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Magneto-oncology: a radical pair primer

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There are few well-established biophysical mechanisms by which external magnetic fields can influence the biochemistry of molecules in living systems. The radical pair mechanism is arguably the most promising. In this mini-review I summarize the characteristics of radical pairs in a way that may be useful to those engaged in the field of magneto-oncology. The intention is to help researchers decide whether an observed biomedical magnetic field effect could have its origin in radical pair biochemistry. Armed with a physically plausible interaction mechanism, it may be possible to devise and refine a theoretical model and thereby iteratively optimise therapeutic protocols. Such an approach may also help identify experimental artefacts

KEYWORDS

radical pair mechanism (RPM), spin chemistry, electron spin, magnetobiology, magnetic field effects (MFE)

Introduction

Magnetic nanoparticles, guided to specific locations by external magnetic fields, have a variety of applications in cancer treatment. They can deliver drugs or genetic material, produce localized heating (magnetic hyperthermia), enhance immune cell activation, and help visualise tumours (magnetic resonance imaging and magnetic particle imaging). The magnetic fields involved are typically stronger than 10 millitesla and the fundamental physics – magnetic forces, radiofrequency heating, spin relaxation, and so on – is well understood. By contrast, the primary interaction mechanisms behind strategies that do not involve nanoparticles are often obscure. The problem is that the energy with which even a 1 tesla magnetic field interacts with a single molecule is a great deal smaller than the energy of the naturally occurring random fluctuations in atomic positions and molecular orientations (1). Even for paramagnetic molecules like free radicals, we can expect that any magnetic field effect on the rates or yields of (bio)chemical reactions should be overwhelmed by thermal noise. No matter how efficient any subsequent amplification mechanisms may be, there can be no magnetic field effect if the primary signal-to-noise ratio is less than one (2).

However, a well-established interaction mechanism does exist for which this thermodynamic argument is irrelevant: the radical pair mechanism (3–10). Over the last fifty years, it has been used, often quantitatively, to account for hundreds of laboratory studies of magnetic field effects on free radical reactions. Although convincing examples in

biology have been scarce, there is no reason why the mechanism could not operate in living systems (11), for instance in the magnetic compass of migratory birds (12–17).

My purpose in writing this article is to summarize the characteristics of the radical pair mechanism in a way that might be useful to those working in the field of magneto-oncology. The intention is to help researchers decide whether an observed biomedical magnetic field effect could have its origin in radical pair biochemistry. Armed with a physically plausible interaction mechanism, it may be possible to devise and refine a theoretical model and thereby iteratively optimise therapeutic protocols. It may also help avoid experimental artefacts, [of which magnetobiology (18–30) seems to have more than its fair share (11)] and allow *in silico* investigation of features of the interaction mechanism that do not readily lend themselves to experimental study. In the course of this primer, little attempt will be made to explain the spin physics

underlying the radical pair mechanism – that can be found elsewhere (3, 9, 31, 32) and in some of the articles cited below. The text starts with a brief summary of the mechanism itself, continues with descriptions of its various manifestations, and ends with a few concluding remarks. Some basic quantitative aspects of the mechanism are summarized in the Supplementary Material.

Radical pair mechanism

Radicals are molecules that contain an unpaired electron whose spin angular momentum (or simply, spin) is associated with a magnetic moment (33–35). In simple terms, the origin of magnetic field effects on pairs of radicals can be understood by reference to Figure 1a. The two unpaired electrons, one in each radical, can be in either singlet (S) or triplet (T) states depending, roughly speaking, on



