR theory proposed in \[34\] is given in Section 4.

To tie the above considerations to the communicated effects on cardiac myocytes and on the heart, we note that according to our theory, the open probability of the relevant K\(^{+}\) channel is increased during the plateau due to the said resonance. Therefore the increased efflux of potassium shortens the action potential, and consequently lowers the peak of the cytosolic calcium concentration, at the expense of increased sodium concentration (see Figures 9 and 10). The shortening of the action potential leads to the shortening of the QT interval (see Figure 11) \[35\]. These theoretical predictions are supported by experimental measurements. Specifically, similar phenomena were communicated in \[24\], \[3\]. Other manifestations of resonance with magnetic fields at 8 and 16 Hz and amplitudes between 160 pT and 160 nT, consistent with the prediction of the modified Luo-Rudy model (see figures \[7\] \[8\], were communicated in \[5\]. The phenomenon of resonance with an alternating electric field in a potassium channel was reported first in \[36\].

## 2 Materials and Methods

Channel expression into *Xenopus* oocytes

Female *Xenopus Laevis* frogs were purchased from Xenopus 1 (Dexter, Michigan, USA). The procedures followed for surgery and maintenance of frogs were approved by the animal research ethics committee of Tel Aviv University and in accordance with the Guide for the Care and Use of Laboratory Animals (1996. National Academy of Sciences, Washington D.C.). Frogs were anaesthetized with 0.15% tricaine (Sigma). Pieces of the ovary were surgically removed and digested with 1mg/ml collagenase (type IA, Sigma) in Ca\(^{2+}\)-free ND96 for about one hour, to remove follicular cells. Stage V and VI oocytes were selected for cRNA or DNA injection and maintained at 18°C in ND96 (in mM: 96 NaCl, 2 KCl, 1.8 mM CaCl\(_2\), 1 MgCl\(_2\) and 5 HEPES titrated to pH = 7.5 with NaOH), supplemented with 1mM pyruvate and 50 g/ml gentamicin. The human KCNQ1 cDNA (in pGEM vector) was linearized by Not1. Capped complementary RNA was transcribed by the T7 RNA polymerase, using the mMessage mMachne transcription kit (Ambion Corp). The cRNA size and integrity was confirmed by formaldehyde-agarose gel electrophoresis. Homomeric expression of human KCNQ1 or \(I_{Ks}\) was performed by injecting 40 nl per oocyte (5 ng cRNA) using a Nanoject injector (Drummond, USA). Several expression experiments were also carried out by microinjecting a recombinant DNA vector (pcDNA3) encoding the human KCNQ1 or \(I_{Ks}\) cDNA directly into Xenopus oocyte nuclei (1 ng into 10 nl). Very similar data were obtained for either cRNA or DNA injections.
2.1 Electrophysiology

Standard two-electrode voltage-clamp measurements were performed at room temperature (22°C-24°C) 2-5 days following cRNA or DNA microinjection. Oocytes were placed into a 100 µl recording chamber and superfused with a modified ND96 solution (containing 0.1mM CaCl₂) under constant perfusion using a fast perfusion system at a rate of 0.48 ml/sec (ALA VM8, ALA Scientific Instruments). Whole-cell currents were recorded using a GeneClamp 500 amplifier (Axon Instruments). Stimulation of the preparation, and data acquisition were performed using the pCLAMP 6.02 software (Axon Instruments) and a 586 personal computer interfaced with a Digidata 1200 interface (Axon Instruments). Stimulation of the preparation, and data acquisition were performed using the pCLAMP 6.02 software (Axon Instruments) and a 586 personal computer interfaced with a Digidata 1200 interface (Axon Instruments). Glass microelectrodes (A-M systems, Inc) were filled with 3M KCl and had tip resistances of 0.2-1 MΩ. Current signals were digitized at 1 kHz and low pass filtered at 0.2 kHz. The holding potential was -80 mV. Leak subtraction was performed off-line, using steps from -120 to -90 mV, assuming that the channels are closed at -80 mV and below. Errors introduced by the series resistance of the oocytes were not corrected and were minimized by keeping expression of the currents below 10 µA.

2.2 Application of the magnetic field

A digital waveform Agilent generator was connected to a copper wire coil with a single wrapping of diameter 5 cm and alternating sinusoidal currents of 16 Hz and amplitude 0.636 mA were passed. The amplitudes of the generated magnetic fields at the center of the loop were 16nT, according to the Biot-Savart law. The copper wire was wound around the oocytes. We repeated the experiments 5 times on separate oocytes.

2.3 Data analysis

Data analysis was performed using the Clampfit program (pCLAMP 8, Axon Instruments), Microsoft Excel 2002 (Microsoft Corporation), SigmaPlot 8.0 (SPSS Inc) and Prism (GraphPad software). To analyze the voltage dependence of channel activation, a double exponential fit was applied to the tail currents at -60 mV or -120 mV and the slow exponential component was extrapolated to the beginning of the repolarizing step. Chord conductance (G) was calculated by using the equation

\[ G = \frac{I}{V - V_{rev}}, \]

where \( I \) is the extrapolated tail current and \( V_{rev} \) is the reversal potential measured in each experiment. The reversal potential value was \( V_{rev} = -98 \pm 2 mV \) (n = 10). The conductance \( G \) was estimated at the tail voltage \( V \) and then normalized to the maximal conductance.
Figure 2: $I_{\text{Ks}}$ current in *Xenopus* oocytes with applied magnetic field of 16 Hz and 16 nT (red) and without (blue)

value $G_{\text{max}}$. Activation curves were fit to the Boltzmann distribution

$$\frac{G}{G_{\text{max}}} = \frac{1}{1 + \exp \left\{ \frac{V_{50} - V}{s} \right\}}$$

where $V_{50}$ is the voltage at which the open probability is 50%, and $s$ is a slope factor.

