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Bioelectromagnetic medicine: The role of resonance signaling

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Only recently has the critical importance of electromagnetic (EM) field interactions in biology and medicine been recognized. We review the phenomenon of resonance signaling, discussing how specific frequencies modulate cellular function to restore or maintain health. The application of EM-tuned signals represents more than merely a new tool in information medicine. It can also be viewed in the larger context of EM medicine, the all-encompassing view that elevates the EM over the biochemical. The discovery by Zhadin that ultrasmall magnetic intensities are biologically significant suggests that EM signaling is endogenous to cell regulation, and consequently that the remarkable effectiveness of EM resonance treatments reflects a fundamental aspect of biological systems. The concept that organisms contain mechanisms for generating biologically useful electric signals is not new, dating back to the nineteenth century discovery of *currents of injury* by Matteucci. The corresponding modern-day version is that ion cyclotron resonance magnetic field combinations help regulate biological information. The next advance in medicine will be to discern and apply those EM signaling parameters acting to promote wellness, with decreasing reliance on marginal biochemical remediation and pharmaceuticals.

Keywords: Bioresonance, coherence domains, electromagnetic medicine, information medicine, ion cyclotron resonance, stem cell differentiation, water structure

Introduction

Although the question of cell signaling is regarded as fundamental, it is usually thought of in a molecular manner, a prime example being the second messenger role played by the calcium ion. An enormous number of downstream effects are connected to this concept. These are rarely, if ever, framed in electric terms. But the experimental record of the past 40 years makes it impossible to dismiss the underlying electromagnetic (EM) nature of cellular signaling. The presently accepted model of calcium as a second messenger is incomplete because it fails to take note of the electrical signal that initiates and is part of the process.

Attempts to study cell function as a problem in electrical engineering have not been fruitful. When asking how much useful information can be transmitted in

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a biological system, some observers simply apply Shannon's theorem to neural elements in the same way as one would to cables, utilizing bandwidth, the number of different frequencies that can simultaneously be transmitted as the key variable. The question reduces to: how well can one receive biologically useful information when the bandwidth is very narrow? This problem, first studied by Weaver and Astumian (1990) and Adair (1991), adopted an approach from electrical engineering, where information transfer is limited by the level of thermal noise to be expected in a circuit element of resistance R and bandwidth $\Delta\nu$ at temperature T, using the expression $(\delta V)^2 = 4kRT\Delta\nu$. However, numerous objections have been raised (Bier, 2005; Vincze, Szasz, & Liboff, 2008; Vincze, Szasz, & Szasz, 2005) to this simplistic application to living tissue, first, because improper values were assigned to the resistance, capacitance and bandwidth, and second, because living tissue is itself actively involved and cannot be treated as a passive circuit element.

Increasingly, it is recognized that life may have an EM basis, either in terms of local field- or potential-dependent functions (Bersani, 1999; Presman, 1970) or more holistically (Liboff, 1994) as a description that complements, if not supplants, the usual biochemical paradigm. We adopt the view that regards life as an expression of the EM field.

Many have speculated in this subject, searching for a role and for a meaning of the presence of EM signals inside and around cells, tissues and living organisms. It is now well known that EM activity can be detected at the level of cell membranes (Becker & Bachman, 1965; Becker & Brown, 1965; Hoelzel & Lamprecht, 1994, 1995; Jelinek et al., 1999; Pelling, Sehati, Gralla, Valentine, & Gimzewski, 2004, 2005, 2007; Pohl, 1980, 1981; Rapp, 1979, 1980) and at the level of microtubules (Pokorny, 1999, 2001; Pokorny, Jelinek, & Trkal, 1998) particularly. One important, recently discovered phenomenon, a resonance effect, is involved in generating communication signals by transferring highly specific and functional information at certain frequencies and intensities. Experiments demonstrate that the use of specific EM signals in the extremely low-frequency (ELF) range can trigger specific biological pathways. Equally important, the amount of useful energy transfer involved in these studies is so low that we must assume that this phenomenon is specifically designed as an information effect, for purposes of control. It is clear that the earlier approach treating EM effects in living things as an exercise in electrical engineering is overly simplistic and without merit.

