

Glycoproteins Bound to Ion Channels Mediate Detection of Electric Fields: A Proposed Mechanism and Supporting Evidence

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The mechanism by which animals detect weak electric and magnetic fields has not yet been elucidated. We propose that transduction of an electric field (E) occurs at the apical membrane of a specialized cell as a consequence of an interaction between the field and glycoproteins bound to the gates of ion channels. According to the model, a glycoprotein mass (M) could control the gates of ion channels, where $M > 1.4 \times 10^{-18}/E$, resulting in a signal of sufficient strength to overcome thermal noise. Using the electroreceptor organ of *Kryptopterus* as a mathematical and experimental model, we showed that at the frequency of maximum sensitivity (10 Hz), fields as low as 2 $\mu\text{V}/\text{m}$ could be detected, and that the observation could be explained if a glycoprotein mass of 0.7×10^{-12} kg (a sphere 11 μm in diameter) were bound to channel gates. Antibodies against apical membrane structures in *Kryptopterus* blocked field transduction, which was consistent with the proposal that it occurred at the membrane surface. Although the target of the field was hypothesized to be an ion channel, the proposed mechanism can easily be extended to include other kinds of membrane proteins. Bioelectromagnetics 28:379–385, 2007. © 2007 Wiley-Liss, Inc.

Key words: field transduction; *Kryptopterus*; electroreceptor; ion channel

INTRODUCTION

The ability to detect weak electric and magnetic fields is exhibited by animals throughout the phylogenetic spectrum [Wachtel and Szamier, 1969; Gavalas-Medici and Day-Magdaleno, 1976; Blake-more, 1982; Wiltschkow and Wiltschkow, 1996; Preece et al., 1998; Pettigrew, 1999], but it has proved difficult to explain on a theoretical or mechanistic basis how such fields can be transduced by animal cells. Strong electric fields can directly alter membrane potentials [Reilly, 1998], but fields below about 0.1 V/m seem capable only of physical effects that are indistinguishable from noise [Astumian et al., 1997]. Models that incorporated a band-limited frequency-response mechanism, signal averaging, or rectification could rationalize detection of weak fields [Weaver and Astumian, 1990; Astumian et al., 1995, 1997], but evidence that these processes occur in cells or actually subserve sensory transduction is lacking. A syncytium structure could possibly explain effects occurring at 1–2 orders of magnitude lower than 0.1 V/m, but this lower field threshold would not be sufficient to explain

how typical environmental electric fields (or tissue electric fields produced by environmental magnetic fields) are transduced.

In some species of fish and mammals the ability to transduce weak fields has been localized to specific neuroepithelial electroreceptor cells and the afferent nerves that synapse on them [Szabo, 1974; Pettigrew, 1999]. It occurred to us that an examination of the anatomic organization of the electroreceptor cells in a field-detecting species might provide insight into a general biological model for transduction of weak

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fields. We chose the glass catfish (*Kryptopterus bicirrhıs*) for this purpose because it contains electroreceptor organs similar in design to those found in many other species [Wachtel and Szamier, 1969; Szabo, 1974]. In *Kryptopterus*, a typical electroreceptor organ consists of an invagination in the skin that contains 5–20 electroreceptor cells that are innervated by a single afferent neuron; the lumen of the organ is filled with glycoprotein molecules [Wachtel and Szamier, 1969]. The organ detects weak fields that occur in the animal's environment and propagate electrotonically to the apical membranes of electroreceptor cells.

Our primary objective was to describe a generally applicable mechanistic model for transduction of weak fields; we used the structure of the electroreceptor organ in *Kryptopterus* as the basis for the model. We propose that transduction occurs at the apical membrane as a consequence of an interaction between the field and glycoproteins bound to the gates of ion channels in the apical membranes of the electroreceptor cells. Our second objective was to calculate the strength of the threshold field detected by *Kryptopterus* to permit an evaluation of the reasonableness of the model. Our third objective was to test the model by showing that transduction occurred at the apical membrane, as proposed; this was accomplished by means of blocking antibodies.

