



Insect magnetoreception: a Cry for mechanistic insights

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Received: 1 February 2023 / Revised: 24 April 2023 / Accepted: 4 May 2023 / Published online: 15 May 2023
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Abstract

Migratory animals can detect and use the Earth's magnetic field for orientation and navigation, sometimes over distances spanning thousands of kilometers. How they do so remains, however, one of the greatest mysteries in all sensory biology. Here, the author reviews the progress made to understand the molecular bases of the animal magnetic sense focusing on insect species, the only species in which genetic studies have so far been possible. The central hypothesis in the field posits that magnetically sensitive radical pairs formed by photoexcitation of cryptochrome proteins are key to animal magnetoreception. The author provides an overview of our current state of knowledge for the involvement of insect light-sensitive type I and light-insensitive type II cryptochromes in this enigmatic sense, and highlights some of the unanswered questions to gain a comprehensive understanding of magnetoreception at the organismal level.

Keywords Magnetoreception · Insect · Cryptochrome · Radical pair mechanism · Migration

Introduction

Magnetoreception, the ability of an organism to sense and use the Earth's magnetic field to accomplish a variety of navigational tasks to locate shelter, food sources or breeding grounds, is widespread in nature (Mouritsen 2018; Putman 2022). We do know that insects, birds, sea turtles, fishes, and amphibians rely on magnetic compass information to point them in the right direction (Wiltschko and Wiltschko 1972, 2005; Lohmann and Lohmann 1993; Bottesch et al. 2016; Phillips and Borland 1994; Guerra et al. 2014; Dreyer et al. 2018). Despite its fundamental role for both short- and long-range navigation, what we do not know is exactly how magnetoreception works, making the magnetic sense the least understood senses in all biology (Nordmann et al. 2017). In this short review, the author aims to integrate recent research outcomes and progress made to understand this enigmatic sense at a mechanistic level from molecules to behavior, with a focus on insects.

With a rich repertoire of navigational behaviors, insects have emerged as promising experimental models to study magnetoreception. Some of the most remarkable examples of animals using the geomagnetic field for navigation are long-distance migratory species. Similar to birds and sea turtles which utilize the geomagnetic field as a compass cue for orientation (Wiltschko and Wiltschko 2005; Lohmann et al. 2004), migratory insects like the diurnal American monarch butterfly (*Danaus plexippus*) and the nocturnal Australian bogong moth (*Agrotis infusa*) appear to rely, at least in part, on magnetic cues for orientation during their migratory journeys (Dreyer et al. 2018; Guerra et al. 2014). Other species of navigators such as desert ants can also use the geomagnetic field for shorter range navigational tasks. *Cataglyphis* desert ants use the geomagnetic field for path integration, a navigation strategy that integrates information of the direction and distance traveled relative to its starting point, allowing them to align their gaze directions toward the nest entrance during their initial learning walks (Fleischmann et al. 2018, 2020). Many more species, including bees, cockroaches, firebugs, and fruit flies, have been shown to be magnetosensitive (Vale and Acosta-Avalos 2021; Netusil et al. 2021; Gould et al. 1978; Bazalova et al. 2016; Fedele et al. 2014b; Gegeer et al. 2008; Oh et al. 2020), although the ecological significance of a magnetic sense in these species remains often unclear.

Handling Editor: Eric J. Warrant.

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Because of its ability to respond to magnetic fields and its genetic tractability, the fruit fly *Drosophila melanogaster* has been used as a genetic model to provide the first in vivo molecular insights into magnetoreception. The lack of clear ecological significance for a magnetic sense in this species has, however, led to questioning whether findings in *D. melanogaster* could apply broadly in other species, including migratory birds and insects. The advent of the CRISPR–Cas9 genome editing system has started and will continue to unlock the potential for similar genetic approaches in other non-conventional model insects, including migratory ones (Wan et al. 2021). Comparative approaches should ultimately help unravel the molecular and cellular bases of the magnetic sense and their evolution across the animal kingdom.

