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Cryptochrome Magnetoreception Mechanism Indicates a New Kind of Magnetometer

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Abstract: Cryptochrome, a blue-light photoreceptor which has high sequence homology to DNA photolyase, is supposed to be the most conceivable magnetoreceptor in avian's magnetoreception. Its light-response mechanism is proposed to result from photoreduction of a protein-bound flavin chromophore through intramolecular electron transfer. We review the cryptochrome magentoreception focusing on the radical pair mechanism, structure of cryptochromes, theoretical and behavioral evidences and the electron transfer models inner cryptochrome protein. Finally, we analysis the superiority of avian's magnetosensitivity and point out that the animal's genius radical pair mechanism may be simulated to develop a new chemical magnetic detection mechanism, or even a new kind of magnetometer, which is different from current magnetic detection technology.

Keywords: cryptochrome; radical pair mechanism; signaling pathway; electron transfer

1. INTRODUCTION

A wealth of evidences demonstrates that many migratory species have the ability to use the earth's magnetic field for orientation and navigation (Mouritsen et al., 2004; Johnsen & Lohmann, 2005; Mouritsen & Ritz, 2005; Leask, 1977; Wiltschko & Wiltschko, 2005). Some studies have proven that plants are also sensitive to the ambient magnetic field (Solov'yov et al., 2007). Decades have been spend to develop the magnetoreception mechanism and the radical pair mechanism is gaining the most supports, which is based on the magneto-sensitive radical pairs formed by photoinduced intramolecular electron transfer reactions (Ritz et al., 2004; Ritz et al., 2000; Timmel & Henbest, 2004). Meanwhile, the blue-light receptor cryptochromes, which are flavoproteins in numerous plants and animals, are proposed to be the

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+magnetoreceptors. And their light-response mechanism is proposed to result from photoreduction of a protein-bound flavin chromophore through intramolecular electron transfer. Many questions have been covered authoritatively and extensively in recent reviews (Johnsen & Lohmann, 2005; Wiltschko & Wiltschko, 2005; Timmel & Henbest, 2004; Rodgers & Hore, 2009; Liedvogel & Mouritsen, 2009).

Here we aim to review the recent advances in this field focusing primarily on (i) structure of cryptochromes, (ii) behavioral experiments and electrophysiological evidences supporting the radical pair mechanism and the cryptochrome magnetoreception, (iii) the structural biology and the functional photochemical process of cryptochrome, (iv) the signal transfer mechanism in animals.

We summarize the main subjects in explaining the cryptochrome magnetoreception and point out that the animal's genius radical pair mechanism reminds us of a new chemical magnetic detection mechanism, which is different from current magnetic detection technology. Finally, we suggest the future researches need further investigation.

2. THE RADICAL PAIR MECHANISM

As well known, the earth's magnetic field is just ≈50μT weak. At first glance, it would be unlikely that an Earth-strength magnetic field can be detected by a chemical reaction. The energy of interaction of a molecular with a ≈50μT magnetic field is about 6 orders of magnitude smaller than the average thermal energy kT at normal temperature, which is 10-100 times smaller than the strength of a chemical bond (Rodgers & Hore, 2009; Brocklehurst, 2002). Therefore, the kinetic energy might be expected to overwhelm any slight magnetic effects. However, the weak magnetic fields might exert an influence on biological molecules and chemical reactions under at least some circumstances and the conditions must be met have been well summarized by Johnsen et al (Johnsen & Lohmann, 2005).

Radicals are molecules that have an odd number of electrons and consequently an unpaired electron spin that may be found in one of 2 spin states: ↑or ↓. And a radical pair is a short-lived reaction intermediate comprising 2 radicals formed in tandem whose unpaired electron spins may be either antiparallel (↑↓, a singlet state, S) or parallel (↑↑, a triplet state, T) (Rodgers & Hore, 2009). If the radical pair was initially born in a singlet state, certain processes and inter-actions may cause its spin state to change from singlet to triplet and vice versa (Timmel & Henbest, 2004). As each electron spin has an associated magnetic moment, the interconversion and chemical fates of the S and T states can be influenced by internal and external magnetic fields. At the same time, electron spins are largely unaffected by thermal noise, and so represent one of only a few molecular features that might plausibly be influenced by the Earth's field.