FIGURE 1

(a) The simplest radical pair reaction scheme. S and T are the singlet and triplet forms of the radical pair. The orange arrows represent the oscillatory interconversion of S and T by hyperfine and Zeeman interactions. S and T react spin-selectively to form singlet and triplet products, P_S and P_{T_r} , respectively. (b) Schematic time-dependence of radical-pair and product states. Starting in the singlet state, S and T interconvert coherently while reacting to give Ps and PT, as in scheme (a). The quantum beat frequencies are typically in the megahertz to gigahertz range depending on the spin interactions of the two electrons. The populations of the products build up to their final levels, Φ_S and Φ_T , where $\Phi_S + \Phi_T = 1$. (c) Schematic changes in the yield of a reaction product, $\Delta \Phi = \Phi(B_0) - \Phi(0)$, induced by a static external magnetic field of strength B_0 . Using the notation $X \to Y$, where X is the initial spin state of the radical pair and Y is the reaction product, this figure is appropriate for $S \rightarrow P_T$ [reaction schemes (a) and (d) (ii)] and $T \rightarrow P_S$ [(a) and (d) (i)]. The sign of $\Delta \Phi$ is inverted for S \rightarrow P_S [(a) and (d) (i)] and T \rightarrow P_T [(a) and (d) (ii)]. The values of B₀ on the horizontal axis give an impression of the magnetic fields at which the various features normally occur for organic radicals with effective hyperfine interactions ≈ 1 mT and $\Delta g \approx 0.001$. The left-hand side shows the behaviour expected for radical pairs with short-lived (red) and long-lived (blue) spin coherence. For the red line, $B_{1/2}$ is the magnetic field at which $\Delta \Phi$ equals half its value at the plateau (in this case when $B_0 \approx 30$ mT). The right-hand side shows two possible effects of the Δg mechanism (green). Effects of exchange and dipolar interactions have been ignored. Δg is defined in the Supplementary Material. (d) Alternative radical-pair reaction schemes. (i) S reacts spin-selectively to form P_S while S and T react non-selectively to give a product P_{ST}. (ii) T reacts spin-selectively to form P_T while S and T react non-selectively to give a product P_{ST}. (e) Schematic field-dependence of the reaction yield for a radical pair with a strong exchange interaction. Using the notation in (c), this figure is appropriate for $S \rightarrow P_T$ [reaction schemes (a) and (d) (ii)] and $T \rightarrow P_S$ [(a) and (d)(i)]. The extremum occurs when $B_0 = 2J$ where J is the strength of the exchange interaction. (f) Schematic spin energylevels of a radical pair in a static magnetic field (i) weaker and (ii) stronger than the hyperfine, exchange and dipolar interactions. v_{HFC} is the maximum resonance frequency in a weak static field, determined mainly by hyperfine interactions. v_L is the Larmor frequency, determined by the strong Zeeman interaction. (g) Schematic B₀-dependence of the reaction yield with and without a weak 150 MHz time-dependent field B₁. The resonance appears when $B_0 = 150/28 = 5.4$ mT.

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whether their spins are mutually aligned antiparallel $(\uparrow\downarrow)$ or parallel $(\uparrow\uparrow)$, respectively. The reactivity of this pair of radicals is subject to spin-selection rules: S-pairs are formed from S-state reactants, and react to give S-state products, and similarly for T-pairs (Figure 1a). Following spin-selective formation, the S and T states interconvert coherently, typically at megahertz or gigahertz frequencies depending on the spin interactions of the two electrons (Figure 1b) (14). An external static, radiofrequency, or microwave magnetic field acting on the two electrons (Zeeman interactions) can alter the extent and timing of S↔T interconversion and hence the probabilities that the pair reacts to form the singlet (P_S) or the triplet (P_T) product (Figures 1a, b). Competition between the two pathways means that an increase in the final yield ($\Phi_{\rm S}$ or $\Phi_{\rm T}$) of one product is matched by a decrease in that of the other. In reality, the pattern of $S \leftrightarrow T$ "quantum beats" is considerably more complex than shown in Figure 1b because each electron spin has (hyperfine) interactions with the spins of several atomic nuclei (e.g. ¹H and ¹⁴N) (36–38).

