are housed in a set of neighboring pontine compartments. The formation of such groups of compartments is a consequence of the highly divergent nature of the cerebro–pontine projection. As discussed in detail in our article, the transformation from a 2D cerebral to a 3D pontine map allows for local sets of pontine compartments whose grouping would not be governed by principles of cerebrocortical somatotopy, a point explicitly acknowledged by Bjaalie and Leergaard[6].

Their second point of disagreement, the presence or absence of overlapping projections, seems to be based on the misconception that a compartmentalized pontine map would impede the 'integration' of signals and, conversely, that such integration would require anatomical overlap of cerebrocortical afferents onto PN neurons. This might be the reason why they try to convince us of the existence of overlapping terminal fields originating in segregated cerebrocortical sites. However, our own studies, which used injections of double anterograde tracers, separated far enough to avoid spillover of tracers, show pure segregation of terminal fields (C. Cavada, P. Thier and U. Ilg, unpublished observations; C. Schwarz and M. Möck, unpublished observations). Even the single 'best' case cited by Bjaalie and Leergaard, which is based on a different approach, clearly emphasizes segregation rather than overlap. The lack of anatomical overlap is, as extensively discussed in our article, in accordance with published physiological data.

Irrespective of these differences in interpretation of the anatomical data, we feel that Bjaalie and Leergaard's assertion that the PN have an 'integrative' role is too noncommittal to subserve as a useful concept of PN function. If our article is read thoroughly, it becomes clear that we went to great lengths to propose that the compartmentalized pontine map is not merely a patchwork of segregated throughput channels, but could have a function, namely the task-dependent binding ('integration') of signals relevant for action.

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REVIEW

The neurobiology of magnetoreception in vertebrate animals

Kenneth J. Lohmann and Sönke Johnsen

Diverse vertebrate animals can sense the earth's magnetic field, but little is known about the physiological mechanisms that underlie this sensory ability. Three major hypotheses of magnetic-field detection have been proposed. Electrosensitive marine fish might sense the geomagnetic field through electromagnetic induction, although definitive evidence that such fish actually do so has not yet been obtained. Studies with other vertebrates have provided evidence consistent with two different mechanisms: biogenic magnetite and chemical reactions that are modulated by magnetic fields. Despite recent progress, however, primary magnetoreceptors have not yet been identified unambiguously in any animal.

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BEHAVIORAL EXPERIMENTS have demonstrated that diverse animals, including representatives of all five vertebrate classes, can sense the earth's magnetic field and use it as an orientation cue while migrating, homing or moving around their habitat[1]. Relatively little is known, however, about the physiological mechanisms that underlie this sensory ability. Theoretical work on mechanisms of magnetoreception has progressed much more rapidly than have empirical physiological studies. Numerous hypotheses have been proposed, including transduction processes mediated by electromagnetic induction[2–4], magnetite[5–7], melanin[8], optical pumping[9] and biradical reactions[10,11]. Yet despite these theoretical analyses, little direct neurobiological or anatomical evidence exists to support any of the proposed mechanisms. In no case yet have primary magnetoreceptors been identified with certainty.

Several factors have made locating magnetoreceptors difficult. One is that magnetic fields pass freely through biological tissue. Thus, magnetoreceptors need not contact the external environment and might plausibly be located nearly anywhere within the body of an animal. Magnetoreceptors might also be tiny and dispersed throughout a large volume of tissue[12], or the transduction process might occur as a set of chemical reactions[10], so that no obvious organ or structure devoted to

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magnetoreception necessarily exists. Moreover, accessory structures such as lenses, which focus sensory stimuli on receptors and are often conspicuous, are unlikely to have evolved for magnetic sensing because few biomaterials affect magnetic field lines.

For now, most of what is known about magnetoreception in vertebrate animals has been inferred from behavioral experiments, from theoretical considerations, and from a limited number of electrophysiological and anatomical studies. This article describes the difference between a magnetic directional (or compass) sense and a magnetic positional (or map) sense, reviews the three main hypotheses of vertebrate magnetoreception, and summarizes the evidence for each.