We shall use the term Bioresonance to describe the situation when resonance signaling occurs within a biological structure such as a specific part of a cell or a tissue or within a living organism as a whole. One type of Bioresonance, currently under intense study (Pokorny, 2001), hypothesizes that endogenous high-frequency signals derived from microtubular generating structures may constitute a form of resonance engineering, acting to maintain cellular homeostasis. Another type of Bioresonance is the selective low-frequency EM stimulation of one or more biological cations at cyclotron resonance (ICR) conditions that are determined by their individual charge-to-mass ratios (Liboff, 1985). ICR stimulation has been widely observed, occurring exogenously as the result of externally applied electric field or magnetic field (MF) and very likely endogenously as well, because of self-generated electric fields at the cell membrane.

EM medicine

To many in the medical community, the term EM medicine refers to a small group of *diagnostic* applications, the foremost example being magnetic resonance imaging

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(MRI). Much less attention has been paid to EM *therapeutic* applications, which have been increasingly shown to be useful in treating widely disparate problems, ranging from bony nonunions to chemotherapeutic stress disorder (Diebert, McLeod, Smith, & Liboff, 1994; Rossi, Corsetti, Sukkar, & Poggi, 2007). Various other types of therapies have reported efficacious clinical results (Brugemann, 1990; Islamov, Balabanova, Funtikov, Gotovskii, & Meizerov, 2002; Islamov, Funtikov, Bobrovski, & Gotovskii, 1999). In addition to the clinical aspects, there have been important advances in the biology of Bioresonance. These include striking resonance effects on amino acid solutions and eukaryotic cell models and human cell lines (Giuliani et al., 2008; Fitzsimmons, Ryaby, Mohan, Magee, & Baylink, 1995; Rozek, Sherman, Liboff, McLeod, & Smith, 1987; Zhadin, Novikov, Barnes, & Pergola, 1998). Most excitingly, we now understand that Bioresonance applied to human stem cells is able to generate modifications in well-defined cells and strongly affect differentiation processes.

It is important to understand that none of this work in resonance signaling, even the now decades-long success with bone repair, can be explained using biochemical processes, beyond knowing that these processes are somehow set into motion by resonance fields. In the eyes of bioscientists, this inability to provide a "classical" explanation makes this research suspect. The clinical concept of EM medicine is difficult to accept because of the belief in the century-old paradigm founded by Pasteur and Koch and elaborated by Watson and Crick. To most clinicians, it is inconceivable that there are other avenues to wellness and longevity than those presently followed and explained biochemically, in terms of molecular biology. At most, EM medicine is regarded as a convenient technological adjunct to diagnostic medicine, providing useful tools such as MRI, electro- and magnetocardiography and electromyography that enable the clinician to further explore patient problems, but always in the context of existing medical understanding. Where EM therapy has proven useful, explanations are attempted with links to physical variables such as heat that can be more readily related to the current physiological paradigm.

But experiments show that there is another side to the clinical use of EM, particularly as regards the application of very weakly intense low-frequency EM signals. Cells are profoundly affected by MFs that are far too weak to be explained by thermal effects. The question then arises by what means are meaningful biochemical changes in living things affected by EM fields if these changes are accompanied by no measurable changes in heat or chemical energy?

We argue that electromagnetism provides an alternate route to molecular biology that can lead to improved medical understanding and efficacious application. It is clear that EM applications can be used to treat illness following pathways that are outside present clinical biochemical regimens. EM medicine, in its most general realization, makes use of interactions that in some cases even go beyond resonance signaling. Some of these EM therapies that do not involve ICR stimulation include repetitive transcranial magnetic stimulation (rTMS) (Figiel et al., 1998; George et al., 1995) to treat depression, EM-induced hyperthermia (Andocs, Szasz, & Szasz, 2009) and electrochemical treatment for late-stage cancers (Chou, McDougall, Ahn, & Vora, 1997) and application of electric fields at hundreds of kilohertz to treat aggressive glioblastoma and lung cancer (Kirson et al., 2007, 2009). Of these, only rTMS has to date gained medical approval in the USA.

