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REVIEW

Photoreceptor-based magnetoreception: optimal design of receptor molecules, cells, and neuronal processing

Thorsten Ritz^{1,*}, Margaret Ahmad², Henrik Mouritsen³,
Roswitha Wiltschko⁴ and Wolfgang Wiltschko⁴

¹*Department of Physics and Astronomy, University of California at Irvine, Irvine, CA 92697, USA*

²*CNRS EAC 7180, University of Paris VI, France*

³*AG Neurosensorik/Animal Navigation, IBU, University of Oldenburg, Germany*

⁴*FB Biowissenschaften, J. W. Goethe-Universität, Frankfurt am Main, Germany*

The sensory basis of magnetoreception in animals still remains a mystery. One hypothesis of magnetoreception is that photochemical radical pair reactions can transduce magnetic information in specialized photoreceptor cells, possibly involving the photoreceptor molecule cryptochrome. This hypothesis triggered a considerable amount of research in the past decade. Here, we present an updated picture of the radical-pair photoreceptor hypothesis. In our review, we will focus on insights that can assist biologists in their search for the elusive magnetoreceptors.

Keywords: magnetic sensing; radical-pair mechanism; photoreceptor

1. INTRODUCTION

It is challenging for nature to detect the weak geomagnetic field with biological materials. Careful models of putative sensory mechanisms often find it hard to explain how a 50 μT magnetic field can result in robust signals in the presence of thermal fluctuations and other sources of noise. With fundamental physical limitations placing constraints on magnetoreception, any mechanism that can in principle allow detection of 50 μT fields is noteworthy. The radical-pair photoreceptor mechanism is one of only three mechanisms considered to be physically viable at the moment, the other two being iron-oxide-based magnetoreception and magnetic sensing through induction in highly sensitive electric sensors (Ritz *et al.* 2002; Johnsen & Lohmann 2005, 2008; Mouritsen & Ritz 2005).

Ultimately, of course, one needs to move beyond discussion of possible mechanisms towards identification of actual magnetoreceptor molecules and cells through molecular biological, genetic and neurobiological approaches. In this regard, the radical-pair mechanism faces a unique challenge, because it is not obvious what cells or organs one should look for. For electromagnetic induction, Lorenzini ampullae are a concrete realization

of an electrically sensitive cell operating in fish. In birds and land-based animals, such cells have not been found, suggesting that induction is not the mechanism for magnetoreception in non-aquatic environments. Iron-oxide-based mechanisms are aided by the unique properties of iron that allow its detection and structural characterization through a number of techniques, thus pointing to possible sensory structures. In the radical-pair mechanism, however, the features distinguishing a putative magnetoreceptor from other, similar, molecules are more subtle, making the direct detection of possible sensory structures much more difficult.

One of the central tenets of the radical-pair mechanism is the need for a light-sensing molecule that changes its oxidation state upon light absorption. Upon light absorption, some, but not all, pigments respond, by transferring electrons to nearby suitable partners. Following a light-induced electron transfer, or change of oxidation state of the pigment, an intermediate state is created in which the pigment together with its electron transfer partner form a radical pair, i.e. a pair of molecules with an unpaired electron each. This intermediate radical pair state is sensitive to external magnetic fields by virtue of the magnetic field effects on the separate electron spins in both radicals, as will be discussed in more detail below. Thus, the first requirement for a candidate photo-magnetoreceptor is that it contains a pigment cofactor that transfers

*Author for correspondence (tritz@uci.edu).

One contribution of 13 to a Theme Supplement 'Magnetoreception'.

electrons upon light absorption. The first and, so far, only candidate fitting this requirement and existing in birds and other organisms of interest is the blue-green light photoreceptor molecule cryptochrome and it was its discovery together with the proof of its existence in animal retinas that prompted the re-suggestion of the radical pair mechanism (Ritz *et al.* 2000), revitalizing the earlier original formulation (Schulten *et al.* 1978).