Magnetic compasses and magnetic maps

At least two types of information can potentially be derived from the earth's magnetic field. An animal with the ability to orient its movements with respect to the geomagnetic field is said to have a magnetic compass sense. A magnetic compass alone, however, is insufficient to guide a long-distance migrant to a specific destination. The animal also needs to know where it is with respect to its goal, so that it can set an appropriate course. For this reason, some animals have been hypothesized to possess an additional sense, called a map sense, which provides the ability to determine position relative to a destination[13]. Several geomagnetic parameters, such as field intensity and the inclination of field lines, vary across the earth's surface in ways that make them suitable for use in a position-finding sense[14,15]. Sea turtles[16,17] and birds[18] can detect at least some of these features. Because the parameters of the earth's field that are important for compass and map information differ, the possibility exists that some species possess two separate magnetosensory systems. Each might detect a different feature of the earth's field, and each might also rely on separate receptors with different underlying physiological mechanisms[19]. Although diverse mechanisms have been proposed that might provide the basis for a magnetic sense in vertebrates, most recent research has focused on three possibilities: electromagnetic induction, magnetic-field-dependent chemical reactions and magnetite.

Electromagnetic induction

An electron moving through a uniform magnetic field experiences a force perpendicular to both its motion and the direction of the field. The magnitude of this force is proportional to the product of the charge, the velocity, and the sine of the angle between the motion and field vectors[20]. Thus, if an electrically conductive bar moves through a magnetic field in any direction except parallel to the field lines, then electrons will migrate to one side of the bar. If the two sides of the bar are connected by a conducting medium that is stationary relative to the field, then the bar and the medium will form an electrical circuit, with the intensity and polarity of the current dependent on the speed and direction of the bar's motion relative to the magnetic field.

This principle, known as electromagnetic induction, has been invoked to explain how elasmobranch fish (sharks, skates and rays) detect the earth's magnetic field[2,21]. According to this hypothesis, structures on the fish known as ampullae of Lorenzini function as the conducting bar; the surrounding sea water functions as the motionless conducting medium, and the highly resistive and sensitive electroreceptors that exist in elasmobranchs detect the voltage drop of the induced current. However, the electric fields induced by ocean currents complicate this simple model considerably because the animal would have to determine which component of the total field that it experiences is attributable to its own motion and which is due to the motion of water[4,21]. Paulin has suggested that this problem might be overcome if the crucial directional information is derived instead from the oscillating electric field that results as the ampullae on the head move back and forth during the swimming movement of the fish[4].

Although sea water is a highly conductive medium, air is not. Thus, birds and other terrestrial animals cannot accomplish magnetoreception by induction in the same way that has been hypothesized for electrosensitive marine fish. While an induction-based system that uses an internal current loop (a closed circuit inside an animal) is possible theoretically, such a loop would need to rotate relative to the earth's field[20] and would also probably require a specialized internal transduction organ several millimeters in diameter[3]. The semicircular canals have some of the necessary features, but no evidence presently exists that magnetoreception occurs in the inner ear, and no likely alternative structure or site has been found in any animal[3].

Evidence for electromagnetic induction

Direct evidence that animals use electromagnetic induction to detect the earth's magnetic field has not yet been obtained. Rays have been conditioned to move towards a specific magnetic direction within an enclosure[22], although whether they are responding to the direction of the field *per se*, or instead to the presence of field anomalies, has been debated[1,23]. Both rays and sharks, however, clearly possess a highly sensitive electric sense with which they detect the weak electric fields generated by the tissues of prey[24]. The sensitivity of this electrosensory system is, in principle, sufficient to permit detection of the earth's magnetic field[25]. Whether elasmobranch fish actually rely on induction for magnetoreception, or use an alternative mechanism instead, remains to be determined.

