6

Magnetic Field Effects on Free Radical Reactions in Biology

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6.1 Introduction

The physical chemistry of spin-correlated free radical pairs offers several mechanisms explaining how magnetic fields may influence biochemical processes. The mechanisms are classified on the basis of the dominating contribution to spin interconversion, and they cover a wide range of field strengths. Of particular interest is what is called the low-field mechanism, which has been extensively developed over the last decade and is now capable of explaining biological effects induced by magnetic fields well below 1 mT.

The principal mechanism behind the free radical mechanism was discovered in the physical problem of magnetic field dependence on positronium decay (Deutsch and Brown, 1952; Halpern, 1954). However, the development of the radical pair mechanism in chemistry has its roots in the work of Kaptein and Oosterhoff (1969), Closs (1969), and Brocklehurst (1969).

An ambitious survey of the literature up to its date of publication is the review of Steiner and Ulrich (1989), which lists some 775 references, 58 of which are themselves reviews on magnetokinetic phenomena. Another, now classic, reference on the subject is the book by Salikhov et al. (1984). McLauchlan and Steiner (1991) published a review including the possible mechanisms at lower fields. The review by Grissom (1995) explored the higher-field mechanisms with particular attention to the context of biological systems. A didactic paper geared toward the issues in biological systems is that of Brocklehurst and McLauchlan (1996). There are also some recent reviews on the free radical mechanism in general (Woodward, 2002) and with particular attention to biological systems (Brocklehurst, 2002).

6.2 Theoretical Background

A radical is an atom or a molecule with an unpaired electron. It tends to be highly reactive, a property that defines their best known roles in biology. A spin-correlated (or geminate) radical pair is typically created by hemolytic cleavage of a covalent bond, that is, each molecule retains one of the electrons that formed the chemical bond that was broken. The electron spins may remain correlated for a significant time (microseconds) after the pair's creation. As the radicals separate, the electron interaction term becomes small, and the electron states of the pair will fluctuate between antiparallel (singlet, or ''S'') and parallel (triplet, or ''T'') because of coherent spin evolution by hyperfine interactions between the electron spin and the nuclei. There is a chance of reencounter between the spin-correlated radicals. Reforming the bond is only permitted by quantum spin selection rules if the electron spins are oriented in the singlet state.

Magnetic fields can affect the electron state in the time before the reencounter; and if singlet and triplet pairs have different chemical fates, we have a basis for magnetic field effects on free radical chemistry (Figure 6.1). In exemplifying the process, we will assume that the radical pair is formed in the singlet state, the normal case for biologically relevant reactions (Eveson et al., 2000).

Many physical transduction mechanisms proposed to explain magnetic field effects in biology are very vulnerable to the randomizing effects of thermal noise at normal temperatures of living systems (Binhi and Savin, 2003). The free radical mechanism is uniquely resistant to this obstacle since it is a nuclear effect and is not strongly coupled to the thermal bath (Adair, 1999).

A quantum mechanical formulation of the free radical mechanism contains many possible contributions to the hamiltonian; Steiner and Ulrich (1989) provide a good categorization of the main components. The stochastic Liouville equation (SLE) is a tool

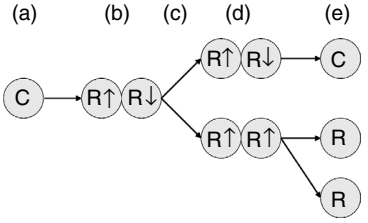

FIGURE 6.1
A molecule ''C'' (a) is split into two radicals (b). After diffusion and spin interconversion (c), the radicals may reencounter while still spin correlated (d). If the encounter occurs in the singlet state (e, top), the radicals may recombine. If the encounter occurs in the triplet state (e, bottom), recombination cannot occur, and the radicals will diffuse apart again and eventually lose their spin correlation. A magnetic field can influence this reaction by changing the rate of spin interconversion as long as the singlet and triplet products have different chemical fates.

for addressing the problem of simultaneous spin mixing and diffusion, but simplified models in which these two components are treated separately are often useful for the great reduction in problem complexity (Brocklehurst and McLauchlan, 1996). Recently, analytical results using a backward SLE have been presented (Pedersen and Christensen, 2004).