All the relevant magnetic interactions of the two electrons with external magnetic fields (Zeeman), with nuclear spins (hyperfine), and with each other (exchange and dipolar) - are normally orders of magnitude smaller than the thermal energy, $k_{\rm B}T$ (Boltzmann's constant times temperature, equivalent to 2.6 kJ mol⁻¹ at physiological temperature). An applied magnetic field cannot therefore break chemical bonds or otherwise initiate new (bio)chemical transformations. It can only modify the yields of existing reactions. Uniquely, this is possible for radical pairs because the electron spins couple so weakly to their surroundings. The nonequilibrium spin states created by spin-selective reactions can persist for times as long as a microsecond before the coherences vanish and the S:T ratio reaches its equilibrium value of 1:3. A spin relaxation time of ~1 µs gives enough time for an external magnetic field stronger than ~100 µT to have a significant effect on the quantum beats and therefore the reaction yields (39, 40). Radical pairs with lifetimes in excess of 1 µs show very weak sensitivity to magnetic fields because the spin correlation decays before any products can be formed. Magnetic fields weaker than ~100 µT would require improbably slow spin relaxation and are therefore highly unlikely to produce significant effects in vivo unless there has been evolutionary pressure to optimise the sensitivity.

More detailed introductory material can be found in ref (14). which aims to "explain the chemical and physical aspects of radicalpair magnetoreception to biologists and the biological and chemical aspects to physicists".

Static magnetic field effects

The most common manifestation of the radical pair mechanism is the dependence of the yields of the reaction products on the strength (magnetic flux density) of a static external magnetic field (Figure 1c). Whether the yield is increased or decreased depends on the properties of the radicals, the strength of the field, the initial spin state (S or T), and which product (P_S or P_T) one looks at.

The shape of Figure 1c (appropriate for the reaction scheme in Figure 1a and the slightly more complicated ones in Figure 1d) has

three origins. In magnetic fields up to about 100 mT, $S \leftrightarrow T$ interconversion is dominated by the hyperfine interactions, and the reaction yields usually have a sigmoidal field-dependence (41-44). The "half-field" parameter, $B_{1/2}$, is normally comparable to the effective hyperfine interaction of the two radicals (defined in the Supplementary Material), typically a few millitesla for organic radicals (41, 45). Larger values of $B_{1/2}$ are expected if one or both radicals undergo rapid spin relaxation (46, 47). If the radicals are long-lived and spin-relax sufficiently slowly, the reaction yields may have an extremum known as the low field effect (31) which boosts the sensitivity to magnetic fields weaker than $B_{1/2}$ and flips the sign of the effect. For stronger fields, $S \leftrightarrow T$ interconversion is driven by the difference in the Zeeman interactions of the two electrons with the applied magnetic field (Δg mechanism) (48, 49). Finally (not shown in Figure 1c), the rate at which spin coherence decays is sometimes field-dependent such that strong magnetic fields give rise to further changes in reaction yields (50).

If the radicals are not randomly oriented, the effect of a static magnetic field may depend on its direction (51-53). This is thought to be the basis of the magnetic compass sense of migratory songbirds (12-14, 39). Exact reversal of the field direction should have no effect on the spin dynamics whether the radicals are oriented or not (54, 55).

The field-dependence of the reaction yields is profoundly different when the exchange or dipolar interaction of the two electrons is larger than the hyperfine couplings. Strong interactions suppress the effects of weak magnetic fields and give rise to a "2*J* resonance" when the Zeeman interaction matches the exchange coupling (Figure 1e) (3, 56). Exchange interactions are generally negligible for radicals separated by more than 1.0 to 1.5 nm; dipolar interactions have a longer range: ~1 mT at 1.4 nm; ~0.1 mT at 3.0 nm (57).