Chemical magnetoreception

A second proposed mechanism of magnetoreception involves chemical reactions that are modulated by earth-strength magnetic fields. At first glance, fields as weak as the earth's appear unlikely to influence any chemical reactions, let alone those in animals. After all, such reactions involve alterations in the energy of electrons, and the energy differences between different orbitals are many orders of magnitude too large for the earth's field to transfer electrons directly from one orbital to another. Moreover, thermal effects at physiological temperatures are significant and might therefore be expected to overwhelm any slight magnetic effect[11].

Weak magnetic fields might nevertheless influence specific chemical reactions by exerting a subtle influence on nuclear and electron spins[11]. The orbital motion of each electron in a reactant forms a current loop and thus creates a small magnetic field. In addition, an electron also rotates about its own axis and this spin results in a second magnetic field. The orientation of the magnetic field produced by an electron's spin relative to the orientation of the field produced by its orbital motion

has a small effect on the total energy of the electron. In addition, the protons and neutrons of the nucleus have spins that sum in a complex way to yield a total nuclear spin. Interactions between the two magnetic fields associated with an electron (see above) and the field produced by the nucleus are responsible for an even smaller effect on the energy of the electron. This final interaction, known as hyperfine coupling, involves energies approaching those of the geomagnetic field.

The following scheme and arguments were developed primarily by Schulten and his colleagues[10,11,26,27]. The sample scheme involves the transfer of an electron from an excited donor molecule A to an acceptor molecule B, leaving each with an unpaired electron. The two electrons either have opposite spins or parallel spins. Either way, the spins precess, meaning that the rotation axis changes slowly in much the same way that a spinning top wobbles around a vertical axis as it slows down. This precession is caused by the resultant magnetic field generated by the spins of the electrons and nuclei, the orbital motion of the electrons, and any external field. After a brief time the electron that was transferred returns to the donor. Until then, however, the speed at which each electron spin precesses depends on the hyperfine couplings involved, and the strength and orientation of the external magnetic field. If electron backtransfer occurs quickly, as takes place in a fast reaction, then the electron spins will have precessed little, and are thus likely to remain in their original opposite or parallel relationship. As a result, A and B remain unchanged. In a long reaction, a small difference in precession rate can change the original opposite or parallel relationship of the two spins. If this occurs, then upon backtransfer of the electron, A and B will differ from the way that they were before the reaction. Such changes affect the chemical properties of the molecules, which in turn can influence subsequent reactions involving A and B, as well as the chemical properties of the reaction products that are produced.

Several conditions must be met for this scenario to be successful. First, the reaction must be slow (lasting at least 100 nanoseconds) to allow the small differences in rate of precession caused by the total ambient field to alter the spin correlation; at the same time, however, it must not be so slow that the correlation is randomized by other disruptive processes[26]. Although most reactions of this type occur much too rapidly, a few exceptions are known, including some reactions that occur within cell membranes[10]. Second, the speed of the reaction and the strength of the hyperfine and fine interactions must be related in specific ways for the earth's field to have a significant effect. Although the existence of reactions influenced by earth-strength magnetic fields has been verified[28], it is not known whether any biomolecules have the correct parameters to be affected by such weak fields. Finally, the initial electron transfer must not randomize the original parallel or opposite spin relationship of the two electrons. This is not true of all electron-transfer processes, but is often true when the transfer is induced by photo-excitation (that is, by the absorption of light)[11,26]. This last consideration suggests that if chemical magnetoreceptors exist, they might also be photoreceptors.

Photoreceptors are an appealing location for chemical magnetoreception for another reason. In order for chemical magnetoreception to yield directional (compass) information, reactions have to vary with the direction an animal faces. Thus, the molecules affected must presumably be held in a fixed orientation relative to the animal. The retina, with its numerous photoreceptors, provides an ordered array of receptor molecules that might potentially be exploited for this purpose[9,29].

