Light-Activated Magnetic Compass in Birds

Ilia A. Solov'yov and Walter Greiner

Abstract Migrating birds fly thousand miles without having a map, or a GPS unit. But they may carry their own sensitive navigational tool, which allows them "see" the Earth's magnetic field. Here we review the important physical and chemical constraints on a possible compass sensor and discuss the suggestion that radical pairs in a photoreceptor cryptochrome might provide a biological realization for a magnetic compass. Finally, we review the current evidence supporting a role for radical pair reactions in the magnetic compass of birds.

1 Introduction

Migratory birds travel spectacular distances each year, navigating and orienting by a variety of means, most of which are poorly understood. Among them is a remarkable ability to perceive the intensity and direction of the Earth's magnetic field [1–3]. Biologically credible mechanisms for the detection of such a weak field (25–65 μ T) are scarce and in recent years two proposals have emerged as front-runners. One, essentially classical, centers on clusters of magnetic iron-containing particles in the upper beak which appear to act as a magnetometer for determining geographical position [4–11]. However, the idea that bird orientation is guided by magnetic-sensing structures in the animals' beaks has been challenged by the suggestion that the iron-containing cells are macrophages, which have no link to the brain [12], i.e., a kind of immune cell that are also involved in iron homeostasis.

W. Greiner

I. A. Solov'yov (🖂)

Beckman Institute for Advanced Science and Technology, Urbana-Champaign, Illinois, USA e-mail: ilia@illinois.edu

Frankfurt Institute for Advanced Studies, Goethe-Universität, Frankfurt, Germany e-mail: greiner@fias.uni-frankfurt.de

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The other mechanism relies on the quantum spin dynamics of transient photoinduced radical pairs [13–29]. Originally suggested by Schulten in 1978 [17] as the basis of the avian magnetic compass sensor, this mechanism gained support from the subsequent observation that the compass is light-dependent [30]. The radical pair hypothesis began to attract increased interest following the proposal in 2000 that free radical chemistry could occur in the bird's retina initiated by photoexcitation of cryptochrome, a specialized photoreceptor protein [20].

The quantum evolution of highly non-equilibrium electron spin states of pairs of transient spin-correlated radicals is conjectured to change the yields of their reaction products in 'wet, warm and noisy' biological surroundings even though the Zeeman interaction with the geomagnetic field is more than six orders of magnitude smaller than the thermal energy per molecule (k_BT). The classical thermodynamic effect of such minuscule interactions on the positions of chemical equilibria and the rates of activated reactions would be entirely negligible. The radical pair mechanism is the only well-established way in which an external magnetic field can influence a chemical reaction [31–34].

The origin of the magnetic field effect (MFE) can be understood by reference to the simple reaction scheme shown in Fig. 1: (1) A pair of radicals A[•]B[•] is formed (e.g. by an electron transfer reaction) in an entangled state which may be either singlet (spin quantum number, S = 0) or triplet (S = 1) depending on the spin of the precursor molecule(s), which is conserved in the reaction. (2) The radical pair is able to recombine from both the S and T states to form chemically distinct products (^SP and ^TP in Fig. 1) with rate constants $k_{\rm S}$ and $k_{\rm T}$ respectively. (3) S and T radical pairs coherently interconvert under the influence of local magnetic fields arising from hyperfine interactions of the electron spins with magnetic nuclei in the two radicals. As a consequence, the fractional yields of the two products are determined not only by $k_{\rm S}$ and $k_{\rm T}$ but also by the extent and timing of the magnetically controlled S \leftrightarrow T interconversion step. (4) This step is also, crucially, enhanced or hindered by electron Zeeman interactions with an external magnetic field. Thus, the fractional yields of the two products and the lifetime of the radical pair become magnetic field-dependent. If the radical pair is immobilized, the tensorial nature of the hyperfine interactions implies a directionality in the response to an external magnetic field which could form the basis of a compass sensor [26, 35-38]. The theory of the radical pair mechanism is well developed and has been successfully used over the last 40 years for the quantitative interpretation of a variety of *in vitro* experimental data—not just

Fig. 1 A simple radical pair reaction scheme



MFEs, but also electron and nuclear spin polarizations [39] and magnetic isotope effects [40].