MATERIALS AND METHODS

Electrical Measurements

Glass catfish (*Kryptopterus bicirrhıs*, approximately 5 cm long) were maintained in tap water (24 mS/m). For study, the fish were immobilized by injection of 10 μ g gallamine (Sigma, G 8134, St. Louis, MO), and anesthesia was maintained using 80 mg/L tricaine methanesulfonate (Argent, Redmond, WA). Current was applied by means of parallel silver wires located on either side of the anal fin (Fig. 1a,b). The current was generated using a function generator (Wavetek, San Diego, CA), or a computer with analog interface (TL-1 DMA, Axon) and a voltage–current converter; galvanic current between the electrodes was neutralized using an Axopatch ID (Axon).

The spike frequency of the electroreceptor nerve was measured using a glass Ag–AgCl microelectrode (10 M Ω) inserted into the opening of an electroreceptor organ (Fig. 1b,c). The micropipette was connected to an amplifier (Axopatch 200B, Axon Instruments, Foster City, CA) by a sepharose gel bridge. The reference electrode was Ag–AgCl. The measured signal was digitized and stored in a computer until analyzed. The experiments were carried out at 25 ± 1 °C.

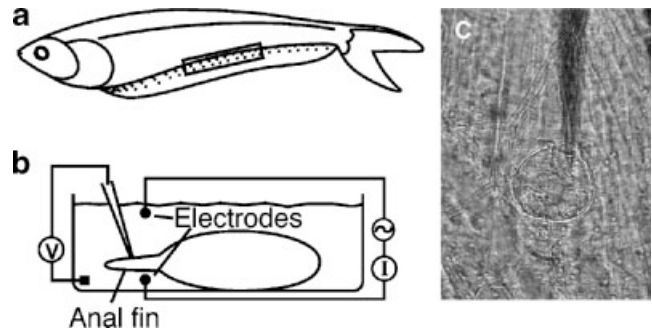


Fig. 1. **a**: Location of electroreceptor organs (shown as dots) on the anal fin of *Kryptopterus bicirrhıs* (1). Rectangle depicts the relative position of the stimulus electrodes (1 cm long, 0.5 mm in diameter; center-to-center separation, 8 mm). **b**: Cross-sectional view depicting voltage measurement inside an electroreceptor organ of an anesthetized fish exposed to an electric field. **c**: Microelectrode inserted into the opening of electroreceptor organ.

Spike frequency was recorded continuously. A trial consisted of the application of a DC or sinusoidal electric field for 2 s (field epoch), followed by a 2-s field-off interval (baseline epoch), except that the epochs were 20 and 6.7 s for the 0.1 and 0.3 Hz stimuli, respectively. The mean \pm SD of the spike frequency was calculated for the field and baseline epochs in 40 consecutive trials, except for 0.1 and 0.3 Hz, where the mean \pm SD of the spike frequency was calculated for 3 and 5 trials, respectively.

To determine the effect of antibodies (see below) on spike frequency, a micropipette was inserted into the same organ whose activity had been studied in the absence and presence of the field, and antibodies or control antibodies were injected at the surface of the electroreceptor cells using low positive pressure, after which the measurement of spike frequency in the absence and presence of the field was repeated. The effect of the antibodies on the field-induced change in spike frequency was evaluated using the paired *t*-test.

