Expert insight into current research

News & views

Sensory biology

Unravelling the enigma of bird magnetoreception

Eric J. Warrant

How animals sense Earth's magnetic field is an enduring mystery. The protein cryptochrome *Er*CRY4, found in the eyes of migratory European robins, has the right physical properties to be the elusive magnetosensor. **See p.535**

Arguably the greatest mystery in sensory biology is magnetoreception – how animals sense Earth's magnetic field and use it as a compass to determine their spatial orientation. Animals as varied as birds, sea turtles, fishes, crustaceans and insects depend on this field for both short- and long-range navigation[1]. The identity of the biological tissue responsible for sensing the field's direction, and the sensory mechanism that underpins this type of navigation, have remained an enigma. In migratory birds, the main contenders are magnetically sensitive proteins called cryptochromes, which are located in the retina[2]. However, proof has been lacking that these proteins truly possess the magnetic sensitivity and physical properties needed to detect Earth's extremely weak magnetic field. On page 535, Xu *et al.*[3] provide this proof *in vitro*, bringing us tantalizingly close to solving the mystery of magnetoreception.

There are currently two main hypotheses for how animals sense Earth's magnetic field[1,4] (as well as some alternative hypotheses put forward in the past few years[5,6]). One proposes that, as an animal changes direction, crystals of the oxidized-iron compound magnetite (Fe_3O_4), located in its body and aligned with the field, exert a rotational force – called torque – on mechanoreceptors with which they are in physical contact. This might thereby signal changes in body alignment through the opening and closing of mechanoreceptor ion channels.

The other main hypothesis (Fig. 1) proposes that, when cryptochrome proteins absorb photons of light and become 'photoexcited', they form magnetically sensitive chemical intermediates known as radical pairs. Variations in the yield of their reaction product (the form of the cryptochrome that contains a radical molecule called FADH$^\bullet$) are thought to signal the animal's direction with respect to Earth's magnetic field[7,8]. These two proposed mechanisms are not mutually exclusive[6] – indeed, migratory birds might possess both, using magnetite for their 'magnetic-map' sense (the ability to sense magnetic characteristics associated with a given location on Earth's surface) and cryptochromes for their magnetic-compass sense (which offers the animal a way to sense its direction relative to magnetic north)[1,2].

Cryptochromes are found both in animals and in plants, and are a type of protein known as a flavoprotein. Cryptochromes bind non-covalently to a molecule called a chromophore, such as FAD, which absorbs photons of blue light when in its fully oxidized state. In animals, cryptochrome proteins termed CRY1 and CRY2 are involved in the regulation of daily (circadian) rhythms[9], and their expression levels in tissue typically cycle over the course of 24 hours. By contrast,