There is no doubt whatsoever that radical pair MFEs rely on coherent quantum dynamics. When a radical pair is formed in a spin-conserving reaction from a singlet or triplet precursor, it is created in a non-stationary coherent superposition of the eigenstates of its spin Hamiltonian. As a consequence, the spin state of the radical pair oscillates coherently at frequencies and with amplitudes determined by the internal and external magnetic interactions. The frequencies typically fall in the $10^7 - 10^9$ Hz range and can be significantly faster than the spin relaxation processes (often $<10^7 \text{ s}^{-1}$) that cause decoherence and loss of spin-correlation. In many cases, there is ample time for weak magnetic interactions to influence the spin dynamics before the radicals react, and therefore to affect the product yields. The clearest experimental demonstrations of this fundamentally quantum mechanical behavior, without which there would be no significant response to an external magnetic field, are the observations of quantum beats in the recombination luminescence of radical ion pairs in non-polar solvents [41-43] and the detection by EPR (electron paramagnetic resonance) of zero-quantum coherences in radical pairs in photosynthetic reaction centers [44-47].

In the following, we review the important physical and chemical constraints on a possible radical-pair-based compass sensor and discuss the suggestion that radical pairs in cryptochromes might provide a biological realization for a magnetic compass. We then summarize pertinent *in vitro* experimental data, and discuss their relevance to detecting the direction of the Earth's magnetic field. Finally, we review the current evidence supporting a role for radical pair reactions in the magnetic compass of birds.

2 Requirements for a Magnetic Compass

To form the basis of an effective compass magnetoreceptor, a radical pair reaction must satisfy a number of conditions [13], which fall into five broad overlapping areas: chemical, magnetic, kinetic, structural and dynamic. (1) The radical pair must be formed in a coherent superposition of its electron-nuclear spin states and at least one of the S and T states should undergo a spin-selective reaction that the other cannot. (2) There should be suitable anisotropic hyperfine interactions. (3) The lifetime of the radical pair must be long enough to allow the weak magnetic field to affect the spin-dynamics, and the rate constants $k_{\rm S}$ and $k_{\rm T}$ should not be too dissimilar. (4) The Zeeman interaction can only modulate the $S \leftrightarrow T$ interconversion if interradical spin-spin (exchange and dipolar) interactions are sufficiently weak. (5) To deliver directional information, the radical pairs must be aligned and immobilized and the spin system should relax sufficiently slowly. These criteria are interlinked and not automatically mutually compatible. For example, (3) places an upper limit on the separation of the radicals, while (4) may require larger inter-radical distances. Both (3) and (4) may constrain the chemistry, e.g. by requiring the magnetically sensitive radical pair to be formed by sequential electron transfers rather than in a

single step [13, 21]. Motional modulation of anisotropic hyperfine interactions is a major source of spin-relaxation in radicals so that (2) may be incompatible with (5) unless the radicals are strongly immobilized.

3 Cryptochrome Magnetoreception

Ritz et al. [20] proposed in 2000 that radical pairs formed photochemically in the protein cryptochrome could form the basis of the compass magnetoreceptor. No other candidate molecule has been put forward in the intervening years. Cryptochromes occur in several of the organisms for which magnetic field effects have been reported, including fruit flies, plants and migratory birds and have been shown to act as photoreceptors in a variety of species [48]. In plants, they serve as photosensors for a number of developmental responses such as hypocotyl growth, leaf expansion, induction of flowering time, and entrainment of the circadian clock. In insects, cryptochromes act as circadian photoreceptors.

Light-induced cryptochrome signalling appears to proceed via electron transfer involving a chain of three tryptophan amino acids (the Trp-triad) and the cofactor, flavin adenine dinucleotide (FAD) [49, 52–54], shown in Fig. 2a. Photo-excitation of



Fig. 2 a Structure of cryptochrome, the protein implicated in avian magnetoreception. Cryptochrome internally binds the FAD (flavin adenine dinucleotide) cofactor which governs the functioning of the protein. The signalling state is achieved via a light-induced photoreduction pathway involving a chain of three tryptophan amino acids, indicated as Trp_{400} , Trp_{377} and Trp_{324} using the amino acid sequence numbers for *Arabidopsis thaliana* cryptochrome-1. **b** The cryptochrome photocycle. The signaling function of cryptochrome is controlled by the oxidation state of its flavin cofactor, which can exist in three interconvertible redox forms, FAD, FADH[•] (or FAD^{•-}), and FADH⁻ (or FADH₂) [49–51]. The FAD form is inactive and is thought to be the resting state of the protein in the dark. Blue light triggers photoreduction of FAD to establish a photo-equilibrium that favors FADH[•] over FAD and FADH⁻. The semiquinone radical FADH[•] state is the signalling state of the protein. FADH[•] can be further reduced to the inactive FADH⁻ form. The FAD→FADH[•] and FADH[•] → FADH⁻ reactions may be affected by an external magnetic field. The excited state of the flavin cofactor, FAD^{*} is a short-lived intermediate in the photocycle