Effects on cell function

For some decades, evidence has accumulated that electromagnetism plays a key, albeit poorly understood, role in physiological outcomes (Aarholt, Flinn, & Smith, 1981;

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Adey & Bawin, 1982; Adey, Bawin, & Lawrence, 1982; Astumian & Robertson, 1989; Astumian, Weaver, & Adair, 1995; Ayrapetyan, Grigorian, Avanesyan, & Stamboltsian, 1994; Barnes, 1996; Basset, 1993; Basset, Pawluk, & Pilla, 1974; Eichwald & Kaiser, 1993; Eichwald & Walleczek, 1996a,b, 1997, 1998; Kaiser, 1996). There is now broad acceptance that cell function is robustly sensitive to specific electric and magnetic signals. Studies have confirmed the reality of the effects of low-frequency MFs on cell characteristics, including membranes, calcium transport, cell proliferation and chromatin conformation.

Electrical properties such as membrane surface charge and potential are especially influenced by weak low-frequency MFs (Blackman, Benane, & House, 1993a,b; Blackman, Benane, House, & Elliot, 1990; Blackman, Kinney, House, & Joines, 1989; Blank & Soo, 1992, 1993a,b; Markin & Tsong, 1991a,b,c; Tsong, Liu, Chauvin, & Astumian, 1989; Tsong, 1990, 1992; Vincze et al., 2005). Lisi, Ledda, et al. (2006) investigated whether exposure to an ELF EM field can affect the molecular biology of pituitary gland-derived AtT20 cells. When continuously exposed to a 2 mT low-frequency EM field, a statistically significant increase in intracellular calcium and membrane depolarization was found. Additional morphological changes, as well as rearrangements in actin filament distribution occur in the plasma membrane.

ELF EM fields can induce depolarization in the cell membrane followed by an increase in $[Ca^{2+}]_i$ and an expression of neurofilament protein. Santoro et al. (1997) reported a decrease in membrane fluidity and reorganized cytoskeletal components after exposure to ELF MF in human B lymphoid (Raji) cells. ELF MFs can influence the structure of protein molecules within the biomembrane and also affect the expression of relevant genes and proteins (Baker, Spadaro, Marino, & Becker, 1974; Baker, Becker, & Spadaro, 1974; Becker, 1967; Becker, 1972; Becker, 1987, 2002; Becker, Chapin, & Sherry, 1974; Becker & Murray, 1970; Becker & Spadaro, 1972; Berg, 1993; Liboff & Jenrow, 2002).

Furthermore, MFs have been shown to stimulate proliferation and differentiation of neuronal cells in culture (Blackman, Blanchard, Benane, & House, 1994; Smith, Liboff, & McLeod, 1992). There is a large body of work (Cossarizza, Monti, Bersani, Cadossi, & Sacchi Franceschi, 1989; Cossarizza, Monti, Bersani, Paganelli et al., 1989; Cossarizza et al., 1993; Grimaldi et al., 1997; Liboff, Rozek, Sherman, McLeod, & Smith, 1987; Lyle et al., 1991; Ross, 1990; Walleczek, 1992; Yost & Liburdy, 1992) establishing the response of human lymphocytes to low-frequency MFs. Liburdy (1992) detected an increase in calcium uptake into mitogen-stimulated rat thymocytes and human lymphocytes during exposure to a 60-Hz ELF field. These and other well-documented effects include altered proliferative response to mitogens as well as changes in calcium uptake and signal transduction. Studies by Belyaev, Alipov, and Harms-Ringdahl (1997), Belyaev and Alipov (2001), Sarimov, Alipov, and Belyaev (2011) greatly reinforced this conclusion, determining that chromatin conformation in human lymphocytes is sharply affected by exposure to weak low-frequency MFs.

ELF resonance fields stimulate embryonic stem cell differentiation into cardiomyocytes by triggering the expression of specific cardiac lineage-promoting genes (Gaetani et al., 2009; Lisi, Ledda, De Carlo, Pozzi, et al., 2008). Cardiac stem cells (CSCs) from human endomyocardial biopsy specimens and mesenchymal stem cells can self-assemble into multicellular clusters known as cardiospheres (CSps) that engraft and partially regenerate infarcted myocardium. CSps and CSp-derived cells were exposed for 5 days in a magnetically shielded room with the cells exposed simultaneously to a weak magnetostatic field and an alternating (AC) low-frequency (7 Hz) MF, close to the cyclotron frequency corresponding to the charge-to-mass ratio of the Ca^{2+} ion. Cardiac markers were upregulated and angiogenic markers

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downregulated. In short, exposure to 7 Hz calcium ICR MF combinations can modulate the cardiogenic versus angiogenic differentiation process of *ex vivo* expanded CSCs. As discussed below, this may pave the way for novel approaches in tissue engineering and cellular therapy.

