Bioelectromagnetics 36:45–54 (2015)

The Effects of Weak Magnetic Fields on Radical Pairs

Frank S. Barnes[1]* and Ben Greenebaum[2]

[1]*Department of Electrical and Computer Engineering, University of Colorado, Boulder, Colorado*
[2]*Department of Physics, University of Wisconsin-Parkside, Kenosha, Wisconsin*

It is proposed that radical concentrations can be modified by combinations of weak, steady and alternating magnetic fields that modify the population distribution of the nuclear and electronic spin state, the energy levels and the alignment of the magnetic moments of the components of the radical pairs. In low external magnetic fields, the electronic and nuclear angular momentum vectors are coupled by internal forces that outweigh the external fields' interactions and are characterized in the Hamiltonian by the total quantum number *F*. Radical pairs form with their unpaired electrons in singlet (S) or triplet (T) states with respect to each other. At frequencies corresponding to the energy separation between the various states in the external magnetic fields, transitions can occur that change the populations of both electron and nuclear states. In addition, the coupling between the nuclei, nuclei and electrons, and Zeeman shifts in the electron and nuclear energy levels can lead to transitions with resonances spanning frequencies from a few Hertz into the megahertz region. For nuclear energy levels with narrow absorption line widths, this can lead to amplitude and frequency windows. Changes in the pair recombination rates can change radical concentrations and modify biological processes. The overall conclusion is that the application of magnetic fields at frequencies ranging from a few Hertz to microwaves at the absorption frequencies observed in electron and nuclear resonance spectroscopy for radicals can lead to changes in free radical concentrations and have the potential to lead to biologically significant changes. Bioelectromagnetics. 36:45–54, 2015.
© 2014 Wiley Periodicals, Inc.

Key words: radical pairs; weak magnetic fields bio-effects; stimulated transitions; ELF; RF

INTRODUCTION

Frequency and amplitude windows in biological systems have been observed for some time and are predicted as the result of the Zeeman shift in the energy levels for electron spin states of radicals at magnetic field levels of millitesla and larger fields. Reviews of this have been done by Grissom [1995] and Steiner and Ulrich [1989]. These reviews show that both changes in nuclear spin states and changes in the orbits for electrons in a molecule occur with variations in the magnetic field. Some effects on chemical reaction rates of nuclear polarizations on some alkyl radicals are described by Kaptein [1968]. This work is followed by numerous papers showing the effects of nuclear polarization and nuclear spin states on chemical reaction rates, including Kaptein and Oosterhoff [1969], Charlton and Bargon [1971], den Hollander et al. [1971], and Buchachenko [2001]. Woodward et al. [2001], among others, found many radio frequency (RF) absorption spectra lines in the 100 μT range. Reviews of dynamic spin chemistry by Nagakura et al. [1999] and by Hayashi [2004] present detailed descriptions of the theory for the conversion of singlet (S) to triplet (T) states for radical pairs and the resulting changes in radical concentrations as a function of magnetic field strength, orientation, and the viscosity of the medium.

Some of the effects of the exposure of biological systems to weak magnetic fields at low frequency are reviewed by Liboff [2007], among others. Several theories have been advanced to describe these results, including ideas about cyclotron frequency resonances [Liboff, 2007] and paramagnetic resonance splitting of vibrational [Lednev, 1991] or Zeeman levels [Blanchard and Blackman, 1994]. However, all of those theories have difficulties [Binhi, 2002] that have prevented their general acceptance by the scientific

---

*Correspondence to: Frank S. Barnes, Department of Electrical and Computer Engineering, University of Colorado, Boulder, CO 80309-0422. E-mail: frank.barnes@colorado.edu

Received for review 28 March 2014; Accepted 8 September 2014

DOI: 10.1002/bem.21883

community at large. Additionally, the lack of a generally accepted mechanism, other than heating, by which weak RF waves can modify biological processes, has contributed to the debate on the possible biological effects of magnetic fields, including whether sources such as cell phones, radar pulses or power lines cause detrimental health effects from these fields.

At present, a leading candidate mechanism for the way fields are transduced to affect biological systems is that they modify the rate of recombination of radical pairs by changing the members of the pair's relative electronic state between S and T, resulting in increased or decreased recombination rates and changing the subsequent radical concentration, thereby producing downstream biological consequences. Adair [1999] calculated the effects on radical pair recombination due to changing the relative state of the electron moments of a separated radical pair by differences in electron spin precession rate in each radical's combined internal and any small, external field, making various simplifying assumptions but not considering resonant transitions between states created by electron and nuclear moments, strongly coupled as they are in a low external field.

Both theoretical and experimental work on the effects of weak magnetic flux densities on free radical concentration has been carried out by the group at Oxford [Brocklehurst and McLauchlan, 1996; Woodward et al., 2001; Henbest et al., 2004; Timmel and Henbest, 2004; Liu et al., 2005; Henbest et al., 2006; Rodgers et al., 2007]. However, these workers have also concentrated at low fields on the spontaneous evolution between S and T states of the spins as they precess (low field effect). Other works on the effects of magnetic fields on radicals has been carried out by Chiabrera et al. [2000], Hansen and Pederson [2006], Wang and Ritz [2006], and Zanetti-Polzi et al. [2013].

In this article we outline a model by which changes in radical concentrations may result from exposures to low intensity magnetic fields, noting that these changes can lead to biologically significant changes in metabolic rates and other processes. At frequencies corresponding to the energy separation between the various states in the external magnetic fields, particularly at low external field intensities, transitions can occur that change the populations of the combined electron and nuclear states, F states, which result in changes in the average population of the S and T states of the electrons in the radical pair. This results in changes in the pair recombination rates, which, in turn, can change radical concentrations and modify biological processes. When the ambient static field is reduced sufficiently the energy differences between some states are smaller than their spontaneous widths and similar transitions may occur.

BACKGROUND

In weak external magnetic fields, molecular magnetic moments are characterized in the quantum mechanical Hamiltonian by a combined angular momentum $F = J + I$, where J is the total electronic angular momentum and I, the total nuclear angular momentum. As the external field strength approaches the strength of the internal field, due to electron spins, this coupling breaks down and the Hamiltonian has separate terms for J and I interactions with the external field [Herzberg, 1950; Townes and Schawlow, 1955]. However, the theoretical articles mentioned in the previous paragraph do not use the F coupling; it is used in the experimental and theoretical analysis of resonance spectra of nitric oxide (NO) by Gallagher et al. [1954] and Kaptein [1972].