the FAD in its fully oxidized state leads to the formation of three consecutive radical pairs by donation of an electron along the Trp-triad to the FAD to form the FADH[•] radical as illustrated in Fig. 2b. It is this state that is thought to be responsible for biological signalling. Any factor that increases (decreases) the yield of this state of the protein should result in an increased (decreased) cryptochrome signal for a given light intensity. In principle, an external magnetic field could alter the yield of the signalling state via its effect on the flavin-tryptophan radical pair [26, 21]. *In vitro*, the FADH[•] state of cryptochrome has a lifetime of about 1–10 ms with respect to reversion to the FAD state [25, 52, 54].

Experimental evidence provides some support for a magnetosensing role for cryptochrome. Growth of Arabidopsis thaliana seedlings in a 500 µT magnetic field has been reported to enhance cryptochrome activity, such that the plants responded as if they had been exposed to higher intensities of blue light than was in fact the case [55]. Magnetically enhanced cryptochrome activity was manifested in shorter hypocotyls and higher anthocyanin levels compared to control plants grown under identical blue-light intensities in weaker magnetic fields. However, none of these effects could be replicated in a subsequent study which also failed to detect responses using substantially stronger magnetic fields where radical pair effects might be expected to be more pronounced [56]. Related effects have been found for the circadian clocks of fruit flies in which cryptochrome acts as a photoreceptor [57]. In response to blue light, cryptochrome activity increases the circadian period in Drosophila, an effect that was found to be more pronounced in the presence of a weak magnetic field, indicating enhanced cryptochrome signalling. Cryptochrome knock-out mutants showed no magnetic field sensitivity, while flies overexpressing cryptochrome in the clock neurons showed enhanced magnetic responses compared to wild type. A recent investigation of behavioral responses of *Drosophila* in applied magnetic fields has also implicated cryptochrome [58, 59]. In these experiments, flies were trained to associate the magnetic field with a food source, and learned to use it as an orientational cue. These responses were absent in cryptochrome-deficient flies.

In the context of avian magnetoreception, it is noteworthy that cryptochromes have been found in birds' retinas [15, 16, 62]. There are some genetic indications of an involvement of cryptochromes in magnetoreception in birds [63], but the lack of transgenic birds has hitherto precluded more clear-cut evidence. Theoretical considerations also provide support for the cryptochrome hypothesis. For example, the theory of electron transfer reactions [64] indicates that a radical pair in a protein environment could have a lifetime as long as 1 μ s if the edge-to-edge inter-radical separation, r_e were less than about 1.5 nm [13]. This appears to be consistent with the crystal structure of *Arabidopsis thaliana* cryptochrome in which $r_e = 1.47$ nm for the FAD cofactor and the terminal residue of the tryptophan triad [65]. A further, related kinetic constraint can be derived from the reasonable assumption that the magnetically responsive radical pair should be formed in less than 1 ns (so as to have a high quantum yield and a pure initial spin state). Estimates, also based on Marcus theory, suggest that this could be achieved if every electron transfer step involved in the formation of the pair had a donor-acceptor separation $r_e < 1.0$ nm, a condition

Fig. 3 Schematic illustration of the visual modulation pattern that might be induced by the geomagnetic field for a bird flying in the eight cardinal directions (N, NE, E, SE, S, SW, W, and NW). The geomagnetic field inclination angle is 66° (appropriate for Frankfurt am Main, Germany) [60, 61]. For details, see [37]



which again is consistent with the FAD/Trp triad structure in *Arabidopsis thaliana* cryptochrome [13].

Finally, we turn to the degree of molecular ordering that would allow an array of cryptochromes to show a significant directional response to a $50\,\mu$ T magnetic field and therefore to act as a compass sensor. Assuming that the magnetic signal-transduction mechanism is linked into the rhodopsin-mediated visual detection system, so that the bird literally sees a representation of the Earth's magnetic field, one can derive a filter function to model the transformation of the visual field produced by a cryptochrome-based magnetoreceptor [37]. Figure 3 shows example of visual modulation patterns simulated in this way for a bird flying horizontally in eight cardinal directions. Such calculations indicate that even modest uniaxial molecular alignment could be sufficient to yield a directional response suitable for compass detection [35–37].