The role of cytosolic Ca^{2+} has long been recognized in the regulation of cellular and molecular interactions. Signal transduction related to Ca^{2+} oscillations can provide molecular cues for cell functions such as differentiation and proliferation. Although Ca^{2+} dynamics are versatile and likely to depend on the cell type, their role in human CSC differentiation as revealed through resonance signaling is yet to be fully elucidated.

The underlying science

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The mid-1980s was marked by the discovery by Blackman and Liboff of a surprising phenomenon (Blackman, Benane, Rabinowitz, House, & Joines, 1985; Liboff, 1985): a low-frequency AC MF is capable of changing free calcium concentrations in brain tissue, but only in the presence of a parallel simultaneously applied static (DC) MF. The most prominent effect was observed at the AC field frequency close to the cyclotron frequency of the calcium ion. Most subsequent ICR cellular studies have focused on the Ca^{2+} ion. As a second messenger, it is involved in regulation at all stages of cellular growth and development, including proliferation and differentiation, and in the assembling and disassembling of cytoskeleton elements.

A confirmation that the charge-to-mass ratio was explicitly involved in this effect was obtained when Liboff substituted isotopic ^{45}Ca for ^{40}Ca in a study on lymphocyte proliferation, showing that the frequency where the maximum ICR effect on proliferation occurred was shifted down by a factor of 12%, exactly what is to be expected for a change of mass of 5 parts out of 40 (Liboff et al., 1987). The angular cyclotron frequency is defined as $\omega = (q/m)B_o$, where q and m are the charge and mass of the ion, and B_o is the DC field. This work in ICR opened a new line of research in studying the interactions between EM fields and living things.

There were three unexpected aspects to this phenomenon: (1) the validity of Lorentz law and the consequent resonance effects in biological systems, (2) profound physiological changes following application of AC and DC MFs tuned to cyclotron frequency resonance conditions and (3) the remarkable effectiveness of very small flux density values of the applied MFs (at first), measured in tens of microtesla, and ELFs of AC MFs, measured in tens of hertz or less. Because these effects appeared to violate simplistic analyses involving magnetic induction, these results evoked much suspicion in the scientific community. However, many subsequent confirmations, performed on different model systems in diverse experimental situations, proved that these weak low-frequency effects are indeed real. It has since become clear that MF combinations, when tuned at ICR, act to regulate the flow of biological information.

There are now dozens of examples from widely different model systems showing that exposures to ICR combined MFs can result in profound physiological changes, not only in animal systems (Smith, Liboff, & McLeod, 1991; Smith, McLeod, Liboff, & Cooksey, 1987; Thomas, Schrot, & Liboff, 1986) but also in plants (Galland & Pazur, 2005; Liboff, 2006). Early experiments verifying this phenomenon were nearly always performed by looking for these changes under separate applications of the DC field alone or the AC field alone, as well as for combined fields. It was repeatedly observed that changes only occurred for combined AC and DC MFs.

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As little as a 10-minute exposure to Ca^{2+} ICR fields will stimulate insulin-like growth factor II and DNA synthesis in human osteosarcoma bone cells (Fitzsimmons et al., 1995). A 1-hour Ca^{2+} ICR field applied to thymic lymphocytes in culture will inhibit calcium influx triggered by the mitogen Concanavalin A (Yost & Liburdy, 1992). The same ICR field application, again on human lymphocytes in culture, is antagonistic to nifedipine, the pharmaceutical employed extensively as a calcium channel blocker (Rozek et al., 1987).

In addition to these and other Ca^{2+} ICR studies, consistent effects have also been reported for K^{+} and Mg^{2+} cyclotron resonance MF applications (Liboff, 2006). ICR fields tuned to Zn^{2+} significantly inhibit cell proliferation, not only in VH-10 human fibroblasts but also, more importantly, in two malignant lines, HeLa cervical cancer and p53 His-273 osteosarcoma (Sarimov, Markova, Johansson, Jenssen, & Belyaev, 2005). The resonance treatment of both bony nonunions and spinal fusion employs the simultaneous application of both Ca^{2+} and Mg^{2+} ICR fields (Diebert et al., 1994). Most recently, two resonance frequencies have been applied simultaneously, in the one case to treat (mouse) ascites caused by cancer and in the other to dissolve Alzheimer's plaque, both with effective results (Bobkova, Novikov, Medvinskaya, & Fesenko, 2005; Novikov, Novikov, & Fesenko, 2009).