Evidence for chemical magnetoreception

No empirical evidence exists at present to support or refute specific models of chemical magnetoreception. Evidence for a link between magnetoreception and the visual system, however, has come from several sources. Electrophysiological responses to magnetic fields have been detected in several parts of the avian nervous system that receive projections from the visual system[1,30]. For example, the nucleus of the basal optic root (nBOR) in pigeons receives projections from retinal ganglion cells, and some neurons in the nBOR respond to directional changes in the ambient magnetic field[31], as might be expected if these cells are components of a magnetic compass sense. Similar responses have been observed in cells within the optic tectum[32]. Responses to magnetic fields in both locations disappeared when the optic nerves were cut[30]. These results suggest that one locus of magnetoreception in birds is in the visual system, perhaps within photoreceptors themselves[1,30].

Another intriguing finding of electrophysiological experiments was that units in the pigeon nBOR responsive to magnetic stimuli exhibited different levels of sensitivity when the eyes were illuminated by light of different wavelengths[32]. These results led to subsequent experiments in which the magnetic orientation behavior of birds[33,34], newts[35] and flies[36] was found to change when the animals were tested under specific wavelengths of light. No consistent pattern has yet emerged between species, but wavelength-dependent effects reported so far include random orientation[33,34,37] and shifts of about 90° in orientation direction[35,36]. Although some results, such as random orientation, might conceivably be explained as an effect of wavelength on motivation[38] or by postulating that light is needed for the processing of magnetic information[30], 90° shifts in direction elicited by specific wavelengths are more difficult to explain as anything other than an effect on a receptor system[35,38].

Several studies have also suggested a link between magnetoreception and the pineal gland[39–42]. Electrophysiological recordings from pigeon pineal cells revealed units responsive to gradual changes in earth-strength magnetic fields[41]. Responses were reduced, but not abolished, when the optic nerves and other sources of input to the pineal were severed, implying that one source of magnetic sensitivity is within the pineal itself[41]. A recent study with newts has also revealed that a 90° shift in magnetic orientation direction that occurs when newts are tested under a specific wavelength of light[35] can be elicited if the pineal complex, but not the eyes, are illuminated with light of the same wavelength[42]. This finding has renewed interest in the pineal gland as a possible locus of magnetoreception in at least some animals.

Taken together, these results suggest that magnetoreception in some vertebrates might occur within specialized photoreceptors, even though the underlying mechanism remains obscure. In birds, photoreceptors in the retina are a possible locus[1,30], whereas in newts, extraocular photoreceptors in or near the pineal gland are good candidates[42]. The precise way in which light

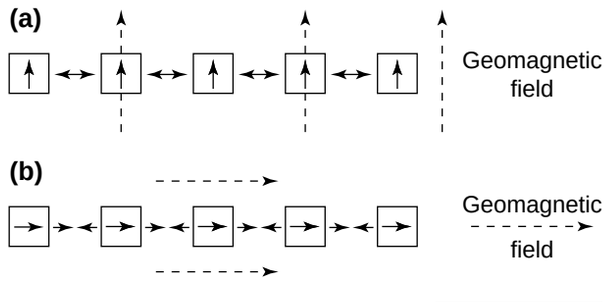

Fig. 1. ***A possible transduction process based on an array of interacting superparamagnetic magnetite crystals.*** *Each box represents a magnetite crystal; the arrow inside it represents the direction of the field the crystal generates. Each crystal field tracks the direction of the earth's field. In* **(a)**, *the orientation of the geomagnetic field and consequent orientation of the crystal fields result in a configuration in which adjacent crystals repel each other. The crystals behave like a row of bar magnets aligned side by side; the resulting interactions stretch the tissue or membrane in which the crystals are embedded. When the animal (and the superparamagnetic array inside it) are oriented differently relative to the earth's field, different interactions arise. A 90° change in ambient field direction relative to the array* **(b)**, *for example, results in adjacent crystals attracting each other like a row of bar magnets aligned end to end. The supporting material is compressed. Expansion and contraction of this type could be detected by stretch receptors or mechanoreceptors, or could activate stretch-sensitive ion channels in cell membranes directly if the crystals exist there.* Modified, with permission, from Ref. 5.

exerts an influence on the detection or processing of magnetic information is not yet known, and whether these results can be generalized to other vertebrates remains to be determined.