4 Evidence for a Radical Pair Mechanism in Birds

4.1 Lack of Evidence for Alternative Mechanisms

Magnetoreception has long been postulated to be based on magnetite or other biogenic magnetic iron-oxide particles. Simple detection of iron-oxide contents in an animal is by itself not sufficient to indicate a role for iron oxides in magnetoreception, unless this is supported by corroborating behavioral observations. In birds, an iron-oxide system has been found in the beaks in the vicinity of the ophthalmic nerve [6, 11, 66]. However, under conditions in which birds show normal magnetic compass orientation in the seasonally appropriate migratory direction, their magnetic orientation responses are unaffected by anesthetization [67] of the beak or lesioning of the trigeminal branch of the ophthalmic nerve [29]. These results show clearly that birds can detect the direction of the magnetic field without using the iron-oxide system in the beak, thus indicating the existence of another, as of yet undiscovered, magnetoreception system. Moreover, the idea that bird orientation is guided by magnetic-sensing structures in the animals' beaks has been recently challenged by the suggestion that the iron-containing cells are macrophages, which have no link to the brain [12].

If this undiscovered system were based on iron-oxide particles, one would expect that a strong magnetic pulse would re-magnetize or re-organize the magnetic material and therefore affect magnetoreception of an iron-oxide based system. In a behavioral test, the bird beak system was anesthetized and a strong magnetic pulse applied prior to testing magnetic compass responses. In these experiments, the birds showed unimpaired magnetic compass orientation, strongly suggesting that the undiscovered magnetoreception system is not based on a mechanism involving iron oxides [68]. It is very likely that the beak iron-oxide system plays some role in magnetoreception, but there is scant evidence suggesting that magnetoreception in birds can occur *only* with the help of iron-oxide based mechanisms: birds can orient magnetically without using the only known iron-oxide system in their beaks and application of a strong magnetic pulse, the standard indirect behavioral test for identifying an iron-oxide based system.

4.2 Neurobiology

The radical pair mechanism postulates that magnetic field effects are perceived as an indirect effect on light sensing. The most likely place for the receptors to be located would be in the eye(s), so as to harness the power and speed of the visual processing system. As mentioned above, the candidate photo-magnetoreceptor molecule cryptochrome has indeed been found in avian retinas. Thus, the question arises whether brain centers have been identified that receive visual inputs and are involved in processing magnetic information. Using genetic markers, a brain area termed Cluster N has been identified in European robins that is most active during magnetic compass orientation experiments at night [69], when European robins migrate, and much less active when the eyes are closed [28, 69]. Cluster N is part of the tecto-fugal visual processing pathway and neuronal tracing has shown that it receives input from the eyes through only one synaptic transition [14, 27]. European robins with bilateral Cluster N lesions cannot perform magnetic compass orientation [29] but are capable of sun and star compass orientation, demonstrating that Cluster N is involved in processing magnetic information. It is unclear whether this area is involved in processing compass information in birds whose compass operates during daytime and seems to show the same functional properties as the compass of night migrants [70].

4.3 Radiofrequency Effects on Magnetic Orientation

An oscillating magnetic field with a frequency that matches an energy-level splitting between radical pair spin states is expected to affect S \leftrightarrow T interconversion, as in the *in vitro* experiments. Such fields could therefore change the sensitivity of a radical pair to the geomagnetic field. Analogous to the application of a strong magnetic pulse to modify the response of an iron-oxide based compass system, one thus expects that the presence of a resonant oscillating field will modify the response of a radical-pair based compass system, leading to re-orientation or disorientation in behavioral experiments when such a field is applied. Frequencies of resonances with typical hyperfine couplings and the free electron Larmor frequency fall into the range 1–100 MHz and one expects such fields to affect magnetic compass orientation. The lack of knowledge of the chemical nature of the hypothetical radical pairs in animal compass systems precludes more accurate predictions.