3. CRYPTOCHROMES AND THE CRY MAGNETORECEPTION

Cryptochromes are flavoproteins and act as blue-light receptors in numerous species on the earth, which have high sequences homology to photolyases (Sancar, 2003; LIN & Shalitin, 2003; LIN, 2000). They have many important physiological functions such as control hypocotyl growth and the transition to flowering in plants, and regulate the circadian rhythms in mammals. The proposal of considering cryptochromes as the magnetorecepor was first raised by Ritz in 2000 (Ritz et al., 2000). He made some theoretical calculations proving that the ratio between singlet and triplet products from radical pair reactions can be modulated by an Earth-strength magnetic field and suggested cryptochromes that had been found in mammalian eyes as a candidate for a radical pair-based magnetoreception.

3.1 Structure of cryptochromes

Cryptochromes were first discovered as blue-light and ultraviolet photoreceptors in plants (Ahmad & Cashmore, 1993) and they were found to be existing in many species. The structure of cryptochromes is high similar to DNA Photolyases. The whole cryptochromes family has an N-terminal photolyase homolyase region (PHR) domain. The difference between cryptochromes and photolyase is the presence of N-terminal expansion and C-terminal expansion in cryptochromes (Müller & Carell, 2009). Until today, however, there are only three structures of cryptochromes that are available, while the expansion domains remain inaccessible.

Lin accomplished a model structure of Arabidopsis thaliana based on the crystal structure of E.coli photolyase (LIN & Shalitin, 2003). The first crystal structure of cryptochrome was reported in 2003, which is identified in Arabidopsis and Synechocystis and homology to Crys from Homo and Drosophila (Cry-DASH) (Brudler et al., 2003). The structure of Cry-DASH is mainly the same as the photolyase-like domain of cryptochrome-1 Arabidopsis thaliana (At Cry-PHR) (Brautigam et al., 2004). Both of them contain two domains, an α/β domain and an α helical domain, connected by a long loop. These domains are consisted by twenty-one α-helicals, one 5-stranded parallel β-sheet and four 310-helices, while the α/β domain is made up of the 5- stranded parallel β-sheet surrounded by four α-helicals and the α helical domain encompasses 14 α-helicals and two 310-helices.

Besides these folds, the Cry family proteins adopts a FAD (flavin adenine dinucleotide) cofactor and a second cofactor (if existed), either MTHF or 8-HDF, in the α/β domain. The FAD cofactor is essential for the physiological function of cryptochromes while the second chromophore is not necessary for catalysis and has no effect on specific enzyme-substrate binding. Actually, the second chromophore plays an antenna role in the protein as their higher extinction coefficient and absorption maximum at longer wavelength than FADH-.

The FAD cofactor binds to the protein in a U-shaped conformation that is conserved both in photolyases and cryptochromes. This groove is positively charged and runs through the enzyme, which is believed to be the DNA-binding site in DNA photolyases. And there is a cavity (FAD-access cavity, Fig.2) on the surface of Crys that leads from the surface to the mostly buried FAD cofactor (Brautigam et al., 2004). Although Crys have lost the ability to repair photolesions, this special conformation is directly related to light-induce electron transduction process which is the initial step of Cry signal transduction.

3.2 Evidences supporting Cryptochromes as the magnetoreceptors

For theoretical consideration of the radical pair mechanism, the radical pair must meet one condition, that the original parallel or opposite spin relationship of the two unpaired electrons cannot be randomized in the electron transfer process (Johnsen & Lohmann, 2005; Cintolesi et al., 2003). This is not true of all electron transfer processes, but is often true when the transfer is induced by photo-excitation. So if the magnetoreceptors do exist, it must be photoreceptors (Ritz et al., 2000). Crys then was considered to be the candidate magnetoreceptor because of its location in retina (Miyamoto & Sancar, 1998) and the influence of ambient magnetic field on regulating circadian rhythms (Cashmore et al., 1999). Many earlier evidences supporting the radical pair mechanism and Cry magnetoreception had been well reviewed authoritatively in recent reviews (Johnsen & Lohmann, 2005; Walker et al., 2002), such as the radical pair reactions could be perturbed by radio frequency field (Henbest et al., 2004), the relationship of the wavelength of light and the radical pair response.