Antibodies

Anal and tail fins, which contain numerous electroreceptor organs [Wachtel and Szamier, 1969], were dissected from approximately 70 fish and pooled. The preparation was kept in buffer (in mM, 120 NaCl, 3 KCl, 1 CaCl₂, 2 MgCl₂, 10 HEPES, pH 7.4) at 4 °C for 1.5 h, and then incubated with 1 g/L hyaluronidase and 1 g/L collagenase for 20 min at 37 °C. The supernatant was homogenized in 0.32 M sucrose buffer, centrifuged at 250g for 10 min at 4 °C, and the resulting supernatant was centrifuged at 60,000g for 30 min at 4 °C. The pellet of crude membranes was resuspended in 1 ml of 50% sucrose buffer in a centrifuge tube; 36% and 25% layers of sucrose buffer (3 ml each) were added to obtain sucrose concentration steps of 50%/36%, and 36%/

25%. Following centrifugation at 54,000g for 3 h at 4 °C, the plasma membrane fraction was collected from the 36%/25% interface, centrifuged at 60,000g in 0.32 M sucrose for 30 min at 4 °C, and frozen at -70 °C until used for production of antibodies.

Antibodies against plasma-membrane fragments were produced using standard methods [Harlow and Lane, 1988]. Briefly, 200 µg of membrane fragments in 150 µl of phosphate-buffered saline were mixed with 150 µl of complete Freund's adjuvant and injected intraperitoneally into mice. The immunization procedure was repeated 2 and 4 weeks later, using incomplete Freund's adjuvant, and the blood was recovered 2 weeks after the last immunization. Immunoglobulin was isolated from the serum of immunized and non-immunized mice using ammonium sulfate.

Histochemistry

Anal fins were fixed in formalin, processed for paraffin embedding using standard techniques, and 5-micron sections cut perpendicularly to the fin were mounted on slides. Odd-numbered slides were stained with hematoxylin and eosin (H&E). When electroreceptor organs were identified, the corresponding even-numbered slides were used for immunohistochemistry (IHC) as follows. The slides were deparaffinized, the antigens were retrieved by steaming for 15 min in citrate buffer, and the slides were treated with 0.3% hydrogen peroxide in methanol to block endogenous peroxidase and with horse serum to block background staining. The slides were then incubated overnight with immunoglobulin from immunized mice, diluted 1:400 in saline. Control slides were incubated in saline only. Gut was used as a control tissue. IHC localization of the membrane proteins was performed using the ABC method (Vectastain, Vector, Burlingame, CA).

Electric Field Calculations

A representative fish was cut into a contiguous series of 1-mm thick transverse sections, and the shape and dimension of each section were used to build a mathematical model for *Kryptopterus*. Assumed conductivities of the skin and internal tissue were 0.8 mS/m [Caputi et al., 1998] and 100 mS/m [Durney et al., 1986], respectively; the conductivity of the water was the measured value (24 mS/m). The electric field (Fig. 3) was calculated in two stages, using Femlab (Comsol, Los Angeles, CA). First, the field was determined at 10 µm above the surface of the anal fin in the vicinity of an electroreceptor organ, and those values were then used as boundary conditions to find the field within the organ. Only a portion of the fish was used in the actual computation in the second stage;

however, restricting the size of the model did not significantly affect the calculated fields (<1% change) because the region of tissue surrounding the organ was much larger than the organ itself.

The apical face of each electroreceptor cell is exposed to the lumen of the organ, and the cell is sealed around its margin by tight junctions [Bennett, 1971]. The group of electroreceptor cells of the organ was therefore modeled as an oblate spheroid (semi-major and semi-minor axes of 26 and 7 µm, respectively) located at the bottom of a glycoprotein-filled spherical cavity 90 µm in diameter. The conductivity of the interior of the spheroid was taken as 100 mS/m; it was bounded by a 5-nm membrane having a conductivity of 0.07 µS/m. The lumen (24 mS/m) was separated from the internal tissue of the fish (100 mS/m) [Durney et al., 1986] by a 5-µm thick membrane (0.8 mS/m) [Caputi et al., 1998] that lined the cavity and was continuous with the skin; the cavity was connected to the water by a circular opening of diameter 20 µm.

The electric field in the electroreceptor organ was calculated in the absence of the microelectrode that was used for measuring spike activity. No correction was made for the presence of the electrode, which decreased the field in the lumen (and consequently decreased electroreceptor sensitivity) by less than 12%, as calculated on the basis of the effective reduction in the diameter of the lumen pore.