The Earth's magnetic field and its detection

Before diving into recent molecular advances in the field, what are the magnetic field cues animals can sense and how these signals could in theory be transduced for navigation behavior? The geomagnetic field, distributed throughout the surface of the globe, can be roughly represented by a field generated by a magnetic dipole that is tilted at an angle of about 11° with respect to the Earth's rotational axis. It originates from the Southern hemisphere, re-enters the Earth in the Northern hemisphere, and varies in three parameters defined in biological terms as intensity, inclination, and declination (Fig. 1). The geomagnetic field intensity varies from $25 \mu\text{T}$ at the magnetic equator to $65 \mu\text{T}$ at each magnetic pole (Fig. 1A). The inclination of the field, which is the angle difference between the magnetic lines and the Earth's surface, is 0° at the magnetic equator when the lines are parallel to the Earth's surface and gradually changes to reach $+90^\circ$ or -90° at the magnetic Northern and Southern poles, respectively (Fig. 1A, B). Finally, the difference between true geographic north and magnetic north, called magnetic declination, varies with geographic location on the Earth's surface. As magnetic North travels, the declination angle changes by units of degrees slowly over decades. Thus, in theory, intensity, inclination, and declination of the Earth's magnetic field provide a reference system for animals to navigate. By providing information on latitudinal position, the inclination of the geomagnetic field can be used as a navigation system for determining the direction of travel relative to the goal. When combined with the field intensity, inclination can also provide unique magnetic characteristics associated with a given location on Earth's surface, helping animals to determine their location (*i.e.*, map position) relative to their destination (Lohmann et al. 2004). Because of its singularity at any location and its usefulness as a cue to discriminate East–West, declination could also contribute

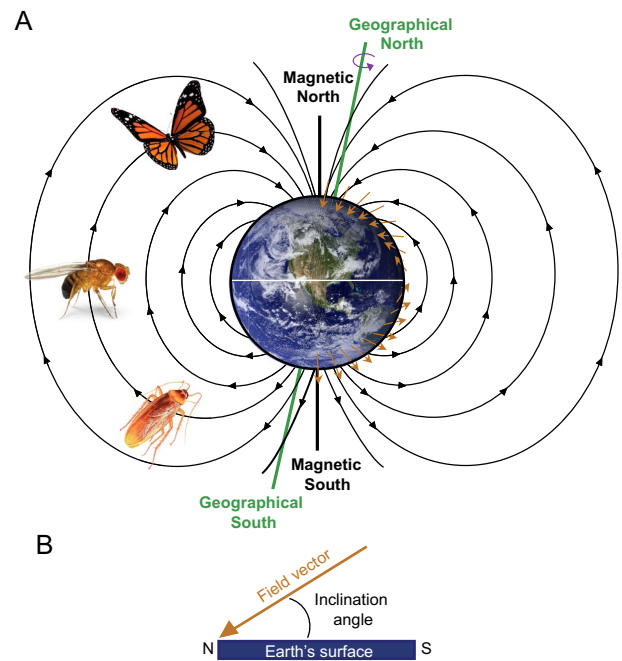


Fig. 1 Characteristics of the Earth's magnetic field. **A** The Earth has two sets of poles, geographic and geomagnetic poles. The geomagnetic field is generated by electric currents in Earth's outer core, and flow out of Earth through the magnetic South pole, extends tens of thousands of kilometers into space before re-entering in the magnetic North pole. The intensity of the field varies at its surface, ranging from $25 \mu\text{T}$ at the magnetic equator (white line) to $65 \mu\text{T}$ at each magnetic pole. The angle of the field between a magnetic pole and a geographic pole corresponds to its declination, and the angle between the field vectors and the Earth's surface is called the inclination (orange arrows). Examples of insect species used as models to study the role of cryptochromes in magnetosensing are shown on the left. **B** Detailed representation of the inclination of Earth's magnetic field, which varies from 0° at the magnetic equator to 90° at each magnetic pole (orange arrows in A)

to an animal's map sense (Akesson et al. 2005; Chernetsov et al. 2017). Unlike birds, sea turtles, fishes, amphibians, and crustaceans in which the use of both a magnetic compass and a magnetic map has been established (for review, (Mouritsen 2018)), long-distance migratory insects have so far only been shown to use magnetic compass cues (Dreyer et al. 2018; Guerra et al. 2014).

How land animals sense the Earth's magnetic field parameters remains far from being fully understood, but three main models have been proposed: (i) an electromagnetic induction-based model in which movement of an animal through the Earth's magnetic field would induce a current in the inner ear (Jungerman and Rosenblum 1980; Nimpf et al. 2019); (ii) a magnetic particle-based model whereby intracellular chains of magnetite (Fe_3O_4) crystals would detect field intensity and function as compass needles (Uebe and Schuler 2016; Bazylinski and Frankel 2004); and (iii) a radical-pair-based model relying on the spin chemistry of

radical-pair reactions initiated by light in specialized photoreceptors (Hore and Mouritsen 2016; Ritz et al. 2000; Schulten et al. 1978).