Here we make no significant attempt to comment on the radical pair mechanism, or to debate the behavioral evidences supporting this magnetioreception. We just try to make clear why the photoreceptor protein cryptochrome is presently the only candidate as the magnetoreceptor.

While the eye is clearly indicated as the site of magnetoreception, and the "radical mechanism" is supported by experimental evidence (Ritz et al., 2004), three cryptochromes (eCRY1a, eCRY1b, eCRY2) were isolated from the retina of robins, which supports a potential role of cryptochromes of transducers for the perception of magnetic compass information in birds. Crys were also found in retina of garden warblers and they acted an concentration response in ganglion cells and in large displaced ganglion cells, which also showed high levels of neuronal activity at night, when the garden warblers performed magnetic orientation (Mouritsen et al., 2004; Mouritsen et al., 2004). Also, the cryptochrome expression levels significantly differed between migratory and non-migratory birds at night. This is the first direct evidence for cryptochromes as the magnetorecepor.

A convincing evidence supporting the Crys as the magnetoreceptor was provided by Gegear et al (Gegear et al., 2008) in 2008. The cryptochromes are light-sensitive in the ultraviolet-A range (350-400nm) with a plateau in the near blue range (430-450nm). Drosophila show significant naive and trained responses to a magnetic field under full-spectrum light, but no respond to the field when wavelengths in the Cry-sensitive, ultraviolet-A/blue-light part of the spectrum are blocked. And the Cry-deficient flies do not show these responses to a magnetic field even under full-spectrum light. This work demonstrated that Crys in animals also act a magnetosensitive function.

Moreover, the Cry-based magnetosensitive response is also found in plants (Ahmad et al., 2007). Crys mediate several blue-light-dependent responses including hypocotyls growth inhibition. In normal Arabidopsis thaliana, growth inhibition was enhanced by an increase in the intensity of the ambient magnetic field under blue-light, while not under red light or darkness. And there was no influence of the increase in the intensity of the ambient magnetic field for Arabidopsis mutants that lack cryptochromes.

3.3 The radical pair in cryptochrome magnetoreception

As described and demonstrated in recent papers (Johnsen & Lohmann, 2005; Rodgers & Hore, 2009; Brocklehurst, 2002; Efimova & Hore, 2008; Rodgers et al., 2007; Rodgers et al., 2005), a magnetic sensitive radical pair must meet many conditions. The minimum requirement is that the radical pair should have a suitable life time, long enough to undergo a spin correlation reaction but not too long, or the spin correlation might be randomized by other disruptive processes. Researches aimed to increase the life time of pairs of radical have been carried on extensively in the simulation of the electron-transfer process of photosynthesis. A typical model is a carotenoid–porphyrin–fullerene molecule, a model system has demonstrated the feasibility of a chemical magnetic compass (Maeda et al., 2008). This chemical compass model could allow a detectable response in Earth-strength magnetic field. Although it is synthesized aiming to stimulate the electron-transfer process of photosynthesis (Kodis et al., 2004) and works at least at -20℃ and below, it bring the first light of imitating the animals' magnetic sensitivity.

In cryptochrome, the magneto-sensitive radical pair was suggested to be formed by photoinduced intramolecular electron transfer reactions. However, the exact mechanism of the electron-transfer process remains obscured.

A promising candidate radical pair comprises the reduced flavin cofactor (FAD) and an oxidized tryptophan residue in a cryptochrome flavoprotein (Solov'yov et al., 2007; Ritz et al., 2000; Liedvogel et al., 2007). There are three tryptophan (Trp) residues in cryptochrome protein, which are high conserved in photolyases and cryptochromes. Researches have shown that a light-induced electron transfer process could happen between the flavin cofactor and Trp residues. The electron transfer process is essential in repairing photolesions in DNA photolyase, as the same, is considered to be forming "the radical pair" in cryptochrome magnetoreception. A FAD-Trp radical pair in DNA photolyase has been shown to be magnetically sensitive in vitro (Henbest et al., 2008). And time-resolve EPR spectroscopy has revealed that FAD-Trp radical pair has sufficient life time for electron spin correlation. The electron transfer process between FAD and Trp residues in the Arabidopsis cryptochrome also has been particularly described (Solov'yov et al., 2007). However, another standpoint was raised up (Liedvogel et al., 2007) based on the detection of the transient absorption spectrum of TyrO$^{\cdot}$. So the FAD-Trp electron transfer process may be followed by an electron transfer from a tyrosine residue to the Trp$^{\cdot}$ to produce a tyrosyl radical, TyrO$^{\cdot}$. Therefore, the life time of the radical pair is remarkable longer than the FAD-Trp mechanism.