In the decade following, a significant body of work, both experimental and theoretical (Stass *et al.* 2000; Weaver *et al.* 2000; Timmel *et al.* 2001; Woodward *et al.* 2001; Weaver 2002; Cintolesi *et al.* 2003; Henbest *et al.* 2004; Ritz *et al.* 2004, 2009; Timmel & Henbest 2004; Vink & Woodward 2004; O’Dea *et al.* 2005; Rodgers *et al.* 2005, 2007; Thalau *et al.* 2005; Vaughan & Weaver 2005; Shakirov *et al.* 2006; Wang *et al.* 2006; Wang & Ritz 2006; Solov’yov *et al.* 2007; Woodward & Vink 2007; Efimova & Hore 2008; Maeda *et al.* 2008; Miura & Murai 2008; Efimova & Hore 2009; Rodgers & Hore 2009; Solov’yov & Schulten 2009; Hill & Ritz 2010; Lau *et al.* 2010), has advanced our information and understanding of how a putative radical-pair magnetoreceptor should be designed so as to be well suited to detect the geomagnetic field. Behavioural studies have provided more information about the functional properties of magnetic compasses in a variety of animals (Rappl *et al.* 2000; Wiltschko *et al.* 2000*a,b*, 2001, 2002*b*, 2003*a*, 2004*a,b*, 2005, 2006, 2007*a,b,c,d*; Åkesson *et al.* 2001; Phillips *et al.* 2001, 2002; Muheim *et al.* 2002, 2006; Irwin & Lohmann 2003; Mouritsen *et al.* 2003, 2004*a*; Cochran *et al.* 2004; Prior *et al.* 2004; Vacha & Soukopova 2004; Freake & Phillips 2005; Gould 2005; Thalau *et al.* 2006; Pazur *et al.* 2007; Schlegel 2007; Voss *et al.* 2007; Wiltschko & Wiltschko 2007; Dommer *et al.* 2008; Feenders *et al.* 2008; Rogers *et al.* 2008; Stapput *et al.* 2008; Vacha *et al.* 2008*a,b*, 2009; Keary *et al.* 2009; Zapka *et al.* 2009; Hein *et al.* 2010; Wilzeck *et al.* 2010) and biophysical and physiological studies have provided more information about the cryptochrome suggestion (Giovani *et al.* 2003; Möller *et al.* 2004; Mouritsen *et al.* 2004*b*, 2005; Ahmad *et al.* 2007; Bouly *et al.* 2007; Heyers *et al.* 2007; Liedvogel *et al.* 2007*a,b*; Freire *et al.* 2008; Gegear *et al.* 2008; Hoang *et al.* 2008; Henbest *et al.* 2008; Biskup *et al.* 2009; Harris *et al.* 2009; Yoshii *et al.* 2009). The goal of this review is to present an updated picture of the radical-pair photoreceptor mechanism, in a manner accessible to an interdisciplinary group of scientists. In this, we adopt a forward-looking approach. We believe that more evidence from behavioural, genetic, molecular biological and neurophysiological studies is necessary before we can conclude what role photoreceptor-based magnetoreception plays in biology. Other, very up-to-date, reviews discuss directional behaviour of birds under different light conditions (Wiltschko *et al.* 2010), as well as the suggestion of cryptochrome as a photo-magnetoreceptor (Liedvogel & Mouritsen 2010). Our focus here is to discuss new constraints and emerging suggestions that can point towards more conclusive studies to be conducted in the future.

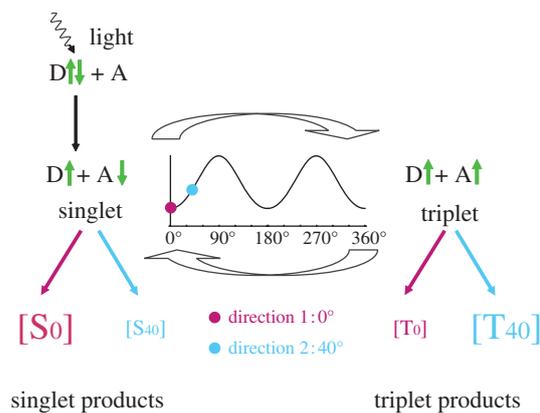


Figure 1. Illustration of the photoreceptor magnetoreception mechanism. Electron spins (green arrows) occur in different relative orientations, corresponding to singlet and triplet spin states. The geomagnetic field alters the dynamics of spin state conversion (black curved arrows), and, ultimately, the relative concentration of product states. The relative yields of singlet and triplet products depend on the orientation of the magnetic field with respect to the radicals, as indicated by the centre and the different sized circles. The size of magnetic field effects depends on details of the reaction, but is typically of the order of a few percent.

2. BIOPHYSICS OF THE PRIMARY MAGNETIC FIELD DETECTION STEP

In the photoreceptor mechanism, absorption of light triggers an electron transfer from a donor to an acceptor molecule (cf. figure 1), thus creating a donor–acceptor pair with one unpaired electron each, a so-called radical pair. This radical pair decays into reaction products on microsecond to millisecond time scales. The two electrons on the donor and acceptor radicals possess a quantum mechanical property, the electron spin that can be thought of as a small magnetic moment. The relative alignment of the two electron magnetic moments at any given time is denoted as the spin state of the radical pair and is a critical determinant for their chemical reactivity. Depending on the spin state, different reaction products will be formed, and at different rates (Schulten *et al.* 1978; Ritz *et al.* 2000; Rodgers & Hore 2009). In essence, the intermediate radical pair state acts like a switch that governs the balance between different product states. If, for example, the singlet products act as a signal for further downstream receptors, then increasing or decreasing the concentration of these products will change the signal. The small geomagnetic field is expected to change concentrations of the order of a few percent (Timmel *et al.* 1998; Rodgers & Hore 2009). Effects of Earth-strength magnetic fields on a radical-pair-based compass were recently demonstrated experimentally in a biradical system (Maeda *et al.* 2008).