Despite being found in many organisms, including bees and ants (de Oliveira et al. 2010; Schiff 1991), magnetite has yet to be demonstrated as a magnetosensory molecule capable of regulating behavior. Similarly, evidence for electromagnetic induction is lacking in insects. More attention has been paid to the radical-pair hypothesis. The theoretical framework underlying the radical-pair mechanism posits that a light-induced electron transfer reaction generates a radical pair that can exist in singlet (antiparallel) or triplet (parallel) spin states. The Earth's magnetic field affects the singlet–triplet interconversion in an orientation-dependent manner relative to the sensor molecule, leading to a change in the singlet–triplet yield. This in turn triggers a signaling cascade in the relevant cells, leading to a physiological and behavioral response (Hore and Mouritsen 2016; Rodgers and Hore 2009). Magnetic field effects on radical-pair reactions have been established by numerous *in vitro* studies (reviewed in Hore and Mouritsen 2016), albeit with field of several orders of magnitude stronger than the one on Earth's. The proof that the photochemistry of a radical-pair mechanism is sensitive to Earth-strength magnetic fields and can function as an inclination compass has, however, been provided using a synthetic carotenoid–porphyrin–fullerene model compound (Maeda et al. 2008; Kerpál et al. 2019), further supporting the idea that a radical-pair mechanism for magnetoreception is plausible. Although not formally demonstrated *in vivo*, an ever-increasing amount of evidence supports this hypothesis.

Cryptochrome: a key player in insect magnetoreception

The light dependency of magnetosensitivity in many species has led the field to postulate that a photoreceptive molecule would be the candidate light-dependent magnetic detector (Ritz et al. 2000). Light-activable opsins, G protein-coupled receptors well known to function in vision, are activated when the bound chromophore retinal undergoes isomerization upon the absorption of a photon of light causing a conformational change that triggers a phototransduction cascade (Terakita 2005). Although this appeared to happen without the production of a radical pair, a recent study using quantum chemical calculations showed evidence that ultraviolet (UV) opsins can generate triplet states in a retinal chromophore (Filiba et al. 2022), rendering them potentially sensitive to the magnetic field. The other photoreceptive molecule proposed to form magnetically sensitive radical pairs of electrons is cryptochrome (CRY) flavoproteins, following photoexcitation of their flavin adenine dinucleotide (FAD) co-factor (Maeda et al. 2012). Magnetically sensitive radical

pair products would be generated when the fully oxidized FAD chromophore is photoreduced via a sequence of electron transfers along a chain of tryptophan residues within the CRY polypeptide (Rodgers and Hore 2009; Wong et al. 2021; Ritz et al. 2000).

Animal CRYs, which are best known for their role in circadian function, can be classified into three categories, *Drosophila*-like type 1 CRYs, mammalian-like type 2 CRYs and bird-like type 4 CRYs. *Drosophila*-like type 1 CRYs (CRY1s) are UV-A/blue-light photoreceptors responsible for the synchronization of the circadian clock to the daily light:dark cycle (Emery et al. 2000; Zhu et al. 2005). Mammalian-like type 2 CRYs (CRY2s) do not appear to be light sensitive and function as transcriptional repressors of the heterodimeric CLOCK:BMAL1 transcription factor that drives the circadian transcriptional feedback loop (Merlin et al. 2013; Michael et al. 2017; Zhu et al. 2005). Bird-like type 4 CRYs are also light sensitive, but unlike type 1 CRYs, do not have any clock function (Zoltowski et al. 2019). In insects, the core oscillator has evolved, giving rise to at least three types of clocks based on the presence/absence of CRY1s and/or CRY2s (Yuan et al. 2007). Mammalian-like type 2 CRYs are found in all insect species examined so far with the exception of flies in the brachyceran lineage, which includes *D. melanogaster* (Yuan et al. 2007; Zhang et al. 2017; Zhu et al. 2005). Thus, *D. melanogaster* expresses only the type 1 CRY, named CRY. Several insects, like mosquitoes, butterflies, and the cockroach *Blattella germanica*, express both CRY1 and CRY2 (Zhu et al. 2005; Bazalova et al. 2016). Others, like the honeybee *Apis mellifera*, the beetle *Tribolium castaneum*, and the cockroach *Periplaneta americana* only express CRY2 (Rubin et al. 2006; Zhu et al. 2005; Bazalova et al. 2016).