Biogenic magnetite

The discovery that crystals of the mineral magnetite (Fe_3O_4) underlie the ability of magnetotactic bacteria to swim along magnetic field lines[43] inspired searches for magnetite in diverse animals. Magnetite was subsequently detected in honeybees, birds, salmon, sea turtles and a number of other animals known to orient to the earth's magnetic field[6]. Most magnetite isolated from animals has been in the form of single-domain crystals similar to those found in magnetotactic bacteria[23]. Such crystals are minute, permanently magnetized bar magnets that twist into alignment with the earth's magnetic field if allowed to rotate freely.

Single-domain magnetite crystals might transduce geomagnetic field information to the nervous system in several different ways[5,44]. One possibility is that such crystals exert pressure or torque on secondary receptors (such as stretch receptors, hair cells or mechanoreceptors) as the particles attempt to align with the geomagnetic field. Alternatively, the movement of intracellular magnetite crystals might open ion channels directly if, for example, cytoskeletal filaments connect the crystals to the channels.

In some animals, magnetite crystals exist in a form that differs from that of single-domain crystals. Crystals of this second type are said to be superparamagnetic; they are smaller than single-domain particles and have different magnetic properties[5]. One characteristic is that the magnetic axis of a stationary superparamagnetic crystal can move about to track the direction of an ambient, earth-strength field. By contrast, the magnetic axis of a single-domain crystal is fixed and stable under the same conditions, and the crystal itself must rotate physically to track the field.

Superparamagnetic crystals generate fields strong enough to attract or repel adjacent crystals. Such intercrystal interactions provide the basis for another possible transduction mechanism (Fig. 1).

Evidence for magnetite-based magnetoreception

For magnetite crystals to function as magnetoreceptors in animals, the magnetite presumably needs to contact the nervous system. Although such a linkage has been hypothesized for more than two decades, direct anatomical evidence remains scarce. The strongest circumstantial case so far has come from studies with trout[45]. Analyses of the trout olfactory lamellae using confocal microscopy have revealed cells that appear to contain magnetite. The region of the trout nose containing these cells is innervated by the ros V nerve, which is one branch of the fifth cranial nerve (the trigeminal). Electrophysiological recordings from this nerve have revealed units that respond to magnetic stimuli consisting of abrupt changes in field intensity. These findings have led to the hypothesis that magnetite-containing cells in the trout nose function as magnetoreceptors and relay information to the brain through the trigeminal nerve. Because reversals of field direction did not elicit responses from units in the ros V nerve, the putative magnetite receptors have been hypothesized to detect field intensity, a parameter that is potentially useful in a map sense.

Similar results have been obtained in the bobolink, a migratory bird. In this case, magnetic material thought to be magnetite has been detected in an area of the upper beak[46,47]. As in the trout, the region that contains the putative magnetite appears to be innervated by the ophthalmic branch of the trigeminal nerve[48]. Specific neurons in the trigeminal ganglion, to which the ophthalmic nerve projects, respond to changes in vertical field intensity as small as about 0.5% of the earth's field[48] (Fig. 2). These cells have been hypothesized to function in a magnetic map sense and to receive input from magnetite-based receptors in the region of the upper beak[30]. Thus, in both a fish and a bird, possible magnetite-based magnetoreceptors have been located in a region of the head that is innervated by a branch of the trigeminal nerve.

Additional evidence suggesting that magnetite has a role in magnetoreception has come from pulse-magnetization experiments. A strong magnetic field of very brief duration can be used to alter the direction of magnetization in single-domain magnetite particles[49]. Such a procedure might therefore alter or destroy magnetite-based magnetoreceptors and thus change the behavior of animals that use such receptors to derive directional or positional information from the earth's field.

In several studies, the application of strong magnetic pulses to birds either randomized the preferred orientation direction or else deflected it slightly relative to controls[37,50–52]. These results have generally been interpreted as evidence for magnetite-based magnetoreceptors[1,37,50–52], although other explanations cannot be ruled out entirely[37].