Detection of the intensity of the geomagnetic field can occur in completely disordered radical-pair systems (Maeda *et al.* 2008). For detecting directions, however, the situation is different, as the alignment of the detecting molecule plays an essential role. For designing a compass out of radical pairs, one needs to consider

the magnetic environment of an electron spin due to the chemical structure of the radicals. Most known radicals contain hydrogen and nitrogen atoms that possess nuclear spins and thus create an internal magnetic field affecting the electron spin. Such internal magnetic fields, in particular those of nitrogens, are highly anisotropic, that is they are much stronger in one direction than in others. This internal magnetic field anisotropy can be exploited to design a compass: the external (or geomagnetic) field will either be aligned with the stronger or the weaker directions of the internal magnetic field, depending on its angle with the radical pair. Therefore, the effect of the geomagnetic field depends not only on its intensity, but also on its direction with respect to the radical pair, thereby potentially creating a magnetic compass (Schulten *et al.* 1978; Ritz *et al.* 2000; Timmel *et al.* 2001; Maeda *et al.* 2008). The physical chemistry of this mechanism is well understood (Brocklehurst 2002; Rodgers & Hore 2009) and the angular dependence is often close to a $\cos(2\theta)$ pattern, as shown in the centre of figure 1. That is, the effect of the geomagnetic field is identical if the field (or the radical pair) is flipped by 180° . One requirement for a radical-pair-based magnetic compass sensor is that the radical pairs are ordered in some way so as not to average out the directional effects. Radicals can readily be anchored within proteins: chlorophyll cofactors in light-harvesting complexes and flavin cofactors in cryptochromes are examples. Proteins, in turn, can be anchored in multiple ways, most easily if they are embedded in membranes, as is, for example, the case for various opsins in visual receptor cells. It remains to be seen whether magnetoreceptor proteins are ordered in a similar fashion. The required level of spatial ordering and possible biological realizations are addressed elsewhere in this supplement (Hill & Ritz 2010; Lau *et al.* 2010).

3. OPTIMAL RADICAL PAIR DESIGN

What are the features that distinguish a radical pair reaction that is sensitive to weak magnetic fields from one that is not? There are three determinants that have been investigated and analysed, but it cannot be ruled out that additional factors may be found in the future. The *kinetics* of the overall reaction scheme matters, as will be discussed further below. The molecular composition of the radical-pair molecule and its surrounding protein determines the strength of magnetic field effects by setting the *internal magnetic environment* for the spin motion and by determining *coherence time* of the radical pair reaction.

Considerable attention has been given to studying the role of the internal magnetic environment. In spin chemistry, many concepts assume that the external magnetic field is the strongest magnetic field present, but for typical radical pairs, the geomagnetic field is actually weaker than internal magnetic fields, precluding a simple application of these concepts to the magnetic sensing situation. Moreover, the exact nature of magnetic field effects depends sensitively on even minor changes of the parameters for the internal

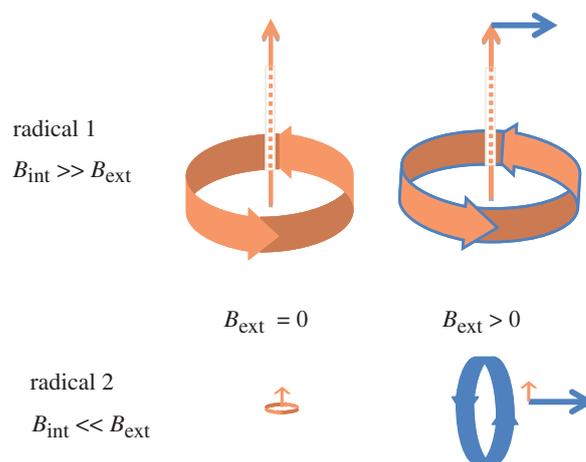


Figure 2. Optimal ‘reference–probe’ design for a radical-pair sensor. Straight arrows indicate strength and direction of internal (orange) and external (blue) magnetic fields in the ‘reference’ radical (top) and ‘probe’ radical (bottom), circular arrows illustrate the resulting electron spin motion around the combined magnetic field axis, with larger arrows suggesting faster motion. In the ‘reference’ radical (top), the spin will precess at a high rate even in the absence of an external magnetic field. Adding the external magnetic field will only slightly perturb the precession rate and direction, because the external field is much smaller than the internal magnetic field. If both radicals had strong internal magnetic fields, the external field would slightly perturb both electron spin motions, thus resulting in small effects of the external field on spin states. However, if a ‘probe’ radical (bottom) has very small or no internal magnetic fields, then the external magnetic field will completely determine precession rate and direction of its spin, resulting in strong sensitivity of the radical pair spin state, i.e. the relative spin orientation, to the external magnetic field.

magnetic field. Given these caveats, the safest approach is to model magnetic field effects on candidate radical pairs by determining all relevant chemical parameters, such as strengths of all internal magnetic fields and kinetics of electron transfer steps.

Nevertheless, for the purpose of this perspective article, we will present one suggestive design idea to illustrate how the internal magnetic environment can affect the strength of magnetic field effects, assuming a simplistic internal magnetic environment with only one anisotropic nucleus. The optimal design can in this case be conceptualized as a ‘reference–probe’ motif. Optimal sensitivity to the direction of an external magnetic field arises when one radical is devoid of internal magnetic fields, whereas the other radical should have very strong internal magnetic fields. To understand why this design is optimal, we consider how the external magnetic field changes the relative arrangement of electron spins, and hence, the spin state of a radical pair. Unlike a compass needle that aligns its direction with that of the local magnetic field and then stops moving, the electrons’ spins never come to rest, but move perpetually in a fashion comparable to that of a gyroscope or spinning top, spinning or ‘precessing’ around the axis of the local magnetic field. The local magnetic field at the position of the electron spins is composed of the external (geomagnetic) field and the, generally stronger, internal magnetic field created by magnetic moments of hydrogen

and nitrogen nuclei. Therefore, the effect of the external magnetic field on the spin motion depends greatly on the internal magnetic field. As illustrated in figure 2, a radical with a strong nucleus and therefore a strong internal magnetic field can be considered a ‘reference’ radical, because its spin motion is essentially unaffected by the external magnetic field, whereas a radical without internal magnetic fields can be considered a ‘probe’ radical, where the spin motion tracks the external magnetic field. In such a ‘reference–probe’ radical pair, the effects of the external fields maximize the difference in spin motion between the two radicals compared with other possible designs.