Driven by the availability of genetic tools and the development of behavioral assays, the fruit fly *D. melanogaster* has been used to provide the first *in vivo* demonstration that light-sensitive type 1 CRYs mediates light-dependent magnetoreception in a wavelength-dependent manner (Fedele et al. 2014a, 2014b; Gegear et al. 2008; Yoshii et al. 2009). Responses of wild-type flies to a magnetic field under full-spectrum light were abolished when wavelengths in the CRY-sensitive, UV-A/blue part of the spectrum (<420 nm) were blocked, as well as in *Cry*-null mutant flies. Unexpectedly, overexpression of monarch butterfly and human CRY2s in CRY-deficient flies restored light-dependent responses to magnetic fields (Foley et al. 2011; Gegear et al. 2010; Fedele et al. 2014a). Other studies, coupling gene knockdown or reverse genetics to behavioral analyses in the cockroaches *P. americana* and *B. germanica*, as well as in the firebug *Pyrrhocoris apterus*, have added support to a possible role of insect CRY2 in magnetoreception (Netušil et al. 2021; Bazalova et al. 2016). Altogether, this suggests the tantalizing possibility that type 2 CRYs may undergo the necessary

photochemical reactions for magnetosensitivity (Fedele et al. 2014a; Gegebar et al. 2010). Because CRY2s lack the structural features to bind FAD and current evidence indicates that, at least in mammals, type 2 CRYs do not bind FAD (Kutta et al. 2017), if CRY2 function in magnetoreception, it is likely that it would do so via an unknown mechanism. However, in striking contrast to the studies mentioned above, a recent study by our group in the monarch butterfly demonstrated that, while CRY1 is necessary for response to changes in the inclination of Earth strength magnetic fields, CRY2 is dispensable (Wan et al. 2021). The contrasting findings between this study and the one in which monarch CRY2 was overexpressed in CRY-deficient flies could be the results of CRY2 overexpression and/or the use of non-physiological magnetic field intensities in the *D. melanogaster* study, in which responses were rescued by monarch CRY2 but only modestly (Foley et al. 2011; Gegebar et al. 2010). Nevertheless, the apparent inconsistencies on the requirement of CRY2 for magnetic responses between insect species cannot be ignored. It is conceivable that insect species that have lost the light-sensitive CRY1 evolved compensatory mechanisms for CRY2 to function in magnetoreception. However, it remains unclear why two species that have both CRY1 and CRY2 such as the monarch butterfly and the cockroach *B. germanica*, would display different requirements of one type of CRY over the other for magnetosensing. One formal possibility is that *B. germanica* CRY1 may have lost its ability to function in magnetoreception and CRY2 took on this function. The divergence of the C-terminal domain of *B. germanica* CRY1 from those of *D. melanogaster* CRY and monarch butterfly CRY1 may support such a possibility (see below). Ultimately, the use of additional insect models possessing either both CRY1 and CRY2 or only CRY2 that would be amenable to genetic manipulations and presenting robust responses to magnetic fields of intensities found on Earth would help resolve this issue.

The magnetosensitive organs: eyes and antennae as prime candidates

The anatomical localization of the site of magnetoreception has also been a sought-after area of investigation. Looking for tissue-specific expression of CRY1 and CRY2 would not yield conclusive results, given that both proteins play important roles within the circadian clock and that circadian clocks operate broadly and autonomously in all peripheral tissues in insects (Glossop and Hardin 2002). Approaches used to identify the location of magnetosensitive cells within tissues have relied on either cell type/tissue-specific rescue in *D. melanogaster* or blocking the light input to candidate organs with black paint in other species in which tissue-specific genetic manipulations are not yet available. In *D.*