RESULTS

First, we describe the model for cellular transduction of weak electric fields. Then we describe the results of a direct determination of the field sensitivity of electroreceptor organ in *Kryptopterus*, and of a calculation of the corresponding electric field at the cell apical membrane of the electroreceptor cells. Lastly, we present evidence that transduction of the field occurred at the apical membrane, as hypothesized.

Model

We postulate that electric fields are detected by means of a process in which the field exerts a force on glycoprotein molecules that are connected to the gate of an ion channel (Fig. 2). Formally, $|q\mathbf{E}\Delta x| \geq U \geq kT/2$, where q is the net negative charge on the molecules, \mathbf{E} is the electric field, Δx is the displacement of the channel gate (~6 nm), U is the potential-energy barrier between closed and opened channel states, k is Boltzman's constant, T is temperature, and $kT/2$ is the thermal energy associated with one degree of freedom. Each glycoprotein molecule contains many negative charges ($q = -eZ$, where e is the elementary charge and Z is the number of charges per molecule); the molecules could

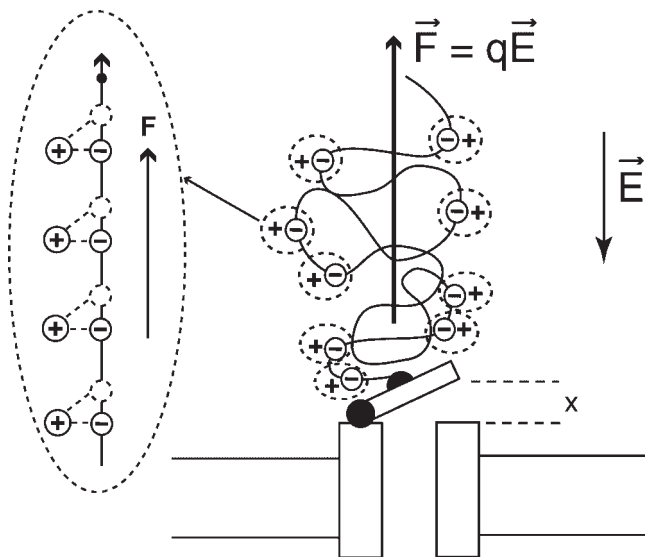


Fig. 2. Proposed model for electroreception. An applied electric field exerts a force F on a negatively charged gel molecule thereby mechanically opening the gate of an ion channel. The molecule may be covalently bound to the gate, or may be interleaved with glyco-groups covalently attached to the gate. The displacement of the channel gate (Δx) is assumed to be 6 nm. It is assumed that the negative glyco-groups rotate slightly with respect to the positive counter-ions. The assumption is reasonable for small displacements.

be connected to each other by covalent or non-covalent bonds. Thus, $neZE\Delta x \geq kT/2$, where n is the number of molecules that control a channel.

To estimate the mass (M) of the glycoproteins that could control a channel gate, we assume that the molecules are polymers and that each monomer has one negative elementary charge, and the same mass, m (assumed to be that of a hyaluronan disaccharide, 6.697×10^{-25} kg). Then, $M = nZm$, and from the inequality above, $M \geq kTm/2eE\Delta x = 1.4 \times 10^{-18}/E$.

Field Sensitivity of Electroreceptor Cells

To estimate E , we measured the sensitivity of the electroreceptor organ and then calculated the field corresponding to maximum sensitivity. In the absence of an applied current, the spike frequency (F) of the afferent nerve was 60–90 Hz, depending on the fish; F increased or decreased, depending on the strength and direction of the current (data not shown). When the response of the electroreceptor organ was assessed by plotting the sensitivity (change in spike frequency per unit of stimulus) as a function of frequency and field strength, a maximum response occurred near 10 Hz (Table 1).