Figure 1 shows that under the low-field effect, a magnetic flux density on the order of tens of microtesla, which is in the vicinity of the earth's magnetic field, can lead to changes in radical concentrations so long as the frequency of the external magnetic field is slow when compared to the lifetime for transitions between the S and T states [Brocklehurst and McLauchlan, 1996]. The lifetime for these transitions is typically in the range of 10^{-10} to 10^{-6} s. Thus, even RF frequencies may be slow compared to the lifetime for these transitions. Except above $\sim$5 mT, at the very peak of the curve around 0.3 mT and, in particular, in the very low-field vicinity of the earth's field of $\sim$45 μT, small changes of magnetic field can modify the transition rate and, therefore, change free radical concentrations. We propose that stimulated transitions between levels in a radical will produce additional level population changes, probably of at least similar magnitude.

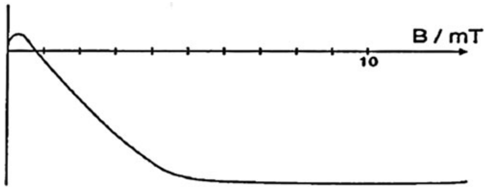

Fig. 1. A schematic representation of the experimentally observed field effect in the pyrene/1,3-DCB system. At the lowest low field values, including that of the geomagnetic field, the effect of the field is to increase the proportion of radicals which survive the geminate period and diffuse into the surroundings, but at high field the reverse happens. The schematic presentation is used since the actual published results measured the derivative of the curve, and to display them would introduce an unnecessary complication [Batchelor et al., 1993].

Chemical reaction rates increase when the energy levels for the initial state and the product approach each other. The maximum rates occur when the energy levels are equal. Thus both electric (e.g., Stark effect or internal quadrupole interactions) and magnetic fields (e.g., Zeeman or hyperfine interactions) can shift the energy levels so as to increase or decrease a chemical reaction rate. It should be noted that magnetic energy shifts, μ_B B, that are small compared to k_BT, can lead to large changes in chemical reaction rates if the initial states are in excited energy levels [Steiner and Ulrich, 1989; Hayashi, 2004]. Examples of this are the number of radicals that survive as a result of the absorption of an ultraviolet (UV) photon or a variety of chemical reactions. Excitations by electric fields keep particles that start in a singlet state in a S state. Free radicals may be created by splitting a molecule so that the surviving fragments each have an odd number of electrons in an orbit. This can be done by hemolytic cleavage of bonds, or thermolysis in solution leading to a pair of radicals in S states, and photolysis in either S or T states. In large molecules, the radical pairs often form in a T state.

In a typical molecule there is an even number of electrons in the outer orbits; and when they are split, one fragment has an electron with spin up and the other with spin down, as shown in Figure 2. These two fragments often recombine in about 10^{-10} s. However, if one of the spins flips, then recombination is forbidden by the Pauli Exclusion Principle and fragments typically survive for about 10^{-5} s. This, in turn, increases the probability that the fragments may drift apart and diffuse through the solution as radicals. The relative energies of the S and T states of a radical pair in a magnetic field as a function of distance between the pair particles are shown in Fossey et al. [1995]. Radicals can be carbon centered and form in a number of common compounds including a variety of methyl and alkyl radicals. They can also be formed in a wide variety of other compounds including radicals centered on nitrogen oxides, phosphorus, oxygen, and sulfur.

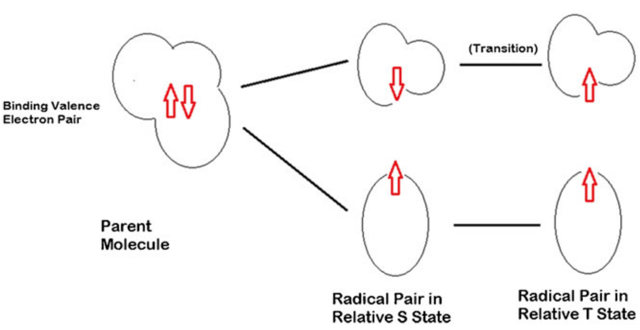

Fig. 2. Formation of radical pairs in relative S or T states.

Biological effects due to low frequency exposures that are sharply defined in frequency and field strengths have been observed by Blackman et al. [1979], Liboff [2007], and others. The effects of low frequency modulation of RF signals have been observed by Bawin et al. [1975], Blackman et al. [1979], and Woodward et al. [2001]. To obtain the narrow line widths on the order of 10 Hz for both the low frequency and for modulated RF signals, energy states with long lifetimes are required. These long lifetimes exist for changes in nuclear spin states and, for many organic molecules, they are in the range from 1 to 100 s [Bovey et al., 1988].

Another phenomenon that we propose may be related to the same mechanism concerns changes seen on reducing the ambient steady and alternating magnetic fields produces changes in biological organisms, compared to controls remaining in the earth's normal magnetic field. Examples may be seen in the work of Prato et al. [2013] with nociception in mice, Mo et al. [2013] with neuroblastoma cell proliferation, and Martino et al. [2010].