### 3 Results

A direct measurement of resonance between an applied periodic magnetic field and the potassium current in a human $I_{\text{Ks}}$ channel, expressed in *Xenopus* oocytes, shows a maximal increase of about 9% in the current at frequency 16 Hz and amplitude 16 nT of the applied magnetic field and membrane depolarization between 0 mV and 8 mV (see Figures 2 and 7). A similar measurement of the potassium current in the KCNQ1 channel, expressed in an oocyte, gives a maximal increase of 16% at the same applied magnetic field and membrane depolarization between -14 mV and -7 mV (see Figure 4).

### 4 Theory

Since the induced electric field is too low to interact with any component of the $I_{\text{Ks}}$ channel, we conjecture that the induced field may interact with locally stable (metastable) configurations of ions inside the selectivity filter [37]. We propose in [34] an underlying scenario for this type of interaction based on the collective motion of three ions in the channel, as represented in the molecular dynamics simulation of [37]. The configurations of three potassium ions in the KcsA channel is represented in [37] in reduced reaction coordinates on a three-dimensional free energy landscape. In our simplified model, we represent the collective
Figure 3: Resonant increase in the $I_{Ks}$ current at magnetic field of 16 Hz and 16 nT

Figure 4: Resonant increase in the KCNQ1 channel current at magnetic field of 16 Hz and 16 nT
Figure 5: Hypothetical energy landscape of two ions in the selectivity filter. The reaction path is marked red. The straight segment in the trough may represent the open state in the channel.

Figure 6: Profile of one-dimensional electrostatic potential landscape biased by a constant electric field.
motion of the three ions in the channel as diffusion of a higher-dimensional Brownian particle in configuration space. An imitation hypothetical energy landscape with a reaction path (indicated in red) is shown in Figure 5. Projection onto a reaction path reduces this representation to Brownian motion on one-dimensional landscape of potential barriers (see Figure 6). The stable states represent instantaneous crystallization of the ions into a metastable configuration, in which no current flows through the channel, that is, they represent closed states of the channel. There is also a pathway in the multidimensional energy landscape that corresponds to a steady current flowing in the channel, e.g., an unobstructed trough in the energy landscape. Transitions from the latter into the former represent gating events. In the scenario of [34] the motion between closed states is simplified to one-dimensional Brownian motion, e.g., in a trough obstructed with barriers, while the interruptions in the current correspond to exits from the unobstructed trough into the obstructed one. Activated transitions over barriers separating two closed states in the obstructed trough affect the probability of transition from closed to open states. Stochastic resonance between two closed states may change the transition rates between them, thus affecting the open (or closed) probability of the channel. The theoretical prediction of [34] claim a relatively narrow window of frequencies and depolarizations, in which the probability of staying on one side of the barrier peaks to about 10-15%, depending on amplitude, above that without the application of the electromagnetic field. These predictions seem to be consistent with the experimental result communicated in this paper.

Both the theoretical and experimental results suggest that the Hodgkin-Huxley equations for channel conductance-voltage response should be modified in the presence of the above mentioned resonance. At the resonance frequency of 16 Hz a bump of about 10-16% should appear in the conductance-voltage response curve at resonance membrane depolarizations, as shown in Figure 2. Alternatively, the response curve can be shifted to the left. Some of the effects of the ELF-EMF on cardiac myocytes, as observed both experimentally [5] and predicted by the Luo-Rudy model [38], with the modified Hodgkin-Huxley equations, are shown in Figures 7 and 8. They consist, among others, in the shortening the duration and lowering the amplitude of the action potential and of the calcium transients.

5 Conclusion and Discussion

Following observations of interactions between ELF-EMF in the heart and in calcium transients in cardiac myocytes, we set out to localize the effect at the molecular level. We find that the \( I_{\text{Ks}} \) and KCNQ1 channels respond to ELF-EMF at the particular frequency of 16 Hz and at membrane depolarization range that corresponds to the plateau of the action potential in the cardiac myocyte. Specifically, we have exposed human \( I_{\text{Ks}} \) and KCNQ1 channels, expressed in a Xenopus oocyte, to a periodic magnetic field of frequency 16 Hz and amplitude 16 nT and varied the membrane depolarization between -100 mV and +100 mV. The observed response was a maximal increase of about 9% in the potassium current at membrane depolarization between 0 mV and 8 mV for the \( I_{\text{Ks}} \) channel (see Figure 3) of 16% at the same applied magnetic field and membrane depolarization between -14 mV and -7 mV for the KCNQ1 channel (see Figure 4). To explain this phenomenon, we offer a scenario of
Figure 7: Action potential without magnetic field (Blue) and with magnetic field (Green)

Figure 8: Action potential duration without magnetic field (Blue) and with magnetic field (Red)
a new kind of stochastic resonance between the induced periodic electric field and the thermally activated transitions between locally stable configurations of the mobile ions in the selectivity filter. Since the induced electric field is too weak to interact with any component of the $I_{Ks}$ or KCNQ1 channel protein, our theory cannot describe the primary gating mechanism of a voltage gated channel. We therefore resort to a new scenario, which postulates interaction of the induced field with configurations of the mobile ions inside the selectivity filter. These configurations may be much more susceptible to the weak induced fields than any components of the surrounding protein, because the potential barriers separating the metastable configurations of the mobile ions can be of any height.

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