Field Calculation

The electric field distribution inside the electroreceptor organ was calculated for the case of the

TABLE 1. Sensitivity ($\Delta F/E$) Versus Stimuli Frequency (f)

f (Hz)	$\Delta F/E$ (Hz/ $\mu\text{V}/\text{m}$)
DC	0.014 ± 0.002
0.1	0.136 ± 0.053
0.3	0.693 ± 0.117
1	1.577 ± 0.671
10	2.927 ± 0.386
20	1.934 ± 0.412

Average of five sensitivity determinations per fish per frequency, averaged for 10 fish (mean \pm SD). The baseline spike frequency (zero stimulus) did not change during the measurements (about 2 h). In our experimental set-up, a field of $1 \mu\text{V}/\text{m}$ was produced by an applied current (I) of 1 nA. Therefore sensitivity can also be expressed as $\Delta F/I$ (Hz/nA).

potential difference that produced an inter-electrode current of 2 nA. The corresponding electric field at the surface of the apical membrane of the electroreceptor cells was $1.5\text{--}2 \mu\text{V}/\text{m}$ (Fig. 3).

Evidence for Transduction at Apical Membrane

To support the idea that field transduction occurred at the apical membrane, we developed anti-

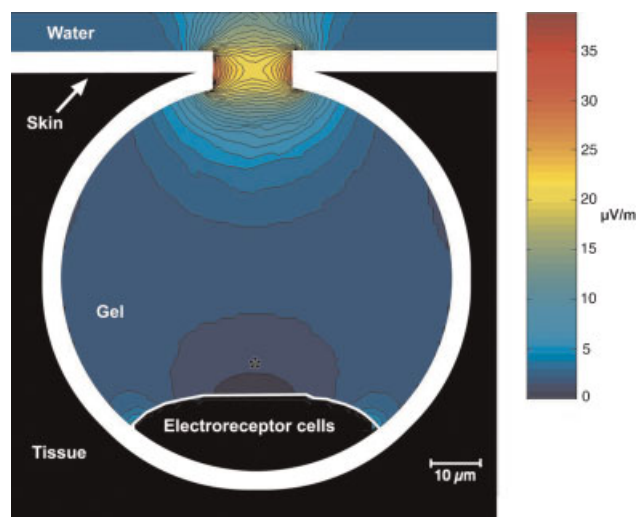


Fig. 3. Calculated electric field inside an electroreceptor organ corresponding to the application of 2 nA (see Fig. 1); the fields associated with higher currents were proportionally greater. Resolution of contour lines, $2 \mu\text{V}/\text{m}$ (First contour (*), $1.5 \mu\text{V}/\text{m}$). Assumed conductivities: water and gel, 24 mS/m; tissue, 100 mS/m [Durney et al., 1986]; cell interior, 100 mS/m; cell membrane, $0.07 \mu\text{S}/\text{m}$; skin, 0.8 mS/m [Caputi et al., 1998]. Under our model, the electric field inside an electroreceptor organ is the effector agent of transduction. Therefore, for clarity, the electric field in the tissue and in the interior of the electroreceptor cells was set to zero in the illustration. [The color figure for this article is available online at www.interscience.wiley.com.]

bodies against proteins in the membrane of electroreceptor cells and showed that the antibodies blocked electroreception. Immunoglobulin from mice that had been immunized with membrane fragments of electroreceptor cells stained the membrane of electroreceptor cells (Fig. 4a) but not that of the epithelial cells in the gut (Fig. 4c), indicating that the immunoglobulin contained antibodies against structures specific to the membrane of electroreceptor cells. The absence of antibody staining of the gut cells suggested that their apical membranes did not contain structures identical to those in electroreceptor cells.