6.2.1 Hyperfine Interaction-Induced Singlet-to-Triplet Conversion

Hyperfine interactions between the spins of the electron and the nucleus cause the electron spins of the radicals to precess and induce singlet-to-triplet conversion. The triplet state has a net magnetic moment, and in the presence of an external magnetic field the energy levels of the triplet states that have a moment aligned with the magnetic field (T_+ and T_-) will be separated by Zeeman splitting. As the applied field strength is increased, the T_+ and T_- energy levels will be shifted away from the singlet state so much that they are decoupled from the spin interconversion process between singlet and triplet states, and only the remaining triplet state (T_0), which has a magnetic moment that is oriented perpendicular to the field, is capable of participating in the spin conversion process. In this way the magnetic field can reduce the number of triplet states that can be converted into singlet states and subsequently reform the original chemical bond. This is the ''normal'' magnetic field effect on free radical chemistry. It becomes relevant for external fields larger than the effective field driving the hyperfine interaction mixing, typically 1–10 mT.

A way in which singlet-to-triplet conversion can be facilitated is when an applied field causes the T_- energy level to cross the nonmagnetic singlet level, which occurs when the Zeeman differential matches the electron exchange interaction energy (cf. Figure 6.2). This effect has been observed for fields as low as 6.6 mT (Werner et al., 1993), but it can in principle be observed for much lower fields if the radical pairs are fixed with an appropriate separation.

6.2.2 High-Field Regime: Spin Rephrasing through the Δg Mechanism

The product of the magnetic field and the Landé g-factor determines the precession of the unpaired electron spin, independent of the hyperfine contribution. If the two radicals have slightly different g-factors, this provides an additional source of spin conversion. Differences are usually quite small, so this mechanism typically becomes significant only for quite large fields, $B > 0.1$–1 T.

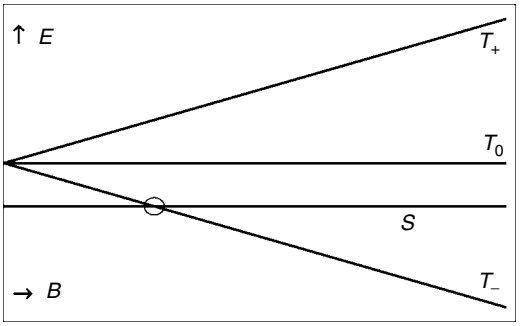

FIGURE 6.2
Energy level diagram for singlet and triplet states of a radical pair. At high fields, T_+ and T_- become completely disconnected from the singlet state, and only the T_0 state is left for singlet–triplet interconversion. At a specific B-field, the Zeeman split causes the T_- state to closely match the singlet state (circled), increasing the likelihood of transitions between the two states.

6.2.3 Low-Field Effect: $B < 1$ mT

At fields below the hyperfine interaction energy, it is still possible to see effects of external fields under certain circumstances. It was found by Brocklehurst (1976) that the selection rules of the hyperfine-induced spin mixing are more restrictive in zero field than when a field is applied (McLauchlan and Steiner, 1991). This becomes relevant, even for a very small field, as long as the coherence of the pair's state is maintained for long periods (100 ns to 1 μs). A helpful vector model to visualize this effect, along with some illustrative numerical examples, is given by Till et al. (1998).

The low-field effect (LFE) can theoretically produce a large (40%) drop in the singlet yield if the conditions are optimal (Timmel et al., 1998), but in practice only smaller effects attributed to this mechanism have been reported in the experimental literature.

Since long coherence times are required, it is necessary to understand spin relaxation effects and under what conditions they may be sufficiently long. Anisotropic hyperfine interactions provide noncoherent spin relaxation in solution, and it appears that the relaxation is slower in the low-field situation than has been generally thought (Fedin et al., 2001, 2003). It is becoming clear that understanding the local environment is crucial for evaluating LFEs (Eveson et al., 2000).

An important way to extend free radical magnetic field effects into the low-field region is to extend the lifetime of the spin-correlated pair. Integrating the magnetic field's influence over a longer time increases its ability to influence the spin evolution. Spin relaxation is not the primary problem here; rather, it is the reencounter probability that needs to be enhanced. There are several ways to achieve this:

1. Increased viscosity to restrict diffusion (Krissinel et al., 1999; Christensen and Pedersen, 2003; Kitahama et al., 2004)
2. Oppositely charged radicals that will oppose a tendency to diffuse apart (Adair, 1999)
3. Physically restricted mobility of the radicals through confining them to a surface or having the reaction taking place inside micelles, which are nanometer-scale compartments that form and reform on microsecond timescales and are able to confine the radical pairs and increase the reencounter probability (Eveson et al., 2000).