Nevertheless, there is no direct evidence for the involvement of FAD-Trp radicals in the cryptochrome magentoreception. Recent researches have suggested that the radical pair may not be FAD-Trp (Ritz et al., 2009). And dioxygen (O_2) and superoxide ($O_2^{\bullet-}$) may be the potential paramagnetic partners for the FAD radical, which was first discussed by Maeda et al (Maeda et al., 2008). Both O_2 and $O_2^{\bullet-}$ are paramagnetic, have no hyperfine interactions and especially O_2 is the dominant oxidizer of reduced flavin cofactor in flavoproteins. This mechanism is that the FAD is reduced via the Trp triad in a photochemical process, and then reoxidised by O_2 or $O_2^{\bullet -}$. Besides the consideration of Zeeman resonances, the involvement of oxygen may also has great advantages over FAD-Trp for magnetoreception (Hogben et al., 2009), which involves a stronger asymmetric distribution of hyperfine coupling across the FAD and oxygen and a fewer hyperfine interaction. The FAD-oxygen mechanism was also be suggested by Solov'yov et al (Solov'yov & Schulten, 2009), which involved the transduction of FAD signaling state to inactive state. Hogben et al (Hogben et al., 2009) gave three reaction forms of the radical pair formed by FAD and O_2 or $O_2^{\bullet -}$ and evaluated the feasibility of this mechanism based on the observation of an in vivo Zeeman resonance at 1.3MHz in a magnetic field of 47 nT. The result shows that neither $O_2^{\bullet -}$ nor $^3O_2$ seems to offer a very credible explanation for the resonance effects observed for birds exposed to radiofrequency magnetic fields, which may indicate an impossible of the FAD-oxygen mechanism. So the biophsiycal mechanism underlying animal magnetoreception remains an open question.

4. GENIUS MAGNETIC SENSITIVITY OF THE AVIAN AND ITS SIMULATION

Animals can sense the Earth-strength magnetic field at physiological temperature. The radical pair mechanism plays an important role in this genius ability. Key features of a radical pair magnetoreceptor have been well summarized by Rodgers and Hore (Rodgers & Hore, 2009), which involves spin chemistry, hyperfine interactions, reaction kinetics and molecular dynamics, geometry, and disorder and motion. Here we just aim to discuss the other aspect of cryptochrome magnetoreception, such as the signal transduction, and to find the reasons of the advantage of organism magnetic sensitivity.

The aforementioned C-P-F triad can form a long-lived radical pair and can detect tiny change of the ambient magnetic field. But this compass only works at very low temperature, which complicates the whole system. While the avian need not so strict temperature condition, their original signal transduction may be totally different from the transient absorption or EPR spectrums that are used in related researches. Just like most well-characterized signal transduction system, cryptochrome signal transduction also involves direct protein-protein interactions (LIN & Shalitin, 2003). Firstly, the change of ambient magnetic field is detected by cryptochrome via radical pair mechanism based on the blue-light irradiation. Then, the magnetic signal is converted to conformational changes which may initiate a chain of protein-protein interactions. Some researchers presume the photoreaction may be the basis of conformational changes that occur in the protein, which is a possible mode of protein interaction. As pointed out the cryptochrome magnetoreception is based on vision system (Mouritsen et al., 2004; Ritz et al., 2000; Möller et al., 2004), the interactions are assumed to end of an optic nerve signal.

Although many proteins have been found to interact with cryptochromes, for example, interact with COP1 in mediating the rhythms of flowering in plants, the receptors of cryptochrome underlying the magnetoreception are still unknown. More researches should be focused on the potential proteins that can interact with cryptochromes to find the receptors in the signal transduction pathway.

For various physiological functions of cryptochromes, the original initiator or mediator is the light. All the functional chemical reactions are initiated by light while the magnetic may be a second factor influencing the reaction result, which can be well validated by many experimental evidences (Solov'yov et al., 2007; Ahmad et al., 2007; Yoshii et al., 2009; Shirdel et al., 2008; Harris et al., 2009). The change of ambient magnetic field has remarkable effect on the inhibition of hypocotyl growth in plants and the circadian rhythms in mammals and insects. Although some models of signalling pathway in circadian rhythms have been predicated, the spatial organization and exact position of cryptochrome protein and the protein-protein interaction are still unknown. It will be really challenging to make the genius of avians magnetosensitivity clear.