melanogaster, three separate anatomical locations were implicated: a subset of CRY-positive clock cells in the brain known as dorsal-lateral clock neurons (LNDs), the antennae, and the eyes (Fedele et al. 2014b). Importantly, specific CRY expression in any one of these cells/organs was sufficient to restore magnetosensitivity of *Cry* loss-of-function mutants, suggesting some level of cellular redundancy (Fedele et al. 2014b). Interestingly, in the monarch butterfly, painting the antennae or compound eyes black resulted, in each case, in a loss of their ability to respond to a reversal of magnetic inclination (Guerra et al. 2014; Wan et al. 2021), indicating that both antennae and eyes are necessary for monarch magnetosensing and that impairing magnetosensitivity in one organ cannot be compensated by the other. Using similar painting experiments, eyes were also found to be necessary for magnetoreception in the cockroach *P. americana* (Bazalova et al. 2016). In this species, CRY2 immunolocalization revealed an orderly pattern of cellular expression just underneath the pigmented layer of the retina, consistent with the widely accepted view that molecules that are necessary for the transduction of a magnetic stimulus into a cellular response should be oriented in an orderly fashion (Hore and Mouritsen 2016). Determining if such a CRY expression retinal pattern is conserved across insect species and in which cells CRY is expressed in the antennae will be necessary to expand our understanding of the cellular bases of the magnetic sense.

Is cryptochrome the *bona fide* magnetoreceptor or a downstream signaling molecule?

While evidence for the involvement of CRYs in magnetoreception is undisputable, whether CRYs serve as *bona fide* magnetoreceptors or signaling molecules functioning downstream of an unknown receptor remains a debated question. As previously mentioned, CRY was originally proposed as a candidate magnetoreceptor based on its ability to initiate an electron transfer cascade along a conserved chain of Trp residues when bound to its co-factor FAD (Ritz et al. 2000; Hore and Mouritsen 2016; Rodgers and Hore 2009). However, a formal test of this hypothesis in *D. melanogaster* cast skepticism as mutating the terminal Trp of the Trp-triad (currently known as the Trp-tetrad) in *D. melanogaster* CRY and monarch CRY1 did not impair the ability of transgenic flies to respond to the magnetic field (Gegebar et al. 2010; Fedele et al. 2014b). Interestingly, the C-terminal (C-ter) domain of *D. melanogaster* CRY, which becomes exposed once CRY undergoes conformational changes triggered by FAD photoreduction (Vaidya et al. 2013), was shown to be required for magnetosensing (Fedele et al. 2014b). As this domain does not contain the canonical FAD-binding domain

and the Trp chain, this suggested that it may function in the intracellular signaling of the CRY response to magnetic fields by modulating downstream protein–protein interactions (Fedele et al. 2014b).

In an unexpected twist, recent work showed that the 52 C-ter amino acids of *D. melanogaster* CRY are not just required, but sufficient to facilitate magnetoreception (Bradlaugh et al. 2023) (Fig. 2A). The single Trp present on this domain does not seem to bind free FAD. Remarkably, the magnetic response mediated by the CRY C-ter can be potentiated in a dose-dependent manner by providing exogenously free FAD that is capable of forming radical pairs on its own, but not by providing its precursor riboflavin that cannot form radical pairs (Bradlaugh et al. 2023). Additionally, it appears that even in absence of the CRY C-ter, high doses of free FAD alone can cause a similar effect, suggesting that FAD may act as a magnetoreceptor at high concentration (Bradlaugh et al. 2023). Together, these results support the existence of a CRY-independent radical-pair mechanism and place CRY in the signaling cascade for magnetoreception, perhaps in addition to its receptor function.

In line with the idea that the C-ter of *D. melanogaster* CRY plays a role in transducing the magnetic signal, the integrity of a putative PDZ-binding motif (EEEV; Fig. 2A) to which scaffold PDZ proteins bind for the assembly and cellular localization of signaling complexes was shown to be required to support a magnetic response, as a single valine to lysine mutation is sufficient to abolish it (Bradlaugh et al. 2023) (Fig. 2A). This discovery may hold the key to deploy molecular approaches for the in vivo identification of protein interactors and perhaps transmembrane

proteins that transduce the radical pair signal into a neural one, ultimately leading to behavioral responses. It may also provide a framework to settle apparent controversies related to which type of CRY (CRY1 vs. CRY2) are involved in insect magnetoreception. As previously mentioned, insect species that have lost the light-sensitive CRY1 may have evolved mechanisms for CRY2 to take on the function in magnetoreception. But what about insect species that possess both CRYs but use either CRY1 or CRY2 in a species-specific way, as is the case for the monarch and the cockroach *B. germanica*? Perhaps the answer lies in the CRY1 C-ter region. Aligning C-ters of *D. melanogaster* CRY and CRY1s from the monarch and the cockroach *B. germanica* reveals that monarch CRY1 C-ter exhibits a high degree of conservation with that of *D. melanogaster* CRY, including the presence of a relatively well-conserved PDZ-binding domain (EDEV), while the most distal end of *B. germanica* C-ter is truncated and lacks this domain (Fig. 2B). If indeed this domain is key for CRY1 function in magnetoreception, it could explain why *B. germanica* is relying on CRY2, and not CRY1, for magnetic responses. Given that most of the experiments conducted by Bradlaugh et al. used non-physiological magnetic fields, validating whether the necessity and sufficiency of the CRY C-ter is conserved in species relying on CRY1 and responding to physiological magnetic fields will be important. This could be achieved in the monarch butterfly via the use of CRISPR/Cas9 for the generation of truncated mutants (Markert et al. 2016; Zhang et al. 2017) and the development of transgenesis for sufficiency tests.