6.2.4 Free Radicals in Radio Frequency Fields

For higher-frequency fields ($f > 1$ MHz) the time modulation of the field starts to correspond to timescales present in the reaction dynamics, and a range of resonant interactions become available (Timmel and Hore, 1996). A detailed treatment of the coenzyme B_{12} system demonstrated resonant phenomena for relatively low-level radio frequency (RF) fields using a variety of mathematical techniques (Canfield et al., 1994, 1995).

6.3 General Characteristics of the Free Radical Mechanism

Free radical reactions are generally quite fast. There is evidence of picosecond reactions (Gilch et al., 1998; Musewald et al., 1999), but many known reactions occur over nanosecond timescales. If the free radical diffusion is constrained by micelles (Eveson et al.,

2000; Christensen and Pedersen, 2003) or by Coulomb attraction (Horiuchi et al., 2003), it may be possible to extend the radical pair lifetimes to hundreds of nanoseconds or even microseconds.

Since the free radical mechanism is practically instantaneous when compared to the timescale of time-varying magnetic fields in the extremely low-frequency regime (<300 Hz), one would expect that the observable output from a biological detection of the field should depend only on the time-averaged absolute field amplitude (Scaiano et al., 1995). However, if there is a downstream system that is able to decode the low-frequency signal, this statement is not necessarily true (Engstrom, 1997; Engstrom and Fitzsimmons, 1999).

6.3.1 Experimental Discrimination of Free Radical Models

The relative orientation of a static and a much smaller oscillating field will provide a discriminating test for a free radical-based model as long as the timescale of the applied field is long compared to the lifetime of the radical pair. In an isotropic system, such as a liquid suspension, described by this field situation, only the amplitude of the magnetic field is relevant. While the smaller parallel field adds linearly to the larger static field, the perpendicular component is effectively reduced by the calculation of vector length and will cause a much smaller variation in field amplitude (Engstrom, 1997).

For oriented systems in which the free radical chemistry steps have spatial preferences, it is possible to have angular dependence with respect to the angle of the applied field, $f(\theta)$. One can argue that some symmetry properties are very likely to be present in that kind of situation (Ritz et al., 2000). Polarity changes are not expected to be relevant, so $f(\theta + 180^\circ) = f(\theta)$. Furthermore, due to the isotropic distribution of nuclear spins in the initial state of the radical pair, one also expects that $f(180^\circ - \theta) = f(\theta)$.

If the free radical mechanism is active for low-frequency fields, one can also expect a response to RF fields in the same system, a property not expected by any other suggested physical transduction mechanisms for magnetic fields (Henbest et al., 2004). In a comparison between static fields in the range 0–2 mT, it was shown that a 300-μT, 5-MHz RF field applied perpendicularly or in parallel with the static field induced a response that was dependent on the magnitude of the static field (Henbest et al., 2004). This is qualitatively, if not quantitatively, similar to the observation that the magnetic sense of migratory birds can be disrupted by a 470-nT, 7-MHz field when the field is applied at an angle with the geomagnetic field (Ritz et al., 2004).

Magnetic isotope effects are another possible discriminating character of free radical effects, and it is possible to differentiate this signature from pure mass effects (Brocklehurst, 1997).

6.4 Free Radicals in Biology

6.4.1 Biological Transduction Mechanisms

Direct detection methods for free radicals have been developed in chemistry only relatively recently (Woodward, 2002). In biological systems, almost all experimental evidence for free radical involvement remains indirect. Generating hypotheses based on the signatures of free radical systems as outlined above are necessary to link free radical chemistry

to magnetic field effects, but there is circumstantial evidence that free radical chemistry underlies some effects reported in the bioelectromagnetics literature.

It has been suggested that complex dynamical systems may have special sensitivity to magnetic field influences (Grundler et al., 1992; Walleczek, 1995). This idea has been elaborated in a series of theoretical models of oscillatory systems (Eichwald and Walleczek, 1996a,b; Kaiser, 1996). These models show that enzyme dynamics involving free radical chemistry may be frequency specific, although only for timescales comparable to or slower than the chemical kinetics of the system (Eichwald and Walleczek, 1997). Field amplitude can influence enzyme dynamics in some instances and this can be used to exert some control over enzyme systems (Eichwald and Walleczek, 1998).