In some theoretical studies, this ‘reference–probe’ design was inadvertently chosen, because low numbers of hyperfine interactions reduce the computational demands, making one-proton, or one-hyperfine interaction models popular (Timmel & Hore 1996; Timmel *et al.* 1998, 2001; Wang *et al.* 2006). The importance of the radical-pair symmetry was realized in further studies and it was shown that weak magnetic field effects become most pronounced when the ratio of hyperfine coupling strengths between the two radicals is maximized (Rodgers *et al.* 2007). There is evidence supporting the ‘probe’ aspect of the ‘reference–probe’ design in several experiments. The experimental realization of a man-made radical-pair compass system sensitive to Earth-strength magnetic fields (Maeda *et al.* 2008) uses a fullerene, almost devoid of hyperfine couplings, as one of the radicals. Recently, several experimental studies applying oscillating magnetic fields in behavioural experiments (Wiltschko *et al.* 2007*d*; Keary *et al.* 2009; Ritz *et al.* 2009; Vacha *et al.* 2009) showed strong effects at frequencies indicative of a ‘free’ electron, i.e. an electron in an environment without internal magnetic fields, suggesting that nature may have indeed selected this optimal design aspect.

Several concerns have been raised with regard to the aforementioned oscillating magnetic fields experiments: (i) they do not use a double-blind protocol, (ii) oscillating magnetic fields might not affect the compass directly, but may provide a different, interrelated, biochemical response, and (iii) the strength of oscillating fields causing disruption is remarkably weak, leading one study to question even the possibility to explain these experiments with the radical-pair model (Kavokin 2009). In addressing these concerns, we wish to point out the similarity in the attempt to disrupt a photochemical-based compass with oscillating fields and the attempt to disrupt an iron-oxide-based compass with strong magnetic pulses. (i) We agree that double-blind experiments are very desirable, but it can be very challenging to perform double-blind behavioural experiments in practice, due to space limitations, manpower, etc. Therefore, virtually no magnetic orientation experiments with birds have been conducted double-blind, including the analogous pulse experiments (e.g. Wiltschko *et al.* 2002*a*). We do not see a reason to hold oscillating magnetic field experiments to a different standard as other, comparable, experiments. (ii) The interpretation of disruptive effects is often difficult and many controls are needed to identify which

system has been affected. So far, control experiments have suggested that not all magnetic orientation responses of birds, but only the regular compass, is affected by oscillating magnetic fields (e.g. Wiltschko *et al.* 2005, 2007*b*) and that the disruptive effect occurs only at certain frequencies and alignments, matching general expectations from a radical pair model (Ritz *et al.* 2000, 2009). At least for one other animal, mole rats, the compass is unaffected by oscillating fields (Thalau *et al.* 2006). Thus, the current control experiments address some of the most obvious alternative interpretations. (iii) How strong oscillating magnetic fields need to be to disrupt a radical-pair-based compass is very closely linked to the question of how robust the compass is to noise and changes in the external magnetic field. In other words, one needs to understand and quantitatively model the signal transduction mechanism that transforms a change of singlet or triplet yield to a nervous signal, before one can make a quantitative prediction about the *absolute* level of oscillating magnetic field effects required to disrupt a radical-pair-based compass. Currently, there is little foundation for the many assumptions required in attempts of such modelling. One expects less dependence on the details of the signal transduction mechanism in conclusions drawn from the *relative* level of oscillating magnetic field effects, on which the suggestion of a ‘free electron’ radical pair was based (Ritz *et al.* 2009).

Beyond the question of whether or not photochemical magnetoreceptors underly the compass of birds, the ability to control spin states is of great importance for scientists interested in controlling quantum processes and designing quantum computers. While the ferromagnetic and electric induction sensing are essentially classical processes, the radical-pair mechanism involves a coherent quantum process. As quantum control theorists gain a better understanding how to optimize controlled spin systems, this will increase our understanding of how nature can optimize magnetic sensing through electron spins. In general, spin-based quantum control processes operate best when the spin motion is protected as much as possible from randomizing effects of thermal and other fluctuations, i.e. when the spin coherence time is long, but other strategies may be conceivable (Cai *et al.* 2009; Rieper *et al.* 2009). In reverse, nature had hundreds of millions of years to optimize a possible spin-based magnetic sensor and may point the way for how we can engineer man-made quantum control systems based on biomimetic principles. In this regard, it is important to realize that a physiological spin-based compass needs to detect Earth-strength magnetic fields at physiological temperatures, whereas the best man-made system (Maeda *et al.* 2008) still fell slightly short of this goal by requiring operating temperatures of -20°C or lower.