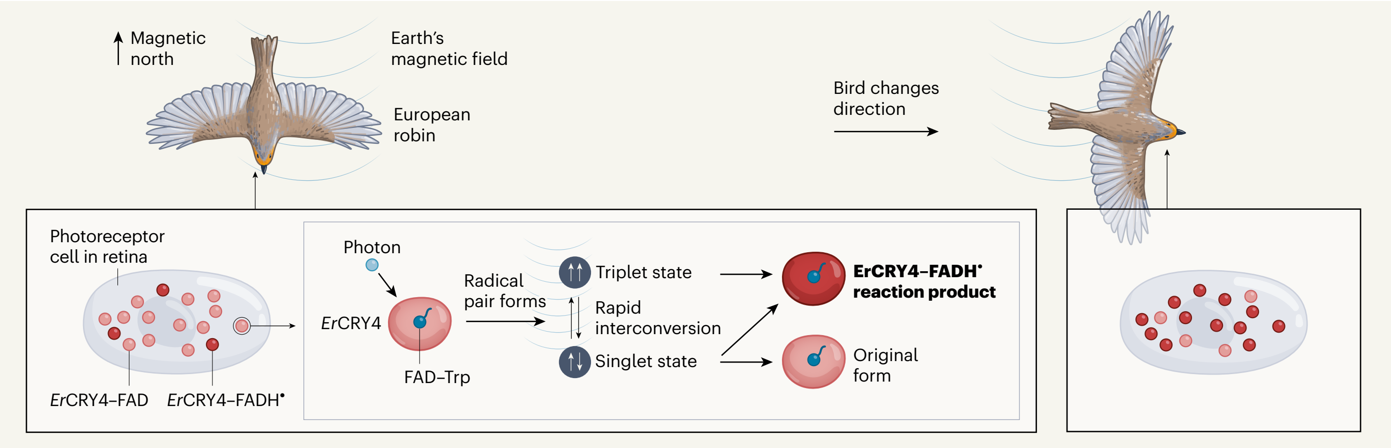

Figure 1 | A model for bird magnetoreception. Birds use Earth's magnetic field to aid their migration[1]. Photoreceptor cells in the retina of the migratory European robin *Erithacus rubecula* contain a protein called *Er*CRY4, which binds to the molecule FAD. The resulting complex is *Er*CRY4–FAD (when FAD is in its ground state) or *Er*CRY4–FADH$^\bullet$ when FAD is in its 'photoexcited' form (a radical, FADH$^\bullet$). When *Er*CRY4–FAD absorbs a photon of blue light, reactive molecules called radical pairs arise. These form through interactions between FAD and a tryptophan (Trp) amino-acid residue of *Er*CRY4, which supplies an electron. The radical pair is sensitive to Earth's magnetic field and oscillates rapidly between a singlet and a triplet state (which have different electron 'spin' states as indicated by the white arrows). The radical pair can generate *Er*CRY4–FADH$^\bullet$ (which is a long-lived reaction product hypothesized to trigger a sensory signalling cascade). Alternatively, *Er*CRY4 might return to its original form (*Er*CRY4–FAD). Which outcome occurs is influenced by the state of the radical pair. If the bird changes direction, the change in the relative orientation of the magnetic field drives a shift in the proportions of the singlet and triplet states, potentially altering the yield of *Er*CRY4–FADH$^\bullet$. Xu *et al.*[3] present data indicating that *Er*CRY4 fulfils the physical requirements needed for this magnetosensing mechanism.

the cryptochrome CRY4 lacks such signs of circadian cycling, suggesting that it has a different biological role, possibly that of magnetoreception[10,11]. CRY4 is found only in birds, fishes and amphibians, which are types of animal with well-documented magnetically guided behaviours. CRY4 has therefore emerged as the leading candidate for enabling cryptochrome-based magnetoreception in vertebrates.

Previous analysis[10] of chickens (*Gallus gallus*) and migratory European robins (*Erithacus rubecula*) indicates that CRY4 is located in the outer segments of two types of photoreceptor cell in the retina – double cones and long-wavelength single cones. This is an ideal location for receiving the light that would excite cryptochromes and thus aid magnetic sensing. Further evidence consistent with a possible role for CRY4 in magnetoreception is that its expression level in the robin retina rises as the migratory season approaches, whereas its level remains permanently low in non-migratory chickens[10].

Xu and colleagues' major advance is the demonstration that the version of CRY4 (dubbed *Er*CRY4) in the migratory European robin has a crucial property needed to sense Earth's magnetic field: the ability to form radical pairs that have high magnetic sensitivity. Radical pairs arise when the FAD bound to *Er*CRY4 is reduced (gains an electron) in the presence of light. Radicals contain an odd number of electrons, and a radical pair consists of two radicals that have been created simultaneously, usually by a chemical reaction. In *Er*CRY4, the radicals' odd electrons are supplied through sequential electron-hopping along a chain of three or four tryptophan amino-acid residues (termed Trp$_{A}$ to Trp$_{D}$) that are located between FAD and the surface of the cryptochrome.

In the case of FAD, the odd electron that arises from reduction in the presence of light makes the radicals intrinsically magnetic. This is because electrons behave as microscopic magnets, with a property that physicists call spin (typically symbolized by an arrow ↑). In a molecule with an even number of electrons, the spins of each electron pair exactly cancel each other out, rendering the molecule non-magnetic.

If the spins of the odd electrons in each of the two radicals in a radical pair are antiparallel (↓↑), the radical pair is said to occupy a singlet state, but when they are parallel (↑↑), the pair occupies a triplet state. When cryptochrome becomes photoexcited, it always forms a radical pair in the singlet state, but it doesn't stay that way for long. Owing to a quirk of quantum mechanics, the radical pair rapidly converts to the triplet state, and then continues to bounce between these two states millions of times per second. Each of these two states can produce a reaction product – the form of CRY4 that contains the radical FADH$^{\bullet}$, which is the proposed signalling molecule for magnetoreception (Fig. 1). But the singlet state can also revert to its oxidized, non-excited ground state, thereby reducing its relative contribution to the generation of reaction products. Thus, if the interconversion of the singlet and triplet states can be manipulated to change the relative amounts of time spent in each of the two states, so too can the yield of the reaction products be manipulated, because a greater fraction of time in the triplet state leads to a higher yield of reaction products.