ENERGY LEVELS OF FREE RADICALS

We will start with the Hamiltonian for the dissociation of a simple hypothetical molecule such as hydrogen (H_2) or nitric oxide (NO) into two parts, H and X, where X has no nuclear spin, following the work of Kaptein and Oosterhoff [1969]. This is a two-step process and, after some time, the pair is completely dissociated and the effective Hamiltonian for the pair becomes

$$\mathrm{H} = \mathrm{H}_z^e + \mathrm{H}_z^n + \mathrm{H}_{ex} + \mathrm{H}_{ss} + \mathrm{H}_{si} \quad (1)$$

where H_z^e and H_z^n are the electron and nuclear Zeeman terms, depending upon the interaction between the external magnetic field *B* and the electronic and nuclear magnetic moments, respectively. These terms take the form $\mu \bullet B$, where μ depends on the appropriate net angular momentum. The total angular momentum is characterized by *F* for low external fields, the net electronic angular momentum is $J = L + S$, the sum of the orbital and spin angular momenta, and the nuclear spin is characterized by *I*. H_{ex} is the exchange term; H_{ss} is the electron–electron dipolar coupling term between the members of the pair; and H_{si} is the hyperfine coupling term, that is, the interaction of the nuclear moment with the local field due to the electronic motion, depending on $J \bullet S$. The H_z^n term is often ignored since it is small compared to other terms. However, H_z^n is a term which we believe may be important for modifying the concentration of the nuclear spin states when driven by a magnetic field at a frequency corresponding to the Zeeman splitting between these energy levels. As will be shown below, different nuclear spin states have different coupling coefficients to the electron spin states. Therefore, changing the distribution of nuclear spin states can affect the electron states and change the average transition rate for the electrons between the S and T states for radical pairs. For polyatomic molecules with more than one atom that has nonzero nuclear spin, there may be a coupling between these spins that leads to narrow absorption lines that are separated by a few cycles [Bovey et al., 1988]. This would add another term to the Hamiltonian, H_{si}^{Z}. This coupling is also weak and may only be important when there are frequency components in the driving signal that correspond to the energy separation. The long lifetimes for the nuclear spin states leads to very narrow frequency absorption bands.

As noted above, it is important to note that at low external magnetic field intensities, where the interactions between the internal magnetic fields and moments associated with *I* and *J* are stronger than interactions of either with the external field, the electronic, and nuclear magnetic moments are coupled together into a total net moment, characterized by $F = I + J$. This is generally the case for external field intensities on the order of the Earth's field, ~45 μT. In this instance, the Hamiltonian is written in terms of *F*, the quantum number characterizing the total state, and not in separate terms for the nuclear and electronic spins. Most nuclear magnetic resonance (NMR) and electron paramagnetic resonance (EPR) spectra are taken at quite high external magnetic field intensities, where *I* and *J* are decoupled and *F* is no longer a good quantum number. However, low-field transitions are between states characterized by *F* and its projection along the applied field direction, M_F, not between purely electronic nor purely nuclear spin states. Finally, if there is a transition in one member of the radical pair that changes the orientation *J*, there can be a transformation of the joint state of the pair from *S* to *T* or vice versa.

POSSIBLE TRANSITION FREQUENCIES: HERTZ TO GIGAHERTZ

There are multiple interactions where weak magnetic fields can change the population distribution in the various spin states: (i) The Zeeman transitions between electron states. These include transitions between states with different angular momentum as well as transitions between electron spin states. The energy values for these transitions are also affected by the magnetic field effects on the orbits of other electrons. These effects are described as changes in the g value or Δg; (ii) Transitions between nuclear spin orientations or the Zeeman states for the nuclear spins, since these couple to the electrons, as discussed below; and (iii) Transitions associated with the coupling between the spins of different nuclei in the same molecule.

Because of the coupling of electronic and nuclear spins at low field where *F* is a good quantum number, low-field transitions affect both the nuclear and electronic spin states. Figure 3 illustrates the large number of transitions that contribute to the NMR spectrum of a radical pair with various combinations of hydrogen (nuclear spin ½) and deuterium (nuclear

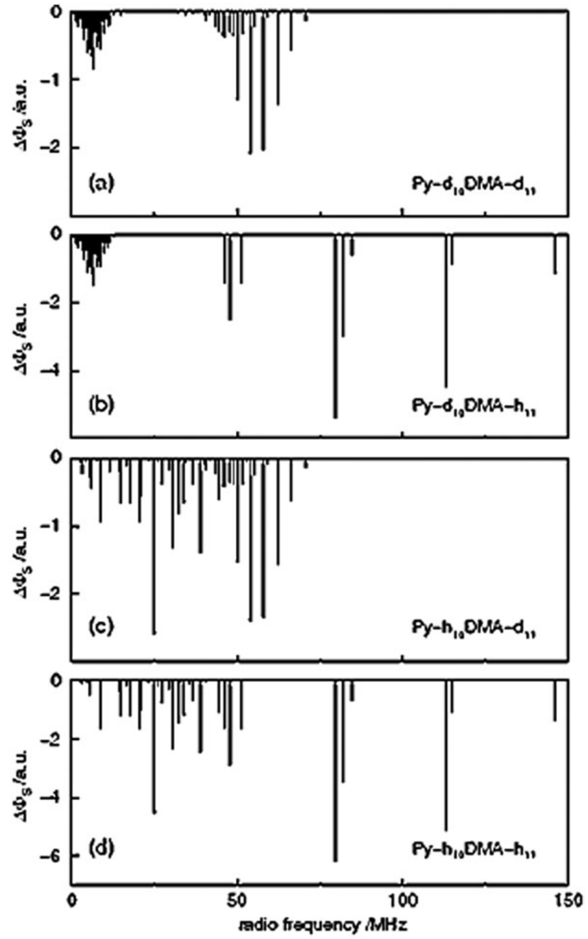

Fig. 3. Calculated magnetic field effect spectra of isotopomeric $Py^{\bullet-}DMA^{\bullet+}$ radical pairs with protons and deuterons in various positions as shown (a-d). Each "stick" represents a magnetic resonance among the electron-nuclear spin states of the radical pair, which produces a change in the yield of the product formed by recombination of singlet radical pairs [from Woodward et al., 2001].

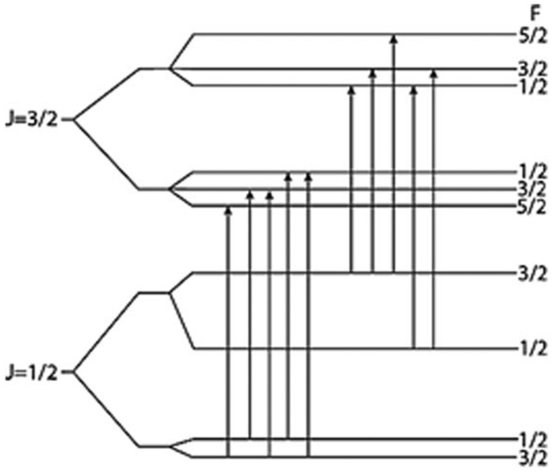

Fig. 4. Energy level diagram and complete spectrum of the $J = ½ \rightarrow 3/2$ rotational transition of the $^2\Pi_{½}$ state of $N^{14}O^{16}$.

spin 1) in the molecule. These transition frequencies were calculated for an external field of 500 μT.