Strong magnetic pulses could hypothetically alter magnetite-based receptors that are part of a compass sense, a map sense, or both. In birds, however, recent findings suggest that the effect might be on a map sense rather than a compass. Pulsed fields influenced the orientation of adult birds, which are thought to rely on map information for navigation, but failed to affect young birds, which complete their first migration by

flying along a consistent compass heading[53]. In addition, anesthetizing the ophthalmic nerve of bobolinks eliminated the effect of pulse magnetization, a result consistent with the hypothesis that the information altered by the pulse originated in the region of the upper beak that contains magnetite[54]. For these reasons, most authors have favored the interpretation that pulse magnetization affects magnetite-based magnetoreceptors involved in assessing positional information.

This tentative conclusion, however, might not hold for all vertebrates. Pulse magnetization also alters significantly the magnetic orientation behavior of mole rats, which have a magnetic compass but are not thought to possess a map sense[55]. These results highlight the possibility that magnetite receptors might have different functional roles in different animals.

Differences between mechanisms

In principle, all three mechanisms we have described can provide an animal with directional information that might be used in a magnetic compass sense. The information derived from the field, however, is not identical in all cases. Some magnetite models and the induction model are capable of detecting field polarity (that is, they can potentially differentiate between magnetic north and south[5,25]). By contrast, no current model of chemical magnetoreception allows for this[11,26]. Thus, a chemically based magnetoreceptor should detect only the axis of the field.

Two functionally different types of magnetic compasses have been discovered in vertebrates. Inclination compasses, which exist in birds[1] and sea turtles[56], do not detect the polarity of the field but instead define 'poleward' as the direction along the earth's surface in which the angle formed between the magnetic-field vector and the gravity vector is smallest. By contrast, salmon[57] and mole rats[58] have compasses that determine north using the polarity of the horizontal field component. Some salamanders possess both types of compasses and use each in different behavioral tasks[59].

Given the two compass types, it is tempting to conclude that each is based on a different mechanism. For example, inclination compasses might be based on chemical magnetoreception because animals with such compasses apparently cannot detect field polarity. Such an inference, however, might be premature because some arrangements of magnetite crystals could also result in receptors indifferent to polarity[5,60]. Moreover, higher-order neural processing might give rise to behavioral outputs that do not mirror precisely the properties of a receptor. At present, the only safe inference appears to be that chemical magnetoreception cannot account for polarity compasses.

The different mechanisms are also likely to have differing sensitivities to some magnetic features that might be used in magnetic maps. For example, magnetite-based receptors might be able to detect very small changes in field intensity[60], but the chemical and induction mechanisms probably cannot[3,10,26]. In the chemical models, the limitation is due to the small effect of field strength on the proposed reactions[10]. In induction models, difficulties arise because the animal would need to determine with great precision both its own velocity and the magnitude of the background (passive) electrical fields in its environment. Thus, given the very small field changes that an animal using a magnetic map would probably need to detect[13], a map sense based on intensity is not likely to be mediated by a chemical or induction mechanism.