On the consideration of magnetic field detection, the "radical pair" mechanism is completely different from the traditional magnetic field detection mechanisms, such as GMI Magnetometer, Fluxgate Magnetometer, SQUID Magnetometer, and Proton Magnetometer. These traditional detection systems usually have big bulk and need strict condition, even though they could achieve an excellent precision. The measurement of magnetic abnormity is more and more important in the analysis of geomagnetic field. And modern magnetic abnormity detector (MAD) is aiming to detect tensor magnetic which is a useful parameter of magnetic field (Chang-da, 2006). It's hard for the traditional magnetometer to be competent for this word because they are complicate and difficult to form array which is essential to the whole system. The avian's magnetosensitivity enlighten us that the radical pair mechanism may be a good candidate mechanism for magnetometer design. In radical pair mechanism, it's a molecule array that senses the magnetic field. They are natural magnetometer array and have no interferer to each other. That's great excellence in tensor magnetic detection.

So if the avian magnetosensitivity could be simulated, a prospective magnetic detection material could be produced. A magnetic sensitive molecule could be designed and synthesized based on the theoretical and computational consideration which has been discussed comprehensively. The magnetoreceptor molecule should be aligned in a special sample, just like the C-P-F triads are frozen in the nematic phase of a liquid crystal, to respond anisotropically to ambient magnetic field. Works on designing and optimizing the magnetosensitive molecules to work at physiological temperatures are being carried on in our group. However, the signaling pathway could never be neglected. A simple and sensitivity signal transfer mode should be developed based on the study on the animal signaling pathway. Then a new magnetometer would be produced despite many intriguing questions remain obscured and how challenging this work it is.

5. CONCLUSIONS

Numerous studies of magnetic compass mechanisms of migratory birds and cryptochrome magnetoreception have been carried on in the past three decades. A lot of evidences supporting the radical pair mechanism and cryptochrome magnetoreception have been provided. And the cryptochromes are considered as the most likely megnetoreceptor in migrant birds and other species. Great progress has been achieved on studies of cryptochrome proteins and their magnetic effect responses. The magnetic compass has also been matured much. Nevertheless, there is still no direct demonstrated evidence proving the cryptochrome is the primary magnetoreceptor and many open questions need to be addressed some of which have been discussed in recent reviews (Rodgers & Hore, 2009; Liedvogel & Mouritsen, 2009; Ritz et al., 2009).

Cryptochrome as the most probable candidate magnetoreceptor underlying light-dependent magnetorecetion, has gain most supports in this field. But it is still very hard to demonstrate this hypothesis convincingly. Moreover, the exact mechanism of cryptochrome magentoreception needs further investigation. The electron transfer pathway in the process of radical pair forming is still unknown. The functional amino residues candidates that interact with FAD cofactor in cryptochrome can be presumed by theoretical and computational studies. And their magnetic response can be studied by site directed mutagenesis of the putatively residues site.

Another question is that there is still no available structure for animal cryptochromes and no reports about the candidates proteins interact with cryptochrome in magnetoreception. So, further experiments on identification and characterization of cryptochromes family and their receptors are necessary. And as a new magnetic sensitive mechanism, the radical pair mechanism could be applied in bionics of designing a new magnetometer.