Several types of transition that are of interest are indicated in Figures 4 and 5, including those between J values of the electronic states, such as between $J = 3/2$ and $J = ½$. A second set of transitions are between nuclear spin states. At low fields where F is a good quantum number, transitions are allowed that result in various combinations of $\Delta M_I = 0$, $\Delta M_I = \pm 1$, $\Delta M_J = \pm 1$, or $\Delta M_J = 0$, where M_I is the quantum number defining the projection of the nuclear spins onto the externally applied magnetic field and M_J is the projection of the electron spins onto the magnetic field. For weak magnetic fields where F is the quantum number, the Zeeman splitting's energy differences between the M states of a given level are equal since the Zeeman Hamiltonian is linear in B; as the external fields become stronger, F becomes a less-good quantum number and this is no longer true. At $B = 0$, the T states for both the electrons and nucleus are degenerate. At higher external magnetic fields, the Zeeman interaction dominates and transitions between I and J states are independent. Figure 6 shows the levels of a diatomic deuterium molecule as a function of external field; each deuterium nucleus has $I = 1$ while the electronic spin in the ground state is $J = 0$. In Figure 6 one can see how the states characterized by F at low fields evolve due to the strong field-electron spin interaction into groups of states characterized by J at high field. The groups are further split by the interactions shown in Figure 5 that are too small

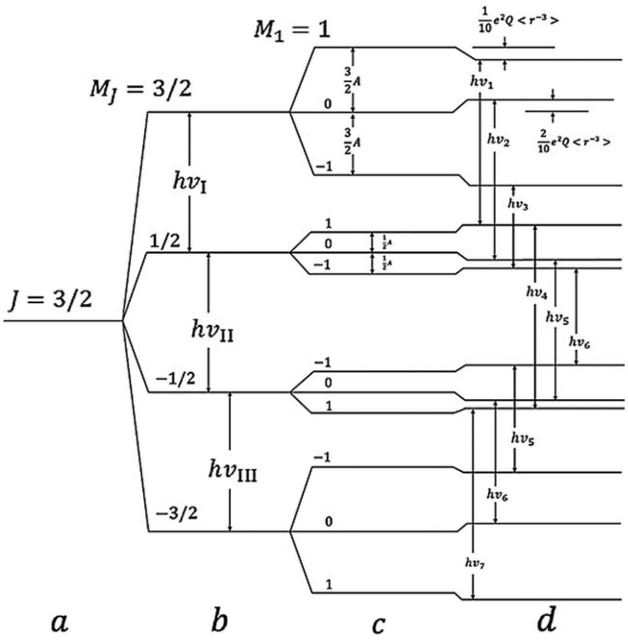

Fig. 5. Energy level diagram of the $J = 3/2$ level of the $^2\Pi_{1/2}$ state of $N^{14}O^{16}$. Stage (a) is in the absence of magnetic field. Stage (b) shows the magnetic levels considering only molecular effects. Stage (c) adds magnetic hyperfine splittings. Stage (d) includes the nuclear electric quadrupole IJ coupling and shows the nine transitions $\Delta M_J = \pm 1$, $\Delta M_I = 0$. Arabic indices on the transitions correspond to the labeling of the observed absorption lines [from Beringer and Castle, 1950].

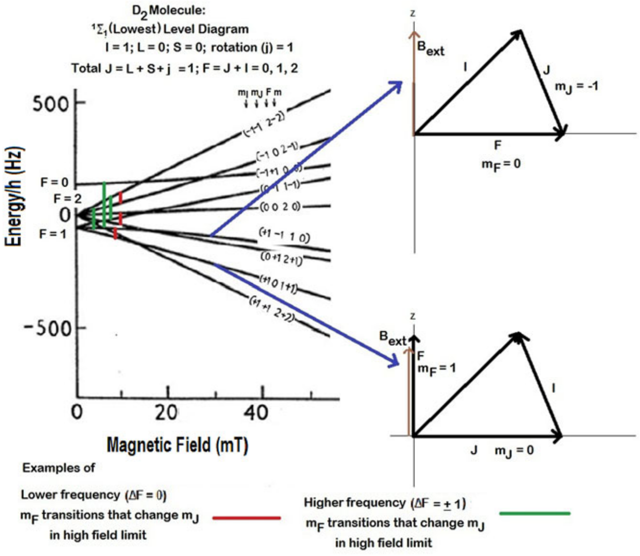

Fig. 6. Left: Energies of D_2 molecule states as a function of magnetic field with low-field (F, m) and high-field (m_J, m_I) quantum number labels. Note linearity of curves in low-field region, where F is a good quantum number, and curvature as well as crossovers as field increases [after Ramsey, 1956]. Vertical lines indicate allowed transitions. Relative orientations of one transition's upper and lower state angular momenta are shown (Right upper and lower). In left diagram, circles indicate possible level-crossing transition points and double arrow indicates region of possible zero-field transitions.

to be shown in Figure 6. Figure 6 also shows the types of allowed transitions in this simple molecule that constitute the basis for our proposal for changes in members of radical pairs.