Electroreception was blocked by immunoglobulin from the immunized mice, but not by immunoglobulin from non-immunized mice (Figs. 5 and 6). In the absence of a DC field, the baseline spike frequency for the fish depicted in Figure 5a–d was about 64 Hz. When 400 nA DC was applied (about 400 $\mu\text{V}/\text{m}$ at the surface of the electroreceptor cell) the spike frequency increased by about 35% (Fig. 5b). Addition of immunoglobulin containing electroreceptor-cell antibodies did not affect baseline spike frequency (Fig. 5c) but the immunoglobulin eliminated the effect of the field (Fig. 5d compared with Fig. 5b). When the experiment was repeated using immunoglobulin that did not contain electroreceptor-cell antibodies, no effect occurred on the ability of the fish to detect the field (Fig. 5f compared with Fig. 5h). Low-frequency fields produced similar results (Fig. 6). In the absence of the fields the baseline spike frequency was 64–66 Hz, depending on the fish. Following application of 10 $\mu\text{V}/\text{m}$ (calculated field at the membrane surface), the spike frequency increased by about 30%. The increase was specifically blocked by antibodies in the immunoglobulin from the immunized mice.

DISCUSSION

The ability to detect weak fields is a sensory modality for which there is no satisfactory mechanistic explanation. In general, detection limits for sensory transduction are set by thermal fluctuations in the detecting system [Bialek, 1987], and the same principle presumably applies to the detection of weak fields [Barnes, 1986]. The problem, therefore, is to explain how weak fields in tissue can produce a deterministic cellular response in the presence of thermal fluctuations, which are ordinarily thought of as being far larger than the predicted displacement caused by the fields. Models have been proposed to rationalize determinism including those based on frequency-band specificity [Weaver and Astumian, 1990], rectification [Astumian et al., 1995], resonance [Astumian et al., 1997], and magnetite [Kirschvink et al., 2001]. Our approach was to focus on a proposed transduction mechanism and describe how it works.

According to our model (Fig. 2), the minimal mass of glycoproteins needed to detect a field of 2 $\mu\text{V}/\text{m}$ is $M \approx 1.4 \times 10^{-18} / 2 \times 10^{-6} \approx 0.7 \times 10^{-12}$ kg, which corresponds to a sphere of about 11 μm in diameter. Electroreceptor cells have diameters of 10–20 μm . If we assume that the glycoproteins form prolate ellipsoids, it is easy to see that they could control the opening of 10–20 ion channels per cell, which could be sufficient to initiate transduction by the same mechanism as that occurring in stretch receptors. A 2-MDa hyaluronan molecule has a length of about 5 μm , and individual hyaluronan molecules can be linked together to form cables >200 μm [Day and de la Motte, 2005]. Thus, the force applied to the glycoproteins by the field could cause a simultaneous response in many cells.

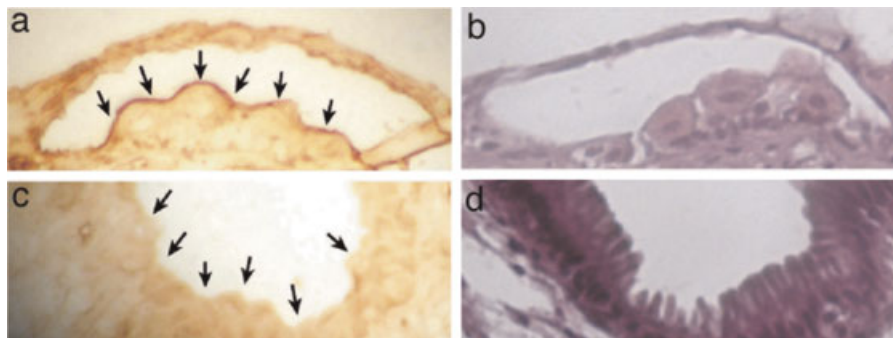


Fig. 4. Histochemistry of tissues from *Kryptopterus* (60 \times). **a**: Section through electroreceptor organ showing staining of the apical membranes of the electroreceptor cells with electroreceptor-cell antibodies (arrows). **b**: A section 15 μm distant, stained with H&E to show individual cells. **c**: A section through the gut to show that the same antibodies did not stain the gut epithelial layer (arrows). **d**: An adjacent section of the gut stained with H&E to show that the epithelial layer was intact. [The color figure for this article is available online at www.interscience.wiley.com.]