Low-frequency magnetic field effects (< 1 MHz)

Radical pairs that show static magnetic field effects rarely have lifetimes longer than 1 µs. This means that oscillating magnetic fields with frequencies much below 1 MHz are effectively static as far as the radical pairs are concerned (58, 59). As there is unlikely to be any correlation between the phase of an external alternating field and the instant at which radical pairs are formed, any observed effect will be an average over a period of the time-dependent field. The result of this averaging is that magnetic fields with frequencies below ~1 MHz should have much smaller effects than a static field of comparable strength. For example, in the presence of the Earth's magnetic field (~50 µT), a 1 µT-strength, 50 or 60 Hz magnetic field is predicted to have a similar effect to that of a ~10 nT change in the Earth's field (58). The latter would be experienced by travelling 2.5 km towards or away from the geomagnetic north pole (58). Similar conclusions apply to any frequency up to ~100 kHz. Stronger time-dependent magnetic fields are expected to lead to larger effects but still smaller than for a static field of similar strength.

High-frequency magnetic field effects (> 1 MHz)

The situation is different for magnetic fields that vary during the lifetime of a radical pair, i.e. for frequencies above ~1 MHz. Magnetic field effects can be expected if the oscillation frequency is in resonance with an S \leftrightarrow T interconversion frequency or, equivalently, if it matches the energy gap between two of the spin energy-levels of the radicals (60–63). Unless the time-dependent field is very strong, non-resonant effects are extremely weak.

In a static magnetic field stronger than the hyperfine, exchange and dipolar interactions, the dominant resonance frequency can be calculated using the conversion factor of 28 MHz per mT, e.g. 2.8 GHz for a 100 mT static field (Figures 1f, g). This "Larmorfrequency" resonance is strongest when the static and timedependent fields are perpendicular to one another and weakest when they are parallel. A magnetic field effect specifically at the Larmor frequency, with this dependence on the relative directions of the two fields, can be used as a diagnostic test for the operation of the radical pair mechanism (64).

By contrast, in weak static fields, comparable to or smaller than the internal magnetic interactions, a specific resonance at the Larmor frequency (e.g. 1.4 MHz for a 50 μ T field) is not normally expected (14, 65). The only exception to this is when the exchange and dipolar interactions and the hyperfine interactions in one of the radicals are all extremely small (an unlikely event) (14, 66). For weak static fields, the maximum resonance frequency corresponds to the separation of the highest and lowest spin energy-levels (Figure 1f) (65), a prediction that has been used to guide behavioural experiments on the orientation of migratory songbirds exposed to radiofrequency magnetic fields (67–71). There may also be changes in reaction yields for frequencies comparable to the strengths of the internal magnetic interactions, e.g. ~28 MHz for ~1 mT hyperfine couplings.

Magnetic isotope effects

Isotopic substitution changes the spin and magnetic moment of a nucleus, and therefore its hyperfine interaction, leading to a "magnetic isotope effect" (62, 72–74) quite distinct from the more familiar mass, or kinetic, isotope effect. Like external magnetic fields, isotopic substitution can increase or decrease reaction yields depending on the initial spin state of the radical pair and the spin state of the product. Other things being equal, the largest magnetic isotope effects are expected when a non-magnetic nuclide is replaced by a magnetic one, or vice versa, for example ${}^{12}C \rightarrow {}^{13}C$ (75) or ${}^{25}Mg \rightarrow {}^{24}Mg$ and/or ${}^{26}Mg$ (76–78). The latter has been suggested as a new way of selectively killing cancer cells (79, 80).

Chemical effects

The discussion so far has considered exclusively "geminate" (G) radical pairs formed in spin-correlated S or T states from S or T

precursors. This situation is very common, especially for photochemical reactions where the precursor is an electronically excited S or T molecule and the radicals are formed by electron or H-atom transfer or homolytic bond cleavage. However, there can also be "F-pairs", arising from the random encounter, e.g. by diffusion in solution, of independently created radicals which initially have uncorrelated electron spins. The spin correlation required for magnetic field effects arises from subsequent spinselective reactions. F-pairs behave qualitatively like triplet G-pairs if the S state reacts faster than the T state, and like singlet G-pairs if the opposite is true (81, 82). The most common case is that S-pairs react to form stable singlet-state products while T-pairs are unreactive. Kinetic competition between the spin-selective reaction of the S-pair and diffusive separation of both S- and Tpairs [Figure 1d(i)] gives rise to the magnetic sensitivity.