Figure 4 shows the experimental arrangement used to investigate the effects of oscillating magnetic fields on the orientation of European robins [24, 71, 72]. In all conditions, the oscillating magnetic field was superimposed on a static magnetic field



Fig. 4 Schematic representation of the experimental arrangement used in Frankfurt to investigate the effects of radiofrequency magnetic fields on the orientation of European robins in the Earth's magnetic field. The birds' responses were recorded in funnel-shaped cages illuminated by diffuse light from above. In addition to the local geomagnetic field, an oscillating magnetic field was applied in each experimental condition. The funnels were lined with coated paper on which the birds left scratches as they moved. Analysis of the distribution of scratch marks allowed the birds' degree of orientation to be determined. For details see [24, 71]

of either $46\,\mu\text{T}$ (geomagnetic field) or an amplified static field of doubled intensity. The linearly polarized oscillating field was vertical, thus forming a 24° angle with the static magnetic field. At an intensity of about 1 % of the geomagnetic field, oscillating fields disrupt orientation of European robins at frequencies between from 0.65 up to 7 MHz, the highest frequency realized in the experimental setup. At frequencies below 30 kHz, the oscillating fields did not affect the robins' orientation. Bimodal orientation results at 0.1 and 0.5 MHz, suggested a transition region between oriented and disoriented behavior. These results suggest that the radical pair lifetime or the spin relaxation time, whichever is shorter, is in the range 2–10 µs [24]. Clearly, an oscillating field with a period longer than the spin-relaxation time would be effectively static, and addition of a weak static magnetic field at 1 % of the geomagnetic intensity is not expected to have a significant effect.

Perhaps the most noteworthy feature of the oscillating field effects is that there is a dramatically stronger disruptive effect at 1.315 MHz, corresponding to the spinonly (i.e. g = 2) electron Larmor frequency in the geomagnetic field of $46 \,\mu$ T. At this frequency, a 15nT RF field led to disoriented behavior, whereas about 30 times stronger fields were necessary to disorient birds at other frequencies. These observations suggest that one of the electron spins is magnetically isolated, i.e. that it is located on a radical with no hyperfine interactions [24]. This suggestion is bolstered by the observation that doubling the static field intensity also doubles the frequency at which a 15 nT field leads to disorientation, as expected for the Zeeman resonance of a g = 2 radical. A particularly strong disruptive effect of oscillating magnetic fields at the spin-only Larmor frequency has been observed in all species for which effects of oscillating fields on magnetic compass orientation have been found, namely in migratory European robins, non-migratory chickens [70] and Zebra finches [73], as well as in cockroaches [74]. This suggests that the magnetically sensitive radical pair reaction has a similar chemical nature in different species. Radicals with an isolated electron spin are unusual in organic environments, as they need to be devoid of hydrogen or nitrogen atoms. The chemical nature of this postulated radical remains unknown. Superoxide and dioxygen have been suggested as possible candidates [22, 24], but cannot be reconciled with known physical properties [75].

The existence of disruptive effects is a first indication supporting the radical-pair mechanism, but it is crucial that additional control conditions be tested to rule out that the change in orientation is due to an unrelated non-specific cause, e.g. a change in motivation due to the presence of the oscillating fields. Oscillating fields had no effect on the magnetic compass of mole rats, a blind, subterranean animal whose compass is probably based on iron-oxide materials [76], indicating that effects of oscillating fields appear not to affect iron-based systems. A key control observation is that the angle of the oscillating fields with respect to the geomagnetic field determines whether birds are oriented or disoriented [71, 72]. Birds were disoriented when the oscillating fields formed a 48° (or 24°) angle with the geomagnetic field, but not when they were collinear with the geomagnetic field. The choice of 48° is particularly meaningful as a control condition, because at this angle, the oscillating field is applied at the same angle relative to the horizontal plane (in which the birds move during the experiments) as in the 0° condition. There is no reason why the birds' motivation

should be affected differently by non-specific effects of oscillating fields of equal intensity, frequency, and direction with respect to the horizontal. It appears much more likely that oscillating fields produce a resonance effect, in which case it is indeed expected that a collinear oscillating field will leave radical pair reactions unaffected [24].

5 Conclusion

The last decade has seen a number of studies from different fields that support the photo-magnetoreceptor and cryptochrome hypotheses. Man-made radical pair reactions have been designed that proved to be sensitive to Earth-strength magnetic fields [23]. Behavioral experiments using radiofrequency fields support the existence of a radical pair mechanism in birds. Studies at the protein level suggest that cryptochromes have properties conducive to magnetic sensing, such as formation of long-lived radical pairs. Magnetic field effects have been observed in several genetic organisms and were absent when cryptochromes were deleted. A visual brain area has been identified that is active during magnetic orientation behavior and without which birds become disoriented in magnetic orientation experiments. At this point, the radical pair hypothesis is not proven. However, support for this hypothesis has strengthened significantly, in particular for migratory birds. If it can be shown conclusively that birds use a radical-pair based compass, this would be a dramatic example of the use of a coherent quantum-mechanical process in a biological system and with clear biological relevance.

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