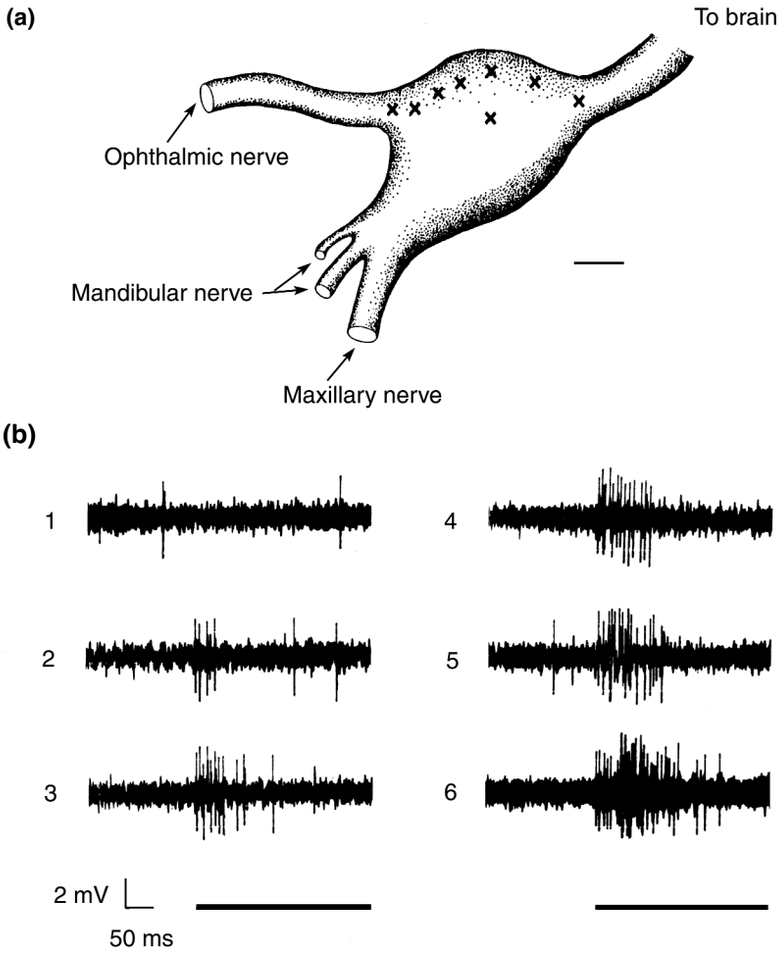

Fig. 2. ***Results of electrophysiological experiments with the bird*** **Dolichonyx oryzivorus** ***(the bobolink).*** **(a)** *The trigeminal ganglion of the bobolink, showing the nerves and locations (x) of neurons that respond with altered electrical activity to changes in the ambient magnetic field.* **(b)** *Recordings from one such ganglion cell during different changes in vertical magnetic-field intensity (these changes also alter the inclination of the field): (1) spontaneous activity; (2) response to 200 nT change; (3) response to 5000 nT change; (4) response to 15 000 nT change; (5) response to 25 000 nT change; (6) response to 100 000 nT change. The earth's field is approximately 50 000 nT. The stimulus onset is indicated by the bar below each series. Scale bar in* (a)*, 1 mm.* Modified, with permission, from Ref. 48.

Field intensity, however, is not the only magnetic feature that might provide map information. Field-line inclination also varies with latitude[14], and at least some animals can distinguish between different magnetic inclination angles[15,16]. To assess inclination, an animal would presumably need to integrate information from its magnetoreception system with information from a gravity-sensing system. No theoretical barrier, however, appears to preclude detection of magnetic inclination by a receptor system based on any of the three mechanisms.

Overview

Primary magnetoreceptors have not yet been identified with certainty in any animal. Circumstantial evidence, however, suggests that several different mechanisms have evolved among vertebrates. For electrosensitive marine fish such as sharks and rays, induction is plausible, but definitive tests remain to be carried out. In birds, the vertebrate group that has been studied most extensively, electrophysiological and behavioral data suggest the existence of two separate magnetoreceptor systems. The first, which is associated with

the visual system, might function to provide directional (compass) information and might be based on chemical reactions similar to those outlined by Schulten and his colleagues[10,11,26,27]. A second set of receptors, based on magnetite and associated with branches of the trigeminal nerve, might be involved in detecting features of the earth's field that can be used in assessing geographic position (map information). These conclusions are at best tentative, however, and the degree to which other vertebrates conform to this putative avian pattern is unclear. Significant differences between taxonomic groups are suggested by at least some results[1,55,58,61].