TRANSITIONS BETWEEN LEVELS

Dependence on Alternating Field Intensity

The Zeeman energies for transitions of electrons for a single unpaired spin in the Earth's magnetic field, ~45 μT, typically fall in the region between 1 and 10 MHz. The Zeeman frequencies for transitions between the nuclear spin states are in the region around 100–1000 Hz. The coupling between nuclei leads to transition frequencies around 10 Hz [Bovey et al., 1988]. Observation of absorption bands in EPR and NMR spectra indicates that the two states have unequal populations. This distribution can be modified by the application of magnetic fields at the resonant frequencies; and with sufficient power, which is usually quite low, the populations become equal and the net absorption goes to zero. For example, the change in the population for nuclear spin states is given by

$$n'_{\mathrm{eq}} = \frac{n_{\mathrm{eq}}}{1 + \gamma^2 B_1 T_2 T_1} \qquad (2)$$

where n_{eq} is the number of radicals in the initial state; n'_{eq} is the population difference between the upper and lower energy levels which, as expected, goes to zero with increasing power; γ is the gyromagnetic ratio; B_1 is the magnitude of the AC magnetic flux density; T_1 is the relaxation time between states and T_2 is the nuclear spin relaxation time [Bovey et al., 1988]. We will assume T_2 to be seconds or longer and T_1 to be between 10^{-6} and 10^{-10} s for transitions from the S to T states of the radical pair. Using $\gamma = 1.933 \times 10^7$ for the nuclear spin transition, we get values for B_1 of between 2.68×10^{-5} and 2.68×10^{-9} T to reduce the value of n'_{eq} by a factor of 2. Other transitions will have different values of γ and give a wide range of values for the significant changes in the populations of n_{eq}. Cai et al. [2012] indicates that the sensitivity of birds to changes in magnetic fields could be as low as few tens of nanotesla by taking advantage of quantum coherence.

Thus, quite low values of B_1 can lead to changes in radical concentrations via their effect on radical recombination processes, especially if the resonant fields cause a transition in one member of the radical pair that shifts the pair's joint electronic state between S and T. The data from the Oxford group [Timmel et al., 1998; Woodward et al., 2001] and others [Simkó, 2007; Usselman et al., 2014] leads to the expectation that these changes in radical concentrations will be in the range of 2% up to 40%, though according to Timmel et al. [1998], the usual values are 10–20%. Other examples of changes in radical concentrations with the application with variations in the magnetic field given by Zmyslony et al. [2004] and Mannerling et al. [2010]. Usselman et al. [2014] show changes in H_2O_2 of 50% and a decrease of O^{*-} of 40% for exposures of rat pulmonary arterial smooth muscle cells (rPASMC) for exposure to 10 μT at 7 MHz along with an increase in growth rate of 40–45% over that for static magnetic fields at 45 μT. From the biological point of view, shifts in radical concentrations that cannot be compensated by feedback and repair processes may have significant downstream consequences.

Energy and Dependence on Applied Frequency

Changes in the absorption or emission rates for applied electric and magnetic fields are expected to change with applied field frequency (*f*) and maximize when the separation between the energy levels (ΔW) for allowed transitions, is equal to *hf*, where *h* is Planck's constant. For electron spin states, this occurs when $\Delta W = g\mu_{\mathrm{o}}B$. Here, μ_{o} is the Bohr magneton, given by $\mu_{\mathrm{o}} = qh/4\pi m_{\mathrm{e}}$ where q is the charge on the electron, m_{e} is the mass of the electron, and B is the magnetic flux density. The g factor takes into account variables such as the vibrational and rotational energy of the molecules and the coupling between electrons in different orbits. It is close to 2 for single electron spins in an outer orbit. In an external magnetic flux density, $B = 45$ μT, and for $g \approx 2$, the resonant frequency (*f*) for inverting the spins is $f \approx 1.26$ MHz. It is to be noted that since we are considering the interaction between two electrons which become unpaired in the formation of the radical pairs, these electronic moments may precess about the applied field at different rates and have different g factors, and the difference between the electrons' frequencies $\Delta f = \Delta g \mu_{\mathrm{o}} B/h$, where Δg can be small, would depend upon the magnetic field. For example, for the radical pair formed on splitting ($CH_3{\cdot}CH_3$ $CH{\cdot}OEt$), $\Delta g = 5.5 \times 10^{-4}$ and $f = 346$ Hz for $B = 45$ μT [Grissom, 1995]. For nuclear magnetic transitions, the magnetic moment is associated with the spins of the protons and neutrons. The Zeeman energy separation between nuclear states in a magnetic field is given by $\Delta W = \mu_n B$. In general, nuclear dipole moment is given to a first approximation by $\mu = g_n(qhI/4\pi M_n)$, where I is the spin quantum number for the nucleus, M_n is the mass of the nucleus and q is the charge on an electron or proton, h is Planck's constant, and I is the quantum number describing the nuclear spin states. This expression is often written in terms of μ_n, the nuclear magneton, which has the same form as the Bohr magneton with the substitution of the mass of the proton for that of the electron ($\mu_n = 5.05 \times 10^{-27}$ J/T). g_n varies with the shielding of the nucleus by the electrons and the proximity of other nuclei. In general, the magnetic energy level spacing decreases with the shielding of the magnetic flux density by the electrons and the spacing between these nuclear spin states changes with the applied magnetic field [Bovey et al., 1988]. The value of I is given by the number of protons and neutrons in the nucleus and the way they pair up (or do not) within each species. Empirically, when both the mass number Z and the atomic number A are even, then $I = 0$. If A is odd, then I will have half-integer values, 1/2, 3/2, 5/2, etc. If A is even and Z is odd, then I will have integer values, 1, 2, 3, etc. [Bovey et al., 1988].

The Zeeman energy level separations in the nucleus are so small that they are often ignored in calculations dealing with the NMR spectra of molecules in a magnetic field [Kaptein and Oosterhoff, 1969; Scaiano, 1996; Binhi, 2002]. We propose here that these transitions may be excited by low frequency magnetic fields or by RF fields that are modulated at low frequencies, especially in the region where the external field coupling with the moment becomes of the same order of magnitude as that of the electrons and the relevance of F begins to break down. Kaptein and Oosterhoff [1969] show, for the case where H_z^n is small, that there is a preferred electronic spin state, on the average, at a particular H atom in a molecule, with the selectivity parameter given by $\Delta^{\pm} = \pm[4aJ^{*}\tau^2/(1 + 4\omega^2\tau^2)]$, where τ is the lifetime, $a = 1/2A$ where A is the hyperfine coupling constant, J^{*} is the exchange integral, and $\omega = (J^{*2} + a^2)^{1/2}$. The important feature of these calculations is that the electron spin states are coupled to the nuclear spin states. It is also true that the strength of the coupling depends on the nuclear spin state and its projection onto the external magnetic field.