4. IDENTIFYING CANDIDATE MOLECULES

How can the fairly abstract quantum mechanical constraints discussed above be actually realized in a

biological molecule and how can they be used to identify potential photo-magnetoreceptor molecules?

Firstly, the molecule in question needs to be a pigment–protein complex that performs photochemistry, i.e. that it can absorb light and change its oxidation state by generating radical pairs. This criterion greatly helps in the selection of candidate molecules as it excludes most non-light sensitive proteins, and retinal-based photoreceptor molecules, but would be fulfilled by flavin-based and chlorophyll-based pigment–protein complexes. Secondly, radical pairs should preferably be long lived, at a minimum for about a microsecond. This criterion can be determined through spectroscopic detection of radical pairs in candidate molecules (Liedvogel *et al.* 2007b; Biskup *et al.* 2009). Interestingly, a lifetime of the order of up to 10 μ s was also suggested by spectroscopic effects in behavioural experiments with birds (Ritz *et al.* 2009). Thirdly, the spin-dependent radical-pair reaction kinetics needs to be relevant for downstream reactions, e.g. by inducing biological activity or by being the slowest step in a kinetic reaction network, thereby determining the overall reaction kinetics. Otherwise, any magnetic field effects would only be observed on intermediates, but not in the biologically relevant outputs. Such appears to be the case in the primary photosynthetic reaction, involving a radical pair generated by light-induced electron transfer between two chlorophylls. Magnetic field effects can be observed when the photosynthetic reaction is arrested in the radical-pair state, but not in regular photosynthetic systems (Liu *et al.* 2005). Cryptochromes, on the other hand, are much better suited because their intermediate semiquinone state, generated via a light-induced radical pair mechanism, is a signalling state and induces biological activity (Bouly *et al.* 2007). Any increase or decrease in redox equilibrium between the fully oxidized, semiquinone, and fully reduced states, shown in figure 3, would thus directly affect the concentration of the signalling state and could thus easily be perceptible, e.g. as an alteration in photoreceptor response in the organism. While current experimental data are consistent with cryptochrome, direct evidence of an involvement of cryptochrome in magnetic orientation, especially in the much studied migratory birds, is still lacking.

The above discussed concept of a ‘probe’ radical pair adds a novel criterion to the search of the candidate photo-magnetoreceptor molecule. In addition to the pigment–protein complex forming radical pairs, one needs to find a reaction partner devoid of internal magnetic fields, i.e. without hydrogens or nitrogens. One potential class of molecules satisfying this criterion are superoxide or peroxide molecules as radical partners and it was suggested that a flavin-superoxide radical pair may be realized in the re-oxidation reaction of cryptochrome (Ritz *et al.* 2009). A role of superoxide or peroxide has been questioned, based on arguments comparing the behavioural action spectra in Ritz *et al.* (2009) to *in vitro* electron spin resonance spectra (Hogben *et al.* 2009). On purely theoretical grounds, it is unclear in how far the strong spin–orbit coupling in a superoxide radical would alter the physics of the

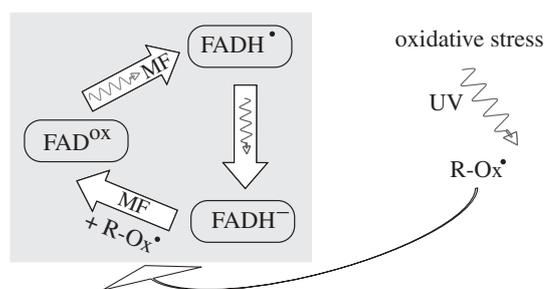


Figure 3. Cryptochrome photocycle and a possible role of oxidative stress in magnetic field effects. Light absorption reduces the photoactive pigment in cryptochromes from the fully oxidized FAD^{ox} to the semiquinone FADH^{\bullet} , and, in a second step to fully reduced FADH^{-} , from which the FAD^{ox} state is recovered through re-oxidation in the presence of suitable oxidizing agents. Magnetic fields (MF) may affect the speed of the photoactivation step from fully oxidized FAD^{ox} and of the re-oxidation step from FADH^{-} via a radical pair mechanism, thereby changing the concentration of the presumed FADH^{\bullet} signalling state. The concentrations of oxygen-based reactive radicals (R-Ox^{\bullet}) may also affect the re-oxidation step or, in reverse, may be affected by magnetic fields. Oxidative stress increases the production of oxygen-based reactive radicals and may thereby change the size of magnetic field effects.

mechanism by which radical pairs detect external magnetic fields.

However, it is noteworthy that many of the molecules devoid of hydrogens and nitrogens that are capable of forming radicals belong, like superoxide or peroxide, to a class of very reactive radicals. These molecules are in general damaging to the organism and are therefore highly regulated. Such reactive radicals are also produced as an effect of oxidative stress. The link between oxidative stress and processes underlying photochemical-based magnetoreception, highlighted in figure 3, has not yet been explored in any detail. It is possible that the magnetic reaction steps change the concentration of reactive radical molecules (Liu *et al.* 2005). Therefore, the reactive radicals, rather than the pigment-based radicals could provide the signal. Alternatively, the presence of reactive radicals may be necessary for magnetic field effects to develop (Solov'yov & Schulten 2009). While we emphasize that the exact nature of the potential reactive radical partner is highly speculative at this point, this speculation does lead to an important question: do oxidative stress levels and the accompanying production of reactive radicals provide a notable, and so far over-looked, factor in variation in magnetic field experiments (Ahmad *et al.* 2007; Harris *et al.* 2009)?