Although exceptions exist, much of what has been learned empirically about magnetoreception mechanisms has come from behavioral experiments. Such an indirect approach is understandable in the absence of a known receptor site, yet behavioral results can ultimately provide only limited insight into transduction mechanisms occurring at or below the cellular level. In no sensory system studied so far has an understanding of receptor function been obtained exclusively through behavioral means. What is needed now are sustained efforts to bring the tools and techniques of neuroscience to bear on magnetoreception research. For now, all mechanisms that have been proposed must be considered hypothetical, and this situation appears unlikely to change until primary magnetoreceptors are identified through neuroanatomical and electrophysiological means.

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From worm to man: three subfamilies of TRP channels

Christian Harteneck, Tim D. Plant and Günter Schultz

A steadily increasing number of cDNAs for proteins that are structurally related to the TRP ion channels have been cloned in recent years. All these proteins display a topology of six transmembrane segments that is shared with some voltage-gated channels and the cyclic-nucleotide-gated channels. The TRP channels can be divided, on the basis of their homology, into three TRP channel (TRPC) subfamilies: short (S), long (L) and osm (O). From the evidence available to date, this subdivision can also be made according to channel function. Thus, the STRPC family, which includes *Drosophila* TRP and TRPL and the mammalian homologues, TRPC1–7, is a family of Ca^{2+}-permeable cation channels that are activated subsequent to receptor-mediated stimulation of different isoforms of phospholipase C. Members of the OTRPC family are Ca^{2+}-permeable channels involved in pain transduction (vanilloid and vanilloid-like receptors), epithelial Ca^{2+} transport and, at least in *Caenorhabditis elegans*, in chemo-, mechano- and osmoregulation. The LTRPC family is less well characterized.

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SEVERAL TYPES of Ca^{2+}-permeable channel regulate Ca^{2+} entry into cells. Of the pore-forming proteins involved, some are well characterized both functionally and at the molecular level, whereas relatively little is known about others. The latter include channels involved in Ca^{2+}-entry mechanisms that are present in nearly all eukaryotic cells and others that are specific to specialized cell types. One of the former mechanisms is observed in cells after stimulation with agonists that bind to receptors coupling to phosphorylation cascades, or via heterotrimeric G proteins to different isoforms of phospholipase C (PLC). After phosphoinositide breakdown to Ins(1,4,5)P_3 and diacylglycerol (DAG), which is catalysed by PLC, a biphasic increase in intracellular Ca^{2+} concentration occurs. The first phase results from transient Ins(1,4,5)P_3-mediated Ca^{2+} release from intracellular stores, the second, more-sustained phase, from Ca^{2+} entry through Ca^{2+}-permeable membrane channels. Proposed roles for the second phase are the refilling of Ca^{2+} stores that have been emptied during the initial phase and the provision of a regulated Ca^{2+}-entry pathway for prolonging the response to the agonist.

Depending on the cell type, different Ca^{2+}-permeable channels, either highly Ca^{2+}-selective channels or Ca^{2+}-permeable nonselective cation channels, are involved in the sustained phase of Ca^{2+} entry (for reviews see Refs 1–3). The first of these channels to be characterized in detail was that mediating the Ca^{2+}-release-activated calcium current (I_{CRAC})[4,5]. These highly Ca^{2+} selective, low-conductance channels, which are activated after depletion of intracellular stores by an as yet unidentified factor, have since been described in a number of nonexcitable cell types[2]. However, despite considerable effort, the channel has not been identified at the molecular level. Other channels involved in receptor-mediated Ca^{2+} entry differ from those that mediate I_{CRAC}, either in their functional properties or in their mechanism of activation. Some, although store-operated, are less Ca^{2+} selective, whereas others are Ca^{2+} selective or nonselective cation channels that are activated by intracellular messenger systems, but are independent of store depletion[1,2,6]. The types of Ca^{2+}-entry mechanism described above have mainly been characterized in peripheral tissues, but are also likely to be of importance in the nervous system, where they might be involved in responses to the stimulation of G-protein-coupled receptors or receptor tyrosine kinases that activate different isoforms of PLC. In addition to signalling pathways such as those described above that are present in most cell types, many specialized cell types possess Ca^{2+}-permeable cation channels that have a key role in their specific function. These cells

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