Figures 4 and 5 give an indication of what the energy level diagram looks like for nitric oxide (NO). Figure 4 shows the basic level structure of the $^2\Pi_{1/2,\,3/2}$ state in the absence of a magnetic field, while Figure 5 shows the various effects of splitting of the $^2\Pi_{3/2}$ levels, including the electronic, but not the smaller nuclear Zeeman shifts. The grouping of $^2\Pi_{3/2}$ levels lies above the $^2\Pi_{1/2}$ levels in energy. In a nonzero magnetic field, all of the levels will be split according to the Zeeman effect. Note that NO is an important molecule and a neural transmitter that provides a biochemical link between the nervous system and the immune system [Kiel, 1995] and that ^{14}N, the most common isotope, has a nuclear spin value $I = 1$, while ^{16}O has $I = 0$ [Heath, 1982].

The coupling between the electrons and the magnetic moment of the nucleus leads to the nuclear hyperfine levels. These energy levels are different for different values of M_J and M_I. Column d of Figure 5 shows that the electric quadrupole moment of the nucleus also modifies the energy separation between the Zeeman levels of the nuclear spin states, but only nuclei with spins of 1 or more can have electric quadrupole moments [Bovey et al., 1988]. At low fields, the energy splitting ΔW of an F level due to the nuclear magnetic moment in an external magnetic field (similar to that in column b of Fig. 5 for the molecular electronic moments, but much smaller), is given by Townes and Schawlow [1955],

$$\Delta W = \Big\{ -\mu_n g_I[I(I+1) + F(F+1) - J(J+1)] - \mu_o g_j[J(J+1) + F(F+1) - I(I+1)] \Big\} \left\{ \frac{m_F B}{2F(F+1)} \right\} \tag{3}$$

where m_F is the quantum number for the projection of the total low-field molecular angular momentum F on the B field. The lifetime for transitions between the nuclear spin states is long, seconds, or more. If we calculate the differences between these energies for levels in the $J = 3/2$ state of NO, as in Figure 4, taking the values for the $J = 3/2$ levels of NO with the nitrogen nuclear magnetic dipole moment, $\mu = g_I \mu_n = 0.4036\,\mu_n$, $I = 1$ and $g_J \approx 0.001$ for these levels [Townes and Schawlow, 1955] we get energy differences for $\Delta m_F = \pm 1$ transitions within the same F state corresponding to frequencies of ~60 to ~1000 Hz, depending on the value of F. Similar transitions in the $J = ½$ state, where $g_J \approx 2$, have frequencies in the vicinity of 500 kHz. Although this calculation uses a formula for a free molecule, it should be taken as an indication of the order of magnitude of the frequency splitting between m_F levels under physiological conditions. Since these transitions reorient the total molecular angular momentum F, they change the relative orientation of the total angular momentum of the two members of a radical pair and can affect whether their relative electronic states are S or T. If the couplings within the molecule are weak enough that F is no longer a good quantum number in external fields with strengths on the order of the Earth's, resonant transition frequencies will still occur that reorient Zeeman states in both I and some values of J for which g_J is small, as in the $J = 3/2$ state in the example above.

The long lifetimes of the nuclear spin states lead to very narrow absorption bands for transitions between nuclear spin states that may be only a few cycles per second—at least for free molecules or very isolated spins. In addition, these lifetimes of seconds are so long compared to the 10^{-6}–10^{-10} s for the S to T transitions of the electrons and the diffusion time for the radicals of the pair to separate that without an exciting field, we can consider the population of the nuclear spin states as constant. If we excite transitions between the nuclear spin states by applying a magnetic field at these frequencies, this distribution is modified. For our example with $J = 3/2$ and $I = 1$, $F = 1/2$, 3/2 and 5/2 and within each F state the allowed hyperfine states are characterized by $m_F = -F, \ -F+1, \ldots, F-1, \ F$, with different energies separating the m_F levels in each F state. If we start with unequally populated spin states after creating a radical pair in a steady background magnetic field B and then apply a time-varying magnetic field at the resonant frequency for the transition between the adjacent m_F states at a strength that saturates the transitions, then the population in the m states gets redistributed so that the populations become equal. Although in thermal equilibrium these states are separated in energy by only small amounts and would be essentially equally populated, this population distribution may not be true upon formation of a singlet-triplet radical pair. If, in addition, we use circularly-polarized RF to induce only $M = +1$ or $M = -1$ transitions but not both, we would create an unequal, nonthermal distribution of M states, similar to that seen in optical pumping of atomic transitions [Happer, 1972].

Reduced Magnetic Fields

A number of experiments [Mo et al., 2013; Prato et al., 2013] have found that reducing the ambient magnetic field through shielding or applying compensating fields has produced changes from samples remaining in the Earth's field and whatever small alternating fields are in the laboratory. Since the splitting between Zeeman levels is linearly proportional to the magnetic field, at some very low field intensity, the energy difference between the levels becomes smaller than their natural line width and the levels become degenerate. In this instance, provided that angular momentum and other selection rules are followed, there is a certain probability of spontaneous transitions between states similar to those described above when the proper frequency-alternating field is applied.

Another source of narrow line widths for transitions that are separated by energies corresponding to a few cycles has been observed in the coupling of the spins between nuclei of adjacent atoms in molecules [Bovey et al., 1988]. This coupling can either be directly between the nuclear spins or through the circulating electrons. Therefore, the electron states can be perturbed by an externally applied magnetic field, which in turn can change the strength of the coupling and the corresponding resonant frequencies.

An example of changes in growth rates of mastacytoma cells with the application of magnetic fields at 60 Hz is shown in Figure 7 [Bingham, 1996]. It should be noted that the growth rate of these cells could both be accelerated and inhibited by changing the average value of the AC magnetic field. Other measurements in this thesis show shifts in these curves with both frequency and the DC magnetic fields. It is hypothesized the changes in growth rate are the result of changes in the rate of generation or of the radical associated with the metabolic processes. The changes in growth rates with magnetic fields may result from changes in the alignment of the energy levels between the fragments of a radical pair or by changing the distribution in the population in the energy levels by applying magnetic fields at the frequency corresponding to transitions between energy levels.