Whatever the molecule underlying light-dependent magnetoreception, an unanswered question is where, in evolutionary history, one finds the first light-dependent magnetoreceptor. Magnetic field effects linked to cryptochrome have been reported in growth responses of plants (Ahmad *et al.* 2007; but see Harris *et al.* 2009), circadian rhythms (Yoshii *et al.* 2009) and orientation of fruit flies (Gegear *et al.* 2008). Two of these studies (Ahmad *et al.* 2007; Gegear *et al.* 2008) suggest absence of magnetic field effects when

cryptochromes are deleted, but in all of these studies the question remains whether the effects are serendipitous, i.e. observations of the potential, latent ability of cryptochromes to be affected by weak magnetic fields, or whether magnetic field effects confer an evolutionary advantage. It has been suggested that the light-dependent magnetoreception is an evolutionary late development (Gould 2008). However, one can also note that flavin-based enzymes are among the most ancient enzymes, being found in about 25 per cent of archae and that the early Earth prior to the creation of the protective ozone layer provided an environment both rich in oxidative stress and blue light, thereby providing a setting suitable for the development of strong magnetic field effects. Local variations of magnetic environments, e.g. close to iron deposits, may have provided differential magnetic field effects, possibly enhancing the ability of organisms to cope with oxidative stress, and thereby conferring an evolutionary advantage at very early stages of evolution. Genetic studies selecting for magnetosensitive phenotypes will be necessary to identify whether photoreceptor-based magnetoreception did indeed confer an evolutionary advantage and if so, at what point during evolution.

5. OPTIMAL STIMULI FOR NEUROPHYSIOLOGY

The question as to how photoreceptor-based magnetic stimuli might be processed neurally is perhaps the least developed aspect of the theory. Nevertheless, there are some immediate consequences that would arise from the postulated mixing of light and magnetic effects at a very fundamental level. In the following, we will outline one possible scenario that assumes that the magnetoreceptor and photoreceptor molecules are closely associated in the same receptor cell and discuss what neural processes would be necessary to separate light and magnetic effects.

Light activates the photo-magnetoreceptor cell. Thus, a magnetic field alone is not expected to affect a photoreceptor-based magnetic sensory system. However, beyond a simple switching 'on', light stimuli would affect the same receptor read-out as magnetic stimuli. In other words, a change in magnetic field may appear to the receptor in the same way as a change in light intensity and it would therefore be impossible for such a single receptor cell to determine whether the light intensity or the magnetic field has changed. This would be analogous to the situation in colour vision, where a single colour receptor cannot determine whether increased activation is due to a general increase of light intensity or a specific increase of intensity in coloured light. The solution is to compare the input of two receptors that differ in their response to the signal (colour, magnetic field). For the magnetic sensor, this can be easily achieved by arranging two (or more) populations of receptor molecules at different angles.

The simplest solution, from the point of view of neuronal processing, involves two populations of receptor molecules in close proximity to each other and arranged

at different, ideally perpendicular, angles. This differential arrangement could be achieved either within one cell or in neighbouring cells of different types. Because of their close proximity, the light input will be approximately the same, but the magnetic field effects will be different. Comparison between the outputs of these two receptor populations could be achieved in early stages of neuronal processing and could then be processed in a specialized neuronal information channel putatively dedicated to magnetic sensing and separate from visual processing.

Given that such a dedicated magnetic processing channel has not yet been identified, it is worth considering a more complicated possible neural processing solution. If the populations of receptor molecules oriented at different angles are not in close proximity, but spread over a wider distance, a further complication will arise. One can now no longer assume that the light inputs are identical, because in any realistic situation where an animal would use a compass, the optical input will show spatial variations. The neural processing task in this case would be to determine whether the light modulation pattern observed is due to variation in light input, i.e. a true optical pattern, or due to the magnetic modulation. There are two strategies that appear particularly promising. The effect of the magnetic field is smooth, gradually changing from one angle to another (see figure 1), whereas optical patterns generally have sharper transitions, such as edges or lines. Low-pass filtering would help to separate magnetic from optical effects. If this strategy is employed, it follows that animals might have problems to obtain accurate magnetic information in settings with smooth optical inputs, i.e. scenes being devoid of sharp patterns.