The inescapable conclusion from this long list of reports is that the ICR mechanism, whatever its molecular basis, is of enormous biological significance. We are able to make reproducible and consistent physiological changes of various sorts in the widest imaginable range of genera simply by applying weak MFs tuned to the charge-to-mass ratio of various biological cations. It is very clear that these ICR applications must be part of a heretofore unknown system that carries physiological information/instructions, and that better understanding will open the way to providing a radically new means of controlling wellness.

Studies on the effects of ICR applications have also been extended in a number of fascinating directions, including the discovery by Zhadin that ICR fields, when tuned to the charge-to-mass ratios of polar amino acids, greatly enhance their aqueous conductivity (Zhadin et al., 1998). In turn, this work led to an increased interest in realizing ICR effects at remarkably small MFs, of the order of 50 nT, and also to the likely involvement of MF-induced changes in water structure as the underlying reason for this strange low-field, low-frequency ICR phenomenon.

Following Zhadin's approach (Zhadin et al., 1998), Giuliani and Grimaldi studied the influence of combined DC and AC parallel MFs on the current through an aqueous solution of glutamic acid (glu) (Giuliani et al., 2008). The results demonstrated for the first time that, for combined DC and AC parallel MFs matching the ICR of a particular charged molecule in biological tissue, an intrinsic weak MF is generated by coherent ion currents in the cell.

It has been difficult to understand the underlying physical mechanisms of these resonance effects. Liboff considered the transport of ions in membrane-bound channels under the action of ICR-tuned combined MFs, suggesting a mechanism similar to the helical motion of charged particles in free space under the influence of the Lorentz force (Figiel et al., 1998; Liboff, Smith, & Mc Leod, 1995; McLeod & Liboff, 1986). But at body temperature, this idea can be realized only at low densities and by including a much larger radius of ionic motion. The idea that parametric resonance might be responsible for such effects is also not very fruitful for lack of a necessary low-frequency harmonic oscillator in cellular systems (Blackman, Blanchard, Benane, & House, 1995, 1999; Blanchard & Blackman, 1994; Lednev, 1991; Vincze et al., 2008). Models employing Larmor precession and other classical approaches have also not proven helpful (Zhadin, 1996, 1998, 2001; Zhadin & Barnes, 2005; Zhadin & Fesenko, 1990; Zhadin & Giuliani, 2006).

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In the most recent attempt to find a reasonable explanation, Preparata's work in quantum electrodynamics (QED) (Preparata, 1995) was used to show that liquid water can be viewed as being in an equilibrium state between coherent and incoherent components. The coherent component is contained within spherical "coherence domains" (CDs) in which all molecules synchronously oscillate with the same phase. CDs are surrounded by the incoherent component where molecules oscillate with random phases (Del Giudice, Galimberti, Gamberane, & Preparata, 1995; Del Giudice & Preparata, 1995). At room temperature, the total volume of such domains is about 40% of the total. The existence of CDs in water has been demonstrated in a set of experiments on pure water exposed to high voltages (Fuchs et al., 2007; Giuliani et al., 2009). Under this condition, the electric field concentrates inside the water, arranging the water molecules to form highly ordered structures.

Because the ions in the immediate vicinity of a structured water domain are in a region where there is total absence of friction, the effects due to viscosity are drastically reduced, which in turn makes the effects of Lorentz forces more likely. An ion trapped around a water CD can behave as if it were in a vacuum. Thus, if a DC uniform MF is applied, the ion will move in a circular path around the CD. If an appropriate additional AC MF is applied with the same frequency of the ion circular frequency (ion cyclotron frequency), the ion will be removed from orbits around the CD and it can jump into the noncoherent water area and become biologically available. Therefore, the ICR problem appears to be solved, at least in part, using the QED approach initiated by Preparata and extended by Del Giudice.