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FIGURES

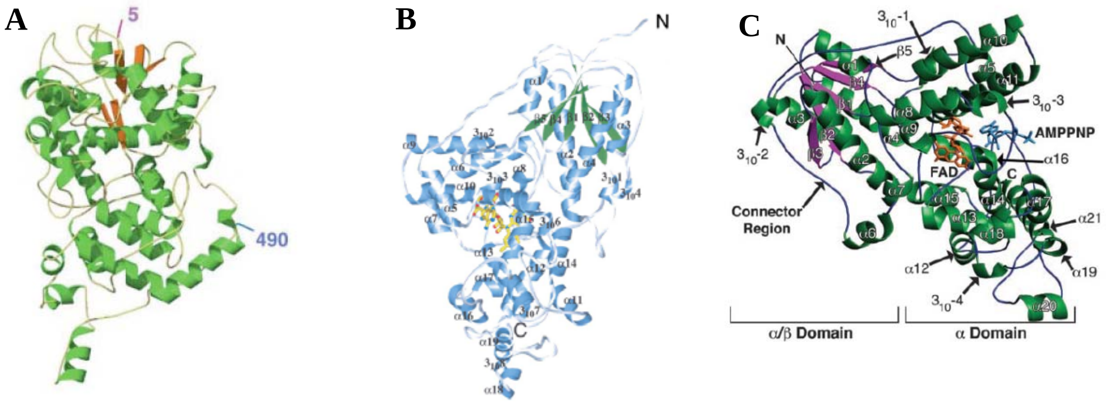

Fig. 1: Structures of *At* Cry2-PHR、Cry-*DASH* and *At* Cry1-PHR (reprinted, Brautigam et al., 2004)

(A) a model structure of *At* Cry2-PHR (LIN & Shalitin, 2003). (B) the overall fold of Cry-*DASH* from Synechocystis sp. PCC6803 Cryptochrome (Brudler et al., 2003). (C) the structure of *At* Cry1-PHR

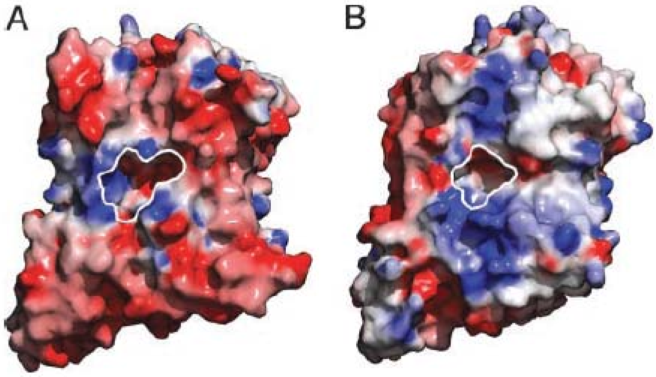

Fig. 2: Structures of FAD-access cavity on the surface of Cry1-PHR(A) and photolyase(B) (reprinted (Brautigam et al., 2004))

The electrostatic potential is color-coded on the surface, with red and blue representing areas of negative and positive electrostatic potential, respectively. The structure of FAD-access cavity in Cry is different from photolyase as many residues are changed in Cry.

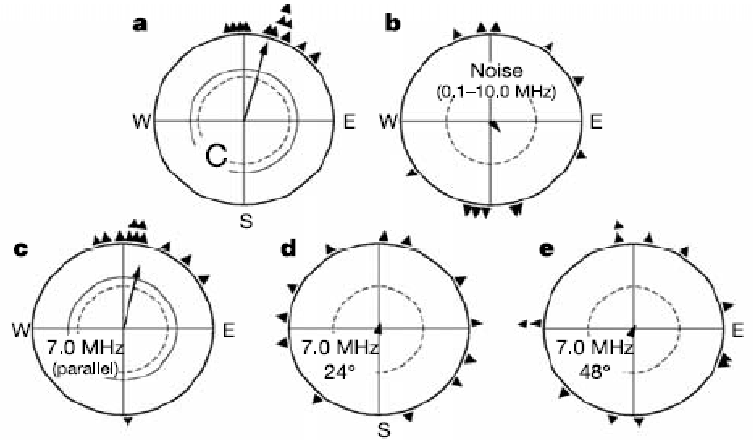

Fig. 3: Effects of oscillating magnetic fields on magnetic orientation behavior of European robins. (reprinted (Ritz et al., 2004))

When the birds are exposed in a oscillating field, their orientation was disturbed in a vertically aligned broadband (0.1–10 MHz)and only at a 24° or 48° in a single-frequency (7-MHz) field, which is consistent with the response effect on singlet-triplet transitions. Triangles indicate the mean orientation of test birds.