The peroxidase–oxidase system has interesting, well-documented dynamical properties (Scheeline et al., 1997). Detailed modeling of this system has shown how a magnetic field-induced perturbation can affect its dynamical behavior (Eichwald and Walleczek, 1998; Moller and Olsen, 1999). The point of interaction in this system is suspected to be electron-transfer enzyme intermediates (Moller and Olsen, 2000; Moller et al., 2000).

Downstream effects from changes in chemistry must be taken into account to evaluate biological significance (Brocklehurst and McLauchlan, 1996). This can both facilitate detection (Walleczek, 1995) as well as introduce interventions that could block the biological significance of a physical detection event.

It may be relevant that other enzyme systems have been studied in detail without the specific intention of addressing free radicals as a possible mechanism. Examples include electric and magnetic field effects in ATPase (Blank and Soo, 2001b). Direct interactions with DNA have been suggested; and electron transfer reactions are proposed interaction targets (Blank and Goodman, 2000; Blank and Soo, 2001a), although not by mechanisms addressed here. Myosin phosphorylation is another enzyme system that has shown sensitivity to time-varying (Markov et al., 1993) and static magnetic fields (Markov and Pilla, 1994), as well as gradient-specific effects (Engstrom et al., 2002).

6.4.2 Role of Freely Diffusing Radicals

Free radicals observed in biology are most commonly oxygen or nitrogen based with an unpaired electron, leading to the terms reactive oxygen species (ROS) and reactive nitrogen species (RNS). A dominant role for these radicals is to act in immunological defense. They are secreted by macrophages and neutrophils and during attempts to kill bacteria, viruses, and tumors (Nathan, 1992). The highly reactive nature of the radicals also means that damage to normal cells is possible, and various defense mechanisms against this have evolved as well (Yu, 1994). This immunological weapon with checks and balances already suggests that there is a signaling system built around free radicals, but it seems that the ROS and RNS also have roles in intracellular cell signaling (Lander, 1997) as well as intercellular communication (Thannickal and Fanburg, 2000).

Consider a biochemical reaction producing a spin-correlated free radical pair in the singlet state. Depending on the specific mechanism at work, the ratio of singlet-to-triplet product at reencounter will be modified. This will increase or decrease the fraction of pairs that tend to recombine because of a reencounter finding the spins in singlet versus the triplet states. For the LFE, the triplet state is favored, and we would see an excess of escape product. The situation is the opposite for the ''normal'' field effect, in which the T_- and T_+ states are decoupled from the interconversion process, increasing the proportion of singlet reencounters leading to a larger amount of cage product and leaving fewer freely diffusing radicals. The Δg mechanism brings the T_- and T_+ states back into play and therefore again boosts the triplet-reencounter escape products.

Given the wide involvement of free radicals in signaling and biological function, it is clear that there is the potential of both subtle and not-so-subtle effects on biological systems if we are able to alter the production of free radicals and thereby change the dynamics of already ongoing processes. The conventional wisdom regarding the deleterious effects of magnetic field effects on free radical recombination has been that more escape product means more radical-induced damage. This may be an oversimplification since the direct effects on cage or escape products are typically fairly small, certainly not larger than tens of percent, implying that drastic biological effects must involve downstream responses that amplify this relatively slight modulation. The answer may lie in the signaling properties of free radicals.

6.4.3 Animal Navigation Models Based on Free Radicals

The free radical mechanism was the first mechanism suggested as an explanation of avian use of magnetic fields for navigation (Schulten et al., 1978; Schulten, 1982). This model has since undergone several iterations of refinement (Ritz et al., 2000; Cintolesi et al., 2003). One interesting aspect of this work is a connection between photosensitivity and magnetoreception (Ritz et al., 2002). Dependence on light is a well-known feature of the avian magnetoreceptor (Deutschlander et al., 1999; Wiltschko et al., 2004a,b), but it has also appeared in other behavioral studies of animal magnetic field sensitivity (Prato et al., 1997, 1998).