Herein lies the heart of the proposed cryptochrome-based magnetosensor: the relative amounts of time spent in the singlet and triplet states and the yield of reaction products are directly manipulated by the direction of Earth's magnetic field. The interaction between a single *Er*CRY4 molecule and the field is, on its own, at least one million times too weak to create the radicals and influence their stability[2], but the energy required is provided by the photon absorbed by FAD. However, for this to work at all, the radical pair must be sufficiently magnetically sensitive, and the reaction product must exist for long enough and have a sufficiently high yield to realistically act as a sensory signalling substance. In a tour de force of biophysical chemistry, Xu and colleagues used a wide range of techniques, such as spectroscopic methods and molecular-dynamics simulations, to show that all of these conditions are satisfied by *Er*CRY4, at least *in vitro*.

Not only does *Er*CRY4 have a much higher magnetic sensitivity than do CRY4 proteins in non-migratory pigeons and chickens, but site-specific mutations of amino-acid residues in *Er*CRY4 also reveal that its Trp$_{D}$ is probably responsible for generating high and long-lasting (of greater-than-millisecond duration) yields of reaction products that would be needed for magnetosensory signalling. Although the evidence provided by Xu and colleagues is not definitive proof that *Er*CRY4 is the elusive magnetoreceptor *in vivo*, the authors have brought us ever closer to solving this abiding mystery of sensory biology.

Eric J. Warrant is in the Lund Vision Group and in the Department of Biology, University of Lund, S-22362 Lund, Sweden.
e-mail: eric.warrant@biol.lu.se

1. Mouritsen, H. *Nature* **558**, 50–59 (2018).
2. Hore, P. J. & Mouritsen, H. *Annu. Rev. Biophys.* **45**, 299–344 (2016).
3. Xu, J. *et al. Nature* **594**, 535–540 (2021).
4. Lohmann, K. J. *Nature* **464**, 1140–1142 (2010).
5. Qin, S. *et al. Nature Mater.* **15**, 217–226 (2016).
6. Nimpf, S. *et al. Curr. Biol.* **29**, 4052–4059 (2019).
7. Schulten, K., Swenberg, C. E. & Weller, A. *Z. Phys. Chem.* **111**, 1–5 (1978).
8. Ritz, T., Adem, S. & Schulten, K. *Biophys. J.* **78**, 707–718 (2000).
9. Griffin, E. A., Staknis, D. & Weitz, C. J. *Science* **286**, 768–771 (1999).
10. Günther, A. *et al. Curr. Biol.* **28**, 211–223 (2018).
11. Pinzon-Rodriguez, A., Bensch, S. & Muheim, R. *J. R. Soc. Interface* **15**, 20180058 (2018).

The author declares no competing interests.

Condensed-matter physics

Plasmons dragged by drifting electrons

Hugen Yan

Plasmons are combinations of light and collective electron oscillations. The demonstration that plasmons can be dragged by drifting electrons in the 2D material graphene could lead to advances in optical physics. **See p.513 & p.517**

A wave passing through a moving medium can be dragged by that medium. Depending on the relative velocity directions of the wave and medium, this effect can either increase or decrease the wave's speed. For a light wave, which typically travels at an enormous speed, the drag effect of a moving medium is negligibly small. Only sensitive optical-interference techniques can detect such a speed change – as shown by a celebrated experiment performed by the French physicist Hippolyte Fizeau in 1851, in which light passes through moving water[1]. On pages 513 and 517, respectively, Dong *et al.*[2] and Zhao *et al.*[3] demonstrate an analogous effect in which plasmons (combinations of light and collective electron oscillations) are dragged by drifting electrons in solids. The groups show that this effect is much more pronounced than that for light travelling through a moving medium.

Waves are said to be transverse if they oscillate perpendicularly to their direction of propagation, and longitudinal if they oscillate parallel to that direction. Light is a transverse