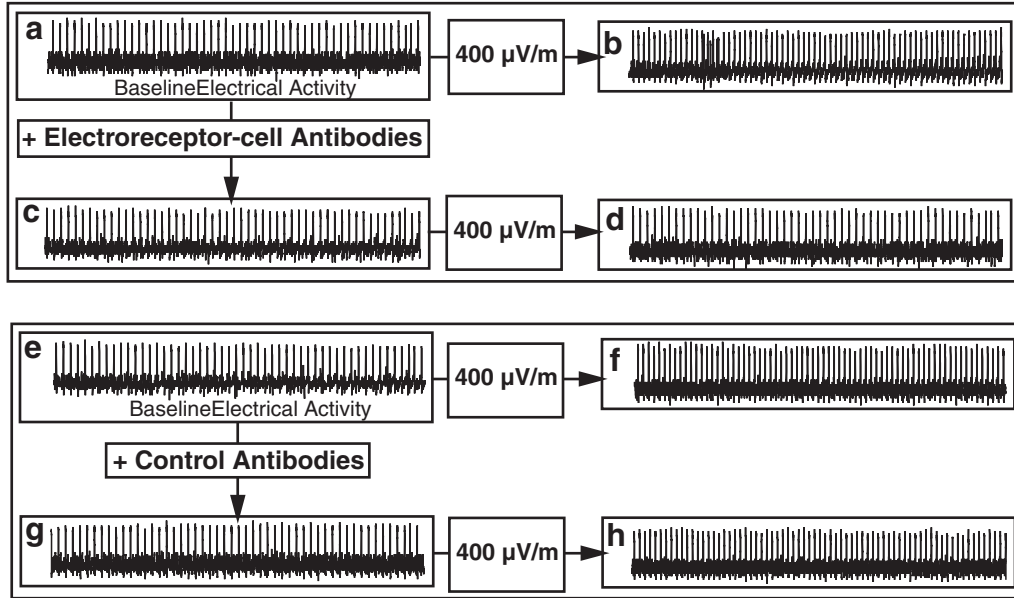


Fig. 5. Extracellular registration of the effect of antibodies to electroreceptor-cell membrane fragments on the response of electroreceptor-nerve spike frequency in *Kryptopterus* to the application of a direct-current electrical stimulus of 400 $\mu\text{V/m}$ (400 nA). **a**: Baseline (pre-stimulus) electrical activity. **b**: Application of electric field. **c**: Baseline activity after addition of mouse antibodies raised against *Kryptopterus* electroreceptor-cell membrane fragments. **d**: Electrical activity in the presence of both the antibodies and the electric field. **e–h**: Same conditions as in **a–d** respectively (using another fish), except using control antibodies. The duration of each record was 0.8 s.

Charge distributions near channel gates result in a highly non-uniform field over nanometer dimensions, with accompanying local changes in conductivity and dielectric constant. Our calculation is limited to the case

where variations occur over much larger distances. However, the field-sensitive element in the mechanism we suggested is located at distances from the membrane of the order of micrometers. At this distance the electric