CONCLUSION

We hypothesize that transitions in weak combined steady and time-varying external fields can reorient the total molecular angular momentum F, changing the relative orientation of the total angular momentum of the two members of a radical pair, and can affect whether their relative electronic states are S or T. We have shown, in one example, that steady fields on the order of the Earth's magnetic field would require frequencies in the extremely low frequency field region for some transitions and in the RF region

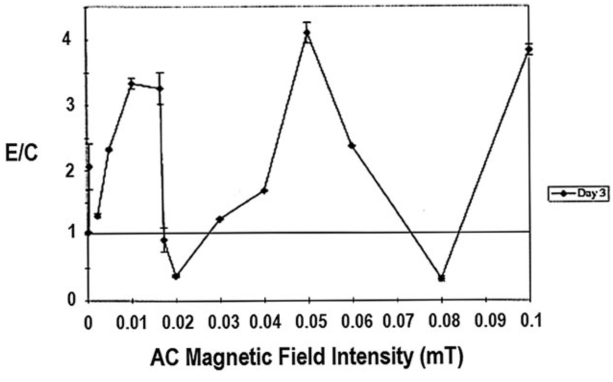

Fig. 7. Growth of P815 Mastacytoma Cells, Bdc = 38 μT, f = 60 Hz [after Bingham, 1996].

for others. If a process creates a pair of radicals that are in a T state relative to each other, for example, then those radicals' recombination rate can be affected if one experiences a time-varying field with a frequency corresponding to the hyperfine splitting caused by the external steady field that changes the combination to a relative S state. For chemical processes that initially generate radical pairs in T states, the change will reduce the number of radicals that are free to drift off and increase the number that recombine into stable molecules. The same would hold true for a pair generated in a relative S state in which an applied field subsequently changes them into a relative T state.

Finally, we suggest that observable magnetic field effects might generally happen under situations where an organism is stressed by other conditions that lead to changes in the radical concentrations so the combination of these stresses and the magnetic field changes take the radical concentrations outside the range of values where they are compensated for by radical scavengers. If this is so, it may explain why it is hard to get reproducible results, as the initial conditions in biological systems are hard to reproduce. This is particularly true in human experiments. In many animal experiments, the conditions are designed to eliminate other stresses so that the compound effects of a magnetic field stress and other stresses are not seen. It is to be noted that radicals are generated as a part of the metabolic processes and their values may vary by more than a factor of 10. However, at the same time these radicals are generated, the generation of radical scavengers is signaled for and the concentrations are brought back to a baseline level. Extended elevation levels of radical concentrations can lead to resetting of the baseline and damage [Droge, 2002]. This in turn may lead to the reason why long term exposure to cell phones may be different from short-term exposures.

Our proposal is, at this point, an outline of a possible mechanism, rather than a fully elucidated theory, and further development is necessary. Of necessity, our discussion draws on evidence from the literature, but has a number of places where direct support is not available. Coupling constants in many molecules and radicals of interest are not measured. Some of the measurements or theories we have drawn upon are for isolated molecules and may not be directly applicable for the case of molecules and radicals in physiological settings, though the interdependence between nuclear and electronic states in solution is clear and measureable, for instance, in line shifts and broadening of NMR and EPR spectra. An experimental check of the proposed hypotheses and variations in our ideas that include excitations at both RF transition frequencies for the Zeeman states of the electrons and modulation at frequencies in the 5–500 Hz region could lead to significant increases in our understanding of how weak magnetic fields can modify biological processes. Ultimately, increasing our understanding of these effects could well lead to additional therapeutic applications and to an understanding of factors under which these conditions might lead to adverse health effects.

ACKNOWLEDGMENTS

The authors wish to express their appreciation to many colleagues in the field who have stimulated their thinking in this area and in particular Carlos Martino and Lucas Portelli, whose experimental work focused their attention on radical pairs.

REFERENCES

Adair RK. 1999. Effects of very weak magnetic fields on radical pair reformation. Bioelectromagnetics 20:255–263.

Batchelor SN, Kay CWM, McLauchlan KA, Shkrob IA. 1993. Time-resolved and modulation methods in the study of the effects of magnetic fields on the yields of free radical reactions. J Phys Chem 97:13250–13258.

Bawin SM, Kazmarek KL, Adey WR. 1975. Effects of modulated VHF fields on the central nervous system. Ann NY Acad Sci 247:74–81.

Beringer R, Castle JG. 1950. Magnetic resonance absorption in nitric oxide. Phys Ref 78:581–586.

Bingham C. 1996. The effects of DC and ELF AC magnetic fields on the division rate of Mastocytoma cells. PhD Thesis, University of Colorado at Boulder.

Binhi VN. 2002. Magnetobiology: Underlying physical problems. London and San Diego: Academic Press. p 473.

Blackman CF, Elder JA, Weil CM, Benane SG, Eichinger DC, House DE. 1979. Induction of calcium-ion efflux from brain tissue by radiofrequency radiation and field strength. Radio Sci 14:93–98.

Blanchard JP, Blackman CF. 1994. Clarification and application of an ion parametric resonance model for magnetic field interactions with biological systems. Bioelectromagnetics 15:217–238.

Bovey FA, Jelinski L, Mirau PA. 1988. Nuclear magnetic resonance spectroscopy. San Diego: Academic Press, Inc. p 653.

Brocklehurst B, McLauchlan K. 1996. Free radical mechanism for the effects of environmental electromagnetic fields on biological systems. Int J Radiat Biol 69:3–24.

Buchachenko AL. 2001. Magnetic isotope effect: Nuclear spin control of chemical reactions. J Phys Chem A 105:9995–10011.

Cai J, Caruso F, Plenio MB. 2012. Quantum limits for the magnetic sensitivity of a chemical compass. Phys Rev A 85: 040304(R).

Charlton J, Bargon J. 1971. Chemically induced dynamic nuclear polarization at zero magnetic field. Chem Phys Lett 8:442–444.

Chiabrera A, Bianco B, Moggia E, Kaufman JJ. 2000. Zeeman-stark modeling of the RF EMF interaction with ligand binding. Bioelectromagnetics 21:312–324.

den Hollander JA, Kaptein R, Brand P. 1971. Chemically induced dynamic nuclear polarization (CIDMP) VII Photoreactions of Alpiphatic Ketones. Chem Phys Lett 10:430–435.

Droge W. 2002. Free radicals in the physiological control of cell function. Physiol Rev 82:47–95.