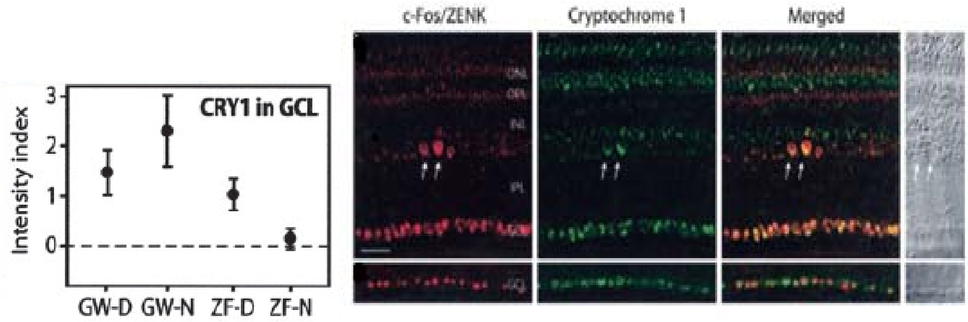

Fig. 4: The left graph shows the different expression levels of garden warblers and zebra finch in day and night(reprinted (Mouritsen et al., 2004))

The right panel shows immunohistochemistry staining of a cross section of a graden warbler retina, indicating from left:the expression pattern of neuronal activity marker proteins (c-Fos/ZENK) in red, the Crys proteins expression pattern in green, and the merged picture which shows colocalization of both proteins in yellow.

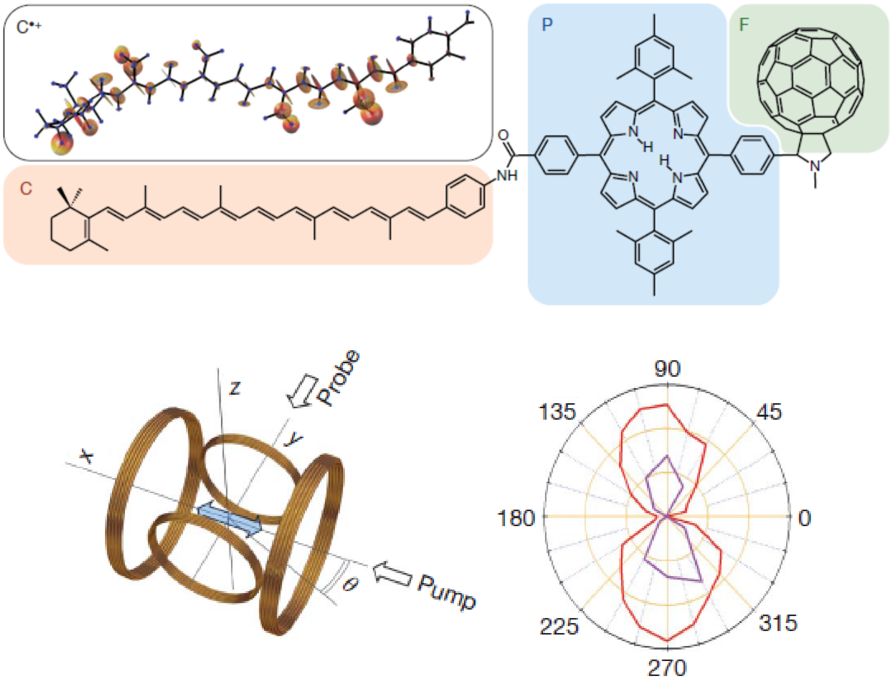

Fig. 5: Structure of the C-P-F triad and the experiment arrangement(reprinted (Maeda et al., 2008))

The top part shows the structure of the C-P-F triad used to demonstrate the principle of a chemical compass. The bottom, left: experiment arrangement used to measure the anisotropy of the magnetic field effect; Right: polar plot of the anisotropy of the magnetic field affect on the transient absorption of $[C^{\bullet +}\text{-}P\text{-}F^{\bullet -}]$.

LIST OF FIGURE CAPTIONS

Fig.1 Structures of *At* Cry2-PHR、Cry-*DASH* and *At* Cry1-PHR(reprinted).

Fig.2 Structures of FAD-access cavity on the surface of Cry1-PHR(A) and photolyase(B) (reprinted (Brautigam et al., 2004)).

Fig.3 Effects of oscillating magnetic fields on magnetic orientation behaviour of European robins. (reprinted (Ritz et al., 2004)).

Fig.4 The left graph shows the different expression levels of garden warblers and zebra finch in day and night(reprinted (Mouritsen et al., 2004)).

Fig.5 Structure of the C-P-F triad and the experiment arrangement(reprinted (Maeda et al., 2008)).