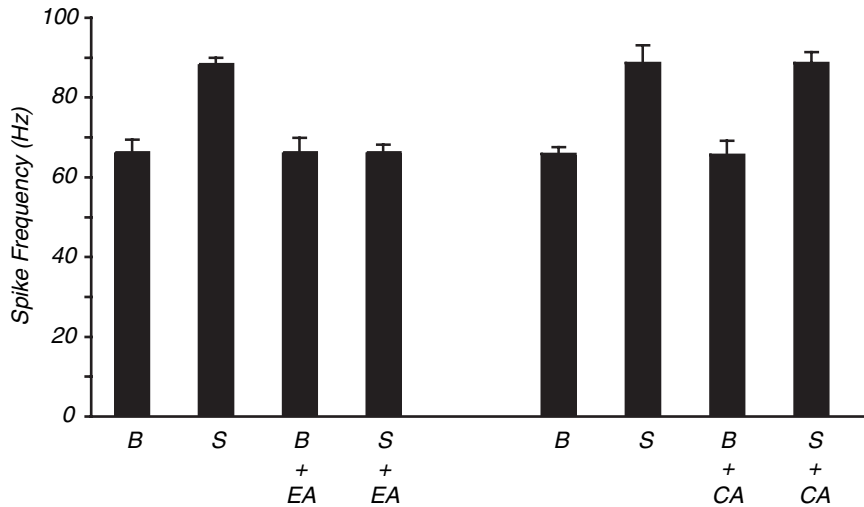


Fig. 6. Effect of antibodies to electroreceptor-cell membrane fragments on the response of electroreceptor nerve activity in *Kryptopterus* to low-frequency electric fields. B, baseline electrical activity. S, 10 $\mu\text{V/m}$ (10 nA), 10 Hz. EA, electroreceptor-cell antibodies. CA, control antibodies. Each group of four measurements was made using a different fish. Each bar is an average of 10 measurements \pm SD. Paired *t*-test for B and S, B + EA and S + EA, B and S, B + CA and S + CA gave the following *t* values: 18, 0.04, 13, 22, which corresponded to the probability of coincidence of B + EA and S + EA of 0.97. The probability of coincidence of other pairs was $<4 \times 10^{-7}$. Application of an electric field at 5 and 20 Hz gave similar results.

parameters of the medium are smooth and uniform (in comparison with those at the channel gate). Thus, despite the limitation of our calculation, we were able to ascertain the field in the area where the charged groups were located.

We wish to emphasize the generality of the model (Fig. 2), and its formal similarity to other forms of transduction. The target in the membrane need not be an ion channel. It could be, for example, an integral membrane protein whose extracellular portion binds to glycoproteins and undergoes a structural modification in the presence of a field resulting in activation of an enzyme at the intracellular terminus of the protein. Transduction occurs at the apical membrane for most other sensory modalities, including sound, touch, and taste, and it is therefore reasonable to expect that such might also be the case for electroreception.

If an interaction between the electric field and structures on the apical membrane of the electroreceptor cells were an essential part of the process of electroreception, then antibodies against the membrane structures might block transduction, and this is what we observed. Response sensitivity was a maximum at about 10 Hz (Table 1). At that frequency, we calculated that the fish could detect a field of approximately 2 $\mu\text{V}/\text{m}$ (Fig. 2). Immunoglobulin containing antibodies raised against membrane fragments from electroreceptor cells stained the apical membranes of the cells (Fig. 4a), and blocked field-induced changes in spike frequency of the afferent neuron which innervated the electroreceptor organ to which the antibodies had been applied (Figs. 5 and 6); such frequency changes can be considered to be the terminal event in the process of transduction. The antibodies did not stain gut epithelial cells (Fig. 4b) and control antibodies did not block electroreception (Figs. 5 and 6), thereby independently indicating that the antibodies were relatively specific for electroreceptor cells. Taken together, this evidence indicated that antibodies against one or more membrane structures blocked transduction of the field. One possibility was that the antibodies became bound to charged structures that directly interacted with the field or were involved in the early part of the signaling pathway, thereby blocking transmission of a signal that coded for the presence of the field.

Although the results showed that an important component of the system responsible for detecting the field was located on the apical membrane, they did not prove that the component necessarily played an active role. The possibility remained that the antibodies merely plugged hypothetical unregulated pores [Bennett, 1971] in the apical membrane, thereby preventing the electric field from passing through

the apical into the cell. If unregulated pores were actually present in the apical membrane, it can be shown that the electric field there (Fig. 3) would propagate to the inner surface of the basolateral membrane. The proposed model (Fig. 2) could then explain transduction on the basis of ion channels in the basolateral membrane.

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