Fossey J, Lefort D, Sorba J. 1995. Free radicals in organic chemistry. New York: Wiley.

Gallagher JJ, Bedard FD, Johnson CM. 1954. Microwave spectrum of $N^{14}O^{16}$. Phys Rev 93:729–733.

Grissom CB. 1995. Magnetic field effects in biology: A survey of possible mechanisms with emphasis on radical pair recombination. Chem Rev 95:3–24.

Hansen MJ, Pedersen JB. 2006. An analytic description of the influence of RF-magnetic fields on radical pair reactions in a strong static field. Chem Phys 326:563–570.

Happer W. 1972. Optical pumping. Rev Mod Phys 44:169–249.

Hayashi H. 2004. Introduction to dynamic spin chemistry. Singapore: World Scientific Publishing Co. p 268.

Heath RL. 1982. Table of the isotopes. In: Weast RC, editor. CRC handbook of chemistry and physics. Boca Raton: CRC Press. pp B-255–B-339.

Henbest KB, Kukura P, Rodgers CT, Hore PJ, Timmel CR. 2004. Radio frequency magnetic field effects on a radical recombination reaction: A diagnostic test for the radical pair mechanism. J Am Chem Soc 126:8102–8103.

Henbest KB, Maeda K, Athanassiades E, Hore PJ, Timmel CR. 2006. Measurement of magnetic field effects on radical recombination reactions using triplet-triplet energy transfer. Chem Phys Lett 421:571–576.

Herzberg G. 1950. Molecular spectra and molecular structure. I. Spectra of diatomic molecules. 2nd edition. Princeton: Van Nostrand. p 308.

Kaptein R. 1968. Chemically induced dynamic nuclear polarization in five Alkyl radicals. Chem Phys Lett 2:261–267.

Kaptein R. 1972. Chemically induced dynamic nuclear polarization. X. On the magnetic field dependence. J Am Chem Soc 94:6269–6280.

Kaptein R, Oosterhoff JL. 1969. Chemically induced dynamic nuclear polarization II. Chem Phys Lett 4:195–197.

Kiel JL. 1995. Type-B cytochromes: Sensors and switches. Boca Raton: CRC Press. p 220.

Lednev VV. 1991. Possible mechanism for the influence of weak magnetic fields on biological systems. Bioelectromagnetics 12:71–75.

Liboff AR. 2007. The ion cyclotron resonance hypothesis. In: Barnes FS, Greenebaum B, editors. Bioengineering and biophysical aspects of electromagnetic fields. Boca Raton: CRC Press. pp 261–292.

Liu Y, Edge R, Henbest K, Timmel CR, Hore PJ, Gasta P. 2005. Magnetic field effect on singlet oxygen production in a biochemical system. Chem Commun 41:174–176.

Mannerling AC, Simkó M, Mild KH, Mattsson MO. 2010. Effects of 50-Hz magnetic field exposure on superoxide radical anion formation and HSP70 induction in human K562 cells. Radiat Environ Biophys 49:731.

Martino CF, McCabe K, Portelli L, Hernandez M, Barnes F. 2010. Reduction of the Earth's magnetic field inhibits growth rates of model cancer cell lines. Bioelectromagnetics 8:649–655.

Mo W-C, Zhang Z-J, Liu Y, Bartlett PF, He R-Q. 2013. Magnetic shielding accelerates the proliferation of human neuroblastoma cell by promoting G1-phase progression. PLoS ONE 8:e54775.

Nagakura S, Hayashi H, Azumi T, editors. 1999. Dynamic spin chemistry. Tokyo, Kodansha and New York: John Wiley & Sons. p 297.

Prato FS, Desjardins-Holmes D, Keenliside LD, DeMoor JM, Robertson JA, Thomas AW. 2013. Magnetoreception in laboratory mice: Sensitivity to extremely low-frequency fields exceeds 33 nT at 30 Hz. J R Soc Interface 10: 20121046.

Ramsey NF. 1956. Molecular beams. Oxford: Clarendon Press. p 237.

Rodgers CT, Norman SA, Henbest KB, Timmel CR, Hore PJ. 2007. Determination of radical re-encounter probability distributions from magnetic field effects on reaction yields. J Am Chem Soc 129:6746–6755.

Scaiano J. 1996. Control of chemical reactions with magnetic fields. Interscientia 1, Number 1. Available from: http://www.uottawa.ca/publications/interscientia/inter.1/magnetic.html [Last accessed 12 Feb 2014].

Simkó M. 2007. Cell type specific redox status is responsible for diverse electromagnetic field effects. Gen Med Chem 14:1141–1152.

Steiner U, Ulrich T. 1989. Magnetic field effects in chemical kinetics and related phenomena. Chem Rev 89:147–151.

Timmel C, Henbest K. 2004. A study of spin chemistry in weak magnetic fields. Phil Trans R Soc London Ser A 362:2573–2589.

Timmel C, Till U, Brocklehurst B, McLauchlan K, Hore P. 1998. Effects of weak magnetic fields on free radical recombination reactions. Mol Phys 95:71–89.

Townes C, Schawlow A. 1955. Microwave spectroscopy. New York: McGraw Hill. p 290.

Usselman RJ, Hill I, Singel DJ, Martino CF. 2014. Spin biochemistry modulates reactive oxygen species production by radio frequency magnetic fields. PLoS ONE 9:e101328.

Wang KF, Ritz T. 2006. Zeeman resonances for radical-pair reactions in weak static magnetic fields. Mol Phys 104: 1649–1658.

Woodward JR, Timmel CR, McLauchlan KA, Hore PJ. 2001. Radio frequency magnetic field effects on electron-hole recombination. Phys Rev Lett 87:077602-1–077602-4.

Zanetti-Polzi L, Marracino P, Aschi M, Daidone I, Fontana A, Apollonio F, Liberti M, D'Inzeo G, Amadei A. 2013. Modeling triplet flavin-indole electron transfer and interradical dipolar interaction: A perturbative approach. Theor Chem Acc 132:1393.

Zmyslony M, Rajkowska E, Mamrot P, Politanski J, Jajte J. 2004. The effect of weak 50 Hz magnetic fields on the number of free oxygen radicals in rat lymphocytes in vitro. Bioelectromagnetics 25:607–6612.