This explanation has been supported by experiments performed in different laboratories studying the behavior of glu at the glutamate ICR condition. Glu solutions in an electrolytic cell were irradiated under controlled conditions for a range of ELFs and the current flowing in the electrolytic cell continuously recorded. When the resonant condition for the charge-to-mass ratio in glu was reached (4.1 Hz), a discrete peak in DC current was recorded (Giuliani et al., 2008).

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Clinical applications

There is potentially a wide diversity to the clinical applications of (nonthermal) resonance signaling. The earliest example dates back to the 1980s when it was applied to the repair of bony nonunions and as an adjunct to healing following spinal surgery. This application used either pulsed MF (PMF) (Basset et al., 1974) or ICR (Diebert et al., 1994), both techniques approved by the US Food and Drug Administration. The PMF approach applies pulses with a repetition rate of 15 Hz, which may be the actual source of the biological stimulation. In the ICR application, MFs tuned jointly to Ca^{2+} and Mg^{2+} are applied for 30 minutes per day for weeks at a time. Very significant responses are consistently observed (often providing a noninvasive alternative to amputation), at success rates approaching 80%.

Resonant MF combinations tuned to amino acid charge-to-mass ratios were used by Novikov to hydrolyze proteins, notably β-amyloid, one of the key markers for Alzheimer's disease (Bobkova et al., 2005). This result, as with many other ICR experiments, illustrates the difficulty in reconciling resonance signaling with conventional biochemistry. The energy supplied by the MF in this work was orders of magnitude less than that required for protein hydrolysis. Using a similar ICR field, Novikov was also able to significantly extend survival rates in mice infected with Ehrlich ascites tumors (Novikov, Novikov, & Fesenko, 2009).

A very different approach to ICR medical therapy is found in the Seqex device (http://www.seqex.it/home_eng.html), which applies an oscillating MF to the

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patient's entire body while simultaneously taking advantage of the local parallel vertical component of the earth's MF to achieve resonance. It has been effectively used to treat the debilitating depression that often accompanies chemotherapy following cancer remediation (Raggi et al., 2008; Rossi et al., 2007). In addition to the fact that this device employs holistic application of the combined fields, it is unique in that the applied ICR frequency is not calculated from ionic charge-to-mass ratios, but is determined by first finding in a prior separate evaluation the specific frequency conditions that sharply alter the whole-body bioimpedance. Once determined, this frequency information is stored on a "smart card" for future treatments on that patient. It is worth noting that the change in whole-body bioimpedance at resonance is consistent with the sharp changes in ionic conductivity that were observed by Zhadin et al. (1998), Giuliani et al. (2008), Pazur (2004) and Alberto et al. (2008).

The most recent clinical application of resonance signaling may also be the most spectacular. Probably the most difficult aspect in treating heart failure is the inability of damaged heart muscle to regenerate, the reason why surgeons are often forced to resort to heart transplants. One objective of stem cell therapy is to provide working replacement of infarcted heart muscle with suitably differentiated heart cells.

The usefulness of the Bioresonance concept to this important current clinical problem was demonstrated by studying the effect of combined DC and AC MFs tuned at Ca^{2+} ICR on a system of human CSCs (Gaetani et al., 2009). It was thought that suitable combinations of EMFs might affect intracellular Ca^{2+} levels, triggering progenitor cell proliferation and differentiation, a reasonable approach, considering that Ca^{2+} ions are essential regulatory components of all organisms. On the basis of previous results obtained with other cellular models, CSCs were exposed for up to 5 days to the ICR frequency corresponding to the charge-to-mass ratio of the Ca^{2+} ion.

These exposures produced several interesting effects. CSCs exposed to ELF EMF had a higher metabolic activity compared with unexposed cells. This can be related to an increase in cell proliferation, as was evidenced by BrdU incorporation curves. This trend was reduced after 3 days of exposure, perhaps due to contact inhibition and/or the beginning of the differentiation process, well documented after 5 days in CSCs at transcriptional and translational levels. Usually proliferation and differentiation are considered mutually exclusive paths, but since CSCs represent heterogeneous populations of progenitor cells at various stages of commitment, one could expect slightly different responses to proliferative and differentiation stimuli at each intermediate stage. To a certain extent, these responses possibly overlap the progressive maturation process of the entire progenitor population.