Amplification mechanisms

There has been a number of suggestions of mechanisms that could amplify small magnetic field effects [briefly reviewed in (58)]. One proposal is that a paramagnetic scavenger, reacting with one of the constituents of a radical pair, could not only boost its sensitivity to magnetic fields but also circumvent the detrimental effects of rapid spin relaxation (83–86). Such a mechanism might allow superoxide-containing radical pairs (see below) to be magnetically sensitive.

A second possibility is that the chemical feedback and autocatalysis that are features of oscillating chemical reactions could permit small magnetically-induced changes in the kinetics of radical pair intermediates to have a disproportionate effect on the amplitude of the oscillations (87–94). Interestingly, it has been proposed that related effects could arise in an intrinsically oscillatory system of coupled mitochondria in cancer cells (95).

Concluding remarks

Magnetobiology has a vast literature, much of it beset by conflicting, implausible or extravagant claims (11). That so many reports of non-thermal biological magnetic field effects have been attributed to the radical pair mechanism seems to owe more to the scarcity of plausible alternatives than to solid experimental evidence of radical pair biochemistry. Assignment of a magnetic field effect to the radical pair mechanism is generally more convincing if the experimental observations do not conflict with theoretical predictions.

The theoretical basis of the radical pair mechanism has become well-established over the last 50 years, to the extent that upper limits on the magnetic sensitivity of radical pair reactions can be estimated quite reliably if enough is known, or can be inferred, about the properties of the radicals involved (58, 71, 96–99). Such calculations can help one decide whether an observed effect is likely to have a radical-pair origin or, sometimes, whether it is likely to be an experimental artefact.

An example of the utility of spin dynamics calculations is provided by the (independently replicated) finding that migratory birds are

prevented from orienting in the Earth's magnetic field (\sim 50 µT) when exposed to astonishingly weak (~1-100 nT) radiofrequency (~1-100 MHz) magnetic fields (66-71, 100-103). Although evidence is accumulating in support of the notion that light-induced radical pairs (formed in cryptochrome proteins located in photoreceptor cells in the birds' retinas) could form the basis of the avian magnetic compass sensor, it is still unclear whether they are sensitive enough to allow small nocturnal migrants to derive a compass bearing with only starlight available to initiate the radical-pair chemistry. It is much more a stretch of the imagination to believe that this sensory mechanism could be disrupted by time-dependent magnetic fields ~1000 times weaker than the geomagnetic field. Computer simulations of realistic spin-systems are being used to guide behavioural experiments by predicting which radiofrequencies should and which should not cause the birds to be disoriented (65, 71). The hope is that such a combination of theory and experiment will reveal whether radiofrequency disorientation is an informative side effect, an experimental artefact or, conceivably, a biologically relevant phenomenon.

Finally, a brief comment on reactive oxygen species (ROS, e.g. O_2^{-} and OH[•]) and reactive nitrogen species (e.g. NO[•]), some of which play crucial roles in cell signalling and oxidative damage. Various ROS-related effects of static, time-dependent and even hypomagnetic (i.e. << 50 μ T) fields, have been discussed in the context of the radical pair mechanism, with the emphasis on superoxide (O_2^{--}) (15, 20, 104–115). A property shared by O_2^{--} , OH[•], and NO[•] is that they all spin-relax much more rapidly (nanoseconds or faster) than the vast majority of organic radicals (116, 117). As a consequence, extremely small magnetic field effects can be expected for radical pairs containing these radicals, even for very strong fields (118, 119). Any radical-pair effects on ROS levels in living systems are much more likely to arise from upstream pairs of slower-relaxing organic radicals (11).

Author contributions

PJH: Writing - original draft, Writing - review & editing.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2025.1539718/ full#supplementary-material

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