A second strategy is to set up a difference between optical and magnetic flow during turns of either the head or the whole animal. If we assume that the receptor cells are perpendicular to a sphere, as is approximately the case for vertebrate rod and cone cells, then a very natural difference between optical and magnetic flow arises, as illustrated in figure 4. Depending on the alignment of the receptor cells with the magnetic field, the signals of the cells will be modulated according to the angular dependence shown in figure 1, with the maximal signal occurring for a receptor cell parallel to the geomagnetic field direction (upward arrows). This receptor cell is marked by an 'x' in figure 4. In figure 4*a*, the brightest spot of the magnetic modulation pattern lies in the line of sight, because the receptor cell in the line of sight is parallel to the magnetic field. After the eye is rotated by a visual flow angle α , the receptor cell parallel to the geomagnetic field (x) is no longer in the line of sight. Projecting the magnetic modulation pattern into the real world shows that this receptor cell is projected to a point halfway between the original viewing direction and the new line of sight. Thus the brightest spot of the magnetic modulation pattern flows with half the speed of the optical flow. If this strategy is employed, care must be taken in neurophysiological experiments not to undercut the mechanism by which the separation of flow speeds is achieved. For example, it is possible

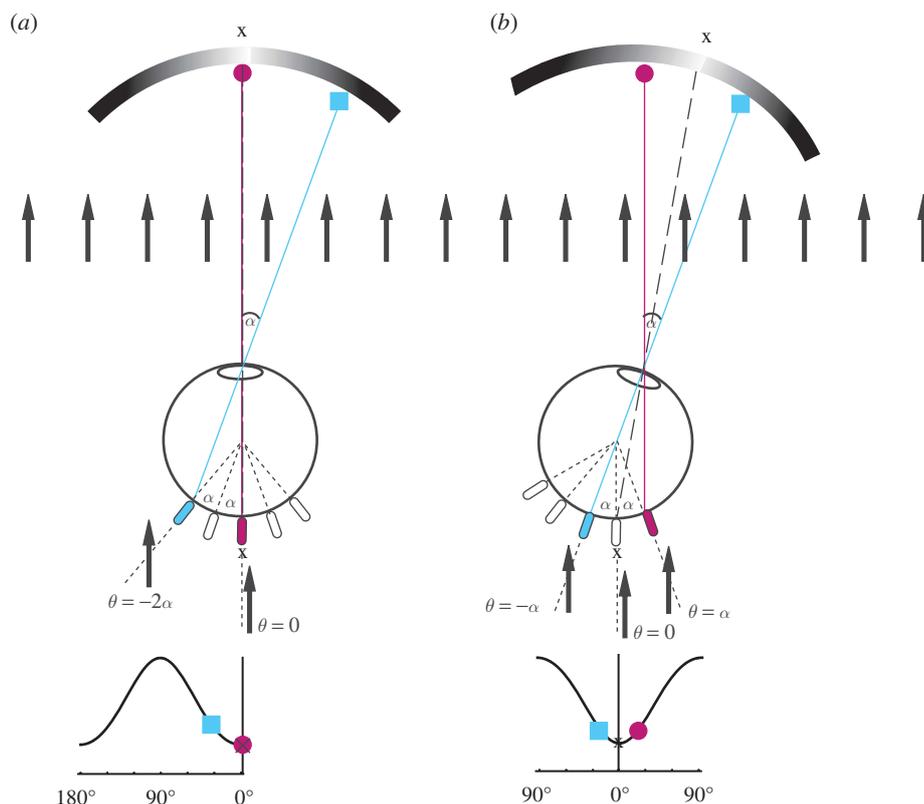


Figure 4. Head (eye) rotations and magnetic modulation. Illustrated is a top view of an eye and two objects (red circle and blue square) in the same plane. The magnetic field is pointing upwards in the figure, as indicated by the arrows. The two objects, separated by the visual field angle, are projected onto two points of the retina. The photo-magnetoreceptor cells at these two positions are aligned with the magnetic field at angles θ that are determined by the eye bearing and by their geometric arrangement with respect to the retina. Here, we assume that photo-magnetoreceptor cells are oriented perpendicular to the retina; but other arrangements could be realized in nature. (a) The line of sight is in the direction of the red circle. Thus, the red circle is projected onto a cell with $\theta = 0^\circ$, and the blue square is projected onto a cell with $\theta = -2\alpha$. This doubling arises from the fact that the visual angle is measured from the lens, but the cell direction is measured from the centre of the eye. The signal of the photo-magnetoreceptor cells is modulated according to the $\cos(2\theta)$ modulation curve from figure 1, as indicated below the eye. In this orientation of the eye, the centre of the magnetic modulation pattern (marked by an 'x') will be projected into the real world as though it is placed in the line of sight of the eye, as indicated by the dashed line and the 'x' above the magnetic modulation pattern (simulated on the grey scale arc part). (b) The eye is rotated by the angle α , i.e. the line of sight is now in the direction of the blue square. Now, the projection of the red circle is onto a cell with $\theta = \alpha$ and the projection of the blue square is onto a cell with $\theta = -\alpha$. The centre of the magnetic modulation pattern would now be projected into the real world at a point between the red circle and the blue square, as marked by the dashed line and by the 'x' above the magnetic modulation pattern. In other words, the centre of the magnetic modulation pattern is neither in the line of sight nor in magnetic north, but trailing the rotation angle by a factor of 2. Consequently, the visual flow speed will be twice as fast as the magnetic pattern flow speed.

that co-processing of head movements and sensory inputs is used to identify the expected visual flow speed, which would make experiments problematic in which the animal's head is fixed. It is interesting to note that 'head scanning' behaviour, i.e. repeated head rotations over more than $\pm 60^\circ$, has been observed in some magnetic orientation experiments. Garden warblers corrected their magnetic orientation towards their mean migratory direction immediately after they performed a head scan (Mouritsen *et al.* 2004a). A seemingly equivalent behaviour has also been observed in sandhoppers (Ugolini 2006). Similarly, experiments, in which the magnetic field is rotated, but the visual input remains fixed, may preclude processing of magnetic information.