The increase in mRNA levels of cardiac specific markers, demonstrated by real-time polymerase chain reaction, was associated with an increase in the corresponding protein expression. Although CSCs spontaneously differentiate toward the cardiogenic phenotype, this process was improved by ICR exposure. The improvement in the differentiation process was cardiac specific, although not terminal. After Ca^{2+} ICR exposure, cardiac markers were upregulated, while vascular markers were either unaffected or reduced. Cardiac-specific differentiation was further evidenced when mRNA levels of cardiac markers of exposed and unexposed cells were compared with those of adult heart tissue from biopsy.

The reduction in the expression ratios of heart tissue versus the Ca^{2+} ICR exposed compared with unexposed samples represents a different and effective means to indicate cardiac differentiation. Confocal analysis confirmed an increase in the expression of cardiac markers. Altogether these results suggest that a lineage-specific differentiation is driven by the exposure to Ca^{2+} ICR Bioresonance signals.

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It is important to understand that the same experiments repeated at other frequencies not matching ICRs of biologically relevant ions did not display any significant effect at the transcriptional level, endorsing the hypothesis that these results were specifically Ca^{2+} mediated. This study demonstrated unequivocally an increased intracellular calcium accumulation in CSCs after chronic exposures to Ca^{2+} ICR, and the interesting observation that this is directly related to information transfer between mitochondria and the cytosol.

Therefore, the modulation of both proliferation and cardiac differentiation observed in Ca^{2+} ICR exposed cells correlates to induced changes in intracellular Ca^{2+} accumulation and mobilization, potentially modulating signal cascade pathways. Independent of the involved mechanisms, the induced differentiation toward the cardiac phenotype has relevant implications for the use of CSCs in tissue engineering and cell therapy. The modulation of cell proliferation and specific differentiation elicited by this system, a result of EM exposure at ICR frequency, may represent an effective, minimally manipulative and safe biotechnological tool to improve patient cardiac regenerative potential.

Conclusions

The Prometheus myth is a fitting model for regenerative medicine. As punishment for giving fire to humanity, Zeus ordered Prometheus chained to a rock and sent an eagle to eat his liver each day. However, Prometheus' liver was able to regenerate itself daily, during nighttime, enabling him to survive. Today we hope to make the legendary concept of regeneration into reality by developing therapies to restore lost, damaged or aging cells and tissues in the human body. It has been shown that ICR differentiation of human adult CSCs is feasible. Thus, it appears that ICR Bioresonance techniques may be extremely useful in advancing the implementation of regenerative medicine and tissue engineering.

But, the clinical potential for resonance signaling is not limited to organ repair and regeneration. Consider, for example, one interesting observation found in ICR studies. In more than a few reports, merely changing the resonance condition from one ion to another resulted in an opposite response. This phenomenon was first observed by Smith in his studies on diatom motility (Baker, Becker, et al., 1974) and later reported by others (Becker, 2002; Belova & Lednev, 2000; Liboff, 2002; Regling, Brueckner, Kimura, & Liboff, 2002; Smith, McLeod, & Liboff, 1993, 1995;

Table 1. Ionic tuning can drastically alter physiological outcome.

Model system	Frequency (Hz)	B_o (μT)	Ion	Response
Diatom motility (Smith et al., 1987)	16	20.9	Ca^{2+}	Motility ↑
	16	41.0	K^+	Motility ↓
Embryonic bone (Smith et al., 1991)	16	20.9	Ca^{2+}	Growth ↑
	16	40.7	K^+	Growth ↓
Embryonic bone (Regling et al., 2002)	16	20.9	Ca^{2+}	Growth ↑
	16	40.7	K^+	Growth ↓
Plant growth (Smith et al., 1993, 1995)	60	78.3	Ca^{2+}	Growth ↑
	60	153.3	K^+	Growth ↓
Rat behavior (Zhadin et al., 1999)	63	50	Mg^{2+}	More active
	38	50	Ca^{2+}	More passive
Gravitropic response (Belova & Lednev, 2000)	35.8	46.5	Ca^{2+}	Up
	54.7	46.5	K^+	Down

Note: This effect is observed for different magnetostatic fields at the same resonant frequency or, equivalently, for different frequencies at the same static magnetic intensity.