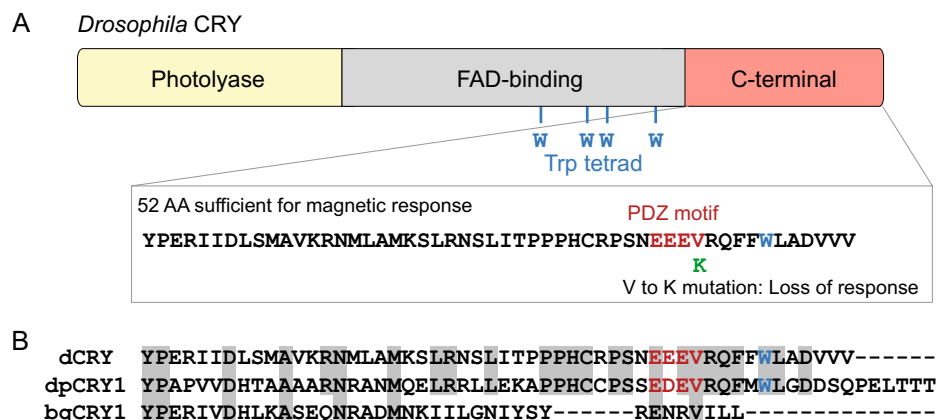


Fig. 2 Role of the *Drosophila melanogaster* CRY C-terminal domain in magnetoreception and sequence conservation/divergence in insects. **A** Schematic of *D. melanogaster* CRY highlighting the different domains, including the Trp (W)-tetrad bearing FAD-binding domain and the 52 amino acids C-terminal (C-ter) domain shown to be sufficient for magnetic responses. The most distal C-ter contains a putative PDZ-binding motif (EEEV; shown in red), whose integrity is essential for CRY function in magnetoreception. When the valine (V)

is mutated to a lysine (K) in the full-length CRY, *D. melanogaster* is no longer able to exhibit responses to the magnetic field. Blue W, single Trp residue in the most distal C-terminus. Modified from (Bradlaugh et al. 2023). **B** Alignment of amino acid sequences of the light-sensitive CRY/CRY1 C-termini of *D. melanogaster* (d), the monarch butterfly *Danaus plexippus* (dp) and the cockroach *Blattella germanica* (bg)

Concluding remarks

Due to the lack of obvious adaptive function of magnetic susceptibility in most insects studied so far, their use for the dissection of the molecular underpinnings of magnetoreception is sometimes questioned. The power of the genetic approaches that can be undertaken in *D. melanogaster* and the existence of a light-sensitive CRY1 and/or light-insensitive CRY2 in many other species make insects, however, uniquely suited for furthering the neurogenetic dissection of the molecular and cellular basis of magnetosensitivity. As discussed in this minireview, there is ample evidence that both types of CRYs play a critical role in magnetosensitivity in a species-specific manner, although it remains to be seen whether they function as a receptor or a downstream signaling molecule. Another major remaining challenge will be to determine how neural signals are transduced and integrated in the brain to give rise to behavioral responses, particularly in migratory insects that use magnetic fields for long-distance orientation and navigation such as the bogong moth and the monarch butterfly. The use of electrophysiological recordings with multi-electrode arrays from brains of tethered flying insects (Beetz et al. 2022) that would be orienting to magnetic fields hold great promise to identify the neural sites of integration of magnetic information and its encoding. Ultimately, forward progress will require highly interdisciplinary approaches, and that the community remains open to unexpected findings as we continue to dig deeper into this fascinating sense.

Acknowledgements The author thanks Dr. Jerome Menet for feedback on the manuscript. This work is supported by a Texas A&M Presidential Impact Fellowship to C.M.

Author contributions CM wrote the manuscript.

Funding Texas A&M University.

Declarations

Conflict of interest The author declares no competing interests.

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