Where should one look for areas processing photoreceptor-based magnetic information in the brain? An obvious location for photo-magnetoreceptors would be in the eye (Wiltschko *et al.* 1993). Magnetic orientation

experiments with birds having one eye covered suggested that magnetic information may be transmitted from the right eye only in two passerines and domestic chickens (Wiltschko *et al.* 2002b, 2003b; Rogers *et al.* 2008). In pigeons, however, the lateralization is much less pronounced (Wilzeck *et al.* 2010). A behavioural study with another passerine species showed no lateralization of the magnetic compass, but still argues for a role of the eyes in transmitting magnetic information (Hein *et al.* 2010).

Assuming one or both eyes as loci for photo-magnetoreceptors, magnetic information should be transmitted through the optic nerve and processed in centres connected to the eye (Mouritsen *et al.* 2005; Heyers *et al.* 2007; Liedvogel *et al.* 2007a; Feenders *et al.* 2008). Behavioural experiments have shown that a brain area called cluster N is most active in both brain hemispheres during magnetic compass orientation in night-active migratory songbirds,

whereas it is much less active during the day (Mouritsen *et al.* 2005; Feenders *et al.* 2008). It was therefore suggested (Mouritsen *et al.* 2005; Heyers *et al.* 2007; Liedvogel *et al.* 2007a) and recently demonstrated (Zapka *et al.* 2009) that cluster N is involved in processing light-dependent magnetic compass information in night-migratory European robins. European robins with bilateral cluster N lesions can perform Sun compass orientation and star compass orientation, but they cannot perform magnetic compass orientation (Zapka *et al.* 2009). It is unclear whether this area is involved in processing compass information in birds like zebra finches, honeyeaters, pigeons and chickens, whose compass seems to show the same functional properties as the compass of night migrants, but operates during day time (Wiltschko *et al.* 2007c). This is theoretically possible because there is some activity in cluster N during the day in zebra finches, the only one of these diurnal species in which cluster N activity has been studied (Mouritsen *et al.* 2005).

When we search for brain areas processing photoreceptor-based magnetic information in the brain, several caveats are notable. Birds may co-process normal visual information with magnetic information to decide whether it is possible to interpret magnetic information reliably and otherwise disregard it (Wiltschko *et al.* 2007a). This could occur in the eye or in higher brain areas as part of the light-dependent processing of magnetic compass information. Furthermore, the theory of photoreceptor-mediated magnetic sensing suggests that magnetic information may be initially encoded as increases and decreases in responses of photoreceptors to light stimuli. Therefore, one does not necessarily expect a general increase in activation levels in response to magnetic stimuli alone in brain areas that process light-dependent magnetic information (Heyers *et al.* 2007; Liedvogel *et al.* 2007a). Searches for such areas with activation markers (Nemec *et al.* 2001, 2005; Mouritsen *et al.* 2005; Liedvogel *et al.* 2007a) are therefore not necessarily expected to produce magnetic field dependent results. Only if and when magnetic stimuli have been separated from optical stimuli can one potentially expect to find brain areas that are activated through magnetic stimuli only. The detection of such areas and neurons responding directly to magnetic stimuli is another remaining challenge of the photoreceptor hypothesis.

6. SUMMARY

Given the relatively short time from the introduction of the radical-pair mechanism to a wider biological audience (Ritz *et al.* 2000), the amount of studies from different fields supporting the photo-magnetoreceptor and cryptochrome hypotheses is promising. However, as described here, fundamental questions remain in all relevant fields. Biophysically, we yet have to understand how nature designed radical-pair receptors so that they can be sensitive to Earth-strength magnetic fields at physiological temperatures, a feat that has been approximated, but not yet fully accomplished in man-made radical pair reactions.

Studies at the protein level suggest that cryptochromes have properties optimal for magnetic sensing, such as formation of long-lived radical pairs. But, we yet have to demonstrate Earth-strength magnetic field effects on cryptochromes or any other concrete candidate photo-magnetoreceptors, both at the protein level, and *in vivo*. Genetic studies suggest absence of magnetic field effects in some organisms when cryptochromes are deleted, but, for magnetoreception, we yet have to find a true model organism for genetic studies. In such a model, one should then show that introducing cryptochromes or regulating the expression levels can create magnetic sensitivity, ideally with a hint of the evolutionary advantage of such sensitivity. Magnetically responsive brain areas and neurons have yet to be identified.

Many of these challenges, especially the absence of genetic models, are not unique to the photoreceptor hypothesis, but remain a problem for the field of magnetoreception in general. By focusing on the photoreceptor hypothesis here, we do not mean to imply in any way that it is the only way to detect magnetic fields. The evidence for magnetite-based magnetoreception is growing concurrently, as reviewed elsewhere in this supplement. In birds, there is evidence that the two mechanisms may exist side by side, probably mediating different types of magnetic information (Wiltschko *et al.* 1994; Mouritsen & Ritz 2005; Wiltschko & Wiltschko 2007). It is our hope that the presentation in this article will facilitate the entry of researchers to the field of magnetoreception and thus pave the way towards conclusive elucidation of the molecules, cells, and neural processes underlying photoreceptor-based magnetoreception.

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