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Zhadin, Deryugina, & Pisachenko, 1999) (Table 1). Liboff (2010) suggested that this effect likely reflects the endogenous nature of Bioresonance, wherein multiple ionic resonances occur simultaneously giving rise to a balanced homeostatic physiologic outcome. If this is true then it should be possible, in principle, to selectively reduce the undesirable in favor of the desirable. Reports (Smith et al., 1992) indicate that ICR applications can increase the rates of proliferation in neuroblastoma cell culture. Is it possible that there exist ICR conditions that would have the opposite effect, namely to reduce the rates of proliferation in cancer cell lines, opening the way to new cancer fighting techniques?

Since the time of Galvani, evidence has accumulated indicating that living systems make use of EM fields. Until recently, this connection between electricity and biology was limited to the nervous system. It now appears that all the major functional structures of living systems can be regarded as EM field sources. Organisms, in turn, can be thought of as EM objects containing atomic and molecular structures.

Medical use of EMF has a long history. Modern medical applications of EMF are used to heal nonunions of bone fractures (Zhadin et al., 1999) and treat some bone-related diseases (e.g. osteoporosis and osteoarthritis), although the specific molecular mechanisms are not understood. The application of EMF to stimulate osteogenesis, for instance, is incorrectly based on the idea of stimulating the natural endogenous streaming potentials in bone. Although EM medicine is still in its infancy, there is much evidence that ICR exposure can tune eukaryotic cells toward cell differentiation and maturation, influencing physiological processes (Berg & Zang, 1993; Bistolfi, 1987; Bistolfi, 1990; Lisi, Foletti, et al., 2006; Lisi, Ledda, De Carlo, Foletti, et al., 2008; Lisi, Rieti, et al., 2006). These data suggest possible future applications of EM protocols, including Bioresonance, for the treatment of a wide range of human diseases by means of specific relevant frequency patterns delivered with specific biomedical technology, thereby providing an important tool in clinical medical practice.

In a certain sense, endogenous resonance signaling represents a more modern version of Carlos Matteucci's nineteenth century work on currents of injury (Matteucci, 1834), rescued from obscurity by Robert Becker, who recognized these currents as an intrinsic feature of living things, a built-in ability that uses electricity to regulate and repair the organism (Becker & Spadaro, 1972). ICR signaling can be regarded as a cellular version of Matteucci's currents of injury.

Apart from its obvious potential as a tool in medicine, there is a deeper question attached to the phenomenon of Bioresonance. What is the underlying biological reason for applications of ICR magnetic stimulation to result in such robust and varied effects, ranging from enhanced cell proliferation to stem cell differentiation, from changing the rates of plant growth to altering the conductivity of glu solutions? This speaks of the likelihood of heretofore unknown biological effects that still remain to be illuminated. One possibility that has been recently hypothesized (Liboff, 2010) is that these various ICR experiments, all involving time-varying MFs, are actually tapping into a basic biological process utilizing time-varying electric fields (Liboff, 1997) stochastically generated at the cell membrane to provide a regulatory system for cell function involving the geomagnetic field. Still another possibility surrounds the remarkable response of lymphocytes to weak ELF MFs, suggesting that the immune system is responsive to EM signals generated by pathogens (Liboff, in press). Both speculations fall within the guiding hypothesis of this work, namely that ELF signaling is an important endogenous feature of living organisms.

We still need to build bridges between biology and physics, particularly QED (Del Giudice, Fleischmann, Preparata, & Talpo, 2002; Del Giudice & Preparata, 1995; Del Giudice et al., 1995; Preparata, 1995), information theory (Foletti, Lisi, Ledda,

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De Carlo, & Grimaldi, 2009; Rubik, 1995; Stuart, 1985a,b) and the theory of open systems (Barbieri, 2004; Becker, 2004; Bertalanffy, 1949, 1950; Fröhlich, 1988; Fröhlich & Kremer, 1983; Liboff, 2004, 2007; Mae-Wan, 1998; Pokorny & Wu, 1998; Popp & Beloussov, 2003; Volodyaev, 2005; Zewail, 2008). In this framework, the concept of resonance signaling can play a unifying role in bridging this gap. Not only can it provide a new tool to help manage biological complexity at the bedside of the sick but perhaps it will also help us find an answer to the old question about the basis to life (Sahu, Hirata, Fujuita, Ghosh, & Bandyopadhyay, in press; Schrodinger, 1944; Dürr, Popp, & Schommers, 2002).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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