The Ritz-Schulten model (Ritz et al., 2000) has an appealing geometrical application. Being integrated into the bird's retina, the suggested compass would appear as a modulation overlay on the bird's field of view. The mechanism operates through the so-called low field effect (LFE), based on a single nuclear spin, and operates near the limit of the theoretical sensitivity, despite omitting degrading effects such as the presence of multiple nuclear spins, dipolar effects, and various spin relaxation process that will start to become relevant for the long radical pair lifetimes (>100 ns) considered in the model.

Cryptochromes provide one possible source of free radicals in a spatially ordered system (Ritz et al., 2002). A recent theoretical model for avian magnetoreception develops that idea by investigating a flavin–tryptophan radical pair with a high degree of homology to the cryptochromes (Cintolesi et al., 2003). This multinucleus model is realistic in that it still manages to provide sensitivity to fields in the geomagnetic field range. Interestingly, it does not operate through the LFE described above (the multinucleus approach appears to remove most signs of that mechanism), but rather it depends on immobilized radicals and assumes that the free radical pair may have a lifetime up to 5 μs.

6.4.4 Coenzyme B_{12}-Dependent Reactions

Magnetic field effects in the coenzyme B_{12} are well explored experimentally with matching theoretical predictions (Harkins and Grissom, 1994; Grissom and Natarajan, 1997; Taoka et al., 1997). While most work on this model system has been concerned with intermediate and higher-field mechanisms, there are also detailed theoretical investigations suggesting that weak (<100 μT), relatively low-frequency (<100 kHz), might be able to affect this system (Canfield et al., 1994, 1995, 1996).

6.4.5 Other Experimental Observations

The addition of iron ions or exposure to a 7-mT static magnetic field (SMF) did not affect the survival of rat lymphocytes *in vitro* when performed in isolation, but combined

exposure led to a significant increase in cell death (Jajte et al., 2002). One possible explanation of this behavior is that the addition of iron ions enhanced levels of ROS and that the field exposure further promoted the creation of free radicals, leading to cell death by both apoptosis and necrosis. An experiment with a similar rationale used added $FeCl_2$ to stimulate ROS production, and a 930-MHz, 5-W/m^2 cell phone-generated field affected a biological marker for ROS production. It should be noted that the vacuum magnetic field associated with this exposure is quite low (approximately 0.14 μT) and the frequency is a relatively unexplored region for this mechanism.

Proliferation of chick fibroblasts was observed to be enhanced by a 100-Hz, 0.7-mT sinusoidal magnetic field (Katsir et al., 1998). In a follow-up study it was found that free radical scavengers (Katsir and Parola, 1998) suppressed this effect, suggesting that that free radicals may have a role in mediating the magnetic field effect on proliferation.

Genotoxic effects from intermediate static magnetic fields (250 mT) have been studied in *Escherichia coli* DNA, both *in vivo* and *in vitro* (Potenza et al., 2004). Free radical formation was stimulated, and the genetic damage was mapped as a function of exposure duration. *In vitro* experiments showed detectable genotoxic effects, but the *in vivo* assays did not, indicating that cellular protective responses may prevent damage in the intact system.

A reported effect on the oxidative burst in neutrophils by a 0.1-mT field was attributed to free radicals (Roy et al., 1995). In that study, the connection to free radicals lies in that the fluorescent probe used to study the neutrophil activity reacts specifically with free radical-derived oxidants that create the fluorescing compounds. Work in neutrophils in humans (Heine et al., 1999) using a much larger field (1.5 T) did not find any effects of magnetic fields on the respiratory burst of human neutrophils or on the production of radical species.

Phagocytosis was observed to be affected by 0.5–1.5-mT, 50-Hz sinusoidal magnetic fields (Simko et al., 2001). An attendant increase in superoxide production may be an indication that the field stimulated the system through a free radical process.

6.5 Conclusion

Free radical reactions are ubiquitous in biology, and recent developments of the low-field mechanisms (Timmel et al., 2001) and the consideration of detailed biochemical systems (Cintolesi et al., 2003) make this mechanism a contender for field effects down to geomagnetic field strengths. The physical transduction step is not vulnerable to thermal perturbations, a significant advantage over competing models.

This model does not produce large (factors >2) changes at the initial field detection step. Theoretical models and direct experimental observations in the low-field region typically operate around or below the 10% level, so we should expect the physical detection mechanism to need cooperation from downstream processes for biologically relevant detection of magnetic fields with free radicals as the starting point.

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